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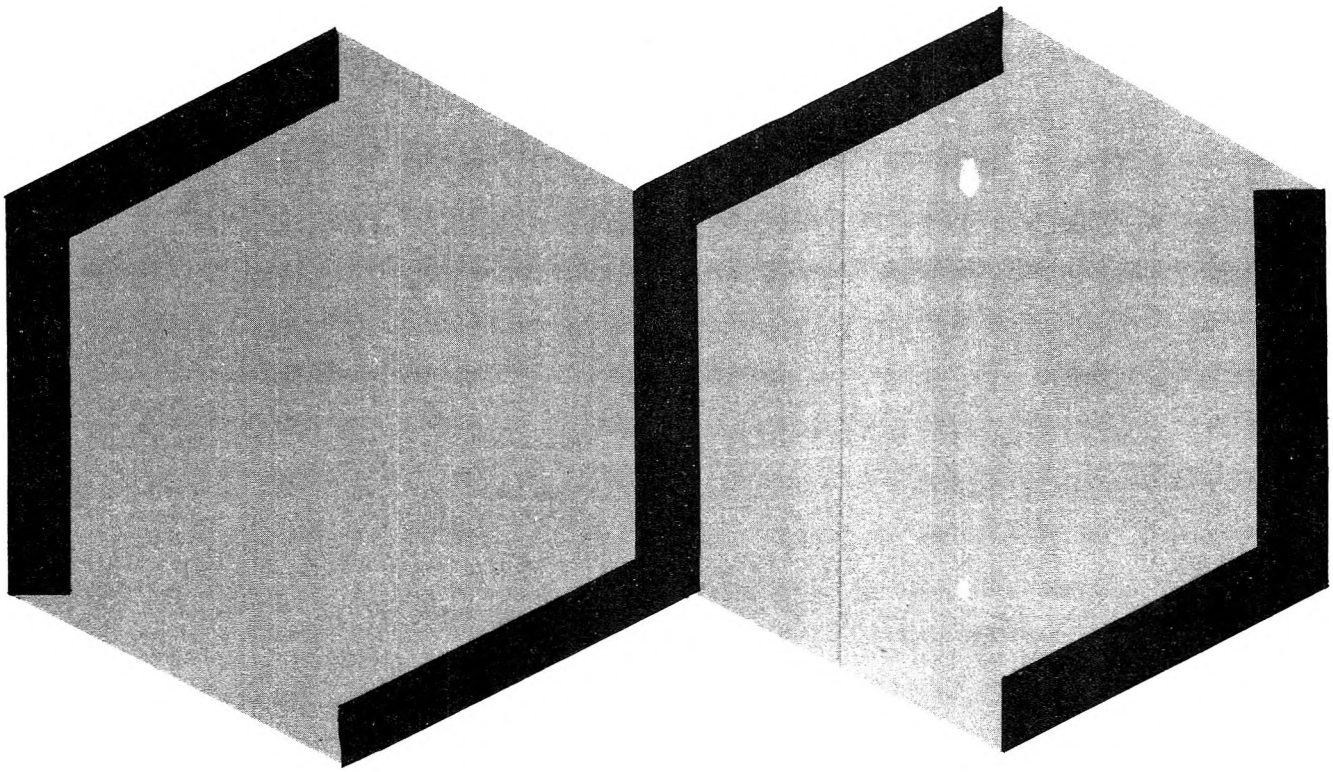

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AUTHOR INDEX

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OCTOBER 31, 1975

2-Halopyrroles. Synthesis and Chemistry[1a]

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Received May 12, 1975

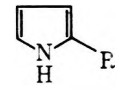
Following the confirmation that both 2-chloropyrrole (1) and 2-bromopyrrole (2) were unstable species, a number of 1-alkyl- and *C*-alkyl-2-halopyrroles were synthesized to investigate the range of instability. The 1-alkyl-2-halopyrroles synthesized were 2-chloro-1-methylpyrrole (14), 2-bromo-1-methylpyrrole (15), 1-benzyl-2-chloropyrrole (47), and 1-benzyl-2-bromopyrrole (46). The *C*-alkyl-2-halopyrroles synthesized were 5-chloro-2-methylpyrrole (26), 2-*tert*-butyl-5-chloropyrrole (36), 5-chloro-2,3,4-trimethylpyrrole (29), and 5-bromo-2,3,4-trimethylpyrrole (20). Also synthesized were the 1-methyl derivatives of 26 and 29. Electrophilic substitution of 2-chloro- and 2-bromopyrroles (1 and 2) under the conditions for formylation and diazo coupling was examined. In the case of the latter reaction no crystalline compounds could be isolated, but diazo coupling of 2-chloro-1-methylpyrrole (14) gave rise to exclusive α substitution. Formylation of 2-chloropyrrole (1) gave the α-substituted derivative but 2-bromopyrrole (2) gave a product arising from the displacement of bromine. 5-chloropyrrole-2-carboxaldehyde (28), in addition to 5-bromopyrrole-2-carboxaldehyde (41).

Electrophilic substitution of simple pyrrole derivatives occurs regioselectively at the 2 position[2] and at a rate considerably faster than in the furan and thiophene series.[3] The simple electrophilic substitution reactions such as nitration,[4] sulfonation,[5] and formylation[6] therefore give rise to the 2-substituted product almost[2] to the exclusion of the 3-substituted derivative. In all cases these products are well-characterized compounds with clearly defined physical constants.[7] However, 2-chloropyrrole (1) and 2-bromopyrrole (2), the expected products of halogenation, are poorly characterized compounds. In addition, there is evidence that these compounds are quite unstable.

Mazzara and Borgo,[8] using sulfuryl chloride in ether as the chlorinating agent, were the first to report the synthesis of 1. Attempted isolation indicated that both 1[8] and 2,5-dichloropyrrole (3)[9] were probably labile. This observation was supported by the work of Hess and Wissing,[10] who heated the pyrrolyl Grignard (4) reagent[11] with chlorine in ether and obtained a highly unstable yellow oil. More recently, a Russian group[5] prepared 2-chloropyrrole (1) but no comment was made as to the stability of the product. Further evidence for the instability of 2-chloropyrrole (1) comes from the work of Hodge and Rickards.[12] Decarboxylation of 5-chloropyrrole-2-carboxylic acid (5) under reduced pressure afforded a yellow oil which rapidly decomposed to a black mass on exposure to air.

There are only two reported attempts to prepare 2-bromopyrrole (2). Bromination of the pyrrolyl Grignard (4) with bromine in ether afforded a highly unstable oil.[13] Attempts to decarboxylate 5-bromopyrrole-2-carboxylic acid (6)[14] also failed to give any 2.

Neither 3-chloropyrrole (7) nor 3-bromopyrrole (8) is known. 3,4-Dichloropyrrole (9) has been prepared on three occasions and has consistently been described as a white, crystalline, stable solid.[15-17]



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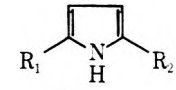
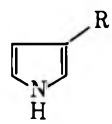
2, R = Br

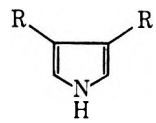


3, R_1, R_2 = Cl
5. R_1 = Cl; R_2 = CO_2H
6, R_1 = Br; R_2 = CO_2H
10. R_1, R_2 = Br
13. R_1, R_2 = CH_3
26, R_1 = Cl; R_2 = CH_3
28, R_1 = Cl; R_2 = CHO
39, R_1 = Cl; R_2 = SO_2OH
41, R_1 = Br; R_2 = CHO

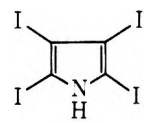
4



7, R = Cl
8, R = Br



9. R = Cl
12. R = CH_3



11

The initial aim of this study was therefore to prepare 2-chloropyrrole (1) and 2-bromopyrrole (2) in a state suitable for thorough analysis.

Preparation of 2-Chloropyrrole (1), 2,5-Dichloropyrrole (3), 2-Bromopyrrole (2), and 2,5-Dibromopyrrole (10). 2-Chloropyrrole (1) was prepared from pyrrole by the two methods[8-10] described previously. A modification of the method due to Mazzara and Borgo[8] was the most effective (see Experimental Section).

NMR and GC[18] analysis of the crude product indicated the presence of a major component and two minor components, one of these being unreacted pyrrole.

The mixture was fractionally distilled with a series of high-boiling aliphatic tertiary amines to inhibit decomposi-

tion.[20] Two main fractions were obtained and NMR examination showed them to contain **1** and **3**.

The pure compounds were obtained in ether solution by precipitation of the quaternary ammonium salt with methyl iodide. The spectral properties of these compounds were consistent with the assigned structures.

A mixture containing 2-bromopyrrole (**2**) was produced by the method of Hess and Wissing[13] and purification effected by column chromatography. The spectral properties of the two compounds isolated were consistent with their formulation as 2-bromopyrrole (**2**) and 2,5-bromopyrrole (**10**).

Properties of 2-Halopyrroles. 2-Chloropyrrole (**1**), a colorless oil with a strong, characteristic odor, was stable in air for periods ranging from 10 sec to 55 min, presumably depending on trace impurities. Decomposition[21] spreads rapidly throughout the liquid, which becomes black, hydrogen chloride is vigorously evolved and the exothermic reaction is complete in 5–10 sec. The black mass remaining proved to be intractable and no spectroscopic data could be obtained. No melting point was observed below 700° and in the process of heating to this temperature, a white solid sublimed which analyzed well for ammonium chloride. Microanalytical data of the black mass were not reproducible, the product apparently adsorbing variable amounts of oxygen. The black mass produced by the spontaneous decomposition of 2-chloropyrrole (**1**) is reminiscent of the material obtained by the thermal decomposition of 2,3,4,5-tetraiodopyrrole (**11**).[22,23]

2-Chloropyrrole (**1**) distilled under high vacuum (10^{-4}–10^{-5} mmHg) as a colorless oil, but decomposition was initiated (5–7 min) on the glass surface.

2-Chloropyrrole (**1**) was recovered in 90–95% yield after treatment with sodium–liquid ammonia, sodium amide–liquid ammonia, or potassium amide–liquid ammonia. In the presence of ethanol, sodium–liquid ammonia effected quantitative removal of the halogen atom to afford pyrrole. Only under vigorous conditions (THF under reflux for 14 hr) was the halogen atom removed by lithium aluminum hydride. 2-Chloropyrrole (**1**) was stable in ether at 0° for several months, but in all other common solvents lifetimes were only 1–2 days. It was found to be very sensitive to acidic reagents such as dry HCl gas, hydroquinone, chloroform, or glacial acetic acid. Decomposition was also accelerated under basic conditions, such as potassium *tert*-butoxide in *tert*-butyl alcohol or alcoholic aqueous potassium hydroxide, or by benzoyl peroxide.

2-Bromopyrrole (**2**), a colorless liquid, decomposed upon removal of solvent within 60 sec. Attempted purification by fractional distillation in the presence of aliphatic tertiary amines failed, owing to thermal decomposition above 40°. The halogen atom was not removed by potassium amide in liquid ammonia, and dry hydrogen chloride gas greatly accelerated the decomposition process.

The dense, colorless liquid, 2,5-dichloropyrrole (**3**), was more stable (2–5 min induction time) than the white solid, 2,5-dibromopyrrole (**10**), which decomposed almost instantaneously upon removal of solvent.

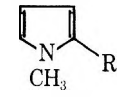
3,4-Dimethylpyrrole (**12**) is not readily autoxidized,[24] certainly not as readily as 2,5-dimethylpyrrole (**13**),[25] a situation parallel to that of the halopyrroles, where 3,4-dichloropyrrole (**9**) is a stable, white, crystalline solid[15–17] and 2,5-dichloropyrrole (**3**) is a very unstable, low-melting solid.

Having confirmed the literature reports[8,10,13] that 2-chloropyrrole (**1**) and 2-bromopyrrole (**2**) are indeed unstable, attention was turned to a study of the alkyl-substituted derivatives.

Studies on the autoxidation of pyrrole[26] and some 1-alkylpyrroles[25] have indicated that labile peroxides are formed in the initial stages of the reaction, and several of the initial products have been isolated and characterized. A *C*-alkylpyrrole such as 2,5-dimethylpyrrole (**13**) was found to consume oxygen at a considerably faster rate than did 1-methylpyrrole.

It was considered that the instability of 2-chloropyrrole (**1**) might be mitigated by the preparation of *N*-alkyl derivatives. Conversely, owing to electronic considerations, it was considered that C-alkylation would decrease the stability of a 2-halopyrrole. Subsequent work confirmed these ideas and gave preliminary information of the structure requirements for stability in the 2-halopyrrole series.

Preparation and Properties of 2-Chloro-1-methylpyrrole (14) and 2-Bromo-1-methylpyrrole (15). 2-



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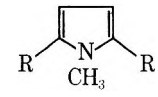
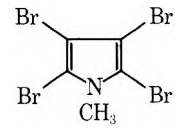
15, R = Br



16, R = Cl
18, R = Br



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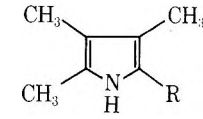


19, R = I
20, R = Br
21, R = H
29, R = Cl

Chloro-1-methylpyrrole (**14**) was prepared by chlorination of 1-methylpyrrole with 1 equiv of sulfuryl chloride in ether at 0°. GC of the ethereal extract after work-up indicated the presence of the 2-chloro and 2,5-dichloro products, **14** and **16**, as established by NMR analysis. The reaction product was found to be quite stable to heat and consequently it was fractionally distilled under reduced pressure without codistillant. It did not decompose to a black mass when in the pure state, but one sample did resinify after some weeks at 0° in a manner characteristic of pyrrole itself.[27] Dry hydrogen chloride gas also produced resinification rather than the decomposition reaction.

2-Chloro-1-methylpyrrole (**14**) was not attacked by lithium aluminum hydride or potassium amide in liquid ammonia; starting material was recovered in good yield. This is in contrast to the thiophene series,[28] where Cine substitution[29] occurs. The chlorine atom of **14** is effectively removed with sodium in liquid ammonia.

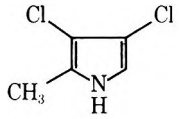
The synthesis of 2-bromo-1-methylpyrrole (**15**) proved to be more difficult and no pure sample was obtained. Bromination of 1-methylpyrrole, by the method of Anderson and Griffiths,[30] gave a complex mixture consisting mainly of the known compound 2,3,4,5-tetrabromo-1-methylpyrrole (**17**)[31] and unreacted 1-methylpyrrole. Similar results were obtained with pyridinium bromide perbromide,[14,32] cupric bromide,[14] and *N*-bromosuccinimide.[14]

The most successful method was to add bromine in carbon tetrachloride to a dilute solution of 1-methylpyrrole, with magnesium oxide as a slurry. Chromatography of the residue, after removal of the tetrabromo derivative by fractional crystallization, afforded a fraction which by NMR was shown to be predominantly (60%) 2-bromo-1-methylpyrrole (**15**), together with some 1-methylpyrrole and 2,5-dibromo-1-methylpyrrole (**18**, 35%).

No *C*-alkyl-2-chloro- or 2-bromopyrroles are known and only one 2-iodo compound, 5-iodo-2,3,4-trimethylpyrrole (**19**), has been described.[33] This compound was fairly stable, decomposing readily in warm solution.

Johnson[34] and Kenner[35] and their respective coworkers attempted without success to prepare 5-bromo-2,3,4-trimethylpyrrole (**20**) by the bromination of 2,3,4-trimethylpyrrole (**21**). Even under mild conditions, however, no compound containing only one pyrrole nucleus could be isolated.

A number of dihalo-*C*-alkylpyrroles are known, and of these several are reported to be highly unstable. 3,4-Dichloro-2-methylpyrrole (**22**) became a "black solid" upon "brief exposure to atmospheric oxygen".[36] 4-Bromo-2-methylpyrrole (**23**) was apparently quite stable, but both 2,3-dibromo-5-methylpyrrole (**24**) and 2,4-dibromo-3,5-dimethylpyrrole (**25**) "reacted immediately upon isolation".[37]



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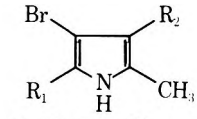
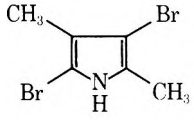


23, $R_1, R_2 = H$

24, $R_1 = Br; R_2 = H$



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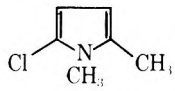


27

It is well known that carbonyl groups attached at the α or β positions of the pyrrole nucleus can be reduced by lithium aluminum hydride to hydrocarbon residues,[38,39] and Hinman and Theodoropoulos[40] have used this as a convenient method for the synthesis of many *C*-alkylpyrroles, mainly by the reduction of carbethoxy and formyl groups.

If "inverse" addition is employed, reduction stops at the hydroxymethyl stage, even under drastic conditions.[39,41]

When the ring nitrogen is substituted by an alkyl group, neither mode of addition affords complete reduction of a carbonyl at the α or β position.[40,42] Invariably, the reaction stops at the hydroxymethyl stage.

Since the halogen atom in 2-chloropyrrole (**1**) was not readily attacked by lithium aluminum hydride, reduction of carbonyl-containing 2-halopyrroles should be an efficient method to prepare *C*-methyl-2-halopyrroles. The carbonyl-containing precursors of these compounds should be fairly stable since they contain an electron-withdrawing group.[16,43-5]

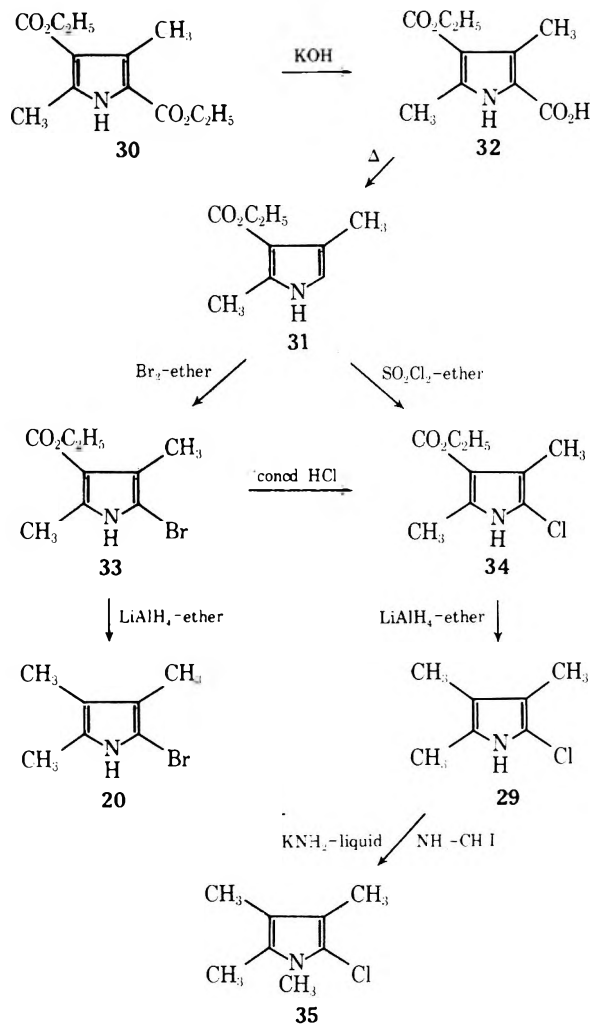
Preparation of 5-Chloro-2-methylpyrrole (26) and 5-Chloro-1,2-dimethylpyrrole (27). Treatment of 5-chloropyrrole-2-carboxaldehyde (**28**) (vide infra) with lithium aluminum hydride in ether under reflux for 14 hr gave a product which was shown by ir, NMR, and TLC to be 5-chloro-2-methylpyrrole (**26**). The product was quite unstable, resinifying in air after 10–12 min.

1-Methylation, using potassium amide and methyl iodide in liquid ammonia, of ethereal 5-chloro-2-methylpyrrole (**26**) followed by chromatography gave rise to extensive decomposition. One fraction was obtained which afforded a white solid melting slowly at room temperature, which was shown to be pure 5-chloro-1,2-dimethylpyrrole (**27**) by TLC and NMR analyses.

Preparation of 5-Chloro- and 5-Bromo-2,3,4-trimethylpyrrole (29 and 20). It was considered desirable to derive a synthetic scheme for the formation of 5-chloro- and 5-bromo-2,3,4-trimethylpyrrole (**29** and **20**) involving lithium aluminum hydride reduction as the terminal step. In this way, the possibility of pyrromethane formation would be essentially eliminated. Additionally, basic ethereal solutions would be involved which would reduce the possibility of decomposition in the reaction medium or during processing.

Knorr's pyrrole, 3,5-diethoxycarbonyl-2,4-dimethylpyrrole (**30**),[46] was used as starting material, and the sequence of reactions leading to the 5-halo-2,3,4-trimethylpyrroles is shown in Scheme I.

Scheme I



30 **32** **31** **33** **34** **20** **29** **35**

A key compound in this scheme is 3-ethoxycarbonyl-2,4-dimethylpyrrole (**31**), which can potentially be chlorinated or brominated. This compound was prepared from Knorr's pyrrole (**30**) in two steps, hydrolysis and decarboxylation.

Selective hydrolysis of the 5-ethoxycarbonyl group was achieved with alcoholic alkali,[46,47] to give the required 5-carboxylic acid (**32**) in good yield.

Decarboxylation and subsequent bromination has been accomplished in the pyrrole series by the use of bromine in acetic acid at 100°.[48] In the aromatic series this reaction may be carried out with the modified Hunsdiecker reaction.[49] This reaction failed when performed on **32**. Knorr describes the decarboxylation of **32** as taking place on melting although no indication of the yield was given.[46] Heating the acid until evolution of carbon dioxide ceased, followed by recrystallization of the resulting solid, afforded 3-ethoxycarbonyl-2,4-dimethylpyrrole (**31**) in very high yield.

Three methods have been used previously for the monobromination of **31**, bromine in ether,[50] bromine in methanol at −60°,[45] and dioxane dibromide.[51] On a small scale each of these methods gave only a low yield (20–30%) of the desired product. On a larger scale, the method of Corwin

and Viohl[45] gave an 84% yield of 5-bromo-3-ethoxycarbonyl-2,4-dimethylpyrrole (**33**).

Treibs and Kolm[33] treated **33** with concentrated hydrochloric acid in glacial acetic acid at room temperature, and obtained the corresponding 5-chloro compound **34**. Repetition of this reaction afforded **34** in high yield.

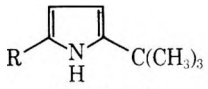
An alternative efficient synthesis of **34** involved the low-temperature chlorination of **31** with 1 equiv of sulfuryl chloride.

Initial attempts to prepare 5-bromo-2,3,4-trimethylpyrrole (**4**) by treatment of **33** with excess lithium aluminum hydride in tetrahydrofuran under reflux gave only 2,3,4-trimethylpyrrole (**21**). However, treatment of **33** with an excess of lithium aluminum hydride in ether under reflux for 1.5–2 hr had the desired effect of reducing the ethoxycarbonyl group without reductive removal of the bromine. NMR analysis indicated that together with 5-bromo-2,3,4-trimethylpyrrole (**20**), a trace of starting material was also present. The mixture was highly unstable and decomposed while the NMR was being run at 0°. Addition of a trace of deuterated pyridine greatly stabilized the solution and permitted the observation of an improved NMR spectrum.

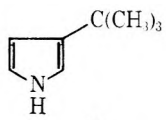
In a similar way, lithium aluminum hydride reduction of **34** in ether under reflux for 1.5 hr gave 5-chloro-2,3,4-trimethylpyrrole (**9**), as shown by ir and NMR analyses.

Preparation of 5-Chloro-1,2,3,4-tetramethylpyrrole (35). It was thought that since a 1-methyl group had a considerable stabilizing effect on 2-chloropyrrole (**1**), it might have a similar effect for its trimethyl homolog; this was found *not* to be the case. Methylation of **29** in the usual way afforded **35**, as shown by NMR. Decomposition to a bright red product was rapid, however. Attempts to prepare **35** by alternative routes failed.

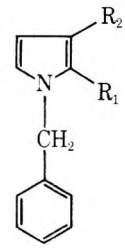
Preparation of 2-*tert*-Butyl-5-chloropyrrole (36). A



36, R = Cl
37, R = H



38



46, R_1 = Br; R_2 = H
47, R_1 = Cl; R_2 = H
48, R_1 = H; R_2 = Br

bulky group at the 5 position to the 2 halogen, even if it has a comparatively large electron-releasing effect, should exhibit a slight stabilizing effect, if the mechanism of the decomposition of 2-chloropyrrole (**1**) involves attack at the opposite α position.

Stabilization, preventing polymerization, by the use of a *tert*-butyl group has previously been observed in the acetylenic series.[52] For example, $(CH_3)_3C(-C{\equiv}C-)_6C(CH_3)_3$ is a stable solid, whereas dodecahexyne, $H(-C{\equiv}C-)_6H$ is a very unstable substance.

2-*tert*-Butylpyrrole (**37**) was previously prepared by Skell and Bean,[53,54] but no electrophilic substitution reactions of this molecule were reported.

The compound was prepared by the alkylation of pyrrylmagnesium bromide with *tert*-butyl chloride,[53] and was separated from the 3 isomer (**38**), unchanged pyrrole, and polyalkyl pyrroles by distillation under reduced pressure, followed by preparative GC of the crude distillate. The pure compound is a white, crystalline solid, but aerial oxidation occurs quite rapidly.

Chlorination of 2-*tert*-butylpyrrole (**37**) with sulfuryl chloride afforded a pale yellow oil, which was shown by NMR and mass spectral analyses to be pure 2-*tert*-butyl-5-chloropyrrole (**36**). No evidence was obtained for the presence of any 4 isomer.

Resinification of **36** occurred in air after about 2 min; the characteristic decomposition reaction was not observed.

No mechanism can be proposed for the decomposition of 2-halopyrroles at this early stage of investigation, but several important conclusions can be drawn.

(a) Oxygen probably plays an important, if only initiating role, in the decomposition reaction; (b) the 2-chloro compounds are in general more stable than the corresponding 2-bromo compounds, possibly owing to the relative strengths of the C–Cl and C–Br bonds; (c) the 2,5-dihalo species are more unstable than the corresponding 2-halo species; (d) introduction of *C*-alkyl groups markedly decreases the stability of 2-halopyrroles whereas 1-methylation tends to increase the stability; (e) hydrogen chloride, one of the products of the decomposition of 2-chloropyrrole, also catalyzes the decomposition, so that the reaction is autocatalytic in nature; (f) ammonia is reported[55] to be one of the products of the ozonolysis of pyrrole, and ammonium chloride has been obtained from the decomposition product of 2-chloropyrrole.

Electrophilic substitution of pyrrole gives rise to predominant attack at the α position,[2] although in the case of an *N*-alkylpyrrole an increasing amount of the β isomer is also obtained.[30,56,57] When a pyrrole contains an electron-withdrawing group at the 2 position, further substitution gives rise to substantial amounts of the 4 isomer[14,16,58] in addition to the 5 isomer. It was of some interest, therefore, to evaluate the susceptibility of 2-chloropyrrole (**1**) and other 2-halopyrroles to further electrophilic attack.

The only previous report of an electrophilic substitution reaction on **1** was the sulfonation, using pyridine–sulfur trioxide, performed by Terent'ev and Yanovskaya[59] which afforded the barium salt of 5-chloropyrrole-2-sulfonic acid (**39**) in moderate yield.

Chlorination or bromination apparently gives rise to the di-α-substituted product, since these are the by-products from the halogenation of pyrrole itself.

Formylation and diazo coupling, both of which proceed readily with pyrrole[2] under conditions which would not be destructive to **1**, were examined for their regioselectivity.

Formylation of 2-chloropyrrole (**1**) with phosphorus oxychloride in dimethylformamide[60,61] gave a white, crystalline material, which was shown by ir, uv, NMR, and mass spectral analyses to be 5-chloropyrrole-2-carboxaldehyde (**28**). No evidence was obtained for the presence of any 4-substituted products.

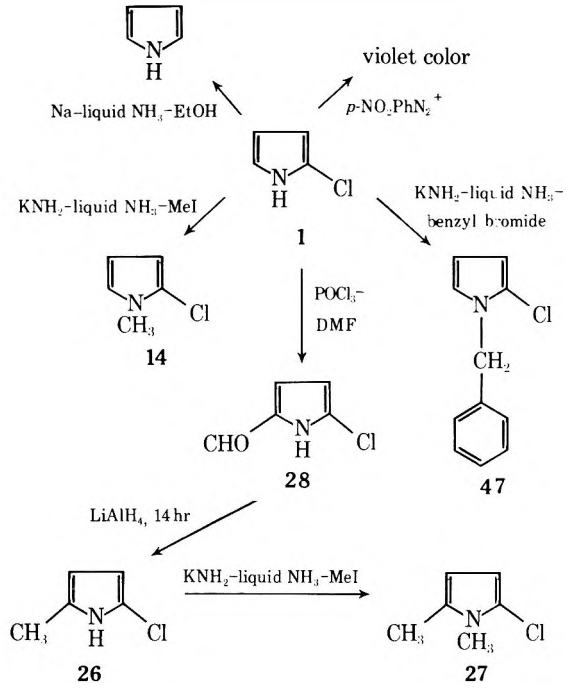
Similarly, treatment of 2-chloro-1-methylpyrrole (**14**) afforded a pale yellow oil, which was shown by ir, uv, NMR, and mass spectral analyses to be 5-chloro-1-methylpyrrole-2-carboxaldehyde (**40**).

Formylation of 2-bromopyrrole (**2**), however, led to a mixture of products. NMR, mass spectral, and GC analyses indicated that two formylated products, in the ratio 2.5:1, were formed. Comparison of retention times with those of authentic samples of 5-chloro- and 5-bromopyrrole-2-carboxaldehyde (**28** and **41**) demonstrated that these were indeed the compounds produced, the bromo compound predominating. An exactly analogous reaction has been observed in the thiophene series.[62,63]

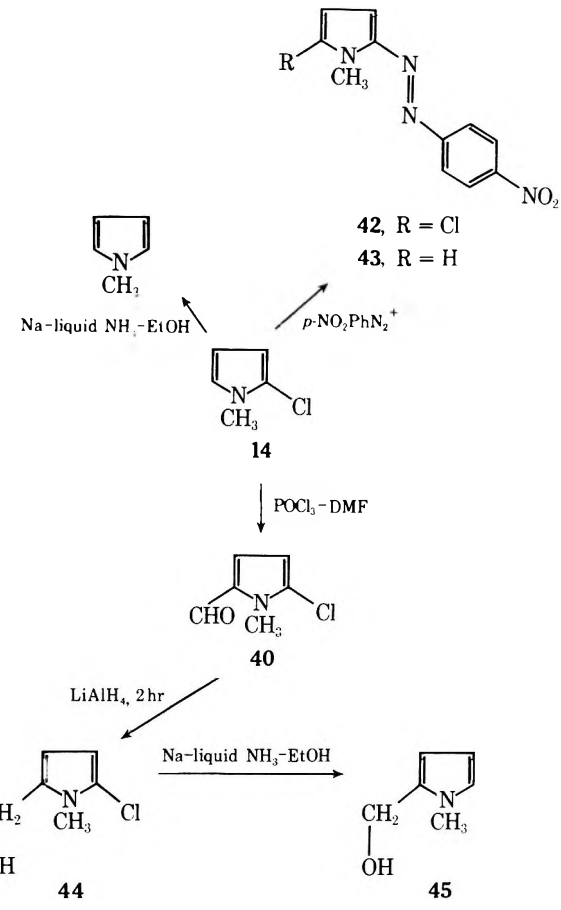
Another electrophilic substitution reaction, which, in the case of pyrrole, gives a fairly stable product is the azo-coupling reaction.[64,65]

Dropwise addition of diazotized 4-nitroaniline to a slightly alkaline solution of **1** in methanol at 5° gave an im-

Scheme II
Reactions of 2-Chloropyrrole (1)



Scheme III
Reactions of 2-Chloro-1-methylpyrrole (14)



mediate deep purple color (λ_{max} 345, 420, and 526 nm), which was stable for 2–3 hr. However, no crystalline derivative could be isolated from the reaction mixture. In a similar way, an alkaline solution of **2** in methanol at 5°, on addition of diazotized 4-nitroaniline solution, afforded an intense maroon color (λ_{max} 348 and 512 nm), but again no crystalline compound could be isolated.

In contrast to this was the reaction of the diazonium solution with a methanolic alkali solution of 2-chloro-1-methylpyrrole (**14**). An immediate red precipitate formed, which was shown by spectral analysis to be 2-chloro-1-methyl-5-(4′-nitrophenylazo)pyrrole (**42**). In a similar way the 2-(4′-nitrophenylazo) derivative of 1-methylpyrrole, **43**, was prepared.

Addition of excess methyl iodide to a mixture of **1** and potassium amide–liquid ammonia gave 2-chloro-1-methylpyrrole (**14**) as shown by ir, NMR, and TLC comparison with authentic material.

The action of lithium aluminum hydride in ether under reflux for 1 hr on 5-chloro-1-methylpyrrole-2-carboxaldehyde (**28**) afforded the unstable 5-chloro-2-hydroxymethyl-1-methylpyrrole (**44**). It was thought that the hydroxymethyl group could be reduced to a hydrocarbon residue by sodium in liquid ammonia in the presence of a proton source such as ethanol.[66] However, treatment of **44** with sodium in liquid ammonia in the presence of ethanol for 4 hr afforded 2-hydroxymethyl-1-methylpyrrole (**45**), as shown by ir, TLC, and NMR comparison with authentic material.

Hydrogenolysis of an aryl halide is known to occur, under these conditions, in the benzene[67] and pyrimidine[68] series. This reduction along with the previously described reductions of **1** and **14** constitute the first reports in the pyrrole series.

1-Benzyl-2-bromopyrrole (46) and 1-Benzyl-2-chloropyrrole (47). Anderson and Griffiths[30] demonstrated that a 1-benzyl group gives a greatly increased proportion of 3 substitution in bromination, nitration, and formylation compared with pyrrole and 1-methylpyrrole.

In view of the surprising regioselective formation of 1-benzyl-3-bromopyrrole (**48**), 1-benzyl-2-bromopyrrole (**46**) was synthesized to compare the NMR data with those obtained by Anderson for the 3 isomer. Addition of benzyl bromide to a mixture of **2** and potassium amide afforded a colorless oil which was shown by NMR and mass spectral analyses to be 1-benzyl-2-bromopyrrole (**46**).

The NMR data clearly indicate that bromination of 1-benzylpyrrole does indeed afford the 3 isomer.

The 1-benzyl derivative of **1** was prepared in an analogous manner, using benzyl bromide in potassium amide–liquid ammonia. 1-Benzyl-2-chloropyrrole (**47**) was stable at room temperature for periods up to 1 week.

Some of the reactions of 2-chloropyrrole (**1**) and 2-chloro-1-methylpyrrole (**14**) are summarized in Schemes II and III.

Details of the mass spectral fragmentation of the 2-halopyrroles synthesized in this study are discussed elsewhere.[69]

Experimental Section

Melting points were determined on covered slides using a Kofler heating stage, and are uncorrected. Infrared (ir) spectra were recorded on either a Perkin-Elmer 237 or 257 instrument. Cells of path 0.5 mm were used for solution spectra. Ultraviolet (uv) spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (NMR) spectra were determined using either a Varian Associates A-60 or HA-100 instrument, an accurate shift from Me_4Si being obtained for at least one signal in each spectrum. Mass spectra were recorded on an A. E. I. MS-9 or MS-12 spectrometer at 70 eV. Thin layer chromatography (TLC) was performed with Silica F plates supplied by Anderman and Co. Ltd. Visualization was effected by a combination of uv lamp and spraying with a 4% solution of ceric sulfate in 1 *M* aqueous sulfuric acid. "Silica" used for column chromatography is silica M. F. C. supplied by Hopkin and Williams Ltd. Analytical gas chromatography (GC) was performed on a Perkin-Elmer F11 instrument using a 10% polyethylene glycol adipate on silanized Embacel 3-ft

glass column, with a nitrogen flow rate of 4 ml/min. Preparative gas chromatography was performed on a Perkin-Elmer F21 instrument using a 6-ft metal column, packed with the same material as for the analytical work. In all preparative work sodium-dried ether was used where appropriate, and solvents were redistilled prior to use. Ether solutions obtained in work-up were dried with potassium carbonate, filtered, and evaporated.

Preparation of Tertiary Amines. Ethyl di-*n*-butylamine, *n*-propyl di-*n*-butylamine, and tri-*n*-butylamine were prepared from di-*n*-butylamine and the appropriate alkyl iodide.

2-Chloropyrrole (1) and 2,5-Dichloropyrrole (3). A. To a mixture of 5 g (0.075 mol) of pyrrole in ether (200 ml) at 0° was added dropwise, a solution of 4.5 g (0.033 mol) of sulfuryl chloride in ether (50 ml). After 2–3 min of stirring, 100 ml of 10% potassium carbonate solution was added and the total mixture was rapidly steam distilled. The steam distillate was extracted with ether after the addition of ammonium chloride and the combined ether extracts processed. TLC on silica eluting with chloroform indicated the presence of three products, R_f 0.75, 0.63, and 0.52, the latter corresponding to pyrrole. GC examination of the chlorination mixture at 60° also confirmed the presence of three products with retention times (% of total) of 11.6 (7.6), 45.2 (86.0), and 60.8 min (6.2). Pyrrole was found to have a retention time of 11.8 min under these conditions.

An equimolar mixture of tri-*n*-propylamine and the synthetic tertiary amines (5 g) was added to the total ether extract from the chlorination reaction and the ether removed. The total residue was fractionally distilled under reduced pressure to afford two main fractions. Fraction 1, bp 52–56° (16 mm), was shown by ir and NMR to be **1** in tertiary amine: NMR (tertiary amine mixture) δ 5.50, 5.16, 5.07 (each 1 H); ir (film) ν_{max} 3450, 3390, 3130, 1140, 1190, 880 cm^{-1}. Fraction 2, bp 92–93° (16 mm), was shown by its ir and NMR spectra to be **3** in tertiary amine: NMR (tertiary amine mixture) δ 4.42 (s, 2, C_3 H, C_4 H); ir (film) ν_{max} 3440, 3360, 3140, 1032, 930 cm^{-1}.

The tertiary amines were removed by treatment of an ethereal solution of the appropriate fraction with excess methyl iodide at 0° for 2 days. Examination of the NMR spectrum after filtration showed that in both cases the impurities were of the order 1–2%. 2-Chloropyrrole (**1**): ^{1}H NMR (CCl_4) δ 5.96 (q, 1, J = 1.75, 3.6 Hz, C_3 H), 6.06 (q, 1, J = 3.05, 3.6 Hz, C_4 H), 6.46 (q, 1, J = 1.75, 3.05 Hz, C_5 H); ir (film) ν_{max} 3260, 1545, 1535, 1440, 1415, 1025, 920, 785, 760, 715 cm^{-1}. 2,5-Dichloropyrrole (**3**): ^{1}H NMR (CCl_4) δ 5.85 (s, C_3 H and C_4 H).

B. 2-Chloropyrrole (**1**) was also prepared by the method of Hess and Wissing.[10] The pale yellow, oily product was shown by TLC and ir analysis to be a mixture of pyrrole and **1** in the approximate ratio 10:1. Because of the easier preparation of a chlorination mixture, and higher content in that mixture using the modified method of Massara and Borgo,[8] this was the method of choice.

2-Bromopyrrole (2) and 2,5-Dibromopyrrole (10). Pyrrolylmagnesium bromide (**4**) was prepared as described previously. To this solution, 100 ml of ether was added, the mixture was cooled to −70°, and 2.64 g (0.016 mol) of redistilled bromine in 10 ml of ether was added. The mixture was stirred for 5 min and transferred to a separating funnel containing 150 ml of 10% potassium carbonate solution, 0.5 g of tertiary amine was added, and the ether layer was processed. TLC eluting with 4:1 petroleum ether–benzene indicated the presence of three products. Chromatography of approximately 300 mg of the bromination product on silica, eluting with 4:1:0.5 petroleum ether–benzene–chloroform, afforded two main fractions other than pyrrole (160 mg). Fraction 1 (~30 mg), a white solid melting slowly at room temperature, was identified as **10** by its ir and NMR spectra: NMR (CCl_4) δ 6.01 (d, 2, J = 2.5 Hz, C_3 H, C_4 H), 9.17 (br d, 1, NH); ir (CCl_4) ν_{max} 3460, 1420, 1410, 1030, 910 cm^{-1}. Fraction 2 (~80 mg), a colorless oil, was identified as **2** by its NMR spectrum: NMR (CCl_4) δ 6.53 (m, 1, C_5 H), 6.13 (m, 1, C_4 H), 6.05 (m, 1, C_3 H), NH not observed.

2-Chloro-1-methylpyrrole (14) and 2,5-Dichloro-1-methylpyrrole (16). To a solution of 5.0 g (0.06 mol) of 1-methylpyrrole in 20 ml of ether at 0° was added a mixture of 8.5 g (0.06 mol) of sulfuryl chloride in 20 ml of ether. After stirring below 10° for 10 min, 70 ml of 10% potassium carbonate solution was added and the mixture was steam distilled. The steam distillate was thoroughly extracted with ether. Processing afforded a pale yellow oil which was fractionally distilled under reduced pressure to afford two main fractions. Fraction 1 (5.34 g, 74%), bp 30–32° (10 mm), was shown to be **14**: NMR (CCl_4) δ 6.40 (q, 1, J = 2.5, 3.0 Hz, C_5 H), 5.92 and 5.90 (m, 2, C_3 H and C_4 H), 3.53 (s, 3, NCH_3); ir (film) ν_{max} 3125, 1295, 1110, 1085, 880 cm^{-1}.

Anal. Calcd for C_5H_6NCl: C, 52.2; H, 5.2; N, 12.2; Cl, 30.4. Found: C, 51.8; H, 5.2; N, 12.3; Cl, 31.7.

Fraction 2 (0.47 g, 5%), bp 40–42° (8 mm), was shown to be 2,5-dichloro-1-methylpyrrole (**16**): NMR (CCl_4) δ 5.96 (s, 2, C_3 H and C_4 H), 3.51 (s, 3, NCH_3).

Attempted Preparation of 2-Bromo-1-methylpyrrole (15). A. Following the method of Anderson and Griffiths,[40] to a solution of 5.01 g (0.06 mol) of 1-methylpyrrole in 20 ml of carbon tetrachloride at −10° was added slowly a solution of 5.5 g (0.034 mol) of bromine in 10 ml of carbon tetrachloride. After stirring for 20 min, the mixture was treated successively with 5% sodium carbonate solution, 5% sodium bisulfite solution, and water. The organic phase was separated and dried with magnesium sulfate. Filtration and removal of solvent afforded a crystalline solid which was recrystallized from alcohol–water to give 2.57 g (13.6%) of white needles, shown to be 2,3,4,5-tetrabromo-1-methylpyrrole (**17**): mp 153–154° (lit.[31] 154°); NMR (CCl_4) δ 3.69 (s, 3, NCH_3); ir (Nujol) ν_{max} 1495, 1315, 1082 cm^{-1}.

B. A solution of 2.7 g (0.017 mol) of bromine in 20 ml of carbon tetrachloride was added to a mixture of 1.2 g (0.015 mol) of 1-methylpyrrole in 150 ml of carbon tetrachloride at 0° containing magnesium oxide as a slurry. After 10 min, 50 ml of 10% potassium carbonate solution was added and the total mixture filtered. The organic phase was washed with 30 ml of 5% potassium bisulfite solution and 25 ml of water, and dried with magnesium sulfate. Removal of the solvent afforded a pale green solid, to which 75 mg of tertiary amine was added and the residue was repeatedly extracted with small quantities of hot petroleum ether. The solid remaining was identified as **17**, mp 153–154°, having spectral properties as before. TLC of the petroleum ether extract, eluting with 4:1 petroleum ether–benzene, indicated the presence of five products. The total residue was chromatographed over silica eluting with 2:1 petroleum ether–benzene to afford 128 mg (10%) of 1-methylpyrrole and two main fractions. Fraction 1 (136 mg) was shown by NMR analysis to be a mixture of the 2,5-dibromo, 2,3,5-tribromo-, and 2,3,4,5-tetrabromo-1-methylpyrroles in the ratio 2.5:4:5. 2,5-Dibromo-1-methylpyrrole (**18**): NMR ($CDCl_3$) δ 6.23 (s, 2, C_3 H and C_4 H), 3.60 (s, 3, NCH_3). 2,3,5-Tribromo-1-methylpyrrole: NMR ($CDCl_3$) δ 6.35 (s, 1, C_4 H), 3.64 (s, 3, NCH_3). Fraction 2, a colorless oil, was shown by NMR to be a mixture of mono- and dibromo derivatives in the ratio 3:2, and a small proportion of 1-methylpyrrole. 2-Bromo-1-methylpyrrole (**15**): NMR (CCl_4) δ 6.55 (q, 1, C_5 H), 6.11 (m, 1, C_4 H), 5.97 (m, 1, C_3 H), 3.63 (s, 3, NCH_3).

Birch Reduction of 1 and 14. Into a mixture of 103 mg (0.001 mol) of **1** in 2 ml of absolute ethanol, 25 ml of ammonia was distilled and 146 mg (0.006 mol) of sodium was added. The mixture was stirred for 4 hr and the ammonia allowed to evaporate. The residue was partitioned between ether and water, and the aqueous phase was thoroughly extracted with ether. Processing afforded 60 mg (90%) of a colorless oil which was shown by its spectral and chromatographic properties to be pyrrole.

Similarly, 116 mg (0.0009 mol) of **14** afforded, upon reduction, 58 mg (84%) of a colorless oil identified as 1-methylpyrrole.

5-Chloro-2-methylpyrrole (26). A solution of 123 mg (0.0011 mol) of **28** in 4 ml of ether was added carefully to 300 mg (0.008 mol) of lithium aluminum hydride in 20 ml of ether and the mixture refluxed for 14 hr. Sodium hydroxide solution (1*N*) was added to destroy the excess lithium aluminum hydride and the aqueous phase was thoroughly extracted with ether. TLC of the residue after processing on silica eluting with benzene indicated the presence of a major product, R_f 0.51. This product, a white, crystalline solid, was identified as **26**: NMR (CCl_4) δ 5.83 (d, 1, J = 3.7 Hz, C_4 H), 5.74 (d, 1, J = 3.7 Hz, C_3 H), 2.18 (s, 3, $-CH_3$); ir (CCl_4) ν_{max} 3470, 2920, 1472, 1410, 1115, 1030 cm^{-1}.

5-Chloro-1,2-dimethylpyrrole (27). An ether solution of **26** [prepared from 521 mg (0.0045 mol) of **28**] was added dropwise to potassium amide [from 756 mg (0.019 mol) of potassium and 50 mg of ferric nitrate] in 150 ml of redistilled liquid ammonia, and the mixture was stirred for 30 minutes. A solution of 1.4 g (0.01 mol) of methyl iodide in 5 ml of ether was added and the mixture was stirred for 5 hr. Excess potassium amide was decomposed by the addition of 10 ml of 1:1 methanol–benzene and the ammonia was allowed to evaporate overnight. Water was added and the aqueous phase was thoroughly extracted with ether. The residue after processing was chromatographed on silica eluting with 10:1 petroleum ether–benzene. Considerable decomposition occurred, but one fraction was shown to be 30 mg (5%) of **27**: NMR (CCl_4) δ 5.74 (d, 1, J = 4.0 Hz, C_4 H), 5.64 (d, 1, J = 4.0 Hz, C_3 H), 3.41 (s, 3, NCH_3), 2.17 (s, 3, $-CH_3$); ir (CCl_4) ν_{max} 2920, 1400, 1300, 1075 cm^{-1}.

3-Ethoxycarbonyl-2,4-dimethylpyrrole-5-carboxylic Acid (32). A solution of 4.97 g (0.021 mol) of **30** and 2.35 g (0.05 mol) of potassium hydroxide in 60 ml of 95% ethanol and 70 ml of water was distilled until 60 ml of distillate had collected. Cooling and acidification give a white solid which was filtered and recrystallized from 95% ethanol to yield 3.25 g (74%) of **32**: mp 203–204° dec (lit.[46] 204°); NMR (pyridine-*d*) δ 4.39 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 3.15 (s, 3, C_2 CH_3), 2.76 (s, 3, C_4 CH_3), 1.34 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 254 nm (log ϵ 4.10), 269 (4.21); ir (Nujol) ν_{max} 3300, 2660, 1690, 1667 cm^{-1}.

3-Ethoxycarbonyl-2,4-dimethylpyrrole (31). Heating 2.75 g (0.013 mol) of **32** to melting, and until carbon dioxide evolution had ceased, gave a pale pink liquid which crystallized on cooling. Recrystallization from petroleum ether gave 1.86 g (86%) of **31** as white needles: mp 78° (lit.[7] 79°); NMR (CCl_4) δ 6.18 (broad s, 1, C_5 H), 4.21 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.42 (s, 3, C_2 CH_3), 2.15 (s, 3, C_4 CH_3), 1.33 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 230 nm (log ϵ 3.91), 258 (3.67); ir (Nujol) ν_{max} 3305, 1665, 1160 cm^{-1}.

5-Bromo-3-ethoxycarbonyl-2,4-dimethylpyrrole (33). Following the method of Corwin and Viohl, **33** was prepared from **31** in 25% yield as pale yellow needles: mp 112–114° dec (lit.[45] 110°); NMR ($CDCl_3$) δ 4.26 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.45 (s, 3, C_2 CH_3), 2.17 (s, 3, C_4 CH_3), 1.33 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 224 nm (log ϵ 3.97), 262 (3.76); ir (Nujol) ν_{max} 3270, 1665, 1315, 770 cm^{-1}.

Repetition of the reaction but starting with 13.5 g of **31** gave a greatly improved (84%) yield of **33**.

5-Chloro-3-ethoxycarbonyl-2,4-dimethylpyrrole (34). A. To a solution of 48 mg (0.0003 mol) of **31** in 2 ml of ether at −70° was added 38 mg (0.0003 mol) of sulfuryl chloride in 2 ml of ether. After 5 min, 5 ml of 10% potassium carbonate solution was added and the aqueous phase was thoroughly extracted with ether. Processing afforded a residue which was chromatographed on silica eluting with chloroform to give 4.2 mg of **31**, identical with an authentic sample. The major product was recrystallized from aqueous alcohol to give 53 mg (91%) of **34** as pale yellow needles: mp 140–142° (lit.[45] 140–141°); NMR ($CDCl_3$) δ 4.27 (q, 2, J = 7.5 Hz, $-CO_2CH_2CH_3$), 2.46 (s, 3, C_2 CH_3), 2.18 (s, 3, C_4 CH_3), 1.35 (t, 3, J = 7.5 Hz, $-CO_2CH_2CH_3$); uv (EtOH) λ_{max} 221 nm (log ϵ 3.92), 264 (3.65); ir (Nujol) ν_{max} 3255, 1670, 1225, 1050 cm^{-1}.

B. Following the method outlined by Treibs and Kolm,[33] 246 mg (0.001 mol) of **33** was suspended in 4 ml of glacial acetic acid, and 0.5 ml of concentrated hydrochloric acid was added. After 10 min at room temperature, 10 ml of water was added. The precipitate was filtered and recrystallized from aqueous ethanol to give 163 mg (81%) of **34** as pale yellow needles, physical and spectral properties as above.

5-Bromo-2,3,4-trimethylpyrrole (20). A solution of 55 mg (0.00022 mol) of **33** in 5 ml of ether was added to a mixture of 100 mg (0.0026 mol) of lithium aluminum hydride in 5 ml of ether and the mixture was refluxed for 2 hr. Processing in the usual way gave an ether solution, which upon evaporation afforded white needles decomposing within 30 sec. Addition of 20 mg of pyridine-d_5 and repeated evaporation from carbon tetrachloride afforded a solution which was shown to contain **20** by NMR at 0°: NMR (CCl_4) δ 2.16 (s, 3, C_2 CH_3), 1.83 (s, 6, C_3 CH_3 and C_4 CH_3); uv (EtOH) λ_{max} 230 nm.

5-Chloro-2,3,4-trimethylpyrrole (29). A solution of 66 mg (0.00033 mol) of **34** in 5 ml of ether was added to a mixture of 100 mg (0.0026 mol) of lithium aluminum hydride in 5 ml of ether and the mixture was refluxed for 2 hr. Processing in the usual way gave an ether solution, which upon evaporation afforded white needles decomposing within 7–8 min. Repeated evaporation from carbon tetrachloride afforded a solution which was shown by NMR to contain only **29**: NMR (CCl_4) δ 2.18 (s, 3, C_2 CH_3), 1.89 (s, 6, C_3 CH_3 and C_4 CH_3); ir (CCl_4) ν_{max} 3480, 1605, 1440, 1295, 1120 cm^{-1}.

5-Chloro-1,2,3,4-tetramethylpyrrole (35). 5-Chloro-2,3,4-trimethylpyrrole (**29**) in ether [prepared from 303 mg (0.0015 mol) of **34**] was added to potassium amide [from 604 mg (0.015 mol) of potassium and 50 mg of ferric nitrate] in 125 ml of redistilled liquid ammonia. After stirring for 30 min, 1.14 g (0.008) of methyl iodide was added and the mixture stirred for 4 hr. At the end of this time 10 ml of 1:1 methanol–benzene was added to destroy the excess potassium amide and the ammonia allowed to evaporate overnight. To this mixture was added 20 ml of saturated ammonium chloride solution and the aqueous phase was thoroughly extracted with ether. TLC indicated the presence of both the NH and NCH_3 compounds in the approximate ratio 1:1.

The N-methylation procedure was repeated on this mixture and the reaction mixture extracted with hexane prior to decomposition of potassium amide to afford pure **35** as a highly unstable, pale yellow solid: NMR (CCl_4) δ 3.32 (s, 3, NCH_3), 2.02 (s, 3, C_2 CH_3), 1.81 and 1.79 (s, 3 each, C_3 CH_3 and C_4 CH_3); uv (EtOH) λ_{max} 231 nm; ir (CCl_4) ν_{max} 1460, 1370, 1290, 1035 cm^{-1}.

2-*tert*-Butylpyrrole (37). The method used was essentially that of Skell and Bean.[53] Analytical GC at 120° showed a complex mixture consisting of pyrrole (35%), retention time 1.25 min, 2-*tert*-butylpyrrole (30%), retention time 2.75 min, 3-*tert*-butylpyrrole (22%), retention time 3.6 min, and polyalkylated pyrroles (5%), retention time 5 min. The total reaction mixture was distilled and the fraction boiling below 120° discarded, and the residue was distilled under reduced pressure (20 mm). The colorless distillate was subjected to preparative GC to afford 17.3 g (28%) of **37** and 11.1 g (18%) of **38**. 2-*tert*-Butylpyrrole (**37**): mp 43–44°; NMR (CCl_4) δ 6.45 (dd, 1, J = 1.5 and 2.75 Hz, C_5 H), 5.91 (dd, 1, J = 2.75 and 3.5 Hz, C_4 H), 5.76 (dd, 1, J = 1.5 and 3.5 Hz, C_3 H), 1.27 [s, 9, $-C(CH_3)_3$]; ir (film) ν_{max} 3380, 3090, 1600, 1560, 1525, 1282, 1260, 1015 cm^{-1}.

2-*tert*-Butyl-5-chloropyrrole (36). A solution of 292 mg (0.0022 mol) of sulfuryl chloride in 2 ml of ether was added to 231 mg (0.0019 mol) of **37** in 8 ml of ether at 0°. After 5 min, 10 ml of 10% potassium carbonate solution was added and the aqueous phase was thoroughly extracted with ether.

The reaction product was chromatographed on silica eluting with 3.5:1 petroleum ether–benzene to afford 255 mg (90%) of **36** as a pale yellow oil: NMR (CCl_4) δ 5.78 (d, 1, J = 3.6 Hz, C_3 H), 2.27 [s, 9, $-C(CH_3)_3$]; ir (CCl_4) ν_{max} 3485, 3280, 3100, 1570, 1280 cm^{-1}.

5-Chloropyrrole-2-carboxaldehyde (28). A solution of 102 mg (0.001 mol) of **1** in 1 ml of ether was added to 160 mg of redistilled phosphorus oxychloride in 4 ml of dimethylformamide and the mixture shaken at room temperature for 30 min. The mixture was cooled in ice and 3 ml of water added. The ether layer was separated and discarded and the aqueous layer treated with 1 ml of 40% sodium hydroxide solution at room temperature for 30 min. The aqueous solution was acidified to pH 3 and thoroughly extracted with ether. Recrystallization of the yellow-white residue from hexane gave 91 mg (78%) of **28** as white needles: mp 110–111° (lit.[12,16] 110–111°); NMR (CCl_4) δ 10.43 (broad s, 1, NH), 9.41 (s, 1, CHO), 6.89 (d, 1, J = 3.9 Hz, C_4 H); uv (EtOH) λ_{max} 240 nm (log ϵ 3.68), 293 (4.285); ir (CCl_4) ν_{max} 3440, 3210, 3080, 2720, 1660, 1290 cm^{-1}.

Formylation of 2-Bromopyrrole (2). A solution of approximately 15 mg of **2** in 1 ml of ether was added to 16 mg of phosphorus oxychloride in 2 ml of dimethylformamide and the mixture allowed to stand at room temperature for 3 hr. Processing as described above afforded an ether solution which by TLC apparently contained a single material. Several techniques, however, indicated that a mixture had been obtained. GC analysis at 150° indicated two components with retention times of 6.8 and 12 min, in the ratio 2.5:1. 5-Chloropyrrole-2-carboxaldehyde (**28**) has retention time 6.9 min and 5-bromopyrrole-2-carboxaldehyde (**41**) has retention time 11.8 min under these conditions. The mass spectrum showed M^+ at m/e 175 and 173 for the 5-bromo compound **41** and M^+, m/e 131 and 129, for the 5-chloro compound **28**. The NMR spectrum in CCl_4 after addition of D_2O indicated two pairs of doublets, each J = 4.0 Hz, at δ 6.87 and 6.16 ppm for **28**, and δ 6.75 and 6.26 ppm for **41**.

5-Chloro-1-methylpyrrole-2-carboxaldehyde (40). A solution of 588 mg (0.0044 mol) of **14** in 3 ml of ether was added to 880 mg of phosphorus oxychloride in 8 ml of dimethylformamide and the mixture allowed to stand overnight at room temperature under nitrogen. Processing as described above afforded a residue which was chromatographed on silica, eluting with 1:1 chloroform–ethyl acetate to give 646 mg (89%) of **40** as a colorless oil: NMR (CCl_4) δ 9.38 (s, 1, CHO), 6.80 (d, 1, J = 4.0 Hz, C_4 H), 3.95 (s, 3, NCH_3); uv (EtOH) λ_{max} 250 nm (log ϵ 3.82), 286 (4.30); ir (CCl_4) ν_{max} 2950, 2710, 1675, 1428, 1310, 1025 cm^{-1}.

Anal. Calcd for C_6H_6ClNO: C, 50.2; H, 4.2; N, 9.7. Found: C, 50.0; H, 3.9; N, 9.7.

2-Chloro-1-methyl-5-(4′-nitrophenylazo)pyrrole (42). A solution of 4-nitroaniline in dilute hydrochloric acid was diazotized with 10 ml of 10% sodium nitrite solution at 5°. An aliquot of this solution was added to 110 mg (0.00095 mol) of **14** in 5 ml of methanolic alkali. After standing for 10 min, the red precipitate was filtered and recrystallized from glacial acetic acid to afford 84 mg (34%) of **42** as fine red needles: mp 137–138°; NMR (acetone-*d*) δ 8.34 and 7.97 (m, 2 each, aromatic H), 6.82 (d, 1, J = 3.8 Hz, C_4 H), 6.39 (d, 1, J = 3.8 Hz, C_3 H), 3.99 (s, 3, NCH_3); uv (EtOH) λ_{max} 434

nm (log ε 4.47); ir (Nujol) ν_{max} 3200, 1600, 1580, 1490, 1310, 1270, 1110, 1040 cm^{-1}.

Anal. Calcd for $C_{11}H_9ClN_4O_2$: C, 50.1; H, 3.4; N, 21.1; Cl, 13.4. Found: C, 49.8; H, 3.4; N, 20.9; Cl, 13.6.

Red needles of **43** were prepared similarly: mp 133–134°; NMR (acetone-*d*) δ 8.33 and 7.94 (m, 2 each, aromatic H), 7.32 (dd, 1, *J* = 1.65 and 2.65 Hz, C_5 H), 6.78 (dd, 1, *J* = 1.65 and 4.35 Hz, C_3 H), 6.36 (dd, 1, *J* = 2.65 and 4.35 Hz, C_4 H), 4.01 (s, 3, NCH_3); uv (EtOH) λ_{max} 414 nm (log ε 4.43); ir (Nujol) ν_{max} 3120, 1510, 1320, 1200, 1095 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O_2$: C, 57.0; H, 4.3; N, 24.8. Found: C, 56.4; H, 4.6; N, 25.1.

2-Chloro-1-methylpyrrole (14). A solution of 106 mg (0.001 mol) of **1** in 5 ml of ether was added to potassium amide [from 212 mg (0.0055 mol) of potassium and 75 mg of ferric nitrate] in 75 ml of redistilled liquid ammonia. After 25 min, a solution of 2.3 g (0.016 mol) of methyl iodide in 3 ml of ether was added and the mixture stirred for 4 hr. Processing in the usual way afforded an ether solution which was chromatographed on silica, eluting with chloroform, to afford 75 mg (63%) of **14** as a colorless oil, having identical spectral properties with the material obtained from the chlorination of 1-methylpyrrole.

1-Benzyl-2-bromopyrrole (46). A solution of approximately 50 mg (0.00033 mol) of **2** in 2 ml of ether was added to potassium amide [from 30 mg (0.00077 mol) of potassium and 50 mg of ferric nitrate] in 25 ml of redistilled liquid ammonia. After 30 min, a solution of 85 mg (0.0005 mol) of benzyl bromide in 2 ml of ether was added and the mixture stirred for 2 hr. Processing in the usual way afforded a mixture of two products, one of which was identified, by TLC, as unreacted **2**. The total residue was chromatographed on silica eluting with 5:1 petroleum ether–benzene to afford unreacted **2** and 31.2 mg (39%) of a colorless oil identified as **46**: NMR (CCl_4) δ 7.3–6.9 (m, 5, aromatic H), 6.60 (m, 1, C_5 H), 6.09 and 6.07 (m, 1 each, C_3 H and C_4 H), 5.07 (s, 2, $-CH_2Ar$); ir (CCl_4) ν_{max} 3040, 2920, 1600, 1495, 1292 cm^{-1}.

1-Benzyl-2-chloropyrrole (47). A solution of 243 mg (0.0024 mol) of **1** in 4 ml of ether was added to potassium amide [from 156 mg (0.0037 mol) of potassium and 72 mg of ferric nitrate] in 40 ml of redistilled liquid ammonia. After 30 min, a solution of 504 mg (0.003 mol) of benzyl bromide in 2 ml of ether was added and the mixture stirred for 4 hr. Processing in the usual way afforded a mixture of three products, one of which was identified, by TLC, as unreacted **1**. The total residue was chromatographed on silica eluting with 5:1 petroleum ether–benzene to afford two fractions other than 86 mg (35%) of **1**. Fraction 1 was 165 mg (61%) of a white solid identified as *trans*-stilbene: mp 122–123° (lit.[7] 124°); NMR (CCl_4) δ 6.96 (s, 2, olefinic H), 7.5–7.1 (m, 10, aromatic H); uv (EtOH) λ_{max} 295 nm, 307, sh 320; mass spectrum *m/e* 180 (M^-, 10%), 77 (100). Fraction 2 was 14 mg (3%) of **47**, a white, crystalline solid: mp 123–124°; NMR δ 7.35–6.90 (m, 5, aromatic H), 6.43 (m, 1, C_5 H), 6.02 and 5.98 (m, 1 each, C_3 H and C_4 H), 5.04 (s, 2, $-CH_2Ar$); ir (film) ν_{max} 3100, 3060, 2920, 1605, 1520, 1290, 1065 cm^{-1}

Anal. Calcd for $C_{11}H_{10}ClN$: C, 69.1; H, 5.2; N, 7.3. Found: C, 68.5; H, 5.3; N, 6.9.

5-Chloro-2-hydroxymethyl-1-methylpyrrole (44). A solution of 94.3 mg (0.00065 mol) of **40** in 5 ml of ether was added to 120 mg (0.0032 mol) of lithium aluminum hydride in 8 ml of ether and the mixture refluxed for 1 hr. Processing in the usual way afforded an ether solution which was evaporated several times from carbon tetrachloride. The final carbon tetrachloride solution was shown to contain only **44**: NMR (CCl_4) δ 5.92 (m, 2, C_3 H and C_4 H), 4.46 (d, 2, *J* = 7 Hz, CH_2OH), 3.67 (s, 3, NCH_3).

Birch Reduction of 44. A solution of **44** [prepared from 190.5 mg (0.001 mol) of **40**] in 5 ml of ether, was added to 0.9 g (0.39 mol) of sodium in 100 ml of redistilled liquid ammonia and 2 ml of ethanol. The mixture was stirred for 2 hr and the ammonia allowed to evaporate. Processing in the usual way afforded 136 mg (92%) of **45** as a pale yellow oil: NMR (CCl_4) δ 6.43 (m, 1, C_5 H), 5.85 (m, 2, C_3 H and C_4 H), 4.41 (s, 2, CH_2OH), 3.63 (s, 3, NCH_3); ir (film) ν_{max} 3360, 2930, 1500, 1305, 995 cm^{-1}.

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Thianaphthen-2-one Chemistry. I. Synthesis of 6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-ones (11-Thiacoumestans)

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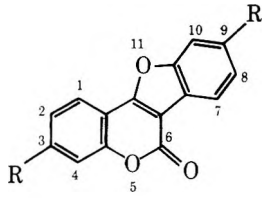
The condensation of thianaphthen-2-one and salicylaldehyde gave 6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (dihydro-11-thiacoumestan). Several analogs were prepared. Oxidation of the dihydro compounds with DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) gave 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans), a new heterocyclic ring system, and the sulfur analog of the naturally occurring 6*H*-benzofuro[3,2-*c*][1]benzopyran-6-one (coumestan) ring system. The reaction of thianaphthen-2-one with 5-nitrosalicylaldehyde and pyridoxal in alcohol gave the corresponding 2-aryl-2,3-dihydrothianaphthene-3-carboxylates.

Derivatives of the 6*H*-benzofuro[3,2-c][1]benzopyran-6-one ring system[1] (commonly called coumestan) have been found in many natural products. 3,9-Dihydroxy-6*H*-benzofuro[3,2-c][1]benzopyran-6-one (coumestrol) was isolated from ladino clover and showed marked estrogenic activity.[2,3] The laboratory syntheses of the coumestans have involved multistep reactions.[1,3-5]



R = H, coumestan
R = OH, coumestrol

This paper reports a convenient two-step synthesis of the corresponding sulfur analogs, 6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (11-thiacoumestans).[6] The first step involves a unique condensation–rearrangement of thianaphthen-2-one (1) and salicylaldehyde to form 6a,11a-dihydro-6*H*-benzothieno[3,2-c][1]benzopyran-6-one (dihydro-11-thiacoumestan, **2a**). Oxidation of the rearrangement product with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) gives 6*H*-benzothieno[3,2-c][1]benzopyran-6-one (Scheme I).

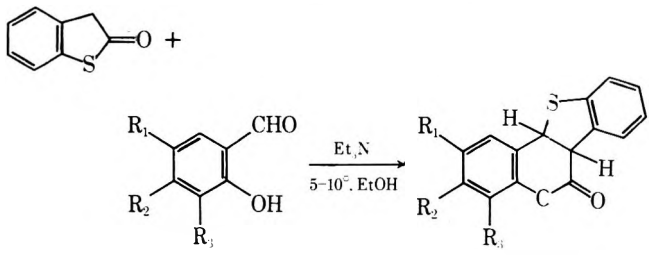
A plausible mechanism for the condensation–rearrangements of thianaphthen-2-one and salicylaldehyde is shown in Scheme I.[7] This suggested pathway has precedent in the mechanism suggested for the Perkin coumarin synthesis.[8] The intermolecular Michael addition of thiophenols to the C-4 position of coumarins is, of course, well known,[9] and an intramolecular addition, proposed herein, is equally likely. Although numerous intramolecular rearrangements of α-salicylidene lactones,[10-14] α-salicylidene oxazolones,[15] and α-salicylidenelactams[16,17] to coumarin derivatives have been reported, this is the first report of such a rearrangement followed by a Michael addition.[18]

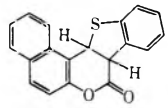
In addition to the parent compound, several substituted dihydrothiacoumestans were prepared (Table I). The dihydro compounds were readily identified by their NMR and ir spectra. The NMR spectra displayed the methinyl protons as characteristic downfield doublets with $J = 7$ Hz (cis methinyls, decoupling collapsing the doublets to singlets). The ir spectra of the dihydrothiacoumestans were characterized by strong carbonyl absorptions at approximately 1755 cm^{-1}.

The 6*H*-benzothieno[3,2-c][1]benzopyran-6-one (**4a**) could be obtained by four different synthetic procedures: (1) direct combination of thianaphthen-2-one and salicylaldehyde in refluxing ethanol with triethylamine as a catalyst (10% yield); (2) heating dihydrothiacoumestan with triethylamine (15% yield); (3) sulfur dehydrogenation of dihydrothiacoumestan (73% yield); and (4) DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) oxidation of dihydrothiacoumestan (75% yield). High yields and simplicity of operation made the DDQ oxidation of the dihydro forms the method of choice for preparation of all thiacoumestans (see Table II).

Wide variations in the relative reactivities observed during the DDQ oxidation of dihydrothiacoumestans to thiacoumestans can be explained by reference to the hydride-abstraction mechanism proposed for DDQ.[19] The dihydrothiacoumestans (**2a–d**) with electron-donating groups were oxidized in good yields by 6–12 hr of reflux. However, the chloro compound **2e** required 59 hr and the naphtho compound **3** required 117 hr for equivalent conversion. Removal by the DDQ of the hydride adjacent to the sulfur would yield a carbonium ion resonance stabilized by both the benzene ring and the sulfur. The more effective stabilization of the benzylic carbonium ion by the electron-donating groups in **2a–d** is reflected in their more rapid oxidation

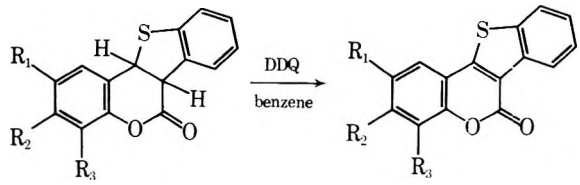
Table I[a]

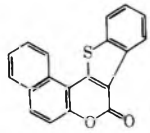


Compd	R_1	R_2	R_3	% yield	Mp, °C	Anal.
2a	H	H	H	79	143.5–145.0	C, H
2b	CH_3O	H	H	80	151.0–153.5	C, H, S
2c	H	OCH_3	H	82	142.0–143.0	C, H, S
2d	H	H	OCH_3	71	173.5–174.5	C, H, S
2e	Cl	H	H	34	226.0–228.0	C, H, S
7[b]	NO_2	H	H	76	198.0–200.0	C, H, S
3				59	215.0–217.0	C, H, S

[a] Satisfactory analytical data (±0.4%) were obtained for the elements indicated. [b] The nitro compound could not be prepared by the general method employed for 2a–e and 3. See Experimental Section for this synthesis.

Table II[a]



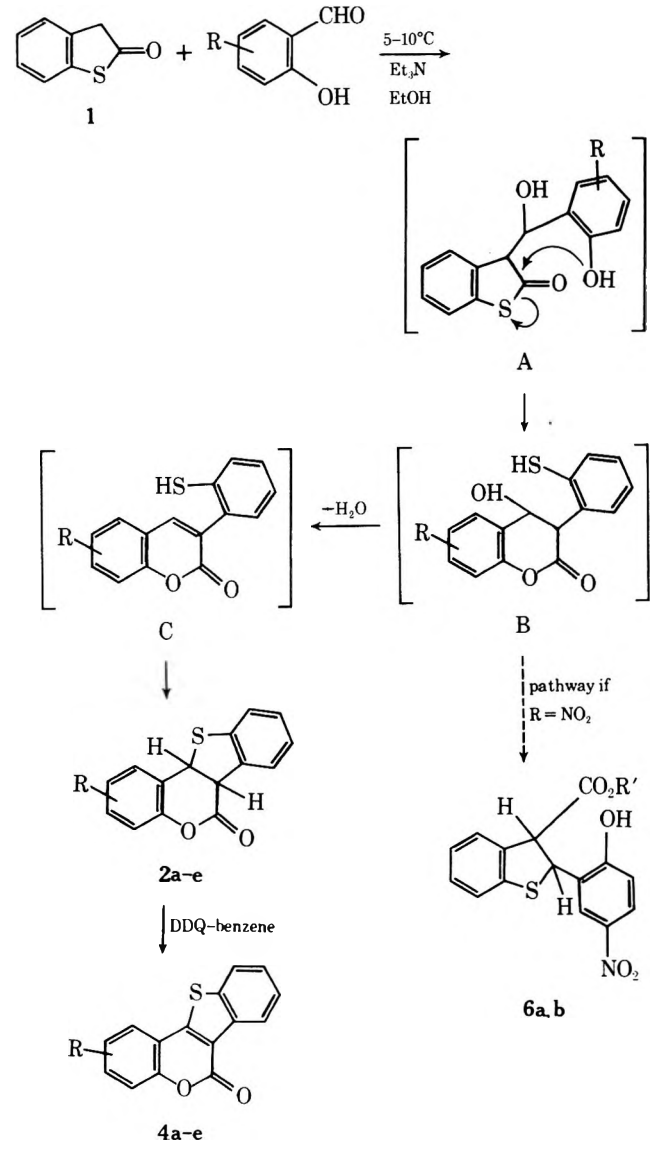
Compd	R_1	R_2	R_3	% yield	Time, hr	Mp, °C
4a	H	H	H	75	11	217.0–217.5
4b	CH_3O	H	H	66	12	187.0–188.0
4c	H	OCH_3	H	66	6	190.0–191.5
4d	H	H	OCH_3	57	10	207.0–208.0
4e	Cl	H	H	57	59	250.5–251.0
8	NO_2	H	H	55	72	261.0–262.0
5				52	117	237.0–239.0

[a] Satisfactory analytical data [±0.4% for C, H, S (N)] were obtained on all compounds listed.

while the longer conversion time required for the oxidation of 2e is apparently due to destabilization of the transient carbonium ion by the *m*-chloro. The extremely slow rate of reaction of the naphtho compound 3 may be rationalized by the peri hydrogen effect of the proton on carbon 1, hindering the DDQ from abstracting the hydride. After the rate-determining hydride loss, the aromatization is completed by removal of the proton α to the carbonyl.

The thiacoumestans were higher melting and less soluble in common organic solvents than their precursor dihydro forms. This diminished solubility made the obtaining of NMR spectra exceedingly difficult and spectra could be obtained only on **4a** and **4b**. These spectra revealed the absence of the typical cis-coupled methinyl proton pair found in the dihydro compounds. The infrared spectra, however, were of considerable assistance in distinguishing the oxidized from the nonoxidized forms for the α,β unsaturation shifted the carbonyl absorption approximately 40 cm^{-1} toward lower wave numbers.

Scheme I

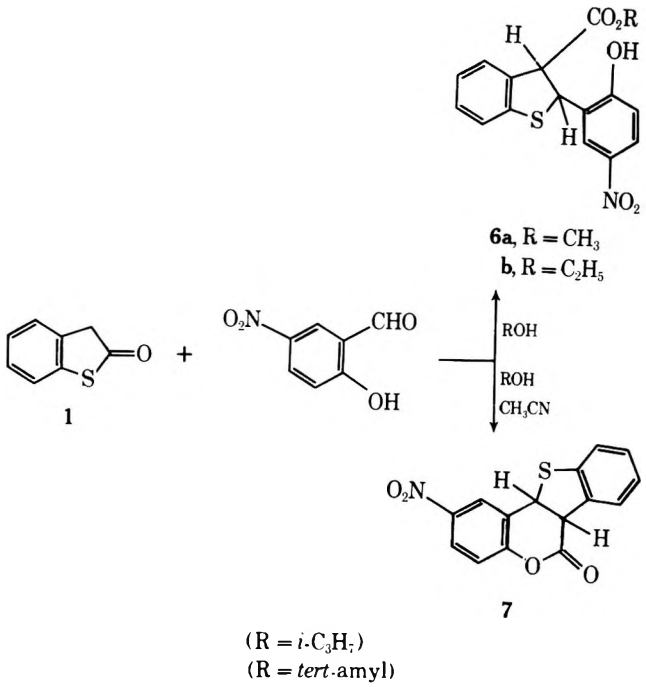


Condensations of Thianaphthen-2-one with 5-Nitrosalicylaldehyde and Pyridoxal. The reaction of 1 and 5-nitrosalicylaldehyde under the normal reaction conditions (ethanol, triethylamine, and cooling in ice) gave ethyl 2-(2-hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (**6b**) instead of the expected 2-nitrodihydrothiacoumestan (**7**) (see Schemes I and II). Since all other salicylaldehydes studied (vide infra) did not yield the 2-(2-hydroxyphenyl)-2,3-dihydrothianaphthene-3-carboxylates but instead yielded the dihydrothiacoumestans, the result obtained with the 5-nitrosalicylaldehyde is unique. Repeating the reaction with methanol gave the corresponding methyl ester (**6a**) but the use of less nucleophilic solvents such as acetonitrile, *tert*-amyl alcohol, and isopropyl alcohol gave the expected 2-nitrodihydrothiacoumestan (**7**).

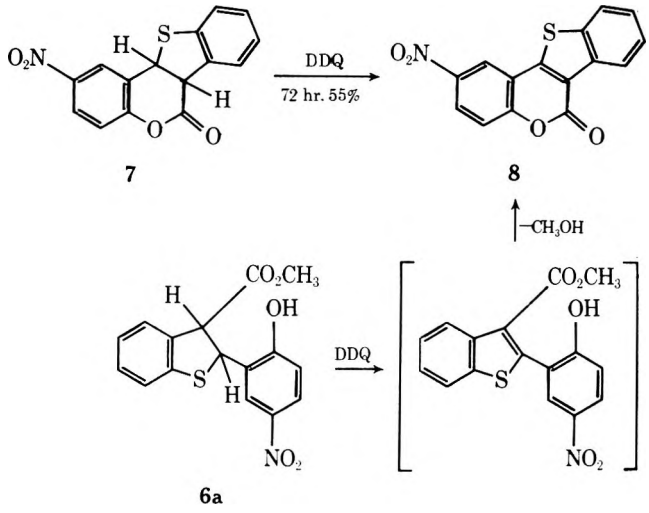
These experimental results implicate a lactone intermediate which is opened by reactive solvents but which proceeds to the 2-nitrodihydrothiacoumestan in less nucleophilic solvents. The fact that 5-nitrosalicylaldehyde is the only salicylaldehyde to undergo this "abnormal reaction" suggests that the nitro group must impart some special properties to this lactone intermediate.

The proposed intermediates A–C and the dihydrothiacoumestan itself (see Scheme I) are all probable species which might be intercepted by methanol or ethanol to produce **6a** or **6b**. No firm experimental evidence establishes

Scheme II



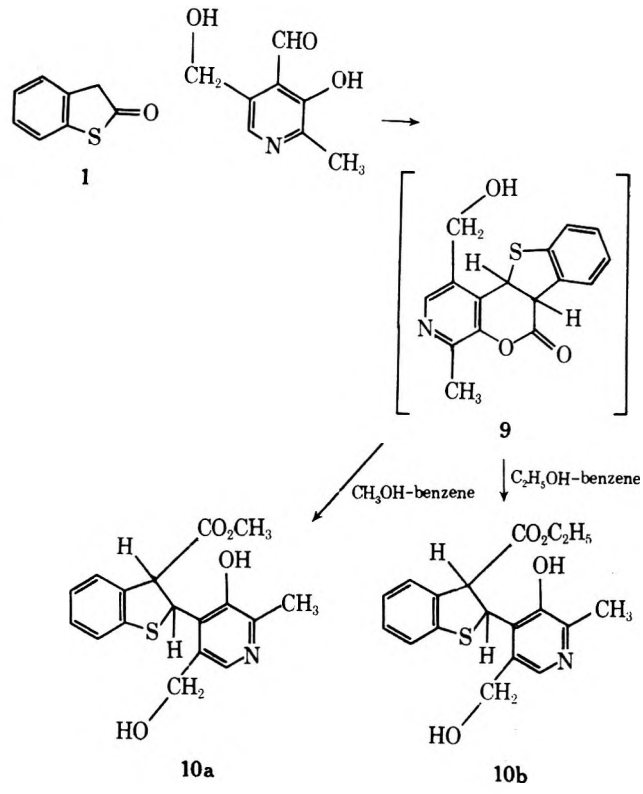
Scheme III



any of these lactones as the precursor of **6a** or **6b** but the authors favor intermediate B. External solvent attack on the thiolactone carbonyl of A as a route to **6a(b)** would not be anticipated to be significantly more likely if R = NO_2 than if R = H. Furthermore, we have found that nitrobenzaldehydes in ethanol form normal benzylidenes without alcoholysis of the thiolactone and an intermediate such as A would be a likely precursor of such benzylidenes. Alcohol attack on the lactone of C would yield a coumarinic ester, a class of compounds known to immediately lactonize to the more stable coumarins.[20] The 2-nitrodihydrothiacoumestan (**7**) when prepared under other conditions was found to be stable to alcoholysis. Thus while no rigorous proof exists, one strong possibility for formation of **6a,b** is the ethanolysis or methanolysis of B followed by its dehydration and thiol-Michael addition. Furthermore, this intermediate B would explain the unique reaction of the 5-nitrosalicylaldehyde, since the nitro group would be expected to enhance the "leaving group" propensity of the phenolate moiety.

2-Nitrothiacoumestan (**8**) was synthesized through three different reaction routes: (1) directly from thianaphthen-2-one and 5-nitrosalicylaldehyde, (2) by DDQ oxidation of 2-nitrodihydrothiacoumestan (**7**), and (3) by DDQ oxidation of the methyl ester **6a**. The oxidation of the methyl ester **6a** to the 2-nitrothiacoumestan 8 was readily predicted from the earlier observations that coumarinate esters (cis cinnamates) immediately lactonize to coumarin.[20] Thus DDQ oxidation of **6a** should yield a labile substituted coumarinate which lactonizes to 8 (Scheme III).

Scheme IV



Thianaphthen-2-one and pyridoxal, upon condensation under the usual reaction conditions with triethylamine catalysis, yielded a crude and labile solid (presumably the pyridopyranone **9**) which upon recrystallization from benzene–methanol gave the methyl ester **10a** and upon recrystallization from benzene–ethanol gave the ethyl ester **10b** (see Scheme IV). The excellent "leaving group" propensity of the 3-hydroxypyridine makes this situation the parallel of the *p*-nitrophenol case previously discussed. Attempts to isolate the presumed intermediate 6*H*-benzothieno[3,2-c]pyrido[4,3-e]pyran-6-one (**9**) were unsuccessful.

Experimental Section

General. Infrared spectra were recorded on a Beckman IR-33 spectrophotometer as Nujol mulls or in solution using 0.1-mm sodium chloride liquid cells. NMR spectra were obtained on a Hitachi Perkin-Elmer R-20A spectrometer with tetramethylsilane as the internal standard. Mass spectra were recorded at the University of Delaware, Newark, Del., on a CED Model 21-110B double focusing spectrometer. Microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N.J. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

General Procedure for the Preparation of 6a,11a-Dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-ones (Dihydro-11-thiacoumestans)(2a–e, 3). Equimolar quantities (6.6 mmol) of thianaphthen-2-one (**1**)[21,22] and the appropriate salicylaldehyde were dissolved or slurried in absolute ethanol (2–6 ml) and cooled with stirring in an ice bath. After the mixture was stirred in the cold for 30 min, 4–5 drops of triethylamine was added and product began to precipitate after an additional 15–30 min. After stirring for several hours in the cold, petroleum ether (bp 60–110°) was added, and the crude product was filtered and washed several times with

cold petroleum ether. The product was recrystallized from benzene–petroleum ether to analytical purity (see Table I).

The characteristic spectral feature of **2a–e** is the coupled methinyl set at δ 4.35 ± 0.02 and 5.14 ± 0.04 ppm (in $CDCl_3$). Compound **2c** was examined in Me_2SO-d_6 owing to insufficient solubility in $CDCl_3$ and the same proton set was observed, δ 4 73 (CHCO) and 5.47 (CHS). The carbonyl absorptions are found at 1760 ± 5 cm^{-1} ($CHCl_3$) for **2a–e** and **3**.

6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-one (4a). Four methods were employed for the synthesis of this substance; the last (oxidation of the dihydro precursors with DDQ) became the general method for synthesis for all analogs of the class (see Table II).

A. Direct Preparation from 1 and Salicylaldehyde. Equimolar quantities (6.6 mmol) of **1** and salicylaldehyde were dissolved in 3 ml of Et_3N and 1 ml of MeOH and the mixture was refluxed for 0.5 hr. Evaporation of the solvents gave a red semisolid which when triturated with boiling MeOH yielded 0.25 g (15%) of **4a:** mp 216.0–217.0°; NMR ($CDCl_3$) δ 6.90–8.80 (m, ArH); ir ($CHCl_3$) 1720 cm^{-1} (C=O); mass spectrum m/e 252 (P).

B. Sulfur Dehydrogenation of 2a. A mixture of 0.25 g (0.98 mmol) of **2a** and 0.06 g (1.96 mmol) of sulfur was fused (H_2S was evolved) in an oil bath at 215°. The melt, after 15 min of heating, solidified and the crude product was dissolved in hot benzene and filtered. Cooling the solution returned 0.18 g (75%) of tan powder (**4a**), mp 215.0–217.0°, mmp 215.0–217.0° (no depression).

C. Refluxing 2a with Triethylamine. A slurry of 0.50 g (1.96 mmol) of **2a**, 8 ml of absolute EtOH, and 8 drops of Et_3N was heated at reflux for 2 hr. Evaporation yielded an oil which when triturated with boiling MeOH gave 0.05 g (10%) of solid (**4a**): mp 213.0–215.0°; identical infrared spectrum with that of previously prepared material.

D. DDQ Oxidation. General Procedure for the Preparation of 6*H*-Benzothieno[3,2-*c*][1]benzopyran-6-ones (11-Thiacoumestans) (4a–e and 5). Equimolar quantities of the 6a,11a-dihydro-6*H*-benzothieno[3,2-c][1]benzopyran-6-one (**2a–e** and **3**) and DDQ in 20 ml of sodium-dried benzene were refluxed for the times stated in Table II. The initially dark black solution became brown during the reaction with the precipitation of the brown hydroquinone. The hydroquinone was removed by hot filtration through a sintered glass funnel and was then washed with hot benzene to ensure complete extraction of the product. The filtrate was partially evaporated and ether was added to precipitate the oxidized product. Upon cooling, crystals precipitated and these were filtered and washed several times with cold ether. One recrystallization from benzene–ether gave the analytical sample (see Table II for data).

Methyl 2-(2-Hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (6a). A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 10 ml of MeOH was cooled to 0°, 5 drops of Et_3N was added, and after 2.5 hr of stirring a solid began to precipitate. After an additional 4 hr, petroleum ether was added and the mixture was filtered to isolate 1.00 g (46%) of white crystals of **6a:** mp 153.0–155.0°C (twice, benzene–petroleum ether); NMR (Me_2SO-d_6) δ 3.30 (s, 3 H, OCH_3), 4.80 (d, 1 H, J = 8 Hz, $CHCOOCH_3$), 5.65 (d, 1 H, J = 8 Hz, SCH), 6.80–8.12 (m, 8 H, ArH and OH); ir (Nujol) 3340 (OH) and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{13}NO_5S$: C, 58.00; H, 3.95; N, 4.23; S, 9.68. Found: C, 58.08; H, 4.18; N, 4.03; S, 9.38.

Ethyl 2-(2-Hydroxy-5-nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylate (6b). A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 10 ml of absolute EtOH was cooled in an ice bath, 5 drops of Et_3N was added, and the slurry was stirred for 3 hr. Petroleum ether was added and the reaction mixture was filtered to yield 1.65 g of a crude product, mp 140–156°. Recrystallization from benzene–ethanol gave 1.17 g (51%) of **6b**, white, fluffy powder: mp 177.0–179.0°; NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, J = 7 Hz, OCH_2CH_3), 3.80 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.87 (d, 1 H, J = 8 Hz, $CHCO_2C_2H_5$), 5.70 (d, 1 H, J = 8 Hz, SCH–), 6.80–7.60 (m, 5 H, ArH), 7.90–8.20 (m, 2 H, ArH), 10.50–11.40 (br, 1 H, OH, D_2O exchangeable); ir (Nujol) 3320 (OH) and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{15}NO_5S$: C, 59.12; H, 4.38; N, 4.06. Found: C, 59.22; H, 4.55; N, 4.10.

2-Nitro-6a,11a-dihydro-6*H*-benzothieno[3,2-*c*][1]benzopyran-6-one (7). A. Acetonitrile Reaction. A slurry of 1.00 g (6.6 mmol) of **1** and 1.10 g (6.6 mmol) of 5-nitrosalicylaldehyde in 5 ml of acetonitrile was cooled in an ice bath for 0.5 hr, 5 drops of Et_3N was added, and a solid began precipitating. After an additional 5 hr of stirring in the cold, the mixture was filtered to isolate 1.50 g (76%) of crude white solid with a melting range of 188–192°. Recrystallizations from acetonitrile gave 0.40 g (20%) of **7** as white granules: mp 198–200°; ir (Nujol) 1760 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.92 (d, 1 H, J = 7.5 Hz, CHCO), 5.72 (d, 1 H, J = 7.5 Hz, CHS), and 7.0–7.7 (m, ArH).

Anal. Calcd for $C_{15}H_9NO_4S$: C, 60.19; H, 3.03; N, 4.68; S, 10.71. Found: C, 60.04; H, 3.25; N, 4.79; S, 10.99.

B. *tert*-Amyl Alcohol Reaction. A slurry of 6.6 mmol each of **1** and 5-nitrosalicylaldehyde in 5 ml of *tert*-amyl alcohol was chilled in an ice water bath, 3 drops of Et_3N was added, and the mixture was agitated in the cold for 7 hr. The product was filtered, washed with cold petroleum ether (bp 30–60°), and dried to yield 1.80 g (91%) of **7**, which, although of broad and low melting point (mp 160–167°), possessed an ir spectrum identical with that of the analytical sample. Two recrystallizations (acetonitrile) raised the melting point to 186–190°. A repeat of the experiment in 2-propanol as solvent gave similar results, an 86% yield crude **7** (mp 168–175°) whose melting point was raised to 190–193° after two recrystallizations from acetonitrile.

Anal. Calcd for $C_{15}H_9NO_4S$: C, 60.19; H, 3.03; N, 4.68; S, 10.71. Found: C, 60.04; H, 3.25; N, 4.79; S, 10.99.

2-Nitro-6*H*-benzothieno[3,2-c][1]benzopyran-6-one (8). A. Directly from Thianaphthen-2-one and 5-Nitrosalicylaldehyde. An orange-yellow solution of 6.6 mmol each of **1** and 5-nitrosalicylaldehyde was cooled in an ice bath, 10 drops of Et_3N was added, and precipitation of product ensued within 10 min. The reaction mixture was stirred at 15° for 6 hr, petroleum ether (bp 30–60°) was added, and the solution was stirred at 35° for 5 hr. Filtration and air drying gave 0.25 g (13%) of the 2-nitrothiacoumestan (**8**) as a tan solid, mp 256–260°, ir ($CHCl_3$) 1725 cm^{-1}. Recrystallization from benzene yielded the analytical sample, mp 261–262°.

Anal. Calcd for $C_{15}H_7NO_4S$: C, 60.60; H, 2.37; N, 4.71; S, 10.78. Found: C, 60.68; H, 2.68; N, 4.56; S, 10.57.

B. DDQ Oxidation of the Methyl Ester 6a. A solution of 0.15 g (0.5 mmol) of the methyl ester **6a** and 0.13 g (0.6 mmol) of DDQ in 20 ml of sodium-dried benzene was refluxed for 72 hr and filtered hot to remove the precipitated hydroquinone. The filtrate was partially evaporated and the fluffy 2-nitrothiacoumestan (**8**) precipitated. Ether (25 ml) was added, the filtrate was chilled, and the fluffy white solid (0.13 g, 97%) was removed, mp 258–260°. Recrystallization from benzene raised the melting point to 263.0–265.0°, mmp 263.5–264.5° (undepressed).

C. DDQ Oxidation of 7 to 8. Following the general procedure previously outlined for DDQ preparation of **4a–e** and **5**, compound **8** (mp 263–265° from benzene) was prepared in 55% yield by oxidation of **7** (see Table II).

Methyl 2-(3-Hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-2,3-dihydrothianaphthene-3-carboxylate (10a). A slurry of equimolar amounts (6.6 mmol) of **1** and pyridoxal hydrochloride in 6 ml of absolute EtOH was cooled to 10°, 5 drops of Et_3N was added, and the medium was stirred for 1 hr. This mixture was then dissolved in water, solid $NaHCO_3$ was added until slight alkalinity was achieved, and the precipitate was filtered, washed with petroleum ether (bp 30–60°), and air dried to give 1.46 g of crude light yellow solid (presumably the lactone **9**: mp 98–106° (unclear melt); NMR (Me_2SO-d_6) δ 2.47 (s, 3 H, pyr-CH_3), 4.67 (s, 2 H, pyr-CH_2OH), 4.80 (d, 1 H, J = 7 Hz, –CHCO), 5.18–5.80 (broad, 1 H, CH_2OH), 5.68 (d, 1 H, J = 7 Hz, CHS), 7.00–7.70 (m, 4 H, ArH), 8.20 (s, 1 H, pyr-H). Recrystallization from 20 ml of 50:50 benzene–MeOH yielded 1.43 g (66%) of the methyl ester as an off-white powder: mp 182.0–185.0° dec; NMR (Me_2SO-d_6) δ 2.43 (s, 3 H, pyr-CH_3), 3.75 (s, 3 H, OCH_3), 4.58 (s 2 H, pyr-CH_2OH), 4.83–5.83 (broad, 1 H, CH_2OH, D_2O exchangeable), 5.12 (d, 1 H, J = 8 Hz, CHS), 7.00–7.50 (m, 4 H, ArH), 7.98 (s, 1 H, pyr-H), D_2O showed two exchangeable protons; ir (Nujol) 3150 (OH) and 1730 cm^{-1} (C=O). An analytical sample of **10a** was prepared by recrystallization from alcohol, mp 191.5–193.0° dec.

Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.62; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.37; H, 5.45; N, 4.04; S, 9.51.

Ethyl 2-(3-Hydroxy-5-hydroxymethyl-2-methyl-4-pyridyl)-2,3-dihydrothianaphthene-3-carboxylate (10b). Following the exact procedure outlined for **10a**, the crude, labile presumed lactone **9** was again isolated and when recrystallized from benzene–EtOH gave 0.51 g of white, fluffy solid **10b:** mp 171.5–173.0° dec; NMR (Me_2SO-d_6) δ 1.20 (s, 3 H, J = 7 Hz, OCH_2CH_3), 2.40 (s, 3 H, pyr-CH_3), 4.17 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.58 (s, 2 H, pyr-CH_2OH), 4.80–5.70 (broad, 1 H, D_2O exchangeable, pyr-CH_2OH), 5.05 (d, 1 H, J = 8 Hz, –CHCO), 5.95 (d, 1 H, J = 8 Hz, –CHS),

7.00–7.40 (m, 4 H, ArH), 7.95 (s, 1 H, pyr-H), D_2O showed two exchangeable protons; ir (Nujol) 3120 (OH) and 1730 cm^{-1} (C=O). A second recrystallization from benzene–EtOH gave 0.35 g of white analytically pure solid **10b**, mp 172.0–173.0° dec.

Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06; S, 9.28. Found: C, 62.75; H, 5.62; N, 3.82; S, 9.51.

Acknowledgments. R.A.C. (Lehigh University, Ph.D., 1974) was a recipient of the Hornor and Buch Graduate Research Fellowships which, in part, supported this study.

Registry No.—**1**, 496-31-1; **2a**, 54711-32-9; **2b**, 54711-33-0; **2c**, 54711-34-1; **2d**, 56404-07-0; **2e**, 56404-08-1; **3**, 56404-09-2; **4a**, 54711-35-2; **4b**, 54711-36-3; **4c**, 54711-37-4; **4d**, 56404-10-5; **4e**, 56404-11-6; **5**, 56404-12-7; **6a**, 56404-13-8; **6b**, 56404-14-9; **7**, 56404-15-0; **8**, 56404-16-1; **9**, 56404-17-2; **10a**, 56404-18-3; **10b**, 56404-19-4; salicylaldehyde, 90-02-8; 5-methoxysalicylaldehyde, 672-13-9; 4-methoxysalicylaldehyde, 673-22-3; 3-methoxysalicylaldehyde, 148-53-8; 5-chlorosalicylaldehyde, 635-93-8; 5-nitrosalicylaldehyde, 97-51-8; sulfur, 7704-34-9; triethylamine, 121-44-8; DDQ, 84-58-2; MeOH, 67-56-1; EtOH, 64-17-5; acetonitrile, 75-05-8; *tert*-amyl alcohol, 75-85-4; pyridoxal HCl, 65-22-5.

References and Notes

(1) Two excellent reviews on coumestan chemistry: (a) F. M. Dean, "The Total Synthesis of Naturally Occurring Oxygen Ring Compounds", in "The Total Synthesis of Natural Products", Vol. 1, J. ApSimon, Ed., Wiley, New York, N.Y., 1973: (b) A. Mustafa, "Furopyrans and Furopyrones", in "The Chemistry of Heterocyclic Compounds", Vol. 23, A. Weissberger, Ed., Wiley, New York, N.Y., 1967.
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Darzens Synthesis of Glycidic Thiol Esters. Formation of a β-Lactone By-product[1]

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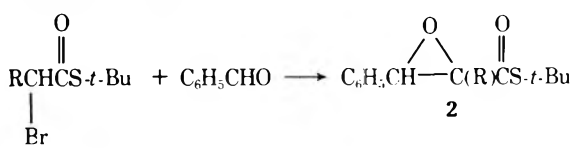
The Darzens condensation has been used in the preparation of glycidic thiol esters. Aliphatic ketones and aromatic and aliphatic aldehydes may be used as substrates. *S*-Benzyl and *S*-*tert*-butyl thiolglycidates were prepared. In general 2-bromothiol esters gave higher yields than the corresponding 2-chlorothiol esters. The low yields obtained with 2-chlorothiol esters are due in part to competing formation of an α-chloro-β-lactone by-product. Results have been obtained that suggest that a carbene intermediate is not involved in the Darzens synthesis of glycidic thiol esters.

A great deal of attention has been given to preparative and mechanistic aspects of the Darzens synthesis of glycidic (oxygen) esters.[2] Recently[1b] we have found that it is also possible to carry out a Darzens synthesis of glycidic thiol esters (2). In the formation of the glycidic thiol esters it is important to use nonnucleophilic bases such as sodium hydride or lithium bis(trimethylsilyl)amide and relatively polar aprotic solvents including tetrahydrofuran and dimethylformamide. We have also found that α-bromothiol ester reactants are preferable in most cases to the corresponding α-chlorothiol esters.[1b]



1a, R = H
b, R = CH_3

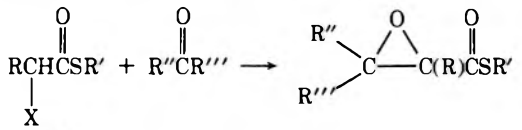
When these facts are kept in mind the Darzens reaction provides the best available method for the synthesis of S-aliphatic glycidic thiol esters.[3] In this report we would like to comment on the generality of this reaction and also certain mechanistic aspects of the process. At the outset it should be pointed out that even when working within the previously described limits[1b] the proper choice of reaction conditions is critical in obtaining a successful reaction. This situation may be contrasted with the wide variety of conditions successfully employed in the normal Darzens glycidic ester condensation.[2] It is important to understand something about these limitations in order to take full advantage of the Darzens reaction in the synthesis of glycidic thiol esters.

Results and Discussion

In this discussion it will be useful to make reference to the currently accepted mechanism[2b,c,d,h,i,l] for the Darzens reaction (Scheme I). Although we have not carried out an extensive examination of the mechanism of the Darzens synthesis of glycidic thiol esters, we have checked certain points to see if major differences are apparent. It has been argued earlier from a study of the reaction of ethyl 2-chlo-

Table I[a]

Glycidic Thiol Esters from α-Halothiol Esters



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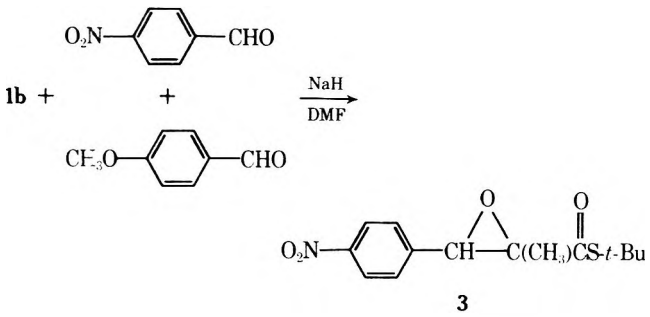
Halo ester	Carbonyl compound	Base	Solvent	Product	R	R'	R"	R"'	Yield, %	Isomer ratio trans:cis
1a	Cyclohexanone	NaH	THF	4	H	*t*-Bu		$-(CH_2)_5-$	69	
1a	Cyclehexanone	NaH	DMF	4	H	*t*-Bu		$-(CH_2)_5-$	28	
$ClCH_2COS$-*t*-Bu (1c)	Cyclohexanone	NaH	THF	4	H	*t*-Bu		$-(CH_2)_5-$	12	
1c	Cyclohexanone	NaH	DMF	4	H	*t*-Bu		$-(CH_2)_5-$	28	
1a	Acetone[b]	NaH	THF	5	H	*t*-Bu	CH_3	CH_3	69	
1a	Acetone[b]	NaH	DMF	5	H	*t*-Bu	CH_3	CH_3	10	
1c	Acetone[b]	NaH	THF	5	H	*t*-Bu	CH_3	CH_3	7	
1c	Acetone[b]	NaH	DMF	5	H	*t*-Bu	CH_3	CH_3	20	
1a	Cyclohexanone	$LiN(SiMe_3)_2$	THF	4	H	*t*-Bu		$-(CH_2)_5-$	92	
1c	Cyclohexanone	$LiN(SiMe_3)_2$	THF	4	H	*t*-Bu		$-(CH_2)_5-$	25	
1a	Acetone[b]	$LiN(SiMe_3)_2$	THF	5	H	*t*-Bu	CH_3	CH_3	60[c]	
1c	Acetone[b]	$LiN(SiMe_3)_2$	THF	5	H	*t*-Bu	CH_3	CH_3	10	
$BrCH_2COSCH_2C_6H_5$ (1d)	Cyclohexanone	$LiN(SiMe_3)_2$	THF	6	H	$C_6H_5CH_2$		$-(CH_2)_5-$	70	
1d	Cyclohexanone	NaH	DMF	6	H	$C_6H_5CH_2$		$-(CH_2)_5-$	10	
1d	Cyclohexanone	NaH	THF	6	H	$C_6H_5CH_2$		$-(CH_2)_5-$	10	
1d	Benzaldehyde	NaH	DMF	7	H	$C_6H_5CH_2$	C_6H_5	H	35[d]	6:4
1a	Benzaldehyde	NaH	DMF	2a	H	*t*-Bu	C_6H_5	H	67[e-g]	3:7
1a	Benzaldehyde	$LiN(SiMe_3)_2$	THF	2a	H	*t*-Bu	C_6H_5	H	59[e]	9:1
1a	Isobutyraldehyde	NaH	DMF	8	H	*t*-Bu	$(CH_3)_2CH$	H	62[f]	4:6
1a	Isobutyraldehyde	$LiN(SiMe_3)_2$	THF	8	H	*t*-Bu	$(CH_3)_2CH$	H	10[h]	9:1
1b	Benzaldehyde	NaH	DMF	2b	CH_3	*t*-Bu	C_6H_5	H	58[e]	9:1
1b	Cyclohexanone	NaH	DMF	9	CH_3	*t*-Bu		$-(CH_2)_5-$ H	60	
$CH_3CH_2CHBrCOS$-*t*-Bu (1e)	Benzaldehyde	NaH	DMF	10	CH_3CH_2	*t*-Bu	C_6H_5	H	59	9:1
$CH_3CHClCOS$-*t*-Bu (1f)	Benzaldehyde	NaH	DMF	2b	CH_3	*t*-Bu	C_6H_5	H	45	All trans
1f	Cyclohexanone	NaH	DMF	9	CH_3	*t*-Bu		$-(CH_2)_5-$	15	

[a] Except where otherwise noted all NaH yields reported in the table were obtained for reactions carried out by adding a mixture of 1 equiv of carbonyl compound and 1 equiv of 2-halothiol ester in DMF (or THF) to 1.3 equiv of NaH in DMF (or THF) at 0° followed by stirring for 30 min at 0° and 30 min at room temperature before work-up. All $LiN(SiMe_3)_2$-THF yields reported in the table were obtained for reactions carried out by adding 1 equiv of base in THF to a mixture of 1 equiv of carbonyl compound and 1 equiv of 2-halothiol ester at 0° followed by stirring for 30 min at 0° and then 30 min at room temperature before work-up. [b] Because of the volatility of acetone, excess (2 equiv) was used and higher yields were thus obtained. [c] A 72% yield was obtained by addition of $LiN(SiMe_3)_2$ to acetone and **1a** at −78° and stirring for 30 min at −78°, followed by warming to room temperature where it was stirred again for 30 min before work-up. [d] No glycidic thiol ester (7) was obtained when the reaction was carried out with $LiN(SiMe_3)_2$ in THF. [e] Reference 1b. [f] No glycidic thiol ester (2a) was obtained when the reaction was carried out with NaH in THF. [g] No glycidic thiol ester (2a) was obtained when 1c was used in place of **1a**. [h] A 28% yield was obtained by adding $LiN(SiMe_3)_2$ to isobutyraldehyde and **1a** in THF at −78° and stirring for 30 min at −78°, followed by warming to room temperature where it was stirred again for 30 min before work-up.

rophenylacetate with a mixture of *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde[2d] that a carbene intermediate is not involved in the Darzens synthesis of glycidic (oxygen) esters. The major Darzens product was that obtained from *p*-nitrobenzaldehyde. If a carbene intermediate were involved the product obtained from *p*-methoxybenzaldehyde would be expected. We thus studied the reaction of a mixture of *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde with *S*-*tert*-butyl 2-bromothiolpropionate (**1b**) using NaH in DMF. The product (**3**) resulting from the reaction of *p*-

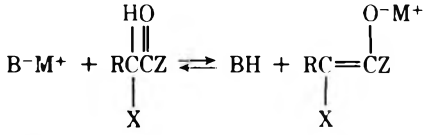


3

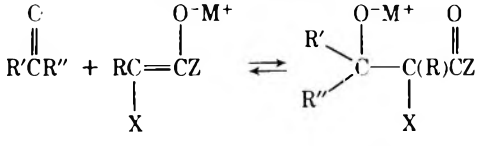
nitrobenzaldehyde was obtained in 75% yield and unreacted *p*-methoxybenzaldehyde (91%) was recovered. No *p*-nitrobenzaldehyde was detected in the reaction mixture. These results suggest that a carbene intermediate is not involved in the mechanism in the formation of glycidic thiol esters. This conclusion is supported by the known high migratory aptitude of the sulfur atom in moving to a carbene center in a Wolff rearrangement process[4] suggesting that if in fact a carbene intermediate was formed in the reaction of **1b** with NaH it would undergo rearrangement preventing formation of the glycidic thiol ester product (**3**). The nature of by-products formed in the Darzens reactions discussed below also tend to support the mechanism in Scheme I.

Scheme I

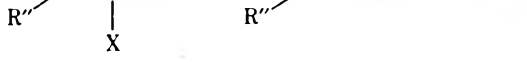
1. Proton Exchange



2. Nucleophilic Addition (Aldolization)



3. Intramolecular Nucleophilic Substitution (Cyclization)



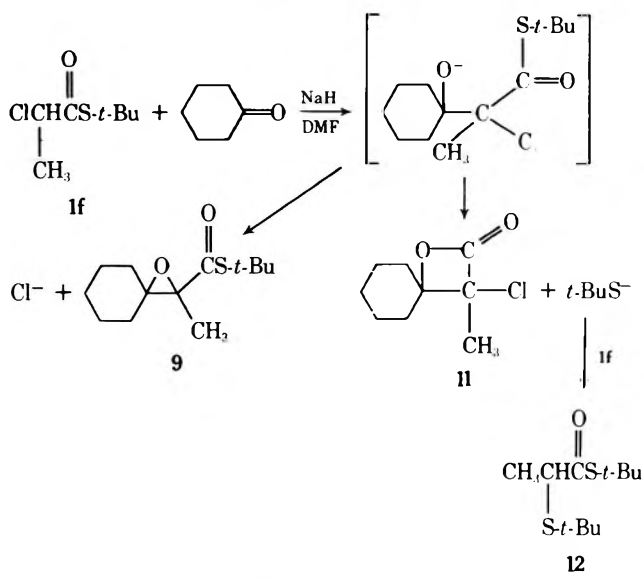
Low yields of thiolglycidates **4** and **5** were obtained in the reaction of cyclohexanone or acetone with *S*-*tert*-butyl 2-chlorothiolacetate (**1c**) using either the NaH–THF, NaH–DMF, or $LiN(SiMe_3)_2$–THF conditions (Table I). High yields of **4** or **5** were obtained using *S*-*tert*-butyl 2-bromothiolacetate (**1a**) and NaH or $LiN(SiMe_3)_2$ in THF. Thus with aliphatic ketones as with aromatic aldehydes,[1b] α-bromothiol esters gave higher yields than the corresponding α-chlorothiol esters. However, even when using α-bromothiol esters it is important to be careful in selecting the reaction conditions in order to achieve a satisfactory yield. For example, low yields of **4** or **5** were obtained with α-bromothiol ester **1a** using NaH in DMF. The use of the polar DMF solvent may favor alkylation of acetone or cyclohexanone by **1a**. Intramolecular as well as intermolecular nucleophilic substitution processes are known to proceed more rapidly as the polarity of the solvent is increased.[2i,l] Also in support of this interpretation we have found that the NaH–DMF conditions work well in the reaction of **1a** with benzaldehyde, which may not undergo this alkylation reaction. It is noteworthy that the NaH–DMF conditions were effective in the reaction of cyclohexanone with *S*-*tert*-butyl 2-bromothiolpropionate (**1b**). In this reaction the alkylation process would occur at a secondary carbon while in the reaction with **1a** a primary carbon is involved. Competing reactions involving alkylation of the ketone substrate have been noted previously in the Darzens synthesis of glycidic (oxygen) esters.[5] This process was shown to be important when α-bromo esters or α-iodo esters were substituted for α-chloro esters. This in part accounts for the preferential use of chloro reactants in the majority of Darzens reactions reported to date.

Another illustration of the need for careful choice of reaction conditions is found in the reaction of *S*-benzyl 2-bromothiolacetate (**1d**) with aldehydes and ketones. In the reaction of **1d** with benzaldehyde a 35% yield of *cis*- and *trans*-*S*-benzyl 3-phenylthiolglycidates (**7**) was obtained using the NaH–DMF conditions although no **7** was found using $LiN(SiMe_3)_2$ in THF. In contrast in the reaction of **1d** with cyclohexanone, a 70% yield of *S*-benzyl thiolglycidate (**6**) was obtained using the $LiN(SiMe_3)_2$–THF conditions although 10% was found using NaH in DMF.

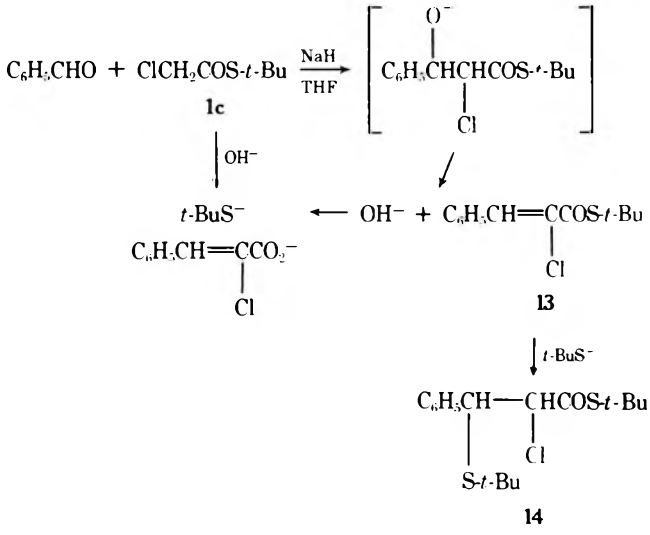
We were interested in learning why α-chlorothiol esters gave low yields in the Darzens synthesis of glycidic thiol esters. In the reaction of cyclohexanone with *S*-*tert*-butyl 2-chlorothiolpropionate (**1f**) using the NaH–DMF conditions we obtained 15% of thiolglycidate **9**. We also isolated two by-products, *S*-*tert*-butyl 2-(*tert*-butylthio)thiolpropionate (**12**) and β-lactone **11**. The NMR spectrum of **12** was unusual in that it gave a doublet at δ 1.41 (21 H) and a quartet at δ 3.42 (1 H). This spectra may be explained if we assume that the two *tert*-butyl peaks are superimposed on the methyl doublet. To confirm this interpretation **12** was prepared independently from **1f** and *tert*-butyl mercaptan in DMF solvent using NaH as a base. The structure of β-lactone **11** is based on analytical data and spectral evidence. **11** had a carbonyl absorption at 1820 cm^{-1} in the ir spectrum and an NMR spectrum which showed a singlet at δ 1.75 superimposed on a multiplet between δ 1.35 and 2.15. The mass spectrum gave intense peaks at *m/e* 144 and 146 ($M^{\cdot+} - CO_2$) and at 109 [$M^{\cdot+}$ − (CO_2 and Cl)]. The formation of β-lactone **11** suggests that an intramolecular nucleophilic acyl substitution reaction may compete with the epoxide forming substitution process in the Darzens synthesis of glycidic thiol esters (Scheme II). The liberated *tert*-butyl thiolate anion is then trapped by starting material (**1f**), leading to the formation of **12**.

A large number of products were obtained in the reaction of benzaldehyde with *S*-*tert*-butyl 2-chlorothiolacetate (**1c**) using NaH in THF. We were able to isolate 2-chlorocinnamic acid along with *erythro*- and *threo*-*S*-*tert*-butyl 3-*tert*-butylthio-2-chloro-3-phenylthiolpropionate (**14**). The isolation of **14** suggests that aldol condensation involving formation of an α-chloro α,β-unsaturated thiol ester derivative such as **13** is another important competing process in the Darzens synthesis of glycidic thiol esters (Scheme III). A similar side reaction has been observed previously in the Darzens reaction of benzaldehyde with ethyl chloroacetate leading to the formation of ethyl 2-chlorocinnamate.[6] α-Chloro ketones are also known to undergo this elimina-

Scheme II



Scheme III



tion process.[7] This reaction may be particularly important with thiol esters, since the acidity of protons adjacent to a thiol ester group is substantially greater than protons α to the (oxygen) ester.[8] A competing elimination process of this type may be used to explain the result that no thiolglycidate **2a** was obtained in the reaction of benzaldehyde with *S-tert*-butyl 2-chlorothiolacetate (**1c**) using NaH in DMF. In this connection it is interesting that under the same conditions 45% of thiolglycidate **2b** was obtained in the reaction of benzaldehyde with *S-tert*-butyl 2-chlorothiolpropionate (**1f**), a reaction which would not be expected to undergo this elimination process. Thiolglycidate **2a** may be obtained in 67% yield from *S-tert*-butyl 2-bromothiolglycidate (**1a**) and benzaldehyde using NaH in DMF.[1b] When the chlorine is replaced by the bromine leaving group, intramolecular substitution (step 3, Scheme I) is able to compete with the side reaction involving proton abstraction.

Experimental Section

General. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60A spectrometer using tetramethylsilane (Me_4Si) as an internal standard. Mass spectral analysis was performed on a Varian MAT CH-5 spectrometer. THF was dried over sodium metal–anthracene complex and distilled prior to use. DMF was initially refluxed with a mixture of potassium hydroxide and calcium oxide overnight. It was then distilled and the distillate was dried over P_2O_5, distilled again, and finally stored over molecular sieves [type 4A (4–8 mesh)]. Benzene was dried over sodium metal while ether was dried over $LiAlH_4$. Both were distilled prior to use. Elemental analysis were performed by M-H-W Laboratories, Garden City, Mich. Melting points and boiling points are uncorrected. The petroleum ether had a boiling point range of 60–110°. The silica gel used in column chromatography was Baker reagent grade (60–200 mesh). Aldehydes and ketones were purified by distillation.

***S-tert*-Butyl 2-Bromothiolacetate (1a).** Pyridine (40 g, 0.51 mol) in chloroform (50 ml) and *tert*-butyl mercaptan (45 g, 0.50 mol) in chloroform (50 ml) were added separately and simultaneously over a 30-min period to a stirred solution of 2-bromoacetyl bromide[9] (101 g, 0.50 mol) in chloroform (150 ml) at 0°. The reaction mixture was stirred for an additional 90 min at 0° and then for 1 hr at room temperature. The chloroform was removed under reduced pressure and the residue was dissolved in ether (300 ml) and extracted once with cold water (200 ml). The water layer was reextracted with ether (150 ml) and the combined ether layers were dried (Na_2SO_4) and concentrated. The residue was purified by fractional distillation to give **1a** as a colorless oil: bp 58–60° (1.3 mm) (63 g, 0.30 mol, 60%); $n^{26}D$ 1.5077; NMR (CCl_4) δ 3.88 (s, 2 H), 1.48 (s, 9 H); ir (thin film) 1690 cm^{-1} (broad).

Anal. Calcd for $C_6H_{11}OSBr$: C, 34.13; H, 5.25; S, 15.19; Br, 37.85. Found: C, 34.23; H, 5.36; S, 15.00; Br, 38.07.

The following 2-halothiolacetates were prepared using a similar procedure.

***S*-Benzyl 2-bromothiolacetate (1d)** was obtained as a colorless oil from 2-bromoacetyl bromide and benzyl mercaptan: 60%; bp 114–116° (0.3 mm); $n^{27}D$ 1.5980; NMR (CCl_4) δ 7.15 (s, 5 H), 4.03 (s, 2 H), 3.80 (s, 2 H); ir (thin film) 1690 cm^{-1} (broad).

Anal. Calcd for C_9H_9OSBr: C, 44.09; H, 3.70; S, 13.08; Br, 32.60. Found: C, 44.12; H, 3.82; S, 12.88; Br, 32.79.

***S*-Phenyl 2-bromothiolacetate** was obtained as colorless plates (decomposes on standing) from 2-bromoacetyl bromide and benzenethiol: 59% mp 38–39° from benzene–petroleum ether; NMR (CCl_4) δ 7.30 (s, 5 H), 3.93 (s, 2 H); ir (KBr) 1695 cm^{-1} (broad).

Anal. Calcd for C_8H_7OSBr: C, 41.57; H, 3.05; S, 13.87; Br, 34.58. Found: C, 41.69; H, 3.09; S, 13.64; Br, 34.53.

***S*-Benzyl 2-chlorothiolacetate** was obtained as a colorless oil from 2-chloroacetyl chloride[9] and benzyl mercaptan: 73%; bp 100–101° (0.1 mm); $n^{26}D$ 1.5782; NMR (CCl_4) δ 7.16 (s, 5 H), 4.03 (s), and 3.99 (s) (4 H); ir (thin film) 1680 cm^{-1} (broad).

Anal. Calcd for C_9H_9OSCl: C, 53.86; H, 4.52; S, 15.98; Cl, 17.66. Found: C, 54.04; H, 4.58; S, 16.16; Cl, 17.54.

***S-tert*-Butyl 2-Bromothiolpropionate (1b).** Pyridine (12.6 g, 0.16 mol) in chloroform (25 ml) and *tert*-butyl mercaptan (14.4 g, 0.16 mol) in chloroform (25 ml) were added separately and simultaneously over a 30-min period to a stirred solution of 2-bromopropionyl bromide[10] (37.5 g, 0.17 mol) in chloroform (50 ml) at 0°. The reaction mixture was stirred for an additional 90 min at 0° and for 1 hr at room temperature. The chloroform was evaporated and ether (200 ml) and water (100 ml) were added. The water layer was extracted with additional ether (100 ml) and the combined ether layers were extracted with 5% $NaHCO_3$ (2 × 50 ml), dried (Na_2SO_4), and concentrated to give an oil which was purified by fractional distillation, bp 68–71° (0.6 mm). **1b** was obtained as a colorless oil (26.7 g, 0.12 mol, 74%): $n^{26}D$ 1.4965; NMR (CCl_4) δ 4.31 (q, 1 H, J = 7 Hz), 1.77 (d, 3 H, J = 7 Hz), 1.48 (s, 9 H): ir (thin film) 1690 cm^{-1} (broad).

Anal. Calcd for $C_7H_{13}OSBr$: C, 37.34; H, 5.82; S, 14.24; Br, 35.49. Found: C, 37.35; H, 5.63; S, 14.06; Br, 35.72.

***S-tert*-Butyl 2-Bromothiolbutyrate (1e).** Using the same procedure **1e** was prepared from 2-bromobutyryl bromide[10] and *tert*-butyl mercaptan: 63%; $n^{26}D$ 1.4940; NMR (CCl_4) δ 4.11 (t, 1 H, J = 7 Hz), 1.97 (m, 2 H), 1.49 (s, 9 H), 1.03 (t, 3 H, J = 7 Hz); ir (thin film) 1685 cm^{-1} (broad).

Anal. Calcd for $C_8H_{15}OSBr$: C, 40.17; H, 6.32; S, 13.41. Found: C, 40.33; H, 6.32; S, 13.55.

***S-tert*-Butyl 2-Chlorothiolpropionate (1f).** Using the procedure described by Dawson[11] for the preparation of *S-tert*-butyl 2-chlorothiolacetate, **1f** was synthesized from *tert*-butyl mercaptan and 2-chloropropionyl chloride:[9] 70%; bp 105° (35 mm); $n^{29}D$ 1.4734; NMR (CCl_4) δ 1.50 (s, 9 H), 1.65 (d, 3 H, J = 7 Hz), 4.32 (q, 1 H, J = 7 Hz); ir (thin film) 1680 cm^{-1} (broad).

Anal. Calcd for $C_7H_{13}OSCl$: C, 46.52; H, 7.27; S, 17.74; Cl, 19.61. Found: C, 46.34; H, 7.32; S, 17.61; Cl, 19.84.

Reaction of 1b with *p*-Nitrobenzaldehyde and Anisal-

dehyde. A 54% NaH dispersion in mineral oil (0.49 g, 11 mmol) was washed with hexane (3 × 10 ml) under nitrogen atmosphere and dry DMF (25 ml) was added. A mixture of anisaldehyde (1.36 g, 10 mmol), *p*-nitrobenzaldehyde (1.51 g, 10 mmol), and **1b** (2.25 g, 10 mmol) in DMF (15 ml) was added to the NaH at 0° over a period of 10 min. After the addition the reaction was stirred at 0° for 30 min and then at room temperature for 75 min. The reaction mixture was extracted with petroleum ether (3 × 50 ml). The combined petroleum ether extracts were washed with water (2 × 50 ml), dried (Na_2SO_4), and concentrated to give an oil that solidified on standing. Water (100 ml) was added to the DMF extract and this was extracted with ether (3 × 50 ml). The combined ether extracts were reextracted with water (2 × 25 ml), dried (Na_2SO_4), and concentrated to give an oil. NMR analysis indicated that the oil obtained from both the ether and petroleum ether extractions contained substantial amounts of anisaldehyde and *trans*- and *cis*-*S*-*tert*-butyl 2-methyl-3-*p*-nitrophenyloxiranecarbothioate (**3**). The fractions were thus combined and subjected to column chromatography on silica gel eluting with 1:3 benzene–petroleum ether. The trans isomer was the first product eluted from the column (1.36 g, 4.6 mmol, 46%). Recrystallization (benzene and hexane) gave faint yellow plates: mp 107–108°; NMR (CCl_4) δ 8.23 (d, 2 H, J = 9 Hz), 7.49 (d, 2 H, J = 9 Hz), 4.17 (s, 1 H), 1.48 (s, 9 H), 1.23 (s, 3 H); ir (KBr) 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}O_4NS$: C, 56.93; H, 5.80; N, 4.74; S, 10.86. Found: C, 56.91; H, 5.78; N, 4.74; S, 10.95.

The cis isomer (0.87 g, 2.9 mmol, 29%) was obtained after further elution with benzene–petroleum ether (1:3). Recrystallization from hexane gave faint yellow plates: mp 81–82°; NMR (CCl_4) δ 8.23 (d, 2 H, J = 9 Hz), 7.60 (d, 2 H, J = 9 Hz), 4.04 (s, 1 H), 1.70 (s, 3 H), 1.22 (s, 9 H); ir (KBr) 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{17}O_4NS$: C, 56.93; H, 5.80; N, 4.74; S, 10.86. Found: C, 57.10; H, 5.68; N, 4.81; S, 10.65.

Finally anisaldehyde (1.24 g, 91%) was recovered by further elution with benzene–petroluem ether (1:3). *p*-Nitrobenzaldehyde was not detected in the NMR spectrum of the crude reaction mixture nor was any isolated from the chromatography column.

***S*-*tert*-Butyl 1-Oxaspiro[2.5]octane-2-carbothioate (4).** A 57% sodium hydride dispersion in mineral oil (0.558 g, 13 mmol) was washed with hexane (4 × 15 ml) under nitrogen atmosphere and anhydrous THF (15 ml) was added. A mixture of cyclohexanone (0.98 g, 10 mmol) and **1a** (2.11 g, 10 mmol) in THF (10 ml) was added at a rate of approximately 1 ml/min to the stirred mixture of NaH in THF at 0°. After the addition the reaction was stirred at 0° for an additional 30 min and then at room temperature for 30 min before filtering through a sintered glass funnel (coarse). The filtrate was added to a mixture of cold water (200 ml) and ether (150 ml). The ether layer was separated and the water layer was extracted again with ether (75 ml). The combined ether extracts were dried (Na_2SO_4) and concentrated to give an oil which was purified by careful column chromatography on silica gel eluting with petroleum ether followed by benzene–petroleum ether (1:1). **4** was obtained as an oil (1.58 g, 6.9 mmol, 69%). Short-path distillation (130–135° bath temperature, 0.6 mm) gave a colorless oil which crystallized on standing overnight under reduced pressure. Recrystallization (hexane) gave colorless plates: mp 31–32°; NMR (CCl_4) δ 3.12 (s, 1 H), 1.45 (s) superimposed on 1.59 (broad singlet), 19 H; ir (KBr)[12] 1665 (strong), 1695 cm^{-1} (medium).

Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.11; H, 8.83; S, 14.04. Found: C, 63.23; H, 8.90; S, 14.24.

Reaction of Benzaldehyde with *S*-*tert*-Butyl 2-Chlorothiolacetate (1c). Using the same NaH–THF procedure benzaldehyde was allowed to react with **1c**[11] to give an oil after evaporation of the ether extract. The NMR spectrum of this oil indicated the presence of a large number of products. It was subjected to column chromatography on silica gel eluting with petroleum ether. A product crystallized from fraction 5 that was purified by recrystallization from hexane to give one of the diastereoisomers of **14**: 6%; mp 75–76°; NMR (CCl_4) δ 7.53–7.18 (m, 5 H), 4.30 and 4.27 (AB quartet, 2 H, J_{AB} = 10 Hz), 1.50 (s, 9 H), 1.20 (s, 9 H); ir (KBr) 1670 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}OS_2Cl$: C, 59.19; H, 7.31; S, 18.59; Cl, 10.28. Found: C, 59.46; H, 7.54; S, 18.39; Cl, 10.09.

From fraction 8 a product crystallized after standing for several days. It was purified by recrystallization from hexane to give the other diastereoisomer of **14**: 4%; mp 90–91°; NMR (CCl_4) δ 7.70–7.20 (m, 5 H), 4.54 and 4.34 (AB quartet, 2 H, J_{AB} = 6.5 Hz), 1.41 (s, 9 H), 1.24 (s, 9 H); ir (KBr) 1660 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}OS_2Cl$: C, 59.19; H, 7.31; S, 18.59; Cl, 10.28. Found: C, 59.35; H, 7.44; S, 18.45; Cl, 10.50.

The basic water layer that remained after the initial ether extraction was acidified with 10% HCl and extracted with ether. Evaporation of this ether extract gave an oil that partially crystallized on standing. Separation of the residual oil from the solid and recrystallization from benzene–hexane gave *trans*-(*Z*)-2-chlorocinnamic acid: 10%; mp 137–139° (lit.[13] 137°). This material was identical (mixture melting point and ir spectrum) with authentic *trans*-(*Z*)-2-chlorocinnamic acid (mp 138–139°) that was prepared by autoxidation of 2-chlorocinnamaldehyde.[9]

***S*-*tert*-Butyl 2-Methyl-1-oxaspiro[2.5]octane-2-carbothioate (9).** A 57% sodium hydride dispersion in mineral oil (0.558 g, 13 mmol) was washed with hexane (4 × 15 ml) under nitrogen atmosphere and dry DMF (20 ml) was added. The mixture was cooled to 0°. Cyclohexanone (0.98 g, 10 mmol) and **1b** (2.25 g, 10 mmol) in dry DMF (10 ml) was added dropwise over a period of 10–15 min. The reaction mixture was stirred for an additional 30 min at 0° and then at room temperature for 30 min before it was filtered through a sintered glass funnel (coarse). The filtrate was extracted with petroleum ether (2 × 150 ml) and the combined petroleum ether extracts were washed with water (2 × 50 ml), dried (Na_2SO_4), and concentrated (below 40°) to give an oil which was chromatographed on silica gel eluting with petroleum ether followed by benzene–petroleum ether (1:1) to give the product (1.4 g, 6.0 mmol, 60%). An analytical sample of **9** was obtained as a faint yellow oil after short-path distillation (118–120° bath temperature, 0.2 mm): $n^{26}D$ 1.4874; NMR (CCl_4) δ 1.40 (s, 3 H), 1.45 (s, 9 H), 1.60 (broad singlet, 10 H); ir (thin film) 1670 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15. Found: C, 64.28; H, 9.34.

The following glycidic thiol esters were prepared using the same procedure.

***S*-Benzyl 3-Phenyloxiranecarbothioate (7).** A 6:4 mixture of *trans*- and *cis*-**7** was obtained from benzaldehyde, **1d**, and NaH in DMF in 35% yield after column chromatography. Fractional recrystallization from hexane gave pure *trans*-**7**: mp 65–66°; NMR (CCl_4) δ 7.29 (s, 10 H), 4.10 (s, 2 H), 3.97 (d, 1 H, J = 1.5 Hz), 3.52 (d, 1 H, J = 1.5 Hz); ir (KBr) 1660 cm^{-1}. The 1.5-Hz epoxide proton coupling constant is consistent with the trans stereochemical assignment.[14]

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22; S, 11.86. Found: C, 71.36; H, 5.16; S, 12.03.

***S*-*tert*-Butyl 3-Isopropyloxiranecarbothioate (8).** A 6:4 mixture of *cis*- and *trans*-**8** was obtained from isobutyraldehyde, **1a**, and NaH in DMF in 62% yield after column chromatography. The mixture was subjected to short-path distillation (bath temperature 95–98°, 0.6 mm) followed by preparative thin layer chromatography (Merck silica gel GF-254) developing six times with benzene–hexane (3:7). The cis (*Z*) isomer traveling with the lower R_f was obtained essentially pure: NMR (CCl_4) δ 3.35 (d, 1 H, J = 4.5 Hz), 2.65 (doublet of doublets, 1 H, J = 4.5, 8.0 Hz), 1.75 (m, 1 H), 1.45 (s, 9 H), 1.08 (d, 3 H, J = 6.0 Hz), 0.86 (d, 3 H, J = 6.5 Hz); ir (thin film) 1670, 1690 cm^{-1}. The 4.5-Hz epoxide proton coupling constant is consistent with the cis stereochemical assignment.[14]

Anal. Calcd for $C_{10}H_{18}O_2S$: C, 59.37; H, 8.97; S, 15.85. Found: C, 59.62; H, 9.23; S, 15.61.

The trans isomer [δ 3.11 (d, J = 1.5 Hz), 2.83 (doublet of doublets, J = 1.5, 6.0 Hz)] traveling with the higher R_f was obtained with a small amount of cis impurity.

***S*-*tert*-Butyl (*E*)-2-Ethyl-3-phenyloxiranecarbothioate (10).** A 9:1 mixture of *trans*- and *cis*-**10** was obtained from benzaldehyde, **1e**, and NaH in DMF in 59% yield after column chromatography. The product was subjected to short-path distillation (140–145° bath temperature, 0.2 mm) to give **10** as a colorless oil (purification by thin layer chromatography on silica gel using petroleum ether as eluent did not result in any change in the spectral data): $n^{23}D$ 1.5253; NMR (CCl_4) δ 7.23 (s, 5 H), 4.03 (s, 1 H), 1.48 (s) superimposed on 2.30–1.10 (m) (11 H), 1.10–0.70 (m, 3 H); ir (thin film) 1675 cm^{-1}. The chemical shift value of δ 1.48 for the *tert*-butyl group is in agreement with the trans stereochemical assignment.[15]

Anal. Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.63; S, 12.13. Found: C, 68.16; H, 7.64; S, 12.33.

Reaction of 1f with Cyclohexanone. Cyclohexanone was allowed to react with **1f** using the NaH–DMF procedure to give an oil which was purified by column chromatography on silica gel eluting with petroleum ether, followed by benzene–petroleum ether (1:4). Fractions 3–6 contained **12** (34%). This material gave the same NMR and ir spectrum as authentic **12** prepared as described below. Fractions 8–10 contained β-lactone **11** (11%) obtained as a solid (mp 66–68°). This was recrystallized from ben-

zene–hexane to give **11** as colorless plates: mp 69–70°; NMR (CCl_4) δ 1.75 (s) superimposed on a multiplet between δ 1.35 and 2.15; ir (KBr) 1820 cm^{-1} (strong); mass spectrum *m/e* (rel intensity) 146 (27), 144 (78) ($M^+ - CO_2$), 109 (98) [$M - (CO_2 + Cl)$], 92 (50), 90 (100), 81 (88), 79 (83), 68 (90), 67 (85), 55 (73). Molecular ion peaks at *m/e* 188 and 190 were not observed.

