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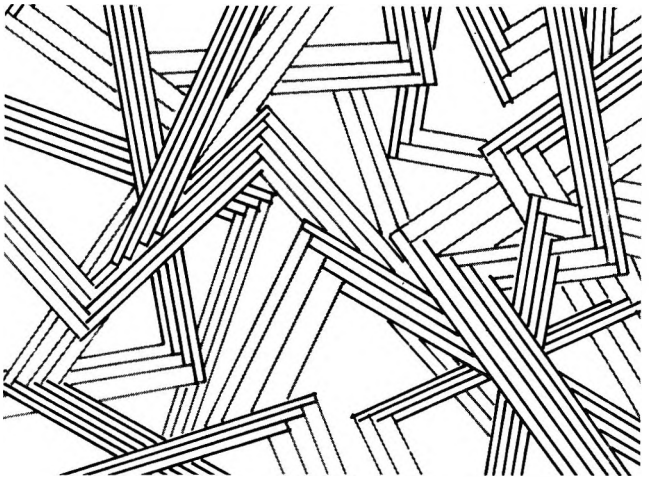

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VOLUME 43, NUMBER 2

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Reactions of Complex Metal Hydrides of Copper with Alkyl Halides, Enones, and Cyclic Ketones

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Received May 4, 1977

A series of stable complex metal hydrides of copper of composition Li_nCuH_{n+1} (n = 1–5), prepared by the reaction of $LiAlH_4$ with the corresponding lithium methylcuprates in diethyl ether, has been allowed to react with selected alkyl halides, enones, and cyclic ketones in both diethyl ether and THF. It has been shown that the different hydrides exhibit different regioselectivities toward enones and different stereoselectivities toward cyclic ketones. These data support the integrity of each hydride as a single compound rather than a physical mixture. Tetrahydrofuran-soluble Li_4CuH_5 has been shown to be the most reactive of the complex metal hydrides of copper toward alkyl halides in that this hydride reduced 1-iodo-, 1-bromo-, and 1-chlorodecane in 100, 100, and 99% yields, respectively. The complex metal hydrides of copper reduce enones predominantly 1,4 (Li_2CuH_3, 96%) or 1,2 (Li_4CuH_5, 95%), depending on the hydride. In most cases, the complex metal hydrides of copper reduce 4-*tert*-butylcyclohexanone predominantly from the axial side, as in the case of $LiAlH_4$. Other cyclohexanones are reduced by the complex metal hydrides of copper similarly to $LiAlH_4$, except with less selectivity.

Application of copper hydride reagents in organic synthesis has been a topic of great interest in the past 10 years. Recently, LiCuHR compounds (where R = 1-pentyne, OBu^t, and SPh) have been prepared and used as selective reducing reagents in order to effect conjugate reduction of α,β-unsaturated carbonyl compounds.[1] Almost at the same time, LiCuHR compounds (where R = alkyl and alkynyl) were evaluated as reagents for the selective removal of halo and mesyloxyl groups from RX compounds as well as for the reduction of α,β-unsaturated ketones.[2] More recently, the mixture obtained by the combination of $2LiAlH(OCH_3)_3$ with CuBr or $NaAlH_2(OCH_2CH_2OCH_3)_2$ with CuBr has been demonstrated to possess the ability to reduce conjugated carbonyl compounds to the corresponding saturated derivatives. The intermediates in these reagents were speculated to be "complex copper hydrides", although no evidence was presented to establish this point.[3] We reported the preparation of the first complex metal hydride of copper, $LiCuH_2$, some time ago by the reaction of $LiAlH_4$ with $LiCu(CH_3)_2$.[4] More recently, we have established the existence of some new organocuprates by variable-temperature NMR, namely, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$,[5] and have shown that these new cuprates behave differently from $LiCu(CH_3)_2$ toward enones[6] and organohalides.[7] In continuation of our present investigations in the field of copper chemistry, we have recently been able to prepare a series of complex metal hydrides of copper, $Li_nCu_mH_{n+m}$ (where n = 1–5 and m = 1–2), which are not only stable at room temperature (except for $LiCu_2H_3$ and $LiCu_3H_5$), but also some of which are soluble in THF ($LiCuH_2$ and Li_4CuH_5). These hydrides are pure compounds and not mixtures, according to x-ray and DTA–TGA data[8] as well as evidence that appears in this study. We now wish to report some reactions of the stable new complex metal hydrides of copper (Li_nCuH_{n+1}) with alkyl halides, enones, and cyclic ketones in Et_2O and THF which should be of considerable synthetic interest.

Results and Discussion

When CH_3Li in diethyl ether was added dropwise to a well-stirred slurry of CuI in diethyl ether at −78 °C, a clear and colorless solution resulted when the CH_3Li:CuI ratio was 2:1. When $LiAlH_4$ in Et_2O was added to this solution, no precipitate was observed at −78 °C; however, when the reaction mixture was allowed to warm to room temperature, a white crystalline solid precipitated. The insoluble solid was separated from the ether-soluble $LiAlH_2(CH_3)_2$ by filtration, and the solid was washed with Et_2O, dried, and characterized by elemental analysis and found to be a complex metal hydride of copper. In this way, a series of complex metal hydrides of copper of composition $Li_nCuH_{(n+1)}$ (where n = 1–5) was prepared by the reaction of $LiAlH_4$ with the corresponding lithium methylcuprates (eq 1 and 2). Specifically, the following compounds were prepared for this study: $LiCuH_2$, Li_2CuH_3, Li_3CuH_4, Li_4CuH_5, Li_5CuH_6.

$$(n+1)CHLi + CuI \xrightarrow[-78°C]{Et_2O} Li_nCu(CH_3)_{n+1} + LiI \quad (1)$$

$$Li_nCu(CH_3)_{n+1} + \left(\frac{n+1}{2}\right) LiAlH_4 \xrightarrow[-78\ °C]{Et_2O} Li_nCuH_{n+1} + \left(\frac{n+1}{2}\right) LiAlH_2(CH_3)_2 \quad (2)$$

The compound $LiCuH_2$ was analyzed as a diethyl ether slurry while other compounds were analyzed as a slurry as well as a solid. It is interesting to note that when the products were dried under vacuum they contained no complexed ether.

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Table I. Analyses and Properties of Complex Metal Hydrides of Copper (Li_nCuH_{n+1})

Compd	Anal. (ratio) Li:Cu:H	Solubility in THF	Thermal decomp[a] (0 °C)
$LiCuH_2$	1.07:1.00:2.01	Soluble	70, 300, 400
Li_2CuH_3	2.07:1.00:2.95	Insoluble	90, 110, 120, 145, 290, 440
Li_3CuH_4	3.05:1.00:3.97	Insoluble	110, 120, 140, 308, 410, 450
Li_4CuH_5	3.95:1.00:4.96	Soluble	120, 145, 300, 365, 430, 480–above 500
Li_5CuH_6	5.09:1.00:5.95	Insoluble	140, 305, 440, 400–above 500

[a] Thermal analysis was carried out on a Mettler Thermoanalyzer II under vacuum with simultaneous DTA–TGA recording.

Table II. Reactions of Complex Metal Hydrides of Copper with Organohalides and Tosylates in THF at Room Temperature for 24 h

Expt	Hydride reagent[a]	Registry no.	Halide substrate	Registry no.	Product(s) and yield(s) (%)[b]
1	$LiCuH_2$	53201-99-3	1-Iododecane	2050-77-3	*n*-Decane (100)
2	$LiCuH_2$		1-Bromodecane	112-29-8	*n*-Decane (85)
3	$LiCuH_2$		1-Chlorodecane	1002-69-3	*n*-Decane (37)
4	$LiCuH_2$		1-Fluorodecane	334-56-5	*n*-Decane (0)
5	$LiCuH_2$		*n*-Octyl tosylate	3386-35-4	*n*-Octane (64)
6	Li_2CuH_3	64010-63-5	1-Iododecane		*n*-Decane (100)
7	Li_2CuH_3		1-Bromodecane		*n*-Decane (100)
8	Li_2CuH_3		1-Chlorodecane		*n*-Decane (35)
9	Li_2CuH_3		1-Fluorodecane		*n*-Decane (0)
10	Li_2CuH_3		*n*-Octyl tosylate		*n*-Octane (80)
11	Li_2CuH_3		Cyclohexyl chloride	542-18-7	Cyclohexane (0)
12	Li_2CuH_3		1-Chlorocyclohexene	930-66-5	Cyclohexene (0)
13	Li_2CuH_3		3-Chlorocyclohexene	2441-97-6	Cyclohexene (0)
14	Li_2CuH_3		Chlorobenzene	108-90-7	Benzene (0)
15	Li_3CuH_4	64010-64-6	1-Iododecane		*n*-Decane (100)
16	Li_3CuH_4		1-Bromodecane		*n*-Decane (90)
17	Li_3CuH_4		1-Chlorodecane		*n*-Decane (34)
18	Li_3CuH_4		1-Fluorodecane		*n*-Decane (0)
19	Li_3CuH_4		*n*-Octyl tosylate		*n*-Octane (39)
20	Li_4CuH_5	64010-65-7	1-Iododecane		*n*-Decane (100)
21	Li_4CuH_5		1-Bromodecane		*n*-Decane (100)
22	Li_4CuH_5		1-Chlorodecane		*n*-Decane (99)
23	Li_4CuH_5		1-Fluorodecane		*n*-Decane (10)
24	Li_4CuH_5		*n*-Octyl tosylate		*n*-Decane (99)
25	Li_4CuH_5		Cyclohexyl chloride		Cyclohexane (0)
26	Li_4CuH_5		1-Chlorocyclohexene		Cyclohexene (0)
27	Li_4CuH_5		3-Chlorocyclohexene		Cyclohexene (10)
28	Li_4CuH_5		Chlorobenzene		Benzene (0)
29	Li_5CuH_6	64010-66-8	1-Iododecane		*n*-Decane (100)
30	Li_5CuH_6		1-Bromodecane		*n*-Decane (100)
31	Li_5CuH_6		1-Chlorodecane		*n*-Decane (80)
32	Li_5CuH_6		1-Fluorodecane		*n*-Decane (0)
33	Li_5CuH_6		*n*-Octyl tosylate		*n*-Decane (69)

[a] The molar ratio of hydride reagent to substrate is 1:1, except $LiCuH_2$ (2:1) ratio.

Interestingly, $LiCuH_2$ and Li_4CuH_5 were found to be soluble in THF, and Li_4CuH_5 was found to be stable in THF at room temperature. All of the complex metal hydrides of copper, except $LiCu_2H_3$, were found to be stable at room temperature in the solid state or as a slurry in diethyl ether. The thermal stability of these compounds is in the order: $Li_5CuH_6 > Li_4CuH_5 > Li_3CuH_4 > Li_2CuH_3 > LiCuH_2 > LiCu_2H_3$. The hydride, Li_5CuH_6, is stable to 140 °C under vacuum and is stable at room temperature for over 1 month. Elemental analysis, solubility, and thermal stabilities of these complexes are given in Table I.

In order to study the reactions of these hydrides with various organic substrates, either a diethyl ether slurry or a THF solution of the hydride of known concentration was prepared and added to the organic substrate in either diethyl ether or THF.

Reactions of Organohalides and Tosylates. Decyl halides (X = I, Br, Cl and F) and *n*-octyl tosylate were allowed to react with each of the stable complex metal hydrides of copper (i.e., $LiCuH_2$, Li_2CuH_3, Li_3CuH_4, Li_4CuH_5, and Li_5CuH_6). In preliminary experiments, both THF and diethyl ether were evaluated as solvents with the results indicating that THF is the better solvent. For example, the reaction of Li_2CuH_3 with 1-iododecane produced 100% *n*-decane in THF within 1 h of reaction time at room temperature

$$Li_nCuH_{n+1} + C_{10}H_{21}I \xrightarrow{THF} C_{10}H_{22}\ (100\%\ \text{yield}) \quad (3)$$

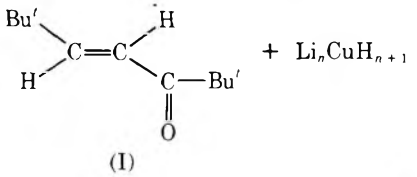
but only 72% *n*-decane was formed in diethyl ether solvent in a comparable experiment over the same period of time. A further difference in the two solvents was indicated in close observations of the reactions of 1-iododecane with Li_2CuH_3. In THF, precipitation of a black solid (Cu°) took place immediately when the reagent and substrate were mixed at 22 °C, whereas in diethyl ether the black solid formed more slowly. The results of these studies are summarized in Table II. Each of the five complex metal hydrides of copper react with 1-iododecane to give 100% *n*-decane. The reactivity of

Table III. Reactions of Complex Metal Hydrides of Copper with 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one at Room Temperature

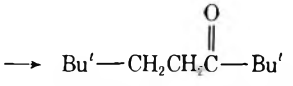
Expt	Hydride reagent	Reaction condition	Enone recovered, %	Products, % 1,4	1,2
34	$LiCuH_2$	Et_2O, 24 h	20	60	20
35	$LiCuH_2$	THF, 24 h	0	11	85
36	Li_2CuH_3	Et_2O, 48 h	0	93	6
37	Li_2CuH_3	THF, 48 h	0	88	12
38	Li_3CuH_4	Et_2O, 48 h	70	5	25
39	Li_3CuH_4	THF, 48 h	50	5	45
40	Li_4CuH_5	Et_2O, 24 h	0	5	90
41	Li_4CuH_5	THF, 24 h	0	5	95
42	Li_5CuH_6	Et_2O, 48 h	58	4	33
43	Li_5CuH_6	THF, 48 h	25	4	71

the substrate toward the hydride reagent has been found to decrease in the order of I > Br > OTs > Cl > F. For example, reactions of $LiCuH_2$ in THF with 1-iododecane, 1-bromodecane, *n*-octyl tosylate, 1-chlorodecane, and 1-fluorodecane produced products in 100, 85, 64, 37, and 0% yield, respectively. This order was followed throughout for the five hydride reagents, except for a small deviation involving Li_5CuH_6. Li_4CuH_5 was found to be the most reactive hydride, presumably due to its solubility in THF. This hydride reacted with 1-iododecane, 1-bromodecane, 1-chlorodecane, and *n*-octyl tosylate to give quantitative yields of the reduction product in each case. Only 10% reaction was observed between Li_4CuH_5 and 1-fluorodecane after 24 h at room temperature (with the reagent still active after the 24-h reaction period); however, the other hydrides did not react at all with 1-fluorodecane. Reactions involving Li_2CuH_3 and Li_4CuH_5 were also carried out with other chlorides, namely, cyclohexyl chloride, 1-chlorocyclohexene, 3-chlorocyclohexene, and chlorobenzene; only in the case of the reaction of Li_4CuH_5 with 3-chlorocyclohexene was any reaction observed (10%).

Reactions of 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one (Enone I). Enone I was chosen as a representative enone for this study. It has been reported that enone I can be reduced quantitatively to the 1,2-reduction product III by $LiAlH_4$ or to the 1,4-reduction product II by H_2AlI. It has also been shown that reaction in THF results in better regioselectivity

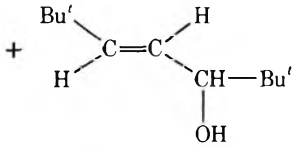


(I)



(1,4-reduction product)

(II)



(1,2-reduction product)

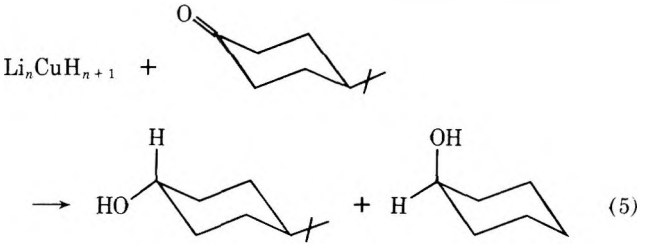
(III)

(4)

than in Et_2O solvent.[9] Reactions of each hydride, Li_nCuH_{n+1}, were carried out in THF and Et_2O solvent at room temperature in order to compare the regioselectivity in each solvent (eq 4). The results are shown in Table III.

A comparison of hydride reactivities (i.e., percent enone recovered) and regioselectivity (i.e., the distribution of 1,4:1,2-reduction products) demonstrates the characteristic differences of the different hydrides. Li_2CuH_3 and Li_4CuH_5 both have high reactivities, but exhibit entirely different regioselectivities. Li_4CuH_5 behaves very much like $LiAlH_4$, whereas Li_2CuH_3 produces the exact opposite regioselectivity, behaving as a good conjugate reducing agent. Li_3CuH_4 and Li_5CuH_6 behave similarly both in reactivity and regioselectivity, whereas $LiCuH_2$ behaves very strangely, producing predominant 1,4-reduction in ether (60:20) and predominant 1,2-reduction in THF (11:85). These data also provide more evidence that these complex metal hydrides of copper are not physical mixtures of each other or combinations of $LiCuH_2$ and LiH, since each stoichiometric compound behaves so differently.

Reactions of 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethycyclohexanone, and 2-Methycyclohexanone. The stereoselective reduction of cyclohexanones by metal hydrides has been studied intensively in recent years. $LiAlH_4$ is considered to be the least sterically hindered hydride, since it produces 90, 76, and 20% axial attack on 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, and 3,3,5-trimethylcyclohexanone, respectively.[10] The more sterically bulky hydrides are subject to "steric approach control" in their approach to any particular cyclohexanone; therefore, the amount of equatorial attack can be considered an indication of the effective bulk of the hydride. Results of the hydride reactions with the cyclohexanones are given in Table IV. Reactions of 4-*tert*-butylcyclohexanone were carried out in both THF and Et_2O solvents (eq 5). It appears that the hydrides in THF



(5)

produce more equatorial attack than in Et_2O except in the case of Li_2CuH_3. The hydride, $LiCuH_2$, in THF provided 78% equatorial attack, which is very unusual compared to $LiAlH_4$ (10% equatorial attack), but gave only 18% equatorial attack in ether solvent. This result suggests a higher effective bulk for $LiCuH_2$ in THF as compared to ether. The results of Table IV show that the amount of axial alcohol increased in the order: $LiCuH_2$ < Li_2CuH_3 < Li_3CuH_4 < Li_4CuH_5 < Li_5CuH_6.

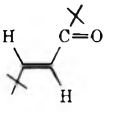
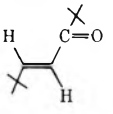
Reaction of 3,3,5-trimethylcyclohexanone and 2-methylcyclohexanane with $LiCuH_2$ in THF and Et_2O and Li_4CuH_5 and Li_5CuH_6 in just THF have also been carried out. In both cases involving $LiCuH_2$, the solvent affects the selectivity in the same way as seen in 4-*tert*-butylcyclohexanone, i.e.,

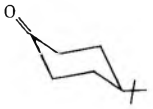
Table IV. Reactions of Complex Metal Hydrides of Copper with 4-*tert*-Butylcyclohexanone, 3,3,5-Trimethylcyclohexanone, and 2-Methylcyclohexane at Room Temperature

Expt	Hydride reagent	Substituted cyclohexanone	Registry no.	Reaction condition	Ketone recovered	Relative yield, % ax-OH	eq-OH
44	$LiCuH_2$	4-*tert*-Butyl	98-53-3	Et_2O, 48 h	0	18	82
45	$LiCuH_2$	4-*tert*-Butyl		THF, 48 h	0	78	22
46	Li_2CuH_3	4-*tert*-Butyl		Et_2O, 48 h	17	43	57
47	Li_2CuH_3	4-*tert*-Butyl		THF, 48 h	20	22	78
48	Li_3CuH_4	4-*tert*-Butyl		THF, 72 h	0	31	69
49	Li_4CuH_5	4-*tert*-Butyl		Et_2O, 72 h	16	11	89
50	Li_4CuH_5	4-*tert*-Butyl		THF, 72 h	40	15	85
51	Li_5CuH_6	4-*tert*-Butyl		Et_2O, 72 h	50	9	91
52	Li_5CuH_6	4-*tert*-Butyl		THF, 72 h	55	14	86
53	$LiCuH_2$	3,3,5-Trimethyl	873-94-9	Et_2O, 24 h	0	86	14
54	$LiCuH_2$	3,3,5-Trimethyl		THF, 24 h	0	98	2
55	Li_4CuH_5	3,3,5-Trimethyl		THF, 24 H	1	82	18
56	Li_5CuH_6	3,3,5-Trimethyl		THF, 24 h	0	91	9
57	$LiCuH_2$	2-Methyl	583-60-8	Et_2O, 24 h	0	42	58
58	$LiCuH_2$	2-Methyl		THF, 24 h	0	50	50
59	Li_4CuH_5	2-Methyl		THF, 24 h	0	35	65
60	Li_5CuH_6	2-Methyl		THF, 24 h	0	33	67

Table V. Comparison of Reactivities of $LiAlH_4$ and Li_4CuH_5 in Equal Molar Ratio in THF at Room Temperature

Expt	Hydride	Substrate	Reaction time	$C_{10}H_{22}$
61	$LiAlH_4$	$C_{10}I$	15 min	98
62		$C_{10}Br$	15 min	85
			1 h	95
63		$C_{10}Cl$	15 min	0
			1 h	0
64	Li_4CuH_5	$C_{10}I$	15 min	100
		$C_{10}Br$	15 min	99
		$C_{10}Cl$	15 min	0
			1 h	3
			24 h	99

				Enone recovered, %	Products, % 1,4	1,2
65	$LiAlH_4$		15 min	0	0	100
66	Li_4CuH_5		15 min	0	5	95

				Ketone recovered, %	Relative yield, % ax-OH	eq-OH
67	$LiAlH_4$		15 min	0	8	92
68	Li_4CuH_5		15 min	0	45	55

98:86% (THF/Et_2O) equatorial attack in the reduction of 3,3,5-trimethylcyclohexanone. $LiCuH_2$ appears to be more selective (higher effective bulk) than the other complex metal hydrides of copper toward all of the cyclohexanones studied.

We have made a comparison of the reactivity of Li_4CuH_5 to that of the well-known $LiAlH_4$ in order to obtain some idea of the strength of the new complex metal hydrides of copper as reducing agents. It would appear from the results in Table IV that the complex metal hydrides of copper in general, and specifically Li_4CuH_5, are weaker reducing agents than $LiAlH_4$ (experiments 49–50). However, the results in Table IV were obtained for Li_4CuH_5 prepared in diethyl ether (expt 49). The solid Li_4CuH_5 was separated from the ether-soluble $LiAlH_2(CH_3)_2$ by filtration or centrifugation followed by total drying of the solid and reslurrying in ether. When THF was described as the solvent (expt 50) the Li_4CuH_5 was prepared in ether; however, the reaction mixture was filtered, producing

a mushy, wet solid, and when THF was added to this mixture all of the solid immediately dissolved. These observations suggest that the product Li_4CuH_5 when prepared contains some complexed ether which can be replaced by the more basic solvent THF, allowing the complex to dissolve. However, if the product Li_4CuH_5 is completely dried under vacuum, the complexed ether is removed, leaving the product in a more stable crystal lattice which exhibits much less solubility in THF. Table V shows the results obtained in a comparison of dissolved Li_4CuH_5 with $LiAlH_4$ in THF. As can be seen from the data, particularly a comparison of reductions of decyl chloride, Li_4CuH_5 is a more powerful reducing agent than $LiAlH_4$. It is also noteworthy that the stereochemistry of reduction of *tert*-butylcyclohexanone by Li_4CuH_5 as a slurry (Table IV, experiment 50; 15:85, axial-OH:equatorial-OH) compared to Li_4CuH_5 in solution (Table V, 45:55, axial-OH:equatorial-OH) is quite different.

In conclusion, results of reactions of new complex metal hydrides of copper with organic substrates have demonstrated their individual integrities and unique properties as reducing agents. In the case of alkyl halides, the new copper hydrides are potentially useful reagents for the reduction to alkanes. Li_4CuH_5, which is soluble in THF, appears to be particularly useful. In the case of enones, it appears that either predominant 1,2- or 1,4-reduction can be obtained depending on the specific hydride used, whereas the new hydrides appear to reduce cyclohexanones similarly to $LiAlH_4$ except in some cases where the reduction is not as selective. A comparison of the rate of reduction for one of the complex metal hydrides of copper (Li_4CuH_5) to $LiAlH_4$ in THF shows that Li_4CuH_5 is a more powerful reducing agent than $LiAlH_4$ toward alkyl halides and possibly toward other substrates as well. The reactivity of the hydrides depends to a large extent on the homogeneous or heterogeneous nature of the hydride, the reactivity being considerably greater when the hydride is soluble in the reaction medium.

Experimental Section

Apparatus and Instrumentation. All operations were carried out either in a nitrogen-filled glove box equipped with a recirculating system[11] to remove oxygen and moisture or at the bench using typical Schlenk tube techniques.[12] All glassware was flash flamed and flushed with nitrogen prior to use. Infrared spectra were recorded in KBr cells using a Perkin-Elmer 621 high-resolution infrared spectrophotometer. The NMR spectra were determined at 60 MHz with a Varian Model T-60-A NMR spectrometer. GLPC analyses were performed on an F and M Model 720 gas chromotograph. Hydrogen analysis was carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the evolved hydrogen with a Toepler pump.[12] Lithium was determined by flame photometry using a Coleman Model 21.[15] Iodide was determined by the Volhard procedure.[16] Copper was determined by electrolytic deposition on a platinum electrode.[17]

Materials. Tetrahydrofuran (Fisher certified reagent grade) was distilled under nitrogen over $NaAlH_4$ and diethyl ether (Fisher Reagent) over $LiAlH_4$ prior to use. Methyllithium in THF and Et_2O was prepared by the reaction of $(CH_3)_2Hg$ with excess lithium metal. Both solutions were stored at −78 °C until ready to use. Cuprous iodide was purified by precipitating from an aqueous KI–CuI solution.[13] The precipitated solid was washed with water, ethanol, and diethyl ether, and then dried at room temperature under vacuum.

A solution of $LiAlH_4$ (Ventron, Metal Hydride Division) was prepared by stirring a diethyl ether slurry overnight, followed by filtration of the slurry through dried Celite analytical grade filter aid. The solution was standardized by aluminum analysis (EDTA).

Halide substrates and authentic samples of products were purchased commercially and used without further purification: iodo-, bromo-, chloro- and fluorodecane (Eastman Organic Chemicals), cyclohexyl chloride (Aldrich Chemical Co.), and 1- and 3-chlorocyclohexene (Friton Laboratories).

n-Octyl tosylate was prepared by reaction of *n*-octanol (7 g, ca. 0.05 M) in pyridine (16 g) with *p*-toluenesulfonyl chloride (10.5 g, ca. 0.055 M) at 20 °C overnight. The workup was by HCl–ice water hydrolysis followed by benzene extraction. The pure product was obtained by distillation: bp 155–156 °C (2 mmHg); NMR ($CDCl_3$) δ 7.66 (2 H, d), 7.25 (2 H, d), 3.94 (2 H, t, CH_2O), 2.40 (3 H, s, benzyl CH_3), 2.0–0.8 (15 H, m, alkyl).

2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one was prepared as previously described.[14] An authentic sample of 1,4-product, 2,2,6,6-tetramethyl-3-heptanone, was synthesized by reaction of 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one with Li/HMPA: bp 108 °C (2 mmHg); NMR (CCl_4) δ 2.36 (2 H, t, O=$COCH_2$), 1.40 (2H, t, CH_2), 1.08 (9 H, s, Bu^t), and 0.87 (9 H, s, Bu^t); IR 1710 cm^{-1} (C=O), no hydroxyl absorption. 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-ol, 1,2-product, was obtained by reaction of 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one with $LiAlH_4$: NMR (CCl_4) δ 5.5 (2 H, m, olefinic), 3.57 (1 H, d, OCH), 1.5 (1 H, s, OH), 0.98 (9 H, s, Bu^t) and 0.78 (9 H, s, Bu^t) IR 3600–3200 (OH), 1485 and 1470 cm^{-1} (C=C), no carbonyl absorption.

4-*tert*-Butylcyclohexanone (Friton), 3,3,5-trimethylcyclohexanone (Chemical Sample Co.), and 2-methylcyclohexanone (Fisher) were purified by vacuum distillation or sublimation.

Preparation of $Li_nCuH_{(n+1)}$ by the Reaction of $Li_nCu(CH_3)_{n+1}$ with $(n + 1/2)LiAlH_4$ in Diethyl Ether. To a well-stirred slurry of cuprous iodide in diethyl ether at −78 °C was added dropwise CH_3Li in diethyl ether in various ratios (MeLi/CuI = 2:1, 3:1, 4:1, 5:1, or 6:1). A clear solution resulted in every case within a few minutes. These reaction mixtures were stirred at −78 °C for 0.5 h. To these solutions was then added $LiAlH_4$ dropwise with stirring [$Li_nCu(CH_3)_{n+1}/LiAlH_4 = (n + 1):(n + 1/2)$]. No precipitation was observed at −78 °C; however, a white crystalline solid formed in every case when the reaction mixture was allowed to warm to room temperature. These reaction mixtures were stirred at room temperature for 1 h, and the solids were centrifuged, separated, washed with fresh diethyl ether, and made a slurry in ether as well as in THF ($LiCuH_2$ and Li_4CuH_5 dissolved in THF immediately). The products were analyzed before reacting with organic substrates. The supernatant solutions which were washed out in all cases showed Al–H stretching at 1710 cm^{-1} (characteristic of $LiAlH_2(CH_3)_2$).

Reactions of Alkyl Halides, *n*-Octyl Tosylate, Enone I, and Cyclic Ketones with Li_nCuH_{n+1}. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush, and then sealed with a rubber septum and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil bubbler. One milliliter of THF or Et_2O solvent was introduced into the reaction vessel; then reactant, e.g., halide substrate (0.5 mL, 0.25 M in THF or Et_2O) with internal standard, was syringed into the vessel. Finally, the calculated amount of the hydride, Li_nCuH_{n+1}, in THF or Et_2O was added. After the designated reaction time, the reaction mixture was quenched with a minimum of distilled water and the resulting solution dried over $MgSO_4$. Analysis of the product and yield data was obtained by GLC, using 6 ft 10% Apiezon L columns. The following oven temperatures and internal standards were used: iododecane, bromodecane, chlorodecane, and fluorodecane, oven temperature 150 °C, internal standard dodecane; *n*-octyl tosylate, 120 °C, decane; cyclohexyl chloride and 1- and 3-chlorocyclohexene, 50 °C, octane; chlorobenzene 50 °C, toluene.

A 10 ft 5% carbowax 20M on Chromosorb W column was used to separate products of enone I. At 90 °C oven temperature and dodecane as the internal standard, recovered enone, 1,4-product, and then 1,2-product were eluted in that order. 4-*tert*-Butylcyclohexanol and 3,3,5-trimethylcyclohexanol were separated by the same column at 150 °C with tetradecane and hexadecane, respectively, as internal standards. The alcohol products of 2-methylcyclohexanone were separated by using a 15-ft 10% diglycerol column (80 °C, internal standard tetradecane). The order of elution for three cyclic ketones was the same—ketone first, axial alcohol second, and equatorial alcohol last.

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Registry No.—*n*-Octanol, 111-87-5; *p*-toluenesulfonyl chloride, 98-59-9; 2,2,6,6-tetramethyl-3-heptanone, 40239-53-0; 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, 20859-13-6; 2,2,6,6-tetramethyl-*trans*-4-hepten-3-ol, 55829-99-7; $LiAlH_4$, 16853-85-3.

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Transition-Metal Peroxide Reactions. Synthesis of α-Hydroxycarbonyl Compounds from Enolates

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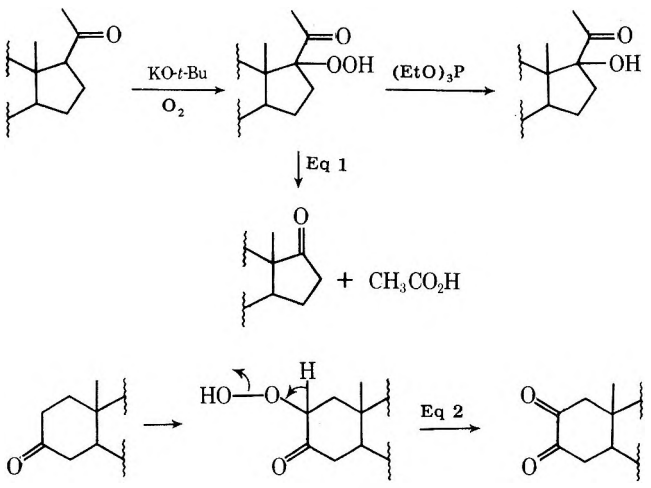
Enolates of ketones, esters, and lactones are oxidized by MoO_5-Py-HMPA (MoOPH) to give α-hydroxy derivatives. The reaction succeeds with carbonyl compounds having α-methylene or α-methine groups, but enolates from methyl ketones give variable results. The hydroxylation process does not afford products of oxidative C–C cleavage which might be formed from an α-hydroperoxycarbonyl intermediate. If the initial intermediate from an enolate and MoOPH is heated, further oxidation to an α-dicarbonyl compound occurs in poor yield. These results suggest an intermediate having the partial structure $R'C(=O)RCHOMoO_4L_2^-$. Hydroxylation of kinetic enolates derived from unsymmetrical cyclic ketones, cyclohexenones, and certain methyl ketones can be achieved. Acyloin regioisomers are not interconverted under the reaction conditions. Hydroxylation of relatively nonhindered ketones is complicated by aldol condensation between unreacted enolate and the oxidation intermediate. This problem can be minimized by working in dilute solution or by using an inverse addition technique (enolate added to MoOPH). Oxidation of enolate analogues prepared from oximes or *N,N*-dimethylhydrazones has been demonstrated, although yields are low. Stabilized enolates of 1,3-dicarbonyl compounds are not hydroxylated using the typical procedure, and the related dianions afford complex product mixtures.

Introduction

The synthetic problem of enolate hydroxylation has been the object of numerous studies.[1,2,5-7] Barton and co-workers achieved the direct enolate oxygenation of pregnan-20-one, and subsequent hydroperoxide reduction gave the 17α-hydroxy derivative.[1a] Gardner et al. found that modified conditions using in situ triethyl phosphite reduction of the hydroperoxides gave superior yields.[2a,b] In the absence of phosphite, oxidative α-carbon cleavage may occur (eq 1, Scheme I), a reaction which has been studied in several analogous systems.[3] The Barton oxidation cannot be used to introduce a hydroxyl group at an enolizable methyl or methylene group because a second fragmentation pathway (eq 2, Scheme I) is available to the resulting α-hydroperoxy ketone.[4] An α-dicarbonyl compound is formed initially, but further oxidation is facile and complex product mixtures are obtained.

Scheme I



Practical oxygenation of carboxylate dianions can be achieved in a number of examples without in situ peroxide reduction by triethyl phosphite.[5] The carboxylate dianion is apparently sufficiently reactive to attack the peroxide O–O bond so that peroxide does not accumulate as oxygen is introduced. If the dianion is added to excess oxygen, the hydroperoxide can be isolated in moderate yield.[5a,c] Oxidation of amide or lactam enolates by the inverse addition method is also feasible.[6] The same technique can be employed for hydroxylation of α-branched esters,[6a,7] but esters having an α-methylene group behave unpredictably.[5a,6a]

A promising method for synthesis of α-hydroxy derivatives of unbranched carbonyl compounds involves the epoxidation of enol silanes.[8] An α-trimethylsiloxycarbonyl compound can be isolated under nonhydroxylic conditions, and facile hydrolysis to the free alcohol is possible. Acetoxylation of enols with reagents such as mercuric acetate or lead tetraacetate might also be considered,[9] but hydrolysis of α-acetoxy derivatives of ketones is often complicated by interconversion of acyloin regioisomers as will be shown later in this account.

A preliminary report[10] from our laboratory described the direct hydroxylation of enolates with the molybdenum peroxide reagent MoO_5-pyridine-HMPA (MoOPH).[11] Representative ketone and ester enolates were reacted with MoOPH in tetrahydrofuran solution, and hydrolysis of the product gave α-hydroxycarbonyl compounds. The details of the oxidation procedure are the subject of this paper.

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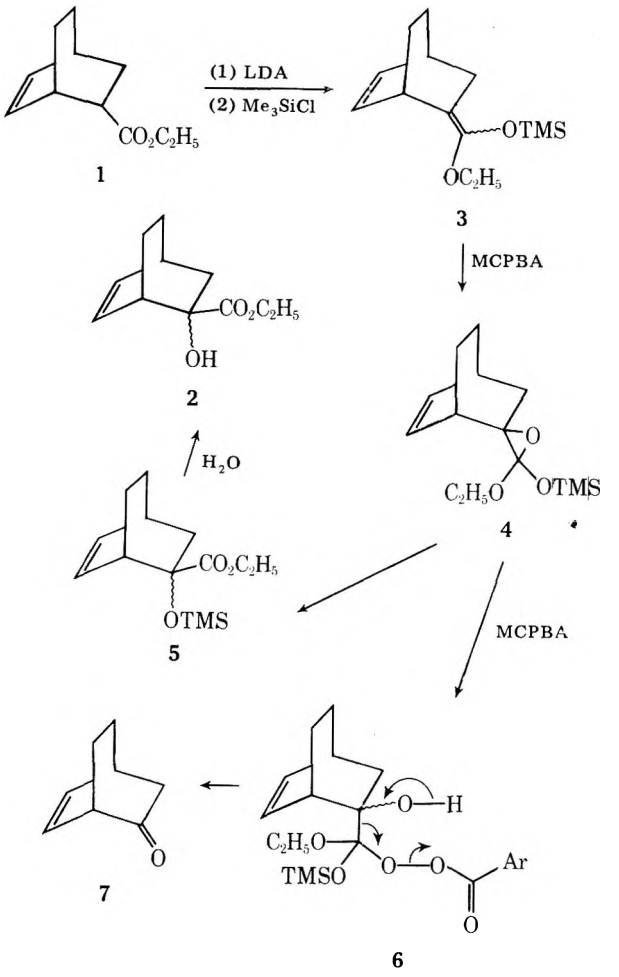
Scheme II



Our interest in enolate hydroxylation began as part of a synthetic project which required conversion of a model ester **1** into the α-hydroxy ester **2**. Small-scale attempts to hydroxylate the enolate with molecular oxygen were not promising, so we examined the oxidation of the derived ketene acetal **3**.

The reaction of **3** with $Pb(OAc)_4$ (1:1 stoichiometry, THF, 0 °C) gave at least three products, and an NMR spectrum of the crude mixture showed only traces of olefinic hydrogens remaining. This reaction was not investigated further. Oxidation with MCPBA did afford some of the desired α-trimethylsiloxy ester **5** (50–60%), but ca. 10% of the cleavage product **7** was inevitably present as well.[12] Since formation of ketone **7** can be explained by epoxidation of **3** and subsequent nucleophilic opening of **4** by a second mole of MCPBA as shown in Scheme II, we turned to the presumably nonnucleophilic epoxidizing agent MoO_5·HMPA.[13] Treatment of **3** with 1 mol of MoO_5·HMPA in methylene chloride at 20 °C resulted in an exothermic reaction, and aqueous workup gave **2** in good yield.

An obvious simplification of the oxidation procedure is to avoid the silylation step and to oxidize the enolate directly. Although this is possible with MoO_5·HMPA, the reagent is hygroscopic and must be dried thoroughly before use. A more convenient reagent for enolate hydroxylation proved to be the highly crystalline and reasonably air-stable complex MoO_5·pyridine·HMPA (MoOPH).[11] This substance reacts with typical enolates in the temperature range −70 to −20 °C, and aqueous workup affords α-hydroxycarbonyl compounds.

Properties of MoO_5·Py·HMPA (MoOPH). Mimoun et al. have described the isolation of crystalline molybdenum peroxides having a variety of ligands.[11] A solution of $H_2Mo_2O_{11}$ is prepared by dissolving MoO_3 in 30% H_2O_2 at 40 °C, and addition of HMPA to this solution affords crystalline MoO_5·H_2O·HMPA in high yield. This operation can be performed routinely by the published method on a 50-g scale, provided that rigorous internal temperature control is maintained during dissolution of MoO_3 (see Experimental Section). Mimoun et al. converted the sparingly soluble MoO_5·H_2O·HMPA directly into MoOPH by treatment with pyridine. We prefer to first prepare MoO_5·HMPA[11] from the hydrate (vacuum desiccator). The anhydrous peroxide is easily soluble in tetrahydrofuran (THF) and addition of one equivalent of pyridine precipitates MoOPH as finely divided crystalline material. In our hands, Mimoun's procedure gave MoOPH contaminated with hydrate, and purification of the product by recrystallization failed because MoOPH decomposes slowly in solution at 25 °C or above.

All of the molybdenum peroxides are light sensitive and decompose to a significant extent after several days of (improper) storage in a clear glass container at room temperature. However, these reagents can be stored for months with no apparent decomposition in a refrigerator shielded from light. We have observed no indication that molybdenum peroxides are shock-sensitive or in any way hazardous in contact with typical organic solvents. Upon heating, small samples of MoOPH decompose with copious gas evolution. Larger samples (0.1–1 g) ignite when placed on a hot plate but do not detonate. We are aware of one instance where a sample of MoO_5·HMPA decomposed with sufficient force to break the jar and char the contents after several weeks of storage at ambient temperature without protection from light.[14] Our experience indicates that no such hazards exist with MoO_5·Py·HMPA (MoOPH) if the reagent is refrigerated between use. Nevertheless, routine precautions are appropriate when handling this high molecular weight peroxide.

Molybdenum peroxides behave as electrophilic oxygen donors and resemble organic peracids in some of their chemical properties. Anionic species such as alkyllithium reagents[15] or nitrile-stabilized carbanions[16] are attacked rapidly by MoO_5·HMPA or by MoOPH at temperatures below 0 °C, resulting in C–O bond formation. Electron-rich neutral substrates including sulfides,[17] *N*-silylamides,[18] or oximes[17] are oxidized more slowly and ambient temperatures are typically necessary. Alkenes can also be oxidized, but temperatures between 40 and 80 °C are usually employed for catalytic epoxidation (Mo catalyst + ROOH)[19] or for stoichiometric epoxidation with MoO_5·HMPA.[13]

Enolate Hydroxylation with MoOPH. The procedure for hydroxylation of carbonyl compounds consists simply of adding the ketone or ester to a 5–10% excess of lithium diisopropylamide in THF–hexane at −70 °C, followed by addition of crystalline MoOPH at a temperature between −70 and −20 °C depending on the individual case. As soon as the sparingly soluble reagent has dissolved, the reaction can be quenched with aqueous sodium sulfite and extracted to recover products. Sodium sulfite apparently reduces unreacted Mo^{VI} species, produces water-soluble salts, and facilitates recovery of organic products. A simple water workup can also be used, but this typically affords emulsions, lower material balance, and highly colored organic-soluble molybdenum-containing side products.

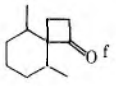
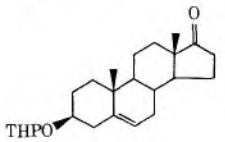
Two reaction pathways can be written for enolate oxidation with MoOPH which are consistent with the known tendency of MoO_5 chelates to transfer one of the peroxidic oxygens rather than the oxo oxygen to potential nucleophiles.[13e] The first (path a, Scheme III) involves cleavage of the O–O bond and formation of **8**, while the second (path b) cleaves an O–Mo bond to give **9**. If path b is the preferred mechanism, then one might expect to isolate α-hydroperoxycarbonyl compounds or their α-carbon cleavage products (Scheme I, eq 1). Since no such products have been detected from any MoOPH hy-

Table I. MoOPH Oxidation of Esters and Lactones[d]

Registry no.	Ester	α-Hydroxy ester	Yield
101-97-3	Ethyl phenylacetate	Ethyl mandelate	58%[a]
106-73-0	Methyl heptanoate	Methyl 2-hydroxyheptanoate	74%[a]
2021-28-5	Methyl 3-phenylpropionate	Ethyl 2-hydroxy-3-phenylpropionate	60%[a]
42858-39-9	Ethyl bicyclo[2.2.2]oct-2-ene-5-carboxylate	Ethyl 5-hydroxybicyclo[2.2.2]oct-2-ene-5-carboxylate	85%[a,c]
19340-56-8	α-Butylbutyrolactone	α-Hydroxy-α-butylbutyrolactone	73%[b]
21303-80-0	γ-Phenyl-γ-methylbutyrolactone	α-Hydroxy-γ-phenyl-γ-methylbutyrolactone	56%[a]

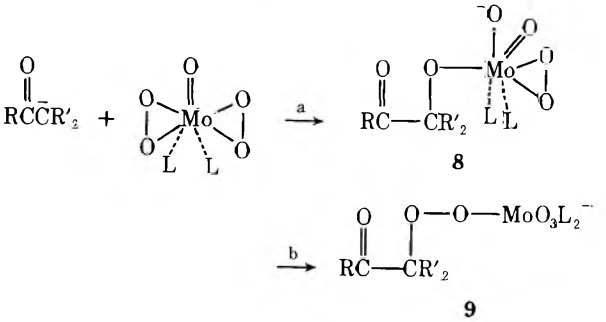
[a] Isolated yield. [b] GLPC yield. [c] Mixture of exo and endo isomers. [d] All oxidations done at −78 °C, 2 h; 1.1 mmol of MoOPH added to enolate from 1 mmol of ester + 1.05 mmol of LDA in THF–hexane.

Table II. Oxidation of Ketones[h]

Registry no.	Ketone	Oxidation temp, °C	α-Hydroxy ketone	α-Diketone
1009-14-9	Valerophenone	−22	60%	13%
		−22[a]	70%	11%
		−44[a]	62%	<2%
451-40-1	Deoxybenzoin	−44	34%	26%
611-70-1	Isobutyrophenone	−22	65%[c]	—
529-34-0	α-Tetralone	−22	48%	*b*
76-22-2	Camphor	−22	70% (endo OH)[d]	<2%
		−22; heat to 60 °C, 16 h	44%[e]	11%
4528-68-1	4,4-Diphenylcyclohexanone	−22	46%	*b*
1444-65-1	2-Phenylcyclohexanone	−44	70% (4:1, 19a–19b)	<5%
64070-08-2		−22	81%[e]	*b*
19637-35-5		−44	75% (16α OH)[g]	*b*

[a] Inverse addition method, enolate added to MoOPH. [b] Yield of α-diketone not established. [c] For NMR data, see ref 20. [d] See ref 31 for characterization of all four possible isomers. [e] Mixture of diastereomers, stereochemistry not determined. [f] B. M. Trost, M. Preckel, and L. M. Leichter, *J. Am. Chem. Soc.*, 97, 2224 (1975). [g] Removal of OTHP at pH 3 gave 3β,16α-dihydroxyandrost-5-en-17-one: A. Hassner and P. Catsoulacos, *J. Org. Chem.*, 31, 3149 (1966); K. Fotherby, A. Colas, S. Atherden, and G. Marrian, *Biochem. J.*, 66, 664 (1957). [h] All oxidations performed by addition of 1.5 mmol of MoOPH to enolate from 1 mmol of ketone + 1.05 mmol of LDA unless noted otherwise, THF–hexane solution. Yields refer to pure material isolated by preparative layer chromatography.

Scheme III



droxylation, path a is considered more plausible.