Anal. Calcd for $C_9H_{13}O_2Cl$: C, 57.29; H, 6.96; Cl, 18.79. Found: C, 57.48; H, 7.08; Cl, 19.00.

Fractions 12–14 contained glycidic thiol ester **9** (15%). Fraction 11 was a mixture of **9** and **11**.

***S-tert*-Butyl 2-(*tert*-Butylthio)thiolpropionate (12).** a mixture of *tert*-butyl mercaptan (2.0 g, 22 mmol) and **1f** (3.6 g, 20 mmol) in DMF (5 ml) was added to sodium hydride (24 mmol or 1.06 g of a 54% dispersion in mineral oil washed three times with hexane) in DMF (15 ml] at 0°. The reaction was allowed to stir for 30 min at 0° and 30 min at room temperature before water (25 ml) was added. The product was extracted into petroleum ether (3 × 50 ml) and the combined petroleum ether extracts were washed with water (2 × 25 ml), dried (Na_2SO_4), and concentrated. The residue was purified by short-path distillation to give **12** as a colorless oil (3.5 g, 15 mmol, 75%): $n^{28}D$ 1.4884; NMR (CCl_4) δ 1.35 (s) and 1.48 (s) (21 H), 3.42 (q, 1 H, J = 7.5 Hz); ir (thin film) 1670, 1690 cm^{-1} (shoulder).

Anal. Calcd for $C_{11}H_{22}OS_2$: C, 56.36; H, 9.46; S, 27.33. Found: C, 56.26; H, 9.69; S, 27.50.

Lithium bis(trimethylsilyl)amide in THF was prepared according to literature methods.[16] *n*-Butyllithium (32 ml of a 1.59 *M* hexane solution) was added slowly over a 15-min period to hexamethyldisilazane (11 ml, 53 mmol) in anhydrous ether (15 ml) under nitrogen atmosphere. The mixture was refluxed for 30 min, the ether was evaporated, and anhydrous THF (50 ml) was added to the residue, all of which dissolved to give a 0.80 *M* solution of $LiN(SiMe_3)_2$. The molarity of this solution was determined by the titration of a 10-ml aliquot with *tert*-butyl alcohol using 4-phenylazodiphenylamine as indicator.[2k]

S-Benzyl 1-Oxaspiro[2.5]octane-2-carbothioate (6). Cyclohexanone (0.98 g, 10 mmol) and **1d** (2.45 g, 10 mmol) were mixed with dry THF (5–10 ml) at 0° under nitrogen atmosphere. To this solution was added $LiN(SiMe_3)_2$ in dry THF (12.5 ml of a 0.80 *M* solution, 10 mmol) over a period of 15 min. The reaction mixture was stirred at 0° for 30 min and at room temperature for an additional 30 min before it was poured into ice water (200 ml) and ether (150 ml). The ether layer was separated and the water layer was extracted again with ether (100 ml). The combined ether layers were dried (Na_2SO_4) and concentrated to give an oil which was purified by column chromatography on silica gel (60 g) eluting with petroleum ether followed by benzene–petroleum ether (1:1) to obtain the product, **6** (1.84 g, 7.0 mmol, 70%) as an oil that crystallized on standing overnight under reduced pressure. Recrystallization (hexane) gave pale yellow needles: mp 32–33°; NMR (CCl_4) δ 7.13 (s, 5 H), 3.98 (s, 2 H), 3.20 (s, 1 H), 1.50 (broad singlet, 10 H); ir (KBr) 1675 (strong), 1695 cm^{-1} (medium).

Anal. Calcd for $C_{15}H_{18}O_2S$: C, 68.67; H, 6.91; S, 12.22. Found: C, 68.76; H, 6.88; S, 12.07.

***S-tert*-Butyl 3,3-Dimethyloxiranecarbothioate (5).** In a similar way **5** was prepared from acetone (2 equiv), **1a** (1 equiv), and $LiN(SiMe_3)_2$ (1 equiv) in THF in 60% yield after column chromatography. The addition of the reactants in the manner described by Borch[2k] involving initial addition of $LiN(SiMe_3)_2$ (1 equiv) to (**1a**) (1 equiv) at −78° followed by the addition of acetone (2 equiv) gave only a 40% yield. This same addition procedure carried out at 0° also gave a 40% yield. However, the addition of base (1 equiv) to **1a** (1 equiv) and acetone (2 equiv) in THF at −78°, stirring for 30 min at −78°, followed by warming to room temperature and stirring for an additional 30 min gave a higher yield (72%) of **5**. The product was obtained as a faint yellow oil after short-path distillation (85–90° bath temperature, 0.6 mm): $n^{25}D$ 1.4702; NMR (CCl_4) δ 3.10 (s, 1 H), 1.40 (s, 9 H), 1.30 (s, 6 H); ir (thin film) 1670 (strong), 1695 cm^{-1} (medium).

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03. Found: C, 57.57; H, 8.79; S, 16.89.

Schotten–Baumann Preparation of 6. Using essentially the same procedure reported[3c] for the preparation of *S*-phenyl 3-methyl-3-phenylthioglycidate, sodium 1-oxaspiro[2.5]octane-2-carboxylate[17] was converted to **6** in 22% yield using oxalyl chloride, pyridine, and benzyl mercaptan. Recrystallization (hexane) gave pure **6** as pale yellow needles (mp 31–32°). This material was identical with **6** prepared from cyclohexanone and **1d** using the $LiN(SiMe_3)_2$–THF Darzens procedure described earlier. The mixture melting point for these two products was not depressed.

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Registry No.—**1a**, 32797-86-7; **1b**, 53635-53-3; **1c**, 56377-45-8; **1d**, 56377-46-9; **1e**, 56403-12-4; **1f**, 56377-47-0; *trans*-**3**, 56403-10-2; *cis*-**3**, 56377-35-6; **4**, 56377-48-1; **5**, 56377-49-2; **6**, 56377-50-5; *trans*-**7**, 56377-37-8; *cis*-**7**, 56377-38-9; *trans*-**8**, 56377-39-0; *cis*-**8**, 56377-40-3; **9**, 56377-54-9; *trans*-**10**, 56377-41-4; *cis*-**10**, 56377-42-5; **11**, 56377-55-0; **12**, 56377-56-1; **14** isomer 1, 56377-43-6; **14** isomer 2, 56377-44-7; *tert*-butyl mercaptan, 75-66-1; 2-bromoacetyl bromide, 598-21-0; benzyl mercaptan, 100-53-8; *S*-phenyl 2-bromothiolacetate, 56377-57-2; benzenethiol, 108-98-5; *S*-benzyl 2-chlorothiolacetate, 56377-58-3; 2-chloroacetyl chloride, 79-04-9; 2-bromopropionyl bromide, 563-76-8; 2-bromobutyryl bromide, 26074-52-2; 2-chloropropionyl chloride, 7623-09-8; *p*-nitrobenzaldehyde, 555-16-8; anisaldehyde, 123-11-5; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; isobutyraldehyde, 78-84-2; $LiN(SiMe_3)_2$, 4039-32-1; acetone, 67-64-1.

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Oxidations By Thionyl Chloride. Mechanism of 3-Thietanone Formation. I[1]

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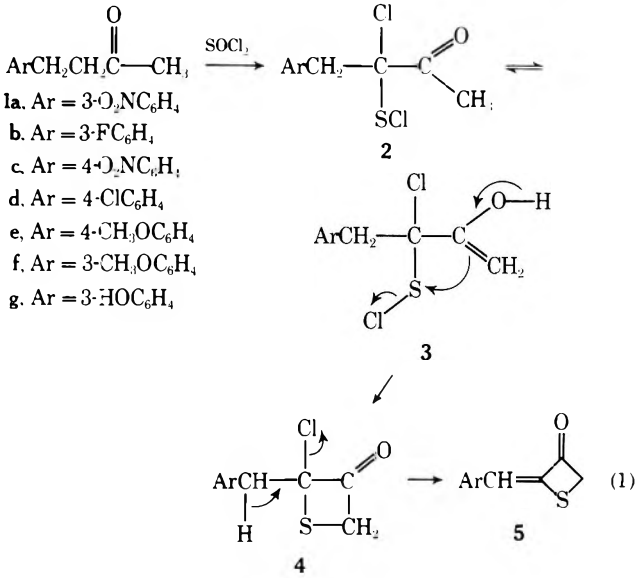
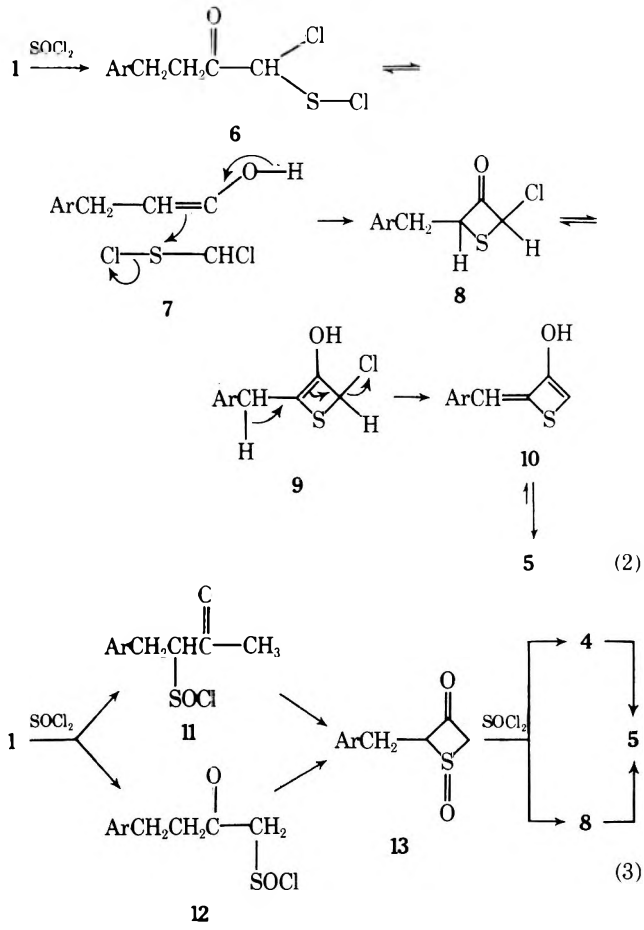
To distinguish between a mechanism in which thionyl chloride oxidizes a methylene group from one in which thionyl chlorides oxidizes a methyl group while converting monosubstituted acetones into 3-thietanones, a series of 4-aryl-2-butanones was subjected to oxidation conditions (thionyl chloride, 25–85°, 5 min–3 hr). Butanones with the following ring substitution gave only 3-thietanones as products: 3-NO_2, 3-F, 4-NO_2, 4-Cl, 4-CH_3O. However, 4-(3-hydroxyphenyl)-2-butanone gave only 2-acetyl-5-hydroxybenzo[*b*]thiophene, and 4-(3-methoxyphenyl)-2-butanone gave both 2-(3-methoxybenzylidene)-3-thietanone and 2-acetyl-5-methoxybenzo[*b*]thiophene as products. The results are consistent only with thionyl chloride oxidation proceeding exclusively at the methylene position.

A few years ago we reported the oxidative conversion of β-aryl carboxylic acids and certain ketones to benzo[*b*]thiophenes[2] and of methyl ketones to 3-thietanones.[3] The unusual nature of these products and the generality of the reactions prompted us to examine the mechanism by which these products were being formed. The results of our investigation of the benzothiophene case have been reported.[2] The key to the mechanism was the intermediacy of sulfenyl chlorides by oxidation of a methylene group adjacent to the carbonyl function.

On the reasonable assumption that the 3-thietanones were being formed through the intermediacy of a structurally similar sulfenyl chloride, we proposed[3] a mechanism for 3-thietanone formation (eq 1). However, this mechanism did not seem to account for the lack of benzothiophene formation in those cases where Ar (in eq 1) is an aromatic ring. If for some reason oxidation of the methyl ketone occurred at the methyl rather than the methylene group, an alternative mechanism (eq 2) for 3-thietanone formation could be proposed that would satisfactorily explain the absence of benzothiophene formation. Disregarding, as far as this paper is concerned,[4] the implications of a third possible mechanism (eq 3) for 3-thietanone formation that seemed to combine the features of both previous mechanisms, we determined to distinguish, if at all possible, between the first two mechanisms. We herewith report our initial findings.





Results and Discussion

The techniques that we had employed quite successfully in the elucidation of the mechanism of benzothiophene formation (e.g., detection, isolation, and/or synthesis of intermediate species) were not easily available to us here, since the reaction usually proceeded readily at room temperature but not at temperatures much below that (e.g. 0°). Furthermore, the major feature of the reaction of thionyl chloride with methyl ketones was the appearance of a nicely intractable black tar from which only the 3-thietanone could be obtained.

To simplify our considerations, we assumed that either **4** or **8**, but not both, was an intermediate leading to **5**. If so, then in the first two mechanisms either **2** or **6** would be formed. If **6** were the intermediate, it was not obvious how

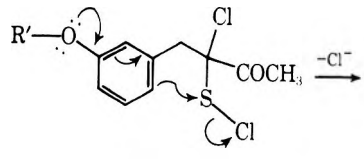
a benzothiophene could arise under any conditions. However, if 2 were the intermediate, then it should be possible to find conditions under which at least some benzothiophene could be detected, i.e., a crossover point between intramolecular cyclization to thietanone vs. benzothiophene should exist at which both products should be observed. This procedure thus would allow us to distinguish between the two mechanisms by a technique, product analysis, that *was* available to us in this case.

We previously had determined[2] that benzothiophenes form readily in a thionyl chloride reaction when (a) there is an electron-withdrawing substituent at the benzylic carbon atom (β to the carbonyl group) or (b) there is a strongly electron-donating ring substituent that can interact through resonance with the sulfur atom of the sulfenyl chloride group in a nucleophilic displacement reaction. We therefore examined the reaction mixtures of thionyl chloride with a number of variously substituted 4-phenyl-2-butanones, anticipating the appearance of benzothiophenes under condition b if 2 were the intermediate. The gross results are reported in Table I.

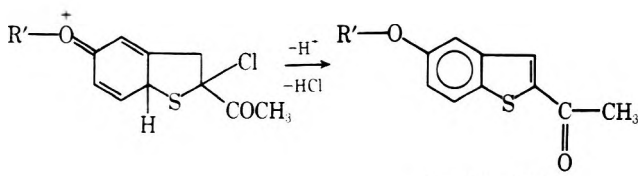
Table I
Products from Reaction of 4-Aryl-2-butanones with Thionyl Chloride

$XC_6H_4CH_2CH_2C(=O)CH_3$, when X is	Conditions	Yield, % Thietanone	Yield, % Benzothiophene
3-NO_2	70°, 45 min	43	
3-F	70°, 40 min	39	
4-NO_2	66°, 35 min	25	
4-Cl	85°, 3 hr	24	
4-CH_3O	85°, 2 hr	11	
3-CH_3O	51°, 12 min	2	13
3-OH	25°, 5 min		17

The data are consistent with the concerted elimination–cyclization (CEC) mechanism proposed earlier,[2e] in that benzothiophene formation occurred under conditions b stipulated above. Such participation should be strong in the case of the 3-hydroxy derivative, **2g**, and indeed no 3-thietanone is observed here. Under these conditions, then, cyclization onto the aromatic ring to form a benzothiophene competes quite favorably with cyclization onto enol **3** to form a thietanone.



2f. R′ = CH_3
g. R′ = H



14a. R′ = CH_3
b. R′ = H

Finally, the absence of thietanone formation in the case of the 3-hydroxy derivative suggests the exclusive operation of the first (eq 1) rather than the second (eq 2) mechanism. Even if the second mechanism operated simultaneously with the first, thietanone formation should be observed in every case. The absence of a 3-thietanone (which, under our work-up conditions, would have been detected even if present in less than 1% yield) in this case eliminates **6** as an intermediate. It would appear that benzothiophene formation competes most effectively with thietanone formation when the benzene ring contains strongly electron-donating substituents.

Experimental Section

Thionyl chloride (purified grade) was distilled from either triphenyl phosphite through a 30-cm Vigreux column or dipentene and then linseed oil;[5] the fraction with boiling range 75–76° was retained. Infrared spectra were obtained on Perkin-Elmer Model 457 or 257 spectrophotometers; solid samples were taken as potassium bromide pellets and liquid samples were taken as a neat film unless otherwise specified. Mass spectra were processed by Mr. Dick Weissenberger with an AEI MS-9 mass spectrometer,[6] unless otherwise noted, at 70 eV. The nuclear magnetic resonance spectra were taken on a Varian Model A-60 spectrometer, using tetramethylsilane as the internal reference and $CDCl_3$ as solvent unless otherwise specified. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Low-boiling petroleum ether (30–60°) was used unless otherwise stated. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

2-(3-Nitrobenzylidene)-3-thietanone (5a). To a mixture of 1.93 g (0.01 mol) of 4-(3-nitrophenyl)-2-butanone[7] (**1a**) and 0.33 ml of pyridine under dry nitrogen and in an oil bath at 70° was added over a 30-sec period 4.17 g (0.035 mol) of thionyl chloride. The mixture darkened and gas evolved after 0.5 min. At the end of 45 min excess thionyl chloride was removed in vacuo, the residue was mixed with 1:4 chloroform–benzene, and solvent was evaporated. This residue was dissolved in chloroform and mixed with 10 g of silica gel (activity III). Solvent was evaporated and the residue was placed on a silica gel column (125 g, activity III). Subsequent elution with 3 l. of 1:1 benzene–petroleum ether afforded a yellow solid which upon crystallization from carbon tetrachloride yielded 0.95 g (43%) of **5a** as yellow grains: mp 138–139.5°; ir 1528 and 1360 cm^{-1}; NMR δ 8.16–8.03 (2 H, m), 7.58–7.45 (2 H, m), 7.18 (1 H, s), and 4.43 (2 H, s); mol wt (mass spectrum) for $^{12}C_{10}{}^{1}H_7{}^{14}N^{16}O_3{}^{32}S$ 221.01479 (calcd 221.01466).

Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19: N, 6.33; S, 14.49. Found: C, 54.20; H, 3.23; N, 5.97; S, 14.30.

2-(3-Fluorobenzylidene)-3-thietanone (5b). To a mixture of 1.66 g (0.01 mol) of 4-(3-fluorophenyl)-2-butanone[8] (**1b**) and 0.33 ml of pyridine under dry nitrogen was added at room temperature over a 1-min period 4.17 g (0.035 mol) of thionyl chloride. No detectable reaction occurred after 7 min. The mixture was placed in an oil bath at 70°, and after 2 min gas evolved steadily. After 40 min excess thionyl chloride was removed in vacuo, the residue was dissolved in 1:4 chloroform–benzene, and solvent was evaporated. The latter residue was dissolved in chloroform, 10 g of silica gel (activity III) was added, and solvent was evaporated. The latter residue was placed on a silica gel column (100 g, activity III). Subsequent elution with 10 l. of 1:9 benzene–petroleum ether afforded a yellow solid, which, upon sublimation (54°, 0.02 mm) and recrystallization from methanol, yielded 0.77 g (39.4%) of **5b** as light yellow needles: mp 96–97°; ir 1745 cm^{-1}; NMR δ 7.16 (4 H, cm), 7.03 (1 H, s), and 4.48 (2 H, s); mol wt (mass spectrum) for $^{12}C_{10}{}^{1}H_7{}^{19}F^{16}O^{32}S$ 194.02063 (calcd 194.02016).

Anal. Calcd for $C_{10}H_7FOS$: C, 61.84; H, 3.63; F, 9.78; S, 16.51. Found: C, 61.74; H, 3.54; F, 10.17; S, 16.80.

2-(4-Nitrobenzylidene)-3-thietanone (5c). Over a 30-sec period 4.17 g (0.035 mol) of thionyl chloride was added to a mixture of 1.93 g (0.01 mol) of 4-(4-nitrophenyl)-2-butanone[9] (**1c**) and 0.33 ml of pyridine surrounded by an oil bath at 66°. The mixture darkened and gas evolved after 3 min. At the end of 35 min excess thionyl chloride was removed in vacuo, the residue was dissolved in 1:4 chloroform–benzene, and solvent was evaporated. The latter residue was dissolved in chloroform and 10 g of silica gel (activity III) was added. Solvent was evaporated and the residue was placed on a silica gel column (100 g, activity III). Elution with 6 l. of 1:2.3 benzene–petroleum ether and 6 l. of 1:1 benzene–petroleum ether, followed by preparative TLC, furnished a yellow solid which, upon recrystallization from methanol, furnished 0.553 g (25%) of **5c** as yellow needles: mp 187–188.5°; ir 1753, 1512, and 1338 cm^{-1}; NMR (Me_2SO-d_6) δ 8.34 (2 H, A of AB quartet, J = 8.8 Hz), 7.73 (2 H, B

of AB quartet, J = 8.8 Hz), 7.50 (1 H, s), and 4.81 (2 H, s); mass spectrum m/e 221 (M^+), 191 (−NO), and 175 ($-NO_2$); mol wt (mass spectrum) for $^{12}C_{10}{}^{1}H_7{}^{14}N^{16}O_3{}^{32}S$ 221.01496 (calcd 221.01466).

Anal. Calcd for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33; S, 14.49. Found: C, 54.39; H, 3.30; N, 6.10; S, 14.31.

Further elution of the column and preparative silica gel TLC produced a dark yellow oil subsequently identified as starting material (48% recovery).

Ethyl 3-(4-Aminophenyl)propanoate. A mixture of 20.81 g (0.094 mol) of ethyl 4-nitrocinnamate dissolved in 150 ml of warm ethyl acetate and 0.5 g of 10% palladium on charcoal was cooled in an ice bath and stirred vigorously magnetically as a total of 8.42 l. of hydrogen (low-pressure hydrogenation apparatus) was absorbed. Catalyst was removed by suction filtration through Celite, and the filtrate was dried ($CaSO_4$) and filtered. Removal of solvent afforded a crude product that was vacuum distilled to yield 17.51 g (96.5%) of ethyl 3-(4-aminophenyl)propanoate as a very pale yellow liquid: bp 127° (0.03 mm) [lit.[10] bp 121–123° (0.02 mm)]; ir 3450, 3375, and 1725 cm^{-1}.

3-(4-Aminophenyl)propanoic Acid Hydrochloride. A mixture of 17.51 g (0.091 mol) of ethyl 3-(4-aminophenyl)propanoate and 4 g (0.1 mol) of sodium hydroxide was dissolved in 50 ml of water, stirred vigorously for 1 hr, and made acidic with concentrated hydrochloric acid. Water was evaporated and the residue was treated with 150 ml of hot absolute ethanol. Insoluble sodium chloride was removed by filtration and solvent by evaporation to yield 16.57 g (91%) of 3-(4-aminophenyl)propanoic acid hydrochloride as grayish-white needles, mp 193–195° dec.

3-(4-Chlorophenyl)propanoic Acid. To a cooled (0°) solution of 16.57 g (0.083 mol) of 3-(4-aminophenyl)propanoic acid hydrochloride in 60 ml of water and 14.1 ml (0.17 mol) of concentrated hydrochloric acid was added a solution of 5.87 g (0.085 mol) of sodium nitrite dissolved in 16 ml of water; the temperature of the mixture was kept between 0 and 5° during the addition and 10 min after addition was complete. The mixture was then added rapidly to a stirred, cold solution of 9.01 g (0.091 mol) of cuprous chloride[11] dissolved in 45 ml of concentrated hydrochloric acid. The immediate formation of a yellow precipitate was accompanied by gas evolution. The mixture was stirred at room temperature for 5 hr and then was extracted with ether (3 × 100 ml). The combined ether layers were extracted with saturated sodium bicarbonate solution until gas evolution ceased, and this aqueous layer was made acidic with concentrated hydrochloric acid and extracted with ether (3 × 100 ml). The latter organic layer was dried ($CaSO_4$) and filtered. Removal of solvent furnished a yellow solid which, upon recrystallization from cyclohexane, yielded 6.84 g (44.8%) of the acid as dark yellow needles, mp 118–120° (lit.[12] mp 126°).

4-(4-Chlorophenyl)-2-butanone (1d). To a magnetically stirred solution of 6.84 g (0.037 mol) of 3-(4-chlorophenyl)propanoic acid dissolved in 125 ml of dry ether was added dropwise at a rate that maintained steady reflux an ethereal solution containing 1.76 g (46 ml, 0.08 mol) of methyllithium (Foote Mineral Co.). The mixture became milky yellow initially but cleared at the end of the addition. The mixture was then stirred for another 10 min. A saturated ammonium chloride solution was added dropwise with vigorous stirring until two clear layers separated. The organic layer was washed twice with water, dried ($CaSO_4$), and filtered. Removal of solvent and distillation afforded 6.30 g (93.3%) of **1d** as a colorless liquid: bp 71–74° (0.02 mm) [lit.[8] bp 107° (0.5 mm)]; ir 1715 cm^{-1} (lit.[8] ir 1715 cm^{-1}); mass spectrum m/e 182 (M^+).

2-(4-Chlorobenzylidene)-3-thietanone (5d). To a magnetically stirred mixture of 1.83 g (0.01 mol) of **1d** and 0.33 ml of pyridine in an oil bath at 85° was added over a 30-sec period 3.57 g (0.03 mol) of thionyl chloride. The mixture darkened and gas evolved. After 3 hr in the oil bath, the reaction mixture was steam distilled (215°) for 8 hr. The condensate was extracted with ether, and the combined extracts were dried ($CaSO_4$) and filtered. Solvent was removed and the residue was placed on a silica gel column (60 g, activity I). Subsequent elution with 4 l. of 1:3 benzene–petroleum ether furnished a yellow solid which, upon sublimation (73°, 0.18 mm) and recrystallization from petroleum ether, afforded 0.500 g (23.7%) of **5d** as yellow needles: mp 87–88°; ir 1743 cm^{-1}; NMR δ 7.31 (4 H, s), 7.17 (1 H, s), and 4.45 (2 H, s); mass spectrum m/e 210 (M^+).

Anal. Calcd for $C_{10}H_7ClOS$: C, 57.01; H, 3.35; Cl, 16.83; S, 15.22. Found: C, 57.01; H, 3.20; Cl, 17.01; S, 15.04.

Elution of the column also produced two oils. These were subsequently identified as mineral oil and starting material (4% recovery).

In a subsequent run, sublimation of the thietanone **5d** left 24.4 mg of a fluffy white powder: mp 153.5–154.6°; ir 2919 (w), 1777 (s), 1747 (m), 1489 (m), 1390 cm^{-1} (w); NMR δ 7.26 (2 H, A of AB, J = 8.6 Hz), 6.85 (2 H, B of AB, J = 8.6 Hz), 4.67 (1 H, s), 4.31 (1 H, A′ of A′B′, J = 15.5 Hz), 4.07 (1 H, B′ of A′B′, J = 15.5 Hz); mass spectrum[13] m/e (rel intensity) 250 and 248 (9 and 13, presumed to be an impurity), 212 (P + 2, 37), 210 (M^+, base), 175 (−Cl, 13), 166/164 ($-CH_2S$, 18/41), 149 (10), 147 (19), 138/136 ($-CH_2S$, −CO, 15/33).

4-(4-Methoxyphenyl)-2-butanone (1e). To a magnetically stirred solution of 18.59 g (0.103 mol) of 3-(4-methoxyphenyl)propanoic acid (Aldrich Chemical Co., recrystallized from cyclohexane) in 1 l. of dry ether was added at a rate to ensure steady reflux 110 ml (4.62 g, 0.21 mol) of ethereal methyllithium (Foote Mineral Co.). After the addition was complete, the mixture was stirred for 5 min and then to it was added with vigorous stirring and until there was a separation of layers a saturated solution of ammonium chloride. The ether layer was washed with saturated sodium bicarbonate solution (once) and water (twice), dried ($CaSO_4$), and filtered. Solvent was removed and the residue was distilled to furnish 16.70 g (91%) of **1e** as a colorless liquid: bp 72° (0.075 mm) [lit.[14] bp 72° (0.02 mm)]: ir 1713 cm^{-1} (lit.[14] ir 1710 cm^{-1}); mass spectrum m/e 178 (M^+).

2-(4-Methoxybenzylidene)-3-thietanone (5e). A mixture of 1.78 g (0.01 mol) of **1e** and 0.33 ml of pyridine under dry nitrogen and surrounded by an oil bath at 85° was treated with 4.17 g (0.035 mol) of thionyl chloride over a 30-sec period. Darkening and gas evolution occurred after 2 min. At the end of 2 hr excess thionyl chloride was removed in vacuo, the residue was dissolved in 1:4 chloroform–benzene and solvent was evaporated. The latter residue was mixed with 10 g of silica gel (activity III) with the aid of chloroform, and this mixture was deposited on a silica gel column (125 g, activity III). Elution with 1:4 benzene–petroleum ether furnished a few milligrams of a yellow oil in the first 5 l. of eluent that was identified as a mixture of the starting ketone and the thietanone **5e**; and in the next 12 l. a yellow solid appeared that was sublimed (80°, 0.02 mm) and recrystallized from cyclohexane to afford 0.212 g (10.6%) of **5e** as clear yellow needles: mp 138–139°; ir 1744 cm^{-1}; NMR δ 7.40 (2 H, A of AB, J = 8.8 Hz), 7.29 (1 H, s), 6.99 (2 H, B of AB, J = 8.8 Hz), 5.54 (2 H, s), and 3.88 (3 H, s); mass spectrum m/e 206 (M^+).

Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 64.11; H, 4.60; S, 15.68.

3-(3-Methoxyphenyl)propanoic Acid. A mixture of 24.27 g (0.136 mol) of 3-methoxycinnamic acid (Aldrich Chemical Co.), 1.1 g of 10% palladium on charcoal, and 210 ml of 95% ethanol was hydrogenated (Paar apparatus) for 18 min, at which time 0.136 mol of hydrogen had been absorbed and further uptake ceased. Catalyst was removed by filtration through Celite and solvent by evaporation to yield 24.48 g (100%) of 3-(3-methoxyphenyl)propanoic acid as a white solid, mp 44–45° (lit.[12] mp 52°).

4-(3-Methoxyphenyl)-2-butanone (1f). To a mixture of 24.48 g (0.136 mol) of 3-(3-methoxyphenyl)propanoic acid and 1 l. of dry ether was added at a rate to maintain steady reflux 150 ml (6.16 g, 0.280 mol) of ethereal methyllithium (Foote Mineral Co.). After an additional 5 min of stirring after completion of the addition, a saturated ammonium chloride solution was added with vigorous stirring until two layers appeared. The ether layer was washed with saturated sodium bicarbonate solution (once) and with water (twice), dried ($CaSO_4$), and filtered. Removal of solvent, followed by distillation, furnished 16.28 g (67.2%) of **1f** as a colorless liquid: bp 152–153° (9 mm) [lit.[14] bp 82° (0.15 mm)]; ir 1713 cm^{-1} (lit.[14] ir 1705 cm^{-1}); mass spectrum m/e 178 (M^+).

Reaction of Thionyl Chloride with 4-(3-Methoxyphenyl)-2-butanone. 2-(3-Methoxybenzylidene)-3-thietanone (5f) and 2-Acetyl-5-methoxybenzo[*b*]thiophene (14a). A mixture of 1.78 g (0.01 mol) of **1f** and 0.33 ml of pyridine under dry nitrogen and surrounded by an oil bath at 51° was treated in 15 sec with 4.17 g (0.035 mol) of thionyl chloride. The mixture darkened and gas evolved after 1 min. After an additional 11 min excess thionyl chloride was removed in vacuo, and 1:4 chloroform–benzene was added and evaporated to remove residual reagent. The residue was mixed with 10 g of silica gel (activity III) with the aid of chloroform, and the resulting dry mixture was deposited on a silica gel column (100 g, activity III). Elution with 4 l. of 1:9 benzene–petroleum ether afforded a light yellow oil that solidified upon standing. Sublimation (60°, 0.30 mm) yielded 30 mg (1.5%) of **5f** as a yellow solid: mp 75–78.5°; ir 1760 cm^{-1}; NMR δ 7.48–7.15 (2 H, cm), 7.09–6.76 (3 H, cm), 4.40 (2 H, s), and 3.79 (3 H, s); mol wt (mass spectrum) for $^{12}C_{11}{}^{1}H_{10}{}^{16}O_2{}^{32}S$ 206.04044 (calcd 206.04015).

Elution with 7 l. of 1:4 benzene petroleum ether furnished a small amount of an oil which, by NMR and ir comparison, appears to be a mixture of the benzothiophene **14a** (see below), starting ketone, and an unidentified material.

Elution with 9 l. of 2:3 benzene–petroleum ether gave a yellow solid that was dissolved in acetone and treated with activated charcoal, sublimed (55°, 0.03 mm), and recrystallized from petroleum ether (bp 60–110°) to yield 0.268 g (13%) of **14a** as yellow needles: mp 95–97°; ir 1660 cm^{-1}; NMR[15,17] (acetone-d_6) δ 8.05 (1 H, br d, H_3, $J_{3,7}$ = 0.7 Hz), 7.84 (1 H, tripled A of AB, H_7, $J_{6,7}$ = 8.9, $J_{3,7}$ = 0.7, $J_{4,7}$ = 0.7 Hz), 7.46 (1 H, br d, H_4, $J_{4,6}$ = 2.5 Hz), 7.18 (1 H, doubled B of AB, H_6, $J_{6,7}$ = 8.9, $J_{4,6}$ = 2.5 Hz), 3.87 (3 H, s), and 2.60 (3 H, s); mass spectrum *m/e* 206 (M^+), 191 ($-CH_3$), and 163 ($-COCH_3$).

Anal. Calcd for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.54. Found: C, 64.00; H, 4.80; S, 15.59.

4-(3-Hydroxyphenyl)-2-butanone (1g). A mixture of 18.89 g (0.098 mol) of **1a**,[7] 17.7 ml (0.19 mol) of concentrated hydrochloric acid, and 150 ml of 95% ethanol was hydrogenated at 15° in a low-pressure apparatus; 6.6 l. of hydrogen was absorbed. Catalyst was removed by suction filtration through Celite and solvent by evaporation to afford a thick red oil. The latter was dissolved in 250 ml of water and to this cold aqueous phase was added 18.50 ml (0.20 mol) of concentrated hydrochloric acid. The solution was cooled to 0° and to it was added over a 12-min period and at 0–3° a solution of 7.10 g (0.103 mol) of sodium nitrite in 60 ml of water. After an additional 15 min in the ice bath the reaction mixture was added dropwise over a 20-min period to 250 ml of boiling water. The latter mixture was cooled in ice and extracted with ether (4 × 200 ml). The ether phase was reduced to a volume of 100 ml, treated with activated charcoal, dried ($CaSO_4$), and filtered. Solvent was removed and the brown solid was distilled to afford 12.49 g of light yellow liquid, bp 132° (0.16 mm), that solidified upon standing. Recrystallization from benzene yielded 12.03 g (75%) of **1g** as a white solid: mp 85–86° (lit.[18] mp 87–88°); mass spectrum *m/e* 164 (M^+), 121 ($-COCH_3$).

2-Acetyl-5-hydroxybenzo[*b*]thiophene (14b). A magnetically stirred mixture of 1.64 g (0.01 mol) of **1g** and 0.3 ml of pyridine under dry nitrogen was treated over a 15-sec period with 4.17 g (0.035 mol) of thionyl chloride. Immediately the mixture turned yellow and gas evolved. At the end of 5 min excess thionyl chloride was removed in vacuo and the resulting black residue was treated with refluxing acetone. This mixture was filtered and to the filtrate was added 10 g of silica gel (activity III). Solvent was evaporated and the residue was placed on a silica gel column (90 g, activity III). Elution with 1:5 ethyl acetate–petroleum ether furnished 11 500-ml fractions, the third and fourth fractions of which were recrystallized twice from chloroform to afford 325 mg (16.9%) of **14b** as a yellow solid: mp 190–191° (analytical sample, mp 191–192°); ir 3338 and 1644 cm^{-1}; NMR[17,19] (acetone-d_6) δ 7.97 (1 H, d, $J_{3,7}$ = 0.7 Hz), 7.75 (1 H, tripled A of AB, $J_{6,7}$ = 8.7, $J_{3,7}$ = 0.7 Hz), 7.37 (1 H, dm, $J_{4,6}$ = 2.4, $J_{3,4}$ = 0.4 Hz), 7.15 (1 H, doubled B of AB, $J_{6,7}$ = 8.7, $J_{4,6}$ = 2.4 Hz), 3.86 (1 H, s), and 2.61 (3 H, s); mass spectrum *m/e* 192 (M^+), 177 ($-CH_3$), and 149 ($-COCH_3$); mol wt (mass spectrum) for $^{12}C_{10}{}^{1}H_8{}^{16}O_2{}^{32}S$ 192.02470 (calcd 192.02450).

Anal. Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19; S, 16.68. Found: C, 62.36; H, 4.30; S, 16.69.

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Registry No.—**1a**, 3506-81-8; **1b**, 3506-77-2; **1c**, 30780-19-9; **1d**, 3506-75-0; **1e**, 104-20-1; **1f**, 29114-51-0; **1g**, 56363-73-6; **5a**, 56363-74-7; **5b**, 56363-75-8; **5c**, 56363-76-9; **5d**, 56363-77-0; **5e**, 56363-78-1; **5f**, 56363-79-2; **14a**, 56363-80-5; **14b**, 56363-81-6; thionyl chloride, 7719-09-7; 3-(4-aminophenyl)propanoic acid hydrochloride, 56363-82-7; ethyl 3-(4-aminophenyl)propanoate, 7116-44-1; 3-(4-chlorophenyl)propanoic acid, 2019-34-3; methyllithium, 917-54-4; 3-(4-methoxyphenyl)propanoic acid, 1929-29-9; 3-(3-methoxyphenyl)propanoic acid, 10516-71-9.

References and Notes

(1) Taken in part from the M.S. Thesis of W.E.S., The Ohio State University, 1971.
(2) (a) A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 5149 (1968); (b) *ibid.*, 4823 (1972); (c) *ibid.*, 125 (1973); (d) *ibid.*, 4515 (1973); (e) *J. Org. Chem.*, in press.
(3) A. J. Krubsack, T. Higa, and W. E. Slack, *J. Am. Chem. Soc.*, **92**, 5258 (1970).
(4) An examination of mechanism 3 currently is in progress and will be reported at a future date.
(5) M. Davis, H. Szkuta, and A. J. Krubsack, *Mech. React. Sulfur Compd.*, **5**, 1 (1970).
(6) We thank the National Science Foundation for a grant (GP-5202) to the chemistry department of The Ohio State University for the mass spectrometer.
(7) Prepared according to the procedure of Boatman, Harris, and Hauser,[8] except that the product was vacuum distilled to yield the ketone (80%) as a light yellow liquid, bp 136° (0.02 mm), that solidified upon standing.
(8) S. Boatman, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 3321 (1965).
(9) Prepared as reported,[8] except that the product was distilled from the black oil to gave the ketone (21.3%) as a light yellow oil, bp 141° (0.10 mm), that crystallized upon standing.
(10) R. Denss, F. Ostermayer, and N. Clauson-Kaas, German Offen. 1,921,651 (1969); *Chem. Abstr.*, **72**, 66802f (1970).
(11) L. F. Fieser, "Organic Experiments", D. C. Heath, Boston, Mass., 1964, p 237.
(12) J. F. Dippy and J. E. Page, *J. Chem. Soc.*, 357 (1938).
(13) We are indebted to Mr. Louis Cazenavette II and to the Chemistry Department of the University of New Orleans for obtaining this spectrum on their Hitachi RMU-6E mass spectrometer.
(14) R. L. Johnston and L. A. Jones, *J. Chem. Eng. Data*, **16**, 112 (1971).
(15) In $CDCl_3$ the NMR positions were δ 7.84 (H_3), 7.73 (H_7), 7.29 (H_4), 7.14 (H_6), 3.85 (OCH_3), and 2.58 ($COCH_3$), with $J_{3,7}$ = 0.85, $J_{4,6}$ = 2.4, and $J_{6,7}$ = 8.8 Hz. Attempts to obtain $J_{4,7}$ through spin decoupling measurements were unsuccessful, the system being too tightly coupled.[16]
(16) We are indebted to Dr. C. E. Cottrell of The Ohio State University nuclear magnetic resonance laboratory for attempting the spin-decoupling experiments at 90 and 100 MHz.
(17) For NMR spectra of substituted benzo[*b*]thiophenes, see (a) K. Takahashi, T. Kanda, and Y. Matsuki, *Bull. Chem. Soc. Jpn.*, **37**, 768 (1964); (b) K. Takahashi, T, Kanda, F. Shoji, and Y. Matsuki, *ibid.*, **38**, 508 (1965); (c) B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Aust. J. Chem.*, **21**, 1853 (1968); (d) N. B. Chapman, D. F. Ewing, R. M. Scrowston, and R. Westwood, *J. Chem. Soc. C*, 764 (1968).
(18) M. Winter, *Helv. Chim. Acta*, **44**, 2110 (1961).
(19) In Me_2SO-d_6 the NMR positions were δ 9.64 (OH), 8.10 (H_3), 7.78 (H_7), 7.38 (H_4), 7.10 (H_6), and 2.61 (CH_3CO), with $J_{6,7}$ = 8.7, $J_{4,6}$ = 2.3, and $J_{3,7}$ = 0.8 Hz. In neither of these cases could $J_{4,7}$ be resolved.

Homolytic Substitution Reactions in Heterocyclic Series. XII.[1] Heteroarylation of Thiophene

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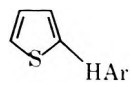
Heteroaryl radicals formed by aprotic diazotization of the corresponding heterocyclic amines in the presence of amyl (or isoamyl) nitrite substitute homolytically on thiophene with the formation of 2-heteroarylthiophenes as main reaction products in overall yields from 20 to 50%. The results of competitive experiments indicate that the reactivity of thiophene in this reaction at 70–80° is slightly higher than that of benzene regardless of the nature of the respective heteroaryl radical. The behavior of thiophene in these reactions is somewhat unusual because its reactivity toward heteroaromatic radicals (which are slightly electrophilic) is lower than the reactivity observed with nucleophilic radicals such as cyclohexyl and benzyl and, to a lesser extent, phenyl radicals. Analytical data (GLC, TLC, and mass spectra) for about 20 heteroarylthiophenes are described. Most of the obtained heteroarylthiophenes are new compounds.

Homolytic substitution reactions of thiophene (arylation,[2] thienylation,[3,4] pyridylation,[5] benzylation,[3a,6] thiylation,[7] amination[8]) have demonstrated, in accordance with previous results,[9] the selective reactivity of the 2 position as compared to the 3 position of this heterocycle.

As a continuation of our systematic studies of heteroarylation in the heterocyclic series, we have decided to investigate the behavior of thiophene toward heteroaryl radicals and to use the selective reactivity of the 2 position in thiophene to synthesize new compounds of general formula A in which HAr represents a heterocyclic group.



A

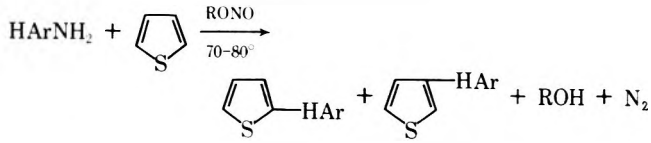
The aprotic diazotization of heteroaromatic amines (pseudo-Gomberg reaction[10,11]) seems to be a better source of heteroaryl radicals than other traditional sources. Our previous work on homolytic thiazolylation reactions in the aromatic[12] and pyridine[1a] series has shown that this radical source possesses many advantages: (i) the amines are generally easily available (commercially or by synthesis), (ii) the reactions are carried out in a homogeneous medium, and (iii) the yields are acceptable. Furthermore, competitive reactions with the system benzene–thiophene should make it possible to study the relative reactivity of these radicals and to compare such results with those obtained in other homolytic substitution reactions.

Results and Discussion

Heteroarylation Products. Decomposition of Heterocyclic Amines in Thiophene in the Presence of Amyl (or Isoamyl) Nitrite. The experimental conditions of this reaction were identical with those previously used in analogous studies in the aromatic and pyridine series. The heteroarylamines were decomposed at 70–80° in excess thiophene in the presence of a slight excess of the nitrite (Table I).

In addition to small amounts of by-products, separation of the crude reaction mixture by preparative thin layer chromatography (TLC) yielded a mixture of two isomers whose structures were assigned on the basis of GLC data and mass spectra (see Assignment of Structures and Mass Spectra).

Table I
Overall Yields of Heteroarylthiophenes Obtained from Aprotic Diazotization of Heteroarylamines in Excess Thiophene at 70–80° [a]



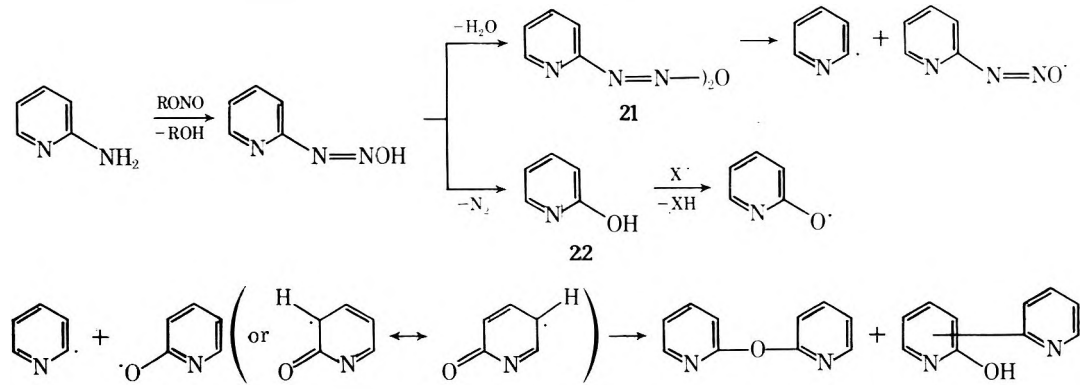
1-10 11-20

Compd	Heterocyclic radical, HAr	Yield, %
1a, 11a	2-Thiazolyl	25
1b, 11b	4-Methyl-5-acetyl-2-thiazolyl	35
1c, 11c	4-Methyl-5-carbethoxy-2-thiazolyl	35
1d, 11d	5-Bromo-2-thiazolyl	20
2, 12	2-Benzothiazolyl	40
3, 13	3-Methyl-5-isothiazolyl	30
4, 14	3,4-Dimethyl-5-isoxazolyl	40
5a, 15a	2-Pyridyl	20
5b, 15b	3-Methyl-2-pyridyl	15
5c, 15c	4-Methyl-2-pyridyl	
5d, 15d	5-Methyl-2-pyridyl	
5e, 15e	6-Methyl-2-pyridyl	
5f, 15f	5-Chloro-2-pyridyl	25
6, 16	3-Pyridyl	42
7, 17	3-Quinolyl	45
8, 18	8-Quinolyl	50
9, 19	2-Pyrazinyl	25
10, 20	2-Pyrimidyl	30

[a] Determined by GLC using an internal standard (usually biphenyl) on PMPE (six ring) or Apiezon L columns. These yields were not altered when reactions were carried out in the presence of oxidizing agents.

Some of the products so obtained were previously described compounds. Thus, 2- and 3-(2′-pyridyl)thiophenes were obtained in low yields by reaction between appropriately substituted thiophenes and pyridine,[5a,13] while 2- and 3-(3′-pyridyl)thiophenes were prepared (47% yield)[5a] using a modified Gomberg reaction generating the 3-pyridyl radical in thiophene according to the procedure described by Rapoport and coworkers[14] for 3-phenylpyridine. These two latter compounds have also been obtained by

Scheme I
By-products Formed in Aprotic Diazotization of 2-Aminopyridine in the Presence of Isoamyl Nitrite



photochemical decomposition of 3-iodopyridine in thiophene.[5b] A synthesis of 2-(2′-thiazolyl)thiophene has been reported.[15] All the other heteroarylthiophenes described in this study seem to be new compounds. Some overall yields reported in Table I are of the same order as those obtained in arylation reactions (20–50%).[11] The similarity between the two reactions is even more striking when isomer ratios are compared as shown in Table II.

Table II
Isomer Ratios in the Arylation and Heteroarylation of Thiophene at 70–80°

Radical	Isomer amounts, %[a] 2	3	Column (temp, °C)[b]
Phenyl	90 (93.1)	10 (6.9)	B, B′ (180)
p-Tolyl	91.6 (93)	8.4 (7)	A, B (190)
m-Methoxyphenyl	88	15	C (200)
p-Methoxyphenyl	87.5 (91)	12.5 (9)	C (200)
m-Nitrophenyl	88.4 (96)	11.6 (4)	A (190)
p-Nitrophenyl	83 (96)	17 (4)	A (190)
2-Thiazolyl	90	10	B′ (200)
3-Pyridyl	85	15	B, B′, C (190)
3,4-Dimethyl-5-isoxazolyl	85	15	C (200)
3-Quinolyl	85	15	A (200)

[a] Values given in parentheses correspond to those reported by Tiecco and coworkers for the same source of aryl radicals but at 30°.[2] [b] See Experimental Section.

In each case, a mixture of two isomers is obtained, always in the same ratio (87% of the 2 isomer and 13% of the 3 isomer), regardless of the radical structure (within the experimental error ±2%).

In these reactions, as in all other homolytic reactions of this type, a certain number of secondary products are also formed. Thus, in the case of azaaromatic amines such as 2-aminopyridine (or its methyl and chloro derivatives), 2-aminopyrimidine, and 2-aminopyrazine, which are resistant toward diazotization or form oxygen-containing products (mainly the corresponding hydroxy derivatives[16]), symmetrical heterocyclic ethers and, to a lesser extent, hydroxy compounds have been found and identified among reaction products.[17]

For example, in the case of 2-aminopyridine (see Scheme I) these products represent an overall yield of 30–35%. The presence of 2-hydroxypyridine and 2-alkoxypyridine was also detected. The existence of these by-products explains why the yields are lower than those observed with other heteroarylamines.

Furthermore, various tars and colored products (easily visible on TLC), as well as bis heterocyclic compounds (traces only) arising from the dimerization of heteroaryl radicals, and the corresponding unsubstituted heterocycles are also formed. The formation of 2,5-disubstituted products observed by certain authors[4,18,19] in homolytic substitution reactions of thiophene cannot be excluded. Finally, no dithienyls could ever be detected contrary to what is observed in thermal decomposition of aryl or heteroaryl peroxides.[2,20,21]

Scheme II
Aprotic Diazotization of Heterocyclic Primary Amines in the Presence of Thiophene (ThioH)

$$HArNH_2 + R{-}O{-}NO \xrightarrow{-H_2O}$$

$$HAr{-}N{=}N{-}OR \rightleftharpoons HArN_2^+RO^- \quad (23)$$

$$HAr{-}N{=}N{-}OR \xrightarrow{-N_2} HAr^\cdot + RO^\cdot$$

$$HArN_2^+RO^- + HArNH_2 \xrightarrow{-ROH} HAr{-}N{=}N{-}NHHAr \quad (24) \xrightarrow{-N_2}$$

$$HAr^\cdot + HArNH^\cdot$$

(a) Coupling in solvent cage

$$HAr^\cdot + HArNH^\cdot \longrightarrow (HAr)_2NH \; (25) + HAr{-}HArNH_2 \; (26)$$

$$HAr^\cdot + RO^\cdot \longrightarrow HArOR$$

$$2(HAr^\cdot) \longrightarrow HAr{-}HAr$$

(b) Radical reaction out of cage

$$HAr^\cdot + ThioH \longrightarrow [HArThioH]^\cdot \; (27) \xrightarrow{X^\cdot} HAr{-}Thio + XH$$

with $X^\cdot = RO^\cdot$ or $HArNH^\cdot$

Mechanism. It is now well established[22] that most five-membered and some six-membered heterocyclic amines such as 3-aminopyridine and 3-aminoquinoline which are readily diazotized behave like normal aromatic amines[10,23,24] and react via diazoate (**23**) and triazene (**24**) intermediates according to Scheme II.

However, no systematic studies of the mechanism of this reaction have been carried out. When these reactions are carried out at low temperatures (0–20°) with isoamyl nitrite in aqueous acetic acid or with sodium nitrite in a dilute acid solution, heteroaryltriazenes are quickly formed. They have been isolated for the following amines: 3-aminopyridine,[23,25] 5-amino-3,4-dimethylisoxazole,[25] 3-amino-1*H*-pyrazole,[26] various substituted 3-aminotriazoles,[27,28] 2-methyl-5-aminotetrazole,[29] 5-aminoisothiazoles,[25,30] and 5-amino-1,2,4-thiadiazoles.[31] The triazenes then undergo thermal decomposition with the formation of nitrogen, heteroaryl, and heteroarylamino radicals.[25]

Table III
Relative Reactivity of Thiophene (with Respect to Benzene) toward Heterocyclic Radicals[a]

Radical, HAr	Relative reactivity[b]
2-Thiazolyl	0.85
5-Bromo-2-thiazolyl	1.3
5-Carbethoxy-4-methyl-2-thiazolyl	1.1
5-Acetyl-4-methyl-2-thiazolyl	1.1
2-Benzothiazolyl	1.0
3,4-Dimethyl-5-isoxazolyl	1.4
3-Methyl-5-isothiazolyl	1.35
1-Methyl-2(1(*H*),3,4-triazol)yl	0.8
2-Pyridyl	0.95
3-Methyl-2-pyridyl	0.75
4-Methyl-2-pyridyl	1.1
5-Methyl-2-pyridyl	1.0
5-Chloro-2-pyridyl	1.15
6-Methyl-2-pyridyl	1.05
3-Pyridyl	1.35
2-Pyrimidyl	1.25
2-Pyrazinyl	1.15
3-Quinolyl	1.35
8-Quinolyl	1.70

[a] Obtained by aprotic decomposition of the corresponding heteroaromatic amines ($\sim 10^{-2}$ *M*) in an equimolar mixture of benzene and thiophene (2 hr at 70–80°). [b] Overall relative reactivity of thiophene toward HAr as compared with that of benzene (=1.0).

Table IV
Relative Reactivity of Thiophene (with Respect to Benzene) toward Aryl and Alkyl Radicals[a]

Radical	Relative reactivity	Radical	Relative reactivity
Phenyl	1.4[b]	1-Naphthyl	1.9
4-Methylphenyl	1.45[b]	2-Naphthyl	1.5
2-Methoxyphenyl	1.2	2-Biphenylyl	2.2
3-Methoxyphenyl	1.16	4-Biphenylyl	1.7
4-Methoxyphenyl	1.06[b]	Cyclohexyl	3.0[c]
2-Acetylphenyl	5.0	3-Cyclohexenyl	2.0[c]
3-Nitrophenyl	1.96	Benzyl	9.0[c]
4-Nitrophenyl	1.3[b]		

[a] Cf. footnotes *a* and *b*, Table III. [b] The corresponding values found by Tiecco and coworkers[2] using the same aryl radical source but at 30° are 2.6 (C_6H_5), 2.4 (4-MeC_6H_4), 1.7 (4-$MeOC_6H_4$), 3.6 (4-$NO_2C_6H_4$). At 40° we found the relative reactivity of thiophene toward phenyl radical equal to 1.75. [c] These radicals were generated by photochemical decomposition of cyclohexane, cyclohexene, or toluene, respectively, in the presence of di-*tert*-butyl peroxide.[3a,37a]

Recombination of these radicals at the position with high unpaired electron density, in the solvent cage, gives the secondary amine (**25**), while the mesomeric forms of heteroarylamino radicals lead to the amino derivatives (**26**). A similar behavior of this type of radicals has been observed in thermal or photochemical rearrangement of diazoamino compounds,[10a] *N*-α-phenethylaniline,[32] *N*-chloroacetanilide,[33] 3-acetamidopyridine,[34] and aryl ethers.[32,35] However, contrary to what is observed with aniline or its N-substituted derivatives, we were not able to show the formation of such by-products, probably because of a longer lifetime of heteroaryl radicals under study. These radicals migrate out of the solvent cage and substitute homolytically on the thiophene ring to give the intermediate σ complex (**27**) which is then oxidized by sufficiently active radicals (alkoxy or heteroarylamino radicals) before dimerization or disproportionation (cf. Scheme I). The presence of commonly used agents (copper, lead tetraacetate, nitrobenzene, etc.) does not alter the reaction yield. This insensitivity to oxidizing agents has also been observed[11f] in the decomposition of pentafluoroaniline at 80° in benzene in the presence of amyl nitrite.

Table V
Relative Retention Times (α_r) of Some 2-Heteroarylthiophenes and Heteroarylbenzenes on Different Columns

Substituent	2-Heteroarylthiophene (α_r relative to 2-phenylthiophene) A (160°)[a]	B′ (200°)[b]	Heteroarylbenzene (α_r relative to biphenyl) A (160°)[a]	B (200°)[b]
Phenyl	1.0	1.0	1.0	1.0
2-Pyridyl	1.4	1.7	1.35	1.65
3-Methyl-2-pyridyl	1.34	1.82	1.31	1.75
4-Methyl-2-pyridyl	2.18	2.7	1.95	2.5
5-Methyl-2-pyridyl	2.27	2.0	2.1	2.1
6-Methyl-2-pyridyl	1.56		1.45	
3-Pyridyl	1.5	1.95	1.48	2.0
2-Pyrimidyl	1.45	1.85	1.38	1.75
2-Pyrazinyl	1.54		1.5	
2-Thiazolyl	1.2	1.52	1.2	1.46
3-Methyl-5-isothiazolyl	1.6		1.54	
3,4-Dimethyl-5-isoxazolyl	2.0		2.1	
5-Chloro-2-pyridyl	*3.0*		*2.8*	
3-Quinolyl	*5.9*[c]		*5.7*	
8-Quinolyl	*5.5*[c]		*5.0*	
5-Bromo-2-thiazolyl		(3.0)		(2.97)
2-Benzothiazolyl		10.4		9.6
4-Methyl-5-carbethoxy-2-thiazolyl		8.2 (7)		8.0 (7)
4-Methyl-5-acetyl-2-thiazolyl		8.0 (7)		8.0 (7)

[a] $\alpha_r = (t'_R)_{HAr\text{-}Thio}/(t'_R)_{2\text{-}Ph\text{-}Thio} \simeq (t'_R)_{HAr\text{-}Ph}/(t'_R)_{Ph\text{-}Ph}$ where t'_R represents the reduced retention time. For biphenyl and 2-phenylthiophene, t'_R = 200 and 220 sec, respectively, on Apiezon L (A) at 160°. [b] Retention times for biphenyl, 2-phenylthiophene, and 3-phenylthiophene on PMPE column (B′) at 200° were 400, 460, and 500 sec, respectively. Values in parentheses are at 220°. Values printed in italics are for 200°. [c] For the isomeric 3-(3′- and 8′-quinolyl)thiophenes α_r = 6.3 and 6.6, respectively.

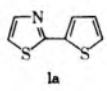
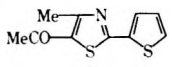
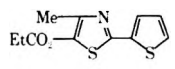
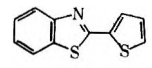
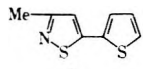
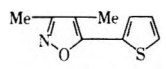
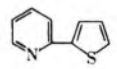
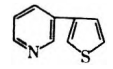
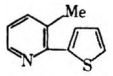
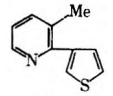
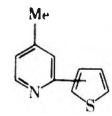
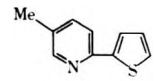
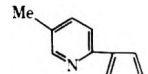
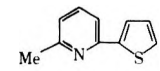
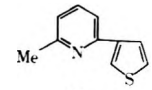
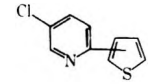
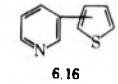
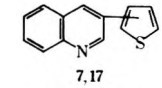
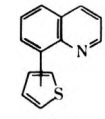
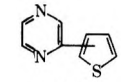
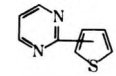
In the case of 2-aminopyridine and other six-membered azaaromatic amines already mentioned, main by-products observed arise from the recombination of 2-pyridyl with 2-pyridyloxy radicals (or their mesomeric forms) generated from diazo anhydride (**21**) and 2-hydroxy derivatives (**22**) (cf. Scheme I) via diazo hydroxide intermediate according to a mechanism similar to that postulated by Rüchardt and coworkers.[36]

Competitive Studies. In order to compare the relative reactivities of the radicals under study, we used the method of competitive reactions with the system benzene–thiophene (equimolar amounts). The experimental conditions were the same as those mentioned above.

The results in Table III show an almost total absence of selectivity of the heteroaromatic radicals toward thiophene, for which the overall reactivity is slightly higher than that of benzene. At the same time the reactivity of the 2 position of thiophene at 80° is roughly three times higher than the reactivity of benzene while that of the 3 position is about three times lower regardless of the nature of the heteroaromatic radical. We have also compared these results with those obtained with hydrocarbon radicals, such as aryl (including biphenyl), benzyl, and cyclohexyl radicals. The latter two were obtained by the photochemical decomposition of di-*tert*-butyl peroxide in toluene[3a] and cyclohexane.[37] These results are presented in Table IV.

It can be seen, first of all, that the relative rates of sub-

Table VI
Mass Spectra of Some 2-Heteroarylthiophene Derivatives, Principal Fragments, and Relative Intensities[a]

Compd	Principal fragments (rel intensity, %)
 1a	169 (10), 168 (10), *167* (96), 110 (4), 109 (3), 69 (5), 60 (6), 59 (5), 58 (100), 57 (5), 45 (8), 39 (5)
 1b	225 (10), 224 (13), *223* (100), 210 (8), 211 (10), 208 (90), 180 (17), 169, 168, 139 (10), 114 (7), 110 (11), 90, 72 (12), 71 (30)
 1c	255 (10), 254 (15), *253* (100), 227, 226, 225 (30), 224 (15), 210, 209, 208 (45), 207 (5), 183, 182, 181 (30), 180 (15), 144, 139, 116 (26), 111 (18), 110 (35), 109 (8), 104, 100, 98 (20), 72 (20), 71 (40), 70 (20), 69 (15), 45 (35)
 2	219 (10), 218 (15), *217* (100), 216 (12.5), 191, 190, 185 (4), 184 (4), 173 (7.5), 172 (5), 140, 109, 108 (32.5), 82 (7.5), 71, 69 (22.5), 58 (10), 43 (5), 44 (10)
 3	183 (11), 182 (12), *181* (100), 180 (5), 153, 149, 148 (6), 142, 141, 140 (30), 110, 109, 108 (8), 96 (35), 82 (5), 74 (9), 69 (9)
 4	181 (4), 180 (10), *179* (100), 138 (6), 122 (8), 121 (6), 111 (50), 110 (44), 109 (12), 96 (9), 85 (6), 83 (7), 77 (8), 68 (17), 66 (11), 51 (7), 45 (8), 43 (8), 42 (11), 41 (13), 40 (8)
 5a	163 (7), 162 (15), *161* (100), 160 (41.6), 135 (8), 134 (6), 133, 128 (10), 117 (26), 116 (10.5), 90 (6.5), 89 (8), 80, 78 (12), 69 (4), 67, 63, 51 (9), 50, 45 (5), 39 (6)
 15a	163 (6.0), 162 (13), *161* (100), 160 (62), 135 (9), 134, 117 (22), 116 (7), 104 (5), 94 (6), 91, 90, 80, 78
 5b	177 (4), 176 (9), *175* (90), 174 (100), 142 (6), 141 (6), 130 (15), 110 (4), 109 (9), 108 (4), 80 (8), 65 (15), 39 (23)
 15b	177 (4.5), 176 (10), *175* (100), 174 (90), 142 (65), 130 (54), 109 (60)
 5c, 15c	177 (6), 176 (16), *175* (100), 174 (30), 173 (6), 160 (4), 149 (4), 147 (4), 143 (5), 131 (6), 130 (9), 109 (7), 92 (4), 81 (4), 65 (6), 51 (3), 45 (3), 39 (9)
 5d	177 (6), 176 (14), *175* (100), 174 (35), 149 (4), 148 (7), 147 (13), 143, 142, 141, 131 (8), 130 (9), 121 (4), 115 (16), 109, 108 (17), 107 (8), 103, 92, 81, 80, 65, 51
 15d	This mass spectrum is very similar to that of its isomer 5d, except for the relative intensities of fragments at 108 (5) and 131 (3).
 5e	177 (7), 176 (4), *175* (100), 174 (30), 160 (4), 149 (3), 147 (3), 143, 142, 141, 131 (7), 130 (9), 108 (6.5), 92 (7), 91 (20), 80, 77, 69, 66, 65, 45, 39
 15e	177 (6), 176 (14), *175* (100), 174 (40), 160 (3), 149, 147, 143, 142, 141, 131 (8), 118, 108 (7), 92, 91 (9), 80, 77, 69, 66, 65, 45, 39
 5f, 15f	198 (12), 197 (35), 196 (16), *195* (100), 171, 162 (6), 160 (9), 151 (10), 133 (4), 116, 115, 114, 113, 89, 76, 69, 63, 62, 58, 51, 50, 45, 39
 6, 16	163 (5), 162 (16), 161 (100), 160 (18.5), 117 (25), 108 (9), 89 (15), 69, 63, 62, 51, 50, 45, 39
 7, 17	213 (7), 212 (17), *211* (100), 210 (17), 183, 167 (9), 166 (9), 140 (4), 105 (6.5), 92 (11), 79 (6), 63, 62, 58, 39
 8, 18	213 (4), 212 (10.5), *211* (70), 210 (100), 178 (28), 141 (10), 140 (14), 139 (14), 101 (14)
 9, 19	164 (6), 163 (10), *162* (100), 135 (10), 109 (55)
 10, 20	164 (5), 163 (8), *162* (100), 161 (4), 135 (3), 110 (7.5), 109 (50), 108 (7), 81 (8), 63, 59, 58, 53, 52, 45, 39

[a] Molecular ions are printed in italics.

stitution of thiophene in the case of aryl radicals are much lower than those observed by Tiecco and coworkers[2] and that the differences in reaction temperature (30° in Tiecco's experiments and 80° in our case) are not sufficient to explain this.

In general, the reactivity of a radical depends on its stability: the lower its stability and the lower its selectivity, the higher is its reactivity.[38] In this respect, the data obtained with cyclohexyl and especially benzyl radicals are in agreement with this principle.

The results obtained by Rüchardt and coworkers[36] on the relative selectivities of aryl and alkyl radicals are similar to our results obtained in the present study. These authors studied the action of structurally very different radicals on the system CCl_4–$CBrCl_3$. They have shown an absence of influence of para substituents on the phenyl radical (except with o-tolyl and 2,4,6-trimethylphenyl radicals, where this is due to steric hindrance), and they have also demonstrated that cyclohexyl and benzyl radicals are respectively 4 and 12 times more selective than phenyl radicals in this reaction.[36a]

Assignment of Structures and Mass Spectra. Our assignment of the structures of heteroarylthiophenes was based on three types of evidence:[39] (a) the preferred formation of 2 isomers in free-radical substitutions of thiophene; (b) the GLC data; and (c) the mass spectra.

Distinction between the isomeric 2- and 3-heteroarylthiophenes was primarily based on the well-known fact that in homolytic substitution reactions occurring on the thiophene ring it is the 2 isomer which is the chief reaction product, regardless of the structure of the radical used in the reaction (cf. Table II).

On nonpolar chromatographic columns, the 2 isomers have a shorter retention time than the 3 isomers. According to Martin's additivity principle,[40] retention increments (α_r or ΔI) of a heteroaryl group must be the same regardless of the nature of the molecule to which this heteroaryl group is bonded. Because of this, relative retention times of 2-heteroarylthiophenes (expressed with respect to 2-phenylthiophene as reference) and those of hereroarylbenzenes (expressed with respect to biphenyl as reference) are in good agreement (Table V). For the same reason, a close similarity must exist between the retention times of 3-heteroarylthiophenes (expressed with respect to 3-phenylthiophene as reference) and the above-mentioned data for arylbenzenes and 2-heteroarylthiophenes (on the same column and at the same temperature).

Finally, coupled GLC–mass spectral data were found to be satisfactory for further confirmation of the structures of heteroarylthiophenes. However, GLC columns used in this case were somewhat less efficient than those used for GLC analysis only (cf. Experimental Section). Because of this, the 3 isomers after separation were slightly contaminated with the 2 isomers. Mass spectra recorded for the compounds **5** and **15** were very similar to those observed for other isomeric substituted thiophenes[41] and, therefore, the assignments of structures in this case were based chiefly on mass spectral data.

The mass spectral data obtained for 2-heteroarylthiophenes are summarized in Table VI. All of the heteroarylthiophenes exhibit the parent molecular ions (base peaks) as the most abundant species in their mass spectra. This observation reflects the great stability of the thiophene ring increased by conjugation with another heteroaromatic ring. The low-intensity fragments (except for 2-thiazolyl derivatives) are characteristic of the cleavage of both the thiophene ring ($M^+ - C_2H_2$, $M^+ - HS$, $M^+ - CS$) and of the heteroaryl substituents.[41]

Experimental Section

Reagents. Most reagents and heterocyclic amines were commercial products: *n*-amyl and isoamyl nitrite (Merck), thiophene (Fluka), di-*tert*-butyl peroxide (Fluka AG Buchs), *p*-toluidine (Prolabo), *m*-anisidine (Koch-Light Laboratories Ltd.), *p*-anisidine (Fluka), *p*-nitroaniline (Prolabo), o-ethylaniline (Fluka), 2- and 4-aminobiphenyl (Fluka), 2-aminopyridine (Fluka), 3-aminopyridine (Eastman), 4-methyl-2-aminopyridine (Eastman), 3-methyl-2-aminopyridine (Eastman), 5-methyl-2-aminopyridine (Eastman), 2-amino-5-chloropyridine (Aldrich), 3- and 8-aminoquinoline (Eastman), 2-aminopyrimidine (Eastman), 2-aminothiazole and 2-aminobenzothiazole (Fluka), 3-amino-5-methylisoxazole (Fluka), and 5-amino-3,4-dimethylisoxazole (Fluka). 5-Substituted 2-aminothiazoles were prepared according to the methods reported in previous work.[12c]

Heteroarylation Procedure. Synthetic scale reactions were generally carried out in the following manner. Isoamyl nitrite (20 g, 0.17 mol) was added to a stirred mixture of the heteroarylamine (0.1 mol) and 500 ml of thiophene in a 1-l. flask equipped with a reflux condenser. The reaction mixture was kept at room temperature for 24 hr and then refluxed for 1 hr. The cooled mixture was filtered to remove tars and thiophene, and isoamyl alcohol and other volatile products were distilled off on a rotary evaporator. The oily residue was first steam distilled in the presence of an acid to eliminate nonbasic impurities and the steam distillation was repeated in the presence of a base. The organic material was then extracted with ether and treated in the usual manner (see Analysis).

In other experiments, the reaction was allowed to proceed at 75–80° and it was sufficiently exothermic to bring the solution to this temperature without external heating.

The less volatile 2-heteroarylthiophenes were separated from colored by-products by preparative TLC.

Competitive Experiments. The following general procedure was followed. Isoamyl nitrite (0.015 mol) was added to a solution of the heterocyclic amine (0.01 mol) and an equimolar (1:1) mixture of benzene and thiophene (0.2 mol) in a 100-ml round-bottomed flask equipped with a reflux condenser. The reaction was allowed to proceed at 75–80° on a bath until the evolution of gas had ceased. Excess of solvents was distilled off in vacuo. The residue was analyzed by gas chromatography.

To determine isomer ratios and relative reactivities more accurately, 2-heteroarylthiophenes were then separated by preparative TLC. The desired fraction was extracted and examined again by GLC. Generally no difference was found between the two chromatograms. All the reactions were carried out in duplicate.

Experiments with arylamines were performed in a similar manner.

Analysis. Details of the analytical conditions are as follows.

TLC. All reaction mixtures were analyzed by TLC according to Stahl's standard procedure.

Preparative TLC was carried out on silica gel $PF_{254+366}$ plates with benzene as eluent for less polar compounds, and with benzene–methanol (20:1) for more polar compounds. The desired fraction, localized mainly in the middle of the plate, was extracted with acetone and examined again by TLC, GLC, and GLC–MS. The R_f values of some aryl- and heteroarylthiophenes are reported in Table VII.

Table VII
R_f Values of Some Aryl- and Heteroarylthiophenes[a]

Compd	R_f
Biphenyl	0.90
2-Phenylthiazole	0.21
2-(2′-Thiazolyl)thiophene	0.23
3-(2′-Thiazolyl)thiophene	0.16
2,2′-Bithiophene	0.28
3,4-Dimethyl-5-phenylisoxazole	0.25
2- and 3-(3,4-Dimethyl-5-isoxazolyl) thiophenes	0.20, 0.25
2- and 3-(2′-Benzothiazolyl)thiophenes	0.32, 0.35
2- and 3-(4′-Methyl-5′-carbethoxy-2′-thiazolyl)thiophenes	0.14
2- and 3-(2′-Pyridyl)thiophenes	0.14, 0.20
2- and 3-(6′-Methyl-2′-pyridyl)thiophenes	0.26, 0.33

[a] On silica gel $HF_{254+366}$ with benzene as eluent in an unsaturated atmosphere. Values for the Stahl dye-test mixture Desaga were 0.06, 0.14, and 0.46, respectively. With more polar compounds such as pyridyl-, pyrazinyl-, and pyrimidylthiophenes, a mixture of benzene and methanol (20:1) was used as eluent. R_f ranged from 0.50 to 0.60.

GLC. The crude products of these reactions and fractions isolated by preparative TLC were analyzed by gas chromatography using an Intersmat IGC 15 gas chromatograph equipped with a flame ionization detector and coupled with a Vidar Autolab integrator. The following three stainless steel 8-in. columns were used: A was a 7-ft column packed with Apiezon L (5%) on Chromosorb W HMDS (80–100 mesh) precoated with 3% KOH. The retention times of biphenyl on this column at 160 and 200° were 200 and 120 sec, respectively. B and B′ were 5- and 10-ft columns packed with polymetaphenyl ether (PMPE six ring, 5%) on Chromosorb W, AW HMDS (60–80 mesh) (retention time of biphenyl was 400 sec on B′ column at 200°). C was a 5-ft column packed with Carbowax 20M (10%) on Chromosorb Q (80–100 mesh) (retention time of biphenyl on this column was 215 sec at 190°). Other columns were also used (OV 225, SE-30). In all cases, the injector and detector temperature was 250°, carrier gas was hemixal (N_2 + He), flow rate 20–25 ml min^{-1}, inlet pressure 28 psi. Difficulty was experienced in finding a suitable column to separate the 2- and 3-aryl and -heteroarylthiophene isomers. The best separation was obtained on the column B′ for more volatile compounds, while for the less volatile compounds (benzothiazolyl, quinolyl, biphenylyl, and naphthylthiophene derivatives) Apiezon L, Silicone SE-30, or OV 225 columns were more suitable. Table V summarizes the relative retention times of some aryl- and heteroarylthiophenes. Kovats indices[43] are reported in Table VIII. These values are usually known as more reproducible than the relative retention times which depend on temperature.

No correction for the average response factors of aryl- and heteroarylthiophenes (in competitive experiments) was applied, these compounds being very similar. However, in the determination of yields with biphenyl as internal standard, an average response fac-

Table VIII
Kováts Indices *I* of Some Heteroarylthiophenes[a]

2-Heteroarylthiophene	*I*
	A (160°)[b]
3-Pyridyl	1705
2-Pyridyl	1692
3-Methyl-2-pyridyl	1690
4-Methyl-2-pyridyl	1795
5-Methyl-2-pyridyl	1800
6-Methyl-2-pyridyl	1720
2-Pyrimidyl	1700
2-Pyrazinyl	1715
2-Thiazolyl	1630
3-Methyl-5-isothiazolyl	1720
3,4-Dimethyl-5-isoxazolyl	1780
	A (230°)[b]
4-Methyl-5-carbethoxy-2-thiazolyl	2190[c]
4-Methyl-5-acetyl-2-thiazolyl	2150
2-Benzothiazolyl	2320[d]
2-Naphthyl	2015
2-Biphenyl	1950
4-Biphenyl	2210
	B′ (200°)[b]
2-(3-Pyridyl)	1965
3-(3-Pyridyl)	2015
2-(2-Pyridyl)	1990
2-(3,4-Dimethyl-5-isoxazolyl	2020
3-(3,4-Dimethyl-5-isoxazolyl)	2060
2-(2-Thiazolyl)	1930

[a] Kováts indices were calculated according to the general formula[43] $I = 200\,[\log(d'_R)_X - \log(d'_R)_Z]/[\log(d'_R)_{Z+2} - \log(d'_R)_Z] + 100Z$, where d'_R represents the reduced retention distance. These values were almost the same on an SE-30 column at 230°. [b] Column and temperature (cf. text). [c] For 2-phenyl-4-methyl-5-carbethoxythiazole, I = 2130. [d] For 2-phenylbenzothiazole, I = 2250.

tor of 2 was used on the column C, whereas 1.4 was used on SE-30 or Apiezon L columns.

GLC–MS. These analyses were performed using Aerograph Model 1400 and Varian MAT 111 instruments at 80 eV, source temperature 200°, accelerating voltage 820 V, and trap current 270 A. Columns used were 5 ft × 0.125 in. Apiezon L (3%), or PMPE six ring (3%) W/W on Varaport (100–120 mesh), operated in programmed temperature 150–250°, 6° min^{-1}. Major peaks and their relative intensities are summarized in Table VI.

The mass spectral data on the heterocyclic ethers of the type HAr–O–HAr have been reported.[20]

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Registry No.—**1a**, 42140-95-4; **1b**, 56421-61-5; **1c**, 56421-62-6; **1d**, 56421-63-7; **2**, 34243-38-4; **3**, 56421-64-8; **4**, 56421-65-9; **5a**, 3319-99-1; **5b**, 56421-66-0; **5c**, 56421-67-1; **5d**, 56421-68-2; **5e**, 56421-69-3; **5f**, 56421-70-6; **6**, 3319-99-1; **7**, 34243-33-9; **8**, 56421-71-7; **9**, 56421-72-8; **10**, 56421-73-9; **11a**, 42140-96-5; **11b**, 56421-74-0; **11c**, 56421-75-1; **11d**, 56421-76-2; **12**, 56421-77-3; **13**, 56421-78-4; **14**, 56421-79-5; **15a**, 21308-81-6; **15b**, 56421-80-8; **15c**, 56421-81-9; **15d**, 56421-82-0; **15e**, 56421-83-1; **15f**, 56421-84-2; **16**, 21298-55-5; **17**, 56421-85-3; **18**, 56421-86-4; **19**, 56421-87-5; **20**, 56421-88-6; isoamyl nitrite, 111-46-3; thiophene, 110-02-1; 2-thiazolamine, 96-50-4; 4-methyl-5-acetyl-2-thiazolamine, 30748-47-1; 4-methyl-5-carbethoxy-2-thiazolamine, 7210-76-6; 5-bromo-2-thiazolamine, 3034-22-8; 2-benzothiazolamine, 136-95-8; 3-methyl-5-isothiazolamine, 24340-76-9; 3,4-dimethyl-5-isoxazolamine, 19947-75-2; 2-pyridinamine, 504-29-0; 3-methyl-2-pyridinamine, 1603-40-3; 4-methyl-2-pyridinamine, 695-34-1; 5-methyl-2-pyridinamine, 1603-41-4; 6-methyl-2-pyridinamine, 1824-81-3; 5-chloro-2-pyridinamine, 1072-98-6; 3-pyridinamine, 462-08-8; 3-quinolinamine, 580-17-6; 8-quinolinamine, 578-66-5; 2-pyrazinamine, 5049-61-6; 2-pyrimidinamine, 109-12-6.

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Reactions of 2,3-Diphenylthiirene 1,1-Dioxide with Nucleophiles

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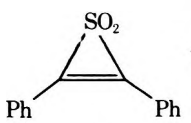
2,3-Diphenylthiirene 1,1-dioxide (**1**) reacts with tertiary phosphines, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), dimethylamine, sodium cyanide, and sodium benzenesulfinate in aprotic solvents by initial attack at the carbon centers of the three-membered ring. The reaction of **1** with dimethylamine in benzene gives a high yield of (*E*)-1,2-diphenyl-1-*N*,*N*-dimethylaminoethene. Tertiary phosphines and DBN react with **1** to give a new class of betaines. The complete X-ray structure of the betaine **3d** derived from **1** and diphenylmethylphosphine is reported. Cyanide and benzenesulfinate ions in DMF add across the carbon–carbon double bond in **1** to give an intermediate anion which undergoes electrocyclic ring opening to vinylsulfinates (**16** and **17**, respectively). These sulfinates were converted into their respective methyl sulfones (**18** and **19**) with methyl iodide.

Although the physical and chemical properties of cyclopropenones[1] indicate that these compounds enjoy a relatively high degree of stability owing to their aromatic character, the corresponding sulfones, thiirene 1,1-dioxides, are not sufficiently well characterized to draw a similar conclusion.[2] A good deal of information is now available on the reactions of cyclopropenones,[1] but far less is known about similar reactions with the unsaturated episulfones. In view of this, we have investigated the reactions of 2,3-diphenylthiirene 1,1-dioxide (**1**) with nucleophiles.

Results and Discussion

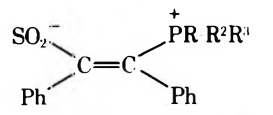
α,β-Unsaturated sulfones,[3] like other alkenes substituted with electron-withdrawing groups,[4] are susceptible to nucleophilic additions. Typical nucleophiles used are alkoxides, amines, thiolates, sulfinates, cyanide, and carbanions.[4] Tertiary phosphines also are reactive, but their reactions with the activated alkenes tend to be highly reversible.[5] Because of the nature of the strained ring system in 2,3-diphenylthiirene 1,1-dioxide (**1**), it seemed likely that **1** would react irreversibly with nucleophiles such as tertiary phosphines either by attack at the sulfur or α-carbon positions. Indeed, **1** reacted rapidly in benzene solvent with a number of reactive tertiary phosphines (**2**) to give 1:1 adducts in quantitative yield.[6] The structure of the adduct of **1** with diphenylmethylphosphine (**2d**) was established as **3d** by an X-ray crystallographic analysis.



1

+ $:PR^1R^2R^3$ $\xrightarrow{\text{benzene}}$

2a, $R^1 = R^2 = R^3 = N(CH_3)_2$
b, $R^1 = R^2 = R^3 = n\text{-Bu}$
c, $R^1 = R^2 = Et$; $R^3 = Ph$
d, $R^1 = R^2 = Ph$; $R^3 = CH_3$

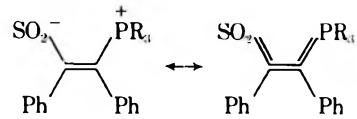


(1)

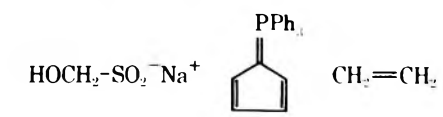
3a, $R^1 = R^2 = R^3 = N(CH_3)_2$
b, $R^1 = R^2 = R^3 = n\text{-Bu}$
c, $R^1 = R^2 = Et$; $R^3 = Ph$
d, $R^1 = R^2 = Ph$; $R^3 = CH_3$

An ORTEP drawing of **3d** from the X-ray determination is given in Figure 2; bond lengths and angles are shown in Figure 1. The A and B phenyl rings, which are attached to the central C=C, are twisted by steric interactions out of the double bond plane by angles of 67 and 47°, respectively. The shortest ring A···ring B distance of 3.37 Å (Figure 2) is virtually identical with the 3.4-Å van der Waals thickness of an aromatic ring. The O(1)–S–O(2) and Ph–P–Ph angles are approximately bisected by the double bond plane, and the orientations of both the SO_2 and PCH_3Ph_2 groups appear to be governed by steric factors. Newman projections illustrating the conformations about C(2)–P and C(3)–S are given in Figure 3. The SO_2 group is pyramidal (the sum of the three angles around S is 315.9°; sum of three perfectly tetrahedral angles, 109.5°, is 328.5°), and with the assumption that the unshared electron pair on S (form I) is positioned, relative to the C and two O atoms, to give a S tetrahedron, it is clear that the SO_2's orientation maximizes the electron pair–P^+ interaction (S···P 3.20 Å).

The resonance structure extremes for **3d** are represented by canonical form I, a sulfinophosphonium betaine, and form II, a phosphonium ylide–sulfene.[7] Bond lengths (Figure 1) for the central P–C–C–S part of the molecule have the usual values for P–C, C=C, and C–S, all of which would pertain to structure I. The P–C(2) distance is typical of P–C (sp^2, phenyl) lengths; phosphonium ylides with some P=C character normally show a distance of about 1.72 Å. Several representative distances are given below.



I II



Bond	C–S[9]	ring-C–P[10]	C–C[11]
Bond length, Å	1.838	1.718	1.34

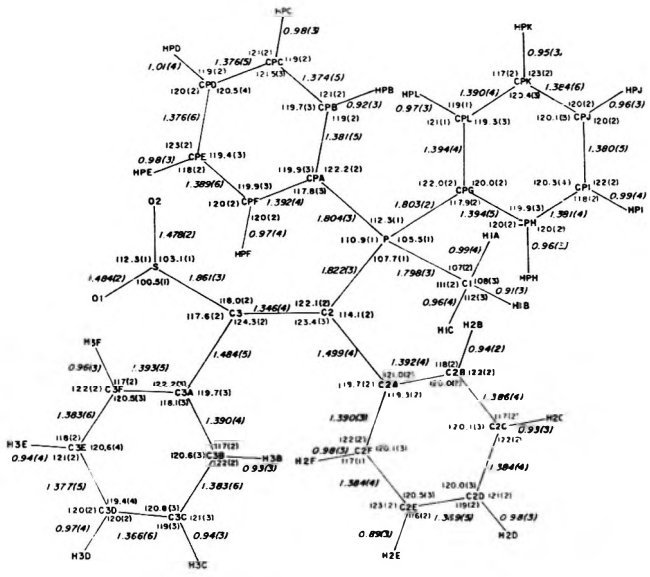
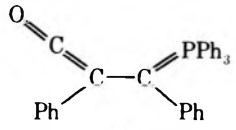


Figure 1. Bond lengths (Å) and angles (degrees) for **3d**. Estimated standard deviations are in parentheses.

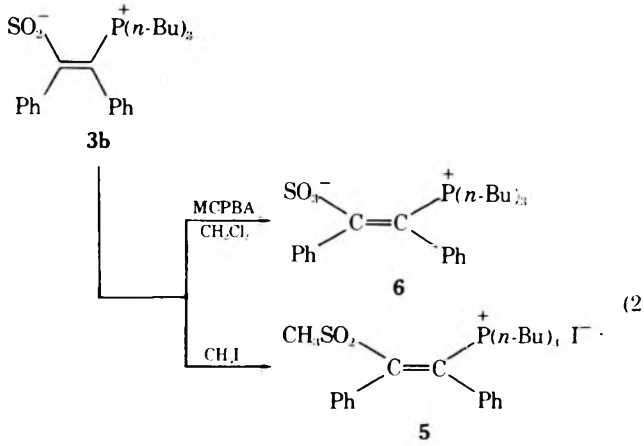
There is no bond length evidence for the P to S delocalization indicated by structure II. The pyramidal shape of the SO_2 and the orthogonal orientation of the S's electron pair to the C=C π electrons are further evidence for structure I.

In contrast to the betaines **3** resulting from the reactions of tertiary phosphines with 1, 2,3-diphenylcyclopropenone reacts with triphenylphosphine to give a 1:1 adduct which is properly represented by the phosphorane structure (**4**).[12]



4

Betaine **3b** reacted with methyl iodide to give the methylsulfonyl phosphonium iodide **5**, and **3b** was oxidized by *m*-chloroperoxybenzoic acid (MCPBA) to the sulfophosphonium betaine **6**.



3b **6** **5** (2)

Interestingly, the sulfinobetaines **3** are yellow-orange colored whereas the sulfobetaines **6** and **7** are colorless. The uv spectrum of **3d** is strongly solvent dependent: λ_{max} (CH_3CN) 390 nm (ϵ 394) and λ_{max} (CH_3OH) 350 nm (ϵ 350). Although it is tempting to ascribe the color of **3d** (bright orange) to a major contribution from the sulfene–ylide form (II), this must be discounted based on the X-ray data (vide supra). The absorption appears to be due to a charge transfer band (eq 3) which undergoes a blue shift going from acetonitrile to methanol, since hydrogen bonding of methanol to the sulfonyl group lowers the ground-state energy of **3d**.[13]

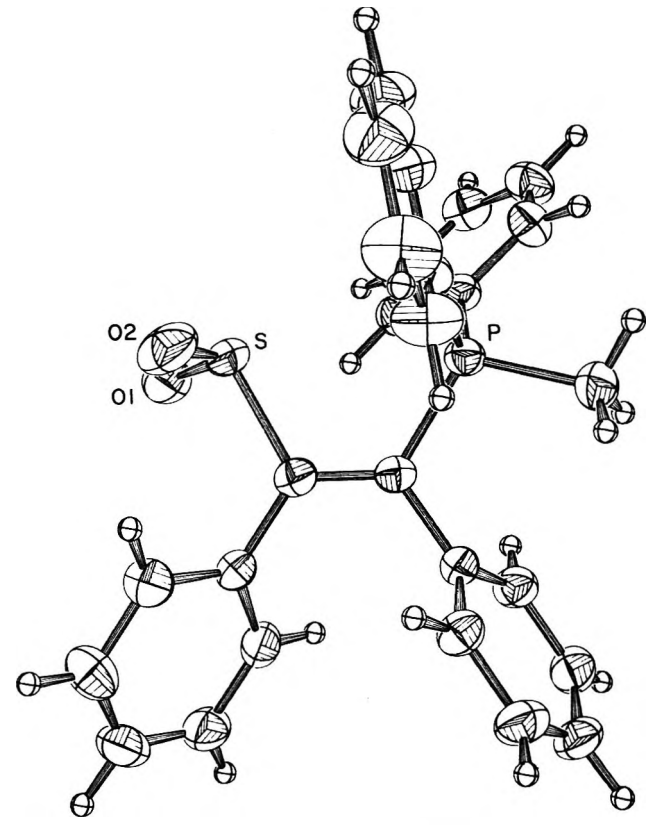
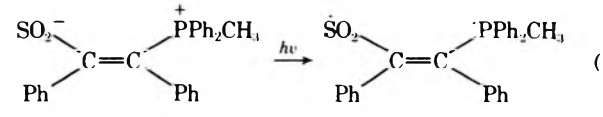
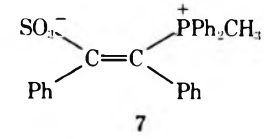


Figure 2. An ORTEP-II drawing of **3d**. The view is normal to the plane of the central C=C.

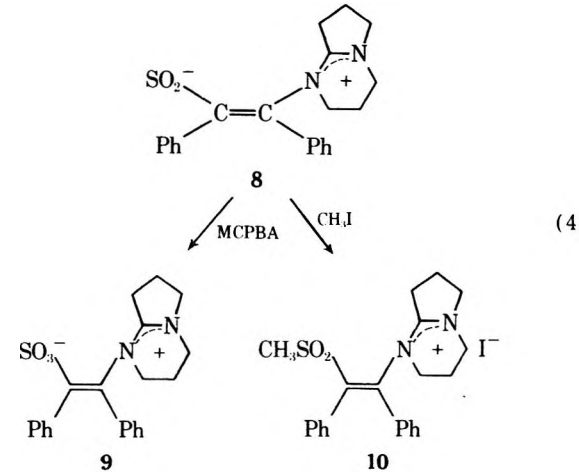


3d (3)



7

In contrast to the reactions of tertiary phosphines, **1** does not react with typical tertiary amines (triethylamine and 1,4-diazabicyclo[2.2.2]octane).[14] However, **1** did react in benzene with the highly reactive tertiary amine, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), to give a 1:1 adduct, the betaine **8**.[6] The yellow-colored betaine **8** was oxidized to the



8 (4)

9 **10**

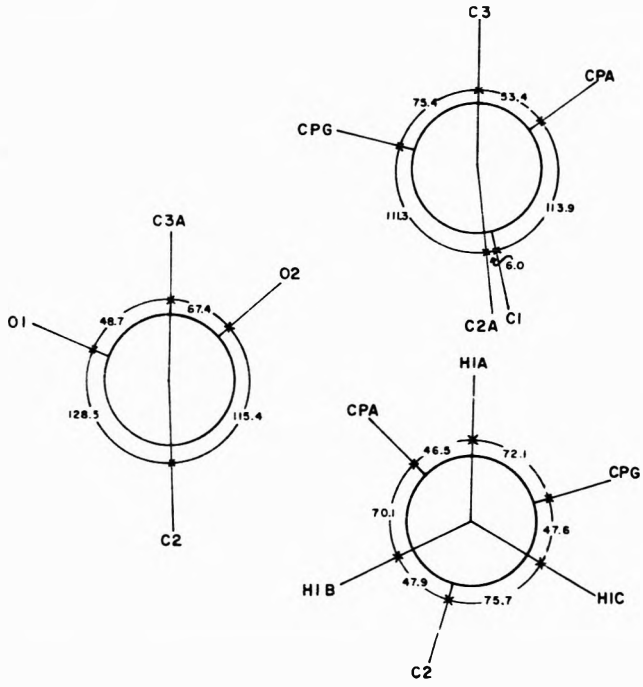
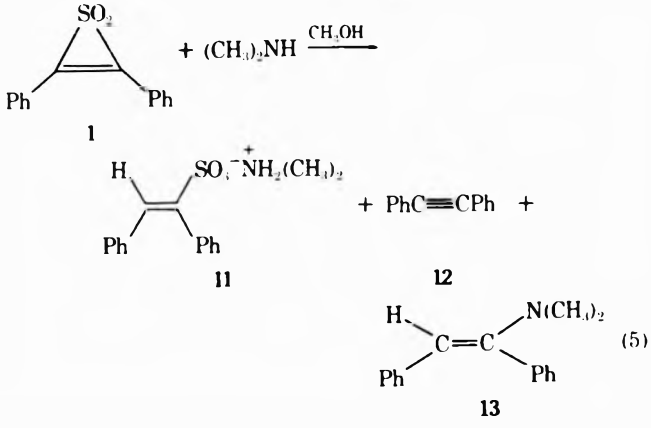


Figure 3. Newman projections for **3d**. Clockwise from the top right, the three projections are for C2 → P, C1 → P, and C3 → S. Dihedral angles are included.

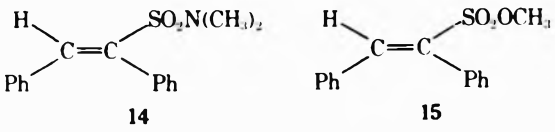
colorless betaine **9** and methylated with methyl iodide to give the sulfone **10.**

Although normal tertiary amines are unreactive toward **1**, dimethylamine reacts with **1** in methanol to give the dimethylammonium sulfonate **11**, a minor amount of diphenylacetylene **12**, and the vinylamine **13**. The salt **11** was



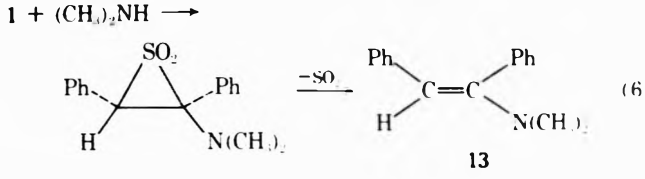
identified by its spectral data and conversion to the known *p*-toluidine salt of 1,2-diphenylethylene-1-sulfonic acid[15] (see Experimental Section).

A possible precursor of **11** is the sulfonamide **14**, which could conceivably have given **11** under the reaction conditions. However, **14** (for synthesis, see Experimental Section) was stable under conditions of eq 5, but methyl sulfonate **15** was rapidly converted to **11** with dimethylamine in



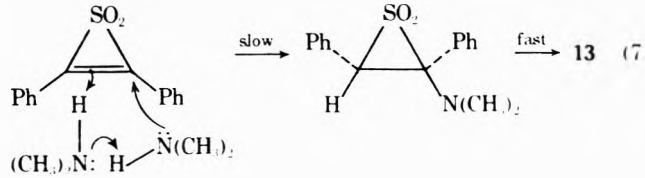
methanol. The methyl sulfonate **15** and diphenylacetylene result from the rapid reaction of **1** with methoxide ion,[16] which is produced by the methanolysis of dimethylamine in methanol. The methanolysis of dimethylamine can be suppressed by running the reaction of **1** with dimethylamine in the presence of dimethylammonium chloride. In the absence of added dimethylammonium chloride, **1** reacts with dimethylamine to give **11** and **13** in a ratio of ca. 8:1, whereas under the same conditions with added 1 *M* dimethylammonium hydrochloride, the ratio of **11:13** is ca. 1:8.

The overall structure of the vinylamine **13** was established through the use of spectroscopy and by the hydrolysis of **13** to benzyl phenyl ketone in quantitative yield. ^{1}H NMR spectroscopy and liquid chromatography showed that the sample of **13** was homogeneous with no indication of a mixture of isomers. Hauser, Taylor, and Ledford[17] reported the synthesis of a vinylamine whose structure they assigned as (*Z*)-1,2-diphenyl-1-*N*,*N*-dimethylaminoethene, mp 30°, from the base-catalyzed elimination of hydrogen cyanide from α-dimethylamino-α-phenylacetonitrile. Thermal elimination of hydrogen cyanide from the above nitrile gave "a liquid enamine" which they suggested was either a geometrical isomer of the 2-vinylamine or a mixture of *E* and *Z* isomers. The assigned stereochemistry of **13** (liquid at room temperature) was based on the above considerations as well as the probable mode of generation (eq 6).



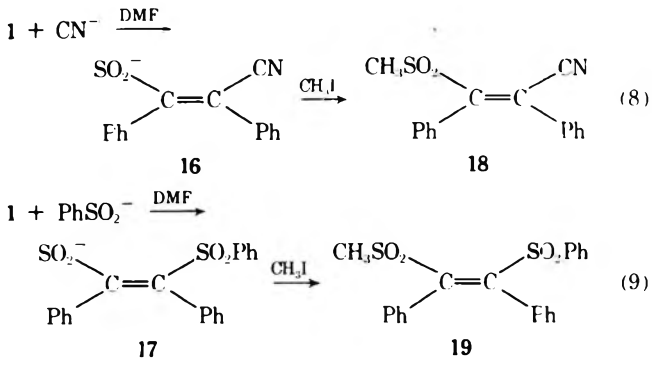
Amines typically add syn to activated olefins[18] and extrusion of sulfur dioxide from episulfones is known to occur with complete retention of configuration.[19]

The reaction of **1** with dimethylamine in benzene gives **13** in high yield accompanied by a small amount of the salt **11**, which presumably arises because of a small amount of water present. The ratio of **13:11** varies with amine concentration (see Experimental Section). A plot of log [**13**]/[**11**] vs. log [$(CH_3)_2NH$] for the reaction of **1** with dimethylamine in benzene gives a straight line (r = 0.994) whose slope is 1.05. This result indicates that in the reaction leading to **13**, the order of the reaction with respect to dimethylamine is one order higher than for the reaction leading to the salt **11**. Assuming that the reaction leading to **11** is first order in amine,[16] then the reaction leading to **13** is second order in amine, which is typical for the additions of amines to olefins in aprotic solvents.[3,4,18] The mechanism below is consistent with the above results and the observed syn addition of dimethylamine to **1**.[20]



At this point it appeared that anions such as alkoxide,[16] hydroxide,[16] and hydride[2a] ions and Grignard reagents[2a] attack the central sulfur atom, whereas neutral nucleophiles such as amines, phosphines, hydroxylamine,[2a] and hydrazine[2a] attacked exclusively the carbon–carbon double bond in the ring of **1**. However, cyanide and benzenesulfinate ions reacted with **1** in DMF to give the vinylsulfinates **16** and **17**, respectively; the sulfinates **16** and **17** were trapped with methyl iodide and isolated as their respective methyl sulfones, **18** and **19** (eq 8 and 9).

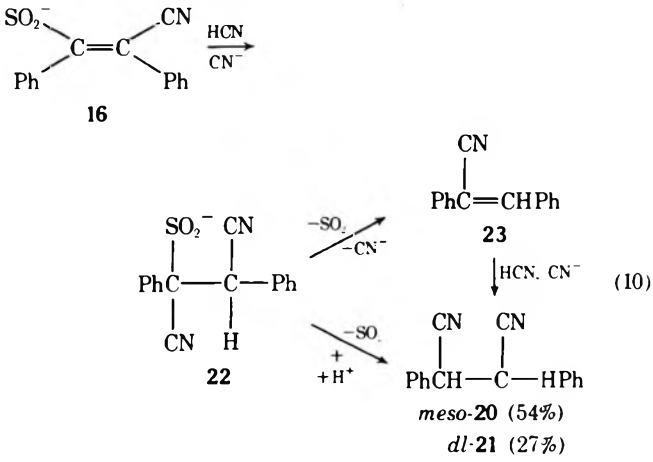
If reaction 8 is run in the presence of excess cyanide ion (ratio of CN^-:**1** of ca. 10:1) a high yield of *meso*- and *dl*-1,2-diphenyl-1,2-dicyanoethane (**20** and **21**) is obtained.[21]



(8)

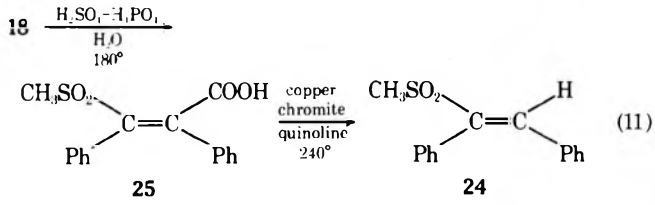
(9)

Under these reaction conditions, α-cyanostilbene (**23**) reacts with excess sodium cyanide in DMF to give **20** and **21** in the same ratio as found above. Although these reactions were run in dry DMF, there no doubt is a small amount of adventitious water present so that hydrogen cyanide could add to **16**. The resulting sulfinate **22** would undergo easily desulfination[22] to give **23** or **20** and **21**, directly (both **20** and **21** are epimerized by sodium cyanide in DMF to a 2:1 mixture of **20**:**21**).



(10)

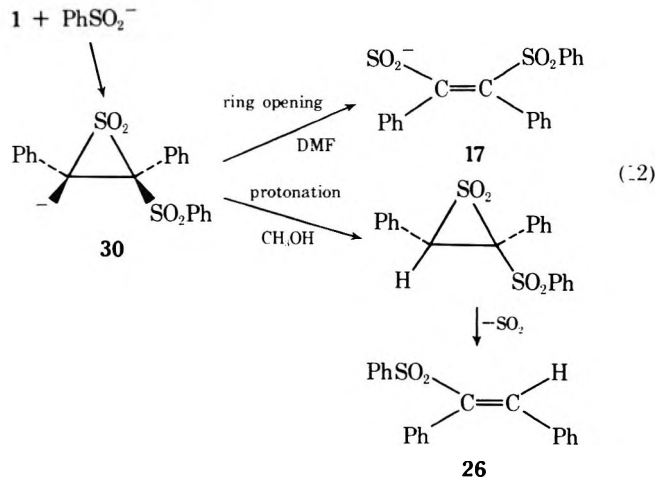
The stereochemical assignment for the vinyl sulfones **18** and **19** rests mainly on the mechanism of their formation; **18** was converted (eq 11) to **24**,[23] a compound which ap-



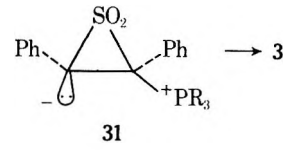
(11)

pears to have been reported earlier but assigned the *Z* configuration.[27]

The reaction of **1** with sodium benzenesulfinate follows a course dependent upon the solvent; in DMF, **17** is formed, but in methanol, **26** is formed (eq 12).[28] Proton transfers to carbanions are fast but well below diffusion controlled.[31] However, electrocyclic ring opening of carbanion **30** apparently is unable to effectively compete with protonation in methanol solvent.[32] The stereochemistry of these electrocyclic ring openings (e.g., **30** → **17**) appears to be governed by the principle of least motion.[33] Although one could argue that the configurationally more stable olefin **17** was the result of steric control, based on a steric argument (*Z*)-**16** should be less stable than its *E* isomer, and yet **16** is the observed product. The stereochemistry of the reactions of phosphines with **1** to give the betaines **3** could be the result either of the strong attraction of the incipient sulfonyl–phosphonium ion sites or of the ring opening of the intermediate betaine **31** accompanied with the least amount of motion of the atoms involved.



(12)



Conclusions

Unlike α,β-unsaturated ketones where nucleophiles add across both the carbon–carbon and carbon–oxygen double bonds, α,β-unsaturated sulfones normally react with nucleophiles to give only addition across the carbon–carbon double bond; the sulfonyl group is attacked by nucleophiles only with difficulty.[34] With α,β-unsaturated ketones, the more highly basic nucleophiles attack the carbonyl carbon while the less basic nucleophiles attack the β-carbon atom.[4b] This also seems to apply to the reactions of **1** with nucleophiles, since the strongly basic nucleophiles attack the sulfonyl sulfur atom while the less basic nucleophiles[35] prefer to attack the unsaturated carbon atoms of the ring.

Experimental Section

Melting points were taken on Fisher-Johns and Mel-Temp apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian Associates A-60D and Varian Associates EM 360 NMR spectrometers operating at ambient temperature. All spectra were taken in carbon tetrachloride or deuteriochloroform with tetramethylsilane (δ 0.00) as an internal standard unless otherwise specified. The ir spectra were taken on a Beckman IR-8 infrared spectrometer as solutions in carbon tetrachloride or as KBr pellets. The Raman spectrum of **18** was recorded on an instrument with a Coherent Radiation Laboratories Argon Ion Laser Model 52, Spec 1401 double spectrometer and EMI 9286-SR photomultiplier tube. The blue line 4880 Å was used. High-pressure liquid chromatography was performed on a Du Pont instrument 830 with a 4-ft analytical Permaphase octadecyl silane (ODS) column at ambient temperature. DMF was distilled once over phosphorus pentoxide in vacuo. Oxygen-free benzene was obtained by passing dry nitrogen through benzene for 15 min before use. Mass spectra were run by Dr. Martha Gay and elemental analyses were performed by Dr. Franz Kasler of the University of Maryland.

The details for the synthesis of the betaines **3**, **6**, **7**, **8**, and **9** and their physical properties are reported elsewhere.[6]

Reaction of 1 with Dimethylamine in Methanol. To a solution of 1.00 g (4.13 mmol) of the thiirene **1** in 150 ml of methanol at room temperature was added ca. 2 ml of dimethylamine. After 10 min, the solvent was removed in vacuo. Recrystallization of the solid residue from dichloromethane–hexane–ether gave 825 mg (65%) of **11**: mp 153°; MS *m/e* 260 [$M^+ - (CH_3)_2NH$]; ir (KBr) 3500 (N–H), 1200 and 1040 cm^{-1} (SO_3^-); ^{1}H NMR ($CDCl_3$) δ 2.4 (t, 6 H), 7.1–7.4 (m, 10 H), 7.6 (s, 1 H), 8.0–8.6 (m, 2 H).

Elemental analysis for **11** was unsatisfactory because the compound proved to be too hygroscopic.

Reaction of 1 with Dimethylamine in Benzene. To a solution

of 1.00 g (4.13 mmol) of 1 in 50 ml of distilled benzene was added 5 ml of dimethylamine. After 5 min, the solvent was removed in vacuo. The resulting yellow oil was put into a 10-ml round-bottom flask. Evaporative distillation (Kugelrohr apparatus, pot temperature 150°, 1 mmHg) gave 775 mg (84%) of (*E*)-1,2-diphenyl-1-*N*,*N*-dimethylaminoethene (**13**)[17] as a viscous yellow oil: ir (neat) 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 2.70 (s, 6 H), 5.52 (s, 1 H), 6.65–7.1 (m, 5 H), and 7.3 (s, 5 H).

Hydrolysis of 13. To a 10-ml beaker with 200 mg (0.89 mmol) of the enamine **13** was added 2 ml of 6 *M* HCl. A white precipitate of 150 mg (86%) of deoxybenzoin was isolated, mp 59° (lit.[36] 60°). Identification was made by ^1H NMR, ir spectroscopy, and mixture melting point.

Preparation of (*E*)-1,2-Diphenylvinylsulfonyl Chloride. To a solution of 1.00 g (3.31 mmol) of **11** in 30 ml of Spectrograde chloroform was added 2.00 g (9.59 mmol) of phosphorus pentachloride. After stirring at room temperature for 3 hr, the solution was washed twice with 30 ml of saturated sodium bicarbonate solution, followed by 30 ml of water. The solvent was dried ($MgSO_4$) and removed in vacuo. Crystallization from methylene chloride–hexane gave 470 mg (49%) of the sulfonyl chloride: mp 130°; ir (CCl_4) 1630 (C=C), 1380 and 1175 cm^{-1} (SO_2); ^1H NMR ($DCCl_3$) δ 8.0 (s, 1 H), 7.6 (s, 5 H), and 7.1–7.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.32; H, 3.98. Found: C, 60.18; H, 4.14.

Preparation of *N*,*N*-Dimethyl-(*E*)-1,2-diphenylvinylsulfonamide (14). To a solution of 300 mg (1.08 mmol) of (*E*)-1,2-diphenylvinylsulfonyl chloride in 50 ml of dry benzene was added 0.3 ml of dimethylamine. The solution was held at reflux for 10 min. The solvent was removed in vacuo. Crystallization from ethanol–water gave 150 mg (47%) of the sulfonamide **14**: mp 153°; ir (CCl_4) 1620 (C=C), 1340 and 1150 cm^{-1} (SO_2); ^1H NMR ($DCCl_3$) δ 2.7 (s, 6 H), 7.1–7.4 (m, 5 H), 7.5 (s, 5 H), and 7.75 (s, 1 H); MS M^+ 287, 179 (PhC=CHPh), and 178 (PhC:CPh).

Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96. Found: C, 66.57; H, 6.20.

Hydrolysis of Methyl (*E*)-1,2-Diphenylvinylsulfonate (15) To a solution of 50 mg (0.18 mmol) of the sulfonate **15**[16b] in 20 ml of Spectrograde methanol was added ~0.5 ml of dimethylamine. The reaction was followed by TLC (silica gel–100% CH_2Cl_2) and was complete in about 1 hr. The solvent was removed in vacuo. Crystallization from methanol–ether gave a white precipitate of dimethylammonium (*E*)-1,2-diphenylvinylsulfonate (**11**), 45 mg (82%). Identification was made by comparison with the authentic sample.

Preparation of *p*-Toluidinium (*E*)-1,2-Diphenylvinylsulfonate. To a solution of 200 mg (0.66 mmol) of the sulfonate **11** in 5 ml of water was added to 1 ml of 6 *M* HCl followed by 100 mg (0.93 mmol) of *p*-toluidine in 5 ml of 6 *M* HCl. A precipitate formed instantaneously. After cooling in an ice bath, the precipitate was collected. Decolorization with neutral Norit and recrystallization from water gave 110 mg (45%) of the salt, mp 196° (lit.[15] 198°).

Qualitative Study of the Reaction of 2,3-Diphenylthiirene 1,1-Dioxide with Dimethylamine with and without Dimethylammonium Chloride. To a vial with ca. 5 mg of 2,3-diphenylthiirene 1,1-dioxide, ca. 5 mg of naphthalene, and 100 mg of dimethylammonium chloride in 1 ml of methanol was added 1 drop of dimethylamine. The reaction was followed by TLC (silica gel–100% methylene chloride) and was complete in about 10 min, at which time 10 drops of 6 *M* HCl was added. This reaction was repeated in the absence of dimethylammonium chloride. The reaction mixtures were analyzed by liquid chromatography (4-ft Permaphase ODS column, 60:40 methanol–water, room temperature, 1000 psi). The products were the ammonium sulfonate **11**, deoxybenzoin, and diphenylacetylene. Deoxybenzoin was isolated from a preparative scale reaction and identified by ir and ^1H NMR spectra and by comparison with an authentic sample. No sulfonamide **14** was detected. Retention times for ammonium sulfonate **11**, deoxybenzoin, sulfonamide **14**, and diphenylacetylene were 2.4, 13.2, 19.6, and 27.8 min, respectively (4-ft Permaphase ODS column, 30:70 methanol–water, room temperature, 1000 psi). The ratio of sulfonate **11**:deoxybenzoin:diphenylacetylene was 1:8:1 in the presence of dimethylammonium chloride but the ratio was 8:1:1 in the absence of dimethylammonium chloride.

Product Ratio Study of the Reaction of Dimethylamine with 1 in Benzene. Twenty milligrams of **1** was put into a 10-ml volumetric flask and dry benzene was added to the mark. A 50-ml volumetric flask with ca. 40 ml of dry benzene was weighed. Anhydrous dimethylamine was added and the weight of dimethylamine was obtained by difference in weight. Dry benzene was added to the mark. The amine solution was transferred to pipette into other volumetric flasks and diluted to the desired concentration. To a vial with 1 ml of **1** solution was added 1 ml of a standard amine solution at room temperature, and the course of the reaction was followed by TLC. After the reaction was complete, the benzene was removed by a steady stream of nitrogen, and methanol was added. The product ratio was analyzed by liquid chromatography (4-ft ODS column, 1000 lb, methanol–water, 40:60) with naphthalene as standard. No significant amount of diphenylacetylene was detected. The results of this experiment are given in Table I.

Table I
Product Ratio of the Reaction of 1 with Dimethylamine in Benzene

[Me_2NH], *M*	[Vinylamine **13**]/[sulfonate **11**]	[Me_2NH], *M*	[Vinylamine **13**]/[sulfonate **11**]
3.45	74.9	0.63	15.0
1.78	35.0	0.45	8.6
1.25	29.8	0.31	5.9
0.89	15.7	0.16	2.9

Reaction of 2,3-Diphenylthiirene 1,1-Dioxide (1) with Sodium Cyanide in DMF. To a solution of 1.00 g (4.13 mmol) of **1** in 10 ml of dry DMF was added in one portion, at room temperature, 215 mg (4.15 mmol) of sodium cyanide in 5 ml of dry DMF. A yellow color appeared immediately. After 10 hr, 1.0 ml of methyl iodide was added. After 3 hr, water was added carefully, and the resulting white precipitate was collected. Recrystallization from dichloromethane–hexane gave 750 mg (65%) of (*Z*)-1,2-diphenyl-2-cyanovinyl methyl sulfone (**18**): mp 161°; ir (KBr) 2940 (CH_3), 1315 and 1140 cm^{-1} (SO_2); Raman 2238 cm^{-1} (C≡N);[37] ^1H NMR ($CDCl_3$) δ 2.9 (s, 3 H) and 7.1–7.3 (m, 10 H); MS (70 eV) 283 (M^+) and 220 [$M^+ - (CH_3SO_2)$].

Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94. Found: C, 67.48; H, 4.63; N, 4.65.

Reaction of 1 with Excess Sodium Cyanide in DMF. A solution of 250 mg (1.08 mmol) of **1** and 500 mg (10 mmol) of sodium cyanide in 8 ml of DMF stood at ambient temperature for 15 hr. The solution was poured into 50 ml of water and extracted with three 30-ml portions of ether. A crystalline solid which was both water and ether insoluble was collected by filtration to give 130 mg (54%) of *meso*-1,2-dicyano-1,2-diphenylethane, mp 236–237° (lit.[38] 236–237°). The ether extracts were combined, and the ether was removed by rotary evaporation. The resulting material was chromatographed over 10 g of silica gel packed in hexane. Elution with 5% benzene in hexane gave 6 mg (3%) of diphenylacetylene. Elution with 20% ether in hexane gave 65 mg (27%) of (±)-1,2-dicyano-1,2-diphenylethane, mp 162–164° (lit.[38] 163–164°).

When α-cyanostilbene[38] was treated with sodium cyanide under the above conditions, an almost quantitative yield of *meso*- and (±)-1,2-dicyano-1,2-diphenylethane (2:1 ratio) was obtained. Treatment of either the meso or racemic diastereomer under the above conditions led to the same 2:1 mixture of diastereomers.

Acid Hydrolysis of 18. In a round-bottom flask containing 300 mg (1.06 mmol) of the sulfone **18** was added 4 ml of 85% phosphoric acid and 1 ml of 75% sulfuric acid. After being heated to 180° for 2 hr, the solution was cooled and ice water added carefully. The white crystals were collected and recrystallized from dichloromethane–hexane to yield 268 mg (86%) of (*Z*)-2,3-diphenyl-3-methylsulfonylacrylic acid (**25**): mp 198°; ir (KBr) 3500–2300 (OH), 1700 (C=O), 1320 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.9 (s, 3 H), 7.25–7.45 (m, 10 H), and 8.35 (s, 1 H).

Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.72; H, 4.82.

Decarboxylation of 25. One milliliter of quinoline was added to a small test tube containing 100 mg (0.34 mmol) of the acid **25** and 20 mg of copper chromite catalyst. The test tube was heated to about 50° and evacuated with a vacuum pump for about 10 min to remove moisture. The tube was heated to 240° for 15 min. To the cooled yellow solution, 20 ml of ether was added, and the catalyst was removed by filtration. Quinoline was removed by extraction with two 10-ml portions of dilute hydrochloric acid, followed by 10 ml of saturated sodium chloride solution. After being dried ($MgSO_4$), the ether was removed in vacuo. Crystallization from carbon tetrachloride–hexane gave 57 mg (44%) of (*E*)-1,2-diphenylvinyl methyl sulfone (**24**): mp 117°; ir (KBr) 1320 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 2.8 (s, 3 H), 7.0–7.2 (m, 5 H), 7.45 (s, 5 H), and 7.82 (s, 1 H).

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.47. Found: C, 69.81; H, 5.44.

Reaction of 1 with Sodium Benzenesulfinate in Methanol. One gram (4.13 mmol) of 1 was dissolved in 150 ml of Spectrograde methanol. Five grams (30.1 mmol) of sodium benzenesulfinate in 30 ml of methanol was added. After 4 days, the precipitate that had formed was collected to give 900 mg (68%) of (*E*)-1,2-diphenylvinyl phenyl sulfone (**26**), mp 182° (lit.[28] 182–183°).

Preparation of *threo*-2-Thiophenoxy-1,2-diphenyl-1-chloroethane. To a warm solution of 10 g (55 mmol) of *cis*-stilbene in 150 ml of glacial acetic acid was added rapidly 8 g (55 mmol) of phenylsulfenyl chloride.[39] After 5 min. the solution was poured over crushed ice. The aqueous solution was extracted twice with 150-ml portions of dichloromethane. The organic solution was washed with water and saturated $NaHCO_3$ followed by water. It was dried ($MgSO_4$) and the solvent was removed in vacuo. Crystallization from pentane–petroleum ether (bp 38–49°) gave 12.4 g (69%) of the sulfide: mp 47–49°; ^1H NMR ($CDCl_3$) δ 4.83 (d, J_{AB} = 7 Hz, 1 H), 5.40 (d, J_{AB} = 7 Hz, 1 H), and 7.1–7.5 (m, 15 H).

Anal. Calcd for $C_{20}H_{17}ClS$: C, 73.94; H, 5.28. Found: C, 74.20; H, 5.50.

Preparation of (*Z*)-1,2-Diphenylvinyl Phenyl Sulfone (27). To a solution of 1.0 g (3.1 mmol) of threo sulfide in 20 ml of Me_2SO was added 0.40 g (3.6 mmol) of potassium *tert*-butoxide in 10 ml of Me_2SO. The mixture was stirred at room temperature overnight, poured into 200 ml of ice water, and extracted twice by 50-ml portions of ether. The ether solution was dried ($MgSO_4$), and the solvent was removed in vacuo. Seventy milliliters of dichloromethane was added, followed by 2.0 g (ca. 10 mmol) of *m*-chloroperoxybenzoic acid (MCPBA). After standing for 3 hr at room temperature, the organic solution was washed twice with saturated sodium carbonate and once with water and dried ($MgSO_4$). The solvent was removed in vacuo. Crystallization from dichloromethane–hexane gave 700 mg (71%) of **27**, mp 131° (lit.[28] 133–134°). When the reaction was run in which the Me_2SO solution was warmed on a steam bath for 30 min and the resulting vinyl sulfide was oxidized with 30% hydrogen peroxide in acetic acid at 80° for 1 min, or with MCPBA in dichloromethane at room temperature for 5 hr, only sulfone **26** was isolated. However, when this reaction was run in which the Me_2SO solution was at room temperature overnight and the resulting vinyl sulfide was oxidized with 30% hydrogen peroxide in acetic acid at 80° for 1 min, **27** was isolated.

Isomerization of (*Z*)-1,2-Diphenylvinyl Phenyl Sulfone (27) to (*E*)-1,2-Diphenylvinyl Phenyl Sulfone (26). In a 50-ml flask containing 10 ml of ethanol was dissolved 100 mg (0.31 mmol) of **27**. The solution was treated with 5 ml of 0.2 *M* ethanolic sodium hydroxide and heated at reflux overnight. The solution was allowed to cool and water was added carefully. The crystals were collected and recrystallization from dichloromethane–hexane gave 40 mg (40%) of crystals, mp 180°. The infrared and ^1H NMR spectra were identical with those of **26**.

Preparation of (*Z*)-1,2-Diphenyl-2-methylsulfonylvinyl Phenyl Sulfone (19). To a solution of 220 mg (1.34 mmol) of sodium benzenesulfinate in 15 ml of dry DMF was added 300 mg (1.24 mmol) of 1. The solution turned yellow. The reaction was followed by TLC (silica gel–100% CH_2Cl_2), and was completed in about 30 min. One milliliter of methyl iodide was added, and the solution was heated at 40° for 1 hr. Water was added, and the solution was extracted three times with 20-ml portions of dichloromethane. The organic solution was dried ($MgSO_4$) and decolorized, and the solvent removed in vacuo. Crystallization from dichloromethane–hexane gave 150 mg (30%) of **19**: mp 172–173°; ir (KBr) 1310 and 1145 cm^{-1} (SO_2); ^1H NMR ($DCCl_3$) 3.37 (s, 3 H), 6.7–7.9 (m, 15 H).

Anal. Calcd for $C_{21}H_{18}O_4S_2$: C, 63.29; H, 4.56. Found: C, 63.35; H, 4.57.

X-Ray Analysis. Recrystallization of diphenylmethyl-(*Z*)-1,2-diphenylvinylsulfinophosphonium betaine (**3d**) from methanol–isopropyl ether gave suitable crystals for an X-ray diffraction analysis. The Laue symmetry, systematic absences, and rough values of the lattice constants were obtained from oscillation and Weissenberg X-ray photographs taken with Cu radiation. The final cell parameter and all intensity measurements were made with monochromatic Mo radiation (by diffraction from a highly oriented graphite crystal, $K\alpha\lambda$ = 0.71069 Å on a Picker FACS-I diffractometer). The crystal, a 0.12 × 0.28 × 0.29 mm parallelopiped with all angles approximately 90°, was mounted and aligned to place the [8, 0, −2] parallel to the ϕ axis of the instrument. The cell constants were calculated by the method of least square using 12 Bragg angles determined from manual measurements of $+2\theta$ and -2θ for each reflection; the average of $|2\theta_o - 2\theta_d|$ was 0.002°. The space group is $P2_1/c$, and cell parameters are a = 9.8970 (7), b = 15.822 (2), c = 15.728 (3) Å, β = 116.045 (6)°. The intensity data were measured using θ–2θ scan methods at a rate of 2° min^{-1} over 2θ range computed from 1.45° + 0.369° tan θ; 10-sec background measurements were made at the start and finish of each scan. Three standard reflections were measured every 100 reflections to monitor intensity fluctuations. Metal foil X-ray attenuators were automatically inserted into the diffracted beam to keep the maximum count rate below 15,000 counts sec^{-1}. A total of 4364 data were measured to a 2θ maximum of 50°; 4062 of the data (including 162 systematic absences) were unique; 2777 of the data were more than three standard deviations above background.[40]

The data were reduced and scaled, $|E|$'s were calculated, and the phases for 687 reflections (295+, 282−) were obtained in a straightforward way, using the direct methods program PHASE.[41] An E map computed with these 687 data revealed the 27 C, 2 O, S, and P atoms and a structure factor calculation gave an R index ($R = \Sigma|F_o - F_d|/\Sigma F_o$) of 0.241.

The structure was refined with the method of full matrix least squares, minimizing the function $\Sigma w(F_o - F_c)^2$; unit weights (w = 1) were used initially, but Hughes-type[42] weights ($w = 1$ if $F_o \leq 50$, $w = (50/F_o)^2$ if $F_o > 50$) were applied in the later refinement cycles. A reflection was included in the calculations only in those cases which I_c was greater than $3\sigma(I_o)$. Hydrogen atoms were located in a different map. The last stages of refinement used anisotropic temperature factors for C, O, S, and P, isotropic terms for H, and included a correction for isotropic secondary extinction [r^* = 0.0069 (2)[43]]. X-Ray scattering factors: C, O, S, P,[44] H.[45] The final R index was 0.036; the weighted R index [$(\Sigma w(F_o - F_c)^2/\Sigma wF_o^2)^{1/2}$] was 0.037. The atomic parameters and the calculated and observed structure factors are listed in the microfilm supplement.

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Registry No.—**1**, 5162-99-2; **11**, 56437-42-4; **13**, 56437-43-5; **14**, 56437-44-6; **15**, 16003-69-3; **18**, 56437-45-7; **19**, 56437-46-8; **24**, 56437-47-9; **25**, 56437-48-0; **26**, 53105-00-3; **27**, 5533-33-5; dimethylamine, 124-40-3; (*E*)-1,2-diphenylvinylsulfonyl chloride, 56437-49-1; phosphorus pentachloride, 10026-13-8; *p*-toluidine, 106-49-0; dimethylammonium chloride, 506-59-2; sodium cyanide, 143-33-9; *threo*-2-thiophenoxy-1,2-diphenyl-1-chloroethane, 56437-50-4; sodium benzenesulfinate, 873-55-2; *cis*-stilbene, 645-49-8; phenylsulfenyl chloride, 931-59-9.

Supplementary Material Available. A listing of observed and calculated structure factors appears in the 1974 microfilm edition of the Journal of the American Chemical Society following p 8094. Photocopies or microfiche (105 × 148 mm, 24× reduction, negatives) of that supplementary material may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th Street, N.W. Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JACS-74-8087.

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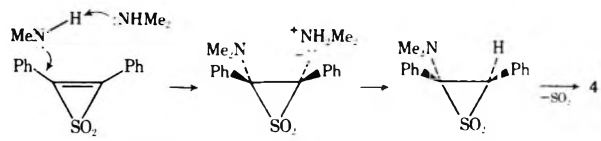
(20) This reaction, **7**, for the sake of economy was represented as a cyclic concerted addition across the carbon–carbon double bond. A similar process was suggested for the addition of amines to *p*-tolyl vinyl sulfone in benzene.[3a] However, reaction **7** could take place stepwise.[4a]



(21) This same result is obtained if excess sodium cyanide in DMF is added to a solution of **16** generated in reaction 8. Treatment of **1** with sodium cyanide in methanol gave the methyl sulfonate **15**, the result of the reaction of **1** with methoxide ion.[16]
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(23) Normally, hydrolysis of the cyano group and decarboxylation of the resulting acid would be expected to take place with no accompanying cis-trans isomerization.[24] However, since the observed product (**24**) is certainly the thermodynamic product,[25] it is possible that the conditions of one or both steps in reaction 11 are sufficient to cause somerization. For example, oxidation (warm peracetic acid) of (*Z*)-1,2-diphenyl-1-benzylthioethene gave a mixture of both (*E*)- and (*Z*)-1,2-diphenyl-1-benzylsulfonylethene.[26]
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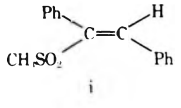
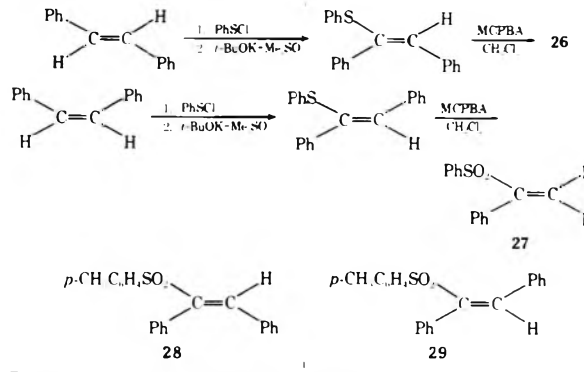
(27) The vinyl sulfone **24**, mp 117°, appears to have been assigned as the *Z* isomer i by earlier workers [M. Oki and A. Kimura, *Bull. Chem. Soc. Jpn.*, **38**, 682 (1965)], based solely on the expected stereochemistry of the base-initiated elimination of hydrogen chloride from *threo*-1-chloro-2-methylthio-1,2-diphenylethane to give (*Z*)-1,2-diphenylvinyl methyl sulfide. This sulfide was oxidized by peracetic acid to a vinyl sulfone, mp 118–119°, which was believed to be i. However, we feel, based on the expected stereochemistry of reactions 8 and 11 as well as the proof of structure for the vinyl sulfone **26**[28] (vide infra), that this sulfone assigned structure i is actually (*E*)-1,2-diphenylvinyl methyl sulfone (**24**).



i

(28) Apparently, sulfone **26** was isolated earlier from the reaction of benzenesulfonyl chloride with phenyllithium but was assigned the *Z* configuration (**27**); an isomeric sulfone said to be **26** was isolated when this reaction was run at low temperature [Y. Shirota, T. Nagai, and N. Tokura, *Tetrahedron*, **23**, 639 (1967)]. Implicit in these assignments was the assumption that (*Z*)-**27** is more stable than (*E*)-**26**. This is certainly not the case, as shown by Cristol and Pappas.[25] We have synthesized stereospecifically sulfones **26** and **27**[29] (see below) and find that with sodium ethoxide in ethanol, **27** is isomerized to **26**.[30] Furthermore, the reported melting point and uv data for the two series of sulfones (**26** and **27** vs. **28** and **29**) are inconsistent; for the *p*-tolyl sulfones (**28** and **29**) the higher melting isomer had a higher λ_{max} and larger ϵ and was assigned the *E* configuration,[25] whereas for the phenyl sulfones **26** and **27**, the higher melting isomer (higher λ_{max} and larger ϵ) was assigned the *Z* configuration by Shirota. The earlier configuration assignments for **26** and **27** should be reversed.



(29) Treatment of *threo*-1-thiophenoxy-2-chloro-1,2-diphenylethane with potassium *tert*-butoxide in dimethyl sulfoxide (Me_2SO) at 25° followed by oxidation with either *m*-chloroperoxybenzoic acid in dichloromethane at 25° (6 hr) or oxidation with hydrogen peroxide in acetic acid at 80° (1 min), gave **27**. However, if the dehydrohalogenation was run in hot Me_2SO (steam bath, 30 min), oxidation led to the vinyl sulfone **26**. Apparently, the strongly basic conditions of potassium *tert*-butoxide in Me_2SO at elevated temperatures is sufficient to cause epimerization of the intermediate vinyl sulfide.
(30) Sodium benzenesulfinate in methanol does not cause the isomerization of **27** to **26**, and therefore sulfone **27** is not involved in the reaction of **1** with sodium benzenesulfinate in methanol.
(31) C. D. Ritchie and R. E. Uschold, *J. Am. Chem. Soc.*, **89**, 2960 (1967).
(32) Although triphenylphosphine does not react with **1** in benzene,[6] it does react in methanol to give at least five products from which a 30% yield of **3**, $R^1 = R^2 = R^3 = Ph$, was isolated. This shows that the electrocyclic ring opening of **31** is at least competitive with protonation by methanol solvent.
(33) O. S. Tee, J. A. Altmann, and K. Yates, *J. Am. Chem. Soc.*, **96**, 3141 (1974), and references cited therein.
(34) R. V. Vizgert, *Russ. Chem. Rev.*, **32**, 1 (1963).
(35) Besides the weakly basic cyanide and benzenesulfinate ions, sulfonium ylides [Y. Hayas, H. Nakamura, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **46**, 667 (1973)] and enamines [M. H. Rosen and G. Bonet, *J. Org. Chem.*, **39**, 3805 (1974)] also give products which appear to arise from initial attack at the ring carbon.
(36) "Handbook of Chemistry and Physics", 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966, p C-388.
(37) The nitrile stretching frequency is nearly undetectable in the ir spectrum (in solid or solution) of **18**.
(38) A. Lapworth and J. A. McRae, *J. Chem. Soc.*, 1699 (1922).
(39) E. Kuhle, *Synthesis*, 561 (1970).
(40) H. L. Ammon, *J. Am. Chem. Soc.*, **95**, 7093 (1973).
(41) All calculations were carried out on a UNIVAC 1108 computer. The crystallographic codes were from J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hull, "The X-Ray System of Crystallographic Programs", TR-192 Computer Science Center, University of Maryland.
(42) E. W. Hughes, *J. Am. Chem. Soc.*, **63**, 1737 (1941).
(43) A. C. Larsen, "Crystallographic Computing", F. R. Ahmed, S. R. Hall, and C. P. Huber, Ed., Munksgaard, Copenhagen, Denmark, 1970, p 291.
(44) D. T. Cramer and J. B. Mann, *Acta Crystallogr., Sect. A*, **24**, 321 (1968).
(45) R. F. Stewart, E. Davidson, and W. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

Revised Structures of Some Tetrahydropyridines Isolated from the Reaction of Pyridine *N*-Oxides with Mercaptans and Acid Anhydrides[1,2]

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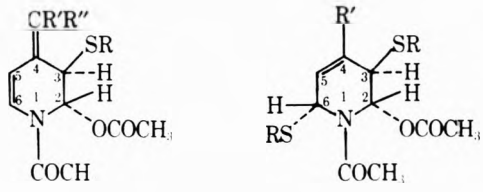
The structures of a number of previously reported tetrahydropyridines were revised. These were established to be 1-acetyl-2-alkylthio-3-hydroxy-4-alkylidene-1,2,3,4-tetrahydropyridines and 1-acetyl-2,6-bis(alkylthio)-3-hydroxy-1,2,3,6-tetrahydropyridines and their corresponding acetoxy derivatives. The change from the published structures involved reversal of the sulfide and oxy functions at C-2 and C-3 in these tetrahydropyridines.