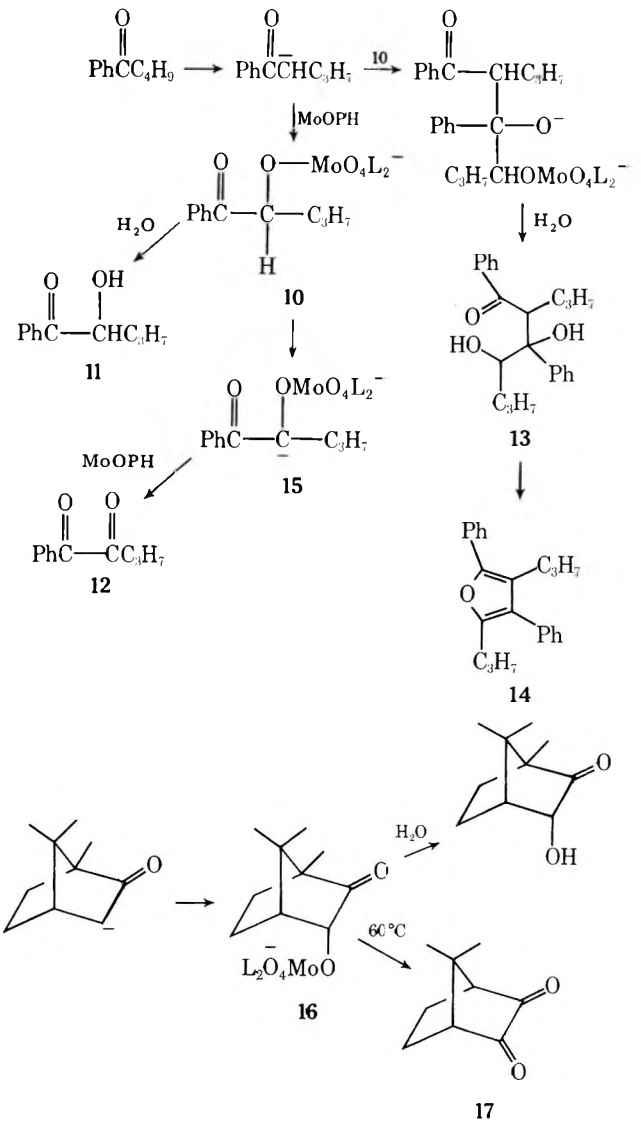
Table I lists typical ester or lactone hydroxylations performed by addition of MoOPH to the enolate at −78 °C. All esters studied were oxidized within 2 h at −78 °C, and no attempt was made to optimize individual cases. By comparison, ketone enolates (Table II) are less reactive. The representative procedure consists of MoOPH addition to the enolate at −22 °C, followed by Na_2SO_3 quenching as soon as the reagent has dissolved (2–5 min). However, results were more reproducible at −44 °C for several of the ketones examined. In general, ketone hydroxylations are more sensitive to reaction conditions, and it is advisable to optimize temperature, concentration, and stoichiometry variables to minimize side reactions.

We have examined the hydroxylation of valerophenone in some detail because this system is especially prone to side reactions under typical conditions (−22 °C, 1.05 *m* LDA, 1.5 mol of MoOPH, 15 min). Although the α-hydroxy ketone **11**[20] is still formed in reasonable yield (60%), the product mixture also contains α-diketone **12**[21] (13%), recovered valerophenone (5%), and two unstable compounds which could not be obtained in pure form. After several hours at room temperature, the unstable products decompose to a new substance (**14**) (22% based on valerophenone) which is assigned the furan structure from NMR data and the absence of carbonyl or hydroxyl absorptions in the infrared spectrum.

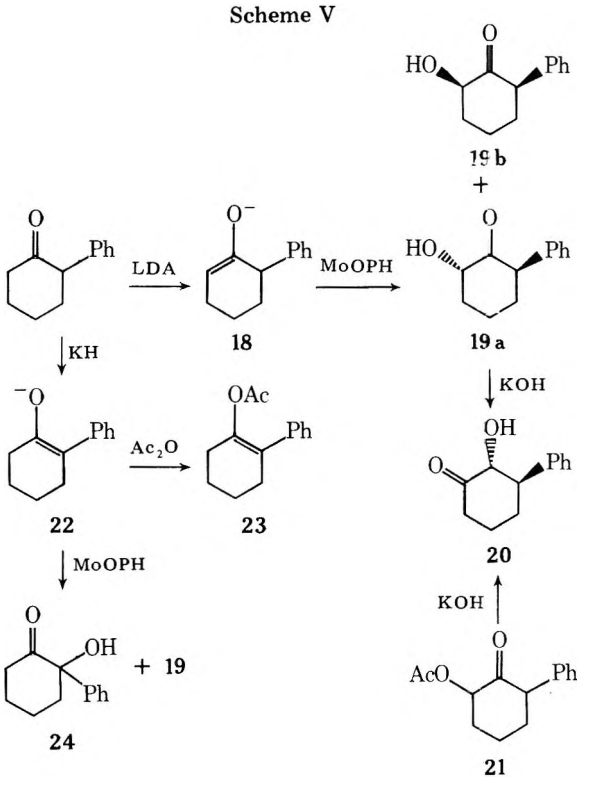
If the experiment is repeated using 1 mol of MoOPH/2 mol of enolate, the yield of **14** increases (42%) at the expense of **11** (43%) and α-diketone **12** (<2%). These conditions maximize contact between starting enolate and the hypothetical oxidation intermediate **10** and allow an aldol condensation to become important (Scheme IV). Cyclization and dehydration of the unstable adduct **13** then leads to the furan **14**. It is significant that 1 mol of MoOPH affords a total of 1.3 mol of products (**11** + **14**) derived from α-oxidation. Clearly, both peroxide rings of MoOPH must be available to some extent for enolate oxidation, and **10** or some derived species must act as the source of electrophilic oxygen after MoOPH is consumed.

Since the formation of **13** is a bimolecular process, it is possible to maximize the yield of **11** by a dilution method. Addition of the enolate to excess MoOPH at −22 °C affords 70% of **11** and 6% of **14** after the usual isolation procedure.

Scheme IV



Scheme V



There is little change in α-diketone yield at −22 °C although an inverse addition experiment at −44 °C gives only traces of **12.**

The pathway leading to α-diketone has not been established, but it seems probable that an anion such as **15** is involved. Direct fragmentation of **15** to **12** and a lower oxidation state of molybdenum is apparently not important at −22 °C since addition of excess LDA *after* addition of MoOPH to the enolate does not change the product ratio. More likely, **15** is subject to further oxidation by MoOPH. As to the origin of **15,** enolate equilibration by proton transfer from **10** to valerophenone enolate provides the simplest rationale and also accounts for the persistent recovery of unreacted starting ketone (5–10%) in spite of all precautions to dry solvents and reagents.

If the solution obtained from MoOPH and valerophenone enolate is heated to 40 °C, the ratio of **12:11** increases. However, numerous other products are formed and the material balance is poor. A more convincing case for thermal fragmentation of a MoOPH oxidation intermediate can be made in the hydroxylation of camphor. At −22 °C, this reaction affords no trace of α-diketone, but thermolysis of the intermediate **16** at 60 °C gives camphor quinone **17**[22] in 11% yield.

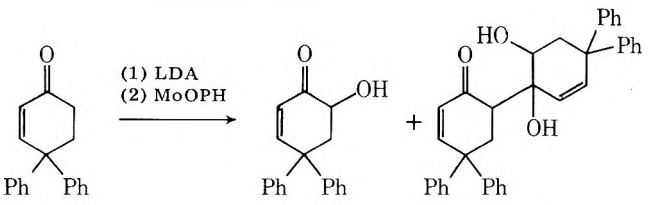
Among the major advantages of MoOPH hydroxylation of lithium enolates is the formation of that acyloin which corresponds to the kinetic enolate in regiochemistry. Thus, addition of 2-phenylcyclohexanone to LDA at −78 °C affords an enolate **18** (Scheme V) and addition of MoOPH at −44 °C gives acyloin diastereomers **19a** and **19b** (7:1) as sole products. Attempts to perform this oxidation at −22 °C result in variable yields and several minor side products. The major diastereomer **19a** is assigned trans stereochemistry on the basis of NMR evidence. One of the low-field methines (4.18 ppm) is a doublet of doublets, J = 11, 6 Hz, while the other methine proton is a broad singlet (4.03 ppm). Clearly, the 4.18 ppm methine is axial while the other is equatorial, a result which is consistent with MoOPH approach from the least hindered enolate face. Treatment of **19a** with methanolic KOH results in rapid conversion into a single acyloin isomer **20.** This substance cannot be detected in the crude MoOPH product by TLC or NMR, so interconversion of acyloin isomers does not occur during MoOPH oxidation or aqueous workup.

Structure **19** has been reported previously by Treibs and Weisenfels as the product obtained from 2-acetoxy-6-phenylcyclohexanone (**21**) by saponification.[23] However, the physical data reported are clearly those of **20** and not of **19a** or **19b.** We have repeated the published sequence (mercuric acetate oxidation of 2-phenylcyclohexanone; KOH saponification) and find that the assigned structure **21** is consistent with NMR data. However, the conditions used to saponify the acetate **21** result in acyloin tautomerization and formation of **20.**

When 2-phenylcyclohexanone is treated with potassium hydride, the more highly delocalized enolate **22** is formed. Enolate trapping by acetic anhydride gives 95% of the tetrasubstituted enol acetate **23.** If the potassium enolate is generated at 20 °C and then treated with 1.05 mol of MoOPH at −44 °C, the acyloin isomer **24**[24] is formed (30%), but the product mixture also contains **19** (24%). Apparently potassium enolate equilibration occurs under these conditions and the less stable enolate **18** is more reactive than **22** toward MoOPH capture. In an attempt to improve conversion to **24,** the enol acetate **23** was treated with methyllithium to form the lithio enolate corresponding to **22** which should be more resistant to enolate equilibration. However, this experiment gave only traces of acyloin products and considerable recovered starting material. Gas evolution was apparent during the experiment,

apparently due to decomposition of MoOPH by the lithium *tert*-butoxide which is present as a product of enol acetate cleavage.

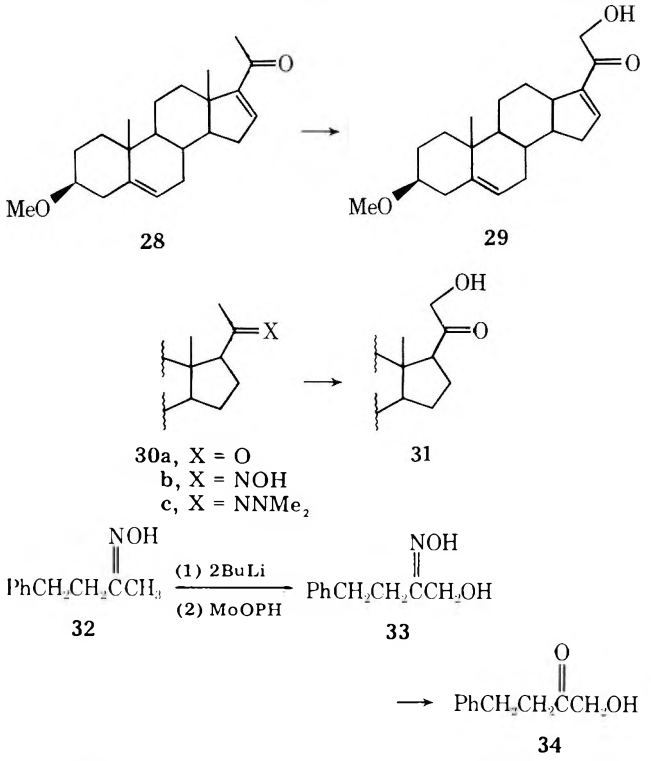
Hydroxylation of cyclohexenone derivatives is unexpectedly difficult according to the standard method (MoOPH added to enolate, −22 °C). Thus, 4,4-diphenylcyclohex-2-enone (**25**)



25 **26** **27**

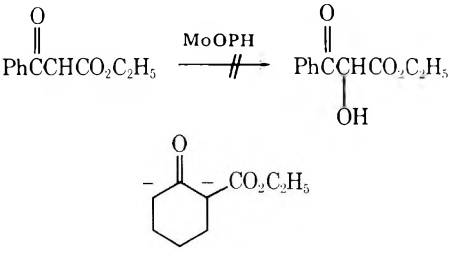
gives only 17% of acyloin **26**. A crystalline substance **27** corresponding to 1:1 condensation of **25** and acyloin **26** is formed in 61% yield. The aldol condensation structure **27** is consistent with the ^{13}C NMR and ^{1}H NMR evidence, and is further supported by the efficient cleavage of **27** to equimolar amounts of **25** and **26** upon LDA treatment. As in the valerophenone case, aldol condensation can be minimized by inverse addition to give **26** (53%), **27** (7%), and recovered starting material (17%).

The aldol condensation problem is most serious for relatively unhindered enolates. As a result, methyl ketone hydroxylation is often difficult to achieve. Unstable high molecular weight products are formed under all conditions examined, and decomposition (presumably to furans) occurs if the crude products are allowed to stand at room temperature. Inverse addition is essential for the isolation of significant yields of acyloin products. Thus, 3-β-methoxypregna-5,16-dien-20-one (**28**)[25] can be converted into the C-21 hydroxylation product **29** in acceptable yield (52% of **29** + 26% recovered starting material). However, the closely analogous α,β-saturated ketone **30a**[26] suffers extensive aldol condensation and affords only ca. 20% of acyloin **31**. One must resort to LDA-induced retro-aldol fragmentation of the crude mixture to raise the isolated yield of **31** to 58% (36% recovered **30a**).



Unhindered 2-alkanone enolates cannot be hydroxylated with MoOPH in practical yield. Thus, 4-phenyl-2-butanone affords a hopeless mixture of at least eight products (TLC analysis) according to the usual method (LDA; MoOPH at −22 °C). However, the α-hydroxy derivative **34** can be obtained in 30–40% yield by MoOPH treatment of the oxime dianion,[27] followed by oxime hydrolysis via the bisulfite adduct.[28] If desired, the α-hydroxy oxime **33** can be isolated prior to hydrolysis in 36% yield, along with recovered **32**, 41%. Numerous attempts to improve the percent conversion failed, even though complete dianion formation could be demonstrated by sulfenylation. Similar hydroxylation and hydrolysis can be used to convert pregnenone oxime **30b** into **31**, but the yield is only ca. 20% and the percent conversion is again quite low. Oxidation of the *N,N*-dimethylhydrazone anion[29] obtained from **30c** with LDA was also examined briefly. Hydroxylation occurred to form a new substance having CH_2OH NMR signals at δ 4.1, but the product could not be purified. Attempts to cleave the crude hydrazone to **31** using published conditions[29] failed, so this approach was not pursued.

One last attempt at hydroxylation of methyl ketones deserves brief consideration. Enolizable β-keto esters might serve as acyloin precursors by hydroxylation and subsequent decarboxylation. Accordingly, the anion of ethyl benzoylacetate was reacted with MoOPH at 25 °C. Although some reaction took place as evidenced by dissolution of the MoOPH, workup with sodium sulfite gave only recovered ethyl benzoylacetate. We assume that a 1,3-dicarbonyl chelate of Mo^{VI} is formed which resists oxidation. Hydroxylation of the dianion **35** of 2-carboethoxycyclohexanone was also attempted.



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However, the product mixture was exceedingly complex and the experiment was not pursued.

Conclusions

The MoOPH oxidation procedure is the only direct method for hydroxylation of α-methylene ketone enolates which is successful in typical examples. Hydroxylation of kinetic enolates derived from α,β-unsaturated ketones or methyl ketones is also possible, but complications due to enolate attack upon the initial oxidation intermediate are common. Hydroxylation of branched ketones or branched and unbranched esters and lactones is easily accomplished from the corresponding enolate.

By comparison with the only other direct enolate hydroxylation procedure (enolate + O_2), MoOPH hydroxylation is superior in all cases involving kinetically generated ketone enolates. Based on more limited literature comparisons, we also believe that MoOPH hydroxylation is superior with enolates from unbranched esters or lactones. However, direct oxygenation of branched ester enolates or carboxylate dianions remains the method of choice for suitable substrates due to the high yields and the obvious advantage in using molecular oxygen as the source of hydroxyl.

Experimental Section

Oxodiperoxymolybdenum(aquo)(hexamethylphosphoric triamide). The procedure of Mimoun et al.[11] was used with additional precautions to maintain temperature control. Thus, a 500-mL three-neck flask was charged with MoO_3 (30 g, 0.2 m) and 30% H_2O_2 (150 mL). The mixture was stirred vigorously with a paddle stirrer and the internal temperature was monitored throughout. An oil bath preheated to 40 °C was used to heat the mixture until a mild exo-

thermic reaction was observed. As soon as the internal temperature reached 35 °C, the heating bath was removed and the reaction temperature was maintained between 35 and 40 °C by cooling with a water bath as necessary. After the initial exothermic period, the mixture was heated at 40 °C for a total of 3.5 h with stirring throughout. Failure to maintain internal temperature control results in formation of amorphous side products.

After cooling to 20 °C, the reaction mixture was filtered to remove solids, and the yellow solution was cooled to 10 °C. Hexamethylphosphoric triamide (37.3 g) was added with stirring, and the crystalline precipitate was collected on a Büchner funnel. Recrystallization from methanol (40 °C maximum temperature) gave $MoO_5 \cdot H_2O \cdot$ HMPA as yellow needles (50 g, 67%).

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)(MoOPH). The anhydrous complex $MoO_5 \cdot$HMPA was prepared as described by Mimoun et al.[11] (vacuum desiccator, 0.2 mm, 24 h over P_2O_5). A solution of 18 g (51.9 mmol) of $MoO_5 \cdot$HMPA in dry THF (40 mL) was stirred magnetically and cooled with a water bath (20 °C) while pyridine (4.11 g, 51.9 mmol, distilled from BaO) was added dropwise. The yellow crystalline precipitate was collected, washed with a small amount of THF (5–10 mL), anhydrous ether (ca. 100 mL), and dried under vacuum to give MoOPH as finely divided, free-flowing crystalline material. The MoOPH was placed in a dark glass bottle and stored in a larger container over Drierite in the refrigerator.

Exposure to sunlight or fluorescent light causes gradual darkening of the crystals. After several days of such exposure at 25 °C, the smell of HMPA and pyridine is apparent and the crystals become "sticky". Use of partially decomposed MoOPH gives lower yields and results in gummy precipitates during aqueous workup of hydroxylation mixtures.

Lithium Diisopropylamide (LDA). A stock solution of LDA was prepared in the following way. A 50-mL Erlenmeyer flask was fused to a high vacuum three-way stopcock as the sole outlet. After flame drying, the stopcock was greased, the flask flushed with nitrogen, and 20 mL of commercial *n*-butyllithium (ca. 1.5 M in hexane) was introduced by syringe through a septum placed over the vertical stopcock inlet. Nitrogen flow was maintained through the stopcock ports by means of syringe needles connected to a nitrogen tank and a mineral oil bubbler. The flask was then cooled to −70 °C and dry diisopropylamine (4.6 mL, 33 mmol, distilled from BaO) was added by syringe while gently swirling the mixture in a dry ice bath. To the gelatinous LDA–hexane mixture was then added dry THF (20 mL, distilled from benzophenone–sodium ketyl). After addition of the first milliliter or so of THF, the LDA crystallized and then slowly redissolved. The solution was then allowed to reach ambient temperature under a slow nitrogen stream throughout. A small amount of flocculent precipitate did not interfere with subsequent use and eventually settled to the bottom of the flask. The LDA solution could be stored for 2–3 weeks at ambient temperature (stopcock closed) without deterioration. However, accidental introduction of air resulted in darkening of the solution from pale yellow (depending on the batch of C_4H_9Li) to brown.

Titration of LDA. A variation of the method of Watson and Eastham[30] was used. Thus, commercial menthol (0.312 g, 2 mmol) was dissolved in dry THF (5 mL) under nitrogen at −70 °C and a few crystals of anhydrous phenanthroline were added. The stock solution of LDA was then added dropwise by syringe until the pale yellow color of lithium menthoxide phenanthroline changed to the characteristic rust color of LDA–phenanthroline. The end point comes with little warning, but is easily detected within ±1 drop from a typical syringe needle. At temperatures above −22 °C, the end point is more difficult to detect, and gradual darkening throughout the LDA addition makes titration at 20 °C impossible. The titration was repeatable to ±2% using a 5-mL syringe; identical results were obtained on a 10-mmol scale, and concentrations of 0.6–0.7 M LDA were typical.

General Procedure for MoOPH Oxidation (Method A). Titrated LDA solution (1.5 mL, 0.7 M, 1.05 mmol) was transferred to a flame-dried, nitrogen-purged 50-mL three-neck flask. The LDA was cooled in a dry ice–acetone bath, and a solution of the carbonyl compound (1.0 mmol) in 10 mL of dry THF was added dropwise over 2–3 min. A slow nitrogen flow was maintained through the system at all times. After 15 min stirring at −78 °C, the solution was brought to the desired temperature for oxidation (−78 °C for esters and lactones, −44 to −22 °C for ketones; see Tables I and II). An excess of MoOPH (0.65 g, 1.5 mmol) was then added at once by means of an L-shaped tube sealed at one end and fitted with a male ground-glass joint at the other. The tube was filled with the calculated amount of MoOPH at the start of the experiment and attached to one neck of the reaction vessel. Rotation of the addition tube into the vertical position resulted in addition of MoOPH over a few seconds to the stirred enolate. If the temperature was sufficient for reaction, the mixture rapidly became orange to red and the MoOPH slowly dissolved. Depending on the substrate and temperature, the color remained red or turned various shades of green-blue. After the crystalline reagent had dissolved (typically to form a slightly opaque solution) the reaction mixture was quenched with saturated sodium sulfite solution (5 mL), warmed to 20 °C, and sufficient water was added to give two homogeneous layers. This mixture was stirred 15 min or until no further color change in the organic layer was evident. The layers were then separated, organic products were extracted with a suitable solvent (usually ether), and the organic extracts were washed with 5% HCl to remove pyridine. After drying ($MgSO_4$) and evaporation, the products were isolated by preparative layer chromatography or other means as appropriate.

Inverse Addition Procedure for MoOPH Oxidation (Method B). The enolate was prepared as above at −78 °C in a single-neck flask stoppered with a septum and flushed with nitrogen via syringe needle inlet and exit. A second flask was charged with MoOPH (1.5–2 mol/mol of enolate) and dry THF (10 mL). This flask was connected through septa to the enolate flask by a U-shaped cannula which could be raised or lowered through the septum caps. With the cannula raised above the liquid levels, nitrogen was swept from the enolate flask through the cannula and vented from the MoOPH flask. After the stirred MoOPH suspension was cooled to the desired temperature, the enolate was introduced dropwise by repeatedly dipping the top of the cannula below the level of enolate solution under *gentle* nitrogen pressure. After enolate transfer was complete, the reaction was allowed to proceed as before and was worked up in the same way.

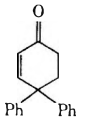
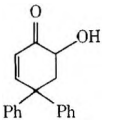
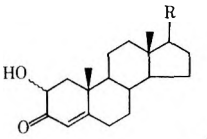
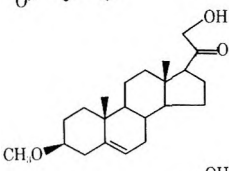
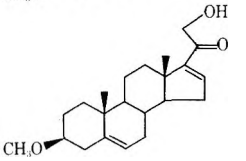
Hydroxylation of Valerophenone Using Method A. The enolate from valerophenone (0.324 g, 2 mmol) was oxidized at −22 °C as described above, with 15 min total oxidation time. After workup with sodium sulfite, the crude product was analyzed by thin-layer chromatography on silica gel, 20% CH_2Cl_2–hexane, two developments. Spots were noted at R_f 0.55, 0.5 (valerophenone), 0.4, 0.25, and 0.2 (major). After 1 h at room temperature in ether solution, a new spot, R_f 0.8, was apparent. After 24 h, the R_f 0.8 spot was intense and the spots of 0.4 and 0.25 had nearly disappeared. Preparative TLC separation gave **14** (0.077 g, 22%, R_f 0.8), diketone **12**[21] (0.043 g, 12%, R_f 0.55), valerophenone (0.015 g, 5%, R_f 0.5), and acyloin **11**[20] (0.195 g, 60%, R_f 0.2). Both **11** and **12** were identified by comparison of NMR spectra with authentic material. The furan **14** was obtained as a colorless oil which darkened slowly upon exposure to oxygen: ^{1}H NMR ($CDCl_3$, δ) 7.6 (2 H, d, J = 8 Hz), 7.1–7.5 (8 H, m), 2.6 (4 H, br t, J = 7 Hz), 1.2–1.8 (4 H, m), 0.95 (3 H, t, J = 7 Hz), 0.82 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$,δ) 151, 146.3, 133.9, 132. 129.6, 128.2, 128, 126.5, 126.2, 125.1, 124.3, 121.6, 28.3, 26.2, 22.9, 21.8, 13.9, 13.6; IR (neat, cm^{-1}) 2960 (s), 2930 (s), 2870 (s), 1595 (m), 1495 (s), 1130 (m), 1070 (m), 990 (m); (no absorptions at <3100, or between 1650 and 1800). Anal. Calcd for $C_{22}H_{24}O$: C, 87.80; H, 7.32. Found: C, 87.91; H, 7.30.

Oxidation of Camphor; Thermolysis of the Intermediate to Give Camphorquinone. Camphor was oxidized according to method A, −22 °C, 10 min total reaction time. After the usual workup, preparative layer chromatography (40% ether–hexane) over silica gel gave *endo*-3-hydroxycamphor, 70% (R_f 0.2), identified by comparison with published NMR data of the possible hydroxycamphor isomers.[31] No other hydroxycamphor isomer was detected; the only other significant zone (R_f 0.5) was recovered camphor, 15%.

The experiment was repeated, but after oxidation at −22 °C the solution from enolate + MoOPH was heated for 18 h at 60 °C under a static nitrogen atmosphere. After the usual workup, preparative layer chromatography gave a yellow zone at R_f 0.45, 11%, which solidified after extraction and evaporation. The yellow solid was identical with camphorquinone by direct NMR and TLC comparison with an authentic sample.[22] Hydroxycamphor was isolated in 44% yield from this experiment, but the isomer ratio was not examined.

Hydroxylation of 2-Phenyleyclohexanone. Oxidation according to method A at −44 °C was performed using 0.348 g (2 mmol) of ketone, 3 mL (2.1 mmol) of LDA solution, and 1.3 g of MoOPH (3 mmol). After 1.5 h at −44 °C only traces of MoOPH crystals remained, and the opaque solution was quenched with Na_2SO_3 and worked up as usual. Preparative layer chromatography (20% ether–hexane, 2 developments) gave recovered 2-phenylcyclohexanone (R_f 0.6, 0.035 g, 10%), *trans*-2-hydroxy-6-phenylcyclohexanone (**19a**) (R_f 0.35, 0.236 g, 62%), and **19b** (R_f 0.2, 0.028 g, 8%). After standing under ca. 1 mL of hexane, **19a** slowly solidified. Recrystallization from hexane gave a sample: mp 88 °C; NMR ($CDCl_3$, δ) 7.28 (5 H, br, s), 4.18 (1 H, dd, J = 11, 6 Hz), 4.03 (1 H, br, s), 3.7 (1 H, br s, exchanged by D_2O), 1.4–2.6 (6 H, m). The minor isomer **19b** did not crystallize: NMR

Table III. Oxidation of Enones and Methyl Ketones; Inverse Addition Method

Registry no.	Ketone	α-Hydroxy ketone	
4528-64-7			(53%)
601-57-0	Cholestenone		(40%)[a]
511-26-2	3β-Methoxypregn-5-en-20-one[d]		(20%)[b] (58%)[c]
64045-69-8	3β-Methoxypregna-5,16-dien-20-one[e]		(52%)

[a] M. Tomoeda, M. Ishizaki, H. Kobazashi, S. Kamatomo, T. Koga, M. Inuzuka, and T. Furuta, *Tetrahedron*, 21, 733 (1965). [b] Yield by inverse addition estimated by NMR. [c] Isolated yield after retro-aldol fragmentation by addition of excess LDA to crude hydroxylation mixture. [d] Reference 26. [e] Reference 25.

($CDCl_3$, δ) 7.3 (5 H, m), 4.21 (1 H, m), 3.5–3.7 (2 H, m; one D_2O exchanged), 1.5–2.7 (6 H, m). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.8; H, 7.47. Found: C, 76.0; H, 7.45.

Conversion of 19a to 20. A solution of *trans*-2-hydroxy-6-phenylcyclohexanone (0.1 g) in methanol (1 mL) was added to a solution of KOH (0.1 g) in methanol (5 mL). After 15 min (20 °C) the mixture was diluted with water and extracted with ether. After drying ($MgSO_4$) and evaporation of ether, a crystalline residue was obtained. Recrystallization from ether–hexane gave colorless needles: mp 118–119 °C, identified as **20** from the NMR spectrum ($CDCl_3$, δ) 7.24 (5 H, br, s), 4.28 (1 H, dd, J = 12, 1.5 Hz; 1.5-Hz coupling disappears after shaking with D_2O), 3.6 (1 H, d, J = 1.5 Hz; D_2O exchangeable), 1.5–2.9 (7 H, m). The same substance (**20**) was obtained by saponification of 2-acetoxy-6-phenylcyclohexanone using KOH–CH_3OH according to the literature procedure[23] claimed to afford **19**. No **19a,b** could be detected by TLC analysis (20% ether–hexane).

Oxidation of the Potassium Enolate of 2-Phenylcyclohexanone. A solution of 0.348 g (2 mmol) of 2-phenylcyclohexanone in dry THF (5 mL) was stirred with ca. 3 mmol of KH (Pressure Chemical Co.) at 20 °C under nitrogen. After 20 min the solution was cooled to −44 °C (acetonitrile–dry ice) and MoOPH (0.91 g, 2.1 mmol) was added at once. The mixture was stirred for 10 min at −44 °C, 20 min at −22 °C, and then quenched and worked up as usual. Preparative layer chromatography gave recovered 2-phenylcyclohexanone (0.09 g, 26%), 2-hydroxy-2-phenylcyclohexanone (**24**)[24] (R_f 0.4, 0.118 g, 30%), and a zone containing ca. 80% **19b** by NMR (R_f 0.2, 0.115 g, yield of **19b** ca. 24%) and contaminated by unknown products. The trans isomer **19a** could not be detected in the crude product by NMR or TLC.

Enol Acetate 23 from the Potassium Enolate. A solution of 2-phenylcyclohexanone (0.076 g) in dry THF (2 mL) was stirred with KH (20 mg) for 30 min. Acetic anhydride (50 μL) was added, and after 10 min the solution was diluted with ether, extracted rapidly with water, dried ($MgSO_4$), and evaporated. The colorless residue was analyzed by NMR (CCl_4): 0.3 H at δ 3.5 (unreacted 2-phenylcyclohexanone), relative integral assuming aromatics = 5 H; methyl singlet at δ 1.8 overlapping CH_2 envelope; no signals between δ 3.6 and 7 which might be due to less substituted enol acetate.

MoOPH Oxidation of the Enolate of 4,4-diphenylcyclohex-2-en-1-one. Method A. The oxidation was performed as usual using 4,4-diphenylcyclohex-2-en-1-one (0.248 g, 1.0 mmol), LDA (1.51 mL, 0.73 N, 1.1 mmol), and MoOPH (565 mg, 1.3 mmol). PLC of the residue with 30% ether in hexane gave starting material (38 mg, 15%, R_f = 0.5) and a mixture of 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one **26** and **27**. A second preparative layer separation of the mixture using 10% ethyl acetate in benzene gave **26** (38 mg, 17%): R_f = 0.48; mp 182–183 °C; NMR ($CDCl_3$, δ) 2.56 (1 H, t, J = 12 Hz), 3.01 (1 H, ddd, J = 2.0 Hz), 3.60 (1 H, OH), 4.17 (1 H, ddd, J = 2.5, 5.0, 12 Hz), 6.20 (1 H, d, J = 10 Hz), 7.0–7.4 (11 H, m); IR (cm^{-1}, $CHCl_3$) 3470 (s), 2985 (m), 1667 (s), 1582 (m), 1440 (m), 1429 (m), 1242 (m), 1136 (w), 1103 (s), 1008 (m), 901 (m), 887 (m), 826 (m), 690 (s), 658 (w); exact mass determined, 264.11493; calcd for $C_{18}H_{16}O_2$, 264.11455; ^{13}C NMR ($CDCl_3$, ppm) 44.03 (td, J = 4, 135 Hz), 51.06 (s), 70.21 (dq, J = 5, 142 Hz), 125.78 (d, J = 167 Hz), 126.96 (dt, J = 7, 161 Hz), 127.01 (dt, J = 6.5, 156 Hz), 127.25 (dt, J = 7, 162 Hz), 127.74 (dt, J = 6.5, 157 Hz), 128.70 (dd, J = 7.0, 161 Hz), 128.74 (dd, J = 7.0, 160 Hz), 142.85 (s), 147.06 (s), 157.19 (dd, J = 7.9, 16 Hz), 200 (s), and the condensation product **27** (160 mg, 61%): R_f = 0.6; mp 153–155 °C; NMR ($CDCl_3$, δ) 2.02–3.1 (6 H, m), 3.65 (1 H, dt, J = 2.0, 10 Hz), 5.90 (1 H, s, OH), 5.85 (1 H, d, J = 11 Hz), 6.20 (1 H, d, J = 10.5 Hz), 7.0–7.5 (22 H, m); IR (cm^{-1}, $CHCl_3$) 3440 (m), 3010 (m), 2960 (w), 1653 (s), 1595 (m), 1492 (s), 1445 (s), 1375 (m), 1230 (s), 1070 (m), 1060 (m), 1037 (w), 932 (m), 840 (w), 691 (s); ^{13}C NMR ($CDCl_3$, ppm) 37.80 (tm, J = 131 Hz), 39.85 (tm, J = 131 Hz), 46.26 (dm, J = 128.5 Hz), 49.34 (s), 50.95 (s), 66.18 (dm, J = 142.5 Hz), 73.39 (s), 126.13 (dt, J = 2.0, 85 Hz), 126.29 (dt, J = 2.0, 8.0 Hz), 126.76 (dt, J = 7, 159 Hz), 127.11 (dt, J = 7, 159 Hz), 127.16 (dt, J = 7, 155 Hz), 127.61 (dt, J = 6.4, 157 Hz), 128.04 (dd, J = 6, 157 Hz), 128.24 (dd, J = 7, 160 Hz), 128.35 (dd, J = 5, 156 Hz), 128.59 (dd, J = 8, 162 Hz), 128.76 (dd, J = 7.8, 161 Hz), 129.32 (d, J = 165.5 Hz), 139.08 (dd, J = 4.6, 157 Hz), 142.13 (sq, J = 65 Hz), 146.23 (sq, J = 8 Hz), 147.66 (sm), 148.06 (sm), 157.16 (dd, J = 7.8, 161 Hz), 204.25 (sm). Anal. Calcd: C, 84.41; H, 6.39. Found: C, 84.41; H, 6.40.

MoOPH Oxidation of 4,4-Diphenylcyclohex-2-en-1-one Using Inverse Addition. Method B. 4,4-Diphenylcyclohex-2-en-1-one (124 mg, 0.5 mmol) was dissolved in dry THF (6 mL) and added to LDA (0.79 mL, 0.70 N, 0.55 mmol) at −23 °C. After 5 min, this solution was added via cannula to MoOPH (282 mg, 0.65 mmol) in THF (10 mL) at −22 °C. An additional amount of THF (2 mL) was used to ensure complete transfer of enolate solution. The light yellow MoOPH solution turned olive green during the addition of the enolate solution. After 5 min, the reaction was quenched with cold saturated sodium sulfite (3 mL). The usual workup and PLC as described previously gave 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one (**26**) (70 mg, 53%), starting material (21 mg, 17%), and self-condensation product **27** (17 mg, 7%).

Retro-aldol Fragmentation of the Condensation Product 27 from MoOPH Oxidation of 4,4-Diphenylcyclohex-2-en-1-one. The condensation product **27** (150 mg, 0.29 mmol) was dissolved in THF (3 mL) and added to LDA (0.93 mL, 0.65 mmol, 0.7 N) at −78 °C. After 5 min at −78 °C, the mixture was stirred at ambient temperature for 30 min. The reaction was quenched with water (5 mL) and extracted with ether (3 × 15 mL), and the combined ether extracts were dried over Na_2SO_4 and evaporated. PLC of the residue as before gave 6-hydroxy-4,4-diphenylcyclohex-2-en-1-one (**26**) (66 mg, 86%) and 4,4-diphenylcyclohex-2-en-1-one (**25**) (64 mg, 89%).

Preparation of 21-Hydroxy-3β-methoxypregna-5,16-dien-20-one (29). Prepared using method B from 3β-methoxypregna-5,16-dien-20-one[25] (164 mg, 0.5 mmol), LDA (0.78 mL, 0.70 N, 0.55 mmol) and MoOPH (283 mg, 0.65 mmol) at −22 °C. PLC of the residue on silica gel using 20% ethyl acetate in hexane as eluent gave colorless needles of **29** (90 mg, 52%, R_f 0.4): mp 138–139 °C (from ether–hexane); NMR ($CDCl_3$, δ) 0.98 (3 H, s), 1.08 (3 H, s), 0.8–2.6 (18 H, m), 3.08 (1 H, m), 4.48 (2 H, AB, J = 21 Hz), 5.37 (1 H, m), 6.68 (1 H, m); IR (cm^{-1}, $CHCl_3$) 3480 (m), 2940 (s), 1664 (s), 1582 (m), 1450 (m), 1432 (m), 1370 (s), 1338 (m), 1322 (s), 1085 (s), 968 (m), 950 (m), 940 (m), 915 (m), 877 (w), 840 (w), 655 (w); exact mass determined, 344.23514; calcd for $C_{22}H_{32}O_3$, 344.23443; starting material (70 mg, R_f = 0.6, 42%).

Preparation of 21-Hydroxy-3β-methoxypregn-5-en-2-one. 3β-Methoxypregn-5-en-20-one[26] (330 mg, 1.0 mmol) in dry THF (6 mL) was added to LDA (1.72 mL, 1.2 mmol, 0.70 N) at −22 °C. The resulting yellow solution was stirred for 10 min at −22 °C and MoOPH (693 mg, 1.6 mmol) was added all at once. After 5 min, the light orange homogeneous mixture was quenched with saturated Na_2SO_3 (6 mL) and the aqueous solution was extracted with chloroform (2 × 20 mL) and with ether (2 × 20 mL). The combined extracts were dried over Na_2SO_4, evaporated, and further dried under vacuum (0.30 mm) over P_2O_5 for 2 h. The crude material (a mixture of acyloin and condensation product) was then dissolved in THF (8 mL), cooled to −22 °C, and LDA (4.3 mL, 3.0 mmol, 0.70 N) was added. The mixture was stirred at ambient temperature for 30 min and quenched with water (10 mL). Extraction with ether (3 × 25 mL) gave an oily solid. PLC of the residue using 30% ether in hexane gave the acyloin **31** (199 mg, 58%): R_f = 0.31; mp 140–141 °C (from acetone); NMR ($CDCl_3$, δ) 0.69 (3 H, s), 3.36 (3 H, s), 0.8–2.5 (21 H, m), 3.92 (1 H, m), 4.15 (1 H, AB, J = 20 Hz), 5.35 (1 H, m); IR (cm^{-1}, CHCl) 3480 (m), 3008 (s), 1702 (s), 1520 (m), 1470 (m), 1432 (m), 1385 (m), 1215 (s), 1020 (s), 1060 (m), 928 (m), 750 (s), 660 (s), 621 (w); exact mass determined, 346.25079; calcd for $C_{22}H_{34}O_{31}$, 346.25079. Starting material (124 mg, R_f = 0.6, 36%) was also isolated.

Preparation of 3β-Methoxypregn-5-en-20-one Oxime (30b). The oxime was prepared by the method of Rao and Price[32] and was recrystallized from acetone: mp 220–222 °C (lit. mp 224–225 °C); NMR ($CDCl_3$, δ) 0.65 (3 H, s), 1.02 (3 H, s), 1.90 (3 H, s), 3.10 (1 H, m), 2.26 (3 H, s), 5.35 (1 H, m), 8.0 (1 H, broad OH), 0.8–2.8 (20 H, m).

Hydroxylation; Hydrolysis of 4-Phenylbutanone Oxime (32). The dianion[27] of **32** was prepared from 0.326 g (2 mmol) of oxime and 4.1 mmol of n-butyllithium (dropwise addition, −22 °C) in THF (10 mL), nitrogen atmosphere. After addition of MoOPH (0.87 g, 2 mmol) at −78 °C, the brown mixture was stirred for 1 h at −78 °C and 20 min at −22 °C, and the resulting green solution was quenched with 5% HCl (10 mL). Sufficient water was added to dissolve precipitated solids (ca. 75 mL), the products were extracted with ether (2 × 25 mL) and dried ($MgSO_4$), and the solvent was removed (aspirator). In an identical run, 1-hydroxy-4-phenyl-2-butan-2-one oxime (**33**) was isolated by preparative TLC (silica gel, 1:1:2 ether–methylene chloride–hexane, R_f 0.3), 0.132 g (36%), together with unreacted **32** (0.134 g, 41%). Traces of **34** were also present, R_f 0.5, ca. 10 mg. The hydroxy oxime **33** was recystallized from ether: mp 37–41 °C; NMR ($CDCl_3$, δ) 2.45–2.60 (2 H, m), 2.60–2.95 (2 H, m), 4.33 (2 H, s), 5.8 (2 H, broad), 7.2 (5 H, s); IR (cm^{-1}, CHCl) 3600 (m), 3360 (m, broad), 2930 (m), 1601 (w), 1494 (m), 1452 (s), 1369 (s), 1078 (m), 1030 (m), 938 (s), 695 (s); exact mass determined 179.09463; calcd for $C_{10}H_{13}NO_2$ 179.09463.

The crude hydroxylation product from the first run was refluxed with 0.6 g of $NaHSO_3$ in 10 mL of 50% ethanol, 3 h (Pines et al.).[28] Ethanol was then evaporated and the white crystalline suspension was stirred with 10% HCl (10 mL) and ether (20 mL) until no solids remained, ca. 20 min. Extraction with ether (2 × 20 mL), drying ($MgSO_4$), and evaporation gave an oil which contained two major spots by TLC (ether–methylene chloride–hexane, 1:1:2) and traces of two other products. Preparative layer separation gave **34** (1-hydroxy-4-phenylbutan-2-one), 0.125 g (38%), as a crystalline solid: mp 43–44 °C (needles, from ether) (lit.[33] mp 44–45 °C); NMR ($CDCl_3$, δ) 3.68 (2 H, m), 2.93 (2 H, m), 3.5 (1 H, OH), 4.10 (2 H, s), 7.17 (5 H, m); IR (cm^{-1}, $CHCl_3$) 3400 (s), 3020 (m), 2970 (m), 1730 (s), 1608 (m), 1505 (m), 1460 (m), 1070 (s), 1085 (s), 750 (s), 700 (s); exact mass determined, 164.08373; calcd for $C_{10}H_{12}O_2$, 164.08383.

MoOPH Oxidation of 3β-Methoxypregn-5-en-20-one Oxime. To 3β-methoxypregn-5-en-20-one oxime (**30b**) (150 mg, 0.44 mmol) in THF (5 mL) at −78 °C was added n-BuLi (0.590 mL, 1.49 M, 0.90 mmol). The cloudy solution was warmed to 0 °C, stirred for 30 min, and MoOPH (189 mg, 4.35 mmol) was added all at once. With the addition of MoOPH, the mixture turned orange and then quickly cleared up to a homogeneous light yellow solution. The mixture was quenched with dilute HCl (4 mL) and was extracted with chloroform (2 × 15 mL) and with ether (2 × 15 mL). After drying the combined extracts over Na_2SO_4 and evaporation of the solvents, the crude oxime mixture was hydrolyzed according to the procedure of Pines et al.,[28] as described for preparation of **34**. PLC of the residue as described previously gave 3β-methoxypregn-5-en-20-one (63 mg, 42%) and 21-hydroxy-3-methoxypreg-5-en-20-one (30 mg, 20%).

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Registry No.—**11,** 20907-23-7; **12,** 20895-66-3; **14,** 64045-70-1; **19a,** 53474-94-5; **19b,** 64045-71-2; **20,** 64045-72-3; **26,** 64045-73-4; **27,** 64045-74-5; **29,** 64045-75-6; **30b,** 64045-76-7; **31,** 64045-77-8; **32,** 6944-54-3; **33,** 64045-78-9; **34,** 20296-07-5; MoOPH, 23319-63-3; MoO_5·H_2O·HMPA, 23319-56-4; pyridine, 110-86-1; *endo*-3-hydroxycamphor, 21488-68-6; camphorquinone, 465-29-2; **24,** 4829-02-1; MoO_5·HMPA, 25377-12-2.

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Studies on the Selective Preparation of Aromatic Compounds. 14. An Attempt to Prepare All the Possible Deuterated Phenols by the Reductive Dehalogenation of the Corresponding Halophenols with Raney Alloys in an Alkaline Deuterium Oxide Solution[1]

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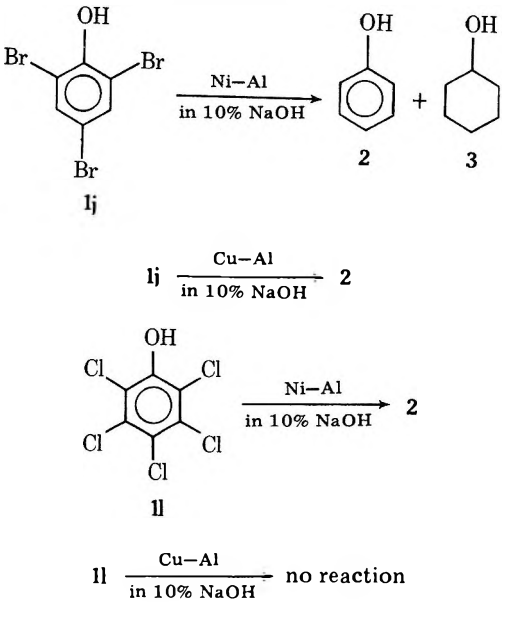
The reductive dehalogenation of the 19 halophenols **1a–s** was carried out with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution in order to obtain all the possible deuterated phenols. It was found that the reaction of the bromophenols with Raney Cu–Al alloy gives fairly selectively the corresponding deuterated phenols, but chlorophenols and bromochlorophenols give extensive further exchange of phenyl hydrogen atoms. 2-Bromophenoxyacetic acid (**6**) was reduced with Raney Ni–Al alloy to afford phenoxyacetic-2-*d* acid (**8**) in high purity without the further exchange of hydrogen atoms.

It has been known that[2-7] some halophenol derivatives could be reduced with Raney Ni–Al alloy in alkaline solution to afford the corresponding phenols. However, we recently found that[8] (i) the reduction of 2,4,6-tribromophenol (**1j**) with Raney Ni–Al alloy in 10% NaOH solution at 80 °C afforded phenol (**2**) with the formation of cyclohexanol (**3**) as a by-product, (ii) Raney Cu–Al alloy gave only **2** without any amount of **3**, and (iii) the former alloy was active for the reduction of chlorophenols as well as bromophenols; however, the latter alloy could reduce only bromophenols but not chlorophenols (Scheme I).

These results suggest that the desired deuterated phenols may be prepared by the reduction of the corresponding halophenols with the Raney alloys in an alkaline deuterium oxide solution.

Scheme I

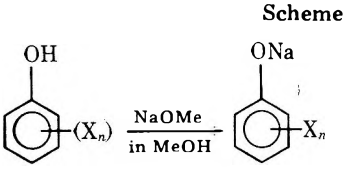


We wish to report the use of the Raney alloys for the reduction of halophenols (**1a–s**) in 10% NaOD–D_2O solution.

Results and Discussion

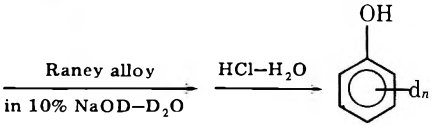
There are 19 possible isomers of the deuterated phenols. In order to obtain all of the possible deuterated phenols, the corresponding halophenols **1a–s** were reduced with Raney alloys such as Ni–Al and Cu–Al in 10% NaOD–D_2O solution which was prepared from D_2O (99.8%) and the calculated amount of NaOMe. To keep the D_2O solution in high isotopic purity, the halophenols **1** were converted to their sodium salts

Scheme II



1 **4**

a, 2-Br	g, 3,5-Br_2
b, 3-Br	h, 2,4-Cl_2, 3-Br
c, 4-Br	i, 2,4,5-Br_3
d, 2,3-Cl_2	j, 2,4,6-Br_3
e, 2,4-Br_2	k, 2,3,4,5-Br_4
f, 2,6-Br_2	l, 2,3,4,5,6-Cl_5



5

a, 2-*d*	g, 3,5-d_2
b, 3-*d*	h, 2,3,4-d_3
c, 4-*d*	i, 2,4,5-d_3
d, 2,3-d_2	j, 2,4,6-d_3
e, 2,4-d_2	k, 2,3,4,6-d_4
f, 2,6-d_2	l, 2,3,4,5,6-d_5

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Table I. The Reduction of Halophenols (1) Via Their Sodium Salts (4) with Raney Alloy in 10% NaOD–D_2O Solution[a]

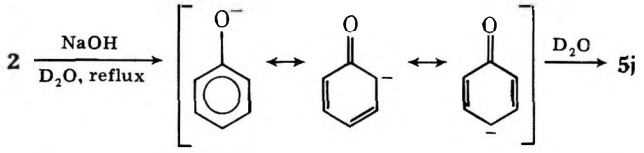
Run	Substance (g)	Registry no.	Alloy (g)	Registry no.	5 (yield %)[b]	Registry no.	Composition of 5 (%)[c] d_0	d_1	d_2	d_3	d_4	d_5
1	**1a** (2.0)	95-56-7	Cu–Al (0.5)	11099-19-7	**5a** (94)	23951-01-1	15	83	2	0	0	0
2	**1b** (2.0)	591-20-8	Cu–Al (0.5)		**5b** (77)	23951-02-2	3	92	5	0	0	0
3	**1c** (2.0)	106-41-2	Cu–Al (0.5)		**5c** (69)	23951-03-3	3	92	5	0	0	0
4	**1d** (3.0)	576-24-9	Ni–Al (4.2)	11114-68-4	**5d** (92)	64045-90-5	2	13	35	31	16	3
5	**1e** (1.72)	615-58-7	Cu–Al (0.8)		**5e** (88)	64045-89-2	1	9	85	5	0	0
6	**1b** (3.5)	608-33-3	Cu–Al (2.0)		**5f** (83)	64045-88-1	0	17	80	3	0	0
7	**1g** (2.22)	06-41-5	Cu–Al (1.00)		**5g** (89)	6264045-87-0	0	12	84	4	0	0
8	**1h** (2.0)	13659-21-7	Ni–Al (4.5)		**5h** (80)	64045-86-9	3	9	27	45	13	3
9	**1i** (4.0)	14401-61-7	Cu–Al (2.0)		**5i** (82)	64045-85-8	0	1	6	92	1	0
10	**1j** (3.38)	118-79-6	Cu–Al (2.0)		**5j** (65)	7329-50-2	0	1	16	80	3	0
11	**1k** (4.5)	4526-58-3	Cu–Al (3.0)		**5k** (77)	64045-84-7	0	0	2	14	82	2
12	**1l** (5.0)	87-86-5	Ni–Al (7.5)		**5l** (74)	4165-62-2	0	0	0	1	13	86

[a] Reaction time was 60 min. [b] The yields isolated are shown. The yields determined by gas chromatographic analyses are almost quatitative in respective cases. [c] The compositions were obtained by mass spectroscopic method.

4 which were obtained from 1 by treatment with the calculated amount of dry NaOMe in MeOH and then dried in vacuo.

The results of the reduction are summarized in Table I. The data of Table I show that the expected deuterated phenols **5a–f** were obtained in good yields, respectively. Although the desired deuterated phenols such as **5a–c,e–g,i–k** were formed in high purities (80–90%) from the corresponding bromophenols with Raney Cu–Al alloy, respectively, **5d** and **5h** were obtained in lower purities (40–50%) from the corresponding halophenols containing one or more chloro atoms with Raney Ni–Al alloy. Also, the reduction of 2,5-dichloro- (**1m**), 3,4-dichloro-(**1n**), 3,5-dibromo-2-chloro- (**1o**), 3-bromo-2,6-dichloro- (**1p**), 3,5-dibromo-4-chloro- (**1q**), 3,5-dibromo-2,4-dichloro- (**1r**), and 3,5-dibromo-2,6-dichlorophenol (**1s**) with Raney Ni–Al alloy gave only in lower purities the deuterated phenols, respectively. However, the expected **5l** was obtained in high purity in the presence of the latter alloy. The former alloy was less active than the latter one so it could not reduce the halophenols containing the chloro atoms.

It should be noted that use of Raney Ni–Al leads to the introduction of more than the expected number of deuterium atoms. It has been reported that[9,10] phenol **2** was refluxed for



a long time in D_2O in the presence of NaOH to afford 2,4,6-trideuterated phenol **5j**.

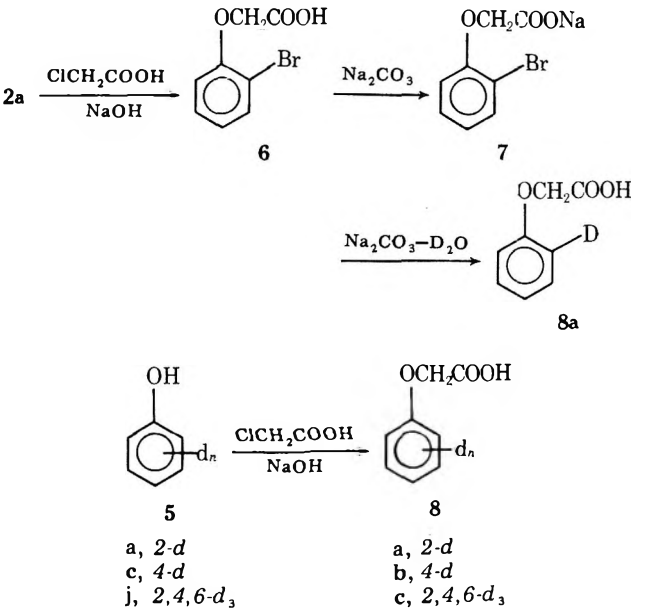
The above reaction might take place in the reduction with Raney Ni–Al as one of the side reactions, since the reaction temperature was somewhat increased when the alloy was added in the alkaline solution.

When sodium 2-bromophenoxyacetate (**7**), which was easily prepared from 2-bromophenoxyacetic acid (**6**) with Na_2CO_3, was treated with Raney Ni–Al in 10% Na_3CO_3–D_2O solution in a similar manner, phenoxyacetic-2-*d* acid (**8**) was obtained in good yield and in high purity (>90%). The deuterated phenoxyacetic acid **8** was also obtained from **5a** and chloroacetic acid in the usual manner.

The result of reduction of **6** with Raney Ni–Al alloy suggests that this reductive method for the introduction of deuterium atoms on the desired position of aromatic ring might be applied to carboxylic compounds as well as phenolic compounds.

The ^1H NMR spectra of **5a–c,g,i–l**, and **8b,c** are shown in Figures 1 and 2. The purities of **8b** and **8c** were calculated from the relative intensities of their methylene and aromatic protons, and agreed well with those obtained from the mass

Scheme III



spectra of **5c** and **5j**. The data of Figures 1 and 2 show also that the deuterium atoms were introduced on the desired positions of the ring of **2** in the reductive system of Cu–Al alloy and bromophenols.

Based on the results described above it might be concluded that, although the attempt to prepare all of the possible deuterated phenols in high purity was not successful, the reduction of bromophenols with Raney Cu–Al alloy in 10% NaOD–D_2O solution might be more a convenient preparative method for the introduction of deuterium atoms on the desired position of aromatic rings than the previously reported methods.[9-14]

Experimental Section

All melting points are uncorrected. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet (ionization energy 70 eV). NMR spectra were determined at 60 MHz with a Hitachi R-20 NMR spectrometer and Me_4Si as an internal reference.

Materials. The halophenols such as **1a–e,m,n,j,l** of commercial grade were used without further purification. The other halophenols were prepared by the reported method and were purified by fractional distillation and/or recrystallization. **1f**:[4,15] mp 57–59 °C; **1q**:[16] mp 81 °C; **1h**:[17] mp 85 °C; **1o**:[18] mp 68 °C; **1p**:[19] mp 67 °C; **1i**:[20] mp 79 °C; **1q**:[18] mp 121 °C; **1r**:[18] mp 121 °C; **1k**:[21] mp 123–125 °C **1s**:[18] mp 128 °C.

Analytical Procedure. The analyses were carried out by gas chromatography using a Yanagimoto gas chromatograph, Yanaco

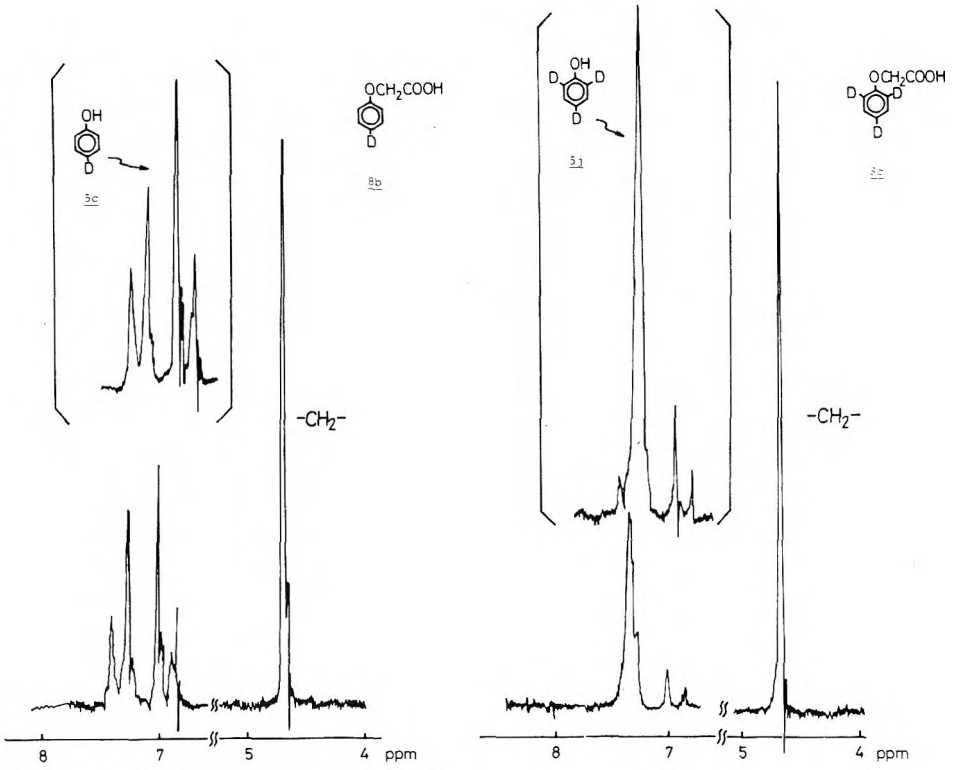


Figure 1. The ^1H NMR spectra of **5c–j** and **8b–c** (Solvent: $CDCl_3$).

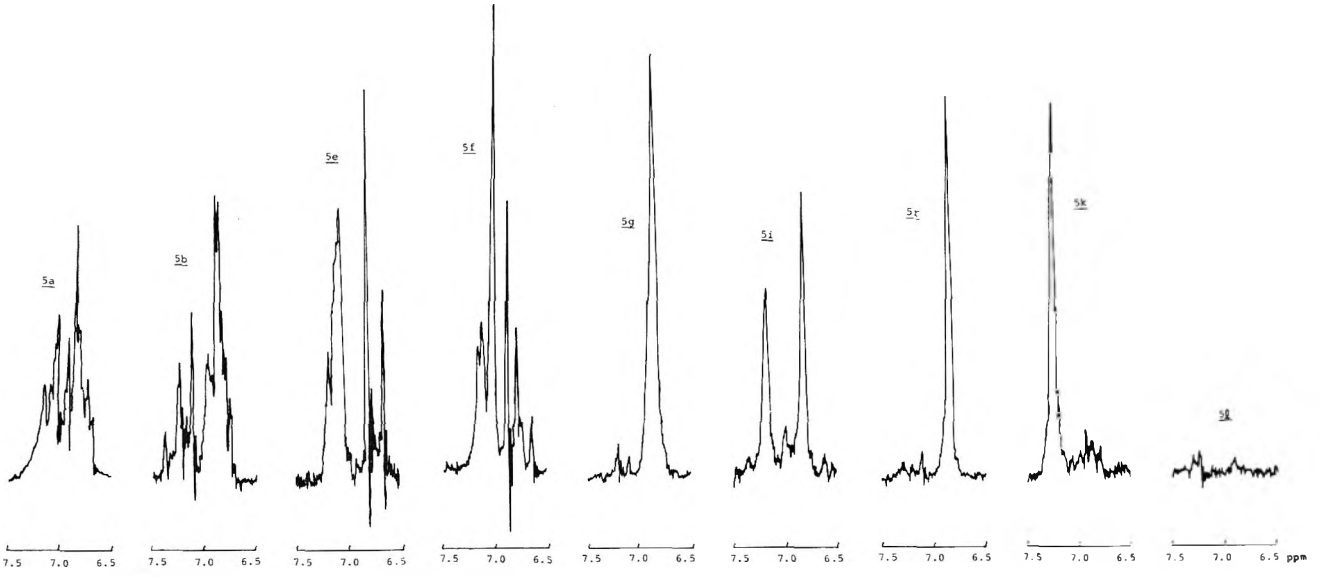


Figure 2. The ^1H NMR spectra of **5a,–l** (solvent $CDCl_3$).

YR-101: column 30% high-vacuum silicon grease, 75 cm; increase rate of column temperature, 12 °C/min; carrier gas, helium, 30 mL/min.

The Typical Procedure for Reduction of 1. To a solution of NaOMe in 50 mL of MeOH, which was prepared from 0.24 g (10.4 mmol) of Na in 50 mL of MeOH, was added 3.38 g (10.2 mmol) of 2,4,6-tribromophenol (**1j**), and then the excess MeOH was evaporated in vacuo to leave the residue which was dried by heating at 120–130 °C over night under reduced pressure affording dry **4j**. The sodium salt **4j** was dissolved in 50 mL of 10% NaOD–D_2O solution which was prepared from 7.37 g of NaOMe and 50 mL of D_2O. To the solution was gradually added at room temperature 2 g of Cu–Al alloy over a period of 10 min. After the reaction mixture was stirred for an additional 50 min, excess D_2O was distilled under reduced pressure, 20—30 mL of D_2O was recovered. The insoluble material was separated by filtration. The filtrate was acidified with 10% HCl solution and extracted with ether. The ether solution was dried over Na_2SO_4 and evaporated to afford **5j** which was analyzed by GC and MS.

The Reduction of 2-Bromophenoxyacetic Acid (6). After 0.2 g of **6** was dissolved in 10 mL of 2 N Na_2CO_3, the solution was evaporated in vacuo to leave colorless crystals (**7**) which were dried at 120 °C for 3 h under reduced pressure. The crystals were dissolved in 10 mL of D_2O and then 0.2 g of Raney Ni–Al alloy was gradually added in a period of 5 min. After the reaction mixture was stirred at 70 °C for 40 min, it was treated and worked up as described above to afford colorless crystals which were recrystallized from *n*-hexane giving 50 mg of phenoxyacetic-2-*d* acid (**8a**), mp 98 °C. The melting point of the unlabeled authentic compound is 99 °C.

Preparation of Deuterated Phenoxyacetic Acid (8) by the Reaction of Chloroacetic Acid with Deuterated Phenols 5a,c,j. The deuterated phenols **5a,c,j** were treated with chloroacetic acid in alkaline solution in the usual manner[22] to afford the corresponding deuterated phenoxyacetic acid.

Registry No.—**4j,** 2666-53-7; **5r,** 64045-83-6; **6,** 1879-56-7; **7,** 13730-99-9; **8a,** 64045-82-5; **8b,** 52199-99-2; **8c,** 21273-28-9.

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Reaction of Silylynamines with Active Triple Bonds

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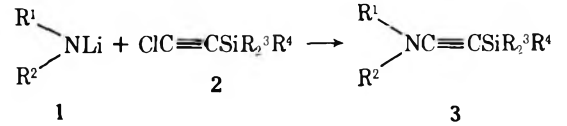
N,N-Disubstituted (triorganosilylethynyl)amines (silylynamines, **3**) reacted with dimethyl acetylenedicarboxylate (**6**), methyl propiolate (**7**), and benzyne (**18**) to give the 1:1 addition products **8**, **9**, and **20**. It appears that these adducts were formed as a result of 1,3-anionic rearrangement of the triorganosilyl group from carbon to carbon in the dipolar intermediates **16** and **19**.

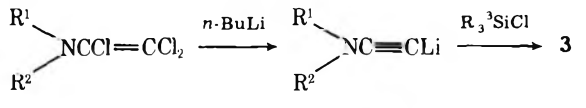
The addition reaction of ynamines with active multibonds provides a versatile tool in the syntheses of amine derivatives.[1] *N,N*-Dialkyl (alkyl or phenylethynyl) amine reacts with dimethyl acetylenedicarboxylate[2] or benzyne[3] in 1:2 mole ratio to give an aniline derivative or a mixture of phenanthrene and anthracene derivatives. These 1:2 addition products may be formed via dipolar intermediates reactive enough to add to another mole of the active triple bond (Scheme I). In this paper, we report the 1:1 addition reaction of N,N-disubstituted (triorganosilylethynyl)amines (silylynamines) with acetylenecarboxylates or benzyne.

Silylynamines **3a–j** were prepared by reaction of lithium diorganoamides **1** with triorganosilylethynyl chlorides **2**

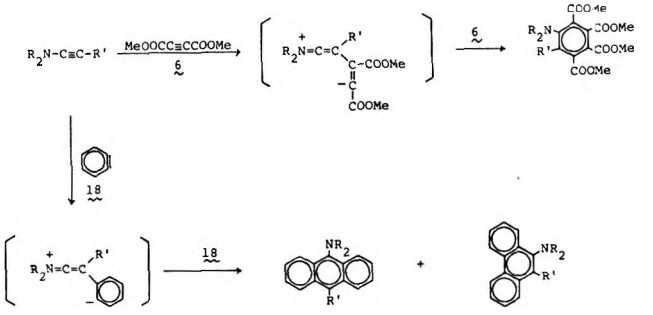
Method A



Method B



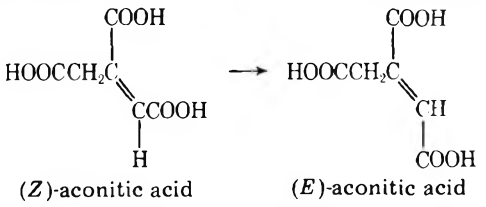
Scheme I



(method A[4]) or from *N*-methyl-*N*-(1,2,2-trichlorovinyl)aniline (**4**) via lithium aminoacetylide (**5**) (method B[5]). Method A gave good yields in the preparation of *N*-(triorganosilylethynyl)dialkylamines **3a–f**, and method B was adequate for *N*-(triorganosilylethynyl)arylamines **3g–j**. The results are summarized in Table I.

When *N,N*-diethyl(trimethylsilylethynyl)amine (**3a**) was mixed with an equimolar amount of dimethyl acetylenedicarboxylate (**6**) in ether, an exothermic reaction occurred immediately at room temperature to give the sole product **8a**. The elemental, NMR, and mass spectral analyses of **8a** indicated this product to be a 1:1 adduct, $C_{15}H_{25}NO_4Si$, and the IR spectrum showed a band at 2180 cm^{-1} indicating the presence of a triple bond. Thus, the structure of **8a** was assumed as (*E*)-*N,N*-diethyl[3,4-bis(methoxycarbonyl)-4-trimethylsilyl-3-buten-1-ynyl]amine (Scheme II).

Acid hydrolysis of **8a** afforded a mixture of two desilylated amides (**10a**) which were assigned to stereoisomers of *E* and *Z* types based on the NMR. Catalytic hydrogenation of the



(*Z*)-aconitic acid (*E*)-aconitic acid

mixture gave a 90% yield of *N,N*-diethyl-3,4-bis(methoxycarbonyl)butanamide (**13**) as a single product. Attempted separation of the stereomers by silica gel column chromatography failed, because both isomers convert to each other at room temperature. In the presence of water, isomerization of (*Z*)-aconitic acid occurs at ambient temperature.[6]

Similar 1:1 addition reactions of silylynamines with **6** were observed in the cases of *N,N*-diethyl(dimethylethylsilylethynyl)amine (**3b**), *N*-(trimethylsilylethynyl)morpholine (**3e**), and *N*-methyl-*N*-(trimethylsilylethylnyl)aniline (**3g**). *N*-Methyl-*N*-(triphenylsilylethynyl)aniline (**3h**) did not react in ether, but did in acetonitrile (see Table II). Acid hydrolysis

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Table I. N,N-Disubstituted (Triorganosilylethynyl)amines 3

Compd[a] 3	Registry no.	R^1	R^2	R^3	R^4	Yield, % Method A	Yield, % Method B	Bp (mmHg) [mp], °C	IR, cm^{-1} (C≡C)
a	33567-68-9	Et	Et	Me	Me	63[b]	44[c]	73–75 (23)	2160
b	64024-61-9	Et	Et	Me	Et	74		68–70 (7)	2140
c	57694-91-4	Et	Et	Ph	Ph	60	0	[42–43]	2140
d	64024-62-0	$-(CH_2)_4-$		Me	Me	49		95–98 (19)	2160
e	64024-63-1	$-(CH_2)_2O(CH_2)_2-$		Me	Me	55		88–90 (9)	2160
f	64024-64-2	$-(CH_2)_2O(CH_2)_2-$		Ph	Ph	80		[120–122]	2140
g	33567-67-8	Me	Ph	Me	Me	9	81[d]	87–90 (1)	2160
h	57694-92-5	Me	Ph	Ph	Ph	0	36	[115–117]	2160
i	64044-70-8	Et	Ph	Me	Me		83	78–79 (0.2)	2160
j	33567-66-7	Ph	Ph	Me	Me	0	78[e]	123–128 (0.5)	2160

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] Lit. 54%, ref 4. [c] Lit. 65%, ref 5. [d] Lit. 85%, ref 5. [e] Lit. 70%, ref 5.

Table II. Reaction of N,N-Disubstituted (Triorganosilylethynyl)amines (3) with Dimethyl Acetylenedicarboxylate (6) or Methyl Propiolate (7)

	R^1	R^2	R^3	R^4	Y	Reaction condition: Solvent[a]	Temp, °C	Time, h	Yield, %
8a	Et	Et	Me	Me	COOMe	E	20	2	82
8b	Et	Et	Me	Et	COOMe	E	Reflux	5	74
8e	$-(CH_2)_2O(CH_2)_2-$		Me	Me	COOMe	E	Reflux	2	43
8g	Me	Ph	Me	Me	COOMe	E	Reflux	10	62
8h	Me	Ph	Ph	Ph	COOMe	E	Reflux	24	0[b]
						A	80	8	40
9a	Et	Et	Me	Me	H	E	Reflux	24	0[b]
						A	80	24	24
9g	Me	Ph	Me	Me	H	E	Reflux	24	0[b]
						A	80	24	0[c]

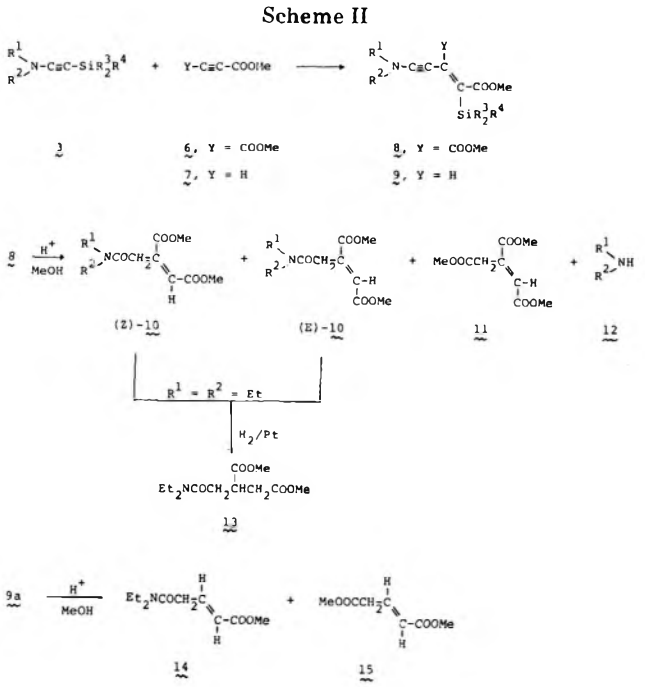
[a] E = ether, A = acetonitrile. [b] No reaction. [c] Polymerization.

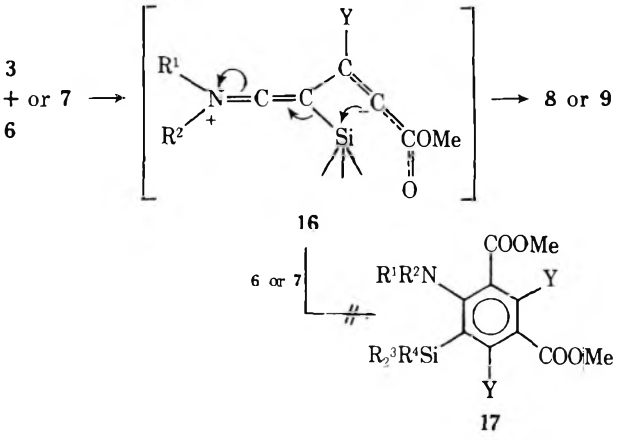
of *N*-methyl-*N*-[3,4-bis(methoxycarbonyl)-4-trimethylsilyl-3-buten-1-ynyl]aniline (**8g**) gave a mixture of (*E*)-**10g** and (*Z*)-**10g** with (*E*)-aconitic acid trimethyl ester (**11**) and *N*-methylaniline (**12**).

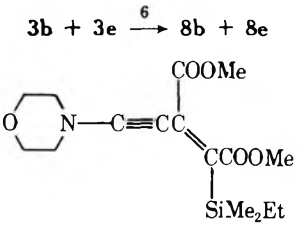
The reaction of **3a** or **3g** with methyl propiolate (**7**) did not occur in ether. However, in boiling acetonitrile a low yield of the 1:1 adduct **9a** was obtained from **3a**, but not from **3g**. Acid hydrolysis of **9a** gave (*E*)-*N*,*N*-diethyl-4-methoxycarbonyl-3-butenamide (**14**) and (*E*)-glutaconic acid dimethyl ester (**15**), which were identical with their authentic samples.

The reaction of silylynamines with acetylenecarboxylates, which is influenced by polarity of the solvent, may take place via a dipolar intermediate **16**, in which an anionic rearrangement of the silyl group giving **8** or **9** precedes the addition of **16** to another mole of **6** or **7** to form the aniline derivative **17**. The intramolecular nature of the silyl migration was confirmed by a crossover experiment. An equimolar amount of **3b** and **3e** was mixed and treated with **6** under the above-mentioned reaction condition. The products in the reaction

Scheme II





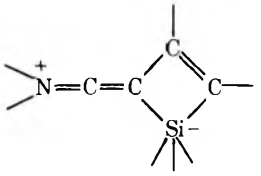


8k

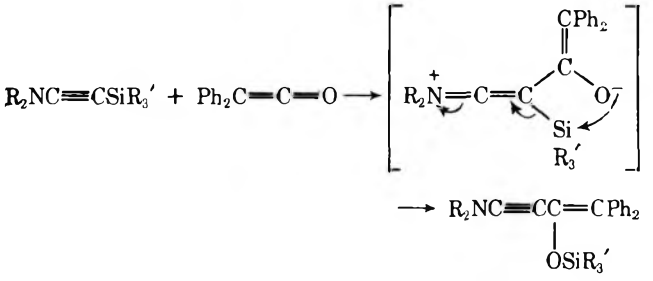
mixture were **8b** and **8e** only, and no crossover products (**8a** and **8k**) were detected.

The reaction of **3a** or **3g** with benzyne (**18**), generated from *o*-fluorobromobenzene and magnesium, also gave the 1:1 addition product **20a** or **20g** and no 1:2 adduct. *N,N*-Diethyl(o-trimethylsilylphenylethynyl)amine (**20a**) was hydrolyzed to amide **21**. Then **21** was reduced by lithium aluminum hydride to *N,N*-diethyl-2-(*o*-trimethylsilylphenyl)-ethylamine (**22**), which was identified by spectral comparison with an authentic sample prepared from *N,N*-diethyl-2-(*o*-bromophenyl)ethylamine (**23**) via a lithiated intermediate **24** (Scheme III).

The benzyne reaction of silylynamines seems to proceed via a similar dipolar intermediate **19** to that of acetylenecarboxylates. The rapid 1,3 rearrangement of the silyl group from carbon to carbon in **16** and **19** may be accelerated by the participation of a pentacoordinated intermediate.



Recently, Himbert reported a 1,3-silyl rearrangement from carbon to oxygen in the reaction of silylynamine with diphenylketene.[7]



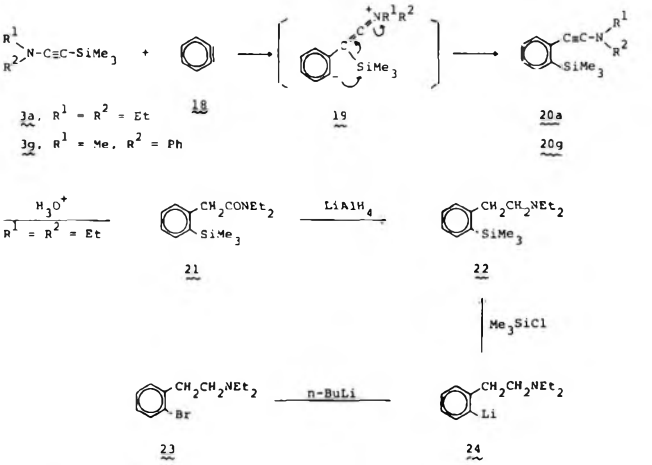
Experimental Section

^{1}H NMR spectra were recorded using a JEOL Model JNM-NH-100 spectrometer employing Me_4Si as internal standard. IR spectra were taken on a JASCO Model IRA-2 spectrometer. Mass spectra were recorded on a Hitachi Model M-52 spectrometer. GLC analyses were performed on a JEOL Model JGC-1100 chromatograph using stainless-steel columns with a nitrogen flow rate of 50 mL/min. Quantitative analysis of the reaction mixtures was carried out by the internal standard method. Fractional distillation was accomplished by a Büchi Model GKR-50 Kugelrohr distillation apparatus. All boiling and melting points are uncorrected. All reactions were carried out under nitrogen atmosphere. Ether and THF were dried by distillation from $LiAlH_4$ just prior to use.

N,N-Disubstituted (Triorganosilylethynyl)amines (3). Method A.[4] A solution of 220 mmol of phenyllithium in ether (150 mL) was added to a solution of 220 mmol of *sec*-amine in ether (150 mL) at 0–10 °C, and stirring was continued for 0.5 h. Then to the reaction mixture was added a solution of 200 mmol of triorganosilylethynyl chloride (**2**) in ether (50 mL) at the same temperature. After 2 h of stirring at room temperature, the reaction mixture was hydrolyzed with saturated aqueous potassium bicarbonate and extracted with ether. The ethereal extract was dried, concentrated, and distilled or recrystallized from hexane, giving **3a–g**.

Characterizing data are summarized in Table I.

Scheme III



Method B.[5] A solution of 125 mmol of *n*-butyllithium in *n*-hexane (80 mL) was added dropwise to a solution of 50 mmol of N,N-disubstituted 1,2,2-trichlorovinylamine (**4**) in ether (100 mL) at 0–10 °C, and stirring was continued for 2 h at room temperature. Then to the reaction mixture was added a solution of 60 mmol of triorganochlorosilane in ether (100 mL) at 0–10 °C. After 2 h of stirring at room temperature, the reaction mixture was hydrolyzed with 20% ammonia water and extracted with ether. The ethereal extract was dried, concentrated, and distilled or recrystallized from hexane, giving **3a,g–j.** Characterizing data are summarized in Table I.

N,N-Disubstituted [3,4-Bis(methoxycarbonyl)-4-trialkylsilyl-3-buten-1-ynyl]amines (8a, 8b, 8e, and 8g). A solution of dimethyl acetylenedicarboxylate (**6**, 1.42 g, 10 mmol) in ether (5 mL) was added dropwise to a solution of 10 mmol of N,N-disubstituted (trialkylsilylethynyl)amine (**3a, 3b, 3e,** or **3g**) in ether (25 mL). The mixture was stirred at reflux (at room temperature in the case of **3a**) for 2–10 h. After removal of the solvent, the residue was distilled to give **8a, 8b, 8e,** or **8g.**

Characterizing data are shown in Tables II and III.

***N*-Methyl-*N*-[3,4-bis(methoxycarbonyl)-4-triphenylsilyl-3-buten-1-ynyl]aniline (8h).** A mixture of *N*-methyl-*N*-(triphenylsilylethynyl)aniline (**3h,** 1.37 g, 3.5 mmol) and **6** (0.50 g, 3.5 mmol) in 30 mL of acetonitrile was heated at 80 °C for 8 h. After removal of the solvent, the residue was recrystallized from ethyl acetate to give 0.743 g (40%) of **8h.** Data are summarized in Table III.

Mixing Experiment. A mixture of **3b** (1.47 g, 8 mmol), **3e** (1.47 g, 8 mmol), and **6** (2.27 g, 16 mmol) in 30 mL of ether was heated at reflux for 2 h. The reaction mixture was analyzed by GLC using a 3 mm × 1 m column filled with 10% silicone SE-30, programed from 150–200 °C at 6 °C/min. The chromatogram showed the presence of **8b** (76%) and **8e** (47%). No crossover products (**8a** and **8k**) were detected.

***N,N*-Diethyl(4-methoxycarbonyl-4-trimethylsilyl-3-buten-1-ynyl)amine (9a).** A mixture of **3a** (3.39 g, 20 mmol) and methyl propiolate (**7**, 1.68 g, 20 mmol) in 40 mL of acetonitrile was heated at 80 °C for 24 h. Distillation of the reaction mixture gave 1.22 g (24%) of **9a.** Characterizing data are shown in Table III.

Acid Hydrolysis of 8a. To a solution of **8a** (1.85 g, 6 mmol) in 5 mL of methanol was added 20 mL of 5% HCl–MeOH. After 5 h of stirring at room temperature, the reaction mixture was neutralized with aqueous potassium bicarbonate, and the methanol was removed under reduced pressure. The ethereal extract of the aqueous layer was dried, concentrated, and distilled giving 1.10 g (72%) of a mixture of (*Z*)- and (*E*)-*N,N*-diethyl-3,4-bis(methoxycarbonyl)-3-butenamide (**10a**): bp 110–113 °C (0.1 mm); NMR (CCl_4) δ 0.95–1.40 (m, NCH_2CH_3), 3.15–3.50 (m, NCH_2), 3.60 and 3.96 (s × 2, $COCH_2$ × 2), 3.64, 3.76, 3.78, and 3.82 (s × 4, OCH_3 × 4), 6.80 and 7.22 (s × 2, vinyl H × 2); IR (neat) 1640 and 1720 cm^{-1} (C=O).

Acid Hydrolysis of 8g. A mixture of a solution of **8g** (1.35 g, 3.9 mmol) in 5 mL of methanol and 20 mL of 5% HCl–MeOH was allowed to react and treated in a similar manner as described above for **8a.** Fractional distillation gave 940 mg (36%) of *N*-methylaniline (**12**), 192 mg (23%) of (*E*)-aconitic acid trimethyl ester[8] (**11**), and 320 mg (24%) of a mixture of (*Z*)- and (*E*)-*N*-methyl-*N*-phenyl-3,4-bis(methoxycarbonyl)-3-butenamide (**10g**): bp 130–135 °C (0.015 mm); NMR (CCl_4) δ 3.22 and 3.30 (s × 2, NCH_3 × 2), 3.12 and 3.85 (s × 2, $COCH_2$ × 2), 3.63, 3.65, 3.70, and 3.76 (s × 4, OCH_3 × 4), 5.74 (s, vinyl H), and 7.10–7.55 (m, aromatic H); IR (neat) 1655 and 1720 cm^{-1} (C=O).

Table III. N,N-Disubstituted [3,4-Bis(methoxycarbonyl)- or 4-Methoxycarbonyl-4-triorganosilyl-3-buten-1-ynyl]amines 8 or 9

Compd[a]	Registry no.	Bp (mmHg) [mp], °C	IR (neat), cm^{-1} C≡C	IR (neat), cm^{-1} C=O	NMR (CCl_4), δ
8a	64024-65-3	120–122 (0.07)	2180	1710 1725	0.26 (s, 9, $SiCH_3$), 1.23 (t, 6, NCH_2CH_3), 3.08 (q, 4, NCH_2), 3.63 (s, 3, OCH_3), and 3.70 (s, 3, OCH_3)
8b	64024-66-4	133–135 (0.2)	2180	1710 1725	0.16 (s, 6, $SiCH_3$), 0.7–1.0 (m, 5, $SiCH_2CH_3$), 1.20 (t, 6, NCH_2CH_3), 3.14 (q, 4, NCH_2), 3.62 (s, 3, OCH_3), and 3.68 (s, 3, OCH_3)
8e	64024-67-5	158–160 (0.6)	2220	1710 1735	0.23 (s, 9, $SiCH_3$), 3.12–3.24 (m, 4, NCH_2), 3.60–3.75 (m, 4, OCH_2), 3.64 (s, 3, OCH_3), and 3.70 (s, 3, OCH_3)
8g	64024-68-6	185–190 (0.15)	2210	1715 1730	0.30 (s, 9, $SiCH_3$), 3.37 (s, 3, NCH_3), 3.69 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), and 6.90–7.30 (m, 5, aromatic H)
8h	64024-69-7	[160–161]	2190[b]	1705 1725	2.46 (s, 3, NCH_3), 3.30 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), and 6.75–7.90 (m, 20, aromatic H)
9a	64024-70-0	121–123 (3)	2180	1690	0.22 (s, 9, $SiCH_3$), 1.25 (t, 6, NCH_2CH_3), 3.12 (q, 4, NCH_2), 3.67 (s, 3, OCH_3), and 7.44 (s, 1, vinyl H)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] KBr disk.

Acid Hydrolysis of 9a. In a similar manner as described for above **8a, 9a** (1.15 g, 4.5 mmol) was hydrolyzed and distilled to give 117 mg (17%) of (*E*)-glutaconic acid dimethyl ester[9] (**15**) and 215 mg (26%) of (*E*)-*N,N*-diethyl-4-methoxycarbonyl-3-butenamide (**14**): bp 133–135 °C (20 mm); NMR (CCl_4) δ 0.95–1.35 (m, 6, NCH_2CH_3), 3.10–3.50 (m, 6, NCH_2 × 2 and $COCH_2$), 5.82 (d, 1, *J* = 16 Hz, =CHCO—), and 6.93 (dt, 1, *J* = 16 and 7 Hz, CH_2CH=); IR (neat) 1640 and 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.17; H, 8.66; N, 7.20.

***N,N*-Diethyl-3,4-bis(methoxycarbonyl)butanamide (13).** A mixture of 100 mg of platinum oxide and the (*Z*)- and (*E*)-**10a** mixture (1.5 g, 5.8 mmol) in 50 mL of methanol was stirred with 100 atm of hydrogen at room temperature for 3 h in an autoclave. After removal of the catalyst, the filtrate was concentrated and distilled, giving 1.35 g (89%) of **13**: bp 128–131 °C (2 mm); NMR (CCl_4) δ 1.00–1.35 (m, 6, NCH_2CH_3), 2.35–2.84 (m, 4, $COCH_2$), 3.00–3.50 (m, 5, NCH_2 × 2 and >CH–), 3.64 (s, 3, OCH_3), 3.66 (s, 3, OCH_3); IR (neat) 1640 and 1735 cm^{-1} (C=O); mass spectrum *m/e* 259 (M^+).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.37; H, 8.15; N, 5.22.

***N,N*-Diethyl(*o*-trimethylsilylphenylethynyl)amine (20a).** A solution of o-fluorobromobenzene (1.58 g, 9 mmol) in ether (5 mL) was added to a boiling mixture of **3a** (1.19 g, 7 mmol) and magnesium turnings (0.22 g, 9 mg-atom). After 1 h of stirring at reflux, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. The ethereal extract was dried, concentrated, and distilled, giving 0.36 g (21%) of **20a**: bp 87–90 °C (0.9 mm); NMR (CCl_4) δ 0.32 (s, 9, $SiCH_3$), 1.26 (t, 6, NCH_2CH_3), 3.00 (q, 4, NCH_2), 6.90–7.40 (m, 4, aromatic H); IR (neat) 2210 cm^{-1} (C≡C).

Anal. Calcd for $C_{15}H_{23}NSi$: C, 73.40; H, 9.45; N, 5.71. Found: C, 73.11; H, 9.43; N, 5.45.

***N*-Methyl-*N*-(*o*-trimethylsilylphenylethynyl)aniline (20g).** A solution of o-fluorobromobenzene (1.76 g, 10 mmol) in THF (10 mL) was added at reflux to a mixture of **3g** (1.02 g, 5 mmol) and magnesium turnings (0.25 g, 10 mg-atom) in THF (20 mL). After 15 h of stirring at the same temperature, the mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. Distillation of the ethereal extract gave 0.22 g (16%) of **20g**: bp 131–133 °C (0.1 mm); NMR (CCl_4) δ 0.38 (s, 9, $SiCH_3$), 3.35 (s, 3, NCH_3), 6.80–7.44 (m, 9, aromatic H); IR (neat) 2220 cm^{-1} (C≡C).

Anal. Calcd for $C_{18}H_{21}NSi$: C, 75.23; H, 8.29; N, 5.48. Found: C, 75.56; H, 8.18; N, 5.40.

***N,N*-Diethyl-*o*-trimethylsilylphenylacetamide (21).** A solution of **20a** (1.00 g, 4.1 mmol) in ether (10 mL) was vigorously stirred with 10 mL of 10% HCl at room temperature for 1 h. The ether layer was separated, dried, and distilled, giving 0.90 g (83%) of **21**: bp 103–105 °C (0.09 mm); NMR (CCl_4) δ 0.32 (s, 9, $SiCH_3$), 1.00–1.25 (m, 6, NCH_2CH_3), 3.04–3.48 (m, 4, NCH_2), 3.70 (s, 2, $COCH_2$), 6.98–7.50 (m, 4, aromatic H); IR (neat) 1645 cm^{-1} (NCO).

Anal. Calcd for $C_{15}H_{25}NOSi$: C, 68.39; H, 9.56; N, 5.32. Found: C, 68.67; H, 9.58; N, 5.43.

***N,N*-Diethyl-2-(*o*-trimethylsilylphenyl)ethylamine (22). A.** A mixture of **21** (0.30 g, 1.1 mmol) and $LiAlH_4$ (0.05 g, 1.3 mmol) in THF (20 mL) was heated at reflux for 8 h. After the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl, the THF layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was dried, concentrated, and distilled, giving 0.26 g (80%) of **22**: bp 117–122 °C (9 mm); NMR (CCl_4) δ 0.34 (s, 9, $SiCH_3$), 1.05 (t, 6, NCH_2CH_3), 2.60 (q, 4, NCH_2), 2.65–2.90 (m, 4, CH_2CH_2), 6.98–7.45 (m, 4, aromatic H); mass spectrum *m/e* 249 (M^+).

Anal. Calcd for $C_{15}H_{27}NSi$: C, 72.22; H, 10.91; N, 5.61. Found: C, 72.40; H, 11.02; N, 5.50.

B. To a solution of *N,N*-diethyl-2-(*o*-bromophenyl)ethylamine (**23**, 1.38 g, 5.4 mmol) in ether (20 mL) was added 15% *n*-butyllithium in *n*-hexane (4.5 mL, 7 mmol). After 3 h of stirring, trimethylchlorosilane (7.6 g, 7 mmol) was added to the reaction mixture and stirring was continued at room temperature for 2 h. Then the mixture was hydrolyzed with saturated aqueous NH_4Cl and extracted with ether. The ethereal extract was dried, concentrated, and distilled, giving 1.07 g (80%) of **22**.

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Registry No.—**1**(R_1, R_2 = Et), 816-43-3; **1**(R_1, R_2 = $-(CH_2)_4-$), 4439-90-1; **1**(R_1, R_2 = $-(CH_2)_2O(CH_2)_2-$), 37828-58-3; **1**(R_1 = Me, R_2 = Ph), 35954-01-9; **2**(R_3, R_4 = Me), 7652-06-4; **2**(R_3 = Me, R_4 = Et), 64024-71-1; **2**(R_3, R_4 = Ph), 18676-70-5; **4**(R_1, R_2 = Et), 686-10-2; **4**(R_1 = Me, R_2 = Ph), 708-88-3; **4**(R_1 = Et, R_2 = Ph), 38488-67-4; **4**(R_1, R_2 = Ph), 727-65-1; **6**, 762-42-5; **7**, 922-67-8; (*E*)-**10a**, 64024-72-2; (*Z*)-**10a**, 64024-73-3; (*E*)-**10g**, 64024-74-4; (*Z*)-**10g**, 64024-75-5; **13**, 64024-76-6; **14**, 64024-77-7; **20a**, 64024-78-8; **20g**, 64024-79-9; **21**, 64024-80-2; **22**, 64024-81-3; **23**, 64024-82-4; Me_3SiCl, 75-77-4; Ph_3SiCl, 76-86-8; *o*-fluorobromobenzene, 1072-85-1.