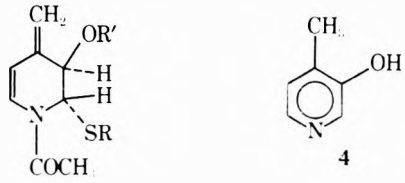
The reaction of pyridine 1-oxides with mercaptans in acetic anhydride afforded a variety of tetrahydropyridyl sulfide esters.[3-5] Two of the most frequently isolated series of tetrahydropyridines were represented by structures **1** and **2**.[5]



1 **2**

New evidence reported in this paper reverses the substituents at C-2 and C-3 in both series and these compounds will then be referred to as shown in **3** and **5**, respectively. Structures based on **3** are discussed first, because their proton magnetic resonance (^{1}H NMR) spectra are considerably less complicated than those of **5**.

The reaction of 4-picoline 1-oxide with *tert*-butyl mercaptan[5] or 1-adamantanethiol (1-AdmSH) in acetic anhydride containing triethylamine provided **3a** [previously formulated as **1**[5] (R = *t*-C_4H_9; R′ = R″ = H)] and **3b**, respectively. Mild alkaline hydrolysis of these esters produced **3c** and **3d**. An analysis of the ^{1}H NMR spectra of these four

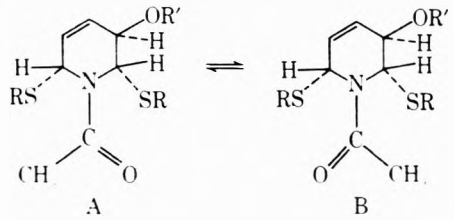


4

3a. R = *t*-C_4H_9; R′ = $COCH_3$
b. R = 1-Adm; R′ = $COCH_3$
c. R = *t*-C_4H_9; R′ = H
d. R = 1-Adm; R′ = H

compounds revealed remarkable similarities. The assignment of chemical shifts for the four ring protons utilized data reported previously.[5] With the assumption that the signal furthest downfield in **3** was due to H-6 and with the aid of a series of decoupling experiments, the chemical shifts of the ring protons were established. Since H-3 was the proton which experienced an upfield shift of about 1 ppm when the esters were converted to the alcohols (–CHOAc → –CHOH), the oxygenated functions in **3** must be attached to C-3. Attempts to obtain ^{1}H NMR spectra of the alcohols, **3c** and **3d**, which would show $J_{H\text{-}3,OH}$, proved unsuccessful.[6] Chemical transformations supported the structure of **3**. Hydrolysis with excess sodium hydroxide converted **3a** or **3c** to a mixture of 4-methyl-3-pyridinol and 2-*tert*-butylthio-4-picoline. Although these data support the structure of **3**, there remains the question of why **3a** pyrolyzed to provide 3-*tert*-butylthio-4-picoline.[5,7a] The mass spectra of the esters or alcohols, **3**, were consistent with their structure. The molecular ion lost the thiyl radical, RS·, followed by losses of ketene, and HO· to produce the molecular ion of 4-picoline, *m/e* 93.

The reaction of a number of pyridine *N*-oxides with *tert*-butyl mercaptan in acetic anhydride without triethylamine produced a series of tetrahydropyridines[3,4] whose structure is represented by **5**. Mild alkaline hydrolysis of these esters



A B

5a. R = *t*-C_4H_9; R′ = $COCH_3$
b. R = *n*-C_4H_9; R′ = $COCH_3$
c. R = 1-Adm; R′ = $COCH_3$
d. R = *t*-C_4H_9; R′ = H
e. R = *n*-C_4H_9; R′ = H
f. R = 1-Adm; R′ = H

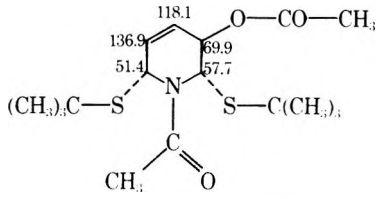
furnished the corresponding alcohols which were also easily reacetylated to the starting esters. The chemical shift of the ring protons of **5a–c** were between 6.6 and 5.8 ppm while in the ^{1}H NMR spectra of the alcohols one of the ring proton signals moved upfield to ~4.5 ppm. This spectral behavior resembled that observed in series **3**.

However, since the ^{1}H NMR spectra of **5** showed rotamers A and B (due to the $NCOCH_3$ group), analyses of these spectra was unduly complicated.[4] By means of an analysis of the 2,6-d_2 analog of **5d**, and a series of decoupling experiments on **5d** and **5f**, it was established that the signal in the 4.5-ppm region arose from H-3. Again, no coupling between H-3 and the OH proton could be observed. In addition, chemical evidence was obtained which supports **5**. Prolonged hydrolysis under alkaline conditions converted **5d** and **5f** to their respective 2-alkylthiopyridines in good yields.[7b]

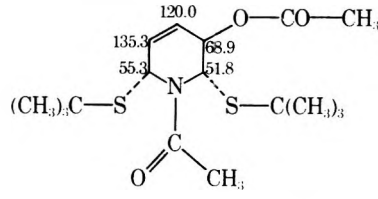
The carbon-13 magnetic resonance (^{13}C NMR) spectra were in accord with structure **5**. Signals due to the various carbons were recorded with the anticipated shifts[8a-f] and those pertinent to the structure proof are discussed only. A full discussion of the ^{13}C NMR spectra of **5a** and **5d** is pre-

Chart I
Carbon-13 Shifts [Parts per Million from $Si(CH_3)_4$] of the Two Rotamers of 5a and 5d

AcCO, 170.4, 167.9
$AcCH_3$, 20.9, 20.9
tert-butyl C, 45.4, 45.4
tert-butyl CH_3, 31.4, 31.4



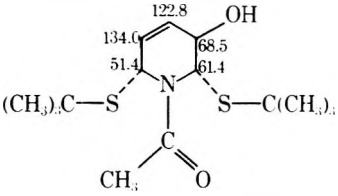
Major rotamer A of **5a**



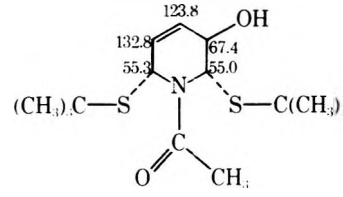
Minor rotamer B of **5a**

AcCO, 170.1, 169.4
$AcCH_3$, 22.4, 21.8
tert-butyl C, 45.3, 45.1
tert-butyl CH_3, 31.9, 31.7

AcCO, 169.3
$AcCH_3$, 22.1
tert-butyl C, 45.0, 45.0
tert-butyl CH_3, 31.4, 31.4



Major rotamer A of **5d**

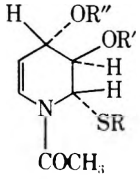


Minor rotamer B of **5d**

AcCO, 170.7
$AcCH_3$, 22.1
tert-butyl C, 45.0, 45.0
tert-butyl CH_3, 31.9, 31.7

sented. From the ^1H NMR spectra, it was determined that rotamer A predominated in $CDCl_3$. Thus, it was possible to sort the duplicate set of ^{13}C resonances to those belonging to A and B of **5a** and **5d**, respectively (Chart I). Chemical shift assignments for the sp^3 ring carbons, C-2 and C-6, was in terms of the anisotropic effect of the amide C=O in rotamer A or B and these are the signals between 51 and 61 ppm. Thus, the signals around 69 ppm arose from the carbinol carbon at C-3 in **5a** and **5d**. The alkene carbon assignments were based on the "β effect" reported for alcohols and their corresponding esters.[8c-f] Briefly, this refers to the relative shifts of the ^{13}C β to the carbinol carbon (which is considered as the α carbon). In system **5**, C-2 and C-4 are "β" carbons, C-5, a "γ" carbon. Thus, in converting the alcohol, **5d**, to the corresponding acetate, **5a**, the "β" carbons exhibited upfield shifts and the "γ" carbons a downfield shift. All other signals in these systems were remarkably constant and are assigned in Chart I.

It was found that[3] the use of *tert*-butyl mercaptan in this deoxidative substitution reaction of pyridine 1-oxide in acetic anhydride produced almost exclusively **5a**. If triethylamine was added to such a reaction mixture, **6a** was isolated as the predominant tetrahydropyridine.[5] However, a



6a, R = *t*-C_4H_9; R′ = R″ = $COCH_3$
b, R = *t*-C_4H_9; R′ = R″ = H
c, R = *n*-C_4H_9; R′ = R″ = $COCH_3$
d, R = *n*-C_4H_9; R′ = H; R″ = $COCH_3$
e, R = 1-Adm; R′ = R″ = $COCH_3$
f, R = 1-Adm; R′ = H; R″ = $COCH_3$
g, R = 1-Adm; R′ = R″ = H

study using two other mercaptans showed that the nature of the tetrahydropyridines could vary. When *n*-butyl mercaptan or 1-adamantanethiol were used in this reaction with pyridine 1-oxide and the temperature of the reaction kept below 80°, products in the **5** series were isolated almost exclusively. However, when the temperature was permitted to rise initially to 110°, these reactions yielded predominantly **6**. The products **6c** had been isolated previously when *n*-butyl mercaptan and triethylamine had been employed.[5] The tetrahydropyridine **6e** had been reported when 1-adamantanethiol had been utilized, with or without triethylamine.[10] In conclusion, it was found that tetrahydropyridines, **5**, were the major products when the temperature was controlled and not permitted to rise initially above 80°.

Experimental Section

Apparati and starting materials used here were described previously.[5] The generous gifts of pyridine and picoline *N*-oxides from Reilly Tar and Chemical Co. and *n*- and *tert*-butyl mercaptans from Phillips Petroleum and the Pennsalt Chemical Co. are gratefully acknowledged. Extreme caution had to be taken in handling *tert*-butyl mercaptan since its odor warns of gas leaks.[5]

1-Adamantanethiol. Considerable difficulty was experienced in recrystallizing and drying this waxy solid. The following modification of the published method[9] provided good yields of pure starting material.

A suspension of *S*-(1-adamantyl)isothiuronium bromide (110 g, 0.36 mol) was stirred for 18 hr at 25° with 5% sodium hydroxide (700 ml) and the mixture then acidified (pH 2) with concentrated hydrochloric acid. The white solid was extracted with benzene (3 × 200 ml) and dried (K_2CO_3), and the benzene removed in vacuo to yield pure thiol (61.5 g, quantitative).

Thin Layer Chromatography. The R_f values were determined on Eastman Chromagram 13181 silica gel sheets with a fluorescent indicator (no. 6060) using the following solvent systems (designated by letters): petroleum ether–ether, 7:3 (A); ether (B).

A. Reaction of 1-Adamantanethiol with Pyridine 1-Oxide. Previous experiments[10] described the isolation of **6e** and **6f**, irrespective of whether or not triethylamine was included in the reaction mixture. It is now reported that with or without triethylamine, that besides **6e** and **6f**, the tetrahydropyridines, **5c** and **5f**, were also isolated. Reexamination of the reaction conditions revealed that the relative proportion of members of the series **5** and **6** depended on the temperatures employed for the reaction. The present work describes the isolation of a number of tetrahydropyridinols. These arose from the hydrolysis of the corresponding acetates during slow chromatographic separations on alumina. The initial crude reaction mixtures contained no tetrahydropyridinols (TLC). The proportion of alcohols to acetates very much depended upon column contact time. Although one of the possible hydroxy acetates, **6f**, was isolated previously from a similar reaction,[10] the corresponding diol (**6g**), whose independent synthesis is described below, was never isolated from a column, even after a prolonged contact time (4 days).

1-Adamantanethiol (18.0 g, 0.1 mol) was added to a solution of distilled pyridine 1-oxide (9.5 g, 0.1 mol) in acetic anhydride (180 ml). The solution was immediately placed in a water bath at 75°, whereupon the temperature rose to 85° for 5 min and then fell to 75°. After an additional 3 hr at 75°, solvents were removed at 20 Torr (water bath 75°). The residue was cooled and stirred at 25° for 1 hr with 100 ml of 50% aqueous potassium carbonate solution to remove acidic by-products and the water-soluble pyridine *N*-oxide. The organic layer was extracted with benzene and dried (K_2CO_3) and the solvent was removed (20 Torr). The oil (25 g) was dissolved in benzene and chromatographed on alumina (Alcoa

F-20, 400 g). The first benzene fractions contained 2- and 3-pyridyl 1-adamantyl sulfides, 1-adamantanethiol, and its acetate.[10] These were not examined further. The later benzene fractions, after evaporation and addition of petroleum ether, yielded pure **5c** (3.0 g): TLC (A) R_f 0.21; mp 196–198°; ^{1}H NMR (C_5D_5N) for rotamer A of **5c**, δ 6.73 (H-2), 5.57 (H-3), ~6.06 (H-4), 6.30 (H-5), 5.57 (H-6) ($J_{2,3}$ = 2.0, $J_{2,4}$ = 1.0, $J_{3,4}$ = 6.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 3.5 Hz); for rotamer B of **5c** δ 5.61 (H-2), 5.45 (H-3), ~6.16 (H-4), 6.25 (H-5), 6.42 (H-6) ($J_{2,3}$ = 2.0, $J_{2,4}$ = 1.0, $J_{3,4}$ = 6.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 3.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 515 (1), 348 (9), 288 (9), 246 (10), 245 (7), 180 (0.5), 168 (2), 135 (100), 93 (16), 79 (23); it is not surprising that the *m/e* 135 ion (1-Adm$^+$) is the base peak in this adamantane derivative.[11] Again, the (M − SR) ion is visible and the loss of acetic acid (348 → 288) is accompanied by a large metastable ion (m*, 238.3). Another prominent m* was observed for the subsequent loss of ketene (288 → 246; m* 210.1). Anal. Calcd for $C_{29}H_{41}NO_3S_2$: C, 67.55; H, 8.01; N, 2.72. Found: C, 67.54; H, 7.99; N, 2.69.

Further elution of this column with chloroform (2 l.) provided a residue which was stirred with petroleum ether to separate **5f** (0.60 g): TLC (B), R_f 0.36; mp 200–201°; ^{1}H NMR (C_5D_5N) for rotamer A of **5f**, δ 6.62 (H-2), 4.69 (H-3), 6.29 (H-4), 6.17 (H-5), 5.64 (H-6) ($J_{2,3}$ = 1.5, $J_{2,4}$ = 1.0, $J_{3,4}$ = 5.2, $J_{4,5}$ = 10.0, $J_{4,6}$ = 1.0, $J_{5,6}$ = 2.5 Hz); rotamer B of **5f** δ 5.54 (H-2), 4.58 (H-3), 6.13 (H-4), 6.11 (H-5), 6.38 (H-6) ($J_{2,3}$ = 1.5, $J_{2,4}$ = 0.5, $J_{3,4}$ = 3.0, $J_{4,5}$ = 10.0, $J_{4,6}$ = 2.0, $J_{5,6}$ = 2.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 473 (2), 306 (22, M − 1-AdmS), 288 (3, M − 1-AdmS − H_2O), 264 (5), 230 (3), 168 (1), 154 (2), 138 (32, M − 1-AdmS − 1-AdmSH), 136 (10), 135 (100), 96 (32), 93 (22), 80 (18), 79 (25). Anal. Calcd for $C_{27}H_{39}NO_2S_2$: C, 68.47; H, 8.30; N, 2.96. Found: C, 68.63; H, 8.19; N, 2.91.

The petroleum ether filtrates from **5f** were evaporated to yield 3-(1-adamantanethio)pyridine (0.61 g), after recrystallization from petroleum ether, TLC (A), R_f 0.44, mp 90.5–91.5° (lit.[10] mp 87–90°). Subsequent chloroform eluates (1 l.) and methanol eluates (0.5 l.) from this original column gave, after crystallization from acetone, pure **6f**[10] (0.5 g), TLC (B), R_f 0.49, mp 191–192° (lit.[10] mp 194–195°).

In order to recover more of compounds of series **5**, the mother liquors of some of the original benzene fractions (those containing **5c**) were rechromatographed on alumina (800 g). Elution with petroleum ether–benzene (1:1, 6 l.) provided first 2-(1-adamantanethio)pyridine (7.4 g), TLC (A), R_f 0.73, mp 82° (lit.[10] mp 82°). Final elution with methanol (0.5 l.) yielded, after crystallization from acetone, pure **5f** (0.80 g).

Based on pyridine 1-oxide, the yield of **5c** was 5.7%, **5f** was 3.0%, and **6f** was 1.4%.

B. Reaction of Pyridine 1-Oxide with *n*-Butyl Mercaptan. The original experiment was conducted in boiling acetic anhydride and no attempt was made to isolate tetrahydropyridines.[12] The success of the present experiment depended on moderating the temperature of the reaction, since it was discovered that these particular tetrahydropyridines were more prone to thermal decomposition than either the *tert*-butyl or the 1-adamantyl analogs. Furthermore, chromatographic separations of the more polar fractions became essential since a large portion of the acetoxy derivatives were hydrolyzed on the alumina to the corresponding polar tetrahydropyridinols.

The thiol (33 ml, 0.33 mol) was added to a stirred solution of distilled pyridine 1-oxide (9.5 g, 0.1 mol) in acetic anhydride (100 ml) at 25°. The temperature rose spontaneously to 80° (5 min) and when the temperature commenced to drop (15 min) the mixture was heated on a steam bath for an additional 1 hr. The mixture was concentrated in vacuo (20 Torr) at a temperature below 75°, then distilled at 0.01 Torr (oil bath ≤60°) to remove pyridyl sulfides and acetates.[12] These distillates were not examined further. Higher oil bath temperatures were avoided to prevent potential pyrolyses of the desired tetrahydropyridines. The residue (25 g) was dissolved in petroleum ether, filtered to remove precipitates, and placed on a column of alumina (Alcoa F-20, 450 g), prepared in petroleum ether. Petroleum ether and benzene eluted primarily 2- and 3-pyridyl sulfides.[12] The first chloroform fraction (1 l.) produced 2.2 g of oil which consisted of a mixture of **5b** (major) [TLC (A), R_f 0.41] with some **5e** [TLC (B), R_f 0.53] with minor quantities of **6c**[5] [TLC (A), R_f 0.29] and the unreported hydroxy acetate, **6d**. This compound was isolated pure from the chloroform fractions of a previously described experiment:[5] TLC (B), R_f 0.59; mp 108–109°; ^{1}H NMR (C_5D_4N) δ 6.42 (H-2), 4.82 (H-3), 5.50 (H-4), 5.40 (H-5), 7.06 (H-6), 7.82 (OH) ($J_{2,3}$ = 2.5, $J_{2,4}$ = 1.2, $J_{2,6}$ ~ 1, $J_{3,4}$ = 1.4, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4.6, $J_{4,6}$ = 1.2, $J_{5,6}$ = 8.2, $J_{3,OH}$ = 4.6 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 287 (6, M$^+$), 96 (100). Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.38; H, 7.44; N, 4.97. Attempts to separate **6d** by crystallization provided impure fractions and this mixture was not rechromatographed further.

Additional chloroform fractions (3.5 l.) provided 3.6 g which consisted primarily of **5e** which contained a trace (TLC) of the hydroxy acetate, **6d**. Additional quantities of pure **5e** (4.1 g) were obtained from chloroform–methanol eluates (95:5, 4 l.).

An analytical sample was recrystallized from ether at −78°, mp 50–52°. The ^{1}H NMR spectrum was unduly complicated because of rotamers. The pattern between δ 6.20 and 5.10 ($CDCl_3$) for four of the five ring protons was identical with that for **5f** in $CDCl_3$ and that for H-3 of A and B was at δ 4.25 and the OH proton δ 4.45 (exchangeable with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 318 (2), 317 (10, M$^+$), 228 (79, M − C_4H_9S), 210 (6), 186 (63), 138 (71, M − C_4H_9S − C_4H_9SH), 113 (11), 96 (100, M − C_4H_9S − C_4H_9SH − CH_2=C=O), 80 (58). Anal. Calcd for $C_{15}H_{27}NO_2S_2$: C, 56.77; H, 8.57; N, 4.41. Found: C, 56.62; H, 8.69; N, 4.38.

The total yield of crude **5b** was estimated to be 6.2% and that of **5e** was 24%, based on pyridine 1-oxide.

C. Reaction of 4-Picoline 1-Oxide with 1-Adamantanethiol in the Presence of Triethylamine. 1-Adamantanethiol (61.5 g, 0.35 mol) was added to a solution of 4-picoline 1-oxide (33.2 g, 0.35 mol) and triethylamine (84 ml, 0.60 mol) in acetic anhydride (400 ml). The reaction was worked up as in procedure A and the residue (114 g) chromatographed over 2 kg of F-20 alumina. The first benzene fractions contained 1-adamantanethiol and its acetate and were not examined further. Further benzene fractions (4 l.) yielded, after crystallization with petroleum ether, pure **3b** (2.5 g): TLC (A), R_f 0.36; mp 126–128°; ^{1}H NMR ($CDCl_3$) δ 6.00 (H-2), 5.40 (H-3), 5.60 (H-5), 6.50 (H-6), 5.22 (H-7, 7′) ($J_{2,3}$ = 2.9, $J_{2,6}$ ~ 1.0, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ ~ 1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 361 (3), 302 (4), 301 (<1), 260 (6), 194 (57), 152 (100), 135 (33), 110 (80), 93 (32), 79 (13). Anal. Calcd for $C_{20}H_{27}NO_3S$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.61; H, 7.66; N, 3.71.

The last benzene fractions (8 l.) gave 3-(1-adamantanethio)-4-picoline (2.0 g), purified by vacuum sublimation (0.01 Torr, 50°): TLC (A), R_f 0.37; mp 70–72°; ^{1}H NMR ($CDCl_3$) δ 8.70 (H-2), 8.45 (H-6), 7.23 (H-5), 2.50 (CH_3), 2.30–1.50 (Adm-H) ($J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 259 (20), 135 (100), 107 (13), 93 (12), 79 (32). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.93; H, 8.27; N, 5.25.

The residues from the chloroform eluates (20 l.) were triturated with petroleum ether and gave **3d** (4.0 g) which was recrystallized from ether (charcoal): TLC (B), R_f 0.44; mp 191–192°; ^{1}H NMR ($CDCl_3$) δ 6.00 (H-2), 4.40 (H-3), 5.65 (H-5), 6.50 (H-6), 5.22 (H-7, 7′), 3.40 (OH) ($J_{2,3}$ = 2.9, $J_{2,6}$ ~ 1.0, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ = 1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 319 (22), 302 (25), 260 (6), 152 (100), 135 (34), 110 (75), 93 (40), 82 (55). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.50; H, 8.02; N, 4.27.

The petroleum ether soluble portion of the residue from the last benzene fractions was rechromatographed over 400 g of F-20 alumina. Petroleum ether–benzene (1:1, 3.5 l.) gave pure 2-(1-adamantanethio)-4-picoline (8.3 g): TLC (A), R_f 0.21; mp 72–73°; ^{1}H NMR ($CDCl_3$) δ 8.35 (H-6), 7.20 (H-3), 6.90 (H-5), 2.25 (CH_3), 2.30–1.60 (Adm-H) ($J_{5,6}$ = 5.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 259 (44), 258 (60), 226 (21), 135 (100), 126 (16), 125 (19), 107 (16), 93 (26), 92 (18), 91 (18), 79 (43). Anal. Calcd for $C_{16}H_{21}NS$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.22; N, 5.17.

The residues from the methanol fraction were recrystallized from petroleum ether to produce more **3d** (1.4 g), mp 189–190°. The yield of **3b** was 2.5 g (2.0%) and the total yield of **3d** was 5.4 g (4.8%), based on 4-picoline 1-oxide.

D. Hydrolysis of Acetates. The ester **5c** (0.30 g, 5.8×10^{-4} mol) was dissolved in warm methanol (50 ml), the solution cooled to 25°, and methanolic sodium hydroxide (0.75 ml, 0.012 g NaOH) added. The solution was concentrated to 20 ml at 25° (20 Torr) and poured onto 50 g of cracked ice. The precipitate was filtered and washed with water to give **5f** (250 mg, 93%), mp 198–200°, identical with the specimen described in procedure A.

A similar hydrolysis of **5a** (1.2 g) gave **5d** (1.01 g, 95%): mp 117–119°; ^{1}H NMR (C_5D_5N) for rotamer A of **5d** δ 6.54 (H-2), 4.61 (H-3), 6.20 (H-4), 6.20 (H-5), 5.56 (H-6) ($J_{2,3}$ = 2.0, $J_{3,4}$ = 3.5 Hz), for rotamer B of **5d** δ 5.46 (H-2), 4.56 (H-3), 6.08 (H-4), 6.08 (H-5), 6.36 (H-6); mass spectrum (70 eV) *m/e* (rel intensity) 317 (5), 260 (2), 228 (44), 210 (1), 186 (11), 172 (10), 138 (47), 130 (23), 113 (11),

112 (9), 96 (100), 80 (33). The major fragments from the molecular ion were successive losses of C_4H_9S, C_4H_9SH, and ketene. Anal. Calcd for $C_{15}H_{27}NO_2S_2$: N, 4.41. Found: N, 4.39.

When the crude reaction mixture from a reaction of pyridine 1-oxide (9.5 g, 0.10 mol), *tert*-butyl mercaptan, and acetic anhydride[3] (after removal of solvents at 20 Torr) was worked up as described under procedure A, it yielded **5a** as expected.[3] However, chromatography (contact time 4 days) over 450 g of F-20 alumina yielded only **5d** (2.2 g, 6.9% based on pyridine 1-oxide), mp 117–119°, as a result of complete hydrolysis of the ester on the column.

Hydrolysis of **5a**-*2,6-d*$_2$[4] (0.18 g) was carried out by refluxing with potassium bicarbonate (0.028 g) in methanol (5.0 ml) for 3 hr. Removal of the solvent (20 Torr) and crystallization of the residue with petroleum ether gave **5d**-*2,6-d*$_2$ (0.062 g, 39%): TLC (B), R_f 0.31; mp 117–118°; ^{1}H NMR (C_5D_5N) for rotamer A of **5d**-*2,6-d*$_2$, δ 4.64 (H-3), 6.20 (H-4), 6.20 (H-5); rotamer B of **5d**-*2,6-d*$_2$, δ 4.56 (H-3), 6.08 (H-4), 6.08 (H-5); mass spectrum (70 eV) *m/e* (rel intensity) 320 (1), 319 (6), 318 (1), 262 (3), 230 (51), 212 (3), 188 (21), 174 (11), 140 (52), 132 (30), 131 (12), 115 (10), 114 (10), 113 (8), 98 (100), 97 (16), 82 (33).

Hydrolysis of **3a** (1.70 g) gave **3c** (after extraction with chloroform, 1.35 g, 93%): mp 137–138°; ^{1}H NMR (C_5D_5N) δ 5.88 (H-2), 4.32 (H-3), 5.59 (H-5), 6.51 (H-6), 5.13, 5.17 (H-7, 7′), 3.40 (OH) ($J_{2,3}$ = 3.0, $J_{2,6}$ = 1.5, $J_{3,5}$ = 1.5, $J_{5,6}$ = 8.0, $J_{5,7}$ = $J_{5,7'}$ ~1.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 242 (6), 241 (30), 224 (9), 182 (4), 152 (100), 110 (90), 109 (15), 93 (21), 92 (15), 82 (70), 80 (27). Anal. Calcd for $C_{12}H_{19}NO_2S$: N, 5.80. Found: 5.77.

A similar hydrolysis of **3b** (0.36 g) gave **3d** (0.32 g, 100%), mp 188–189°, identical with the sample in procedure C.

Hydrolysis of bisacetate **6e** (0.80 g) with $KHCO_3$ (0.24 g) in refluxing methanol gave diol **6g** (0.55 g, 86%): mp 164–165°; TLC (B), R_f 0.25; ^{1}H NMR ($CDCl_3$) δ 5.95 (H-2), 4.36 (H-3), 3.90 (H-4), 5.35 (H-5), 6.70 (H-6), ~3.30 (OH) ($J_{2,3}$ ~ 1.0, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4.5, $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 323 (5), 156 (6), 138 (41), 135 (43), 114 (9), 96 (39), 79 (25), 78 (100). Anal. Calcd for $C_{17}H_{25}NO_3S$: N, 4.33. Found: N, 4.11.

Diol **6g** was similarly obtained by the hydrolysis of the hydroxy acetate **6f**.[10]

Hydrolysis of bisacetate **6a** (2.0 g, 6.1 × 10^{-3} mol) with $KHCO_3$ (0.61 g) in refluxing methanol gave diol **6b** (1.3 g, 86%): TLC (B), R_f 0.23; mp 109–110°; ^{1}H NMR ($CDCl_3$) δ 5.90 (H-2), 4.36 (H-3), 3.90 (H-4), 5.35 (H-5), 6.70 (H-6), ~3.30 (OH) ($J_{2,3}$ = 1.5, $J_{3,5}$ = 1.8, $J_{4,5}$ = 4., $J_{5,6}$ = 8.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 245 (10), 156 (14), 138 (45), 114 (24), 96 (100), 86 (8), 84 (7), 80 (3). Anal. Calcd for $C_{11}H_{19}NO_3S$: N, 5.71. Found: N, 5.58.

E. Acetylation of Alcohols. Alcohol **5f** (2.0 g, 4.2 × 10^{-3} mol) was dissolved in pyridine (10 ml) and acetic anhydride (10 ml) added. After 18 hr at 25°, the mixture was diluted with water (100 ml) and the solid filtered and washed with water to give **5c** (2.1 g, 96%), mp 201–202°.

Alcohol **5e** (1.0 g, 3.2 × 10^{-3} mol) was similarly acetylated. From the ether extract was obtained **5b** (1.1 g, 100%), pure by TLC and ^{1}H NMR. Attempts to distil the oil (0.01 Torr, 50°) resulted in partial decomposition and codistillation of 3-*n*-butylthiopyridine.[5] Crystallization from ether (−78°) gave a white solid: mp ~−20°; TLC (A), R_f 0.41; the ^{1}H NMR ($CDCl_3$) spectrum for the four ring protons is identical with that of **5a** in $CDCl_3$ absorbing as multiplets, δ 6.4–5.7 and 5.5–5.1; mass spectrum (70 eV) *m/e* (rel intensity) 359 (2), 270 (9), 210 (32), 180 (4), 168 (100), 112 (14), 96 (43), 80 (65). Anal. Calcd for $C_{17}H_{29}NO_3S_2$: N, 3.90. Found: N, 3.90.

Similar acetylations of **5d**, **3c**, and **3d** gave **5a** (88%), **3a** (65%), and **3b** (56%), respectively.

Extensive Hydrolysis. A solution of **3a** (1.44 g, 0.004 mol) in methanol (35 ml) containing sodium hydroxide (3.2 g, 0.08 mol) was refluxed for 1 hr. Methanol was removed, and the residue was diluted with water. Extraction with chloroform provided a mixture (0.094 g) which contained a small quantity of 2-*tert*-butylthio-4-picoline[14] (identified by TLC). The basic solution was neutralized with dilute hydrochloric acid and reextracted with chloroform. This extract yielded 4-methyl-3-pyridinol (0.187 g, 43%) which crystallized from benzene–petroleum ether: mp 120–121° (lit.[13] mp 120–121.2°); ^{1}H NMR ($CDCl_3$) δ 11.70 (OH, exchangeable), 8.20, 7.95 (H-2, H-6), 7.15 (H-5), 2.30 (CH_3); mass spectrum *m/e* (rel intensity) 109 (100), 91 (15), 80 (68), 64 (11), 53 (27).

The same products were observed when **3c** was subjected to a similar experiment.

A similar extended hydrolysis on **5d** (0.317 g, 0.001 mol) with 8 ml of 10% methanolic sodium hydroxide (18 hr) yielded, from the basic aqueous layer, 2-*tert*-butylthiopyridine (0.127 g, 76%), identified by TLC (B), R_f 0.77, and ^{1}H NMR spectrum.[14] No pyridinol could be isolated from the aqueous layer after the basic solution had been neutralized.

Extensive hydrolysis of **5f** (0.160 g, 0.005 mol) yielded, on similar work-up, a mixture (0.087 g) of 2-(1-adamantanethio)pyridine,[10] TLC (A), R_f 0.71, and 1-adamantanethiol, TLC (A), R_f 0.56, which was also substantiated by ^{1}H NMR.

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Registry No.—**3a**, 56363-48-5; **3b**, 56363-49-6; **3c**, 56363-50-9; **3d**, 56363-51-0; **5a**, 56363-52-1; **5a**-*2,6-d*$_2$, 56363-53-2; **5b**, 56391-05-0; **5c**, 56363-54-3; **5d**, 56363-55-4; **5d**-*2,6-d*$_2$, 56391-06-1; **5e**, 56363-56-5; **5f**, 56363-57-6; **6a**, 31579-91-6; **6b**, 56363-58-7; **6d**, 56363-59-8; **6e**, 56363-60-1; **6f**, 54851-58-0; **6g**, 56363-61-2; 1-adamantanethiol, 34301-54-7; *S*-(1-adamantyl)isothiuronium bromide, 30771-94-9; sodium hydroxide, 1310-73-2; pyridine 1-oxide, 694-59-7; 3-(1-adamantanethio)pyridine, 54476-12-9; 2-(1-adamantanethio)pyridine, 54476-11-8; *n*-butyl mercaptan, 109-79-5; 4-picoline 1-oxide, 1003-67-4; 3-(1-adamantanethio)-4-picoline, 56363-62-3; 2-(1-adamantanethio)-4-picoline, 56363-63-4; 4-methyl-3-pyridinol, 1121-19-3.

References and Notes

(1) Part XII. The Oxidative Substitution of Pyridine *N*-Oxides.
(2) Support for this work by Research Grant CA-13964 from the National Cancer Institute, NIH, U.S. Public Health Service, is most gratefully acknowledged.
(3) F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 660 (1969).
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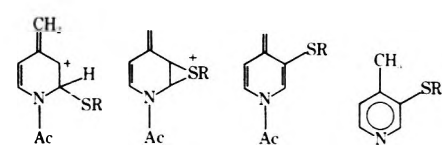
(6) Molecular sieve was heated at 350° for 18 hr, then permitted to cool in a desiccator over P_2O_5. All subsequent operations were conducted in a drybox, over P_2O_5. Me_2SO-d_6 was allowed to stand over the dried molecular sieve for 18 hr and used to prepare the solution for the ^{1}H NMR experiment.
(7) (a) It is suggested that the pyrolysis of **3a** involved migration of the sulfide group. Initial formation of an allylic carbonium ion A, from **3a**, could facilitate migration of the thioether group via B and C to produce the thioether D eventually. (b) It should be noted that the results from this



A B C D

wet method differed considered from prior pyrolyses of these compounds. Part of the reason for the original structure assignment, 1, rested on the pyrolysis of the esters in this series, which afforded 3-alkylthiopyridines (ref 3). Similar pyrolyses of the corresponding alcohols also yielded the 3-pyridyl sulfides. No mechanisms are advanced at present for these transformations.
(8) (a) Carbon-13 spectra in $CDCl_3$ were recorded by means of a Varian Fourier transform XL-100 spectrometer operating at 25.2 MHz, using $(CH_3)_4Si$ as internal standard. (b) ^{13}C resonances exhibited chemical shifts in ranges expected for the diverse carbons in **5a** and **5d**: J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972. (c) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975). (d) H. J. Reich, M. Jautelat, M. T. Messe, J. F. Weigert and J. D. Roberts, *ibid.*, **91**, 7445 (1969). (e) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, *ibid.*, **92**, 1338 (1970). (f) Y. Senda, S. Imaizumi, S. Ochiai, and K. Fujita, *Tetrahedron*, **30**, 539, 3813 (1974).
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Stereochemistry of Amine Additions to Acetylenic Sulfones[1]

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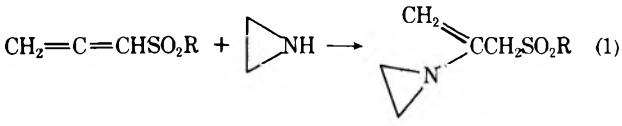
Nucleophilic addition of aziridine to sulfonylacetylenes ($RSO_2C{\equiv}CR'$) in benzene proceeds predominantly in a trans fashion. Increasing the bulk of R′ results in lowering the rate of addition as well as trans stereoselectivity. A weak solvent and temperature effect was observed in the propynyl sulfones. Postisomerization was shown to occur spontaneously during work-up of some of these 1:1 adducts and was also catalyzed by acetic acid, but was inhibited by tertiary amines.

Nucleophilic additions of amines to activated acetylenes have received considerable attention over the past several years, especially with respect to the stereochemistry of the 1:1 adducts. Aziridine has gained prominence as the amine in the recent studies[2-7] because of the reported greater resistance of its adducts to undergo postisomerization under the reaction conditions.

The early workers[4,8] in the field of amine additions to sulfonylacetylenes utilized primary and secondary amines (except aziridine), whose adducts were subject to thermodynamic equilibration under the reaction conditions. The *Z*–*E* isomer ratios for primary amine adducts were found to be solvent dependent, whereas only the *E* isomer was observed with secondary amines. Low-temperature (−25°) studies[4] of diethylamine and *n*-propylamine with *p*-tolylsulfonylacetylene demonstrated that the kinetic product (*Z* isomer) was formed initially, but gradually isomerized to the more stable *E* structure.

Aziridine additions to terminal acetylenic[4] and propynyl sulfones[2,4] appeared to be inconsistent, the terminal acetylenes undergoing ≥95% trans addition in benzene while the propynyl sulfones appeared to be nonstereoselective, giving a mixture of *Z* and *E* isomers, and exhibiting some solvent and temperature dependency. The addition of aziridine to propynyl sulfones was thought to be complicated by the intermediacy of an allene,[4,8a] followed by 1,2 or 2,3 addition; however, this was ruled out when it was found that 1,2 addition predominated in the addition of aziridine to ethylsulfonylpropadiene and *p*-tolylsulfonylpropadiene leading to the nonconjugated adduct[2] (eq 1).



(1)

The proposed mechanism for these additions involves attack by aziridine on the β carbon of the sulfonylacetylene with initial formation of an intramolecularly stabilized

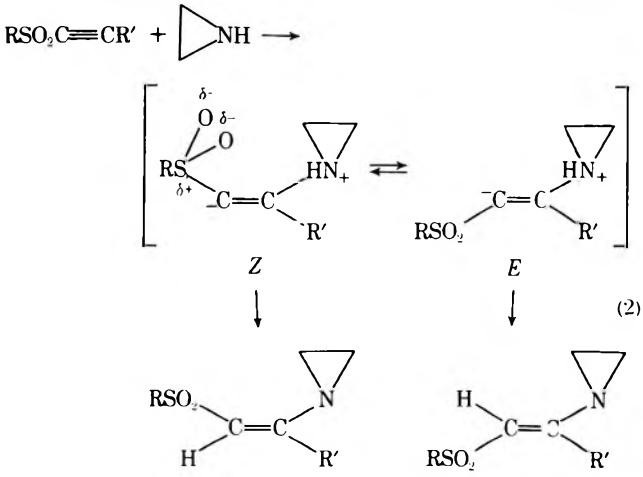


Table I
Reaction of Aziridine with $CH_3C{\equiv}CSO_2C_6H_4R$-*p* in Benzene

R	Temp, °C	Reaction time, hr	Configuration, %[a] Z	E
H	Room temp	4	81	19
CH_3[b]	24–25	4	87	13
OCH_3[c]	24–25	4	78	22
NO_2[c]	24–25	4	83	17

[a] The ratios of *Z* and *E* isomers were determined by NMR analysis of the crude reaction mixture. [b] Under identical conditions ref 2 reports 80% *Z* and 20% *E*. [c] Reference 9.

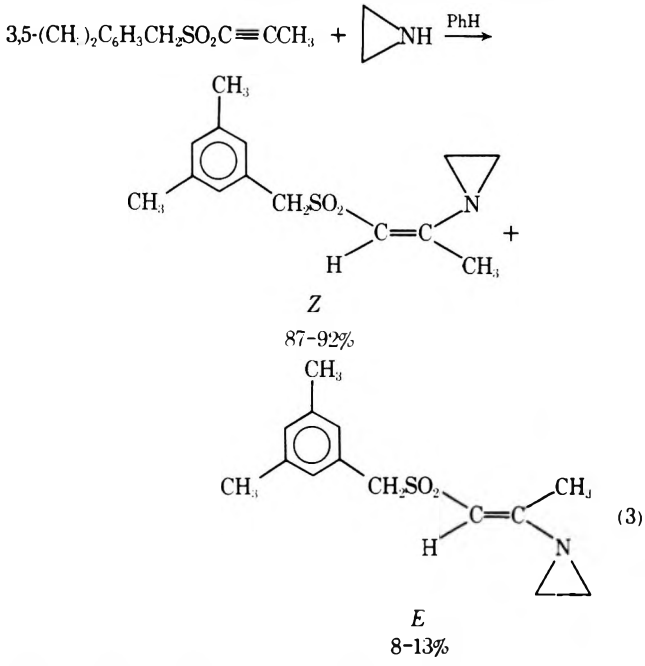
(electrostatic or hydrogen bonded) angular dipolar *Z* intermediate (eq 2). This intermediate can then proceed to the *Z* adduct by protonation (kinetic control) or isomerize to the *E* angular intermediate. Protonation of the *E* intermediate leads to the *E* adduct and thermodynamic control.

A modification of this mechanism was proposed[2] when there appeared to be an effect in the propynyl sulfones on the isomer ratio by an aromatic ring attached to the sulfonyl moiety or contained in an attached chain. This neighboring group participation (π hydrogen bonding of the *Z* aziridinium center to the aromatic nucleus) presumably is operative when attached directly to the sulfonyl moiety or only one carbon removed. However, two arguments may be raised concerning the feasibility of such a π hydrogen bonded intermediate. First, since the reaction is conducted in benzene solvent, it would seem that the π-electron clouds of the numerous solvent molecules would compete favorably for the aziridinium center and might be expected to have a higher electron density than the aromatic ring attached to the electron-withdrawing sulfonyl moiety. A second consideration would be the attractive force of the negative oxygens of the sulfone group toward the positively charged aziridinium center in comparison to that of the π-electron cloud of the aromatic ring.

The influence of electron-withdrawing and -donating substituents on the electron density of the aromatic ring of the sulfone should be reflected in the *Z*–*E* ratio of isomers. In the reaction of aziridine with the variously substituted phenylsulfonylpropynes (Table I) in benzene at ambient temperatures no definite trend was observed; however, it is significant that all gave a preponderance of the *Z* isomer, which arises from trans addition of the aziridine molecule across the acetylenic bond.

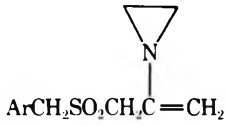
Hydrogen bonding to the π cloud of electrons of an aromatic ring has precedent in the literature,[10,11] as well as the effect of substituents[11] on the strength of the hydrogen bond. It has been shown that increased methyl substitution enhances the capacity of the ring to form a hydrogen bond. As a further test, 1-(3,5-dimethylbenzylsulfonyl)propyne was prepared and treated with aziridine under the reaction

conditions. 1-Benzylsulfonylpropyne had been reported[2] to give a preponderance (72%) of the *Z* isomer so that the dimethyl substituted compound might be expected to give a larger proportion of the *Z* isomer if π hydrogen bonding were involved. In a series of three runs under similar conditions (26–31°, 4–5 hr) the products shown in eq 3 were obtained. The high preference for *Z* isomer is supportive of



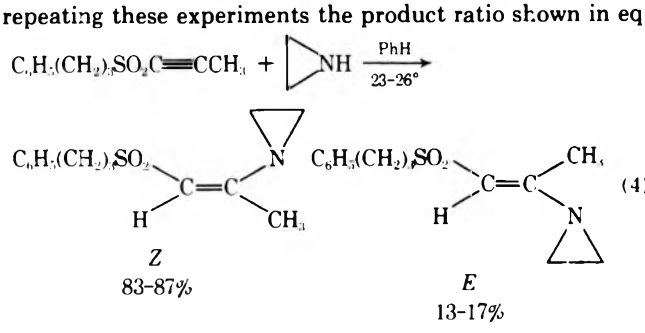
(3)

the postulated π hydrogen bonding phenomenon, but yet does not eliminate the possibility of stabilization of the *Z* intermediate by attractive forces between the sulfonyl oxygens and the aziridinium center. To ascertain that the *Z* isomer was the kinetic isomer in this system the reaction product was isomerized with potassium hydroxide in THF to give an equilibrium mixture containing 5% *Z*, 90% *E*, plus 5% of the nonconjugated isomer



As was the case with the adduct of 1-benzylsulfonylpropyne and aziridine, an upfield shift of the vinyl methyl protons of the *E* isomer was observed in the NMR relative to those of the *Z* isomer in 1-(3,5-dimethylbenzylsulfonyl)-2-aziridinopropene. It has been suggested[2] that this shift is the result of diamagnetic shielding[12] by the aromatic ring of the protons of the methyl group located on the same side of the double bond. The pertinent NMR data are given in Table IV.

An extension of the homologous series $C_6H_5(CH_2)_nSO_2C{\equiv}CCH_3$ to n = 3 could provide information concerning the π hydrogen bonding hypothesis, since, when n = 0, 1, and 2, the percent of *Z* isomer obtained with aziridine in benzene solvent appeared to decrease.[2] However, on repeating these experiments the product ratio shown in eq



(4)

Table II
Reaction of Aziridine with 1-Cyclopentylsulfonylpropyne in Benzene

Run	Temp, °C	Reaction time, hr	Configuration, %[a] Z	E
1[b]	29–31	4	53	47
2[b]	22–24	4	55	45
3[c]	23–24	15 min	85	15
4[b,d]	23–24	4	58	42
5[e]	24–25	2	81	19
6[f]	27–30	4	89	11

[a] The ratios of *Z* and *E* isomers were determined by NMR analysis of the crude reaction mixtures. [b] Normal run procedure: aziridine added to benzene solution of acetylene; solution stirred for specified time; solvent removed in vacuo at room temperature; residue dissolved in $CDCl_3$ for NMR. [c] Reaction carried out in NMR tube. Less than the stoichiometric amount of aziridine added to benzene solution of acetylene. [d] The aziridine was freshly distilled before use. [e] One equivalent of pyridine was added to the reaction mixture before aziridine addition. [f] One-half equivalent of tripropylamine was added after 4 hr, but before work-up.

4 was observed. The *E* isomer was likewise the thermodynamic product in this case. A neighboring group participation by the phenyl ring nine atoms removed seems unlikely in accounting for the preponderance of the *Z* isomer in this reaction; however, stabilization might be afforded by the oxygens of the sulfonyl group.

Another approach to this problem involved the replacement of the aromatic ring by a saturated ring with similar size and steric characteristics, but without the capability to form a π hydrogen bond. For this purpose 1-cyclopentylsulfonylpropyne was prepared and allowed to react with aziridine in benzene under the usual conditions.[2] Two runs under similar conditions provided 53–55% *Z* isomer. This result seemed inconsistent with the preceding data, so successive runs were made to determine if this was the true isomer ratio (Table II). The NMR-monitored reaction was complete in 15 min, but at 27 min elapsed time the ratio had changed slightly to 81% *Z* and 19% *E* adducts while at 43 min the ratio was 65% *Z* and 35% *E*, the *E* isomer increasing at the expense of the *Z* isomer. After standing overnight the ratio had fallen to 39% *Z* and 61% *E* adducts. Obviously, a postisomerization of the initially formed adducts is occurring in this system and likewise occurred in the two initial runs with this acetylene.

Huisgen[13] has noted that catalytic amounts of acid cause rapid isomerization of the amine adducts of methyl propiolate and dimethyl acetylenedicarboxylate. Spontaneous isomerization of these adducts occurred in benzene solution alone at 25°, the rate being very slow; however, when an equimolar amount of triethylamine was added to the solution, the rate of isomerization decreased by a factor of 27 in the case of methyl 3-cyclohexylaminoacrylate. This reduced rate of isomerization was attributed to the scavenging of any free acid in the solution by the triethylamine. Presumably the addition of base in runs 5 and 6 is functioning similarly in this system. The presence of more basic tertiary amines, e.g., triethylamine and tripropylamine, in the reaction mixture initially causes isomerization of the acetylene to the allene.[2,4]

The study of aziridine addition to 1-cyclopentylsulfonylpropyne has demonstrated that postisomerization can occur with aziridine adducts under normal reaction and work-up conditions. An, as yet unidentified, acidic impurity appears to be responsible for this isomerization, since small amounts of tertiary amine decrease the isomerization rate drastically. This postisomerization has not been observed in all systems studied; however, a reexamination of

the previously reported[2] propynyl systems, 1-ethylsulfonylpropyne and 1-(2-phenylethylsulfonyl)propyne, was necessary as well as an in-depth study of other alkylsulfonylpropynes, being alert for postisomerization and factors responsible for it.

The following propynyl sulfones were prepared and treated with aziridine in benzene (with the results recorded in Table III): 1-methylsulfonylpropyne, 1-(2-propylsulfonyl)propyne, 1-(2-methyl-2-propylsulfonyl)propyne, and 1-(2-phenylethylsulfonyl)propyne. In all of the propynyl sulfones studied a high degree of stereoselectivity for formation of the *Z* isomer by trans addition of aziridine was observed. Only with 1-methylsulfonylpropyne was it necessary to utilize a tertiary amine to decrease the postisomerization rate. In the absence of tripropylamine, postisomerization occurred so rapidly under normal reaction and work-up conditions that a ratio of 7% *Z* and 93% *E* adducts was obtained.

As noted in Table III, both 1-ethylsulfonylpropyne and 1-(2-phenylethylsulfonyl)propyne were shown to undergo addition of aziridine to give a preponderance of the *Z* isomer from trans addition. Obviously, the earlier reported[2,4] ratios of isomers for these compounds were those in which postisomerization had already occurred, presumably during work-up, and thus gave an erroneous trend which led to a postulation of a neighboring group participation (π hydrogen bonding) by an aromatic group attached to the sulfonyl moiety. The data in Table III do not support the published trend nor the π hydrogen bonding modification of the proposed mechanism.

Table III
Reaction of Aziridine with $RSO_2C{=}CCH_3$ in Benzene

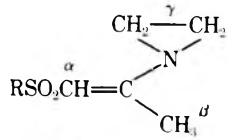
R	Temp, °C	Reaction time, hr	Configuration, %[a] *Z*	*E*
C_6H_5	Room temp	4	81	19
p-$CH_3C_6H_4$	24–25	4	87	13
p-$CH_3OC_6H_4$[b]	24–25	4	78	22
p-$NO_2C_6H_4$[b]	24–25	4	83	17
$C_6H_5CH_2$[c]	28–29	4	72	28
3,5-$(CH_3)_2C_6H_3CH_2$	29–31	4	92	8
$C_6H_5CH_2CH_2$	27–31	4.3	84	16
$C_6H_5CH_2CH_2CH_2$	23–26	4	87	13
CH_3	24–26	2	94	6
CH_3CH_2	23–25	4	96	4
$(CH_3)_2CH$	23–25	4	91	9
	27–30	4	89	11
$(CH_3)_3C$	23–25	4	96	4

[a] The ratios of *Z* and *E* isomers were determined by NMR analysis of the crude reaction mixture. These isomer ratios represent minimal values (greater than or equal to) for the *Z* isomer for this reaction. [b] Reference 9. [c] Reference 2.

Configurational assignments were based on NMR analysis of the reaction mixture and are similar to those previously published[2,4] for these compounds. The pertinent chemical shifts are given in Table IV. A downfield shift of 0.12–0.19 ppm was noted for the vinyl proton of the *E* isomer relative to that of the *Z* isomer which would be consistent with a deshielding of this proton by the electronegative nitrogen of the aziridino group on the same side of the double bond in the *E* isomer. Likewise, a downfield shift of 0.17–0.34 ppm was observed for the aziridino protons in the *Z* isomer relative to those in the *E*, as well as a downfield shift of 0.21–0.37 ppm for the vinyl methyl protons of the *E* isomer relative to those of the *Z* (with the exception of those in the two benzylsulfonyl systems as noted above), both of which can be attributed to a deshielding by the sulfonyl moiety on the same side of the double bond.

Numerous attempts were made to effect a postisomerization under the reaction conditions used with the 1-ethylsulfonylpropyne–aziridine system. Shortening the reaction time to 30 min decreased the *Z* isomer insignificantly (91% on a 70% completion of the reaction). Utilizing a mole ratio of 1.5 (acetylene:aziridine) over 4 hr reaction time caused another decrease to 88% *Z* adduct and 12% *E*. Inverse addition of the acetylene to aziridine gave 91% of the *Z* isomer. Analysis in carbon tetrachloride or $CDCl_3$[14] gave identical isomer ratios of 94–95% *Z* isomer and 5–6% *E* isomer following a 4-hr run period. A slow isomerization was observed when the crude reaction mixtures were allowed to stand in carbon tetrachloride: elapsed time 4 hr, *Z*:*E* ratio 94:6; 72 hr, 70:30; 144 hr, 61:39; 360 hr, 50:50. However, this postisomerization could be effectively reduced to zero by the addition of a small amount of tertiary amine, e.g., no isomerization was noted after 6 days when 10 mol % trieth-

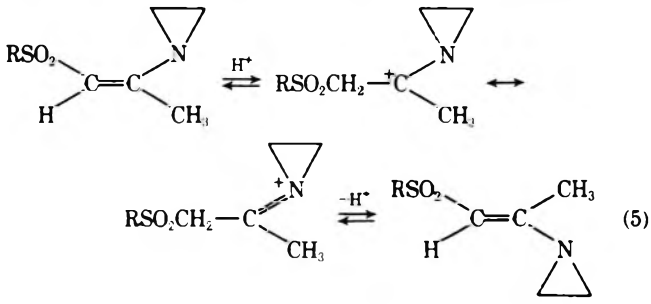
Table IV
NMR Data for



R	Solvent	α[a] *Z*	α[a] *E*	β[a] *Z*	β[a] *E*	γ[a] *Z*	γ[a] *E*
C_6H_5	$CDCl_3$	5.54	5.73	1.87	2.23	2.27	1.98
p-$CH_3C_6H_4$	$CDCl_3$	5.51	5.68	1.85	2.20	2.24	1.95
$C_6H_5CH_2$[b]	$CDCl_3$	5.19	5.38	1.80	1.73	2.15	1.85
3,5-$(CH_3)_2C_6H_3CH_2$	$CDCl_3$	5.25	5.41	1.91	1.86	2.25	1.96
$C_6H_5CH_2CH_2$	$CDCl_3$	5.35	5.47	1.85	2.22	2.25	1.91
$C_6H_5CH_2CH_2CH_2$	$CDCl_3$	5.33	5.49	1.81	2.16	2.15	1.92
CH_3	CCl_4	5.47	5.63	1.92	2.19	2.26	2.02
CH_3CH_2	$CDCl_3$	5.37	5.53	1.90	2.25	2.29	2.05
$(CH_3)_2CH$	$CDCl_3$	5.26	5.39	1.94	2.21	2.23	2.06
	$CDCl_3$	5.38	5.54	1.95	2.26	2.30	2.03
$(CH_3)_3C$	CCl_4	5.20	5.35	1.97	2.18	2.23	2.02

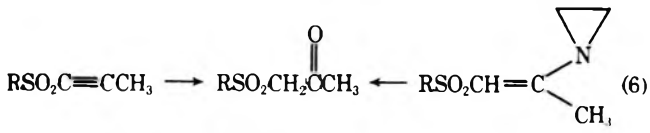
[a] Positions given in parts per million (δ) relative to Me_4Si. The α, β, and γ peaks were all singlets. [b] Reference 2.

ylamine was added to a carbon tetrachloride solution of 94% *Z* and 6% *E* isomers. It was only after the addition of a small amount of acetic acid to one of these reaction mixtures that an exothermic reaction and a reversal in the isomer ratio was noted. Within 5 min the isomer ratio had changed from 93% *Z* and 7% *E* to 8% *Z* and 92% *E* adducts. This rapid isomerization by an organic acid is suggestive of the mode of postisomerization which may be operative in these systems (eq 5). The reaction solvent, the NMR sol-



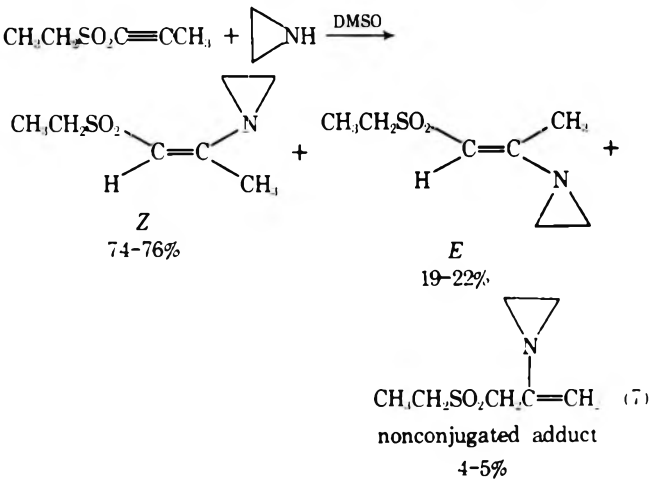
(5)

vent, and aziridine have been eliminated as sources of acidic impurities. One of the remaining suspects is the acetylenic sulfone, which could form the moderately acidic β-keto sulfone[15] through a hydrolysis step. Likewise, a hydrolysis of the adducts (enamines) could lead to the same β-keto sulfones (eq 6).



(6)

A solvent effect has been alluded to earlier in this discussion and reported previously for aziridine additions to acetylenic sulfones,[2,4] acetylenic carboxylic esters,[3,4,5a,6] and nitriles.[3] The reaction of aziridine with 1-*p*-tolylsulfonylpropyne in four different aprotic solvents gave a decreasing amount of stereoselectivity for trans addition with increasing polarity of the solvent,[2] e.g., CCl_4, 81% *Z* isomer; C_6H_6, 80%; Et_2O, 74%; Me_2SO, 68%. Since 1-ethylsulfonylpropyne had been shown to be highly stereoselective toward trans addition (96%) in benzene, it was of interest to study the addition in the polar solvent dimethyl sulfoxide. Analyzing the crude reaction mixture prior to distillation gave the results shown in eq 7. Although this solvent effect is not as



(7)

great as that which was claimed earlier,[16] it is still significant and consistent with the proposed mechanism.[2]

This is the first instance in which the nonconjugated isomer has been observed in the product reaction mixture of aziridine addition to 1-propynyl sulfones. A possible explanation for the appearance of this isomer is that some ethylsulfonylpropadiene[17] is being formed during the reaction with subsequent addition of aziridine. Facile isomerization[2,4,8a,18] of 1-propynyl sulfones to the isomeric allenes is favored under sufficiently basic conditions. The base strength of aziridine in benzene is not sufficient to facilitate this isomerization; however, in the highly polar dimethyl sulfoxide, its base strength may be enhanced to effect such an isomerization.

A temperature effect was found to be operative in the earlier study[2] and was supportive of the mechanism (eq 2). The results indicated below with 1-ethylsulfonylpropyne and 1-*p*-tolylsulfonylpropyne substantiate the temperature effect in nonterminal acetylenes, but also suggest that the effect is considerably less than originally thought. It appears that some postisomerization clouded the picture in the earlier 1-*p*-tolylsulfonylpropyne study[2] (where 31% *Z* isomer was reported at a reaction temperature of 53–54°, in benzene), since under identical conditions, 64% *Z* isomer was observed in the present study. This isomer ratio was confirmed with two subsequent runs in which 10 mol % of a tertiary amine was added to the reaction mixture to retard any postisomerization. A run made with 10% pyridine in benzene at 55–57° showed 65% *Z* and 35% *E* isomers while the run containing 10 mol % 1,8-bis(dimethylamino)-naphthalene[19] at 53–54° gave 72% *Z* and 28% *E* isomers. These results, when compared with the 87% *Z* isomer at 24–25°, reflect an effect of temperature on the reaction.

As with 1-*p*-tolylsulfonylpropyne, the addition of aziridine to 1-ethylsulfonylpropyne at 52–57° in benzene gave a slight decrease in the amount of trans addition compared to addition at 23–24°. A series of five runs gave between 82 and 91% *Z* isomer at the higher temperature compared to 96% at room temperature.

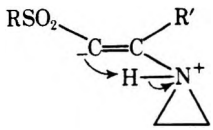
The preceding investigation of the propynyl sulfone system revealed that the alkyl and aryl groups attached to the sulfonyl moiety, as well as the temperature and solvent, had an effect, albeit relatively small, on the course of addition of aziridine to these acetylenes; however, a thorough study of the effect of substituents, R′, on the acetylenic β carbon was lacking ($RSO_2C{\equiv}CR'$). In the addition of *n*-propylamine to $CH_3CH_2SO_2C{\equiv}CR'$, it was shown[4] previously that as the steric bulk of R′ increased, the equilibrium was shifted toward the *Z* adduct, owing to greater steric effects in the *E* isomer. The addition of aziridine to this series where R′ = H,[16] CH_3,[2,4] and CH_2CH_3[2] was reported, but postisomerization appears to have complicated the picture. The results shown in Tables V and VI for the addition of aziridine to $CH_3CH_2SO_2C{\equiv}CR'$ and *p*-$CH_3C_6H_4SO_2C{\equiv}CR'$ in benzene indicated a trend toward nonstereoselectivity as the bulk of R′ increases, but yet the predominance of trans addition was observed throughout (67% or greater). This trend may be explained on the basis of steric retardation of protonation in the *Z* intermediate

Table V
Reaction of Aziridine with $CH_3CH_2SO_2C{\equiv}CR'$ in Benzene

R′	Temp, °C	Reaction time, hr	Configuration, %[a] *Z*	*E*
H[b]	Room temp	4	100	
CH_3	23–24	4	96	4
$CH(CH_3)_2$[c]	26–27	6	76	24
$C(CH_3)_3$[d]	29–32	28	75	25

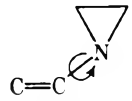
[a] The ratios of *Z* and *E* isomers were determined by NMR analysis of the crude reaction mixture. [b] Reference 16. [c] The reaction was only 83% complete at the end of 4 hr. Analysis was carried out in acetone or carbon tetrachloride since the *Z* and *E* vinyl protons overlapped in $CDCl_3$. [d] The reaction was only 14% complete at the end of 4 hr and 42% complete at 28 hr.

leading to a shift in equilibrium to the *E* intermediate, wherein protonation could occur in a four-center process from the aziridinium group as shown (or via a six-center process involving a second aziridine associated with the first).



The rate of reaction observed for both systems where R′ was *tert*-butyl was significantly diminished (14–17% complete after 4 hr) when compared to the less sterically bulky members in the series (where reaction was complete in 6 hr or less). Longer reaction times, where R′ = *tert*-butyl, improved the extent of reaction with similar isomer ratios being observed. The addition of the sterically larger secondary amine, diethylamine, to 1-(*p*-tolylsulfonyl)-3,3-dimethyl-1-butyne was unsuccessful (no adducts were present even after 38 hr in benzene), thus supporting the evidence that nucleophilic approach to the β carbon of the *tert*-butyl-substituted sulfonylacetylene is severely restricted.

The pertinent NMR data for the adducts in these series are tabulated in Table VII and support the structural assignments. However, it should be noted that the difference ($\Delta\alpha$) in chemical shift between the *Z* and *E* vinyl proton decreases as the steric bulk increases and becomes negative at *tert*-butyl. The greater downfield shift of the *Z* vinyl proton in the *tert*-butyl substituted acetylene adducts may be due to the hindrance by the bulky *tert*-butyl group to free rotation about the sp^2 carbon to nitrogen bond



thus reducing the amount of deshielding by the electronegative nitrogen on the proton in a cis relationship to it. All other shifts in the adducts are consistent with those previously published.[2,4]

Table VI
Reaction of Aziridine with *p*-$CH_3C_6H_4SO_2C{\equiv}CR'$ in Benzene

R′	Temp, °C	Reaction time, hr	Configuration, %[a] *Z*	*E*
H[b]	0, room temp	4	95	5
CH_3	24–25	4	87	13
CH_2CH_3[c]	Room temp	4	76	24
$CH(CH_3)_2$	Room temp	4	73	27
$C(CH_3)_3$[d]	Room temp	4	67	33
C_6H_5	Room temp	4	85	15

[a] The ratios of *Z* and *E* isomers were determined by NMR analysis of the crude reaction mixture. [b] Reference 4. [c] Reference 20. [d] The reaction was only 17% complete after 4 hr. After 52 hr the ratio of isomers remained the same and the reaction was 74% complete.

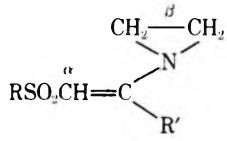
Experimental Section[21]

Materials. Aziridine was obtained from Dow Chemical Co. and stored in the cold over caustic soda pellets. Phenylacetylene, 3-methyl-1-butyne, and 3,3-dimethyl-1-butyne were purchased from Farchan Research Laboratories, methanethiol from Pennsalt Chemical Corp., cyclopentyl mercaptan from Columbia Chemical Co., sodium *p*-toluenesulfinate, propargyl bromide, 2-propanethiol, 2-methyl-2-propanethiol, 3-phenyl-1-propanethiol, and *m*-chloroperbenzoic acid from Aldrich Chemical Co., and ethanesulfonyl chloride from Eastman Chemical Co. Samples of the following chemicals were supplied by the persons indicated of this laboratory: 1-(*p*-tolylthio)propyne, J. Allison; *cis*-1,2-bis-(ethylthio)ethene, L. D. Markley; 1-(*p*-tolylsulfonyl)-3-methyl-1-butyne, G. C. Wolf; and 1-(*p*-tolylsulfonyl)-3,3-dimethyl-1-butyne, G. Tichenor.

Preparation of 3,5-Dimethylbenzyl Bromide (1). *N*-Bromosuccinimide (89 g, 0.5 mol) was added to freshly distilled mesitylene (60 g, 0.5 mol) dissolved in 3300 ml of carbon tetrachloride and refluxed for 2.5 hr under illumination.[35] After cooling, the precipitated succinimide was filtered from the solution and the filtrate concentrated in vacuo and distilled to give 58.56 g (58.9%) of **1**, bp 86° (1.85 mm), mp 39–41° [lit.[22] bp 75–77° (1.5 mm)].

Preparation of 3,5-Dimethylbenzyl Mercaptan (2). Utilizing the established method[23] for alkyl thiol synthesis, a solution of **1** (58.24 g, 0.293 mol) in 165 ml of 95% ethanol was refluxed with thiourea (22.27 g, 0.293 mol) for 4.5 hr and then allowed to cool. After the addition of aqueous sodium hydroxide (17.6 g, 0.44 mol in 150 ml of water) the mixture was again refluxed for 2 hr. The cooled solution formed two layers. The aqueous lower layer was acidified (7 ml of concentrated H_2SO_4 in 50 ml of water) and extracted with benzene. After the organic layer was combined with

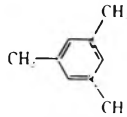
Table VII
NMR Data for



R	R′	Solvent	α[a] *Z*	α[a] *E*	Δα[b]	β[a] *Z*	β[a] *E*	Δβ[c]
p-$CH_3C_6H_4$	H	$CDCl_3$	5.59 (d, J = 8.8 Hz)	5.82 (d, J = 13 Hz)	0.23	2.23	2.00	0.23
	CH_3	$CDCl_3$	5.51	5.68	0.17	2.24	1.95	0.29
	CH_2CH_3[d]	$CDCl_3$	5.54	5.66	0.12	2.23	1.95	0.28
	$CH(CH_3)_2$	$CDCl_3$	5.51	5.55	0.04	2.28	1.97	0.31
	$C(CH_3)_3$	$CDCl_3$	5.63	5.47	−0.16	2.38	2.00	0.38
	C_6H_5	$CDCl_3$	5.92	6.03	0.11	2.35	1.89	0.46
CH_3CH_2	H[e]	$CDCl_3$	5.48 (d, J = 9 Hz)	5.78 (d, J = 13 Hz)	0.30	2.25	2.09	0.16
	CH_3	$CDCl_3$	5.37	5.53	0.16	2.29	2.05	0.24
	CH_2CH_3[e]	$CDCl_3$	5.35	5.47	0.12	2.30	2.05	0.25
	$CH(CH_3)_2$	CCl_4	5.22	5.30	0.08	2.28	2.02	0.26
	$C(CH_3)_3$	$CDCl_3$	5.50	5.34	−0.16	2.45	2.08	0.37

[a] Positions given in parts per million (δ) relative to Me_4Si. The α and β peaks appeared as singlets except for R′ = H, where the α peaks were doublets. [b] Difference in α position, *E*-*Z*. [c] Difference in β position, *Z*-*E*. [d] Reference 20. [e] Reference 16.

Table VIII
Preparation of $HC{\equiv}CCH_2SR$

R	% Yield	Bp, °C (mm)	Reaction time, hr	Note	Compd
CH_3	32.7	108–109.5 (760)	2	*a*	3
$CH(CH_3)_2$	78.4	63–65.5 (49)	Overnight	*b*	4
$C(CH_3)_3$	74	76.8–78 (52)	2	*c*	5
	80.2	124–126 (68)	2	*d*	6
	81.6	128 (2.55)	Overnight	*e*	7
$CH_2CH_2C_6H_5$	79.1	85–88 (0.3)	2	*f*	8
$CH_2CH_2CH_2C_6H_5$	59.1	88–93 (0.2)	2 (reflux)	*g*	9

[a] NMR (CCl_4) δ 2.19 (s, 3 H, CH_3S), 2.33 (t, 1 H, J = 2.7 Hz, $-C{\equiv}CH$), 3.24 (d, 2 H, J = 2.7 Hz, $-SCH_2C{\equiv}C-$). [b] Reference 24. [c] Reference 25. [d] Anal. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62; S, 22.86; mol wt, 140.25. Found: C, 68.41; H, 8.84; S, 22.61; mol wt, 144.6. [e] Anal. Calcd for $C_{12}H_{14}S$: C, 75.74; H, 7.42; S, 16.85; mol wt, 190.31. Found: C, 75.95; H, 7.21; S, 16.95; mol wt, 191 1. [f] Reference 2. [g] Reference 9.

the benzene extracts, the mixture was washed with water, dried over sodium sulfate, concentrated in vacuo and distilled to give 36.02 g (8?%) of **2**: bp 97° (4.15 mm); NMR ($CDCl_3$) δ 1.68 (t, 1 H, J = 7.3 Hz, –SH), 2.26 (s, 6 H, aromatic CH_3), 3.62 (d, 2 H, J = 7.3 Hz, $-CH_2S$), 6.90 (broad singlet, 3 H, aromatic ring protons).

Anal. Calcd for $C_9H_{12}S$: C, 71.00; H, 7.94; S, 21.06; mol wt, 152.26. Found: C, 71.10; H, 7.91; S, 20.76; mol wt, 156.

General Procedure for the Preparation of 3-Propynyl Sulfides.[24] One equivalent each of sodium thiolate and propargyl bromide was combined in methanol and stirred for a specified time. The reaction mixture was diluted with water and extracted with either chloroform or methylene chloride. The extracts were dried ($MgSO_4$) and then distilled to obtain the desired product listed in Table VIII.

General Procedure for the Preparation of 1-Propynyl Sulfides.[8a] The corresponding 3-propynyl sulfides were dissolved in a tetrahydrofuran solution containing excess undissolved potassium hydroxide and stirred until isomerization was complete. The solid was removed by filtration and the filtrate distilled to obtain the 1-propynyl sulfides listed in Table IX.

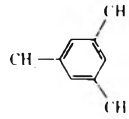
Preparation of 1-(Ethylthio)propyne (18). To a cooled (−46°, Dry Ice–cyclohexane bath) solution of sodium amide (28 08 g, 0.72 mol) in 500 ml of ammonia was added, dropwise, (*Z*)-1,2-bis(ethylthio)ethene (3.28 g, 0.36 mol). After stirring for 6 hr, methyl iodide (102.6 g, 0.72 mol) was added slowly and then the ammonia was allowed to evaporate overnight. Water and diethyl ether (100 ml of each) were added to the residue, the layers separated, and the organic layer dried ($MgSO_4$) and distilled to give 21.14 g (58.7%) of **18**: bp 59.5–61° (48 mm) (lit.[28] bp 134–144°); NMR ($CDCl_3$) δ 1.34 (t, 3 H, J = 7.2 Hz, CH_3CH_2S-), 1.93 (s, 3 H, $-SC{\equiv}CCH_3$), 2.66 (q, 2 H, J = 7.2 Hz, CH_3CH_2S-).

General Procedure for the Preparation of 1-Propynyl Sulfones from Sulfides. Two equivalents of 85% m-chloroperbenzoic acid (MCPBA) in chloroform were added to a chloroform solution of the sulfide (1 equiv) maintained at 0°. After 24 hr, during which time the reaction mixture warmed to room temperature, the precipitated *m*-chlorobenzoic acid was removed. The filtrate was washed with a saturated $NaHCO_3$ solution containing a small amount of Na_2SO_3, dried over $MgSO_4$, and concentrated in vacuo. The 1-propynyl sulfone was purified by either recrystallization if it was a solid or distillation if a liquid. See Table X.

Preparation of 1-Phenylsulfonylpropyne (28). Oxidation was carried out using hydrogen peroxide in glacial acetic acid. To a solution of **17** (10.5 g, 0.071 mol) in 100 ml of glacial acetic acid was added 30% hydrogen peroxide (32.2 g, 0.284 mol). The resulting mixture was heated to reflux for 2 hr and then poured into 500 ml of ice water. The excess peroxide was destroyed with Na_2SO_3. The crude sulfone was collected, dissolved in $CHCl_3$, dried ($MgSO_4$), and concentrated to give 7.2 g; mp 63–70°. Recrystallization from pentane–chloroform afforded 4.87 g (38%) of **28**: mp 70–72° (lit.[31] mp 68.5–69.5°); NMR ($CDCl_3$) δ 2.02 (s, 3 H, $-C{\equiv}CCH_3$), 7.52–7.82 (m, 3 H, aromatic ring protons), 7.88–8.14 (m, 2 H, aromatic ring protons).

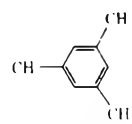
Preparation of Sodium Ethanesulfinate (29). This compound was prepared by alternately adding small portions of ethanesulfonyl chloride (47.5 g, 0.37 mol) and sodium bicarbonate (61.3 g, 0.73 mol) to an aqueous solution of sodium sulfite (92 g, 0.73 mol in 400 ml of H_2O) held at 86°. After an additional 30 min of stirring the

Table IX
Preparation of $CH_3C{\equiv}CSR$

R	% yield	Bp, °C (mm)	Note	Compd
CH_3	75	111 (760)	*a*	10
$CH(CH_3)_2$	83	67–68 (45)	*b*	11
$C(CH_3)_3$	84.8	69 (35)	*c*	12
	69.7	85–87 (12)	*d*	13
	88	100 (0.5)	*e*	14
$CH_2CH_2C_6H_5$	86.8	82.5–83 (0.27)	*f*	15
$CH_2CH_2CH_2C_6H_5$	68	91–93 (0.3)	*g*	16
C_6H_5	70	56.5–58.5 (0.2)	*h*	17

[a] Reference 26. [b] Reference 27. [c] Reference 28. [d] Anal. Calcd for $C_8H_{12}S$: C, 68.51; H, 8.62; S, 22.86; mol wt, 140.25. Found: C, 68.75; H, 8.86; S, 22.66; mol wt, 144.2. [e] Anal. Calcd for $C_{12}H_{14}S$: C, 75.74; H, 7.42; S, 16.85; mol wt, 190.31. Found: C, 75.66; H, 7.12; S, 16.57; mol wt, 188.0. [f] Reference 2. [g] Reference 9. Anal. Calcd for $C_{12}H_{14}S$: C, 75.74; H, 7.42; S, 16.85; mol wt, 190.31. Found: C, 76.02; H, 7.29; S, 16.65; mol wt, 190. [h] Reference 29, 30, and 31.

Table X
Preparation of $CH_3C{\equiv}CSO_2R$

R	% yield	Mp or bp, °C (mm)	Note	Compd
CH_3	57	75 (0.4)	*a*	19
CH_2CH_3	82.9	81.5 (0.58)	*b*	20
$CH(CH_3)_2$	84	87.5–89.5 (0.45)	*c*	21
$C(CH_3)_3$	87.3	78–79.5	*d*	22
	83.9	110 (0.23)	*e*	23
	94.4	121–122	*f*	24
$CH_2CH_2C_6H_5$	89.3	45.5–47	*g*	25
$CH_2CH_2CH_2C_6H_5$	52		*h*	26
$C_6H_4CH_3$-*p*	88.4	98–99.5	*i*	27

[a] Mp 36–39°C. Anal. Calcd for $C_4H_6O_2S$: C, 40.66; H, 5.12; S, 27.14; mol wt, 118.16. Found: C, 40.44; H, 5.14; S, 27.31; mol wt, 120.12. [b] Reference 4. [c] Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93; mol wt, 146.21. Found: C, 49.52; H, 6.77; S, 21.83; mol wt, 148.9. [d] Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55; S, 20.01; mol wt, 160.24. Found: C, 52.58; H, 7.67; S, 20.19; mol wt, 162. [e] Anal. Calcd for $C_8H_{12}O_2S$: C, 55.79; H, 7.02; S, 18.62; mol wt, 172.25. Found: C, 55.96; H, 7.15; S, 18.42; mol wt, 173.91. [f] Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.83; H, 6.35; S, 14.42; mol wt, 222.31. Found: C, 64.62; H, 6.31; S, 14.62; mol wt, 224.9. [g] Reference 2. [h] Attempted distillation led to decomposition.[32] Purification was effected by elution from a column of silica gel with diethyl ether–petroleum ether (bp 35–37°). [i] Reference 8d.

solvent was removed in vacuo and the resulting dry salts leached with boiling ethanol. Solvent evaporation and vacuum drying afforded 37.12 g (86%) of **29** as a fluffy white solid.

Preparation of *p*-Tolylsulfonyl Iodide (30). To a vigorously stirred solution of sodium *p*-toluenesulfinate (17.8 g 0.1 mol) in 1200 ml of water was added iodine (25.0 g, 0.099 mol) in 450 ml of ethanol. The resulting yellow precipitate was collected, washed with cold petroleum ether (bp 35–37°), and recrystallized from carbon tetrachloride, giving 21.75 g (78%) of **30**: mp 90–94° dec (lit.[34] mp 90–91° dec); NMR ($CDCl_3$) δ 2.48 (s, 3 H, aromatic CH_3), 7.36 (d, 2 H, J = 8.2 Hz, aromatic ring protons), 7.75 (d, 2 H, J = 8.2 Hz, aromatic ring protons).

In Situ Preparation of Ethylsulfonyl Iodide (31). This sulfonyl iodide rapidly decomposes,[33] as evidenced by the liberation of iodine, so was prepared freshly in a benzene solution for each addition and used immediately. The general procedure follows. To a vigorously stirred benzene solution of iodine was added a slight excess of sodium ethanesulfinate in water. After a short time (5 min) the benzene layer turned from purple to orange indicating the formation of **31** so the layers were separated. The benzene layer was dried briefly over anhydrous magnesium sulfate and then used in the acetylene additions.

Preparation of 1-Iodo-1-phenyl-2-(*p*-tolylsulfonyl)ethene (32). To a solution of **30** (21.15 g, 0.075 mol) in 200 ml of diethyl ether was added phenylacetylene (7.65 g, 0.075 mol) in 100 ml of Et_2O with illumination.[35] After 12 hr the solvent was removed and the residue recrystallized from ethanol–water, affording 25.9 g (90%) of **32**: mp 83–84.5° (lit.[33] mp 83–84°); NMR ($CDCl_3$) δ 2.32 (s, 3 H, aromatic CH_3), 7.0–7.61 (m, 10 H, aromatic ring protons, vinyl proton).

Preparation of 1-Ethylsulfonyl-2-iodo-3-methyl-1-butene (33). To 31 (60.91 g, 0.24 mol of I_2 and 33.64 g, 0.29 mol of $EtSO_2Na$) in benzene was added 3-methyl-1-butyne (17.68 g, 0.26 mol) with illumination[35] (4 hr) and the solution was stirred overnight. The reaction mixture was washed with sodium thiosulfate solution, dried over magnesium sulfate and decolorizing carbon, and concentrated in vacuo giving 41.02 g of yellow liquid. Distillation provided a reddish material[36] in the forerun and then 25.56 g (37%) of **33**: bp 119–123° (1 mm); NMR ($CDCl_3$) δ 1.02 [d, 6 H, J = 6.3 Hz, $-CH(CH_3)_2$], 1.39 (t, 3 H, J = 7.3 Hz, $CH_3CH_2SO_2-$), 3.02 (q, 2 H, J = 7.3 Hz, $CH_3CH_2SO_2-$), 3.13 [septet, 1 H, J = 6.3 Hz, $-CH(CH_3)_2$], 6.93 (s, 1 H, vinyl proton).

Anal. Calcd for $C_7H_{13}IO_2S$: C, 29.19; H, 4.55; I, 44.05; S, 11.13. Found: C, 29.14; H, 4.74; I, 44.21; S, 11.10

Preparation of 1-Ethylsulfonyl-2-iodo-3,3-dimethyl-1-butene (34). To a benzene solution of **31** (60.91 g, 0.24 mol of I_2 and 30.76 g, 0.26 mol of $EtSO_2Na$) was added 3,3-dimethyl-1-butyne (21.32 g, 0.26 mol) with illumination[35] (4.5 hr). The reaction mixture was washed with sodium thiosulfate solution, dried over $MgSO_4$, decolorized with carbon, and concentrated in vacuo to 44.81 g of orange liquid. NMR analysis showed two isomers,[37] cis-addition isomer predominating over the trans-addition isomer, 56:44. Pure Z isomer was obtained by cooling to −78° causing the formation of a glass; subsequent warming to room temperature and addition of petroleum ether provided 14.41 g of (*Z*)-**34**. Recrystallization from 2-propanol–water gave a white solid: mp 77–78°; NMR ($CDCl_3$) δ 1.27 [s, 9 H, $-C(CH_3)_3$], 1.37 (t, 3 H, J = 7.4 Hz, $CH_3CH_2SO_2-$), 3.26 (q, 2 H, J = 7.4 Hz, $CH_3CH_2SO_2-$), 6.91 (s, 1 H, vinyl proton).

Anal. Calcd for $C_8H_{15}IO_2S$: C, 31.80; H, 5.00; I, 42.00; S, 10.61; mol wt, 302.18. Found: C, 32.00; H, 5.07; I, 41.80; S, 10.40; mol wt, 299.4.

Distillation of the filtrate provided a reddish material[38] in the forerun, bp 37–38° (0.25 mm), and then 24.33 g of the Z and E isomers, bp 109–117.5° (0.2 mm). Pure (*E*)-**34** was obtained by adsorption chromatography using a silica gel column with benzene–diethyl ether as the eluent. Recrystallization from petroleum ether gave white platelets: mp 44.5–45.5°; NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7.4 Hz, $CH_3CH_2SO_2-$), 1.47 [s, 9 H, $-C(CH_3)_3$], 3.11 (q, 2 H, J = 7.4 Hz, $CH_3CH_2SO_2-$), 7.14 (s, 1 H, vinyl proton).

Anal. Calcd for $C_8H_{15}IO_2S$: C, 31.80; H, 5.00; I, 42.00; S, 10.61. Found: C, 31.60; H, 5.04; I, 42.28; S, 10.49.

The combined yield of (*Z*)- and (*E*)-**34** was 38.74 g (53.4%).

General Procedure for the Dehydroiodination of Vinyl Iodides to Acetylenes.[33] A warm (50–60°) methanol solution of the vinyl iodide was treated with an equivalent amount of aqueous potassium carbonate and stirred for 0.75–1.5 hr. Water was then added to the cooled solution inducing crystallization if the acetylene was a solid. The liquid acetylenes were extracted into diethyl ether, dried with $MgSO_4$, and distilled.

***p*-Tolylsulfonylphenylacetylene (35).** **32** (25.85 g, 0.067 mol) in 250 ml of methanol and potassium carbonate (9.25 g, 0.067 mol) in 40 ml of water gave 13.03 g (76%) of **35** after recrystallization from ethanol–water: mp 84–85.5° (lit.[39] mp 80–81°); NMR ($CDCl_3$) δ 2.43 (s, 3 H, aromatic CH_3), 7.13–7.97 (m, 9 H, aromatic ring protons).

1-Ethylsulfonyl-3-methyl-1-butyne (36). To **33** (23.11 g, 0.80 mol) in 150 ml of methanol was added K_2CO_3 (11.04 g, 0.08 mol) in 75 ml of water. Work-up and distillation afforded 11.32 g, bp 78–82° (0.25 mm); however, a carbonyl[40] band at 1733 cm^{-1} was noted in the infrared spectrum as a minor impurity. After a 10% NaOH wash, which removed the impurity, the material was redistilled, giving 6.6 g (52%) of **36**: bp 86–88° (0.5 mm); NMR ($CDCl_3$) δ 1.26 [d, 6 H, J = 6.3 Hz, $-CH(CH_3)_2$], 1.44 (t, 3 H, J = 7.4 Hz, $CH_3CH_2SO_2-$), 2.80 [septet, 1 H, J = 6.3 Hz, $-CH(CH_3)_2$], 3.18 (q, 2 H, J = 7.4 Hz, $CH_3CH_2SO_2-$).

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55; S, 20.01; mol wt, 160.237. Found: C, 52.72; H, 7.48; S, 20.22 mol wt, 160.4.

1-Ethylsulfonyl-3,3-dimethyl-1-butyne (37). To 52% (*E*)- 48% (*Z*)-**34** (30.2 g, 0.1 mol) in 250 ml of methanol was added K_2CO_3 (13.8 g, 0.1 mol) in 100 ml of water. Work-up and distillation provided 14.37 g (82.6%) of **37**: bp 78–86° (0.38 mm); NMR ($CDCl_3$) δ 1.31 [s, 9 H, $-C(CH_3)_3$], 1.44 (t, 3 H, J , 7.4 Hz, $CH_3CH_2SO_2-$), 3.18 (q, 2 H, J = 7.4 Hz, $CH_3CH_2SO_2-$).

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.40; mol wt, 174.266. Found: C, 55.25; H, 8.26; S, 18.55; mol wt, 170.

General Procedure for the Addition of Aziridine to Sulfonyl Acetylenes. For most of the addition reactions 1 molar equiv of aziridine was added by means of a syringe directly into a magnetically stirred solution of the sulfonyl acetylene. After the specified length of stirring time, the solvent was removed in vacuo at room temperature with the resulting residue taken up in $CDCl_3$ or CCl_4 for NMR analysis. The ratio of Z and E isomers reported here is that of the crude reaction mixture before any purification. The yield of the crude material was essentially quantitative by NMR, except where noted. Pertinent chemical shifts are given in Tables IV and VII.

1-Methylsulfonyl-2-aziridino-1-propene (38). Runs 1 and 2. To **19** (0.51 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). After stirring for 4 hr at 23–25°, solvent was removed at room temperature and NMR analysis in CCl_4 showed 7% (*Z*)- and 93% (*E*)-**38**. Distillation[41] of combined runs 1 and 2 gave 0.74 g (53.6%) of (*Z*)-**38** (8%), (*E*)-**38** (86%), and $CH_3SO_2CH_2C(Az)=CH_2$ (6%; Az = aziridinyl), bp 110–114.5° (0.35 mm).

Run 3. To aziridine (0.36 g, 0.0086 mol) in 10 ml of benzene was added **19** (0.51 g, 0.0043 mol) in 10 ml of benzene, followed by stirring for 2 hr at 24–26°. Tripropylamine (0.3 g) was added and the solvent removed in vacuo. NMR analysis showed 94% (*Z*)- and 6% (*E*)-**38** (Table III).

1-Ethylsulfonyl-2-aziridino-1-propene (39).[4] **Run 1.** To **20** (0.57 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol) followed by stirring for 4 hr at 23–24°. Solvent evaporation and NMR analysis gave 95% (*Z*)- and 5% (*E*)-**39**.

Run 2. To **20** (0.57 g, 0.0043 mol) in 20 ml of dimethyl sulfoxide was added aziridine (0.18 g, 0.0043 mol), and the solution was stirred for 4 hr at 22–23°. Solvent removal under vacuum (0.23 mm) and up to 52° bath temperature gave a residue, which contained 74% (*Z*)- and 22% (*E*)-**39** as well as 4% of the nonconjugated isomer, $CH_3CH_2SO_2CH_2C(Az)=CH_2$.

1-(2-Propylsulfonyl)-2-aziridino-1-propene (40). Run 1. To **21** (0.63 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol) and the solution was stirred for 4 hr at 23–25°. Solvent removal and NMR analysis of the residue showed 4% **21** and 91% (*Z*)- and 9% (*E*)-**40** (Table III).

Run 2. To **21** (1.26 g, 0.0086 mol) in 40 ml of benzene was added aziridine (0.36 g, 0.0086 mol) and the solution was stirred for 6 hr at 29–31°. Tripropylamine (0.3 g) was added and then the solvent removed in vacuo and the residue analyzed in $CDCl_3$ [89% (*Z*)- and 11% (*E*)-**40**]. Distillation[41] provided 1.10 g (67.9%) of (*Z*)-**40** (81%), (*E*)-**40** (16%), and $(CH_3)_2CHSO_2CH_2C(Az)=CH_2$ (3%), bp 117° (0.4 mm).

1-(2-Methyl-2-propylsulfonyl)-2-aziridino-1-propene (41). A solution of **22** (0.69 g, 0.0043 mol) in 20 ml of benzene and aziridine (0.18 g, 0.0043 mol) was stirred for 4 hr at 23–25°. Solvent removal and NMR analysis of the residue showed 10% of **22** and 96% (*Z*)- and 4% (*E*)-**41** (Table III).

1-Cyclopentylsulfonyl-2-aziridino-1-propene (42). Runs 1 and 2. To **23** (0.74 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). The solution was stirred for 4 hr. The

residue after solvent removal showed 55% (*Z*)- and 45% (*E*)-**42** (Table II).

Run 5. Under conditions identical with those of runs 1 and 2, except that tripropylamine (0.3 g) was added before solvent removal, 89% (*Z*)- and 11% (*E*)-42 were obtained. Distillation[41] provided 0.36 g (38%) of (*Z*)-42 (50%), (*E*)-42 (40%), and c-$C_5H_9SO_2CH_2C(Az)=CH_2$ (10%), bp 144–146° (0.37 mm).

1-(3,5-Dimethylbenzylsulfonyl)-2-aziridino-1-propene (43). To **24** (0.95 g, 0.0043 mol) dissolved in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). Stirring was carried out for 4 hr at 29–31°. NMR analysis showed 92% (*Z*)- and 8% (*E*)-**43**. Recrystallization from benzene–hexane gave 0.57 g of white needles, mp 107.5–110.5° [95% (*Z*)-**43**], while another 0.24 g of solid was obtained from the mother liquor, total yield 0.81 g (72%).

Anal. Calcd for $C_{14}H_{19}NO_2S$: C, 63.36; H, 7.22; N, 5.28; S, 12.08; mol wt, 265.37. Found: C, 63.23; H, 7.32, N, 5.38; S, 12.00; mol wt, 266.1.

1-(2-Phenylethylsulfonyl)-2-aziridino-1-propene (44).[2] To **25** (0.89 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). The solution was stirred for 4.3 hr at 27–31°. Solvent evaporation and NMR analysis of the residue showed 84% (*Z*)- and 16% (*E*)-**44** (Table III).

1-(3-Phenylpropylsulfonyl)-2-aziridino-1-propene (45). To **26** (0.95 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). Stirring for 4 hr at 23–26° and solvent removal left 1.28 g of crude oil,[42] which showed 87% (*Z*)- and 13% (*E*)-**45** as well as some benzene solvent (Table IV).

1-(*p*-Tolylsulfonyl)-2-aziridino-1-propene (46).[2] To **27** (0.83 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). After stirring for 4 hr at 24–25°, analysis of the whole residue in $CDCl_3$ showed 87% (*Z*)- and 13% (*E*)-**46**.

1-Phenylsulfonyl-2-aziridino-1-propene (47). To **28** (1.2 g, 0.0067 mol) in 24 ml of benzene was added aziridine (0.29 g, 0.0067 mol) followed by stirring for 4 hr at room temperature. Solvent removal left 1.53 g of white solid, mp 83–89° [81% (*Z*)- and 19% (*E*)-**47**]. Recrystallization from benzene–hexane gave 0.94 g (63%) of 95% (*Z*)-**47**, mp 92.5–94°.

1-Aziridino-1-phenyl-2-(*p*-tolylsulfonyl)ethene (48). To **35** (1.1 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol) followed by stirring for 4 hr at room temperature. NMR analysis of the crude residue showed 85% (*Z*)- and 15% (*E*)-**48**. Recrystallization (benzene–hexane) gave 0.97 g (76%) of **48**, mp 87–100.5°. Successive recrystallizations provided pure (*Z*)-**48**, mp 101.5–103.5°.

Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71; mol wt, 299.4. Found: C, 67.98; H, 5.63; N, 4.70; S, 10.48; mol wt, 302.7.

1-Ethylsulfonyl-2-aziridino-3-methyl-1-butene (49). To **36** (0.69 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol). Stirring was continued for 6 hr at 26–27°. NMR analysis of the residual oil (0.88 g) in CCl_4 showed 75% (*Z*)- and 25% (*E*)-**49** (Table V).

1-(*p*-Tolylsulfonyl)-2-aziridino-3-methyl-1-butene (50). To 1-(*p*-tolylsulfonyl)-3-methyl-1-butyne (0.4 g, 0.0018 mol) in 6.5 ml of benzene was added aziridine (0.07 g, 0.0018 mol); the solution was stirred for 4 hr at room temperature. Solvent evaporation provided 0.47 g (100%) of (*Z*)-**50** (73%) and (*E*)-**50** (27%), mp 88.5–94° (Table VI).

1-Ethylsulfonyl-2-aziridino-3,3-dimethyl-1-butene (51). To **37** (0.75 g, 0.0043 mol) in 20 ml of benzene was added aziridine (0.18 g, 0.0043 mol) followed by stirring for 28 hr at 29–32°. Solvent removal and NMR analysis indicated that 58% of the starting sulfonyl acetylene, **37**, remained unreacted, but also that product formation had occurred giving 75% (*Z*)- and 25% (*E*)-**51** (Table V).

1-(*p*-Tolylsulfonyl-2-aziridino-3,3-dimethyl-1-butene (52). To 1-(*p*-tolylsulfonyl)-3,3-dimethyl-1-butyne (1.01 g, 0.0043 mol) in 15.6 ml of benzene was added aziridine (0.18 g, 0.0043 mol); the solution was stirred for 4 hr at room temperature. Solvent removal and NMR analysis of the residue showed 17% completion of the reaction with a ratio of 67% (*Z*)- and 33% (*E*)-**52**. This residue was again dissolved in benzene, treated with more aziridine (0.18 g), and stirred for an additional 24 hr. Work-up and analysis indicated 62% completion with a ratio of 68% (*Z*)- and 32% (*E*)-**52**. Successive treatment with aziridine over a total of 191 hr brought the reaction to 92% completion with some postisomerization being noted at 124 hr. Final isomer ratio was 91% (*Z*)- and 9% (*E*)-**52**. Recrystallization from benzene–hexane gave pure (*Z*)-**52**, mp 109.5–111.5°.

Anal. Calcd for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58; N, 5.01; S, 11.48; mol wt, 279.46. Found: C, 64.28; H, 7.50; N, 5.02; S, 11.66; mol wt, 282.

Equilibration of Sulfonylaziridinopropenes to the Thermodynamic Mixture. The propenyl adducts are isomerized to the thermodynamic equilibrium mixture with potassium hydroxide in tetrahydrofuran.[2]

Isomerization of 43. To **43** (0.55 g, 0.0025 mol, 95% *Z* and 5% *E*) in 50 ml of THF was added 85% KOH pellets (1.65 g, 0.025 mol); the mixture was stirred for 65 hr at room temperature. Solvent evaporation after filtration left 0.59 g of oil, which analyzed as 5% (*Z*)-**43**, 90% (*E*)-**43**, and 5% of the nonconjugated isomer, $Ar\text{-}CH_2SO_2CH_2C(Az)=CH_2$. Crystallization occurred upon the addition of petroleum ether, giving 0.33 g, mp 91–92.5° [pure (*E*)-**43**]. A second crop of 0.16 g gave a total yield of 89.1%.

Isomerization of 45. To **45** (2.09 g, 0.0079 mol, 39% *Z* and 61% *E*) in 50 ml of THF was added 85% KOH pellets (5.20 g, 0.079 mol); the mixture was stirred for 71 hr at room temperature. Filtration of the solid and solvent removal provided 1.42 g (68%) of orange oil, which analyzed as 4% (*Z*)-**45**, 87% (*E*)-**45**, and 9% of the nonconjugated isomer, $C_6H_5CH_2CH_2CH_2SO_2CH_2C(Az)=CH_2$.

Registry No.—**1**, 27129-86-8; **2**, 38360-81-5; **3**, 26842-65-9; **4**, 14272-25-4; **5**, 17277-57-5; **6**, 56480-82-1; **7**, 56480-83-2; **8**, 25558-00-3; **9**, 56480-84-3; **10**, 22174-51-2; **11**, 56480-85-4; **12**, 1595-36-4; **13**, 56480-86-5; **14**, 56480-87-6; **15**, 25558-02-5; **16**, 56480-88-7; **17**, 6212-77-7; **18**, 13597-15-4; **19**, 56480-89-8; **20**, 13596-73-1; **21**, 56480-90-1; **22**, 56480-91-2; **23**, 56480-92-3; **24**, 56480-93-4; **25**, 25558-04-7; **26**, 56480-94-5; **27**, 14027-53-3; **28**, 2525-41-9; **29**, 20035-08-9; **30**, 1950-78-3; **31**, 42790-83-0; **32**, 56480-95-6; **33**, 56480-96-7; (*Z*)-**34**, 56480-97-8; (*E*)-**34**, 56480-98-9; **35**, 28995-88-2; **36**, 56480-99-0; **37**, 52323-96-3; (*Z*)-**38**, 56481-00-6; (*E*)-**38**, 56481-01-7; (*Z*)-**39**, 13894-50-3; (*E*)-**39**, 13894-33-2; (*Z*)-**40**, 56481-02-8; (*E*)-**40**, 56481-03-9; **40** nonconjugated isomer, 56481-04-0; (*Z*)-**41**, 56481-05-1; (*E*)-**41**, 56481-06-2; (*Z*)-**42**, 56481-07-3; (*E*)-**42**, 56481-08-4; **42** nonconjugated isomer, 56481-09-5; (*Z*)-**43**, 56481-10-8; (*E*)-**43**, 56481-11-9; (*Z*)-**44**, 25558-49-0; (*E*)-**44**, 25558-44-5; (*Z*)-**45**, 56481-12-0; (*E*)-**45**, 56481-13-1; (*Z*)-**46**, 25558-47-8; (*E*)-**46**, 25558-42-3; (*Z*)-**47**, 56481-14-2; (*E*)-**47**, 56481-15-3; (*Z*)-**48**, 56481-16-4; (*E*)-**48**, 56481-17-5; (*Z*)-**49**, 56481-18-6; (*E*)-**49**, 56481-19-7; (*Z*)-**50**, 56481-20-0; (*E*)-**50**, 56481-21-1; (*Z*)-**51**, 56481-22-2; (*E*)-**51**, 56481-23-3; (*Z*)-**52**, 56481-24-4; (*E*)-**52**, 56481-25-5; propargyl bromide, 106-96-7; sodium methanethiolate, 5188-07-8; sodium 2-propanethiolate, 20607-43-6; sodium 2-methyl-2-propanethiolate, 29364-29-2; sodium cyclopentanethiolate, 56481-26-6; sodium 3,5-dimethylphenylmethanethiolate, 56481-27-7; sodium 2-phenylethanethiolate, 13423-07-9; sodium 3-phenylpropanethiolate, 56481-28-8; (*Z*)-1,2-bis(ethylthio)ethene, 14044-67-8; ethanesulfonyl chloride, 594-44-5; sodium sulfite, 10579-83-6; sodium *p*-toluenesulfinate, 824-79-3; iodine, 7553-56-2; phenylacetylene, 536-74-3; 3-methyl-1-butyne, 598-23-2; 3,3-dimethyl-1-butyne, 917-92-0; aziridine, 151-56-4; 1-(*p*-tolylsulfonyl)-3-methyl-1-butyne, 28995-91-7; 1-(*p*-tolylsulfonyl)-3,3-dimethyl-1-butyne, 28995-90-6.

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(38) This compound was identified as $(CH_3)_3C{-}C(I){=}CH(I)$ from its mass spectrum molecular ion *m/e* 336, and its NMR ($CDCl_3$): δ 1.40 [s, 9 H, $(CH_3)_3C-$], 7.24 (s, 1 H, vinyl proton).
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(41) Thermal isomerization of the conjugated adducts to the nonconjugated adduct appears to have occurred during distillation.
(42) Elution chromatography of this crude oil on a column of silica gel caused isomerization to the more stable trans isomer and the nonconjugated isomer $PhCH_2CH_2CH_2SO_2CH_2C(Az){=}CH_2$, as well as hydrolysis of some of the material to the ketone $(PhCH_2CH_2CH_2SO_2CH_2COCH_3)$.

Stereochemistry of β-Lactams Derived from α-Keto-γ-lactams by Ring Contraction. X-Ray Analysis and Differential Behavior with Shift Reagents of Difunctional β-Lactams

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The configurations of the α,α-disubstituted β-lactams **2**, **3**, and **4** were determined by X-ray analysis, and the results are used to explain the stereochemistry of β-lactams derived from α-keto-γ-lactams by oxidative ring contraction with periodate. The X-ray data provide indirect support for the proposed correlation of biological activity with the pyramidal nature of bonding to the β-lactam nitrogen. The behavior of the esters **7** and **8** toward the lanthanide shift reagents $Eu(dpm)_3$ and $Eu(fod)_3$ in both CCl_4 and $CDCl_3$ was also examined. Different results arose depending upon both ligand (dpm or fod) and solvent, and the differences are explained by invoking for $Eu(fod)_3$ a 2:2 bridged complex in CCl_4 and a mixture of bridged complex and 1:1 chelated complex in $CDCl_3$. In addition, $Eu(fod)_3$ was shown to be unstable to the carboxylic acids **1–4**, indicating a limitation on its utility for the characterization of carboxylic acids. Perturbation of conformational equilibria by coordination to shift reagents is illustrated.

The formation of β-lactams from α-keto-γ-lactams by oxidative ring contraction with periodate[1] can lead to two orientations for the new carboxyl group at the α carbon of the β-lactam. The mechanism of this rearrangement reaction has been investigated using 1-methyl-2,3-piperidinedione as the prototype,[2] and the proposed mechanism is illustrated in Scheme I for β-substituted α-keto-γ-lactams. It was anticipated that stereochemistry would be governed by the relative size of substituents in an orientation-determining stage approximated by structures **11** or **12**. Consistent with this view, only the trans isomer **1** was obtained when X = H.[1] When X = methyl, again only one isomer, **2**, was produced; however both isomers, **3** and **4**, occurred when X = bromine,[1] and this provided the possibility of defining the requirements for generating the isomer with the carboxyl group oriented cis (β) to the fused ring. Accordingly, we undertook the determination of the stereochemistry of β-lactams **2**, **3**, and **4** by X-ray crystallographic analysis, and we now report the results of these studies along with their mechanistic implications.

It was also anticipated that use of a lanthanide shift reagent (LSR) could lead to definition of relative stereochemistry. The shift reagent $Eu(dpm)_3$ (dpm = dipivaloylmethanato) differentiated between the bromo isomers, and the limitations on its use for determining stereochemistry are discussed. On the other hand, use of $Eu(fod)_3$ (fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) led to essentially no differentiation. The results of the use of both reagents in CCl_4 and $CDCl_3$ are discussed in terms of composition of LSR–substrate complexes.

In addition, perturbation of conformational equilibria by coordination to shift reagents is illustrated, and limitations on the use of chelate shift reagents with carboxylic acids are discussed.

Results and Discussion

Previously the syntheses of compounds **9** (X = H) and **10** (X = CH_3 and Br) were described along with their reaction with periodate to form the β-lactams **13**.[1] For X = H and CH_3 only one isomer was formed, but for X = Br both iso-

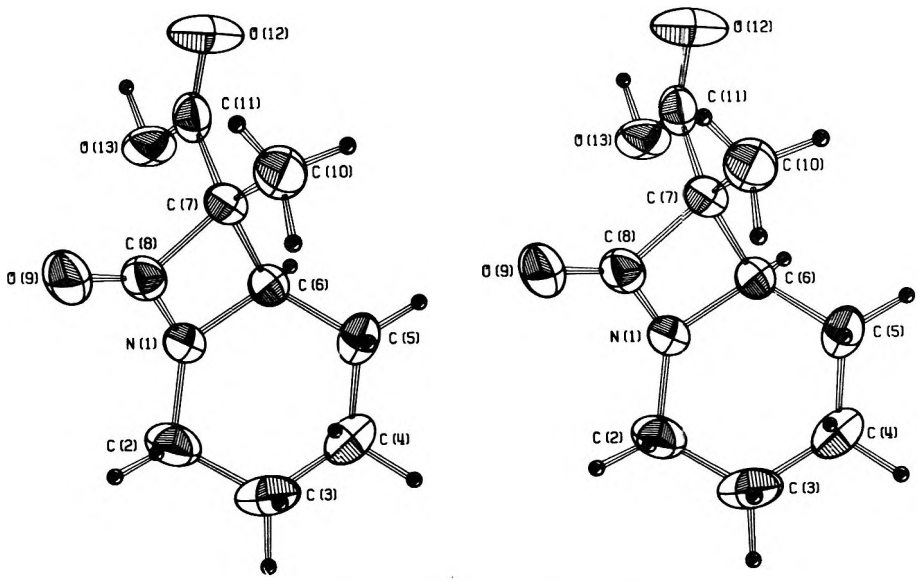
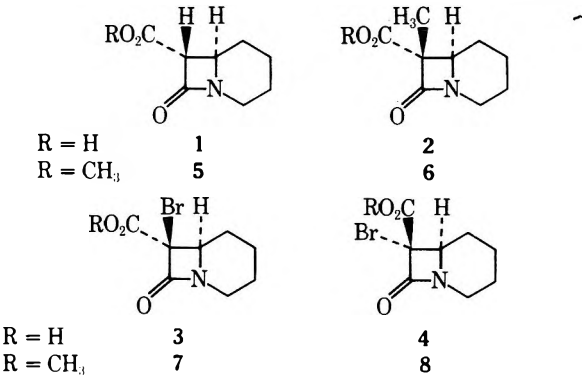


Figure 1. Stereoplot of 7α-carboxy-7β-methyl-8-oxo-6α*H*-1-azabicyclo[4.2.0.]octane (2).

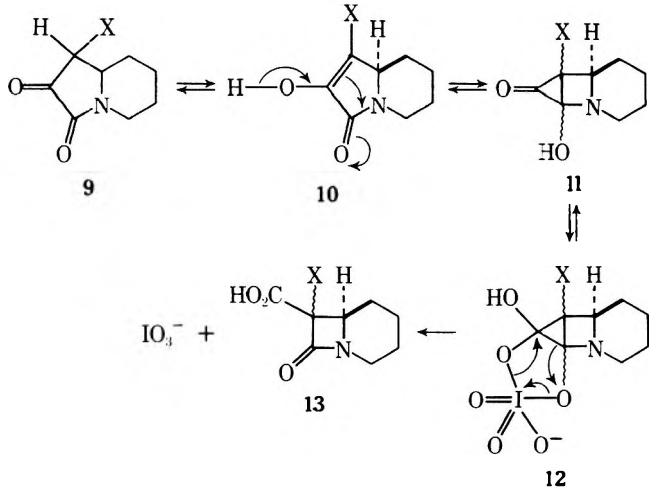
mers were produced in a ratio of 9:1. The configurations of the methyl (2, Figure 1) and bromo (3, 4) compounds were determined by X-ray analysis and are given below, with



structure 3, the 7β-bromo compound, corresponding to the major bromo isomer. Two modes of reaction for an intermediate such as 11 have been proposed;[2] since the minor mode is not available for β-substituted α-ketoacyl derivatives, only the major mode of reaction is illustrated in Scheme I.

The 7β-methyl group of 2 and the bromine of the major isomer 3 both have the same orientation as the 7 proton in 1, i.e., cis to the fused ring. The β-lactams of this series (1, 2, 3) have the carboxyl on the less hindered face of the β-lactam ring, consistent with the proposal that the size of the substituent X determines the stereochemistry in the β-lactams 13. Measurements which appear to reflect the effective size of substituents suggest that bromo is somewhat larger than, or at least comparable to, the methyl group.[3] For this simple carbocyclic system, formation of the minor bromo isomer 4 then suggests that an effective size approximating bromo defines a lower limit for substituents which will force a change in stereochemical preference.

Scheme I
Mechanism of Oxidative Ring Contraction of β-Substituted α-Keto-γ-lactams



X-Ray Analyses. The refined crystallographic structures were stereographically plotted (e.g., Figure 1) using the ORTEP computer program.[4] An estimate of errors in positional parameters, bond lengths, and bond angles is summarized in Table I. Bond distances and angles are given in Table II. The degree of planarity of the β-lactam ring is reflected in the measurements shown in Table IIIA, and dihedral angles involving the ring fusion are given in Table IIIB. Atomic parameters and structure factor tables appear in Tables V, VI, and VII.[5]

Among those fused ring β-lactams which have been studied in detail by X-ray diffraction,[6] the biologically active compounds (e.g., penicillin G,[6a] cephaloridine,[6b] and cephaloglycine[6b]) contain the β-lactam nitrogen at the apex of a pyramid with the nitrogen atom raised about 0.24 Å (cephalosporins) to 0.40 Å (penicillin G) above the plane of the attached atoms. On the other hand, biologically inactive 7β-phenoxyacetamido-Δ²-deacetoxycephalosporanic acid[6b] and the fused β-lactam 14[6c] contain the β-lactam nitrogen raised only about 0.07 Å above the plane of the attached atoms. Based on the data from penicillin G and the cephalosporins, it has been suggested that, as one among a number of factors, biological activity may be correlated

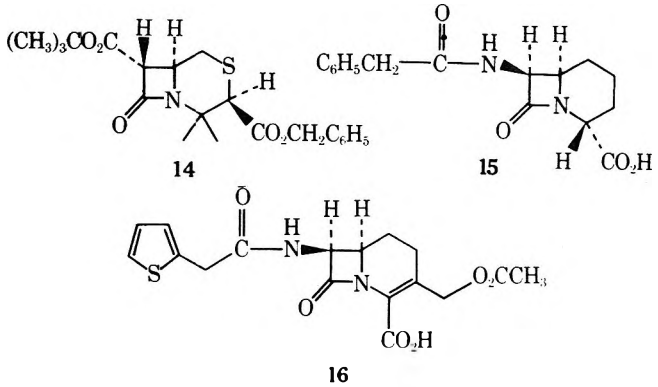


Table I

Compd	2	3	4
A. Refinement Parameters			
R index ($R = \Sigma \|\|F_0\| - \|F_c\|\| / \Sigma \|F_0\|$)	0.079	0.055	0.045
Weighted R ($R' = w(F_0^2 - F_c^2)^2 / \Sigma w F_0^4$)	0.028	0.017	0.009
Final calculated shifts, fraction of standard deviation	0.00	0.25	0.00
Positional uncertainty, Å			
C	0.009	0.008	0.007
N	0.007	0.007	0.006
O	0.007	0.005	0.006
Br		0.0008	0.0007
Bond distance uncertainty, Å			
C–C	0.016	0.010	0.010
C–N	0.014	0.009	0.009
C–O	0.012	0.009	0.009
C–Br		0.006	0.007
Bond angle uncertainty, deg	0.9	0.7	0.6
B. Crystal Parameters			
Formula	$C_9H_{13}NO_3$	$C_8H_{10}BrNO_3 \cdot H_2O$	$C_8H_{10}BrNO_3$
Crystallization media	Acetone–hexanes	Chloroform–hexanes	Chloroform–hexanes
Crystal habit	Acicular	Prismatic	Acicular
Crystal size, mm	0.10 × 0.10 × 0.15	0.30 × 0.50 × 0.80	0.05 × 0.15 × 0.25
Cell dimensions, Å	a = 8.164 (3)	a = 7.709 (1)	a = 8.049 (3)
	b = 10.825 (2)	b = 12.577 (2)	b = 10.306 (6)
	c = 15.356 (6)	c = 11.588 (2)	c = 12.524 (6)
	β = 135.70 (2)°	β = 109.23 (1)°	β = 113.55 (3)°
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
Molecules/unit cell	4	4	4
Density observed, g/cm^3	1.29	1.62	1.69
Density calculated, g/cm^3	1.28	1.67	1.73
Number of reflections	973	1093	970
Nonzero reflections	848	1061	898
Linear absorption coefficient μ, cm^{-1}	8.1	57.8	63.1

Table II
Bond Distances and Angles for Compounds 2–4

Atom	Atom[a]	Distance, Å 2	3	4	Atom	Atom	Atom	Angle, deg 2	3	4	Atom	Atom	Atom	Angle, deg 2	3	4
N(1)	C(2)	1.46	1.44	1.43	C(6)	N(1)	C(2)	126	125	125	R(10)	C(7)	C(6)	119	118	114
N(1)	C(6)	1.48	1.48	1.48	C(8)	N(1)	C(2)	136	135	137	C(11)	C(7)	C(6)	114	114	116
N(1)	C(8)	1.33	1.33	1.33	C(8)	N(1)	C(6)	96	96	97	R(10)	C(7)	C(8)	114	113	111
C(2)	C(3)	1.54	1.52	1.53	C(3)	C(2)	N(1)	107	108	109	C(11)	C(7)	C(8)	112	118	116
C(3)	C(4)	1.52	1.53	1.52	C(4)	C(3)	C(2)	113	111	112	C(11)	C(7)	R(10)	112	107	112
C(4)	C(5)	1.54	1.54	1.54	C(5)	C(4)	C(3)	112	112	112	C(7)	C(8)	N(1)	94	92	92
C(5)	C(6)	1.51	1.52	1.53	C(6)	C(5)	C(4)	108	108	107	O(9)	C(8)	N(1)	134	133	133
C(6)	C(7)	1.57	1.56	1.57	C(5)	C(6)	N(1)	111	109	109	O(9)	C(8)	C(7)	133	135	135
C(7)	C(8)	1.54	1.53	1.54	C(7)	C(6)	N(1)	87	85	86	O(12)	C(11)	C(7)	125	123	122
C(7)	R(10)	1.52	1.93	1.94	C(7)	C(6)	C(5)	122	122	121	O(13)	C(11)	C(7)	111	112	113
C(7)	C(11)	1.52	1.51	1.52	C(8)	C(7)	C(6)	84	86	85	O(13)	C(11)	O(12)	124	125	125
C(8)	O(9)	1.24	1.23	1.23												
C(11)	O(12)	1.19	1.19	1.19												
C(11)	O(13)	1.33	1.30	1.31												

[a] R = Br for compounds 3, 4; R = CH_3 for compound 2.

with the degree of nonplanarity of the β-lactam nitrogen atom.[6b]

The pyramidal character of the β-lactam nitrogen of compounds 2–4 is reflected in the measurements given in Table IIIC. Not surprisingly, the deviations for all three β-lactams lie well below the range observed for active compounds. If the variation among the three β-lactams can be taken as a rough indication of the magnitude of the effect of peripheral groups on skeletal structure, then the deviation from planarity for the cephalosporin analog 15[7] would be expected to lie approximately in the range found for β-lactams 2–4, that is, below the range apparently required for activity. The observed inactivity of 15 accordingly can be viewed as consistent with the proposed correlation of biological activity with the pyramidal character of the β-lactam nitrogen.

Table III

Compd	2	3	4
A. Planarity of β-Lactam Ring[a]			
Atom, deviation, Å			
N(1)	−0.009	−0.045	0.000
C(6)	0.008	0.038	0.000
C(7)	−0.007	−0.037	0.000
C(8)	0.009	0.044	0.000
O(9)	0.071	0.151	0.002
C(11)	−1.317	−1.311	1.224
B. Dihedral Angles Involving the Ring Fusion			
Dihedral angle, deg			
7–8–1–2	163.7	166.1	166.7
7–6–1–2	166.2	169.0	169.0
8–1–6–5	121.3	115.3	121.7
8–7–6–5	111.6	104.0	110.1
C. Pyramidal Nature of N(1)[b]			
Derivation, Å			
N(1)	−0.121	−0.143	0.089
C(11)	−1.103	−1.231	1.411

[a] Atoms 1, 6, 7, and 8 were used to define the least-squares plane. Atoms 9 and 11 were given zero weight. Atom 11 serves to define the positive and negative directions. [b] Atoms 2, 6, and 8 were used to define the plane. Atoms 1 and 11 were given zero weight. Atom 11 serves to define the positive and negative directions.

The recently synthesized cephalosporin analog **16** has been shown to have antimicrobial activity comparable with the activity of cephalothin.[8] From the above point of view, a deviation from planarity about the β-lactam nitrogen of 0.24–0.40 Å, probably close to 0.30 Å, would be predicted. This increased nonplanarity undoubtedly would result from introduction of the C(2)–C(3) double bond into the six-membered ring.

Shift Reagent Analyses. The β-lactam esters **7** and **8** contain two functional groups which might coordinate with a shift reagent: the lactam and ester carbonyls. If there is any preference for coordination at the ester carbonyl, then the distance from the lanthanide atom to the bridgehead proton would be greater in 7β-methoxycarbonyl isomer **8** than in 7α-methoxycarbonyl isomer **7**. If the angle dependence of the lanthanide induced shifts (LIS) is negligible, then the simplified McConnell–Robertson relationship suggests that the difference in distance will be reflected linearly in a difference in the induced shift for the bridgehead proton.[9-11] Accordingly, we examined the behavior of Eu(dpm)$_3$ and Eu(fod)$_3$ in order to ascertain their utility in stereochemical studies of α,α-disubstituted β-lactams.

Initial studies with Eu(fod)$_3$ indicated that this reagent differentiates only insignificantly between the isomers **7** and **8**; however, use of Eu(dpm)$_3$ led to significant differences in the induced shift for the bridgehead proton which will be considered later. Our interpretation of the behavior of the β-lactams **7** and **8** in the presence of shift reagents rests on a suggestion of apparent changes in preferred coordination site depending upon both shift reagent and solvent. A position of preferred coordination is in turn inferred from relative induced shifts for various substrate protons. The actual coordination site is of no concern, since we are interested only in changes in apparent coordination site relative to other potential sites.

In the general structure **17** the protons of particular interest are those attached to C-2 (H-2α and H-2β) and to the bridgehead carbon (H-6). Signals for all three protons have been assigned[7] on the basis of line shape, the anisotropic effect of the lactam carbonyl on the chemical shifts for the C-2 protons, and comparison with spectra of similar compounds.[13] In addition, we have confirmed the H-6 assignment by spin decoupling experiments with ester **5** in the presence of Eu(fod)$_3$.[5]

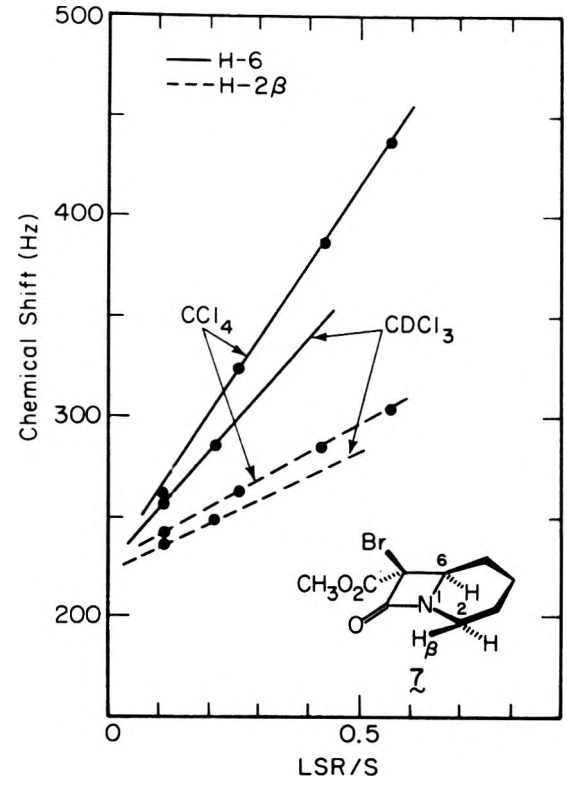
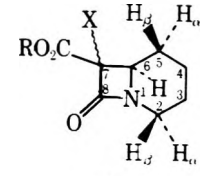


Figure 4. Lanthanide induced chemical shifts for H-6 and H-2β of **7** in $CDCl_3$ and CCl_4 as a function of increasing Eu(dmp)$_3$ concentration: $[7]_{CDCl_3} = 0.30\ M$, $[7]_{CCl_4} = 0.16\ M$.



17

In Figures 2 and 4, the induced shift for H-6 is much greater than the roughly comparable shifts seen for H-2α and H-2β, suggesting that with Eu(dpm)$_3$ a site of significant coordination is the ester carbonyl. As expected for europium coordination at the ester, the induced shift for H-6 was found to be greater for 7α-methoxycarbonyl isomer **7** than for 7β-methoxycarbonyl isomer **8**.[5] However, the magnitude of this difference was not large and was found to be comparable to the variance in the ratio of H-2β/H-6 shifts seen for **5** and **7** with Eu(fod)$_3$, indicating significant sensitivity to the size of the substituent, X. The method thus appears to be useful only when both isomers are available for comparison and when the substituent, X, can be expected not to coordinate with the shift reagent.

Since the completion of these investigations, Eu(fod)$_3$ has been reported to be stable to carboxylic acids.[14] It was conceivable that use of the acids **3** and **4** with Eu(fod)$_3$ could at least attenuate the severe limitations on use of the ester, but it was found that Eu(fod)$_3$ was unstable to all of the acids **1**–**4**.[5]

Perturbation of the conformation of the fused six-membered ring of esters **5**, **7**, and **8** was detected in the presence of both Eu(fod)$_3$ and Eu(dpm)$_3$ by monitoring the line shape for H-6.[5] The example represented by these fused bi-

cyclic molecules is somewhat unique in that the conformationally mobile portion, the six-membered ring, is fused to an immobile portion, the four-membered lactam with the shift reagent binding to the immobile portion and the bridgehead proton (H-6) available as monitor.

Although our intent was to determine the utility of shift reagents for defining the stereochemistry of α,α-disubstituted β-lactams, other features of the behavior of these fused ring β-lactams with shift reagents were evident. These features are the subject of the following comments.

Factors Affecting Complex Composition. In Figures 3[5] and 5 (for CCl_4), the induced shift for H-2β is seen to be greater than the comparable shifts seen for H-6 and H-2α, suggesting that with Eu(fod)$_3$ in CCl_4 the site of preferred coordination is the β-lactam carbonyl. In contrast, we found that with Eu(dpm)$_3$ in CCl_4 coordination at the ester carbonyl is significant. As illustrated in Figures 4 and 5, results in $CDCl_3$ are qualitatively unchanged with Eu(dpm)$_3$ but significantly different with Eu(fod)$_3$. For Eu(dpm)$_3$ the reduction in the absolute value of induced chemical shifts on change of solvent from CCl_4 to $CDCl_3$ can be attributed to greater solvent association with the shift reagent in $CDCl_3$,[9] but it is evident from comparison of relative slopes that a change in solvent has not affected significantly the site of preferred coordination. On the other hand, a similar comparison of relative slopes in Figure 5 indicates that for Eu(fod)$_3$ a change in solvent from CCl_4 to $CDCl_3$ has altered significantly the apparent average position of the europium atom. This new position can be viewed as an average between the two previously inferred positions.

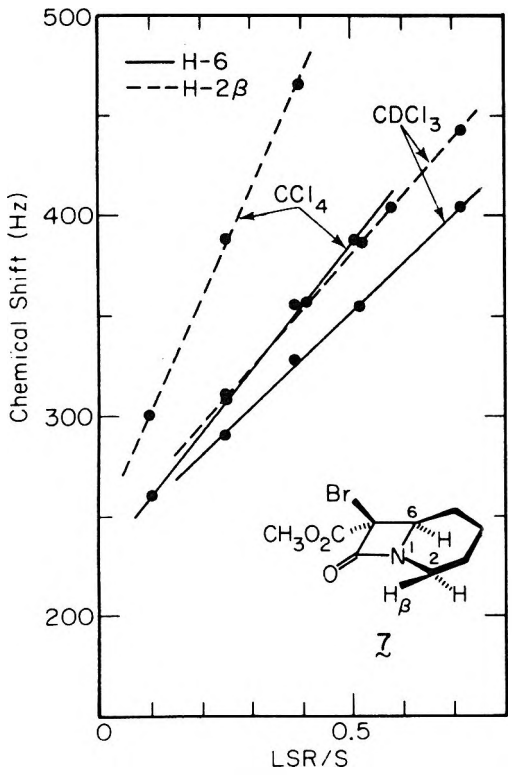


Figure 5. Lanthanide induced chemical shifts for H-6 and H-2β of **7** in $CDCl_3$ and CCl_4 as a function of increasing Eu(fod)$_3$ concentration: $[7]_{CDCl_3} = 0.38\ M$, $[7]_{CCl_4} = 0.30\ M$.

These data suggest the importance of a fundamental difference between the two shift reagents, and we propose that the apparent change in coordination site can be attributed primarily to a difference in type of shift reagent–substrate complex.[15] The results with Eu(dpm)$_3$ are readily accommodated by the 1:1 monomeric complex usually proposed for this reagent. The lactam carbonyl would be expected to be more basic than the ester carbonyl, and the available data indeed suggest that amides are stronger donors than esters.[9] Preferred coordination at the lactam is thus expected and chelation with the ester carbonyl would introduce the observed differentiation between isomers.[17] However, it is evident in comparison that coordination at the ester is negligible with Eu(fod)$_3$. To account for this result and for the difference in solvent effects, we suggest that Eu(fod)$_3$ in CCl_4 forms with these fused ring β-lactams a 2:2 bridged complex in which each substrate molecule functions as a bridging ligand between the two europium atoms.[18] In such a bridged, eight-coordinate complex, chelation by substrate is not possible, and a preference for coordination at the more basic lactam carbonyl is viewed as the dominant force.[19]

Support for the proposal of this rather exclusive difference in complex structure can be drawn from a number of considerations.[20] The preponderance of evidence suggests that Eu(dpm)$_3$ is monomeric in solution, regardless of solvent and concentration. On the other hand, Eu(fod)$_3$ forms aggregates whose concentrations increase in the order chloroform, carbon tetrachloride, *n*-hexane, self-association being negligible in $CHCl_3$ but quite significant in CCl_4.[21] It also appears, as previously mentioned, that for Eu(dpm)$_3$ the principal complex formed between reagent and substrate is a monomeric 1:1 adduct; but for the fod reagents, a variety of complexes has been suggested, including the bridged complex proposed above.[9,18,20]

One property in particular appears to provide a unifying explanation. That is the varying tendency of europium to undergo coordinative expansion depending upon its acidic character. The basics of the argument have been presented[20] with the implication that the dominating difference between Eu(fod)$_3$ and Eu(dpm)$_3$ with regard to self-association is the increase in the tendency of the europium atom toward coordinative expansion caused by a change in ligand from dpm to the much more electron-withdrawing fod. A preference toward eight-coordination instead of seven-coordination has also been noted.[20] In this context Eu(dpm)$_3$, with its reduced tendency toward coordinative expansion and its large effective size, is viewed as having an aversion toward oligomer formation and a preference for only 1:1 substrate adducts; whereas Eu(fod)$_3$, with its increased tendency toward coordinative expansion and its reduced effective size, prefers oligomer formation and other than monomeric 1:1 substrate adducts, all of these latter complexes being eight-coordinate if possible. It is then reasonable to propose that Eu(fod)$_3$–nonpolar substrate adducts of apparent 1:1 composition in CCl_4 are best represented by an eight-coordinate 2:2 bridged complex.[22]

The solvent effect on Eu(fod)$_3$ behavior can be explained using the same argument. The change in medium polarity on going from CCl_4 to $CDCl_3$ can stabilize the polarity introduced by the fod ligands, in this way reducing the tendency toward coordinative expansion. The result is reduced self-association[21] and a proposed increase in the presence of monomeric 1:1 substrate adducts as chelates. The data for **7** and Eu(fod)$_3$ in $CDCl_3$ can accordingly be viewed as reflecting an equilibrium between a bridged complex and a monomeric 1:1 chelated complex.

No change in LIS was seen with *n*-hexanoic acid and Eu(fod)$_3$ on change of solvent from CCl_4 to $CDCl_3$.[5] This result is expected if *n*-hexanoic acid is considered to provide polarity sufficient for eradication of the tendency of Eu(fod)$_3$ toward self-association, thus allowing the acid to form with Eu(fod)$_3$ a monomeric complex in either solvent. Consequently, even in CCl_4, it appears likely that for Eu(fod)$_3$ there is an undefined range with regard to sub-

strate polarity within which there will exist both a bridged and a monomeric complex. To extract quantitative information about substrate structure by use of the McConnell–Robertson relationship it is necessary that there be only one complex in solution. It therefore appears that the utility of $Eu(fod)_3$ for structural studies of this type is quite limited.

Experimental Section

X-Ray Analysis of 2–4. The crystal structures of compounds 2–4 were concluded in a routine manner. Since all three analyses were similar, they will be reported together. Suitable crystals were grown from appropriate solvents (see Table VII) by the slow evaporation technique. The crystals were surveyed and 1 Å intensity data sets (maximum $\sin\theta/\lambda = 0.5$) were obtained on a Syntex P1 diffractometer using copper radiation (λ = 1.5418 Å) at 22°C. Crystal density was measured by the flotation technique in aqueous zinc chloride. Final unit cell dimensions were obtained using a least-squares fit of ten high angle reflections ($2\theta > 40°$). The diffractometer was equipped with a graphite incident beam monochromator mounted in the perpendicular mode. During data collection a θ–2θ scan technique was employed, the scan rate was 2°/min in 2θ, the scan range was 1.0° above $K\alpha_2$ and 1.0° below $K\alpha_1$, and the background was counted for half the scan time on each side of the peak. A single check reflection was monitored every 30 reflections and indicated no crystal damage since it was reproducible within counting statistics.

The diffractometer output was processed using subprograms of the CRYM crystallographic computer system.[23] The processing included corrections for background and for Lorentz and polarization effects. The polarization effect due to the graphite monochromator was included in these corrections.[24] No corrections were made for absorption. The data processing also included calculation of the F^2 value and its standard deviation for each reflection. The standard deviations were assigned on the basis of the equation

$$\sigma^2(I) = S + \alpha^2(B_1 + B_2) + (dS)^2$$

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and α is the scan time to total background time ratio. All intensities with a value less than two times the standard deviation were set equal to zero with zero weight. Finally, the data sets were placed on an approximately absolute scale by means of Wilson statistics.

Determination of Structure and Refinement. Trial structures for compounds 3 and 4 were obtained by conventional Patterson and Fourier techniques. In both cases the first electron density map revealed every nonhydrogen atom. A trial set of phases for compound 2 was obtained through the reiterative application of Sayre's equation.[25,26] A trial structure was obtained with the first E map. The trial structure for compounds 2 and 4 refined routinely to an acceptable R index. A difference Fourier was required in compound 3 to locate a water of crystallization. Upon the inclusion of the water molecule, refinement proceeded smoothly to an acceptable R index (see Table I). The latter stages of the refinement procedure included a full matrix least-squares treatment of coordinates, anisotropic temperature factors, and scale factor in one matrix. Methylene and methine hydrogen positions were calculated; all other hydrogen positions were located by difference Fourier techniques. While hydrogen positions were added to the structure factor calculations in the latter stage of refinement, their positions were not refined. The quantity minimized by the least-squares procedure was $\Sigma w(F_o^2 - F_c^2)^2$, where $w = 1/\sigma^2(F_o^2)$. Parameters pertinent to the refinement procedure are summarized in Table I. In each case a final difference Fourier revealed no missing or misplaced atoms.

Shift Reagent Studies. Materials. The acids 1–4 and the esters 5, 7, and 8 were prepared as described previously.[1] $Eu(dpm)_3$, obtained from Bio-Rad Laboratories, and $Eu(fod)_3$, obtained from Norell Chemical Co., were stored over $CaCl_2$ prior to use. Reagent grade CCl_4 (Mallinckrodt) and economy grade $CDCl_3$ (Bio-Rad) were used as solvents with Me_4Si as internal reference.

Sample Preparation. The substrates were dissolved in appropriate solvents, and weighed amounts of shift reagent were added in increments directly to the NMR tube.

NMR Measurements. Spectra were recorded on a Varian T-60 spectrometer and all shifts are given in hertz relative to Me_4Si. Decoupling experiments were carried out on a Varian HA-100 spectrometer, employing the frequency sweep mode.

Acknowledgment. We thank Judy Lyding for carrying out the decoupling experiments.

Registry No.—1, 42599-31-5; 2, 54409-84-6; 3, 54409-86-8; 4, 54409-87-9; 5, 53618-26-1; 6, 54409-85-7; 7, 42599-40-6; 8, 42599-41-7; $Eu(dpm)_3$, 15522-71-4; $Eu(fod)_3$, 17631-68-4.

Supplementary Material Available. Detailed discussion of proton signal assignments; the use of $Eu(dpm)_3$ for the determination of stereochemistry (including Figures 2 and 3, from which the data in Figures 4 and 5 with regard to studies in CCl_4 were taken); limitations on the use of $Eu(fod)_3$ with carboxylic acids and the conformational equilibrium perturbation; Table IV of coupling constants for H-6 as a function of increasing [LSR]; and Tables V, VI, and VII listing atomic parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3208.

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Stereochemistry of the 4-Phenylquinolizidin-1-ol Diastereoisomers. Conformational Free Energy of the Quinolizidine Ring Fusion, and of Their Intramolecular OH···N Hydrogen Bonds

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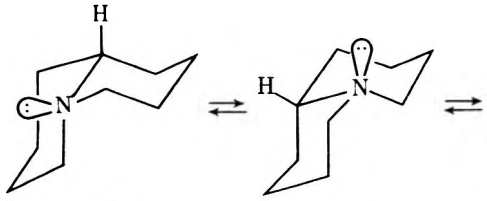
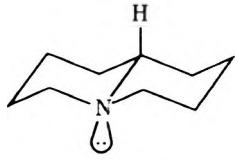
The four diastereoisomers of 4-phenylquinolizidin-1-ol have been synthesized and separated, and their relative configurations assigned. Three of the isomers contain an intramolecular OH···N hydrogen bond. From dilute solution ir spectra, the position of the conformational equilibrium in each of the isomers has been determined. By conformational analysis, the inherent free energy difference between the cis and trans quinolizidine ring fusion ($\Delta G°_Q$) and the conformational free energy of their intramolecular hydrogen bonds ($\Delta G°_{OH-N}$) have been rigorously and independently derived. In this system, $\Delta G°_Q$ was found to be 2.0 kcal/mol, in favor of the trans conformation, and $\Delta G°_{OH-N}$ to be 0.6 kcal/mol (attractive), for $\Delta\nu_{OH} \sim 83$ cm^{-1}, at 33°.