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Synthesis of Organosilanes and Polysiloxanes with Nitro and Fluoro Substituents[1]

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Nitrite ion displacement of (3-bromopropyl)trimethylsilane, (4-bromobutyl)trimethylsilane, and (3-bromobutyl)trimethylsilane gave the corresponding nitro compounds, which on oxidative nitration gave the *gem*-dinitro compounds. Fluorination of salts of (3,3-dinitropropyl)trimethylsilane and (4,4-dinitrobutyl)trimethylsilane with elemental fluorine or perchloryl fluoride gave (3-fluoro-3,3-dinitropropyl)trimethylsilane and (4-fluoro-4,4-dinitrobutyl)trimethylsilane. Trimethylsilylmethyl triflate and 2-fluoro-2,2-dinitroethanol gave trimethylsilylmethyl 2-fluoro-2,2-dinitroethyl ether. Nitrite displacement, oxidative nitration, and fluorination converted (3-bromopropyl)methyldiphenylsilane to (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane, and dephenylation with bromine gave (3-fluoro-3,3-dinitropropyl)methyldibromosilane, which was hydrolyzed to give polysiloxanes. The latter reacted with hydrofluoric acid to give (3-fluoro-3,3-dinitropropyl)methyldifluorosilane, which with sodium methoxide and aqueous acid gave the corresponding difluorodisiloxane. Bis(3-bromopropyl)diphenylsilane was converted to bis(3-fluoro-3,3-dinitropropyl)diphenylsilane. Stepwise dephenylation with bromine and hydrolysis gave the cyclic trisiloxane.

Although the chemistry of organosilicon compounds has been studied extensively,[2] few examples of this class of compounds with nitro substituents are known. The hydrosilylations of 3-nitropropene, 4,4,4-trinitrobutene, and 4,4-dinitrobutene with trichlorosilane and methyldichlorosilane have been reported,[3,4] and patent literature describes N_2O_3 addition to allylsilanes[5] and silver nitrite displacement of (3-iodopropyl)triethoxysilane.[6] The most commonly used methods of forming carbon–silicon bonds, the reaction of Grignard reagents and similar organometallics with silicon halides and the reaction of elemental silicon with alkyl halides at high temperatures, are not compatible with nitro substituents.

The present study involved the synthesis of *gem*-dinitro- and fluorodinitrosilanes and polysiloxanes by the stepwise introduction of nitro and fluorine moities. Polysiloxanes are usually obtained by the hydrolysis of silicon–halogen bonds, and these bonds are not stable to displacement, nitration, and fluorination reaction conditions. A hydrolytically stable silicon blocking group is therefore needed.

Convenient starting materials for the synthesis of simple nitrosilanes are (3-bromopropyl)trimethylsilane,[7] (4-bromobutyl)trimethylsilane,[8] and (3-bromobutyl)trimethylsilane.[8] Kornblum[9] has reported that the reaction of alkyl bromides with sodium nitrite in dimethyl sulfoxide gives nitroalkanes, with alkyl nitrites as byproducts. These trimethylsilyl compounds underwent this displacement reaction normally.

$$(CH_3)_3Si(CH_2)_nBr \xrightarrow[Me_2SO]{NaNO_2} (CH_3)_3Si(CH_2)_nNO_2 + (CH_3)_3Si(CH_2)_nONO \qquad n = 3, 4$$

$$(CH_3)_3SiCH_2CH_2CHBrCH_3 \rightarrow (CH_3)_3SiCH_2CH_2CH(NO_2)CH_3 + (CH_3)_3SiCH_2CH_2CH(ONO)CH_3$$

The oxidative nitration reaction[10] was applied to (3-nitropropyl)trimethylsilane, (4-nitrobutyl)trimethylsilane, and (3-nitrobutyl)trimethylsilane to prepare (3,3-dinitropropyl)-trimethylsilane, (4,4-dinitrobutyl)trimethylsilane, and (3,3-dinitrobutyl)trimethylsilane, respectively. Yields were 57–72%.

$$(CH_3)_3Si(CH_2)_nCH_2NO_2 \xrightarrow[NaNO_2,\ OH^-]{AgNO_3} (CH_3)_3Si(CH_2)_nCH(NO_2)_2 \qquad n = 2, 3$$

$$(CH_3)_3SiCH_2CH_2CH(NO_2)CH_3 \rightarrow (CH_3)_3SiCH_2CH_2C(NO_2)_2CH_3$$

The direct fluorination of terminal *gem*-dinitro compounds in aqueous alkaline solution was reported previously to give fluorodinitro compounds.[11] This reaction with (3,3-dinitropropyl)trimethylsilane, using the theoretical amount of base, gave (3-fluoro-3,3-dinitropropyl)trimethylsilane in 31% yield. In the fluorination of (4,4-dinitrobutyl)trimethylsilane, after fluorine uptake ceased, additional base and fluorine were added; a 61% yield of (4-fluoro-4,4-dinitrobutyl)trimethylsilane was obtained. A difficulty in these reactions was that dilute solutions were used because of low solubility of the nitronate salts in water, and acid was formed by competing fluorination of water. Another fluorination reagent that has been used with dinitro compounds, perchloryl fluoride,[12] allows the use of a broader range of solvents. This reagent was used to fluorinate the potassium salt of (3,3-dinitropropyl)-trimethylsilane in equal parts of water, methanol, and dimethylformamide. The fluorodinitro compound was obtained in 85% yield.

$$(CH_3)_3Si(CH_2)_nCH(NO_2)_2 \rightarrow (CH_3)_3Si(CH_2)_nCF(NO_2)_2 \qquad n = 2, 3$$

A fluorodinitroalkylsilane with an ether linkage was obtained by the alkylation of 2-fluoro-2,2-dinitroethanol. Alkyl triflates are sufficiently reactive to alkylate this alcohol in methylene chloride in the presence of a mild heterogeneous base such as potassium carbonate.[13] Under these conditions, trimethylsilylmethyl triflate and 2-fluoro-2,2-dinitroethanol gave trimethylsilylmethyl 2-fluoro-2,2-dinitroethyl ether. This triflate was prepared by the reaction of trifluoromethanesulfonic anhydride with (hydroxymethyl)trimethylsilane, obtained by the published procedure.[14]

$$(CH_3)_3SiCH_2OH + (CF_3SO_2)_2O \rightarrow (CH_3)_3SiCH_2OSO_2CF_3$$

$$(CH_3)_3SiCH_2OSO_2CF_3 + FC(NO_2)_2CH_2OH \xrightarrow[K_2CO_3]{CH_2Cl_2} (CH_3)_3SiCH_2OCH_2CF(NO_2)_2$$

Polysiloxanes are generally prepared by the hydrolysis of dialkyldihalosilanes, and if fluorodinitro-substituted polysiloxanes are to be synthesized by the above methods the silicon–halogen bonds must be generated after the nitro and fluorine groups are introduced. Silicon halides, as well as silicon acetates, silicon methoxides, and similar derivatives,

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would not survive the hydrolytic reaction conditions.[2] However, carbon–silicon bonds can be cleaved by bromine, and the cleavage of phenyl–silicon bonds in this way is particularly facile.[15] Therefore, the approach was taken to build up fluorodinitro groups starting with dialkyldiphenylsilanes containing reactive sites on the alkyl chains.

One such starting material is (3-bromopropyl)methyldiphenylsilane. This compound was obtained initially by the bromination of the hydroboration product of allylmethyldiphenylsilane, prepared, in turn, from allylmagnesium bromide and methyldiphenylchlorosilane.

$$CH_2{=}CHCH_2MgBr + (C_6H_5)_2SiCH_3Cl \rightarrow CH_2{=}CHCH_2Si(C_6H_5)_2CH_3$$

$$\xrightarrow[BF_3]{NaBH_4} \xrightarrow[NaOCH_3]{Br_2} CH_3(C_6H_5)_2SiCH_2CH_2CH_2Br$$

A more convenient route to this bromide was based on the hydrosilylation of allyl acetate with methyldiphenylsilane with chloroplatinic acid[16] as catalyst to give a 49% yield of (3-hydroxypropyl)methyldiphenylsilane after hydrolysis. A molar excess of allyl acetate was required. The use of allyloxytrimethylsilane instead of the acetate gave a 71% yield of the alcohol with only a 10% excess of olefin. The use of tris(triphenylphosphine)rhodium chloride[17] as the catalyst instead of chloroplatinic acid increased the yield to 98%. This alcohol was converted to the toluenesulfonate in 62% yield with toluenesulfonyl chloride and pyridine in methylene chloride. The toluenesulfonate was converted to the bromide with lithium or sodium bromide in dimethyl sulfoxide. The yield of this displacement was essentially quantitative on the basis of NMR analysis, and for preparative purposes it was not necessary to isolate the bromide; the subsequent step was carried out with the same solvent.

$$CH_3(C_6H_5)_2SiH + CH_2{=}CHCH_2OSi(CH_3)_3 \rightarrow CH_3(C_6H_5)_2SiCH_2CH_2CH_2OSi(CH_3)_3$$

$$\xrightarrow[H_2O]{H^+} CH_3(C_6H_5)_2SiCH_2CH_2CH_2OH$$

$$\xrightarrow[Pyr,\ CH_2Cl_2]{TsCl} CH_3(C_6H_5)_2SiCH_2CH_2CH_2OSO_2C_6H_4CH_3\text{-}p$$

$$\xrightarrow[Me_2SO]{NaBr} CH_3(C_6H_5)_2SiCH_2CH_2CH_2Br$$

The displacement of the bromide[18] with sodium nitrite in dimethyl sulfoxide gave the nitro compound, as well as the corresponding nitrite and alcohol. The nitro compound was separated from the other products by extracting the mixture with potassium hydroxide, and the isolated yield was 50%. Oxidative nitration of (3-nitropropyl)methyldiphenylsilane gave (3,3-dinitropropyl)methyldiphenylsilane in 70% yield, an undistillable oil characterized by NMR. Salts of this *gem*-dinitro compound had low solubility in water, and attempted fluorinations in this medium with elemental fluorine were unsuccessful. Fluorination with perchloryl fluoride in methanol, however, gave a 79% yield of (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane. Heating this fluorinated compound with bromine then gave (3-fluoro-3,3-dinitropropyl)methyldibromosilane in 78% yield. The dibromide was too labile hydrolytically for elemental analysis but was identified spectrally and by its hydrolysis product.

$$CH_3(C_6H_5)_2SiCH_2CH_2CH_2Br$$

$$\xrightarrow[Me_2SO]{NaNO_2} CH_3(C_6H_5)_2SiCH_2CH_2CH_2NO_2$$

$$\xrightarrow[NaNO_2,\ OH^-]{AgNO_3} CH_3(C_6H_5)_2SiCH_2CH_2CH(NO_2)_2$$

$$\xrightarrow[CH_3OH]{FClO_3} CH_3(C_6H_5)_2SiCH_2CH_2CF(NO_2)_2$$

$$\xrightarrow{Br_2} CH_3Br_2SiCH_2CH_2CF(NO_2)_2$$

The hydrolysis of this dibromide gave cyclic polysiloxanes, with the number of units depending on the hydrolysis conditions. Thus, treating the dibromide in ether solution with ice gave the tetramer on the basis of vapor osmometric molecular weight. The same molecular weight was obtained when a sample of the neat dibromide was hydrolyzed by atmospheric moisture. On the other hand, when a methylene chloride solution was hydrolyzed, a molecular weight corresponding to the trimer was obtained.

The polysiloxane reacted with hydrofluoric acid in aqueous ethanol to give an 80% yield of (3-fluoro-3,3-dinitropropyl)methyldifluorosilane. The dibromide also gave the difluoride, probably via an in situ hydrolysis. The difluoride reacted with sodium methoxide to give a compound assigned on the basis of NMR spectra to be (3-fluoro-3,3-dinitropropyl)methylmethoxyfluorosilane. A pure sample of this compound was not isolated. Advantage was taken of the relative stability of fluorine–silicon bonds toward acids.[19] Treating the crude methoxyfluoride with aqueous acid gave 1,3-bis(3-fluoro-3,3-dinitropropyl)-1,3-dimethyl-1,3-difluorodisiloxane, isolated readily by distillation.

$$\left[CH_3SiCH_2CH_2CF(NO_2)_2\right]_n \xrightarrow{HF} CH_3SiF_2CH_2CH_2CF(NO_2)_2$$

$$\xrightarrow{NaOCH_3} CH_3SiF(OCH_3)CH_2CH_2CF(NO_2)_2$$

$$\xrightarrow[H_2O]{H^+} FC(NO_2)_2CH_2CH_2Si(CH_3)F{-}O{-}Si(CH_3)FCH_2CH_2CF(NO_2)_2$$

The synthesis of bis(3-fluoro-3,3-dinitropropyl)polysiloxanes was also undertaken with the use of phenyl as a blocking group. The starting material for this work was prepared initially using a rearrangement of haloalkoxysilyl ethers to hydroxyalkylsilanes as reported by Speier.[20] Bis(3-chloropropoxy)diphenylsilane was prepared by the reaction of dichlorodiphenylsilane and 3-chloropropanol with ammonia in benzene. This product reacted with sodium and chlorotrimethylsilane in refluxing toluene to give bis(3-trimethylsilyloxypropyl)diphenylsilane. Hydrolysis with acid gave bis(3-hydroxypropyl)diphenylsilane.

$$(C_6H_5)_2SiCl_2 + ClCH_2CH_2CH_2OH$$

$$\xrightarrow[C_6H_6]{NH_3} (C_6H_5)_2Si(OCH_2CH_2CH_2Cl)_2$$

$$\xrightarrow[(CH_3)_3SiCl]{Na,\ Toluene} (C_6H_5)_2Si[CH_2CH_2CH_2OSi(CH_3)_3]_2$$

$$\xrightarrow[EtOH]{H^+} (C_6H_5)_2Si(CH_2CH_2CH_2OH)_2$$

Another route to a difunctional starting material involved hydroboration. Borane in tetrahydrofuran was added to diallyldiphenylsilane, and the resulting borane was brominated to give bis(3-bromopropyl)diphenylsilane in 24% overall yield.

$$(C_6H_5)_2Si(CH_2CH{=}CH_2)_2 \xrightarrow{BH_3} (C_6H_5)_2Si(CH_2CH_2CH_2B)_2$$

$$\xrightarrow{Br_2} (C_6H_5)_2Si(CH_2CH_2CH_2Br)_2$$

A reaction scheme analogous to that used to prepare the

(2-fluoro-2,2-dinitropropyl)methylsilane derivatives provided a more practical route to the preparation of bis(2-fluoro-2,2-dinitropropyl)silicon compounds. Thus, the hydrosilylation of allyloxytrimethylsilane with diphenylsilane catalyzed by tris(triphenylphosphine)rhodium chloride gave, after hydrolysis, a 68% yield of bis(3-hydroxypropyl)diphenylsilane. Lower yields resulted from the use of allyl acetate as the olefin or chloroplatinic acid as the catalyst. The alcohol was converted to the *p*-toluenesulfonate which, in turn, was treated with sodium bromide in dimethyl sulfoxide to give the dibromide in 84% overall yield. The dimethyl sulfoxide solution could be used in the nitrite reaction without workup. The dibromide was also prepared from the alcohol with phosphorus tribromide in 67% recrystallized yield.

$$(C_6H_5)_2SiH_2 + CH_2{=}CHCH_2OSi(CH_3)_3 \rightarrow (C_6H_5)_2Si[CH_2CH_2CH_2OSi(CH_3)_3]_2$$

$$\xrightarrow[H^+]{H_2O} (C_6H_5)_2Si(CH_2CH_2CH_2OH)_2$$

$$\xrightarrow[\text{1. TsCl, Pyr, } CH_2Cl_2\quad \text{2. NaBr, } Me_2SO]{PBr_3 \text{ or}} (C_6H_5)_2Si(CH_2CH_2CH_2Br)_2$$

The reaction of bis(3-bromopropyl)diphenylsilane in dimethyl sulfoxide with sodium nitrite gave bis(3-nitropropyl)diphenylsilane in 34% yield. Oxidative nitration of this compound gave bis(3,3-dinitropropyl)diphenylsilane in 38% yield. Fluorination of the potassium salt of this compound was carried out in a mixture of water, methanol, and dimethylformamide with perchloryl fluoride as the fluorinating agent. An 85% yield of bis(3-fluoro-3,3-dinitropropyl)diphenylsilane was obtained.

$$(C_6H_5)_2Si(CH_2CH_2CH_2Br)_2 \xrightarrow[Me_2SO]{NaNO_2} (C_6H_5)_2Si(CH_2CH_2CH_2NO_2)_2$$

$$\xrightarrow[NaNO_2,\ OH^-]{AgNO_3} (C_6H_5)_2Si[CH_2CH_2CH(NO_2)_2]_2$$

$$\xrightarrow{FClO_3} (C_6H_5)_2Si[CH_2CH_2CF(NO_2)_2]_2$$

This diphenylsilane could not be dephenylated completely with bromine under the conditions that were used with (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane; the reaction ceased when approximately half of the phenyl groups were cleaved. However, when water was added after this initial reaction was completed, bromine consumption resumed. A white solid, mp 207–209 °C, was isolated in 67% yield and was identified by molecular weight and analysis as the cyclic trisiloxane. Apparently, the second fluorodinitropropyl group inhibits the dephenylation to the extent that only one phenyl group is removed. The accelerating effect of water on the dephenylation is rationalized on the basis of the hydrolysis of the initially formed phenylbromosilane. The resulting silanol or its dimer is dephenylated more readily than the bromosilane.

$$(C_6H_5)_2Si[CH_2CH_2CF(NO_2)_2]_2 \xrightarrow{Br_2} C_6H_5SiBr[CH_2CH_2CF(NO_2)_2]_2$$

$$\xrightarrow[Br_2]{H_2O} C_6H_5Si(OH)[CH_2CH_2(NO_2)_2]_2$$

$$\rightarrow BrSi(OH)[CH_2CH_2CF(NO_2)_2]_2$$

$$\xrightarrow{-HBr} [FC(NO_2)_2CH_2CH_2]_2Si\underset{O}{\overset{[CH_2CH_2CF(NO_2)_2]_2}{\overset{|}{Si}}}O\underset{|}{\overset{|}{}}Si[CH_2CH_2CF(NO_2)_2]_2$$

Experimental Section

NMR and IR spectra were recorded with a Varian T-60 spectrometer and a Perkin-Elmer 700 spectrometer, respectively. Molecular weights were determined with a Mechrolab 301A vapor osmometer. A Varian 920 gas chromatograph with a 12 ft × 3/8 in aluminum column packed with 12% QF-1 on 60–80 mesh Chromosorb W was used for GLC separations. Previously described safety precautions for fluorodinitro compounds[11,12] were observed.

(3-Nitropropyl)trimethylsilane. A solution of 10 g (0.145 mol) of sodium nitrite and 11.3 g (0.055 mol) of (3-bromopropyl)trimethylsilane[8] in 120 mL of dimethyl sulfoxide was stirred for 3 h at ambient temperature. Water (500 mL) was added, and the product was extracted with three 50-mL portions of carbon tetrachloride. The NMR spectrum showed (3-nitropropyl)trimethylsilane (69% yield), (3-nitritopropyl)trimethylsilane (25%), and starting material and the alcohol (5% combined). Distillation gave 2.2 g (9.5%) of (3-nitritopropyl)trimethylsilane, bp 48–50 °C (16 mm), and 5.9 g (60%) of 95% pure (3-nitropropyl)trimethylsilane, bp 62–64 °C (1 mm). An analytical sample was isolated by GLC: NMR (CCl_4) δ 4.20 (t, J = 7 Hz, 2 H, CH_2NO_2), 1.87 (m, 2 H, CH_2CH_2Si), 0.50 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); IR (CCl_4) 2970, 1545, 1430, 1380, 1250 cm^{-1}. Anal. Calcd for $C_6H_{15}NO_2Si$: C, 44.69; H, 9.38; N, 8.68. Found: C, 44.74; H, 9.38; N, 8.67.

The nitrosation[21] of (3-hydroxypropyl)trimethylsilane provided an independent synthesis of (3-nitrotopropyl)trimethylsilane: NMR (CCl_4) δ 4.50 (t, 2 H, CH_2ONO), 1.7 (m, 2 H, CH_2CH_2Si), 0.5 (m, 2 H, CH_2Si), 0.0 (s, 9 H $(CH_3)_3Si$); IR (film) 1645, 1605, 1260, 850, 800 cm^{-1}.

(4-Nitrobutyl)trimethylsilane. A solution of 1.9 g (0.028 mol) of sodium nitrite and 2.92 g (0.014 mol) of (4-bromobutyl)trimethylsilane[8] in 30 mL of dimethyl sulfoxide was stirred for 3 h at ambient temperature. Water (30 mL) was added, and the product was extracted with three 15-mL portions of carbon tetrachloride. The carbon tetrachloride solution was washed with 10 mL of water and was dried over magnesium sulfate. Distillation gave 1.1 g (45%) of (4-nitrobutyl)trimethylsilane, bp 54–56 °C (0.9 mm). An anlytical sample was isolated by GLC: NMR (CCl_4) δ 4.27 (t, J = 7 Hz, 2 H, CH_2NO_2), 2.02 (q, J = 7 Hz, 2 H, $CH_2CH_2NO_2$), 1.4 (m, 2 H, CH_2CH_2Si), 0.50 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); IR (CCl_4) 2960, 1545, 1435, 1385, 1255 cm^{-1}. Anal. Calcd for $C_7H_{17}NO_2Si$: C, 47.96; H, 9.77; N, 7.99. Found: C, 47.95; H, 9.70; N, 8.11.

(3-Nitrobutyl)trimethylsilane. A solution of 4.3 g (0.020 mol) of (3-bromobutyl)trimethylsilane and 4.1 g (0.06 mol) of sodium nitrite in 50 mL of dimethyl sulfoxide was stirred at ambient temperature for 3 h. The solution was diluted with 200 mL of water, and the product was extracted with three 25-mL portions of carbon tetrachloride. The NMR spectrum of the solution indicated a 55% yield of (3-nitrobutyl)trimethylsilane, a 25% yield of (3-nitritobutyl)trimethylsilane, and 12% unreacted bromide. Distillation gave 1.0 g of a mixture of nitrite and bromide, bp 56–62 °C (10 mm), and 2.0 g of 80% pure (3-nitrobutyl)trimethylsilane (45% yield), bp 58–60 °C (1 mm). Redistillation gave 95% pure product (NMR), and an analytical sample was isolated by GLC: NMR (CCl_4) δ 4.30 (sextet, 1 H, $CHNO_2$), 1.75 (m, 2 H, CH_2CH_2Si), 1.42 (d, 3 H, CH_3CHNO_2), 0.4 (t, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); IR (film) 2970, 1545, 1260, 865, 845 cm^{-1}. Anal. Calcd for $C_7H_{17}NO_2Si$: C, 47.96; H, 9.77; N, 7.99. Found: C, 48.09; H, 9.66; N, 7.68.

The nitrite was identified by hydrolysis with acetic acid in methanol to give the alcohol, which was isolated by preparative GLC: NMR (CCl_4) δ 3.48 (sextet, 1 H, CHOH), 2.9 (broad s, 1 H, OH), 1.3 (m, 2H, CH_2Si), 1.05 (d, 3 H, CH_3CHOH), 0.40 (m, 2 H, CH_2Si), 0.0 (s, 9 H $(CH_3)_3Si$); IR 3350 (OH), 2950, 1250, 860, 850, 840 cm^{-1}.

The alcohol was reconverted by a standard procedure[21] to the nitrite with identical spectra: NMR (CCl_4) δ 5.30 (sextet, 1 H, CHONO), 1.7 (m, 2 H, CH_2CH_2Si), 1.40 (d, J = 7 Hz, 3 H, CH_3CH), 0.55 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); IR (film) 2970, 1640, 1600, 1260, 880, 850, 800 cm^{-1}. The 1640-, 1600-, and 800-cm^{-1} peaks are assigned[22] to ONO.

(3,3-Dinitropropyl)trimethylsilane. A solution of 5.6 g (0.035 mol) of (3-nitropropyl)trimethylsilane, 2.58 g (0.039 mol) of potassium hydroxide, and 2.7 g (0.039 mol) of sodium nitrite in 25 mL of water and 25 mL of methanol was added quickly to a well-stirred mixture of 13.3 g (0.078 mol) of silver nitrate in 25 mL of water and 50 mL of ether. The mixture was stirred for 2 h at room temperature, and 25 mL of saturated sodium chloride was added. The silver deposits were filtered off, and the ether layer was separated, dried, and distilled to give 5.7 g (71%) of 90% pure (3,3-dinitropropyl)trimethylsilane, bp 70–72 °C (0.2 mm). An analytical sample was obtained by GLC: NMR (CCl_4) δ 5.88 (t, J = 7 Hz, 1 H, $CH(NO_2)_2$), 2.38 (m, 2 H, CH_2CH_2Si),

0.55 (m, 2 H, CH_2Si), 0.08 (s, 9 H, $(CH_3)_3Si$); IR (CCl_4) 2970, 1570, 1335, and 1260 cm^{-1}. Anal. Calcd for $C_6H_{14}N_2O_4Si$: C, 34.94; H, 6.84; N, 13.58. Found: C, 35.28; H, 6.90; N, 13.47.

(4,4-Dinitrobutyl)trimethylsilane. A mixture of 0.6 g (0.015 mol) of sodium hydroxide, 2.62 g (0.015 mol) of (4-nitrobutyl)trimethylsilane, and 6 mL of water was stirred at 80 °C until a solution was formed. The solution was cooled to room temperature, and 1.1 g (0.015 mol) of sodium nitrite was added. The resulting solution was added quickly to a well-stirred, ice-cooled mixture of 5.1 g (0.030 mol) of silver nitrate, 12 mL of water, 12 mL of ether, and 2 drops of 1 N sodium hydroxide. The mixture was stirred at room temperature for 2 h and filtered, and the precipitate was washed with ether. The ether layer of the filtrate, combined with the washings, was dried over magnesium sulfate and distilled to give 1.9 g (57%) of (4,4-dinitrobutyl)trimethylsilane, a colorless oil, bp 71–74 °C (2 mm). An analytical sample was isolated by GLC: NMR (CCl_4) δ 5.97 (t, J = 7 Hz, 1 H, $CH(NO_2)_2$), 2.43 (q, 2 H, CH_2CH), 1.47 (m, 2 H, CH_2CHSi), 0.57 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); IR (CCl_4) 2970, 1570, 1330, 1250 cm^{-1}. Anal. Calcd for $C_7H_{16}N_2SiO_4$: C, 38.17; H, 7.32; N, 12.72. Found: C, 38.38; H, 7.32; N, 12.66.

(3,3-Dinitrobutyl)trimethylsilane. A mixture of 5.95 g (0.34 mol) of (3-nitrobutyl)trimethylsilane, 3 g of potassium hydroxide, 30 mL of water, and 30 mL of methanol was heated with stirring at 65 °C until a homogeneous solution was formed. Sodium nitrite (3.0 g, 0.043 mol) was added, and the solution, at room temperature, was added rapidly with stirring to a mixture of 100 mL of ether and 15 g (0.088 mol) of silver nitrate in 50 mL of water. The mixture was stirred 1.5 h, and 50 mL of saturated aqueous sodium chloride was added. The silver deposits were filtered off, and the ether layer was separated, dried, and distilled to give 5.38 g (72%) of (3,3-dinitrobutyl)trimethylsilane: bp 77–79 °C (0.1 mm); NMR (CCl_4) δ 2.34 (m, 2 H, $(NO_2)_2CCH_2$), 2.02 (s, 3 H, $(NO_2)_2CCH_3$), 0.40 (m, 2 H, CH_2Si), 0.05 (s, 9 H, $(CH_3)_3Si$); IR (CCl_4) 2970, 1565, 1330, 1260, 1195 cm^{-1}. Anal. Calcd for $C_7H_{16}N_2O_4Si$: C, 38.16; H, 7.32; N, 12.72. Found: C, 37.98; H, 7.19; N, 11.71.

(3-Fluoro-3,3-dinitropropyl)trimethylsilane. A solution of 1.6 g (0.0078 mol) of (3,3-dinitropropyl)trimethylsilane and 0.44 g (0.0078 mol) of potassium hydroxide in 250 mL of water was fluorinated[11] at 0 °C until the solution became colorless. The product was extracted with three 20-mL portions of ether, dried, and distilled to give 0.9 g (31% yield) of 60% pure (3-fluoro-3,3-dinitropropyl)trimethylsilane, by 66–71 °C (0.5 mm). An analytical sample was obtained by GLC: proton NMR (CCl_4) δ 2.57 (m, 2 H, CH_2CF), 0.50 (m, 2 H, CH_2Si), 0.08 (s, 9 H, $(CH_3)_3Si$); fluorine NMR ϕ 106.0 (broad t); IR (CCl_4) 2970, 1590, 1320, 1260, 1190 cm^{-1}. Anal. Calcd for $C_6H_{13}N_2O_4SiF$: C, 32.13; H, 5.84; N, 12.49. Found: C, 32.34; H, 5.62; N, 12.43.

A solution of 5.13 g (0.025 mol) of (3,3-dinitropropyl)trimethylsilane and 2.0 g (0.03 mol) of potassium hydroxide in a mixture of 30 mL of water, 30 mL of methanol, and 30 mL of dimethylformamide was fluorinated with perchloryl fluoride[12] at ambient temperature until the gas was no longer absorbed by the solution. The solution was diluted with water, and the product was extracted with carbon tetrachloride and distilled to give 4.8 g (85%) of (3-fluoro-3,3-dinitropropyl)trimethylsilane, bp 68–71 °C (0.5 mm).

(4-Fluoro-4,4-dinitrobutyl)trimethylsilane. A solution of 1.45 g (0.0066 mol) of (4,4-dinitrobutyl)trimethylsilane and 0.5 g (0.0076 mol) of potassium hydroxide in 250 mL of water was fluorinated at 0 °C until the solution became colorless. An additional 0.4 g (0.006 mol) of potassium hydroxide was added, and fluorination was continued until the solution again became colorless. The product was extracted with three 20-mL portions of ether, dried over magnesium sulfate, and distilled to give 1.05 g (61%) of 90% pure (4-fluoro-4,4-dinitrobutyl)trimethylsilane. An analytical sample was obtained by GLC: proton NMR (CCl_4) δ 2.67 (d of 5, J_{HF} = 19, J_{HH} = 7 Hz, 2 H, CH_2CF), 1.44 (m, 2 H, CH_2CH_2Si), 0.53 (m, 2 H, CH_2Si), 0.0 (s, 9 H, $(CH_3)_3Si$); fluorine NMR (CCl_4) ϕ 102.8 (broad t, $(NO_2)_2CF$); IR (CCl_4) 2970, 1590, 1350, 1255 cm^{-1}. Anal. Calcd for $C_7H_{15}N_2O_4SiF$: C, 35.28; H, 6.34; N, 11.76. Found: C, 35.24; H, 6.30; N, 11.64.

Trimethylsilylmethyl Trifluoromethanesulfonate. A solution of 4.5 g (0.0435 mol) of (hydroxymethyl)trimethylsilane[14] and 3.43 g (0.0435 mol) of pyridine in 30 mL of methylene chloride was added with stirring over a 45-min period to a solution of 12.2 g (0.043 mol) of trifluoromethanesulfonic anhydride in 30 mL of methylene chloride. After 15 min the solution was poured over ice. The methylene chloride solution was dried over sodium sulfate and distilled to give 7.0 g (68%) of trimethylsilylmethyl triflate, bp 49–51 °C (9 mm). An analytical sample was isolated by GLC: proton NMR (CCl_4) δ 4.07 (s, 2 H, CH_2Si), 0.08 (s, 9 H, $(CH_3)_3Si$); fluorine NMR ϕ 74.3 (s); IR (film) 1410, 1210, 1150, 960, 870 cm^{-1}. Anal. Calcd for $C_5H_{11}O_3F_3SiS$: C, 25.40; H, 4.69. Found: C, 25.23; H, 4.66.

Trimethylsilylmethyl 2-Fluoro-2,2-dinitroethyl Ether. Potassium carbonate (6 g) was added to a solution of 3.5 g (0.0148 mol) of trimethylsilylmethyl trifluoromethane sulfonate and 2.3 g of 2-fluoro-2,2-dinitroethanol in 5 mL of methylene chloride, and the mixture was stirred for 16 h. This suspension was added with stirring to a mixture of 30 mL of ice water and 30 mL of carbon tetrachloride. The carbon tetrachloride layer was washed with 10 mL of water, dried over magnesium sulfate, and distilled to give 1.56 g (45%) of trimethylsilylmethyl 2-fluoro-2,2-dinitroethyl ether, bp 52 °C (0.75 mm). An analytical sample was prepared by GLC: proton NMR (CCl_4) δ 4.35 (d, 2 H, J = 18 Hz, CH_2CF), 3.23 (s, 2 H, CH_2Si), 0.02 (s, 9 H, $(CH_3)_3Si$); fluoride NMR (CCl_4) ϕ 110.25 (broad t); IR (film) 2975, 2925, 1600, 1320, 1250, 1125, 870, 860 cm^{-1}. Anal. Calcd for $C_6H_{13}N_2O_5SiF$: C, 29.99; H, 5.45; N, 11.66. Found: C, 30.22; H, 5.33; N, 11.75.

Allylmethyldiphenylsilane. A solution of 1452 g (12 mol) of allyl bromide in 2.5 L of absolute ether was added dropwise with stirring, over a period of 3.5 h, to a suspension of 389 g (16 mol) of magnesium turnings in 2.5 L of absolute ether. An efficient reflux condenser was used, equipped with a drying tube. Excess magnesium was removed by filtration, and 1862 g (8 mol) of chloromethyldiphenylsilane was added dropwise over a 1 h period. The solution was refluxed for 1 h and was allowed to stand overnight at room temperature. A solution of 642 g (12 mol) of ammonium chloride in 2 L of water and then 3 L of water were added slowly, using a reflux condenser to control the exotherm. The aqueous layer was separated and extracted with three 1-L portions of ether. The combined ether solutions were dried over magnesium sulfate and distilled to give 1397 g (73%) of allylmethyldiphenylsilane: bp 93 °C (0.1 mm); NMR (neat) δ 0.0 (s, 3 H, CH_3Si), 1.5 (d, J = 7 Hz, 2 H, $C{=}C{-}CH_2Si$), 4.3 (m, 2 H, $CH_2{=}C$), 5.3 (m, 1 H, $C{=}CHCH_2Si$), 6.6–6.9 (m, 10 H, C_6H_5); IR (film) 1640, 1440, 1270, 1170, 1130 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_2Si$: C, 80.67; H, 7.56. Found: C, 80.45; H, 7.56.

(3-Bromopropyl)methyldiphenylsilane from Allylmethyldiphenylsilane. A solution (150 mL) of 29.6 g (208.3 mol) of boron trifluoride etherate in dry tetrahydrofuran was added over a 1 h period, with stirring, to 350 mL of a tetrahydrofuran solution of 119 g (0.50 mol) of allylmethyldiphenylsilane and 5.94 g (0.156 mol) of sodium borohydride. The mixture was heated at reflux for 2.5 h, and then 10 mL of methanol was added. Then, 27.3 mL (0.50 mol) of bromine and sodium methoxide solution (from 14.4 g, 0.625 mol of sodium and 300 mL of methanol) were added simultaneously at such a rate as to maintain a yellow color in the mixture. The temperature was kept at 25–30 °C by means of an ice bath. The mixture was agitated with 250 mL of 50% potassium carbonate and 250 mL of cyclohexane until the strong yellow color faded. The layers were separated, and the aqueous layer was extracted with three 100 mL portions of cyclohexane. The combined organic layers were washed with three 300-mL portions of water and 150 mL of saturated sodium chloride, dried over potassium carbonate, and distilled to give 79 g (49.5%) of (3-bromopropyl)methyldiphenylsilane: bp 176–210 °C (0.3 mm); NMR ($CDCl_3$) δ 0.5 (s, 3 H, CH_3Si), 1.1 (m, 2 H, CH_2Si), 1.8 (m, 2 H, CH_2CH_2Si), 3.2 (t, J = 7 Hz, 2 H, $BrCH_2$), 7.2 (m, 10 H, C_6H_5). Anal. Calcd for $C_{16}H_{19}BrSi$: C, 60.19; H, 5.96. Found: C, 60.36; H, 6.01.

(3-Hydroxypropyl)methyldiphenylsilane. Allyloxytrimethylsilane[23] (1162 g, 8.94 mol) was added dropwise to a mixture of 1539 g (7.77 mol) of methyldiphenylsilane and 80 mg of tris(triphenylphosphine)rhodium chloride at 130 °C over a 3 h period. The solution was added dropwise with stirring, over a 1.5 h period, to a solution of 3 L of methanol and 800 mL of 1 N hydrochloric acid. The mixture was stirred overnight, and an equal volume of water was added. The aqueous solution was extracted with 3 L of methylene chloride. The combined methylene chloride solution was washed with water and saturated salt solution and was dried with sodium sulfate. The solvent was removed by distillation to give 1950 g (98%) of (3-hydroxypropyl)methyldiphenylsilane: bp 130–140 °C (0.03 to 0.07 mm); NMR ($CDCl_3$) δ 0.48 (s, 3 H, CH_3), 0.95 (m, 2 H, CH_2Si), 1.4 (m, 2 H, CCH_2C), 2.0 (s, 1 H, OH), 3.12 (t, J = 6 Hz, 2 H, CH_2O), 7.0 (s, 10 H, C_6H_5). Anal. Calcd for $C_{16}H_{20}SiO$: C, 74.95; H, 7.86. Found: C, 74.80; H, 8.07.

(3-*p*-Toluenesulfonatopropyl)methyldiphenylsilane. Toluenesulfonyl chloride (1597 g, 8.38 mol) and then 766 mL (9.53 mol) of pyridine were added to a solution of 1950 g (7.62 mol) of crude (3-hydroxypropyl)methyldiphenylsilane in 1950 mL of methylene chloride at 4 °C. The mixture was stirred overnight and was poured into water. The methylene chloride layer was separated, and the aqueous layer was extracted once with methylene chloride. The combined methylene chloride solution was washed with water, with 1 N hydrochloric acid, and with saturated salt solution and was then dried with sodium sulfate. Most of the solvent was removed by dis-

tillation. The product was crystallized from 1200 mL of ethyl ether and 1200 mL of Skelly F to give 1925 g (62%) of (3-*p*-toluenesulfonatopropyl)methyldiphenylsilane: mp 68–69 °C; NMR ($CDCl_3$) δ 7.3 (d of d, 4 H, CC_6H_4Si-*p*), 7.2 (broad s, 10 H, C_6H_5), 3.85 (t, J = 6.5, 2 H, CH_2O), 2.40 (s, 3 H, $CH_3C_6H_5$), 1.6 (m, 2 H, CH_2CH_2Si), 1.0 (m, 2 H, CH_2Si), 0.50 (s, 3 H, CH_3Si). Anal. Calcd for $C_{23}H_{26}O_3SiS$: C, 67.28; H, 6.38. Found: C, 67.44; H, 6.48.

(3-Bromopropyl)methyldiphenylsilane from Toluenesulfonate. A solution of 3.5 g (0.04 mol) of lithium bromide and 5.98 g (0.0146 mol) of (3-propyl)methyldiphenylsilane *p*-toluenesulfonate in 25 mL of dimethyl sulfoxide was stirred at ambient temperature for 3 h. Water (10 mL) was added, and the product was extracted with three 10-mL portions of carbon tetrachloride. The combined organic layers were washed with 10 mL of water, dried, and stripped of solvent. The residue consisted of 4.2 g (90%) of 90% pure (3-bromopropyl)-methyldiphenylsilane.

(3-Nitropropyl)methyldiphenylsilane. The addition of 99.6 g (1.26 mol) of sodium nitrite to a solution of 101 g (0.317 mol) of (3-bromopropyl)methyldiphenylsilane in 500 mL of dimethyl sulfoxide resulted in a temperature rise to 30 °C over a 40 min period. The mixture was added to 2.5 L of water, and the product was extracted with four 300-mL portions of carbon tetrachloride. The carbon tetrachloride solution was washed with three 600-mL portions of water and 300 mL of saturated sodium chloride, and the solvent was removed. The NMR spectrum of the residue showed a 52% yield of the nitro compound (δ 4.2), a 20% yield of the nitrite (δ 4.4), and a 15% yield of the alcohol and/or bromide (δ 3.3).

The mixture was stirred for 1 h with 80 mL of 5 N potassium hydroxide, and 320 mL of water was added. The mixture was extracted with two 100-mL portions of ether. The aqueous solution was acidified to pH 6 with acetic acid, and the product was extracted with four 100-mL portions of methylene chloride. The methylene chloride solution was dried over magnesium sulfate and evaporated to give 45.4 g (50%) of (3-nitropropyl)methyldiphenylsilane. An analytical sample was obtained by molecular distillation: bp 152 °C (0.22 mm); NMR ($CDCl_3$) δ 0.3 (s, 2 H, CH_3Si), 1.2 (m, 2 H, CH_2Si), 2.1 (m, 2 H, CH_2CH_2Si), 4.2 (t, J = 7 Hz, 2 H, CH_2NO_2), 7.3 (m, 10 H, C_6H_5); IR (film) 1550, 1435, 1395, 1260, 1190, 1165, 1125 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2Si$: C, 67.37; H, 6.67; N, 4.91. Found: C, 67.57; H, 6.62; N, 4.64.

(3,3-Dinitropropyl)methyldiphenylsilane. A mixture of 68.4 g (0.24 mol) of (3-nitropropyl)methyldiphenylsilane and 53 mL of 5 N potassium hydroxide was stirred for 1 h. The resulting solution was diluted with 212 mL of water, and 22.9 g (0.29 mol) of sodium nitrite in 200 mL of water was added. The solution was cooled with an ice bath, and a cold solution of 90 g (0.53 mol) of silver nitrate in 400 mL of water and 800 mL of cold ether were added rapidly with efficient stirring. The mixture was stirred for 30 min at 0 °C and for 90 min at room temperature. Saturated sodium chloride solution (100 mL) was then added, and after 15 min the mixture was filtered and the precipitate was washed with water and ether. The combined filtrate and washings were acidified to pH 6 with acetic acid, and the layers were separated. The aqueous layer was extracted with ether, and the combined ether solutions were washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The ether was removed, and NMR analysis of the residue, 64 g, showed a 70% yield of (3,3-dinitropropyl)methyldiphenylsilane and 8% starting material: NMR ($CDCl_3$) δ 0.7 (s, 3 H, CH_3Si), 1.3 (m, 2 H, CH_2Si), 2.6 (m, 2 H, CH_2CH_2Si), 6.0 (t, J = 7 Hz, 1 H, CH), 7.4 (m, 10 H, C_6H_5).

(3-Fluoro-3,3-dinitropropyl)methyldiphenylsilane. The above crude product containing 53.5 g (0.162 mol) of (3,3-dinitropropyl)-methyldiphenylsilane was dissolved in a solution of 0.217 mol of potassium hydroxide in 900 mL of methanol. The solution was placed in a 2-L flask equipped with a glass dip tube for introducing perchloryl fluoride, a thermometer, a magnetic stirrer, and an ice bath. The flask was vented to the fume-hood atmosphere by means of a mineral oil bubbler, and another bubbler as well as an inverted vacuum trap (to prevent suck back) were placed between the dip tube and a perchloryl fluoride cylinder. Perchloryl fluoride was passed into the solution at 10 °C until it was no longer absorbed (2 h). Then, 1000 mL of water was added, and the solution was stirred 1 h at room temperature. An additional 1500 mL of water was added, and the mixture was made basic (pH 12) with potassium hydroxide. The product was extracted with four 400-mL portions of methylene chloride. The methylene chloride solution was washed with three 1000-mL portions of water, dried, and stripped of solvent. The residue, 58.5 g, was chromatographed on a 750 g column of dry silica gel, using carbon tetrachloride (30 L) for elution, to give 44.5 g (79%) of (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane: proton NMR ($CDCl_3$) δ 0.6 (s, 3 H, CH_3Si), 1.1 (m, 2 H, CH_2Si), 2.7 (m, 2 H, NO_2CCH_2), 7.2 (m, 10 H, C_6H_5); fluorine NMR ($CDCl_3$) φ 104.4 (t, J = 22 Hz); IR (film) 1590, 1440, 1370, 1330, 1270, 1200, 1120 cm^{-1}. Anal. Calcd for $C_{16}H_{17}N_2O_4FSi$: C, 55.17; H, 4.88; N, 8.04. Found: C, 55.02; H, 5.12; N, 8.09.

(3-Fluoro-3,3-dinitropropyl)methyldibromosilane. A mixture of 12.5 mL (0.230 mol) of bromine and 20.0 g (0.0574 mol) of (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane was heated at 100 °C for 2 h under nitrogen. The product was evacuated at 25 mm at room temperature for 90 min. Distillation gave phenyl bromide, bp 60 °C (0.15 mm), a 0.5-g intermediate fraction, and 15.8 g (78%) of (3-fluoro-3,3-dinitropropyl)methyldibromosilane, a colorless liquid: bp 68 °C (0.14 mm); proton NMR ($CDCl_3$) δ 1.1 (s, 3 H, CH_3Si), 1.4 (m, 2 H, CH_2Si), 2.9 (m, 2 H, CH_2Si); fluorine NMR ($CDCl_3$) φ 103.5 (t, J = 17 Hz). The material was too hygroscopic for commercial microanalysis.

(3-Fluoro-3,3-dinitropropyl)methylpolysiloxane. A solution of 14.2 g (0.0401 mol) of (3-fluoro-3,3-dinitropropyl)methyldibromosilane in 50 mL of ether was poured onto 75 g of crushed ice, and the mixture was stirred for 30 min. The ether layer was washed with two 50-mL portions of water and 50 mL of saturated sodium chloride solution. The solution was dried over magnesium sulfate, and the solvent was removed. The residue was dried for 3 h at 90 °C (0.07 mm) to give 7.7 g (91.4%) of an oily product: proton NMR ($CDCl_3$) δ 0.2 (s, 3 H, CH_3Si), 0.7 (m, 2 H, CH_2Si), 2.7 (m, 2 H, CH_2CH_2Si); fluorine NMR ($CDCl_3$) φ 104.1 (t, J = 17 Hz); IR (film) 3600, 3450, 2900, 2650, 1600, 1440, 1380, 1330, 1280, 1210, 1190, 1080 cm^{-1}. Anal. Calcd for $C_4H_7N_2FO_5Si$: C, 22.86; H, 3.33; N, 13.33. Found: C, 22.98; H, 3.55; N, 13.41; mol wt, 834.

The use of methylene chloride as the hydrolysis solvent gave a similar product with mol wt 562.

(3-Fluoro-3,3-dinitropropyl)methyldifluorosilane. (3-Fluoro-3,3-dinitropropyl)methylpolysiloxane (13.5 g, 64.3 mmol of monomer) was dissolved in 50 mL of ethanol, 25 mL of 48% hydrogen fluoride, and 15 mL of water. The mixture was agitated for 24 h and then diluted with water. The product was extracted with methylene chloride, and the methylene chloride solution was washed with water and saturated salt solution and dried over sodium sulfate. The solvent was evaporated, and the residue was distilled to give 12 g (80%) of (3-fluoro-3,3-dinitropropyl)methyldifluorosilane: bp 67 °C (3 mm); NMR ($CDCl_3$) δ 0.4 (t, J = 6 Hz, 3 H, CH_3Si), 0.9 (m, 2 H, CH_2Si), 2.9 (m, 2 H, $CH_2CF(NO_2)_2$); fluorine NMR ($CDCl_3$) φ 104.5 (t, J = 16 Hz, 1 F, $F(NO_2)_2C$), 132.3 (sextet, J = 6 Hz, 2 F, SiF_2); IR (film) 1600, 1435, 1370, 1325, 1275, 1220, 1190, 1065, 1025, 930, 910, 870, 860, 830, 805 cm^{-1}. Anal. Calcd for $C_4H_7F_3N_2O_4Si$: C, 20.69; H, 3.02; H, 12.07. Found: C, 20.67; H, 2.88; N, 12.52.

A mixture of 33 g (0.0932 mol) of (3-fluoro-3,3-dinitropropyl)-methyldibromosilane and 15.7 g (0.373 mol) of sodium fluoride was dissolved in 100 mL of ethanol, 25 mL of 48% hydrogen fluoride, and 15 mL of water with agitation. After 3 days, the mixture was poured into water and extracted twice with methylene chloride. The organic solution was washed with water and saturated salt solution and dried over sodium sulfate. The solvent was evaporated, and the residue was distilled to give 17.8 g (82%) of (3-fluoro-3,3-dinitropropyl)methyldifluorosilane.

Reaction of (3-fluoro-3,3-dinitropropyl)methyldifluorosilane with Sodium Methoxide. A solution of 5.4 g (0.1 mol) of sodium methoxide in 30 mL of dry methanol was added dropwise to 23.2 g (0.1 mol) of (3-fluoro-3,3-dinitropropyl)methyldifluorosilane with ice bath cooling. After 0.5 h, the methanol was evaporated and the residue was distilled at 79–85 °C (3 mm) to give a mixture of starting material (20%), dimer (18%), and product (62%). The yield of (3-fluoro-3,3-dinitropropyl)methylmethoxyfluorosilane was 13.9 g (57%) by quantitative NMR: NMR ($CDCl_3$) δ 0.3 (d, J = 6 Hz, 3 H, CH_3Si), 0.8 (m, 2 H, CH_2Si), 2.8 (m, 2 H, $CH_2C(NO_2)_2F$), 3.5 (s, 3 H, CH_3OSi); fluorine NMR ($CDCl_3$) φ 104.7 (T= J = 16 Hz, 1 F, $CF(NO_2)_2F$), 138.1 (sextet, J = 6 Hz, 1 F, FSi); IR (film) 1600, 1440, 1375, 1330, 1275, 1215, 1195, 1100, 1065, 1030, 915, 880, 855, 835, 810 cm^{-1}.

1,3-Bis(3-fluoro-3,3-dinitropropyl)-1,3-dimethyl-1,3-difluorodisiloxane. A solution containing 1.25 g (5.12 mmol) of (3-fluoro-3,3-dinitropropyl)methylmethoxyfluorosilane in 25 mL of methanol, 5 mL of water, and 1 mL of concentrated sulfuric acid was stirred for 20 h. The solution was poured into water, and the product was extracted with methylene chloride, washed with water and saturated salt solution, and dried over sodium sulfate. The solvent was evaporated, and the residue was distilled to give 0.7 g (62%) of 1,3-bis(3-fluoro-3,3-dinitropropyl)-1,3-dimethyl-1,3-difluorodisiloxane: bp 158 °C (0.2 mm); NMR (neat) δ 0.3 (d, J = 6 Hz, 6 H, CH_3Si), 0.9 (m, 4 H, CH_2Si), 2.9 (m, 4 H, CH_2CF); fluorine NMR (neat) φ 105.5 (t, J = 20 Hz, 2 F, $FC(NO_2)$), 132.0 (sextet, J = 6 Hz, 2 F, FSi); IR (film) 1590, 1435, 1365, 1320, 1235, 1100, 1025, 970, 910, 875, 855, 820, 800, 780

cm^{-1}. Anal. Calcd for $C_8H_{14}F_4N_4O_9Si_2$: C, 21.72; H, 3.17; N, 12.67. Found: C, 21.88; H, 3.05; N, 13.50.

Bis(3-chloropropoxy)diphenylsilane. Anhydrous ammonia was passed through a stirred solution of 81.6 g of 93% pure dichlorodiphenylsilane (0.30 mol) and 56.7 g (0.60 mol) of 3-chloropropanol in 600 mL of dry benzene at 5 °C until it was no longer absorbed. The solution was filtered and distilled to give 93.5 g (84.5%) of bis(3-chloropropoxy)diphenylsilane: bp 176–179 °C (0.21 mm); NMR ($CDCl_3$) δ 1.95 (quintet, J = 6 Hz, 4 H, $CH_2CH_2CH_2$), 3.55 (t, J = 6 Hz, 4 H, CH_2OSi), 3.8 (t, J = 6 Hz, 4 H, $ClCH_2$), 7–7.7 (m, 10 H, C_6H_5). Anal. Calcd for $C_{18}H_{22}O_2Cl_2Si$: C, 58.54; H, 5.96. Found: C, 58.19; H, 5.90.

Bis(3-hydroxypropyl)diphenylsilane from Bis(3-chloropropoxy)diphenylsilane. A round-bottom flask containing 175 mL of dry toluene and 22.2 g (0.964 mol) of sodium was fitted with a stirrer, a thermometer, a reflux condenser, and a dropping funnel containing 103 g (0.963 mol) of chlorotrimethylsilane. The toluene was refluxed, and sufficient chlorotrimethylsilane was added to lower the boiling point to 101 °C. Bis(3-chloropropoxy)diphenylsilane (80.6 g, 0.2185 mol) was mixed with the remaining chlorotrimethylsilane, and the mixture was added dropwise into the flask with vigorous stirring over a 30 min period. The solution was filtered and, the solvent was removed under reduced pressure. The residue was dissolved in 150 mL of absolute ethanol, and 30 mL of 5% hydrochloric acid was added slowly with cooling. The mixture was stirred for 1 h, and the ethanol and water were then removed under vacuum. The product was washed with 100 mL of saturated potassium carbonate and distilled to give 33.5 g (51%) of bis(3-hydroxypropyl)diphenylsilane: bp 178–185 °C (0.07 mm); mp 83–84 °C, NMR ($CDCl_3$) δ 0.7–1.7 (m, 8 H, CH_2CH_2Si), 2.58 (s, 2 H, OH), 3.2 (t, J = 6 Hz, 4 H, OCH_2), 6.9 (m, 10 H, C_6H_5); IR (film) 3300, 3050, 2900, 1430, 1190, 1120 cm^{-1}. Anal. Calcd for $C_{18}H_{24}O_2Si$: C, 72.00; H, 8.00. Found: C, 71.68; H, 8.26.

Bis(3-bromopropyl)diphenylsilane from Diallyldiphenylsilane. A solution of borane in tetrahydrofuran (35.02 mL, 0.96 M) was added dropwise with stirring under nitrogen to a solution of 13.2 g (0.05 mol) of diallyldiphenylsilane in 100 mL of dry tetrahydrofuran at 0 °C. The solution was stirred for 30 min at 0 °C and for 30 min at 20 °C. Then 1 mL of methanol was added to destroy excess borane. Bromine (5.4 mL, 0.101 mol) and sodium methoxide solution (from 2.53 g, 0.110 mol, of sodium and 30 mL of methanol) were added simultaneously at a rate such that the reaction mixture remained yellow. The reaction temperature was maintained at 23–30 °C by means of a water bath. Cyclohexane (100 mL) was added, and the solution was extracted with 100 mL of 50% potassium carbonate. The aqueous layer was extracted with three 50 mL portions of cyclohexane. The combined organic layers were washed with two 100 mL portions of water and 100 mL of saturated sodium chloride and dried over anhydrous potassium carbonate. Distillation gave 5.1 g (24%) of bis(3-bromopropyl)diphenylsilane, bp 182 °C (0.06 mm), spectrally identical to the compound characterized below. This material was handled as an oil; seed crystals were not available.

Bis(3-hydroxypropyl)diphenylsilane by Hydrosilylation. A mixture of 1500 g (7.33 mol) of 90% diphenylsilane, 0.1 g of tris(triphenylphosphine)rhodium chloride, and 200 g of allyloxytrimethylsilane was heated to 100 °C. Heating was stopped and the temperature rose to 120 °C. Additional allyoxytrimethylsilane, a total of 2800 g (21.6 mol), was added at a rate sufficient to maintain reflux. This solution was added to a solution of 15 mL of concentrated HCl and 600 mL of water in 3 L of methanol. After 24 h, the product was extracted with methylene chloride. Crystallization from methylene chloride and Skelly F yielded 1500 g (68%) of bis(3-hydroxypropyl)-diphenylsilane.

Bis(3-bromopropyl)diphenylsilane from PBr_3. Bis(3-hydroxypropyl)diphenylsilane (1490 g, 4.96 mol) was added to a solution of 1043 g (3.86 mol) of phosphorus tribromide in 3 L of ether, which was maintained at room temperature by a water bath. The mixture was stirred for 72 h and then was added to ice. The product was extracted with water, dried, stripped of solvent, and extracted into Skelly F, giving 1683 g of semicrystalline, 90% pure bis(3-bromopropyl)diphenylsilane. Recrystallization from ethanol gave 1400 g (67%) of bis(3-bromopropyl)diphenylsilane: mp 48–49 °C; NMR ($CDCl_3$) δ 1.2 (m, 4 H, CH_2Si), 1.8 (m, 4 H, CH_2CH_2Si), 3.25 (t, J = 6 Hz, 4 H, $BrCH_2$), 7.15 (m, 10 H, C_6H_5). Anal. Calcd for $C_{18}H_{22}Br_2Si$: C, 50.72; H, 5.20. Found: C, 50.74; H, 5.17.

Bis(3-*p*-toluenesulfonatopropyl)diphenylsilane. Pyridine (11.3 g, 0.14 mol) and 25 g (0.13 mol) of *p*-toluenesulfonyl chloride were added to a solution of 15 g (0.050 mol) of bis(3-hydroxypropyl)diphenylsilane in 50 mL of methylene chloride at 0 °C. After a 20 h reaction period at room temperature, the mixture was washed successively with water, 1 N hydrochloric acid, water, and saturated sodium bicarbonate. The solution was dried over magnesium sulfate, and the solvent was removed to give 31.6 g (85% yield) of 85% pure bis(3-*p*-toluenesulfonatopropyl)diphenylsilane, an oil. An analytical sample was isolated by column chromatography on silica gel using methylene chloride as the elution solvent: NMR ($CDCl_3$) δ 7.4 (d of d, 8 H, $-C_6H_4-(p)$), 7.2 (m, 10 H, C_6H_5), 3.97 (t, 4 H, CH_2O), 2.47 (s, 6 H, $-C_6H_4CH_3-p$), 1.7 (m, 4 H, CH_2CH_2Si), 1.0 (m, 4 H, CH_2Si). Anal. Calcd for $C_{32}H_{36}O_6S_2Si$: C, 63.28; H, 5.96. Found: C, 63.20; H, 6.29.

Bis(3-bromopropyl)diphenylsilane from *p*-Toluenesulfonate. A solution of 19.8 g (0.0325 mol) of bis(3-*p*-toluenesulfonatopropyl)diphenylsilane and 10 g (0.115 mol) of lithium bromide in 60 mL of dimethyl sulfoxide was stirred for 4 h. Water (150 mL) was then added, and the product was extracted with three 40 mL portions of carbon tetrachloride. The carbon tetrachloride solution was washed with 30 mL of water, dried, and stripped of solvent to give 11.3 g (74% yield) of 90% pure (by NMR) bis(3-bromopropyl)diphenylsilane. Identical results were obtained using sodium bromide instead of lithium bromide.

A solution of 1200 g (6.2 mol) of *p*-toluenesulfonyl chloride and 480 g (6.1 mol) of pyridine in 1600 mL of methylene chloride was added, with stirring and ice bath cooling, to 900 g (3.0 mol) of bis(2-hydroxypropyl)diphenylsilane in 1600 mL of methylene chloride. An additional 40 g (0.5 mol) of pyridine was added 1 h after this addition was completed. The mixture was stirred for 2 h at room temperature and was then washed with four 400 mL portions of water, dried over magnesium sulfate, and stripped of solvent. The residue was added to 825 g (8 mol) of sodium bromide and 2000 mL of dimethyl sulfoxide, and the mixture was stirred for 94 h. Water (4000 mL) was added, and the aqueous layer was extracted with two 250-mL portions of carbon tetrachloride. The combined organic layers were washed with 1000 mL of water and dried over sodium sulfate. Skelly F (5 L) was added, and the precipitated material was dried under vacuum to give 1135 g of 95% pure (NMR) bis(3-bromopropyl)diphenylsilane (84% yield).

Bis(3-nitropropyl)diphenylsilane. A solution of 530 g (7.7 mol) of sodium nitrate and 723 g (1.7 mol) of bis(3-bromopropyl)diphenylsilane in 6 L of dimethyl sulfoxide was stirred for 1.5 h and then was diluted with 12 L of water. The product was extracted with three 1000 mL portions of carbon tetrachloride, washed with 1000 mL of water, dried over sodium sulfate, and stripped of solvent. Crystallization and recrystallization from carbon tetrachloride and Skelly F gave 203 g (33%) of bis(3-nitropropyl)diphenylsilane, white crystals: mp 84.5–85.5 °C; NMR ($CDCl_3$) δ 7.3 (s, 10 H, C_6H_5), 4.3 (t, 4 H, CH_2NO_2), 2.0 (m, 4 H, CH_2CH_2Si), 1.1 (m, 4 H, CH_2Si); IR (CCl_4) 1540, 1430, 1380, 1120, 710 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_4N_2Si$: C, 60.31; H, 6.19; N, 7.81. Found: C, 60.15; H, 6.04; N, 7.62.

Bis(3,3-dinitropropyl)diphenylsilane. Bis(3-nitropropyl)-diphenylsilane (73 g, 0.204 mol) was added with stirring to 33 g (0.5 mol) of potassium hydroxide in 50 mL of water and 250 mL of methanol. When solution was complete, 200 mL water and 34.5 g (0.5 mol) of sodium nitrite were added. This solution was quickly added to an ice bath cooled mixture of 170 g of silver nitrate (1 mol) in 300 mL water and 500 mL of ether. After the mixture was stirred at room temperature for 2 h, 200 mL of saturated sodium chloride solution was added. The silver precipitate was filtered, and the solution was made slightly acidic with acetic acid. The ether layer was separated, washed, dried, and stripped. The product was crystallized from methylene chloride and Skelly F, giving 34.5 g (38% yield) of bis(3,3-dinitropropyl)diphenylsilane: mp 96–97 °C; NMR ($CDCl_3$) δ 7.40 (3, 10 H, C_6H_5), 6.01 (t, J = 7 Hz, 2 H, $CH(NO_2)_2$), 2.4 (m, 4 H, CH_2CH_2Si), 1.2 (m, 4 H, CH_2Si); IR ($CHCl_3$) 1570, 1330, 1120 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4O_8Si$: C, 48.21; H, 4.50; N, 12.49. Found: C, 48.32; H, 4.59; N, 12.29.

Bis(3-fluoro-3,3-dinitropropyl)diphenylsilane. Perchloryl fluoride was bubbled into a vigorously stirred solution of 40 g of bis(3,3-dinitropropyl)diphenylsilane (0.009 mol) and 13.2 g of potassium hydroxide (0.2 mol) in 150 mL of water, 200 mL of methanol, and 200 mL of dimethylformamide at room temperature. When gas uptake stopped, water was slowly added and the product precipitated out. Filtration yielded 42 g of a light tan solid. Recrystallization gave 36.6 g (85% yield) of white crystalline product: mp 85–86 °C; proton NMR ($CDCl_3$) δ 7.35 (s, 10 H, C_6H_5), 2.63 (m, 4 H, CH_2CH_2Si), 1.17 (m, 4 H, CH_2Si); fluorine NMR ($CDCl_3$) ϕ 105.7 (J_{HF} = 18 Hz); IR (KBr) 1590, 1430, 1320, 1260, 1200, 1100, 700 cm^{-1}. Anal. Calcd for $C_{18}H_{18}O_8N_4F_2Si$: C, 44.63; H, 3.75; N, 11.57. Found: C, 44.84; H, 3.85; N, 11.39.

1,1,3,3,5,5-Hexakis(3-fluoro-3,3-dinitropropyl)cyclotrisiloxane. A solution of 10 g (0.021 mol) of bis(3-fluoro-3,3-dinitropropyl)-diphenylsilane in 25 mL of methylene chloride and 25 mL of acetic acid was stirred with 10 g (0.0625 mol) of bromine for 3 days. Water

(10 mL) was added, and the reaction mixture was stirred for 24 h. The solution was washed with water, and the solvent was removed. The product was redissolved in methylene chloride, and 2 g of bromine was added. Crystals slowly formed and after 4 days 4.8 g (67% yield) of 1,1,3,3,5,5-hexakis(3-fluoro-3,3-dinitropropyl)cyclotrisiloxane was isolated by filtration. The product was recrystallized from ethyl acetate and Skelly F to give white crystals: mp 207–209 °C; proton NMR (acetone-d_6) δ 3.14 (m, 4 H, CH_2CF), 1.20 (m, 4 H, CH_2Si); fluorine NMR (acetone-d_6) ϕ 106.0; IR (KBr) 1590, 1320, 1270, 1210, 1090 cm^{-1}. Anal. Calcd for $C_6H_8N_4O_9F_2Si$: C, 20.83; H, 2.33; N, 16.19. Found: C, 21.00; H, 2.36; N, 16.17; mol wt (vapor phase osmometer/EtOAc), 1010 ± 5% (trimer = 1038).

Registry No.—Sodium nitrite, 7632-00-0; (3-bromopropyl)trimethylsilane, 10545-34-3; (3-nitropropyl)trimethylsilane, 64035-55-8; (3-hydroxypropyl)trimethylsilane, 2917-47-7; (4-bromobutyl)trimethylsilane, 18379-55-0; (4-nitrobutyl)trimethylsilane, 64035-56-9; (3-bromobutyl)trimethylsilane, 18379-54-9; (3-nitrobutyl)trimethylsilane, 64035-57-0; (3-hydroxybutyl)trimethylsilane, 18387-24-1; (3-nitrotobutyl)trimethylsilane, 64035-58-1; (3,3-dinitropropyl)trimethylsilane, 64035-59-2; (4,4-dinitrobutyl)trimethylsilane, 64035-60-5; (3,3-dinitrobutyl)trimethylsilane, 64035-61-6; (3-fluoro-3,3-dinitropropyl)trimethylsilane, 64035-62-7; (4-fluoro-4,4-dinitrobutyl)trimethylsilane, 64035-63-8; (hydroxymethyl)trimethylsilane, 3219-63-4; trimethylsilylmethyltriflate, 64035-64-9; 2-fluoro-2,2-dinitroethanol, 17003-75-7; trimethylsilylmethyl 2-fluoro-2,2-dinitroethyl ether, 64035-65-0; allyl bromide, 106-95-6; chloromethyldiphenylsilane, 144-79-6; allylmethyldiphenylsilane, 17922-43-9; (3-bromopropyl)methyldiphenylsilane, 64035-66-1; allyloxytrimethylsilane, 18146-00-4; (3-hydroxypropyl)methyldiphenylsilane, 64035-67-2; toluenesulfonyl chloride, 98-59-9; (3-*p*-toluenesulfonatopropyl)methyldiphenylsilane, 64035-68-3; (3-nitropropyl)methyldiphenylsilane, 64035-69-4; (3,3-dinitropropyl)methyldiphenylsilane, 64035-70-7; (3-fluoro-3,3-dinitropropyl)methyldiphenylsilane, 64035-71-8; (3-fluoro-3,3-dinitropropyl)methyldibromosilane, 64035-72-9; (3-fluoro-3,3-dinitropropyl)methyldifluorosilane, 64035-73-0; (3-fluoro-3,3-dinitropropyl)methylmethoxyfluorosilane, 64035-74-1; 1,3-bis(3-fluoro-3,3-dinitropropyl)-1,3-dimethyl-1,3-difluorodisiloxane, 64035-75-2; dichlorodiphenylsilane, 80-10-4; 3-chloropropanol, 627-30-5; bis(3-chloropropoxy)diphenylsilane, 63802-06-2; bis(3-hydroxypropyl)diphenylsilane, 34564-72-2; diallyldiphenylsilane, 10519-88-7; diphenylsilane, 775-12-2; bis(3-bromopropyl)diphenylsilane, 64035-76-3; bis(3-*p*-toluenesulfonatopropyl)diphenylsilane, 64035-77-4; bis(3-nitropropyl)diphenylsilane, 64035-78-5; bis(3,3-dinitropropyl)diphenylsilane, 64035-79-6; bis(3-fluoro-3,3-dinitropropyl)diphenylsilane, 64035-80-9; 1,1,3,3,5,5-hexakis(3-fluoro-3,3-dinitropropyl)cyclotrisiloxane, 64035-81-0; $(CF_3SO_2)_2O$, 358-23-6.

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^{13}C–^{13}C Spin Coupling Constants within the Bicyclo[2.2.2]octane and Bicyclo[3.2.1]octane Systems

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A series of eight derivatives of the bicyclo[2.2.2]octane and the bicyclo[3.2.1]octane system with a ^{13}C label have been synthesized. The ^{13}C–^{13}C spin coupling constants have been measured and interpreted in terms of substituent and conformational dependence.

The early work on carbon–carbon spin coupling constants mainly centered on directly bonded carbon atoms. The substituent dependence, the effect of orbital hybridization, and the sign of these coupling constants were investigated by the research groups of Roberts,[1] Grant,[2] and Maciel.[3] Early theoretical work by Pople[4] again focussed on the interpretation of $^1J_{C,C}$. More recently the interest shifted to two- and three-bond coupling constants,[5] both in experimental[6] and in theoretical[7] work. The current interest in ^{13}C–^{13}C couplings apparently seems to be threefold: (i) in a series of papers[8] the usefulness of both direct and long-range coupling constants in determining biosynthetic pathways is demonstrated; (ii) the conformational dependence of carbon coupling constants is investigated;[9] and (iii) the mechanism of carbon coupling constant transmission in π systems is open to question.[10]

Very recent theoretical predictions on the angular dependence of ^{13}C–^{13}C spin couplings[11] led us to continue our studies of compounds[9] in which the labeled carbon atom is directly part of a rigid bi- or tricyclic system, whereby the carbon–carbon long-range coupling constants are not subject

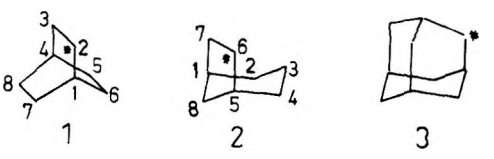

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Table I. ^{13}C Chemical Shifts of the Derivatives of 1, 2, and 5[a]

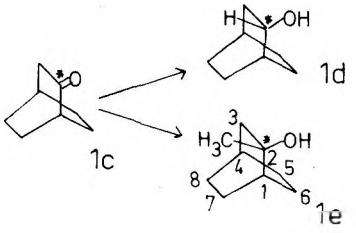
Compd	Registry no.	Carbon atom 1	2	3	4	5	6	7	8
1a	64162-90-9	50.9	212.9	43.3	27.9	38.0	54.4	17.3	24.2
b	64200-02-8	50.5	211.4	43.9	28.4	37.7	55.2	22.7	23.3
c	64162-91-0	41.6	217.3	44.6	27.9	24.7	23.3	23.3	24.7
d	64162-92-1	31.6	69.5	37.5	24.9	25.7	18.7	23.8	24.6
e[b]	64162-93-2	36.6	71.7	44.1	26.2	24.4[c]	21.1	23.3	24.6[c]
2a	64162-94-3	32.0	26.0	28.3	58.5	53.5	216.2	42.9	31.5
b	64162-95-4	32.0	30.5	18.7	30.3	45.9	221.2	43.3	37.0
c	64162-96-5	34.3	32.6	19.5	26.8	39.3	75.0	38.0	37.9
5a	64162-97-6	30.5	31.3	125.7	126.9	24.7	28.4	40.9	179.8
b	64162-98-7	30.5	30.2	124.4	126.4	24.0	27.4	52.8	172.0

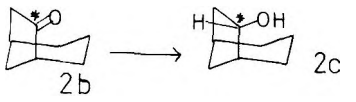
[a] ppm vs. internal Me_4Si. [b] CH_3, 30.3 ppm. [c] Relative assignment is tentative.

to conformational or rotational averaging. In this work, we report the ^{13}C–^{13}C spin couplings in the bicyclo[2.2.2]octane system (1) labeled at C-2 and the bicyclo[3.2.1]octane system (2) labeled at C-6 and compare these with the results of the adamantane system (3) previously reported.[9]

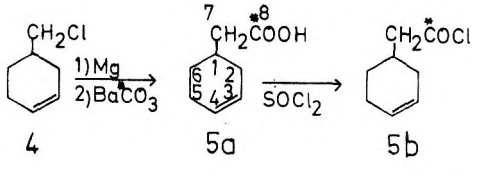
Results and Discussion

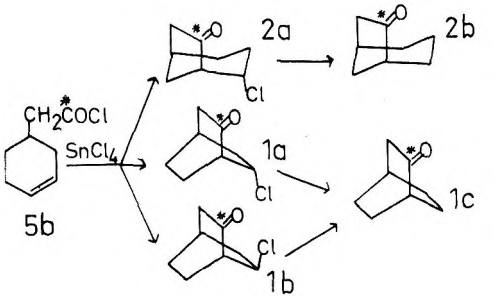
Synthesis of the Labeled Compounds. Monti and White[12] recently reported a new synthesis for bicyclo[2.2.2]octan-2-one (**1c**) which seemed feasible for labeling purposes. Thus, we prepared from 3-cyclohexene-1-methylene chloride (**4**) the carboxyl-^{13}C-labeled 3-cyclohexene-1-acetic acid (**5a**) and its acid chloride (**5b**). On intramolecular Friedel–Crafts reaction, **5b** yields three keto chloride isomers, separable by preparative





GLC. Monti and White[12] assigned the structures **1a** and **2a** to two of the isomers. Contrary to their work, we were able to reduce all three isomers by tri-*n*-butyltin hydride. Since the third isomer yields, like **1a**, bicyclo[2.2.2]octan-2-one (**1c**) on reduction, we assign the *endo*-chloro ketone structure **1b** to





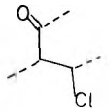
it according to the spectroscopic results outlined below. **1c** was further reduced to the alcohol **1d** and to the methyl alcohol **1e**. **2b** was reduced to the alcohol **2c**. The limited amount of labeled material did not allow further transformations.

^{13}C Chemical-Shift Assignments. The ^{13}C chemical shifts of the derivatives of **1**, **2**, and **5** are given in Table I. The chemical-shift assignment of **1c** follows the assignment of Stothers,[13] who investigated in detail the bicyclo[2.2.2], -[2.2.1], and -[3.2.1] systems. From these results and the incremental shift values for chlorine in the bicyclo[2.2.1] system,[14] it was possible to assign the exo and endo structures of the two bicyclo[2.2.2]keto chlorides **1a** and **1b**. Stothers has shown that substituents cause similar incremental shifts in both the bicyclo[2.2.2] and the bicyclo[2.2.1] systems. For **1a** there is a typical γ shielding effect for C-7 of 6 ppm if one compares its shift position with the chemical shift of C-7 in **1c**. Compound **1d** has already been reported, and our values are in agreement with the literature.[13] The closely resonating carbon atoms C-5, C-7, and C-8 were distinguished using the incremental shifts of the OH group.[14] The addition of a methyl group to the same C-2 already bearing a hydroxyl group in **1e** deshields the resonance of C-2 only by 2.2 ppm. Its effect on the chemical shift of C-3 and C-1, however, is in the predicted range. C-6, being in a γ anti position with respect to the methyl group, is deshielded by 2.4 ppm, and C-7 moves only slightly upfield to 23.2 ppm, a value quite comparable with that of the corresponding carbon atom of 2,2-dimethylbicyclo[2.2.2]-octane.[13] The relative assignment of C-5 and C-8 is tentative.

The ^{13}C chemical shifts of bicyclo[3.2.1]octan-6-one (**2b**) have been reported.[15] For bicyclo[3.2.1]keto chloride **2a**, where only one isomer was isolated, the exo structure was determined from the chemical-shift values of C-8 and C-2, both of which again show the typical γ upfield effect. All the other chemical-shift values in this isomer are in reasonably good agreement with shift values calculated by the incremental shifts for chlorine.[14] The chemical shifts of **2c** were very recently discussed by Stothers.[16]

The chemical shifts for the cyclohexene compounds **5a** and **5b** were assigned with the help of the data from Lippmaa,[17] who studied a variety of substituted cyclohexenes. All the assignments given in Table I have been checked by off-reasonance spectra.

^{13}C–^{13}C Spin Coupling Constants. The ^{13}C–^{13}C spin coupling constants of the derivatives of **1**, **2**, and **5** are given in Table II. The one-bond coupling constants do not vary much; their relative insensitivity to structural changes has already been pointed out.[2] However, it might be noted that starting from the unsubstituted ketone **1c**, $^1J_{C\text{-}2,C\text{-}1}$ decreases for the chloro ketone **1a** and increases for the endo isomer **1b**. This might further support the correctness of the structural assignment of **2a** since the lowering of $^1J_{C\text{-}6,C\text{-}5}$ compared to that in **2b** would emphasize a structure in which the carbonyl



group and the chlorine atom are in a transoid arrangement. The open chain compounds (**5**) show $^1J_{C,C}$ values in the known range for acetic acid derivatives.[3]

The geminal coupling constants in the bicyclo[2.2.2] system (**1**) tend to be smaller than the vicinal ones. This confirms our findings from the adamantane system.[9] As in the adamantane system, the carbon atom syn to the polarizing substituent (C-6 in **1d** and **1e**) shows the higher geminal coupling constant. Thus, we can possibly conclude that this is a general feature of geminal ^{13}C–^{13}C coupling constants in aliphatic compounds.

The vicinal coupling constants in butane were calculated by Barfield et al.[7] to be 1.94 Hz for a dihedral angle of 60°. In a later paper,[11] the authors gave values ranging from 0.86 to 2.54 Hz using different refinements of their INDO FPT approach. In the bicyclo[2.2.2] series (**1**), a dihedral angle of 60° between the labeled C-2 atom and the vicinal coupling partners C-5 and C-8 applies. Our experimental values range from 1.4 to 2.4 Hz, as in the adamantane series where the same dihedral angle applies.

In the bicyclo[3.2.1] system (**2**) the geminal coupling constants show a remarkable change. C-1 shows in all three compounds measured the normal magnitude already found in the bicyclo[2.2.2]octane series. The geminal coupling constant of C-4 can not be resolved in **2a**; the other two compounds again show normal values. Unexpectedly high, however, are the values for C-8 in all three compounds (**2a–c**). The value of 6.1 Hz in **2c** is probably the highest reported geminal coupling constant in aliphatic compounds. Currently we have no reasonable explanation for this circumstance. The vicinal coupling constants for C-2 are not resolvable; in **2b** and **2c** the vicinal coupling constants to C-3 are very small. Theoretically[11] one expects no resolvable coupling constant for C-2 in these systems since the dihedral angle between the bonds C-6, C-7, and C-1, C-2 can be estimated to be about 90°. If one assumes a flattening of the six-membered ring in the bicyclo[3.2.1]octane derivatives,[18] the dihedral angle between the bonds C-6, C-5 and C-4, C-3 can get close to 90° as well. Thus, if the theoretical predictions are valid, the very small vicinal ^{13}C–^{13}C coupling constant in these compounds would indicate a flattening of the six-membered ring. Finally, the open-chain compounds (**5**) show the largest vicinal coupling constants of the series reported here, a result which probably supports the idea of impinging back lobes[11] reducing the coupling constants for stereochemically rigid compounds.

Conclusions

In this work, we have shown that the principal results found earlier in the adamantane series regarding the directional substituent dependence for geminal and vicinal coupling constants between carbon atoms are also valid in the bicyclo[2.2.2] system. The values for the bicyclo[3.2.1] system possibly indicate a flattened six-membered ring; however, there are only limited examples. It is evident that further studies of labeled and geometrically fixed systems are needed to check the theoretical results.

Experimental Section

Materials. 3-Cyclohexene-1-methylene chloride (**4**) was prepared[19] from 1-hydroxymethylene-3-cyclohexene (EGA Chemie). 3-Cyclohexene-1-[^{13}C]acetic acid (**5a**) was prepared[20] by reacting a Grignard solution of **4** (300 mmol in 100 mL of dry ether) on a high-vacuum line as described by Murray and Williams[21] with $^{13}CO_2$ developed from 90% enriched $BaCO_3$ and concentrated H_2SO_4; yield 80%. Acid chloride **5b** was prepared by stirring **5a** with an equimolar amount of $SOCl_2$. *exo*-6-Chlorobicyclo[2.2.2]octan-2-one (**1a**), *endo*-6-chlorobicyclo[2.2.2]octan-2-one (**1b**), and *endo*-4-chlorobicyclo[3.2.1]-octan-6-one (**2a**) were prepared according to Monti and White.[12] They were separated by preparative GLC (Aerograph A 90 P, Carbowax 20 M on Chromosorb G, 60–80 mesh, 1.8 m, ¼ in, 180 °C, 70–80 mL of He).

Tri-*n*-butyltin hydride reduction of these compounds was achieved according to the procedure given by Monti and White[12] with the exception that a spatula tip of azoisobutyric acid dinitrile was added. Under these conditions, all three isomers could be reduced.

Compounds **1d**, **1e**, and **2c** were obtained by $LiAlH_4$ reduction of **1c** and **2b** and by methyllithium addition to **1c** via standard procedures. The physical constants of all compounds reported here are already in the literature.[12,13,22,23]

NMR Measurements. The ^{13}C spectra were obtained on a Varian XL-100-15 spectrometer equipped with a 16K 620 L computer and a Varian disc system. Thus, 32K FT spectra were obtained with no exponential filtering and with a digital resolution of less than 0.2 Hz/point. Where no coupling constants are given in Table II, the value is lower than 0.35 Hz. Spectra were mostly taken three times in rather diluted solutions of $CDCl_3$ due to the limited amount of material. Agreement between the different runs was excellent.

Table II. ^{13}C–^{13}C Spin Coupling Constants (Hz) in the Derivatives of 1, 2, and 5

Compd	Carbon atom 1	2	3	4	5	6	7	8
1a	36.5		35.5	1.2	1.4	1.1	2.0	2.4
b	39.4		35.6	1.6	1.8	2.7	1.8	2.7
c	38.6		34.6	1.5	2.2	1.7	1.7	2.2
d	36.0		34.7	1.0	2.4	1.9	0.7	2.4
e[a]	36.7		35.4	1.2	1.7	1.7		1.8
2a	2.2				35.0		36.7	3.9
b	2.3		0.7	2.0	37.4		35.6	4.4
c	1.7		0.4	2.2	35.6		36.3	6.1
5a		3.4	0.4			2.6	55.1	
b	1.9	3.9	0.3			4.0	52.9	

[a] $^1J_{C\text{-}2,CH_3}$ = 40.2 Hz.

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Para-Substituted Toluenes. Evaluation of Long-Range Carbon–Hydrogen Coupling Constants

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Carbon-13 NMR spectra for a series of para-substituted toluenes were obtained and the proton-coupled spectra were analyzed. It is shown that the coupling patterns observed are characteristic for each type of carbon signal and can be used as "fingerprints". One-bond carbon–hydrogen coupling constants J_{77} and J_{22} were found to vary systematically and were analyzed using the Swain–Lupton $\mathcal{F}$ and $\mathcal{R}$ treatment. Chemical-shift substituent effects were found to be similar in direction and magnitude to those obtained for monosubstituted benzenes.

A great number of studies concerning the carbon-13 NMR spectral properties of aromatic compounds, particularly benzenoid systems, have been reported over the last few years.[1b-e] While considerable attention has been devoted to chemical-shift data and substituent effects, natural-abundance carbon-13–hydrogen coupling constant data have been generally neglected.[2] (In favorable instances, one-bond carbon–hydrogen coupling constants have been obtained from the carbon-13 satellites appearing in proton NMR spectra.[3]) Natural-abundance long-range carbon-13–hydrogen coupling-constant investigations of benzene derivatives are indeed rare, limited only to benzene,[4] halobenzenes,[5] toluene[6] and some substituted phenols.[7] The major problem associated with obtaining proton-coupled carbon-13 spectra is inherent in the nature of the carbon-13 nucleus.[8] However, recent advances in instrumentation, especially the introduction of "gated-decoupling,"[9] have facilitated the measurement of proton-coupled spectra. Additionally, a spectrometer system equipped with a crystal filter[10a] or quadrature detection[10b] can reduce the total time necessary to obtain a spectrum by ca. one-half.

The information contained in the proton-coupled spectrum can be perceived in a study of ortho-disubstituted benzenes, whereby carbon-13 shift assignments were made by simple inspection of the coupling "fingerprint."[11] (The use of "fingerprints" in proton NMR aromatic shift assignments is exemplified in an investigation by Zanger.[12]) While the above example represents the ideal situation, careful inspection of the more complex proton-coupled spectrum of monosubstituted benzenes can often lead to the carbon-shift assignments.[7,13] The purpose of the present report is to evaluate the proton-coupled carbon-13 spectra for a series of para-substituted toluenes.

Experimental Section

All compounds used in this study were commercially available materials requiring no further purification as indicated by the lack of significant additional signals in both the proton and carbon-13 NMR spectra. Sample concentrations, in deuteriochloroform, were ca. 20% w/v for chemical-shift determinations, and ca. 60% w/v for coupling-constant data. Sample tubes with an o.d. of 10 mm were used. The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a JEOL FX-60 spectrometer system operating at 15.03 MHz, and equipped with a Texas Instruments computer with 24K memory.

General NMR spectral and instrumental parameters used were: internal deuterium lock to solvent, spectral width of 2500 Hz for decoupled spectra and 500 Hz for proton-coupled spectra, a pulse width of 4 μs, corresponding to a 36° pulse angle, and a pulse repetition time of 1.8 s. All proton-coupled spectra were obtained in the "gated" mode, and the free induction decay signal was worked up without a window function. For all decoupled spectra 8K data points were used, while for proton-coupled spectra 16K data points were employed.

All chemical shifts are referenced to internal Me_4Si and are esti-

Table I. Carbon-13 Chemical Shift Values (δ_c) for a Series of Para-Substituted Toluenes[a]

X	Registry no.	C_1	C_2	C_3	C_4	C_7
H	108-88-3	137.8	129.3	128.5	125.6	21.3
F	352-32-9	133.4	130.4	115.0	161.3	20.5
Cl	106-43-4	136.2	130.4	128.3	131.2	20.7
Br	106-38-7	136.5	130.7	131.1	119.0	20.8
I	624-31-7	136.9	130.9	136.9	90.2	20.9
OH	106-44-5	130.2	130.2	115.4	152.8	20.3
OMe	104-93-8	129.7	129.9	113.8	157.7	20.4
SH	106-45-6	126.7	129.7	129.7	135.2	20.8
NH_2	106-49-0	127.5	129.7	115.2	144.0	20.5
CN	104-85-8	143.8	130.0	131.9	109.3	21.7 (119.1)
NO_2	99-99-0	146.2	129.9	123.4	146.2	21.5
CH_3	106-42-3	134.6	129.0	129.0	134.6	20.9

[a] In parts per million from internal Me_4Si.

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Table II. Substituent Chemical Shifts for a Series of Para-Substituted Toluenes

X	C_1	C_2	C_3	C_4	C_7
F	−4.4[a]	1.1	−13.5	36.7	−0.8
Cl	−1.4	1.1	−0.2	5.6	−0.6
Br	−1.3	1.4	2.6	−6.6	−0.5
I	−0.9	1.6	8.4	−35.4	−0.4
OH	−7.6	0.9	−13.1	27.2	−1.0
OMe	−8.1	0.6	−14.7	32.1	−0.9
SH	−11.1	0.4	1.2	9.6	−0.5
NH_2	−10.3	0.4	−13.3	18.4	−0.8
CN	6.0	0.7	3.4	−16.3	0.4
NO_2	8.4	0.6	−5.1	20.6	0.2
CH_3	−3.2	−0.3	0.5	9.0	−0.4

[a] Negative numbers indicate an upfield shift.

mated to be accurate to ±0.05 ppm. Coupling-constant data were measured from expanded spectra, and relative line positions are believed to be accurate to ±0.06 Hz. The observed coupling constants themselves are probably accurate to at least ±0.2 Hz.

Results and Discussion

Chemical-Shift Values. The carbon-13 chemical shift values for the para-substituted toluene series are given in Table I, and the substituent chemical shifts ($\Delta\delta = \delta_{toluene} - \delta_{obsd}$, negative sign indicates upfield shift) are listed in Table II. The substituent effects are not greatly affected by the *p*-methyl moiety and compare well with the substituent effects reported for monosubstituted benzenes.[1d] Carbon assignments were made on the basis of the substituent effects and of the appearance of the proton-coupled spectrum (vide infra). In a recent investigation, Taft et al. suggested that caution should be exerised when making carbon-13 assignments simply from substituent effect additivity based solely on monosubstituted benzene data because the substituent shifts depend upon the nature of the fixed substituent.[14] However, the fixed methyl substituent does not cause any large deviations from the monosubstituted benzene data.

Coupling-Constant Data. For ease of discussion, the coupling-constant data obtained for each carbon type will be presented separately (see Table III). Certain coupling-con-

Table III. Carbon-13–hydrogen Coupling Constants in Para-Substituted Toluenes

		J, Hz		
C_1	$C_{2(6)}$	$C_{3(5)}$	C_4	C_7
		H[a]		
−6.0 (H_7)	4.6 (H_7)	157.6 (H_3)	0.8 (H_7)	126.0 (H_7)
0.5 (H_2)	155.9 (H_2)	7.9 (H_5)	7.8 (H_2)	5.0 (H_2)
7.6 (H_3)	6.6 (H_6)		1.1 (H_3)	−0.4 (H_3)
		Cl		
6.4 (H_7)	4.9 (H_7)	163.4 (H_3)	1.1 (H_7)	126.4 (H_7)
	160.0 (H_2)	4.6 (H_5)	10.6 (H_2)	4.3 (H_2)
6.4 (H_3)	6.6 (H_6)		0.6 (H_3)	0.4 (H_3)
		Br		
6.2 (H_7)	5.0 (H_7)	165.2 (H_3)	1.1 (H_7)	126.4 (H_7)
	159.1 (H_2)	6.3 (H_5)	10.5 (H_2)	4.3 (H_2)
6.2 (H_3)	6.7 (H_6)		0.6 (H_3)	0.4 (H_3)
		I		
6.3 (H_7)	4.9 (H_7)	165.2 (H_3)	1.1 (H_7)	126.4 (H_7)
1.2 (H_2)	158.6 (H_2)	6.3 (H_5)	10.5 (H_2)	4.3 (H_2)
6.3 (H_3)	6.5 (H_6)		0.6 (H_3)	0.4 (H_3)
		OH		
6.3 (H_7)	5.0 (H_7)	158.5 (H_3)		125.8 (H_7)
	157.1 (H_2)	3.8 (H_5)	7.4 (H_2)	4.0 (H_2)
6.3 (H_3)	6.2 (H_6)			0.6 (H_3)
		SH		
6.2 (H_7)	4.8 (H_7)	158.0 (H_3)		125.4 (H_7)
	157.9 (H_2)	4.9 (H_5)	7.2 (H_2)	4.4 (H_2)
6.2 (H_3)	5.7 (H_6)			
		NH_2		
6.2 (H_7)	4.9 (H_7)	161.2 (H_3)		125.7 (H_7)
0.6 (H_2)	155.3 (H_2)	5.4 (H_5)	8.4 (H_2)	4.3 (H_2)
6.2 (H_3)	7.1 (H_6)			0.4 (H_3)
		OMe		
6.4 (H_7)	5.0 (H_7)	159.3 (H_3)		126.0 (H_7)
0.8 (H_2)	156.2 (H_2)	4.5 (H_5)		4.3 (H_2)
6.4 (H_3)	6.8 (H_6)			0.4 (H_3)
		CN		
6.5 (H_7)	5.1 (H_7)	164.6 (H_3)		126.9 (H_7)
0.8 (H_2)	161.7 (H_2)	5.8 (H_5)	8.0 (H_2)	4.3 (H_2)
6.5 (H_3)	5.3 (H_6)			0.7 (H_3)
		NO_2		
6.2 (H_7)	5.0 (H_7)	162.7 (H_3)		127.1 (H_7)
0.7 (H_2)	162.7 (H_2)	4.5 (H_5)		4.3 (H_2)
6.0 (H_3)	6.8 (H_6)			0.6 (H_3)

[a] M. Hansen and H. J. Jakobsen, *J. Magn. Reson*, **20**, 520 (1975).

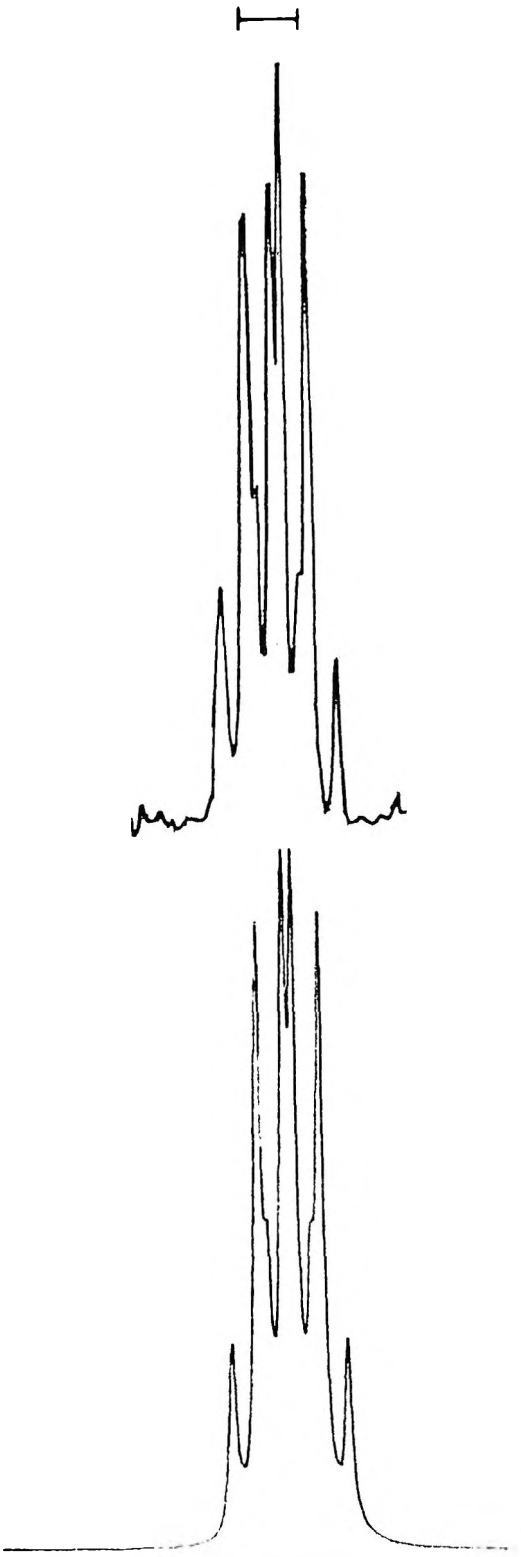
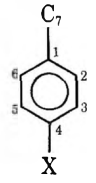


Figure 1. Top: lower-field half of the proton-coupled carbon-13 spectrum of C_2 in *p*-chlorotoluene. Bottom: calculated spectrum for C_2 using *p*-chlorotoluene data. Measure bar is 10 Hz.

stant data were unobtainable even at spectral widths that would allow better than 0.06-Hz data-point resolution. These carbon–hydrogen coupling constants were of the two or four bond variety, whose magnitudes in this type of aromatic system are generally on the order of 1 Hz or less.[4–6] The numbering sequence is shown below.