Quinolizidine, the bridgehead nitrogen analog of decalin, occurs as a substructure in many natural products.[1] Whereas decalin exists as separable cis and trans isomers, quinolizidine exists as an equilibrium mixture of cis (two) and trans conformers, which rapidly interconvert at ordinary temperature by simple ring flip (cis ⇄ cis), and pyramidal inversion[2] of the nitrogen (cis ⇄ trans). This equilibrium is



cis cis



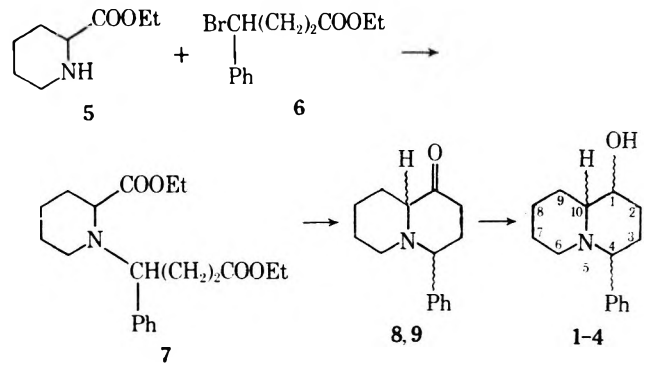
trans

known to favor, strongly, the trans-fused conformer, if to an uncertain degree, what with values of 2.6[3] and 4.4 kcal/mol[4] having been reported. Suitable substituents can shift this equilibrium to a point where appreciable quantities of both cis- and trans-fused species are present,[3,5] or further, to where a cis-fused form largely predominates.[6-9] In no case, however, have a pair of stable conformers been isolated.[10] Thus, earlier claims[11-13] for two forms of substituted quinolizidines, that differ only in the stereochemistry of the ring fusion, were subsequently shown[6,14,15] to have been erroneous structural assignments.[7,16,17]

Apart from the question of the equilibrium position in the unsubstituted parent, the conformational assignments of substituted quinolizidines have been almost invariably given as simply cis or trans, corresponding to the ring fusion of the major species (in solution). More quantitative assignments of such equilibria are necessary, however, if one is to assess the conformational factors that operate in the quinolizidine ring system. Accordingly, we now report a study of the 4-phenylquinolizidin-1-ol isomers, from which the free-energy difference between the cis and trans ring fusion in the interesting *trans*-4,10-*H*-4-phenylquinolizidine system[8] is rigorously derived.

Results

4-Phenylquinolizidin-1-ol was synthesized by the following route. In this synthesis, the product obtained from a



Dieckmann condensation of the diester **7** was hydrolyzed and decarboxylated to a mixture of epimeric ketones **8** and **9**, from which a pure sample of major isomer **8** was obtained. Reductions of small amounts of **8** gave mixtures of alcohol isomers **1** and **2**. However, since the ketones (especially minor isomer **9**) were found to deteriorate on standing, the ketone mixture was not separated in the large-scale run, but was directly reduced to alcohol isomers **1–4**. The composition of this carbinol mixture (**1** plus **2** and **3** plus **4**) corresponds to that of the ketone mixture from which it was obtained, based upon the configurational assignments given below. A pure sample of each alcohol was obtained by adsorption chromatography on alumina, the separation being monitored by GLC on Carbowax 20M. The isomers are numbered according to their order of elution, and the same order was obtained from both the alumina and Carbowax columns. The ir spectrum of each alcohol isomer was recorded in dilute CCl_4 solution (Figure 1), where intermolecular hydrogen bonding has been eliminated. The data are given in Table I. Only isomer **2** was found to contain 100% free OH. For intramolecular bonded isomers **1**, **3**, and

Table I
Ir Spectral Data for 4-Phenylquinolizidin-1-ol Isomers in Dilute CCl_4 at 33°

		Free OH			Bonded OH···N	
Isomer	Mp, °C	ν_{OH}, cm^{-1}	B, l. mol^{-1} cm^{-2}	Mol %	ν_{OH}, cm^{-1}	$\Delta\nu_{OH}$, cm^{-1}
1	109–111	3630	300	7.5	3552	78
2	117–118	3637[a]	3970	100		
3	Liquid	3635	600	15	3549	86
4	133–134	3630	3200	80.5	3550	80

[a] Shoulder at 3610 cm^{-1}, assigned to a free OH rotamer form.[18]

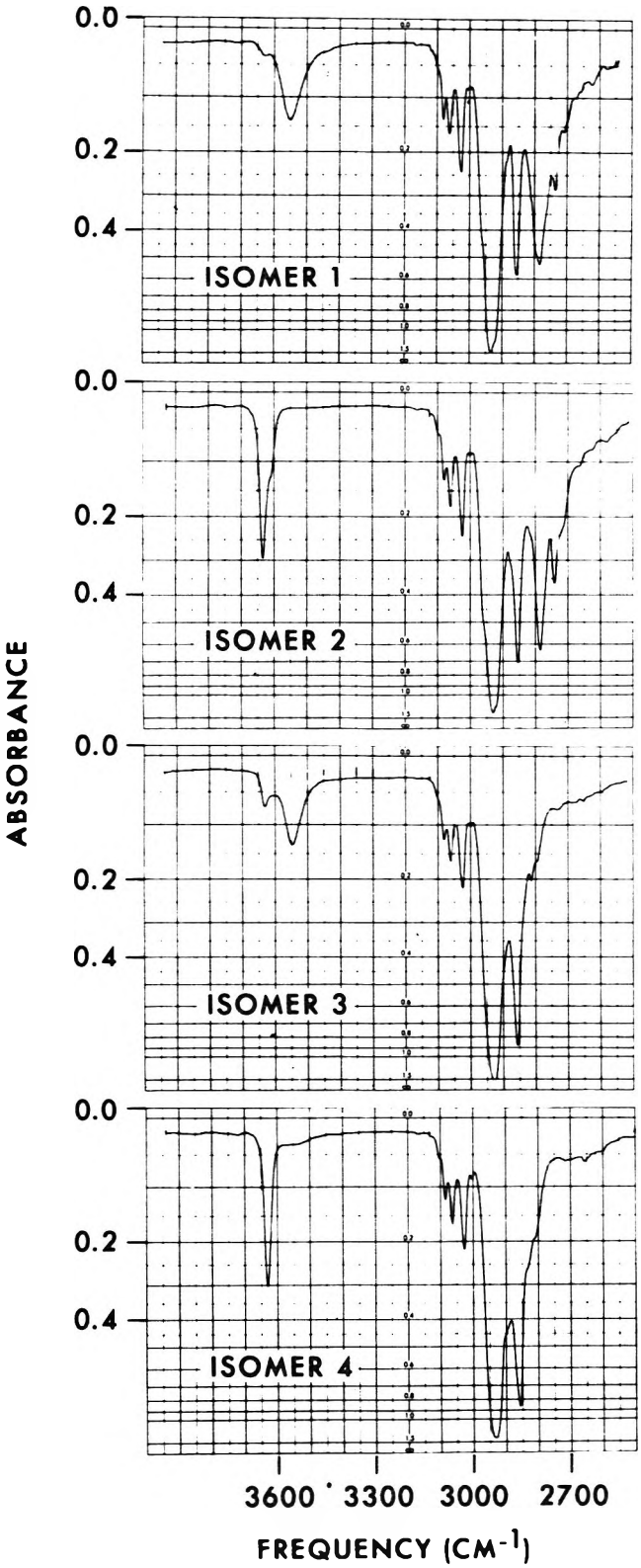
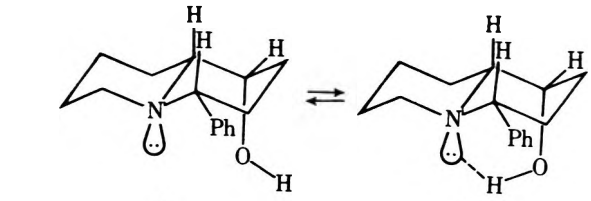


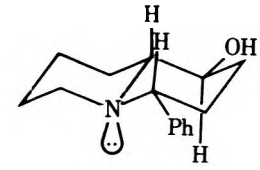
Figure 1. Dilute solution ir spectra of the 4-phenylquinolizidin-1-ol isomers in CCl_4, all at 2.6×10^{-3} *M*, 2-cm cell path.

4, the percentage of free OH was calculated from the area (*B*) of the free OH band of each, relative to that of isomer 2, as the 100% free-OH reference model.[18] For these closely related structures, the values are assumed to be accurate to ±3 mol %.

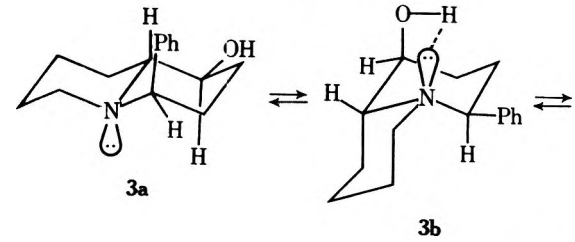
The NMR spectral data are given in the Experimental Section. The proton signals have been assigned by analogy to literature data, and are consistent with the configurational and conformational assignments given below.

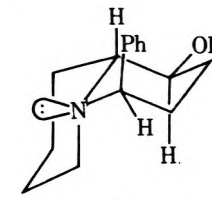


cis-1,4,10-H

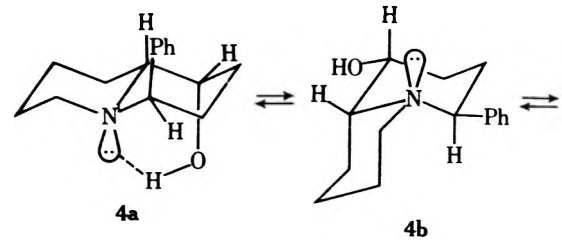


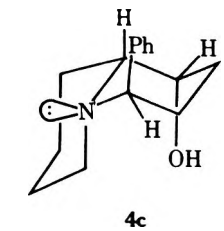
cis-4,10-H





cis-1,4-H

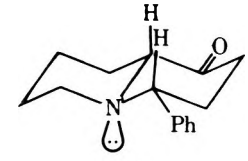




cis-1,10-H

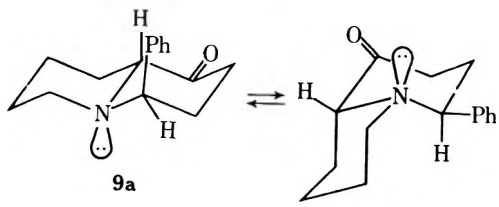
Discussion

Ketone Epimers 8 and 9. Ketone 8 is assigned a trans ring fusion with a preferred equatorial 4-phenyl substituent (hence, cis-4,10-H configuration, as shown), based on the strong Bohlmann bands[19] observed in the 2700–2800-cm^{-1} region of its ir spectrum. Conversely, an 8–9 mixture



cis-4,10-H

had only weak absorption in this region, which suggests that **9** exists in solution in an equilibrium, which contains an appreciable amount (predominant if calculated by methods given below) of the cis quinolizidine form (**9b**).



9a ⇌ **9b**

trans-4,10-H

Regardless of the exact equilibrium position, however, the ir data are consistent with a **9** trans-4,10-H configuration, since even the trans-fused form **9a** should absorb relatively weakly in the Bohlmann region, because it has a 4-axial substituent, hence contains only one *secondary* hydrogen anti-trans to the N-electron pair.[20]

Alcohol Isomers 1–4. The structural formulas and conformational equilibria of these isomers have been assigned as discussed below. Although each isomer, of course, exists in equilibrium between one trans- and two cis-fused conformers, except for structure **4c**, only those forms which are present in any significant concentration are shown. Also, only one enantiomer of each isomer is depicted, although they all exist (also 8 and **9**) as a racemic pair. Thus, a trans ring fusion for amino alcohol isomers **1** and **2** and a predominantly cis ring fusion for isomers **3** and **4** are assigned from the presence and absence, respectively, of the Bohlmann ir bands, corresponding to a preferred equatorial 4-phenyl substituent for each, in agreement with the assignment of the 4-phenylquinolizidine isomers.[8] Previously, the 1- and 3-hydroxyquinolizidines were found to exist with a trans ring fusion, and this stereochemistry was not affected by an intramolecular OH···N hydrogen bond that would be formed in a cis-fused form.[21] Therefore, the configuration of each hydroxyl group in **1–4** may be assigned based on whether it is predominantly free or hydrogen bonded in its dilute solution ir spectrum. For **1**, the 7.5 mol % free OH absorption at 3630 cm^{-1} is assigned to an OH rotamer form (**1a**), in which the axial OH group is oriented away from the nitrogen electron pair. Such a rotamer form (i.e., band) has been observed in weakly bonded OH···N systems,[22] but was not detected in the bonded isomers of 1- and 3-hydroxyquinolizidine,[21] apparently because of their slightly stronger hydrogen bonds ($\Delta\nu \sim 100$ cm^{-1} in CCl_4),[18] compared to **1**. An alternate possibility, whereby this free OH band might be due to a cis ring-fused conformer of **1**, is excluded by the extremely unfavorable syn-axial steric interactions that exist in such a structure.

In the case of isomers **3** and **4**, the presence of both free OH and OH···N bonded species is undoubtedly due, based on conformational analysis, to the presence of a significant concentration of both cis- and trans-fused quinolizidine conformers in the equilibrium mixture. Therefore, for these isomers, all three ring-fused species must be considered. In **4**, however, the concentration of **4c** can be ignored, owing to the unfavorable syn-axial OH–CH_2 interactions that are present in this form. In **3**, a small percentage of **3c** can also be ignored, to a first approximation, in order to simplify the calculations. Then, as shown below, the results can be corrected to reflect the presence of this species. First, the total free OH observed for **3** and **4** (Table I) must be divided into that which is due to equatorial OH conformations **3a** and **4b**, and that which is due to a nonbonded OH rotamer form of axial OH conformations **3b** and **4a**, respectively. Therefore, taking the 7.5:92.5 ratio observed for the comparably strongly bonded (based on $\Delta\nu_{OH}$, Table I) **1a–1b** equilibrium, and applying it to **3** and **4**, one calculates 7 mol % free OH rotamer form associated with 85 mol % **3b**, and about 1.5 mol % free OH rotamer form with 19.5 mol % **4a**. On this basis, one calculates free OH species **3a** equal to 8 mol % (15 − 7%), and **4b** to 79 mol % (80.5 − 1.5%), respectively. Then, as calculated for conformational equilibria in other hydrogen-bonded systems,[23] the **3a–3b** equilibrium may be defined by the free-energy difference between the two conformations, as

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = \Delta G^\circ_{\mathbf{3b}} - \Delta G^\circ_{\mathbf{3a}} \quad (1)$$

The $\Delta G^\circ_{\mathbf{3a}}$ and $\Delta G^\circ_{\mathbf{3b}}$ values in turn are calculated from the algebraic sum of the individual syn-axial and peri[24a] conformational interactions, taking repulsive interactions as positive, and attractive interactions as negative, in sign. Thus, **3b**, the dominant species, is favored by the conformational free energy of the hydrogen bond ($\Delta G^\circ_{OH\cdots N}$), but is opposed by the inherent conformational preference for the trans quinolizidine ring fusion (ΔG°_Q).[3,4] In addition, **3b** is opposed by both a syn-axial interaction of the OH group with the 3β hydrogen (ΔG°_{OH-H}) and a peri interaction of the phenyl group with the 6α hydrogen, that is essentially equivalent to a syn-axial Ph–H interaction. Conformation **3a**, in turn, is opposed by three syn-axial Ph–H interactions (involving the 2, 6, and 10β hydrogens), plus a peri interaction of the hydroxyl group with the 9β hydrogen that is essentially equivalent to a syn-axial OH–H interaction. Therefore, the **3** equilibrium may be defined, according to eq 1, by

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = (\Delta G^\circ_Q + \Delta G^\circ_{OH-H} + \Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH\cdots N})_{\mathbf{3b}} - (3\Delta G^\circ_{Ph-H} + \Delta G^\circ_{OH-H})_{\mathbf{3a}} \quad (2)$$

which reduces to

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = \Delta G^\circ_Q - 2\Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH\cdots N} \quad (3)$$

By a similar analysis of the **4a–4b** equilibrium, in which the intramolecular OH···N bond is now in conformational opposition to the dominant species (**4b**), the system may be defined by

$$-RT \ln (\mathbf{4b})/(\mathbf{4a}) = (\Delta G^\circ_Q + \Delta G^\circ_{Ph-H} + \Delta G^\circ_{OH-H})_{\mathbf{4b}} - (3\Delta G^\circ_{Ph-H} + 2\Delta G^\circ_{OH-H} - \Delta G^\circ_{OH\cdots N})_{\mathbf{4a}} \quad (4)$$

which reduces to

$$-RT \ln (\mathbf{4b})/(\mathbf{4a}) = \Delta G^\circ_Q - 2\Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH-H} + \Delta G^\circ_{OH\cdots N} \quad (5)$$

Conformational Free Energy of the Intramolecular Hydrogen Bond ($\Delta G^\circ_{OH\cdots N}$). If one subtracts eq 5 from eq 3, and substitutes (from above) the values of **3a** (8%), **3b** (85%), **4a** (19.5%), and **4b** (79%), one obtains

$$-0.6 = -2\Delta G^\circ_{OH\cdots N} + \Delta G^\circ_{OH-H} \quad (6)$$

Substituting here for ΔG°_{OH-H} 0.35 kcal/mol (from one-half the conformational value of the hydroxyl group in aprotic media[24b]) gives $\Delta G^\circ_{OH\cdots N}$ = 0.5 kcal/mol (attractive) in **3b** and **4a**, *independent of the actual values of* ΔG°_Q *and* ΔG°_{Ph-H}. If one now refines this calculation to reflect (see below) the presence of 3% of free OH species **3c**, a corrected concentration for **3a** of 5% should have been used in eq 3. On this basis, subtracting eq 5 from eq 3 gives

$$-0.85 = -2\Delta G^\circ_{OH\cdots N} + \Delta G^\circ_{OH-H} \quad (7)$$

from which $G^\circ_{OH\cdots N}$, corrected, is calculated to be 0.6 kcal/mol. The value of $\Delta G^\circ_{OH\cdots N}$ thus derived (for $\Delta\nu$ 83 ± 3 cm^{-1}) is in good agreement with that (0.5 kcal/mol, for $\Delta\nu$

100 cm^{-1}) recently calculated (but less rigorously) for other OH···N systems.[23]

Conformational Free Energy of the Quinolizidine Equilibrium ($\Delta G°_Q$). If one defines the **3b–3c** equilibrium, as above, one obtains

$$-RT \ln (\mathbf{3c})/(\mathbf{3b}) = (2\Delta G°_{Ph\text{-}H} + \Delta G°_{OH\text{-}H})_{\mathbf{3c}} - (\Delta G°_{Ph\text{-}H} + \Delta G°_{OH\text{-}H} - \Delta G°_{OH\cdots N})_{\mathbf{3b}} \quad (8)$$

which reduces to

$$-RT \ln (\mathbf{3c})/(\mathbf{3b}) = \Delta G°_{Ph\text{-}H} + \Delta G°_{OH\cdots N} \quad (9)$$

Substituting for $\Delta G°_{Ph\text{-}H}$ 1.55 kcal/mol (from one-half the conformational value of a phenyl group[24b]) and for $\Delta G°_{OH\cdots N}$ 0.5 or, corrected, 0.6 kcal/mol gives 3% **3c** in equilibrium with 85% **3b** at 33°. On this basis, one calculates **3a** equal to 5 mol % (8–3%), when corrected for free OH species **3c** that is also present. If one now adds eq 3 and 5, taking the corrected value of **3a** (5%), one obtains

$$-2.55 \text{ kcal/mol} = 2\Delta G°_Q - 4\Delta G°_{Ph\text{-}H} - \Delta G°_{OH\text{-}H} \quad (10)$$

Substituting for $\Delta G°_{OH\text{-}H}$ 0.35 kcal/mol and for $\Delta G°_{Ph\text{-}H}$ 1.55 kcal/mol gives $\Delta G°_Q$ 2.0 kcal/mol, in favor of the trans quinolizidine ring fusion. As here derived, this result is *essentially independent of the actual value of* $\Delta G°_{OH\cdots N}$, but reasonably assumes that $\Delta G°_{OH\cdots N}$ is essentially the same (if not identical, based on $\Delta\nu_{OH}$ 83 ± 3 cm^{-1}) in **3b** and **4a**. Any difference in $\Delta G°_{OH\cdots N}$ in these two species will reflect in the probable error of $\Delta G°_Q$. In these calculations, no specific conformational value was assigned to the nitrogen electron pair, hence its conformational factor (if any) will be contained within $\Delta G°_Q$.

Probable Error in $\Delta G°_{OH\text{-}N}$ and $\Delta G°_Q$ Values, and Application of the Results to Other Systems. By directly comparing the **3** and **4** equilibria, values for the individual syn-axial interactions need not be assigned (except for $\Delta G°_{Ph\text{-}H}$ and $\Delta G°_{OH\text{-}H}$ in eq 10, and $\Delta G°_{OH\text{-}H}$ in eq 6 and 7), since they are presumably equivalent in either system. Therefore, the probable error in the calculated values of $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$ is mainly due to the uncertainty in the measured values (Table I) of the free OH band areas of **2**, **3**, and **4**. For these closely related systems, **2** should be the perfect 100% free OH reference model. We find that an absolute deviation of ±5 mol % in the assigned values for each of **3a**, **3b**, **4a**, and **4b** results in a probable error of ±0.35 kcal/mol in the calculated values of $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$, while a ±3 mol % error in the individual conformer assignments corresponds to a probable error of ±0.2 kcal/mol in each of the two calculated values. We believe that the probable error in the conformer assignments is less than ±5 mol %. In view of the various other assumptions and assignments that are required in these calculations, however, we estimate the reliability of the values calculated above for $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$ to be on the order of ±0.35 kcal/mol.

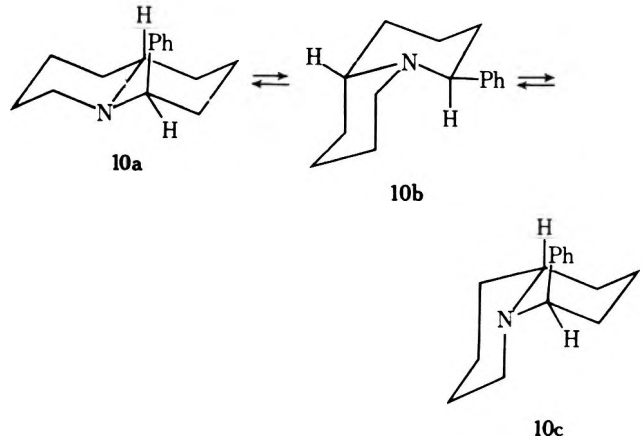
From the above results, the conformer population of *trans*-4,10-*H*-4-phenylquinolizidine[8] (**10**) can now be readily assigned. Thus, the **10** equilibrium may be defined, in part (for **10a**, **10b**), according to eq 1, by

$$-RT \ln (\mathbf{10b})/(\mathbf{10a}) = (\Delta G°_Q + \Delta G°_{Ph\text{-}H})_{\mathbf{10b}} - (3\Delta G°_{Ph\text{-}H})_{\mathbf{10a}} \quad (11)$$

and in part (for **10b**, **10c**) by

$$-RT \ln (\mathbf{10c})/(\mathbf{10b}) = (2\Delta G°_{Ph\text{-}H})_{\mathbf{10c}} - (\Delta G°_{Ph\text{-}H})_{\mathbf{10b}} \quad (12)$$

Substituting for $\Delta G°_Q$ 2.0 ± 0.35 kcal/mol and $\Delta G°_{Ph\text{-}H}$ 1.55 kcal/mol as above, and solving these two equations (taking **10a** + **10b** + **10c** = 100%), one calculates 86 ± 6% cis-fused species (80% **10b** and 6% **10c**) in the equilibrium mixture at 25°.



These results are particularly applicable to the conformational analysis of other 4-aryl substituted quinolizidine systems, including the Lythraceae alkaloids.[25] Vertaline, for example, which has been found to exist as a cis quinolizidine (as the hydrobromide) in the crystal,[26] as the *free base* should exist in solution as an equilibrium mixture which, according to our calculations, should actually favor the trans-fused conformation, by ~0.4 kcal/mol.

It should be noted that the value of $\Delta G°_Q$ derived above is specifically applicable only to derivatives of *trans*-4,10-*H*-4-phenylquinolizidine; it is only approximately applicable to other systems. Thus, for example, the value of $\Delta G°_Q$ for completely unsubstituted quinolizidine will actually differ from 2.0 kcal/mol by the difference in the conformational contribution of a gauche interaction of a phenyl–nitrogen electron pair (in **3b** and **4b**), compared to that of a gauche hydrogen–nitrogen electron pair interaction in the unsubstituted parent. This difference is probably small, however, and may even be within the experimental error of these methods, if one assumes that $\Delta G°_Q$ in the unsubstituted parent is approximately 2.6 kcal/mol,[27] as suggested by our earlier study,[3] and as calculated from the three gauche CH_2–H interactions that are present in the cis- but absent in the trans-fused form.[24c] However, a rigorous determination of $\Delta G°_Q$ for unsubstituted quinolizidine would better be obtained from the study of other quinolizidinol compounds.

Experimental Section

Dilute solution ir spectra (Figure 1) were recorded on a Perkin-Elmer 521 spectrophotometer and the mole percent values were calculated as described;[18] all other ir spectra were recorded on a Perkin-Elmer 237B spectrophotometer. NMR spectra were recorded on a Varian A-60D spectrometer, and mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer.

Ethyl Pipecolate (5). Ethyl picolinate (20 g, Aldrich Chemical Co.) was hydrogenated in an excess of aqueous HCl over platinum dioxide (0.75 g, J. Bishop & Co.) at 60 psig for 18 hr at room temperature in a Parr hydrogenator. After the catalyst was filtered off, the solution was brought to pH 10 and extracted with chloroform. The organic solution was then dried (Drierite), concentrated, and distilled at a pot temperature below 65°, recovery 17 g (85%) of **5**, bp 36–38° (0.3 mm). The product is best stored in the freezer, since it slowly dimerizes (with elimination of ethanol) on standing at room temperature.[28]

Ethyl 4-Bromo-4-phenylbutyrate (6). 5-Phenyldihydrofuranone (5-phenyl-γ-butyrolactone, Regis Chemical Co.) (20 g, 0.12 mol) was dissolved in 60 ml of absolute ethanol in a 200-ml round-bottom flask equipped with a thermometer, drying tube, and magnetic stirring bar. The stirred solution, maintained at 15°, was saturated during 3 hr with anhydrous HBr (Mathieson Gas Products), introduced through a Drierite tower. The mixture was allowed to warm overnight to room temperature, then was shaken with an equal volume of water, and the aqueous phase was extracted with ether. The combined ether–organic phase was washed

three times with sodium bicarbonate solution, then dried (Drierite) and concentrated on a rotary evaporator under reduced pressure at room temperature. An oil (28 g) was obtained, which contained 74% of **6** (62% yield), calculated from the weight of sodium bromide that precipitated, when an aliquot of the solution was warmed on the steam bath with an excess of sodium iodide in acetone. Except for residual solvent, the product appeared to be relatively pure, based on its ir spectrum (CCl_4): 1738 cm^{-1} (C=O), with only a trace of starting lactone (1795 cm^{-1}). For fear of possible dehydrohalogenation, no attempt was made to distil the product, or to remove the remaining solvent by heating under vacuum.

Diethyl Pipecolate-1-(4-phenyl-4-butyrate) (7).[29] Compound **6** (31 g, 0.072 mol based on 80% purity, by sodium iodide assay described above) was added in 5 min, dropwise with stirring, to 16 g (0.10 mol) of **5** in 75 ml of anhydrous acetone, which contained 28 g (0.20 mol) of a suspension of anhydrous potassium carbonate. After being stirred for 30 min at room temperature, the mixture was refluxed with stirring for 2 hr, then left to stand at ambient temperature over a 3-day weekend. The salts were filtered and washed with acetone, and the filtrate was concentrated under reduced pressure with gentle warming, at which time a precipitate began to form. After standing overnight, the residual oil was dissolved in ether, and the mixture was filtered to give ~1 g of (presumably) ethyl pipecolate hydrobromide, needles, mp 183–185°. Apparently, the original reaction had not been fully completed, and this salt was formed from the continued reaction of residual **5** and **6**, after the K_2CO_3 had been removed. The ethereal solution thus obtained was dried ($MgSO_4$), filtered, and concentrated on the steam bath, then under reduced pressure on a rotary evaporator to give 38 g of the crude product. This product (7 g) was subjected to a molecular distillation at 1 μ, and after a low-boiling forerun was removed (75–88° bath), the desired **7** was collected (5 g, 85%) at an oil bath temperature of 125–155°. This product appeared to be about 97% pure by GLC (retention time of 8 min, 10-ft column of 10% SE-30 at 255°, 30 ml/min): ir (CCl_4) 1735 (C=O, singlet), with (phenyl) bands at 3045, 3075, and 3100 cm^{-1}. It was not further characterized, but was used directly in the next step.

1-Oxo-4-phenylquinolizidine (8 and 9).[30] To a suspension of 1.5 g of sodium hydride (Ventron Corp., 57% in oil, 0.035 mol) in 40 ml of sodium-dried toluene in a 250-ml round-bottom flask equipped with a nitrogen inlet tube, dropping funnel, reflux condenser with drying tube, and magnetic stirrer was added 5.2 g (0.015 mol) of **7** in 60 ml of dry toluene. No evidence of any hydrogen evolution was observed until the mixture was heated. It was refluxed until hydrogen evolution had ceased (3 hr), then cooled in an ice bath, and 100 ml of 6 *N* hydrochloric acid was slowly added. A gummy precipitate formed. The mixture was refluxed, carbon dioxide evolution occurred, and the precipitate slowly dissolved. After 5 hr, carbon dioxide evolution could no longer be detected. The mixture was then cooled to room temperature, and the layers were separated. The aqueous phase was cooled in an ice bath and brought to pH 9 by slowly adding a concentrated sodium hydroxide solution. The product precipitated as a tan solid mixture of **8** and **9**, and was filtered off. The filtrate was brought to pH 10, and a little additional product was obtained. As described below, these ketones were found to be unstable; therefore, the two crops were combined and used directly (wet) in the next step. From the yield of alcohol isomers **1–4**, isolated in the next step, about a 90% yield of **8** and **9** had been obtained.

In an earlier experiment, the **8–9** product mixture (95% **8**, by GLC) obtained in this way was found to be completely soluble in ether. However, this product deteriorated on standing to produce an ether-insoluble residue, accompanied by a decrease (GLC) in the relative percentage of isomer **9** in the mixture. A 0.4-g sample of the mixture was chromatographed on 40 g of neutral alumina (Woelm, Grade I), and eluted with 1:1 ether–petroleum ether. The eluent was collected in 20-ml fractions, and the solvent was removed on a rotary evaporator. The composition of each fraction was determined by GLC on a 10-ft column of 10% SE-30 at 240°, at 85 ml/min helium flow. Under these conditions, the relative retention times were 5.0 (**8**) and 5.8 min (**9**), with irregular tailing of the peaks, possibly owing to some decomposition. Fractions 2 plus 3 gave 0.22 g of pure **8**, mp 89–92°, as white, crystalline stars, which darkened even when stored in the refrigerator: ir (CCl_4) 1725 (C=O), 3035, 3070, and 3090 (phenyl), 2720 (sh), 2740, 2750 (sh), and 2790 cm^{-1} (CH, Bohlmann bands). Fractions 4 plus 5 gave 41 mg of a yellowish oily product which contained (GLC) about 33% of **9**. Although the pure **9** was not isolated, the relative intensity of the Bohlmann bands in the ir spectrum of this mixture was much smaller than that of the pure **8**. Ketones **8** and **9** were not further characterized, but were reduced to the corresponding amino alcohols under a variety of chemical and catalytic conditions.[31] The best preparative route to the total carbinol isomer mixture (i.e., which gave the largest percentage of minor isomer **3**) is reported below.

4-Phenylquinolizidin-1-ol Isomers (1–4). The mixture of isomers **8** and **9** (from 5.2 g of **7**) was dissolved in 75 ml of methanol, and shaken in a Parr hydrogenator at 50 psig hydrogen with 0.2 g of platinum dioxide (J. Bishop Co.) for 40 min, at which time the hydrogen uptake had ceased. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator to give a mixture which consisted (GLC)[32] of 80% **1**, 16% **2**, 1% **3**, and 3% **4**. The remaining methanol was then removed, and the residue was taken up in ether, filtered to remove a small insoluble residue, concentrated to about 25 ml, cooled, and seeded with a crystal of **1** (obtained from earlier hydrogenation experiments) to give 1.3 g of mainly **1**, mp 103–107° (from GLC, 93% **1**, 6% **2**, a trace of **3**, and about 1% of **4**). The filtrate was concentrated to dryness, and the residue (1.3 g) was chromatographed on 170 g of Woelm neutral alumina (1 × 11 in. column) in ether, using ether as the eluent, and a slight positive pressure to speed the flow. After 100 ml of blank solvent was collected, the product began to elute. It was collected in 25-ml fractions, which were concentrated under reduced pressure, and examined by GLC. Fractions 1 and 2 contained a total of 0.55 g of pure **1**, mp 109–111°. Fractions 6–9 contained 82 mg of **2**, 97% pure by GLC (3% **1**), which was recrystallized from ether–petroleum ether to give 46 mg of pure **2**, mp 117–118°. Fractions 14–21 were combined to give pure **3**, obtained as 41 mg of pale yellow oil, after being pumped to constant weight over phosphorus pentoxide at 10 μ. This isomer could not be induced to crystallize. Fractions 25–38 gave 0.13 g of pure **4**, mp 133–134°. The melting points of **1** and **4**, above, did not change on recrystallization from ether–petroleum ether. Including the mixed isomer fractions, a quantitative recovery was obtained from the separation.

The mass spectra of the four isomers were very similar. All had major peaks (*m/e*) at 231 (mol wt) and 230 (loss of H), with the next major peaks (loss of H_2O) at 213 and 212, then 136 (loss of phenyl).

The NMR spectra of these isomers in $CDCl_3$ (internal Me_4Si) follow: **1**, δ 7.3 (s, 5, Ph), 3.8–3.4 (m, 1, CHOH), 3.1–2.4 (m, 3, OH, CHPh, and C_6 eq H), and 2.3–1.1 (m, 12); **2**, 7.25 (s, 5, Ph), 3.75–3.15 (m, 1, CHOH), 3.1–2.45 (m, 2, CHPh and C_6 eq H), and 2.4–1.0 (m, 13, including OH at 1.6); **3**, 7.3 (m, 5, Ph), 4.15–3.8 (m, 1, probably CHOH), 3.8–3.4 (m, 2, OH and probably CHPh), 3.35–2.1 (m, 3, C_6H_2 and $C_{10}H$), and 2.1–0.8 (m, 10); **4**, 7.3 (m, 5, Ph), 4.25–3.8 (m, 2, CHOH and CHPh), 3.5–3.1 (m, 1, $C_{10}H$), 2.95–2.4 (m, 2, C_6H_2), 2.25 (s, 1, OH), and 2.4–0.8 (m, 10). The position of the OH proton was assigned from the change in the spectrum obtained by either heating the solution or adding D_2O. The other proton assignments were made by analogy to those reported for the quinolizidin-1-ol[21] and 4-phenylquinolizidine[8a] systems.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.1. Found: **1**, C, 77.6; H, 9.5; N, 6.0; **2**, C, 77.7; H, 9.5; N, 6.2; **4**, C, 77.5; H, 9.6; N, 6.1.

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Registry No.—**1**, 56454-11-6; **2**, 56454-12-7; **3**, 56454-13-8; **4**, 56454-14-9; **5**, 15862-72-3; **6**, 56454-15-0; **7**, 56454-16-1; **8**, 56454-17-2; **9**, 56454-18-3; ethyl picolinate, 2524-52-9; 5-phenyldihydrofuranone, 1008-76-0; ethyl pipecolate HBr, 56454-19-4.

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Some Reactions of DL-*trans*-4,5-Dicarbomethoxy-2-phenyl-2-oxazoline

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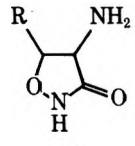
The synthesis and some anomalous reactions of the title compound (4) are discussed. Treatment of 4 with hydroxylamine caused oxazoline ring opening to form the amidoxime 5. When the diester 4 was saponified, the *O*-benzoyl zwitterion 6 crystallized from solution in excellent yield. The structure of 6 was secured by its rearrangement into DL-*threo*-*N*-benzoyl-β-hydroxyaspartic acid (10) and its conversion into DL-*threo*-β-hydroxyaspartic acid dimethyl ester. In contrast, the oxazoline ring in monoester 2 (R = H; R′ = CH_3) is stable to both hydroxylamine and alkali.

We have been interested in the synthesis of derivatives and analogs of the antibiotic cycloserine (1, R = H) for many years. Recently, we have been working toward the synthesis of a 5-carbamido analog (1, R = $CONH_2$) of cycloserine, since this compound might reasonably be expected to inhibit asparagine synthetase. Since the original synthesis[1] of cycloserine proceeded through an oxazoline intermediate, 2 (R = H), we decided to investigate a synthetic scheme using the oxazoline dicarboxylic acid (2, R = COOH; R′ = H).



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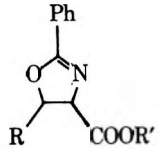
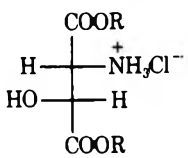


2

The starting material for this approach was β-hydroxyaspartic acid, the synthesis and stereochemistry of which we had investigated previously.[2] Esterification of the threo amino acid (3, R = H) followed by conversion of the ester into the oxazoline (4, R = CH_3) by reaction with ethyl benzimidate[3] was uneventful. The oxazoline ester was a crystalline compound, which was unstable at ambient temperatures but could be kept indefinitely in a refrigerator.



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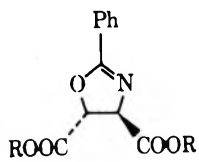
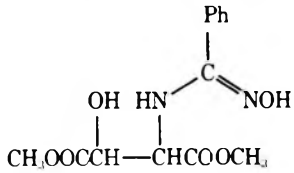


4

The difficulties with the oxazoline approach to 1 (R = $CONH_2$) began when attempts were made to convert the oxazoline ester into the corresponding dihydroxamic acid (4, RO = NHOH). The use of the standard methods of hydroxamic acid synthesis, i.e., treatment of the diester with at least 2 equiv of hydroxylamine in basic or neutral solution,[4] gave only highly colored products of a polymeric nature. All attempts to crystallize salts of the desired product from the mixture failed. Treatment of the crude product with ethanolic cupric acetate followed by isolation of the precipitated salts and liberation of the organic conjugate acids with hydrogen sulfide gave only tarry products. When, however, 4 was treated with 1 equiv of methanolic hydroxylamine, a white crystalline product, $C_{13}H_{16}N_2O_6$, was obtained in yields of 35–71%. The empirical formula indicated that 1 mol of oxazoline had combined with 1 mol of hydroxylamine. Significantly, the ester functions of the starting material were still present in this product as shown by infrared, NMR, and ^{13}C NMR spectroscopy. It gave a negative $FeCl_3$ test, but showed positive Tollens and Griess[5] tests indicating the presence of a reducing group, probably –NHOH or =NOH, in the molecule. Of all the possible structures considered, only the amidoxime structure 5 was consistent with all the spectral and chemical data. Importantly, when the proton decoupled ^{13}C NMR spectrum of the ester 4 (R = CH_3) was compared with that of the unknown compound, a signal at 152.2 ppm in the

spectrum of the latter had to be assigned to the carbon atom which had appeared at the 2 position in the oxazoline ring. This chemical shift is too far upfield for a carbonyl or oxazoline carbon atom, but was very close to the amidoxime carbon in benzamidoxime (150.8 ppm). These data, thus, confirmed the structure 5 for that of the hydroxylamine adduct. The reaction of imino esters with hydroxylamine to form amidoximes has been reported,[6] but, to our knowledge, the conversion of an oxazoline (cyclic imino ester) into an amidoxime has not been reported. This specific case of amidoxime formation seems to us even more unexpected in light of the conversion by hydroxylamine of the oxazoline ester (2, R = H; R′ = CH_3) into a hydroxamic acid in excellent yield.[4] It is difficult to understand why the presence of the 5-carbomethoxy group should cause the results of this reaction to be so completely different.



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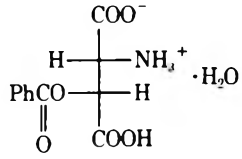
The enhanced reactivity of 4 at C-2 is reflected also in the opening of the oxazoline ring in the saponification of 4. The acid obtained on acidification crystallized as a hydrate[7] which on drying lost 1 mol of water. The spectral and analytical data and a positive ninhydrin reaction indicated that the acid was not the expected oxazoline 4 (R = H), but rather DL-*threo*-*O*-benzoyl-β-hydroxyaspartic acid monohydrate (6). This structure was consistent with the fact that when 6 was treated with thionyl chloride at room temperature, a hydrochloride (7) rather than an oxazoline



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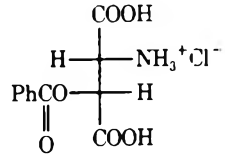
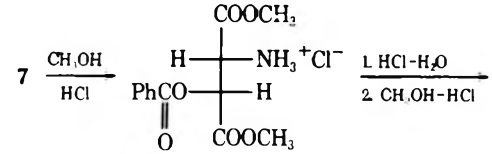


7

acid chloride hydrochloride was obtained. Dilute bicarbonate converted 7 back to 6 in excellent yield. The structure and configuration of 7 was confirmed by its conversion to the known DL-*threo*-β-hydroxyaspartic acid dimethyl ester hydrochloride[2,8] (9). Direct methanolysis of 7 to 9 failed



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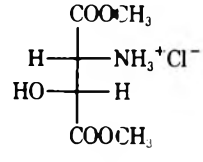

9

when it was found that 8 was the only product. Surprisingly, 8 was stable to refluxing saturated methanolic hydrogen chloride for 5 days. It was necessary to *hydrolyze* 8 to the crude acid and subsequently to convert the acid into the ester 9. This extreme difficulty of ester methanolysis is reminiscient of difficulty experienced in the acid hydrolysis of an α-amino acetal in which the proximity of the positively charged amino function presumably retarded the reaction.[9] The fact that the threo ester (9) was finally obtained shows that no inversion of configuration had occurred in the formation of the acid 6 from 4. One of the most interesting aspects of the acid 6 was its slow (72 hr) conversion in Me_2SO-d_6 into DL-*threo*-*N*-benzoyl-β-hydroxyaspartic acid (10). Both 10 and its erythro isomer were synthesized by benzoylation of the amino acids for spectral comparison with the rearrangement product. This is an example of a very slow O → *N*-acyl migration under very mildly basic (Me_2SO solution) conditions. In fact, when 6 was allowed to stand in aqueous basic solution overnight, 10 was obtained in excellent yield.

The fact that the oxazoline ring in 4 (R = CH_3) was destroyed under the saponification conditions was not unexpected, but the isolation of a highly crystalline water-insoluble zwitterion like 6 was very much unexpected. In one case, the dipotassium salt of the saponification product was isolated and its ^1H NMR and ^{13}C NMR spectra were determined. The C-4 and C-5 protons were present as in the oxazoline, not as they appear in the *N*-benzoyl derivative, 10, and the C-2 carbon atom appeared as expected at 167.2 ppm (Me_2SO-d_6). Apparently the oxazoline ring *was* intact until the solution was acidified giving the fortuitously insoluble zwitterion, 6. Under similar conditions of saponification, the oxazoline monoester 2 (R = H; R′ = CH_3) gave the corresponding oxazoline acid in excellent yield.

The exhanced reactivity of the oxazoline 2 position in 4 (R = CH_3) as compared to 2 (R = H; R′ = CH_3) can be rationalized by invoking the electron-withdrawing inductive effect of the 5-carbomethoxy group, but it would seem to be only a partial explanation for the apparent total redirection of the reaction of 4 with hydroxylamine.

Experimental Section

All melting points were taken on a Nalge-Axelrod hot stage and are uncorrected. Infrared spectra were recorded on either a Perkin-Elmer Infracord Model 257 or Model 631. The proton NMR spectra were recorded using either a Varian T-60 or HA-100 spectrometer and were calibrated by the side band modulation technique with either tetramethylsilane (Me_4Si) or 3-(trimethylsilyl-)propanesulfonic acid sodium salt as the internal standard. ^{13}C NMR spectra were recorded on a Jeol spectrometer using Me_4Si as a standard and chemical shifts were determined by computer scan. Radial paper chromatography was carried out on 31-cm Whatman No. 1 circles having a 1-cm diameter center hole. Compounds were visualized using ninhydrin (N). Thin layer chromatography was carried out on Kodak ultraviolet-sensitive silica gel sheets and was visualized in a uv lamp box.

Starting Materials. DL-*threo*-β-Hydroxyaspartic acid and DL-*erythro*-β-hydroxyaspartic acid were prepared by the method of Jones and Stammer[2] in 93% yield and benzamidoxime was prepared according to the method of Tiemann.[10]

DL-*trans*-2-Phenyl-4,5-dicarbomethoxy-2-oxazoline (4).[11] To a solution of 4.9 g (26 mmol) of ethyl benzimidate hydrochloride in 50 ml of *N*,*N*-dimethylformamide (DMF) was added 4 ml (29 mmol) of triethylamine and the solution was stirred for 10 min. A solution of 5.4 g (26 mmol) of 3 (R = CH_3) hydrochloride in 30 ml of DMF was added and the reaction mixture was stirred at room temperature for 24 hr. The resulting orange solution was concentrated in vacuo and 50 ml of water and 100 ml of ether were added. The resulting water layer was extracted with three 100-ml portions of ether and the combined ether layers were extracted with three 100-ml portions of water. After drying with anhydrous magnesium sulfate, the ether solution was percolated through a thin pad of Woelm No. 1 grade neutral alumina to remove the reddish-orange color. The resulting colorless solution was concentrated to yield 3.30 g of 4 which was recrystallized from ether–petroleum ether: 3.2 g (54%); mp 59–60°; ir (Nujol) 1750 (C=O), 1660 cm^{-1} (C=N); ^1H NMR (Me_2SO-d_6) δ 4.0 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 5.7 (d, 1 H, CHN, J = 6 Hz), 6.3 (d, 1 H, CHO, J = 6 Hz), 8.0 ppm (m, 5 H, Ph); ^{13}C NMR (off resonance, Me_2SO-d_6) 169.1 (s, C=O), 168.3 (s, C=O), 163.5 (s, C=N), 131.7–125.4 (m, phenyl), 77.6 (d, C—5), 71.7 (d, C—4), 52.4 (q, CH_3, both esters).

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 58.89; H, 5.07; N, 5.48.

DL-*threo*-*N*-(1-Hydroxyiminobenzyl)-β-hydroxyaspartic Acid Dimethyl Ester[12] **(5).** To a solution of 262 mg (3.8 mmol) of

NH_2OH·HCl in 15 ml of absolute methanol was added 8.0 ml (3.8 mmol) of 0.48 *N* sodium methoxide and the solution was stirred for 10 min. The mixture was filtered and the filtrate was added to a solution of 1.00 g (3.8 mmol) of **4** (R = CH_3) in absolute methanol. The solution was stirred at 25° for 1 hr after which the white precipitate (239 mg) was collected. A second crop was obtained (146 mg) after allowing the filtrate to stand at 5° overnight, bringing the total yield to 385 mg of **5** (35%): mp 163–166° dec; ir (Nujol) 3448 (OH), 3390 (NH), 1754 (C=O, esters), 1645 (C=N, oxime); ^{1}H NMR (Me_2SO-d_6) δ 4.1 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3), 5.1 (m, 2 H, CHN and CHO), 7.8 ppm (m, 5 H, Ph); ^{13}C NMR (off resonance, Me_2SO-d_6) 170.4 (s, C=O), 169.6 (s, C=O), 152.2 (s, C=NOH), 131.1–127.1 (m, phenyl), 70.4 (d, MeO_2C-CHOH), 58.2 (d, MeO_2C-CHNH), 51.7 (q, CH_3 esters).

Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.45. Found: C, 52.81; H, 5.43; N, 9.27.

DL-*threo*-*N*-Benzoyl-β-hydroxyaspartic Acid (10). In a 250-ml round-bottom flask equipped with a stirrer and pH electrode, 1.0 g (6.7 mmol) of DL-*threo*-**3** (R = H) was placed in 14 ml of 1 *N* LiOH and the mixture was stirred mechanically until the solid dissolved. After addition of 3 ml of dimethoxyethane (DME) to the mixture, 940 mg (6.7 mmoles) of benzoyl chloride dissolved in 3 ml of DME was slowly added. The pH of the mixture was kept above 10.0 by the slow addition of 7.0 ml of 1.0 *N* LiOH and after 1 hr the solution was acidified to pH 1.8 with 1.0 *N* HCl. The acidic reaction mixture was extracted with three 50-ml portions of ethyl acetate, and the combined extracts were dried over anhydrous $MgSO_4$ and evaporated to dryness in vacuo to a pale yellow oil which solidified within a few minutes. The white crystals were washed with ether and dried in vacuo to yield 1.60 g (95%) of crude benzoyl derivative. The product was recrystallized from water: mp 173–175°; ir (Nujol) 3380 (NH), 1760 (C=O, acid), broad 1740 (C=O, acid), 1650 cm^{-1} (C=O, amide); ^{13}C NMR (Me_2SO-d_6) (proton decoupled, Me_4Si external standard) 172.4 (C=O, acid), 170.7 (C=O, acid), 166.4 (C=O, amide), 133.6–127.2 (phenyl), 70.7 (β carbon), 55.6 ppm (α carbon); ^{1}H NMR (Me_2SO-d_6) δ 4.66 [*d*, 1 H, *J* = 3 Hz, -CH(OH)-], 5.01 (q, 1 H, *J* = 3, 8 Hz, -CHNHCOPh), 7.70 (m, 5 H, phenyl), 8.16 ppm (d, 1 H, *J* = 8 Hz, -NHCOPh).

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.25; H, 4.40; N, 5.46.

DL-*erythro*-*N*-Benzoyl-β-hydroxyaspartic Acid. This compound was prepared by the same procedure used for **10**. DL-*erythro*-**3** (R = H) (1.12 g) afforded 1.30 g (68%) of the erythro isomer, mp 157. Recrystallization from ethyl acetate–hexane (1:1) gave an analytical sample: mp 160–161°; ir (Nujol) 3455 (OH), 3390 (NH), 1745 and 1705 (C=O, acid), and 1625 cm^{-1} (CONH); ^{1}H NMR (Me_2SO-d_6) δ 4.44 [d, 1 H, *J* = 3 Hz, -CH(OH)], 5.10 (q, 1 H, *J* = 3, 8 Hz, -CHNH), 7.73 (m, 5 H, phenyl), 8.33 ppm (d, 1 H, *J* = 8 Hz, -CONH-); ^{13}C NMR (Me_2SO-d_6, proton decoupled; Me_4Si external standard) 172.2 (COOH), 170.3 (COOH), 166.2 (-CONH-), 133.7–127.3 (phenyl), 70.9 (β carbon), 55.8 ppm (α carbon).

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.38; H, 4.41; N, 5.61.

DL-*threo*-*O*-Benzoyl-β-hydroxyaspartic Acid (6) Monohydrate. One gram (3.8 mmol) of **4** (R = CH_3) was placed in 55 ml of DME to which 304 mg (7.6 mmol) of NaOH pellets previously dissolved in 20 ml of water was added. The solution was stirred at room temperature for 10 min and the resulting clear solution was acidified with 0.1 *N* HCl to pH 2.0. A fine white precipitate was filtered and recrystallized from water to give 900 mg (93%) of pure **12**: mp 190–191°; ir (Nujol), 3500 (NH), 3240, 3350 (OH), 1720 (C=O, acid); 1670 cm^{-1} (NH-H_2O); ^{1}H NMR (Me_2SO-d_6, Me_4Si external standard) δ 7.8 (m, 5 H, phenyl), 6.7 (m, 6 H, H_2O, NH. 2 CO_2H, OH), 5.7 (d, 1 H, HC-5, *J* = 8 Hz), 4.3 ppm (d, 1 H, HC-4, *J* = 8 Hz); ^{13}C NMR (Me_2SO-d_6, Me_4Si external standard proton decoupled) 167.8 (C=O, acid), 167.6 (C=O, acid), 164.3 (PhC=O), 133.3–128.2 (phenyl), 70.2 (COC), 52.5 ppm (CNH).

Anal. Calcd for $C_{11}H_{13}NO_7$: C, 48.71; H, 4.83; N, 5.16. Found: C, 48.78; H, 4.84; N, 5.18.

DL-*threo*-*O*-Benzoyl-β-hydroxyaspartic Acid (6). Drying 383.7 mg (1.42 mmol) of **6** monohydrate in an Abderhalden apparatus for 3 days at 82° and 0.025 Torr gave 359 mg (100%) of **6**: mp 185–187°; ir (Nujol) 3190 (NH), 3090 (OH), and 1715 cm^{-1} (COOH); ^{1}H NMR (Me_2SO-d_6) δ 4.24 (d, 1 H, *J* = 8 Hz, HC-4), 5.44 (d, 1 H, *J* = 0 Hz, HC-5), 7.7 ppm (m, 6 H, phenyl, NH).

Anal. Calcd for $C_{11}H_{11}NO_6$: C, 52.18; H, 4.38; N, 5.53. Found: C, 52.33; H, 4.42; N, 5.43.

DL-*threo*-*O*-Benzoyl-β-hydroxyaspartic Acid Hydrochloride (7). A suspension of 2.21 g (8.16 mmol) of **6** monohydrate in 13 ml of thionyl chloride was stirred magnetically for 16 hr. The suspended white solid was filtered and dried in vacuo, giving 2.24 g (94%) of **7**: mp 138–140°; ir (Nujol) 3190–3060 (broad NH_3^+), 1695 cm^{-1} (COOH); ^{1}H NMR (Me_2SO-d_6) δ 4.62 (d, 1 H, *J* = 3 Hz, -CH-), 5.80 (d, 1 H, *J* = 3 Hz, -CH-), 7.90 (m, 5 H, phenyl), 10.56 ppm (broad s, 4 H, COOH, NH_3^+); ^{13}C NMR (Me_2SO-d_6) (proton decoupled; Me_4Si external standard) 167.1 (COOH), 166.7 (COOH), 164.3 (PhCOO-) 134.0–128.0 (phenyl), 70.1 (β carbon), 52.7 (α carbon).

Anal. Calcd for $C_{11}H_{12}O_6NCl$: C, 45.61; H, 4.18; N, 4.84. Found: C, 45.57; H, 4.17; N, 4.85.

DL-*threo*-*O*-Benzoyl-β-hydroxyaspartic Acid Dimethyl Ester Hydrochloride (8). To a solution of 15 ml of acetyl chloride in 50 ml of methanol was added 1.0 g (3.47 mmol) of **7**. The solution was refluxed for 16 hr and the solvent was evaporated in vacuo, giving 0.97 g of an amorphous solid. Crystallization from isopropyl alcohol–ether gave 0.85 g (77%) of an analytical sample of **8**: mp 142–145°; ir (Nujol) 1750, sh 1740 cm^{-1} ($COOCH_3$); ^{1}H NMR (Me_2SO-d_6) δ 4.78 (d, 1 H, *J* = 4 Hz, -CH-), 5.86 (d, 1 H, *J* = 4 Hz, -CH-), 7.95 (m, 5-H, phenyl); ^{13}C NMR (Me_2SO-d_6, proton decoupled, Me_4Si external standard) 166.1 (PhCOO-), 165.7 ($COOCH_3$), 164.2 ($COOCH_3$), 134.1–127.5 (phenyl), 69.9 (β carbon), 53.4 (both CO_2CH_3) 52.6 ppm (α carbon).

Anal. Calcd for $C_{13}H_{16}NO_6Cl$: C, 49.20; H, 5.04; N, 4.41. Found: C, 49.15; H, 4.92; N, 4.55.

DL-*threo*-β-Hydroxyaspartic Acid Dimethyl Ester (9) from 8. A solution of 579 mg (1.8 mmol) of **16** and 25 ml of concentrated HCl was refluxed for 16 hr and the solvent was evaporated in vacuo. The oily product was dissolved in methanol saturated with dry HCl and after 3 hr the solvent was evaporated in vacuo and the oily residue was redissolved in methanol and evaporated in dryness in vacuo. Crystallization of the crude residue from methanol–ether gave 166 mg (43%) of **9**, mp 133–135° (lit.[10] 134–136°).

Registry No.—DL-*threo*-**3** (R = CH_3), 13515-98-5; DL-*threo*-**3** (R = H), 4294-45-5; DL-*erythro*-**3** (R = H), 6532-76-9; **4** (R = CH_3), 56454-02-5; **5**, 56454-03-6; **6**, 56454-04-7; **7**, 56454-05-8; **8**, 56454-06-9; **10**, 56454-07-0; **10** erythro isomer, 56454-08-1; ethyl benzimidate hydrochloride, 5333-86-8; NH_2OH·HCl, 5470-11-1; benzoyl chloride, 98-88-4; methanol, 67-56-1.

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(8) The β-hydroxyaspartic acids themselves have rather nondescript infrared spectra and very broad melting points, especially as hydrochlorides. Their conversions to the diesters allow easy identification.
(9) Unpublished results.
(10) F. Tiemann, *Chem. Ber.*, **17**, 126 (1884).
(11) This compound was first prepared in these laboratories by T. W. Kethley, Jr.
(12) This compound was first prepared in these laboratories by Mrs. Ann McCall.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy in Conformational Analysis of 9-Azabicyclo[3.3.1]nonane Derivatives

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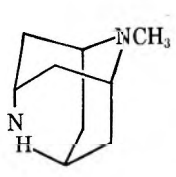
Carbon-13 NMR spectroscopy is demonstrated to be a powerful tool in conformational analysis and stereochemical assignment of 9-azabicyclo[3.3.1]nonanes. Endo alcohol **2** is shown to have the chair–boat conformation **2a** while exo alcohol **3** exists in the double chair conformation. Similarly quaternary ammonium chloride **13** is shown to exist in a chair–boat conformation in spite of a severe steric interaction. 9-Alkyl-9-azabicyclo[3.3.1]nonan-3-ones **6–9** are shown to prefer conformations with the *N*-alkyl group over the piperidone side of the molecule rather than over the piperidine side.

Carbon-13 nuclear magnetic spectroscopy[1,2] is a powerful tool for structure determination of organic compounds and is an exceedingly sensitive probe for conformational analysis because of the dependence of carbon chemical shifts upon steric effects within molecules.[3-5] Most of the effort has been directed toward cyclohexanes and their fused polycyclic counterparts (i.e., decalins[6] and perhydroanthracenes[7]). Spirocyclic compounds have also been studied.[8] The bridged polycyclic substrates which have been examined in detail are those of rather rigid molecular structures, such as the norbornyl,[9] bicyclooctyl,[10c] and adamantyl[10a,b] skeletons. Very little attention has been accorded to conformationally flexible bridged bicyclic structures. We have undertaken an investigation of the conformational manifestations of steric effects in the 9-azabicyclo[3.3.1]nonane (granatanine) system by carbon-13 NMR spectroscopy. This ring system was selected on account of its being composed of two six-membered rings, the symmetry of which facilitates chemical shift assignments, and in particular because of the delicate balance between chair–chair and chair–boat conformations as a function of substituent stereochemistry. The 9-azabicyclo[3.3.1]nonane ring system is known[11] to adopt a double chair conformation which is slightly flattened to relieve the transannular steric interactions of the endo hydrogens on carbons 3 and 7 (see formula 1). A 3-endo substituent larger than hydrogen forces



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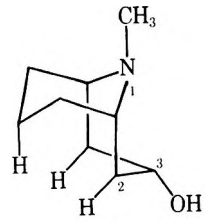
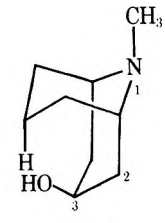
the substituted bridge to flip so that the substituted piperidine ring has a boat conformation as shown in **2a**.[11]

Results and Discussion

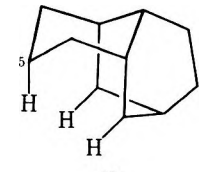
Table I collects the carbon-13 chemical shifts for the granatanine substrates we have studied in this investigation. Assignments were made on the basis of relative signal intensities and with the aid of coupled spectra. We focus first on the granatanols **2** and **3**, which differ structurally only in the configuration of the hydroxyl group at carbon 3. The major difference in the ^{13}C NMR chemical shifts is at carbon 7, the atom most remote from the site of the stereochemical difference. We attribute this difference to the fact that the endo isomer **2** exists predominantly in the chair–boat conformation **2a** in order to relieve the transannular steric interactions in the chair–chair conformation **2b**.[12,13] However, in conformation **2a**, the endo-7-hydrogen atom is in a gauche relationship with the endo hydrogens at carbons 2 and 4, and thus, according to the findings of Grant and coworkers, carbon 7 should be sterically shielded by approximately 5 ppm compared to a suitable model. Employing the parent amine **1** as the model, we find that indeed α-granatanol (**2**) has its 7-carbon signal shifted upfield by 5.9 ppm relative to the 3(7) carbon of **1**. β-Granatanol (**3**), which exists predominantly in the double-chair conformation,[12,13] displays its 7 carbon at 19.8 ppm, only 0.6 ppm upfield of the corresponding carbon signal of granatanine (**1**). In support of our interpretation is the carbon-13 NMR spectrum of homotwistane (**10**), which contains an unusually high field signal (15.2 ppm) for carbon 5, attributed to the gauche interactions that carbon experiences as a consequence of the rigid chair–boat conformation.[14] Lawton and Haslanger have observed similar differences in ^{13}C spectra of 3-exo and 3-endo substituted bicyclo[3.3.1]nonanes.[15] Somewhat surprising is the fact that carbons 2 and 4 of endo alcohol **2** show essentially the same chemical shift difference with respect to **1** as shown by carbons 2 and 4 of exo alcohol **3**. The observed shift (approximately 9.5 ppm) is that which would be expected for the introduction of a β hydroxyl group.[16] Grant has also observed the lack of reciprocity for the chemical shifts of sterically interacting moieties.[4]



2a



2b



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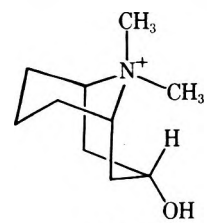
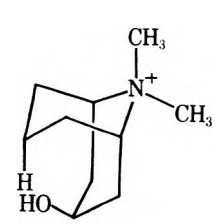
We have also measured the carbon-13 NMR spectra of the quaternary ammonium chlorides **11–13**; Table II presents the ^{13}C chemical shifts. Again the most striking difference in chemical shifts is that found for carbon 7: in endo isomer **12**, carbon 7 resonates 5.4 ppm upfield of the corresponding carbons of the parent salt **11** while the 7 carbon of the exo epimer **13** is within 0.2 ppm of carbon 3(7) of **11**. Thus, we conclude that endo alcohol **12** also exists preferentially in the chair–boat conformation **12a**. This finding is interesting since it implies that the transannular 3,7 in-

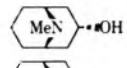
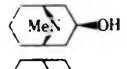
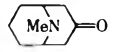
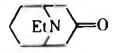
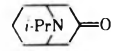
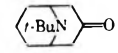


12a



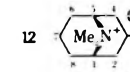
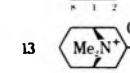
12b

Table I
Chemical Shifts of 9-Azabicyclo[3.3.1]nonane Derivatives[a,b]

	Compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	N-C-C
1		52.3	26.4	20.4	(26.4)	(52.3)	(26.4)	(20.4)	(26.4)	40.9
2		51.9	34.9	62.0	(34.9)	(51.9)	25.1	14.5	(25.1)	40.4
3		53.9	35.3	64.4	(35.3)	(53.9)	27.4	19.8	(27.4)	40.5
4		79.4	37.9	21.7	29.5	50.9	(29.5)	(21.7)	(37.9)	
5		82.5	33.8	22.0	25.6	57.6	(25.5)	(22.0)	(33.8)	34.2
6		55.8	41.8	210.0	(41.8)	(55.8)	29.7	16.1	(29.7)	41.1
7		53.6	42.4	210.1	(42.4)	(53.6)	30.0	16.8	(30.0)	46.4[c]
8		50.6	42.7	211.3	(42.7)	(50.6)	30.3	16.6	(30.3)	47.5[c]
9		48.4	47.0	212.7	(47.0)	(48.4)	32.3	17.2	(32.3)	54.1[c]

[a] Downfield from internal tetramethylsilane. [b] Chemical shifts of symmetry-related atoms are enclosed in parentheses. [c] Chemical shifts for N-C-C: 7, 13.7; 8, 21.9; 9, 32.3.

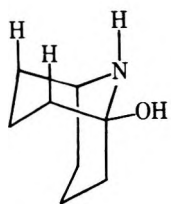
Table II
Chemical Shifts of 9-Azoniabicyclo[3.3.1]nonane Compounds[a,b]

	Compd	C-1	C-2	C-3	C-6	C-7	N-C	N-C'
11		65.0	27.2	18.4			53.0	
12		63.9	35.3	59.4	26.9	13.0	52.8	53.4
13		66.3	36.6	63.2	26.8	18.2	52.6	53.5

[a] Measured in D_2O with external $NaO_3SCH_2CH_2CH_2Si(CH_3)_3$. [b] Chemical shifts for symmetry-related atoms are omitted.

teraction associated with conformation **12b** is more severe than the steric crowding between the methyl group and the hydrogen at the flagpole positions of the boat portion of the molecule.

We next address the question of the steric effect of the substituent attached to nitrogen on the chemical shifts of various carbon atoms. The bridgehead alcohols **4** and **5** are



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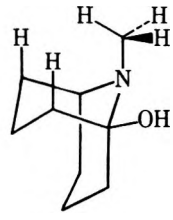

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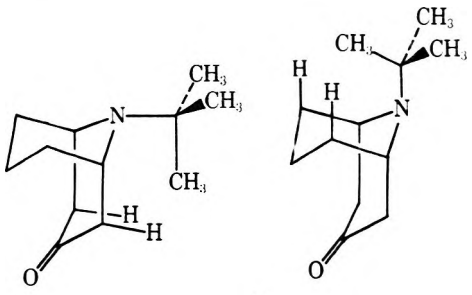
useful for this purpose. Upon substitution of methyl for hydrogen, carbons 2(8) and 4(6) undergo upshield shifts of 4.1 and 3.9 ppm, respectively. A substituent at the 9 position of the bicyclo[3.3.1]nonane system must be axial to one of the six-membered rings, and because of pyramidal inversion at nitrogen, the *N*-methyl group has axial character alternately in each ring. The axial nature of the methyl group introduces gauche steric interactions with the carbons 2, 4, 6, and 8 and thus the observed upfield shifts for these carbons are expected based on the findings of Grant.[4] A similar methyl-induced shift (approximately 3 ppm) has been reported for nortropane and tropane.[17]

Finally, we note the small difference in chemical shift for carbons 6 (and 8) in the isomeric alcohols **2** and **3**. Exo alcohol **3**, with the double-chair conformation, should have its *N*-methyl axial in each piperidine ring approximately 50% of the time. Carbons 6 and 8 of **3** experience γ-gauche interactions with the *N*-methyl group 50% of the time and resonate at δ 27.4. Endo alcohol **2**, with the chair–boat conformation, has its *N*-methyl group axial to the chair ring and in a γ-gauche relationship to carbons 6 and 8 nearly all the time. In alcohol **2**, carbons 6 and 8 resonate at δ 25.1, 2.3 ppm upfield from the corresponding resonance for **3**. Significantly, the chemical shifts of carbons 6 (and 8) of quaternary salts **12** and **13** are virtually identical.

The pseudopelletierine derivatives **6–9** also provide valuable information relating carbon-13 chemical shifts to conformational ramifications of steric interactions induced by substituents on nitrogen. Of particular interest are carbons 2, 4, 6, and 8, which show only small downfield shifts (about 0.3 ppm) as two of the methyl hydrogens of pseudopelletierine (**6**) are sequentially exchanged for methyl groups to provide the ethyl and isopropyl substrates **7** and **8**. When the final hydrogen is replaced by a methyl group, a substantial downfield shift is observed. The direction and magnitude of the observed shifts are in accord with Stothers' results for δ-steric effects.[18] In the case of *tert*-butyl derivative **9**, a methyl group must be situated in the midst of the axial hydrogens on carbons 2, 4, 6, and 8, thus introducing severe δ-steric interactions. The most significant feature of these sterically induced shifts is that the shift in-

crements per methyl group are greater, especially with *tert*-butyl derivative **9**, at carbon 2(4) than at carbon 6(8). From



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this we infer that, as the nitrogen atom undergoes pyramidal inversion, the *tert*-butyl group spends more time on the piperidone side of the molecule than on the piperidine side. This is probably due to flattening of the piperidone bridge in accommodating the sp^2-hybridized carbonyl carbon which diminishes somewhat the severity of the steric interactions. We have observed similar steric effects with the syn and anti epimers of 9-phenyl-9-phosphabicyclo-[3.3.1]nonan-3-one 9-oxide.[19]

Conclusion

With the results reported here, we have demonstrated the power of carbon-13 NMR spectroscopy in determining conformational preferences in bridged bicyclic substrates. Specifically, ^{13}C NMR spectroscopy can be utilized to ascertain simply the conformations and the configuration of 3-substituted and 9-substituted bicyclo[3.3.1]nonanes.

Experimental Section

The carbon-13 NMR spectra were measured at 25.15 MHz with a Jeol JNM PS-100 spectrometer interfaced with a Nova 1200 computer. The amines **1–9** were run in deuteriochloroform with tetramethylsilane as internal standard. The quaternary ammonium chlorides **11–13** were run in D_2O with the sodium salt of 3-trimethylsilylpropanesulfonic acid in D_2O as external reference. In all cases 10-mm tubes were employed and the sample concentrations were on the order of 0.5 *M*.

All of the amines utilized in this study were prepared according to literature procedures: **1**,[20] **2**,[21] **3**,[22] **4**,[23] **5**,[20] and **6–9**.[24] The quaternary ammonium chlorides **10–13** were prepared by the addition of excess methyl iodide to a solution of the corresponding amine in methylene chloride. The resulting precipitate was collected by filtration and then dissolved in hot water and passed through a 25 × 1 cm column packed with Amberlite IRA-401 ion exchange resin in the chloride form. Concentration of the eluent afforded the desired methochloride salts.

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Registry No.—**1**, 491-25-8; **2**, 2038-40-6; **3**, 6376-00-7; **4**, 56258-83-4; **5**, 56258-84-5; **6**, 552-70-5; **7**, 27092-59-7; **8**, 56258-85-6; **9**, 56258-86-7; **11**, 56258-87-8; **12**, 56258-88-9; **13**, 56258-89-0; methyl iodide, 74-88-4.

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Reaction of Azulene with Tetracyanoethylene Oxide

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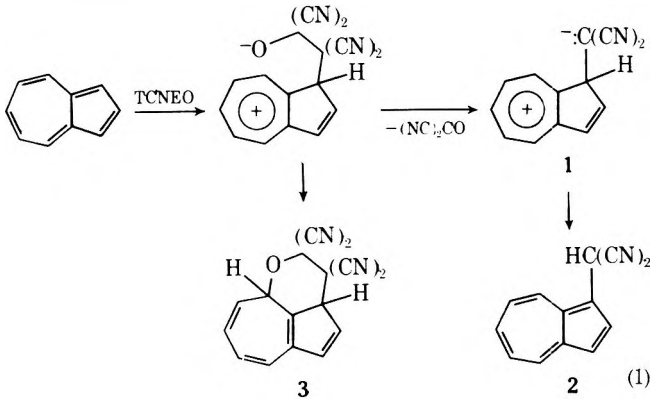
Azulene reacts with tetracyanoethylene oxide (TCNEO) to give 1-dicyanomethylazulene (**2**), 1-azuloyl cyanide (**4**), and 1-azulyltricyanoethylene (**6**) as the principal stable products. The major product was **4** (49%). The formation of **4** appears to involve carbon–carbon cleavage of the epoxide ring in TCNEO. A number of minor, unstable products were not characterized.

Tetracyanoethylene oxide (TCNEO) has been found to react readily with nucleophiles,[2,3,6] alkenes and alkynes,[2,4,5,7] aromatic rings,[2,4,5] Schiff bases,[6] and reducing agents.[5] The nucleophiles gave products derived from degradative scission of the epoxide ring, the alkenes gave stereospecific 1,3-dipolar-like addition, and the reducing agents abstracted oxygen and generated TCNE. With the aromatic compounds studied, which were all benzenoid and included benzene, naphthalene, anthracene, phenanthrene, furan, and thiophene, two distinct modes of reaction were

found: addition and oxidation. Oxidation was observed (accompanied by addition) for those systems having ionization potentials of 8.02 eV or less (anthracene, durene).

The nonbenzenoid azulene could act toward TCNEO as a nucleophile. This could lead to the electrophilic substitution product (2) via the established carbon–oxygen opening of the epoxide ring,[6] or the initial intermediate could undergo cycloaddition to form 3 (eq 1). Calculation of the ion-



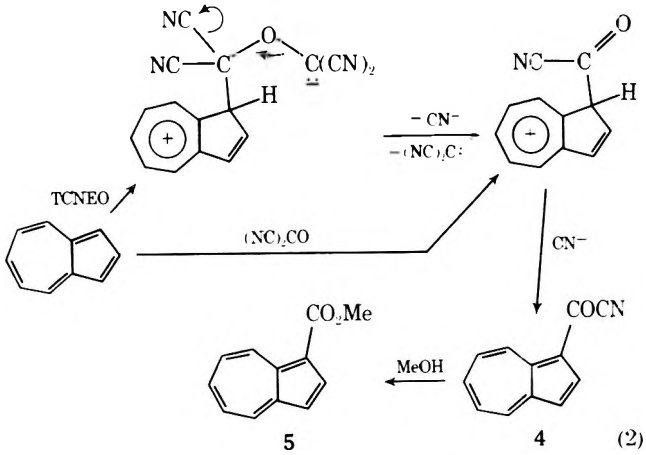
(1)

ization potential of azulene from the oxidation potential[8] gave a value of 6.867 eV, so oxidation would also be expected, probably with the generation of TCNE. To determine which of these reactions would occur, we have allowed azulene to react with TCNEO.

From the reaction in benzene at room temperature was obtained an almost black solid. Chromatography of this enabled the isolation of three stable products totaling 65.6% yield. In addition there were formed several unstable compounds which were not isolated in pure form and were not characterized.

The first product isolated was violet crystals which were identified to be 1-dicyanomethylazulene (2, 7.75%). The anticipated reactions leading to 2 thus possibly occurred, but to a perhaps surprisingly minor extent in view of striking reactivity of azulene to even weakly electrophilic reagents.[9]

The major product was 1-azuloyl cyanide (4), obtained as red-orange crystals (49%), a compound which had not been predicted. Two reasonable routes for the formation of 4 are shown (eq 2). The first involves opening of the epoxide ring



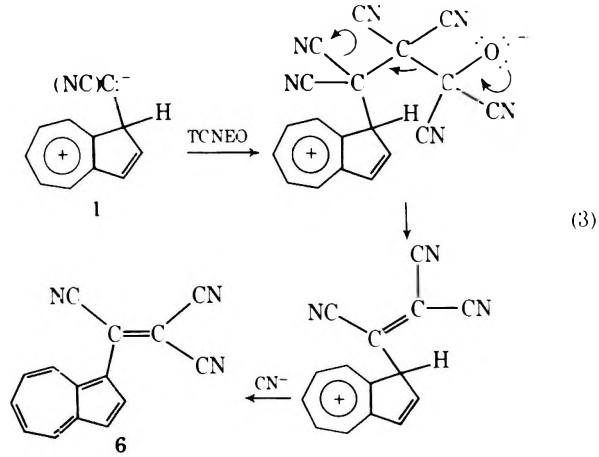
(2)

by carbon–carbon bond cleavage and thus possibly provides one of the few examples of this process.[10] The dicyanocarbene which would be generated could react with azulene to form 1. This provides an alternative path to 2. Evidence for this was provided by the reaction of azulene with bromomalononitrile, a precursor of dicyanocarbene, which gave 2 and also 6. The finding of the latter, which in this case must arise from the reaction of azulene with tetracyanoethylene,[13] establishes the formation of dicyanocarbene in the reaction. Azulene apparently acts as the base needed. If pyridine was added prior to work-up, no 6 was isolated, indicating a reaction of this product with the base. Curiously, in the presence of triethylamine the products were 1,3-dibromoazulene and 6. This result calls for an electrophilic bromine compound and the bromotriethylammonium ion is suggested.

The second route is direct electrophilic substitution by reaction with carbonyl cyanide, and its simplicity makes it attractive. The plausibility of this was shown by a test reaction which afforded 4 in 80% yield. This route requires, however, a source of carbonyl cyanide corresponding to the amount of 4 formed. The reaction yielding 1 would provide only ca. 8% and other sources for the additional 41% were not evident. Therefore, the indirect path is considered to be the more probable.

Additional characterization of 4 was provided by its reaction with methanol to form the known methyl 1-azuloate (5)[11] in essentially quantitative yield, and its preparation from azulene by reaction with phosgene and then cuprous cyanide. Compound 4 was also formed (87%) during the chromatography of 2 on Florisil[12] in the presence of wet ether. As the material moved down the column, the green color from 2 gradually changed to orange. This reaction involves an oxidation, yet the $MgO{\cdot}SiO_2$ with ca. 0.5% Na_2SO_4 composition of the adsorbent would not seem to provide this. The nature of the oxidizing agent was not determined.

A third stable product was 1-azulyltricyanoethylene (6, 8.8%), which has been shown to be formed from the reaction of azulene with TCNE[13] or chlorotricyanoethylene.[14] The isolation of 6 and the fact that a number of unstable products were observed in other chromatographic fractions is consistent with TCNE being formed from a reaction of TCNEO with azulene wherein the latter is oxidized. An alternative route to 5 would require that the second intermediate (1) leading to 2 exist long enough to react with a second molecule of TCNEO as shown (eq 3). This is considered to be less likely.



(3)

Experimental Section

Melting points are corrected. Uv and visible spectra were recorded on a Cary Model 14 recording spectrophotometer. Ir spectra were recorded with a Perkin-Elmer Model 21 instrument. NMR spectra were taken on a Varian Model A-60 or T-60 with Me_4Si as internal reference. Analyses were performed by Mr. Dave Harsch at the University of Idaho or by Chemalytics, Inc., Tempe, Ariz. All solvents were reagent grade or purified prior to use. Silica gel for chromatography was Davison or, for final purification, Mallinckrodt SiliAR CC-7.

Reaction of Azulene with Tetracyanoethylene Oxide. To a stirred solution of 522.3 mg (4.08 mmol) of azulene[15] in 20 ml of dry benzene at room temperature was added dropwise over 1 hr a

solution of 579.9 mg (4.03 mmol) of freshly sublimed, pure (mp 179–179.5°) TCNEO[16] in 130 ml of benzene and the mixture was stirred for an additional 1 hr. Removal of the solvent (reduced pressure) left an almost black solid which was dissolved in 30 ml of benzene and chromatographed on a silica (70 g) column with benzene (1 l.), THF (1 l.), and MeOH (1 l.) as the eluents in that order. The last appeared to contain only unstable products which were not characterized.

The residue (570.1 mg) from the benzene eluate contained three products (TLC on silica gel, R_f 0.13, 0.18, and 0.22 with benzene) and the benzene eluate (ca. 0.5 l.) from the chromatography of this on silica gel (40 g) was collected first in ca. 10-ml fractions and these were then combined according to color into seven fractions. From fraction 1 was obtained 0.5 mg of unchanged azulene. Chromatography of an ether solution of the residue (104.2 mg of brown crystals) from fraction 2 on silica gel (60 g) afforded 58.6 mg (7.54%) of 1-dicyanomethylazulene (2) as violet crystals which formed plates when crystallized from *n*-hexane–benzene: mp 140.3–141.3°; uv ($HCCl_3$) 223 nm (log ϵ 4.72), 241 (sh, 4.24), 268 (sh, 4.48), 274 (sh, 4.66), 278 (4.78), 283 (4.74), 288 (4.77), 339 (3.74), and 355 (3.60); visible ($HCCl_3$) 473 nm (sh, ϵ 172), 512 (366), 560 (522), 600 (453), and 656 (sh, 177); ir ($HCCl_3$), 2265 (CN), 2915 and 2880 cm^{-1} (CH); NMR ($DCCl_3$) δ 5.63 (s, 1, –CH<), 7.44 (d, 1, J = 4.0 Hz, H-3), 7.30–7.98 (AB_2, 3, H-5, H-6, H-7), 8.07 (d, 1, J = 4.0 Hz, H-2), 8.42 (d of d, 1, J = 9.8 and 1.2 Hz, H-4), 8.52 (d, 1, J = 9.8 and 1.2 Hz, H-8).

Anal. Calcd for $C_{13}H_8N_2$: C, 81.23; H, 4.20; N, 14.57. Found: C, 81.35; H, 4.20; N, 14.20.

Rechromatography of fraction 3 (12.3 mg of reddish brown crystals) gave an additional 2.2 mg of 2 for a total yield of 60.8 mg (7.83%).

Rechromatography of the residue (313.2 mg of orange crystals) from fraction 4 on 20 g of silica gel separated 304.4 mg (40.4%) of 1-azuloyl cyanide (oxo-1-azulylethanenitrile) as reddish orange crystals, mp 140.2–140.5° after recrystallization from *n*-hexane–benzene: uv ($HCCl_3$) 222 nm (log ϵ 4.53), 2.77 (4.08), 323 (4.36), 403 (4.16), and 419 (4.17); visible ($HCCl_3$) 500 (ϵ 1021), 541 (sh, 685) and 586 (sh, 180); ir ($HCCl_3$) 1635 (CO) and 2330 cm^{-1}, (CN); NMR ($DCCl_3$) δ 7.38 (d, 1, J = 4.5 Hz, H-3), 7.60–8.30 (ABC, 3, H-5, H-6, H-7), 8.46 (d, 1, J = 4.5 Hz, H-2), 8.65 (d of d, 1, J = 9.8 and 2.0, H-4), 9.75 (d of d, 1, J = 9.5 and 2.0 Hz, H-8); MS (70 eV) *m/e* (rel intensity) 181 (59.4) (P^+), 155 (100) (P – CN), and 127 (36.9) (P – CNCO).

Anal. Calcd for $C_{12}H_7NO$: C, 79.55; H, 3.89; N, 7.75. Found: C, 79.55; H, 3.92; N, 7.75.

From the rechromatography of fractions 2 and 3 (see above), fraction 5 (9.1 mg of red crystals), and fraction 6 (70.7 mg of dark brown solid) was obtained 25.5 mg of 4 for a combined yield of 329.9 mg (45.1%). The residue (492.5 mg) from the original THF eluate was chromatographed on 75 g of silica gel with ca. 0.5 l. of THF–5% MeOH as the eluent as described above for the benzene eluate fraction except that the small fractions were combined into nine fractions according to color. The last seven were found to contain small quantities of unstable products which were not characterized. Rechromatography twice more of the combined residues from fraction 1 (19 mg of reddish brown crystals) and fraction 2 (224.9 mg of brown oil), and of fraction 7 (22.6 mg of brown solid) from the benzene eluate fraction, with benzene as the eluent gave an additional 32 mg of 4 for a total yield of 361.9 mg (49.44%).

From the above chromatograph of fraction 4 was obtained 1.2 mg of red-brown crystals which was combined with the major component of fraction 6. Rechromatography of the combined material (15 g of silica gel, benzene) afforded 65.2 mg (7.06%) of 1-azulyltricyanoethylene (6) as reddish brown needles: mp 202.8–203.2° (lit.[13,14] 201–202°) after recrystallization from benzene; uv ($HCCl_3$) 234 nm (log ϵ 4.13), 256 (4.12), 302 (4.06), 366 (3.80), and 384 (sh, 3.72); visible ($HCCl_3$) 495 (4.43), 530 (sh, 4.23), and 567 (sh, 3.66); ir ($HCCl_3$) 1585, 1605 (C=C), and 2230 cm^{-1} (CN); NMR (Me_2SO-d_6) δ 7.78 (d, 1, J = 4.8 Hz, H-3), 7.88–8.48 (AB_2, 3, H-5, H-6, H-7), 8.57 (d, 1, J = 4.8 Hz, H-2), 8.95 (d of d, 1, J = 9.5 and 1.5 Hz, H-4), and 9.27 (d of d, 1, J = 9.5 and 1.5 Hz, H-8).

From the rechromatography of fractions 1 and 2 of the original THF eluate (see above) was obtained an additional 16 mg to make the total yield 82.3 mg (8.9%) of 6.

1-Azuloyl Cyanide (4). A. From 1-Azulyldicyanoethylene (2). A solution of 2.9 mg (0.015 mmol) of 2 in 2 ml of ether was chromatographed on 10 g of Florisil.[12] The violet color changed to green as the material was adsorbed, and then gradually to orange as the chromatogram developed. Ether saturated with water was the eluent and the time on the column was 2 hr. The residue (2.8 mg) from the orange eluate was rechromatographed in the same manner to give 2.3 mg (87%) of 4 identified by comparison of its ir spectrum and TLC behavior with those of an authentic sample.

B. From Azulene, Phosgene, and CuCN. A saturated solution of phosgene (ca. 2 mmol) in 0.4 ml of dry benzene was added slowly (syringe) to a stirred, ice-cooled solution of 12.8 mg (0.1 mmol) of azulene in 2 ml of dry benzene. The mixture was allowed to come to room temperature as stirring was continued (3 hr). Two further additions [ca. 3 mmol (0.6 ml) and 5 mmol (1 ml)] of the phosgene solution were made at hourly intervals with stirring continued for 1 hr after the last addition. The dark red, semisolid residue (presumed to contain 1-azuloyl chloride) was stirred with 13.5 mg (0.15 mmol) of dried (110°) CuCN and 8 ml of dry pyridine for 4 days. Evaporation of the pyridine (vacuum pump) left a dark red solid which was chromatographed on silica gel (7 g). Elution with benzene afforded 0.1 mg of unchanged azulene and 2.7 mg (15%) of 4 as orange-red crystals identical (ir and TLC) with the material from A. Elution with THF removed 12.4 mg of dark violet crystals (three components by TLC) which were not investigated further.

C. From Azulene and Carbonyl Cyanide. To an ice-cooled solution of 12.8 mg (0.1 mmol) of azulene in 2 ml of dry benzene was added dropwise (5 min) with stirring 8 mg (0.1 mmol) of carbonyl cyanide.[3] The cold mixture was stirred for an additional 25 min and then the solvent was slowly removed under reduced pressure at 0°. Chromatography of the residue on 5 g of SiO_2 with benzene as the eluent gave 2 mg (16%) of unchanged azulene and then 14.5 mg (80.1%) of 4 as orange crystals identical (TLC and ir) with an authentic sample.

Methyl 1-Azuloate (5) from 1-Azuloyl Cyanide (4). A solution of 21.9 mg (0.121 mmol) of 4 in 4 ml of absolute MeOH was shaken occasionally for 30 min, during which time the color changed from orange to red to purple. The solution was then refluxed for 10 min. After removal of the solvent (reduced pressure), the residue was chromatographed on silica gel (15 g, benzene eluent) and 22.3 mg (99.2%) of 5 was obtained as a purple liquid identical (TLC, ir) with an authentic sample.[9b]

Reaction of Azulene with Bromomalononitrile. A. A solution of 18 mg (0.12 mmol) of bromomalononitrile[17] in 1 ml of dry acetonitrile was added dropwise to 12.8 mg (0.1 mmol) of azulene dissolved in 2 ml of acetonitrile. After 16 hr, the solvent was carefully evaporated (reduced pressure) and a solution of the residue in 3 ml of benzene was chromatographed on 7 g of SiO_2. Following a small yellow oil fraction which was not characterized, there was obtained 2.8 mg (15%) of 2 as violet crystals identical (TLC, uv, ir) with an authentic sample, and 4.5 mg (20%) of 6 as red crystals identical (TLC, ir) with the product previously obtained.

B. To an ice-cooled solution of 12.8 mg (0.1 mmol) of azulene and 12 mg (0.12 mmol) of triethylamine in 2 ml of dry acetonitrile under N_2 was added dropwise with stirring a solution of 18 mg (0.12 mmol) of bromomalononitrile in 1 ml of acetonitrile. The mixture was stirred for 5 min, the solvent was carefully removed under reduced pressure, and the residue was chromatographed (benzene) on 7 g of SiO_2. The first blue fraction yielded 7.5 mg (26%) of 1,3-dibromoazulene, and the red eluate yielded 0.3 mg (1%) of 6 identical (TLC, ir) with authentic samples of each.

Registry No.—2, 56454-36-5; 4, 56454-37-6; 6, 56454-38-7; azulene, 275-51-4; tetracyanoethylene oxide, 3189-43-3; bromomalononitrile, 1885-22-9.

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Substitution and Elimination Reactions in Chloro Olefins. II.[1] Reactions of Methyl β-Chlorocinnamates with Methoxide and Ethoxide Ions

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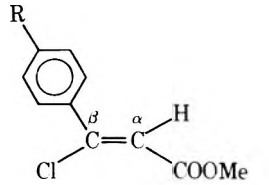
The rates of the base-catalyzed eliminations of a series of trans para-substituted methyl β-chlorocinnamates have been determined in methanol and ethanol using methoxide and ethoxide ions as bases. Elimination products are obtained exclusively, and the rates of the reactions show a Hammett correlation with ρ values of 1.7 and 2.0 for methoxide and ethoxide ions, respectively, which suggests a certain carbanionic character of the transition state. An E2 mechanism, presumably with an E1cB-like transition state, has been suggested.

Simple vinyl halides are known for their inertness toward bimolecular nucleophilic substitution and base-catalyzed dehydrohalogenation compared to alkyl halides. The reactivity of vinyl halides toward nucleophiles can, however, be greatly enhanced by the presence of strongly electron-attracting groups attached directly to the alkene double bond. The activating groups not only enhance β-eliminations but also substitutions. The competition between substitution and elimination is, indeed, one of the most intriguing features of the reactions of vinylic compounds with nucleophiles. This competition is generally controlled by the nature of the nucleophile, by the leaving group, and by the configuration of the substrate. In most cases vinylic substrates were found to react with a nucleophile either by direct substitution, which may merge in an addition–elimination mechanism, or by elimination which may or may not be followed by addition of solvent to the initially formed acetylene. The mechanisms of the reactions of vinyl halides with nucleophiles have attracted considerable interest in recent years and comprehensive reviews on this subject are available.[2-6]

Whereas aromatic substitutions are satisfactorily correlated[7] by the Hammett equation, the rates of vinylic substitutions do not always follow the sequence predicted by either σ or σ^-. On the other hand, when the effects of substituents not directly bonded to the β-ethylenic carbon are considered, good Hammett correlations are observed with positive values of ρ.[8] A Hammett correlation has been also reported for elimination reactions of several saturated alkyl halides with phenyl substitution on the β carbon and in particular in the 2-phenylethyl system.[9]

To our knowledge no such Hammett correlation has been reported for the rates of vinylic eliminations. From our interest in the kinetics and mechanisms of alcoholysis of chloro olefins, the present work is designed to study the reactions of *trans*-methyl β-chlorocinnamates (Ia–d) with



Ia, R = H; b, R = *p*-CH_3; c, R = *p*-NO_2; d, R = *p*-Cl

methoxide and ethoxide ions, and the effect of substituents on the phenyl ring on a carbanion developed at the α carbon.

Results and Discussion

A convenient route for the synthesis of *trans*-β-chlorovinyl acids by the reaction of phosphorus pentachloride with the appropriate β-keto esters was recently reported by us.[10] The isolation of only the trans isomer from this reaction can be visualized to take place by a mechanism similar to that suggested for the reactions of ketones with phosphorus pentachloride.[11] The assignment of the trans configuration to methyl β-chlorocinnamates (I) came from NMR and uv measurements for both the acids and esters. The data are compared with that reported for *cis*- and *trans*-methyl α-cyanocinnamates[12] and methyl α-chlorocinnamates.[13a] The chemical shifts of the vinylic protons and the carbomethoxy groups appear constantly for the trans isomer at lower field than that of the cis, and are quite identical with those of the compounds (Ia–d). Furthermore, the calculated chemical shifts,[13b] applying the NMR rules of additivity,[14,15] of *trans*-β-chlorocinnamic acid and its methyl ester are found to be in excellent agreement with the observed values. A summary of the spectral properties of Ia–d is collected in Table I.

Table I
Ir,[a] Uv,[b] and NMR[c] Spectra for Ia–d

R	C=O, cm^{-1}	C=C, cm^{-1}	λ_{max}, nm	ε	Trans OCH_3	Vinyl proton
H	1725	1620	272	16,240	3.92	6.73
p-CH_3	1720	1615	282	17,990	3.70	6.45
p-NO_2	1730	1625	290	17,600	3.97	7.22
p-Cl	1730	1620	277	19,320	3.88	7.13

[a] Nujol. [b] Absolute ethanol. [c] For solvent see Experimental Section; δ values are used for the chemical shifts.

The rates of the reactions of compounds Ia–d with methoxide and ethoxide ions in methanol and ethanol, respectively, were measured at various temperatures. They always follow a second-order kinetic equation. As expected, the rates with ethoxide ion are faster than with methoxide ion (ca. 13 times for Ia and 30 for Ic) because of its well-known higher nucleophilic power and higher basicity.[16] The rate coefficients together with the derived Arrhenius parameters are reported in Table II.

The reactions of compounds Ia–d with either methoxide or ethoxide ions are similar to those observed in other nucleophilic reactions of activated ethylenic halides.[17,18] The configuration of the substrates determines the mechanism of the reactions. Consequently, all compounds react by elimination because of the favorable steric arrangement of the hydrogen trans to the halogen. The small positive entropy of activation is that expected for β anti elimination reactions. Under the kinetic conditions the formed acetylenic products do not undergo further addition as observed with *p,p'*-dinitrotolan obtained from the reactions of *cis*- and *trans*-1-chloro-1,2-di(*p*-nitrophenyl)ethylene with methoxide and ethoxide ions.[1]

Figure 1 shows a Hammett plot for the reactions of the compounds Ia–d with methoxide and ethoxide ions with ρ values of 1.7 and 2.0, respectively. The ρ value in a Ham-

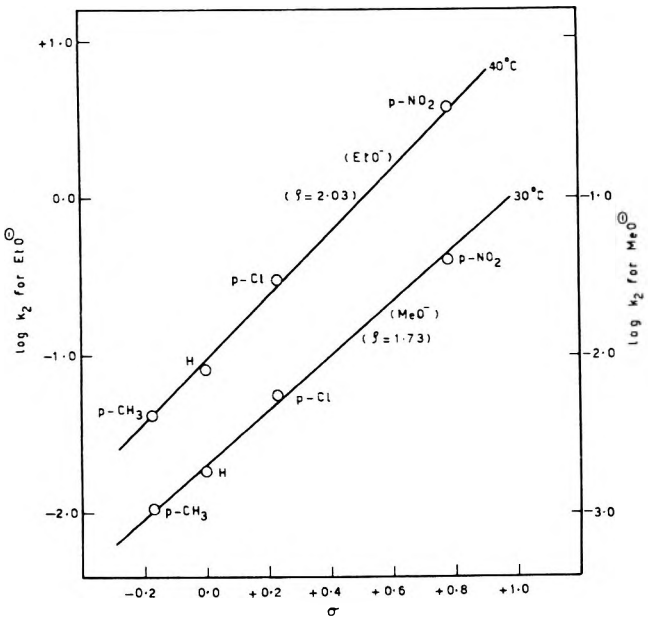
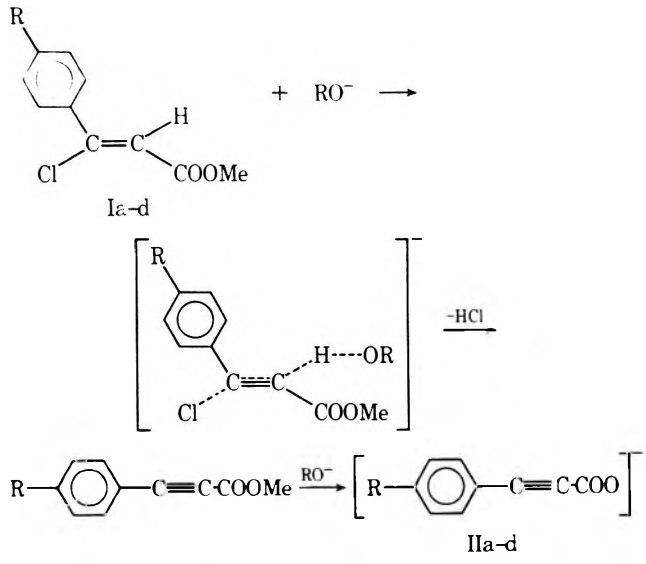


Figure 1. A plot of log k_2 for base-catalyzed elimination reaction against Hammett σ constants.

mett correlation has been taken as a measure of the carbanion character developed in the transition state of an elimination reaction.[19] The ρ values obtained in this study are comparable to those reported for the base-catalyzed eliminations of various saturated and vinylic systems where transition states of varying degrees of carbanionic character have been postulated.[8,19,20] As shown in Figure 1, the ρ value is larger with the stronger base ethoxide ion, which indicates that the negative charge is greater in the transition state with stronger base.[20a]

In conclusion, an E2 mechanism, presumably going through an E1cB-like transition state, is suggested for the elimination reactions studied as shown in the following scheme.



Experimental Section

Infrared and ultraviolet spectra were taken on Unicam SP 200 and SP 800 spectrometers, respectively. The NMR spectra[29] were measured at 60 MHz using tetramethylsilane as internal standard. Microanalyses were done at Cairo University microanalytical laboratory; melting points and boiling points are uncorrected.

Ethyl benzoylacetate was prepared in 70% yield as described earlier,[21] colorless liquid, bp 130–140° (2.5–3.5 mm).

β-Chlorocinnamic Acid. Ethyl benzoylacetate (14 g, 0.073 mol) was added dropwise (1 hr) to a cold suspension of phosphorus pentachloride (43.5 g, 0.21 mol) in dry benzene (50 ml) with stirring. The reaction mixture was refluxed for 0.5 hr and then thoroughly decomposed with ice-cold water. The benzene layer was separated and the aqueous layer was extracted twice with benzene. The combined benzene extract was washed with water and extracted with a saturated solution of sodium carbonate. Evaporation of benzene gave a sticky, oily product proved to be composed mainly of unreacted material, phosphorus pentachloride, besides other materials under investigation. Acidification of the cold carbonate extract gave a solid (5 g, 38%), mp 139–145°. This mixture of cis and trans acids was treated with a 30% ammonia solution and then a saturated solution of barium chloride. The barium salt of the trans isomer separated immediately and was collected and acidified to give a solid (4.2 g), crystallized from carbon tetrachloride as colorless needles, mp 145–146° (lit.[22] mp 142°). Anal. Calcd for $C_9H_7ClO_2$: C, 59.17; H, 3.84; Cl, 19.45. Found: C, 59.16; H, 3.81; Cl, 19.46. Ir strong bands at 1700, 1610, 780, and 725 cm^{-1}; uv λ 218 nm (ϵ 9499), λ_{max} 262 nm (ϵ 13,170); NMR ($CDCl_3$) multiplet centered at δ 7.33 (aromatic protons, 5 H) and a singlet at δ 6.42 (=CH).

***trans*-Methyl β-Chlorocinnamate (Ia).** *trans*-β-chlorocinnamic acid was converted to Ia by reaction with thionyl chloride and addition of absolute methyl alcohol to the formed acid chloride. The ester was purified by repeated distillation in vacuo to give a colorless liquid, bp 128–130° (2.5 mm), which solidified on cooling, mp 29°. Anal. Calcd for $C_{10}H_9ClO_2$: Cl, 18.06. Found: Cl, 18.30. Ir strong bands at 2990, 1725, 1620, 770, and 690 cm^{-1}; uv λ 218 nm (ϵ 9761), λ_{max} 272 nm (ϵ 16,240); NMR ($CDCl_3$) multiplet centered at δ 7.72 (aromatic protons, 5 H), a singlet at δ 6.73 (=CH), and a singlet at δ 3.92 ($-OCH_3$).

Ethyl *p*-methylbenzoylacetate was prepared by the condensation of ethyl acetoacetate with *p*-methylbenzoyl chloride following the procedure of ethyl benzoylacetate, bp 160–170° (2–4 mm), ir strong bands at 3075, 1750, 1690, 1620, and 815 cm^{-1}.

***trans*-β-Chloro-*p*-methylcinnamic Acid.** Ethyl *p*-methylbenzoylacetate was converted to the acid by refluxing with phosphorus pentachloride in dry benzene for 7 hr. Work-up as before gave a solid separated from benzene in colorless plates (34% yield), mp 178°. Anal. Calcd for $C_{10}H_9ClO_2$: C, 61.07; H, 4.58; Cl, 18.06. Found: C, 61.30; H, 4.60; Cl, 18.00. Ir strong bands at 1695, 1600, 825, and 715 cm^{-1}; uv λ 216 nm (ϵ 13,514), λ_{max} 265 nm (ϵ 21,007); NMR (Me_2SO-d_6) quartet centered at δ 7.58 (aromatic protons, 4 H), singlet at δ 6.73 (=CH), and a singlet at δ 2.38 (*p*-CH_3).

***trans*-Methyl β-Chloro-*p*-methylcinnamate (Ib).** The above acid was converted to Ib following the usual procedure, separated from methanol in colorless plates, mp 71–72°. Anal. Calcd for $C_{11}H_{11}ClO_2$: C, 62.71; H, 5.23; Cl, 16.86. Found: C, 63.10; H, 5.4; Cl, 17.10. Ir strong bands at 1720, 1615, 820, and 710 cm^{-1}; uv λ 227 nm (ϵ 8322), λ_{max} 282 nm (ϵ 17,990); NMR ($CDCl_3$) quartet centered at δ 7.28 (aromatic protons, 4 H), singlet at δ 6.45 (=CH), singlet at δ 3.70 ($-OCH_3$), and singlet at δ 2.35 (*p*-CH_3).

Ethyl *p*-Nitrobenzoylacetate. The procedure of Bülow and Hailer[23] for the synthesis of ethyl *p*-nitrobenzoylacetoacetate was modified as follows. Ethyl acetoacetate was treated successively with small equal amounts of sodium ethoxide in absolute ethanol and *p*-nitrobenzoyl chloride in ether while cooling and stirring.

Table II
Rate Coefficients and Activation Parameters for Reactions of *trans*-Ia–d ($1.0–0.25 \times 10^{-2}$ *M*) with Methoxide and Ethoxide Ions ($5.0–0.25 \times 10^{-2}$ *M*) in Methanol and Ethanol

Compd	Base	$k_2 \times 10^3$, mol^{-1} l. sec^{-1} 15[d]	20	25	30	35	40	E_a, kcal mol^{-1}[b]	$\Delta S^{\ddagger}$,[c] eu
Ia	MeO⁻				1.8	3.3	5.9	21.8	−1
	EtO⁻				23.8	42.2	81.2	21.7	−4
Ib	MeO⁻				1.1	2.1	4.0	24.3	−6
	EtO⁻				14.5	25.6	42.2	20.3	−2
Ic	MeO⁻			23.4	41.0	69.2		19.9	−1
	EtO⁻	215	356	661			3677[a]	20.8	−8
Id	MeO⁻				5.6	9.7	17.6	21.5	−1
	EtO⁻			51.9	101	176	300[a]	20.9	−4

[a] Extrapolated values. [b] Values from plots of log k_2 vs. $1/T$. [c] $\Delta S^{\ddagger}/4.576 = \log k_2 - 10.753 - \log T + E_a/4.576T$ at 40°C. Rate constants are calculated by the standard deviation method and errors estimated to be within 1–6%. [d] Temp, °C.

When addition was completed, the separated solid was filtered, dried, and acidified to give ethyl *p*-nitrobenzoylacetoacetate (84% yield), mp 54°. This ester (30 g) was hydrolyzed by treatment with an alcoholic ammonia solution (450 ml of 10%) while shaking gently from time to time at 45° for 30 min. The solution was cooled and the separated solid filtered and dried. This solid was suspended in water and acidified and the separated solid filtered and crystallized in yellow prisms from alcohol (15 g, 59%), mp 73° (lit.[23] mp 71°).

***trans*-β-Chloro-*p*-nitrocinnamic Acid.** Ethyl *p*-nitrobenzoylacetate (3 g, 0.013 mol) was refluxed with phosphorus pentachloride (9 g) in dry benzene for 40 hr. Decomposition and work-up gave a solid (1.4 g, 47%), crystallized from benzene, mp 196–198°. Experiments carried out with larger amounts gave a low yield. Anal. Calcd for $C_9H_6NClO_4$: C, 47.46; H, 2.64; N, 6.15; Cl, 15.60. Found: C, 47.22; H, 2.78; N, 6.29; Cl, 15.50. Ir strong bands at 1705, 1615, 1355, 760, and 720 cm^{-1}; uv λ 217 nm (ε 10,764), λ_{max} 304 nm (ε 12,384); NMR (Me_2SO-d_6) quartet centered at δ 8.33 (aromatic protons, 4 H) and singlet at δ 7.23 (=CH).

***trans*-Methyl β-Chloro-*p*-nitrocinnamate (Ic).** The above acid was converted to Ic in the usual manner, crystallized from methanol–benzene mixture in pale yellow needles, mp 157–158°. Anal. Calcd for $C_{10}H_8ClO_4$: C, 49.69; H, 3.31; N, 5.79; Cl, 14.69. Found: C, 49.30; H, 3.50; N, 6.00; Cl, 14.37. Ir strong bands at 1730, 1625, 1520, 1355, 850, and 700 cm^{-1}; uv λ 215 nm (ε 15,600), λ_{max} 290 nm (ε 17,600); NMR (Me_2SO-d_6) quartet centered at δ 8.37 (aromatic protons, 4 H), singlet at δ 7.22 (=CH), and singlet at δ 3.97 (-OCH_3).

Ethyl *p*-chlorobenzoylacetate was prepared (88% yield) by the condensation of ethyl acetoacetate with *p*-chlorobenzoyl chloride following the method of ethyl benzoylacetate, as a pale yellow liquid: bp 170–180° (4.5–5.5 mm); ir strong bands at 3025, 1745, 1720, 1600, 860, 780, and 745 cm^{-1}.

***trans*-β-Chloro-*p*-chlorocinnamic Acid.** Ethyl *p*-chlorobenzoylacetate was refluxed with phosphrous pentachloride for 20 hr in dry benzene. Work-up gave a solid (30% yield), separated from benzene in colorless needles, mp 178–180°. Anal. Calcd for $C_9H_6Cl_2O_2$: C, 49.76; H, 2.77; Cl, 32.72. Found: C, 49.50; H, 2.89; Cl, 32.80. Ir strong bands at 1680, 1605, 840, and 715 cm^{-1}; uv λ 225 nm (ε 6595), λ_{max} 275 nm (ε 16,390); NMR (Me_2SO-d_6) quartet centered at δ 7.93 (aromatic protons, 4 H) and singlet at δ 7.07 (=CH).

***trans*-Methyl β-chloro-*p*-chlorocinnamate (Id)** was prepared by the esterification of β-chloro-*p*-chlorocinnamic acid in the usual manner, separated from methanol as colorless prisms, mp 43–44°. Anal. Calcd for $C_{10}H_8Cl_2O_2$: C, 51.95; H, 3.46; Cl, 30.74. Found: C, 52.30; H, 3.50; Cl, 30.40. Ir strong bands at 1730, 1620, 835, and 740 cm^{-1}; uv λ 226 nm (ε 7663), λ_{max} 277 nm (ε 19,320); NMR (Me_2SO-d_6) quartet centered at δ 7.93 (aromatic protons, 4 H), singlet at δ 7.13 (=CH), and singlet at δ 3.88 (-OCH_3).

Reaction Products. The following procedure was adopted for all compounds (Ia–d). The compound (0.5 g) was dissolved in absolute methanol or ethanol (50 ml) and the equivalent amount of metallic sodium (ten times the molarity of the compound) was added. The solution was thermostated at 40° for 10 half-lives in each case. The reaction mixture was diluted with a large volume of water, acidified with dilute sulfuric acid, and extracted with ether. The ethereal layer was extracted twice with a saturated solution of sodium carbonate. The ether extract was washed, dried, and evaporated to give no materials in all cases. Acidification of the sodium carbonate extract gave the product (yields more than 80%). All the products were proved to be the corresponding acetylenic compounds (IIa–d), characterized by the presence of the sharp acetylenic band at 2225 cm^{-1} in the infrared spectra,[24] and by melting points and mixture melting points with authentic samples in some cases. The products obtained from the reactions of compounds Ia–d with base are respectively phenylpropiolic acid (IIa, needles from carbon tetrachloride), mp and mmp 139° (lit.[25] mp 137°); *p*-methylphenylpropiolic acid (IIb, needles from water), mp 151–152° (lit.[26] mp 151°); *p*-nitrophenylpropiolic acid (IIc, yellow needles from water), mp and mmp 180–181° (lit.[27] mp 180°); *p*-chlorophenylpropiolic acid (IId, needles from water), mp 186° (sealed tube) (lit.[28] mp 185°).

Kinetic Measurements. The rates of reaction were determined by following the rates of liberation of chloride ions by the electrometric method as previously reported.[1] Most reactions were followed to 70–80% completion, and in all cases the infinity titer was found to agree with the calculated. The results are quite reproducible and the reactions showed simple second-order kinetics. Rate coefficients and activation parameters were calculated in the usual way and are collected in Table II.

Registry No.—Ia, 56377-29-8; Ib, 56377-28-7; Ic, 56377-30-1; Id, 56377-31-2; β-chlorocinnamic acid, 18819-66-4; ethyl benzoylacetate, 94-02-0; phosphorus pentachloride, 7647-19-0; ethyl *p*-methylbenzoylacetate, 27835-00-3; *trans*-β-chloro-*p*-methylcinnamic acid, 56377-32-3; ethyl *p*-nitrobenzoylacetate, 838-57-3; ethyl acetoacetate, 141-97-9; *p*-nitrobenzoyl chloride, 122-04-3; *trans*-β-chloro-*p*-nitrocinnamic acid, 56377-33-4; ethyl *p*-chlorobenzoylacetate, 2881-63-2; *p*-chlorobenzoyl chloride, 122-01-0; *trans*-β-chloro-*p*-chlorocinnamic acid, 56377-34-5.

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Aromatic Nucleophilic Substitution Reactions of Ambident Nucleophiles. III.[1] Reactivity of the Nitrite Ion

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The reactivity patterns in the SNAr reactions of the ambident nitrite ion with nitrohalobenzenes depend on the solvent, the leaving group, and the position of substituents. The rate-determining step can be either the formation or decomposition of the intermediate complex, depending on the leaving group and mode of attack by the nitrite ion. The activating effect of a para relative to the same ortho substituent depends on the leaving group and on whether nitrite is attacking via its nitrogen or oxygen atom. The nitrite ion is of comparable nucleophilicity to azide ion, but is a much weaker carbon base than azide when attacking through its nitrogen atom, although it is a strong carbon base when attacking through oxygen. The reactivity patterns of nitrite ion in SNAr reactions are compared with those of other nucleophiles, such as N_3^-, SCN^-, the halides, RS^- and RO^-.

In Part II[1] we gave further evidence for a mechanism (Scheme I) first proposed by Rosenblatt, Dennis, and Goodin[2] for the reactions of nitrite ion with aromatic compounds, ArX, which are suitably activated for aromatic nucleophilic substitution. A number of rate constants were reported and used to support the mechanism. This paper takes those rate constants and some new ones and discusses reactivity patterns,[3] i.e., nucleophilicities, leaving group tendencies, solvent effects, and substituent effects in these reactions and in reactions involving related nucleophiles, such as azide, thiocyanate, and the halides.

The ambident nitrite ion[2,4] bonds to aromatic carbon via its nitrogen or its oxygen atom (N-attack or O-attack), but the end product of reaction with ArX is always the phenoxide, ArO^-, owing to the reactivity of the nitro intermediate $ArNO_2$, which can be isolated in certain reactions.[1,2]

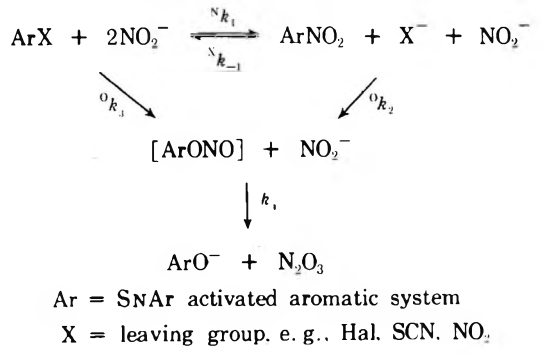
The reactions of nitrite ion have similarities to the SNAr reactions of the ambident thiocyanate ion, which were discussed in Part I.[5] Thus the compounds ArSCN and $ArNO_2$ are reactive intermediates, and SCN^- and NO_2^- are weak carbon bases. The nitrite ion has a soft[6] nitrogen atom and two harder[6] oxygen atoms, whereas SCN^- has soft sulfur and harder nitrogen. These properties cause interesting variations in leaving group tendencies,[3] in the activating effect of substituents,[3] and even in the effect of solvents on rates and mechanism, as discussed below.

Results and Discussion

Rate constants were measured and processed as described in Parts I[5] and II.[1]

Leaving Group Tendencies.[3] Table I compares the rates of reaction of three sets of fluoro-, chloro-, and iodonitro-substituted benzenes, ArX, with nitrite ion, via N-attack as log $^Nk^X$, and O-attack as log $^Ok^X$. Three comparisons are made, $^Nk^X/^Ok^X$ (the ratio of N- to O-attack), log $^Nk^F/^Nk^{Cl}$, and log $^Ok^F/^Ok^{Cl}$. The latter two comparisons show leaving group tendencies of fluorine relative to chlorine for N- and O-attack, respectively. In some cases, only upper or lower limits to these ratios have been recorded because the other rate constant was too slow to measure in competition with other reactions. However, even these ratios give useful information. All three sets of ratios show substantial changes with one or more of the variables of solvent, leaving group, or substituent. These changes are related to changes of mechanism, e.g., formation or decomposition of the SNAr intermediate as rate-determining step.[3] As shown in Table I, for N-attack by nitrite ion, fluorine is displaced less rapidly than chlorine in both protic and dipolar aprotic solvents, except in the reactions of 4-fluoro- and 4-chloronitrobenzene. For O-attack by nitrite ion, fluorine is displaced more rapidly than chlorine from the 2,4-dinitrohalobenzenes in methanol, but not in Me_2SO, DMF, or HMPA. In contrast to the 2,4-dinitrohalobenzenes, in Me_2SO, fluorine is replaced more rapidly than chlorine by O-attack of nitrite ion on both the 2- and the 4-nitrohalobenzenes in Me_2SO.

Scheme I



Ar = SNAr activated aromatic system

X = leaving group, e.g., Hal, SCN, NO_2

Variations in the relative rates of displacement of fluorine, relative to other halogens in SNAr reactions, have long been used as a probe into whether formation of the SNAr intermediate or its decomposition is rate determining.[3] If fluorine is displaced much more rapidly than other halogens, then formation of the intermediate is rate determining but if fluorine is displaced less rapidly then its decomposition is rate determining. Hard nucleophiles which are strong carbon bases,[7] e.g., methoxide ion, displace hard fluorine much more rapidly than they displace other halogens, whereas soft nucleophiles, which are weaker carbon bases, e.g., SCN^-,[5] PhS^-,[3,8] and Br^-,[3] displace fluorine more slowly or only as fast as they displace the other halogens.

Leaving group tendencies of fluorine, chlorine, and the nitro group relative to iodine are compared in Table II. The variation is considerable, e.g., k^F/k^I decreases by more than 10,000 for reactions of the 2,4-dinitrohalobenzenes in the order of nucleophile/solvent: Pip/MeOH ≈ OMe^-/MeOH ≃ N_3^-/MeOH ≈ ONO^-/MeOH > SCN^-/DMF > PhS^-/MeOH > ONO^-/DMF > SCN^-/DMF ≈ SCN^-/MeOH > NO_2^-/DMF, where the atom which is bonding to carbon is boldfaced. Iodine can be replaced up to ten times *more* rapidly than fluorine, chlorine, or nitro by soft nucleophiles, but with some hard nucleophiles, iodine is replaced up to 1000 times *less* rapidly than fluorine or nitro and up to five times less rapidly than chlorine. A spectrum of leaving

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Table I
SNAr Reaction of Nitrite Ion with Halonitrobenzenes. Leaving Group Tendencies and Effect of Leaving Group and Solvent on Ratio of N-Attack to O-Attack

Substrate ArX	Solvent	Temp, °C	Log $^{N}k^{X}$ [a,b]	Log $^{O}k^{X}$ [a,b]	$^{N}k^{X}/^{O}k^{X}$	Log $^{N}k^{F}/^{N}k^{Cl}$	Log $^{O}k^{F}/^{O}k^{Cl}$
Ar″F	MeOH	45	<−3	−1.97	<0.1	<0.7	>+2.4
Ar″Cl	MeOH	45	−3.72	<−4.4	>5		
Ar″I	MeOH	45	−3.96	<−4.7	>5		
Ar″F	Me_2SO	25	<−1.5	−0.85[c]	<1	<−1	≤−0.6
Ar″Cl	Me_2SO	25	−0.40	−0.22	0.67		
Ar″I	Me_2SO	25	−0.57[c]		>1		
Ar″F	DMF	25	<−1	−0.62[c,d]	<1	<−1	≤−1.3
Ar″Cl	DMF	25	0.48[d]	0.65[f]	0.67		
Ar″I	DMF	25	0.15[c,d]		>1		
Ar″F	HMPA	25	<0.5	1.0[c,d]	<1	<−2	≤−1.8
Ar″Cl	HMPA	25	2.66[d]	2.84[d]	0.67		
Ar″I	HMPA	25	2.12[c,d]		>1		
o-Ar′F	Me_2SO	100	−3.98	−3.50	0.33	−0.41	+0.24
o-Ar′Cl	Me_2SO	100	−3.57	−3.74	1.5		
o-Ar′I	Me_2SO	100	−3.1	−4	7		
p-Ar′F	Me_2SO	100	−2.89	−3.50	4	+0.86	+0.55
p-Ar′Cl	Me_2SO	100	−3.75	−4.05	2		
p-Ar′I	Me_2SO	100	−3.3	−4.2	8		

Ar″F = 1-F-2,4$(NO_2)_2C_6H_3$, *o*-Ar′F = 1-F-2$NO_2C_6H_4$, *p*-Ar′F = 1-F-4$NO_2C_6H_4$, etc.

[a] Taken from ref 1 unless otherwise stated. [b] $^{N}k^{X}$ and $^{O}k^{X}$ are the rate constants for N- and O-attack, respectively, in l. mol^{-1} sec^{-1} with X-Hal as the leaving group. [c] Only this mode of attack could be detected. [d] This work.

group tendencies is shown by the reactions of the ambident nitrite ion (Table II), which behaves as a rather soft nucleophile and is softer when attacking through nitrogen than when attacking through oxygen.

The log $^{O}k^{F}/^{O}k^{Cl}$ value for the SNAr reaction of nitrite ion via O-attack on the 2,4-dinitrohalobenzenes is high in methanol but low in dipolar aprotic solvents (Table I). This effect has long been anticipated,[5,8] but rarely if ever observed in SNAr reactions[7,8] with other nucleophiles. It suggests that formation of the intermediate complex is rate determining in methanol but decomposition of the intermediate complex is rate determining in dipolar aprotic solvents. A reason could be that small anions, like F^-, have a much more endoenergetic free energy of transfer from methanol to the poorly solvating dipolar aprotic solvents than do anions like nitrite and especially the intermediate complex anion.[7] Thus loss of fluoride ion from a fluorine-containing complex anion requires a much higher activation energy in dipolar aprotic relative to that for the formation of the complex from NO_2^- and Ar″F than it does in methanol.

As shown in Table II, the nitrite ion is a very labile leaving group, compared to iodide ion in most SNAr reactions. As with fluorine, the lability depends on the nucleophile; e.g., NO_2 is not particularly labile when displaced by NO_2^- (O- or N-attack), but is very labile when displaced by the small azide ion.

It is believed that the strong electronegativity of the nitro group and of fluorine when bound to carbon accounts for the high reactivity of ArF and $ArNO_2$ relative to ArI in SNAr reactions for which formation of the intermediate complex is rate determining.[3] However, when the decomposition of the intermediate complex is rate determining, nitro and fluorine are much less labile, relative to iodine. Examples of both types of reaction are in Table II.

Substituent Effects.[3] The relative rates of SNAr reactions of aromatic compounds activated by a para vs. the same ortho substituent show differences which can tell us something about the mechanism of SNAr reactions.[3,9-11] There are of course steric interactions of the reaction center with ortho groups, but not with para groups in SNAr reactions. Reactivity patterns for reactions with azide ion and nitrite ion in Me_2SO are presented as para/ortho ratios for NO_2, F, and Cl as leaving groups in Table III. Para/ortho rate ratios are rates of reaction of a para isomer divided by the rate of the corresponding reaction of the ortho isomer under identical conditions.

Nitro substituents para to a leaving NO_2 or Cl are *less* effective in enhancing rate of attack by nitrite ion in Me_2SO than are ortho nitro substituents; however, when the much smaller fluorine is the leaving group, a para is *more* effective than an ortho nitro substituent (Table III). This may be related to the fact, confirmed by X-ray work, that halogens twist ortho nitro groups in halonitrobenzenes. The twisting is minor for fluorine but naturally is greater with increasing size of the halogen.[12] Thus *o*-dinitrobenzene and o-nitrochlorobenzene, with their bulky substituents, are likely to be more reactive species than their para isomers. Examination of models show that the twisting of the nitro group in the ortho isomers is likely to be relieved in the transition state for formation of the SNAr complex as the carbon at the reaction center becomes sp^3 hybridized.[3] The larger the leaving group, the greater the relief. Thus nitroaromatics with bulky leaving groups ortho to the nitro group react more rapidly than the corresponding para isomers, leading to low para/ortho rate ratios. This reasoning, applied to Table III, is valid for Me_2SO as solvent, but special solvent effects must be considered for reactions in some protic solvents.[10,11]

With fluorine as leaving group, the steric effect of fluorine on an ortho nitro group is small, so that para/ortho ratios close to unity are expected. The value of 12 for N-attack by nitrite ion in Me_2SO on the *o*- and *p*-nitrofluorobenzenes is anomalous in terms of a bond-forming rate-determining step. Leaving group tendencies (Table II) have suggested that this pair of reactions is likely to be one in which decomposition of the intermediate—not formation—is rate determining and the high para/ortho ratio supports this. Thus the fluorine- and nitro-containing intermediate, in which there is no steric interaction between reaction

Table II
Effect of Nucleophiles and Solvent on Leaving Group Mobility of Groups X Relative to Iodide in SNAr Reactions

Nucleophile	Solvent	Temp, °C	Substrate[a]	Log k^X − log k^I X = F	Cl	NO_2
PhS^-	MeOH[e]	30	Ar″	1.3	−0.2	
PhS^-	MeOH[f,g]	30	*p*-Ar′			2.1
$Ar''S^-$	MeOH[g]	100	Ar″	0.6	−0.6	2.6
SCN^-[b]	MeOH[g]	100	Ar″	−1.0	−0.8	
SCN^-[b]	DMF[g]	75	Ar″	−1.1	−0.5	1.7
SCN^-[b]	DMF[g]	75	Ar″	1.9	0.2	≤1.9
N_3^-	MeOH[h,i]	25	Ar″	2.8	0.2	3.6
N_3^-	MeOH[j]	100	*o*-Ar′	1.6		
N_3^-	MeOH[j]	100	*p*-Ar′	1.8		
N_3^-	DMF[j]	100	*p*-Ar′	2.0	−0.1	
N_3^-	DMF[h]	−16	Ar″	>2	0.7	
Pip	MeOH[k]	0	Ar″	3.5	0.6	2.9
Pip	EtOH[l]	50	*o*-Ar′	2.7	0.1	
Pip	EtOH[l]	50	*p*-Ar′	3.05	0.4	
Pip	Me_2SO[m]	50	*p*-Ar′	3.2	0.6	
NO_2^-[b]	MeOH[s]	45	Ar″	<1	0.2	~1.2[c]
NO_2^-[b]	DMF[s]	25	Ar″	<−1	~0.3	~1.4[a,d]
NO_2^-[b]	Me_2SO[s]	100	*o*-Ar′	−0.9	−0.5	0.5
NO_2^-[b]	Me_2SO[s]	100	*p*-Ar′	0.4	−0.45	−0.5
ONO^-[b]	MeOH[s]	45	Ar″	>2	0–1	>1
ONO^-[b]	DMF[s]	25	Ar″	~0		>2[c]
ONO^-[b]	Me_2SO[s]	100	*o*-Ar′	0.5	0.3	1.3
ONO^-[b]	Me_2SO[s]	100	*p*-Ar′	0.7	0.15	0.2
MeO^-	MeOH[n,o]	30	Ar″	3.3	0.7	2.9
MeO^-	MeOH[p]	100	*o*-Ar′	2.7	0.2	
MeO^-	MeOH[q]	100	*p*-Ar′	2.6	0.4	
Br^-	DMF[g,r]	73	Ar″		−1.1	
Cl^-	DMF[r]	73	Ar″		−0.9	

[a] *o*-Ar′ = 2-$NO_2C_6H_4$, *p*-Ar′ = 4-$NO_2C_6H_4$, Ar″ = 2,4-$(NO_2)_2C_6H_3$. [b] Mode of attack for ambident nucleophiles is boldfaced to show which atom is bonding to carbon. [c] Assuming an N:O ratio similar to that for *o*-dinitrobenzene and o-nitroiodobenzene in Me_2SO. [d] Solvent is Me_2SO. [e] J. F. Bunnett and W. S. Merritt, *J. Am. Chem. Soc.*, 79, 5967 (1957). [f] Reference 8. [g] D. E. Giles, Ph.D. Thesis, University of Western Australia, 1970. [h] B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker *J. Chem. Soc. B*, 152 (1966). [i] K. C. Ho, J. Miller, and K. W. Wong, *J. Chem. Soc.*, 310 (1966). [j] J. Miller and A. J. Parker, *J. Am. Chem. Soc.*, 83, 117 (1961). [k] J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Am. Chem. Soc.*, 79, 385 (1957). [l] N. B. Chapman, R. E. Parker, and P. W. Soanes, *J. Chem. Soc.*, 2109 (1954). [m] H. Suhr and H. Grube, *Ber. Bunsenges. Phys. Chem.*, 70, 544 (1966). [n] A. L. Beckwith, J. Miller, and G. D. Leahy, *J. Chem. Soc.*, 3552 (1952). [o] J. Miller and K. W. Wong, *Aust. J. Chem.*, 18, 117 (1965). [p] B. A. Bolto, J. Miller, and V. A. Williams, *J. Chem. Soc.*, 2926 (1955). [q] G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *J. Chem. Soc.*, 1265 (1954). [r] M. Ruane, Honors Thesis, University of Western Australia, 1965. [s] This work.

Table III
Reactions of Azide and Nitrite Ion with 1-X-2-Nitro- and 1-X-4-Nitrobenzene at 100° in Me_2SO. Variation of Para:Ortho Rate Ratios

Nucleophile	k_p/k_o[a] X = NO_2	F	Cl
ONO^-[b]	0.1	1.0	0.5
NO_2^-[b]	0.14	12	0.65
N_3^-	0.2[c]		0.2[d]

[a] Rate of reaction of the para isomer divided by the rate of reaction of the ortho isomer. [b] The atom which bonds to carbon is boldfaced for ambident nucleophiles. [c] Reaction is at 40°. [d] $k_n = 3.8 \times 10^{-4}\ M^{-1}\ sec^{-1}$.

center and ortho nitro group, is decomposing in the rate-determining step through a transition state, whose structure is tending toward the product, o-dinitrobenzene. In this product there are strong unfavorable interactions between the ortho substituent nitro group and the entering nitro group. Thus the "bond breaking reaction" of o-nitrofluorobenzene with nitrite ion (N-attack) is slowed relative to the reaction of the para isomer and the para/ortho ratio becomes anomalously high, when compared with SNAr reactions of fluoroaromatics in which formation of the intermediate is rate determining.

Nitrite Ion as a Nucleophile. Nucleophilic tendencies[3] of bases toward methyl iodide (SN2 reactions)[7] and toward 1-iodo-2,4-dinitrobenzene (SNAr reactions) are compared in Table IV. Two sets of nucleophilicities are given. One has chloride ion in methanol as reference nucleophile, the other has chloride in DMF. Solvent effects on nucleophilic tendencies are very substantial,[7] so comparisons can only be made within one solvent system. Table IV allows interesting comparisons of nucleophilicity for displacement of iodide from saturated and aromatic carbon, respectively.

Table IV
SNAr and SN2 Nucleophilicity (Log ^Bk − log ^{Cl}k) of Bases B^- Relative to Chloride Ion in Methanol and DMF. Leaving Group Iodine

Nucleophile B^-	SNAr reactions of Ar″I[b] MeOH	DMF	SN2 reactions of MeI[c] MeOH	DMF
PhS^-	11.0[l]	9.4[d,l]	~5[x,y]	~4[x,z]
$Ar''S^-$	9.3[f,m]	3.4[e,m]		
MeO^-	7.7[n]	6.5[d,n]	1.8[y]	1.6[y]
PhO^-	~6.8[g,o]	8[d,o]	1.3[u]	0.3[u]
p-Ar′O^-[a]	~3.9[g,o]	1.5[d,o]	0[u]	−2.2[u]
$Ar''O^-$	−0.7[d,p]	−3.3[e,p]	−1.7[u]	−4.4[u]
N_3^-	6.5[q,r]	5.2[f,q,r] 5.9[e,f,p]	1.5[q]	0.1[q]
NO_2^-[h]	5.2[aa]	~3.7[f,aa]	1.2[i]	0.4[i,j]
ONO^-[h]	4.4[aa] <4[k,s]	2.7[f,aa]		
SCN^-[h]	4.5[m,q]	−0.3[m,q]	2.5[q]	−1.5[q]
SCN^-[h]		−3.6[m] −4.1[e,p]	<1.0[w]	<−3.0[w]
I^-	2.5[m,t]	−3.3[m,t] −3.5[e,p]	2.25[i,r]	−1.7[d,r]
Br^-	1.3[r]	−1.3[r] −2.6[e,p]	1.3[v]	−0.4[v]
F^-	>0[aa]	>0[aa]		
Cl^-	0[b,r]	0[b,r]	0[c,v]	0[c,v]

[a] *p*-Ar′ = 4-$NO_2C_6H_4$, Ar″ = 2,4-$(NO_2)_2C_6H_3$. [b] Log ^{Cl}k (Ar″I) = −8.86 in MeOH at 50°, E_a = 32.1 kcal/mol, $\Delta S^\ddagger$ = −2 eu; −2.53 in DMF at 50°, E_a = 23.7 kcal/mol, $\Delta S^\ddagger$ = −1 eu. [c] Log ^{Cl}k (MeI) = −7.0 in MeOH at 0°, −0.62 in DMF at 0°. [d] Estimated from $^M\gamma^{DMF}$ for B^- and Cl^- assuming $^M\gamma^{DMF}$ for substrate and transition state is negligible. Reference 7. [e] Reaction of Ar′ SCN. Log ^{Cl}k (Ar″SCN) ≈ log ^{Cl}k (Ar″I) (ref 5). [f] Values corrected to same temperature using E_a and $\Delta S^\ddagger$ quoted in footnote *b*. [g] Reaction of Ar″Cl with B^- relative to reaction of Ar″I with Cl^-. [h] Mode of attack boldfaced for ambident nucleophiles. [i] Reaction of *n*-BuI at 25°. [j] In Me_2SO. [k] In CH_3CN-H_2O. [l] Footnote *e*, Table II. [m] Footnote *g*, Table II. [n] Footnote *o*, Table II. [o] G. O. Leahy, M. Liveris, J. Miller, and A. J. Parker, *Aust. J. Chem.*, 9, 382 (1956). [p] Reference 5. [q] Footnote *h*, Table II. [r] Footnote *r*, Table II. [s] Reference 2, but corrected from <1 by agreement following correspondence with Drs. Rosenblatt and Dennis. [t] F. H. Kendall and J. Miller, *J. Chem. Soc. B*, 119 (1967). [u] D. Cook, I. P. Evans, E. C. F. Ko, and A. J. Parker, *J. Chem. Soc. B*, 404 (1966). [v] A. J. Parker, *J. Chem. Soc.*, 4398 (1961). [w] No isothiocyanato compound detected. [x] Reaction of *n*-BuBr. [y] Reference 7. [z] A. J. Parker, M. Ruane, D. A. Palmer, and S. Winstein, *J. Am. Chem. Soc.*, 44, 2228 (1972). [aa] This work and ref 1.

SN2 reactions are synchronous and have a single transition state. This is "looser" than either of the transition states for formation or decomposition of the SNAr intermediate.[7] In a loose transition state, entering and/or leaving groups have only weak covalent bonding interactions with carbon. The looser the SN2 transition state, the smaller the difference in reactivity between the strongest and weakest nucleophiles,[7] the tighter the transition state, the greater the difference in nucleophilicity. Thus the very tight SNAr transition state allows a wide range of reactivity for nucleophiles. There are other differences too between SN2 and SNAr reactions, associated with the two-step formation and decomposition of the SNAr intermediate and the steric consequences of a four- (SNAr) vs. a five- (SN2) coordinate transition state.[3]

A feature of Table IV is that methoxide, phenoxide, azide, and nitrite ions are $>10^5$ times more reactive than chloride ion in SNAr reactions, but these ions are of similar reactivity to chloride ion in SN2 reactions. In the SNAr reactions, the nucleophilicity is strongly influenced by the ability of the base to form strong bonds with carbon. Nitrite ion (N-attack) has a nucleophilicity which is comparable with azide ion toward 1-iodo-2,4-dinitrobenzene.