Before proceeding with the discussion concerning the carbon–hydrogen coupling constants, an understanding of the method used to obtain those values is warranted. The carbon-13 proton-coupled spectrum of the methyl carbon C_7 and ring carbons C_1 and C_4 represent the X part of separate AA′BB′M_3X spin systems, while ring carbons C_2 (C_6) and C_3 (C_5) represent the X part of separate ABCDM_3X spin systems. Because of the unobservable long-range couplings of the two and four bond variety, these complex spin systems were found to be amenable to analysis by a more simplified notation. For example, the C_2 spin system was analyzed assuming it to be an ABM_3X system, while C_1 simplifies to AA′M_3X. In *principle*, the J_{AX} and J_{BX} values can not be obtained directly from the relative line positions, only the sum ($J_{AX} + J_{BX}$) can be directly measured, the true values being obtained by computer simulation. However, there is strong precedence in the literature indicating that in certain systems direct measurement of observed spectral splittings of the proton-coupled carbon-13 spectrum yields excellent values for the coupling constants.[7,15] Under such conditions (AA′X type spin systems), Roberts et al. obtained the coupling-constant values for benzene.[4] In addition, the directly observed values should be of more use to the practicing organic chemist.

In order to substantiate the premise that useful coupling constants for the para-substituted toluenes could be read directly from the spectrum, noniterative spectral analysis of the C_2 coupling pattern was performed. C_2 was chosen because its coupling pattern was of reasonable complexity. If the values obtained by first-order analysis are useful, then there should be little difference between the directly measured splittings and splittings dictated by the input data. In all of the instances (including selected examples involving C_1 and C_3), the correlation between measured splittings and input data was excellent, within the ±0.1 Hz experimental accuracy. A comparison of the observed and calculated spectrum for C_2 is shown in Figure 1. It may be noted that there is some intensity skewing in the observed spectrum, indicating that these systems are not strictly first order.

A less extensive study done in this laboratory of unsymmetrical meta-disubstituted benzenes indicates a limitation on the use of first-order rules. The apparent problem associated with the meta series lies in the nonsymmetrical nature of the paired splitting patterns. The coupling patterns in the para series did not suffer from this problem and in view of the above discussion the values obtained by first-order analysis are believed to be useful.

Methyl Carbon (C_7). The proton-coupled carbon-13 spectrum of the methyl carbon C_7 appears grossly as a quartet of triplets, arising from a large one-bond coupling to the three directly attached protons, J_{77}, and a three-bond coupling to the protons at carbons 2 and 6, J_{72}. Inspection of the triplets at a larger sweep width indicates further coupling arising from protons on carbons 3 and 5, J_{73}. From the data in Table III, it is noticed that the size of the one-bond coupling J_{77} is affected by the para substituent. Analysis of the J_{77} values using a dual substituent parameter equation[16] with the Swain–Lupton $\mathcal{F}$ and $\mathcal{R}$ values[17] yields regression coefficients of 0.88 and 0.84, respectively, $\bar{r} = 0.98$, average error 0.07 Hz. This result is consistent with the values recently reported by Yoder et al.[18] The J_{72} value appears to be unaffected by the para substituent.

Carbon 1. Carbon 1 is a nonprotonated center and appears in the proton-coupled spectrum as a first-order sextet with peak-area ratios of almost exactly 1:5:10:10:5:1. This spectral pattern arises as a consequence of the equality of the coupling constants to the methyl protons, J_{17}, and the three-bond coupling to the protons on carbons 3 and 5, J_{13}. In some cases,

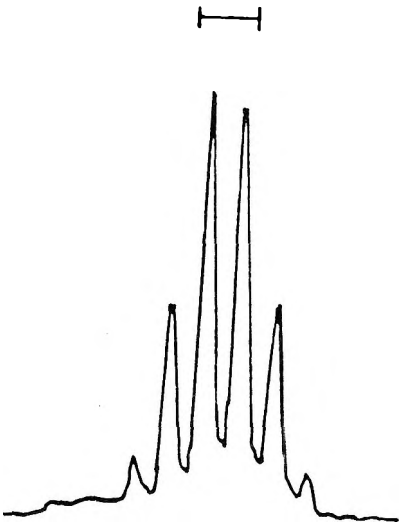


Figure 2. Proton-coupled carbon-13 spectrum of C_1 in *p*-chlorotoluene. Measure bar is 10 Hz.

careful inspection of the central two peaks (because of their greater intensity) reveals another small coupling attributable to protons on carbons 2 and 6, J_{12}; thus, each peak in the sextet is further split into a triplet. The data in Table III indicate that J_{17} and J_{13} remain fairly constant, with J_{13} reduced in magnitude vs. the analogous coupling constant found for toluene and J_{17} being slightly larger than the toluene value.

Carbon 2 (6). Each half of the proton-coupled spectrum of carbon 2 (6) appears as an octet. This pattern arises from the coupling with the methyl protons. J_{27}, being further split by the coupling of the ring protons 2 (6) and 6 (2). In the instance of *p*-cyanotoluene, this spectral pattern appears as a quintet owing to the near equality of the J_{27} and J_{26} coupling constants. From the coupling-constant data given in Table III, it can be seen that J_{27} is larger than that found for toluene and this value remains fairly constant. This result is consistent with recent theoretical calculations which indicate that para substitution increases the J_{27} coupling constant.[20] The coupling constant across the methyl moiety, J_{26}, varies from 5.3 to 7.1 Hz with an average value of 6.4 Hz. No apparent trend (correlation with dual substituent shift equation or with group electronegativity is poor) is observed for the J_{26} coupling constant values.

The one-bond carbon–hydrogen coupling, J_{22}, is seen to vary in a regular manner. Using the Swain–Lupton $\mathcal{F}$ and $\mathcal{R}$ values and the dual substituent parameter equation, a regression coefficient of 5.5 $\mathcal{F}$ and 2.7 $\mathcal{R}$ is obtained, $\bar{r} = 0.98$, average error 0.4 Hz. This result may be rationalized as follows. The presence of an electron-withdrawing group increases the effective electronegativity of the aromatic ring which causes increased polarization of the C–H bond, resulting in a larger coupling constant.[21] Conversely, for electron-donating groups a decrease in the s character of the C–H bond occurs and a smaller coupling constant is obtained. This observation is seen to parallel the data for J_{77}, the one-bond methyl coupling constant.

Carbon 3 (5). Each half of the proton-coupled spectrum of $C_{3\,(5)}$ appears as a sharp doublet owing to a three-bond coupling to the proton on $C_{5\,(3)}$. (Under a number of different spectral parameter conditions, no other long-range couplings to this carbon could be observed.) All of the one-bond coupling constants, J_{33}, are seen to be larger than that found for toluene. The long-range coupling constant J_{35} varies from 3.8 to 6.3 and is smaller than the analogous toluene values. This reduction in the coupling constant across an electronegative moiety parallels the calculated reduction of the analogous coupling in fluorobenzene.[20] No correlation with the Swain–Lupton values was obtained.

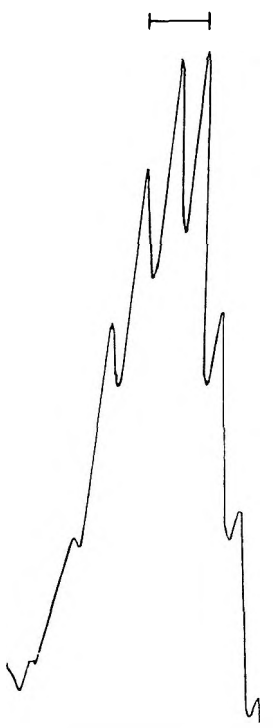


Figure 3. Expanded view of the central peak of the proton-coupled carbon-13 spectrum of C_4 in *p*-iodotoluene. Measure bar is 1 Hz.

Carbon 4. The coupling pattern for C_4, by preliminary inspection, appears as a simple triplet; however, an expanded spectrum reveals, in some cases, a very complex pattern. In the instance of para-halo toluenes, long-range coupling to the methyl protons could clearly be observed. The central peak of the proton-coupled pattern for carbon 4 in *p*-iodotoluene is shown in Figure 3. No general trends were observed in the J_{42} coupling constant.

Conclusions. It has been found that the proton-coupled carbon-13 spectra of para-substituted toluenes yield "fingerprint" patterns which can be readily utilized for making signal assignments. In the instance of para-substituted toluenes, the proton–carbon coupling constants can be read directly from the spectrum. The coupling constants J_{22}, J_{33}, J_{35}, and J_{24} are substantially influenced by the nature of the para substituent. This can be rationalized, in part, to be due to changes in the hybridization of the individual C–H bonds. It is clear, however, that other factors such as changes in excitation energy[22] and π-bond orders[15b] play an important role in determining the magnitude of these long-range coupling constants.

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$$\delta = f\mathcal{F} + r\mathcal{R} = i$$

where i is the intercept of the equation and f and r are the regression coefficients; see ref 18. $\mathcal{F}$ and $\mathcal{R}$ are contributions arising from field and inductive effects taken together and resonance effects, respectively.
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Highly Stereoselective Methanolysis of Diazaoxyphospholenes

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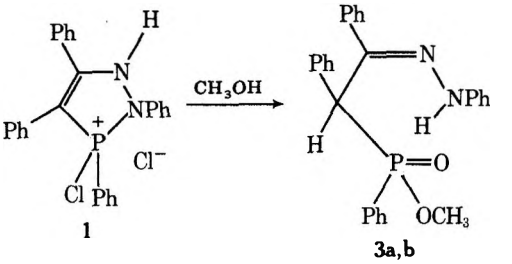
When the diazaoxyphospholene *cis*-**2** is placed in a neutral absolute methanol solution, it gives both isomerization to *trans*-**2** and ring opening with exclusive formation of only one (**3b**) of the four possible diastereomeric β-phenylhydrazone methylphosphinates **3**. In the same conditions the isomer *trans*-**2** gives the same diastereomer **3b**. The relative configuration of the two chiral centers in **3b** is tentatively assigned. The high stereoselectivity is explained in terms of pentacoordinate phosphorus intermediates, in which steric factors have a considerable influence on their stability.

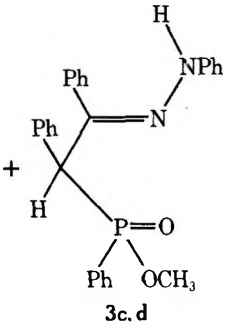
The discovery of the role played by a small ring containing phosphorus in determining the behavior of the nucleophilic displacement reaction at a phosphoryl center has led to wide research in this field.[1-5] Generally these attacks on phosphorus contained in a five- or four-membered ring are rationalized by assuming the formation of intermediates with pertacoordinated phosphorus.[5,6]

Considerable information is now available[6-8] on the factors which effect the stability of such phosphorane derivatives and control the process of ligand reorganization within them. Two factors turn out to be important in this connection: (a) the preference of electronegative groups for the apical positions and (b) the preference of a small-membered ring for an apical–equatorial situation.[7-10] However, the reaction stereochemistry may also be dependent on the steric interactions as well as on the specific reaction conditions.

In this paper we report a case in which a steric effect is the main factor in highly stereoselective stereochemical results.



1 3a,b



3c,d

Results

In previous communications we reported that the diazaphospholene cycloadduct **1** undergoes exclusive ring opening when treated with neutral absolute methanol,[11] while ring retention was observed when the adduct was treated with water under the same reaction conditions.[12] This unexpected behavior was rationalized[11] on the basis of the relative apicophilicities of hydroxyl and methoxy groups compared to the diaza group. Each one of the four diastereomeric β-phenylhydrazone methyl phosphinates **3** was isolated in pure form.

Configurational assignment about the C=N has been determined by proton NMR spectroscopy. From the data presented in Table I, it should be noted that the methine proton in isomers **3a** and **3b** resonates at lower magnetic fields (deshielded) than that of **3c** and **3d**, suggesting[13] that isomers **3a** and **3b** have the syn configuration defined as that in which the anilino and benzylic groups are on the same side of the C=N bond. Moreover, our NMR data were in good agreement with Karabatsos[14] on the analysis of the anisotropic effects of the benzene ring on the syn and anti methinic hydrogens.

Another NMR correlation which is potentially useful for configurational assignments involves the chemical shift difference in the NH proton resonance of diastereomers **3**. The NH of **3a** and **3b** is strongly intramolecularly bonded as evidenced from the low-resonance value.

In contrast the NH of the other forms **3c** and **3d**, incapable of this hydrogen bonding, resonates at higher magnetic field (masked by aromatic protons). Hence, in the diastereomers

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Table I. NMR Spectra of β-Phenylhydrazonephosphinates 3

Compd	Solvent	δ $POCH_3$	J_{POCH_3}	δ PCH	J_{PCH}	δ arom	δ NH
3a	$CDCl_3$	3.70 (d)	10.5	5.03 (d)	20.7	6.70–8.00 (m)	11.05
	C_6D_6	3.05 (d)	10.5	4.88 (d)	20.2	6.40–7.75 (m)	11.64
3b	$CDCl_3$	3.75 (d)	10.5	5.15 (d)	22.2	6.50–7.80 (m)	10.50
	C_6D_6	3.10 (d)	10.5	4.97 (d)	21.7	6.10–7.90 (m)	11.09
3c	$CDCl_3$	3.45 (d)	10.5	4.25 (d)	18.0	6.50–7.70 (m)	*b*
	C_6D_6	3.15 (d)	10.5	4.30 (d)	17.2	6.35–7.80 (m)	*b*
3d	$CDCl_3$	3.49 (d)	10.5	4.32 (d)	21.7	6.30–7.60 (m)	*b*
	C_6D_6	3.25 (d)	10.5	4.40 (d)	21.0	6.25–7.70 (m)	*b*

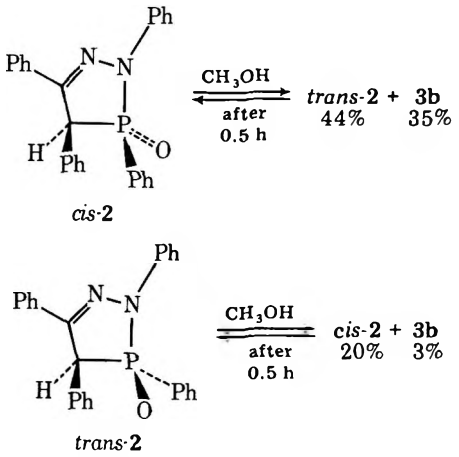
[a] Concentrations of 3–5 mol % phenylhydrazone were used; chemical shifts in parts per million from Me_4Si; *J* values in hertz. [b] Masked by aromatic protons.

Table II.[a] Methanolysis of *trans*- and *cis*-2

Time, h	% trans	% cis	% 3b	% 3a
		trans-2		
0	100	0	0	0
0.5	82	15	3	0
1	74	20	6	0
2	65	26	8	0
4	58	29	13	0
8	49	25	26	0
24	40	20	40	0
96	23	11	66	Traces
		cis-2		
0	0	100	0	0
0.5	43	21	36	0
1	38	19	43	0
2	35	18	45	0
4	27	14	59	0
8	21	10	69	0
24	19	8	70	3
96	18	7	68	7

[a] The ratios (±5%), determined as stated in the text, are the average of four separate reactions.

Scheme I[a]



[a] Only one enantiomer of each compound is shown in Scheme I, although racemic mixtures were used in this study.

3a and **3b** the NH and PO groups interacted and must therefore be on the same side of the C=N bond. The same relationship was confirmed by the infrared spectra (in chloroform solutions) of the isomers **3** (see the Experimental Section).

The UV spectra show the maximum of **3a** and **3b** (ε 18 000) displayed by +47 nm relative to the isomers **3c** and **3d** (ε 11 000). On the assumption that this bathochromic and hyperchromic shift must be the result of a change in configuration about the C=N bond, the isomer which absorbs with greater intensity at a longer wavelength is taken as the syn isomer. The anilino and conjugated aromatic ring are then on the opposite sides of the C=N bond and can attain coplanarity; this is not possible in the other configuration. Examples of analogous assignments are reported[15] in the literature for similar systems.

It is interesting to note that such isomers **3** are not interconvertible in several solvent solutions ($CDCl_3$, CH_2Cl_2, C_6H_6), even after many hours at room temperature under neutral conditions, while interconversion of isomers **3** was observed to occur slowly under acidic conditions.

We now report that when the diazaoxyphospholene *cis*-**2** (3,4-dihydro-2,3,4,5-tetraphenyl-2*H*-1,2,3-diazaphosphole 3-oxide)[16] is placed in a neutral absolute methanol solution at room temperature, after only 0.5 h both isomerization to *trans*-**2** and ring opening with exclusive formation of **3b** are obtained.

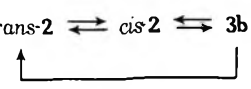
In the same conditions the isomer *trans*-**2** interconverts to *cis*-**2** but with a slower formation of the same diastereomer **3b** (Scheme I). The course of the reaction was followed by ^1H NMR appearance of the new $POCH_3$ and NH peaks and of the characteristic methine absorptions. The course of the reaction can also be conveniently monitored by TLC (silica gel). The different proportions at different times of each reaction are reported in Table II.

This methanolysis reaction can be considered highly *stereoselective* because both isomers **2** give exclusively the ring-opening isomer **3b**. The good stability observed in neutral methanol solution of these β-phenylhydrazone methyl phosphinates excludes the possibility of rapid isomerization of these compounds in the reaction mixture and confirms the "syn" configuration for the isomer **3b**.

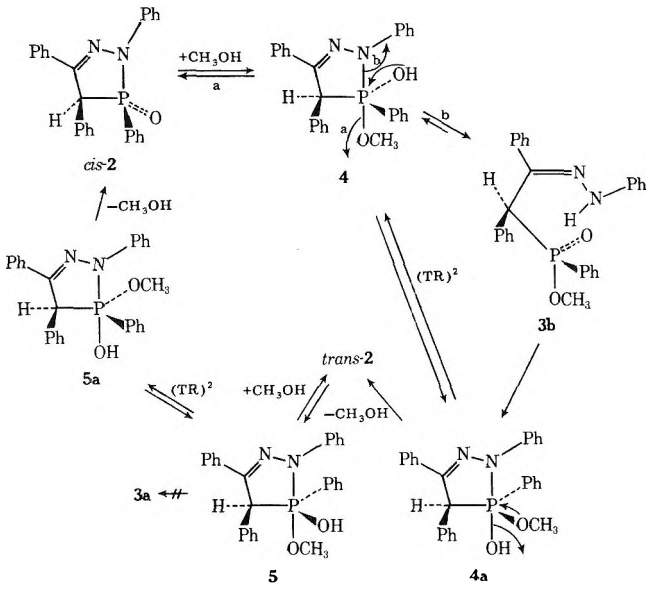
The observation that in the first times of the reaction the methanolysis of the *cis*-**2** isomer gives a larger extent of **3b** than *trans*-**2** could suggest that only the *cis*-**2** isomer undergoes direct ring opening. This could also be evidence of the fact that at first the *trans*-**2** must isomerize to *cis*-**2** and then *cis*-**2** undergoes ring opening.

Moreover, it should be noted that after about 4 days this methanolysis reaction leads to a *trans*-**2**:*cis*-**2**:**3b** ratio of about 20:10:70 in both cases; after 4 days this ratio remains constant if we neglect the increase of isomer **3a** which appears after longer reaction times.

On the other hand, when **3b** is left in a methanol solution, a slow recyclization with formation of both isomers is observed (as well as a slower collateral isomerization to **3a**) and after 4 days a *trans*-**2**:*cis*-**2**:(**3b** + **3a**) ratio of about 20:10:70 is obtained. In this mixture the **3b**:**3a** ratio is about 4:1. Then, if one neglects the slower collateral reaction of isomerization of ring-opening compounds **3**, the methanolysis reaction is simplified to



Scheme II[a]



[a] The TR and $(TR)^3$ processes[18] are neglected in Scheme II because they lead to unfavorable phosphorane intermediates with the NPh group in the equatorial position. However, the same stereochemical conclusions can be deduced if we assume that these intermediates are participating in the process.

Discussion

The large number of relatively stable phosphoranes[6,17] and the theoretical background that now exists on their structure and dynamic stereochemistry[5,8,9] provide an adequate interpretation for our findings. The mechanism we propose for the methanolysis here described (see Scheme II) involves the formation of metastable phosphoranes which presumably are sufficiently long-lived to allow stereomutation or positional interchange at pentacoordinated phosphorus by a Turnstile rotation (TR)[18] or a resultwise equivalent Berry pseudorotation (BPR).[19] However, the latter is less likely to be applied here because of the presence of the five-membered ring.[9]

The transformation of the tetracoordinate phosphorus compound **2** into the pentacoordinate species such as **4** results from an apical attack of methanol at the tetrahedral phosphorus atom.

Another set of phosphoranes enantiomeric with structure **4** is generated by attack at a different enantiotopic face of the phosphorus tetrahedron. However, as a rule,[6,9] five-membered rings are unable, for reasons of strain, to occupy the diequatorial position of the trigonal bipyramid and, therefore, only conformers with apical–equatorial rings are considered to participate in the permutational process. This preference in our heterocyclic system is strongly supported by the results[20] of an x-ray analysis of a *cis*-**2** parent compound (where there is a benzyl in C_5) which indicates that the C–P–N ring angle is 90°. This provides a considerable driving force for the formation of a trigonal-bipyramidal phosphorane intermediate such as **4** by the addition of a nucleophile to the phosphorus involving relatively small additional bond angle deformations.

On the other hand, since more electronegative atoms tend to prefer the apical positions,[8,9] the pentacoordinated structures with apical nitrogen may be favored over those with apical ring carbon; thus, we propose that the favored attack of the methanol is at the face opposite the P–N bond with formation of **4** which leads to **4a** after a $(TR)^2$ process.[18] Since there is an intramolecular overcrowding in trigonal-bipyramidal structures,[21] the steric factors will have a considerable influence on the stability of such phosphoranes. One consequence of this structural feature is that **4a** may be favored over **4** because it will avoid the steric interaction of P-phenyl with C_4-phenyl.

Apical departure (requirement of microscopic reversibility[2,22,23]) of the hydroxyl group from **4a** will yield the *trans*-**2.** Another possibility for the form **4** is to return to tetracoordination by apical cleavage of the P–N bond with formation of **3b** with inversion of the P chirality. Compound **3b** is expected to be thermodynamically more stable than **2** because ring strain is the main factor of instability in tetracoordinate phosphorus[21] (while the corresponding cyclic phosphoranes gain in stability). When methanol attacks the *trans*-**2** the hypothetical phosphorane **5,** which can also isomerize to **5a** by a $(TR)^2$, is obtained.

The form **5** should be more stable than **4** and **5a,** having less steric interference between the two phenyl groups. This gain in stability of **5** relative to **4** should reduce considerably the formation of **3a** via the ring opening of **5.** This is in agreement with the fact that **3b** appears exclusively also when pure *trans*-**2** is used in the methanolysis reaction, and in this case the slower formation of **3b** may be evidence that at first *trans*-**2** interconverts to *cis*-**2** which subsequently undergoes ring opening.

The data on recyclization are consistent with the proposed mechanism which involves in recyclization of **3b** the same hypothetical intermediate **4** (involved in ring opening). However, from our findings, we cannot exclude the possibility of formation of the intermediate **4a** in recyclization. This would represent an "irregular isomerization" [7] of **4** and **4a.** It is evident also that isomerization of **2** can proceed by this irregular process. That is

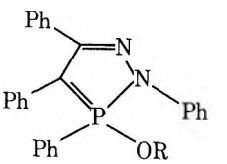
$$cis\text{-}\mathbf{2} \leftrightarrows \mathbf{4} \rightleftarrows \mathbf{3b} \rightarrow \mathbf{4a} \rightarrow trans\text{-}\mathbf{2}$$

However, the small amounts of **3b** in the first times of reduction suggest that this "irregular process" should not be the only process of isomerization of **2.** Both the **4** → *trans*-**2** and **5a** → *cis*-**2** conversions may be explained on the basis of a nucleophilic attack by hydroxyl (after its apical departure) at the methoxy carbon with C–O bond cleavage.

An analogous mechanism has been observed in phospholanium and phosphorinanium salts.[24] The rupture of the P–OH bond and the formation of the new C–O bond may be synchronous. Since there is more back-donation of electrons from the equatorial position than from the apical position toward the central phosphorus,[8] the equatorial methoxy carbon is activated to undergo the nucleophilic attack by the apical hydroxy.

The relatively strong apicophilicity of the diaza group[8,11] may be a further factor which favors this nucleophilic attack at carbon. In competition with this S_N2 attack at carbon the formation of an ylide form such as **6a** is possible, which may also be considered as an alternative route for stereomutation of **2.**

Indeed we have noted that deuterium exchange occurs when *cis*-**2** is dissolved in CH_3OD, but this exchange is slower than



6a, R = CH_3
b, R = H

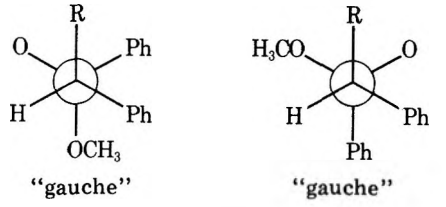
isomerization. Moreover, the formation of **6** is favored by its possible "aromatic character".[25]

However, an exclusive mechanism via ylide for stereomutation of **2** would require the involvement of pentacoordinate species in order to understand the other results. Similar ste-

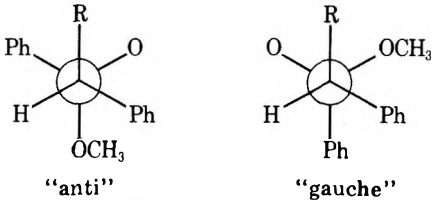
reoselective results in trichlorosilane reduction of this heterocyclic system were explained[26] on the basis of pentacoordinate intermediates.

From the proposed mechanism, the relative configuration of the two chiral centers in **3b** should be the one reported in Scheme II (*dl*-erythro form). The favored formation of an intramolecular hydrogen bonding between NH and P=O groups[27] in the isomer **3b** may favor the "gauche" rotamers with respect to the "anti" rotamer. On the other hand, in the isomer **3a** (*dl*-threo form) the same hydrogen bonding will favor only one of the "gauche" forms and the "anti" form.

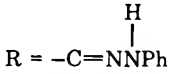
An examination of these assumed predominant conformations reveals that there is a larger *cis*-Ph character in **3a** than in **3b**, as the Newman projections show. This is supported



3b, *dl*-erythro form



3a, *dl*-threo form



by the NMR data reported in Table I. The methine proton is more shielded and has a smaller value for coupling constant J_{PCH} in **3a** than in **3b**. An equal behavior is observed for the methoxy group of those isomers. This configurational assignment of **3b** would confirm the proposed mechanism.

In conclusion, we think that our results clearly indicate that, because of the greater crowding in trigonal-bipyramidal phosphoranes, steric factors play a large part in determining the stereochemistry of nucleophilic attack on phosphorus and emphasize the fine balance between pseudorotation and product formation in phosphorane intermediates.

Experimental Section

All reactions were carried out with rigorous exclusion of oxygen under a nitrogen atmosphere. Methanol was freshly dried with magnesium. **1** was prepared by the previously[12] described method. Melting points were determined on a Kofler hot-stage and are uncorrected.

The IR spectra were determined on a Perkin-Elmer spectrometer Model 257 and the UV spectra on a Perkin-Elmer Model 402. The NMR spectra were recorded on a Jeol JMMC 60 HC spectrometer. ^1H NMR chemical shifts are expressed in parts per million from internal Me_4Si. The microanalyses were performed on mixtures of the isomers as well as on pure isomers. The results obtained were practically identical.

Reaction of 1 with Methanol. Separation of β-Phenylhydrazone Phosphinates 3. A slight excess of dry methanol (1 mL) was added to 9.2 g (0.02 mol) of **1** in 70 mL of dry methylene chloride. An exothermic reaction and evolution of CH_3Cl were observed. The mixture was stirred for 20 min at 20 °C and then titrated with 20% sodium hydroxide to pH 7. This solution was extracted with 5 × 100 mL of CH_2Cl_2. The combined organic layers were dried over sodium sulfate and evaporated to give a crude solid which after crystallization from CH_2Cl_2–hexane gave 5.70 g (65%) of **3**. Only small amounts (~10%) of **2** were obtained. The NMR spectrum ($CDCl_3$) of the crude product showed (**3a** + **3b**) and (**3c** + **3d**) in 30:70 ratio.

Separation of small amounts of the diastereomers was accomplished by chromatography on a silica gel column [elution with benzene–ether (8:2) mixture]. The isomer **3a** (R_f 0.55) had mp 126–128 °C; UV max ($CHCl_3$) 340 nm (ε 18 000); IR ($CHCl_3$) 3240 (NH), 1235 cm^{-1} (P=O). **3b** (R_f 0.48) had mp 157–159 °C; UV max ($CHCl_3$) 340 nm (ε 18 000); IR ($CHCl_3$) 3240 (NH), 1240 cm^{-1} (P=O). **3c** (R_f 0.16) had mp 154–156 °C; UV max ($CHCl_3$) 293 nm (ε 11 000); IR ($CHCl_3$) 3330 (NH), 1260 cm^{-1} (P=O). **3d** (R_f 0.10) had mp 119–121 °C; UV max ($CHCl_3$) 293 nm (ε 11 000); IR ($CHCl_3$) 3330 (NH), 1260 cm^{-1} (P=O).

In all the four isomers of **3**, strong bonds in the infrared region (KBr) were caused by the P=O stretching vibrations (1210 and 1260 cm^{-1}), by the $POCH_3$ stretchings (1020 and 1110 cm^{-1}), and the PPh stretching (1440 cm^{-1}). Strong bonds were found also at 1600 and 1500 cm^{-1}.

The NMR data ($CDCl_3$ and C_6D_6) are reported in Table I. Anal. Calcd for $C_{27}H_{25}N_2O_2P$: C, 73.62; H, 5.67; N, 6.36. Found: C, 73.86; H, 5.64; N, 6.20.

Methanolysis of *cis*-2. A solution of pure *cis*-**2** (1.22 g) in dry methanol (420 mL) was kept at room temperature under nitrogen in a flask sealed with a serum cap. At appropriate intervals of time (until no further appreciable changes were noted) aliquots (40 mL) were removed from the flask by using a hypodermic syringe, in order to prevent contact of the reaction solution with moisture. The solvent was stripped off and the residue was dissolved into $CDCl_3$.

NMR analysis of these samples showed the presence of *trans*-**2** and the exclusive formation of the ring-opening isomer **3b**. After 4 days a mixture was obtained in which the *trans*-**2**:*cis*-**2**:**3b** ratio was ca. 20:10:70 (obtained by integration of the methoxy and methinic NMR absorptions). The composition of the samples is reported in Table II. No changes were observed after 4 days if we neglected the slow increase of isomer **3b** which appeared after longer reaction times.

A separate but identical reaction was allowed to proceed for 4 days and the whole resulting mixture was chromatographed using benzene–ether as eluent yielding the following: first fraction **3a**, mp 126–128 °C (5%); second fraction **3b**, map 157–159 °C (65%); third fraction *trans*-**2**, mp 202–204 °C (17%); fourth fraction *cis*-**2**, mp 174–177 °C (10%). Identification of the products was based on comparison of their spectroscopic data with those of pure isomers obtained from **1**.

Methanolysis of *trans*-2. The same procedure as above was followed using 1.22 g of pure *trans*-**2** in 420 mL of dry methanol. Interconversion of isomer **2** was observed but in the first times of the reaction the percent of **3** was smaller than the one given by *cis*-**2**.

After 4 days a product ratio which was almost identical with that obtained with the cis isomer was observed. The reaction was repeated several times with each isomer and the ratios at different intervals of time reported in Table II are the average of four separate reactions.

Sometimes these ratios may vary for separate reactions and this variability appears to be caused by traces of water in the used methanol. In fact, when the methanol was freshly dried with magnesium, when care was taken to clean and dry the apparatus thoroughly, and when the methanolysis flask was sealed with a serum cap, then the yield of **3b** after 96 h was ~70%. When 1 equiv of water was deliberately added, the yield of **3b** fell to 11%.

When pure isomer *cis*-**2** (0.66 g) was dissolved in CH_3OD (21 mL), a detectable exchange of methine protons and isomer crossover without exchange was observed. The percent exchange was followed by integration of the area in the methine region relative to the area of aromatic protons. After 24 h ~30% exchange in the products was observed.

Recyclization of 3b in Methanol Solution. A solution of pure **3b** (0.66 g) in dry methanol (210 mL) was kept at room temperature under nitrogen in a flask sealed with a serum cap. Aliquots (40 mL) were removed at appropriate intervals of time, the solvent was stripped off, and the residue was dissolved into $CDCl_3$.

NMR analysis of these samples showed the presence of **2** (cis and trans) and of **3a**.

After 4 days a *trans*-**2**:*cis*-**2**:**3b**:**3a** ratio of 16:8:61:15 was obtained. After 8 days this ratio became 17:8:53:22. After 10 days **3c** and **3d** were detectable in appreciable extent. No recyclization was obtained when pure **3c** (or **3d**) was dissolved in dry methanol under the same conditions of **3b**.

Acknowledgements. We wish to thank the Italian CNR for financial support.

Registry No.—**1** (charged form), 51849-77-5; **1** (uncharged forms), 64057-38-1; *cis*-**2**, 64057-39-2; *trans*-**2**, 64057-40-5; **3a**, 64090-79-5; **3b**, 64090-78-4; (*z*)-*dl*-*erythro*-**3**, 64129-88-0; (*Z*)-*dl*-*threo*-**3**, 64090-77-3.

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Kinetic Study of the *N*-Bromosuccinimide Bromination of Some 4-Substituted 3-Cyanotoluenes

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Twelve 4-substituted 3-cyanotoluenes (3-X) were prepared from 4-substituted 3-aminotoluenes, 4-amino-3-nitrotoluene, or *m*-tolunitrile (3-H). The relative rates of NBS bromination of 3-X vs. 3-H were determined in benzene at 80 °C. These relative rates, k/k_0, increased in the following substituent order: $NO_2 < CN < Ac < F < Cl < Br < I < H < Ph < CH_3 < N{=}NPh < OCH_3$. The substituent effects were discussed in terms of polar transition state and bond dissociation energy arguments. A linear dependence on σ^+ was found with $\rho = -1.13 \pm 0.12$. Several withdrawing substituents were believed to provide "extra" resonance in this free-radical reaction.

Substituent influences on the homolytic process have been studied in a wide variety of reactions. In spite of this, the effects, both stabilizing and destabilizing, of substituents on free-radical sites are not nearly as well understood as the corresponding substituent influences on positive and negative sites in a molecule. Linear free-energy studies of the Hammett type have proven to be a major tool used to help elucidate organic reaction mechanisms of both the heterolytic and homolytic types. One of the systems that has yielded much valuable information about free-radical substituent effects is the H atom abstraction reactions of substituted toluenes. Most common free radicals have been reacted with substituted toluenes. Russell[1] and Pryor[2] list nearly 20 different free radicals that have been studied in this reaction including: H·, Ph·, CH_3·, *t*-BuO·, Cl·, Br·, etc. Because of this wealth of information available on the benzyl free radical, it was chosen as the substrate in this study.

Many H atom abstraction reactions are known to be dependent on σ or σ^+. The usual explanation of this is illustrated by eq 1, where Y–H represents a substituted toluene, ·Z the abstracting radical, and Y· a benzyl radical. The susceptibility of the transition state to polar influences is represented by **2b** and **2c**, where **2b** is important when Z is electronegative and **2c** is important when Z is electropositive. This explanation had become so well accepted that if polar effects were possible they were expected to overshadow the free radical influences.

Recently, a paradigm shift[3] from this polar transition state explanation to a bond dissociation energy (E) explanation was attempted by Zavitsas.[4] Pryor[5] and Henderson[6] have successfully defended the polar transition state explanation by finding several reactions that have positive ρ values consistent with contributions of **2c** above but inconsistent with Zavitsas' explanation. It is also very difficult experimentally to determine accurate bond dissociation energies for benzyl C–H bonds whose only difference is a meta or para substituent.

$$\underset{\mathbf{1}}{Y\text{–}H} + \cdot Z \rightarrow [\underset{\mathbf{2a}}{\dot{Y}\dot{H}Z} \leftrightarrow \underset{\mathbf{2b}}{Y^+\dot{H}Z^-} \leftrightarrow \underset{\mathbf{2c}}{Y^-\dot{H}Z^+}]^{\ddagger} \rightarrow Y\cdot + H\text{–}Z \quad (1)$$

Most attempts to study free-radical influences in H atom abstraction reactions have been to decrease the electronegativity of Z in eq 1 so that the polar effects will become less important. This has been successfully accomplished by using ·Z = ·CH_3,[7] ·Ph,[8] or ·H;[2] and sure enough ρ was found to be near zero in each case. The approach used in this work is to diminish the polar effects by a substrate change (addition of a *m*-CN group) instead of a change in Z. The strongly electron-withdrawing cyano substituent should increase the potential energy of the benzyl cationic contributor **2b**, and consequently the free-radical contributor **2a** should be relatively more important. This is another way of saying the polar effects should not be as important in this free radical reaction.

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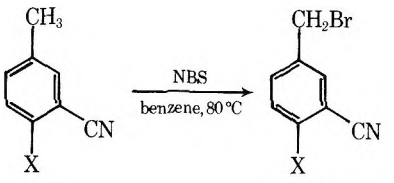
Since the abstracting radical is Br·, **2c** is not important in the transition state of this reaction.

The model system chosen for study was the *N*-bromosuccinimide (NBS) bromination of 4-substituted 3-cyanotoluenes (3-X) vs. *m*-tolunitrile (3-H) in benzene at 80 °C, see eq 2. This



3 4 (2)

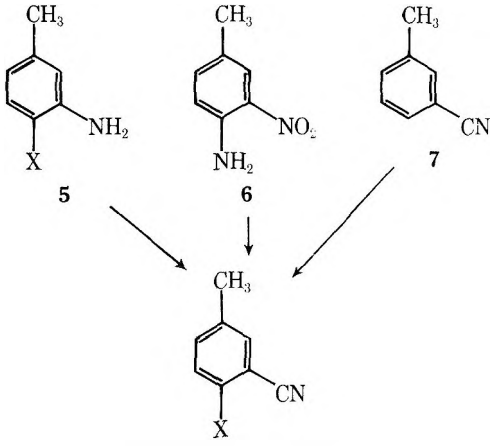
reaction was chosen because its mechanism is well established.[9] Twelve substituents (X) were studied here, covering the entire range of electron donor and acceptor substituents.

Results

Toluene Syntheses. The 4-substituted 3-cyanotoluenes (**3**) used in this work were prepared from one of three different precursors: 4-substituted 3-aminotoluenes (**5**), 4-amino-3-nitrotoluene (**6**), or *m*-tolunitrile (**7**); see eq 3.

Three commercially available amines, 3-amino-4-chlorotoluene, 3-amino-4-methoxytoluene, and 2,5-dimethylaniline, were each diazotized and then reacted with CuCN via a Sandmeyer reaction to give 3 (X = Cl, OCH_3, CH_3).

Three toluenes **3** (X = CN, I, Ph) were prepared from **6** by way of **5**. Diazotization of 4-amino-3-nitrotoluene (**6**) was followed by treatment with CuCN, KI, or benzene and base (Gomberg reaction). Reduction of the 3-nitro group in these three compounds with iron and acetic acid gave the three amines **5** (X = CN, I, Ph). These amines were then converted to **3** (X = CN, I, Ph) by repetition of the sequence used above to convert **5** to **3**.



(3)

3, X = Cl, CH_3, OCH_3, from **5**
X = CN, I, Ph, Ac from **6**
X = NO_2, –N=NPh, F, Br from **7**

4-Acetyl-3-cyanotoluene was prepared by an interesting series of reactions. Hydrolysis of 4-cyano-3-nitrotoluene with 50% sulfuric acid gave the benzoic acid derivative which was then converted to the acid chloride with thionyl chloride. The acid chloride was then added to an ether slurry of ethoxymagnesium malonate to form the benzoyl malonate derivative using a procedure developed by Hauser.[10] Hydrolysis and decarboxylation gave 4-acetyl-3-nitrotoluene in 52% yield. The 3-nitro group was then converted into the nitrile in the same manner as above, giving **3**-Ac.

The last four toluenes were made from *m*-tolunitrile (**7**). Nitration of **7** gave a 60% yield of **3**-NO_2 after removal of 5-cyano-2-nitrotoluene by steam distillation. Reduction of 4-nitro-3-cyanotoluene with iron and acetic acid gave 4-amino-3-cyanotoluene, which was then converted to **3**-N=NPh by addition of nitrosobenzene. 4-Amino-3-cyanotoluene was diazotized and then converted to **3**-F by the Shiemann reaction and to **3**-Br by the Sandmeyer reaction.

Table I. Relative Rates of NBS Bromination of Some Toluenes

X	Registry no. (3-X)	k/k_0 3-X	k/k_0 *p*-X-Ph-CH_3[a]
OCH_3	53078-70-9	10.34 ± 0.85	12.39
N=NPh	57495-20-2	3.55 ± 0.06	1.66[b]
CH_3	13730-09-1	2.70 ± 0.04[c]	2.62
Ph	64113-85-5	2.41 ± 0.02	1.83[b]
H	620-22-4	1.00	1.00
I	42872-86-6	0.90 ± 0.01	0.64[b]
Br	42872-83-3	0.90 ± 0.01	0.60[b]
Cl	4387-32-0	0.82 ± 0.04	0.72
F	64113-84-4	0.72 ± 0.02	1.28[b]
$C(O)CH_3$	64113-87-7	0.63 ± 0.02	0.19[b]
CN	63089-50-9	0.24 ± 0.03	0.11
NO_2	64113-86-6	0.13 ± 0.01	0.07[b]

[a] Reference 9a. [b] Estimated using σ^+ and $\rho = -1.46$. [c] Value for bromination at the 5-methyl only of 2,5-dimethylbenzonitrile.[11]

Kinetic Results. The competitive rates of NBS bromination of each toluene **3**-X vs. the reference toluene **3**-H were done in benzene solvent at 80 °C. These conditions provide a homogeneous solution and thus simplify the kinetics. Good reproducibility was found if the initial amounts of each toluene were precalculated (after a preliminary run) so that approximately equal amounts of benzyl bromide products were formed.

Table I shows the results of these relative rate studies. The most reactive toluene, **3**-OCH_3, was 80 times more reactive than the least reactive one, **3**-NO_2. For sake of comparison, the kinetic data for the monosubstituted toluenes[9a] are also shown in Table I.

Six other toluenes **3**-X were also prepared and relative rate studies were attempted on these. The kinetics of bromination of these compounds were unsuccessful for a variety of reasons. Toluenes **3**-NHAc and **3**-NHBz were insoluble under the reaction conditions. **3**-NH_2 and **3**-SPh underwent side reactions that interfered with the primary reaction. In **3**-CHO the aldehyde H, not the benzylic H, was brominated. **3**-CO_2CH_3 brominated in the correct position, but the carbomethoxy H's interfered with the benzyl H's in the NMR of the benzyl bromide products, making analysis impossible.

Discussion

The NBS bromination of monosubstituted toluenes in benzene at 80 °C was studied by Pearson and Martin.[9a] By studying six substituents they found an excellent correlation with σ^+, $\rho = -1.46$, $r = 0.997$. The mechanism of this reaction has been shown to involve bromine atoms in the H-abstraction step,[9a] with the NBS acting as a source of bromine. The substituent effects for this reaction have normally been explained by the polar transition state argument. This was illustrated earlier in eq 1, where **2b** represented the polar influence on the transition state of this free-radical reaction. This explanation is also illustrated in Figure 1. The placement of a substituent on toluene Y–H causes the transition state of this reaction to be stabilized (OCH_3) or destabilized (CN) with the appropriate increase or decrease in rate. Thus, *p*-methoxytoluene reacts 113 times as fast as *p*-cyanotoluene in the reaction. Zavitsas' bond dissociation energy (E) argument would predict the same result for this reaction by postulating the origin of the substituent effect, residing in the E's of the C–H bonds being broken in the reaction. This explanation is illustrated

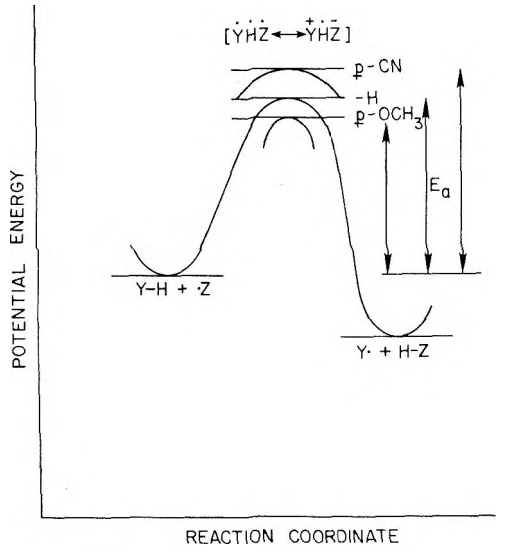


Figure 1. Potential energy diagram for a H-abstraction reaction showing the polar transition state explanation for substituent effects in free-radical reactions.

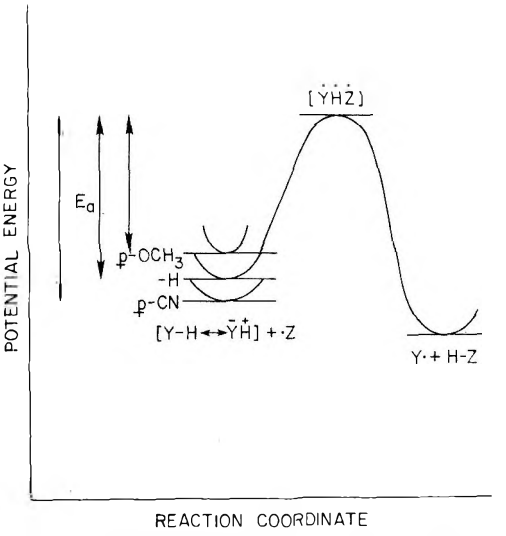


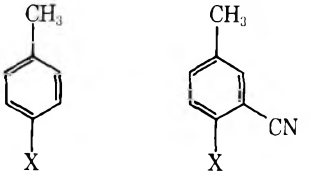
Figure 2. Potential energy diagram for a H-abstraction reaction showing the bond dissociation energy explanation for substituent effects in free-radical reactions.

in Figure 2. In this case the transition state is assumed to be the same for each substituent, but the benzyl C–H bond of *p*-cyanotoluene is considered stabilized by the cyano substituent. This argument puts the emphasis on ground-state influences instead of transition-state influences. Note the net result is the same in each case: the cyanotoluene is slowest. Essentially the BDE argument places the polarity in the ground state instead of in the transition state. The point of agreement is that the activation energy for *p*-cyanotoluene is larger than that of *p*-methoxytoluene.