SNAr nucleophilicities toward 1-iodo-2,4-dinitrobenzene in methanol decrease in the order $PhS^- > Ar''S^- > MeO^- > PhO^- > N_3^- > NO_2^- > SCN^- > I^- > Br^- > ONO^- > Cl^- > F^-$. As one might expect from the substantial effects of different leaving groups and solvents on reactivity, SNAr nucleophilicity toward 1-fluoro-2,4-dinitrobenzene in DMF is very different,[13] i.e., $PhS^-, PhO^- > N_3^- \gg ONO^- > Ar''S^-, NO_2^-, F^- > Cl^- > SCN^-, SCN^- > Br^- > I^-$. SN2 nucleophilic tendencies toward methyl iodide in methanol decrease in yet a different order: $PhS^- \gg SCN^- > I^- > MeO^- > PhO^-, N_3^- > NO_2^-, Br^- > SNN^-, Cl^-$.

N- vs. O-Attack. It is now apparent (see preceding discussion) why the relative rates of N-attack vs. O-attack in SNAr reactions of the ambident nitrite ion change with the solvent, the leaving group, and substituents. The following examples highlight these interesting effects, which can be explained using the principles outlined herein.

An example of the solvent effect on this ambident ion is the reaction of NO_2^- with 1-chloro-2,4-dinitrobenzene, where N-attack is more than five times faster than O-attack in methanol, but in Me_2SO O-attack is faster than N-attack (Table I).

An example of the leaving group effect on ambident NO_2^- is the reaction of the 1-halo-2,4-dinitrobenzenes with nitrite ion in methanol. Here N-attack is more than ten times *slower* than O-attack on the fluoro compound but N-attack is more than five times *faster* than O-attack for reaction with the iodo compound (Table I).

An example of the substituent effect on reactions of the ambident nitrite ion are the reactions of *o*- and *p*-fluoronitrobenzene with nitrite ion in Me_2SO at 100°. Here N-attack is three times *slower* than O-attack on the ortho isomer, but N-attack is four times *faster* than O-attack on the para isomer.

Registry No.—Ar''F, 70-34-8; Ar''Cl, 97-00-7; Ar''I, 709-49-9; *o*-Ar'F, 1493-27-2; *o*-Ar'Cl, 88-73-3; *o*-Ar'I, 609-73-4; *p*-Ar'F, 350-46-9; *p*-Ar'Cl, 100-00-5; *p*-Ar'I, 636-98-6; PhS^-, 13133-62-5; $Ar''S^-$, 56437-88-8; SCN^-, 302-04-5; N_3^-, 14343-69-2; Pip, 26330-84-7; NO_2^-, 14797-65-0; MeO^-, 3315-60-4; Br^-, 24959-67-9; Cl^-, 16887-00-3; PhO^-, 3229-70-7; *p*-Ar'O^-, 14609-74-6; Ar''O^-, 20350-26-3; I^-, 20461-54-5; F^-, 16984-48-8.

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The Nucleophilic Step of the Ring Opening Reactions of Cyclopropanes with Electrophiles. Mechanism and Stereochemistry. I. Reaction of 1-Phenylbicyclo[4.1.0]heptane with Mercuric Salts

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The regio- and stereoselectivity of the cyclopropane ring opening reactions of 1-phenylbicyclo[4.1.0]heptane (1) with mercuric salts has been investigated. The stereoselectivity of the mercuration of 1 is highly variable, ranging from a syn:anti ratio of 13.5:86.5 to one of 82.5:17.5, and it is influenced by the type of mercuric salt and by the solvent. The observed results can be accounted for by a mechanism implying transition states or intermediates with high degree of development of positive charge on the benzylic carbon, in analogy with what was found in the case of the ring opening of aryl-substituted oxiranes and oxetanes in acidic media.

The ring opening reactions of cyclopropanes with electrophiles have been the subject of many recent investigations,[1-4] and in most cases a regiospecificity in accordance with the Markovnikov rule has been observed, with some exceptions.[5,6]

As to the stereochemistry of the ring opening it has been found that the electrophilic attack can occur with either retention or inversion of configuration depending on the nature and configuration of the ring substituents, whereas the nucleophilic step is highly stereoselective with complete or

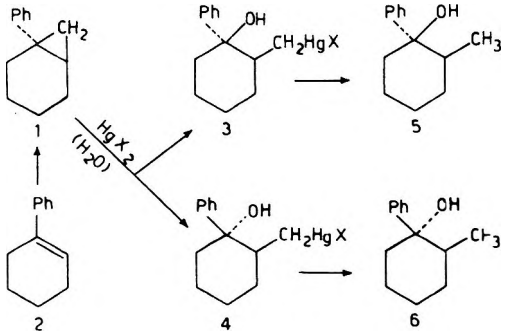
strongly predominant inversion of configuration in the majority of the reported cases.[1-4]

Mercuric salts and protic acids (H^+ and D^+) have been the most studied electrophiles in these reactions, but the latter afford very often significant amounts of elimination and/or rearrangement products.[1]

Previous work in our laboratory on the steric course of the ring opening reactions in acidic media of small ring heterocycles such as oxiranes,[7] aziridines,[8] and oxetanes[9] bearing aryl substituents on the ring has shown that the regio- and stereochemistry of these reactions are strongly influenced by the structure of the heterocycle, the nature of the substituents, the reaction condition, etc., the attack by the nucleophile taking place with courses ranging from complete retention to complete inversion of configuration.[7-9]

In connection with these studies we started an investigation on the ring opening reactions of cyclopropanes in order to establish possible correlations between the steric course of the nucleophilic stage of these reactions and that of the ring opening of small ring heterocycles in acid media. We wanted in particular to find out what analogies, if any, exist between the latter reactions, involving oxygen or nitrogen as the leaving atom, and the former ones, in which carbon exerts this function. We are reporting here the results of the ring opening reactions with mercuric salts of 1-phenylbicyclo[4.1.0]heptane (**1**), an analog of heterocycles[7a-c,8,9] that have previously been extensively investigated by our group.

Cyclopropane **1** has been obtained by the Simmons–Smith reaction of olefin **2**, and has been purified by its treatment with ozone followed by chromatography. Levina and coworkers[10] reported that the ring opening reaction of **1** with mercuric acetate in water leads to 70% 1-phenyl-2-acetoxymercurimethylcyclohexanol, without giving any detail on the stereochemistry of the product. We have, therefore, reexamined this reaction and determined the composition and the stereochemistry of the products by reductive demercuration of the crude reaction mixture with sodium borohydride,[11] followed by GLC analysis. The known 1-phenyl-*cis*- (**5**) and -*trans*-2-methylcyclohexanol (**6**)[12] were thus obtained in a ratio of 13.5:86.5 (see Table I), indicating a similar ratio of the corresponding organomercurials **3a** and **4a** in the initial reaction mixture. Pure **4a** was obtained through crystallization of the crude oxymercuration product.



a, X=OOCCH3; b, X=OOCCF3; c, X=½SO4; d, X=NO3; e, X=ClO4

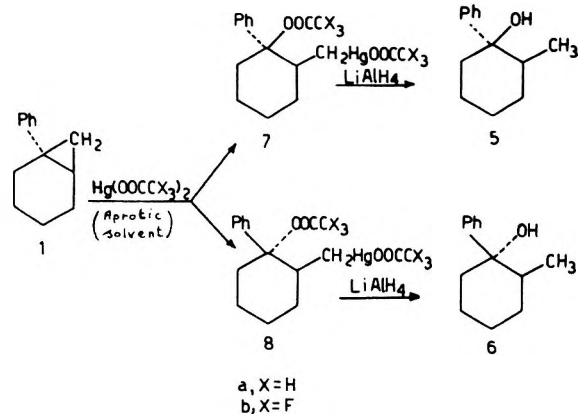
The hydroxymercuration reactions were also carried out with other mercury salts (Table I) and it was found that the **3**:**4** ratio increased when salts of stronger acids were used. Pure **4b** was obtained by crystallization of the crude oxymercuration products. Higher percentages of cis adducts were also formed when 1:1 THF–water was used as the solvent.

Cleavage of **1** with $Hg(OOCCH_3)_2$ in acetic acid gave a mixture of the cis (**7a**) and trans diacetate (**8a**) which was reduced by $LiAlH_4$ to the alcohols **5** and **6** in a ratio of 45:55; when this reaction was carried out in CH_2Cl_2 the amount of syn opening of the cyclopropane ring increased to 58.0%. The presence of free acetic acid in the reaction medium did not substantially modify the result (Table I).

Table I
Stereochemistry of the Nucleophilic Step of the Mercuration of 1

Mercuric salt	Added nucleophile	Solvent	% 5	% 6
$Hg(OOCCH_3)_2$		H_2O	13.5	86.5
$Hg(OOCCF_3)_2$		H_2O	19.5	80.5
$HgSO_4$		H_2O	22.5	77.5
$Hg(NO_3)_2$		H_2O	22.5	77.5
$Hg(ClO_4)_2$		H_2O	23.0	77.0
$Hg(OOCCH_3)_2$		THF–H_2O (1:1)	25.5	74.5
$Hg(OOCCF_3)_2$		THF–H_2O (1:1)	28.5	71.5
$Hg(OOCCH_3)_2$		CH_3COOH	45.0	55.0
$Hg(OOCCH_3)_2$		CH_2Cl_2	58.0	42.0
$Hg(OOCCH_3)_2$	1 *M* CH_3COOH	CH_2Cl_2	54.5	45.5
$Hg(OOCCF_3)_2$		Cyclohexane	69.5	30.5
$Hg(OOCCF_3)_2$	H_2O (satd)	Cyclohexane	69.0	31.0
$Hg(OOCCF_3)_2$		CCl_4	62.0	38.0
$Hg(OOCCF_3)_2$		$CHCl_3$	82.5	17.5
$Hg(OOCCF_3)_2$		CH_2Cl_2	75.0	25.0
$Hg(OOCCF_3)_2$	H_2O (satd)	CH_2Cl_2	73.0	27.0
$Hg(OOCCF_3)_2$		Benzene	71.0	29.0
$Hg(OOCCF_3)_2$	H_2O (satd)	Benzene	68.5	31.5
$Hg(OOCCF_3)_2$		CH_3NO_2	72.0	28.0

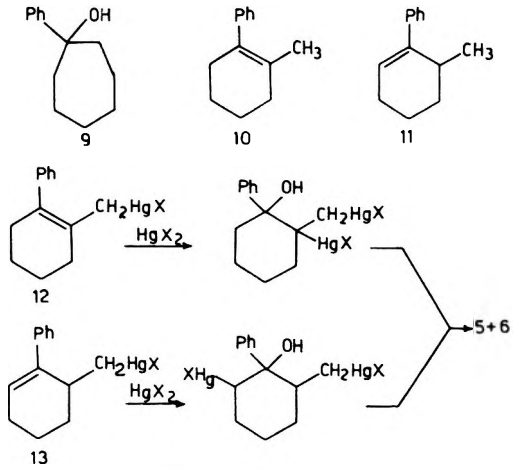
The use of mercury trifluoroacetate in aprotic solvents gave products **7b** and **8b**, with a high prevalence of the former, reaching 82.5% in $CHCl_3$ (Table I). From the reaction mixtures pure **7b** was obtained by crystallization. The presence of water in the aprotic medium does not modify substantially the trend of the reactions, except for making them slightly less syn stereoselective.



a, X=H
b, X=F

In all the mixtures obtained after reductive demercuration of the cleavage products of **1** with mercuric salts no trace was revealed of the alcohol **9**, that should have been formed from the electrophilic attack of the mercuric salt on the secondary cyclopropylic carbon of **1** followed by the ring opening in the direction of the more stable benzylic cation.

Furthermore, it was thought suitable to ascertain whether the results obtained in the cleavage of **1** with mercuric salts were due entirely to a direct opening of the cyclopropane or to a more complex sequence of reactions,[13] such as intermediate formation of the unsaturated organomercurials **12** and **13**, followed by reaction with further mercuric salt affording products which, on reductive demercuration, should have given mixtures of alcohols **5** and **6**. We there-



fore tested the reactivity of olefins **10** and **11**, structurally analogous to **12** and **13**, with mercuric acetate. It was found that **10** and **11**, when treated with $Hg(OOCCH_3)_2$ in water under the same conditions used for the ring opening of **1**, were recovered practically unreacted. These results agree with the very low reactivity of 1-phenylcyclohexene (**5**) with $Hg(OOCCH_3)_2$ in THF–H_2O reported by Brown.[11]

The main point of interest in our results is in the highly variable stereoselectivity ranging from a syn:anti ratio of 13.5:86.5 to one of 82.5:17.5, in contrast with what would be expected on the basis of previous results[1,2,4] indicating that in the mercuration of cyclopropanes the nucleophile attacks exclusively, or nearly so, with inversion of configuration. On the other hand, the complete regiospecificity of the ring cleavage is in accordance with expectations.[1,2,4,14]

As for the stereochemistry of the nucleophilic step, the fact that the stereoselectivity is influenced by the type of mercuric salt and by the solvent and that high percentages of syn adducts are obtained when the mercurations are effected in aprotic media points to a mechanism (Scheme I) implying transition states or intermediates with a high degree of development of positive charge on carbon, in which electron release by the phenyl probably plays an important role. Similar explanations were given in order to rationalize the steric course of the ring opening of phenyl-substituted oxiranes and oxetanes in acidic media.[7,9]

In aprotic solvents, the corner-mercurated intermediate,[1,2,4] obtained by the attack of the mercury (as Hg_X_2)[14] on the least hindered carbon of **1**, can evolve through an incipient carbenium ion **16** to an intimate ion pair (like **19**) in which the anion of the mercuric salt and the benzylic carbenium ion are probably held together by electrostatic interactions.[7,9] Because of the low degree of bond breaking of the C–C bond in the incipient carbocation **16**, the attack of the nucleophile at this stage occurs from the trans side leading to the anti adduct **15**. On the contrary, for the ion pair **19** direct collapse to the cis product **18** would be particularly favorable.

When the reactions are carried out in protic solvent, the benzylic carbenium ion formed can be selectively solvated to intermediates like **17** in which the mercury is coordinated with the solvent and the solvent itself is the effective nucleophilic agent because of the higher availability. Also, in the present case, combination of the solvated ion **17** should cause the preferential formation of the syn adduct **20**, whereas the attack of the solvent on **16** should give the anti adduct **14**. The higher trans stereoselectivity obtained in the reactions carried out in protic solvents, that has been observed also in the reactions of aryl-substituted small ring heterocycles in acidic media,[7-9,15] may be due to the attack by the protic solvent on the incipient carbenium ion **16** from the anti side before the complete rupture of the C–C bond which is favored by the high availability of nucleophilic molecules.

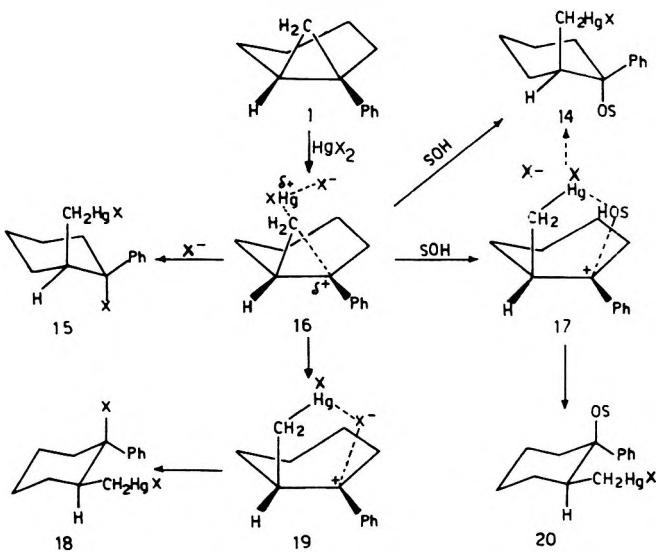
Clearly every factor which favors the development of positive charge on the benzylic carbon should increase the syn:anti ratio. As a matter of fact, when, in the mercuration of **1** in water, the mercuric salt is changed from mercuric acetate to more highly ionic salts, the higher electrophilicity of the mercury should make the rupture of the C–C bond more effective and therefore favor the path leading to the syn adduct **20** through carbenium ion **17**, in accordance with the observed increase of the cis adduct **3** on going from $Hg(OOCCH_3)_2$ to $Hg(ClO_4)_2$.[16] The same trend is observed in methylene dichloride, where the increase in syn adduct on going from $Hg(OOCCH_3)_2$ to $Hg(OOCCF_3)_2$ is considerably larger than in water or water–tetrahydrofuran. However, it should be pointed out that in the reactions carried out in methylene dichloride, the nucleophiles are different and the higher nucleophilicity of the acetate may make the attack at the stage **16**, affording the trans adduct **15**, more facile.

The high syn stereoselectivity in the reactions carried out in aprotic solvent is in agreement with our previous results on the ring opening of small ring heterocycles in acidic media.[7-9] The aprotic solvents should permit the ion-pair mechanism leading to the cis adduct to work efficiently. An added nucleophile (H_2O or CH_3COOH) affects only slightly the stereoselectivity of the mercuration reactions in aprotic solvents, showing that the ion pair **19** is sufficiently stable in the reaction conditions.

Further support for the existence of the mechanism proposed by us on the basis of the stereochemical results is given by the high negative ρ value (−3.2) found for a Hammett-type plot of the mercuration rates of arylcyclopropanes in acetic acid against the σ^+ constants.[14] In fact, the ρ value for the cleavage reactions approaches the ρ value for the solvolysis of aryldimethylcarbinyl chloride,[17] clearly a reaction with substantial carbenium ion character.

In conclusion, it is noteworthy that, in contrast with previous statements, the steric course of the nucleophilic step of the mercuration of cyclopropanes can change from complete trans stereoselectivity to nearly complete syn stereoselectivity depending on the substituents on the cyclopropanes, the reaction conditions, and the mercury salt which is used. The type of mercuric salt used may be of some importance in determining the steric course of mercuration reactions; therefore it ought to be stressed that the indiscriminate use of different mercuric salts may not be quite correct.

Scheme I



Experimental Section

All melting points were taken on a Kofler micro hot stage and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137 on paraffin oil mulls. The NMR spectra were determined on ca. 10% $CDCl_3$ solutions with a Jeol C-60 HL spectrometer using tetramethylsilane as internal standard. All GLC analyses were performed on a Perkin-Elmer apparatus Model F-11 using a glass column (2.5 mm × 2 m) packed with 15% Carbowax 20M on 80–100 mesh silanized Chromosorb W, temperatures column 200°, evaporator 230°, detector 230°, nitrogen flow 30 ml/min. The order of increasing retention times follows: **10, 11, 5, 6, 9.** The relative percentages of **5** and **6** were obtained from two or more separate runs on each experiment. All comparison between compounds were made on the basis of ir and NMR spectra and GLC. $MgSO_4$ was always used as drying agent. Evaporations were made in vacuo (rotating evaporator). Petroleum ether refers to the fraction boiling at 40–70°. Cyclohexane, benzene, CCl_4, and $CHCl_3$ were distilled from P_2O_5; CH_2Cl_2 was dried on P_2O_5 and CH_3NO_2 on molecular seives (3 Å).

1-Phenylbicyclo[4.1.0]heptane (1). A mixture of zinc dust (46.0 g, 0.70 g-atom) and cuprous chloride (6.88 g, 0.069 mol) in anhydrous ether (50 ml) was stirred rapidly and refluxed vigorously for 45 min in a nitrogen atmosphere.[18] After cooling, a few crystals of iodine and then 1-phenylcyclohexene (**2**,[19] 20.0 g, 0.12 mol) were added to the zinc–copper couple. The well-stirred mixture was then treated dropwise with methylene iodide (93.0 g, 0.35 mol) to maintain spontaneous refluxing. When the addition was complete the mixture was stirred and refluxed for an additional 24 hr. After cooling the ether layer was decanted from the unreacted couple, which was then washed with ether. The organic portion was washed with saturated NH_4Cl solution, 5% hydrochloric acid, and water and dried to yield crude **1** (18.3 g). The crude **1** was ozonized in $CHCl_3$ at 0° for 30 min in order to eliminate traces of olefinic products. Then the chloroformic solution was washed with 2 *N* Na_2CO_3 and water and evaporated to dryness and the residue was chromatographed on a 2.5 × 29 cm column of Al_2O_3 (activity I) using petroleum ether as the eluent and collecting 50-ml fractions. The second and the third fraction yielded pure **1** (14.0 g) (GLC), $n^{25}D$ 1.5404 (lit.[10] $n^{20}D$ 1.5425).

1-Phenyl-*cis*- (5) and -*trans*-2-methylcyclohexanol (6). A 94:6 mixture of **5** and **6** was obtained by the Grignard reaction of 2-methylcyclohexanone and phenylmagnesium bromide according to Luderer,[12a] bp 113–118° (2.5 mm) [lit.[12b] bp 93–96° (0.38 mm)]. The carbinol mixture (10 g) was chromatographed on a 2.9 × 60 cm silica gel column, eluting in succession with petroleum ether (6.0 l.), 98:2 petroleum ether–ether (6.0 l.) and 97:3 petroleum ether–ether (6.0 l.). Elution with 98:2 petroleum ether–ether afforded pure **5** (5.8 g), $n^{25}D$ 1.5333 (lit.[12a] $n^{22}D$ 1.5331), and with 97:3 petroleum ether–ether gave mixtures of **5** and **6.**

1-Phenyl-2-methylcyclohexene (10) and 1-Phenyl-6-methylcyclohexene (11). A mixture of **10** and **11** in a ratio of 59:41 was obtained in a modification of the method of Garbisch.[20] The 94:6 mixture of **5** and **6** (2.0 g) was stirred for 60 sec with a 20% sulfuric acid–acetic acid solution and then processed as described by Garbisch.[20]

10 and **11** were separated by preparative GLC (Carbowax 20M) and their physical and NMR data agreed with those reported by Garbisch.[20]

1-Phenylcycloheptanol (9) was obtained by Grignard reaction of cycloheptanone with phenylmagnesium bromide, mp 32–34° (from petroleum ether) (lit.[21] mp 23°).

1-Phenyl-*trans*-2-acetoxymercurimethylcyclohexanol (4a). A suspension of **1** (1.0 g, 5.8 mmol) in water (100 ml) was treated with mercuric acetate (1.85 g, 5.8 mmol) and then stirred at room temperature for 48 hr. After this time the reaction mixture was extracted with CH_2Cl_2 and the extracts, washed with water, were evaporated to dryness. The solid residue (2.1 g) on recrystallization from ethyl acetate yielded **4a** (1.5 g), mp 150–151°, λ_{OH} 2.98, λ_{CO} 6.40 μ (lit.[10] mp 143–146°).

1-Phenyl-*trans*-2-trifluoroacetoxymercurimethylcyclohexanol (4b). Mercuric trifluoroacetate[22] (1.24 g, 2.9 mmol) was added to a suspension of **1** (0.5 g, 0.29 mmol) in water (50 ml). The mixture was stirred for 48 hr at room temperature and then extracted with CH_2Cl_2. Evaporation of the washed (water) organic extracts yielded a solid residue (1.3 g) which, on crystallization from petroleum ether (bp 80–100°), gave **4b** (0.6 g), mp 105–107°, λ_{OH} 2.91, λ_{CO} 5.97 μ. Anal. Calcd for $C_{15}H_{17}F_3HgO_3$: C 35.81; H, 3.38. Found: C, 36.90; H, 3.40.

1-Phenyl-*cis*-2-trifluoroacetoxymercurimethyl-1-trifluoroacetoxycyclohexane (7b). A solution of **1** (0.300 g, 1.74 mmol) in anhydrous benzene (30 ml) was treated with mercuric trifluoroacetate (0.665 g, 1.56 mmol) and then stirred for 24 hr at room temperature. The reaction mixture was washed (water, saturated $NaHCO_3$, and water) and evaporated to yield a solid residue (0.68 g) which on crystallization from hexane afforded **7b** (0.27 g), mp 114–116°, λ_{CO} 5.61, 5.96 μ. Anal. Calcd for $C_{17}H_{16}F_6HgO_4$: C, 34.07; H, 2.67. Found: C, 34.21; H, 2.54.

1-Phenyl-*trans*-2-methylcyclohexanol (6). A. A suspension of **4a** (0.600 g, 1.33 mmol) in water (20 ml) and tetrahydrofuran (10 ml) was treated with 4 *N* NaOH (3 ml) and sodium borohydride (0.150 g, 3.8 mmol) and stirred at room temperature for 10 min. The reaction mixture was diluted with water and extracted with ether. Evaporation of the washed (water) and dried ether extracts yielded a solid residue (0.220 g) consisting of **6** (GLC) which on crystallization from petroleum ether (bp 30–50°) at −5° yielded pure **6** (0.150 g), mp 60–62° (lit.[12b] mp 61–63°).

B. Reduction of **4b** (0.300 g, 0.59 mmol) as described above for **4a** yielded a crude residue (0.070 g) consisting of **6** (GLC).

1-Phenyl-*cis*-2-methylcyclohexanol (5). A solution of **7b** (0.100 g, 0.17 mmol) in anhydrous ether (15 ml) was treated with lithium aluminum hydride (0.100 g, 2.63 mmol), stirred for 5 min at room temperature, and then refluxed for 15 min. After this time the excess of hydride was decomposed with the minimum amount of water and 2 *N* NaOH and the ether solution was dried and evaporated to yield an oily residue (0.025 g) which consisted of **5** (GLC).

Reaction of 1 with Several Mercuric Salts in Water. A suspension of **1** (0.100 g, 0.58 mmol) in water (10 ml) was treated under stirring with the appropriate mercuric salt (0.52 mmol) at room temperature. After 3 hr the mixture was treated with tetrahydrofuran (8 ml), 4 *N* NaOH (1 ml), and sodium borohydride (0.060 g, 1.58 mmol), left stirring for a further 10 min, diluted with water, and extracted with ether. Evaporation of the washed (water) and dried extracts gave a residue which was analyzed by GLC. The ratios of **5** to **6** are shown in Table I. Reactions of **1** carried out under the same reaction condition but reducting after 6 hr yielded the same product ratio within the experimental error. However, in the case of the reactions with mercuric salts of stronger acids, much longer contact times showed a slow epimerization of **6** into **5.** When olefins **10** and **11** were treated with mercuric acetate, as described above, they were recovered practically unchanged.

Reaction of 1 with Mercuric Acetate and Mercuric Trifluoroacetate in Tetrahydrofuran–Water. A solution of **1** (0.100 g, 0.58 mmol) in 1:1 (v/v) tetrahydrofuran–water mixture (10 ml) was treated with mercuric acetate or mercuric trifluoroacetate (0.52 mmol) and stirred at room temperature (6 hr for the reaction with the acetate and 1 hr for the reaction with the trifluoroacetate). Then 4 *N* NaOH (1 ml) and sodium borohydride (0.060 g, 1.58 mmol) were added and stirring was continued for 10 min. Work-up was carried out as in the case of the reactions in water and the residue obtained was analyzed by GLC (Table I). Reaction of **1** with each salt carried out under the same conditions but stopping after relatively longer contact times yielded the same product ratio within the experimental error.

Reaction of 1 with Mercuric Acetate in Acetic Acid. A solution of **1** (0.100 g, 0.58 mmol) in glacial acetic acid (10 ml) was treated under stirring with mercuric acetate (0.165 g, 0.52 mmol) for 1 hr. Then the reaction mixture was diluted with water and extracted with ether. The ether extracts were washed (water, saturated $NaHCO_3$, and water), dried, and evaporated to dryness. The residue (0.24 g) (λ_{CO} 5.78 and 6.17 μ) was dissolved in anhydrous ether (15 ml), treated with lithium aluminum hydride (0.100 g, 2.63 mmol), stirred for 5 min at room temperature, and then refluxed for 15 min. The excess of hydride was decomposed with the minimum amount of water and 2 *N* NaOH, and the dried ether layer was evaporated to dryness to yield a residue which was analyzed by GLC. The ratio of **5** to **6** is shown in Table I. Reactions of **1** carried out under the same reaction conditions but stopping after relatively longer contact times (2 hr) showed the same ratio of **5** to **6** within the experimental error.

Reactions of 1 with Mercuric Salts in Several Aprotic Solvents. A solution of **1** (0.100 g, 0.58 mmol) in the appropriate solvent (10 ml) was treated with the mercuric salt (0.52 mmol) (see Table I), stirred at room temperature (15 min for the reactions with mercuric trifluoroacetate and 2 hr for the reactions with mercuric acetate), then diluted with CH_2Cl_2, washed immediately with water, dried, and evaporated. The residue [λ_{CO} 5.78, 6.17 μ for the reactions with $Hg(OOCCH_3)_2$ and λ_{CO} 5.61, 5.96 μ for the reactions

with $Hg(OOCCF_3)_2$] was taken up in anhydrous ether (15 ml) and reduced with lithium aluminum hydride (0.100 g, 2.63 mmol) under the same conditions used for the mercuration reaction in acetic acid to give a residue which was analyzed by GLC. The ratios of 5 to 6 are reported in Table I. Reactions of 1 with each salt carried out for each solvent under the same conditions but stopping after relatively longer contact times (1 hr for the reactions with the trifluoroacetate and 4 hr for the reactions with the acetate) yielded the same product composition within the experimental error. However, much longer contact times showed changes in the ratios between 5 and 6.

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Registry No.—**1**, 2415-82-9; **2**, 771-98-2; **4a**, 56437-51-5; **4b**, 56437-52-6; **5**, 30689-79-3; **6**, 30689-80-6; **7b**, 56437-53-7; mercuric acetate, 1600-27-7; mercuric trifluoroacetate, 13257-51-7.

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Mercury in Organic Chemistry. VI.[1] A Convenient Stereospecific Synthesis of α,β-Unsaturated Carboxylic Acids and Esters via Carbonylation of Vinylmercurials

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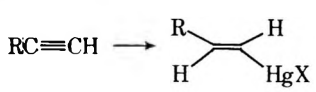
Vinylmercuric chlorides readily react with carbon monoxide (atmospheric pressure), lithium chloride, and palladium chloride in an alcohol solvent at low temperatures (<−20°) to give near-quantitative yields of α,β-unsaturated carboxylic esters in which the chloromercuri group is stereospecifically replaced by a carboalkoxy group. α,β-Unsaturated carboxylic acids may be obtained in an analogous fashion by employing 1–5% aqueous tetrahydrofuran as the solvent. The reaction accommodates a variety of functional groups and can also be effected using only catalytic amounts of palladium chloride or palladium on carbon if cupric chloride is used as a reoxidant. A mechanism involving vinyl- and acylpalladium intermediates is suggested.

The direct carbonylation of organomercurials is exceedingly difficult, requiring high temperatures and pressures and usually resulting in only very poor yields of carboxylic acids or their derivatives.[2,3] The addition of palladium salts generates organopalladium compounds[4] which are much more readily carbonylated.[5] Both the palladium exchange[6] and carbonylation[7] reactions have been determined to proceed with stereochemical retention of configuration. Unfortunately, the palladium-promoted carbonylation of alkyl-[6] and arylmercurials[8] gives poor yields of carboxylic acids or their derivatives and these reactions appear to be of rather limited synthetic utility. With the ready availability of a number of vinylmercurials through acetylene addition reactions (eq 1, 2)[9-11] and the ability of these reactions to accommodate a wide variety of functional groups, we were encouraged to examine some possible synthetic applications of these compounds. We wish to report now that the extremely facile palladium-promoted carbonylation of vinylmercurials provides an excellent new method for the preparation of α,β-unsaturated carboxylic acids and esters.



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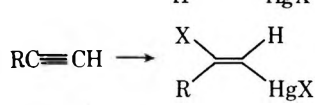
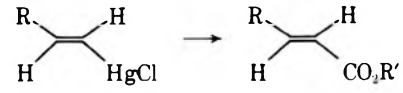


(2)

Results and Discussion

α,β-Unsaturated Esters. In order to determine the best conditions for converting vinylmercurials into α,β-unsaturated carboxylic esters, we have examined the stoichiometry of this reaction. Both styrylmercuric chloride (1 mmol) and *trans*-1-hexenylmercuric chloride (1 mmol) were treated with varying amounts of palladium chloride, lithium chloride, and methanol or ethanol under 1 atm of carbon monoxide at low temperatures, and the yield of ester determined by GLC analysis (eq 3). The results are indicated in Table I.

Several points are obvious from this study. Although excellent yields are obtained in almost all reactions, the combination of 1 equiv of palladium chloride and 2 equiv of

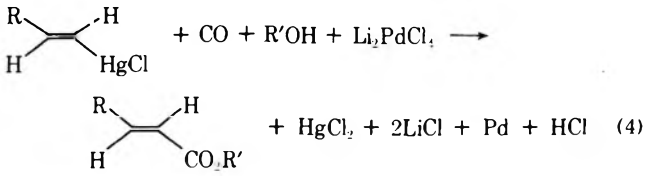


(3)

$R = C_6H_5, n\text{-}C_4H_9$
$R' = CH_3, C_2H_5$

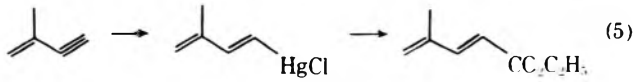
lithium chloride gives the best results. Styrylmercuric chloride gives higher yields than *trans*-1-hexenylmercuric chloride under comparable conditions and the yields in methanol are superior to those in ethanol. Use of a cosolvent resulted in sharply reduced yields of esters. The best yields are obtained by mixing the reagents at −78° where no reaction appears to occur and allowing the reaction mixture to slowly warm on its own to room temperature, at which time the reaction is complete.

Treatment of a wide variety of other vinylmercurials with carbon monoxide (1 atm), lithium chloride (2 equiv), and palladium chloride (1 equiv) in an alcohol solvent at low temperatures (−78° to room temperature) also results in near-quantitative yields of the corresponding α,β-unsaturated esters (eq 4) (see Table II). It should be noted that



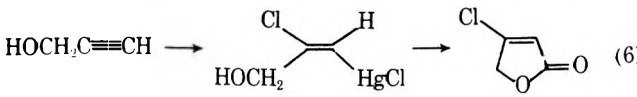
(4)

not only cyano and ester groups are readily accommodated by this reaction, but that the dienylmercurial derived from isopropenyl acetylene also gives an excellent yield of the α,β-γ,δ-unsaturated carboxylic ester (eq 5). Particularly in-



(5)

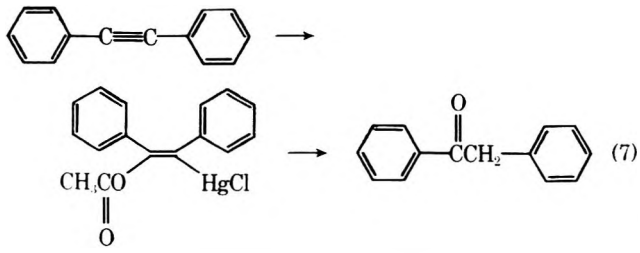
teresting is the last entry in Table II. Progargyl alcohol readily reacts with saturated aqueous solutions of mercuric chloride to give the *trans*-β-chlorovinylmercurial.[12] Subsequent carbonylation in diethyl ether provides the corresponding β-chlorobutenolide in 96% crude yield (eq 6). We



(6)

are currently extensively studying this novel new route to butenolides.

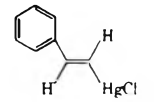
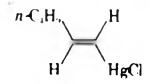
Several other β-substituted vinylmercurials were less successful, however. *trans*-3-Acetoxy-2-butenylmercuric chloride[13] gave several unidentified products in about equal amounts. On the other hand, *cis*-β-acetoxystilbenylmercuric chloride[14] gave a near-quantitative yield of deoxybenzoin characterized by comparison with an authentic sample (eq 7). We presently have no mechanistic explana-



(7)

tion for formation of this product other than simple protonolysis of the vinylmercurial or -palladium compound and subsequent hydrolysis of the enol acetate upon ammonium chloride work-up.

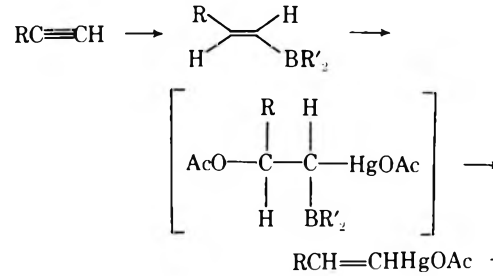
Table I
Stoichiometry of Vinylmercuric Chloride Carboalkoxylation

Vinylmercuric chloride	$PdCl_2$, mmol	LiCl, mmol	Alcohol	Temp, °C	Ester yield, %[a]
	0.5		CH_3OH	0	85
	0.5	1.0			95
	1.0				87
	1.0	2.0			100
			C_2H_5OH		88
			CH_3OH		88
				−20	95
				−78	99
			C_2H_5OH	0	67
				−20	95
				−78	95

[a] GLC analysis using an internal standard.

In most of these carbonylation reactions 1–2% yields of the stereochemically inverted product were obtained. However, 1-decenylmercuric chloride and methyl 11-chloromercuri-10-undecenoate give approximately 1:2 and 1:1.3 ratios of cis:trans mixtures, respectively. It was subsequently observed, however, that repeated recrystallization of the 1-decenylmercuric chloride eventually resulted in a mercurial which upon carbonylation gave pure (>99%) methyl *trans*-2-undecenoate in 98% isolated yield. However, the other vinylmercurial could not be as easily purified. These results suggest that the exchange and carbonylation reactions are highly stereospecific, but that the vinylmercurials themselves contain small amounts of the opposite isomer.

The low isomeric purity of the vinylmercurials obtained by the hydroboration–mercuration of 1-decyne and methyl 10-undecynoate is most unusual. We believe that stereospecificity is lost during mercuration of the intermediate vinylborane, possibly through a nonstereospecific addition–elimination sequence (eq 8). However, it is not at all clear

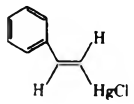
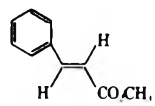
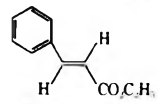
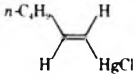
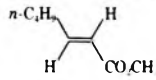
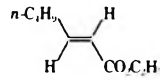
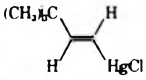
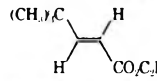
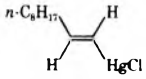
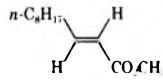
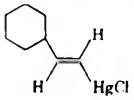
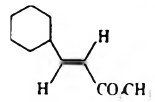
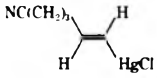
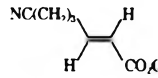
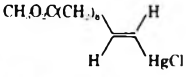
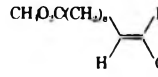
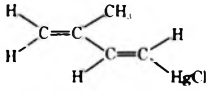
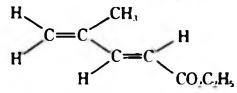
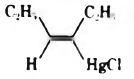
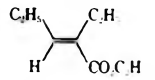
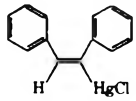
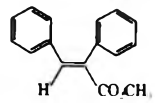
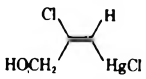
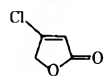


(8)

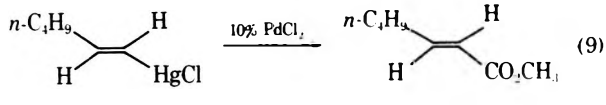
how the carbon chain length might affect the stereochemistry of such reactions. Side products in these mercuration reactions are also suggestive of attack upon the double bond of the vinylborane by mercuric acetate.[9] Furthermore, the halogenation of vinylboranes proceeds with exclusive attack upon the carbon–carbon double bond.[15,16] These results suggest that perhaps even the protonolysis of vinylboranes is proceeding by a highly stereospecific addition–elimination sequence and not direct electrophilic cleavage as previously assumed.[17]

The carbonylation reactions would achieve even greater synthetic utility if they could be carried out utilizing only catalytic amounts of palladium. This can indeed be accomplished very nicely by employing catalytic amounts of either palladium chloride or palladium on carbon and stoichiometric amounts of anhydrous cupric chloride (2 equiv) (eq 9–11).

Table II
Preparation of α,β-Unsaturated Carboxylic Esters

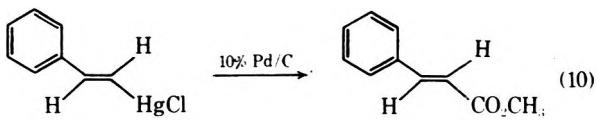
Vinylmercuric chloride	Registry no.	Carboxylic ester	Registry no.	% yield
	36525-03-8		1754-62-7	100[a]
			4192-77-2	99[a]
	50874-36-7		38693-91-3	98[a]
			54340-72-6	93[a]
	36525-02-7		22147-62-2	90[a]
	56453-77-1		56453-83-9	98
	36525-01-6		26429-99-2	96
	56453-78-2		56453-84-0	98
	56453-79-3 56453-80-6		13038-20-5 13038-18-1	98[b]
	56453-81-7		13369-24-9	93[a]
	36525-04-9		22147-74-6	85[a]
	16188-35-5		36854-27-0	99
	56453-82-8		56453-85-1	96[c]

[a] Yield by GLC analysis using an internal standard. [b] Vinylmercurial and ester are a mixture of cis and trans isomers. [c] Carbonylation in diethyl ether.



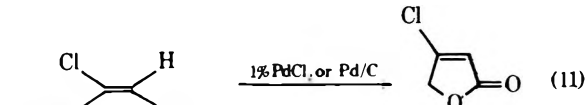
(9)

100%



(10)

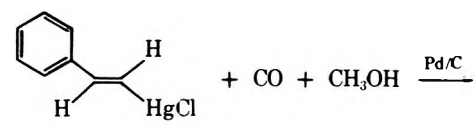
96%

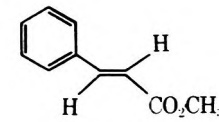


(11)

96%

We have also examined possible palladium catalysis in the absence of added cupric chloride. Modest yields of ester can be obtained by employing 1 equiv of palladium on carbon (eq 12). Unfortunately, lesser amounts of palladium (10%) gave dismal yields (1–2%). In view of the hazardous nature of this reaction (two out of three caught fire!) and the low yields, Pd/C catalysis appears to be of little synthetic utility. Tetrakis(triphenylphosphine)palladium(0)

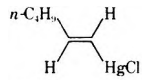
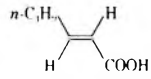
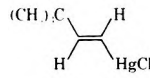
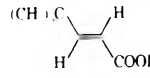
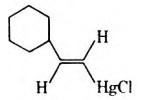
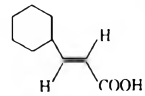
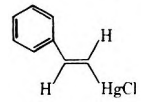
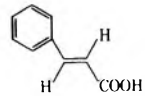
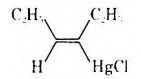
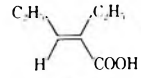
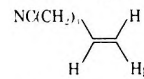
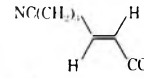
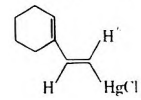
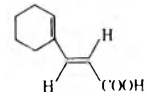




+ Hg^0 + HCl (12)

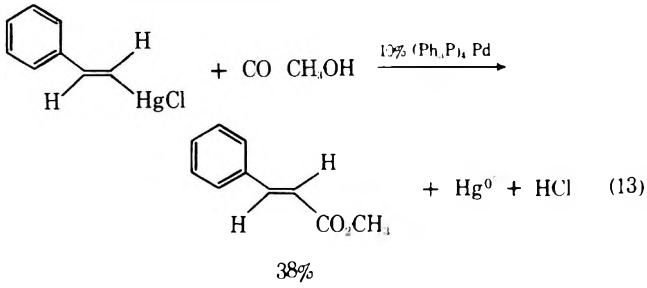
54%

Table III
Preparation of α,β-Unsaturated Carboxylic Acids

Vinylmercuric chloride	% aqueous THF	Carboxylic acid	Registry no.	% yield
	5		10352-88-2	98[a]
	2			99[a]
	5		16666-45-8	98
	5		56453-86-2	65
	2			82
	1			90
	0.5			77
	5		140-10-3	80
	1			30
	5		16403-07-9	85[a]
	2			60[a]
	5		56453-87-3	72
	2			65
	5		56453-88-4	45
	2			72
	1			57

[a] Yield by GLC analysis using an internal standard. [b] Registry no., 56453-89-5.

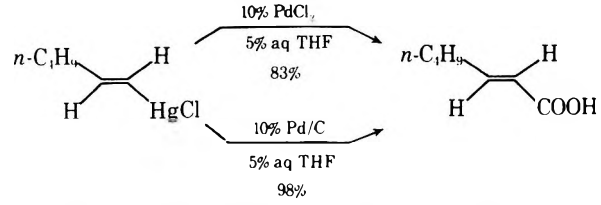
has also been examined as a possible catalyst, but was found wanting (eq 13). Thus, cupric chloride appears essential for high yields of ester.



(13)

α,β-Unsaturated Acids. Several obvious difficulties arose in attempting to extend the carbonylation reaction to the preparation of α,β-unsaturated carboxylic acids. The carboalkoxylation reactions required low temperatures (<20°) and alcohol as the solvent. Obviously we could not obtain homogeneous aqueous solutions of organomercurials at such very low temperatures. Instead we examined a variety of aqueous organic solvent systems (acetone, ether, tetrahydrofuran, dimethoxyethane) at the lowest of possible temperatures. Although an occasional reaction gave high yields, most of the reactions gave only poor yields and were highly irreproducible. We observed, however, that the yields seemed to improve by reducing the amount of water present in the system. With less than 10% water in tetrahydrofuran (THF) we were able to lower the temperature of the reaction to −78° and obtain reproducible results. Some representative yields of α,β-unsaturated acids are included in Table III. In most cases the highest yields were obtained by using 5% aqueous THF. In two examples, however, we obtained higher yields with lesser amounts of water. The aqueous carbonylation of styrylmercuric chloride also proved considerably more difficult than the analogous alcohol reactions which produced excellent yields under almost all conditions. In fact, carbonylation with 50% aqueous acetone at −20° produced *trans,trans*-1,4-diphenylbutadiene as the major product. In general, the yields of α,β-unsaturated carboxylic acids are slightly less than the corresponding esters.

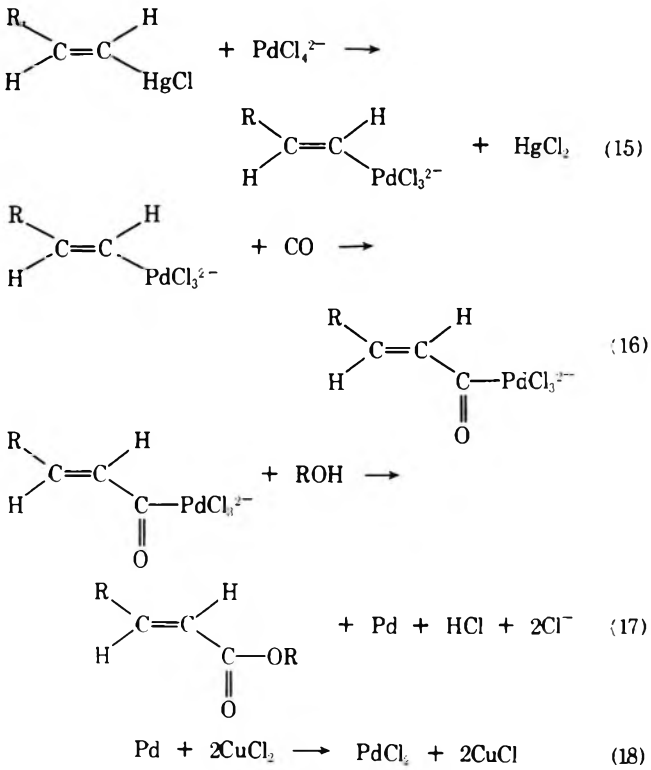
Once again we were able to effect these reactions using only catalytic amounts of either palladium chloride or palladium on carbon if cupric chloride (2 equiv) was employed (eq 14). Cupric acetate and 10% $PdCl_2$ under identical conditions gave only a 30% yield of *trans*-2-heptenoic acid.



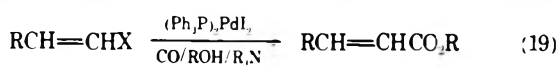
(14)

α,β-Unsaturated Amides. We have attempted to extend the carbonylation of vinylmercurials to the synthesis of the corresponding amides. Carbonylation of styrylmercuric chloride in diethylamine under conditions identical with those used in the preparation of α,β-unsaturated esters resulted in 92% recovery of starting vinylmercurial. On the theory that the very basic diethylamine was coordinating too strongly with the palladium salt to allow exchange with the vinylmercurial, we examined the analogous reaction of much less basic pyrrole. Addition of pyrrole to the palladium salt resulted in a vigorous reaction, presumably electrophilic substitution on the aromatic ring. No further amidation reactions were attempted.

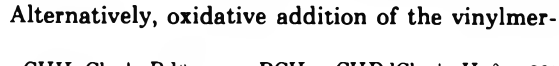
Mechanism. The palladium-promoted carbonylation of vinylmercurials undoubtedly proceeds by an initial mercury–palladium exchange reaction (eq 15), carbon monoxide insertion into the resultant vinylpalladium compound (eq 16), and subsequent solvolysis to give the α,β-unsaturated acid or ester and palladium metal (eq 17). In the catalytic reactions the palladium metal is reoxidized to palladium(II) by cupric chloride (eq 18). Support for this mech-



anism is found in the many analogous reactions reported previously.[5] Presumably similar steps are involved in Heck's palladium-catalyzed carboalkoxylation of vinyl halides (eq 19).[18] The carbonylation reactions using palladi-



um on carbon or tetrakis(triphenylphosphine)palladium(0) in the absence of cupric chloride presumably involve initial mercury–palladium interchange via oxidation–reduction (eq 20). Alternatively, oxidative addition of the vinylmer-



curial to palladium(0) might provide a species capable of undergoing carbonylation.

Conclusion

Although the palladium-promoted carbonylation of alkyl-[6] and arylmercurials[8] has been observed previously, the reaction appears to be of little synthetic value owing to the low yields of carboxylic acids and derivatives obtained. We report here the first carbonylation of vinylmercurials. The ready availability of a wide variety of functionally substituted vinylmercurials, the exceedingly mild reaction conditions, the high stereospecificity, and the excellent yields of α,β-unsaturated carboxylic acids and esters suggest considerable preparative utility for this reaction.

Experimental Section

Reagents. All chemicals were used directly as obtained commercially unless indicated otherwise. *trans*-3-Acetoxy-2-butenylmercuric chloride,[13] *cis*-β-acetoxystilbenylmercuric chloride,[14] and (*E*)-2-chloro-3-hydroxy-1-propenylmercuric chloride[12] were prepared according to literature procedures. All other vinylmercuric chlorides were prepared by hydroboration–mercuration of the appropriate alkyne.[9,10]

The following vinylmercurials have apparently not previously been reported.

trans-1-Decenylmercuric chloride, mp 102.5–103°.

Anal. Calcd for $C_{10}H_{19}ClHg$: C, 32.00; H, 5.10; Hg, 53.45. Found: C, 31.98; H, 5.20; Hg, 53.43.

trans-5-Cyano-1-pentenylmercuric chloride, mp 89.5–90°.

Anal. Calcd for C_6H_8ClHgN: C, 19.17; H, 2.53; Hg, 62.82. Found: C, 19.06; H, 2.54; Hg, 62.72.

Methyl *cis*- and *trans*-11-chloromercuri-10-undecenoate, mp 54–?.

Anal. Calcd for $C_{12}H_{21}ClHgO_2$: C, 33.26; H, 4.88; Hg, 46.29. Found: C, 33.21; H, 4.96; Hg, 46.43.

trans-3-Methyl-1,3-butadienylmercuric chloride: pale yellow crystals unstable toward heat or light; melts with decomposition; ^1H NMR peaks at δ 1.83 (s, 3 H, CH_3), 5.06 (s, 2 H, $=CH_2$), 6.00 (d, J = 18 Hz, 1 H, vinyl), and 6.58 (d, J = 18 Hz, 1 H, vinyl).

Anal. Calcd for C_5H_7ClHg: C, 19.81; H, 2.33; Hg, 66.17. Found: C, 19.61; H, 2.48; Hg, 66.02.

trans-(1-Cyclohexenyl)ethenylmercuric chloride, mp 170.5–171°.

Anal. Calcd for $C_8H_{11}ClHg$: C, 28.00; H, 3.23; Hg, 58.44. Found: C, 27.95; H, 3.36; Hg, 58.58.

Stoichiometry of Carboalkoxylation. The appropriate alcohol (5 ml), lithium chloride, palladium chloride, and a suitable hydrocarbon GLC internal standard were placed in a 25-ml round-bottom flask containing a septum inlet. A pressure-equalizing addition funnel containing the vinylmercuric chloride (1 mmol) and 5 ml of alcohol was placed on top of the flask. After cooling the reaction mixture to the appropriate temperature and flushing the system with carbon monoxide (a balloon works fine), the vinylmercurial was slowly added to the reaction mixture. After 1 hr at the low temperature the reaction mixture was allowed to slowly warm to room temperature and maintained there overnight. GLC analysis using an appropriate hydrocarbon internal standard gave the yields indicated in Table I.

Preparation of α,β-Unsaturated Carboxylic Esters. The following procedure for the preparation of methyl *trans*-β-cyclohexylacrylate is representative. Anhydrous lithium chloride (20 mmol), palladium chloride (10 mmol), and 100 ml of methanol were added to a well-dried 250-ml round-bottom flask containing a septum inlet and carbon monoxide inlet tube. The flask was cooled to −78° and *trans*-cyclohexylethenylmercuric chloride (10 mmol) was added. The flask was flushed thoroughly with carbon monoxide and the well-stirred reaction mixture was then allowed to slowly warm to room temperature over a 4-hr period and stirred overnight while maintaining a slight positive pressure of carbon monoxide. Ether and activated carbon were added to the reaction mixture, which was filtered, washed with saturated ammonium chloride, and dried over anhydrous sodium sulfate. Removal of the solvent provided 1.61 g (96%) of ester (essentially pure by GLC and ^1H NMR): ir max (neat) 2920, 2850, 1730, 1655, 1275, and 1170 cm^{-1}; ^1H NMR peaks (CCl_4) at δ 1.0–2.3 (br, 11 H, cyclohexyl), 3.63 (s, 3 H, OCH_3), 5.66 (d, J = 16 Hz, 1 H, vinyl), and 6.82 (dd, J = 9 and 16 Hz, 1 H, vinyl); *m/e* 168.1152 ± 0.0009 (calcd for $C_{10}H_{16}O_2$, 168.1150).

The following compounds were prepared in a similar fashion. Methyl *trans*-2-undecenoate: ir max (neat) 2915, 2840, 1730, 1660, 1270, and 1195 cm^{-1}; ^1H NMR peaks (CCl_4) at δ 0.89 (t, J = 5 Hz, 3 H, CCH_3), 1.30 (br, 12 H, CH_2), 2.13 (m, 2 H, allyl), 3.65 (s, 3 H, OCH_3), 5.69 (dt, J = 1 and 16 Hz, 1 H, vinyl), and 6.86 (dt, J = 7 and 16 Hz, 1 H, vinyl); *m/e* 198.1623 ± 0.0010 (calcd for $C_{12}H_{22}O_2$, 198.1620). Methyl *trans*-6-cyano-2-hexenoate: ir max (neat) 2940, 2240, 1750, 1660, 1275, and 1205 cm^{-1}; ^1H NMR peaks (CCl_4) at δ 1.5–2.0 (m, 2 H, CCH_2C), 2.0–2.5 (m, 4 H, CH_2CN and allyl), 3.58 (s, 3 H, CCH_3), 5.75 (dt, J = 1 and 16 Hz, 1 H, vinyl), and 6.78 (dt, J = 7 and 16 Hz, 1 H, vinyl); *m/e* 153.0799 ± 0.0015 (calcd for $C_8H_{11}NO_2$, 153.0790). Methyl 2-dodecenedioate, cis and trans mixture. Methyl α-phenylcinnamate, mp 77° (lit.[19] mp 77°). β-Chloro-$\Delta^{\alpha,\beta}$-butenolide, mp 52.5–53.0° (lit.[20] mp 52–53°).

All GLC yields were determined on reactions run on one-tenth the scale of the above preparative reactions using hydrocarbon internal standards. All retention times were identical with those of authentic samples.

Catalytic Esterification Reactions. β-Chloro-$\Delta^{\alpha,\beta}$-butenolide was prepared by modifying the above preparative procedure. The $PdCl_2$ was replaced by anhydrous $CuCl_2$ (20 mmol) and either 10% Pd/C (0.1 mmol) or $PdCl_2$ (0.1 mmol). Anhydrous diethyl ether replaced the alcohol solvent.

The methyl cinnamate and methyl *trans*-2-heptenoate yields were determined by GLC analysis using an appropriate hydrocarbon internal standard, carbon monoxide, the vinylmercuric chloride (1 mmol), methanol (10 ml), anhydrous cupric chloride (2 mmol), anhydrous lithium chloride (2 mmol), and either 10% Pd/C (0.1 mmol) or palladium chloride (0.1 mmol). Methyl cinnamate was prepared at 0°, methyl *trans*-2-heptenoate at −78°.

The stoichiometric Pd/C reaction was run just as above except

that the amount of Pd/C was increased to 1 mmol and the cupric chloride was omitted. Caution—fire hazard!

The yield of methyl cinnamate prepared by tetrakis(triphenylphosphine)palladium(0) catalysis was determined by GLC analysis on a reaction run at −78° employing methanol (10 ml), styrylmercuric chloride (1 mmol), carbon monoxide, and catalyst (0.1 mmol). No lithium chloride was added. The reaction was allowed to slowly warm on its own to room temperature and stirred overnight before analysis.

Preparation of α,β-Unsaturated Acids. Both preparative and GLC reactions were run in a manner identical with the above ester reactions except that 0.5–5% aqueous THF replaced the alcohol solvent.

The following procedure for the preparation of 4,4-dimethyl-*trans*-2-pentenoic acid is representative. Anhydrous lithium chloride (20 mmol), palladium chloride (10 mmol), 5 ml of water, and 95 ml of THF were added to a 250-ml round-bottom flask containing a septum inlet and carbon monoxide inlet tube (a balloon will suffice). The flask was cooled to −78° and 3,3-dimethyl-*trans*-1-butenylmercuric chloride (10 mmol) was added. The flask was thoroughly flushed with carbon monoxide. The well-stirred reaction mixture was then allowed to slowly warm to room temperature over a 4-hr period and stirred overnight while maintaining a slight positive pressure of carbon monoxide. Ether and activated carbon were added to the reaction mixture, which was filtered, washed with saturated ammonium chloride, and finally extracted several times with saturated sodium bicarbonate solution. The bicarbonate solution was acidified with cold hydrochloric acid and extracted several times with ether. After drying over anhydrous Na_2SO_4 and removal of the solvent, one obtains 1.25 g (98%) of acid (essentially pure by GLC and ^1H NMR), mp 62–62.5° (hexane) (lit.[21] mp 61–62°).

The following α,β-unsaturated carboxylic acids were obtained in a similar manner. *trans*-β-Cyclohexylacrylic acid, mp 57° (hexane) (lit.[22] mp 57–58°). Cinnamic acid, mp 132° (H_2O) (lit.[23] mp 132.6–132.8°). *trans*-6-Cyano-2-hexenoic acid: mp 69.5–70°; ir max (neat) 3600–2000, 2240, 1705, 1640, 1310, 1295, and 1210 cm^{-1}; ^1H NMR peaks ($DCCl_3$) at δ 1.90 (m, 2 H, CCH_2C), 2.1–2.7 (m, 4 H, $NCCH_2$ and allyl), 5.88 (dt, J = 1 and 16 Hz, 1 H, vinyl), 7.03 (dt, J = 7 and 16 Hz, 1 H, vinyl), and 11.06 (s, 1 H, COOH); *m/e* 121.0524 ± 0.0006 (calcd for $C_7H_9NO_2$, 121.0528). *trans*-β-(1-Cyclohexenyl)acrylic acid: mp 116.5–117.5° (hexane); ir max (KBr) 3300–2000, 1675, 1600, 1410, 1305, and 1275 cm^{-1}; ^1H NMR peaks ($DCCl_3$) at δ 1.66 (m, 4 H, CH_2CH_2), 2.18 (m, 4 H, allyl), 5.73 (d, J = 16 Hz, 1 H, CHCO), 6.20 (m, 1 H, vinyl), 7.35 (d, J = 16 Hz, 1 H, vinyl), and 11.28 (br, 1 H, COOH); *m/e* 152.0838 ± 0.0008 (calcd for $C_9H_{12}O_2$, 152.0837).

The catalytic carboxylic acid reactions were run exactly as those of the esters except that 5% aqueous THF was employed as the solvent and saturated ammonium chloride and ether were added to the reaction before GLC analysis.

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The Palladium Dichloride Complex of 4-Vinylcyclohexene

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In our hands the reported rearrangement of 4-vinylcyclohexene to 1,5-cyclooctadiene upon reaction with bisbenzonitrilepalladium dichloride does not occur. A variety of conditions were explored to try to induce rearrangement. NMR analysis of the product and its reactions with nucleophiles indicate that the product is the unrearranged π,π complex of 4-vinylcyclohexene. The reaction of related alkyl-substituted dienes with bisbenzonitrilepalladium dichloride is discussed.

The ability of transition metals to effect skeletal rearrangements of olefins is well documented.[1b] Wilkinson et al. reported the conversion of 4-vinylcyclohexene to 1,5-cyclooctadiene using an iridium salt.[2] This same conversion was reported using $(PhCN)_2PdCl_2$,[3] but an analogous reaction with Na_2PtCl_4 gave no rearranged product.[4a] In addition, no rearrangement occurred with 4-substituted 4-vinylcyclohexenes via the palladium complex.[4b]

In connection with our studies on the effect of diene structure on nucleophilic additions to palladium complexes, we investigated the reaction of 4-vinylcyclohexene with $(PhCN)_2PdCl_2$ and now report that the palladium complex remains unrearranged, in contrast to earlier reports.[3] We also report on the tendency of some related dienes to complex with palladium.

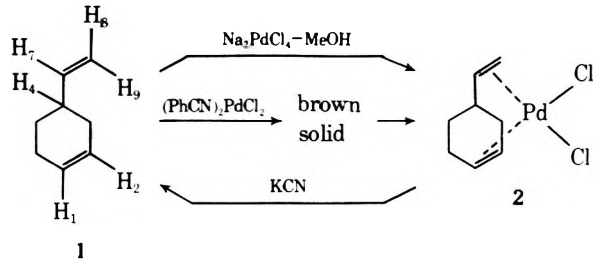
Results

The reaction between 4-vinylcyclohexene and bisbenzonitrilepalladium dichloride [$(PhCn)_2PdCl_2$] in benzene immediately produces a dark brown solid, which on standing

at room temperature is transformed into a gold-colored solid, in agreement with Frye's observation.[3] However, in our hands, decomposition of this solid with KCN gave 4-vinylcyclohexene as the only organic product, and not 1,5-cyclooctadiene as Frye reported. The gold-colored solid could also be prepared in acetone or chloroform without the intermediacy of the brown solid.

Paiaro reported the formation of 2 from 4-vinylcyclohexene and Na_2PdCl_4.[5] We repeated this reaction and found the product to be identical with our gold-colored solid. These results are depicted in Scheme I.

Scheme I



Since Frye's observation has been widely cited as one of a few samples of a rearrangement initiated by palladium, we examined possible ways to induce this rearrangement: allowing the brown solid to stand in the presence of trace amounts of acetic acid, methanol, NaOH, excess diene, PhCN, $CHCl_3$, or acetone always resulted in the same transformation to 2. In addition, heating a benzene solution of this solid to reflux with traces of PhCN, $CHCl_3$, or excess 4-vinylcyclohexene likewise produced 2.

NMR analysis of 2 further supports the unrearranged π,π structure. Figure 1 depicts the olefinic region of 2 as

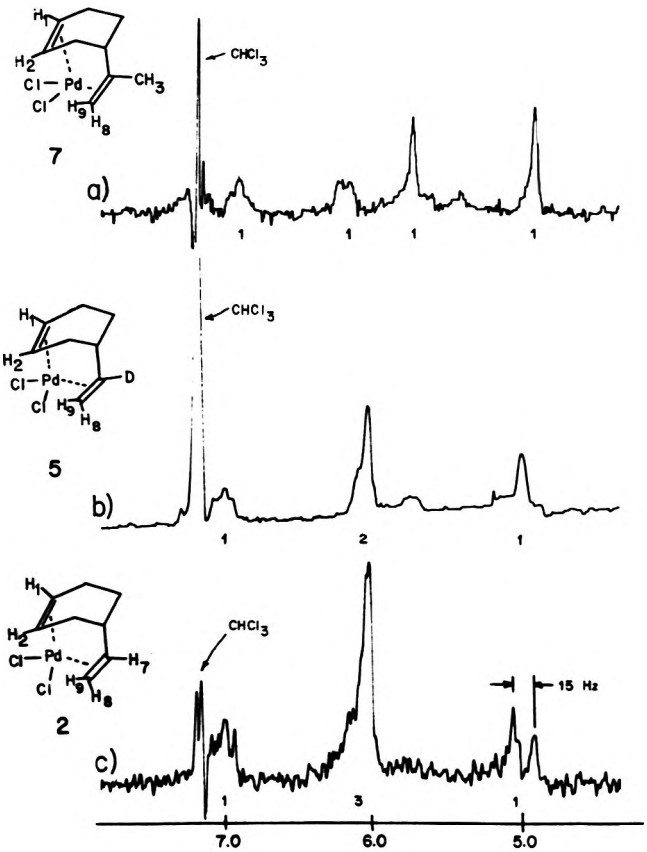
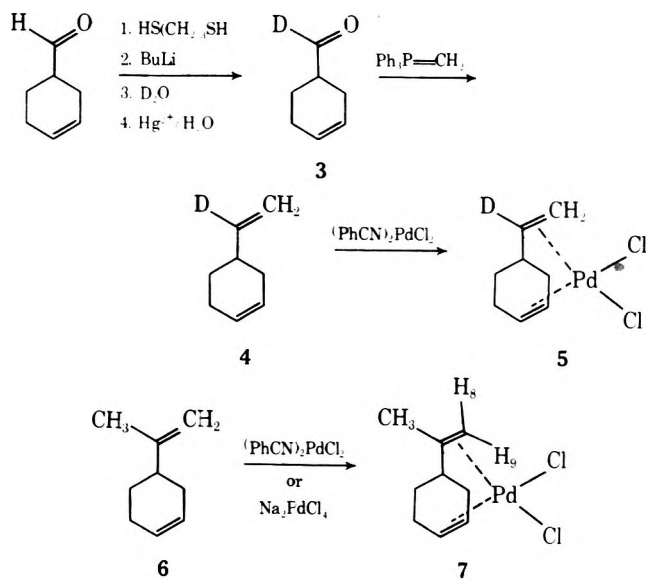


Figure 1. NMR spectra (100 MHz) of the olefinic region of complexes (a) 7, (b) 5, and (c) 2 in $CDCl_3$ with Me_4Si as internal standard after 70 scans with CAT.

Scheme II



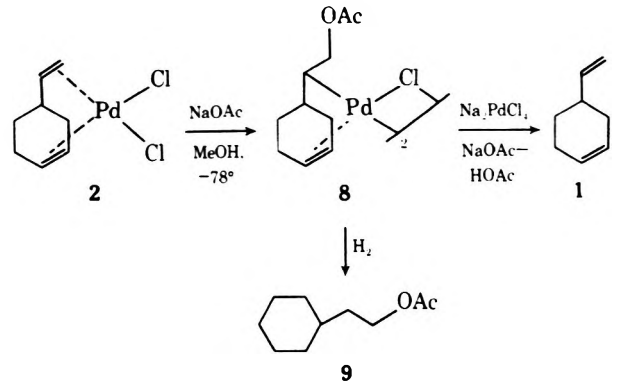
well as a deuterated and a methyl derivative (5 and 7, respectively). These were prepared as shown in Scheme II.

The magnetically nonequivalent cyclohexene protons in compound 7 (Figure 1a) appear as broad absorptions at δ 6.82 and 6.14 ppm. The sharper absorptions at δ 5.62 and 4.70 ppm are H_8 and H_9, respectively. The increased shielding of H_9 arises from the diamagnetic anisotropy of the C-5–C-6 bond, above which it is constrained to lie in order for the diene to be favorably aligned for π,π-complex formation.[6]

Compounds 2 and 5 (Figures 1c and 1b) likewise display broad absorptions for the cyclohexene protons at δ 7.01 and 6.0 ppm. Replacement of H_7 by deuterium results in a disappearance of the absorption at δ 6.01 ppm and in a loss of coupling (J = 15 Hz) in the doublet at δ 5.0 ppm in 2; this doublet is assigned to H_9. The splitting arises from trans coupling with H_7.[6] The remaining resonance at δ 6.01 ppm in 2 may be assigned to H_8. The cis coupling between H_7 and H_8 cannot be discerned because of the accidental equivalence of H_7, H_8, and $H_{1(2)}$.

Reaction of 2 with acetate ion lends additional supports for our structural assignment.[5] In methanol at room temperature, reduction to the metal occurs. However, at −78°, a light, gray solid forms which can be isolated by filtering in the cold. An identical solid results from reaction of 4-vinylcyclohexene with Na_2PdCl_4 in HOAc–NaOAc at room temperature. Elemental analysis of this solid indicates the empirical formula $C_{10}H_{15}ClO_2Pd$, and reduction with hydrogen affords 2-cyclohexylethyl acetate (9). These results suggest that complex 2 has undergone nucleophilic attack by acetate ion to give complex 8 (Scheme III).

Scheme III



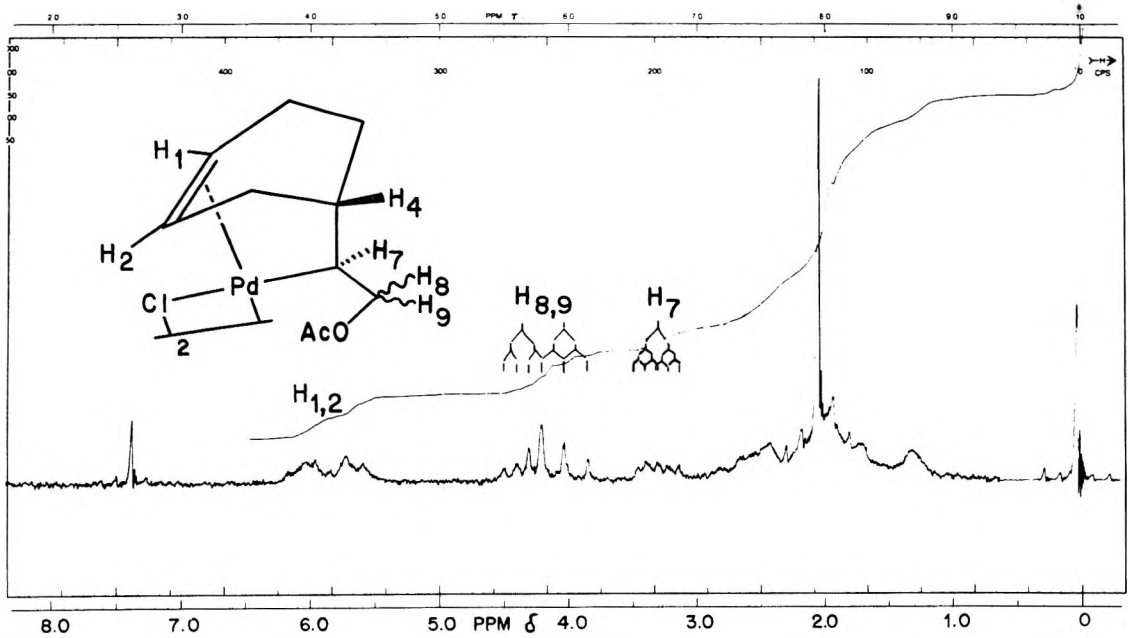
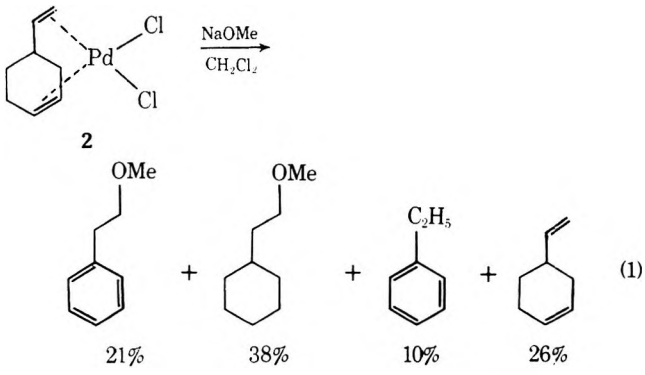


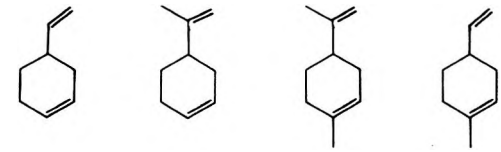
Figure 2. NMR spectrum (60 MHz) of complex 8 in $CDCl_3$ with Me_4Si as internal standard ($J_{4,7}$ and $J_{7,8}$ = 6, $J_{7,9}$ and $J_{8,9}$ = 11.5 Hz).

The 60-MHz NMR spectrum of 8 (Figure 2) shows the typical broad absorptions for the olefinic protons (δ 5.6–6.2 ppm), and a sharp acetoxy methyl group at δ 2.02 ppm. The methylene protons (H_8 and H_9) are magnetically nonequivalent since they are adjacent to a chiral center (C-7).[6] These give rise to two AB patterns at δ 4.35 and 4.0 ppm with a geminal coupling of 11.5 Hz. The complex pattern at δ 3.28 is assigned to H_7, which couples with H_8 and H_9 (J = 11.5 and 6.0 Hz) and H_4 (J = 6.0 Hz).

The instability of 8 when prepared in MeOH was thought to be due to a competition between acetate and methoxide ion. Attempts to prepare the methoxy analog of 8 by the reaction of 2 with MeOH–Na_2CO_3 failed; palladium metal and a sweet-smelling liquid (11 products by VPC) were isolated. A similar mixture was obtained from the reaction of 4-vinylcyclohexene with $PdCl_2$ or Na_2PdCl_4 in MeOH–Na_2CO_3. However, reaction of 2 with CH_2Cl_2–NaOMe gave four main products (eq 1) which were identified by VPC comparison with the pure compounds. The methyl ethers presumably result from nucleophilic attack on the olefins, and the aromatic products arise from disproportionation of the olefins.[7]



The addition of dienes 1 and 7 to solutions of palladium salts results in a discharge of the deep red color and precipitation of the diene complex. Under identical conditions, dipentene (10) fails to discharge the color and no precipitation occurs. Similarly, 1-methyl-4-vinylcyclohexane (11) behaves like dipentene and apparently fails to coordinate with the metal. It thus appears that the ring methyl substituent to 10 and 11 destabilizes the diene toward complex formation.

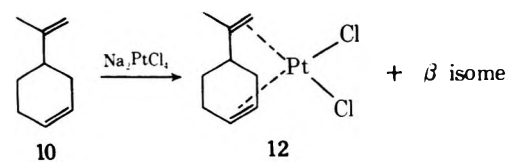


1 7 10 11

Discussion

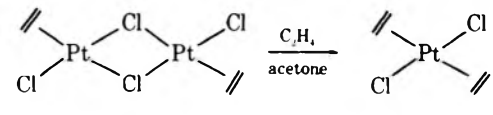
The foregoing evidence clearly indicates that the rearrangement of 4-vinylcyclohexene to 1,5-cyclooctadiene via a palladium complex did not occur; the nature of the brown, intermediate solid still remains to be determined.

Chatt and Wilkins[8] found that dipentene (10) forms two complexes with platinum. X-Ray crystallography revealed the more stable α isomer to be the normal 1,3-diene complex 12, but the structure of the β isomer remains unknown. Chatt proposed a structure in which Pt–Cl had added across one olefin bond. However, the insolubility of the complex argues against this since most σ, π complexes of this type are very soluble in the solute used.[9] The insolubility of 2 and 15 also prevent osmometric molecular weight determination.

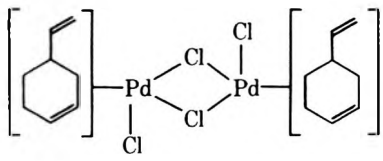


10 12

Chatt and Wilkins also observed the formation of 14 from dimer 13 in the presence of excess ethylene and acetone.[10] In this reaction acetone functions to cleave the μ bridge in 13. We suggest that the brown complex is a di-



13 14

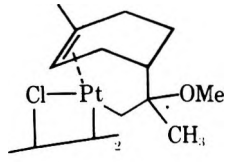


15

meric complex **15** analogous to **13** which is kinetically formed in nonpolar solvents. In polar solvents, the μ bridges are cleaved, resulting in the formation of the more thermodynamically stable gold-colored complex **2**.

The NMR spectra of **2**, **5**, and **8** can be interpreted in light of current theory on the spectrum of palladium and platinum olefin complexes.[11,12] The olefinic protons are markedly deshielded in these complexes as is expected;[12] coordination of palladium results in a shift of electron density from the olefin to the metal, thereby reducing the electron density near the proton and causing a downfield shift. Palladium and platinum are unique in this respect, since upfield shifts are observed with all other uncharged metal complexes.[11] In addition to being deshielded, H_1 and H_2 in complexes **2**, **5**, and **8** are widely separated relative to the parent hydrocarbon ($\Delta\delta$ 0.8 ppm) owing to the unsymmetrical disposition of the olefin bond with respect to the palladium atom.[11]

Two interesting features of the acetate addition to diene complex **2** are the orientation and the selectivity of the addition. The anti-Markovnikov orientation of the product parallels that observed with other nucleophiles[13] as well as additions to other diene complexes (1,5 hexadiene[14] and 5-vinylbicyclo[2.2.2]oct-2-ene). However, addition of methoxide ion to the dipentene platinum complex gives the Markovnikov addition product **16**.[15,16] In this case, the yield is



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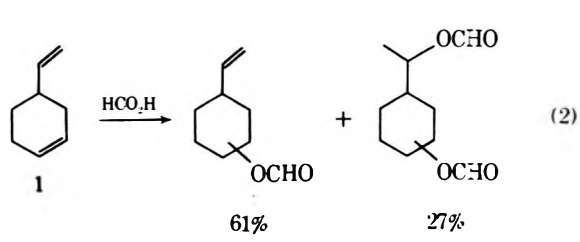
very low (2.7%), and it could be that the anti-Markovnikov addition product is formed, but is unstable under the reaction conditions.

The selectivity does not parallel observations with other diene complexes (dipentene,[16] dicyclopentadiene,[16] 5-vinyl-2-norbornane[17]) in which nucleophilic additions to the complexes occur with the same selectivity as do ionic additions to the free dienes.[18] In the case of 4-vinylcyclohexene, nucleophilic additions to the complex occur at the acyclic double bond, but ionic additions to the free diene take place preferentially at the cyclohexene bond (eq 2).[19]



(2)

Considerably more research is necessary to determine if there is any significance in this type of comparison.

The finding that **1** and **7** form palladium π complexes whereas **10** and **11** do not suggests that, at least with palladium, the complex can tolerate an alkyl group on the acyclic double bond, but not on the cyclohexenyl double bond. Although the electron-donating effect of a methyl group should tend to destabilize the complex,[20] the difference between **7** and **11** must be steric. In **7**, there can be some rotation about the acyclic single bond which skews the double bonds, but puts the methyl group further away from the metal. In **11**, the methyl group is constrained by the ring which leads to effectively a larger steric congestion.

In the case of the platinum dipentene complex, the greater stability of the platinum–olefin bond relative to that of palladium[21] is apparently able to overcome the steric destabilization.

Experimental Section

Melting points were taken on a Mel-Temp apparatus, and are uncorrected. Spectral measurements were made on the following instruments: NMR, Varian Associates Model A-60 and A-100; ir, Perkin-Elmer Model 237B grating spectrophotometer; VPC, Varian Associates Aerograph, Model 90-P, SE-30 column; CAT, Varian Model C-1024. Elemental analyses were performed by Schwarzkopf Microanalytical Lab, Woodside, N.Y. Bisbenzonitrilepalladium dichloride was prepared by the method of Kharasch.[22] All other chemicals were reagent grade materials.

General Procedure for the Reaction of Dienes with Palladium Salts. The palladium salt and the solvent were placed in an erlenmeyer flask, a serum cap was attached, and the flask was flushed with nitrogen. The diene was injected and the contents were stirred at room temperature until either a new solid formed, or a color change indicated completion of reaction. The contents were filtered, and the precipitate was washed with ligroin and dried in a desiccator. Additional solid could be obtained by diluting the solvent layer with ligroin and filtering as before.

Reaction of 4-Vinylcyclohexene with $(PhCN)_2PdCl_2$ in Benzene. The general procedure was followed using 0.192 g (0.5 mmol) of $(PhCN)_2PdCl_2$ and 0.5 ml of the diene in 10 ml of benzene. A dark brown precipitate formed immediately. Upon standing for 8 hr at room temperature, the solid turned bright yellow. This was isolated to give 0.099 g (70%) of gold-colored flakes (**2**), mp 132–136° dec. Anal. Calcd for $C_8H_{12}Cl_2Pd$ (285): C, 33.68; H, 4.21; Cl, 24.91. Found: C, 33.44; H, 4.12; Cl, 25.11 (Schwarzkopf B21756).

The procedure was repeated, but the brown solid was isolated immediately after precipitating. Three separate analyses on this solid gave inconsistent results, the chloride analysis being consistently high, mp 128–134° dec. This solid changed into the gold-colored flakes upon contact with polar solvents (acetone, $CHCl_3$, acetic acid, methanol).

In $CHCl_3$ or Acetone. The above procedure was repeated using chloroform and acetone as solvents. A bright golden solid was formed immediately upon contact of the diene with the palladium solution. These were isolated to give 92 and 78% yields of the same gold-colored complex (**2**), respectively.

Reaction of 4-Vinylcyclohexene with Na_2PdCl_4. Using the general procedure, 0.588 g (2.0 mmol) of the palladium salt was allowed to react with 1.0 ml of the diene in 20 ml of $CHCl_3$. After stirring for 1.5 hr, golden crystals had formed. These were isolated to give 0.544 g (94%) of a gold-colored solid (**2**), mp 129–134° dec (lit.[5] mp 128–130° dec). The NMR and ir spectra of this and the previously prepared compound were identical. Aside from the olefinic protons (see Figure 1), the aliphatic region appeared as a broad band at δ 1.8–3.4 ppm, ir (KBr) ν 1505 cm^{-1} (lc coordinated C=C).

Decomposition of Complex 2 with KCN. Each of the above complexes (complex **2**) was stirred with a solution containing 5 ml of 1.5 *M* KCN and 5 ml of CCl_4. After 0.5 hr, the solids had dissolved, leaving a colorless liquid. Stirring was continued for an additional 0.5 hr, after which time the layers were separated. The organic layer was dried over $MgSO_4$ and the solvent was removed to leave a clear liquid which gave NMR and VPC retention data identical with those of 4-vinylcyclohexene.

Reaction of 2 with NaOAc. Complex **2** (0.298 g, 1.0 mmol), NaOAc (0.172 g, 2.0 mmol), and 10 ml of methanol were stirred in a Dry Ice–acetone bath for 0.5 hr. The pale yellow solution was allowed to warm, whereupon the solution turned gray. The solution was immediately filtered, and the precipitate was washed with ligroin and dried in a desiccator to give 0.244 g (79%) of **8** as a light gray solid: mp 95–103° dec; ir (KBr) ν 1736 (s, C=O), 1510 cm^{-1} (w, coordinated C=C).

Reaction of 4-Vinylcyclohexene with Na_2PdCl_4 in HOAc–

NaOAc. The general procedure was followed using 0.294 g (1.0 mmol) of Na_2PdCl_4, 0.164 g (2.0 mmol) of NaOAc, and 0.5 ml of the diene in 10 ml of HOAc. Within 5 min, a pale yellow solid formed. This was stirred for 0.5 hr and the solution was filtered. The solid was washed repeatedly with ligroin and water and dried in a desiccator to give 0.2377 g (73%) of **8** as a yellow solid: mp 103–105° dec; ir identical with that prepared above; NMR, see text. Anal. Calcd for $C_{20}H_{30}Cl_2O_4Pd_2$ (618.16): C, 38.86; H, 4.89; Cl, 11.47. Found: C, 38.99; H, 4.85; Cl, 11.81 (Hoffmann-La Roche 92735).

Hydrogenation of 8. The complex (0.162 g, 0.25 mmol) in 10 ml of THF was hydrogenated on a Paar apparatus for 0.5 hr at 20 psi. The solution was filtered, and the solvent was evaporated to give 0.042 g of a clear liquid. NMR, ir, and VPC data were identical with those of 2-cyclohexylethyl acetate (**9**) prepared from the commercially available alcohol.

Deuterio-3-cyclohexenecarboxaldehyde (3). The dithiane of 3-cyclohexenecarboxaldehyde was prepared in 94% yield according to Seebach;[25] analytical data were in accord with the proposed structure. The dithiane was deuterated by the method of Seebach[24] to afford the product in 91% yield as a clear liquid. bp 130° (4 mm); NMR integration indicated 99% deuterium incorporation.

The deuterated dithiane was hydrolyzed in 90% aqueous acetone according to the method of Seebach.[24] The deuterated aldehyde (**3**) was obtained as a clear liquid in 40% yield: bp 62° (30 mm); ir (CCl_4) ν 2045 (m, C–D), 1718 (s, C=O), 1650 cm^{-1} (w, C=C); NMR (CCl_4) δ 5.67 (2 H, s, CH=CH), 1.7–2.5 ppm (7 H, mound, ring H) and the absence of aldehyde H.

4-(α-Deuteriovinyl)cyclohexene (4). The method of Corey[25] was employed using 1.1 g (10.0 mmol) of aldehyde **3** and 10.0 mmol of methylenetriphenylphosphorane. The mixture was stirred for 15 min at room temperature, and the product was distilled. The fraction boiling below 40° (4 mm) was collected in a cold trap. This liquid was diluted with pentane, washed with water, and dried over $MgSO_4$. The clear liquid was passed through a short alumina column (Woelm neutral, activity I) using pentane as eluent. Evaporation of the solvent gave 0.24 g (23%) of diene **4**: ir (CCl_4) ν 1650 cm^{-1} (w, C=C) and absence of aldehyde C=O; NMR (CCl_4) δ 5.59 (2 H, s, CH=CH), 4.91 (2 H, mound, C=CH_2), and 1.05–2.5 ppm (7 H, mound, ring H).

4-(α-Deuteriovinyl)cyclohexenepalladium Dichloride (5). The deuterated diene (**4**) was added to a solution of 0.1 g of $(PhCN)_2PdCl_2$ in 2 ml of benzene. The dark brown solid which formed immediately was allowed to stand in the mother liquor for 8 hr, and then filtered. The dark gold-colored solid was washed with ligroin and dried in a desiccator to give 55.9 mg of **5**: mp 129–133° dec; ir (KBr) ν 1510 cm^{-1} (w, C=C); NMR ($CDCl_3$), see Figure 1.

4-Isopropenylcyclohexene (6). The procedure employed was identical with that used in the preparation of **4** starting from 12.4 g (0.1 mol) of 4-acetylcyclohexene (prepared according to literature report[26]). The crude product was passed through an alumina column (Woelm neutral, activity I) using pentane as eluent. After removing the solvent, 7.23 g (60%) of **6** was obtained as a clear liquid: bp 157° (760 mm) [lit.[27] bp 39–40° (10 mm)]; ir (CCl_4) ν 1643 cm^{-1} (w, C=C); NMR (CCl_4) δ 5.7 (2 H, s, CH=CH), 4.73 (2 H, s, C=CH_2), 1.8–2.4 (7 H, br mound, ring H), 1.7 ppm (3 H, s, C=CCH_3).

4-Isopropenylcyclohexenepalladium Dichloride (7). Using the general procedure, complex **7** was prepared in 62% yield from Na_2PdCl_4–$CHCl_3$, 82% yield from $(PhCN)_2PdCl_2$–$CHCl_3$, and 73% yield from $(PhCN)_2PdCl_2$–benzene. The dark, golden granules had identical melting behavior as well as ir and NMR spectra: mp 73–76° dec; ir (KBr) ν 1534 and 1515 cm^{-1} (w, coordinated C=C); NMR ($CDCl_3$), see text. Anal. Calcd for $C_9H_{14}Cl_2Pd$ (299): C, 36.12; H, 4.70; Cl, 23.7; Pd, 36.10.) Found: C, 35.65; H, 4.83; Cl, 23.74; Pd, 36.25 (Schwarzkopf B23617).

1-Methyl-4-vinylcyclohexene (11). The procedure employed for the preparation of **4** was followed, using 12.4 g (0.1 mol) of 4-methyl-3-cyclohexenecarboxaldehyde (prepared according to the literature[26]). The crude product was passed through an alumina column (Woelm neutral, activity I) using pentane as eluent. Evaporation of the solvent gave 5.98 g (49%) of **13** as a clear liquid: bp 152° (760 mm) [lit.[28] bp 87–90° (100 mm)]; ir (CCl_4) ν 1640 cm^{-1} (w, C=C) and the absence of aldehyde C=O; NMR (CCl_4) δ 5.8 (1 H, ABC pattern, CH=CH_2, $J_{1,3}$ = 17, $J_{2,3}$ = 10, $J_{3,4}$ = 5.8 Hz), 4.88 [1 H, m, CH=CH_2 (H_2)], 4.95 [1 H, m, CH=CH_2 (H_3)], 1.6–2.1 (7 H, mound, ring H), 1.66 ppm (3 H, br s, C=CCH_3).

Reaction of 2 with NaOMe. The general procedure was followed using 0.285 g (1.0 mmol) of complex **2** and 0.1 g (2.5 mmol) of NaOMe in 10 ml of CH_2Cl_2. After 0.5 hr, the contents had blackened. The mixture was filtered, and the solvent was reduced. VPC of the liquid (10% SE-30,110° column temperature) indicated the presence of four main products, and unidentified products with less than 3 min retention (eq 1). The four main products were identified by VPC comparison with pure compounds.

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Registry No.—**1**, 100-40-3; **2**, 41660-18-8; **3**, 56454-09-2; **4**, 56454-10-5; **5**, 56468-31-6; **6**, 26325-89-3; **7**, 56468-32-7; **8**, 56468-33-8; **11**, 17699-86-4; $(PhCN)_2PdCl_2$, 14220-64-5; $NaPdCl_4$, 13820-53-6; 4-acetylcyclohexene, 7353-76-6.

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Oxidative Acetoxylation of Methyl Oleate with Palladium Catalysts[1]

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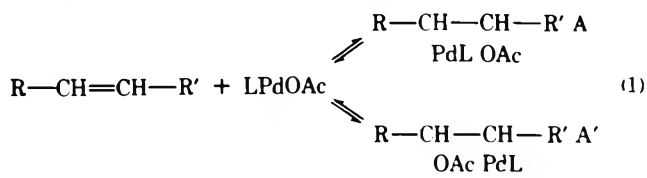
Catalytic acetoxylation of methyl oleate in acetic acid produces allylic acetoxy fatty esters in high yield. These derivatives are related to products of autoxidation. Useful catalyst systems include $PdCl_2$ + $CuCl_2$ + NaOAc, $PdCl_2$ or $Pd(OAc)_2$ + $LiNO_3$, Pd/Al_2O_3 or Pd/C + $LiNO_3$, and Pd/C. Esters produced in 50–97% conversion at 70–120° and O_2 at 1 atm pressure or 20–45 psig include acetoxy (20–63%) and diacetoxy (20–47%) octadecenoate. Monooxygenated products characterized by GC–MS of the silyl ether derivatives were mainly a mixture of 8-acetoxy-9(*cis/trans*)-, 10-acetoxy-8(*cis/trans*)-, 9-acetoxy-10(*cis/trans*)-, and 11-acetoxy-9(*cis/trans*)-octadecenoate. Dioxygenated products had both 1,2- and 1,4-diacetoxy allylic structures: –CH(OAc)CH(OAc)CH=CH– and –CH(OAc)CH=CHCH(OAc)–. 1,3-Disubstituted isomers were ruled out by NMR. The Pd–$LiNO_3$ catalyst system proved to be highly selective for the allylic acetoxylation of methyl oleate. A mechanism involving allylic $Pd(Cl/OAc)_x$ complex intermediates explains the formation of allylic acetoxy esters. For diacetoxylation a direct pathway from oleate is invoked that involves interconversion of σ-oxypalladation, π olefin, and π-allyl complex intermediates.

The Pd(II)-catalyzed oxidation of ethylene to acetaldehyde in aqueous solution is the basis for the commercial Wacker process.[2] When the aqueous reaction medium in this process is replaced by acetic acid, olefins are acetoxylated. Unsaturated esters are made commercially by this method.[3] Lower olefins are converted to vinyl acetates when the double bond is terminal and to allyl acetates mainly when the double bond is internal. With higher olefins, the products become quite complicated.[4]

Although acetoxylation processes have been studied in considerable detail, results are conflicting, especially with higher olefins. Much care is needed in interpreting some of the results in the literature because of the complexity of the Pd(II) catalyst systems.[4] The course of catalytic acetoxylation depends on reaction parameters (ligand, solvents, presence of oxygen) and the structure of olefinic substrates.[4,5] Cu(II) salts[6a] and other oxidants, such as nitrates,[7] have been used as redox couples to make the acetoxylation catalytic in Pd(II). The presence of these oxidants and other reagents, such as acetates, affects significantly product distribution from higher olefins, and their mechanism of action is not too clear.[4] The oxidation of *cis*- and *trans*-2-butene in the presence of $CuCl_2$ in acetic acid produces 2,3- and 1,3-diacetates and chloroacetates, in addition to the unsaturated acetates formed in the absence of $CuCl_2$.[6a,b]

A mechanism involving the formation of oxypalladation complexes (A, A′) has been generally accepted for the oxidation of 1- and 2-butenes and pentenes[6,8] (eq 1).



(1)

The allylic products obtained with internal olefins have been explained by β-elimination of HPdL from the oxypalladation complexes. Isomerization of these complexes before reaction with Cu(II) has been suggested to explain the disubstituted products from butenes.[6] Olefinic and allylic isomerization may also complicate the interpretation of isomeric product distribution. With 1-hexene a high selectivity for primary monoacetates was observed, together with the formation of 1,2-diol mono- and diacetates.[9] The greater amount of 2 than 3 substitution observed with 2-hexene was considered larger than expected from an oxypalladation mechanism. A two-carbon insertion pathway was postulated to explain 2-substitution products and 1,2-diol mono- and diesters, and a one-carbon insertion pathway to explain 1-substitution products and 1,1-diacetates from olefins.[9] No direct evidence was presented, however, for 1,1-disubstitution products.

The intervention of π-allyl intermediates has been discounted because product distribution from 1- and 2-butene was different even though they were expected to give similar π-allyl complexes.[6] However, with cyclohexene-d_4, π-allylic routes have been supported by evidence based on deuterium distribution in the allylic acetate product.[10a] Oxypalladation was considered a minor competing reaction producing mainly homoallylic acetate. Further solvolysis studies with different organopalladium compounds showed that a π-allyl palladium chloride complex can be an intermediate in the allylic oxidation of cyclohexene but the corresponding π-allyl palladium acetate cannot.[10b] The formation of 90% secondary acetate by neutral solvolysis of π-crotyl and π-cinnamyl palladium acetate in acetic acid was explained by neutral depalladation of σ-allyl intermediates.[11]

Much attention has been given to the allylic oxidation of methyl oleate with mercuric salts and selenium,[12] but none with palladium salts. The contrasting mechanisms of allylic oxidation of short-chain olefins with mercuric and palladium acetate[8] stimulated our interest in studying the palladium salt oxidation of methyl oleate. We found that the catalytic acetoxylation of methyl oleate with Pd compounds leads to allylic acetoxy fatty esters related to products of autoxidation. In light of the mechanisms proposed for Pd(II) oxidation of higher olefins, we postulate possible reaction pathways for mono- and diacetoxylation.

Results

Methyl oleate was catalytically acetoxylated with various Pd-containing systems in acetic acid solution made anhydrous with acetic anhydride.[13] Data in Table I are from runs carried out in the presence of O_2 at either 1 atm pressure or 20–45 psi in the temperature range of 70–120°. Among catalyst systems tried the most useful include $PdCl_2$ + $CuCl_2$ + NaOAc, $PdCl_2$ or $Pd(OAc)_2$ + $LiNO_3$, and Pd/Al_2O_3 or Pd/C + $LiNO_3$. Analysis by GLC shows conversion of methyl oleate into acetoxy and diacetoxy fatty esters of 50–97%. Significant amounts of diacetoxy esters were formed during the initial stages, and their proportion increased at longer reaction times. With the $PdCl_2$–

Table I
Catalytic Acetoxylation of Methyl Oleate (0.1 Mol)

Run no.	Apparatus[a]	Catalyst	Oxidants and other reagents (0.1 mol)	Temp, °C	Time, hr	Acetate,[b] % Mono-	Di-	Total
1	P	$PdCl_2$	$CuCl_2$, NaOAc	100	24	35.2	44.8	80.0
2	P	$PdCl_2$	$CuCl_2$, NaOAc	120	18	30.4	30.4	60.8
3	P	$PdCl_2$	$LiNO_3$	100	24	19.8	32.1	51.9
4	P	$PdCl_2$	$LiNO_3$ NaOAc	100	24	31.3	19.5	50.8
5	P	$PdCl_2$	$LiNO_3$	80	6	45.8	26.6	72.4
					12	55.9	38.4	94.3
6	F	$PdCl_2$	$CuCl_2$, NaOAc	80	6	17.6	19.9	37.5
					24	29.6	32.8	62.4
7	F	$PdCl_2$	$LiNO_3$	70	6	41.1	12.0	53.1
					24	60.2	27.0	87.2
8[c]	F	$PdCl_2$	$LiNO_3$	80	24	46.9	43.3	90.2
9	F	$PdCl_2$	$LiNO_3$	90	6	52.5	31.7	84.2
					24	45.9	39.0	84.9
10	F	$PdCl_2$	$LiNO_3$ LiOAc	80	6	56.8	23.5	80.3
					24	54.2	29.2	83.4
11	F	$Pd(OAc)_2$	$LiNO_3$ LiCl	80	6	54.4	28.5	82.9
					24	54.9	29.6	84.5
12	F	$Pd(OAc)_2$	$LiNO_3$	80	6	63.2	16.8	80.0
					24	62.9	25.1	88.0
13	F	Pd/Al_2O_3	$LiNO_3$	80	6	45.0	24.9	69.9
					24	46.0	47.0	93.0
14[c]	F	Pd/C	$LiNO_3$	80	24	60.5	36.6	97.1
15	F	Pd	$LiNO_3$	80	6	15.8	17.7	33.5
					24	26.9	26.5	53.4

[a] P = pressure reactions, 20-45 psi O_2, Parr hydrogenation apparatus, 90 ml HOAc + 10 ml Ac_2O + 0.002 mol catalyst (runs 1-4) and 0.005 mol catalyst for run 5; F = open flask reactions, 1 atm pressure, O_2 bubbling, 125 ml HOAc + 10 ml OAc_2 + 0.005 mol catalyst (runs 13-14: 0.53 g Pd). [b] Analyses made by GLC on crude filtered and solvent stripped samples before work up. Percents based on 96% purity of starting material. [c] See rate curves in Figure 1.

$CuCl_2$ system little or no conversions were obtained (less than 10%) without NaOAc. In contrast, with the $PdCl_2$–$LiNO_3$ system, conversions of more than 90% were obtained without acetate; addition of acetate to this system increased the relative proportion of monoacetates (compare runs 3 and 4, 8 and 10). Optimum reaction temperature with this system was 80°. $Pd(OAc)_2$ with or without added chloride was as effective as $PdCl_2$ (runs 11 and 12). Pd supported on either Al_2O_3 or C provided one of the most effective catalyst systems (runs 13 and 14). Unlike the supported catalysts, Pd metal + $LiNO_3$ was practically inactive (run 15).

Although $LiNO_3$ was an effective oxidant, significant amounts of nitrate esters formed with it, as previously observed with olefins.[14] Ir analyses showed varying absorptions at 1630 ($RONO_2$), 1550 and 1520 (α,β-unsaturated RNO_2), and 855 cm^{-1} (NO_3^-).[15] These nitrate esters could be removed readily by hydrogenolysis.

The course of acetoxylation was studied further by sequential analyses of reaction mixtures. Kinetic runs with $PdCl_2$–$LiNO_3$ and Pd/C–$LiNO_3$ at 80° were plotted (Figure 1). Analysis by GLC shows that the disappearance of methyl oleate is followed by rapid monoacetoxylation and diacetoxylation. With $PdCl_2$ + $LiNO_3$ (run 8) monoacetoxy esters peak around 12 hr and decrease at later stages of the reaction. With Pd/C + $LiNO_3$ (run 14), the monoacetoxy esters reach a higher concentration and level off at 12 hr. With both catalytic systems acetoxylation is slowed down markedly after 6 hr and the formation of diacetoxy esters levels off at 24 hr. Initial rapid formation of diacetoxy products indicates a direct diacetoxylation path from oleate. The decrease of monoacetoxy products observed at later stages of the reaction suggests also secondary oxidation of mono- to diacetates. This decrease of monoacetates

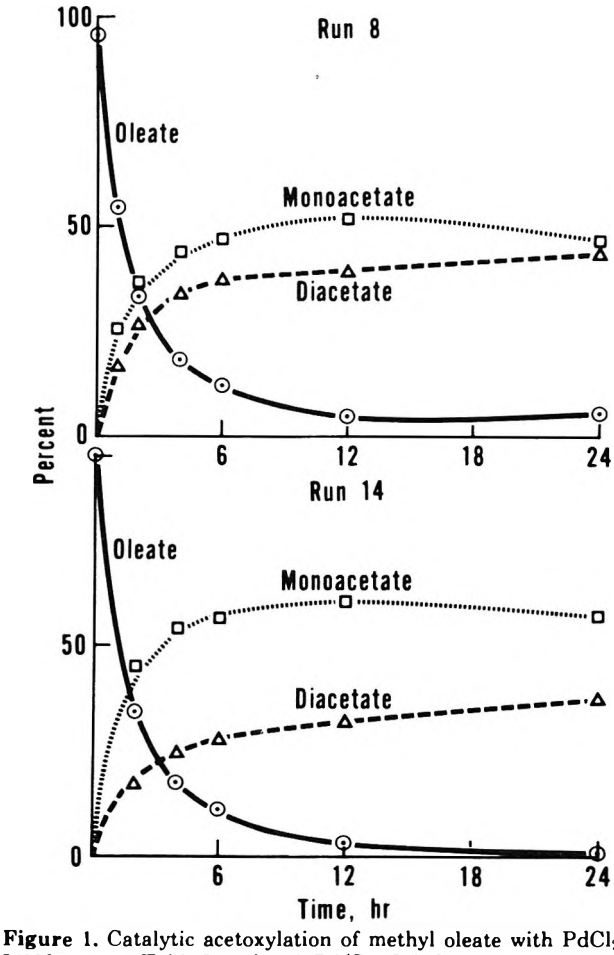
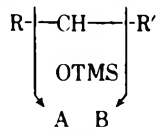


Figure 1. Catalytic acetoxylation of methyl oleate with $PdCl_2$ + $LiNO_3$ (run 8, Table I) and with Pd/C + $LiNO_3$ (run 14, Table I).

Table II
Isomer Distribution of Monohydroxy Derivatives by GC–MS of Silyl Ethers

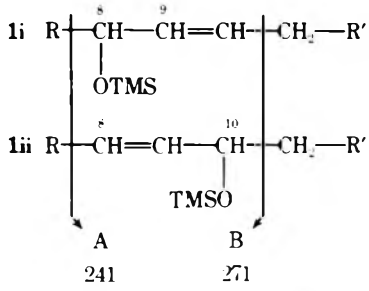
		Before hydrogenation[a]					After hydrogenation[a]			
		Allylic, %[b]					Saturated, %			
Run	Time, hr	8-OH Δ^9 (1i)	9-OH Δ^{10} (1iii)	10-OH Δ^8 (1ii)	11-OH Δ^9 (1iv)	Nonallylic,[c] %	8-OH	9-OH	10-OH	11-OH
1	24	3.6	14.0	14.6	6.3	61.5	12.6	28.4	39.7	19.3
6	6	10.0	27.6	27.6	13.0	21.8	12.6	35.1	37.4	14.9
	24	7.2	23.6	18.3	8.7	42.2	12.2	35.4	38.0	14.4
7	24	17.7	19.2	20.0	19.6	23.5	23.1	24.8	27.2	25.0
8	1	18.8	21.2	22.5	24.2	13.3	21.6	24.8	26.8	26.8
	2	18.2	21.3	21.6	23.3	15.6	21.4	25.3	26.8	26.5
	6	17.4	20.8	22.4	23.5	15.9	20.9	24.8	27.3	27.0
	24	17.1	19.6	21.8	23.4	18.1	20.8	24.0	27.8	27.4
13	24	18.9	20.9	23.5	26.3	10.4	21.3	24.0	26.7	28.0
14	24	24.2	25.5	26.4	23.9	0	24.2	25.5	26.4	23.9

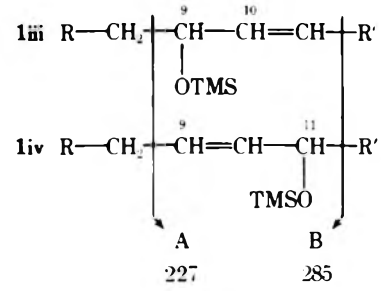
[a] With Pd/C–HOAc, room temperature at 50 psi H_2. Fragment type



	A	B
8-OH	243	245
9-OH	229	259
10-OH	215	273
11-OH	201	287

[b] Based on MS analyses before and after double bond hydrogenation. Fragment type

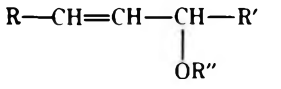




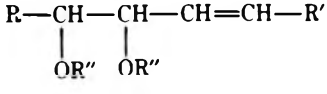
[c] Calculated: total saturated OH ester (100%) − allylic OH esters. [d] See Table I and Figure 1: relative percent, assuming that relative intensities of mass fragments are independent of position of OTMS (silyl ether) substituent in the fatty chain.

may not be as great as would be expected from stepwise oxidation because the catalyst may be partially inactivated after 6–12 hr.

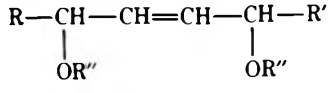
The longer reaction times that increase conversions also permit more accurate product distribution to be determined. Distilled products were isolated chromatographically as either the acetoxy or free hydroxy derivatives. The main products were characterized chemically and spectrally as acetoxy- (**1a**) and allyl diacetoxy- (**2a, 3a**) octadecenoates.[16] The double bond is approximately 50% trans in both products (ir analysis). Mass spectrometry (MS),[16] as well as other evidence, also indicated varying amounts of nonallylic unsaturated acetoxy products.



1. R″ = H
1a. R″ = Ac
1b. dihydro derivative of **1a**



2. R″ = H
2a. R″ = Ac
2b. dihydro derivative of **2a**



3. R″ = H
3a. R″ = Ac
3b. dihydro derivative of **3a**

$R/R' = CH_3(CH_2)_x—/—(CH_2)_yCOOCH_3$

$x + y = 13$ in **1a**
12 in **2a**, **3a**

GC–MS of silyl ethers (OTMS) gave the most detailed structural analysis of the hydroxy ester derivatives. By this procedure the four possible allylic hydroxy isomers from methyl oleate were characterized clearly by their allylic fragmentation (Table II). This type of fragmentation was reported for naturally occurring allyl alcohols[17] but was unrecognized for the corresponding oleate hydroperoxide derivatives.[18] The expected mixture of 8-, 9-, 10-, and 11-acetoxyoctadecanoates (**1b**) was produced by hydrogenation of **1a**. This isomeric distribution corresponds to that determined directly on the saturated acetoxy derivatives.[16] The allylic hydroxy esters estimated from MS analyses before and after hydrogenation include 8-OH, Δ^9 (4–24%); 9-OH, Δ^{10} (14–28%); 10-OH, Δ^8 (15–28%); and 11-OH, Δ^9 (6–26%) octadecenoate (Table II). The total allylic hydroxy esters (**1**) varied from 38.5% with the $PdCl_2$–$CuCl_2$–NaOAc catalyst system to 100% with the Pd/C–$LiNO_3$ catalyst system (runs 1 and 14, Table II). With both catalyst systems the positional distribution of the acetoxy isomers (between C-8 and C-11) does not change significantly during the reaction. However, the proportion of allylic hydroxy isomers to the total hydroxy esters decreases significantly during the reaction with the $PdCl_2$–$CuCl_2$–NaOAc system but not with the Pd/C–$LiNO_3$ system (runs 6 and 8, Table II). Evidently the supported Pd–$LiNO_3$ catalyst system is highly selective for allylic acetoxylation of methyl oleate.

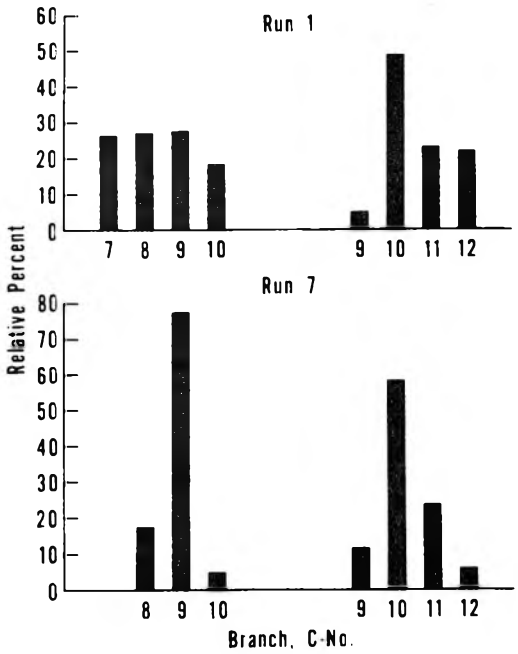


Figure 2. Isomeric distribution by mass spectrometry of dihydroxyoctadecanoate derivatives (**2b** + **3b**): $PdCl_2$ + $CuCl_2$ + NaOAc (run 1, Table I); $PdCl_2$ – $LiNO_3$ (run 7, Table I).

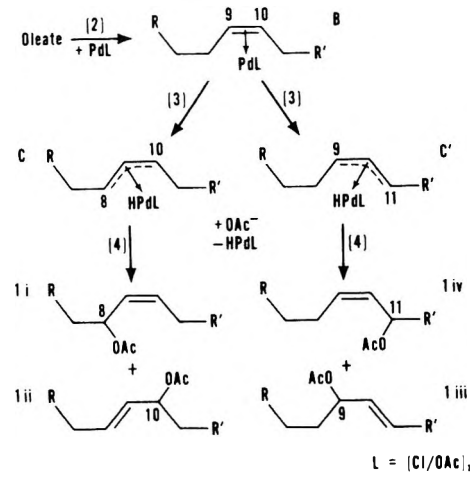
Mass spectra[16] of silyl ethers of dihydroxy derivatives (**2** + **3**) are quite complex. Fragmentation schemes are based on the spectra of allyl monohydroxy esters. Evidence for allylic fragmentation supports the structure of dihydroxy ester **2**. The mass spectra of saturated diOTMS derivatives (of **2b** + **3b**) are more straightforward and simpler than those of corresponding unsaturated derivatives. Quantitative analyses of saturated diOTMS ethers were based on data involving two reference compounds (9,10- and 10,12-dihydroxyoctadecanoate). Analyses of two acetoxylation samples show that one hydroxy substituent is scattered between C-7 and C-10 and the other hydroxy between C-9 and C-12 (Figure 2). Since 1,3-disubstituted isomers were ruled out by NMR,[16] the MS analyses are consistent with the saturated 1,2 isomers (**2b**) being mixtures of 8,9-, 9,10-, and 10,11-dihydroxyoctadecanoate and the 1,4 isomers (**3b**) being mixtures of 7,10-, 8,11-, and 9,12-dihydroxyoctadecanoate.

Discussion

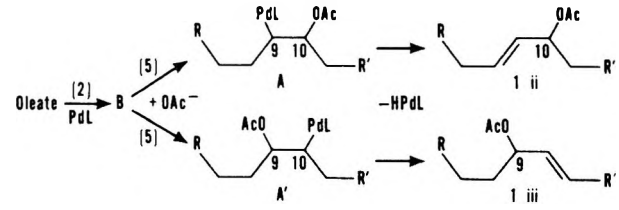
In earlier studies with short-chain acyclic olefins π-allyl routes were ruled out in favor of oxypalladation–dehydropalladation.[6,8] Although there is evidence for π-allyl PdCl complex formation during Pd(II)-catalyzed oxidation of 1-hexene, the function of this complex is uncertain.[9] Under mild conditions (25°, 1 atm O_2), reaction of both 1- and *cis*-2-hexene with $Pd_3(OAc)_6$ formed allylic complexes $Pd_3(1,2,3\text{-}H^3C_6H_{11})_2(OAc)_4$ and $Pd_2(1,2,3\text{-}H^3\text{-}C_6H_{11})_2(OAc)_2$.[19] However, because the oxidation of 2-hexene was extremely slow (4% conversion after 7 days), the addition–elimination mechanism was considered improbable and an alternative free-radical route was supported by the kinetic data.

In contrast to short-chain olefins, methyl oleate undergoes allylic acetoxylation and diacetoxylation preferentially without saturated mono- and disubstituted products being formed. Monosubstitution was limited to carbons 8, 9, 10, and 11 (Table II) and disubstitution to carbons 7 to 10 on one hand and carbons 9 to 12 on the other (Figure 2). Why only the four possible allylic acetoxy esters from methyl oleate are formed can best be explained in terms of olefinic–PdL and allylic HPdL intermediates (eq 2 and 3, Scheme I). Allyl complex C acetoxylates on either carbon 8 or carbon 10 to give 8-acetoxy-*cis*-9-octadecenoate (**1i**) and 10-acetoxy-*trans*-8-octadecenoate (**1ii**). In the same way complex C′ gives 9-acetoxy-*trans*-10-octadecenoate (**1iii**) and 11-acetoxy-*cis*-9-octadecenoate (**1iv**).

Scheme I



Scheme II



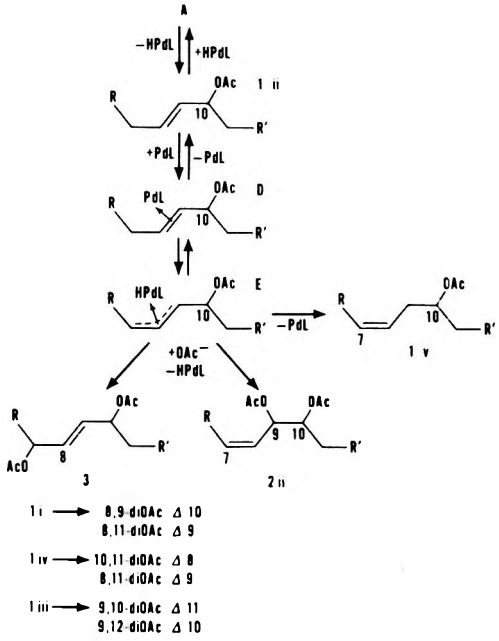
The alternate oxypalladation mechanism would be expected to produce two allylic acetoxy esters with oleate (**1ii** and **1iii**) (eq 5, Scheme II). Since substitution on carbons 9 and 10 was greater with $CuCl_2$ than with $LiNO_3$ (68–73% vs. 51–52% saturated 9-OH and 10-OH esters, Table II), oxypalladation may become important with the former oxidant. However, the stereochemistry of HPdL elimination would not be completely opposite to that of the oxypalladation step, as reported for cyclohexene,[20] because the products observed are 50% in the trans configuration.

The problem of distinguishing between olefinic and allylic isomerization has been discussed previously.[9] Although the relative amount of allylic unsaturation varied with catalysts and conditions (Table II), the positional distribution of acetoxy isomers was narrow (between C-8 and C-11). This positional specificity would be lower if allylic ester isomerization occurred during acetoxylation. Therefore, nonallylic monooxygenated isomers must form from double bond isomerization after acetoxylation and must not involve the acetoxy substituent. A reasonable pathway involves dissociation of complexes D and E (Scheme III) to produce a mixture of allylic (**1ii**) and homoallylic (10-acetoxy-*cis*-7) esters (**1v**).

Alternatively, interconversion of the σ-oxypalladation complex A with a π-allyl complex of type E through the intermediacy of a π-olefin complex D (Scheme III) would also produce a mixture of allylic and homoallylic acetoxy esters. The lower proportion of allylic acetates obtained with $CuCl_2$ than with $LiNO_3$ may be attributed to the easier formation of complexes D and E from the trans-unsaturated 9- and 10-acetoxy esters (**1ii** and **1iii**) than from the corresponding cis-unsaturated 8- and 11-aeetoxy esters (**1i** and **1iv**).

For diacetoxylation, the data in Figure 1 indicate a direct pathway from oleate and a mechanism may be operative

Scheme III



different from that for monoacetoxylation. If oxypalladation is postulated as an initial step (eq 5, Scheme II), then our results can be explained by assuming the same path as isomerization (Scheme III). 1,3-Acetoxylation of the π-allyl system in complex E would produce a mixture of 1,2- (mainly 9,10-) and 1,4-diacetoxy *cis*- and *trans*-octadecenoate consistent with the results of Figure 2.[16] Consecutive oxidation of mono- to diacetoxy esters is apparently another pathway (Figure 1). This reaction (1ii ⇌ D) can also involve intermediate π-olefin and π-allyl complexes of type D and E undergoing 1,3-acetoxylation as above (Scheme III). This secondary oxidation of allylic acetoxy esters does not involve acetylated oxypalladation intermediates because a mixture of allylic 1,2- and vinylic 1,3-diacetoxy esters would then be produced and no 1,4 isomers. This work showed no evidence of either vinylic or 1,3-diacetoxy esters. A study of the Pd(II)-catalyzed reaction of isolated monoacetate intermediates would shed more light on the mechanism of diacetoxylation.

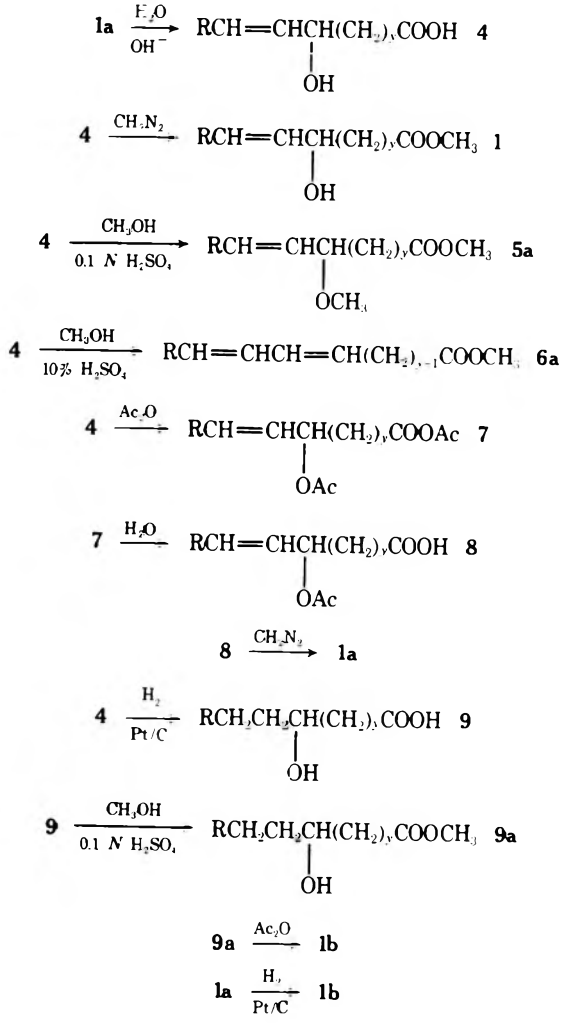
A free-radical mechanism[19] may also account for the high selectivity toward allylic acetoxy esters produced with Pd–$LiNO_3$. However, before this possibility can be considered seriously, a study is needed on the influence of typical free-radical initiators and inhibitors in the polar acetic acid solvent medium.

Interestingly, the allylic products from methyl oleate are similar to corresponding derivatives from hydroperoxides formed by autoxidation,[18] as well as by allylic oxidation with mercuric salts or selenium.[12] Pd-catalyzed acetoxylation provides not only a more efficient route to these allylic oxidation products, but also high yields of diacetoxy esters. Our work suggests that similar allylic dioxygenated products may also be formed under certain conditions during autoxidation of methyl oleate. Consequently, catalytic acetoxylation should provide a useful synthetic route for model compounds needed for the characterization of secondary autoxidation products of unsaturated fatty esters.

Experimental Section

Materials. The catalysts—$PdCl_2$ (Fisher Scientific Co.),[1] palladium(II) acetate (Strem Chemicals, Inc.), Pd on alumina or Pd (10%) on carbon (Engelhardt Industries), Pd black (Matheson Coleman and Bell)—and other reagents—$CuCl_2$, $LiNO_3$, NaOAc, HOAc, Ac_2O, and LiCl (Baker reagents)—were used as purchased. Methyl oleate was redistilled from esterified commercial oleic acid

Scheme IV



(Pamolyn-100, Hercules, Inc.) and analyzed 96% by GLC (impurities included 2.4% stearate and 1.6% linoleate).

Acetoxylations. A. Pressure Reaction (Run 1, Table I). Methyl oleate (0.1 mol), $PdCl_2$ (0.002 mol), $CuCl_2$ (0.1 mol), NaOAc (0.1 mol), HOAc (90 ml), and Ac_2O (10 ml) were placed in a 500-ml pressure bottle. The contents were pressurized with O_2 at 20 psi in a Parr hydrogenation apparatus and heated to 100° under thermostatic control. The pressure was maintained between 20 and 45 psi during the course of the reaction. After oxidation, the cooled mixture was filtered, concentrated by removing most of the HOAc on a rotating evaporator, poured into water saturated with Na_2CO_3, and extracted with petroleum ether. The ether extract was washed three times with Na_2CO_3 (each wash was extracted with petroleum ether) and then with water. The solution was dried (Na_2SO_4), the solvent was removed in vacuo, and after the dark brown residue (26.5 g) was molecularly distilled at 120–210° (0.02 mm), it gave 22.0 g (83%) of a yellow material containing 36% monoacetoxy and 40.5% diacetoxy esters (by GLC on a JXR silicone column[21] programmed from 180 to 260° at 4°/min): ir (neat) 1740 (C=O), 1235 ($OCOCH_3$), 1015 (C–O), and 960 cm^{-1} (trans C=C).

B. Open-Flask Reactions (Run 7, Table I). $PdCl_2$ (0.005 mol), $LiNO_3$ (0.1 mol), HOAc (125 ml), and Ac_2O (10 ml) were placed in a three-necked 250-ml flask provided with an O_2 inlet, attached to an HOAc trap and a bubbler, and with a reflux condenser, attached to a water trap. The solution, stirred magnetically, was first bubbled with O_2 saturated with HOAc and then heated. When the temperature reached 60°, methyl oleate (0.1 mol) was added through the reflux condenser. After an exothermic rise of 10° occurred, the temperature was controlled at 70°. Acetoxylation was followed by sequential GLC analysis. The cooled and filtered product was worked up as in run 1 (34 g). A 20-g fraction was molecularly distilled to give 18.2 g (91%) of a pale yellow material containing 59.9% monoacetoxy and 22.9% diacetoxy esters by GLC: ir on distillate 1740 (C=O), 1620 ($RONO_2$), 1550, 1520 (RNO_2), 1235 ($OCOCH_3$), 1010 (C–O), 960 (trans C=C), 855 cm^{-1} (ionic NO_3^-); distillation residue same ir spectrum except additional bands at

3440 (OH), 1690 (COOH), and no trans band at 960 cm^{-1}. Another sample of crude product was reactylated by refluxing with excess Ac_2O. The product was molecularly distilled, but the yield increased little (92.9%). Apparently some thermolysis of acetoxy products occurs during distillation.

Run 14 (Table I). This reaction was carried out the same way as run 7, except that 5.3 g of 10% Pd/C was the catalyst and the reaction temperature was 80°. A portion of the HOAc solution of crude product was transferred unfiltered into a pressure bottle and hydrogenated in a Parr apparatus at room temperature and 20 psi H_2 until no uptake was observed (3 hr). Analysis by GLC before hydrogenation gave 58.1% monoacetoxy and 35.1% diacetoxy esters; after hydrogenation saturates increased from 2.5 to 13.2% and acetoxy esters (42.3% mono- and 38.6% diacetoxy) decreased correspondingly. Hydrogenolysis of acetoxy esters is also accompanied by hydrogenolysis of nitrate esters as shown by ir: 3440 (OH^-) and no bands at 1630 ($RONO_2$) and 860 cm^{-1} (NO_3^-).

Product Separations. Distilled products (runs 1 and 7, Table I) were fractionated by silicic acid chromatography.[22] Mono- and diacetoxy esters were isolated in 90–97% purity by eluting successively with mixtures of 5:95 and 10:90 diethyl ether–petroleum ether. The free hydroxy esters could also be separated chromatographically, but the allylic components were easily dehydrated with silicic acid, and useful separations could only be achieved with the saturated hydroxy derivatives.

Methyl Acetoxyoctadecenoate. Compound **1a** was characterized by comparing chromatographic behavior (GLC and TLC) with that of methyl acetyl ricinoleate and by other spectral characteristics.[16] Quantitative analyses by ir (CS_2) showed isolated trans (960 cm^{-1}) estimated as 53.9%, if methyl elaidate is the reference and if difference in molecular weight is corrected.

Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14, H, 10.80. Found: C, 70.58, H, 11.00.

Methyl Acetoxyoctadecanoate. Compound **1b** was isolated chromatographically after catalytic hydrogenation of crude acetoxylation products with 5% Pt/C in hexane at room temperature and 50 psi for 1 hr. Spectral and chromatographic data are given in the supplementary material.[16] Analyses by ir showed no trans unsaturation (965 cm^{-1}).

Anal. Calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 71.20; H, 11.36.

Methyl Diacetoxyoctadecenoate (2a + 3a). Although several GLC peaks were obtained for **2a + 3a**, the principal one from **2b + 3b** (hydrogenated **2a + 3a**) corresponded to that of 9,10-diacetoxyoctadecanoate (Table III). No suitable solvent systems proved useful for TLC separation of diacetoxy ester components. Because only saturated reference compounds were available, other functional characterizations were based on data obtained before and after double bond hydrogenation.[16] Quantitative analyses by ir (CS_2) gave a value for isolated trans (960 cm^{-1}) of 53.6% (run 1, Table I).

Anal. Calcd for $C_{23}H_{40}O_6$: C, 66.96; H, 9.77. Found: C, 67.06; H, 10.34.

Methyl Diacetoxyoctadecanoate (2b + 3b). Functional characterization data are given in the supplementary material.[16]

Anal. Calcd for $C_{23}H_{42}O_6$: C, 66.63, H, 10.21. Found: C, 66.70; H, 10.26.

Characterization by Proton NMR.[16] Mono- and diacetoxy fractions showed signals due to OAc (δ 1.98–2.04) and CHOAc (δ 4.82–5.15). Monoacetoxy fractions showed absorptions due to olefinic protons (δ 5.4–5.6) as established by a double resonance experiment; diacetoxy fractions also showed absorptions in this region (δ 5.3–5.6). When used as reference, acetyl ricinoleate (methyl 12-acetoxy-*cis*-9-octadecenoate) gave similar signals as **1a** but a double resonance experiment established that the triplet at δ 2.26 (4 H) is due to both methylenes α to ester carbonyl (on C-2) and α to the double bond (on C-11). With both the monoacetoxy ester **1a** and diacetoxy esters (**2a + 3a**), the absorption at δ 2.28 (2 H) is due only to the methylene α to the ester carbonyl (C-2). The methylene protons α to the double bond would absorb at about δ 2.0, in the same place as the acetoxymethyl protons. The allylic acetoxy structures of **1a**, **2a**, and **3a** are thus confirmed.

The two reference compounds 9,10- and 10,12-diacetoxyoctadecanoate were distinguished by the quartet in the latter at δ 1.8 due to the methylene on C-11 flanked by two methine protons (AcO-$CHCH_2CH$OAc) as established by a double resonance experiment. The absence of this allylic methylene signal at δ 1.8 in **2b** and **3b** (hydrogenated **2a** and **3a**) rules out the presence of 1,3-diacetoxy isomers in the acetoxylation products. Although the two signals in the olefinic proton region may be due to the different allylic structures of **2a** and **3a**, no suitable reference compounds were available to confirm this assignment.

Chemical Characterization. Reactions in Scheme IV were carried out on crude (1 g) and chromatographically purified (30–50 mg) acetoxy esters from runs 1, 13, and 14 (Table I). Characterization data are given in the supplementary material.[16]

Acetoxy esters **1a** were saponified by refluxing for 1 hr in a 95% ethanol solution containing 5% KOH. The isolated hydroxy acids (**4**) from runs 13 and 14 were free of nitrate esters (as shown by ir). The allyl hydroxy acid **4** from **1a** could only be esterified to **1** with diazomethane. The allylic methoxy esters (**5a**) were obtained by treating **4** with weakly acidic methanol (refluxing 1.5 hr in methanol containing 0.1 *N* H_2SO_4, by allowing a methanol solution to stand at room temperature for 2 hr either in the presence of 1% trimethyl orthoformate and 1% HCl (w/v) or 50% dimethoxypropane (v/v) and 1% *p*-toluenesulfonic acid). Under mildly acidic conditions, the etherification of related conjugated dienols and allylic alcohols takes place readily.[23] On refluxing **4** with methanol containing 10% H_2SO_4, partial dehydration occurred as shown by formation of 16% conjugated diene **6a** (by GLC). Refluxing in benzene containing *p*-toluenesulfonic acid resulted in more efficient dehydration.[24]

After dehydration, conjugated fatty esters from purified monohydroxy (**1**) ester fractions were separated from nonallylic hydroxy components by column chromatography.[25] Fatty esters from monohydroxy esters of run 1 and 13 contained, respectively, 76.7 and 89.1% conjugated diene (by GLC on a DEGS column operated isothermally at 200°; mainly cis,trans and trans,trans and a little cis,cis). Analyses by uv (isooctane) gave ϵ values at 230 nm of 18105, and 21030, respectively. Smaller amounts of enol (about 5% in run 13, Table I, and 20% in run 1, as estimated by GLC) were neither converted to the ether **5a** nor dehydrated, and were therefore considered nonallylic.

Acetylation of hydroxy acids **4** by refluxing for 1 hr in neat acetic anhydride gave the mixed anhydride **7**, which was readily hydrolyzed to the acetoxy acid **8** by refluxing in acetone solution containing 20% (v/v) water. The acetoxy esters **1a** were regenerated by treating an ether solution of the acetoxy acid **8** with excess diazomethane.

Compound **4** was catalytically hydrogenated with 5% Pt/C in methanol or Pd/C in HOAc in a Parr apparatus at room temperature and 50 psi H_2 for 1 hr. Adams catalyst (PtO_2 in methanol) caused excessive hydrogenolysis of **4** to methyl oleate and stearate. Esterification of the saturated hydroxy acid **9** by refluxing with methanol containing 0.1 *N* H_2SO_4 gave the corresponding hydroxy ester **9a** but no ether. Therefore, formation of the allyl methoxy ester **5a** is due to the special reactivity of the allyl hydroxy function in **4a**. Acetylation of hydroxy ester **9a** with neat Ac_2O gave the same saturated acetoxy ester **1b** as that from catalytic hydrogenation (Pt/C) of the starting allylic acetoxy ester **1a**.

When the diacetoxy components (**2a + 3a**) were subjected to the reactions in Scheme IV, the same chemical transformations were observed by ir; e.g., saponification, etherification, acetylation, and double bond hydrogenation. However, dehydration of the dihydroxy derivatives (**2 + 3**) formed conjugated trienes. Fatty esters from dehydrated dihydroxy esters of run 1 contained 15.6% conjugated triene (ϵ at 268 nm, 9516). This formation can be attributed to the 1,4-dihydroxy allyl ester **3** since the 1,2-dihydroxy compound **2** should not dehydrate.

Mass Spectral Analyses.[16] Isomeric analysis of **1a** shows prominent peaks due to saturated C-8 and C-9 ester fragments and much less intense peaks due to unsaturated C-10 and C-11. After double bond hydrogenation, isomeric analysis by MS becomes more definitive, and **1b** is shown to be a mixture of 8-, 9-, 10-, and 11-acetoxyoctadecanoate. With diacetoxy components it was possible to determine the position of the first acetoxy substituent (between C-7 and C-11 and mostly at C-9) but not the position of either the second acetoxy substituent or of the double bond.

Isomer Analysis by GC–MS. Ester samples were separated through a gas chromatograph (Packard Model 740 with a 6 ft × 3/16 in. glass column packed with 3% JXR on Gas-Chrom Q 100/120 mesh, Applied Science) attached to a mass spectrometer (Nuclide 12-90-DF) with a direct valve connection to allow a portion of GLC effluents to enter directly into the ionization chamber. The spectrometer was set to scan every 9 sec from *m/e* 10 to 450. Output of the MS detector was electrically connected to a computer magnetic tape system. Later processing provided total ion plots and mass spectra of individual scans. Hydroxy ester derivatives (**1** and **2 + 3**) were silylated with bis(trimethylsilyl)trifluoroacetamide (Regis Chemical Co.). The data in Table II and Figure 2[16] were based on

analyses before and after double bond hydrogenation, comparisons with reference compounds [methyl 9(10)- and 12-hydroxy-9-octadecenoate, 12-hydroxyoctadecanoate, and 9,10- and 10,12-dihydroxyoctadecanoate] and reported fragmentation schemes.[17,18,26] The 9,10-dihydroxy (threo) compound is derived from methyl oleate; the 10,12-dihydroxy (threo) compound, from methyl ricinoleate (by microbial hydration[27]).

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Registry No.—*cis*-**1a** 8-OAc, Δ^9, 56437-68-4; *trans*-**1a** 8-OAc, Δ^9, 56437-69-5; *cis*-**1a** 10-OAc, Δ^8, 56437-70-8; *trans*-**1a** 10-OAc, Δ^8, 56437-71-9; *cis*-**1a** 9-OAc, Δ^{10}, 56437-72-0; *trans*-**1a** 9-OAc, Δ^{10}, 56437-73-1; *cis*-**1a** 11-OAc, Δ^9, 56437-74-2; *trans*-**1a** 11-OAc, Δ^9, 56437-75-3; **1b** 8-OAc, 2379-99-9; **1b** 9-OAc, 2380-00-9; **1b** 10-OAc, 2380-02-1; **1b** 11-OAc, 2380-04-3; **2a**, 8,9-dihydroxy, 56437-76-4; **2a**, 9,10-dihydroxy, 56437-77-5; **2a**, 10,11-dihydroxy, 56437-78-6; **2b**, 8,9-dihydroxy, 56437-79-7; **2b**, 9,10-dihydroxy, 56437-80-0; **2b**, 10,11-dihydroxy, 56437-81-1; **3a**, 7,10-dihydroxy, 56437-82-2; **3a**, 8,11-dihydroxy, 56437-83-3; **3a**, 9,12-dihydroxy, 56437-84-4; **3b**, 7,10-dihydroxy, 56437-85-5; **3b**, 8,11-dihydroxy, 56437-86-6; **3b**, 9,12-dihydroxy, 56437-87-7; methyl oleate, 112-62-9; $PdCl_2$, 7647-10-1; $Pd(OAc)_2$, 3375-31-3; Pd, 7440-05-3.