Our system compares the relative rates of NBS bromination of 4-substituted 3-cyanotoluenes (**3**-X) with the reference substrate *m*-tolunitrile (**3**-H). Compounds **3**-X are disubstituted toluenes with a *m*-cyano group on each toluene in addition to the variable 4-substituent. The *m*-cyano group was added because it is a strong electron-withdrawing group and should increase the activation energy of **3**-X relative to the toluenes without the *m*-cyano group. In the polar transition state explanation, this increase in E_a for the cyano group makes the polar form **2b** of higher energy and therefore less important. This diminished importance would be seen experimentally as a smaller value of ρ in the disubstituted series **3**. Two other factors that normally affect the magnitude of ρ were kept constant here. These are the amount of bond breaking in the transition state and the electronegativity of the H-abstracting species ·Z. The linear geometry of the cyano group provided a minimum steric interference with adjacent 4-substituents compared to other electron-withdrawing groups like nitro or acetyl.

Some substituents are known to give "extra" resonance to free-radical sites due to strong direct resonance between the substituent and the free-radical site. The *p*-cyano group has been postulated to provide such additional stability in the free-radical methylation of benzonitrile[12] and the unusual stability of the tricyanomethyl radical.[13] This type of "extra" resonance would be possible for a 4-substituent that can directly resonate with a benzyl free-radical site. This "extra" resonance would also stabilize free-radical form **2a** in a manner analogous to that given the polar form **2b** already discussed. Substituents that stabilize **2a** but destabilize **2b** would be of special interest. Electron-withdrawing substituents fit this category.

Some of the kinetic data of Table I will be cited here that relates to the concept of "extra" resonance. The compounds whose rates are to be compared are formed by placing a 4-substituent on toluene and *m*-tolunitrile, respectively. The first two cases, CN and Ac, provide a relative rate increase in **3** that is 2.2 and 3.3 times that seen in **8**. This is a fairly large increase. In contrast F causes a rate decrease in **3** relative to **8**. The "extra" resonance of the Ac group is probably also retarded by steric inhibition of resonance from the 3-cyano group.



8	**3**	$k(3)/k(8)$
$k_{CN/H} = 0.11$	$k_{CN/H} = 0.24$	2.2
$k_{Ac/H} = 0.19$	$k_{Ac/H} = 0.63$	3.3
$k_{F/H} = 1.28$	$k_{F/H} = 0.72$	0.6

Some general comments need to be made about the importance of steric inhibition of resonance in those benzyl radicals where the 3-cyano substituent can interfere with the planarity of the 4-substituent. This interference should be important for three substituents—NO_2, Ac, and Ph. The effect should be most pronounced for phenyl, since it is the largest of the three. This steric situation is analogous to optically active ortho-substituted biphenyls where coplanarity is not possible due to the steric interaction. In the benzyl free-radical from **3**-Ph, it is estimated that that the two phenyl groups are about 60° out of plane. This steric effect and the small electron-withdrawing nature of the phenyl group probably account for the lack of much "extra" resonance from the phenyl substituent.

A statistical analysis was performed to see if our kinetic data of Table I was linearly correlated with some of the more common Hammett substituent constants. The results are shown in Table II. The best correlation was found with σ^+ as expected, with $\rho = -1.13 \pm 0.12$, $r = 0.950$. The other correlations fall into the so-called region of noncorrelation with $r < 0.9$. This ρ^+ value of -1.13 is appreciably less than the value of -1.46 found in the monosubstituted toluene series, see Figure 3. This smaller ρ^+ value is consistent with polar influences being less important in **3**-X than in **8**-X. The correlation with σ was much poorer than σ^+ as measured by both correlation coefficient and standard deviation of ρ. This was

Table II. Correlations of Log k/k_0 with Some Hammett Substituent Constants for 3-X

Substituent constant	Ref[a]	ρ	r	n
σ^+	17	−1.13 ± 0.12	0.950	12
σ^n	18	−1.43 ± 0.29	0.869	10
σ	19, 20	−1.38 ± 0.27	0.854	12
σ^-	19, 21	−0.92 ± 0.31	0.774	8
σ'	22	−1.52 ± 0.55	0.659	12
σ_R[b]	19, 20, 22	−1.32 ± 0.61	0.566	12
E_s	22	0.29 ± 0.25	0.399	9

[a] Values of substituent constants used are given in these references. [b] $\sigma_R = \sigma_p - \sigma'$.

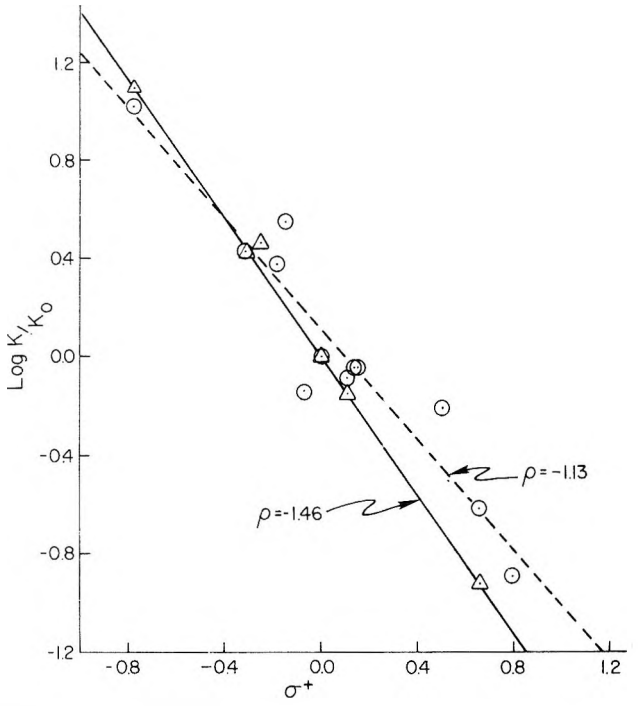


Figure 3. Plot of rates of NBS bromination vs. σ^+ for monosubstituted toluenes (triangles) and for 3-X (circles).

also the case with monosubstituted toluenes 8. Some other parameters were also checked for correlations and found to be poorer than those listed in Table II. These include σ_R^+,[14] molar refractivity,[15] van der Waals volume,[16] and lipophilicity.[15]

In conclusion, the rates of NBS bromination of toluenes 3-X are adequately explained by the usual polar transition state explanation involving a reduced dependence on polar effects compared with monosubstituted toluenes. "Extra" resonance is believed to be found for several electron-withdrawing substituents.

Experimental Section

Materials. Benzene, *N*-bromosuccimimide (Aldrich), phthalide (Aldrich), and 2,2′-azobisisobutyronitrile (K&K) were all purified by standard procedures prior to use. *m*-Tolunitrile (K&K) was distilled and a center cut used.

All infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded with a Varian A-60. Elemental analyses were performed by Galbraith Laboratories, Inc.

4-Chloro-3-cyanotoluene (3-Cl). 3-Amino-4-chlorotoluene (Eastman), 21.2 g (0.15 mol), was added to a cold solution of sulfuric acid and diazotized with 11.25 g (0.16 mol) of sodium nitrite. The diazonium solution was added to a warm solution of 44.5 g (0.5 mol) of cuprous cyanide and 33.5 g (0.5 mol) of potassium cyanide in a typical Sandmeyer reaction. After heating for 1 h on a steam bath, the mixture was cooled, extracted with ether, washed with water, 6 M hydrochloric acid, and 5% sodium bicarbonate, and dried with magnesium sulfate. Removal of solvent followed by recrystallization from 50% ethanol gave 6.3 g (28%) of 4-chloro-3-cyanotoluene: mp 56–57 °C; IR (CCl_4) 2225 cm^{-1} (C≡N); NMR (CCl_4) δ 7.2–7.5 (m, 3 H, Ar-**H**), 2.3 (s, 3 H, Ar-CH_3).

Anal. Calcd for C_8H_6ClN: C, 63.38; H, 4.00; N, 9.24. Found: C, 63.31; H, 3.84; N, 9.05.

2,5-Dimethylbenzonitrile (3-CH_3). A Sandmeyer reaction was used to convert 12.0 g (0.1 mol) of 2,5-dimethylaniline to the nitrile: yield 6 g (47%); bp 66–67 °C (1.4 Torr) [lit.[23] bp 104–105 °C (18 Torr)].

3-Cyano-4-methoxytoluene (3-OCH_3). Using the Sandmeyer procedure as above, 3-amino-4-methoxytoluene, 20.5 g (0.15 mol), was converted into 9 g (41%) of 4-cyano-4-methoxytoluene: bp 85–86 °C (0.4 Torr) [lit.[24] bp 148–150 °C (18 Torr)].

3,4-Dicyanotoluene (3-CN). 4-Amino-3-nitrotoluene (Baker), 75 g (0.5 mol), was converted to 4-cyano-3-nitrotoluene by the Sandmeyer procedure. Reduction of the crude 4-cyano-3-nitrotoluene with iron and acetic acid followed by recrystallization from 30% ethanol gave 15 g (23%) of 3-amino-4-cyanotoluene: mp 93–95 °C (lit.[25] mp 92.0–94.5 °C). The method of Findeklee[26] was then used to convert 3.0 g (0.022 mol) of 3-amino-4-cyanotoluene into 0.75 g (23%) of 3,4-dicyanotoluene: mp 118–120 °C (lit.[26] mp 118–120 °C).

3-Cyano-4-iodotoluene (3-I). 4-Iodo-3-nitrotoluene was prepared from 4-amino-3-nitrotoluene in 67% yield by the procedure of Carlin and Foltz.[27] 4-Iodo-3-nitrotoluene, 25 g (0.095 mol), was added to 28 g of iron filings and 140 mL of 50% aqueous acetic acid. The mixture was heated for a few minutes to start the reaction and was kept below 50 °C for 1 h. Neutralization followed by steam distillation gave 18 g (81%) of the amine, mp 33–35 °C (lit.[28] mp 37.5 °C). The method of Hodgson[29] was then used to convert the amine to 3-cyano-4-iodotoluene in 28% yield. Recrystallization from petroleum ether gave orange crystals: mp 49–51 °C; IR (CCl_4) 2225 cm^{-1} (C≡N); NMR (CCl_4) δ 7.0–8.0 (m, 3 H, Ar-H), 2.4 (s, 3 H, Ar-CH_3).

Anal. Calcd for C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 40.42; H, 2.36; N, 6.00.

3-Cyano-4-phenyltoluene (3-Ph). Using the procedure of Ritchie,[30] 71 g (0.46 mol) of 4-amino-3-nitrotoluene was converted to 46 g (46%) of 3-nitro-4-phenyltoluene, bp 140–142 °C (0.3 Torr) [lit.[30] bp 207–208 °C (28 Torr)]. 3-Nitro-4-phenyltoluene, 20 g (0.094 mol), 20 g of mossy tin, and 100 mL of concentrated HCl were refluxed overnight. The mixture was filtered, made basic, and extracted with ether. Evaporation of the solvent left 10 g of the crude amine, which was converted to the nitrile by the usual diazotization procedure. Recyrstallization from hexane gave 2.0 g (19%) of 3-cyano-4-phenyltoluene: mp 79–80 °C; IR (CCl_4) 2225 cm^{-1} (CN); NMR (CCl_4) δ 7.3–8.1 (m, 8 H, Ar-**H**), 2.5 (s, 3 H, Ar-CH_3).

Anal. Calcd for $C_{14}H_{11}N$: C, 87.00; H, 5.75; N, 7.25. Found: C, 87.10; H, 5.52; N, 7.19.

4-Acetyl-3-cyanotoluene (3-Ac). The procedure of Joachim and Claus[31] was used to convert 4-cyano-3-nitrotoluene to 4-methyl-2-nitrobenzoic acid. The acid chloride was then obtained from the acid and thionyl chloride. An ether solution of the acid chloride was treated with an ether solution of ethoxymagnesium malonate using the method of Hauser.[10] After refluxing for 1 h, the magnesium complex was hydrolyzed with 20% sulfuric acid. Removal of the ether gave a dark oil which was hydrolyzed and decarboxylated by refluxing with an aqueous mixture of acetic and sulfuric acid. Purification gave a 59% yield of 4-acetyl-3-nitrotoluene. The reduction of 4-acetyl-3-nitrotoluene to the amine was carried out by the procedure of Kenneford.[32] A 46% yield of 4-acetyl-3-aminotoluene, mp 54–55 °C (lit.[32] mp 55–56 °C), was obtained. The amine was then converted to 4-acetyl-3-cyanotoluene by the method of Hodgson and Heyworth.[29] 4-Acetyl-3-cyanotoluene was obtained as a white solid: mp 73–74 °C; IR ($CHCl_3$) 2225 (CN), 1710 cm^{-1} (C=O); NMR (benzene) δ 3.0 (s, 3 H, Ar-CH_3), 1.2 (s, 3 H, Ac).

Anal. Calcd for $C_{10}H_9NO$: C, 75.44; H, 5.71; N, 8.80. Found: C, 75.76; H, 5.63; N, 8.88.

3-Cyano-4-nitrotoluene (3-NO_2). *m*-Tolunitrile, 15 g (0.13 mol), was nitrated by the method of Macovski[33] to give 13 g (65%) of the nitro product. Recrystallization from 50% ethanol (charcoal) gave the white solid 3-cyano-4-nitrotoluene: mp 93–94 °C (lit.[26] 93–94 °C).

4-Amino-3-cyanotoluene (3-NH_2). 3-Cyano-4-nitrotoluene, 14 g (0.086 mol), was reduced with iron and acetic acid to give a yellow solid. Recrystallization from 30% ethanol (charcoal) yielded 8.0 g (71%) of 4-amino-3-cyanotoluene as a white solid: mp 59–61 °C (lit.[26] 63 °C).

3-Cyano-4-phenylazotoluene (3-N=NPh). 4-Amino-3-cyanotoluene was converted to 3-cyano-4-phenylazotoluene in 22% yield:[19] mp 100–102 °C.

3-Cyano-4-fluorotoluene (3-F). 4-Amino-3-cyanotoluene was converted to the fluoro compound by the Schiemann reaction. Diazotization of 6.3 g (0.046 mol) of 4-amino-3-cyanotoluene in 40% fluoboric acid at 0 °C gave the diazonium salt, which was filtered and dried. The salt was heated slowly with a low flame in a flask fitted with a condenser. After the decomposition, the reaction mixture was dissolved in ether, washed with water and 5% sodium bicarbonate, and dried. Removal of solvent and crystallization from petroleum ether gave 0.9 g (15%) of 3-cyano-4-fluorotoluene: mp 44–46 °C; IR (CCl_4) 2225 cm^{-1} (CN); NMR (CCl_4) δ 6.6–7.8 (m, 3 H, Ar-**H**), 2.3 (s, 3 H, Ar-CH_3).

4-Bromo-3-cyanotoluene (3-Br). 4-Amino-3-cyanotoluene, 5.0 g (0.018 mol), was converted to 4.0 g (54%) of 4-bromo-3-cyanotoluene by the Sandmeyer reaction. Steam distillation of the resulting mixture gave a white solid that melted at 64–65 °C (lit.[34] mp 65 °C) after recrystallization from 40% methanol.

Kinetic Procedure. The relative rates of NBS bromination of toluenes **3** were determined by the method of Martin and Pearson.[9a] A mixture of 577.3 mg of 4-chloro-3-cyanotoluene, 297.8 mg of *m*-tolunitrile, 103.7 mg of NBS, and a catalytic amount of AIBN were diluted to 10.0 mL with benzene. The mixture was degassed three times using a freeze–thaw procedure and dry ice–acetone cooling. The tube containing the degassed mixture was sealed and placed in a bath thermostated at 80 °C for 3 h. A UV lamp was placed about 20 cm from the tube to ensure efficient initiation. The cooled mixture was evaporated to 2 mL and then analyzed by NMR using added phthalide (45.1 mg) to determine the yield of the reaction. The relative amounts of benzyl bromide products were determined by integration of the benzyl H's near δ 4.4 with an average of ten integrals taken for each determination. The identity of the benzyl singlets was determined by adding a known solution of *m*-cyanobenzyl bromide and observing the increase in area of one of the singlets. Duplicate runs at different concentrations agreed with 5%.

The relative rates were obtained using the integrated form of the competitive kinetic equation $k/k_0 = \log((A - X)/A)/\log((B - Y)/B)$, where A and B are the amounts of **3**-X and **3**-H, respectively, and X and Y are the amounts of the corresponding benzyl bromide products.

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Registry No.—3-Amino-4-chlorotoluene, 95-81-8; 2,5-dimethylaniline, 85-78-3; 3-amino-4-methoxytoluene, 120-71-8; 4-amino-3-nitrotoluene, 89-62-3; 4-cyano-3-nitrotoluene, 26830-95-5; 3-amino-4-cyanotoluene, 26830-96-6; 3-amino-4-iodotoluene, 13194-69-9; 3-nitro-4-phenyltoluene, 39556-87-5; 4-amino-3-cyanotoluene, 5925-93-9; 2-cyano-4-methylbenzenediazonium tetrafluoroborate, 64163-00-4.

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Substituent Effects in Free-Radical Reactions. A Study of 4-Substituted 3-Cyanobenzyl Free Radicals

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An extended Hammett treatment of the kinetic data of the NBS bromination of 4-substituted 3-cyanotoluenes led to a free-radical substituent constant, $\sigma\cdot$. The substituent order of free-radical stabilization found in this work was: F < OCH_3 < CH_3 < H < Cl < Ph < I < Br < NO_2 < N=NPh < CN < Ac. This order was further analyzed in terms of the ability of each substituent to stabilize a free radical. Two substituents—F and OCH_3—were found to be destabilizing in this system.

One of the major tools available to help elucidate organic reaction mechanisms is that of quantitative structure–reactivity relationships. The ability of a substituent to stabilize a cation, an anion, or a polar transition state by direct resonance is well understood in terms of σ^{+1} and σ^{-}.[2] The comparable influence of a substituent on a free-radical intermediate ($\sigma\cdot$ or σ^{H})[3] is not as well understood. Which substituents best stabilize a free-radical intermediate? Do all substituents

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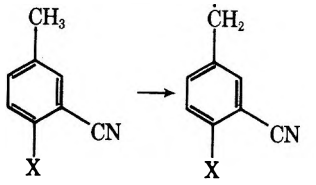
Table I. Model Systems Used to Define Some Free-Radical Substituent Constants

Substituent constant	Ref	Defining eq	Reaction
1. $\sigma\cdot$	25	$\log k/k_0 = \rho\sigma^+ + \sigma\cdot$	1 → 2
2. E_R	5c	$\log k/k_0 = \rho\sigma + \gamma E_R$	$XArCH(CH_3)_2$ + polystyryl radical
3. E_D	18	$\log k/k_0 = \rho\sigma^+ + E_D$	$XArCH{=}CH_2 + \cdot CCl_3 \rightarrow$
4. τ_p	19	$\log k/k_0 = \rho\sigma + \tau_F$	$ArX + YPh\cdot \rightarrow$
5. log Q	5a	$\frac{k_{11}}{k_{12}} = \frac{Q_1}{Q_2}\rho^{-e_1(e_1-e_2)}$	$-CH_2\dot{C}HX + CH_2{=}CHY \rightarrow$

stabilize a free radical in contrast to ionic behavior? Are there some substituents that do not stabilize a free radical? The answers to these fundamental questions concerning free-radical stabilization by substituents are not known with any degree of certainty even though much work has been done on the problem.

Our current understanding of the relationships between structure and reactivity in the homolytic process has been obtained from a wide variety of studies including: bond dissociation energies;[4] free-radical vinyl copolymerizations;[5] decompositions of peroxides,[6] peresters,[7] and azo compounds;[8] spectroscopic[9] and polarographic studies;[3a,10] atom abstraction reactions;[3b,11] etc. One of the most common approaches of those just mentioned is the H-atom abstraction reactions of substituted toluenes.

Our study[12] of the NBS bromination of 4-substituted 3-cyanotoluenes (1), see eq 1, led us to consider the general



1 2 (1)

problem of substituent effects in free-radical reactions. The transition state for this H-abstraction reaction is normally represented as **3** where Y· is **2** and ·Z, the abstracting radical, is Br·. The NBS bromination of monosubstituted toluenes has an excellent correlation with σ^+, where $\rho = -1.46$.[13a] This large negative ρ was interpreted as being consistent with a large contribution of polar form **3b** and dependence on σ^+ because direct resonance was possible between electron-donor substituents and **3b**. The reaction of monosubstituted toluenes with the nucleophilic *tert*-butyl radical[14] has a ρ value of +0.99 consistent with contribution of polar form **3c** to the transition state of this reaction. These two H-abstraction reactions are both consistent with the polar transition state explanation just given, whereas only the former is consistent with Zavitsas' BDE explanation.[15]

$$[\dot{Y}H\dot{Z} \leftrightarrow Y^+H\bar{Z} \leftrightarrow \bar{Y}H\dot{Z}^+]$$
3a **3b** **3c**

To get a substituent effect that is only related to free-radical stabilities and not polar influences, the latter must be eliminated. Alternatively, a system could be designed where polar effects are not important. This has been accomplished by using an abstracting free radical, ·Z, that has approximately the same electronegativity as ·Y. The reactions of monosubstituted toluenes with $\cdot CH_3$,[16] ·Ph,[17] and ·H[3b] have been studied and ρ was found to be near zero in each case. The remaining rate effects are so small that very accurate measurements are required and interpretation is difficult.

The approach used in this study is not to eliminate the polar effects, but to diminish them. This is to be accomplished by a substrate change (addition of a *m*-cyano group) instead of a change in Z. In our system, polar form **3c** is not important because of the electronegativity of the H-abstracting Br·. The addition of electron-withdrawing groups to Y make the polar form **3b** have a higher energy and therefore not contribute as much to this transition state. Some electron-withdrawing 4-substituents should also be able to destabilize **3b** and at the same time stabilize free radical form **3a** by direct resonance. A free-radical substituent constant is developed in this work to measure this "extra" resonance.

Model Systems. There are many problems associated with establishing a free-radical substituent constant.[3,5c,18-22] What free-radical system is general enough to cover all situations? How are polar effects to be removed? How can transition-state effects be separated from ground-state effects? Is the extended Hammett treatment valid for free-radical reactions? It is doubtful if any system can satisfy all these demands. The two radicals studied most in this context are the benzyl and the cyclohexadienyl systems. Our system has something positive to say on this topic, but is not the ultimate system, and does not answer all of the questions raised. It is hoped that this work will stimulate new approaches that may ultimately lead to the ideal system.

Several attempts to develop a free-radical substituent constant have used an extended Hammett approach that is similar to the Yukawa–Tsuno approach; see Table I. The Yukawa–Tsuno equation,[23] $\log k/k_0 = \rho[\sigma + r(\sigma^+ - \sigma)]$, is used for reactions with variable resonance contributions from one reaction series to another of similar mechanism. When $r = 0$, usual σ dependence is observed; when $r = 1$, σ^+ dependence is found. In general r can vary from zero to values >1. The Yukawa–Tsuno equation is a special example of a general four-parameter linear free-energy equation as illustrated in the equation

$$\log k/k_0 = aX + bY \qquad (2)$$

where aX and bY represent separate influences of the substitutents that directly affect the rates of the reaction. Other examples of eq 2 include the Edwards equation,[2] the Swain–Lupton equation,[24a] and Hansch's multiple parameter analysis.[24b] In Table I, aX represents normal Hammett behavior with dependence on σ or σ^+, and bY represents any deviation from normal behavior. In eq 1, 3, and 4 of Table I, b is taken as 1.0 for the defining equations. Reactions that are different from the model systems could have different values of b.

A good variety of free-radical reactions are represented in Table I. Two reactions involve H-atom abstractions from toluene and cumene systems, respectively; two reactions involve free-radical additions to vinyl monomers; and one is a homolytic aromatic substitution reaction. Equation 2 of Table I is the work of Yamamoto and Otsu[5c] and their substitution constant is called E_R for resonance substituent constant. Sakurai[18] studied the effects of substituents on styrene to the addition of $\cdot CCl_3$ and developed a delocalization substituent constant, E_D, related to the Q value of Alfrey and Price. Simamura[19] has suggested the substituent constant τ to measure the free-radical stabilizing effect of substituents to phenylation. The last entry in Table I is the *Qe* scheme of Alfrey and

Table II. Values of Some Free-Radical Substituent Constants[a]

Substituent	Registry no.	$\sigma\cdot$	E_R	E_D	τ_p	Log Q	σ^{2c}
F	64113-73-1	−0.25					0.00
OCH_3	64113-74-2	−0.12	0.11	0.19	0.14	0.13	0.07
CH_3	64113-75-3	−0.02	0.03	0.11	0.09	0.04	0.03
H	61142-85-6	0.00	0.00	0.00	0.00	0.00	0.00
Cl	64113-76-4	0.08	0.10	0.07	0.16	0.01	0.05
Ph	64113-77-5	0.12					0.00
I	64113-78-6	0.16	0.12			0.07	0.03
Br	64113-79-7	0.17	0.12			0.04	0.05
NO_2	64113-80-0	0.27	0.41	0.27	0.90	0.21	0.61
N=NPh	64113-81-1	0.33			0.9[b]		0.07
CN	64113-82-2	0.34	0.24	0.32		0.27	0.44
Ac	64113-83-3	0.53	0.24				0.25

[a] See Table I for the definitions of these substituent constants. [b] Reference 27. [c] Reference 20.

Price,[5a] which has found much utility in the study of vinyl copolymerizations.

The extended Hammett approach[18] as applied to free-radical reactions has been used mainly to separate inductive and resonance effects. The inductive effects are usually measured experimentally by ρ_m found by using only meta substituents. Then any deviations of para substituents from this line are assumed to be resonance effects. A major problem with this approach arises in free-radical reactions because the resonance effects measured can involve both polar and radical stabilization. The term "extra" resonance[26] is often used to refer to any direct resonance between the substituent and the reaction site that is not possible in the reactant. The Hammett substituent constants σ^+ and σ^- measure this "extra" resonance as it applies to positive and negative reaction sites. The Hammett free-radical substituent $\sigma\cdot$ is the analogous measure of the "extra" resonance between a substituent and a free-radical site. A separation of the polar and radical "extra" resonance is required for a measure of $\sigma\cdot$. In this work we are attempting to separate the resonance effects on radical form **3a** from the resonance effects on polar form **3b** by use of a substrate change.

$\sigma\cdot$. Some general criteria that need to be met in a model system used to define $\sigma\cdot$ are: (1) the effect studied must involve a direct interaction between the substituent and the free-radical site; (2) the mechanism of the reaction should be well understood; (3) the kinetic effects should be reasonably large, and an accurate method should be available to measure the kinetic effects; (4) a wide range of substituents should be studied to give generality to the study; (5) outside influences (like steric effects, solvent effects, etc.) should be kept to a minimum.

The 4-substituted 3-cyanotoluene system (1) chosen here, while not the ultimate choice of a model system, nonetheless measures up nicely to each of the five criteria just listed. A benzyl free radical can be directly stabilized by resonance with para substituents on it. The mechanism of NBS bromination of toluenes has been determined by a variety of studies[13] and is believed to involve a hydrogen-atom abstraction by a bromine atom. The use of benzene solvent in this reaction provides a homogeneous medium and accurate kinetics are easily obtained. Twelve substituents were chosen varying from methoxyl to nitro on the extremes. Steric inhibition of resonance can come into play for only three substituents, and this will be discussed in more detail later.

Using the form of a general four-parameter linear free-energy equation, $\sigma\cdot$ is defined by the equation

$$\log k/k_0 = \rho\sigma^+ + \sigma\cdot \qquad (3)$$

The relative rate data for 1 given in Table I of our earlier work[12] provides the log term on the left. The aX term is represented by $\rho\sigma^+$, which is $-1.46\sigma^+$ for the NBS bromination of monosubstituted toluenes. By rearranging the terms in eq 3, the definition of $\sigma\cdot$ results as $\sigma\cdot = \log k/k_0 - \rho\sigma^+$. This is a measure of the difference in substituent effects between the monosubstituted toluenes and the 4-substituted 3-cyanotoluenes for the NBS bromination reaction. The values of $\sigma\cdot$ thus calculated are listed in Table II along with values of the other substituent constants mentioned in Table I. There are other ways $\sigma\cdot$ could be defined that more closely resemble the Yukawa–Tsuno equation, but eq 3 seems the simplest and is more in harmony with the other extended Hammett equations of Table I.

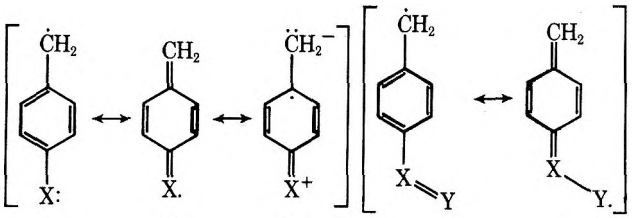
The ρ^+ for monosubstituted toluenes is believed to contain both inductive and direct resonance effects between electron-donor groups and **3b**. Probably some direct resonance between the 4-substituents and radical form **3a** is present, but it is believed to be overshadowed by the polar resonance as indicated by the excellent σ^+ correlation. The "extra" resonance looked for here is that which is possible in the transition state of the bromination of 1 but is not important in the transition state of the same reaction with the monosubstituted toluenes. Our reference value of ρ in eq 3 is not a ρ_m because we were not interested in only separating inductive and resonance effects of the polar type. It was assumed that the ρ^+ value of −1.46 has both resonance and inductive polar influences in it.

Of the six substituent constants in Table II, only $\sigma\cdot$ has negative values. A negative value indicates destabilization by a substituent. The idea that all substituents should stabilize a free radical originated in studies of homolytic aromatic substitution reactions. Free-radical substitution of monosubstituted benzenes are normally faster than benzene, and the ortho and para products are more favored than the meta products for virtually all substituents. Cammarata[20] has suggested that this is equivalent to saying that free-radical substituent effects should be correlated with σ^2. Several such correlations were found,[20] but some substituents such as $N\text{–}Me_3^+$ and S–Me must not be used in this type of correlation. These exceptions raise questions about the generality of direct resonance between both electron-donor and electron-acceptor substituents and free-radical sites.

The electron-withdrawing groups NO_2, CN, and Ac are good free-radical stabilizing substituents as measured by all six substituent constants of Table II. The relative order of the three vary, however, and each is favored in at least one system.

Individual Substituents. The benzyl free radical is a class S radical in the classification of Walter,[28] in spite of the fact that a large number of Hammett correlations have been ob-

served for it. A class S radical is one that both electron-donor and -acceptor substituents affect in the same manner. Transition state **3** would, however, be class O. It is well established that only donor substituents can stabilize a positive site and only acceptor substituents can stabilize a negative site by direct resonance. It is often stated that both electron-donor and acceptor substituents can have direct resonance with a free radical. The situation is illustrated in structure **4** with an electron-donor substituent and in structure **5** with an electron-acceptor substituent. Resonance in **5** is directly analogous to negative ion delocalization and looks favorable for a single electron also. For electron donor substituents the situation is different. When an electron-donor group stabilizes a free radical in the same manner as a positive site, **4c** results which is charge separated and consequently is considered to be of higher energy than noncharge-separated structures like **4a** and **4b**. Structure **4b** involves delocalization of the odd electron to the donor atom and results in an expansion of its octet by one electron. This is possible with higher period elements with low-lying d orbitals and by hyperconjugation when the substituent is methyl. However, when the donor atom is a first-row element like O, N, or F, no such stabilization is possible. These general considerations seem to be confirmed by the results of this study.



4a **4b** **4c** **5a** **5b**

The values of $\sigma\cdot$ in Table II vary from F to Ac with the former the least stabilizing and the latter the most stabilizing substituent. In general the electron acceptor substituents stabilized the benzyl free radical the best, presumably by resonance structures like **5**. Of the resonance electron donor groups, the phenylazo and all of the halo substituents but fluoro also provide stabilization for the free radicals. Two substituents, fluoro and methoxyl, are actually destabilizing in this study.

The best four free-radical-stabilizing substituents found here were NO_2, N=NPh, CN, and Ac, respectively, with Ac decidedly the best. These four substituents are all good electron-withdrawing substituents as measured by σ. Inductively, the nitro substituent is the best electron acceptor of the group as measured by σ'. The ability to withdraw electrons by resonance is usually measured by $\sigma_R = \sigma_p - \sigma'$. The Ac substituent is the best of the four at resonance electron withdrawal. The σ_R values for N=NPh, CN, NO_2, and Ac are +0.05, +0.07, +0.15, and +0.25, respectively.[25,29] Even though steric inhibition of resonance is probably important for both the nitro and acetyl substituents, its effect should be about the same for each substituent. The linear CN group should not have steric problems and this would relatively enhance its ability at "extra" resonance. It is concluded that the Ac substituent is the best substituent of those studied here at stabilizing a free radical because it can best delocalize the odd electron by resonance.

Steric inhibition of resonance is possible in **3** for the three substituents NO_2, Ac, and Ph. The 4-substituents must be in the plane of the benzyl ring to effectively resonate with the odd electron at the benzyl position. The 3-cyano substituent in **2** can interfere with the planarity of these three 4-substituents. This steric effect should be most pronounced for phenyl, since it is the largest of the three. It is estimated that the

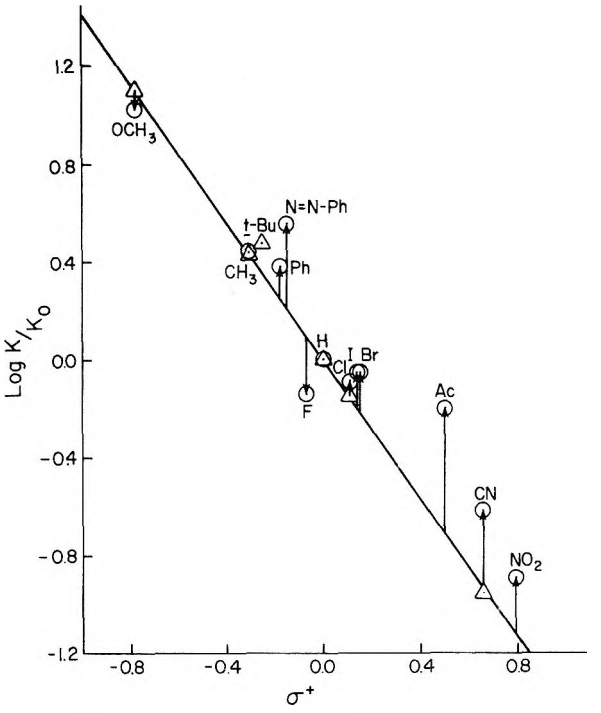


Figure 1. Plot of log k/k_0 vs. σ^+ for monosubstituted toluenes (triangles) and for 1-X (circles). The line is for the monosubstituted toluene data where $\rho = -1.46$. The vertical arrows represent the sign and magnitude of $\sigma\cdot$.

4-phenyl substituent is about 60° out of plane. Correction for this steric effect would enhance the value of $\sigma\cdot$ for Ph by a factor of several fold. Undoubtedly this steric effect is the reason the phenyl group is not more prominent in this study. Correction for the steric effects of the Ac and NO_2 substituents would enhance their $\sigma\cdot$ values by an approximately equal amount and would not affect the relative positions of these two substituents.

The methoxyl substituent is an interesting case. It is such a strong electron donor by resonance that its σ^+ value is −0.78 vs. a σ value of −0.27. From theoretical calculations, Taft[30] has estimated the methoxyl substituent to be less than one-third as efficient at stabilizing a free radical as a positive charge when either is located on the carbon atom adjacent to the substituent. Timberlake,[8b] in a study of azo compounds, found little if any stabilization by the methoxyl substituent in both aliphatic and benzylic systems. Delocalization of the benzylic odd electron to the OCH_3 group would necessitate placing it on a higher energy orbital of oxygen, such as the 3s orbital. This should be unfavorable but has been suggested by Gould[31] to be important for substituted triphenylmethyl radicals.[32] Resonance structures of the type **4** would be unfavorable here due to the electronegativity of the hydrogen-abstracting atom (Br·). Our value of $\sigma\cdot$ lends support to Timberlake's conclusion that the methoxyl substituent cannot effectively stabilize a free radical, and in fact seems to destabilize it.

Hyperconjugation would be required for the methyl substituent to resonance stabilize this benzyl free radical. The lack of any enhancement by the methyl substituent ($\sigma\cdot$ is essentially zero for methyl) is interpreted as the lack of hyperconjugation in this case.

The halo substituents provide an interesting insight into the problem of free-radical stabilization. The σ^+ value of F is negative. The other three halo substituents have positive σ^+ values, indicating that F being a first-row element is the most efficient cation stabilizing substituent by resonance, and this outweighs the fact the F is also the most electronegative of the

halogens. To stabilize a free radical, however, electron withdrawal is required, not electron donation. The odd electron ends up being delocalized into a d orbital on the halo substituent. Since F cannot expand its octet, it does not stabilize the benzyl free radical, but the other three halo substituents with low-lying d orbitals have favorable $\sigma\cdot$ values.

Because of the importance of the azo linkage, –N=N–, to azo dyes and some free-radical initiators, the phenylazo substituent has been discussed elsewhere.[25,33] The phenylazo substituent can both donate and accept electrons by resonance, and consequently stabilize cations, anions, and free radicals.

In summary, the free-radical stabilizing ability of the 12 substituents studied here is graphically illustrated in Figure 1. The straight line in Figure 1 is for the NBS bromination of monosubstituted toluenes. The deviation from this line is shown by an arrow for each substituent, where the up direction represents free-radical stabilization and the down direction destabilization. The direction and magnitude of these vectors represent the sign and magnitudes of the σ·'s. It is not claimed that complete separation of the polar and radical effects was achieved here, but progress was made in that direction. The relative order of substituent stabilization found here is probably more significant than the magnitudes of the σ·'s. Also, comparisons within the series of electron-withdrawing substituents and within the series of electron-donor substituents is probably more significant than comparisons between the two series, because of the polar nature of the transition state 3 found in the NBS brominations of toluenes.

Registry No.—1 (R = F), 64113-84-4; 1 (R = OMe), 53078-70-9; 1 (R = CH_3), 13730-09-1; 1 (R = H), 620-22-4; 1 (R = Cl), 4387-32-0; 1 (R = Ph), 64113-85-5; 1 (R = I), 42872-86-6; 1 (R = Br), 42872-83-3; 1 (R = NO_2), 64113-86-6; 1 (R = N=NPh), 57495-20-2; 1 (R = CN), 63089-50-9; 1 (R = Ac), 64113-87-7; 1 (R = *t*-Bu), 64113-88-8.

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(32) The dimers of the triphenylmethyl radicals discussed by Gould[31] are now known not normally to be hexaphenylethanes, but this does not affect the argument of whether the oxygen atom of a methoxyl group can easily expand its octet by resonance with a free radical site para to it.
(33) The σ· value reported earlier[25] of 0.28 is slightly different from the value of 0.33 reported here due to a difference in the kinetic equation used. In the earlier work, the kinetic equation $k/k_0 = M_H A_X / M_X A_H$ was used, where M_X is the moles of X and A_X is the area of the X benzyl H's in the NMR of the product mixture. This equation is used in competative reactions involving small conversions of reactants to products.

Structure Elucidation with Lanthanide-Induced Shifts. 3. Acyclic Aliphatic Nitriles[1]

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The structures of a series of acyclic aliphatic nitriles have been studied with lanthanide-shift reagents. The experimental values of the bound shifts induced by $Eu(fod)_3$ are compared with the values obtained by a priori calculation for a proposed structure using a parameterized form of the pseudocontact equation. The agreement between predicted and experimental data allows assessment of the validity of the proposed structure. The method permits direct determination of conformer populations, as well as of gross molecular structure.

Knowledge of the structure of organic molecules is of considerable importance in terms of understanding chemical reactivity, particularly in the case of conformationally flexible molecules in solution. While diffraction techniques can afford accurate and detailed information about molecular structure, they are not applicable to the liquid state. The most powerful tool for organic chemists has been NMR spectroscopy,[3] although many difficulties are still encountered with this method. For example, conformational analysis frequently has relied on the interpretation of coupling constants, using empirical relationships to estimate the values of coupling constants of the individual conformers.[4] We report here the successful use of lanthanide-induced shifts (LIS) to evaluate the structures in solution of the series of aliphatic nitriles **1–7** (Table I).

Results and Discussion

We have previously shown[1,5] that the bound shifts[6] of nitriles are accurately correlated with molecular structure according to the dipolar form of the pseudocontact equation (eq 1). Parameterization of eq 1 for a series of substituted adamantanecarbonitriles with $Eu(fod)_3$ in CCl_4 afforded[5] a value of 760 for k and a nitrogen–carbon bond length (R_{LX}) of 1.89 Å. With these parameters in hand it is possible to evaluate a proposed structure by a priori prediction of the bound shifts (Δ_1) with eq 1 followed by comparison with the experimentally determined LIS. A point of particular importance here is that, unlike much of the previous work[7–9] in this area, we are not adjusting the parameters of eq 1 or structural parameters such as R_{LX} in order to obtain the best fit between relative induced shifts and the experimental data; rather, eq 1 is used to predict the absolute magnitudes of the LIS which can be directly compared with experimental values.

$$\Delta_1 = \frac{k(3\cos^2\theta - 1)}{r^3} \qquad (1)$$

Bound shifts [with $Eu(fod)_3$ in CCl_4] for the series of nitriles **1–7** were calculated with eq 1 using $k = 760$, $R_{LX} = 1.89$ Å, and using standard bond lengths and angles.[10,11] The resulting bound shifts for hydrogens in each of the possible orientations corresponding to a stable conformation are illustrated in the composite molecular structure of Figure 1. For hydrogens in the β and γ positions, several nonequivalent locations (with respect to the cyano group) are possible, and the actual shift for a given hydrogen will be the weighted average of the shifts for each of the individual conformers. In cases (e.g., methyl-group rotation) where the conformers have the same energy, the weighting will be the same for each and the calculated Δ_1 will be the simple arithmetic mean of the individual values. This is the situation for the methyl groups (β-hydrogens) of **2–4**; similarly, the calculated Δ_1 for the methyl groups (γ-hydrogens) of **7** is the average of the values for the nine possible orientations shown in Figure 1.

The situation is somewhat more complicated for butyronitrile (**5**) and isovaleronitrile (**6**) where the different conformations (Figure 2) are not equivalent. As shown in Figure 2, each of these compounds may exist in either conformation I (which possesses a plane of symmetry) or conformation II (which is actually a mixture of enantiomers IIa and IIb). Since the sum of the mole fractions of the conformers is unity and the mole fractions of enantiomers IIa and IIb must be equal in an achiral environment, the conformational equilibrium is related to the lanthanide-induced shift of a given hydrogen by eq 2.

$$\Delta_{1[\text{obsd}]} = (n_I)(\Delta_{1[I]}) + \frac{1}{2}(1 - n_I)(\Delta_{1[IIa]}) + \frac{1}{2}(1 - n_I)(\Delta_{1[IIb]}) \qquad (2)$$

Using the experimental bound shifts for the γ (methyl) hydrogens[12] and the values for $\Delta_{1[I]}$, $\Delta_{1[IIa]}$, and $\Delta_{1[IIb]}$ calculated from eq 1 (i.e., the averages of the values shown for the three hydrogens of each methyl group in Figure 1), eq 2 yields direct determinations of the conformational equilibria of **5** and **6**. These are summarized in Table III together with estimates based on analysis of the H_α–H_β coupling constants. The results obtained from these two methods are in quite good agreement. A crucial point here is that we have measured the conformational equilibrium of the LS complexes and have extended the results to the free substrates; this requires that the conformational equilibrium I $\rightleftarrows$ II be unaffected by complexation. While there are literature reports indicating that complexation can alter the conformational equilibrium for some functional groups,[13] nitriles appear to be much less sensitive to such perturbations, since the lanthanide ion must be located on an extension of the linear C—C≡N array and is unlikely to suffer significant steric interaction with the remainder of the organic moiety.[1,14] In any event, the magnitudes of the H_α–H_β coupling constants for **5** and **6** are unaffected by complexation,[15] thus demonstrating that the relative populations of I and II are essentially the same for both the complexed and free substrate.

Having determined the relative conformer populations of nitriles **5** and **6**, it was possible to predict the bound shifts of each hydrogen in compounds **1–7**.[19] As discussed above, the weighting of different conformations was equal for **1–4** and **7**; for **5** and **6**, eq 2 was employed using the conformation populations determined from the LIS data for the γ-hydro-

Table I

RC≡N	$RCH_2C{\equiv}N$	R
1	**2**	CH_3
2	**5**	C_2H_5
3	**6**	i-C_3H_7
4	**7**	t-C_4H_9

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Table II. Conformer Populations of Butyronitrile (5) and Isovaleronitrile (6)

	Δ_1, γ-Hydrogens[a]			$J_{\alpha\beta}$[b]		
	n_I	n_{II}	ΔG, kcal	n_I	n_{II}	ΔG, kcal
5	0.45	0.55	−0.12	0.54	0.46	0.10
6	0.24	0.76	−0.69	0.25	0.74	−0.65

[a] Populations calculated using eq 2 (see text). [b] Coupling constants for the individual conformers were estimated from the data of A. A. Bothner-By [*Adv. Magn. Reson.*, **1**, 225–227 (1965)]; for **5**, J_{180} = 12.85, J_{60} = 4.0 Hz; for **6**, J_{180} = 12.0, J_{60} = 3.7 Hz.

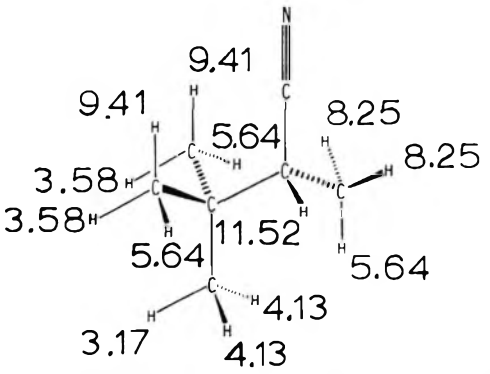

Figure 1. Composite structure illustrating the various possible stable orientations of hydrogen atoms in aliphatic nitriles with chain lengths of four or fewer carbons. The bound shifts shown are values predicted for each of the hydrogen atoms in a static conformation having standard bond lengths and angles.

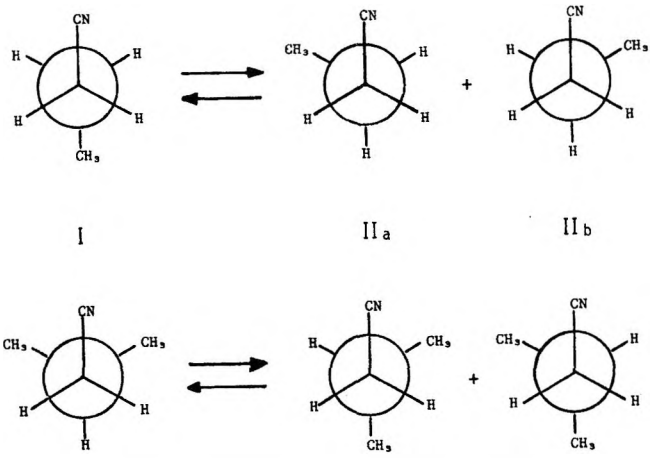

Figure 2. Conformational equilibria of butyronitrile (**5**) (top) and of isovaleronitrile (**6**) (bottom).

gens. The results of these calculations together with the experimental LIS data are presented in Table III.