Supplementary Material Available. Characterization data by ir, GLC, TLC, NMR, MS, and GC–MS will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3247.

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α Anions. VII. Direct Oxidation of Enolate Anions to 2-Hydroperoxy- and 2-Hydroxycarboxylic Acids and Esters[1]

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2-Hydroperoxy acids were obtained by direct low-temperature oxygenation of enolate dianions of straight-chain and branched-chain aliphatic carboxylic acids. Esters of 2-hydroperoxy acids were similarly obtained from ester enolate anions or by diazomethane reaction with 2-hydroperoxy acids. Alternatively, 2-hydroxy acids are formed directly and nearly quantitatively by dianion oxygenation at ambient temperatures. Stabilities, decompositions, and products of decomposition of the hydroperoxy acids and their esters are described.

Although 2-hydroperoxy esters of aliphatic[3] and araliphatic[4] acids were prepared a decade ago, attempts to derive the parent 2-hydroperoxycarboxylic acids through hydrolysis of the 2-hydroperoxycarboxylic esters[5,6] or by free-radical autoxidation of fatty acids were ineffective.[7] In the course of our studies on enolate dianions,[8a] we indicated the reactivity of the dianions to oxygen and subsequently presented the reaction as a route to 2-hydroperoxy- and 2-hydroxycarboxylic acids.[1] The present paper describes the details of the oxygenation reaction and further provides a facile preparation of 2-hydroperoxycarboxylic esters which has advantages in scope and convenience over those previously reported.[3,4] The decomposition of several hydroperoxycarboxylic acids and esters were also examined.

Simultaneously with our presentation of this work,[1] Adam and Liu[5] reported two methods for deriving 2-hydroperoxy acids. The photodecarboxylation of an ether solution of di-*n*-butylmalonoyl peroxide in the presence of hydrogen peroxide gave 2-butyl-2-hydroperoxyhexanoic acid, which resisted purification. Their more successful alternate method employed the enolate dianion of 3,3-dimethylbutyric acid, which on silylation, oxygenation, and hydrolysis in methanol gave the desired 2-hydroperoxy acid. Although quantitative yields of hydroperoxy acid were reported for

Table I
Preparation of 2-Hydroperoxycarboxylic Acids

Starting acid	Registry no.	% oxidation[a]	% 2-OOH[b]	Registry no.	% yield[c]	Mp, °C
Octanoic	124-07-2	86	50	53705-92-3	30	67–68
Tetradecanoic	544-63-8	93	50	53705-94-5	30	89-90
2-Methylpentanoic	97-61-0	92	72		*d*	Liquid
2-Methyldecanoic	24323-23-7	65	55	53705-99-0	43	45–46
2-Ethyldecanoic	2874-76-2	89	70		*d*	Liquid
2-Methyltetradecanoic	6683-71-2	88	68	53705-97-8	66	57–58
2-Ethyltetradecanoic	25354-93-2	93	78	53705-98-9	67	Liquid
2-Propyltetradecanoic	53705-91-2	90	75	53705-96-7	65	Liquid
2-Heptyldecanoic	53705-90-1	93	30		*e*	
cis-Δ^9-Octadecenoic (oleic)	112-80-1	98	30		*e*	
trans-Δ^9-Octadecenoic (elaidic)	112-79-8	98	45	56363-64-5	11	79–80
trans-3-Hexenoic	1577-18-0	96	49		*e*	
Phenylacetic	103-82-2	89	0[f]			

[a] Percent oxidation (total of hydroperoxy and hydroxy acid) determined by GLC analysis of esterified crude product. [b] Percent hydroperoxide determined by iodometric analysis of the crude product. [c] Percent yield based on isolated pure product. [d] Pure product was not isolated. [e] Hydroperoxy acid was unstable and decomposed prior to and during efforts at purification. [f] Products were benzaldehyde (60%), 2-hydroxyphenylacetic acid (25%), and benzoic acid (4%).

their given example, the scope of reactions was not examined for general utility. Their method also introduced the additional steps of silylation and methanolysis.

The direct oxygenation of dianions to 2-hydroperoxy acids is generally accompanied by formation of 2-hydroxy acids as side products. Moersch and Zwiesler[9] recently described the preparation of the latter compounds by this route, but failed to observe formation of the hydroperoxy acids. However, we have observed that either oxygenated derivative may be substantially obtained by appropriate adjustments in procedure. The present direct preparation of 2-hydroxycarboxylic acids is notably superior for branched-chain species[10] that formerly became available only through low-yield multistep syntheses.[10,11,12]

Experimental Section

Materials. Dry, oxygen-free diethyl ether and tetrahydrofuran (THF) were each obtained by distillation from sodium and benzophenone under nitrogen. Hexamethylphosphoramide (HMPA) was distilled at reduced pressure from sodium hydride and stored under nitrogen. *n*-Butyllithium (1.6 *M* in hexane solution) was obtained from Foote Mineral Co.[13] Diisopropylamine was distilled over calcium hydride and maintained under nitrogen.

Analytical Procedures. Conversions of carboxylic acids and esters to hydroperoxide derivatives were determined by a combination of iodometric and GLC analyses. Hydroperoxide contents of the product mixture and purity of isolated compounds were determined by a standard iodometric method.[14] GLC analyses were obtained on esters that were prepared by reaction of carboxylic acids and derivatives with diazomethane. Analytical GLC was performed with an F & M Model 5750 gas chromatograph using 25% DEGA–2% phosphoric acid as column substrate. Esters of 2-hydroperoxy acids were determined from decomposition products thermally generated in the injection port (180°) and resolved on column at temperatures ranging from 150° for methyl 2-hydroperoxyoctanoate to 180° for methyl 2-hydroperoxytetradecanoate. Methyl 2-hydroxyalkanoates were also determined by GLC. Nuclear magnetic resonance spectra were recorded on a Jeolco C-60H NMR spectrometer. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer. Physical constants of the hydroperoxy acids, hydroperoxy esters, and hydroxy acids are listed in Tables I, II, and IV, respectively.

Representative Oxygenations. The following typical preparations of 2-hydroperoxy acids and esters and 2-hydroxy acids illustrate the small variation in procedure that applies to each homologous class.

I. Preparation of 2-Hydroperoxycarboxylic Acids. A. 2-Hydroperoxytetradecanoic Acid. Anhydrous THF (150 ml) and diisopropylamine (10.1 ml, 77.3 mmol) were added to a dry flask flushed with nitrogen and cooled to −30°. *n*-Butyllithium (48.7 ml, 77.3 mmol) was added followed by tetradecanoic acid (8.0 g, 35 mmol) in THF (25 ml) and HMPA (6.33 ml, 35 mmol) while maintaining the temperature at −30°. Dianion formation was completed by heating the solution to 50° for 30 min and then cooling to room temperature. The dianion solution was added dropwise over a period of 1–2 hr to oxygen-saturated diethyl ether (150 ml) at −75°. The addition was made with a dropping funnel bearing an elongated stem with the tip immersed below the ether surface. The reaction mixture was acidified with dilute acid in the cold, the water layer was separated and extracted with ether, the combined ether layers were dried over sodium sulfate, and the products were recovered at ambient temperature by rotary evaporation. Iodometric analysis in conjunction with GLC analysis indicated 7% unreacted tetradecanoic acid, 50% 2-hydroperoxytetradecanoic acid, and 43% 2-hydroxytetradecanoic acid. Pure 2-hydroperoxytetradecanoic acid (30% yield, mp 89–90°) was obtained by crystallization from hot hexane upon cooling to 25°.

Anal. Calcd for $C_{14}H_{28}O_4$: C, 64.62; H, 10.77. Found: C, 64.31; H, 10.77.

B. 2-Hydroperoxy-2-methyltetradecanoic Acid. Dry THF (150 ml) was distilled under nitrogen into a dry flask. Diisopropylamine (5.05 g, 50 mmol) was added and the contents cooled to −10°. *n*-Butyllithium (31.5 ml, 50 mmol) and 2-methyltetradecanoic acid (5.5 g, 22.7 mmol) dissolved in THF (25 ml) were added in sequence while maintaining the temperature below 0°. Dianion formation was completed by heating to 50° for 2 hr and then cooling the solution to ambient temperature. The dianion solution was added dropwise to oxygen-saturated diethyl ether over a period of 1–2 hr at −75° from a dropping funnel as described in A above. The mixture was acidified in the cold with dilute hydrochloric acid solution, extracted with ether, dried over anhydrous sodium sulfate, and rotary evaporated at reduced pressure and ambient temperature. Analysis of the crude product gave 12% unreacted carboxylic acid by GLC, 68% 2-hydroperoxy-2-methyltetradecanoic acid by iodometry, and 20% 2-hydroxy-2-methyltetradecanoic acid by difference. Purification of the titled peroxide (4.45 g, 66% yield) was attained by silicic acid chromatography using CH_2Cl_2–ether (1:1) as the eluting solvent mixture.

Anal. Calcd for $C_{15}H_{30}O_4$: C, 65.69; H, 10.95. Found: C, 65.74; H, 10.88.

C. 2-Hydroperoxyelaidic Acid. The preparation of the dianion and its subsequent oxygenation and product isolation was equivalent to that described in IA. Immediate crystallization of the crude product from pentane (5 ml/g) followed by subsequent crystallizations from pentane–ether (10:1) mixture (22 ml/g) at 5° yielded pure 2-hydroperoxyelaidic acid [11% yield; mp 79–80°; ir ($CHCl_3$) 965 (trans C=C), 1720 (C=O), 3510 cm^{-1} (OH); NMR (Me_4Si, $CDCl_3$) δ 4.57 (t, 1, α CH), 5.85 (m, 2, trans C=C), 10.2 (s, 2, COOH and OOH)].

II. Preparation of 2-Hydroperoxy Esters. A. Methyl 2-Hydroperoxyoctanoate. Anhydrous THF (100 ml) and *N*-isopropyl-

Table II
Preparation of 2-Hydroperoxy Esters

Starting ester	Registry no.	% oxidation[a]	% 2-OOH[b]	Registry no.	% yield[c]	Mp, °C
Methyl octanoate	111-11-5	82	65	56363-66-7	55 (2)[d]	Liquid
Methyl octanoate[e]		30	23		(15)[d]	
Methyl 2-hexylnonanoate	56363-65-6	99	78	56363-67-8	69	Liquid
tert-Butyl dodecanoate	7143-18-2	92	73	56363-68-9	61	41–41.5
Methyl oleate	112-62-9	72	61	35277-31-7	43	Liquid
Ethyl *trans*-3-hexenoate	26553-46-8	93	13	56363-69-0	*f*	

[a] Percent oxidation (total hydroperoxy and hydroxy esters) determined by GLC of crude product. [b] Percent 2-hydroperoxide determined by iodometric analysis of crude product. [c] Percent yield determined by isolation of pure product. [d] Claisen condensation product. [e] Inverse addition of enolate solution to oxygen saturated ether solution. [f] Hydroperoxy ester unstable and decomposed prior to and during efforts at purification.

N-cyclohexylamine (3.76 ml, 20 mmol) were added to a dry flask and cooled to −75°. *n*-Butyllithium (20 mmol) and methyl octanoate (3.16 g, 20 mmol) in THF (50 ml) were added while the solution was maintained at approximately −75°, then stirred for an additional 15 min to complete enolate anion formation. HMPA (3.58 ml, 20 mmol) was added, stirring was continued for 15 min, and oxygen was bubbled into the solution for 1 hr. The solution was acidified and the product was isolated by ether extraction and evaporation as described in the foregoing illustrations. Analysis indicated 65% conversion to methyl 2-hydroperoxyoctanoate by iodometry, 18% unreacted methyl octanoate, and 2% Claisen condensation product by GLC, and 15% methyl 2-hydroxyoctanoate by difference. Purification of methyl 2-hydroperoxyoctanoate (1.60 g, 55% yield) was obtained by silicic acid chromatography: ir (film) 1735 (C=O), 3400 cm^{-1} (OH); NMR (Me_4Si, CCl_4) δ 3.8 (s, 3, OCH_3), 4.45 (t, 1, α CH), 9.78 (br s, 1, OOH).

B. Diazomethane Esterification of 2-Hydroperoxy Acids. Methyl esters of the hydroperoxy acids described above were alternatively prepared by reaction with diazomethane. Reaction of diazomethane was specific with the carboxylic acid functionality and gave no evidence of attack at the hydroperoxide group.

1. Methyl 2-Hydroperoxytetradecanoate: ir (CCl_4) 1740 (C=O), 3480 cm^{-1} (OOH); NMR (Me_4Si, CCl_4) δ 3.78 (s, 3, OCH_3), 4.4 (t, 1, α CH), 10.25 (br s, 1, OOH).

2. Methyl 2-Hydroperoxy-2-methyltetradecanoate: ir (CCl_4) 1738 (C=O), 3475 cm^{-1} (OOH); NMR (Me_4Si, CCl_4) δ 1.43 (s, 3, α Me), 3.80 (s, 3, OCH_3), 8.96 (s, 1, OOH).

3. Methyl 2-Hydroperoxyelaidate. Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.51; H, 10.98. Found: C, 69.11; H, 10.84.

III. Preparation of 2-Hydroxy Acids. A. 2-Hydroxyoctanoic Acid. The dianion of octanoic acid was prepared as described for tetradecanoic acid in IA. The reagents and quantities used were diisopropylamine (4.45 g, 44 mmol) in THF (100 ml), *n*-butyllithium (44 mmol), octanoic acid (2.88 g, 20 mmol) dissolved in THF (25 ml), and HMPA (3.6 ml, 20 mmol). Oxygen was bubbled directly into the dianion solution at room temperature for 30 min and the product isolated as described in IA for the hydroperoxy acid. The crude product consisted of 2% 2-hydroperoxyoctanoic acid by iodometry, 4% unreacted octanoic acid by GLC, and 94% 2-hydroxyoctanoic acid by GLC. Crystallization gave pure 2-hydroxyoctanoic acid (2.0 g, 63% yield, mp 70°, lit. 69.5°): ir ($CHCl_3$) 1720 (C=O), 3515 cm^{-1} (OH); NMR (Me_4Si, CCl_4) δ 4.2 (t, 1, α CH), 7.62 (br s, 1, OH).

Anal. Calcd for $C_8H_{16}O_3$: C, 60.00; H, 10.00. Found: C, 60.36; H, 10.16.

B. 2-Hydroxy-2-methylvaleric Acid. The dianion was prepared as described in IB with reagents and amounts as follows: diisopropylamine (9.55 g, 94.6 mmol) in THF (150 ml), *n*-butyllithium (94.6 mmol), and 2-methylvaleric acid (5 g, 43 mmol) in THF (25 ml). The solution was oxygenated by direct passage of oxygen at 25° for 30 min and the product isolated as described in previous examples. Analysis of the crude oily product indicated the presence of 12% 2-hydroperoxy-2-methylvaleric acid and ~1% 2-methylvaleric acid. Crystallization from petroleum ether gave pure 2-hydroxy-2-methylvaleric acid (3 g, 53% yield, mp 52–53°, lit. 54°): ir (CCl_4) 1732 (C=O), 3550 cm^{-1} (OH); NMR (Me_4Si, CCl_4) δ 1.43 (s, α Me), 7.23 (br s, OH).

Anal. Calcd for $C_6H_{12}O_3$: C, 54.53; H, 9.15. Found: C, 54.54; H, 9.25.

Results and Discussion

2-Hydroperoxy Acids and Esters. The quantitative generation of enolate anions from acids[8b] and esters[15,16] prior to oxidation is essential for the optimization of oxygenated products (Tables I and II). The primary oxygenation reaction that is formulated in eq 1 for conversion of

$$RR'\bar{C}CO_2^- + O_2 \xrightarrow{-75°} RR'C(O_2^-)CO_2^- \quad (1)$$

I II

enolate dianions I (R, R′ = H or alkyl) to 2-peroxy carboxylate dianions II is accompanied by carbanion reduction of II leading to 2-hydroxycarboxylic acids (anion III, eq 2).

$$RR'C(O_2^-)CO_2^- + RR'\bar{C}CO_2^- \longrightarrow 2RR'C(O^-)CO_2^- \quad (2)$$

II I III

The competitive reduction was minimized by adaptation of Walling's[17] technique of inverse addition of carbanions to oxygen-saturated ether.

2-Hydroperoxy esters were similarly prepared from ester enolates. Direct oxygenation was preferred to inverse addition, since warming of enolate on transfer gave significant amounts of Claisen condensation product VI (eq 3 and

$$2R\bar{C}HCO_2Et \longrightarrow R\bar{C}HC(O^-)(OEt)CHRCO_2Et \xrightarrow{H^+} R(R)CHCOCH(R)CO_2Et + EtOH \quad (3)$$

IV V VI

Table II). Methyl esters were also conveniently obtained for analytical purposes by reaction of hydroperoxy acid with diazomethane which specifically methylated the carboxylic acid group. The reaction's specificity was confirmed by iodometric and elemental analysis and by spectral (ir and NMR) comparisons of the products with preparations from ester enolate anions. Since simple hydroperoxides are alkylated by diazoalkanes,[18] the diminished reactivity of hydroperoxide in α-hydroperoxy acids may be attributed to intramolecular hydrogen bonding as depicted by structure VII.

VII

The majority of 2-hydroperoxycarboxylic acids prepared and listed in Table I were stable and easily separated from 2-hydroxycarboxylic acids by silicic acid chromatography. 2-Heptyl-2-hydroperoxydecanoic acid was least stable and was recoverable only in impure form. A solution of the peroxide completely decomposed overnight to a mixture of heptyl octyl ketone and 2-hydroxy-2-heptyldecanoic acid whereas its methyl ester was stable at room temperature. The araliphatic derivative, 2-hydroperoxyphenylacetic acid, which was not isolable gave benzaldehyde (60%), 2-hydroxyphenylacetic acid (25%), and minor amounts of benzoic acid as products. Since carbinol is derived by carbanion reduction of hydroperoxide, 2-hydroxyphenylacetic acid provides evidence of the initial hydroperoxide formation. Benzaldehyde was, therefore, assumed to arise by decarboxylative dehydration of the intermediate 2-hydroperoxyphenylacetic acid[9] and benzoic acid by oxidation of benzaldehyde.

Unsaturated 2-hydroperoxycarboxylic acids (Table I) were surprisingly unstable in comparison with saturated members. The long-chain trans isomer, 2-hydroperoxyelaidic acid, was more stable than the oleic isomer but stability of the latter was enhanced by esterification. The cause of a long-range interaction inducing destabilization of the hydroperoxide 7–8 carbon atoms distant from the olefinic site remains unanswered. 2-Hydroperoxy-*trans*-3-hexenoic acid and the methyl ester were both unstable. This instability may be related to the physical state of the unsaturates, i.e., the liquids may be more unstable than the solids which are more often the saturated analogs. Rapid decomposition is also observed for the saturated branched-chain 2-hydroperoxy-2-heptyldecanoic acid (a liquid), whereas the solid branched-chain compounds are relatively stable for long periods.

The oxygenation of *trans*-3-hexanoate dianion followed an unexpected reaction pathway. Selective α-oxygenation was anticipated on the basis of our previous studies of substitutions of 2- and 3-hexenoate dianions with alkyl halide[19] and cyclohexanone,[20] which had established the near-exclusive formation of 2-substituted 3-hexenoic acids. The initially formed unstable hydroperoxide derivative decomposed to a mixture of 2-hydroxy-3-hexenoic acid (α-substitution), 4-hydroxy-2-hexenoic acid (γ-substitution) and 4-oxo-2-hexenoic acid (γ-substitution). While α-oxygenation predominated, γ-oxygenation was substantial and produced products in a proportion dependent on temperature, i.e., the α/γ ratio was about 3:1 at −75° and 9:1 at 25°.[21] The relatively high proportion of γ-oxygenated product was at variance with our former conclusions of selective α-substitution in hexenoic acids.[19,20] The apparent contradiction in these results has, therefore, prompted further inquiry into the oxygen substitution pattern which is currently under study.

Structure and Decomposition. Infrared and NMR spectral data provide evidence for free and hydrogen-bonded structures of 2-hydroperoxycarboxylic acids and esters. The infrared absorptions of methyl 2-hydroperoxytetradecanoate in CCl_4 showed marked changes in ν (OH) with concentration. At high concentration (7.3×10^{-1} *M*) a broad absorption at 3425 cm^{-1}, presumably due to intermolecular and intramolecular hydrogen-bonded OOH, is observed. Upon dilution, a movement to higher frequency and narrowing of this band is apparent. At tenfold dilution, the OH band has shifted to 3480 cm^{-1} approaching the region associated with free OH absorption. In branched-chain 2-hydroperoxy esters such as methyl 2-ethyl-2-hydroperoxytetradecanoate, different spectral absorption characteristics with dilution were noted. At high concentration (6.6×10^{-1} *M*) absorption of predominantly hydrogen-bonded OH was observed at 3450 cm^{-1}. However, unlike the straight-chain analog above, the shift of the major band was small within tenfold dilution. In addition, a new relatively sharp shoulder indicative of free OH was observed at 3520 cm^{-1}. Similar absorption characteristics for the closely related α-hydroperoxy ketones have been reported by Richardson and Steed.[22] Their assignments suggest that the narrow, high-frequency band (3546 cm^{-1}) is due to a free hydroperoxide species.

Table III
Chemical Shifts of Acidic Protons and p*K* Values of Peroxy Compounds

Compd	Chemical shift, ppm[a]	pK_a
Peroxycarboxylic acids[b]	10.9–11.8[c]	7–8
Straight-chain 2-hydroperoxy esters	9.8	
Branched-chain 2-hydroperoxy esters	8.9–9.0	
Hydroperoxides[b]	7.6–9.2	11.6–12.8

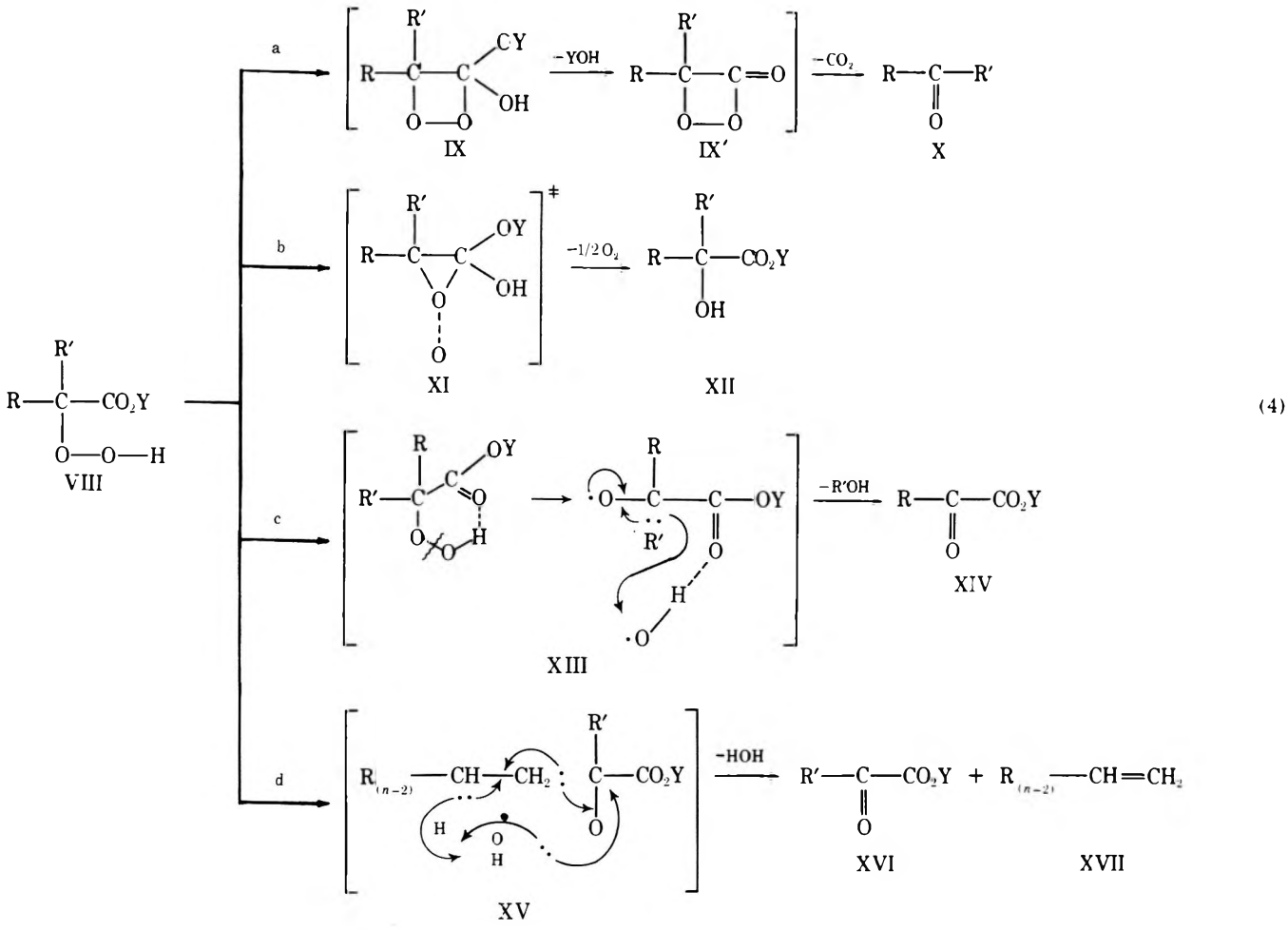
[a] Downfield from Me_4Si as internal reference in 10% CCl_4 solutions. [b] L. S. Silbert in "Organic Peroxides", Vol. II, D. Swern, Ed., Wiley, New York, N.Y., 1971, p 702. [c] Spectra obtained in $CDCl_3$.

The position of the proton shifts of free OOH protons of straight-chain 2-hydroperoxy esters suggests their relative acidity to be intermediate to alkylhydroperoxides and peroxycarboxylic acids (Table III). Both increased acidity and lowered chemical shift are attributable to facile intramolecular bonding with the adjacent carbomethoxy carbonyl as depicted by structure VII. Branched-chain 2-hydroperoxy esters exhibit free OOH resonances at slightly higher fields relative to the straight-chain species because of the electron-donating effects of the 2-alkyl substituent (Table III).

It is well known that the free OH proton resonances of hydroperoxides shift upfield with dilution.[23] The same phenomenon is observed for 2-hydroperoxy ester OOH resonances. Sixfold dilution (CCl_4) from 0.585 to 0.098 *M* of methyl 2-hydroperoxytetradecanoate produced a moderate upfield shift of 0.37 ppm for the OOH resonance. Although this dilution shift is small relative to those observed for alcohols, it nevertheless demonstrates the presence of distinct hydrogen-bonded species.

The hydroperoxycarboxylic acids and esters decomposed primarily to carbonyl and carbinol products (eq 4a,b). Straight-chain hydroperoxy acids (VIIIi) such as 2-hydroperoxyoctanoic acid decomposed in benzene at 70–75° to aldehyde (Xi, 44% heptaldehyde) and hydroxy acids (XIIi, 56% 2-hydroxyoctanoic) and α-branched chain hydroperoxy acids (VIIIii) decomposed in aromatic solvents (benzene, chlorobenzene, xylene)[24] to dialkyl ketones (Xii, 85%) and to 2-hydroxy acids (XIIii, 15%).

The more stable methyl esters were subject to decomposition at higher temperatures. Decomposition and analysis were conveniently carried out by direct injection into a gas chromatograph. The methyl esters of unbranched 2-hydroperoxy acids (VIIIiii, eq 4b,c) decomposed to only two products, methyl α-keto ester (XIViii) and methyl α-hydroxy ester (XIIiii). The structures of XIIiii and XIViii were substantiated by comparison of their spectra (ir, NMR, mass spectra) with authentic materials. By maintaining constant instrumental conditions, the products were obtained in the constant ratio of 85:15, though the ratio varied with changes in injection port temperature. The simplicity of the technique provided a rapid method of analysis that complemented iodometric analyses. The methyl esters of 2-hydroperoxy branched-chain acids de-



(4)

i, R = alkyl; R′ = H; Y = H
ii, R = R′ = alkyl; Y = H
iii, R = alkyl; R′ = H; Y = CH_3
iv, R = R′ = alkyl; Y = CH_3

composed to a more complex mixture of products. In illustration of the products and percentages obtained, methyl 2-methyl-2-hydroperoxydecanoate (VIIIiv) gave rise to four products: methyl 2-methyl-2-hydroxydecanoate (XIIiv, 53%), methyl octyl ketone (Xiv, 19%), methyl 2-ketopropionate (XVIiv, 13%), and 1-octene (XVIIiv, 13%) (eq 4a,b,d).

On the basis of limited evidence, a generalized but speculative scheme to account for products of decomposition is proposed below. Either of the basic oxygen atoms in the hydroperoxide group may cyclize with the polarizable carbonyl in formation of reactive intermediates or transition states. Cyclization with the terminal peroxide oxygen and loss of YOH (CH_3OH or H_2O) leads to an α-peroxylactone IX′. This intermediate, which was recently prepared by Adams and Liu,[5] decomposes to ketone X (or aldehyde for unbranched hydroperoxy acids) with loss of carbon dioxide. α-Hydroxy acids or esters may be derived by cyclization with the penultimate oxygen to an assumed transition state XI of α-lactone hydrate or hemiacetal with concerted loss of nascent oxygen. α-Keto esters XIV arising from unbranched esters cannot originate from a peroxylactone intermediate. A probable mechanism may involve homolytic rupture of the hydroperoxide to hydroxyl radical that is intramolecularly maintained by hydrogen bonding (XIII) to abstract α hydrogen. Finally, decomposition of α-branched esters yielded two additional products, α-keto ester XVI and olefin XVII, in equivalent amounts. The α-keto ester cannot arise by any of the forestated pathways such as c since there is no α hydrogen available for abstraction. Thus XVI must be produced simultaneously with olefin via pathway d, which involves intramolecular β-hydrogen abstraction by hydroxyl radical and electronic rearrangement to products as depicted by structure XV.

Attempts to measure the kinetics of decomposition of the hydroperoxy acids were fraught with difficulties that were incompletely resolved. The α-hydroperoxy acids are sensitive to catalytic decomposition initiated at wall surfaces of Pyrex NMR tubes, Pyrex volumetric flasks, and Teflon bottles. Inconsistent decomposition rates were obtained in NMR tubes that were either pretreated by potassium hydroxide solution or used without pretreatment.

In illustration of a decomposition in deuterated benzene solutions in the NMR spectrometer, 2-hydroperoxyoctanoic acid decomposed completely to aldehyde and α-hydroxy acid in untreated tubes but no decomposition ensued in 10 hr in treated tubes; 2-methyl-2-hydroperoxydecanoic acid decomposed solely to ketone by a zero-order reaction (ketone formed vs. time) to the extent of 50% decomposition in 5 hr in untreated tubes and in 32 hr in base-washed tubes. These results suggested the intervention of acid catalysis at the wall surface of untreated tubes. The effects of the type and concentration of acid (acetic, trichloroacetic, and ethanesulfonic acid), iron catalyst, and container material (glass, Teflon) on the decompositions were therefore examined.

Table IV
Preparation of 2-Hydroxyalkanoic Acids

Starting acid	Temp, °C	% 2-OOH[a]	% 2-OH[b]	% yield[c]	Mp, °C	Registry no.
Octanoic	−10	17	65			617-73-2
Octanoic	25	2	94	63	69–70 (69.5)[d]	
Tetradecanoic	40		74	69	82–83 (81.5–82)[d]	2507-55-3
2-Methylvaleric	−10	39	60			28892-68-4
2-Methylvaleric	25	12	87	53	52–53 (54–54.5)[d]	

[a] Determined by iodometric analysis of crude product. [b] Determined by GLC analysis of esterified crude product. [c] Isolated pure product. [d] Literature values taken from common reference sources.

The decompositions carried out under these varied conditions gave irreproducible k values. The first-order kinetic rate constant for 2-hydroperoxy-2-methyltetradecanoic acid decompositions in an untreated Teflon bottle (5×10^{-2} hr^{-1} at 75° in chlorobenzene) was 10–20 times larger than values in Teflon bottles preconditioned by peroxide decompositions. Unfortunately, the k values for decompositions carried out in preconditioned bottles varied significantly during successive experiments. Under these conditions, first-order rate constants for 2-hydroperoxytetradecanoic and 2-hydroperoxy-2-alkyltetradecanoic acids (alkyl = Me, Et, Pr) ranged within 10^{-1} to 10^{-2} hr^{-1} but confidence in the accuracy of individual values is low owing to the forestated inconsistencies in reproducibility. The effect of larger alkyl substituents was demonstrated by the greater instability of 2-hydroperoxy-2-heptyldecanoic acid which suggested that higher rates of decomposition were induced by longer α-branched chains. However, since this compound is a liquid, it is unclear whether its physical state is responsible for its enhanced instability. The qualitative kinetic evidence has, nevertheless, implicated structural effects on the stability of solid saturated α-hydroperoxy acids that may be tentatively summarized in the order unbranched > small R α-branched > large R α-branched.

2-Hydroxy Acids. Direct passage of oxygen into anion solutions allows for competitive reduction of hydroperoxide anion II through reaction with excess anion I in formation of alkoxide III (eq 2). The reduction step formulated in eq 2 proceeds rapidly at room temperature so that only small amounts of hydroperoxide survive as the contaminant in α-hydroxy acid preparations. The results of oxygenations recorded in Table IV illustrate the lower degree of hydroperoxide formation at 25° relative to oxygenations at −10° and the associated increase in hydroxy acid formation. Since this method works well for both straight- and branched-chain acids, it is superior to previous methods for the preparation of 2-hydroxy acids.[10-12]

While the present study of direct oxidation was in progress, a similar method of preparation of 2-hydroxy acids was reported by Moersch and Zwiesler.[9] Aeration of the appropriate dianion solution by their procedure produced 2-hydroxy acids in 14–18 hr. Our method employing pure oxygen reduced reaction times to 30 min with high conversions of carboxylic acids to α-hydroxy acids.

Registry No.—Methyl 2-hydroperoxytetradecanoate, 56363-70-3; methyl 2-hydroperoxy-2-methyltetradecanoate, 56363-71-4; methyl 2-hydroperoxyelaidate, 56363-72-5.

References and Notes

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(2) Agricultural Research Service, U.S. Department of Agriculture.
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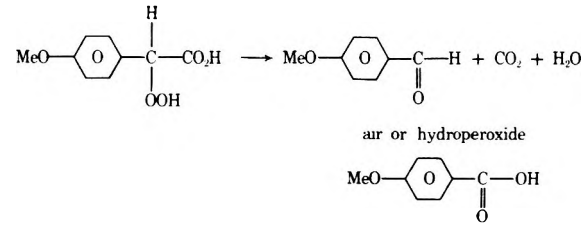

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(16) Rathke's procedure was employed for the generation of ester enolate anions. Anion concentration as determined by CO_2 quenching was 94–98% in both the presence and absence of HMPA. However, yields of the 2-hydroperoxy esters were increased with the addition of a molar equivalence of HMPA prior to oxygenation. Previous authors [T. Cuvingney, D. Reisdorf, and H. Normant, *C. R. Acad Sci., Ser. C*, **268**, 419 (1969)] have also observed a similar effect of HMPA for the autoxidation of carbanions of aromatic hydrocarbons.
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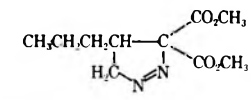
(21) Carbonation at −75° gave the anticipated α-substituted product $CH_3CH_2CH{=}CHCH(CO_2H)_2$. Although α-substtitution was correspondingly predominant at 25°, the acidity of malonate C–H rendered the allylic moiety labile to isomerization which at the higher temperature in basic media led to extensive isomerization to the ethylidene derivative $CH_3CH_2CH_2CH{=}(CO_2H)_2$. Reaction of the latter with diazomethane for GLC analysis gave the corresponding pyrazoline which pyrolyzed in the heated chamber with formation of two alkylated products,



$CH_3(CH_2)_2C(CH_3){=}C(CO_2CH_3)_2$ and $CH_3(CH_2)_3CH{=}C(CO_2CH_3)_2$, and a trace of a third of presumed cyclopropane structure.
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(24) With xylene as the solvent for the decomposition of 2-hydroperoxy-2-methyltetradecanoic acid, a small quantity of tolualdehyde was formed by hydroperoxide oxidation.

Stable Carbocations. CLXXXVIII.[1] Bicyclo[3.1.0]hexenyl Cations

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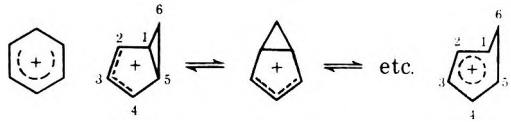
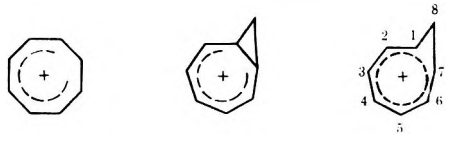
A series of bicyclo[3.1.0]hexenyl and benzobicyclo[3.1.0]hexenyl cations were prepared under stable ion conditions. Based on ^{13}C NMR data, these ions are considered to be cyclopentenyl-like cations with charge delocalization into the fused-on cyclopropane ring. They show no homoantiaromatic or Möbius-type character. ^{13}C NMR spectra of related cyclohexadienyl cations (benzenium ions) which photochemically rearrange to the corresponding bicyclo[3.1.0]hexenyl cations are also reported for comparison.

Photochemical transformation of cyclohexadienyl cations to bicyclo[3.1.0]hexenyl cations in fluorosulfuric acid–SO_2 (or SO_2ClF) solution at low temperature has received considerable attention.[2] The reaction was shown to occur largely with retention of configuration.[3] Both the parent cyclohexadienyl (**1**)[4] and bicyclo[3.1.0]hexadienyl (**2**)[2c] cations have recently been prepared and characterized by ^1H



1 **2** **3**

NMR. Although **1** and **2** are structurally related isomeric carbocations, the former has been shown to possess no antiaromatic homocyclopentadienyl cation (**3**)[4] nature, and the latter contains a fully formed cyclopropane ring with charge delocalization involving the C_1–C_6 and C_5–C_6 (instead of C_1–C_5) bonds, undergoing stereospecific degenerate circumambulation of the cyclopropane ring about the cyclopentenyl cation system. In contrast, when going from the cyclohexadienyl to the cyclooctatrienyl (**4**) cation the strong 1,7 overlap in the latter makes the C_7 system homoaromatic.[5] Neither of the isomeric C_8 cations **4** and **5** were directly observable. Hehre[6] has suggested that the bicyclo[3.1.0]hexenyl cation could be termed as a 6-π "Möbius aromatic" system, similar to the homotropylium ion. Both systems have been shown, however, to exhibit geometrical structures consistent with normal Hückeloid type character and Möbius structures are not considered to be of importance.[7]



4 **5** **6**

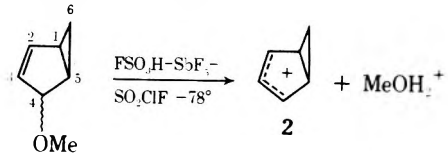
We have recently reported the ^{13}C NMR spectrum of the homotropylium ion **6**, showing that the methylene-bridge carbon (C_8) is hardly deshielded, while both C_1 and C_7 bear substantial positive charge.[8] In contrast, in the bicyclo[3.1.0]hexenyl cations positive charge should be delocalized through the electron-rich external cyclopropane bonds unto C_6, instead of unto C_1 and C_5. It was, therefore, of great interest to study these systems.

We now report the ^{13}C NMR spectroscopic study of the parent and substituted bicyclo[3.1.0]hexenyl cations, showing that, indeed, there is substantial positive charge delocalized unto the methylene-bridge carbons. The structural aspects of the ions were also compared to their corresponding cyclohexadienyl (benzenium) ions.

Interested in the ability of the cyclopropane ring to interact with an adjacent carbocationic center,[9] and to compare it when competing with a fused-on benzene ring, we also extended our studies to a series of novel benzobicyclo[3.1.0]hexenyl cations.

Results and Discussion

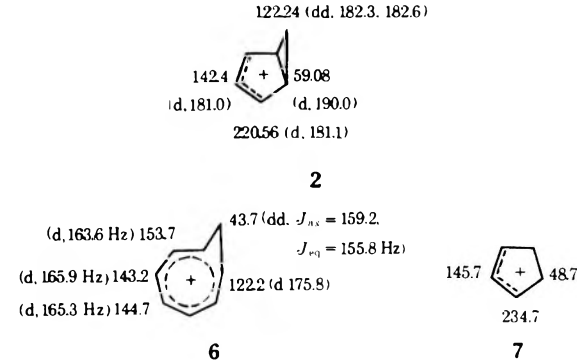
A. Bicyclo[3.1.0]hexenyl Cations. The parent bicyclo[3.1.0]hexenyl cation (**2**) was prepared from 4-methoxybicyclo[3.1.0]hexene in FSO_3H–SbF_5–SO_2ClF solution at −78°. The ^1H NMR spectrum of the solution of **2** at −78°



2

was identical with that previously reported.[2c] The proton noise-decoupled ^{13}C NMR spectrum (Figure 1a) consisted of four carbon resonances (in addition to the methyl signal of protonated methanol). Assignments were made with the aid of the proton coupled spectrum (Figure 1b).

It is interesting to compare the ^{13}C NMR parameters of ion **2** with those of the homotropylium (**6**)[8] and cyclopentenyl (**7**)[10] cations, as shown.



2 **6** **7**

There is a significant difference in carbon shifts for the methylene-bridge carbons in the bicyclo[3.1.0]hexenyl cation **2** and the homotropylium ion **6**.[8] Likewise, the two bridgehead carbons (C_1 and C_5) in **2** are much less deshielded than the corresponding ones (C_1 and C_7) in **6**. Undoubtedly, charge delocalization in the former does not substantially involve the internal fused cyclopropane bond (C_1–C_5), while substantial charge delocalization forming the homoaromatic 6-π system is evident in the latter. One further notices that the bridge methylene carbon (C_6) in **2** is about 60 ppm *downfield* from the other cyclopropane-ring carbons (C_1 and C_5), while the opposite is found in the case of homotropylium ion **6** (C_8 is about 80 ppm *upfield* from C_1 and C_7). The one-bond ^{13}C–H coupling constants for the cyclopropane ring carbons in **2** are substantially larger than the corresponding ones in **6**. This also is in

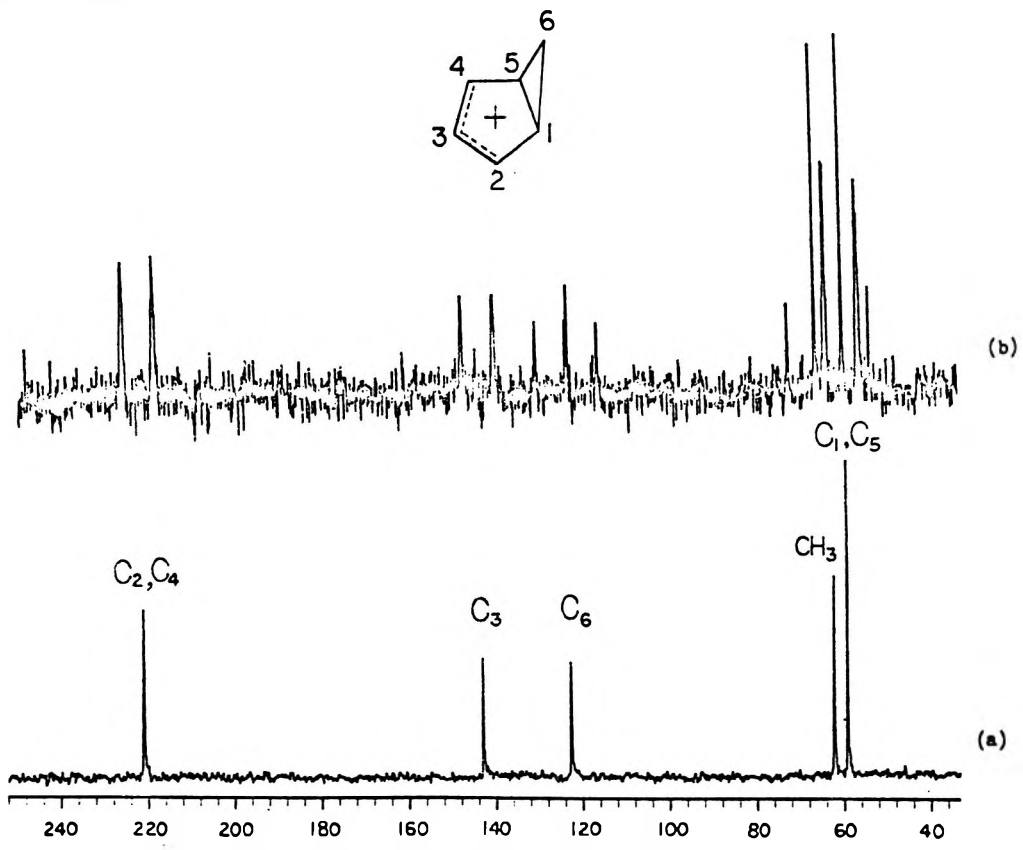
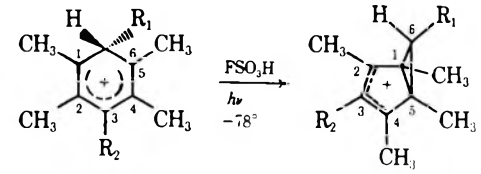


Figure 1. (a) Proton noise-decoupled ^{13}C NMR spectrum of the parent bicyclo[3.1.0]hexenyl cation in FSO_3H–SbF_5–SO_2ClF solution at −75°. Carbon resonance at δ ^{13}C 62.08 is due to the protonated methanol. (b) Proton-coupled ^{13}C NMR spectrum of 1.

agreement with the presence of a cyclopropane ring in 2.[9] Furthermore, comparison of bicyclic ion 2 and the cyclopentenyl cation 7 indicates that the parent bicyclo[3.1.0]hexenyl cation, indeed, is best represented as a cyclopentenyl cation with charge delocalization into the fused cyclopropane ring.

Bicyclo[3.1.0]hexenyl cations are known to be also formed photochemically from their corresponding cyclohexadienyl cations.[11] We have, therefore, examined the ^{13}C NMR spectra of several polymethylated benzenium ions[4] 8–10 and their photochemically rearranged products 11–13 in FSO_3H–SO_2ClF solution. ^{13}C NMR parameters, including the chemical shifts, multiplicities, and coupling constants, are summarized in Table I along with their assignments.

Although carbon shifts cannot be used as a direct measure of charge density, comparison of shift difference among closely related system gives a good indication of the



8, $R_1 = R_2 = H$
9, $R_1 = H$; $R_2 = CH_3$
10, $R_1 = R_2 = CH_3$

11, $R_1 = R_2 = H$
12, $R_1 = H$; $R_2 = CH_3$
13, $R_1 = R_2 = CH_3$

general trend of charge distribution.[12] For cyclohexadienyl cations, C_1 (and C_5) and C_3 are generally much more deshielded than C_2 (and C_4), indicating that positive charge is heavily delocalized unto C_1, C_3, and C_5 positions. This is also shown by the fact that methyl carbons at the C_1, C_3, and C_5 positions in these ions are more deshielded than those at C_2 and C_4 positions. In their photochemically rearranged products, 11–13, C_2 and C_4 become more deshielded

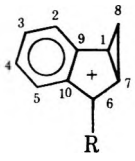
Table I
^{13}C NMR Parameters of Bicyclo[3.1.0]hexenyl and Cyclohexadienyl Cations (Benzenium Ions) in FSO_3H Solutions at −78°

Ion	C_1, C_5	C_2, C_4	C_3	C_6	C_1 CH_3	C_2 CH_3	C_3 CH_3	C_6 CH_3
8	194.25 (s)	142.36 (s)	175.32 (d, 162.5)	57.90 (t, 117.5)	23.08 (q, 130.0)	17.15 (q, 127.5)		
9	186.39 (s)	141.35 (s)	192.65 (s)	55.08 (t, 116.4)	23.11 (q, 129.5)	14.50 (q, 128.3)	23.11 (q, 129.5)	
10	193.85 (s)	139.52 (s)	191.85 (s)	57.58 (d, 134.2)	23.26 (q, 129.5)	14.50 (q, 128.7)	23.26 (q, 129.5)	20.51 (q, 129.0)
11	61.31 (s)	237.69 (s)	137.42 (d, 181.9)	106.52 (dd, 164.5, 167.6)	9.87 (q, 130.4)	22.97 (q, 131.0)		
12	59.40 (s)	232.74 (s)	145.44 (s)	105.56 (dd, 167.9, 176.5)	9.56 (q, 130.0)	20.74 (q, 130.0)	8.76 (q, 128.8)	
13	65.48 (s)	228.70 (s)	149.08 (s)	124.50 (d, 161.5)	11.13 (q, 130.2)	21.48 (q, 129.4)	11.13 (q, 130.2)	8.34 (q, 130.0)

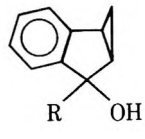
than C_3, while both C_1 and C_5 are much more shielded. The bridge cyclopropane-ring carbons (C_6), on the contrary, become more deshielded than their corresponding ones in the precursor cyclohexadienyl cations. C_2 and C_3 in the rearranged ions **11–13** show chemical shifts in the region of those in the allylic cation **7**. Again, the methyl carbons in these ions display corresponding effects.

Positive charge, as shown, is substantially delocalized over C_2, C_4, and C_6 in bicyclo[3.1.0]hexenyl cations, which are best represented as cyclopentenyl-type carbenium ions with charge delocalization into the cyclopropane ring. The increase of one-bond $J_{^{13}C-H}$ of C_6 in these ions further substantiates the formation of the cyclopropane ring.

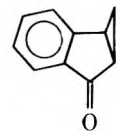
B. Benzobicyclo[3.1.0]hexenyl Cations. The parent secondary ion **14**-H and tertiary ions **14**-R were prepared from the corresponding alcohols **15** (or ketone **16**[13]) in either FSO_3H–SO_2ClF or FSO_3H–SbF_5 solutions at −78°.



14-R



15-R



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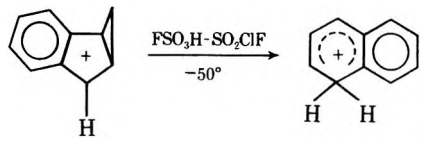
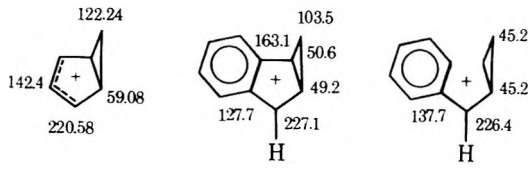
The secondary ion **14**-H slowly underwent ring opening to give the naphthalenium ion[14] above −50°, while tertiary ions are more stable.



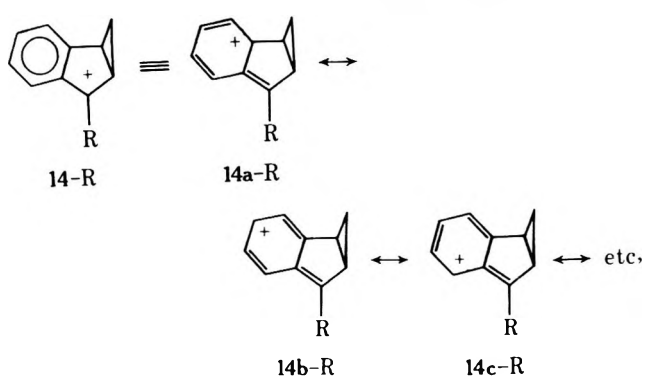
14-H

The complete ^1H and ^{13}C NMR parameters for ions **14**-R are summarized, with their assignments, in Table II. Assignments, multiplicities, and coupling constants (J_{CH} in hertz) were made with the aid of proton-coupled FT ^{13}C NMR spectra. Typical are the spectra shown in Figure 2 for ions **14**-R.

The methylene-bridge carbons in the benzobicyclo[3.1.0]hexenyl cations (C_8) and those (C_6) in bicyclo[3.1.0]hexenyl cations are substantially more deshielded than the rest of the cyclopropane carbons, indicating



charge delocalization through the external cyclopropyl carbon–carbon bonds (C_1–C_8 and C_7–C_8 in **14**-H). C_8 in the



14-R **14a**-R **14b**-R **14c**-R

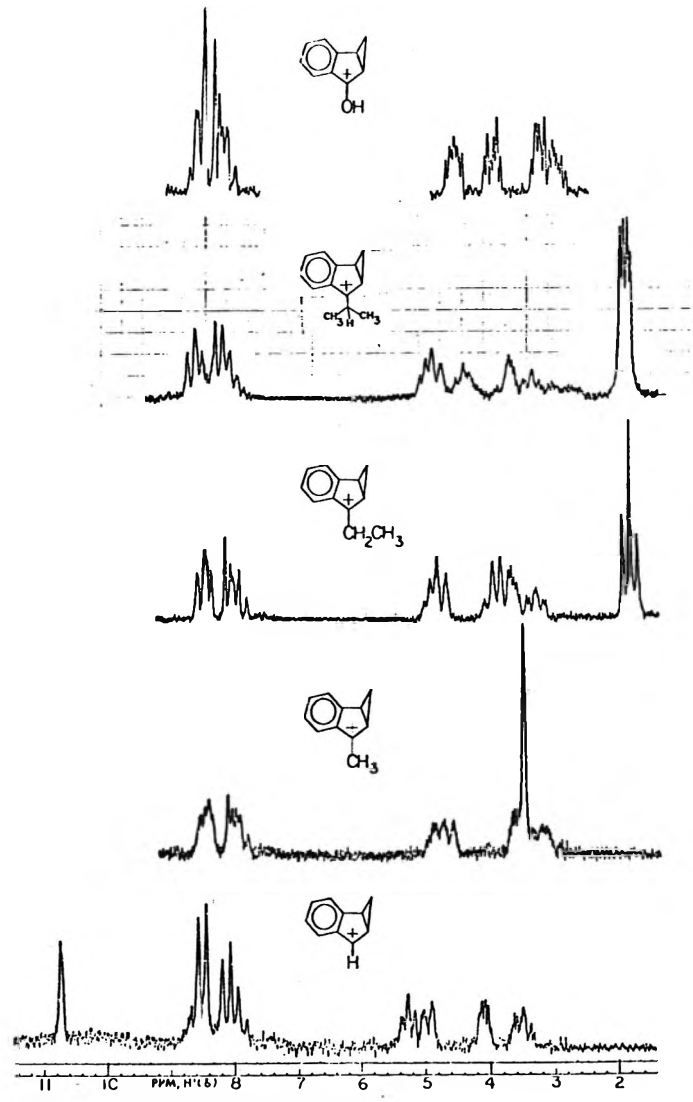
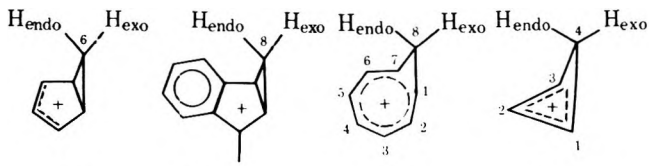


Figure 2. 60-MHz ^1H NMR spectra of benzobicyclo[3.1.0]hexenyl cations at −75° in FSO_3H–SO_2ClF solution.

parent benzobicyclo[3.1.0]hexenyl cation **14**-H is about 10 ppm less deshielded than the corresponding C_6 carbon in the parent bicyclo[3.1.0]hexenyl cation, owing to the presence of the fused-on benzene ring in the former so that positive charge is shared by a relatively larger π system.

The benzobicyclo[3.1.0]hexenyl cations could also be considered as cyclopentenyl cation derivatives with charge delocalization into both the cyclopropane and benzene rings. Substitution at C_6 with alkyl groups, from methyl to isopropyl groups, causes graduate deshielding at C_6 and shielding at the cyclopropane ring carbons, while the benzene ring positions do not vary much.

In the parent bicyclo[3.1.0]hexenyl cation **2**, $H_{6,exo}$ and $H_{6,endo}$ show different chemical shifts at δ 3.98 and 4.28, respectively.[2c] The difference between $H_{8,exo}$ and $H_{8,endo}$ in the parent benzobicyclo[3.1.0]hexenyl cation **14**-H and its related tertiary ions (Table I) falls in similar order. The smaller chemical shift difference ($\delta_{endo} - \delta_{exo}$) of the methylene-bridge protons (+0.30 ppm in **2** and +0.60 ppm in **14**-H) of bicyclo[3.1.0]hexenyl-type cations is in contrast to



2 **14a**-H **6** **17**

Table II
^1H and ^{13}C NMR Parameters of Benzobicyclo[3.1.0]hexenyl Cations[a]

	14-H		14-CH_3		14-CH_2CH_3		14-$CH(CH_3)_2$		14-OH[b]	
Position	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C	δ ^1H	δ ^{13}C
1	5.30	49.2 (d, 183.3)	4.85	49.0 (d, 186.5)	4.74	47.2 (d, 187.2)	4.86	45.0 (d, 185.8)	4.40	30.9 (d, 184.5)
2	8.15	131.9 (d, 169.5)	8.05	130.8 (d, 169.7)	8.15	130.7 (d, 169.0)	8.16	130.4 (d, 169.4)	7.90	129.7 (d, 168.7)
3	8.58	139.4 (d, 169.9)	8.42	134.4 (d, 169.3)	8.50	133.8 (d, 170.5)	8.45	132.9 (d, 170.4)		126.5 (d, 167.9)
4	7.98	127.2 (d, 169.9)	7.95	126.7 (d, 170.7)	7.98	126.7 (d, 172.0)	7.92	126.9 (d, 171.4)	8.52	129.7 (d, 168.7)
5	8.50	151.9 (d, 163.4)	8.50	149.1 (d, 165.1)	8.49	148.8 (d, 169.8)	8.56	148.3 (d, 169.2)		143.8 (d, 164.3)
6	10.78	227.1 (d, 183.4)		249.6 (s)		255.0 (s)		259.0 (s)		219.5 (s)
7	4.95	50.6 (d, 190.3)	4.64	44.3 (d, 185.2)	4.78	43.9 (d, 185.6)	4.70	43.3 (d, 185.1)	3.82	33.1 (d, 184.8)
8	3.68, exo 4.28, endo	103.5 (dd, 170.2, 172.9)	3.22, exo 3.60, endo	89.1 (dd, 171.7, 174.4)	3.28, exo 3.62, endo	89.3 (dd, 172.0, 172.9)	3.26, exo 3.60, endo	89.0 (dd, 171.6, 172.8)	2.85, exo 3.10, endo	60.2 (dd, 171.4, 171.5)
9		173.3 (s)		169.6 (s)		169.3 (s)		169.4 (s)		163.1 (s)
10		142.4 (s)		140.3 (s)		139.5 (s)		139.1 (s)		127.7 (s)
CH_3			3.48	24.6 (q, 131.2)	1.78	11.8 (q, 131.1)	1.40	20.4 (q, 129.7)		
							1.62	21.7 (q, 130.0)		
CH_2					3.89	32.5 (t, 129.2)				
CH							4.28	39.7 (d, 131.4)		

[a] Both proton and carbon chemical shifts are in parts per million from external Me_4Si (capillary). [b] δ_{OH} = 10.85 (singlet). [c] Multiplicities and coupling constants are given in parentheses.

that ($\delta_{H_{8,endo}} - \delta_{H_{8,exo}}$ −5.8 ppm) in the homotropylium ion **6**.[5] This corresponds to the difference in J_{CH} in these three systems indicating that both **14** and **2** are different in nature from **6**. The homoaromatic nature of **6** thus causes a substantial ring current effect to shield the $H_{8,endo}$ proton, while the effect is relatively small in charge-delocalized cyclopentenyl type ions **14** and **2**. This finding is also in accord with our recent results showing that 1,3-orbital interaction to produce homoaromaticity is more important in smaller cycloalkenyl cations, such as the parent cyclobutenyl cation **17** ($\delta_{H_{4,endo}} - \delta_{H_{4,exo}}$ −0.82)[15]. The latter has been shown to be the truly homoaromatic 2-π system, i.e., the homocyclopropenyl cation.[15]

Experimental Section

Materials. 4-Methoxybicyclo[3.1.0]hexene was prepared by direct irradiation of a solution of benzene in methanol at room temperature according to the literature procedure,[16] and purified by GLC.

1,1a,6,6a-Tetrahydrocycloprop[*a*]inden-6-one (**16**) was prepared from *trans*-2-phenylcyclopropanecarboxylic acid chloride according to literature procedures,[13] bp 79–81° (0.4 mm).

1,1a,6,6a-Tetrahydrocycloprop[*a*]inden-6-ol (**15-H**) was prepared by reduction of **16** with $LiAlH_4$ in anhydrous ether in the usual manner: mp 83.5–84.3°; NMR ($CDCl_3$, capillary Me_4Si) δ 7.78 (4 H, s, aryl H), 6.14 (1 H, d, J = 6.4 Hz, H_6), 2.95 (1 H, m, benzyl H), 2.70 (1 H, s, OH), 2.58 (1 H, m, H_7), 1.50 (1 H, m, anti H_8), and 1.04 (1 H, m, syn H_8).

6-Methyl-1,1a,6,6a-tetrahydrocycloprop[*a*]inden-6-ol (**15-CH_3**) was prepared from **16** and methylmagnesium bromide in anhydrous ether: mp 47–48°; NMR ($CDCl_3$, capillary Me_4Si) δ 7.74 (4 H, s, aryl H), 2.94 (1 H, m, benzyl H), 2.40 (1 H, m, H_7), 2.43 (1 H, s, OH), 2.14 (3 H, s, CH_3), 1.58 (1 H, m, anti H_8), and 0.95 (1 H, m, syn H_8).

6-Ethyl-1,1a,6,6a-tetrahydrocycloprop[*a*]inden-6-ol (**15-CH_2-CH_3**) was prepared from **16** and ethylmagnesium bromide in anhydrous ether: bp 232–233°; NMR ($CDCl_3$, capillary Me_4Si) δ 7.66 (4 H, s, aryl H), 2.82 (1 H, m, benzyl H), 2.78 (1 H, s, OH), 2.40 (2 H, q, CH_2), 2.30 (1 H, m, H_7), 1.42 (1 H, m, anti H_8), 1.36 (3 H, t, CH_3), and 0.92 (1 H, m, syn H_8).

6-Isopropyl-1,1a,6,6a-tetrahydrocycloprop[*a*]inden-6-ol [**15-CH-$(CH_3)_2$**] was similarly prepared from **16** and isopropylmagnesium bromide in anhydrous ether: bp 197° dec; NMR ($CDCl_3$, capillary Me_4Si) δ 7.70 (4 H, S, aryl H), 2.90 (1 H, m, benzyl H), 2.44 (1 H, m, H_7), 1.60 (1 H, h, CH), 1.60 (3 H, d, CH_3), 1.30 (3 H, d, CH_3), 1.34 (1 H, m, anti H_8), 0.94 (1 H, m, syn H_8), and 0.60 (1 H, s, OH).

Preparation of Ions. The parent bicyclo[3.1.0]hexenyl cation **2** was prepared by careful addition of 4-methoxybicyclo[3.1.0]hexene in SO_2ClF at −78° to FSO_3H–SO_2ClF solution with stirring. The ion was formed cleanly without any formation of benzenium ion, and it showed similar thermal decomposition at higher temperature as previously described.[2c]

Methyl-substituted bicyclo[3.1.0]hexenyl cations **11–13** were prepared by irradiation of the solution of their corresponding benzenium ions, which were prepared by addition of methyl-substituted benzene to FSO_3H–SO_2ClF solution at Dry Ice–acetone bath temperature (ca. −78°), at low temperature with a Hanovia 450-W mercury arc lamp. The progress of the reaction was allowed for maximum conversion after about 8–12 hr.

Benzobicyclo[3.1.0]hexenyl cations **14-R** were also prepared in a similar way from their corresponding alcohols in either FSO_3H–SO_2ClF or FSO_3H–SbF_5–SO_2ClF solutions at Dry Ice–acetone bath temperature (−78°).

Proton and Carbon-13 NMR Spectroscopy. ^1H NMR spectra were obtained using Varian Associates Models A56/60A and HA-100 NMR spectrometers, equipped with a variable-temperature probe. Tetramethylsilane was used as reference. ^{13}C NMR spectra were obtained using a Varian VFT, XL-100-15 spectrometer equipped with a broad-band proton noise decoupler and a variable-temperature probe. The instrument was operated in the pulse Fourier transform mode. Carbon shifts were measured from the ^{13}C signal of capillary Me_4Si (5% enriched).

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No.—**2**, 32730-99-7; **8**, 31426-84-3; **9**, 40854-61-3; **10**, 27458-89-5; **11**, 53966-99-7; **12**, 53966-98-6; **13**, 52059-03-7; **14-H**, 56377-03-8; **14-CH_3**, 56377-04-9; **14-CH_2CH_3**, 56420-55-4; **14-$CH(CH_3)_2$** 56377-05-0; **14-OH**, 56377-06-1; **15-H**, 22228-27-9; **15-CH_3**, 56403-16-8; **15-CH_2CH_3**, 56403-17-9; **15-$CH(CH_3)_2$**, 56403-18-0; **16**, 5771-62-0; methyl bromide, 74-83-9; ethyl bromide, 74-96-4; isopropyl bromide, 75-26-3; 4-methoxybicyclo[3.1.2]hexene, 56377-02-7.

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Stereochemical Studies on Some Reactions Proceeding via α-Fluoro- and α-Chlorocyclopropyl Radicals[1]

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The stereochemistry of the brominative decarboxylation of 7-*endo*-fluoro- (**1a**), 7-*exo*-fluoro- (**1b**), 7-*endo*-chloro- (**2a**), and 7-*exo*-chlorononcarane-7-carboxylic acid (**2b**), as well as the thermal decomposition of their *tert*-butyl peroxy esters in toluene, cumene, or bromotrichloromethane, has been examined. The degree of stereospecificity observed in these reactions has revealed that (i) the 7-fluoro-7-norcaryl radical is configurationally very stable and its bromine abstraction under the brominative decarboxylation conditions (0 or 77°) or from bromotrichloromethane (110°) occurs much more rapidly than its inversion of configuration, (ii) its hydrogen abstraction from toluene or cumene occurs less rapidly and can compete with its inversion, and (iii) the inversion of the 7-chloro-7-norcaryl radical occurs more rapidly than that of the corresponding fluoro radical, and as a result the stereospecificity of the reaction involving the chloro radical decreases. Similar reactions of 7-unsubstituted norcarane-7-carboxylic acids (**3a** and **3b**) and their peroxy esters have shown that the 7-norcaryl radical is configurationally unstable and behaves like a planar radical in these reactions.

Based on many spectrochemical data, ordinary alkyl radicals have been recognized either to have a pyramidal structure but be subject to rapid inversion of configuration, or to have a planar structure. For example, the trifluoromethyl radical has been proved to be pyramidal by ir[2] and ESR[3] spectroscopy and by photoionization studies.[4] The fluoro- and hydroxymethyl radicals are also considered to be pyramidal,[5] whereas electronic[6] and ESR[7] spectra have provided evidence supporting a planar structure for the methyl and unsubstituted alkyl radicals.

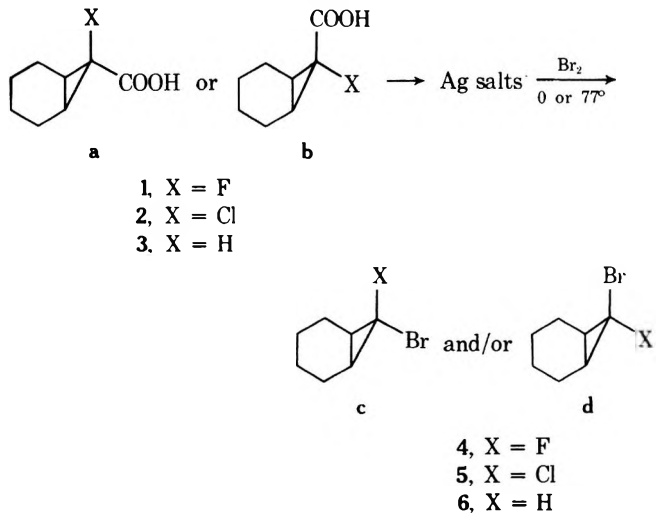
Recent chemical studies on the nature and, in particular, the configurational stability of vinyl[8] and cyclopropyl[9] radicals have favored a bent and a nonplanar configuration, respectively, at the tervalent carbon. Thus, we reported earlier that the reduction of some *gem*-halofluorocyclopropanes with tri-*n*-butyltin hydride proceeded with complete retention of configuration.[9a,b] The results were rationalized by postulating a pyramidal structure for the intermediate α-fluorocyclopropyl radical and the slow rate of its inversion relative to its hydrogen abstraction, which came from the high configurational stability, or the high energy barrier for inversion, of α-fluorocyclopropyl radicals.

The validity of this assumption has now been examined by studying the stereochemistry of some reactions which are believed to involve α-fluoro (or -chloro)cyclopropyl radicals, viz., the brominative decarboxylation (Hunsdiecker reaction) of 7-halonorcarane-7-carboxylic acids and the thermal decomposition of their peroxy esters.

Results

Brominative Decarboxylation of 7-Halonorcarane-7-carboxylic Acids (1, 2, and 3). Two isomers of 7-fluoronocarane-7-carboxylic acid (**1a** and **1b**) (Scheme I) were obtained by carbonation of 7-fluoro-7-norcaryllithium followed by fractional recrystallization. The configurational assignment to the isomers was made from their ^{19}F NMR spectra based upon the generalization that in fluorocyclopropanes the ring fluorine is more strongly coupled with cis than with trans hydrogen,[10] and that in alkyl- and aryl-substituted cyclopropanes the ring fluorine is shielded by cis and deshielded by trans substituents.[11] Isomers of 7-chlorononcarane-7-carboxylic acid (**2a** and **2b**) were prepared according to the method of Köbrich and Goyert.[12] The 7-unsubstituted acids, **3a** and **3b**, were prepared as follows: norcarane-7-*exo*-carboxylic acid (**3a**) was obtained by the reaction of ethyl diazoacetate with cyclohexene followed by alkaline hydrolysis and fractional recrystallization. Endo acid **3b** was obtained by the reduction of methyl 7-bromonorcarane-7-carboxylate with tri-*n*-butyltin hydride followed by hydrolysis. Their spectral data were in good agreement with the reported ones.[12,13,14]

Scheme I



The silver salts of the acids were separately prepared in the conventional manner and were allowed to react with bromine in carbon tetrachloride under the conditions indicated in Table I. The brominated cyclopropanes were identified by comparison of their retention times and spectral properties with those of an authentic sample of 7-bromo-7-fluoronorcarane, 7-bromo-7-chlorononcarane, or 7-bromonorcarane. The yields of these bromides were determined from their peak areas in GLC, calibrated against authentic sample solutions of known concentrations.

Thermal Decomposition of *tert*-Butyl Peroxy Esters (7 and 8). *tert*-Butyl 7-fluoro- and 7-chlorononcarane-7-peroxycarboxylates were prepared in good yields by treatment of the corresponding acid chloride with *tert*-butyl hydroperoxide in *n*-pentane at −20°. The peroxy esters were purified by chromatography on Kiesel gel prior to use. All four peroxy esters gave satisfactory spectral analyses. Two of the four peroxy esters were solids at room temperature (**7a**, mp 40.0–41.0°; **8a**, mp 46.5–47.5°), which minimized

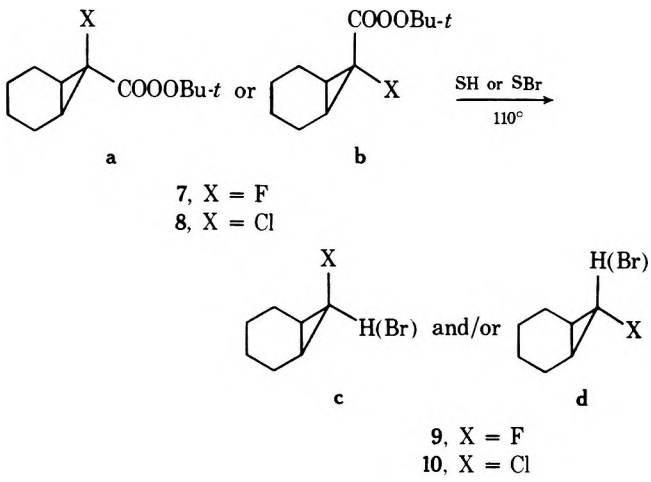
Table I
Brominative Decarboxylation of Acids 1, 2, and 3

Compd	Time, hr	Temp, °C	Yield, %	Isomer ratio retn:invn
1a	2	0	71	100:0
	2	77	75	100:0
1b	2	0	75	100:0
	2	77	71	100:0
2a	2	0	68	88:12
	2	77	73	72:28
2b	2	0	71	82:18
	2	77	74	43:57
3a	2	0	70	81:19
	2	77	73	84:16
3b	2	0	72	16:84
	2	77	76	15:85

contamination problems, and the others (**7b** and **8b**) were liquids at room temperature. The structural assignment of all peroxy esters was made on the basis of the stereochemistry of the starting acids.

Degassed solutions of the peroxy esters in toluene, cumene, or bromotrichloromethane as scavenging solvent were heated in sealed Pyrex ampoules at 110° for 24 hr (Scheme II). Infrared analysis revealed no remaining per-

Scheme II



oxy esters at the end of the reaction. The yields of the products are given in Table II together with the reaction conditions. The products formed by hydrogen (or bromine) abstraction, RH or RBr, were identified by comparison with authentic samples and their yields were measured by the internal standard method (GLC). Where only relative yields (isomer distributions) were desired, no internal standard was added. The yields of acids, RCOOH, were determined by calibration of the carboxyl absorption intensity against those of solutions of known concentrations. The isolated acids were found to have retained the geometry of the starting peroxy esters in all cases.

Discussion

As shown in Table I, the brominative decarboxylation of 7-fluoronorcarane-7-carboxylic acid (**1**) occurred with complete retention of configuration, whereas that of the chloro acid **2** occurred with only partial stereospecificity to give a mixture of two geometrical isomers. The high stereospecificity observed with the fluoro acid means that the inversion of configuration of the 7-fluoro-7-norcaryl radical oc-

Table II
Thermal Decomposition of Peroxy Esters 7 and 8

Compd	Solvent	Yield, %[a] RCOOH	Yield, %[a] RH or RBr	Isomer ratio retn:invn
7a	Toluene	13	61	94:6
	Cumene	15	65	96:4
	$CBrCl_3$		53	100:0
7b	Toluene	16	65	90:10
	Cumene	16	58	93:7
	$CBrCl_3$		49	100:0
8a	Toluene	17	64	78:22
	Cumene	18	56	80:20
	$CBrCl_3$		38	82:18
8b	Toluene	18	68	23:77
	Cumene	19	55	21:79
	$CBrCl_3$		47	18:82

[a] R stands for 7-fluoro- or 7-chloro-7-norcaryl group.

curs much more slowly than its bromine abstraction, and can be ascribed to the extremely high configurational stability of the α-fluorocyclopropyl radical intermediate as previously cited.[9b] On the other hand, the stereochemical behavior of the chloro acid suggests that the configurational stability of the 7-chloro-7-norcaryl radical is not so high as that of the corresponding fluoro radical, and that the inversion of the chloro radical occurs at a rate comparable to its bromine abstraction. Table I also shows that, as is the case in the reduction of cyclopropyl bromides with tri-*n*-butyltin hydride,[9b] the ratio of retention to inversion decreases as the temperature increases.

In the reaction of the corresponding 7-unsubstituted acid (**3**) under the same reaction conditions, the isomer distributions in the products were nearly identical in all runs, irrespective of the geometry of the starting acid. This indicates that the unsubstituted 7-norcaryl radical is either pyramidal but inverts its configuration so rapidly that it behaves like a planar radical, or in fact it is planar.

From the above-described results, it follows that both the α-fluoro and the α-chloro substituents can stabilize the pyramidal configuration of the cyclopropyl radical, but the effect of fluorine is much stronger than that of chlorine.

Further evidence supporting this view is provided by the thermal decomposition of the *tert*-butyl peroxy esters of 7-fluoro- and 7-chloronorcarane-7-carboxylic acid (**7** and **8**).

The significant yields of the acids suggest that a one-bond homolysis[15] operates with these peroxy esters. However, decarboxylation also occurs as indicated by the moderate to high yield of RH (Table II). As is clear from the data in Table II, the hydrogen abstraction of the 7-fluoro-7-norcaryl radical from toluene or cumene is not so rapid as the bromine abstraction from bromotrichloromethane and can compete with the inversion of configuration. It should be noted that the degree of stereospecificity is closely related to the bond-dissociation energy of the C–H or the C–Br bond in scavenger molecules.

In contrast to the fluoro peroxy esters, the isomer compositions of the products from the chloro peroxy esters are essentially the same, regardless of their stereochemistry. It means that, at least at this reaction temperature, the inversion of configuration of the chloro radical takes place much more rapidly than the hydrogen or bromine abstraction from the solvents, though more efficient scavenging systems might lead to partial or complete specificity. The preferential formation of *endo*-chloronorcarane and *endo*-chloro-*exo*-bromonorcarane (**10c**) is most easily explained

by stereoselectivity in the hydrogen or bromine abstraction step, i.e., the approach of the scavenging agent toward the 7 position from the exo side being sterically less hindered than that from the endo side.

A similar trend has been noted in studies on the 9-decalyl systems[16] where a change of solvent from cyclohexene to cumene leads to an increase in *cis*-decalin in the product mixture.

From the stereochemical results described herein, it may be concluded that in comparison with the α-fluorocyclopropyl radical, the configurational stability of the α-chloro radical is lower, but not so low as that of the α-unsubstituted one.

Generally, the configurational stability of free radicals can be regarded as being dependent upon the s character of the odd-electron orbital.[17] Thus, vinyl radicals are configurationally more stable than cyclopropyl radicals, since the odd-electron orbital of the former is sp^2 hybridized and that of the latter is $sp^{2.4}$ or $sp^{2.5}$ hybridized.[18] If the α hydrogen is replaced by an electronegative atom or group such as fluorine or chlorine, the s character of the carbon orbital forming the C–F or the C–Cl bond decreases relative to that of the C–H bond, and as a result the s character of the odd-electron orbital increases. It may be expected, therefore, that the more electronegative the α substituent is, the less rapidly the inversion of configuration will occur.

The results reported herein are in accordance with this expectation. An analogous tendency has been observed with α-substituted vinyl radicals,[8] and the calculation of the energy barrier for inversion of some cyclopropyl and vinyl radicals by CNDO/2[9c] or MINDO/3[19] also suggests the significance of the electronegativity effect of α substituents. The work of Altman et al.[9d] on the α-(trifluoromethyl)cyclopropyl radical reveals, however, that the electronegativity can not be the only factor that determines the configurational stability of cyclopropyl radicals. No doubt more work must be done, both theoretically and experimentally, in order to solve the problem.

Experimental Section

All boiling and melting points are uncorrected. Infrared spectra were taken on a Shimadzu IR-27 infrared spectrometer using a polystyrene film for calibration. Proton NMR spectra were measured for solutions in carbon tetrachloride with tetramethylsilane (Me_4Si) as an internal standard with a Varian Associates T-60 or A-60 or a Jeolco H-60 spectrometer. Fluorine NMR spectra were recorded on a Hitachi H-60 spectrometer (56.4 MHz) in carbon tetrachloride with trifluoroacetic acid (TFA) as an external reference. The proton and fluorine chemical shifts are expressed in parts per million downfield from Me_4Si and in parts per million upfield from TFA, respectively. Gas chromatographic (GLC) analyses were performed with a Shimadzu GC-2C or a Hitachi K23 gas chromatograph by use of a 3 m × 3 mm column with 7% Apiezon L or 7% Silicon DC 550 on 80–100 Celite 545, or a 45 m × 0.25 mm Golay column with Apiezon L or butanediol succinate (BDS). Isomer distributions were calculated from peak areas in gas chromatograms. The values of the isomer ratios listed in Tables I and II are accurate within ±2%.

Materials. All chemicals were reagent grade and used without further purification. Solvents were distilled (or vacuum distilled) through a 25-cm Vigreux column and, if necessary, were purified in the usual manner prior to use. Authentic samples were prepared as follows: 7-bromo-7-fluoronorcarane and 7-bromo-7-chloronorcarane were obtained by the reaction of cyclohexene with bromofluorocarbene[9a,20] and bromochlorocarbene,[21] respectively, generated by basic decomposition of the corresponding trihalomethane.

7-Fluoronorcarane-7-carboxylic Acid (1). To a solution of 29 g (0.15 mol) of 7-bromo-7-fluoronorcarane (mixture of isomers) in 200 ml of tetrahydrofuran–ether (1:1), cooled to −140° by immersing in a bath of liquid nitrogen and methylcyclohexane–*n*-hexane (4:1), was added, under nitrogen atmosphere, 200 ml of a 0.7 *N* solution of *n*-butyllithium in *n*-hexane at such a rate that the temperature should not rise above −130°. After the addition was over, the reaction mixture was stirred for 20 hr at −150 to −140°, and then an excess of solid carbon dioxide was carefully added. The mixture was warmed up to room temperature, poured onto ice water, and was worked up as usual. From the acid fraction, 2.1–2.5 g of 7-fluoronorcarane-7-carboxylic acid was obtained together with 3–4 g of *n*-valeric acid. The neutral fraction gave 6–7 g of unchanged 7-bromo-7-fluoronorcarane (*exo*-F:*endo*-F 9:1), ca. 2 g of 7-(2-tetrahydrofuryl)norcarane, and a small amount of some unidentified products. The crude acid thus prepared was fractionally recrystallized from petroleum ether to yield 1.4–1.7 g of the *exo*-fluoro isomer (**1b**), mp 99.0–99.5°, and 0.2–0.4 g of the *endo*-fluoro isomer (**1a**), mp 112.5–113.0°.

1a: ir (KBr) 1720 (vs), 1440 (s), 1308 (m), 1265 (s), 1250 (s), 1176 (s), 1122 (s), 1035 (m), 980 (m), 790 (m), 755 (m), 680 cm^{-1} (m); ^1H NMR δ 1.1–2.3 (complex m, 10 H) and 11.94 (s, 1 H); ^{19}F NMR δ_F 146.0 (J_{HF} = 5.9 Hz).

Anal. Calcd for $C_8H_{11}O_2F$: C, 60.75; H, 7.01; F, 12.01. Found: C, 61.02; H, 7.22; F, 12.02.

1b: ir (KBr) 1703 (vs), 1690 (vs), 1440 (vs), 1300 (s), 1220 (vs), 1195 (s), 1122 (s), 1095 (s), 1040 (m), 910 (s), 850 (m), 780 cm^{-1} (s); ^1H NMR δ 0.8–2.2 (complex m, 10 H) and 11.85 (s, 1 H); ^{19}F NMR δ_F 98.2 (J_{HF} = 22.3 Hz).

Anal. Calcd for $C_8H_{11}O_2F$: C, 60.75; H, 7.01; F, 12.01. Found: C, 60.83; H, 6.93; F, 12.14.

7-Chloronorcarane-7-carboxylic acid (2) was prepared according to the method of Köbrich and Goyert.[12]

2a: mp 92.0–92.5°; ir (KBr) 1680 (vs), 1440 (m), 1290 (s), 1170 (m), 1105 (m), 1000 (m), 900 (m), 780 (m), 728 cm^{-1} (m); ^1H NMR δ 1.0–2.2 (complex m, 10 H) and 12.63 (s, 1 H).

2b: mp 108.0–109.0°; ir (KBr) 1683 (vs), 1440 (s), 1310 (s), 1221 (s), 1170 (m), 1060 (m), 975 (m), 840 (m), 780 (m), 750 cm^{-1} (m); ^1H NMR δ 1.1–2.0 (complex m, 10 H) and 12.42 (s, 1 H).

Norcarane-7-carboxylic Acid (3). To 74 g (0.9 mol) of cyclohexene in the presence of ca. 0.5 g of anhydrous cupric sulfate was very carefully added, at room temperature, a solution of 34 g (0.3 mol) of ethyl diazoacetate which had been diluted with an equal volume of ether. After the addition, the mixture was stirred until the evolution of nitrogen ceased, and then was worked up as usual. Vacuum distillation of the organic layer afforded, together with ethyl maleate, an isomeric mixture of ethyl norcarane-7-carboxylate (exo ester:endo ester 9:1), bp 72–77° (3 mm), which was hydrolyzed with potassium hydroxide in 50% aqueous ethanol. After a usual work-up, the acid fraction was distilled in vacuo to give crude acid, bp 111–113° (3 mm). Recrystallization from petroleum ether gave 5.5 g of pure norcarane-7-*exo*-carboxylic acid (**3a**) in an overall yield of 13%: mp 95.0–96.0°; ir (KBr) 1673 (vs), 1450 (s), 1310 (s), 1233 (s), 1000 (m), 785 (m), 698 cm^{-1} (m); ^1H NMR δ 0.9–2.0 (complex m, 11 H) and 12.38 (s, 1 H). The reduction of 23 g (0.1 mol) of methyl 7-bromonorcarane-7-carboxylate with 35 g (0.12 mol) of tri-*n*-butyltin hydride at 0° gave 13.9 g of an isomeric mixture (endo ester:exo ester 13:1) in 90% yield, bp 93–94° (19 mm). By a similar treatment as above, 7.0 g of norcarane-7-*endo*-carboxylic acid (**3b**) was obtained as a crystalline solid: 51% yield; mp 77.0–78.0°; ir (KBr) 1690 (vs), 1450 (s), 1345 (m), 1205 (vs), 1170 (s), 1140 (m), 980 (m), 940 (m), 870 (m), 780 cm^{-1} (m); ^1H NMR δ 0.9–2.1 (complex m, 11 H) and 12.18 (s, 1 H).

Brominative Decarboxylation of Acids (1, 2, and 3). In a three-necked flask equipped with a thermometer, a dropping funnel, a stirrer bar, and a condenser with a drying tube at the top was placed 5–10 mmol of the silver salt of **1**, **2**, or **3** and 20 ml of carbon tetrachloride. This suspension was maintained at a constant temperature (0 or 77°) and a solution of 1.2 equiv of bromine in 10 ml of carbon tetrachloride was rapidly added with stirring. After being kept at the same temperature for 2 hr, the reaction mixture was brought to room temperature. The silver-containing precipitates were removed by filtration and washed with a small amount of carbon tetrachloride. The filtrate was concentrated by vacuum evaporation below 30°. The residue was carefully distilled under reduced pressure. The isomer composition of the product was determined by GLC prior to distillation and is shown in Table I.[22]

General Procedure for Preparation of *tert*-Butyl Peroxy Esters (7 and 8). A solution of pyridine (15 mmol) and the acid chloride (10 mmol), prepared by conventional methods from thionyl chloride, in 10 ml of *n*-pentane was cooled in an ice–salt bath, and to it was added a solution of 98% *tert*-butyl hydroperoxide (50 mmol) in 10 ml of *n*-pentane. The mixture was stirred for 3 hr at −15 to −20° and for 1 hr at room temperature. The organic layer was washed successively with cold 10% sulfuric acid, cold 10% aqueous sodium carbonate, and water. It was dried over anhydrous sodium sulfate and concentrated in vacuo to a slightly green oil.

The product was purified by chromatography on Kiesel gel G (Merck) to give a clear oil or a solid in 55–61% yields.

7a: mp 40.0–41.0°; ir (CCl_4 solution) 1760 (vs), 1375 (s), 1350 (s), 1050 (s), 1032 cm^{-1} (s); ^1H NMR δ 1.39 (s, 9 H) and 1.2–1.9 (complex m, 10 H).

7b: colorless liquid; ir (film) 1770 (vs), 1365 (s), 1328 (s), 1200 (s), 1150 (vs), 1080 (vs), 1030 cm^{-1} (s); ^1H NMR δ 1.39 (s, 9 H) and 1.2–2.0 (complex m, 10 H).

8a: mp 46.5–47.5°; ir (CCl_4 solution) 1755 (vs), 1370 (s), 1215 (vs), 1190 (s), 1155 (vs), 1052 (m), 1030 cm^{-1} (m); ^1H NMR δ 1.36 (s, 9 H) and 1.3–2.0 (complex m, 10 H).

8b: colorless liquid; ir (film) 1775 (vs), 1365 (s), 1295 (s), 1176 (s), 1145 (vs), 1080 (s), 1025 cm^{-1} (m); ^1H NMR δ 1.36 (s, 9 H) and 1.3–2.0 (complex m, 10 H).

Thermal Decomposition of *tert*-Butyl Peroxy Esters (7 and 8). A solution of 0.5–1.0 mmol of the peroxy ester in a tenfold molar quantity of toluene, cumene, or bromotrichloromethane was placed in a pressure-resistant Pyrex ampoule. It was degassed with pure nitrogen and was heated at 110° for 24 hr. After the reaction was over, the reaction mixture was cooled to 0°, and the ampoule was very carefully opened. The isomer distribution in the product was determined by GLC prior to any treatments and is shown in Table II.[22]

The free acids were isolated by conventional extraction methods. The comparison of the spectral properties and melting points of the isolated acids with those of authentic samples showed the geometry of the starting peroxy esters being retained.

Registry No.—**1a**, 56403-11-3; **1b**, 56377-36-7; **2a**, 18688-20-5; **2b**, 18688-19-2; **3a**, 21448-77-1; **3b**, 21448-76-0; **4c**, 19144-91-3; **4d**, 19144-90-2; **7a**, 56403-13-5; **7b**, 56377-51-6; **8a**, 56377-52-7; **8b**, 56377-53-8.

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(21) Bromochlorocarbene was generated by the treatment of dibromochloromethane with potassium *tert*-butoxide at −20 to −10°.
(22) It was confirmed, by separate experiments, that the isomer ratios given in Tables I and II showed no appreciable change, and no ring-opening products were detected by GLC, after the reaction mixture was kept under the reaction conditions for an additional 4 and 10 hr, respectively.

Substituent Effects on the Thermal Decomposition of *I,I*-Dibenzoyldioxyiodobenzenes in Chloroform. An Observed Linear Free Energy Relationship[1]

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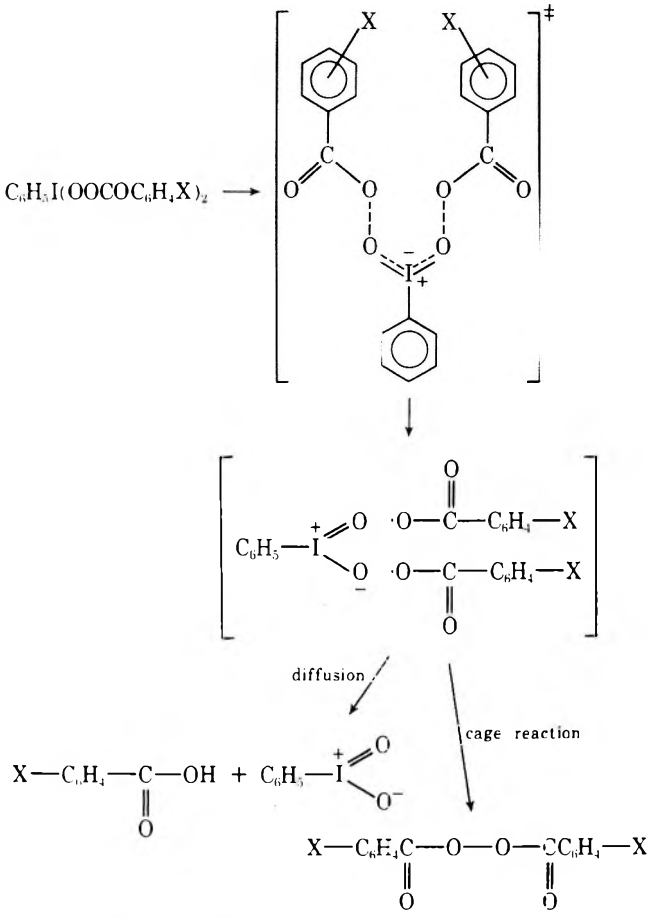
The preparation and characterization of 14 symmetrically substituted *I,I*-dibenzoyldioxyiodobenzenes, Ar-I(OOCOAr-X)$_2$, are reported. A quantitative study of the decomposition for seven of these compounds in chloroform (0.008–0.030 *M*) at 28–38° has been undertaken. Under these conditions the reaction is kinetically of the first order and yields iodoxybenzene (identified as a new polymorphous modification), benzoic acid, dibenzoyl peroxide, and hexachloroethane as the major products. A Hammett plot of the rates of decomposition of meta- and para-substituted compounds vs. σ values gives a ρ of −0.29 (r = 0.93). The effect of substituents on decomposition is discussed in terms of increased or decreased electron densities on the peroxidic oxygens. A unimolecular free-radical mechanism, with a transition state in which some rotational restrictions appear (partial ionic character), is proposed to be the major reaction path. *The explosive properties of compounds under investigation are pointed out.*

The chemistry of compounds ArI(OCOAr)$_2$, usually formed in the reaction of iodobenzene with peroxy acid,[2] has received intensive study in the past and is now rather well understood mainly by the efforts of Leffler and coworkers.[3,4] On the other hand, compounds of the type Ar-I(OOR)$_2$ have been only scarcely investigated. Milas et al. reported the results of a study of the reaction of iodosobenzene with *tert*-butyl hydroperoxide in methylene chloride, and proposed ArI(OOBu-*t*)$_2$ to be an intermediate of short lifetime below −80°.[5]

As a part of our continuing interest in organic polyvalent iodine compounds, we wish to report in the present paper details concerning the preparation and characterization of symmetrically substituted *I,I*-dibenzoyldioxyiodobenzenes together with the results of the thermal decomposition in chloroform.

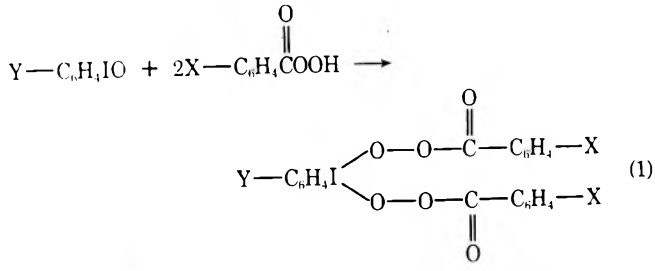
Scheme I



I,I-Dibenzoyldioxyiodobenzenes are the first class of compounds with peroxide functional groups directly bound to iodine. Aromatic peroxides with iodine as a substituent in the ortho position have already been reported to decompose rather quickly owing to the anchimerically assisted cleavage.[6-8]

Results and Discussion

Preparation and Characterization. *I,I*-Dibenzoyldioxyiodobenzenes were prepared from iodosobenzene and substituted peroxybenzoic acids in chloroform (or methylene chloride) at −5°, eq 1, in yields ranging from 60 to



(1)

Y = F, Cl, CH_3; X = F, Cl, Br, NO_2, *t*-Bu

70%. Derivatives of aliphatic peroxy acids could not be isolated; i.e., iodoxybenzene was identified as the major product in the reaction of iodosobenzene with peroxyacetic acid.

I,I-Dibenzoyldioxyiodobenzenes possess three "active" oxygens per molecule as determined by iodometric titration. Iodobenzene and benzoic acid are the end products of this reduction.

The infrared spectra of compounds under investigation show some similarities with those of the corresponding parent peroxybenzoic acid. Carbonyl stretching frequencies

Table I
Rate Constants and Activation Parameters for the Decomposition of *I,I*-Dibenzoyldioxyiodobenzenes, $ArI(OOCOArX)_2$, in Chloroform

Substituent, X	Concn. *M*	Temp, °C	$k \times 10^5$, sec^{-1} [a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
4-*t*-Bu	0.025	28.0	1.94 (±0.06)		
	0.026	38.0	5.15 (±0.04)	17.5	−21.8
4-F	0.025	38.0	3.80 (±0.03)		
4-Cl	0.025	28.0	1.35 (±0.07)		
	0.025	38.0	3.80 (±0.04)	18.6	−19.0
3-Cl	0.022	38.0	3.08 (±0.05)		
4-Br	0.026	38.0	3.96 (±0.06)		
3-NO_2	0.019	38.0	2.49 (±0.09)		
4-NO_2	0.022	38.0	2.70 (±0.08)		

[a] Average of at least three runs with standard deviations rentheses.

Table II
Products of Decomposition of *I,I*-Dibenzoyldioxyiodobenzenes, $ArI(OOCOArX)_2$, in Chloroform

Substituent, X	Concn. *M*	Temp, °C	Products, mol/mol of peroxide [a]		
			$ArIO_2$	X−$ArCO_2H$ (X−ArCOO)$_2$ [b]	
4-Cl	0.010	28.0	0.85	1.60	0.15
	0.030	38.0	0.80	1.70	0.10
4-Br	0.025	38.0	0.83	1.65	0.08

[a] Hexachloroethane was determined qualitatively in all decompositions by mass spectrometry. [b] The correct value for diaroyl peroxide (X = 4-NO_2) in ref 1 is 0.15.

are located a little higher but with the same type of splitting of the carbonyl band (ca. 20 cm^{-1}), indicating a covalent rather than ionic structure.[9] Attempts to obtain some stereochemical data on *I,I*-dibenzoyldioxyiodobenzenes by a dipole moment study met with no success.[10] Nevertheless, it seems reasonable to assume, on the basis of only one signal for *tert*-butyl protons (−60 to 30°) in the 60-MHz ^1H NMR ($CDCl_3$) spectrum of $C_6H_5I(OOCOC_6H_4$-*t*-Bu$)_2$, centered at δ 1.37 (18 H) (aromatic multiplet, 13 H, δ 7.19–8.30), that these compounds appear in solution in a single conformation,[11] most probably a symmetrical (C_{2v}) one, with both functional groups in a mirror position (Scheme I).[12]

Kinetics and Products of Decomposition. The decomposition in chloroform at 28–38° obeys a first-order rate law over a concentration range 0.008–0.030 *M*. Each reaction was followed for at least 2 half-lives of the starting material. The rate constants and activation parameters are listed in Table I.

As can be seen from Table I, electron-repelling substituents increase the rate of decomposition whereas electron-attracting groups retard. A plot of the rates of decomposition against Hammett σ constants gives a reasonable correlation (r = 0.93) with ρ −0.29 (Figure 1). The products under various conditions for two representative compounds are summarized in Table II.

The decomposition products and first-order kinetics are in accord with an unimolecular free-radical decomposition as the predominant reaction path as proposed in Scheme I. The effect of substituents could be explained as being due to an inductive effect removing or adding the excess of electron density on the peroxidic oxygens, stabilizing or destabilizing in this way both peroxidic bonds with respect to homolytic cleavage (dipole–dipole repulsion).[13] The low enthalpy of activation together with a rather large negative

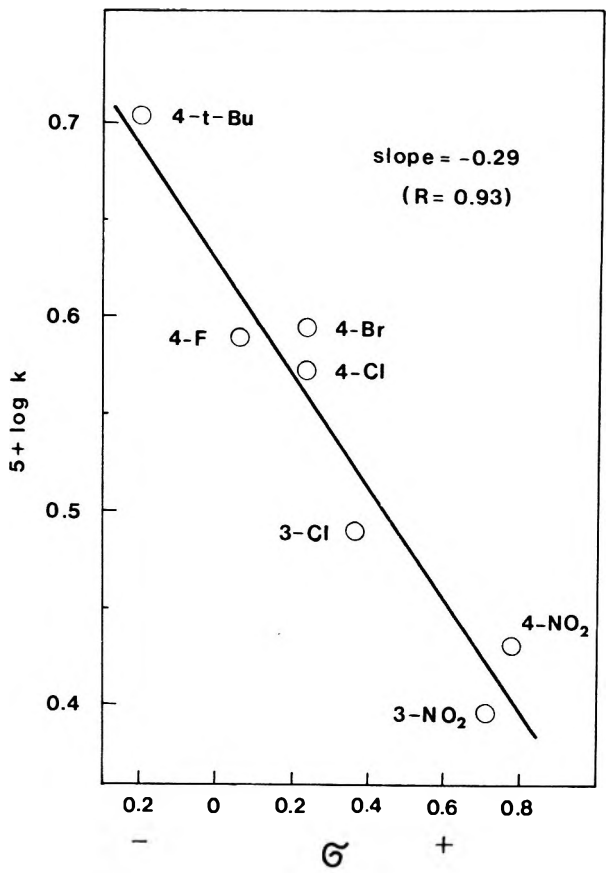
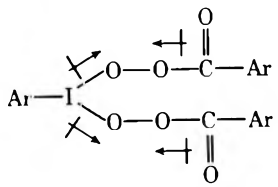


Figure 1. Plot of the logarithms of the rates of decomposition (38°) of *I,I*-dibenzoyldioxyiodobenzenes, $ArI(OOCOArX)_2$, against Hammett σ values of the substituents.



entropy of activation seem to indicate considerable rotational restrictions in, as well as a partially ionic character of, the transition state.[14-16]

Some comments regarding the decomposition products are appropriate. Iodoxybenzene (B) formed in the decomposition had a sharp melting point (223°), i.e., much lower than that of the authentic sample (A), mp 236–237° (lit.[17] 230°), prepared by two independent methods.[17] Infrared spectra of both compounds also differ considerably, especially in the ν C–H, C=C, and I–O regions of the spectrum (Figure 2). The presence of symmetric and asymmetric I–O stretching bands in the ir spectra of both compounds (710–770 cm^{-1}), together with the fact that B can be transformed to A by recrystallization from water, indicate that A and B are polymorphous modifications of the same compound.[18] It is interesting to mention that $4F\text{-}C_6H_4I(O_2COC_6H_4\text{-}4Cl)_2$ decomposes in chloroform to give *p*-fluoroiodoxybenzene (B), mp 214° (authentic sample, mp 248°), with A and B showing the same general features in the infrared spectra.[19] The formation of iodoxybenzene in the decomposition of *I,I*-dibenzoyldioxyiodobenzenes indicates that both reported synthetic methods which are in use for the preparation of iodoxybenzene, i.e., the reaction of iodobenzene with excess of peroxyacetic acid[17] and peroxybenzoic acid,[20] proceed via corresponding *I,I*-diacyl- or *I,I*-dibenzoyldioxyiodobenzenes as intermediates. The mechanism of these reactions was believed previously to involve the nucleophilic attack of the iodine lone electron pair in iodobenzene and iodosobenzene (which is formed first) at the electrophilic oxygen of the peroxy acid.[21] Benzoyloxy radicals formed initially in the decomposition appear to have sufficient lifetime under conditions investigated to be rapidly trapped by the abstraction of hydrogen from the solvent.[22-26] Absence of any products which would indicate the abstraction of chlorine is rather surprising, but is in accord with the findings reported previously for the decomposition of dibenzoyl peroxides in the same solvent.[27]

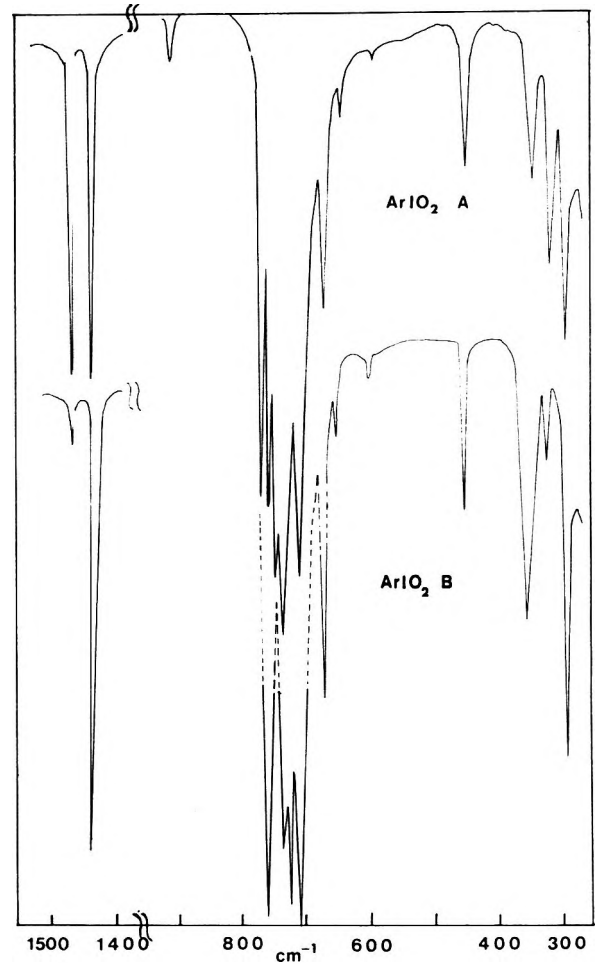


Figure 2. Segments of the infrared spectra of iodoxybenzene A and B.

Relatively small amounts of dibenzoyl peroxides formed in the decomposition, most probably as a result of geminate recombination, could be explained with a rather great initial distance of benzoyloxy radicals formed as well as with a low viscosity of the solvent used.[28,29]

The study of decomposition in other conventional solvents requires higher initial temperatures owing to a low solubility of peroxides investigated. For example, decomposition in CCl_4 (79.9°) does not follow the first-order law well; small amounts of benzoic acids are formed in this solvent, indicating induced (or free-radical and polar) decomposition. These reactions are not well understood at present and additional work is being done to clarify them.

Experimental Section

Chloroform was shaken with sulfuric acid and washed with sodium hydrogen carbonate solution and water. After successive 24-hr periods of drying over anhydrous $MgSO_4$ it was fractionally distilled and kept over 3A molecular sieves.

Substituted peroxybenzoic acids were prepared by direct oxidation of the corresponding benzoic acids by 95% hydrogen peroxide in methanesulfonic acid,[30] and were found to be over 99% pure by iodometry (recrystallization from chloroform–hexane).

Iodosobenzene was made by hydrolysis of the iodobenzene dichloride with 5% sodium hydroxide solution.[31] Iodometric titration showed this product to be over 99.5% pure. Owing to its tendency to disproportionate the iodosobenzene was prepared freshly before use.

Iodoxybenzene (A) was prepared by two independent methods, i.e., direct oxidation of iodobenzene by 40% peroxyacetic acid[17b] and by disproportionation of iodosobenzene.[17a] The crude product was recrystallized from water, giving white needles, mp 236–237° (100% pure by iodometry).

Iodoxybenzene (B) obtained in the decomposition had mp 223°.

Anal. Calcd for $C_6H_5IO_2$: C, 30.50; H, 2.12; 0, 13.55. Found: C, 30.48; H, 2.13; O, 13.55.

***I,I*-Dibenzoylidoxyiodobenzenes.** In a typical preparation, iodosobenzene (20 mmol) was suspended under magnetic stirring in 60 ml of chloroform at −5°. Peroxybenzoic acid (45 mmol) was added slowly within a few minutes. Stirring was continued for about 15 min. The reaction mixture was then filtered and the solvent removed on a rotary evaporator below room temperature. The crude product was washed several times with small portions of diethyl ether and dried in vacuo over P_2O_5. All peroxides were found to be over 97% pure by iodometry. See Table III.

Table III
Melting Points and Ir (NMR) Data for *I,I*-Dibenzoyldioxyiodobenzenes

	$YC_6H_4I(OOCOC_6H_4X)_2$			
	Y	X	Mp, °C[a]	Ir[b] (NMR)[c]
I[d]	H	3-Cl	96–98 dec	1744, 1725
II[d]	H	4-Cl	89–90 dec	1740, 1723
III[d]	H	3-NO_2		
IV[d]	H	4-NO_2	114–116 dec	1749, 1729
V[d]	H	3-Br	95–96 dec	1738, 1720
VI[d]	H	4-Br	93–95 dec	1740, 1722
VII[d]	H	4-F	77–78 dec	1745, 1720
VIII[d]	H	4-*t*-Bu	99–101 dec	($CDCl_3$) δ 1.37 (s, 18 H), 7.19–8.30 (m, 13 H)
IX[d]	2-CH_3	3-Cl	61–63 dec	
X[d]	3-CH_3	3-Cl	67–69 dec	
XI[d]	4-CH_3	3-Cl	74–76 dec	
XII[d]	4-F	3-NO_2	93–94 dec	
XIII[d]	4-Cl	3-NO_2	90–91 dec	
XIV[d]	4-F	4-*t*-Bu	88–89 dec	($CDCl_3$) δ 1.36 (s, 18 H), 7.07–8.27 (m, 12 H)

[a] Melting points were taken on a Kofler micro hot stage and are not corrected. [b] Infrared spectra were recorded on Perkin-Elmer Models 521 and 180 spectrometers (Nujol). [c] The nuclear magnetic resonance spectra were obtained with a Varian Model A-60 and Jeol JNM-C-60HL spectrometers ($CDCl_3$, Me_4Si). [d] Satisfactory analytical data for C, H, and "active" O (iodometric) were provided for these compounds. Ed.

Caution. Although this procedure was repeated several times without incident, the use of safety shielding is strongly recommended. Particular caution should be observed when solvent is removed on a rotary evaporator and in handling pure, dry materials. For example, a small sample of I detonated when it was touched by a metal spatula, although previous samples had been handled in the same way without incident.

Kinetic experiments were carried out in sealed, degassed tubes, and the remaining peroxide was determined (after removal of the unsoluble iodoxybenzene) by an iodometric titration already described.[32] First-order rate constants and correlation coefficients were obtained from a linear least-squares program. Activation parameters were calculated by the usual methods.

Product Analysis. The products were determined by a combination of techniques. Iodoxybenzene was removed by filtration. Benzoic acids were extracted with bicarbonate or determined by infrared in the decomposition mixture prior to any work-up procedure. Diaroyl peroxides were determined by infrared[33] and by thin layer chromatography.[34] The quantities reported are probably good within 7% of their reported values. The presence of hexachloroethane in the reaction mixture (prior to any work-up procedure) was confirmed by mass spectrometry.

In a typical run, approximately 0.025 *M* solution was decomposed, and the solution was subjected to the analysis described. The absence of other volatile products was confirmed by gas–liquid chromatography.

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Registry No.—I, 30242-75-2; II, 56391-39-0; III, 56391-40-3; IV, 30030-30-9; V, 56391-41-4; VI, 56391-42-5; VII, 56391-43-6; VIII, 56391-44-7; IX, 56391-45-8; X, 56391-46-9; XI, 56391-47-0; XII, 56391-48-1; XIII, 56391-49-2; XIV, 56391-50-5; iodosobenzene, 536-80-1; iodoxybenzene, 696-33-3; 3-chloroperoxybenzoic acid, 937-14-4; 4-chloroperoxybenzoic acid, 937-22-4; 3-nitroperoxybenzoic acid, 2453-41-0; 4-nitroperoxybenzoic acid, 943-39-5; 3-bromoperoxybenzoic acid, 5106-10-5; 4-bromoperoxybenzoic acid, 13020-00-3; 4-fluoroperoxybenzoic acid, 1514-03-0; 4-*tert*-butylperoxybenzoic acid, 1711-40-6.

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(11) The NMR argument holds for the case that the barriers to rotation about I–O bonds are higher than ca. 10–12 kcal/mol; otherwise an "apparent" single conformation would be seen even at −60° in the 60-MHz NMR spectrum.
(12) Even if dipole moments had been measured, the interpretation would be difficult. On the other hand, the principle of estimating conformation part by part, according to simpler model compounds, might be quite promising. The dihedral angle ∠O═C–O–O is almost certainly ~0–30°, according to esters and peroxy esters [F. D. Verderame and J. G. Miller, *J. Phys. Chem.*, **66**, 2185 (1962)]; the dihedral angle ∠C–O–O–I is very probably ~100–120°, according to peroxides; and ∠O–O–I–C is perhaps ~180°, according to *I,I*-diacyloxyiodobenzenes [O. Exner and B. Plesnicar, *J. Org. Chem.*, **39**, 2812 (1974)].
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Successful Direct Fluorination of Oxygen-Containing Hydrocarbons

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New methods which have been recently developed for direct fluorination have enabled practical syntheses in high yields of oxygen-containing perfluorocarbons from their hydrocarbon analogs. These syntheses have been successful on several important classes of oxygen-containing hydrocarbons and most functional groups survive these gentle fluorinations. The syntheses of perfluoro-1,2-dimethoxyethane, perfluorobis(2-methoxyethyl) ether, perfluoro-1,2-diethoxyethane, perfluoro-1,4-dioxane, perfluoroethyl acetate, perfluorodimethylmalonyl difluoride, and perfluoropivaloyl fluoride from their hydrocarbon analogs are discussed. The monohydro species α-hydrotetrafluoroethyl trifluoroacetate, monohydroctafluoropivaloyl fluoride, and 1-hydrononafluoro-2,5-dioxahexane have also been prepared and characterized.

A substantial body of oxygen-containing and functional perfluoroorganic compounds have been prepared and characterized over the last 30 years and their physical properties investigated. Some have been prepared by fluorination using fluorinating agents such as cobalt trifluoride, but the majority have been prepared by the industrially important hydrogen fluoride electrochemical cell techniques pioneered by Simons.[1b] Relatively few successful syntheses of such species have been reported using elemental fluorine as the fluorinating agent. For example: "Fluorination by fluorine is unlikely to be used in normal organic syntheses".[2] A new technique for direct fluorination developed by Lagow and Margrave[3] has led to practical methods[4-7] for the synthesis of oxygen-containing perfluorocarbons from their hydrocarbon analogs. These new direct fluorination techniques for preparing functional and oxygen-containing fluorocarbons promise to develop into an important synthetic method yielding many unreported fluorocarbon compounds and better syntheses for many known compounds. In addition, direct fluorination is particularly valuable for preparing fluorocarbon compounds which are impossible or difficult to obtain by methods such as the cobalt trifluoride or electrochemical methods. The use of direct fluorination to prepare fluorocarbon species such as esters and some ethers whose hydrocarbon analogs are spontaneously decomposed in the hydrogen fluoride solvent used in the electrochemical cell establishes that there are many unique applications for such synthetic techniques.

Several new fluorocarbon compounds which are perfluoro analogs of structurally basic hydrocarbon species are reported in this paper (see Figure 1). Every synthesis reported in this paper represents the highest yield of perfluoro analog yet obtained with any method involving fluorination of the respective starting materials. The yields obtained for the present syntheses of perfluoro-1,4-dioxane, perfluoro-1,2-dimethoxyethane, perfluorobis(2-methoxyethyl) ether, perfluoro-1,2-diethoxyethane, perfluorodimethylmalonyl difluoride, and perfluoropivaloyl fluoride are the highest obtained by any synthetic method.

Experimental Section

Mass spectra were measured on a Hitachi RMU6B mass spectrometer at 70 eV. NMR spectra were taken on a Perkin-Elmer R20-B spectrometer at 70 MHz for protons and 56.466 MHz for fluorine. Gas chromatography separations were made using either a Varian Moduline 2700 or a Bendix Model 2300 gas chromatograph. Either a 10% SE-30 or Chromosorb P on a fluorosilicone QF1-0065 10% on Chromosorb P column (10 m × 0.375 in.) was used; however, the fluorosilicone column generally provided better separation.

Molecular weight determinations were performed on 20–50-mg samples sealed in preweighed capillaries and broken into a 66-cm^3 bulb attached to a manometer calibrated for volume change with pressure. Precision was about 0.5%.

Carbon, hydrogen, and fluorine analyses were done by Schwarzkopf Microanalytical Laboratory on 4–10-mg samples sealed under nitrogen into preweighed capillaries. Precision using this technique usually was 0.2–0.3% for fluorine analyses.

The reactor system used is illustrated in Figure 2, except that for the fluorination of pivaloyl fluoride and dimethylmalonyl difluoride a six-zone cryogenic reactor was used. The dimensions of the reactor have been previously described.[4] Physical properties of reactants are important in the cryogenic fluorination reactor. An ideal compound should have a reasonably high vapor pressure in the solid state. The combination of volatility and exposure in the solid phase, except during transfer, permits the renewal of the reactant surface as the more volatile products are produced and the dissipation of heat into the lattice and ultimately to the supporting copper turnings, walls, and cooling system in the reactor. A large initial surface area formed by sublimation of the reactant into the reactor permits fluorine at very low concentrations (less than 2%) to react with a large percentage of the hydrocarbon molecules.

Initial fluorination of a hydrocarbon decreases the volatility of the species. At about 50% fluorination, a maximum boiling point or minimum vapor pressure occurs. Under such conditions, hydrogen bonding and other associative interactions are at a maximum. After such a minimum vapor pressure of the reactant is obtained, each successive substitution of a fluorine for a hydrogen atom increases the vapor pressure. If at this point a temperature gradient is produced in the reactor, the more highly fluorinated products will be volatilized, exposing less highly fluorinated, less volatile species to interaction with fluorine. By repeating the above procedure, essentially complete fluorination of the hydrocarbon can occur under conditions which maintain a slow controllable rate of reaction. In the initial stages of the reaction, this rate of reaction is controlled by a high dilution of the fluorine and by cryogenic temperatures which reduce the reaction rate. As the reaction proceeds and more protons have been replaced by fluorine, the concentration of fluorine is increased and the temperature gradient applied to maintain a more constant rate of reaction. The amount of fluorine used is carefully controlled and is usually between 30 and 150 mmol/day. Should combustion occur, all the fluorine in the reactor is consumed and the reaction terminates until more fluorine is delivered. Therefore, the only adverse effect is an unsuccessful reaction. This is an important safety factor.

Perfluoro-1,2-dimethoxyethane. 1,2-Dimethoxyethane (4.015

* Alfred P. Sloan Fellow.

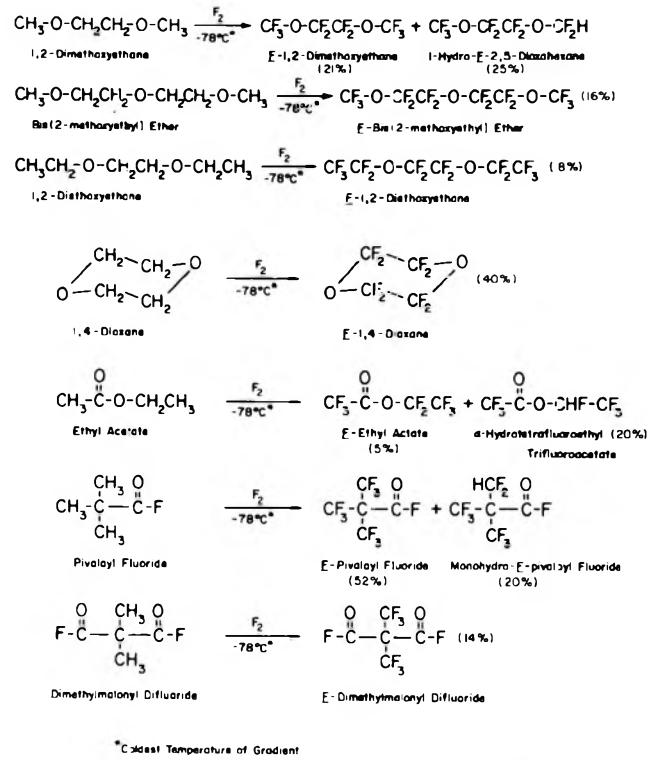


Figure 1. Direct fluorination of oxygen-containing hydrocarbons.

g, 0.045 mol) was evaporated employing a flow of 50–100 cm^3 of helium into a gradient reactor containing four distinct zones which were maintained at −78°, a temperature below the freezing point of the ether (−58°). An initial flow of 0.5 cm^3/min fluorine and 20 cm^3/min helium was started and after 12 hr the fluorine was increased to 1.0 cm^3/min. After an additional 12 hr, zone 1 was allowed to run out of Dry Ice. Twelve hours after zone 1 was clear of Dry Ice the fluorine was increased to 1.5 cm^3/min while still maintaining helium flow at 20 cm^3/min. The fluorine flow was maintained at 1.5 cm^3/min. On alternate days the helium was reduced to 10 cm^3/min followed by allowing one additional zone to clear of Dry Ice. Subsequent reductions to 5, then to 0 cm^3/min helium flow were followed each time by warming of one additional zone.[8] Finally, as the reactor warmed under a flow of pure fluorine, the fluorinated ether was passed through a metal trap filled with sodium fluoride pellets and into a glass trap maintained at −78°. The raw fluorocarbon ethers collected represented a mass which corresponds to between 50 and 100% of the expected yield based on moles of the parent ether. This mixture contained several hydrofluoro ethers and other hydrolytically unstable and corrosive products along with a smaller amount of perfluorinated fragments. In earlier work with the four-zone reactor, the yield of the hydrofluoro ethers in most cases exceeded the yield of perfluoro ethers owing to incomplete reaction. These products were removed by aqueous alkali hydrolysis and the hydrolytically stable ethers fractionated. The bulk of the desired products was collected in the −95 and −130° traps (combined weight 2.48 g, 20.6%). Final purification was accomplished using gas–liquid chromatography using a 0.375-in. fluorosilicone (QF-1-0065, 10% on Chromosorb P, 60/30 mesh) column.

Perfluoro-1,2-dimethoxyethane is a gas at room temperature (bp 16.7°). The molecular weight determined by the ideal gas method was 269 (cf. 270 for $C_4F_{10}O_2$). The ^{19}F NMR consisted of a triplet at +59.54 ppm and a quartet at +94.19 ppm relative to $CFCl_3$[9] with coupling constant 9.2 Hz and relative intensities 3:2. The infrared spectrum exhibited bands at 1410 (w), 1295 (s), 1250 (s), 1200 (w), 1170 (sh), 1155 (s), 1105 (w), 923 (w), 887 (m), 865 (w), 819 (w), and 690 cm^{-1} (w). The mass spectrum contained no parent peak but showed strong peaks at *m/e* 135 corresponding to the symmetrical cleavage of the molecule (CF_3–O–CF_2). Other strong peaks were *m/e* 119, C_2F_5; 100, C_2F_4; 69, CF_3; 50, CF_2 and 47, CFO. The yield was 21%.

Anal. Calcd for $C_4F_{10}O_2$: C, 17.79; F, 70.36. Found: C, 17.41; F, 70.08.

1-Hydrononafluoro-2,5-dioxahexane. If the products of the previously described reaction were not hydrolyzed, a second major product may be isolated which in some cases exceeds the amount of perfluoro-1,2-dimethoxyethane. This ether was a liquid with a disagreeable odor and may be quite toxic. Its molecular weight was determined to be 251 (cf. 252 for $C_4HF_9O_2$). Its ^{19}F NMR spectrum exhibited a triplet at +59.22 ppm and a quartet at +93.63 ppm with a coupling constant of 9.4 Hz and relative intensity of 2:2 respectively: a doublet centered at +88.36 (J = 70.0 Hz) split into triplets (J = 4.4 Hz) and a triplet at +92.47 ppm (J = 4.6 Hz) relative to $CFCl_3$ with relative integrals of 2:2. The proton NMR consisted of a triplet at −6.26 ppm relative to external Me_4Si, with coupling constant equal to 68.6 Hz in good agreement with the doublet splitting in the ^{19}F NMR. If the proton was irradiated the ^{19}F doublet decayed into a singlet. This information is consistent with a structure containing a proton in the α position (Chart I).

Chart I
1-Hydrononafluoro-2,5-dioxahexane

$$\underset{+59.22}{CF_3}\text{—}O\text{—}\underset{+93.63}{CF_2}\text{—}\underset{+92.47}{CF_2}\text{—}O\text{—}\underset{+88.36}{CF_2}\text{—}\underset{-6.26^b}{H}$$

(9.2) (<1) (4.5) (6.93)

The mass spectrum supports this conclusion. The two peaks corresponding to "symmetrical" cleavage at *m/e* 135, C_2F_5O, and *m/e* 117, C_2HF_4O, were both strong with relative intensities of 1:1.5, respectively, as are the very strong peaks at *m/e* 69, CF_3, and *m/e* 51, CHF_2, of relative intensities 1:1.5. Other, less intense peaks support this conclusion.

The infrared spectrum contains a weak proton absorption at 3028 cm^{-1} in addition to carbon–fluorine and carbon–oxygen bands at 1400 (w, br), 1370 (w), 1295 (s), 1250 (s), 1192 (m), 1179 (sh), 1159 (s), 1125 (s), 1040 (m), 910 (m), 853 (w), 818 (m), 700 cm^{-1} (w). The yield was 0–25%.

Perfluorobis(2-methoxyethyl) Ether. Bis(2-methoxyethyl) ether (1.79 g, 0.0134 mol) was evaporated at 50° into the four-zone cryogenic reactor (zone 1, −40°; zones 2–4 at −78°) using a 80–100 cm^3/min flow of helium gas. After 6–8 hr the helium flow was reduced to 20 cm^3/min and a 0.5 cm^3/min flow of fluorine was started. A similar procedure to that used for 1,2-dimethoxyethane was used to complete the reaction. The raw products were fractionated through −63, −78, −95, and −196° traps. Perfluorobis(2-methoxyethyl) ether was collected from the −78 and −95° traps (yield 0.83 g, 16.1%). Perfluorobis(2-methoxyethyl) ether is a volatile liquid, bp 60–63°. Its molecular weight was determined to be 385 (cf. 386 for $C_6F_{14}O_3$). The ^{19}F NMR exhibited a triplet at +59.30 ppm and a quartet at +92.84 ppm (J = 9.4 Hz) and a singlet at +91.61 ppm relative to $CFCl_3$. The relative integrals of the absorptions were 3:2:2, respectively.

The infrared spectrum contained bands at 1385 (w), 1295 (s), 1250 (s), 1220 (sh, w), 1200 (w), 1165 (s), 1145 (s), 920 (sh), 910 (m), 770 (m), 697 (w), and 681 cm^{-1} (sh).

The mass spectrum contained strong peaks at *m/e* 185, C_3F_7O; 135, C_2F_5O; 119, C_2F_5; 100, C_2F_4; 69, CF_3; and 50, CF_2. The yield was 16%.

Anal. Calcd for $C_6F_{14}O_3$: C, 18.67; F, 68.90. Found: C, 18.64; F, 69.94.

Perfluoro-1,2-diethoxyethane. A 1.81-g (0.0153 mol) sample of 1,2-diethoxyethane was injected into the evaporator of a cryogenic reactor.[4] The sample was evaporated into the reactor (Z_1 = −30, Z_2 = −50, Z_4 = −78°) using a 175 cm^3/min flow of helium. After 17 hr, zones 1–4 were cooled to −78°, the helium flow was reduced to 30 cm^3/min, and a flow of 0.5 cm^3/min of fluorine was started. After 12 hr, the fluorine flow was increased to 0.75 cm^3/min and zone 1 was allowed to warm to equilibrium (−40°). After 8 hr, the fluorine flow was increased to 1.0 cm^3/min and the helium flow reduced to 20 cm^3/min. After 22 hr the fluorine flow was increased to 1.5 cm^3/min and zone 2 allowed to warm (Z_1 = −30, Z_2 = −50, Z_4 = 78°). After 30 hr, the fluorine flow was increased to 2.0 cm^3/min. After 24 hr the helium flow was reduced to 10 cm^3/min and zone 3 was allowed to warm. After 24 more hr, the helium flow was shut off and zone 4 was allowed to warm from −80 to 25° at a rate of 20°/day. The fluorine flow was terminated and the product which had collected in the −196° collection trap was hydrolyzed with 25 ml of 2.0 M KOH and fractionated on a vacuum line. The product which collected in the −95 and 78° traps was purified by gas chromatography (13% fluorosilicone QF-1-0065 on Chromosorb P).

Perfluoro-1,2-diethoxyethane is a clear, colorless, water-stable liquid (bp ~62°). The molecular weight determined by the ideal gas method was 370 (cf. 371 for $C_6F_{14}O_2$). The ^{19}F NMR consisted

of a closely spaced quartet (J = = 1.6 Hz) at +92.05 ppm and a pentet (J = 1.6 Hz) at +91.0 ppm of intensity 4:3, respectively. The infrared spectrum exhibited bands at 1245 (vs), 1220 (sh), 1155 (s), 1140 (s), 1102 (m), 837 (w), 788 (w), 733 (w), 703 (m), 690 (w), 648 (w), 550 (sh), 525 cm^{-1} (w). The mass spectrum contained strong peaks at m/e 185, C_3F_7O; 119, C_2F_5; 100, C_2F_4; 97, C_2F_3O; 69, CF_3; and 50, CF_2. The yield was 18%.

Anal. Calcd for $C_6F_{14}O_2$: C, 19.48; F, 71.88. Found: C, 19.53; F, 71.52.

Perfluoro-1,4-dioxane. In a typical experiment for the preparation of perfluoro-1,4-dioxane, approximately 3 ml (3.324 g, 0.0347 mol) of 1,4-dioxane was syringed into the evaporator (50°) of the fluorination reactor.[4] The design of the reactor has been previously reported[4] and is used as described. A flow of 160 cm^3/min of helium was used to evaporate the material into the gradient reactor. Zone 4 of the reactor was maintained at −78° and zone 1 at approximately 0 to −5°. After about 20 hr all four reactor zones were filled with Dry Ice. The flow of helium was reduced to 20 cm^3/min and a fluorine flow of 0.5 cm^3/min was initiated. After 12 hr, the fluorine flow was increased to 1.0 cm^3/min. Twelve hours later zone 1 started to warm. After equilibrium temperature was reached in zone 1 (~−40°) the fluorine flow was raised to 1.5 cm^3/min. Twelve hours later, zone 2 was allowed to warm (Z_1 = −20, Z_2 = −40° at equilibrium). When the equilibrium gradient temperatures stabilized (~12 hr), the helium flow was reduced to 12.5 cm^3/min and 12 hr later reduced to 7.5 cm^3/min. Twenty-four hours later the helium flow was reduced to 2.5 cm^3/min and zone 3 was allowed to warm. At equilibrium (Z_3 = −40, Z_2, −20, Z_1, −5°) the helium flow was stopped. A flow of 1.5 cm^3/min of fluorine was continued for 24 hr, then zones 1 and 2 were filled with ice and water. After 12 hr, zone 4 was allowed to warm and the glass collection trap initially maintained at −78° was cooled to −196° and a flow of 3.0 cm^3/min of helium was started. After 12 hr, the reactor was at ambient temperature and 6.9 g of volatiles had collected in the collection trap. The volatiles were condensed into a 500-ml bulb containing approximately 25 ml of frozen (−196°) 2.0 M KOH and sealed. The contents were allowed to warm over 1 hr to −78° and then to ambient overnight. The aqueous contents were frozen at −15° and the liquid and gas removed and fractionated. GLC assay of the contents of the −95 and −131° traps yielded 3.37 g (38.5%) of perfluoro-1,4-dioxane and 0.4 g (4%) of perfluoro-1,2-dimethoxyethane. The −196° trap contained 4.23 g (48%) of essentially pure perfluorodimethyl ether.

Perfluoro-1,4-dioxane is a gas at room temperature (bp 15.9°). The molecular weight determined by the ideal gas method was 232.7 (cf. 232.0 for $C_4F_8O_2$). The ^{19}F NMR consisted of a singlet at φ +90.78 ppm (relative to $CFCl_3$, external). The infrared spectrum exhibits bands at 1435 (w), 1369 (w), 1311 (sh), 1303 (s), 1232 (vs), 1163 (sh), 1149 (s), 1113 (s), 890 (m), 665 cm^{-1} (m). The mass spectrum shows no parent peak but shows a peak at m/e 213 corresponding to the molecular ion minus a fluorine $C_4F_7O_2$. Other strong peaks are m/e 119, C_2F_5; 100, C_2F_4; 69, CF_3; 50, CF_2; and 47, CFO.

Anal. Calcd for $C_4F_8O_2$: C, 20.706; F, 65.503. Found: C, 20.63; F, 65.67.

Perfluoro(ethyl acetate). In the preparation of perfluoro(ethyl acetate), ethyl acetate (1.74 g, 0.0198 mol) was syringed into the evaporator of the four-zone gradient reactor system. A flow of 150 cm^3/min helium evaporated the ethyl acetate into the gradient reactor which was maintained at −100°. After 6 hr, a flow of 0.5 cm^3/min of fluorine was initiated and the helium flow was reduced to 20 cm^3/min. After 16 hr, the fluorine flow was increased to 1.0 cm^3/min. After 8 hr, the fluorine was increased to 1.5 cm^3/min and the helium flow reduced to 10 cm^3/min while zone 1 was warmed to equilibrium (−70°). After 24 hr, the helium flow was reduced to 5 cm^3/min and zone 2 was warmed to equilibrium gradient (Z_1, −40, Z_2, −70°). After 12 hr, the helium flow was stopped. Twelve hours later, zone 3 was warmed to equilibrium gradient (Z_1, −30, Z_2, −50, Z_3, −70, Z_4, −100°). Twelve hours later the fluorine flow was increased to 2.0 cm^3/min. After 24 hr, zone 4 was warmed to −80° (Z_1, 10, Z_2, 0, Z_3 −45, Z_4, −80°). After an additional 24 hr, Z_4 was warmed to −45° and over the next 24 hr to ambient temperature (24°). The system was purged with helium and the product which had collected in the −196° trap was vacuum line fractionated through −63, −84, −95, −104, and −196° slush-cooled traps. Gas chromatographic separations (fluorosilicone QF1-0065, 13% in Chromosorb P) of the products collected in the −63 through −104° traps yielded the following products: $CF_3CO_2C_2F_5$, 0.23 g (5%); $CF_3CO_2CHFCF_3$, 0.85 g (20%); $CF_3CO_2CF_2CF_2H$, 0.05 g (1.2%); FCO_2CHFCF_3, 0.5 g (1.4%); the −196° trap also contained

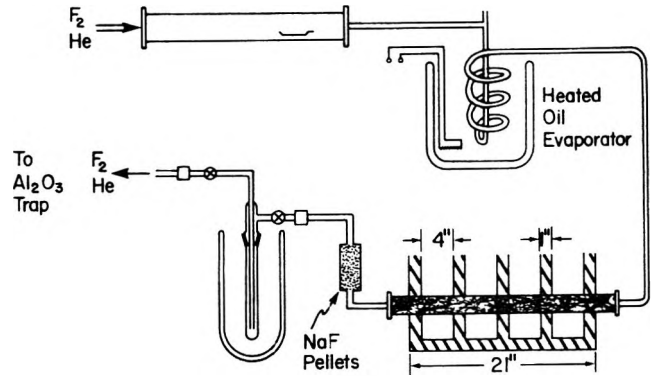


Figure 2. Multizone cryogenic reactor. Volatile liquids are vaporized into the first zone of the reactor from a nickel boat. Less volatile liquids are injected into the heated oil evaporator and vaporized into the reactor. After the reaction is complete, hydrogen fluoride is removed from products using a sodium fluoride pellet trap and products are collected in the liquid nitrogen trap. The excess fluorine is treated with 8–14 mesh Al_2O_3 to produce AlF_3 and release molecular oxygen.

2 g of a mixture of about equal parts CF_3CFO and CHF_2CFO.

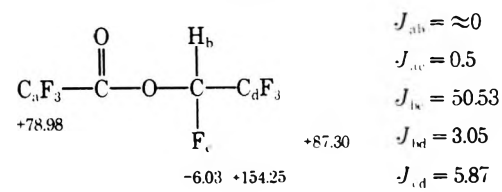
Anal. Calcd for $C_4F_8O_2$: C, 20.706; F, 65.503. Found: C, 20.65; F, 65.48.

Perfluoro(ethyl acetate) is a moisture-sensitive gas (bp 21.4°) which was easily dissociated to 2 mol of trifluoroacetyl fluoride. The infrared spectrum of perfluoro(ethyl acetate) exhibits bands of 1848 (s) (νC=O), 1332 (m), 1245 (vs), 1213 (s), 1200 (s), 1173 (ms), 1109 (vs), 1089 (s), 855 (w), 832 (m), 677 (m), 618 cm^{-1} (sh). The ^{19}F NMR as a neat liquid relative to external $CFCl_3$ in carbon tetrachloride consisted of a sharp triplet (J = 0.4 Hz) at +79.78 ppm, a quartet (J = 2.4 Hz) at +95.45 ppm split into quartets (J = 0.4 Hz) end a triplet at +90.79 ppm (J = 2.4 Hz). The relative integrals were 3:2:3, respectively. The data are rationalized in Chart II, and compare well with those published by Shreeve and cowork-

Chart II

ers.[10] The major product isolated from the reaction of ethyl acetate and elemental fluorine was the trifluoroacetic acid ester of the unstable alcohol α-hydrotetrafluoroethyl alcohol. This fluoro alcohol ester is a moisture-sensitive liquid (bp 31.7°) which can be dissociated by a Lewis base into an equimolar mixture of trifluoroacetyl fluoride and trifluoroacetaldehyde. The product was identified by a molecular weight determination [214.2 (cf. 214 for $C_4F_7HO_2$)], infrared, and ^{19}F and ^1H nuclear magnetic resonance. The infrared spectrum exhibits bands at 2995 (w), 1830 (s) (νC=O), 1420 (w), 1370 (w), 1331 (w),) 00 (s), 1248 (s), 1218 (vs), 1198 (vs), 1140 (s), 1105 (vs), 1062 (m), 920 (m), 733 (m), 698 (m), 628 (w), 580 (w), 550 cm^{-1} (w). The ^{19}F and ^1H nuclear magnetic resonance spectrum is summarized in Chart III. A major factor affecting yields in this re-

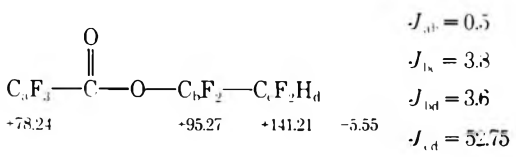
Chart III



action is presumed to be the rearrangement of perfluoro(ethyl acetate) to 2 mol of trifluoroacetyl fluoride catalyzed by the hydrogen fluoride by-product and perhaps by the fluoride ion from the sodium fluoride pellets used to absorb the hydrogen fluoride liberated in the reaction. In fact, no perfluoro(ethyl acetate) was obtained from the reaction unless the sodium fluoride charged hydrogen fluoride trap was cooled to at least −10°.

The β-hydrotetrafluoroethyl trifluoroacetate was characterized by an ideal gas method molecular weight determination (214.9, cf. 214.1) and its ^{19}F and ^{1}H NMR which is summarized in Chart IV.

Chart IV



The infrared spectrum contained bands at 3030 (w), 2995 (w), 1850 (m), 1833 (m), 1340 (w), 1302 (m), 1275 (w), 1250 (vs), 1206 (vs), 1150 (vs), 1132 (sh), 1101 (vs), 885 (w), 845 (w), 735 cm^{-1} (w).

The most important by-products, CF_3CFO and CHF_2CFO, are often obtained in yields as high as 40%; CF_4, OCF_2, and possibly $FCO_2C_2F_5$ are also produced in the reaction.

Perfluorodimethylmalonyl Difluoride. A 2.54-g (18.7 mmol) sample of dimethylmalonyl difluoride (mp 2°) was injected into the evaporator of the six-zone fluorination reactor. The first zone of the reactor was maintained at −8° and the dimethylmalonyl difluoride was evaporated at 20° into the first zone of the cryogenic reactor using a helium flow of 150 cm^3/min. After 24 hr the reactor was cooled to −78°, and a 0.5 cm^3/min flow of fluorine and a 20 cm^3/min flow of helium was initiated. This flow was maintained at this level for 3.5 days (95% total F_2 calculated for the reaction) at which time it was raised to 1.0 cm^3/min. On the first and second days the first and second zones were allowed to warm to equilibrium and on day 2.5 the helium was reduced to 10 cm^3/min. At day 4.0 the third zone was allowed to warm and the helium flow was reduced to 5 cm^3/min. On day 4.5 the helium was shut off. On day 5.5 the fluorine was increased to 1.5 cm^3/min and zone 4 was allowed to warm followed by zone 5 on day 6.5. On day 7.5 the temperature of zone 6 was raised to −50° by a temperature controller and zone 1 was heated to 20° by an immersion heater. On day 8.5 zone 6 was increased to 0° and one day later to 25°. The reactor was purged with helium for several hours, the glass trap was removed, and the contents were fractionated through −45, −78, −104, −130, and −196° traps. The major products, perfluorodimethylmalonyl difluoride (0.25 g, 5.5%) and difluoro-2-methylpropanoyl fluoride (0.51 g, 14%), and octafluoropropane were isolated from the −78 and 104° traps, respectively. The above materials were purified on a 0.375 in. × 10 m GLC column packed with fluorosilicone QF1-0065 (10% on 60–80 mesh Chromosorb P).

Perfluorodimethylmalonyl difluoride is a very volatile liquid above 11° (mp 10.5–11°, sealed tube). The molecular weight determined by the ideal gas method is 243.3 (cf. 244, $C_5F_8O_2$). The ^{19}F NMR consists of a heptet (J = 9.7 Hz) at ϕ −3.97 ppm and a triplet at ϕ +68.2 ppm with relative intensities 1:3. The mass spectrum exhibited a parent ion at m/e 244, a P − F at 225, a P − COF_2 at 178, a P − COF_3 at 159; 137, $C_4F_3O_2$; 69, CF_3; 47, CFO; the m/e 178, 69, and 47 peaks are the most intense.

Anal. Calcd: C, 24.25; F, 62.02. Found: C, 24.609; F, 62.279.

Perfluoropivaloyl Fluoride. For the preparation of perfluoropivaloyl fluoride, a 2-ml sample (1.961 g, 0.0188 mol) was injected into the evaporator of the fluorination reactor (a six-zone modification).[4] The reactor was maintained at −32° and the pivaloyl fluoride was evaporated at 25° into the first zone of the reactor using a helium flow of 150 cm^3/min. After 12 hr, the reactor was cooled to −78°; a 0.5 cm^3/min flow of fluorine and a 20 cm^3/min flow of helium were initiated. This flow was maintained at this level for 3 days (65% total F_2 calculated for reaction) during which time zones 1, 2, and 3 were warmed to their equilibrium temperature on successive days. On the fourth day, the helium was reduced to 10 cm^3/min and zone 4 was warmed. The fluorine flow was then increased to 1.0 cm^3/min for 3 more days (150% total F_2 calculated for reaction). At the end of the first day, the helium was reduced to 5 cm^3/min and then stopped completely on the second day. On the fourth day, the fluorine was increased to 1.5 cm^3/min and zone 6 was allowed to warm up by ≈25°/day until the reactor was warmed to 40° and maintained there by a thermostatic heater. The latter steps ensured that the crowded *tert*-butyl group would be completely fluorinated.

A crude yield of 4.4 g of material containing perfluoroisobutane, perfluoro-3,3-dimethyl-1-oxacyclobutane, perfluoropivaloyl fluoride, and monohydroctafluoropivaloyl fluoride was obtained. From this mixture, 2.6 g (52% id) of perfluoropivaloyl fluoride was isolated. The monohydroacyl fluoride still makes up approximately 20% of the molar yield, the other two products making up most of the remaining material. The product is a very volatile solid (mp 38–38.5°, sealed tube) which sublimes readily at room temperature. The product has been characterized by ^{19}F NMR (a 95% solution in CCl_4) and consists of a dectet (J = 11.3 Hz) centered at −42.34 ppm and a doublet (J = 11.4 Hz) centered at +67.08 ppm relative to external $CFCl_3$–CCl_4. The relative integrals were 1:9.5. The mass spectrum contained a molecular ion at m/e 266, a P − F at 247, a P − COF_2 at 200, and other strong peaks at 181, C_4F_7; 178, C_4F_6; 159, C_4F_5O; 131, C_3F_5; 69, CF_3 (strongest peak); and 47, COF_2.

The infrared spectrum exhibited bands at 1880 (m, C–O), 1855 (sh), 1312 (sh), 1290 (vs), 1215 (m), 990 (s), 739 (w), 710 (w), 660 (w), 540 cm^{-1} (w).

Anal. Calcd for $C_5F_{10}O$: C, 22.574; F, 71.412. Found: C, 22.21; F, 71.47.

Results and Discussion

The direct fluorination of oxygen-containing hydrocarbons as a class of compounds represents a significant extention of the "LaMar" direct fluorination process to structures other than those containing only carbon and hydrogen. The term "oxygen containing" has been limited in this case to those compounds containing only carbon, hydrogen, oxygen, and fluorine. This group of compounds, a significant percentage of all functional hydrocarbons, includes acids, acyl fluorides, anhydrides, ketones, esters, ethers, and aldehydes. This paper is concerned primarily with the fluorination of ethers, esters, and acyl fluorides.

The carbon–oxygen single bond in hydrocarbons is of comparable strength with that of the carbon–carbon bond and therefore should resist fragmentation to an extent comparable to that found for the carbon–carbon bond. In general, this is found to be true; only in those cases where bonds are unstable in hydrogen fluoride or where unstable radicals can be formed, such as the acyl radical, are significant difficulties encountered. The first problem is due to the large amount of hydrogen fluoride liberated in the fluorination reactions; however, this problem can be reduced by keeping the system cold. The second problem is encountered in the acid derivatives which are converted to acyl fluorides via an intermediate acyl radical. This latter problem can be resolved by first converting the acid derivative to the acyl fluoride before fluorination of the alkyl group is attempted.

One of the significant problems in the electrolytic fluorination of ethers and especially ethylene glycol based diethers is the "β cleavage", the rupture of a carbon–carbon bond β to the ether linkage(s). The successful preparation of the "glyme" ethers, perfluoro-1,2-dimethoxyethane, perfluoro-1,2-diethoxyethane, and perfluorobis(2-methoxyethyl) ether, as well as the cyclic diether, perfluoro-1,4-dioxane, in good yields demonstrates that the problem of "β cleavage" is much less important in the system described herein. By contrast, the electrochemical fluorination of 1,4-dioxane, an example of "β cleavage", in which only perfluoro-1,2-dimethoxyethane was produced in 4% yield,[11] is the only previous synthesis reported for this compound.

The fluorination of hydrocarbon esters is one area in which direct fluorination yields the perfluorinated esters and other methods produce only the corresponding fluorocarbon acids. The direct fluorination of ethyl acetate represents the first successful fluorination of an ester. This is a difficult result to obtain even with direct fluorination and the primary reason for this difficulty is the instability of the ester linkage toward the hydrogen fluoride produced by the fluorination. However, the production of the perfluoroethyl and α-hydrotetrafluoroethyl trifluoroacetate esters in 5 and 20% yields, respectively, indicates that significant amounts of the ester products do survive under the conditions of the reaction. Recovery of the perfluorinated esters

is also hampered by the very facile dissociation of the esters to two acyl fluoride functions in the presence of catalytic amounts of fluoride ion. In fact, the recovery of perfluorinated ester is not accomplished unless the sodium fluoride charged hydrogen fluoride trap is cooled to about −10°. This presumably reduces the activity of the sodium fluoride toward dissociation of the perfluoro ester. The reverse reaction is also known; fluoride ion functions as a catalyst in the production of a perfluorinated ester from 2 mol of acyl fluoride.[8] The α-hydro ester is also labile, but to a lesser extent. It can be produced by the reaction of trifluoroacetyl fluoride with trifluoroacetaldehyde in the presence of a Lewis base such as a tertiary amine.[12] The fact that the β-hydro ester is also produced in low yields indicates that it is the lability of the ester linkage in esters possessing the $-(CO)OCF_2-$ linkage which significantly reduces yields of the β-hydro (2%) and perfluoro esters (5%) relative to the α-hydrotetrafluoroethyl trifluoroacetate ester (20%). This is reasonable because the major difference between the α- and β-hydro esters is this lability, and statistically, one would expect them to be produced in comparable yields. It has also been noted that the purified β-hydro ester does not undergo spontaneous dehydrofluorination. The β-hydrotetrafluoroethyl trifluoroacetate ester can also be produced by fluoride ion catalyzed condensation of trifluoroacetyl fluoride and difluoroacetyl fluoride, although a mixture of products is obtained. On the other hand, condensation of difluoroacetyl fluoride yields the ester, $CHF_2(CO)OCF_2CHF_2$. Dehydrofluorination of the alcohol part could produce $CHF_2(CO)OCF{=}CF_2$, a potentially interesting monomer, and preliminary studies have been undertaken in this area.

The fluorination of highly branched hydrocarbons is an area in which direct fluorination has a distinct advantage. The direct fluorination of pivaloyl fluoride [$(CH_3)_3CCFO$], which yields perfluoropivaloyl fluoride in 52% yield, is a good example. By contrast, when potassium tetrafluorocobaltate(III) is the fluorinating agent pivaloyl fluoride is recovered unchanged.[13] This example shows that these are species for which direct fluorination is not only the best method but possibly the only suitable method. Previously, it had been proposed that highly branched hydrocarbons are more difficult to fluorinate.[14] The fluorination of highly branched structures by direct fluorination requires only that more reaction time at higher fluorine concentrations be used to replace the last few remaining hydrogens on these very crowded systems.

Perhaps one of the more interesting compounds prepared during the course of this work is perfluorodimethylmalonyl difluoride. This compound has many interesting possibilities. The most obvious is, of course, as a difunctional acid monomer in condensation reactions. Other interesting possibilities exist and are currently being investigated. The low yields of perfluorodimethylmalonyl difluoride are partially attributable to the instability of the hydrocarbon parent, dimethylmalonyl difluoride, which decomposes spontaneously at ambient temperature in a sealed tube (with about a 1-day half-life). The fluorocarbon appears to be stable.

The decomposition of the hydrocarbon produces a solid residue and gaseous products; however, decomposition may be arrested by storage at −15° or lower. The rather large relative yield of perfluoro-2-methylpropanoyl fluoride during the fluorination indicates that this system tends to undergo decarboylation at one point, possibly during evaporation of the hydrocarbon into the reactor which takes about 12 hr. If this is the case it should be possible to increase the yield dramatically by modification of the reactor system.

A discussion of the utility and important parameters for the cyrogenic reactor is presented in the Experimental Section. Although it is an idealization and simplification of the actual fluorination process, it is a helpful guide in designing a workable reaction program of flow rates and gradients. Maximization of parameters still requires trial and error, but knowledge of operation procedure for the system is approaching science rather than art.

Because the direct fluorination process described here is predominantly a radical process, complications can occur in systems which rearrange under these conditions. Protective groups, primarily steric, could be utilized to prevent extensive rearrangement or polymerization of sensitive functions. Radical recombination problems have been minimal despite the fact that the fluorination occurs in a condensed phase. Presumably this is because the radical sites occur in a scattered pattern among a group of molecules at high dilution of fluorine and since the bulk of the material remains solid, few radical sites can approach one another and combine. Also, as the system is fluorinated, steric and fluorine–fluorine repulsions become more important.

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Registry No.—Perfluoro-1,2-dimethoxyethane, 378-11-0; 1-hydrononafluoro-2,5-dioxahexane, 40891-98-3; perfluorobis(2-methoxyethyl) ether, 40891-99-4; perfluoro-1,2-diethoxyethane, 356-70-7; perfluoro-1,4-dioxane, 32981-22-9; perfluoro(ethyl acetate), 30950-31-9; α-hydrotetrafluoroethyl trifluoroacetate, 54214-47-0; β-hydrotetrafluorethyl trifluoroacetate, 54214-49-2; perfluoro-dimethylmalonyl difluoride, 42139-57-1; perfluoropivaloyl fluoride, 1813-18-9; fluorine, 7782-41-4; 1,2-dimethoxyethane, 110-71-4; bis(2-methoxyethyl) ether, 111-96-6; 1,2-diethoxyethane, 629-14-1; 1,4-dioxane, 123-91-9; ethyl acetate, 141-78-6; dimethylmalonyl difluoride, 870-75-7; pivaloryl fluoride, 430-71-7.

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Preparation and Determination of Absolute Configurations and Rotations of 1,2-Dimethyl-5-norbornen-2-yl Derivatives[1]

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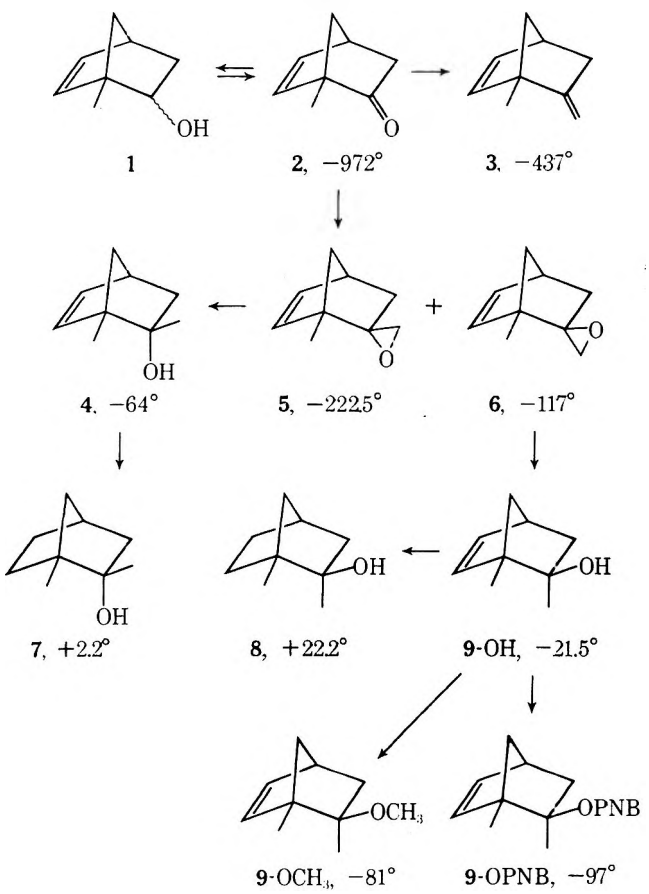
Racemic and optically active 1-methyl-5-norbornen-2-one (2) have been converted into 1,2-dimethyl-5-norbornen-*exo*-2-yl derivatives (9) and 1,2-dimethyl-5-norbornen-*endo*-2-ol (4). Absolute configurations have been established by correlation of optically active 9-OH and 4 with the corresponding saturated analogs, 1,2-dimethyl-*exo*-2-norbornanol (8) and 1,2-dimethyl-*endo*-2-norbornanol (7). Enantiomeric compositions of active compounds were determined directly with an optically active NMR shift reagent, tris(3-heptafluorobutyryl-*d*-camphorato)europium(III).

We have recently investigated the symmetry properties of ionic intermediates involved in solvolytic reactions of 1,2-dimethyl-5-norbornen-*exo*-2-yl *p*-nitrobenzoate (9-OPNB).[2] This paper describes the preparation of the necessary compounds and the correlations of optical configurations and rotations required for that investigation.

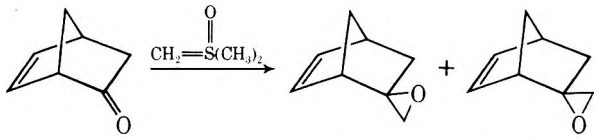
Racemic and optically active 1-methyl-5-norbornen-2-one (2) were converted into the 1,2-dimethyl-5-norbornen-*exo*-2-yl system (9) as outlined in Chart I. The ketone 2 was also converted to 2-methylene-1-methyl-5-norbornene (3) by the Wittig reaction. The latter was an expected solvolysis product for 9-OPNB.

Optically active 1-methyl-5-norbornen-2-one (2) was obtained as follows. Lithium aluminum hydride reduction of racemic 2[3] gave a 90:10 exo:endo mixture of 1-methyl-5-norbornen-2-ols (1). This mixture was converted into the acid phthalate derivative, which was resolved by recrystallization of the brucine salt. Saponification of the active acid phthalate gave (−)-1 (96% endo isomer), which was converted into (−)-2 by Oppenauer oxidation. The most active samples of (−)-2 were shown to be about 90% optically pure (see below).

Chart I



The bicyclic ketone 2 was converted into the desired 1,2-dimethyl-5-norbornen-2-yl system by a method reported by Bly and coworkers[4] for similar transformations of dehydronorcamphor (10). These workers observed that dimethyloxosulfonium methylide attacks 10 primarily from the endo direction to give a 71:29 mixture of the exo (11) and endo (12) oxiranes.



10 11 (71%) 12 (29%)

Similar results were obtained with 2. In this case a 73:27 mixture of spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (6) and spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (5) was obtained. The isomeric oxiranes were separated by preparative GC and converted to the corresponding tertiary alcohols, 9-OH and 4, by reduction[4] with lithium aluminum hydride. The overall yield for the two-step conversion of 2 to the desired exo tertiary alcohol (9-OH) was about 50%. The endo tertiary alcohol (4) was also prepared directly from 2 by reaction with methylmagnesium bromide. As in the case of the parent dehydronorcamphor (10),[4] this reaction involves about 97% exo attack.

Absolute configurations are shown in Chart I. These were established by conversion of (−)-1,2-dimethyl-5-norbornen-*endo*-2-ol (4) to (+)-1,2-dimethyl-*endo*-2-norbornanol (7) by reduction with diimide. Similarly, (−)-1,2-dimethyl-5-norbornen-*exo*-2-ol (9-OH) was converted to (+)-1,2-dimethyl-*exo*-2-norbornanol (8). Absolute configurations of the saturated tertiary alcohols (7 and 8) are known;[5] thus, these correlations establish absolute configurations for all of the compounds in the chart.

Absolute rotations[6] are included in Chart I. These were determined from observed rotations of homogeneous samples of known enantiomeric composition. Except for the hydrocarbon 3 and the bicyclic methyl ether 9-OCH_3, enantiomeric compositions were determined directly with an optically active NMR shift reagent, tris(3-heptafluorobutyryl-*d*-camphorato)europium(III) [Eu(hfbc)$_3$].[7] Observed shift differences for enantiotopic signals are tabulated in the Experimental Section. It is noteworthy that the absolute rotations determined in the present work for 7 and 8 are in excellent agreement with values obtained earlier[5] by other methods. The absolute rotation for 2-methylene-1-methyl-5-norbornene (3) was determined by correlation with the precursor (2).

1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH) was converted into the *p*-nitrobenzoate derivative (9-OPNB) by a conventional method.[5] The most active sample was 91% optically pure. The tertiary alcohol 9-OH was also converted into the methyl ether 9-OCH_3 by the Williamson method. This was an expected methanolysis product for 9-OPNB. The absolute rotation of 9-OCH_3 was deduced by correlation with active 9-OH.

Experimental Section

A 100-ft SE-30 capillary column was used for analytical GC and a 5 ft × 0.25 in. column packed with 10% FFAP on Chromosorb W 60/80 was used for preparative GC. NMR spectra were determined with a JEOL MH-100 spectrometer. Melting points are not corrected.

(−)-1-Methyl-5-norbornen-2-ol (1). A solution of 20 g (0.164 mol) of 1-methyl-5-norbornen-2-one[3] in dry ether was added slowly to a solution of 7 g of lithium aluminum hydride in 220 ml of dry ether at a rate so that gentle reflux was maintained. The reaction mixture (under dry nitrogen) was refluxed for an additional 6 hr. Work-up in the usual manner gave 19 g (94%) of **1-methyl-5-norbornen-2-ol** (1) consisting of about 90% endo isomer and 10% exo isomer. A solution of 19 g (0.153 mol) of this mixture and 28.1 g (0.19 mol) of purified phthalic anhydride in 400 ml of anhydrous pyridine was heated on a steam bath for 4 hr. After cooling the mixture was poured onto a slurry of ice and 500 ml of 10% hydrochloric acid. The resulting mixture was extracted four times with chloroform. The extracts were combined, washed once with cold 5% hydrochloric acid and twice with water, and dried over magnesium sulfate. Removal of solvent gave 40 g (95%) of residual crude **1-methyl-5-norbornen-2-yl acid phthalate.** After recrystallization from a benzene–pentane mixture the acid phthalate had mp 96°; NMR (CCl_4) δ 9.6 (s, 1 H, acid), 7.5–7.96 (m, 4 H, aromatic), 6.3 (q, 1 H, olefin), 5.87 (d, 1 H, olefin), 5.3 (q, 1 H), 2.8 (s, 1 H), 2.3–2.56 (m, 1 H), 1.4 (s, 3 H), 1.0–1.48 (m, 3 H).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.71; H, 5.96.

The above acid phthalate was resolved as follows. In a typical resolution a solution of 40 g (0.147 mol) of the above crude acid phthalate and 58 g (0.147 mol) of brucine in a mixture of 500 ml of methanol and 300 ml of acetone was concentrated with a rotary evaporator to a volume of about 300 ml. The resulting solution was chilled in a refrigerator (−20°) for 2 days. Filtration gave a first crop of 71.4 g of brucine salt. Three additional recrystallizations of this crop from a 5:3 methanol–acetone mixture gave 40 g of brucine salt. The acid phthalate was regenerated from the brucine salt as follows. The above 40 g of salt was dissolved in 200 ml of methylene chloride and the solution was extracted with four 90-ml portions of cold 5% aqueous sodium hydroxide. The extracts were combined, shaken with methylene chloride, acidified with cold dilute hydrochloric acid, and extracted with chloroform. After drying ($MgSO_4$) and removal of the solvent, 11 g of colorless **(−)-1-methyl-5-norbornen-2-yl acid phthalate,** $[\alpha]^{25}D$ −22° (*c* 0.8, $CHCl_3$), was obtained.[8]

A solution of the above optically active acid phthalate in 45 ml of 20% aqueous sodium hydroxide was steam distilled until 250 ml of distillate was collected. The distillate was saturated with sodium chloride and extracted several times with pentane. The pentane extract was dried ($MgSO_4$) and removed under reduced pressure. Analytical GC (71°) showed that the residue consisted of 96% *endo*- and 4% **(−)-*exo*-1-methyl-5-norbornen-2-ol** (1). After purification by preparative GC (65°) this sample of (−)-1 had mp 53–55° (sublimation), $[\alpha]^{25}D$ −67.2° (*c* 0.53, $CHCl_3$).[8]

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.26; H, 9.66.

(−)-1-Methyl-5-norbornen-2-one (2). Oxidation of a 4-g sample of the above (−)-1 with quinone and aluminum *tert*-butoxide in benzene by a procedure described earlier[9] gave 3.61 g (90%) of (−)-2 which was isolated by short-path distillation (54°, 12 mm). After purification by preparative GC (65°) this colorless liquid sample of (−)-2 had $[\alpha]^{25}D$ −884° (*c* 0.43, $CHCl_3$).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$[7] showed that this sample was 91% optically pure.

Reaction of (−)-1-Methyl-5-norbornen-2-one (2) with Dimethyloxosulfonium Methylide. To a stirred suspension of 1.416 g (0.06 mol) of sodium hydride in 24 ml of dimethyl sulfoxide (Me_2SO) under dry nitrogen was added 6.5 g (0.03 mol) of trimethyloxosulfonium iodide.[10] After hydrogen evolution ceased a solution of 3.6 g (0.03 mol) of the above (−)-2 in 10 ml of Me_2SO was added dropwise with cooling. After addition of the (−)-2, which required about 15 min, the reaction mixture was stirred at room temperature for 2 hr and then at 60° for 1 hr. The solution was cooled, diluted with 100 ml of water, and extracted with pentane. The pentane extract was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Analytical GC indicated that the residue consisted of 68% spiro[1-methyl-5-norbornen-*exo*-2,2′-oxacyclopropane] (6), 25% spiro[1-methyl-5-norbornen-*endo*-2,2′-oxacyclopropane] (5), and 7% of an unidentified product. Pure (−)-6 and (−)-5 were obtained by preparative GC (65°).

The (−)-6 had mp 44–46°: $[\alpha]^{25}D$ −106° (*c* 0.43, $CHCl_3$); NMR (CCl_4) δ 6.20 (q, 1 H), 5.7 (d, 1 H), 2.8 (s, 1 H), 2.59 (s, 2 H), 1.5–1.82 (m, 4 H), 1.0 (s, 3 H). The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.40; H, 8.85.

The colorless liquid sample of pure (−)-5 had $[\alpha]^{25}D$ −222.5° (*c* 0.73, $CHCl_3$); NMR (CCl_4) δ 6.28 (q, 1 H), 5.84 (d, 1 H), 2.76 (s, 1 H), 2.68 (s, 2 H), 1.2–2.1 (m, 4 H), 1.0 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.35; H, 8.90.

1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH). Racemic and optically active 9-OH were obtained as described below for preparation of (−)-9-OH. A slurry of 1.743 g (13 mmol) of the above (−)-6 and 800 mg of lithium aluminum hydride in 40 ml of ether was refluxed for 6 hr, after which the mixture was cooled and hydrolyzed with 15% aqueous sodium hydroxide. The precipitated salts were removed by filtration and the dried ethereal solution ($MgSO_4$) concentrated to give 1.70 g (96%) of colorless needles, mp 65° (sublimation). An analytical sample of **(−)-1,2-dimethylnorbornen-*exo*-2-ol (9-OH)** was prepared by preparative GC (65°): $[\alpha]^{25}D$ −19.5° (*c* 0.38, $CHCl_3$); NMR δ 6.01 (q, 1 H), 5.66 (d, 1 H), 2.66 (s, 1 H), 1.0–1.9 (m, 5 H), 1.16 (s, 3 H), 1.1 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.32.

Correlation of (−)-1,2-Dimethyl-5-norbornen-*exo*-2-ol (9-OH) with (+)-1,2-Dimethyl-*exo*-2-norbornanol (8). To a rapidly stirred solution of 200 mg (1.45 mmol) of the above (−)-9-OH and 20 g (103 mmol) of dipotassium azodicarboxylate[11] in 50 ml of methanol under nitrogen was added 12.5 ml of glacial acetic acid. The dropwise addition resulted in gas evolution and reflux was controlled by the rate of addition. The solution was stirred for an additional 5 hr and then cooled and diluted with 50 ml of water. The resulting mixture was extracted with several portions of pentane and after drying ($MgSO_4$), the pentane was removed under reduced pressure. The residual product was purified by preparative GC (65°). The resulting homogeneous (+)-8 had $[\alpha]^{25}D$ 21.1° (*c* 0.11, $CHCl_3$). The NMR spectrum was indistinguishable from that of an authentic sample of 8.[5,8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

1,2-Dimethyl-5-norbornen-*exo*-2-yl *p*-Nitrobenzoate (9-OPNB). Racemic and optically active 9-OPNB were prepared as described below for the preparation of (−)-9-OPNB. A solution of 1.64 g (12 mmol) of the above (−)-9-OH in 20 ml of anhydrous tetrahydrofuran under nitrogen was refluxed over 601 mg (15 mmol) of potassium for 4 hr. The solution was chilled to −78° and slowly mixed with a similarly chilled solution of 2.78 g (15 mmol) of purified *p*-nitrobenzoyl chloride in 35 ml of tetrahydrofuran. After mixing, the resulting solution was stirred at −78° for an additional 5 hr and then warmed to room temperature and diluted with benzene. The resulting solution was shaken with water and the benzene solution dried ($MgSO_4$) and concentrated to a yellow residue. This material was purified by column chromatography (Al_2O_3 with benzene as eluent) followed by recrystallization from ether–pentane. The resulting (−)-9-OPNB was nearly colorless and had mp 133–133.5°: $[\alpha]^{25}D$ −88.3° (*c* 0.46, $CHCH_3$); NMR (CCl_4) δ 8.06–8.4 (m, 4 H), 6.26 (q, 1 H), 5.76 (d, 1 H), 2.76 (s, 1 H), 1.2–2.4 (m, 4 H), 1.52 (s, 3 H), 1.44 (s, 3 H).[8] The NMR spectrum in the presence of Eu(hfbc)$_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96. Found: C, 66.96; H, 6.03.

1,2-Dimethyl-5-norbornen-*endo*-2-ol (4). A 335-mg (2.45 mmol) sample of the above (−)-5 was converted into (−)-4 by the procedure described above for conversion of 6 into 9-OH. After pu-

Table I
Data for Determination of Enantiomeric Compositions of Compounds in Chart I[a]

Compd	R/S	ΔΔδ (ppm)
2	0.79	0.18
4	0.38	0.14
5	0.64	0.18
6	0.56	0.22
7	0.62	0.12
8[b]	0.63	0.12
9-OH[b]	0.42	0.14
9-OPNB	0.68	0.20

[a] Enantiotopic methyl signals used for determinations. Downfield methyl signal used for dimethyl compounds. [b] Both methyl signals were isolated from other resonances and suitable for determination of enantiotopic compositions.

rification by preparative GC (65°) the homogeneous liquid sample of (−)-4 had $[\alpha]^{25}D$ −5.77° (c 0.90, $CHCl_3$); NMR (CCl_4) δ 6.3 (q, 1 H), 5.82 (d, 1 H), 2.64 (s, 1 H), 1.04–1.92 (m, 5 H), 1.3 (s, 3 H), 1.22 (s, 3 H).[8] The NMR spectrum in the presence of $Eu(hfbc)_3$ indicated that this sample was 91% optically pure.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.19; H, 10.23.

This compound was also prepared directly from a sample of the above-described (−)-2 by reaction with methylmagnesium bromide in the usual manner.[9] The sample of (−)-4 obtained by this method was purified by preparative GC and had the same rotation and NMR spectrum as the sample described above.

Correlation of (−)-1,2-Dimethyl-5-norbornen-*endo*-2-ol (4) with (+)-1,2-Dimethyl-*endo*-2-norbornanol (7). Diimide reduction of a 200-mg sample of the above (−)-4 by the method described above for reduction of 9-OH gave (+)-7, $[\alpha]^{25}D$ 2.0° (c 0.6, $CHCl_3$). The NMR spectrum was indistinguishable from that of an authentic sample.[5,8] The NMR spectrum in the presence of $Eu(hfbc)_3$ indicated that this sample was 91% optically pure.

1-Methyl-2-methylene-5-norbornene (3). A sample of (+)-2, $[\alpha]^{25}D$ 627° (c 0.46, $CHCl_3$) (65% optically pure), was converted to (+)-3 by the Wittig reaction using a general procedure described earlier.[5] The (+)-3 was isolated and purified by preparative GC (50°) and had $[\alpha]^{25}D$ 282°; NMR (CCl_4) δ 6.04 (q, 1 H), 5.66 (d, 1 H), 4.74 (d, 2 H), 2.88 (s, 1 H), 1–2.5 (m, 4 H), 1.3 (s, 3 H). Since this sample should have the same optical purity as the (+)-2 from which it was derived, the calculated absolute rotation for 3 is 437°.

1,2-Dimethyl-*exo*-2-methoxy-5-norbornene (9-OCH_3). A mixture of 343 mg (2.49 mmol) of (+)-9-OH, $[\alpha]^{25}D$ 13.3° (c 0.2, $CHCl_3$), and 97 mg (2.49 mmol) of potassium in 10 ml of tetrahydrofuran under dry nitrogen was refluxed for 5 hr, cooled to room temperature, and mixed with a solution of 353 mg (2.49 mmol) of iodomethane in 5 ml of tetrahydrofuran. The resulting mixture was stored at room temperature for 1 hr and then diluted with water and extracted with ether. The extract was dried ($MgSO_4$) and concentrated. The residual (+)-9-OCH_3 was isolated and purified by preparative GC. Homogeneous (+)-9-OCH_3 was obtained as a colorless liquid and had $[\alpha]^{25}D$ 49.8° (c 0.59, $CHCl_3$); NMR (CCl_4) δ 6.10 (q, 1 H), 5.75 (d, 1 H), 3.2 (s, 3 H), 2.7 (s, 1 H), 1.0–2.0 (m, 4 H), 1.1 (s, 3 H), 1.04 (s, 3 H). Assuming that there is no loss of optical configuration in this transformation the absolute rotation for 9-OCH_3 is 81°.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.71; H, 10.47.

Determination of Enantiomeric Compositions. Enantiomeric compositions of active samples were determined directly with an NMR shift reagent, $Eu(hfbc)_3$, as outlined previously.[7] Isolated corresponding enantiotopic signals were expanded and relative peak areas determined with a planimeter. Pertinent data are summarized in Table I, which shows the $Eu(hfbc)_3$/substrate molar ratio (R/S) and the observed magnitudes of nonequivalence (ΔΔδ). Carbon tetrachloride was the solvent in all determinations. Enantiotopic methyl signals were used in each case. For dimethyl compounds the downfield signal was used.

Registry No.—(±)-*exo*-1, 56292-49-0; (±)-*endo*-1, 56292-50-3; (−)-*exo*-1, 56324-12-0; (−)-*endo*-1, 56324-13-1; (±)-2, 56292-51-4; (−)-2, 56324-14-2; (+)-2, 56324-15-3; (+)-3, 56292-52-5; (−)-*endo*-4, 56292-53-6; (−)-*endo*-5, 56292-54-7; (−)-*exo*-6, 56324-16-4; (+)-7, 18366-96-6; (+)-8, 56389-60-7; (−)-9-OH, 56324-17-5; (+)-9-OH, 56324-18-6; (−)-9-OPNB, 56292-55-8; (+)-9-OCH_3, 56292-56-9; phthalic anhydride, 85-44-9; (±)-*endo*-1-methyl-5-norbornen-2-yl acid phthalate, 56292-57-0; (±)-*exo*-1-methyl-5-norbornen-2-yl acid phthalate, 56292-58-1; brucine, 357-57-3; (−)-*endo*-1-methyl-5-norbornen-2-yl acid phthalate, 56324-19-7; (−)-*exo*-1-methyl-5-norbornen-2-yl acid phthalate, 56324-20-0; dimethyloxosulfonium methylate, 5367-24-8; tris(3-heptafluorobutyryl-*d*-camphorato)europium(III), 34788-82-4.

References and Notes

(1) This work was supported by the National Science Foundation (GP-6555X) and the Air Force Office of Scientific Research (AFOSR-71-1974).
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Notes

Thermal Decarboxylation of *N*-Alkoxycarbonylimidazoles. An Improved and Convenient Procedure for N-Alkylation of Imidazoles

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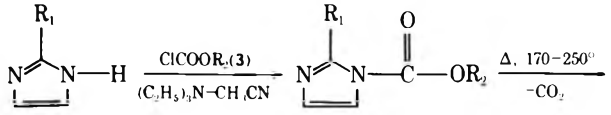
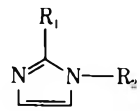
Alkylation of imidazoles at the nitrogen atom is normally achieved by reaction of imidazoles with alkyl halides or dialkyl sulfates under strongly basic conditions in organic solvents or in water. Yields are often low owing to strong water solubility of the reaction products and partial quaternization[1a,b].

In 1935 John reported that 1-carbethoxyimidazole, prepared by the reaction of imidazole with ethyl chloroformate, upon heating at 250° for 20 sec gave 1-ethylimidazole. This reaction proved to be applicable only on microscale; on scale-up large amounts of starting material remained. Reexamination of this work, however, showed that extension of the pyrolysis time solved this problem and made this reaction an attractive preparative procedure for alkylation of imidazoles.

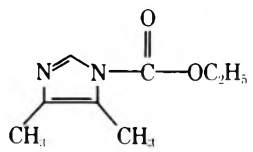
Reaction of equimolar amounts of imidazoles **1** and alkyl chloroformates **3** in the presence of 1 equiv of triethylamine in acetonitrile led to the corresponding carbamate esters **2a–h** and **5** in almost quantitative yields.



1 **2a-h**



4a-h



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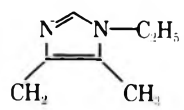

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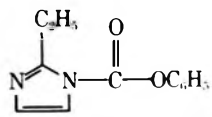

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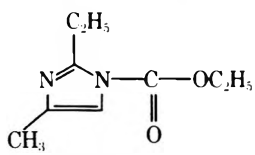

8a, $R_1 = H$; $R_2 = C_2H_5$
b, $R_1 = R_2 = C_2H_5$
c, $R_1 = n\text{-}C_3H_7$; $R_2 = C_2H_5$
d, $R_1 = i\text{-}C_3H_7$; $R_2 = C_2H_5$
e, $R_1 = C_2H_5$; $R_2 = i\text{-}C_4H_9$
f, $R_1 = n\text{-}C_3H_7$; $R_2 = i\text{-}C_4H_9$
g, $R_1 = C_6H_5$; $R_2 = C_2H_5$
h, $R_1 = CH_3$; $R_2 = C_2H_5$

The crude esters were heated neat to the temperatures at which carbon dioxide evolution began and heating was prolonged for an additional 10 min. Distillation of the reaction mixtures afforded the alkylated imidazoles **4a–g** and **6** in good yields.

1-Ethyl-2-methylimidazole (**4h**) could only be obtained in 15% yield after chromatography of the tarry reaction mixture. The results are summarized in Table I.

Table I
N-Alkylated Imidazoles

Compd	Empirical formula	Yield %	Bp, °C (mm)	Decarbo temp, °C	Picrate salt[a] mp, °C
4a[b]	$C_5H_8N_2$	68	40–41(0.5)	170	170–171
4b[c]	$C_7H_{12}N_2$	65	52–53(0.01)	250	125–126
4c[d]	$C_3H_{14}N_2$	66	60–64(0.04)	200	123–124
4d	$C_3H_{14}N_2$	75	60–62(0.05	200	141–142
4e	$C_3H_{16}N_2$	59	71–72(0.1)	220	137–138
4f[d]	$C_{10}H_{18}N_2$	61	78–81(0.1)	230	129–130
4g	$C_{11}H_{12}N_2$	69	86–89(0.01)	220	173–174
4h[e]	$C_5H_{10}N_2$	15	63–67(0.02)	210	171–172
6	$C_7H_{12}N_2$	60	118–121(18)	190	170–171

[a] Satisfactory analytical data were obtained for picrate salts of all compounds listed in the table (±0.3 for C, H, and N). Ed. [b] W. John, *Ber.*, 68, 2283 (1935). [c] B. Oddo and Y. Mingoia, *Gazz. Chim. Ital.*, 58, 584 (1928); *Chem. Abstr.*, 23, 1638 (1929). [d] J. B. Rieger, *Monatsh. Chem.*, 9, 607 (1888). [e] A. Heymans, *Ber.*, 65, 320 (1932).

Attempts to synthesize N-arylated imidazoles in this manner were unsuccessful. Upon heating 1-carbophenoxy-2-ethylimidazole (**7**) at temperatures up to 290° no detectable carbon dioxide evolution took place and only darkening of the reaction mixture was observed.

Mechanistically this reaction might be regarded as an O → N shift and as such is comparable with the Chapman rearrangement[3] and a more recently reported rearrangement of *N*-(*p*-tolylsulfonyl)imidocarbonate.[4]

The use of this reaction in the synthesis of asymmetrically substituted imidazoles seems limited. Whereas reaction of ethyl chloroformate and 2-ethyl-4(5)-methylimidazole led to 1-carbethoxy-2-ethyl-4-methylimidazole (**8**) with more than 95% regioselectivity, the subsequent decarboxylation afforded a 3:1 mixture of 1,2-diethyl-4-methylimidazole and 1,2-diethyl-5-methylimidazole.

Experimental Section

General. The NMR data were obtained with a Varian T-60 spectrometer, using Me_4Si as an internal standard. The substituted imidazoles and the chloroformate esters were commercially available. A typical experiment procedure is illustrated by the synthesis of 1-ethyl-4,5-dimethylimidazole (**6**).

1-ethyl-4,5-dimethylimidazole (6). To a solution of 9.60 g (0.1 mol) of 4,5-dimethylimidazole and 11 g (0.11 mol) of triethylamine in 100 ml of acetonitrile was added with stirring at 10° a solution of 10.8 g (0.1 mol) of ethyl chloroformate in 20 ml of ether. After stirring at ambient temperature for 1 hr the mixture was filtered and the filtrate was taken up in 300 ml of ether. Upon washing, drying, and evaporation of the organic phase 16 g of **5** remained as a colorless oil: NMR ($CDCl_3$) 1.41 (t, 3, CH_3), 2.12 (s, 3, CH_3), 2.32 (s, 3, CH_3), 4.38 (q, 2, $-CH_2-$), 7.86 ppm (s, 1, H-2 imidazole). The crude product was heated with stirring in a round-bottom flask until a vigorous carbon dioxide evolution began (190°). After the reaction had ceased, heating was prolonged for an additional 10 min at 200°. The dark reaction mixture was distilled and afforded 7.4 g (60%) of **6** as a yellowish oil: bp 118–121° (20 mm); NMR

($CDCl_3$) δ 1.32 (t, 3, CH_3), 2.18 (s, 6, CH_3), 3.72 (q, 2, $-CH_2-$), 7.21 (s, 1, H-2 imidazole). Anal. Calcd for $C_7H_{12}N_2$: C, 67.74; H, 9.77; N, 22.50. Found: C, 67.79; H, 10.01; N, 22.38.

1-Carbethoxy-2-ethyl-4-methylimidazole (8). To a solution of 11.0 g (0.1 mol) of 2-ethyl-4(5)-methylimidazole and 11 g (0.11 mol) of triethylamine in 100 ml of acetonitrile was added dropwise with stirring at 0–5° a solution of 10.8 g (0.1 mol) of ethyl chloroformate in 30 ml of ether. After stirring for an additional 1 hr at 0° the reaction mixture was filtered. Upon washing, drying, and evaporation of the organic phase 17.3 g (95%) of 8 remained as a colorless oil: NMR ($CDCl_3$) δ 1.32 (t, 3, CH_3), 1.37 (t, 3, CH_3), 2.18 (s, 3, CH_3), 3.01 (q, 2, CH_2), 4.41 (q, 2, CH_2), 7.04 (s, 1, H-5). No traces of isomer could be detected.

On decarboxylation of 8 under the conditions used for 6 (210°), 51% of product was obtained, bp 81–85° (0.1 mm). Anal. Calcd for $C_8H_{14}N_2$: C, 69.56; H, 10.14; N, 20.28. Found: C, 69.59; H, 10.29; N, 20.12.

The NMR spectrum and TLC revealed the presence of two isomeric imidazoles in the ratio 3:1 (based on integrals). The major isomer could be identified as the normal product 1,2-diethyl-4-methylimidazole: NMR ($CDCl_3$) δ 1.38 (t, 3, CH_3), 1.41 (t, 3, CH_3), 2.25 (s, 3 CH_3), 2.64 (q, 2, CH_2), 3.87 (q, 2, CH_2), 6.58 (s, 1, H-5). The minor compound must be assigned as the isomeric 1,2-diethyl-5-methylimidazole: NMR ($CDCl_3$) δ 1.31 (t, 3, CH_3), 1.37 (t, 3, CH_3), 2.24 (s, 3, CH_3), 2.63 (q, 2, CH_2), 3.87 (q, 2, CH_2), 6.64 (s, 1, H-4).

Acknowledgment. The authors wish to thank Dr. H. M. Buck for continuous interest and encouragement.

Registry No.—**1a**, 288-32-4; **1b**, 1072-62-4; **1c**, 50995-95-4; **1d**, 36947-68-9; **1g**, 670-96-2; **1h**, 693-98-1; **2a**, 19213-72-0; **2b**, 56468-36-1; **2c**, 56468-37-2; **2d**, 56468-38-3; **2e**, 56468-39-4; **2f**, 56468-40-7; **2g**, 56468-41-8; **2h**, 56468-42-9; **3a**, 105-39-5, **3e**, 13361-35-8; **4a**, 7098-07-9; **4b**, 51807-53-5; **4c**, 56468-43-0; **4d**, 56468-44-1; **4e**, 56468-45-2; **4f**, 46056-02-4; **4g**, 56468-46-3; **4h**, 21202-52-8; **5**, 56468-47-4; **6**, 56468-48-5; **7**, 56468-49-6; **8**, 56468-50-9; 4,5-dimethylimidazole, 2302-39-8; 2-ethyl-4(5)-methylimidazole, 931-36-2; 1,2-diethyl-4-methylimidazole, 56468-51-0; 1,2-diethyl-5-methylimidazole, 56468-52-1.

Supplementary Material Available. NMR data for all compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3279.

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Conformational Analysis of the Dibenzo[*a*,*g*]quinolizidines by Spectroscopic Methods

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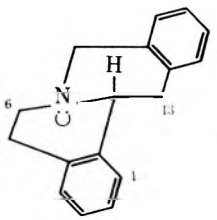
The dibenzo[*a*,*g*]quinolizidine structure forms the skeleton of the tetrahydroprotoberberine alkaloids. If rings B and C of the dibenzo[*a*,*g*]quinolizidine assume half-chair conformations, it exists in the equilibrium of one trans (**1**) and two cis conformation (**2** and **3**). The unsubstituted di-



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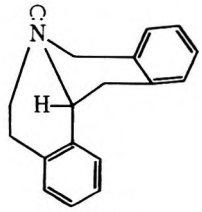

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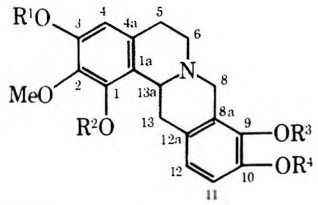

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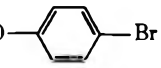
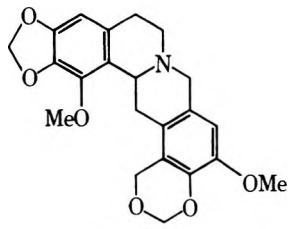
4. $R^1 = R^3 = R^4 = Me$; $R^2 = H$
5. $R^1 = R^3 = H$; $R^2 = R^4 = Me$
6. $R^1 = R^3 = Me$; $R^2 = H$; $R^4 = CO$—  —Br
7. $R^1 = R^2 = R^3 = R^4 = Me$
8. $R^1 = R^3 = Me$; $R^2 = R^4 = H$



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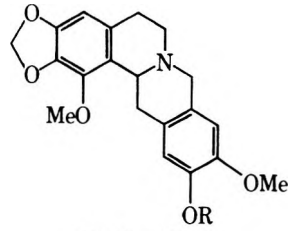
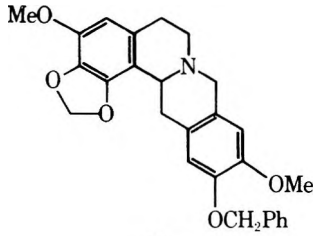


10, R = CH_2Ph
11. R = H



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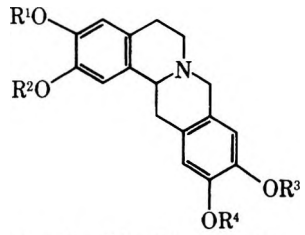
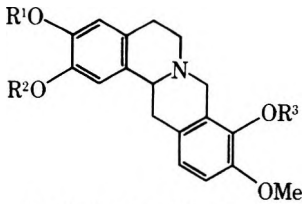
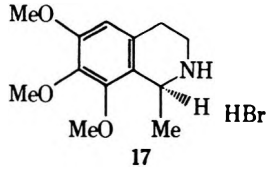


13, $R^1 = R^2 = R^3 = R^4 = Me$
14, $R^1 + R^2 = R^3 + R^4 = CH_2$



15, $R^1 + R^2 = CH_2$; $R^3 = Me$
16, $R^1 = R^2 = Me$; $R^3 = H$



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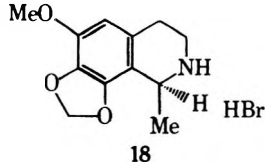

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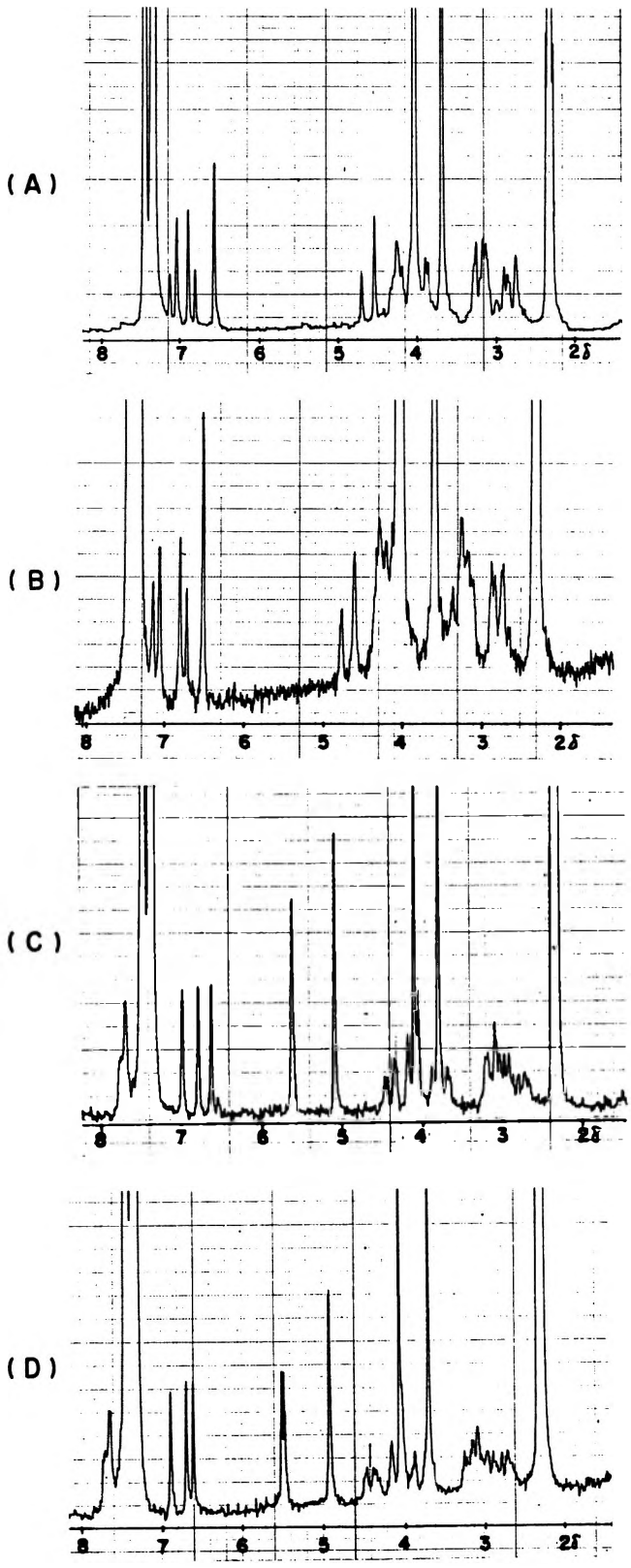

Figure 1. Proton NMR spectra of tetrahydroprotoberberines in deuteriotoluene at room temperature and −88°: (A) *O*-methylcapaurine (7) at room temperature; (B) *O*-methylcapaurine (7) at −88°; (C) the base 10 at room temperature; (D) the base 10 at −88°.

benzo[*a*,*g*]quinolizidine exists mainly in the thermodynamically stable *trans*-quinolizidine.[1] X-Ray analyses of the hydrobromides of (−)-capaurine (4) and (±)-isocapaurimine (5) and (−)-capaurimine *p*-bromobenzoate (6) by us revealed that they exist in the *cis*-quinolizidine form (2) in the crystalline state.[2-4] It was considered that an energetically unfavorable nonbonded interaction of the C-1 substituent with the C-13 hydrogens destabilized the trans form (1). Such an unfavorable interaction still remains in the other cis form (3), which may be the least preferred one. Thus, cis form 2 becomes more important for the 1-substituted tetrahydroprotoberberines. In the course of the synthesis of orientalidine (9),[5] we observed that (±)-3-methoxy-1,2-methylenedioxytetrahydroprotoberberine derivatives, for example 12, showed strong Bohlmann bands in their ir spectra. We therefore became interested in the conformational analysis, using spectroscopic methods, of the dibenzo[*a*,*g*]quinolizidines varying oxy substituents in the A and D rings, and now wish to describe our findings.

Ir Spectroscopy. The presence or absence of Bohlmann bands in the ir spectra in solution has been utilized to distinguish the *trans*- from *cis*-quinolizidines,[6,7] although some workers have found that these absorptions were not definitive.[8,9] The ir spectra of (−)-*O*-methylcapaurine (7) and (±)-1-methoxy-2,3-methylenedioxytetrahydroprotoberberines (9, 10, and 11)[5] in chloroform solution did not show Bohlmann bands between 2700 and 2900 cm^{-1}. On the other hand, (±)-3-methoxy-1,2-methylenedioxytetrahydroprotoberberines showed considerably strong absorptions between 2700 and 2900 cm^{-1}, comparable to that of 1-nonsubstituted tetrahydroprotoberberines. It was therefore assumed that these derivatives exist mainly in the trans conformation in solution.

When the ir spectra of the tetrahydroprotoberberines were taken in the crystalline states, peculiar behavior was observed. Crystals of (−)-capaurimine *p*-bromobenzoate (6), whose X-ray analysis revealed the *cis*-quinolizidine,[4] and (−)-capaurimine (8) in potassium bromide did not show absorptions between 2700 and 2900 cm^{-1}. On the other hand, (±) compounds (10, 12), optically active (−)-capaurine (4), and (−)-*O*-methylcapaurine (7) showed strong absorptions in the same region. However, the racemates of capaurine (4) and *O*-methylcapaurine (7), prepared by the racemization of the corresponding optically active compounds with Adams catalyst,[10] showed no Bohlmann-type absorptions. The ir spectra of some tetrahydroprotoberberines between 2400 and 3100 cm^{-1} are given in supplementary pages. Bohlmann bands in the crystalline state provide ambiguous criteria, and there is a possibility that the conformation of the 1-substituted tetrahydroprotoberberines in the crystalline state may depend upon the crystal structure (see paragraph at end of paper regarding supplementary material).

Proton NMR Spectroscopy. The angular proton of a trans conformation in benzo[*a*]- and indolo[*a*]quinolizidines resonates at a higher field than δ 3.8 ppm, whereas cis conformations are characterized by a signal below 3.8 ppm for this proton.[11] However, it is normally difficult to observe the signal due to the angular proton from the proton NMR spectra of the tetrahydroprotoberberines in deuteriochloroform solution, because the signals due to methoxyl groups appeared around 3.8 ppm. When the spectra were taken in deuteriotoluene, the signals due to the angular protons were shifted downfield and separated from the signals due to the methoxyl groups. The chemical shifts of the angular proton and the protons at the C-8 position of some tetrahydroprotoberberines in deuteriotoluene are shown in Table I, together with the coupling constants. (−)-*O*-Methylcapaurine (7), (±)-orientalidine (9), and (±)-10 showed the angular proton at 4.26, 4.24, and 4.37 ppm, respectively, as a quartet (J = 12 and 4 Hz). On the other hand, the angular proton of the bases (12 and 14) appeared at 3.96 and 3.50 ppm, respectively, as a quartet (J = 15 and 4 Hz). From the above chemical shifts, it is estimat-

Table I[a]
Chemical Shifts and Coupling Constants of the Protons at C-13a and C-8 Positions of Some Tetrahydroprotoberberines in Deuteriotoluene at Room Temperature

Compd	13a-H, ppm (J, Hz)	8-H eq, ppm (J, Hz)	8-H ax, ppm (J, Hz)
7	4.26 (4 and 12)	4.62 (16)	4.16 (16)
9	4.24 (4 and 12)	4.12 (15)	*b*
10	4.37 (4 and 12)	4.25 (16)	3.95 (16)
12	3.96 (4 and 15)	4.02 (15)	3.76 (15)
14	3.50 (4 and 15)	3.74 (15)	3.49 (15)

[a] The δ values were calculated from the signal due to the methyl group of toluene, 2.32 ppm. [b] The signal was not distinguishable.

For example, the proton NMR spectra of 7 and 10 in deuteriotoluene at room temperature and −88° are shown in Figure 1. It is therefore assumed that the equilibration between *cis* and *trans*-quinolizidines is very fast.

^{13}C NMR Spectroscopy. The assignments of the ^{13}C chemical shifts of some tetrahydroprotoberberines are based on the comparison of the spectra[12-14] and on the splitting patterns which are observed in the off-resonance decoupled spectra. The values are shown in Table II.

It was expected that some of the carbons of the *cis*-quinolizidines would resonate at a higher field than in the *trans*-quinolizidine owing to γ effects.[15] Although the chemical shifts of C(5), C(8), and C(13a) in the dibenzo[*a*,*g*]quninolizidine are expected to be influenced directly by the substituents on the adjacent benzene ring, the preferential conformation can be determined by the compari-

Table II[a]
Carbon-13 Chemical Shifts of Tetrahydroprotoberberines

Carbon	7	8	10	11	12	13	14	15	16
C-1	151.9	146.4[c]	147.5	147.8	142.4	108.5[b]	105.6	105.5	109.1
C-2	140.2	143.6	134.5	134.5	133.4	147.3	146.1	145.9[c]	147.5
C-3	150.1	150.6[c]	140.2	140.4	145.3	147.3	146.1	146.1[c]	147.5
C-4	107.4	104.0	102.9	103.1	107.0	111.3	108.5	108.4	111.5
C-4a	130.6[b]	131.3	128.6	128.5	129.5	126.6	127.9	127.7	127.0
C-5	30.0	30.6	30.1	30.1	30.0	29.0	29.6	29.6	29.2
C-6	48.3	49.3	47.1	46.9	51.1	51.3	51.3	51.4	51.5
C-8	53.3	53.6	57.2	57.3	58.0	58.2	58.7	54.0	53.7
C-8a	128.3[b]	127.9[b]	126.6[b]	124.8[b]	126.8[b]	126.2	127.4	127.7[b]	121.4
C-9	150.9	146.4[c]	109.7	108.7	109.8	109.5[b]	106.5	150.2	141.6
C-10	145.3	146.6[c]	146.6	145.3	146.8	147.3	146.1	145.0	144.2
C-11	110.9	114.2	147.9	144.3	148.0	147.3	146.1	110.9	109.1
C-12	124.0	125.3	114.3	114.6	114.5	111.3	108.5	123.9	119.3
C-12a	128.6[b]	128.5[b]	127.6[b]	127.3[b]	127.8[b]	126.2	127.4	128.6[b]	128.1
C-13	33.0	32.9	31.9	31.6	34.0	36.3	37.1	36.5	36.5
C-13a	55.5	56.0	54.9	54.7	57.1	59.5	59.9	59.6	59.4
C-13b	124.2	117.9	123.6	123.9	114.1	129.6	130.9	130.8	129.9
$-OCH_3$	60.6 (× 2)	61.2	59.2	59.5	56.5	55.8 (× 4)		60.1	56.2 (× 3)
	60.1	60.9	56.0	56.1	56.3			55.8	
	55.8 (× 2)	56.3							
$-OCH_2O$			100.5	100.7	101.2		100.8 (× 2)	100.7	
$-OCH_2Ph$			70.9		71.2				
$-OCH_2C_6H_5$			137.2		137.3				
			128.3		128.5				
			127.1		127.4				
			126.4		126.8				

[a] All shifts are in parts per million from Me_4Si. [b,c] The assignments may be reversed.

ed that the former three compounds adopt predominantly the cis conformation. The splitting pattern of the angular proton suggests that the cis form is not 3, but 2. The difference between the chemical shifts of 3-methoxy-1,2-methylenedioxytetrahydroprotoberberine (12) and 14 is due to the anisotropy of the oxygen substituent at the C-1 position. This was confirmed by ^{13}C NMR spectroscopy (vide infra). Furthermore, the protons at C-8 in (−)-*O*-methylcapaurine (7) appeared at low field owing to the presence of the methoxyl group at the C-9 position.

Proton NMR spectroscopy of the tetrahydroprotoberberines in deuterioacetone or deuteriotoluene was also studied at variable temperatures. The proton NMR spectra in deuterioacetone from −90° to room temperature showed no change. When the compounds 7, 10, 12, and 13 were measured in deuteriotoluene from −90 to 100°, the chemical shifts of some signals in all the spectra gradually changed, but separate conformations were not observed.

son of the chemical shift of C(6). (±)-Tetrahydroprotoberberines (13–16), which have a hydrogen at C-1 position, showed the signal due to C(6) at about 51.4 ± 0.1 ppm even if the pattern of the substitutents on ring A and D is changed. (±)-3-Methoxy-1,2-methylenedioxytetrahydroprotoberberine (12) also showed the signal at 51.1 ppm, indicating the preferential *trans*-quinolizidine. The fact is consistent with the presence of Bohlmann bands in chloroform solution and the chemical shift of the angular proton in deuteriotoluene, which has been already methioned above. Based on these results and in consideration of the results of X-ray analyses of *O*-methylanhalonidine hydrobromide (17) and anhalonine hydrobromide (18),[16] the methylenedioxy group at the peri position does not cause as serious an interaction as either the hydroxy or the methoxy group.

For (−)-capaurimine (8), (−)-*O*-methylcapaurine (7), and (±) compounds (10 and 11), the signal due to C(6) ap-

peared at 49.3, 48.3, 47.1, and 46.9 ppm, respectively. Owing to the steric interaction between the C-1 OR and C-13 hydrogens, these four compounds must be shifted over toward the cis form (2), because the C-6 signal always appears at a lower field (~δ 51.4, as shown above), when the system exists in the *trans*-quinolizidine form. It seems that the conformation of tetrahydroprotoberberines having a substituent at C-1 position is governed by the degree of steric interaction between the C-1 substituent and C-13 hydrogens. The chemical shift due to C(6) would depend upon the position of equilibrium between cis form 2 and trans form 1. Therefore it was estimated that (−)-capaurimine (8) exists as a mixture of cis and trans in the equilibrium. This is consistent with the observation of weak absorptions in the region of 2800–2700 cm^{-1} of the ir spectrum of (−)-capaurimine in solution[17] and the finding by Shamma and his coworkers that (−)-capaurimine showed an intermediate rate for methiodide formation as compared with the cis and trans model compounds.[18] Estimation of the position of equilibrium by the ^{13}C chemical shifts have been recently reported.[19,20]

It is probably worthwhile to mention the difference of the C(8) chemical shifts between the 9,10- and 10,11-substituted tetrahydroprotoberberines. The C(8) of the 9,10-substituted compounds appeared at a higher field than 54.0 ppm, while the C(8) of the 10,11-substituted ones resonates at a lower field than 57.0 ppm. The steric perturbation by the C-9 substitutent caused this difference, a fact which is useful for the structure determination of the natural products.

Experimental Section

Ir spectra were taken in chloroform or potassium bromide with a Hitachi EPI-3 recording spectrometer. Proton NMR spectra were taken with a JNM-PS-100 spectrometer operating at 100 MHz. ^{13}C NMR spectra were obtained in deuteriochloroform (0.3–0.7 *M*) with a JNM-PFT-100 system equipped with a JNM-PS-100 spectrometer operating at 25.15 MHz. Optical rotations were measured with a JASCO PIP-SL automatic polarimeter.

Racemization of (−)-*O*-Methylcapaurine (7). To a suspension of 30 mg of Adams catalyst in 10 ml of methanol which was previously saturated with hydrogen, 30 mg of (−)-*O*-methylcapaurine (7) was added. The mixture was shaken for 50 hr at room temperature and atmospheric pressure. After filtration of the catalyst, the combined filtrate and washing were evaporated and the residue was recrystallized from methanol to give 20 mg of (±)-*O*-methylcapaurine as colorless needles, mp 142–144° (lit.[21] mp 140–142°), $[\alpha]^{25}D$ 0° (MeOH). The ir (in $CHCl_3$) and NMR (in $CDCl_3$) spectra were superimposable on those of (−)-*O*-methylcapaurine.

Racemization of (−)-Capaurine (4). To a suspension of 60 mg of Adams catalyst in 10 ml of methanol which was previously saturated with hydrogen, 60 mg of (−)-capaurine (4) was added and the mixture was shaken for 96 hr under the same condition as above and worked up as before to give 40 mg of (±)-capaurine, mp 207–209° (from methanol) (lit.[21] mp 208°), $[\alpha]^{25}D$ 0° (methanol). The ir (in $CHCl_3$) and NMR (in $CDCl_3$) spectra were superimposable on those of the optically active compound (4).

Acknowledgments. We wish to express our gratitude to Dr. K. Takahashi and Dr. T. Honda, Pharmaceutical Institute, Tohoku University, for their help in the preparation of samples. We also thank Dr. T. Kobari, Mitsui Pharmaceutical Co. Ltd., Miss R. Kato and Miss R. Suenaga of this institute, and Mr. m.|Kunugi of JEOL Ltd. for the spectral measurements.

Registry No.—(−)-4, 478-14-8; (±)-4, 478-15-9; (±)-5, 56437-89-9; (−)-6, 30758-82-8; (−)-7, 6033-73-4; (±)-7, 6033-71-2; (−)-8, 30758-81-7; (±)-9, 56437-90-2; (±)-10, 52346-06-2; (±)-11, 52346-07-3; (±)-12, 56437-91-3; (±)-13, 13407-95-9; (±)-14, 36295-42-8; (±)-15, 29074-38-2; (±)-16, 7762-76-7.

Supplementary Material Available. The ir spectra in potassium bromide for compounds (±)-4, -7, -10, -12, and -13 and (−)-4, -6, -7, and -8 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C., 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3280.

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A New Synthesis of Benzo[*a*]pyrene-6,12-quinone[1]

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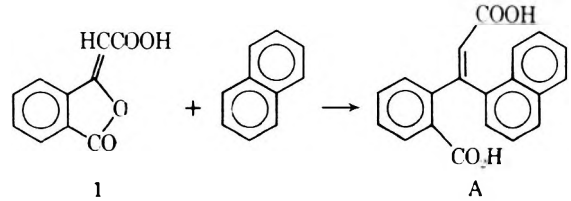
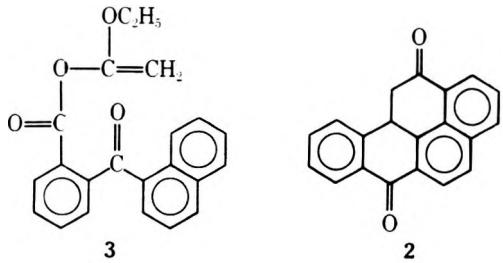
The condensation of phthalideneacetic acid (1) with naphthalene in anhydrous hydrogen fluoride to yield benzo[*a*]pyrene-6,12-quinone (2) has been described.[3] An unsaturated acid, A, was suggested[3] as an intermediate in the formation of 2. Because of previous work on the thermal re-



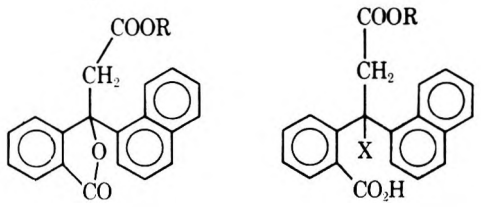
1 A

arrangement of 1-ethoxyvinyl esters of o-benzoylbenzoic acids[4] we were led to study the pyrolysis of 1-ethoxyvinyl o-(1-naphthoyl)benzoate (3) in the hope of obtaining 4, a compound which might be convertible to A. Although we were unable to obtain A by pyrolysis of 4 or of the hydrolysis product 5, we did obtain 3-carboethoxymethyl-3-(1-naphthyl)phthalide (4), which could be hydrolyzed to 3-(*o*-carboxyphenyl)-3-hydroxy-3-(1-naphthyl)propanoic acid (5) and reduced to ethyl 3-(*o*-carboxyphenyl)-3-(1-

naphthyl)propanoate (6) in high yields. Both 4 and 5 could be cyclized to 2 in good yield by anhydrous HF. Attempts to cyclize 6 or 6a to a dihydrodiketone analogous to 2 were

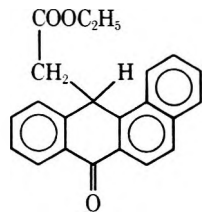


3 2



4. R = C_2H_5 5. R = H; X = OH
4a. R = H 6. R = C_2H_5; X = H
6a. R = X = H

unsuccessful because only the quinone 2 was obtained with HF or polyphosphoric acid (PPA) in addition to quantities of 12-carboethoxymethyl-7-benz[*a*]anthrone (7). If any



7

dihydroketone is formed it must be dehydrogenated in the reaction medium.

Thus, although our original objective to prepare A was unsuccessful, we have been able to effect a new synthesis of 2 and to provide a route which may be useful in preparing derivatives of benzo[*a*]pyrene. The new synthesis involves an intermediate which is closely related to the postulated intermediate, A, in the benzo[*a*]pyrene-6,12-quinone synthesis referred to.[3] However, judging from the fact that the synthesis involving 1 gave appreciable yields only in the case of naphthalene,[3] we believe that the present synthesis offers more versatility.

Experimental Section[5]

1-Ethoxyvinyl 2-(1-Naphthoyl)benzoate* (3). To a solution at −5° of 12.6 g (0.18 mol) of ethoxyacetylene[6] and 0.5 g of mercuric acetate in 100 ml of methylene chloride was added a solution of 16.6 g (0.06 mol) of 2-(1-naphthoyl)benzoic acid,[7] mp 164–167°, in 500 ml of dry CH_2Cl_2 during 30 min while maintaining the temperature below 0°. After 2 hr at room temperature the solvent was removed on a rotary evaporator under reduced pressure and the residue was crystallized from ethyl acetate–petroleum ether (bp 30–60°) to yield 20.76 g (92%) of 3, mp 86–87°, ir bands similar to those of 1-ethoxyvinyl o-benzoylbenzoate.[4] In attempts to purify crude 3 by column chromatography on silica gel, it was converted mainly (ca. 80%) into the n,ψ anhydride[8] of 2-(1-naphthoyl)benzoic acid, mp and mmp 200–201°. The authentic anhydride* was prepared in 79% yield (+15% of recovered keto acid) by treating 5 mmol of ethoxyacetylene with 10 mmol of keto acid in CH_2Cl_2 without mercuric acetate. A pure sample, mp 202–203°, ir bands at 5.6, 5.78, and 6.0 μ, was prepared by recrystallization from ethyl acetate–petroleum ether.

3-Carboethoxymethyl-3-(1-naphthyl)phthalide* (4). In the best of several experiments in which time and temperature of pyrolysis and method of isolation of product were varied, 15.0 g of 3 was heated at 170–180° for 12 hr. Vacuum distillation at 0.5 mm yielded a distillate (12 g) which was recrystallized from methanol to yield 7.6 g (50%) of 4, mp 140–141°, ir bands at 5.68 and 5.8 μ. No pure compound was isolated from the mixture remaining in the mother liquors.

3-(*o*-Carboxyphenyl)-3-hydroxy-3-(1-naphthyl)propanoic Acid (5). A solution of 6.9 g of 4 in 50 ml each of water and methanol containing 8 g of NaOH was refluxed for 3 hr. The solvents were evaporated and an aqueous solution of the residue was extracted with ether (discarded). Acidification afforded crude acid which was recrystallized from benzene–petroleum ether to yield 6.5 g (92%) of 5: mp 222–224° dec; NMR (Me_2SO-d_6) δ 2.45 (s, 2, CH_2), 6.1 (s, 1, OH), 7.2–8 (m, 11, ArH). Although the C, H analysis was 0.4 low for both C and H, 5 was completely converted into 4a on heating with dilute HCl.

3-(Carboxymethyl)-3-(1-naphthyl)phthalide* (4a). On heating 5 with 6 *N* HCl for 2 hr a solid was obtained which afforded pure 4a, mp 206–208, broad ir band from 5.7 to 5.9 μ, in almost quantitative yield.

Ethyl 3-(*o*-Carboxyphenyl)-3-(1-naphthyl)propanoate* (6). A stirred mixture of 4.5 g of 4 and 30 g of zinc (activated by stirring with 10% HCl followed by washing with water, acetone, and anhydrous ether) in 150 ml of glacial acetic acid was held at reflux for 96 hr. After a usual work-up 4.3 g (96%) of 6, mp 132–133°, ir 5.82 and 5.95 μ, NMR ($CDCl_3$, Me_4Si) δ 1.02 (t, J = 7 Hz, 3, CH_3CH_2), 3.15 (d, J = 7.5 Hz, 2, CH_2CH), 4.0 (q, J = 7 Hz, 2, CH_3CH_2), and 6.5 (t, J = 7.5 Hz, 1, CH_2CH), was obtained by crystallization from benzene–petroleum ether.

3-(*o*-Carboxyphenyl)-3-(1-naphthyl)propanoic Acid* (6a). Alkaline hydrolysis followed by acidification afforded 6a, mp 205–207°, in almost quantitative yield after recrystallization from benzene–petroleum ether.

Benzo[*a*]pyrene-6,12-quinone (2). A. HF Cyclizations. To about 50 g of liquid HF condensed in a 200-ml stainless steel bomb[9] held at −10° by a cooling bath was added 1.0 g of 5. The sealed bomb was held at 40–45° for 40 hr. The contents (cooled to below 0°) were poured into ice water and the product was worked up as usual to yield 0.65 g (77%) of 2, mp 320–322° (lit.[3] mp 327° in a block after sublimation and recrystallization). In a similar experiment 1.4 g of 4 was converted into 0.7 g (62%) of 2. Similarly, 0.7 g of 6 afforded 45% of 2 and 0.25 g (38%) of 7,* mp 115–117°, ir bands at 5.8 and 6.05 μ.

B. PPA Cyclizations. A mixture of 2.5 g of 6 and 100 ml of PPA was stirred at 80° for 24 hr and then poured on ice. After the usual work-up there was obtained 1.7 g (72%) of 7 and 0.4 g (20%) of 2 (much less soluble, slower moving on silica gel chromatography), mp 320–324°. Similarly, when 0.64 g of 6a was held at 80° with 40 ml of PPA for 4 hr, there was obtained 0.45 g (80%) of 2 but no dihydrodiketone.

Registry No.—2, 3067-12-7; **3,** 56437-61-7; **4,** 56437-60-6; **4a,** 56437-59-3; **5,** 56437-58-2; **6,** 56437-57-1; **6a,** 56437-56-0; **7,** 56437-55-9; ethoxyacetylene, 927-80-0; 2-(1-naphthoyl)benzoic acid, 5018-87-1; 2-(1-naphthoyl)benzoic acid n,ψ-anhydride, 56437-54-8.

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(5) All melting points and boiling points are uncorrected. Microanalyses by M-H-W Laboratories, Garden City, Mich. The term "worked up in the usual way" means that an ether–benzene solution of the products was washed with suitable aqueous solutions to remove certain impurities, and with saturated salt solution, and dried by dripping through a cone of anhydrous magnesium sulfate. The solvents were then removed by distillation or by use of a rotary evaporator. All new compounds whose analysis agrees with the theoretical within ±0.3% are marked with an asterisk.
(6) Obtained from the Farchan Laboratories, Willoughby, Ohio 44094, and redistilled, bp 50–52°, just before use.
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(8) See ref 4 for discussion concerning the n,ψ structure for the anhydride of o-benzoylbenzoic acid.
(9) Model 4753 from the Parr Instrument Co., Moline, Ill. 61265.

β,β,β′,β′-Tetrabromoazoethenes. Synthesis, Bromine Addition, and Molecular Decomposition

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Ahrens and Berndt[1] have recently succeeded in preparing the first example of a divinyl azo compound (or azoethene), namely, $(t\text{-Bu})_2C{=}CHN{=}NCH{=}C(t\text{-Bu})_2$ (**1**) (in only 4% yield). The uv spectrum of **1** is reminiscent of aromatic dyes and this azoethene was found to be stable upon heating to 180°C. It was of interest to prepare further examples of the azoethene series and to compare the physical properties and chemical reactivity of these compounds with those of aromatic and aliphatic azo compounds.

In the present paper, the debromination of perbrominated ketazines (PBK), $Br_3C{-}CR{=}N{-}N{=}CRCBr_3$ (**2**, R = Ph, and **3**, R = $CHBr_2$), to give β,β,β′,β′-tetrabromoazoethenes, $Br_2C{=}CRN{=}NCR{=}CBr_2$ (**4**, R = Ph, and **5**, R = $CHBr_2$), in 70–75% yield is described and the mechanism of this reaction in various solvents is discussed.

Perbromination of acetophenone azine to give 2,2,2-tribromoacetophenone azine, $Ph(CBr_3)C{=}N{-}N{=}C(CBr_3)Ph$ (**2**), and of acetone azine to give pentabromopropanone azine, $CBr_3(CHBr_2)C{=}N{-}N{=}C(CHBr_2)CBr_3$ (**3**), is accomplished by adding bromine directly to refluxing methylene chloride solutions of the original ketazines. Yields are in the vicinity of 50%. Conversion of **2** to bright red 1,1′-diphenyl-2,2,2′,2′-tetrabromoazoethene (**4**) is achieved by brief refluxing in a mixture of methanol, ethyl acetate, and cyclohexene. This debromination method is inapplicable for **3** apparently as a result of its extreme insolubility. Debromination of **3** is accomplished by refluxing overnight in cyclohexene to give grayish purple 1,1,1′,1′,3,3,3′,3′-octabromo-2,2′-azopropene (**5**).

Perbrominated ketazines **2** and **3** are interesting examples of "bromine carriers", that is, compounds which readily liberate Br_2 upon heating and are regenerated by bromine addition to the resultant olefin at room temperature. While no obvious advantages of these PBK as brominating agents over *N*-bromosuccinimide (NBS) are seen, the liberation of Br_2 by a nonradical mechanism in methanol (and, perhaps, less polar solvents) may have possible utility.

An efficient "bromine carrier" system requires (1) easy removal of Br_2 from a dibromide upon heating and (2) facile addition of bromine to the original double-bond system, i.e.

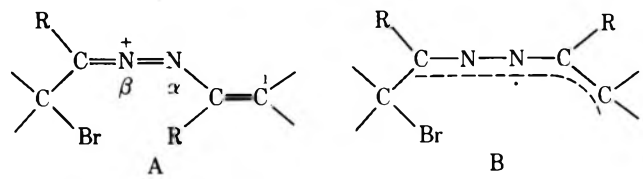
$$X + Br_2 \underset{\Delta}{\overset{\text{room temp}}{\rightleftharpoons}} X{-}Br_2$$

The low exothermicity of bromine addition to carbon double-bond systems (e.g., $CH_2{=}CH_2 + Br_2 \rightarrow CH_2BrCH_2Br$, $\Delta H° = -21.8$ kcal/mol)[2] and the relatively low C–Br bond energy (67 kcal)[3] suggest the possibility of facile removal of bromine from bromine-addition products at elevated temperatures.

A number of bromine carrier systems have been studied which consist of halogenated olefins such as tetrachloroethylene and their bromide-addition products.[4] The electron-withdrawing nature of the geminal halogen atoms in such bromine-addition products reduces the polarity of the $C^{\delta+}{-}Br^{\delta-}$ bond, thereby reducing the C–Br bond energy [e.g., *E* ($Br_3C{-}Br$) = 49 kcal].[3] The bromine transfer from these carriers to alkanes and alkenes appears to involve radical chain reactions and often requires radical initiation.

Unfortunately, the electron-poor double bonds of the halogenated olefins obtained upon loss of Br_2 are not prone to easy electrophilic bromine addition. In fact, bromine addition to such compounds is usually effected through a radical process with the generation of Br· from Br_2 by intense illumination.[5] Furthermore, the debromination of the addition product is not facilitated by the formation of well-stabilized intermediate cations or radicals. Thus, both the Br_2 addition and loss steps are not particularly facile for such haloalkene–alkane systems.

Perbrominated ketazines such as **2** and **3** appeared to be natural candidates for good bromine carriers as a result of (1) the weakening of the C–Br bonds owing to the inductive effect of the geminal bromine atoms, (2) the considerable steric strain resulting from the nonbonding geminal interaction of the CBr_3 and R groups, especially in **3**, and (3) the participation of the central C=N–N=C system to allow facile bromination and debromination through structures such as ionic intermediate A or radical intermediate B. The

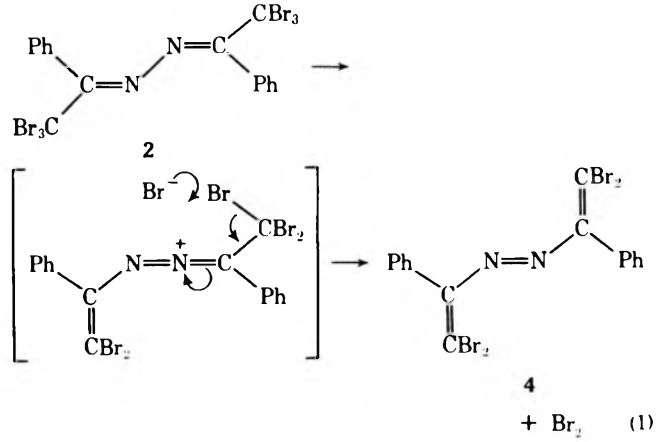


A B

role of structures of type A in the extremely facile solvolyses of α,α′-dichloroazoalkanes has been demonstrated in our earlier work.[6]

The debromination mechanism in the conversion of **2** to **4** was probed in mixed methanol–cyclohexene solvent. Heating **2** overnight at reflux in methanol–cyclohexene (70:30 v/v) gives 45% *trans*-1,2-dibromocyclohexane and 55% *trans*-1-bromo-2-methoxycyclohexane. These results are very close to those obtained by Chretien et al.[7] for the addition of Br_2 to cyclohexene–methanol mixtures and strongly indicate that an ionic reaction obtains in this reaction.

It has long been recognized that the allylic bromination of olefins by NBS involves attack of Br·;[8] NBS bromination of cyclohexene gives ca. 90% 3-bromocyclohexene and *no* addition product.[9] Therefore, the complete absence (<1%) of allylic products is further evidence that Br· is not produced in the initial debromination step. A reasonable ionic mechanism is



2 4

+ Br_2 (1)

It is interesting that the type A cation proposed in reaction 1 does not react by adding MeOH but rather undergoes 100% elimination. This behavior may be attributed, at least in part, to steric hindrance at C_1 and also to the localization of the positive charge on the β-N relative to C_1.

Debromination of **2** by heating in pure cyclohexene at reflux overnight either in ordinary room light or in the dark gives about 70% 3-bromocyclohexene and 30% 1,2-dibromo-

cyclohexane. This result does not lead to an unequivocal mechanistic conclusion.

McGrath and Tedder[10] found that the reaction of molecular bromine with cyclohexene in refluxing CCl_4 yields largely 3-bromocyclohexene. This reaction is very sensitive to the local Br_2 and HBr concentrations. The addition product, 1,2-dibromocyclohexane, was also found. The authors propose a radical mechanism for this reaction through Br·, though competing ionic addition and elimination reactions of Br_2 could also explain the observed results. At any rate, it is clearly impossible on this basis to decide whether Br· or Br_2 (or both) is the attacking species derived from **2** in pure cyclohexene, though the 30% yield of addition product is an indication that at least some Br_2 is formed by a nonradical process as the NBS radical bromination of cyclohexene does not give any additional product (vide supra).

It should be noted that the debromination of **2** in pure cyclohexene is a thermal and not a photoinduced process. Thus, a control solution of **2** held in cyclohexene for 24 hr under ordinary room illumination does not undergo any reaction.

Upon heating to 150° in *o*-dichlorobenzene for 30 min, pentabromopropanone azine (**3**) loses bromine in 80% theoretical yield. The bromine gas evolved may be collected by employing a gentle stream of nitrogen through the reaction solution and into a methylene chloride trap at 0°. The azooctabromide **5** is obtained upon cooling the solution. Thus, **3** is an efficient carrier of molecular bromine.

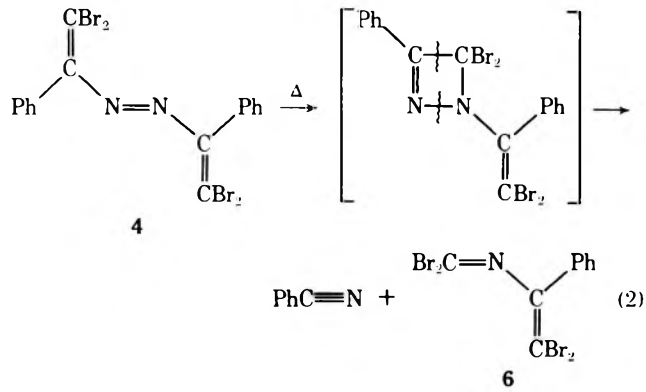
Attempts to follow the apparently first-order kinetics of the loss of Br_2 from **3** in *o*-dichlorobenzene–1-octene at 108° were unsuccessful as other colored products arise, probably from further reaction of **5**. A half-life of about 30 min can be estimated at this temperature by following the growth in the uv band at 502 nm for the products, **5**.

Both azoethenes **4** and **5** react quantitatively with Br_2 in CH_2Cl_2 solution at room temperature. The bromine addition to **4** is essentially instantaneous and with **5** requires 30 min for complete reaction; the sluggishness of **5** may be attributed to both the greater steric hindrance in the addition product **3** relative to **2** as well as to extreme insolubility of **5**. Azoethene **4** is inert to both Cl_2 and I_2 in CH_2Cl_2 at room temperature. The lack of reaction with Cl_2 is likely a result of the unfavorable interaction of highly electrophilic chlorine with the electron-poor double bonds in **4**. The failure of the addition of I_2 to **4** is probably due to steric hindrance and/or thermodynamic factors, i.e., the release of I_2 by the possible iodine-addition product of **4** proceeds more rapidly at room temperature than the I_2 addition.

The uv absorptions of these $\beta,\beta,\beta',\beta'$-tetrabromoazoethenes are reminiscent of aromatic azo compounds. Thus, for **4** (in benzene), λ_{max} 353 nm (log ϵ 4.36), 478 (2.59), for **5** (in benzene), λ_{max} 354 nm (log ϵ 4.38), 502 (2.52), and for (*E*)-azobenzene (in EtOH),[11] λ_{max} 319 nm (log ϵ 4.34), 443 (2.71).

Azoethene **1** was found to be stable upon heating to 180°C.[1] On the other hand, heating **4** at reflux in chlorobenzene for a few hours leads quantitatively to a colorless, crystalline product $C_9H_5NBr_4$ with the probable structure $Br_2C{=}NC(Ph){=}CBr_2$ (2-aza-3-phenyl-1,1,4,4-tetrabromo-1,3-butadiene, **6**). This same product may also be obtained by heating neat **3** to 190° in a test tube, whereupon melting with decomposition occurs; PhCN is obtained on the walls of the test tube. The ir, NMR, and uv spectral evidence is consistent with the proposed structure **6**; the ir bands at 1674 and 1623 cm^{-1} can be assigned to C=N and C=C bond stretching, respectively.

A possible mechanism for this molecular rearrangement involves prior conrotatory ring closure.



4

(2)

6

The rate of the first-order conversion of **4** to **6** at 119° in chlorobenzene subjected to prior bubbling with a nitrogen stream was followed by the disappearance of the peak at 478 nm and found to be 5.46×10^{-3} min^{-1}.

Azoethene **4** is stable upon heating neat to 190° but undergoes decomposition at 220°. Dibromoacetonitrile was not found among the decomposition products.

Experimental Section

2,2,2-Tribromoacetophenone Azine (2). A solution was prepared containing 10.0 g (0.042 mol) of acetophenone azine in 50 ml of CH_2Cl_2 in a round-bottomed flask equipped with a condenser. A dropping funnel with an equalizer arm was attached on top of the condenser. Bromine (41 g, 0.26 mol) was added dropwise over 40 min while the solution was heated at reflux with magnetic stirring. Heating at reflux was continued for 1 hr after bromine addition. The solvent was removed by rotary evaporation and the dark red mass remaining triturated with methanol. The unstable yellow crude product was collected on a Buchner funnel, then dissolved at room temperature in CH_2Cl_2 (10 ml per 1 g of crude product) and recrystallized at −20°, giving light yellow needles of **2** which slowly decompose upon standing in the air (11.9 g, 40%): mp 170° dec; ir (Nujol) 1715, 1610, 1592, 1449, 1250, 1080, 1028, 824, 781, 747, 730, 710, 650 cm^{-1}; NMR ($CDCl_3$) τ 2.50 (apparent s).

Anal. Calcd for $C_{16}H_{10}N_2Br_6$: C, 27.08; H, 1.42; N, 3.95; Br, 67.55. Found: C, 27.01; H, 1.36; N, 3.90; Br, 67.62.

Pentabromopropanone-2 Azine (3). This preparation, involving the bromination of acetone azine, was analogous to the preparation of **2** described above. After bromine addition, the reaction solution was heated at reflux overnight. The crude product was recrystallized from toluene (50 ml per 1 g of crude product) to give yellow needles of **3** (yields were about 60%), mp 227° dec, which are stable in the air: ir (KBr) 3010, 1660, 1610, 1390, 1150, 900, 785, 760, 730 cm^{-1}; MS (100 eV, 180° probe temperature) M^+ (rel intensity, 2, 11-line pattern for 10 Br), $(M - Br)^+$ (100), $(M - C_2H_2Br_4N)^+$ (70).

Anal. Calcd for $C_6H_2N_2Br_{10}$: C, 8.00; H, 0.22; N, 3.11; Br, 88.67. Found: C, 8.08; H, 0.19; N, 3.09; Br, 88.70.

1,1′-Diphenyl-2,2,2′,2′-tetrabromoazoethene (4). Crude **2** (10 g, 0.014 mol) was added to a mixture of 30 ml of methanol, 30 ml of ethyl acetate, and 0.5 ml of cyclohexene and heated to reflux. Shortly before the onset of reflux, bright red crystals appeared in the solution mixture and heating at reflux was continued for an additional 5–10 min until all **2** was debrominated, giving **4**. The solution was cooled rapidly and crude **4** was recrystallized from EtOAc–EtOH (2:1 v/v) (45 ml for 1 g) to give brilliant red platelets which are stable in a sealed evacuated ampoule, decompose after a few days in a closed nonevacuated vial, but are stable in the open air for about 1 month: mp 192° dec; 5.4 g (70%); ir (Nujol) 1540, 1265, 1180, 1092, 1080, 1035, 1005, 894, 811, 761, 703, 655 cm^{-1}; uv (benzene) λ_{max} 353 nm (log ϵ 4.36), 478 (2.59); NMR ($CDCl_3$) τ 2.5–3.0 (m). Bromine addition (in CH_2Cl_2): 1.2675 g of **4** gives 1.6358 g of **2** (99.99%).

Anal. Calcd for $C_{16}H_{10}N_2Br_4$: C, 34.95; H, 1.83; N, 5.09; Br, 58.13. Found: C, 35.01; H, 1.87; N, 5.10; Br, 58.05.

1,1,1′,1′,3,3,3′,3′-Octabromo-2,2′-azopropene (5). Crude **3** (3.0 g, 3.3 mmol) was added to cyclohexene and heated at reflux for 24 hr. The resulting red solution was cooled and grayish purple, circular platelets of **5** (1.83 g, 75%) were collected: mp 179° [from 10 ml of EtOAc–C_6H_6 (1:1 v/v) for 1 g]: ir (Nujol 1534, 1260, 1220, 1150, 938, 872, 739, 700 cm^{-1}; uv (benzene) λ_{max} 354 nm (log ϵ 4.38), 502 (2.52); NMR (CCl_4) τ 2.87 (s); MS (100 eV, 150° probe tempera-

ture) M^+ (rel intensity, 22, nine-line pattern for 8 Br) $(Br_2C{=}N{=}CBr_2)^+$ (100).

Anal. Calcd for $C_6H_2N_2Br_8$: C, 9.72; H, 0.27, N, 3.78; Br, 86.23. Found: C, 9.55; H, 0.25; N, 3.64; Br, 86.39.

2-Aza-3-phenyl-1,1,4,4-tetrabromo-1,3-butadiene (6). A sample of azoethene **2** (1.0 g, 1.8 mmol) was heated neat in a test tube to 190°. The black mass obtained was cooled and 5 ml of methanol was added. White square platelets (0.65 g, 80%) of azabutadiene **6** were obtained, mp 60° (MeOH). The liquid droplets condensed on the test tube wall were shown to be benzonitrile by ir.

Similarly, **6** was prepared by heating a solution of **2** (1.0 g, 1.8 mmol) in chlorobenzene at reflux for 4 hr until the originally deep red solution was practically colorless, evaporation of the solvent, and trituration with MeOH: yield 0.80 g of **6** (100%, 71% after MeOH); ir (CCl_4) 3062, 1674, 1623, 1490, 1447, 1060, 870, 697, 650 cm^{-1}; uv (methanol) end absorption; NMR (CCl_4) τ 2.61 (apparent s); MS (100 eV, 150° probe temperature) M^+ (rel intensity, 14, five-line pattern for 4 Br), $(M - Br_2CN)^+$ (100).

Anal. Calcd for $C_9H_5NBr_4$: C, 24.19; H, 1.13; N, 3.14; Br, 71.54. Found: C, 24.19; H, 1.25; N, 3.13; Br, 71.35.

Bromine Generation from Ketazine 3. A solution was prepared containing 12 g (0.033 mol) of ketazine **3** in 20 ml of o-dichlorobenzene in a 50-ml round-bottomed flask connected to a trap containing methylene chloride at 0°. The solution was heated at 150–170° for 30 min with a nitrogen stream bubbling through the system. The bromine collected in the trap was titrated with 850 mg of cyclohexene (10.3 mmol, 77%) and azopropene **5** (8.8 g, 89%) was recovered as a crystalline solid.

Registry No.—**2**, 56454-39-8; **3**, 56454-40-1; **4**, 56454-41-2; **5**, 56454-42-3; **6**, 56454-43-4; acetophenone azine, 729-43-1; bromine, 7726-95-6; acetone azine, 627-70-3.

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A Novel High-Yield Synthesis of γ Esters of Glutamic Acid and β Esters of Aspartic Acid by the Copper-Catalyzed Hydrolysis of Their Diesters

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Benzyl esters have a unique place in peptide synthesis for the reversible protection of side-chain carboxyl groups.[1] These esters are relatively stable to the mildly acidic and basic conditions of peptide synthesis, but can be easily removed at the end of the synthesis by strongly acidic or reductive cleavage.[2] A problem with benzyl esters, however, is that they are not completely stable to reagents commonly used to remove the α-NH_2 *tert*-butyloxycarboxyl protecting group (e.g., trifluoroacetic acid–dichloromethane, 1:1) and are slowly hydrolyzed by these reagents.[3]

This lability can cause difficulties in long syntheses, giving rise to cumulative loss of side-chain protection and hence to branching of the peptide chain. To prevent the occurrence of this problem, more stable carboxyl-protecting groups are needed. These groups are also useful for the solid-phase synthesis of protected peptide fragments, which can be achieved by the use of side-chain protecting groups[4] which are completely stable to the reagents used to cleave the peptide from the resin (e.g., HBr in acetic acid).

For these reasons, substituted benzyl esters have been used by several workers[5-7] for side-chain carboxyl protection, although the use of such esters has been hindered by a lack of methods for their facile preparation. For example, the *p*-nitrobenzyl esters of Schwarz and Arakawa[5] can best be prepared by the procedures of Ledger and Stewart,[6] which involve the preparation of the copper complex of the amino acid, and the subsequent esterification of this copper complex with *p*-nitrobenzyl halide. This method is lengthy, however, and yields are low. The selective hydrolysis of aspartic and glutamic acids diesters which is described in this communication provides a method for the preparation in high yield of a wide range of monoesters by a very simple procedure.

In this procedure the amino acid is converted to the appropriate diester salt, using well-established procedures.[1,8,9] Without further purification the diester is then hydrolyzed by aqueous copper sulfate, and the copper complex of the desired monoester is isolated by filtration. After the copper complex has been decomposed with EDTA by the method of Ledger and Stewart,[6] the monoester can be isolated in a pure form by a single recrystallization.

In a typical copper hydrolysis, glutamic acid dibenzyl ester *p*-toluenesulfonate (10 g, 20 mmol) was dissolved in ethanol (140 cm^3) and aqueous $CuSO_4 \cdot 5H_2O$ (20 g, 80 mmol in water, 350 cm^3) was added. The pH was raised to 8.0 with 1 *M* NaOH, and the solution was maintained at that pH and 32°C for 60 min. The pH was then lowered to 3.0 with 3 *M* HCl and the precipitate of the copper complex of Glu(γOBzl)[10,11] was filtered off and washed with water, ethanol, and ether. Ethylenediaminetetraacetic acid disodium salt (7.8 g, 21 mmol) in 100 cm^3 of water was added, the solution was boiled and filtered, and on cooling, glutamic acid γ-benzyl ester precipitated out. The product was collected by filtration and washed with water, ethanol, and ether: yield 3.5 g (14.8 mmol, 74%); mp 169–170°; $[\alpha]^{22}D$ +19.3° (c 5.49, acetic acid) (lit. mp 169–170°, $[\alpha]^{25}D$ +19.2).[6]

The yields for various esters of glutamic and aspartic acids are given in Table I.

Terashima et al.[12] have proposed a structure for the copper complexes of aspartic and glutamic acids where both the amino nitrogen and one of the carboxyl oxygens are coordinated to the copper atom only if a five-membered ring is formed. This proposal was confirmed by the absence in the hydrolysis product of any trace of the α-monoesters of aspartic and glutamic acid or of the free amino acids.[13]

The mechanism of the copper-catalyzed hydrolysis of amino acid esters has been suggested[14] to proceed by OH^- attack on the carbonyl group of the copper coordinated ester linkage. If this is the case, the rate of hydrolysis should be increased by electron-withdrawing substituents on the ester group. To test this hypothesis, the rate of the copper hydrolysis reaction for various glutamic acid diesters was measured. Samples of the reaction mixture were quenched with dilute acid, treated with EDTA, and chromatographed on silica gel plates, using a 1-butanol–acetic acid–pyridine–water (15:3:10:12) solvent. The γ-ester spots

Table I
Yield of Asp and Glu Diesters Prepared by the Copper-Catalyzed Hydrolysis of Corresponding Diesters

Ester	Crude yield,[a] mol %	Yield of recrystd ester, mol %	Mp, °C	Lit. mp, °C	Registry no.
Glu (OBzl)	95	74	169–170	169–170[b]	1676-73-9
Glu (OBzl-*p*-Cl)	93	54[c]	169–170	176[d]	20806-20-6
Glu (OBzl-*p*-NO_2)	87	54[c]	158–159[e]	171–172[f]	3940-62-3
Glu (OMe)	99		180[d]	182[d,g]	1499-55-4
Glu (OEt)	96		192–194	194[g]	1119-33-1
Asp (OBzl)	98	67	220–222	221[h]	2177-63-1
Asp (OBzl-*p*-Cl)	98	83	208–210	208[h]	14335-22-9
Asp (OBzl-*p*-NO_2)	97	88	193–195	189–190[f]	3940-63-4
Asp (OMe)	98		188–190[i]	191–193[g,i]	2177-62-0

[a] Measured by TLC of an aliquot of the reaction mixture. [b] J. Noguchi, *Chem. Abstr.*, 59, 10238 (1963). [c] The reduced yield of these esters is possibly due to their very low solubility in all common solvents. [d] M.-H. Loucheux and M. J. Parrod, *C. R. Acad. Sci., Ser. C*, 267, 614 (1968). [e] It has been observed that this compound may show more than one distinct melting point, presumably because of the existence of several crystalline forms. [f] Reference 6. [g] Reference 1, p 929. [h] M. Hashimoto and J. Aritomi, *Bull. Chem. Soc. Jpn.*, 39, 2707 (1966). [i] As hydrochloride.

Table II
Rate Constants for the Cu(II)-Catalyzed Hydrolysis of Glutamic Acid Diesters

Diester	Rate[a], min^{-1}	Registry no.
Glu (OBzl-*p*-NO_2)$_2$	0.54	47662-90-8
Glu (OBzl)$_2$	0.54	2768-50-5
Glu (OBzl-*p*-Cl)$_2$	0.14	56437-39-9
Glu (OMe)$_2$	0.070	6525-53-7
Glu (OEt)$_2$	0.067	16450-41-2
Glu (OEt 2-Cl)$_2$	0.050	56437-40-2

[a] pH 8, 32°.

were visualized with ninhydrin and the ninhydrin color eluted with ethanol and measured at 250 nm. The rates of the reaction are given in Table II.

The rates are consistent with the mechanism proposed, in that the ethyl ester reacts more slowly and the benzyl ester more rapidly than the methyl ester. Esters substituted with chlorine, however, react more slowly than do unsubstituted esters, in spite of the electron-withdrawing nature of the chlorine moiety. This anomaly is probably due to the large volume occupied by a chlorine atom, as reactions of amino acid copper complexes appear to be very susceptible to steric hindrance.[12]

Registry No.—Dibenzyl aspartate, 2791-79-9; *p*-chlorodibenzyl aspartate, 56437-41-3; *p*-nitrodibenzyl aspartate, 47636-64-6; dimethyl aspartate, 6384-18-5.

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Simple, Novel Deaminations. VII.[1,2] The High-Yield Conversion of Primary and Secondary Carbinamines to Alcohol and Formate Esters via Nucleophilic Substitution of Protonated Sulfonimide Derivatives

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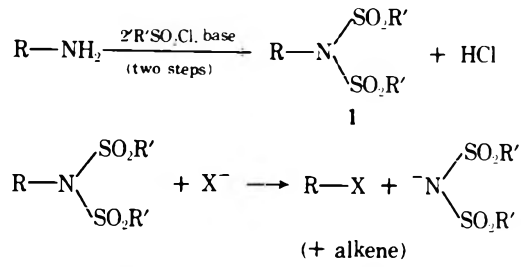
The conversion of the aliphatic primary amino group to the primary hydroxyl group has been, historically, relatively difficult to achieve. Until now the apparent best yielding procedures (25–90%) involve the pyrolysis of *N*-nitrosoamides[4] or the treatment of arylalkyl triazenes with carboxylic acids.[5] Both of these methods exclusively produce esters as the carbon–oxygen product. To obtain the alcohol, a subsequent ester hydrolysis is obligatory. Moreover skeletal rearrangements are common, although in nonpolar solvents the occurrence of this problem is reduced, presumably because the mechanism in nonpolar solvents is usually SN2.[4-6]

In previous papers in this series,[1-3,7,8] it has been found that various sulfonimide activating groups (1), analogous to various sulfonate ester activating groups in the alcohol series, are readily susceptible to nucleophilic substitution (Scheme I). These processes occur with ease, most probably because sulfonimide anions are weak bases compared to NH_2^- anions, and consequently sulfonimide anions are relatively good leaving groups. For example, in these and other laboratories, primary and secondary carbinamines have been converted, usually in high yields, to alkyl halides,[2,3,8,9] to alkenes,[1-3,7-9] to ketones,[1] and to alkanes[12] and other functional groups.[2,3,8,9,11,13]

Results

However, all our attempts to convert these activated sulfonimide derivatives (1) to alcohols via the use of the hydroxide anion as a nucleophile have been essentially unsuc-

Scheme I



where R = various primary or secondary alkyl groups
R′ = *p*-$CH_3C_6H_4$, C_6H_5, *p*-BrC_6H_4, *p*- and *m*-$NO_2C_6H_4$, and CF_3
X = Cl^-, Br^-, I^-, SH^-, N_3^- and aniline

cessful, presumably owing to the highly preferential saponification at the sulfur–nitrogen bond. If, however, conditions could be designed to increase the susceptibility of the C–N bond to nucleophilic cleavage and/or to decrease the susceptibility of the S–N bond to saponification, then the conversion of the C–N bond to the C–O bond may be easily achieved. Such conditions are apparently obtained when various sulfonimides (**2**, **4**–**8**) are heated at 50–130° with ca. 58% aqueous hydrogen iodide in dimethylformamide (DMF); under these conditions, the already good sulfonimide leaving group is apparently further activated by protonation.[14a] For example, when *N*-*n*-hexyl-*N*,*N*-di(*p*-toluene)sulfonimide (**2**) is treated with a two- to threefold molar excess of 58% aqueous HI in DMF for 94 hr at 125°, a 98% conversion of the C–N bond to the C–O bond is indicated by the isolation and characterization of 1-hexanol (60.3%), 1-hexyl formate (37.6%), and the di(*p*-toluene)sulfonimide leaving group (**3**) in 99% yield.

Results under various conditions are summarized in Table I. These results indicate that the method worked essentially as well for a typical secondary carbinamine as for a typical primary carbinamine. Not surprisingly, however, activated cyclohexylamines (**7** and **8**) gave only cyclohexene. Under analogous conditions similar results were obtained when known iodocyclohexane or known cyclohexanol were substituted for sulfonimide-containing cyclohexyl substrates. In fact, cyclohexyl substrate **8** has been shown to undergo thermal elimination (in up to 70% yield by gas chromatography) simply by refluxing in DMF without added nucleophiles or acid.

The experimental procedures involved in characterizing and isolating the products of these deaminations are simple. In particular, a very efficient procedure for preparing sulfonimides has been developed in our laboratories,[2,3,8,9] and all the acid-induced runs on these substrates were clean and efficient. Most important, all of the runs proceeded to give 90–98% yields of products *without any observed skeletal rearrangement*.

The products were qualitatively and quantitatively analyzed with the aid of GLC, ir, and NMR, as well as by comparison with known synthetic or commercial standards. The alcohols were further characterized via their 3,5-dinitrobenzoate ester derivatives. The protonated sulfonimide leaving groups were isolated as crystalline compounds and identified by comparison of various physical properties with those of known materials synthesized by other means. Since the yields of the protonated sulfonimide leaving group in these runs were in the order of ~99%, the present-

Table I
Products[a] from Reaction of Various *N*-Alkyl-*N*,*N*-disulfonimides with Aqueous HI in DMF

Compd	Structure[b]	Conditions[c]	Products[d] (% yield)[e]
2	*n*-Hexyl-$N(Ts)_2$	DMF, 125°	1-Hexanol (60.3)
	mp 114.9–115.2°	94 hr	1-Hexyl formate (37.6)
			3 (99.0)
4	*n*-Hexyl-$N(Bs)_2$	DMF, 130°	1-Hexanol (55.5)
	mp 99.8–100.0°	72 hr	1-Hexyl formate (35.6)
			$(Bs)_2NH$ (97.7)
5	*n*-Hexyl-$N(Ns)_2$	DMF, 100°	1-Hexanol (57.5)
	mp 132.8–133.1°	47 hr	1-Hexyl formate (38.6)
			$(Ns)_2NH$ (99.6)
	(1-Iodohexane)[f]	DMF, reflux	1-Hexanol (50.4)
		96 hr	1-Hexyl formate (35.0)
6	*dl*-2-Heptyl-$N(Ns)_2$	DMF, 50°	2-Heptanol (8.0)[g]
	mp 129.0–131.0°	24 hr	2-Heptyl formate (89.6)
			$(Ns)_2NH$ (98.0)
7	Cyclohexyl-$N(Bs)_2$	DMF, 100°	Cyclohexene (73.7)[h]
	mp 189.0–190.0°	46 hr	$(Bs)_2NH$ (98.2)
8	Cyclohexyl-$N(Ns)_2$	DMF, 85°	Cyclohexene (90.2)[h]
	mp 193.0–195.0°	48 hr	$(Ns)_2NH$ (98.6)

[a] All products were isolated directly, independently separated, and fully characterized. [b] The synthesis, purification, structural assignments, and further physical data for each of these starting materials are thoroughly outlined in ref 3. Abbreviations: Ts = *p*-toluenesulfonyl, Bs = *p*-bromobenzenesulfonyl, and Ns = *p*-nitrobenzenesulfonyl. [c] Solvent, temperature (°C), and reaction time. Reaction times were extended in order to maximize yields; it is likely that shorter times in some instances could produce similar yields. [d] All volatile products were characterized by ir, proton NMR, and GLC behavior in comparison with known synthetic or commercial standards. The alcohols were additionally converted into their 3,5-dinitrobenzoate esters. The protonated leaving group, **3**, and its analogs, were fully characterized as noted in ref 3. [e] Numbers listed indicate *mole* percentages of each compound based on the disulfonimide as limiting reagent; i.e., the sum of the percent yield for alcohol and ester is a direct measure of the total C–N to C–O conversion. Each reaction was run at least in duplicate and the yields noted are easily reproducible. In the cases of alcohol–ester mixtures, quantitative analysis was performed by the internal standard GLC method (cf. Experimental Section) on the in-hand, isolated, two-component mixture. [f] Known, control reaction; no evidence of iodoalkane at end of reaction period. [g] Trace amounts of *cis*- and *trans*-2-heptene also noted in this run. The 2-heptenes (with the trans isomer predominating) are artifactual side products derived presumably from the initially produced substitution products. Under kinetically controlled conditions, the olefins(s) can be noted to accumulate later in the reaction period; the amount of olefinic product, which can be significant at elevated temperatures, can be controlled and essentially eliminated by lower temperatures and shorter reaction times. [h] No substitution products elicited by GLC. See also discussion in text.

ly reported reaction may also be considered to be an excellent procedure for making sulfonimides. No previously reported procedures give such good yields of these sulfonimides.[14b] For a complete detailed listing of physical properties, melting points, literature citations, etc., see ref 3, Table V.

A hypothetical mechanism for the reaction is given in Scheme II. A detailed discussion of the mechanism of this reaction will be presented in a later paper.

Scheme II

Step 1[10] $R{-}N(SO_2Ar)_2 + HI \rightleftharpoons R{-}\underset{+}{NH}(SO_2Ar) + I^-$ (9)

Step 2 $9 + I^- \rightleftharpoons R{-}I + HN(SO_2Ar)_2$

Step 3 $RI + H_2O \rightleftharpoons [ROH_2^+]I^- \overset{base}{\rightleftharpoons} ROH$

Step 4 $ROH + \underset{\text{(from DMF)}}{HCO_2H} \overset{H^+}{\rightleftharpoons} ROC(=O){-}H + H_2O$

Experimental Section

Materials. All chemicals used in these preparations were reagent grade or better. The DMF was spectrophotometric grade (Fisher Scientific Co.) and the *o*-dichlorobenzene was Aldrich reagent grade.

Instrumentation. Melting points, ir, proton NMR, and analytical gas–liquid partition chromatography (GLC) were performed on instruments described in Part V in this series.[3] The reaction mixtures were routinely examined for homogeneity, maximum number of products, or diagnostic experiments (such as GLC of known mixtures, peak enhancement experiments, temperature programming, etc.) on various columns of varying polarity which included 10% QF-1 and 10% Carbowax 20M on 60/80 mesh Chromosorb W, and 10% SE-30, 5 and 10% DEGS, and 10% FFAP on 80/100 Chromosorb W. (All solid supports were acid washed, DMCS treated.) The quantitative analysis of the liquid mixtures was performed on an F & M Scientific Hewlett-Packard Model 407 high-efficiency gas chromatograph using the 10% Carbowax 20M column (6 ft × 0.125 in.), a column temperature of 95°, and helium as the carrier gas. These conditions were used for both the standardizations and the unknown determinations. Response factors for the 1-hexanol and 1-hexyl formate vs. the internal standard, *o*-dichlorobenzene, were obtained from the least-square slopes of the plots of known weight ratios vs. area ratios. GLC peak areas in this study were estimated by chromatographing, cutting out the peaks directly, and weighing in triplicate, and the average value was taken for each solution. The response factors were validated for the concentration range normally encountered.

For quantitative purposes commercial reagent grade 1-hexanol and 1-hexyl formate (both of which had several unidentified impurities by analytical GLC) were both preparatively chromatographed on a Hewlett-Packard 776 Prepmaster Jr. instrument using an 80 × 0.75 in. 20% Carbowax 20M column at 85°. The analytically pure samples thus obtained were then used to obtain the response factor vs. the internal standard as noted above. With the aid of these factors, quantitative analytical GLC was used to determine the compositions of the mixtures noted in Table I.

Deaminations in DMF with Aqueous Hydriodic Acid (Methods). The results of all trials are recorded in Table I. All experiments were similarly conducted, and only samples will be presented in detail. It should be noted that all isolations of liquids included bulb-to-bulb distillations. It was essential for maximum efficiency (and yield) in these distillations to wrap the glass tubing between the bulbs with a 4 ft × 0.75 in. heating tape (Glas-Col), and to maintain magnetic stirring of the reaction mixture after one freeze–evacuation (to ca. <0.1 mmHg)–thaw cycle.

The *N*-alkyl-*N*,*N*-di(sulfonimides) (**2**, **4**–**8**) were prepared and identified by the procedures previously described in Part V in this series.[3]

Deamination of 2 with Aqueous HI in DMF. 2 (40.96 g, 0.10 mol), mp 114.9–115.2°, was dissolved in 100 ml of DMF and 43.88 g (0.20 mol) of 58.3% HI added. The mixture was heated to ca. 125° for 94 hr under reflux. The reaction mixture was then bulb-to-bulb distilled; the distillate was mixed with 50 ml of water and extracted with ten 20-ml portions of diethyl ether. The combined ether extracts were then washed with two 50-ml portions of water and dried (Na_2SO_4). The ether was distilled off and nitrogen was passed over the remaining water-white liquid for 10 min. This residue was then washed with 2 × 10 ml of water and dried over type 4A molecular sieves. The product obtained, a mixture of 1-hexanol and 1-hexyl formate, totaled 11.06 g. Quantitative GLC determination of the product mixture yielded 4.90 g of 1-hexyl formate (37.6 mol%) and 6.16 g of 1-hexanol (60.3 mol%). In addition, similar mixtures from other runs of this preparation were separated and independently isolated by preparative GLC. Both products thus derived were identical with known standards in ir, proton NMR, and analytical GLC retention behavior. The 1-hexanol was also characterized by its 3,5-dinitrobenzoate ester derivative (mp 58.0°, lit.[15] mp 58.4°). This derivative had an ir, melting point, and mixture melting point identical with those of the 3,5-dinitrobenzoate of known 1-hexanol.

The solid residue left behind in the bulb-to-bulb distillation was recrystallized from 1500 ml of benzene, yielding 29.67 g of **3**, mp 168–169° (lit.[3] mp 168–169°). Concentration of the mother liquor yielded 2.53 g more of **3**, mp 168–169°. Thus a total yield of protonated leaving group of 32.20 g (99.0%) was obtained. Isolated **3** also had an ir and proton NMR identical with those of known **3**.

Disulfonimides **4** and **5** were similarly deaminated, worked up, the resultant products GLC analyzed, and the results noted in Table I.

Deamination of 7 with HI in DMF. 7 (13.43 g, 0.025 mol), mp 189–190°, was dissolved in 40 ml of DMF, 10.97 g (0.050 mol) of 58.3% HI was added, and the mixture was heated at ca. 100° for 46 hr under reflux. After bulb-to-bulb distillation, the distillate was fractionally distilled to yield 1.51 g (73.7 mol%) of cyclohexene, bp 82–83°, which was homogeneous to GLC. The product had an ir spectrum (neat) which was identical with that of an authentic sample of freshly distilled cyclohexene. The protonated leaving group was recrystallized from 100 ml of 4:1 (v:v) water–acetone, yielding 9.25 g of di(*p*-bromobenzene)sulfonimide, mp 232–233° (lit.[3] mp 232–233°). Concentration of the mother liquor gave 2.03 g more, mp 232–233°. Thus a total yield of 11.28 g (98.2%) was isolated. As in the above preparation, the isolated protonated leaving group had ir and proton NMR identical with those of known material synthesized by literature methods (for citations see ref 3).

Cyclohexyl substrate **8** was similarly treated and analyzed.

The HI runs on the *dl*-2-heptyl substrate (**6**) were performed and analyzed analogously. The 3,5-dinitrobenzoate ester of the product 2-heptanol had mp 49.0–50.5° (lit.[16] mp 48.5–50°); the ir spectrum (CCl_4), melting point and mixture melting point of known 2-heptyl 3,5-dinitrobenzoate and the derivatized reaction product were identical. Known 2-heptyl formate was made by the method of Staab[17] using *N*-formyl imidazolide. This product was used for the internal standard GLC analysis, and was identical in all respects (ir, NMR, and analytical GLC behavior) with the ester product formed in the reaction.

In an identical run on the 2-heptyl substrate, the product mixture after ethereal extraction was further diluted and then refluxed overnight with a 3 molar excess of freshly opened $LiAlH_4$. Work-up included decomposition of the excess hydride with very dilute aqueous H_2SO_4, filtration, washing, drying (4A molecular sieves), and removal of the ether. These procedures provided an essentially pure (only a trace of unreduced 2-heptyl formate was elicited by GLC) 2-heptanol in 94.7% yield (based on **6**), which was identical in all respects with known material.

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Registry No.—**2**, 24332-41-0; **3**, 3695-00-9; **4**, 52374-06-8; **5**, 24332-42-1; **6**, 52374-08-0; **7**, 52374-15-9; **8**, 24332-44-3; 1-hexanol, 111-27-3; 1-hexyl formate, 629-33-4; $(Bs)_2NH$, 1156-18-9; $(Ns)_2NH$, 4009-06-7; 2-heptanol, 543-49-7; 2-heptyl formate, 56282-06-5; cyclohexene, 110-83-8.

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A Novel Method for Sulfinylation Reaction of Lithioamines Using Sulfur Dioxide

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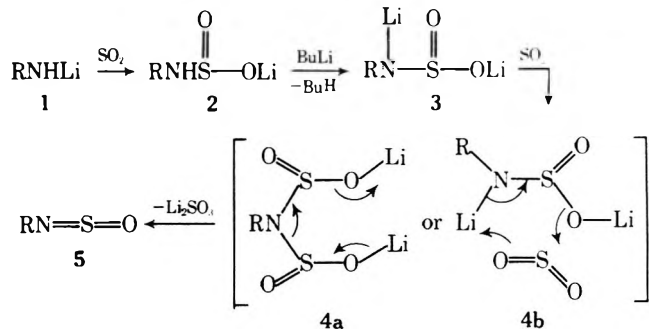
Thionyl chloride is usually used as a sulfinylating reagent of amines or amides in the presence of base such as pyridine or trimethylsilyl amide.[1-9] In connection with a utilization of sulfur dioxide, we have found a novel and direct sulfinylation reaction of lithioamines with sulfur dioxide to afford *N*-sulfinylamines.

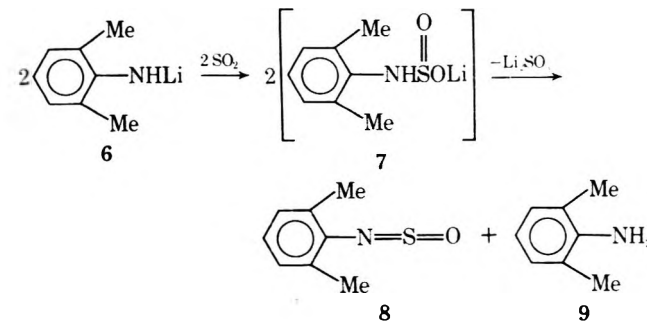
The lithioamine **1** prepared in situ from primary amine and butyllithium in tetrahydrofuran was treated with an equimolar amount of sulfur dioxide to form lithium aminosulfinate **2**. The A_2B_2 signals in the NMR spectra were shifted downfield from δ 6.07 and 6.47 for **1** to 6.39 and 6.59 for **2** (R = *p*-$CH_3C_6H_4$). Lithium *N*-(*p*-tolyl)aminosulfinate (**2**) was allowed to react with butyllithium to afford butane and the *N*-lithio-*N*-tolylaminosulfinate **3** (R = *p*-$CH_3C_6H_4$), which showed a new broad singlet at δ 6.66 in the NMR spectrum. Subsequently, introduction of a second mole of sulfur dioxide caused exothermic reaction and the characteristic bands of ν_{NSO} appeared at 1280 and 1157 cm^{-1} in the ir spectrum of the reaction mixture. After refluxing, the reaction mixture was distilled to separate *N*-sulfinyltoluidine **5** (R = $CH_3C_6H_4$).



The formation of *N*-sulfinyltoluidine by heating the intermediate **2** or **3** could not be observed even in the ir and NMR spectra of the reaction mixture, so the role of the second mole of sulfur dioxide is essential in the preparation reaction for *N*-sulfinylamine **5**. On the other hand, in the presence of the second mole of sulfur dioxide, **3** was easily decomposed to afford **5** and lithium sulfite which was detected by the $\nu_{SO_3^{2-}}$ bands of inorganic sulfite at 1010 and 960 cm^{-1} in the ir spectrum of solid mass in a distillation residue. Although the intermediate or transition state, **4a** or **4b**, could not be identified even by spectroscopic method such as ir or NMR, it will be postulated to explain the observed accelerating effect of the second mole of sulfur dioxide in the decomposition reaction of **3**. The same phenomena have also reported in the cases of the reaction of lithium *N*-lithiocarbamate with carbon disulfide to give isothiocyanate[10] and of the exchange reaction of heterocumulenes using organostannyl compounds.[11]

In usual cases for preparation of sulfinylamines, 2 mol each of butyllithium and sulfur dioxide per 1 mol of amine were used stepwise. The NMR data for the product mixtures indicated the complete and selective conversion of amines to sulfinylamines, but the yields shown in Table I were rather low, probably owing to hydrolysis of *N*-sulfinylamines.

The behavior of *N*-lithio-2,6-xylidine (**6**) was different from those of other *N*-lithioamines: it reacted exothermically with an equimolar amount of sulfur dioxide to afford an equimolar mixture of free xylidine and *N*-sulfinylxylidine in the absence of the second mole of sulfur dioxide, the latter being characterized by the comparisons of the ir and NMR spectra of the reaction products with those of the mixture of the authentic **8** and **9**.



The abnormal behavior of *N*-lithio-2,6-xylidine was assumed to be due to the steric effect of two *o*-methyl groups on the stability of **7** or **8**, although detailed investigations are now in progress.

Table I
Sulfinylamines Prepared by the Reaction of Primary Amines with 2 Mol Each of Butyllithium and Sulfur Dioxide

Amine used (RNH_2)	Registry no.	RNSO: Bp, °C (mm)	RNSO: Yield, %	RNSO: ν_{NSO}	Lit.
$C_6H_5NH_2$	62-53-3	55–60 (10)	46	1280, 1160	1
2-$MeC_6H_4NH_2$	95-53-4	83–85 (13)	59	1285, 1167	2
4-$MeC_6H_4NH_2$	106-49-0	75–80 (10)	58	1280, 1157	3
2,6-$Me_2C_6H_3NH_2$	87-62-7	97–100 (15)	52	1280, 1178	4
2-$MeOC_6H_4NH_2$	90-04-0	75–80 (0.2)	60	1286, 1156	2
3-$MeOC_6H_4NH_2$	536-90-3	66–72 (0.2)	50	1292, 1154	5
4-$MeOC_6H_4NH_2$	104-94-9	80–84 (0.5)	47	1305, 1157	6, 7
4-$ClC_6H_4NH_2$	106-47-8	100–105 (12)	45	1292, 1166	1
n-$C_3H_7NH_2$	107-10-8	80–90	30	1230, 1140	1
n-$C_4H_9NH_2$	109-73-9	80–90	20	1240, 1115	1
c-$C_6H_{11}NH_2$	108-91-8	55–60 (16)	14	1245, 1120	1

Experimental Section

All melting and boiling points were uncorrected. The ir and NMR spectra were determined with a Jasco Model IRA-1 spectrometer and a Hitachi Perkin-Elmer Model R-24 spectrometer, respectively. Solvents, amines, and sulfur dioxide were dried by common methods. Reactions were performed under dry nitrogen atmosphere. Identification of the products isolated was carried out by comparisons of boiling point, ir, and NMR spectra of authentic samples prepared by published methods.[1-9]

Standard Method for Preparation of *N*-Sulfinylamines. A. *N*-Sulfinyltoluidine. Under dry nitrogen atmosphere, *p*-toluidine (5.3 g, 50 mmol) was dissolved in dry tetrahydrofuran (50 ml) in a flask equipped with a mechanical stirrer, a condenser, a drying tube, a dropping funnel, and a nitrogen inlet, and treated with butyllithium (55 mmol in 40 ml of petroleum ether) at room temperature. After stirring for 30 min, sulfur dioxide gas was slowly introduced to the solution of *N*-lithiotoluidine (**1**, R = *p*-$CH_3C_6H_4$; δ 6.07, 6.47, dd, in tetrahydrofuran). Lithium *N*-tolylaminosulfinate (**2**, R = *p*-$CH_3C_6H_4$; δ 6.39, 6.59, dd) was formed exothermically. The muddy solution of **2** thus prepared in situ was treated again with butyllithium (55 mmol) with cooling to give a pale yellow suspension of lithium *N*-lithio-*N*-tolylaminosulfinate (**3**, R = *p*-$CH_3C_6H_4$; δ 6.66, br s). Sulfur dioxide (57 mmol) was allowed to react slowly with **3**, to give the reddish-orange solution of *N*-sulfinyltoluidine (**5**, R = *p*-$CH_3C_6H_4$), containing insoluble powders of lithium sulfite. The NMR spectrum of the solution was nearly the same as that of pure **5**. After refluxing for 2 hr, separation of insoluble materials by decantation method, and evaporation of solvent, the liquid layer was distilled in vacuo to afford *N*-sulfinyltoluidine: yield 3.2 g (40%); bp 85–90° (11 mm); ir (neat) ν_{NSO} 1280 and 1156 cm^{-1}. The ir and NMR spectra were in good agreement with those of the authentic sample prepared by the published method.[3] The solid mass obtained from the residue in the decantation or in the distillation showed the ir bands at 1010 and 960 cm^{-1} which were ascribable to $\nu_{SO_3^{2-}}$ bands of lithium sulfite.

Other aromatic *N*-sulfinylamines were also prepared and isolated in the same manner described above, and the structure of **5** obtained was identified by the comparison of ir and NMR spectra with those of authentic samples.[1-9]

In a separate experiment, the suspension of **2** or **3** (R = *p*-$CH_3C_6H_4$) was heated at 180° under reduced pressure (20 mm), but *N*-sulfinylamine (R = *p*-$CH_3C_6H_4$) was never obtained. The residue was hydrolyzed by dilute acid to recover toluidine in good yield (80–90%).

B. Aliphatic *N*-Sulfinylamines. Aliphatic *N*-sulfinylamines were prepared in the same procedure mentioned above. However, aliphatic *N*-sulfinylamine is readily hydrolyzed by moisture, so the suspension containing **5** and lithium salt in tetrahydrofuran was directly distilled in vacuo, and the distillate was trapped by cooling using liquid nitrogen. The distillate was fractionally redistilled to separate **5** (R = alkyl).

Equimolar Reaction of *N*-Lithio-2,6-xylidine with Sulfur Dioxide. Sulfur dioxide (50 mmol) was introduced slowly into the solution of *N*-lithio-2,6-xylidine (50 mmol) prepared in situ in tetrahydrofuran with cooling. The NMR and ir spectra of the reaction mixture coincided well with those of an equimolar mixture of free 2,6-xylidine (**6**) (multiplet at δ 6.2–6.8; ν_{NH_2} at 3380 and 3450 cm^{-1}) and *N*-sulfinyl-2,6-xylidine (**8**) (br singlet at δ 6.94; ν_{NSO} at 1280 and 1178 cm^{-1}). Isolation of *N*-sulfinylxylidine from the mixture failed by distillation.

Registry No.—**5** (R = Ph), 1122-83-4; **5** (R = 2-MeC_6H_4), 15182-74-8; **5** (R = 4-MeC_6H_4), 15795-42-3; **5** (R = 2,6-$Me_2C_6H_4$), 17420-02-9; **5** (R = 2-$MeOC_6H_4$), 17419-98-6; **5** (R = 3-$MeOC_6H_4$), 17420-00-7; **5** (R = 4-$MeOC_6H_4$), 13165-69-0; **5** (R = 4-ClC_6H_4), 13165-68-9; **5** (R = C_3H_7), 53437-16-4; **5** (R = C_4H_9), 13165-70-3; **5** (R = c-C_6H_{11}), 30980-11-1.

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Solvolysis of Covalent Arylsulfonylmethyl Perchlorates. General Base Catalysis by Dipolar, Aprotic Solvents

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Dimethyl sulfoxide (Me_2SO) as well as the Me_2SO–H_2O binary system are valuable reaction media for many organic reactions. The solvation properties of Me_2SO are characteristic of those of dipolar, aprotic (DPA) solvents and have been reviewed in detail.[1-3] In Me_2SO–H_2O strong intermolecular interactions occur between the components and recent studies indicate that the behavior of these mixtures may be rationalized by assuming the formation of thermolabile, nonstoichiometric 1:2 complexes and by considering the effect of Me_2SO on the diffusionally averaged water structure.[4-6]

In this paper we focus our attention on the dynamic basicity (also referred to as "kinetic basicity") of Me_2SO and Me_2SO–H_2O mixtures employing the rates of irreversible deprotonation of two carbon acids as a kinetic probe. The carbon acids are the covalent arylsulfonylmethyl perchlorates **1** and **2** which hydrolyze via a mechanism involving general base catalysis (Brönsted β ca. 0.5, primary kinetic

$$RSO_2CH_2OClO_3 + B \xrightarrow{slow} [RSO_2\bar{C}HOClO_3] + BH^+$$

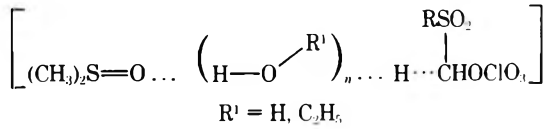
1, R = *p*-$NO_2C_6H_4$; 2, R = *p*-$CH_3C_6H_4$

$$[RSO_2\bar{C}HOClO_3] \xrightarrow{H_2O,\ fast} RSO_2H + HCOOH + ClO_4^-$$

deuterium isotope effect, k_H/k_D ca. 6).[7,8] Since 1 and 2 show a coveniently fast "water reaction" (B = H_2O), the rates of hydrolysis may serve as a specific probe for the dynamic basicity of aqueous and mixed aqueous solutions in the absence of other active Brönsted bases.[8]

In view of our earlier work[8] and results obtained by Hibbert and Long[9] for the rate-determining detritiation of tritiated malononitriles in Me_2SO–H_2O, it was anticipated that the initial addition of Me_2SO to water would cause a rate acceleration and that a kinetic maximum would be reached around the solvent composition for which a maximum in the diffusionally averaged water structure has been claimed (mole fraction of water, n_{H_2O}, ca. 0.7–0.8). This expectation was not borne out in practice. Instead, we observe a continuous and strong increase in rate upon the gradual addition of Me_2SO until at n_{H_2O} = 0.62 the rate becomes too fast to be measured with our kinetic equipment (Table I; rates relative to that in pure water are plotted as a function of n_{H_2O} in Figure 1). It may be noted that the pseudo-first-order rate constants (k_{obsd}) increase much more rapidly than a linear relationship with the Me_2SO concentration would require. The small change of the magnitude of the primary kinetic deuterium isotope effect (k_H/k_D) as a function of n_{H_2O} indicates that in the Me_2SO-rich mixtures the mechanism of hydrolysis does not change from a base-catalyzed process to nucleophilic substitution. Presumably, the increase in k_{obsd} may be attributed to general base catalysis by Me_2SO, most likely by stabilizing the transition state for water-catalyzed deprotonation.[10] A similar explanation may be advanced for the Me_2SO-catalyzed ethanolysis (Table I). A schematic representation of the transition state is depicted in Chart I, taking into account

Chart I



R^1 = H, C_2H_5

the known strong interaction between Me_2SO and hydrogen bonding donors like water and ethanol. Previously, Benoit and Lam[11] have demonstrated that H_3O^+ will be more strongly solvated by Me_2SO than by water. An additional factor that may contribute to transition state stabilization in Me_2SO–H_2O is the better solvation[1] of the charge dispersed transition state by Me_2SO than by H_2O.[12] In the highly aqueous mixtures (n_{H_2O} > 0.8) we cannot exclude the possibility that a rate-accelerating "water structure effect" is superimposed on the Me_2SO-catalyzed process,[13] but reliable experimental support for this effect is lacking.

As shown in Table I, other dipolar, aprotic solvents like sulfolane (tetramethylene sulfone, TMS), *N*,*N*-dimethylformamide (DMF), and hexamethylphosphortriamide (HMPA) also exert rate-accelerating effects on the hydrolysis of 1 and/or 2. The effect of the poor hydrogen bond acceptor TMS[14] is only modest. The relative efficiencies of Me_2SO, DMF, and HMPA as base catalysts are reasonably correlated with their hydrogen bonding acceptor abilities.[15]

It is difficult to establish the number of water molecules (n) present in the transition state viewed in Chart I, but the $\Delta S^\ddagger$ values for the H_2O–Me_2SO mixtures (Table I) are difficult to reconcile with n > 2. Since the decrease of the solvent deuterium isotope effect (k_{H_2O}/k_{D_2O}, Table I) upon

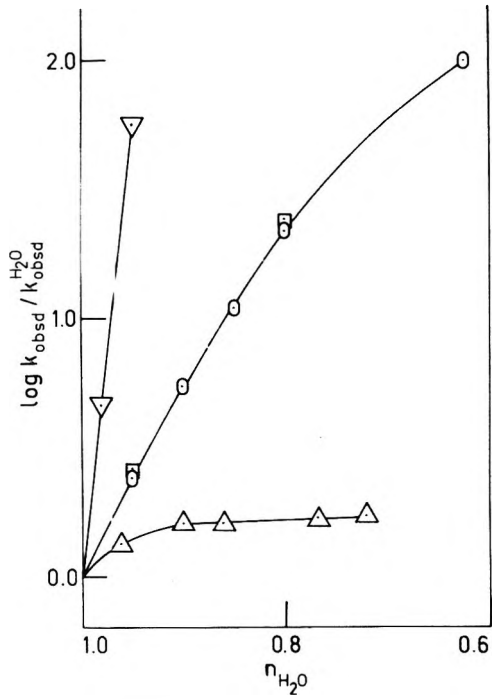


Figure 1. Relative rates of solvolysis of 1 and 2 vs. mole fraction of water: △, 2 in H_2O–TMS; ○, 1 in H_2O–Me_2SO; □, 2 in H_2O–Me_2SO; ▽, 1 in H_2O–HMPA.

increasing Me_2SO concentration could be indicative of solvolysis via a transition state for which n = 0, we have investigated the reaction of 1 with Me_2SO, DMF, and HMPA in an inert medium like anhydrous 1,4-dioxane (Table I).[16] Fairly rapid solvolysis occurs and the reaction products formed from 1 in dioxane–Me_2SO (n_{Me_2SO} = 0.10) are identical with those formed upon hydrolysis (see Experimental Section). The magnitude of the primary kinetic deuterium isotope effect (Table I) provides compelling evidence[17] for rate-determining deprotonation of the substrate. Highly efficient catalysis by traces of hydroxide ion[18] can be excluded because of the nearly identical rates of solvolysis in the presence of different concentrations of HCl or $HClO_4$. Catalysis by small amounts of water is also very unlikely, since addition of minor quantities of water (0.3–1.3 *M*) decreased rather than increased the rates of solvolysis of 1 in dioxane–Me_2SO (n_{Me_2SO} = 0.10). Consequently, we assume that 1 solvolyzes via rate-determining proton transfer to Me_2SO, DMF, and HMPA; approximate second-order rate constants are, respectively, 51 × 10^{-3} M^{-1} sec^{-1} (n_{Me_2SO} = 0.00–0.10), 9.6 × 10^{-3} M^{-1} sec^{-1} (n_{DMF} = 0.00–0.10), and 1130 × 10^{-3} M^{-1} sec^{-1} (n_{HMPA} = 0.00–0.05). The superior hydrogen bonding capability of HMPA is again reflected in the high efficiency of this molecule as a general base.

The significantly greater dynamic basicities of Me_2SO, DMF, and HMPA as compared with water in the deprotonation of 1 and 2 in water as well as in dioxane as the solvent are noteworthy. Often, acids are less dissociated in Me_2SO and in Me_2SO–H_2O mixtures than in water, mainly owing to weaker solvation of the conjugate anions when the possibility of hydrogen bonding interaction is reduced.[19] Our results support Bordwell's recent conclusion[20] that in a particular medium kinetic acidities provide only a rough guide to carbanion stabilities. In the solvolysis of 1 and 2, the transition state is reached early on the reaction coordinate (Brönsted β coefficient[7] ca. 0.5) and its free enthalpy most likely will be primarily dependent on the strength of the hydrogen bonding interaction between substrate and base which precedes proton transfer.[21] This sit-

Table I
Pseudo-First-Order Rate Constants (k_{obsd}), Activation Parameters, and Deuterium Isotope Effects for the Solvolysis of 1 and 2 in Different Solvents at 25°

Compd	Solvent	n_{H_2O}[a]	$k_{obsd} \times 10^3$, sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_H/k_D[b]	k_{H_2O}/k_{D_2O}[c]
1	H_2O	1.000	3.25	18.4 ± 0.3	−8 ± 1	5.6	1.7
1	H_2O–Me_2SO	0.950	7.83	19.2 ± 0.3	−4 ± 1		
1	H_2O–Me_2SO	0.900	17.7	18.0 ± 0.3	−6 ± 1		
1	H_2O–Me_2SO	0.850	35.5	17.8 ± 0.3	−5 ± 1		
1	H_2O–Me_2SO	0.800	70.6	16.3 ± 0.3	−9 ± 1	6.3	1.3
1	H_2O–Me_2SO	0.625	322				1.1
1	H_2O–HMPA	0.980	15.1				
1	H_2O–HMPA	0.950	185				
1	H_2O–DMF	0.900	24.7				
1	H_2O–DMF	0.800	71.5				
1	EtOH	1.000[d]	4.51	15.8 ± 0.3	−16 ± 1		
1	EtOH–Me_2SO	0.900[d]	18.4				
1	Dioxane–Me_2SO	0.100[e]	62.8	12.8 ± 0.3	−21 ± 1	8.0	
1	Dioxane–HMPA	0.010[f]	13.0				
1	Dioxane–HMPA	0.030[f]	37.2				
1	Dioxane–HMPA	0.050[f]	67.0				
1	Dioxane–DMF	0.100[g]	11.5				
1	Dioxane–DMF	0.200[g]	29.0				
1	Dioxane–DMF	0.300[g]	53.8				
2	H_2O	1.000	0.605	19.7 ± 0.3	−7 ± 1		
2	H_2O–Me_2SO	0.950	1.58				
2	H_2O–Me_2SO	0.800	14.7				1.25
2	H_2O–DMS	0.950	0.688				
2	H_2O–TMS	0.960	0.814				
2	H_2O–TMS	0.900	0.967				
2	H_2O–TMS	0.860	0.965				
2	H_2O–TMS	0.768	1.01				
2	H_2O–TMS	0.720	1.04				

[a] Mole fraction of water. All solvent systems contained 10^{-3}–10^{-2} *N* HCl or $HClO_4$ to suppress catalysis by other bases than the solvent molecules. Me_2SO = dimethyl sulfoxide, HMPA = hexamethylphosphortriamide, DMF = *N,N*-dimethylformamide. DMS = dimethyl sulfone, TMS = tetramethylene sulfone (sulfolane). [b] Primary kinetic deuterium isotope effect. [c] Solvent deuterium isotope effect. [d] Mole fraction of EtOH. [e] Mole fraction of Me_2SO. [f] Mole fraction of HMPA. [g] Mole fraction of DMF.

uation may be contrasted with the deprotonation reaction of malononitriles,[9] for which the proton is transferred almost completely in the transition state (Brönsted β ca. 1.0). In this case the Brönsted basicity rather than the hydrogen bond basicity of the base will be the dominating factor. This will explain the sharp decrease of the rate of deprotonation in Me_2SO–H_2O mixtures below n_{H_2O} = 0.3 as found by Hibbert and Long.[9]

Experimental Section

Materials. The perchlorates 1 and 2 used in the kinetic experiments were analytically pure compounds which were prepared as described previously.[7] The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. Deuterium oxide (99.75% D_2O) was obtained from Merck (uvasol quality) and was used as such. The organic solvents were obtained from Merck and were of the best grade available (water content below 0.1%). Dioxane was filtered through active, neutral alumina in a nitrogen atmosphere and stored under nitrogen at 0°. Solvent mixtures were usually made up by weight.

Product Analysis. The products formed upon complete solvolysis of 1 in dioxane–Me_2SO (n_{Me_2SO} = 0.10) were examined using spectroscopic techniques. The uv spectrum of the reaction mixture was identical with that of *p*-nitrobenzenesulfinic acid and differed significantly from that of the corresponding sulfonic acid. The formation of chloric acid was shown by a positive test with manganous sulfate and polyphosphoric acid.[22] The sharp peak at δ 8.5 ppm in the NMR spectrum of the reaction mixture revealed the formation of formic acid. After rate-determining deprotonation by Me_2SO, the final reaction products are most likely formed via rapid product-forming steps involving traces of water (< 0.1%) present in the solvent mixture.

Kinetic Measurements. Pseudo-first-order rate constants, k_{obsd}, were obtained using the uv technique described previously.[7,8] Solvolysis was accurately first order in all cases. Rate constants were reproducible to within 2%. The thermodynamic quantities of activation were calculated from k_{obsd} values at three to five temperatures between 25 and 45°.

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Registry No.—1, 26452-84-6; 2, 14894-56-5.

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Halogen Interchange in Alkyl Halides Using Molybdenum(V) Chloride[1a]

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The interconversion of haloalkane congeners by halide exchange (Finkelstein halide interchange) is a synthetically useful procedure when applied to primary and, to a lesser degree, secondary alkyl halides. Most frequently these interchanges involve the replacement of chloride or bromide with iodide, occur by an SN2 mechanism,[2] and are usually accomplished by treating the alkyl halide with sodium iodide in an appropriate solvent.[3] In general, the replacement of iodide by bromide or chloride, or of bromide by chloride, requires a large excess of the inorganic halide and elevated temperatures.[7,8] Alkyl fluorides do not undergo halide interchange under these conditions.[11,12]

We wish to report that alkyl iodides, bromides, and *fluorides* can be converted to alkyl chlorides in modest to good yields by reaction with molybdenum(V) chloride.

$$RX \xrightarrow[CH_2Cl_2]{MoCl_5} RCl$$

A summary of the results obtained on treatment of various representative substrates is given in Table I.

Several specific points related to the data in Table I deserve brief comment. First, this reaction sequence seems applicable to the conversion of secondary and tertiary alkyl fluorides, bromides, and iodides to the corresponding chloride. As suggested by the nearly quantitative recovery of 1-bromooctane, molybdenum(V) chloride does not affect halogen interchange in primary alkyl bromides. By comparison, 1-iodo- and 1-fluorooctane react readily. This dramatic difference in reactivities suggests the possibility of selective halogen interchange such as, for example, the conversion of a secondary alkyl bromide, iodide, or fluoride to the corresponding chloride in the presence of a primary alkyl bromide (cf. last entry in Table I).

Second, the conversion of 1-iodooctane to 1-chlorooctane is accompanied by the formation of some of the rearranged isomer, 2-chlorooctane. In contrast, the reaction of 1-fluorooctane occurs with extensive rearrangement.

Third, in a effort to probe the mechanism of halogen interchange we have examined the stereochemistry of the product produced by the reaction of molybdenum(V) chloride with (−)-(*R*)-2-bromooctane[13] (α_{589}^{20} −38.4°, 90% optical purity). The resulting 2-chlorooctane was completely racemic. It is, however, not possible to make a definitive statement concerning the stereochemistry of the carbon–chlorine bond-forming step, since under comparable conditions both optically active 2-chlorooctane[13] (α_{589}^{20} −30.7°, 97% optically pure) and optically active 2-bromooctane are completely racemized in less than 6 min.[14] One conceivable mechanism that accounts for these observations, as well as the 1,2 migrations observed with certain substrates, involves a Lewis acid assisted ionization of the carbon–halogen bond followed by conversion of this carbonium ion to chlorocarbon by reaction with a halometallo–ate complex.

Table I
Reaction of $MoCl_5$ with Various Alkyl Halides[a]

RX (concn, *M*)	Registry no.	Alkyl chloride	Registry no.	Yield,[b] % (recovered RX, %)
2-Fluoro-2-methylpropane[c] (2.0)	353-61-7	2-Chloro-2-methylpropane	507-20-0	49
2-Fluorooctane (2.0)	407-95-4	2-Chlorooctane	628-61-5	71
1-Fluorooctane[d] (4.5)	463-11-6	1-Chlorooctane	111-85-3	12
		2-Chlorooctane		58
2-Bromo-2-methylpropane (2.0)	507-19-7	2-Chloro-2-methylpropane		69
2-Bromooctane (2.0)	5978-55-2	2-Chlorooctane	51261-14-4	60
1-Bromooctane (1.0)	111-83-1	1-Chlorooctane		5 (94)
2-Iodo-2-methylpropane (1.5)	558-17-8	2-Chloro-2-methylpropane		48
2-Iodooctane (1.5)	557-36-8	2-Chlorooctane		67
1-Iodooctane (1.0)	629-27-6	1-Chlorooctane		66
		2-Chlorooctane		13
1-Iodo-2-phenylethane (1.5)	17376-04-4	1-Chloro-2-phenylethane	622-24-2	60
Fluorocyclohexane (3.0)	372-46-3	Chlorocyclohexane	542-18-7	62
Bromocyclohexane (2.0)	108-85-0	Chlorocyclohexane		60
1,1-Difluorocyclohexane (1.5)[e]	371-90-4	1,1-Dichlorocyclohexane	2108-92-1	31
1,3-Dibromobutane (2.0)	107-80-2	1-Bromo-3-chlorobutane	56481-42-6	61

[a] Unless otherwise indicated all reactions were carried out in CH_2Cl_2 solution at room temperature under an inert atmosphere of dry nitrogen. The concentration of molybdenum(V) chloride was ~1.0 *M*. [b] Yields were determined by quantitative vapor phase chromatography and are based on alkyl halide. [c] Carried out at −50°. [d] Performed at −78°. [e] Under similar conditions α,α,α-trifluorotoluene does not react with $MoCl_5$.

The intermediacy of carbonium ions in the reaction of alkyl halides with molybdenum(V) chloride is supported by the fact that treatment of 1-iodo-2-phenylethane-2,2-d_2[10] (1) with molybdenum(V) chloride produces a 1:1 mixture of 1-chloro-2-phenylethane-2,2-d_2 and 1-chloro-2-phenylethane-1,1-d_2. When this experiment was carried to ~50% completion, the recovered starting halide was found to consist of a 1:1 mixture of 1 and 1-iodo-2-phenylethane-1,1-d_2.[15,16]

Synthetically, the reaction of alkyl halides with molybdenum(V) chloride expands the utility of halogen interconversion to alkyl fluorides in particular, and to tertiary halides in general. Moreover, the conversion of alkyl halides to alkyl chlorides using molybdenum(V) chloride can be accomplished selectively and under conditions that are comparatively milder than those required for the analogous conversion involving displacement by chloride ion. As such, the replacement of fluoride, bromide, and iodide by chloride using molybdenum(V) chloride offers a useful compliment to halide interconversion procedures that proceed by SN2 displacement.

Experimental Section[18]

Molybdenum(V) chloride was prepared by the literature procedure.[19] 2-Fluorooctane,[13] 1-iodo-2-phenylethane,[10] and 1,1-difluorocyclohexane[20] were prepared using known procedures.

Procedures for Halogen Interchange. Similar procedures were used to effect the halogen interchange listed in Table I.

Conversion of 2-Fluorooctane to 2-Chlorooctane. Molybdenum(V) chloride (1.20 g, 4.39 mmol) was placed in a flame-dried, 25-ml flask containing a Teflon-coated stirrer bar. Methylene chloride (3 ml) was added by syringe followed by the slow addition of a solution of 2-fluorooctane (1.16 g, 8.78 mmol) in methylene dichloride (2 ml) over a 5-min period. This mixture was stirred for 2 hr, then cautiously hydrolyzed with water (1 ml). The organic layer was separated, dried ($MgSO_4$), and passed through a short column of alumina. GLC analysis of the eluent indicated a 71% yield of 2-chlorooctane. A collected sample had the retention time and ir spectrum equivalent to that of authentic 2-chlorooctane.

Conversion of 1-Iodo-2-phenylethane to 1-Chloro-2-phenylethane. A solution of 1-iodo-2-phenylethane (2.35 g, 10.1 mmol) in dichloromethane (8 ml) was added by syringe to a solution of molybdenum(V) chloride (4.25 g, 15.6 mmol) in methylene chloride (7 ml) contained in a 25-ml, dried flask equipped with Teflon-coated stirrer bar and capped with a rubber septum. The resulting mixture was stirred for 2 hr at room temperature before cautiously adding water (1 ml). The organic layer was separated, dried ($MgSO_4$), and passed through a short column of alumina. Analysis of the eluent indicated a 60% yield of 1-chloro-2-phenylethane. The infrared spectrum and retention time of sample collected from GLC was equivalent to that of authentic 1-chloro-2-phenylethane.

Conversion of 1,3-Dibromobutane to 1-Bromo-3-chlorobutane. Molybdenum(V) chloride (1.27 g, 4.66 mmol) was placed in a 25-ml, flame-dried flask equipped with a Teflon-coated stirrer bar and capped with a rubber septum. Dichloromethane (3 ml) was added by syringe followed by a solution of 1,3-dibromobutane (1.80 g, 8.32 mmol) in dichloromethane (2 ml). After stirring for 10 hr at room temperature, the reaction mixture was cautiously hydrolyzed with water (1 ml) and the organic layer was dried and passed through a short column of alumina. Analysis of the eluent by GLC indicated the major product (66%) to be 1-bromo-3-chlorobutane: M^+ *m/e* 170; ir (CS_2) 803 cm^{-1} [s, ν(C–Cl)]; ^1H NMR (CCl_4) δ 4.18 (sextet, 1 H), 3.49 (t, 2 H), 2.13 (quart, 2 H), 1.55 (d, 3 H).

Conversion of 1,1-Difluorocyclohexane to 1,1-Dichlorocyclohexane. Molybdenum(V) chloride (1.69 g, 6.20 mmol) was placed in a 25-ml, flame-dried flask equipped with Teflon-coated stirrer bar and capped with a rubber septum. Dichloromethane (3 ml) was added by syringe followed by a similar addition of a solution of 1,1-difluorocyclohexane in methylene chloride (3 ml). After 5 hr and a work-up similar to that described above, the reaction mixture was analyzed by GLC. The principal product (31%) as revealed by its retention time, mass, and infrared spectra, was 1,1-dichlorocyclohexane.[21]

Registry No.—$MoCl_5$, 10241-05-1.

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(14) Under similar conditions, optically active 2-fluorooctane[13] (α^{20}_{589} −9.44°, 95% optically pure) is 11% racemized by $MoCl_5$ in 1 hr.
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(16) The interchange of chloride or bromide for fluoride using mercury(II) fluoride also proceeds through the intermediacy of carbonium ions;[10] however, in contrast to the stereochemistry of chloride interchange using molybdenum(V) chloride, the reaction of (−)-(*R*)-2-bromooctane with mercury(II) fluoride in pentane at 25° yields (+)-(*S*)-2-fluorooctane (α^{20}_{589} 4.65°, 47% optical purity), indicating that reaction has occurred with a 74% net *inversion* of configuration. Neither optically active 2-bromo- nor 2-fluorooctane suffers any racemization under these conditions.[17]
(17) J. San Filippo, Jr., and L. Romano, unpublished results.
(18) Infrared spectra were determined within sodium chloride cells on a Perkin-Elmer Model 137 spectrophotometer. NMR spectra were determined with a Varian T-60 NMR spectrometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-7E mass spectrometer. Analytical GLC analyses were performed on a Hewlett-Packard Model 5750 flame ionization instrument. Absolute product yields were calculated from peak areas using internal standard techniques with response factors obtained from authentic samples. Dichloromethane was distilled from phosphorus pentoxide immediately prior to use. GLC analysis were determined on a 20 ft × 0.25 in. column of 7.5% SE-30 on Gas-Chrom Z. All reactions and transfers of solids and liquids were performed under a nitrogen atmosphere. Unless otherwise indicated, starting halides and authentic product samples were obtained from commercial sources.
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Introduction of *N*-Vinyl Group into Tautomeric Heterocycles by the Exchange Reaction

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Vinyl exchange between vinyl acetate and a nitrogen heterocyclic compound is a valuable one-step preparation of *N*-vinyl heterocycles, and thus is important in the synthesis of polymers.[1] The reaction is acid catalyzed and is believed to proceed through two successive equilibria[1] as shown in eq 1.

$$\text{HetN–H} + CH_3COOCH{=}CH_2 + Hg(OCOCH_3)_2 \rightleftarrows \text{HetN}(CH_3COO)CHCH_2HgOCOCH_3 + CH_3COOH \rightleftarrows \text{HetN–CH}{=}CH_2 + CH_3COOH + Hg(OCOCH_3)_2 \quad (1)$$

Use of this reaction brings two problems—it is not clear which of the possible isomeric *N*-vinyl compounds may be formed and the isolation of the product is often tedious. In this work we focus on both these problems.

In many cases several isomeric *N*-vinyl derivatives could arise from a single heterocycle; nevertheless, in all examples described to date, only one isomer has been isolated. In the pyrimidine series, of the two possible (1 or 3) isomers, only the 1-vinyl compounds were obtained. The following compounds were investigated: 4-ethoxy-2-pyrimidinone (yield of vinyl derivative 55%),[2] 2-ethoxy-4-pyrimidinone (yield 10%),[3] 2,4-bis(trimethylsiloxy)pyrimidine (yield 40%),[4] and 2-trimethylsiloxy-4-trimethylsilylaminopyrimidine (yield 21%).[4] In the purine series, of the four possible isomers (1, 3, 7, and 9) only the 9-vinyl compounds were formed. The following compounds were studied: 6-chloropurine (yield 70%),[2] 2,6-dichloropurine (yield 80%),[2] adenine (yield 2%),[5] and 6-benzoyladenine (yield 65%).[5]

In surprising contrast, two major products and one minor one were formed when purine was used in the vinyl exchange reaction. The major products, obtained in approximately equal yields, were hydrogenated, compared with the known *N*-ethylpurines,[6–8] and identified as 7-vinylpurine and 9-vinylpurine. When the vinyl exchange reaction was used on theophylline (1,3-dimethyl-2,6-purinedione), only one product was formed. This was 7-vinyltheophylline, previously synthesized by another method.[9,10] The position of the vinyl group was further confirmed by hydrogenation of this compound to the known 7-ethyltheophylline.[11]

Considerable data have been collected on the direction of alkylation and acylation of purine derivatives;[12] the position of vinylation and the position of alkylations or acylation do not seem to correspond. On the other hand, a reasonable correlation is obtained between the position of the tautomeric hydrogen atom in the parent heterocycle and the position of vinyl substitution. All the purine derivatives investigated to date are either 7H or 9H tautomers. In purine, both 7H and 9H tautomers have the same stability;[12–16] in theophylline the 7H tautomer is favored[17,18] while in adenine,[13,19] 6-chloropurine,[18] and 2,6-dihloropurine[18] the 9H tautomers are favored. The position of the proton in the most stable tautomeric form is also taken by the vinyl group in this reaction. 2-Ethoxy-4-pyrimidinone exists in nonpolar solutions as the 3H tautomer, while in polar solutions both forms are present.[3] In this particular compound, however, positions 1 and 3 are very different sterically and this may override other factors in the vinylation reaction.

We investigated the possibility that the position of the vinyl group in the product is determined by the relative thermodynamic stability of the product, but found that this is not the case. When purine is used in the vinyl exchange reaction, approximately the same amounts of 7- and 9-vinylpurine are obtained. When pure 7- and 9-vinyl derivatives were used in the vinyl exchange reaction no isomerization was noticed. Apparently equilibria as given by eq 1, for all the isomeric *N*-vinyl compounds, are not established under the mild conditions used. Thus the ratio of isomeric vinyl derivatives is apparently kinetically controlled.

Isolation of the products from the vinyl exchange reaction is a tedious process because vinyl acetate forms decomposition products which appear to form emulsions and interfere with extractive isolation. We now find that simple filtration of the reaction mixture through a short column of activated alumina gives directly a colorless solution of the *N*-vinyl compound in vinyl acetate; the catalysts, the unreacted starting material, and the decomposition products are much more strongly adsorbed than the product. This labor-saving procedure furthermore improves the yields considerably. Thus, 1-vinyl-4-ethoxy-2-pyrimidinone was obtained in 70% instead of the previously obtained 55% yields.[2]

Experimental Section

Melting points were determined on a hot stage and are not corrected; ultraviolet spectra were measured in a Cary 15 spectrophotometer in phosphate buffer (0.15 *M* NaCl, 0.01 *M* sodium phosphate, pH 7.3), and infrared spectra in a Beckman IR12 spectrophotometer. All products, before any identification operation, were sublimed in vacuo (0.1 mm).

Vinylation Reactions. To a suspension of 0.5 g of mercuric acetate in 150 ml of vinyl acetate (stabilized, practical grade) contained in a glass pressure flask was added a solution of 0.1 ml of sulfuric acid in 2 ml of ethyl acetate. After a solution was formed, 1–1.5 g of the heterocyclic compound was added and nitrogen was bubbled through the suspension for 10 min. Thereafter, the closed flask was kept for 3–4 days at 40°C (water bath). The red-brown reaction mixture was then filtered through neutral activated alumina (100 ml was used for 4 g of starting compound) in a separatory funnel. The alumina was washed with 100 ml of ethyl acetate and the slightly yellow filtrate was evaporated in vacuo to yield a crystalline product.

A. Purine. The product from the vinylation of 4 g of purine was recrystallized from ethyl acetate to yield pure 7-vinylpurine (925 mg): mp 137–138°; uv λ_{max} 225 nm (ϵ 4000), 260 (6000), 274 (shoulder). Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: 57.25; H, 4.03; N, 38.51. The mother liquors were concentrated in vacuo and applied to six preparative thin layer chromatography plates (PLC silica gel 60F-254, E. Merck, Darmstadt: 2 mm layer with the fluorescent indicator) and developed by ethyl acetate. Three main bands were observed with the following colors under uv light: violet (R_f 0.9), violet (R_f 0.6), blue (R_f 0.3). Extraction with ethyl acetate of the blue band yielded more 7-vinylpurine (total 1225 mg, 25%). The violet (R_f 0.9) band on extraction yielded a small amount of material which darkened rapidly in air and therefore could not be satisfactorily identified. It may be noted that 1-ethylpurine, unlike all its isomers, was found to be unstable.[6] The violet (R_f 0.6) band on extraction yielded 9-vinylpurine which after recrystallization from ethyl acetate had mp 113°; λ_{max} 219 nm (ϵ 15000), 263 (5000); yield 22% (1050 mg). Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.50; H, 4.06; N, 38.29. The 7 and 9 isomers may be identified by ir bands at 600 and 635 cm^{-1} (KBr pellet), respectively. Each of these peaks are unique for each respective isomer.

B. Theophylline. Vinylation of theophylline (4 g) yielded only one product which after recrystallization from benzene had mp 177–178°, yield 75% (3.4 g) (lit.[9] mp 173–174°; lit.[10] 176–177°).

Hydrogenation of Vinyl Derivatives. The vinyl derivative (25 mg) was dissolved in water, 25 mg of Pd (10%) on C was added, and the mixture was stirred in a hydrogen atmosphere at atmospheric pressure and room temperature for 5 hr. The mixture was clarified by filtration with filtration aid (Hyflo Super Cel, Fisher Scientific Co., Fair Lawn, N.J.) and evaporated in vacuo and the residue was sublimed in vacuo. 7-Ethylpurine was identified by mp 102–104° and uv spectra: λ_{max} 267 nm (pH 7) and 258 (1 *N* HCl) [lit.[6] mp 107°, uv spectra λ_{max} 267 nm (pH 7) and 258 (pH 1)]. 9-Ethylpurine was identified by its ir spectrum in CCl_4 (identical with previously obtained material[2]). 7-Ethyltheophylline was identified by mp 154–155° (lit.[11] mp 154°).

Equilibration of 7- or 9-Vinylpurines. Purified isomer (10 mg) was treated in the same way as described under Vinylation Reaction. Only the starting isomers were detected by thin layer chromatography (silica gel Eastman sheet 6060 with fluorescent indicator, developed by ethyl acetate). To ascertain that the catalytic components were still fully active, a sample of purine (10 mg) was added to either reaction mixture. After 4 days at 40°C both 7- and 9-vinylpurines were in either reaction mixture.

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Registry No.—Vinyl acetate, 108-05-5; purine, 270-26-7; 7-vinylpurine, 56468-28-1; 9-vinylpurine, 56468-29-2; theophylline, 58-55-9; 7-vinyltheophylline, 22247-84-3; 7-ethylpurine, 39253-23-1; 9-ethylpurine, 5427-23-6; 7-ethyltheophylline, 23043-88-1.

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Addition of Trichloromethane Phosphonyldichloride and Its Derivatives to Vinylic Monomers and Other Olefins

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The addition of trichloromethyl compounds to olefins under iron or copper chloride catalysis is a general process, without almost any restriction on the olefin, and provides for high yields of 1:1 adducts without telomerization.[1]

Trichloromethane phosphonyldichloride reacts in a similar fashion, via a redox chain. The phosphonylchloride function is retained in the adducts, as expected.

$$2CuCl_2 + C{=}C \longrightarrow 2CuCl + Cl{-}C{-}C{-}Cl \quad \text{initiation} \quad (a)$$

$$CuCl + CCl_3POCl_2 \rightleftharpoons CuCl + {\cdot}CCl_2POCl_2 \quad (b)$$

$$C{=}C + {\cdot}CCl_2POCl_2 \longrightarrow C{-}C{-}Cl_2POCl_2 \quad \text{propagation} \quad (c)$$

$$CuCl_2 + {\cdot}C{-}C{-}CCl_2POCl_2 \longrightarrow CuCl + Cl{-}C{-}C{-}CCl_2POCl_2 \quad (d)$$

Reactions of trichloromethane phosphonyldichloride with 1-butene at 110 and 125° with *tert*-butyl perbenzoate as the initiator gave only a 10% yield of adduct, together with unconverted material and heavier products.[2] In comparison, catalysis by iron chloride afforded 90% adduct. Copper chloride (for the vinylic monomers) likewise gave high yields (Table I).

Dimethyl and diethyl trichloromethanephosphonate also gave clean reactions, which, however, stopped at low conversion (compare, e.g., the reactions of butadiene in Table I). This seems to be the result of a gradual alkylation of chloride ions, since dialkyl phosphonates alkylate chloride ion,[3] and especially the dialkyl trichloromethanephosphonates are known[4] to be good alkylating agents. Without chloride ligands on copper(II) or iron(III) ion, radicals formed in c are not trapped anymore by the metal salt as in d[5] (dialkyl ester instead of dichloride), and the redox chain breaks down. In accord with this view, the dichloride and the diphenyl ester, which do not alkylate chloride ions, were fully converted into the corresponding adducts. Also, the reaction of butadiene with dimethyl trichloromethanephosphonate stopped after only 25% conversion of the latter, whereas the diethyl ester, which can be expected to be a less powerful alkylating agent, reached 50% under the same conditions. Finally, in a copper chloride catalyzed addition of diethyl trichloromethanephosphonate to acrylonitrile at 100°, an explosive polymerization of the monomer took place. This is only possible in the absence of chloride ions[5] and never occurred in additions of the phosphonyldichloride instead of the diester.

Twofold Addition. Under more drastic conditions, excess ethylene reacted with trichloromethane phosphonyldichloride to give mainly the "twofold" addition product (2) as distinguished from the 2:1 telomer $Cl(CH_2CH_2)_2CCl_2POCl_2$. Such "twofold" addition products have been mistaken for the isomeric 2:1 telomers in reactions of excess methyl acrylate with carbon tetrachloride, chloroform, or ethyl trichloroacetate under drastic conditions.[6] The isomers are readily distinguished by NMR, the "twofold" adducts having spectra which are very similar to the corresponding 1:1 adducts.

The NMR spectrum of the carbon tetrachloride "twofold" addition product of ethylene $CCl_2(CH_2CH_2Cl)_2$, mp 34–35[7] [δ 2.7 (4 H, t) and 3.8 (4 H, t)], is also very close to that of **2**, whereas the spectrum of the isomeric 2:1 telomer $Cl(CH_2CH_2)_2CCl_3$ is quite different: δ 1.9 (4 H, m), 2.7 (2 H, m), and 3.6 (2 H, m).

Experimental Section

NMR was on a Varian A-60 instrument.

The solvents were dried over calcium chloride; anhydrous iron(III) chloride and triethylammonium chloride were Merck analytical. Copper(II) chloride hydrate was made anhydrous by heating at 120° until constant weight. Dimethyl and diethyl trichloromethanephosphonate[8] and trichloromethane phosphonyldichloride[9] were prepared by published procedure. The latter compound (mp 156°) was frequently used as a concentrated (~50%), distilled solution in 1,2,4-trichlorobenzene or in *o*-dichlorobenzene, boiling range 93–98 and 80–95° (25 mm), respectively. Such solutions were easier to handle than the solid phosphonyldichloride, and the solvent served as an internal standard for monitoring the conversion by GLC. Also, unconverted phosphonyldichloride was entrained by the high-boiling solvent without clogging the condenser. The concentration of these stock solutions was determined either by GLC (2 ft × 0.25 in. column, 10% UC-W98 on Chromosorb P, 100–200°, 15° min^{-1}) or by titration of chloride ion after hydrolysis (see below).

Analytical. A convenient, quantitative determination of trichloromethane phosphonyldichloride and its adducts was based on their hydrolysis according to $RCCl_2POCl_2 + H_2O \rightarrow RCCl_2PO(OH)Cl + HCl$, in aqueous DMF.[10] A sample was dissolved in three to four times its weight in DMF containing 30% water, under considerable evolution of heat. After standing at room temperature for 1 hr, the solution was made up to 500 ml with water, and chloride ion was titrated in an aliquot by standard procedure.

Correct chlorine analyses were obtained, either by hydrolysis or by combustion. The NMR spectra of the reported adducts are consistent with the assigned structure. The signal for protons on carbon separated from ^{31}P by not more than an -O- or a $-CCl_2$ linkage is split by phosphorus, as was reported for numerous organic phosphorus compounds.[11]

Reactions. The reactions were carried out in sealed glass ampoules in the absence of air, and in the case of ethylene and propylene, in a glass-lined autoclave. (see Table I). Upon completion of the reaction, the conversion of trichloromethane phosphonyldichloride or the corresponding diester and the yield of adduct was

Table I
Addition of Trichloromethane Phosphonyldichloride and Esters (0.05 Mol) to Olefins[f]

Compd no.		Solvent, ml CH_2Cl_2	Solvent, ml MeCN	Temp, °C	Time, hr	Conversion, %	Yield[a] %	Adduct structure	Bp, °C (mm)
				Trichloromethane Phosphonyldichloride					
1	Ethylene (0.2)		5	125	24	90	80	$CH_2ClCH_2CCl_2POCl_2$	105–107 (4)
1	Ethylene (0.2)[b]	5		110	24	75	75	$CH_2ClCH_2CCl_2POCl_2$	
2	Ethylene (0.2)[c]	15	2	150	48	95	68	$(CH_2ClCH_2)_2CClPOCl_2$ + 20% (1)	mp 60–62
3	Vinyl chloride (0.1)		5	125	24	90	90	$CHCl_2CH_2CCl_2POCl_2$	66–67 (0.1)
4	Vinylidene chloride (0.1)		5	125	17	90	85	$CCl_3CH_2CCl_2POCl_2$	69 (0.04)
5	1-Butene (0.1)[b]	10		110	5.5	50	90	$C_2H_5CHClCH_2CCl_2POCl_2$	64–66 (0.05)
6	Butadiene (0.1)	20		110	7.5	100	78	$CH_2ClCH{=}CHCH_2CCl_2POCl_2$	92–93 (0.05)
7	Methyl acrylate (0.1)		5	125	20	100	90	$CH_3O(O)CCHClCH_2CCl_2POCl_2$	83 (0.04)
8	Acrylonitrile (0.1)			110	15	85	77	$N{\equiv}CCHClCH_2CCl_2POCl_2$	90–91 (0.04)
				Diethyl Trichloromethanephosphonate					
9	Vinyl chloride (0.1)[d]		10	125	24	25	87	$CHCl_2CH_2CCl_2PO(OC_2H_5)$	108–110 (0.15)
10	1-Butene (0.1)[b]		10	110	9	65	62	$C_2H_5CHClCH_2CCl_2PO(OC_2H_5)_2$	95–96 (0.1)
11	Butadiene (0.1)		10	110	9	50	80	$CH_2ClCH{=}CHCH_2CCl_2PO(OC_2H_5)_2$	120–125 (0.15)
				Dimethyl Trichloromethanephosphonate					
12	Butadiene (0.1)		10	110	9	25	83	$CH_2ClCH{=}CHCH_2CCl_2PO(OCH_3)_2$	119–122 (0.15)
				Diphenyl Trichloromethanephosphonate					
13	Ethylene (0.6)[e]	30	15	150	44	95	68	$CH_2ClCH_2CCl_2PO(OC_6H_5)_2$	mp 73.4–74
14	Propylene (0.5)[e]	30	15	150	44	95	63	$CH_3CHClCH_2CCl_2PO(OC_6H_5)_2$	mp 39.5–40.5

[a] Based on converted phosphonyldichloride or ester and on GLC. [b] Catalyst: 1 mmol Fe(III) chloride, 2 mmol triethylammonium chloride. Initiator: 1 mmol benzoin. [c] Catalyst: 2 mmol Cu(II) chloride, 3 mmol triethylammonium chloride. [d] Initiator: 5 mmol isobutyraldehyde. [e] 0.15 mol diphenyl phosphonate, 6 mmol Cu(II) chloride, 9 mmol triethylammonium chloride. [f] Catalyst: 1 mmol Cu(II) chloride, 1.5 mmol triethylammonium chloride.

assessed by GLC (2 ft 10% UC-W98, 100–250, 15° min^{-1}). The catalyst was extracted with ice-cold 1 *N* HCl and water. After drying on calcium chloride, the adducts were isolated by fractionation in vacuo. Yields based on actual isolation were considerably lower than those based on GLC, owing to partial hydrolysis on treatment with water.

Diphenyl Trichloromethanephosphonate. To a solution of 71 g (0.3 mol) of trichloromethane phosphonyldichloride and 56.5 g (0.6 mol) of freshly distilled phenol in 400 ml of dry methylene chloride, 61 g (0.6 mol) of triethylamine in 100 ml of methylene chloride was added at such a rate that the temperature did not rise above 5°. Stirring and cooling were continued for 1 hr. The reaction vessel was protected from moisture by a calcium chloride tube. The amine hydrochloride precipitated, and was dissolved in 0.1 *N* HCl. After two additional extractions with water, the organic layer was dried over calcium chloride and methylene chloride was removed by distillation, first at atmospheric pressure and then in vacuo. According to GLC, diphenyl dichloromethanephosphonate and triphenyl phosphate are also formed in small amounts. The residue solidified, and was recrystallized from 2-propanol, mp 64–65° (72 g). Anal. Calcd for $C_{13}H_{10}Cl_3O_3P$: Cl, 30.30. Found: Cl, 29.72.

Addition of Ethylene to Diphenyl Trichloromethanephosphonate (13). A solution of 52.7 g (0.15 mol) of diphenyl trichloromethanephosphonate, 804 mg (6 mmol) of Cu(II) chloride, and 1236 mg (9 mmol) of triethylammonium chloride in 15 ml of acetonitrile and 30 ml of methylene chloride was heated with 17 g (0.6 mol) of ethylene at 150° during 44 hr, after displacement of air, in a glass-lined autoclave of 300 ml. During this time, the pressure decreased from 1800 to 1400 psi. After cooling and release of excess ethylene, the dark brown solution was washed twice with 0.5 *N* HCl and once with water, and dried over calcium chloride. The solvent was evaporated in vacuo, and the residue was refluxed with active charcoal in 200 ml of 2-propanol. Filtering and cooling afforded 20 g of **13**, mp 72.5–73.5°. A second crop of 13 g (mp 70–72.5°) was obtained after concentrating and cooling again. After an additional crystallization from hexane, the melting point was 73.5–74°.

Addition of Propylene to Diphenyl Trichloromethanephosphonate (14). The above experiment was repeated with 20 g (0.5 mol) of propylene instead of ethylene. Diphenyl trichloromethanephosphonate was no longer present (GLC). Evaporation in vacuo at 50° left 47 g of residue, which was dissolved in 80 ml of 2-propanol and kept at 0° overnight. Adduct **14** crystallized (25 g), mp 39–40°, after recrystallization from hexane mp 39.5–40.5°.

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Registry No.—**1**, 39981-18-5; **2**, 56172-72-6; **3**, 39950-62-4; **4**, 39981-19-6; **5**, 37696-45-0; **6**, 39950-70-4; **7**, 39950-72-6; **8**, 39950-68-0; **9**, 56172-73-7; **10**, 56172-74-8; **11**, 56172-75-9; **12**, 56172-76-0; **13**, 56172-77-1; **14**, 56172-78-2; ethylene, 74-85-1; vinyl chloride, 75-01-4; vinylidene chloride, 75-35-4; 1-butene, 106-98-9; butadiene, 106-99-0; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; propylene, 115-07-1; trichloromethane phosphonyldichloride, 21510-59-8; diethyl trichloromethanephosphonate, 866-23-9; dimethyl trichloromethanephosphonate, 29238-81-1; diphenyl trichloromethanephosphonate, 23614-63-3.

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One-Electron Oxidation of a Naphthoquinol Monoacetate

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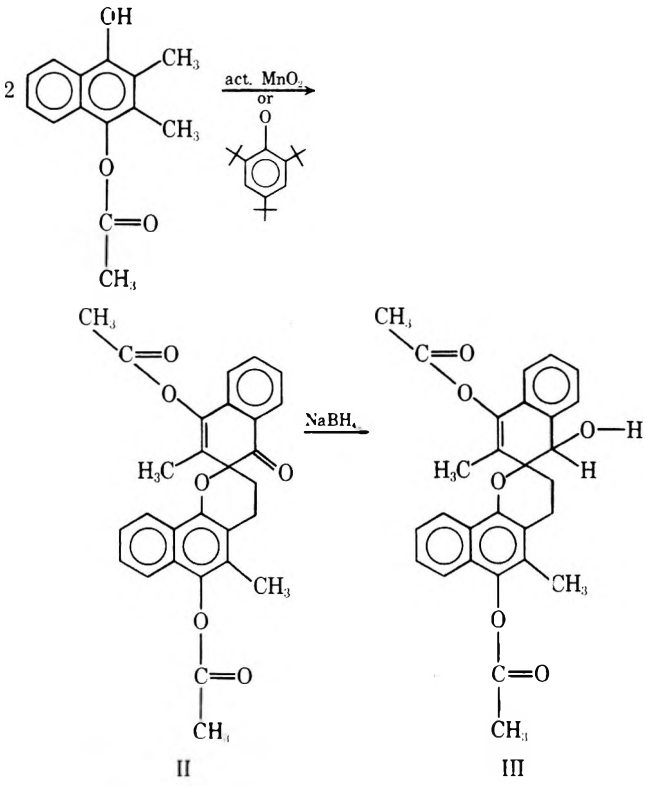
The oxidations of quinol monoesters have elicited interest owing to their possible relationship to oxidative phosphorylation, wherein the oxidative process generates a labile phosphoryl or acyl group suitable for anhydride formation. Several model reactions, wherein a quinol monoester was oxidized to an intermediate that contained the active precursor, were carried out with oxidants such as bromine,[1] periodic acid,[2] or high-potential quinones[3] such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in polar solvents. The mode of such oxidations were either clearly two-electron oxidations or one-electron oxidations followed by a heterolytic cleavage. We have sought to determine the products of a quinol monoacetate oxidation by mild one-electron oxidants.

The quinol ester, 2,3-dimethyl-1,4-naphthalenediol monoacetate (I), is a model for the Vitamin K series. It was stirred overnight in methylene chloride over activated manganese dioxide at room temperature. The yellow, glassy residue of this reaction was chromatographed on silica gel several times. The major component, whose crude yield was 70%, was assigned the structure II, 3,4-dihydro-3′,5-dimethyl-4′,6-dihydroxyspiro[2*H*-naphtho[1,2-*b*]pyran-2,2′-naphthalen-1′-one] diacetate, mp 148–150°. The infrared spectrum of II had carbonyl peaks at 1745 and 1690 cm^{-1}. The latter band was lacking in the reduction product III, which possessed a hydroxyl band at 3400 cm^{-1}. Whereas II did not volatilize in the mass spectrum, compound III (mp 184–185.5°) did do so to display a parent peak at 458, a molecular weight corresponding to oxidative dimerization. The same product II was obtained by the oxidation of I with the stable free radical, 2,4,6-tri-*tert*-butylphenoxyl.

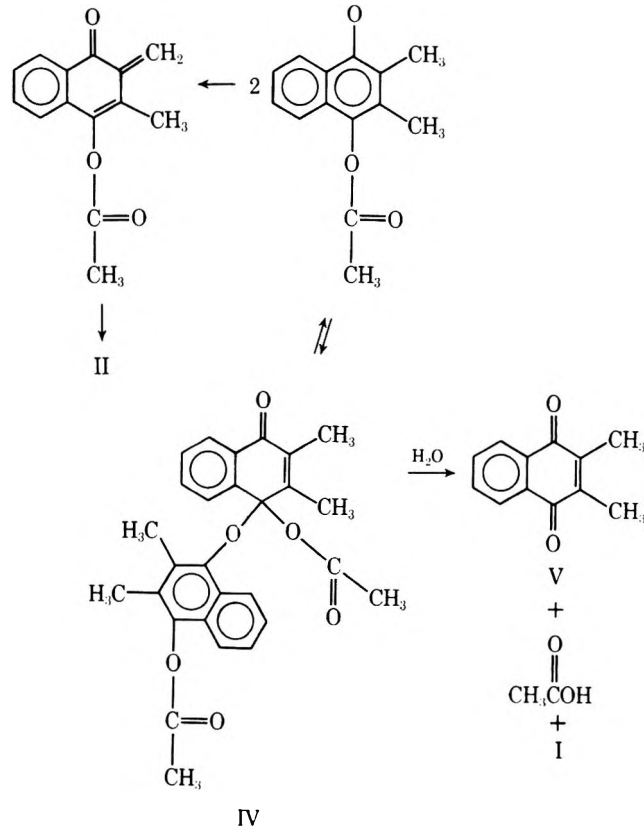


II III

In the nuclear magnetic resonance spectrum of II there are four methyl singlets at 2.48, 2.41, 2.18, and 1.98 ppm. In III the values for the methyl groups are 2.48, 2.34, 2.18, and 1.66 ppm. Since the 2.48 and 2.18 peaks did not shift, they are in an environment unaffected by the reduction. Hence, the former may be assigned to the methyl of the ester C-6 of the naphtho[1,2-*b*]pyran ring of II and the latter assigned to the methyl at the C-5 of that ring system. The values for the other ester methyl and vinyl methyl of the naphthalen-1′-one ring of II are then 2.41 and 1.98 ppm, respectively. Multiplets at 2.7 and 2.8 ppm can be assigned to the four pyran protons. In the aromatic region of both II and III there is a multiplet (1 H) at about 8.22 ppm which is reported to be characteristic of the C-10 hydrogen of such naphthopyran structures.[4] Since the neighboring unresolved doublet at 7.94 ppm (1 H) of II does not appear in the NMR of III, it can be assigned to the 8′ H in the naphthalen-1′-one system. A neighboring multiplet at 7.62 ppm (2 H) is assignable to the hydrogens at C-7 and C-5′, peri to the ester groups. The remaining four hydrogens can be assigned to the 7.16–7.53-ppm multiplet.

The structures II and III agree with the proposed mode of coupling for an o-quinone methide intermediate with carbon to carbon rather than oxygen to carbon coupling. Such couplings are common to related oxidations such as those of tocopherols,[5] 2,4-di-*tert*-butyl-6-methylphenol, and 4-substituted 2,6-dimethylphenols.[6] Although oxidations of these classes of compounds lead to trimers as well as dimers, we have no evidence for trimer formation in these oxidations of I.

In both oxidation reactions 2,3-dimethyl-1,4-naphthoquinone (V) was formed in 10–25% yields. This would be the expected product if coupling had proceeded to an active acetate species IV, which reacted subsequently with a nucleophile. Such a species could have formed, but in the nonpolar solvents and in the absence of any nucleophile save for the water of oxidation in the MnO_2 reaction it would have reverted to radicals which can also disproportionate to the *o*-quinone methide.



II IV

With the knowledge of the behavior of I with mild one-electron oxidants we proceeded to the study of the oxidation of I with its parent quinone V. If this compound served as an oxidant, a reaction more akin to a biochemical event would be at hand. Such an oxidation would proceed through charge-transfer complexes to radicals, whose products would be either IV or another active acetate. When I and V were mixed in benzene or benzene–methanol, only starting materials were recovered. Evaporation of the benzene solution did afford a highly colored quinhydrone. Similar results were obtained with the duroquinone and 2,3-dimethyl-5,6-dimethoxy-1,4-benzoquinone and their respective hydroquinone monoacetates. Although addition of catalytic quantities of *p*-toluenesulfonic acid had no effect on these combinations, the presence of at least 1 mol of base leads to products currently under examination. These latter reaction are complicated by the base reactions of V[7] or duroquinone[8] to afford products formed by the Diels–Alder addition of *o*-quinone methides to quinones.

The high-potential quinone DDQ did react with I at room temperature in benzene to give a 1:1 adduct. This adduct formed principally II and reduced DDQ when it was treated with hot methanol or benzene solutions of 2,6-xylenol, mesidine, pyridine, or acetic acid.

Experimental Section

Materials were reagent grade and were purchased from the Aldrich Chemical Co. and the J. T. Baker Chemical Co. Elemental analyses were determined by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined on a Thomas-Hoover Unimelt apparatus, whose thermometer was checked periodically with melting point standards supplied by A. H. Thomas Co., Philadelphia, Pa. The following instruments were used: infrared, Perkin-Elmer Model 137; nuclear magnetic resonance, Varian Associates Model A-60; mass spectra, Varian Associates Model M-66. Thin layer chromatography was performed on precoated silica gel plates with uv indicator supplied by the Woelm Co.

2,3-Dimethyl-1,4-naphthalenediol Monocetate (I). A modified procedure of Wieland and Aguila was used.[9] To a stirred solution of 2.3 g of 2,3-dimethyl-1,4-naphthohydroquinone in 10 ml of pyridine was added a solution of 1.4 g of acetyl chloride in 10 ml of chloroform over a 15-min period. After being stirred for an additional 1 hr, the liquid was transferred to a separatory funnel. The solution was washed three times with 50-ml portions of 7% HCl. After being washed with water and dried over $MgSO_4$, the chloroform solution was evaporated to a brown solid, which was chromatographed on a silica gel column with chloroform as eluent. The middle fractions contained the monoester, which was recrystallized three times from hexane–benzene to give 0.487 g of white crystals: mp 152–153° (lit. mp 153–154°); mass spectrum (70 eV) *m/e* (rel intensity) 230 (7) and 187 (100); NMR (CCl_4) δ 7.83 (m, 1), 7.44 (m, 1), 7.26 (m, 2), 5.52 (m, 1), 2.50 (s, 3), 2.06 (s, 3), and 1.64 ppm (s, 3); ir (Nujol) 3450 (s), 1730 (s), 1600 (m), 1570 (w), 1490 (w), 1275–1200 (tr, vs), 1175 (m), 1090 (m), 1060 (s), 1020 (m), 975 (m), 910 (m), 860 (m), 810 (m), 770 cm^{-1} (s).

Oxidation of I with Activated Manganese Dioxide. A solution of 2.30 g of I in 175 ml of methylene chloride was stirred for 3 days at room temperature with 1.305 g of activated manganese dioxide (Beacon-Winthrop). The brown mixture was filtered twice and the solvent was evaporated. The yellow glassy residue weighed 2.39 g and was chromatographed on a silica gel column with chloroform as the initial solvent. A second 50-ml fraction containing 1.81 g was chromatographed further on a dry silica gel column with benzene–chloroform mixtures as eluents. The center fraction of 1.06 g was chromatographed on a preparative TLC plate. The midband of the plate was extracted and recrystallized from hexane–benzene, mp 148–150°. This material (II) could neither be sublimed nor volatilized in the mass spectrum: NMR ($CDCl_3$) δ 8.22 (m, 1), 7.94 (d, 1, J = 8), 7.62 (m, 2), 7.16–7.53 (m, 4), 2.70 (m, 2), 2.48 (s, 3), 2.41 (s, 3), (m, 2), 2.18 (s, 3), and 1.98 ppm (s, 3); ir (Nujol) 1745 (s), 1690 (s), 1660 (w), 1630 (w), 1590 (s), 1570 (m), 1350 (s), 1300 (m), 1260 (m), 1160–1200 (vs), 1120 (s), 1060 (s), 1030 (m), 1000 (m), 960 (m), 940 (m), 890 (s), 870 (m), and 760 cm^{-1} (s).

Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 74.65; H, 5.45.

Oxidation of I with 2,4,6-Tri-*tert*-butylphenoxyl. A 0.100-g sample of I was placed in an erlenmeyer flask equipped with magnetic stirrer and connected with an addition funnel and a sintered glass addition funnel upon which was mounted a third addition funnel. All funnels had side arms so that the entire system could be maintained under a slightly positive nitrogen pressure after evacuation of air. In the first funnel was 5 ml of benzene which was added to dissolve the monoester I. In the sintered glass funnel was a bed of 2.0 g of $NaBiO_3$, to which was added a solution of 2.0 g of 2,4,6-tri-*tert*-butylphenol in benzene. As the dark blue radical solution was added dropwise to the stirred monoester solution, the color was discharged. When the blue color persisted, addition was stopped and the mixture was stirred for an additional 90 min. The solvent was removed in vacuo with occasional warming on a steam bath. The residue of 0.32 g was washed with hexane. The hexane-soluble material weighed 0.196 g and was identified as 2,4,6-tri-*tert*-butylphenol by infrared spectra. The hexane-insoluble material (0.087 g) possessed the same ir spectrum as the product of the MnO_2 oxidation of I.

Reduction of Oxidation Product of I. Sodium borohydride was added in small portions to a solution of 0.100 g of compound II in 20 ml of methanol. (Compound II is stable in refluxing methanol.) The mixture was poured into a separatory funnel containing 125 ml of 2% HCl and was extracted with ether. Evaporation of the ether after a water wash and drying with $MgSO_4$ afforded 0.088 g of an off-white solid. Crystallization from hexane–benzene gave a white powder: mp 184–185.5°; mass spectrum (70 eV) *m/e* (rel intensity) 457 (5), 415 (10), 355 (10), 229 (20), 200 (15), 187 (100), and 171 (75); NMR ($CDCl_3$) δ 8.24 (m, 1), 7.64 (m, 2), 7.26–7.52 (m, 4), 7.12 (m, 1), 5.40 (d, 1, J = 3 Hz), 2.64–2.84 (m, 2), 2.56 (d, 1, J = 3 Hz), 2.48 (s, 3), 2.34 (s, 3), 2.18 (s, 3) 2.00 (m, 2), and 1.6 ppm (s, 3), ir (Nujol) 3300–3500 (tr, m), 1745 (s), 1600 (w), 1570 (w), 1160–1220 (tr, s), 1100 (m), 1050 (s), 1000 (m), 890 (m), and 760 cm^{-1} (s).

Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.71. Found: C, 73.35; H, 5.87.

Reaction of DDQ with I. To a solution of 0.100 g of I in 12 ml of benzene was added a solution of 0.100 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 8 ml of benzene. The mixture stood overnight. The precipitate was filtered and washed with benzene and methylene chloride. It weighed 0.191 g. It had no definite melting range and did not give a mass spectrum. No NMR spectrum was obtained owing to insolubility in CCl_4, $CDCl_3$, and C_6H_6 and decomposition in polar solvents such as CD_3COCD_3. The infrared spectrum (Nujol) was as follows: 3100–3300 (tr, m), 2240 (m), 1740 (s), 1660 (s), 1600 (m), 1550 (m), 1330 (m), 1280 (m), 1240 (s), 1200 (s), 1070 (w), 1030 (m), 990 (m), 960 (s), 890–920 (tr, s), 860 (s), 770 (s), 750 (s), and 715 cm^{-1} (s).

Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_5$: C, 57.78; H, 3.09; N, 6.15. Found: C, 56.46; H, 3.17; N, 6.03.

A solution of 0.100 g of this adduct in 10 ml of methanol was heated on a steam bath for 25 min. After evaporation of the methanol, the residue was treated with benzene. The insoluble material weighed 0.031 g and displayed an ir spectrum identical with that of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone. The benzene filtrate was evaporated to 0.050 g of a residue whose ir spectrum was almost identical with that of II. Similar products were obtained when benzene solutions of 2,6-xylenol, mesidine, pyridine, or acetic acid were used to treat the adduct.

Registry No.—I, 25181-86-6; II, 56292-32-1; III, 56292-33-2; V, 2197-57-1; 2,3-dimethyl-1,4-naphthohydroquinone, 38262-43-0; acetyl chloride, 75-36-5; manganese dioxide, 1313-13-9; 2,4,6-tri-*tert*-butylphenoxyl, 2525-39-5; DDQ, 84-58-2.

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Regeneration of Ketones from Tosylhydrazones, Arylhydrazones, and Oximes by Exchange with Acetone

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Derivatives of carbonyl compounds such as tosylhydrazones serve as important synthetic intermediates and are at the same time very useful for purification and characterization. However, their utility is limited to some extent because of resistance to hydrolytic cleavage to the parent carbonyl compounds. Most of the known methods of regenerating carbonyl compounds from their nitrogenous derivatives require strongly oxidative or reducing, acidic, or basic media, or tedious procedures and/or expensive reagents.[1]

Among the earliest reported regeneration methods are the exchange reactions with other carbonyl compounds such as pyruvic[2] or levulinic acid.[3] We report here that a wide variety of ketones can be regenerated from their tosylhydrazones (Table I) by simply allowing them to react with an excess of acetone at temperatures between 20 and 80° (eq 1).

$$R_1R_2C{=}N{-}NHTS + Me_2C{=}O \rightleftharpoons R_1R_2C{=}O + Me_2C{=}N{-}NHTS \quad (1)$$

Using acetone as the exchange reagent offers some advantages over the reported exchange procedures as it involves a nonacidic reaction medium, simple work-up, and inexpensive reagents. The reaction is most easy to perform. After equilibrium is reached, the excess acetone is removed by distillation and the acetone tosylhydrazone formed is precipitated from the reaction mixture with pentane. The carbonyl compound is recovered from the concentrated pentane solution by crystallization, distillation, or, when the reaction has been performed on a very small scale, VPC separation.

This procedure is not limited in its applicability to tosylhydrazones but works also for regenerating ketones from other derivatives such as oximes, phenylhydrazones, or 2,4-dinitrophenylhydrazones. The yields are normally acceptable. The preparative applicability of this method is limited to the regeneration of ketones, as aldehydes can be recovered only in low yields. It appears that a certain thermal stability of the carbonyl compound is required.

This method is very useful for the incorporation of deuterium into carbonyl compounds during their regeneration. We observed that the reaction of tosylhydrazones of enolizable ketones with acetone-d_6 produced ketones which are perdeuterated in the α positions (Table II). The enolizable ketone when heated with acetone-d_6 alone under the same conditions does not exchange its α hydrogens. However, when a 1:1 mixture of the ketone and its tosylhydrazone is heated in acetone-d_6, all of the isolated carbonyl compound is perdeuterated in the α positions. This implies that the tosylhydrazone or free tosylhydrazide serves as base in this efficient deuterium exchange.[4]

Experimental Section

Tosylhydrazones were prepared in the usual way by reaction of the carbonyl compounds with equimolar amounts of tosylhydrazide in methanol. They were recrystallized from methanol.

General Procedure for the Regeneration of Ketones from Tosylhydrazones. The tosylhydrazone (1.0 g) was dissolved in 5

Table I
Carbonyl Compounds Regenerated from Their Tosylhydrazones and Other Derivatives by Exchange with Acetone

Carbonyl compd	Registry no.	Derivative	Registry no.	Reaction time, hr	Reaction temp °C	Yield, %
Cyclopentanone	120-92-3	*a*	17529-98-5	18	50	75
		d	2057-87-6	20	75	79
Cyclohexanone	108-94-1	*a*	4545-18-0	24	65	78
		b	100-64-1	100	80	72
		c	946-82-7	100	80	60
		d	1589-62-4	20	75	84
Pentan-3-one	96-22-0	*a*	28495-72-9	48	75	83
		d	1636-83-5	20	75	80
Phenyl *tert*-butyl ketone	938-16-9	*a*	24379-40-6	70	60	68
7,7-Dimethylbicyclo-[3.2.0]hept-2-en-6-one	767-85-1	*a*	56454-20-7	18	60	87
Pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$$0^{4,7}$]-nonan-9-one (homocubanone)	15231-18-6	*a*	56454-21-8	48	25	84
Carvone	99-49-0	*a*	21195-60-8	24	65	69
6,6-Dimethylcyclohex-1-en-3-one	1073-13-8	*a*	21195-63-1	48	80	52
6,6-Dimethylcyclohexa-1,4-dien-3-one	1073-14-9	*a*	24832-83-5	48	80	27
Benzaldehyde	100-52-7	*a*	1666-17-7	16	75	5

[a] Tosylhydrazone. [b] Oxime. [c] Phenylhydrazone. [d] 2,4-Dinitrophenylhydrazone.

Table II
α-Perdeuterated Ketones from Nitrogenous Derivatives by Exchange with Acetone-d_6

Ketone	Registry no.	Derivative	Yield, %[d]	Deuterium incorporation in the α positions
Cyclopentanone	3994-89-5	*a*	62	*e*
		c	58	
Cyclohexanone	1006-03-7	*a*	59	*e*
		b	55	*e*
		c	50	
Pentan-3-one	6400-97-1	*a*	66	*e*
		c	52	

[a] Tosylhydrazone. [b] Oxime. [c] 2,4-Dinitrophenylhydrazone. [d] Ketones were isolated by preparative VPC. [e] >95%; no α-hydrogen atoms could be detected by NMR.

ml of reagent grade acetone. The solution was heated in a sealed glass tube until equilibrium had been established (analysis by TLC or VPC). The excess acetone then was removed under reduced pressure and 30 ml of pentane added. The precipitate of acetone tosylhydrazone was removed by filtration and the remaining solution concentrated in vacuo. The carbonyl compound was isolated either by recrystallization or distillation from the residue.

α-Perdeuterated Ketones from Tosylhydrazones by Exchange with Acetone-d_6. The tosylhydrazone (150 mg) was dissolved in 0.6 ml of acetone-d_6 and heated in a sealed NMR tube until equilibrium was reached (analysis by NMR). The excess acetone-d_6 then was removed by distillation in vacuo and 5 ml of pentane was added to the residue. The solution was filtered from the precipitate and concentrated. The α-perdeuterated ketone was recovered by preparative VPC.

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Registry No.—Acetone, 67-64-1; acetone-d_6, 666-52-4.

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Solvent Effects in the Solvolysis of Aryldi-*tert*-butylcarbinyl *p*-Nitrobenzoates in Aqueous Acetic Acid. Substituent Effects on Transition State Charge Separation

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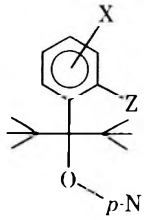
The Grunwald-Winstein equation,[1] $\log k/k_0 = mY$, has proved invaluable in solvolysis studies because of the possibility of using m as an empirical criterion of reaction mechanism. However, recent data[2] on the solvolysis of phenyldi-*tert*-butylcarbinyl *p*-nitrobenzoate (**1d**) in aqueous acetone indicate an m value of 0.32 at 100°, substantially lower than is usual for limiting solvolysis without nucleophilic solvent assistance[3] or anchimeric assistance.[4,5]



1. Z = H
2. Z = Me

We have now determined the solvolysis rates of some aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates **1** and **2** in aqueous acetic acid (0–8 *M* in water, 0.01 *M* in sodium acetate) by the uv spectroscopic method.[6] The m values range from 0.26 (**2b**) to 0.42 (**1g**) at 85° (Table I). The calculated value[7] for *tert*-butyl chloride under these conditions being 0.75, these values are indeed abnormally low. However, these molecules contain several features which are known to reduce m. Firstly, low solvent sensitivity is associated with leaving groups which are able to disperse the developing negative charge; m decreases in the order Cl > Br > OTs[8] and, more pertinently, Cl > *p*-NB > thionbenzoate.[9] Secondly, relief of steric strain in the solvolysis of congested tertiary derivatives leads to an early transition state with little charge separation.[3,10] The unusually small ρ value reported for **1** in 70% aqueous acetone at 100° (−1.79),[2a] is approximately confirmed in the present work[11] and is consistent with an early transition state. A further factor which could reduce m is steric inhibition of solvation of the incipient cation,[12] but its role has not yet been clearly demonstrated.

Table I
Grunwald-Winstein *m* Values for the Solvolysis of Aryldi-*tert*-butylcarbinyl *p*-Nitrobenzoates in Aqueous Acetic Acid at 85°

Compd	Substituent X	$10^4 k_{HOAc,\ 100\%}$, sec^{-1}	m^a
1a	*p*-MeO	6.18	0.316
1b	*p*-Me	1.74	0.384
1c	*m*-Me	1.26	0.383
1d	H	0.805	0.370
1e	*p*-Cl	0.220	0.370
1f	*m*-Cl	0.100	0.402
1g	*m*-CF_3	0.0364	0.425
2b[b]	*p*-Me	393 (9.67)[c]	0.259
2c[b]	*m*-Me	332 (7.78)[c]	0.265
2d[b]	H	220 (4.93)[c]	0.274

[a] Standard deviation on k, 1–4%; standard deviation on m, less than 0.01 (**1**) or 0.02 (**2**). [b] Values at 85° were estimated from data at 30–60°; values in parentheses are at 50.5°. [c] Corresponding rate constants in 97.7% aqueous ethanol follow: **2b**, 2.74×10^{-4}; **2c**, 2.30×10^{-4}; **2d**, 1.56×10^{-4} sec^{-1}.

Notwithstanding some scatter, there is a well-defined trend in the relationship between solvent sensitivity and reactivity: as the reactivity ($\log k$) of these aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates increases, m tends to decrease linearly (Figure 1). The substituent dependence of m[13] raises an interesting point regarding the Hammett and

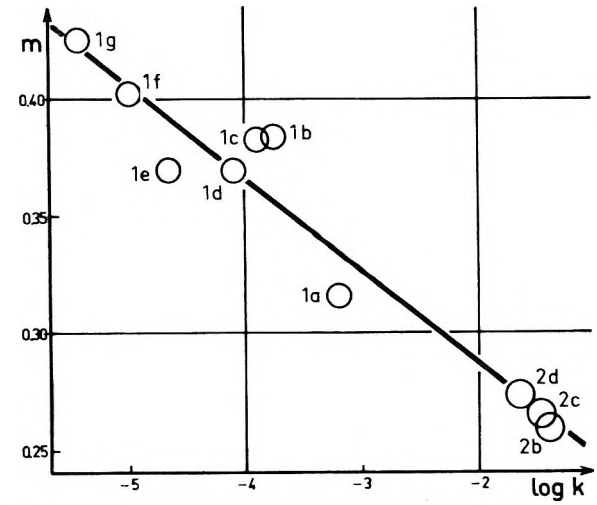


Figure 1. Linear relationship between reactivity ($\log k$) and solvent effect (m) in the solvolysis of aryldi-*tert*-butylcarbinyl *p*-nitrobenzoates.

Grunwald–Winstein correlations. Both ρ and m are widely considered to indicate the extent of charge separation in the transition state, but both substituents and solvent must also modify the charge. We anticipate that ρ_2 would be smaller (less negative) than ρ_1 but the m values show that there is a *continuous* variation in the extent of charge separation. The value of ρ must be taken, therefore, as an *averaged* measure of the charge separation. The assumption that the charge separation is invariant within a reaction series[19] only leads to confusion.

The trend in the m–log k relationship observed here is in accord with the Hammond postulate[20] but not with Thornton's "push–pull" model of the SN1 mechanism.[21] This model, however, requires weak nucleophilic solvent participation which is scarcely conceivable, owing to the congestion of the reaction center, and which, moreover, is absent even in *tert*-butyl chloride solvolysis.[22] The values of $(k_{aqEtOH}/k_{HOAc})_Y$[23] determined at 50.5° for **2** (0.28–0.32) are similar to those of 1- and 2-adamantyl tosylates in which solvent is sterically excluded from the backside of the reaction center.[8,22,24] Values below unity are commonly encountered where hydrogen bonding to the leaving group occurs[4b,c] or where electrophilic catalysis by acetic acid is possible,[24] as in the present case. We have no direct evidence regarding the extent of ion-pair return in these systems. Nevertheless, it can be deduced from the low values of m and of $(k_{aqEtOH}/k_{HOAc})_Y$ that this is not an important process; the high values of $\Delta S^{\ddagger}$ (1.8, 2.1, and 2.4 eu for **2b**, **2c**, and **2d**, respectively) tend to confirm this conclusion.[22,24]

Registry No.—**1a**, 40601-70-5; **1b**, 40544-04-5; **1c**, 56437-67-3; **1d**, 40544-05-6; **1e**, 40544-06-7; **1f**, 56437-66-2; **1g**, 56437-65-1; **2b**, 56437-64-0; **2c**, 56437-63-9; **2d**, 56437-62-8.

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A New Approach to Triaminopyrimidine *N*-Oxides

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2,4-Diamino-6-(substituted amino)pyrimidine 3-oxides have useful hypotensive activity in man.[1] A general route to these compounds is reported below.

Generally, pyrimidine *N*-oxides are prepared (a) by modification of a preexisting pyrimidine *N*-oxide, (b) by direct N-oxidation, or (c) by cyclization reactions.[2] In the past, 6-aminopyrimidine *N*-oxides have been prepared in this laboratory by reaction of various amines with 2,4-diamino-6-chloropyrimidine 3-oxide.[3] The literature contains very few examples of the second general route, direct N-oxidation of triaminopyrimidines.[4] This paper describes a cyclization approach which uses hydroxylamine as a condensation agent in the synthesis of triaminopyrimidine *N*-oxides. Hydroxylamine[5–7] and its derivatives, benzyloxyamine,[8,9] hydroxyurea,[10,11] benzyloxyurea,[10,12,13] and amidooxime ethers[14] have been used to introduce the requisite N–O bond of pyrimidine *N*-oxides. However, the preparation of a triaminopyrimidine *N*-oxide by cyclization with hydroxylamine or its derivatives has not yet been reported.

Results and Discussion

Formally, triaminopyrimidine *N*-oxide **6** is an adduct of hydroxyguanidine and cyanoacetamide **2** or a suitable derivative such as **3**. In our hands, neither compounds **2** nor **3** gave pyrimidine **6** when reacted with hydroxyguanidine. Therefore, compound **5** was constructed from smaller molecular fragments (see Chart I).

Reactions of ethyl cyanoacetate with a variety of amines efficiently produced the corresponding cyanoacetamides **2** (see Chart I). Amide **2** was O-methylated with either methyl fluorosulfonate or trimethyloxonium fluoroborate (see Chart I). The resultant salt was treated with either potassium carbonate or sodium methoxide to give enol ether **3**. Compound **3** reacted with cyanamide in alcoholic solvent to give cyanoiminopropionitrile **4**. When NR^1R^2 was piperidine, the tautomeric structure **4** (3-cyanoimino-3-piperidinopropionitrile) was suggested by NMR (CH_2 singlet at δ 3.93) and by ir (lack of N–H stretch). In the normal application of this synthesis, compound **4** was not isolated, but was treated with hydroxylamine to form triaminopyrimidine *N*-oxide **6**, presumably via postulated intermediate **5**. Yields for the three-step process from amide **2** to crystalline pyrimidine *N*-oxide **6** range in most cases from 40 to

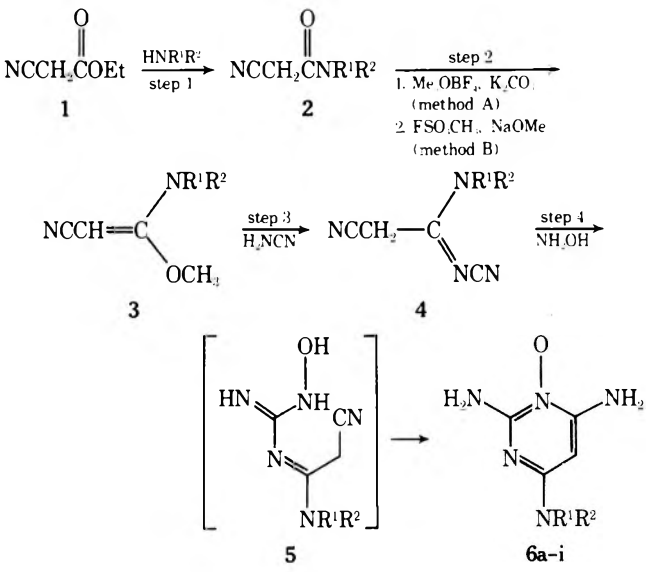
Table I
Preparation of Triaminopyrimidine *N*-Oxides (6) by Method A

Compd 6	NR^1R^2	Reaction time, hr: Step 2	Step 3	Step 4	% yield of 6 from 2	Mp of 6,[h] °C
a[a]	Ethylamino	16	6	15	49	275 dec
b[b]	*n*-Butylamino	4	1.6	17	45	221–221.5
c[c]	*n*-Decylamino	28	9	15	46	118
d[d]	Cyclohexylamino	3.3	2.5	15	43	218–220
e	Di-*n*-butylamino	7.5	16	48	23	186.5–188
f	Dicyclohexylamino	24	40	68	33	246 dec
g[e]	Piperidino	24	6	1.6	43	260 dec
h[f]	Pyrrolidino	24	19	30	46	278 dec
i[g]	Methylamino	16	10	80	73	188 dec

[a] From *N*-ethyl-2-cyanoacetamide: K. G. Naik and Y. N. Bhat, *Q. J. Indian Chem. Soc.*, 4, 547 (1927). [b] From *N*-(*n*-butyl)-2-cyanoacetamide (mp 72–73° from Et_2O). [c] From *N*-(*n*-decyl)-2-cyanoacetamide (mp 78–79° from Et_2O–hexane). [d] From *N*-cyclohexyl-2-cyanoacetamide.[17] [e] From *N*-(2-cyanoacetyl)piperidine.[17] Method B for the preparation of **6g** is described in the Experimental Section. [f] From *N*-(2-cyanoacetyl)pyrrolidine: T. S. Osdene and A.A. Santilli, U.S. Patent 3,138,592 (1964). [g] From *N*-methyl-2-cyanoacetamide: E. C. Kornfeld and E. G. Fornefeld, U.S. Patent 2,749,353 (1956). [h] Compounds recrystallized from MeOH–CH_3CN.

50% (see Table I). Compound **6g** prepared by the method of Chart I was identical with a sample which was prepared

Chart I
Synthesis of 2,4-Diamino-6-(substituted amino)pyrimidine 3-Oxides



by reaction of piperidine and 2,4-diamino-6-chloropyrimidine 3-oxide.[3]

In step 4 we assume that hydroxylamine attacks the more electron-deficient *N*-cyano group rather than the relatively electron-rich aliphatic cyano to give **5** which has never been observed. In the cyclization of **5**, both the amino and the hydroxyamino groups can react with the nitrile function. Preferential attack by the hydroxyamino group is the only observed reaction. Such preferential closures to form heterocyclic *N*-oxides rather than hydroxylamine substituted heterocyclic derivatives have been reported.[5,12,15,16]

Compounds of type **6** can be prepared from 2,4-diamino-6-chloropyrimidine by *m*-chloroperbenzoic acid oxidation to the 3-oxide and subsequent reaction with aliphatic amines to give 2,4-diamino-6-(amino)pyrimidines. In general, the method of Chart I gives higher yields, requires less chromatography, and is substantially more economical than the route via the chloro *N*-oxide.

Experimental Section

Melting points were determined in capillary tubes with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Model 421 infrared spectrophotometer as Nujol mulls. NMR spectra were recorded on a Varian A-60 spectrophotometer. NMR peaks are recorded in parts per million downfield from tetramethylsilane. Samples for NMR were generally dissolved in Me_2SO-d_6. The diagnostic singlet for the C-5 hydrogen of compound **6** occurs between 5.15 and 5.38 ppm in all the cases of Table I. Mass spectra were run at 70 eV on an Atlas Model CH-4 spectrometer. Reactions were monitored by an HPLC (high-pressure liquid chromatography) unit consisting of a Milton-Roy minipump, Chromatronix injector, and glass columns (0.125 in. × 150 cm), and an LDC LUV monitor. Columns were packed with floated TLC grade silica gel. Satisfactory analytical data (±0.4% for C, H, N) were obtained for all the new compounds of Table I and compound **4g** unless otherwise stated.[17]

The amides of cyanoacetic acid were prepared by the method of Whitehead and Traverso.[18] Elemental analyses were not obtained for these amides. The melting points and crystallization solvents for new compounds of this class are cited in Table I.

6-Piperidino-2,4-diaminopyrimidine 3-Oxide (6g). Method A. A solution of 11.44 g (0.0753 mol) of *N*-(2-cyanoacetyl)piperidine (mp 87–89°, from EtOAc) and 10.95 g (0.0739 mol) of trimethyloxonium fluoroborate[19] was stirred in 120 ml of dry CH_2Cl_2[20] for 24 hr under N_2. The reaction mixture was poured with vigorous stirring into 10.95 g of K_2CO_3 and 11 ml of H_2O. After stirring for 30 min, the organic phase was decanted from the coagulated potassium fluoroborate. The residue was washed several times with methylene chloride. The combined organics were washed quickly with 10% aqueous K_2CO_3, dried by passage through K_2CO_3, and concentrated in vacuo. The NMR indicates that cis–trans isomers are present. The concentrate was dissolved in 180 ml of absolute EtOH and 3.22 g (0.0753 mol) of cyanamide was added. The reaction mixture was stirred at 25° for 6 hr under N_2. Then 21.9 g (0.158 mol) of K_2CO_3, 8.27 g (0.119 mol) of hydroxylamine hydrochloride, and 90 ml of absolute EtOH were added and the mixture was stirred at 25° for 16 hr. The reaction mixture was filtered and the residue washed with MeOH. The filtrate was concentrated and chromatographed on silica gel (15% MeOH–1% NH_4OH–CH_2Cl_2) to give 6.77 g (43%) of crystalline product. This was recrystallized from MeOH–CH_3CN to give 5.48 g (35%), mp ca. 260° dec.

The spectral properties and decomposition points of this compound are identical with those of 6-piperidino-2,4-diaminopyrimidine 3-oxide prepared by reaction of piperidine and 6-chloro-2,4-diaminopyrimidine 3-oxide.[3]

6-Piperidino-2,4-diaminopyrimidine 3-Oxide (6g). Method B. A solution of 50.0 g (0.329 mol) of *N*-(2-cyanoacetyl)piperidine and 41.25 g (0.362 mol) of methyl fluorosulfonate (Aldrich, magic methyl) in 250 ml of CH_2Cl_2[20] was stirred for 72 hr. The reaction mixture was cooled to 0° and 78 g (0.362 mol) of 25% NaOMe in MeOH was added. The cooling bath was removed and the reaction mixture was stirred for 20 min. The reaction mixture was filtered through Celite to remove sodium fluorosulfonate. The residues

were washed with CH_2Cl_2, and the combined organic phases were concentrated in vacuo. The residue was stirred with 13.82 g (0.329 mol) of cyanamide in 200 ml of MeOH for 6 hr. A mixture of 27.44 g (0.395 mol) of hydroxylamine hydrochloride, 54.48 g (0.395 mol) of K_2CO_3, and 500 ml of MeOH was added. After stirring for 15 hr at 50° the reaction mixture was cooled to room temperature and filtered through Celite. The residues were washed with MeOH. The combined organics were concentrated, diluted with 500 ml of H_2O, and continuously extracted with CH_2Cl_2 to give the product, which was triturated with CH_3CN and then crystallized from MeOH–H_2O to give 27.9 g of product. Silica gel chromatography of the residues from trituration and recrystallization gave an additional 6.1 g of recrystallized product. Total yield was 34.0 g (49%), mp ca. 265° dec. The product obtained by method B was identical with that obtained by method A.

3-Cyanoimino-3-piperidinopropionitrile (4g). The portion of method A applicable to preparation of this compound was followed. A mixture of 5.00 g (0.0329 mol) of *N*-(2-cyanoacetyl)piperidine and 5.00 g (0.0338 mol) of trimethyloxonium fluoroborate[19] was first stirred in 50 ml of CH_2Cl_2[20] for 23 hr. The product was isolated and stirred with 1.38 g (0.0329 mol) of cyanamide in 25 ml of absolute EtOH for 5 hr and the mixture was concentrated in vacuo. The product mixture was chromatographed by HPLC on 30–50 μ silica gel in MeOH–$CHCl_3$ to afford 2.12 g of pure 3-cyanoimino-3-piperidinopropionitrile: mp 73–74.5°; NMR ($CDCl_3$) δ 1.75 [br, s, 6, $-CH_2-)_3$], 3.48–3.91 [m, 4, $N(CH_2)_2$], 3.93 (s, 2, CH_2); uv (EtOH) end absorption, λ_{max} 252 nm (ϵ 19000); mass spectrum *m/e* (rel intensity) 176 (749), 122 (698), 109 (999), 96 (334), 83 (556); ir (Nujol) 2260 (C≡N), 2180 (NC≡N), 1595 cm^{-1} (C=N), no N–H.

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Registry No.—**2** (R^1 = H; R^2 = Et), 15029-36-4; **2** (R^1 = H; R^2 = Bu), 39581-21-0; **2** (R^1 = H; R^2 = decyl), 52493-40-0; **2** (R^1 = H; R^2 = cyclohexyl), 15029-38-6; **2** (R^1 = R^2 = Bu), 53807-36-6; **2** (R^1 = R^2 = cyclohexyl), 56487-99-1; **2** (R^1, R^2 = piperidino), 15029-30-8; **2** (R^1, R^2 = pyrrolidino), 14227-95-3; **2** (R^1 = H; R^2 = Me), 6330-25-2; **4g**, 56488-00-7; **6a**, 55921-54-5; **6b**, 55921-55-6; **6c**, 55921-56-7; **6d**, 55921-57-8; **6e**, 55921-62-5; **6f**, 55921-63-6; **6g**, 38304-91-5; **6h**, 55921-65-8; **6i**, 55973-02-9.

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(20) Dried by passage through Woelm basic alumina, activity grade I.

A Convenient Synthesis of the Sesquiterpene (±)-α-Curcumene. VI. Application of Alkylation–Reduction to the Total Synthesis of Terpenes

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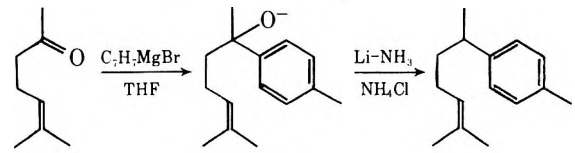
This laboratory has been developing the concept of tandem alkylation–reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons by the lithium–ammonia–ammonium chloride reduction of benzyl alkoxides generated in situ by alkylation.[1] Recently we extended this convenient procedure to the selective synthesis of rather complex aromatic hydrocarbons in excellent isolated yields by the phenylation–reduction of appropriate aldehydes and ketones.[2] One of the purposes of that study, which demonstrated that challenging organic structures could be rapidly assembled by the proper selection of the requisite carbonyl system, was to explore the potential applicability of this simple procedure to the total synthesis of aromatic terpenes. Herein we wish to report an example of the use of the procedure, which is performed in the same reaction vessel without the isolation or purification of intermediates, for the total synthesis of (±)-α-curcumene (**3**). The entire synthesis consumed only ca. 8 hr and the overall isolated yield of the pure aromatic sesquiterpene **3** was in the range of 90–92% in repeated runs.

Addition of 6-methyl-5-hepten-2-one (**1**) to a THF solution of *p*-tolylmagnesium bromide, generated in situ from *p*-bromotoluene and a dark gray suspension of highly reactive magnesium metal[3] in THF in a metal–ammonia reaction vessel, produces the intermediate benzyl alkoxide **2**. Subsequently ammonia is distilled into the vessel, excess lithium foil is quickly added, and the resultant dark blue mixture is quenched with ammonium chloride. The latter are conditions that protonate the benzyl alkoxide **2** and then rapidly reduce the resultant benzyl alcohol to the sesquiterpene (±)-α-curcumene (**3**) before all the excess lithium is destroyed, thereby completing the synthesis.



1 2 3

Although there have been numerous methods reported for the total synthesis of this racemic sesquiterpene,[4] the best overall yield starting from commercially available material seems to be ca. 35%.[4d]

Since α-curcumene has previously been reduced to β-curcumene in sodium–ammonia–ethanol (92% yield)[4d] and cyclized in phosphoric acid to calamenene (80% yield),[5] this tolylation–reduction procedure constitutes a convenient method for the preparation of these sesquiterpenes as well.

Experimental Section[6]

General Comments. The entire reaction sequence was performed under a static argon (prepurified) atmosphere, which is connected by a T tube to the assembly and to a soda lime drying trap that is connected in series to an oil bubbler, and is operated at a moderate flow rate throughout the synthesis. All glassware was oven dried and cooled to room temperature in a large box desiccator, and then quickly assembled. Anhydrous magnesium chloride was weighed in a nitrogen atmosphere. Potassium metal was wiped

free of oil, cut into small pieces, and rinsed in petroleum ether just prior to use. Lithium wire (0.32 cm, high purity, Foote Mineral Co.) was wiped free of oil, hammered flat between sheets of aluminum foil, cut into 0.5-cm pieces, and rinsed in petroleum ether just prior to use. Tetrahydrofuran (THF) was freshly distilled under nitrogen from $LiAlH_4$. Commercially available *p*-bromotoluene and 6-methyl-5-hepten-2-one (1) were redistilled. Anhydrous ammonia was distilled, through a tower of potassium hydroxide pellets, directly into the reaction vessel. Gas chromatography (GLC) analyses were performed on a 100 × 0.4 cm (i.d.) glass column, packed with 3% silicon gum rubber OV-17 (methyl phenyl) supported on 80–100 mesh HP Chromosorb W, using a 40 ml/min carrier gas flow rate, with a Hewlett-Packard Model 7610A (flame detector) chromatograph. Purification of the product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) by elution with petroleum ether. Evaporative distillations were performed in a Kügelrohr oven. The boiling point is uncorrected.

(±)-α-Curcumene (3). A stirred mixture containing 7.08 g (74.4 mmol) of magnesium chloride and 5.20 g (133 mg-atoms, five pieces) of potassium in 180 ml of THF was refluxed (oil bath, 78–80°) for 2 hr. After the dark gray suspension was allowed to cool to 25° (ca. 30 min), a solution of 5.80 g (33.9 mmol) of *p*-bromotoluene in 15 ml of THF was slowly added (ca. 5 min). After 25 min the stirred mixture was cooled to ca. −78° (Dry Ice–acetone bath) and then a solution of 3.15 g (25.0 mmol) of 6-methyl-5-hepten-2-one (1) in 15 ml of THF was added dropwise (ca. 10 min). After 20 min at −78°, the cooling bath was removed and the stirred mixture was allowed to warm to 25°. After 1 hr, 210 ml of ammonia was carefully distilled (ca. 30 min) into the reaction vessel and then 0.694 g (100 mg-atoms, 40 pieces) of lithium foil was quickly added. After ca. 10 min, the dark blue color of the reaction mixture was discharged by the rather continuous addition (ca. 15 min) of excess ammonium chloride[7] (ca. 23 g) and then the ammonia was allowed to evaporate. After the residue had been taken up in water, adjusted to pH 7 with 1 *N* HCl, and extracted with ether, the organic phase was dried ($MgSO_4$), filtered, and concentrated at water aspirator pressure. The resultant colorless oil (4.85–5.00 g, 96–99%) exhibited one product peak on GLC (6-min retention time at 120°). Following column chromatography 4.55–4.65 g (90–92%) of (±)-α-curcumene (3) was obtained as a colorless oil: bp 125–127° (15 mm); $n^{26}D$ 1.4996; ir (film) 3095, 3050, 3025, 2965, 2925, 2865, 1515, 1450, 1375, 810, 720 cm^{-1}; NMR (100 MHz, $CDCl_3$, 250 scans) δ 7.08 (4 H, s), 5.09 (1 H, apparent t. J = *ca.* 7 Hz), 2.65 (1 H, apparent sextet, J = 6.8 Hz), 2.31 (3 H, s), 2.0–1.7 (2 H, m), a broad multiplet at 1.7–1.3 (2 H, m) on which is superimposed two perturbed singlets at 1.66 (3 H, s) and 1.52 (3 H, s), 1.21 (3 H, d, J = 6.8 Hz); mass spectrum *m/e* (rel intensity) 202 (M^+, 17), 188 (5), 173 (2), 159 (3), 145 (22), 132 (76), 131 (41), 119 (100), 105 (55), 91 (33), 83 (21), 77 (17), 69 (26), 55 (48), 41 (81), 39 (29).

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.92; H, 10.95.

The physical and spectral data are consistent with those available in the literature.[4b-d]

Acknowledgments. The authors wish to thank Abbott Laboratories, Hoffmann-La Roche Inc., the Charles and Johanna Busch Memorial Fund (Rutgers University), and the National Institutes of Health (Biomedical Sciences Support Grant) for grants supporting our natural products programs; and Dr. F. Scheidl, Hoffmann-La Roche Inc., Nutley, N.J., for the microanalyses.

Registry No.—**1**, 110-93-0; **3**, 3649-81-8; *p*-bromotoluene, 106-38-7;

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(2) Part IV: S. S. Hall and F. J. McEnroe, *J. Org. Chem.*, **40**, 271 (1975).

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(4) (a) For an excellent review and discussion of the various synthetic approaches to this and related terpenes see C. H. Heathcock in "The Total Synthesis of Natural Products", Vol. 2, J. ApSimon, Ed., Wiley-Interscience, New York, N.Y., 1973, pp 241–247; (b) A. P. Krapcho and E. G. E. Jahngen, Jr., *J. Org. Chem.*, **39**, 1322 (1974); (c) F. D. Carter, J. L. Simonsen, and H. O. Williams, *J. Chem. Soc.*, 451 (1940); (d) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(5) N. H. Andersen, D. D. Syrdal, and C. Graham, *Tetrahedron Lett.*, 905 (1972).

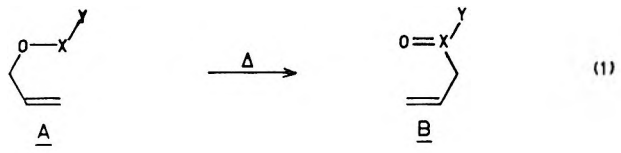
(6) The refractive index was determined with a Bausch and Lomb refractometer. The ir spectra were determined with a Beckman Model AccuLab 6 infrared spectrophotometer. The NMR spectra were determined at 100 MHz with a Jeol Model JNM-PS-FT-100 Fast Fourier transform NMR spectrometer. The chemical shifts values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with an AEI Model MS-30 mass spectrometer (70 eV) to which is interfaced a Pye Unicam Model 104 gas chromatograph.

(7) The ammonium chloride is most conveniently introduced by attaching a glass bulb tube filled with the salt to a side arm by means of tygon tubing. When the ammonium chloride is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

The Formation of an Unusual Bicyclic Sultone by Means of Thermally Induced Rearrangement of a Dipropargylic Sulfite

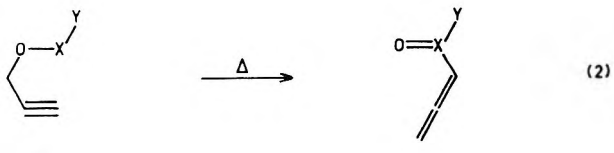
Summary: On pyrolysis the sulfite from 4,4-dimethyl-2-yne-1-pentanol undergoes a [2,3] sigmatropic rearrangement followed by intramolecular cycloaddition.

Sir: There is now adequate evidence that on thermal activation sigmatropic rearrangements occur readily with allylic (A → B, eq 1) and propargylic (C → D, eq 2) sulfenates (X = S; Y = R),[1] sulfoxylates (X = S; Y = OR),[2] and sulfinates (X = SO; Y = R).[2,3] Related rearrangements of sulfonium ylides also are known[4] and similar structural mobility likewise is seen in the transformations of propargylic sulfides to isomeric allenes.[5]



(1)

A B

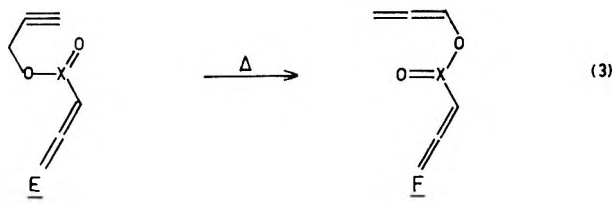


(2)

C D

We report here evidence for what we believe to be the first example of sigmatropic rearrangement of a propargylic sulfite (C, X = SO, Y = OR), thereby setting the stage for a remarkable cycloaddition of an allene and an acetylene.

The experiment was carried out with a dipropargylic sulfite with the thought that there would be formed E, through a [2,3] sigmatropic process, or possibly F, from E through [3,3] sigmatropic conversion (eq 3), which com-

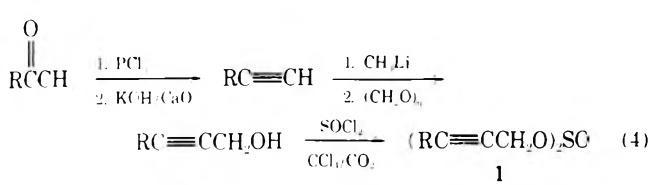


(3)

E F

pounds were anticipated to be particularly suitable substrates for realization of intramolecular cycloaddition. Such reactions have previously drawn our attention.[6]

Sulfite 1 (R = t-C_4H_9) was prepared as shown in eq 4.



(4)

1

Pyrolysis of neat 1 above 180° leads to tarry material from which in 22% yield (not maximized) an isomeric substance, mp 141.3–141.4°,[10] was isolated. Consideration of the spectral data[7] in the light of reasonable mechanistic hypotheses led to **2** or **3**. Attempts to probe chemically into the structure (see below) gave, however, no basis for a distinction.

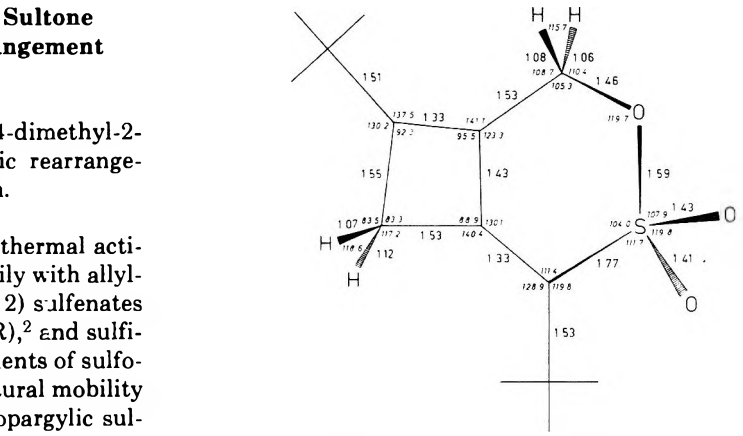


Figure 1. Bond distances in Å and angles in degrees for **3** (data for the *tert*-butyl groups are omitted).

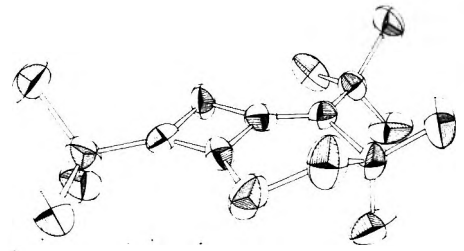
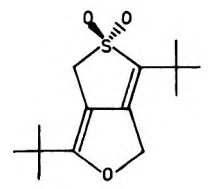
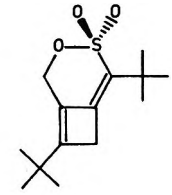


Figure 2. ORTEP plot of **3** (hydrogen atoms omitted).



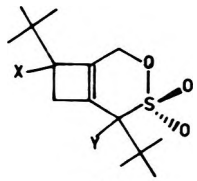
2



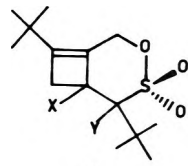
3

By x-ray diffraction the correct structure was shown to be **3**. The crystal data follow: triclinic, a = 9.82, b = 9.80, c = 7.96 Å, α = 84.9, β = 101.8, γ = 96.8°, U = 742 Å, Z = 2, space group $P\bar{1}$. The structure was solved by direct methods,[9] followed by a least-squares refinement with 1589 independent reflections, which were measured on an Enraf–Nonius four-circle diffractometer at room temperature using Mo Kα radiation. The weighted index R decreased to 0.121. Pertinent angles and bond lengths are depicted in Figure 1. An ORTEP plot of **3** is shown in Figure 2. The ring system present in **3** has never before been reported.

Compound **3** is remarkably stable. It is recovered unchanged on attempted hydrolysis with NaOH in dioxane–water or HCl in the same medium; it is stable to treatment with zinc in acetic acid, sodium in ethanol, hexachlorodisilane, potassium *tert*-butoxide in *tert*-butyl alcohol, or to *N*-bromosuccinimide under brominating conditions. It is stable to irradiation and pyrolysis. Several addition reactions do take place. Addition of bromine gives a single dibromide, mp 119.2–120.1°, which on the basis of spectral data[10] is assigned structure **4a** or **5a**. A rather unstable ad-



4

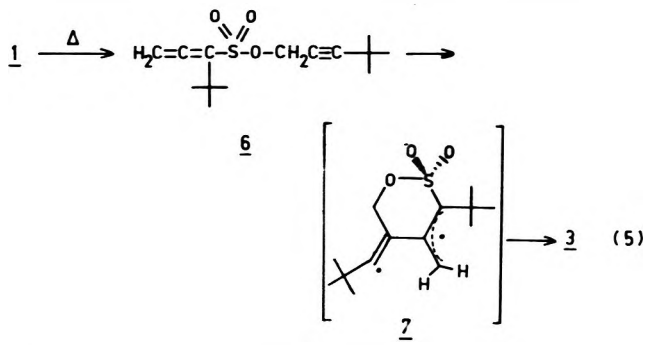


5

a. X = Y = Br
b. X = H, Y = I
c. X = H, Y = OH
d. X = Y = H

duct **4b** or **5b** is obtained with HI; this on treatment with $AgNO_3$ in THF–water affords unstable **4c** or **5c**. Treatment with triethylamine causes **4/5a** to revert to **3** whereas **4/5b** and **4/5c** revert to **3** on chromatography. Hydrogenation of **3** (Pd/C) gives a complex mixture of reduced products; reduction (Zn/HOAc) of **4/5b** gives **4/5d**. Ozonolysis of **3** produces a stable ozone addition product, mp 83.3–83.8° dec, the structure of which is under investigation.[10]

The structure of **3** makes probable that it is preceded by **6**, which we have been unable to observe, suggesting its great proclivity toward cycloaddition, even through the uncommon allene–acetylene mode.[11] It is likely that the latter reaction passes through diradical **7** (eq 5).[11a] A superficially



(5)

related reaction has been observed by Braverman and Segev.[2a] The structure **2** originally considered as an alternative would become accessible were **6** to undergo a subsequent [3,3] sigmatropic rearrangement (eq 3), followed by the well-known allene dimerization through a 2,2′-bisallyl diradical.[6,11g]

Further investigations are underway.

Acknowledgment. We are indebted to Professor Dr. A. Vos of the Department of Structural Chemistry of this university for making available equipment for crystallographic work.

Supplementary Material Available. A listing of crystallographic data (atomic coordinates and thermal parameters, interatomic distances, bond angles and least square planes) as well as physical data for **3**, **4/5a-d** and the ozone adduct will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journal Division, American Chemical Society, 1155 16th Street, N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3308.

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(6) (a) T. Beetz and R. M. Kellogg, *J. Am. Chem. Soc.*, **95**, 7925 (1973); (b) T. Beetz and R. M. Kellogg, paper in preparation.
(7) Spectral data for **3**: ^1H NMR (CCl_4) δ 1.15 [s, 9, $(CH_3)_3C$–], 1.33 [s, 9, $(CH_3)_3C$–], 3.15 (dd, 2, J = 3.5, 2.4 Hz, $-CH_2$–),[8] and 5.06 (dd, 2, J = 3.5, 2.4 Hz, $-CH_2$–); ir (KBr) 1335 and 1155 cm^{-1} (sulfur–oxygen bonds); uv (C_2H_5OH) λ_{max} 246 nm (ϵ 8750). In the coupled ^{13}C NMR spectrum there is seen in addition to the $(CH_3)_3C$– absorptions (relative to TMS) δ 158.1 (s, vinylidene C), 139.8 (s, vinylidene C), 132.7 (s, vinylidene C), 129.1 (s, vinylidene C), 68.2 (t, J_{CH} = 153 Hz, $-CH_2$–), and 36.5 (t, J_{CH} = 143 Hz, $-CH_2$–).
(8) Coupling constants confirmed by computer simulation [LAME: C. W. Haigh, *Annu. Rep. NMR Spectrosc.*, **4**, 311 (1971)].
(9) MULTAN computer program: G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
(10) Correct elemental analyses have been obtained for all new compounds save **4/5b,c**, which were too unstable for analysis, and **4/5d**. Spectral data were all in accord with the proposed structures. See also note concerning microfilm edition.
(11) Examples of this type of reaction are reported by (a) B. E. Kirk and D. R. Taylor, *J. Chem. Soc. Perkin Trans. 1*, 1844 (1974); (b) R. E. Banks, W. R. Deem, R. N. Hazeldine, and D. R. Taylor, *J. Chem. Soc., C*, 2051 (1966); (c) D. E. Applequist and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 4012 (1956); (d) Ya. M. Slobodin, Yu. A. Tallier, and I. Ismailova, *Zh. Org. Khim.*, **3**, 1529 (1967) (English translation, p 1484). (e) A failed attempt to realize this reaction has been reported by H. A. Staab and H-A. Kurmeier, *Chem. Ber.*, **101**, 2897 (1968). (f) The addition of benzyne to allenes could be considered a variant on this reaction: H. H. Wassermann and J. M. Fernandez, *J. Am. Chem. Soc.*, **90**, 5322 (1968); H. H. Wasserman and L. S. Keller, *Chem. Commun*, 1483 (1970). (g) For general references on allene cycloadditions, see J. E. Baldwin and R. H. Fleming, *Fortsch. Chem. Forsch.*, **15**, 281 (1970); D. Seebach, Houben-Weyl Methoden der Organischen Chemie, George Thieme Verlag, Stuttgart, 1971, IV/4, p 151 et seq.

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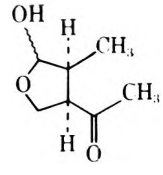
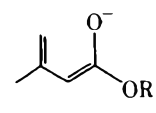
The Stereochemistry of Ester Dienolate Anions. A Stereoselective Route to Botryodiplodin

Summary: A three-step total synthesis of the antibiotic and antileukemic agent botryodiplodin by means of the stereoselective Claisen rearrangement of *cis*-crotyl senecioate is described.

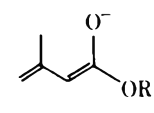
Sir: A short, stereoselective total synthesis of the antibiotic and antileukemic agent botryodiplodin[1,2] (**1**) has been achieved by a route which also provides evidence for the configuration of ester dienolate anions. Several recent re-



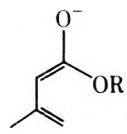
1



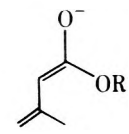
2. *E* (s-cis)



3. *E* (s-trans)

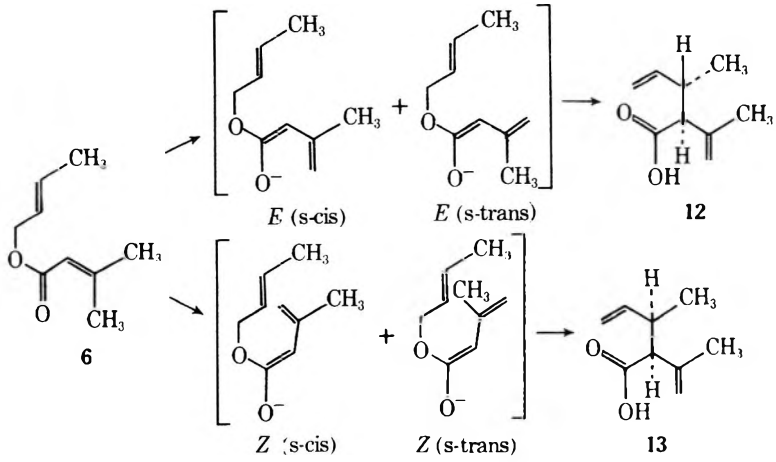


4. *Z* (s-cis)



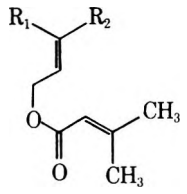
5. *Z* (s-trans)

Scheme I

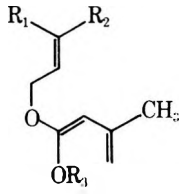


ports have appeared concerning the alkylation[3] or aldol condensation[4] of dienolate anions of α,β-unsaturated carboxylic acids or esters. These anions may adopt either *E* configuration **2** (s-cis) and **3** (s-trans) or *Z* configuration **4** (s-cis) and **5** (s-trans). It has been suggested[3c] that the dienolate **2** (R = Na) should be the most stable.

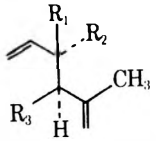
The recent extensions of the Claisen rearrangement to ester enolates,[5] and the high degree of stereoselectivity[6] well known in the vinyl ether Claisen rearrangement suggests that the rearrangement of *cis*- and *trans*-crotyl ester dienolate anions might be used as a probe to examine the initial stereochemistry of ester dienolates. Rearrangement of trans ester **6** (Scheme I) should give (2*S*),(3*S*)-acid **12**[7] via the *E* (s-cis or s-trans) dienolate anion or (2*S*),(3*R*)-acid **13** via the *Z* (s-cis or s-trans) dienolate. The opposite should hold true for the cis ester **7**.



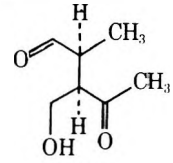
6, $R_1 = H$; $R_2 = CH_3$
7, $R_1 = CH_3$; $R_2 = H$



8, $R_1 = H$; $R_2 = CH_3$; $R_3 = TMS$
9, $R_1 = CH_3$; $R_2 = H$; $R_3 = TMS$



10, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2TMS$
11, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2TMS$
12, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2H$
13, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2H$
14, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2CH_3$
15, $R_1 = CH_3$; $R_2 = H$; $R_3 = CO_2CH_3$
16, $R_1 = H$; $R_2 = CH_3$; $R_3 = CH_2OH$
17, $R_1 = CH_3$; $R_2 = H$; $R_3 = CH_2OH$



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trans-Crotyl senecioate (**6**) and *cis*-crotyl senecioate (**7**) were prepared by standard methods. Treatment of **6** with lithium 2,2,6,6-tetramethylpiperidide[8] (THF, −78°, 15 min), followed by trimethylchlorosilane, gave silyl ketene acetal (**8**) which on heating to reflux rearranged to silyl ester **10**. This material hydrolyzed on work-up to the (2*S*),(3*S*)-acid **12**, in 95% overall yield (bp ~75° at 2.5 mm, mp 34–36°) (see Table I).[9,10] Similar treatment of the cis ester **7** gave (2*S*),(3*R*)-acid **13** in 88% yield (mp 29.5–31°).

The stereoselectivity[11] is 68% for the trans ester **6** and 82% for the cis ester. This is lower than the ~95% usually observed in the Claisen rearrangement and implies a 10–20% concentration of *Z* dienolate anion **4,5** with the *E* dienolate **2,3** predominating.[12]

Table I
Stereoselective Crotyl Senecioate Rearrangements

Ester	Conditions	Ratio[a] of 12:13	% yield[b]
6	LDA,[c] 25°	79:21	53
6	LiTMP,[d] −78°, TMSCl, Δ	84:16	95
7	LiTMP, −78°, TMSCl, Δ	9:91	88

[a] Ratios of isomers were determined by NMR integration of the methyl doublet (proton C, Table II) and by GLPC analysis of the methyl ester (CH_2N_2) on a 200-ft DB-TCP capillary column operating at 60°C. [b] Isolated yield of distilled or crystallized product. [c] Lithium diisopropyl amide. [d] Lithium 2,2,6,6-tetramethylpiperidide.

The reaction can be utilized for the construction of stereochemistry in acyclic systems such as botryodiplodin (**1**). Acid **13** was reduced with excess lithium aluminum hydride in ether to the alcohol **17** in 83% yield (bp 75° at 50 mm). Ozonolysis (O_3, CH_2Cl_2, −78°, Zn, AcOH) gave ketoaldehyde **18** which spontaneous cyclized to the lactol *dl*-botryodiplodin (**1**, 63%, bp ~130° at 5 mm). Spectral properties of *dl*-botryodiplodin and its acetate were identical with those reported by McCurry.[2a,b]

Acknowledgment. The authors gratefully acknowledge the generous support of the Indiana University Department of Chemistry and the Indiana University Research Funds.

Supplementary Material Available. Table II, containing 220-MHz PMR data for compounds **12–17** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St. N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3309.

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(7) All new compounds reported in this paper are racemic but for convenience only one stereoisomer is drawn. Thus compound **12** is (2*S*),(3*S*) and (2*R*),(3*R*); compound **13** is (2*S*),(3*R*) and (2*R*),(3*S*).
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(9) All new compounds possessed satisfactory analytical and spectral data. NMR spectral data for compounds **12–17** are collected in Table II (microfilm edition).
(10) Fractional crystallization of acids **12** and **13** substantially increased the purity of the major isomer. Care was taken, however, to assure that the isomer ratios in Table I were accurate by examination of the total crude product.
(11) Stereoselectivity is defined as (% major isomer − % minor isomer); see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 10.
(12) An alternative explanation involves increased proportion of reaction proceeding via boat transition state.

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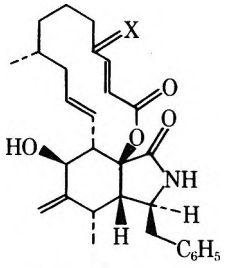
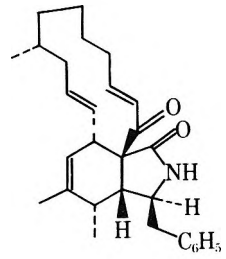
Synthesis of the Isoindolone Nucleus of the Cytochalasins

Summary: The isoindolone skeleton of the cytochalasins has been constructed stereospecifically via an intramolecular Diels–Alder reaction.

Sir: The cytochalasins are a group of microbial metabolites producing a variety of unusual biological effects upon living cells.[1] The members of this group of natural products are all characterized structurally by a saturated isoindolone skeleton fused to an 11- to 14-membered macrocyclic ring,[2-4] as shown in cytochalasins A (**1**), B (**2**), and proxiphomin



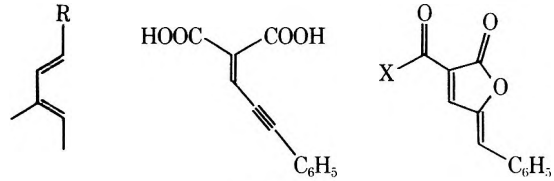
1, X = O
2, X = α-OH, β-H



3

(**3**).[5] Although these compounds represent an exciting and difficult challenge for the synthetic chemist, to our knowledge no work has yet been reported in this area. We now wish to describe a stereospecific approach to the isoindolone nucleus of the cytochalasins.

Condensation of tiglic aldehyde with trimethyl phosphonoacetate (sodium hydride, benzene) produced methyl γ-methylsorbate (**4**) in 80% yield. Reduction of **4** to the alcohol **5**[6] [bp 40–45° (0.2 mm)] was effected in 87% yield with lithium aluminum hydride in ether. Diacid **6**, prepared as described[7] by condensation of malonic acid and phenyl propargaldehyde, was cyclized to the known butenolide **7**[8] by refluxing in *o*-dichlorobenzene. Compound **7** could be converted into the corresponding acid chloride **8** upon treatment with thionyl chloride in chloroform. The crude



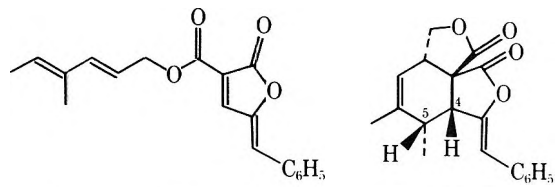
4, R = $COOCH_3$
5, R = CH_2OH

6

7, X = OH
8, X = Cl

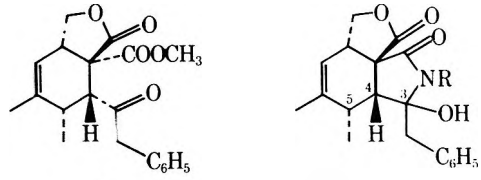
acid chloride **8** was treated with a solution of alcohol **5** in pyridine at room temperature to produce the stable, crystalline ester **9** (80%), mp 106–108°.

Heating ester **9** in refluxing *o*-dichlorobenzene produced the crystalline tricyclic dilactone **10**: NMR ($CDCl_3$) δ 1.38



9 10

(3 H, d, J = 8 Hz), 1.80 (3 H, br s), 2.5 (1 H, m), 3.2 (1 H, m), 3.56 (1 H, d, J = 7 Hz), 4.65 (1 H, t, A of ABX), 5.25 (1 H, dd, B of ABX), 5.68 (1 H, s), 6.00 (1 H, m), 7.2–7.7 (5 H, m). One would expect that an endo transition state is preferred for this intramolecular Diels–Alder reaction,[9,10] thus producing the stereochemistry shown in structure **10**. The C-4–C-5 hydrogen coupling constant of 7 Hz in compound **10** supports assignment of a cis relationship to these protons.[11] Tricyclic lactone **10** was quite difficult to isolate because of its propensity for reaction with nucleophiles during chromatography. It was discovered that refluxing a methanolic solution of **10** led to formation of keto ester **11**:



11

12, R = H
13, R = $CH_2C_6H_5$

NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.90 (2 H, s). The high reactivity of the butenolide ring of **10** toward nucleophiles was used in introducing nitrogen into the system.

Thus, on heating a dilute *o*-dichlorobenzene solution of ester **9** for 2.5 hr, followed by cooling in ice, and saturating with ammonia, crystalline tricyclic lactam **12** could be readily isolated (32% yield from **9**): mp 174–175°[12]; ir (film) 3400, 3300, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (2 H, AB q, J = 14 Hz).

Similarly, treatment of the crude Diels–Alder product **10** with benzylamine produced lactam **13**[11,12] (36% frm **9**): ir ($CDCl_3$) 3350, 1740, 1700 cm^{-1}; *m/e* found 417.19520. Work is now in progress to utilize systems such as **12** and **13** in a total synthesis of the cytochalasins.

Acknowledgment. This research was supported by Grants HL 18450 and CA12568 from the National Institutes of Health and by Eli Lilly. We thank Mr. D. Kim for 100-MHz NMR spectra, Mr. R. Comi for preparation of intermediates, and Dr. C. E. Costello, MIT, for high resolution mass spectra.

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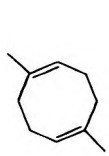
Transannular Cyclizations. A Stereoselective Synthesis of the Cyclopentanoid Monoterpenes

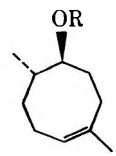
Summary: A highly stereoselective method of cyclopentanoid ring formation by transannular cyclization of cyclooctane systems is described. Its utility is illustrated by a total synthesis of the monoterpene iridomyrmecin.

Sir: We wish to report an approach to the synthesis of the cyclopentanoid class of monoterpenes which commences with the novel head-to-tail isoprene dimer 1,5-dimethyl-1,5-cyclooctadiene[1] (1) and which makes use of a transannular cyclization[2] to construct the carbon framework of a key intermediate in a stereoselective manner. The route, illustrated by the total synthesis of the naturally occurring insecticide iridomyrmecin, isolated from the Argentine and *Iridomyrmex humilis*, could potentially be diverted at suitable points to synthesize many of the cyclopentanoid monoterpenes.[3]

The diene 1[4] was converted into alcohol **2a**[5] (75% yield)

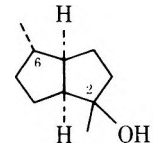


1



2a, R = H
b, R = SO_2CH_3

by a selective monohydroboration–oxidation sequence employing 9-borabicyclo[3.3.1]nonane,[6] and thence to the sulfonate ester **2b** with methanesulfonyl chloride and triethylamine in methylene chloride.[7] Without purification, this ester was subjected to solvolysis for 12 hr at 60° in aqueous dioxane in the presence of an excess of sodium carbonate. The alcohol **3** (60% yield overall from **2a**) thereby produced has the indicated orientation of the C-6 methyl group (exo- to the cis-fused bicyclo[3.3.0]octane system) that both follows from and is required for a successful synthesis of iridomyrmecin. The stereochemical control observed in this cyclization is the result of π-electron participation in the solvolytic removal of the sulfonyloxy group and thus the exo orientation at C-6 can be attributed directly to the trans relationship of the methyl group and the sulfonate moiety in **2b**. Though the reaction could have alternatively occurred without assistance while still generating the product of transannular cyclization, consideration of molecular models indicates that the C-6 epimer would be expected to be the predominent product of such a process.[8] Alcohol **3** was transformed into olefin **4** (70% yield) by a *p*-



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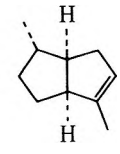

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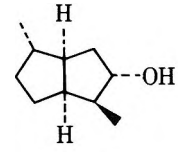
toluenesulfonic acid catalyzed dehydration in pentane at reflux to effect azeotropic removal of water. A second hydroboration–oxidation sequence using diborane served to convert olefin **4** into alcohol **5** (60% yield) containing a small amount of a second alcohol, possibly that resulting from attack by diborane on the endo face of olefin **4**. Alcohol **5** was converted into the corresponding ketone (**6**, 90%



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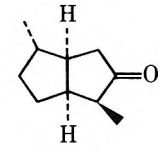
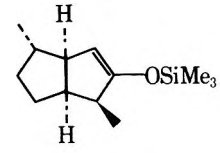


6

yield) by Jones oxidation.[9] The kinetic enolate of this ketone was generated with lithium diisopropylamide in tetrahydrofuran solution and then trapped by trimethylsilyl chloride to form the unstable enolsilyl ether **7**. Without isolation of intermediates, the enol ether **7** was cleaved with



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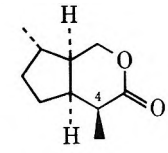

iridomyrmecin

ozone in methanol–methylene chloride solution,[10] the resulting acid–aldehyde was reduced with sodium borohydride, and the hydroxy acid was subjected to aqueous hydrochloric acid to effect lactonization. The crude material thus formed (40% overall yield from ketone **6**) crystallized spontaneously and could be recrystallized from pentane to afford needles with mp 57–58° (lit. 59° for racemic iridomyrmecin).[11,12] Further confirmation of the structure was provided by the conversion of iridomyrmecin into the more stable C-4 epimer, isoiridomyrmecin, by the known procedure.[11,12]

Acknowledgment is gratefully made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research.

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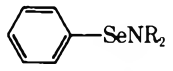
Organoselenium Chemistry. Preparation and Reactions of Benzeneselenenamides

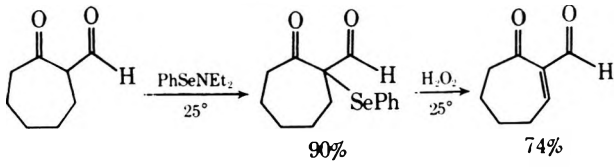
Summary: *N,N*-Dialkylbenzeneselenenamides react with β-dicarbonyl compounds to give β-dicarbonyl selenides, with acetic anhydride to give benzeneselenenyl acetate, and with some enones to give α-phenylseleno-β-dialkylamino ketones.

Sir: The chemistry of the amides of selenenic acids (selenenamides) has been little studied.[1] We have prepared several simple *N,N*-dialkylbenzeneselenenamides (**1a–c**) by reaction of secondary amines with PhSeCl, PhSeBr, or PhSeOH (generated in situ by selenoxide syn elimination) and examined their chemistry.[2] Compound **1a**[3a] is rather easily hydrolyzed and should be handled with appropriate care. The more hindered diethyl (**1b**)[3b] and diisopropyl (**1c**)[3b] derivatives are substantially more resistant to hydrolysis.

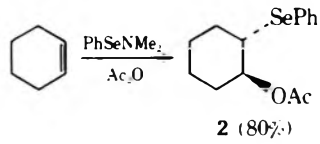


1a, R = CH_3
b, R = CH_2CH_3
c, R = $CH(CH_3)_2$

Selenenamides undergo a number of reactions similar to those of the analogous sulfenamides. For example, 2-formylcycloheptanone is selenenylated cleanly and rapidly by reaction with **1b** or **1c**.[3c,d] Careful oxidation of the selenide with hydrogen peroxide (2 equiv) then leads to β-dicarbonyl enone.[4,5a-c]

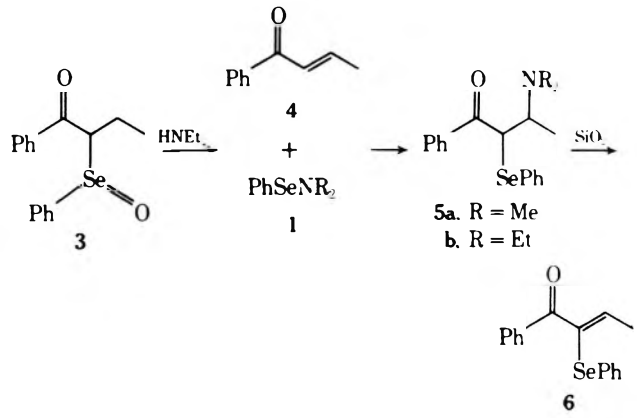


Compound **1a** reacts with acetic anhydride in the presence of cyclohexene to give the adduct **2**. Apparently benzeneselenenyl acetate ($PhSeO_2CCH_3$)[5d,6,7] is formed under these conditions.



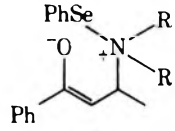
2 (80%)

A reaction of selenenamides which appears to have no parallel in sulfur chemistry[3] is the addition to electron-deficient olefins. This reaction was discovered when **3** was warmed in the presence of diethylamine. Selenoxide syn elimination gives a mixture of enone **4** and selenenamide[9] **1b**. These compounds then react with each other slowly at 25° to give a new product identified from its spectral data as **5b**.[10] Similar results were obtained when pure **1a** or **1b** and **4** were allowed to react. Attempted purification of **5** by chromatography on silica gel resulted in elimination of dialkylamine giving **6** (88% yield using **1a**).

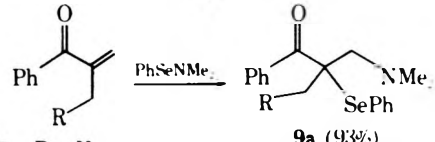


The formation of **5** probably occurs by a Michael addition leading to **7**, followed by an intramolecular selenenylation. Indirect evidence for a long-lived reversibly formed intermediate is provided by the observation that the cis isomer of **4** is isomerized to **4** in the presence of **1b**.[11]

The addition of selenenamides to α,β-unsaturated carbonyl compounds is successful only with some of the more reactive Michael acceptors.[12] and **1a** is significantly more reactive than **1b** or **1c**. Benzene and chloroform are the preferred solvents for the addition. Addition of **1a** in chloroform to compound **8a** is complete in 18 hr, **8b** requires 3 days, while 2-ethyl-1-phenyl-2-buten-1-one is incomplete after several weeks.



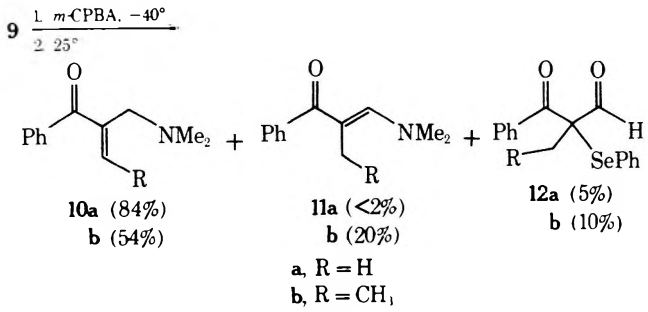
7



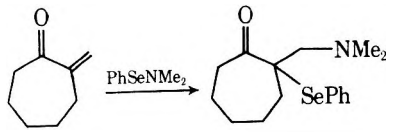
8a, R = H
b, R = CH_3

9a (93%)
b (94%)

Of several possible transformations of the adducts **9** we have examined oxidation and subsequent selenoxide elimination. Oxidation of **9a** with *m*-chloroperbenzoic acid at −40° followed by warming to room temperature leads to **10a** in good yield. Only trace amounts of the products **11a** and **12a** resulting from elimination toward the dimethylamino group are formed. The additional substituent in **9b** almost equalizes the ratio of elimination directions. The product **12b** is apparently formed by reaction of **11b** with an active selenenylating reagent (PhSeOH or a dispropor-



tionation product of it)[5b,13] produced in the course of the selenoxide elimination. Quite similar results are found for **13** where products analogous to **10**, **11**, and **12** are formed in 48, 6, and 22% yields, respectively.



Pronounced control of selenoxide eliminations away from hydroxy-, alkoxy-, and acetoxy-substituted carbons has been previously reported.[5e,6,7,14] The dimethylamino group, at least in these carbonyl substituted systems, appears to exert a much less pronounced control of the elimination. In fact, a methyl substituent apparently retards elimination toward a carbon almost as effectively as dimethylamino (compare **9a** and **9b**).

Preliminary attempts to add *N,N*-dimethylbenzenesulfenamide to enones have not been successful.

Acknowledgment. We thank the National Science Foundation and the Research Corporation for financial support of this research.

References and Notes

(1) (a) H. Rheinboldt in "Houben Weyl. Methoden der Organischen Chemie, Schwefel-, Selen-, Tellurverbindungen", Vol. IX, 1955, p 1178; (b) D. L. Klayman and W. H. H. Gunther, Ed., "Organic Selenium Compounds: Their Chemistry and Biology", Wiley, New York, N.Y., 1973, p 108; (c) Von O. J. Scherer and J. Wokulat, *Z. Anorg. Allg. Chem.*, **357**, 92 (1968).

(2) All new compounds (except **5** and the selenoxides, which were unstable) gave satisfactory elemental analyses or elemental compositions.

(3) (a) **1a** was prepared in 62% yield by addition of PhSeCl to 2 equiv of dry dimethylamine in hexane at 0°, filtration, and distillation: pale yellow liquid; bp 39–40° (0.1 mm); ^{1}H NMR δ (CCl_4) 2.81 (s, 6 H), 7.28 (m, 3 H), 7.56 (m, 2 H); ^{13}C NMR δ^{TMS} ($CDCl_3$) 51.0 (*N*-CH_3), 128.9 (C-1), 134.5 (C-2), 128.5 (C-3), 128.2 (C-4) (J_{C_2Se} = 9.7 Hz). (b) **1b** and **1c** were prepared as above (59% yield of **1b** and 24% yield of **1c**) except that reaction was performed at 50°. (c) 2-Carbomethoxybutyrophenone (92%), 2-formylbutyrophenone (80%), and 2-acetylcyclohexanone (92%) have similarly been converted to selenides. Use of **1a** results in cleavage (reverse Claisen) of some selenides. (d) Sulfenamides also react with β-dicarbonyl compounds: T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Lett.*, 5115 (1970).

(4) The crude enone was a 56:44 mixture of keto to enol forms; almost complete enolization occurred during distillation. In less readily enolized systems, this method usually gives only traces of the enol form.[5b,c]

(5) (a) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *ibid.*, **97**, 5434 (1975); (c) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Org. Chem.*, **39**, 2133 (1974); (d) H. J. Reich, ibid., **39**, 428 (1974); (e) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **97**, 3250 (1975).

(6) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974).

(7) D. L. J. Clive, *Chem. Commun.*, 100 (1974).

(8) N. E. Heimer and L. Field [*J. Org. Chem.*, **35**, 3012 (1970)] have studied the reaction of *N*-ethylthiopiperidine with N-substituted maleimides and ethyl acrylate. They obtained the amine adducts.

(9) The selenenamides (**1b** and **1c**) survive aqueous work-up under mildly basic conditions.

(10) **5b**: NMR δ ($CDCl_3$) 0.72 (t, $J \simeq 7$ Hz, 3H), 1.24 (d, $J \simeq 6.5$ Hz, 3 H), 2.38 (m, 2 H), 3.56 (dq, $J \simeq 11,6.5$ Hz, 1 H), 4.46 (d, $J \simeq 11$ Hz, 1 H, 7.0–7.7 (m, 8 H), 7.80 (m, 2 H); ir ($CDCl_3$) 1672, 1599, 1581 cm^{-1}. A second stereoisomer was formed in 4–5% yield.

(11) Support for a mechanism involving intramolecular selenenylation is provided by the observation of cis addition to dimethyl acetylenedicarboxylate (H. J. Reich, J. M. Renga, and J. E. Trend, unpublished results).

(12) Methyl acrylate, phenylacetylene, cyclohexene, and ethyl 2-phenylcrotonate did not react with **1a**. Cyclohexenone, cyclopentenone, 2-*p*-tolylidenecyclohexanone, and *N*-methylmaleimide react with **1a** to give mixtures of products.

(13) Thermolysis of **3** in the presence of **11b** results in partial conversion (~66%) to **12b**.

(14) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

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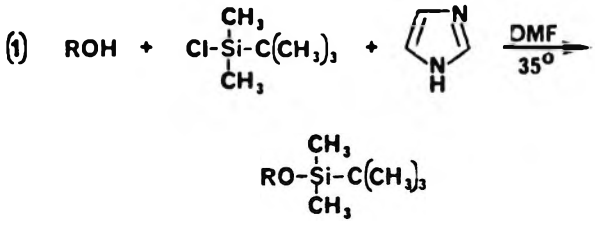
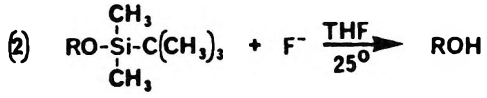
tert-Butyldimethylsilyl Chloride

For the protection of hydroxyl groups

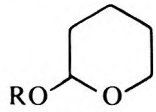
The formation of *tert*-butyldimethylsilyl ethers by the reaction of ***tert*-butyldimethylsilyl chloride** with alcohols is a very useful method for protecting alcohols.[1] These silyl ethers have no additional chiral centers and are frequently crystalline. They are stable to neutral and basic hydrolyses, yet are easily removed under acidic conditions or by treatment with tetra-*n*-butylammonium fluoride in THF.[1] The masked or protected alcohols are suitable for gas chromatographic or mass spectral analysis and for use in metal hydride reductions, Grignard reactions, Wittig reactions, Jones oxidations and the phosphorylation of nucleosides.[2]





The *tert*-butyldimethylsilyl group has been employed in the synthesis of prostaglandins[1] and in the selective blockage of the coordination of estradiol with a lanthanide shift reagent in proton NMR spectroscopy.[3]

In many synthetic processes, the chemist may wish to have only one of several hydroxyl groups unprotected. For a hypothetical molecule containing six blocked hydroxyl groups, Corey and Venkateswarlu[1] have proposed that the protecting groups may be selectively removed in a number of ways including the following two sequences:

Possible Orders of Removal		Derivative	Cleaving Reagent
1	4	ROAc	K_2CO_3/CH_3OH
2	3	$ROCH_2CCl_3$	Zn/CH_3OH
3	5	$ROCH_2Ph$	H_2/Pd
4	1	$ROSi(CH_3)_2C(CH_3)_3$	F^-/THF
5	2		$H_2O/HOAc$
6	6	$ROCH_3$	BBr_3

References:

1) E.J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).
2) K.K. Ogilvie, *Can. J. Chem.*, **51**, 3799 (1973).
3) H. Hosoda, K. Yamashita, and T. Nambara, *Chem. Ind.*, 650 (1975).