Clearly, the agreement between observed and calculated values of bound shifts is quite good. The agreement factors are comparable to those reported by previous workers[8,9] who have treated k and R_{LX} as variable parameters in order to minimize disagreement between calculated and observed shifts. Even if the data for α-hydrogens (for which the calculation of Δ_1 is not totally a priori because of the inclusion of a contact shift correction) are excluded, the mean relative error increases only from 0.039 to 0.056. The determination of conformer populations by this method offers an excellent alternative to other techniques based on vicinal coupling

Table III. Calculated and Experimentally Observed Values of Lanthanide-Induced Shifts (Δ_1) for Aliphatic Nitriles[a]

Substrate	Registry no.	Position	Calcd[b]	Exptl[c]	calcd − obsd[d] / obsd	Agreement[e] factor
1 $CH_3C{\equiv}N$	75-05-8	α	13.19	13.16 ± 0.33	0.002	0.002
2 $CH_3CH_2C{\equiv}N$	107-12-0	α	13.19	12.99 ± 0.04	0.015	0.053
		β	7.38	6.64 ± 0.01	0.113	
3 $CH_3CHC{\equiv}N$ (CH_3)	78-82-0	α	13.19	13.17	0.002	0.026
		β	7.38	7.00	0.054	
4 $CH_3CC{\equiv}N$ (CH_3, CH_3)	630-18-2	β	7.38	7.47 ± 0.18	0.012	0.012
5 $CH_3CH_2CH_2C{\equiv}N$	109-74-0	α	13.19	12.91	0.022	0.054
		β	7.53	6.75	0.116	
		γ	5.12	5.12	0.000	
6 $CH_3CHCH_2C{\equiv}N$ (CH_3)	625-28-5	α	13.19	13.16	0.002	0.036
		β	7.62	7.05	0.081	
		γ	5.30	5.30	0.000	
7 $CH_3CCH_2C{\equiv}N$ (CH_3, CH_3)	3302-16-7	α	13.19	14.02	0.059	0.061
		γ	5.41	5.82	0.070	

[a] Shifts are reported in ppm. [b] Calculated using eq 1. The shifts for the α-hydrogens also include a contact shift contribution of 1.67 ppm. [c] Errors reported are standard errors for multiple determinations. [d] Relative error. The mean relative error is 0.039 for all data; if the data for the α-hydrogens is excluded, the mean relative error is 0.056. [e] The mean agreement factor for all compounds is 0.035.

constants. While the approximations involving "standard" geometries and lack of conformational perturbation by the shift reagent undoubtedly place some limitations on the accuracy of the method, we believe these limitations are minor. For example we conclude from the data in Table II that the populations of the anti and gauche (I and II) conformations of butyronitrile are nearly equal; the agreement factor calculated for butyronitrile existing to the extent of 75% in the anti conformation is 0.090, a value substantially larger than any of those reported in Table III. Thus, the present work effectively demonstrates that the use of bound shifts together with a chemically reasonable parameterization of the pseudocontact equation allows lanthanide-induced shifts to be used for rigorous and accurate evaluation of the molecular structures of conformationally mobile molecules.

Experimental Section

Nitriles. Acetonitrile (**1**) was obtained from Fisher Scientific Co. (catalog no. A-21) and was dried over Linde 4-Å molecular sieves prior to use. Propionitrile (**2**) was obtained from Eastmen Organic Chemicals (catalog no. 528) and was dried over Linde 4-Å molecular sieves prior to use. Isobutyronitrile (**3**), trimethylacetonitrile (**4**), and butyronitrile (**5**) were all purchased from Aldrich Chemical Co. (catalog no. I-1,560-2, T-7200-1, and B-10,380-2, respectively) and were each dried over Linde 4-Å molecular sieves prior to use. Isovaleronitrile (**6**) was purchased form K &K Chemicals and was purified by preparative gas chromatography (Carbowax 20M). *tert*-Butylacetonitrile (**7**)[20] was prepared from the corresponding acid chloride (ALDRICH NO/ B-8,880-2) via conversion to the amide followed by dehydration with P_2O_5 according to the procedure of Kent and McElvain for isobutyronitrile.[21]

Tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanediona-to)europium (Aldrich, Resolve-Al EuFOD™, no. 16,093-8) was sublimed (160–165 °C, 0.05 Torr) and stored in a vacuum dessicator over P_2O_5 for at least 48 h prior to use.

Nuclear magnetic resonance spectra were obtained using Varian EM-360 and A-60 spectrometers. All spectra were recorded at either 600 (EM-360) or 500 Hz (A-60) sweep widths. Chemical shifts were measured relative to internal Me_4Si, and sweep widths were calibrated with an external audio oscillator. When the widths of spectra exceeded the sweep widths, offset spectra were recorded, and peak positions were measured relative to a Me_4Si audio side band.

Shift reagent runs utilized the incremental dilution method[6] in which a CCl_4 solution containing both shift reagent (0.6 M) and the nitrile (0.2 M) was successively diluted with a 0.2 M CCl_4 solution of the nitrile. The precise concentrations of shift reagent and nitrile were determined gravimetrically for each sample, and spectra were recorded for a total of 25 different concentrations (including zero) of shift reagent.

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Registry No.—$Eu(fod)_3$, 17631-68-4.

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(12) Use of the bound shifts for the β-hydrogens does not afford satisfactory results; for example, a negative mole fraction (−0.15) is calculated for conformation I of **5**. We believe that this is a result of dev ation from the "standard" geometries[10] assumed for our calculations. Small distortions would result in the greatest errors when the hydrogen is relatively close to the lanthanide ion; such is the case for two of the three possible orientations of a β-hydrogen (cf. Figure 1).
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(15) For both **5** and **6**, plots of $J_{\alpha\beta}$ vs. [Eu]/[R–CN] are horizontal lines having slopes of zero within experimental error (linear-regression analysis).
(16) That butyronitrile (**5**) exists to the extent of approximately 50% in conformation II (which appears to have increased steric interactions relative to I) might initially seem surprising. However, it should be recalled that the steric requirements of a cyano group are small[17] and that for both **5** and **6** conformation II (a *d,l*-pair) is favored by an entropy term of $R \ln 2$.[18]
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Reactions of Derivatives of 1,2,3-Triphenylcyclopropene with Iron Salts[1-3]

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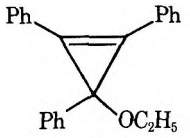
The reaction of 3-ethoxy-1,2,3-triphenylcyclopropene (1) with ferric chloride in refluxing ethanol gives 1,2,3-triphenylcyclopropene (3) and 2,3-diphenylindenone (4) as major products. It has been found that 1,2,3-triphenylcyclopropenylium bromide (5) reacts with ethanol or 2-propanol without iron(III) to give 3 and products associated with acid-catalyzed rearrangement of 3: 1,2-diphenylindene and ethers of 1,2,3-triphenylprop-2-en-1-ol. When 2-propanol was used, acetone was detected as a product. Thus, the formation of 3 in the reaction of 1 in the presence of ferric chloride is reduction of the triphenylcyclopropenylium cation (or the corresponding ether coordinated with an acid) by solvent. The pathway suggested for formation of 4 is equilibration to give 3-hydroxy-1,2,3-triphenylcyclopropene (11), followed by oxidation with iron(III) to give a ring-opened vinyl radical 12 which can be trapped with oxygen or by ligand transfer oxidation. The path to 4 involves cyclization either of 12 or the cation corresponding to it. Several other reaction pathways are ruled out on the basis of control experiments. In an attempt to generate 12 independently, treatment of 1,2,3-triphenylcyclopropenylium tetrafluoroborate (29) with potassium nitrite gives benzil, benzoic acid, 2-phenylisatogen, and benzonitrile in substantial amounts, but less than 1% of 4.

When 3-ethoxy-1,2,3-triphenylcyclopropene (1) is refluxed with ferric chloride in ethanol or 1,2,3-triphenylcyclopropenylium tetrachloroferrate (2) is treated with 1 equiv



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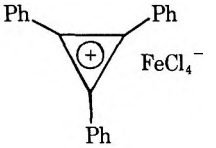
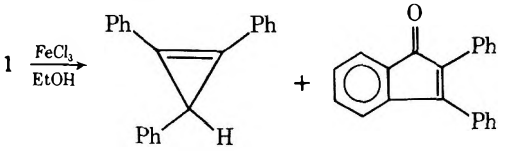


2

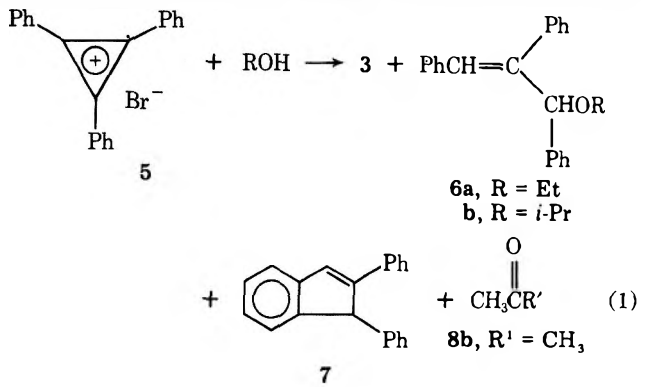
of base under the same conditions, the major products are 1,2,3-triphenylcyclopropene (3) (15%) and 2,3-diphenylindenone (4) (65%).[4] The reaction to give 3 does not require the



3 4

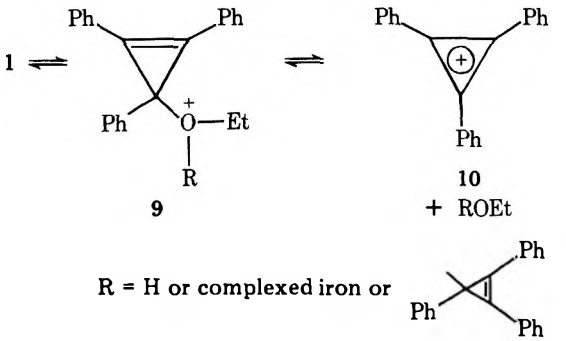
presence of iron, while the formation of 4 does. Thus, possible pathways to these products will be discussed separately. Our studies to elucidate the mechanism of formation of 4 illustrate the variety of reactions that free radicals can undergo in the presence of iron(III) which depend on the ligand on iron, the solvent, the temperature and the presence of oxygen.

Mechanism of Formation of 3. The evidence indicates that the presence of iron(III) or iron(II) is not necessary for the formation of 3 from 1. For example, in both refluxing ethanol and 2-propanol, 1,2,3-triphenylcyclopropenylium bromide (5) alone will react to give 3 and/or products which can be explained on the basis of acid-catalyzed rearrangement of 3 (see eq 1).[5] Reaction conditions and results are given in Table I. Of note is that specially prepared "acid-free" 5 does not give acid-catalyzed rearrangement products of 3. Compound 5, prepared in the usual manner[6] and not carefully recrystallized, contains some hydrogen bromide as evidenced by the evolution of a gas acidic to litmus when 5 is heated in acetonitrile. Results with 2 parallel those from 5 (see Table II), although under these conditions indenone formation competes. Methanol and *tert*-butyl alcohol give at the most traces of 3.



5 6a, R = Et; b, R = *i*-Pr 7 8b, R' = CH_3 (1)

There are other results which indicate that the reaction of 1 to give 3 is acid catalyzed. For example, 1 is stable in refluxing ethanol. Also, treatment of 2 in ethanol with 2 equiv of base leads to an 86% yield of 4 but no 3. Thus, when 3 is formed from 1 in the presence of ferric chloride we favor the following mechanism. Acid present in the solution, either as a proton formed by solvolysis of ferric chloride (solutions are acidic to indicator paper and the response of a glass electrode indicates protons), some iron species, or 10[7], facilitates the following equilibrium. In fact, there may be significant quantities of cation 10 present, because when 2 is treated with an equivalent of sodium hydroxide in methanol under nitrogen, conditions under which reduction does not take place and oxidation is limited, roughly 35% of a triphenylcyclopropenyl cation and no 3-methoxy-1,2,3-triphenylcyclopropene was isolated. Furthermore, we would expect more of 10 than 9 to be present at equilibrium, since the pK_as of ordinary aliphatic



9 10 + ROEt

R = H or complexed iron or

ethers are −2 or less,[9] while the pK_{R+} of 5 is 2.80.[6] Either 9 or 10 can react to give 3: 9 by an intramolecular hydride transfer or 10 by an intermolecular hydride transfer from the solvent. Clearly, an intermediate protonated ether can be formed from either 5 or 2 as well as 1. The isolation of acetone from the reaction of 5 in 2-propanol substantiates the hydride-transfer mechanism. The reason for lack of formation of 3 with 2 and *tert*-butyl alcohol is now obvious: there are no

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Table I. Reaction of 5 with Various Alcohols[a]

mmol of 5	Solvent (mL)	Product in % yield 1	3	5	6a or b[b]	7	CH_3CCH_3 (O)
0.43	EtOH (100)		17		44		
0.43	EtOH (110)			15	26[e]	29[e]	
0.43[f]	EtOH (100)	18	65				
0.45	*i*-PrOH (50)		59		14		
5.81	*i*-PrOH (100)[g]				40	32	6[i]
0.30	MeOH (20)			100[j]			

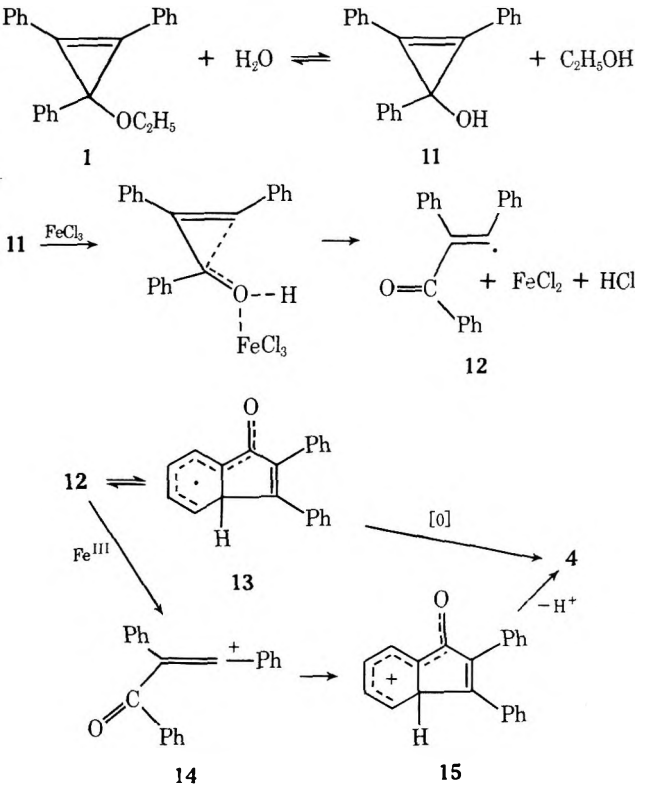
[a] All reactions were run in air, bath temperature 120–130 °C, 20–24 h. [b] Authentic samples of 6a and b were prepared from (*E*)-1,2,3-triphenylprop-2-en-1-ol,[c] acid, and ethanol and 2-propanol, respectively. Spectroscopic and analytical data appear under Experimental Section. These syntheses parallel the synthesis of the corresponding methyl ether.[c] Although the assignment of the stereochemistry (*E*) is based on weak evidence,[c] formation of the *E* isomer can be rationalized on the basis that other acid-catalyzed ring-opening reactions of 1,2-diphenylcyclopropenes have given exclusively the allyl isomer in which the two phenyls are cis.[d] [c] R. E. Lutz and E. H. Rinker, Jr., *J. Am. Chem. Soc.*, 77, 368 (1955). [d] G. A. Kudryautseva and O. A. Nesmeyanova, *Izv. Akad, Nauk Kaz. SSSR, Ser. Khim.*, 2357 (1974); J. A. Pincock, R. Morchat, and D. R. Arnold, *J. Am. Chem. Soc.*, 95, 7536 (1973). [e] Based on recovered starting material. [f] Acid-free cation was prepared by refluxing the material in acetonitrile containing Linde molecular sieve 4-A for 0.5 h after HBr evolution ceased (as detected by wet pH paper), decanting the solution, and collecting the product in the usual manner. Presumably, the first two entries in the table differ because of differing amounts of acid in different samples of the cation which are not treated in this manner. [g] Roughly 5% of a product was isolated which was tentatively identified as (*Z*)-1,2,3-triphenylpropene. It had an infrared spectrum very similar to the infrared (kindly supplied by Professor G. Griffin) of an authentic specimen and UV similar to that reported: λ_{max} (EtOH) 259 (lit.[h] 260 nm). [h] G. W. Griffin, A. F. Marcantonio, H. Kristinsson, R. C. Petterson, and C. S. Irving, *Tetrahedron Lett.*, 2951 (1965). [i] Isolated as 2,4-DNP derivative prepared from first 20 mL of distillate from the reaction mixture. Isopropyl alcohol is not oxidized in a detectable amount by air under the reaction conditions. [j] Since recovered starting material melted 230–250 °C (dec), small amounts of impurities could have been present. Infrared was identical to that of starting material.

Table II. Reaction of 2 in Various Alcohols

Solvent 2 + $^-$OH	% yield 3	4
MeOH[a]	0	85
EtOH[a]	15	65
EtOH[b]	0	86
i-PrOH[a]	24[c]	56[c]
t-BuOH[a]	Trace ?	65

[a] 0.152 g (0.33 mol) of 2, 0.35 mmol of NaOH in 20 mL of solvent, 0.34 mL of H_2O, reflux 20 h. [b] 1.029 g (2.22 mmol) of 2, 4.36 mmol of NaOH in 45 mL of solvent, reflux 20 h. [c] Average of two runs.

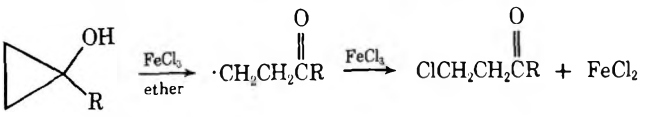
Scheme I



hydrogens appropriately situated to give hydride transfer. It may seem anomalous that the reduction does not occur in methanol. However, it has been found that, although the reduction of triphenylcarbinol to triphenylmethane in acid proceeded well with ethanol and 2-propanol, suitable conditions could not be found for the same reduction in methanol.[10]

Mechanism of Indenone Formation. An outline of our conclusions concerning the mechanism of the formation of 4 appears in Scheme I. The important features of this scheme are formation of 3-hydroxy-1,2,3-triphenylcyclopropene (11) which is oxidized to give a ring-opened radical 12. The pathways to 4 from 12 can involve reversible cyclization to radical 13 which is subsequently oxidized and/or oxidation to 14 followed by cyclization to cation 15 which loses a proton to give 4.[11]

Evidence for a Cyclopropenol Intermediate. Particularly suggestive is the fact that when 2 is treated with an equivalent of base in refluxing water the two major products are 4 (48%) and 1,2,3-triphenylprop-2-en-1-one (16) (35%). The latter has typically been presented as the product of base-catalyzed ring opening of 11.[12] Also, because of the acid catalysis necessary for the formation of 3, it is highly probable that both 1 and 11 are present in the reaction mixture with 10 as an intermediate between them (see above). Finally, the formation of vinyl radical 12, which we have unequivocally trapped as an intermediate (see below), from the cyclopropenol and iron(III) has precedence in the redox chemistry of cyclopropanols studied by Th. Deboer, Depuy, and their coworkers.[13] In particular, ferric chloride produces β-ketoalkyl radicals which undergo ligand transfer oxidation to the corresponding chloro ketones.[13a] Only ring-opened radicals can be detected by ESR even though stereochemical studies suggest attack at the O–H bond rather than at a C–C bond.[13b]



Thus, if cyclopropoxy radicals are formed, they have a very short lifetime. Because the strain energy of cyclopropenes is so much higher than that of cyclopropanes, it is highly likely that a cyclopropenoxy radical would not be a discrete intermediate and that 11 would ring open directly to 12 in the presence of iron(III).

Our results leave little doubt about 11 as an intermediate to the formation of 4.[14] Unfortunately, more direct evidence for the intermediacy of 11 has not been possible, since despite many attempts we and others have been unable to synthesize it.[15]

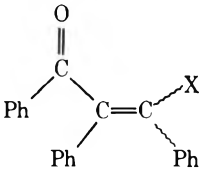
Evidence for a Vinyl Radical. In order to obtain infor-

Table III. Reaction of 1 with FeX_3 at Room Temperature

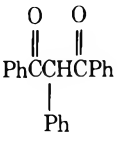
1 →	4	17a or + b	+ 18	+ PhC(=O)CPh(=O)	+ $PhCO_2H$[a]
$CH_3CN/FeCl_3$	18%	9	14		22
$CH_3CN/FeCl_3$[b] degassed	26	5	None		None
$EtOH/FeCl_3$	2	33	c	19	56
$CH_3CN/FeBr_3$	Trace?	50	6		70

[a] Yield based on possible 1 mol of benzoic acid produced/mol of 1. [b] 46% of 1 was recovered. [c] A small quantity might have been present in the reaction mixture.

mation about any intermediates between 11 and 4, the course of the reaction was observed in aqueous ethanol and aqueous acetonitrile at ambient temperatures (Table III). The use of acetonitrile as solvent precludes the reduction leading to 3. We were particularly hopeful, in light of Depuy's work (see above), that products of ligand transfer oxidation of radical 12 might be obtained. We were therefore most pleased to find significant amounts of 3-halo-1,2,3-triphenylprop-2-en-1-ones (17; analytical data and alternate syntheses are given in the



17a, X = Cl
b, X = Br



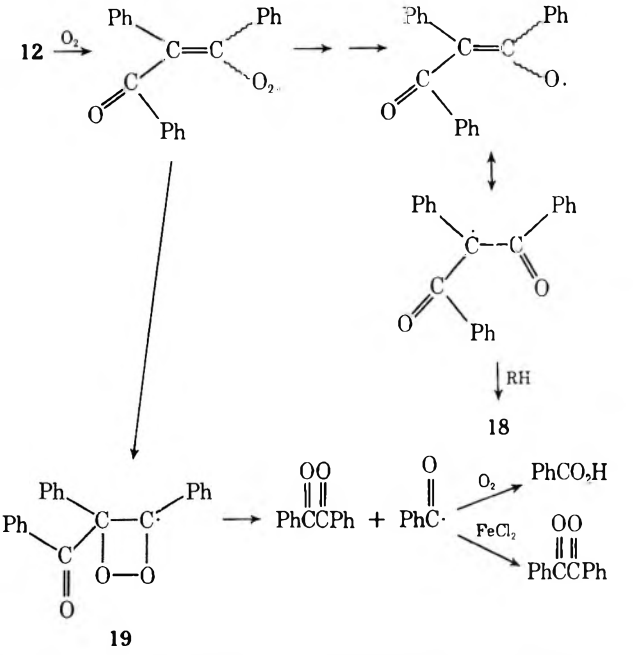
18

Experimental Section) as products, particularly when ferric bromide was the oxidant.[16] That these reactions represent ligand transfer oxidation and not halogenation due to disproportionation of the ferric halides in solution[17] is shown by several control experiments. Both 3 and 3-hydroxymethyl-1,2-diphenylcyclopropene are stable to ferric halides under these reaction conditions.[18] The fact that the reaction of 1 with ferric bromide in acetonitrile does not give significant amounts of indenone while ferric chloride does can be explained by the fact that ferric bromide is a better ligand transfer agent than ferric chloride.[19]

In addition to the halovinyl ketones 17, dibenzoylphenylmethane (18),[16] benzil, and benzoic acid were isolated from the reactions run at room temperature.[20] All three are the result of radical 12 reacting with molecular oxygen as evidenced by their diminished yield at reflux temperatures[21] and absence when the reaction is run in degassed solvent.[22] The simplest mechanism for the formation of these products is shown in Scheme II (of course, others are possible). Several groups of workers have demonstrated that radicals like 19 cleave readily in the manner shown.[23] The oxidation of acyl radicals to carboxylic acids is a well-known process, and it has been shown that iron(II) may facilitate the coupling of benzoyl radicals to form benzil.[24]

Cationic vs. Radical Cyclization to Form 4. While none of our experiments have unequivocally demonstrated whether the cyclization leading to 4 is a reversible homolytic process or an electrophilic process,[25] at this time we favor the electrophilic mechanism (see Scheme I) as the major pathway at room temperature. The critical experiment which led us to consider these alternatives was the drastic solvent effect on the reaction pathway when ferric chloride was used as the oxidant. That is, in aqueous acetonitrile at room temperature the major product is 4, while in aqueous ethanol the major products are the isomeric chloro ketones 17a (see Table III). Recently, Nonhebel has convincingly shown that phenyl radical addition to aromatics is a reversible process.[27b] How-

Scheme II



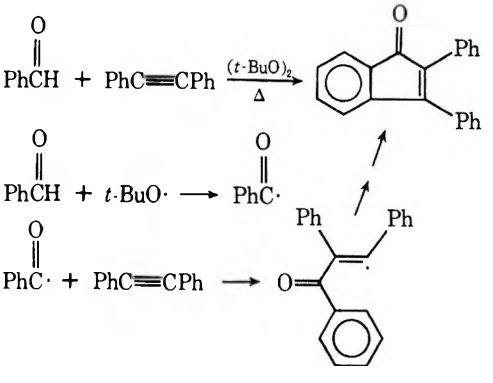
19

ever, complete equilibration does not take place at temperatures below 100 °C, and the reversibility of the process is reduced when Cu(II) is added to oxidize the intermediate radical. Both of these observations lead us to believe that if a reversible radical addition were taking place in our system substantial amounts of radical 13 should be oxidized in the presence of ferric chloride even in aqueous ethanol. The solvent effect is best rationalized by assuming that the oxidation potential of ferric chloride in acetonitrile is higher than it is in ethanol[28] and thus the oxidation of 12 to 14 takes place only in acetonitrile. The minor amounts of indenone 4 produced in ethanol may be the result of a radical cyclization. Either pathway is possible at elevated temperature.

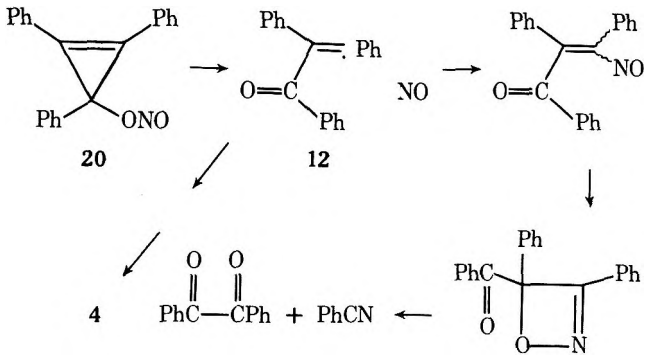
That the radical 12 can cyclize is illustrated by the formation of 4 in 11% yield when benzaldehyde, diphenylacetylene, and *tert*-butyl peroxide are refluxed in bromobenzene (see Scheme III).[29]

Another approach to the investigation of the reactivity of radical 12 would be through thermolysis of 1,2,3-triphenylcyclopropenyl nitrite (20). Although Jones and Kobzina synthesized a compound which was either a nitro or nitrite derivative of 1,2-diphenylcyclopropene,[30] work with cyclopropyl nitrites[31] led us to believe that a cyclopropenyl nitrite would not be stable at ordinary temperatures. In order to generate nitrite 20, we simply mixed 1,2,3-triphenylcyclopropenyl tetrafluoroborate with an excess of potassium nitrite in aqueous acetonitrile at room temperature. The following products were obtained: 4 (<1%), benzil (22%), benzoic acid (10%), 2-phenylisatogen (11%),[4] and benzonitrile (substantial

Scheme III



Scheme IV



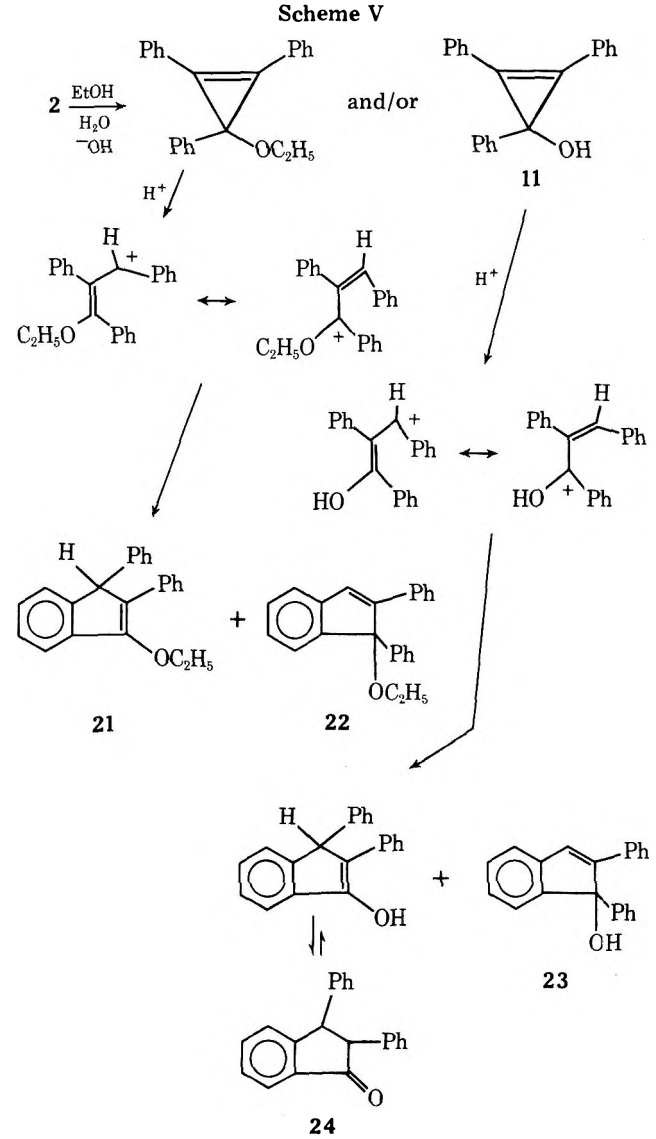
amounts). Under degassed conditions about the same amount of indenone and benzil were produced, starting with 1,2,3-triphenylcyclopropenylium bromide and sodium nitrite in ether–water. The other products might have been present, but were not looked for.

The most reasonable explanation for formation of **4**, benzil, and benzonitrile is shown in Scheme IV. The initially formed nitrite **20** loses nitric oxide to give **12**. This radical can cyclize to give **4** or it can react with nitric oxide to give a vinylnitroso compound. This can rearrange to give benzil and benzonitrile, a process with ample precedent in the literature.[32] Because capture of the radical **12** by nitric oxide is such a favorable process, these experiments do not say anything about the mechanistic pathway to **4** in our experiments with **1** and iron salts.

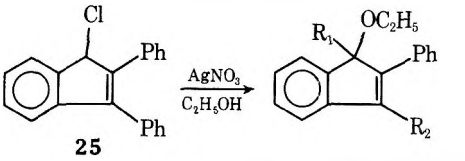
Several other possible mechanisms for indenone formation which we have considered and ruled out are discussed in the next two sections.

Possible Friedel–Crafts Reaction. Formation of 2,3-diphenylindenone might be the result of two successive reactions: Friedel–Crafts cyclization of an intermediate formed from **1** or 3-hydroxy-1,2,3-triphenylcyclopropene (**11**) (see Scheme V) followed by oxidation to **4**. Precedent for the cyclization is the previously cited rearrangement of **3** to 1,2-diphenylindene catalyzed by acetic acid–sulfuric acid.[5b] The reaction is also catalyzed by $[(C_2H_4)PtCl_2]_2$.[33] Thus, we first investigated the reaction of 1,2,3-triphenylprop-2-en-1-one (**16**), the product of ring-opening of **11**,[11] with ferric chloride under the reaction conditions. It did not undergo cyclization; in fact, it was recovered almost quantitatively. Thus, the Friedel–Crafts pathway became doubtful, since it was unlikely that the carbonium ions formed on ring opening of **1** or **11** would retain excess energy from the relief of strain long enough to undergo cyclization before this energy was dissipated to the solvent. However, to have an unequivocal answer, we decided to test for **21–24** as intermediates by ascertaining whether or not they were oxidized to **4** under the reaction conditions.

Scheme V



Compound **21** was available from the reaction of **1** with cuprous bromide (see Experimental Section). Compound **22** was prepared by the solvolysis of 1-chloro-2,3-diphenylindene (**25**)[34] in ethanolic silver nitrate. In fact, **25** gave two products, **22** and **26**; **22** being the minor product of the reaction. Although **23** was known,[35] its synthesis was most easily effected by the solvolysis of **25** in acetone–water–silver nitrate. Again,



22, R_1 = Ph; R_2 = H
26, R_1 = H; R_2 = Ph

the desired compound was the minor product. Compound **24** was synthesized by a method in the literature.[36] The results of treatment of **21–24** with **1** and 2 mol of ferric chloride under the usual reaction conditions are given in Table IV. Although minor amounts of **21–24** or their degradation products with ferric chloride might have been missed in the workup of the reaction of **1** with ferric chloride, none of these compounds was present in significant amount. Since **21–24** are not oxidized to **4** to any large extent, none of them is considered to be an important intermediate in the formation of the indenone.

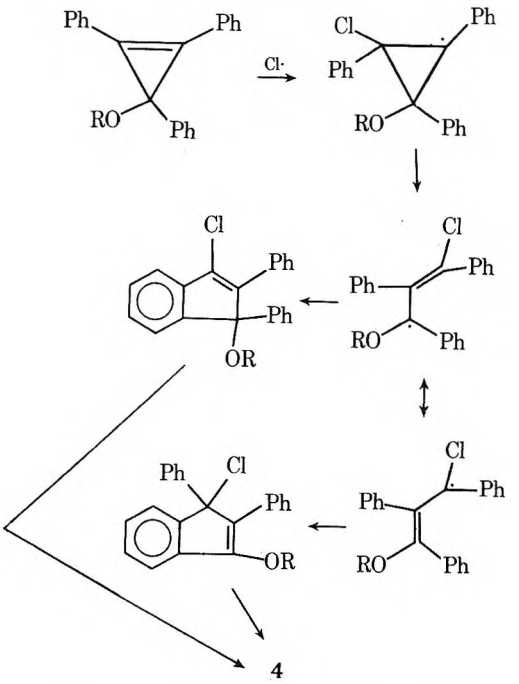
Possible Reaction of Chlorine Radical. Another mechanism which has been ruled out is one in which the ligand on iron is the essential reactant. Such a reaction with a chlorine atom is indicated in Scheme VI.[37] However, we have checked the reaction of **1** with two other iron compounds, ferric nitrate nonahydrate and ferric perchlorate hexahydrate in ethanol under the usual reaction conditions. The nitrate and **1** gives 74% of **4**, while the perchlorate gives 54% of **4** and 20% of **7** or **3**. Although nitrate radicals do sometimes add to olefins in oxidation reactions,[38] we have not found a precedent for this kind of reaction with perchlorate salts.

Experimental Section

All melting points were uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 137 spectrophotometer. Ultraviolet spectra were recorded with a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were taken with a Varian A-60 NMR spectrometer.

Gas chromatography was performed with a Varian 70 Aerograph

Scheme VI



Model 90-P gas chromatograph on a 10-ft, 20% SE-30 on Anakron A (60–80 mesh) column at 160 °C. TLC layers were prepared according to Stahl with silica gel GF. The size of the thick-layer plates (1 mm in thickness) was 20 × 20 cm. Eluants were reagent grade. Microanalyses were performed by Baron Consulting Co., Orange, Conn.

Preparation of 1,2,3-Triphenylcyclopropenylium Tetrachloroferrate (2). In a 150-mL beaker, 0.650 g (2.1 mmol) of 3-ethoxy-1,2,3-triphenylcyclopropene (**1**)[39] was dissolved in 50 mL of anhydrous ether to which 0.324 g (2.0 mmol) of ferric chloride in 30 mL of anhydrous ether was slowly added with stirring. A yellow powder precipitated, yield 0.870 g (125%), mp 240–245 °C. Recrystallization (CH_3CN) gave fine yellow crystals, mp 251 °C [lit.[40] mp 253–254 °C]. The IR spectrum was identical to that of 1,2,3-triphenylcyclopropenylium bromide.

Anal. Calcd for $C_{21}H_{15}Cl_4Fe$: C, 54.19; H, 3.23; Cl, 30.45; Fe, 12.0. Found: C, 54.37; H, 3.25; Cl, 30.76; Fe, 10.6.

Characterization of 6a and 6b. Compound **6a** is white needles (EtOH in the cold): mp 67–68 °C; IR (KBr) 6.25, 6.7, 9.0, 14.3 μm; UV (EtOH) λ_{max} 260 nm (log ε 4.20); NMR ($CDCl_3$) δ 1.2 (3 H, t, J = 7 Hz, Me), 3.6 (2 H, q of d, J = 7, 3 Hz, CH_2), 5.0 (1 H, br s, >CHO–), 6.2–7.4 ppm (16 H, m, vinylic + Ph).

Anal. Calcd for $C_{23}H_{22}O$: C, 87.86; H, 7.05. Found: C, 88.14; H. 7.29.

An authentic sample was prepared in a manner completely analogous to that reported for the preparation of 1-methoxy-1,2,3-triphenylprop-2-ene[41] and was identical (IR, mixture mp) to the samples isolated from the reaction of **5** with ethanol.

Compound 6b is white needles (*i*-PrOH): mp 82.5–83.5 °C; IR (KBr) 6.25, 6.7, 9.15, 14.3 μm; UV (EtOH) λ_{max} 260 nm (log ε 4.21); NMR ($CDCl_3$) δ 1.2 [6 H, d, J = 6 Hz, $(CH_3)_2C$], 3.9 (1 H, m, J = 6 Hz, >CHO–), 5.2 (1 H, br s, CHPh), 6.8–7.6 (16 H, m, vinylic + Ph).

Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 87.64; H, 7.32.

An authentic sample was prepared by refluxing for 20 h 0.1 g (0.35 mmol) of (*E*)-1,2,3-triphenylprop-2-en-1-ol[41] in 50 mL of isopropyl alcohol containing 0.010 g of *p*-toluenesulfonic acid. The solution was cooled, poured into water, and extracted with ether which was dried ($MgSO_4$) and removed in vacuo to give a white solid, mp 81.5–83.5 °C. This sample and samples isolated from the reaction of **5** with isopropyl alcohol were identical (IR, mixture mp).

Preparation of Lower Melting 3-Chloro-1,2,3-triphenylprop-2-en-1-one (17a). To phenylmagnesium bromide in 150 mL of ether prepared from 15.7 g (0.1 mol) of bromobenzene and 2.43 g (0.1 g atom) of Mg was added 20 g (0.08 mol) of 3-chloro-2,3-diphenylpropenal[42] dissolved in 300 mL of benzene. After all the benzene had been added, the mixture was refluxed for 2 h, allowed to cool to room temperature, poured into saturated ammonium chloride, and worked up in the usual manner to give a yellow oil. This was crystallized with difficulty from ethyl acetate–petroleum ether to give 20 g (75%) of yellow needles of 3-chloro-1,2,3-triphenylprop-2-en-1-ol (**30**), mp 45–55 °C, mp 93–100 °C after drying in vacuo. An analytical sample (white needles, ether–hexane) gave mp 110–111 °C; IR (KBr) 2.8 (O–H), 9.6, 14.3 μm; UV (EtOH) sh 245 nm (log ε 3.98); NMR ($CDCl_3$) δ 2.2 (1 H, br s, OH), 5.8 (1 H, br s, >CH), 6.9–7.8 ppm (15 H, m, Ph).

Anal. Calcd for $C_{21}H_{17}ClO$: C, 78.62; H, 5.34; Cl, 11.05. Found: C, 78.42; H, 5.28; Cl, 11.43.

Oxidation of 3.20 g (0.01 mol) of **30** by the method of Ratcliffe and Rodehorst[43] gave 2.8 g (88%) of **17a**, mp 98–100 °C. A sample prepared for analysis (EtOH) had mp 99.5–100.5 °C, IR (KBr) 6.0, 6.1, 7.9, 13.0, 14.4 μm; UV (EtOH) λ_{max} 256 nm (log ε 4.33); NMR ($CDCl_3$) δ 6.8–8.1 ppm (m), actually two contiguous multiplets ca. 6.8–7.8 ppm (13 H) and 7.7–8.1 ppm (2 H, ortho H on benzoyl). The IR of this compound was nearly identical to that of higher melting **17b**.

Anal. Calcd for $C_{21}H_{15}ClO$: C, 79.12; H, 4.74; Cl, 11.12. Found: C, 79.11; H, 4.84; Cl, 11.49.

Preparation of Higher Melting 3-Chloro-1,2,3-triphenylprop-2-en-1-one (17a). To 1 g (3.2 mmol) of **1** in 60 mL of acetonitrile was added 1.105 g of $CuCl_2 \cdot 2H_2O$ dissolved in 2.5 mL of water and 5 mL of acetonitrile.[44] The solution was stirred for 1 h, poured into water, and extracted twice with ether which was washed, dried ($MgSO_4$), filtered, and removed under reduced pressure to give an oil. This was chromatographed on alumina. Elution with petroleum ether gave an oil which, upon scratching in ethanol at dry ice temperatures, crystallized. Fractional crystallization (EtOH) gave 0.142 g (14%) of lower melting **17a**, mp 94–97 °C, and 0.050 g (5%) of higher melting **17a**, mp 105–106 °C: IR (KBr) 6.0, 14.4 μm; UV (EtOH) λ_{max} 257 (log ε 3.97), sh 280 nm (log ε 3.72); NMR ($CDCl_3$) δ 7.9–8.3 (1.5 H, m, H ortho on benzoyl), 6.7–7.7 ppm (13.5 H, m, all other phenyl hydrogens); mass spectrum, calcd for $C_{21}H_{15}ClO$: mol wt 318.0811; found: 318.0803. IR and mixture melting point showed higher melting **17a** to be identical to the crystalline chloro ketone obtained from $FeCl_3$ and **1** in CH_3CN–H_2O at room temperature (see Table V). The IR of this compound was very similar to the IR of the lower melting **17b**.

Preparation of Higher Melting 3-Bromo-1,2,3-triphenylprop-2-en-1-one (17b). The 3-bromo-2,3-diphenylpropenal was synthesized by the method of Arnold and Holy[45] in 32% yield: mp 157–161 °C [lit.[45] mp 165 °C]. To phenylmagnesium bromide in ether, prepared from 7.2 g (0.046 mol) of bromobenzene and 1.1 g (0.045 g-atom) of Mg was added 11 g (0.038 mol) of 3-bromo-2,3-diphenylpropenal, mp 161–164 °C, partially dissolved in 100 mL of dry benzene. The cloudy reaction mixture was refluxed for 2 h, allowed to cool to room temperature, and poured into ammonium chloride–water. The water layer was extracted two times with ether which was washed with water, dried ($MgSO_4$), and removed in vacuo to give an oily solid. Recrystallization (benzene–hexane) gave 9.5 g, mp 128–131 °C, and 1.85 g, mp 121–125 °C, yield 11.35 g (81%). An analytical sample (ethyl acetate–hexane) gave mp 133–134 °C: IR (KBr) 2.94, 9.7, 14.4 μm; UV (EtOH) sh 261 (log ε 3.82), 230 nm (log ε 4.27); NMR ($CDCl_3$) δ 2.4 (1 H, br s, OH), 5.7 (1 H, s, >CH), 6.7–7.9 ppm (15 H, m, Ph).

Anal. Calcd for $C_{21}H_{17}BrO$: C, 69.05; H, 4.69. Found: C, 69.35; H, 4.84.

Oxidation of 3.65 g (0.01 mol) of the above alcohol by the method of Ratcliffe and Rodehorst[43] gave 2.6 g (71%) of higher melting **17b**, mp 106–108 °C. A sample prepared for analysis (benzene–hexane) had mp 107–108 °C: IR (KBr) 6.0, 6.1, 7.9, 13.0, 14.4 μm; UV (EtOH) λ_{max} 252 (log ε 4.38) nm; NMR ($CDCl_3$) δ 7.7–7.9 (2 H, m, H ortho on benzoyl), 6.9–7.6 ppm (13 H, m, all other phenyl hydrogens).

Anal. Calcd for $C_{21}H_{15}BrO$: C, 69.43; H, 4.16; Br, 22.00. Found: C, 69.75; H, 4.20; Br, 22.29.

Synthesis of Lower Melting 3-bromo-1,2,3-triphenylprop-2-en-1-one (17b). A mixture of 0.502 g (1.6 mmol) of **1** and 0.284 g (1.6 mmol) of *N*-bromosuccinimide (purified by the method of Dauben and McCoy)[46] in 25 mL of CCl_4 was refluxed for 22 h. After 5 h almost all of the solid had dissolved and the solution was colorless. Almost all of the solvent was removed in vacuo to give a thick oil to which was added 5 mL of anhydrous acetonitrile. After standing in the freezer, 0.413 g (53%) of colorless crystals, of what is probably 1-bromo-3-ethoxy-3-succinimido-1,2,3-triphenylpropene (**27**), mp 167–168.5 °C, was collected. A sample prepared for analysis (benzene–hexane) had mp 184–185 °C: IR (KBr) 5.8, 7.6, 8.6, 13.3, 14.3 μm; UV (CH_3CN) sh 266 nm (log ε 3.69); NMR ($CDCl_3$) δ 1.0 (3 H, t, J =

Table IV. Extent of Oxidation of Possible Intermediates

	21	22	23	24
1 mol of $FeCl_3$ % indenone	9	None	Trace	6
2 mol of $FeCl_3$ % indenone	20	None	Trace	9

7 Hz, CH_3), 2.9 (4 H, s, CH_2CH_2), 3.5 (2 H, q, J = 7 Hz, CH_2), 7.1–8.0 ppm (m, 15 H, Ph); mass spectrum, parent peaks m/e 489, 491.

Anal. Calcd for $C_{27}H_{24}BrNO_3$: C, 66.01; H, 4.90; N, 2.86; Br, 16.34. Found: C, 65.75; H, 4.81, N, 2.60; Br, 16.72.

After several months in a stoppered flask, the residue was treated with ether, giving 0.035 g of fluffy solid, mp 197–200 °C. A sample recrystallized for analysis (EtOH) gave white fluffy needles, mp 205–206.5 °C, probably 1,2,3-triphenyl-3-succinimidoprop-2-en-1-one (**28**): IR (KBr) 5.9 (succinimide C=O), 6.05 (PhC=O), 7.3, 8.6, 13.4, 14.3 μm; UV (EtOH) λ_{max} 258 nm (log ε 4.28); NMR ($CDCl_3$) δ 2.5 (br s, 4 H, $-CH_2CH_2-$), 6.7–8.2 ppm (m, 15 H, Ph).

Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.73; H, 5.02; N, 3.68. Found: C, 78.74; H, 5.09; N, 3.57.

Further treatment of the residue by refluxing in 6:1 acetonitrile–water for 30 min left an oil from which was isolated, by treatment with ether, 0.013 g of **28**. Thick-layer chromatography gave 0.120 g of a mixture of the higher and lower melting isomers of **17b**, NMR analysis showing the higher melting isomer predominating 2:1. Also, about 0.010 g of dibenzoylphenylmethane (**18**) was isolated from the thick-layer plate.

Hydrolysis of 0.186 g of **27** was effected by refluxing in 6 mL of water/acetonitrile (1:5) for 30 min. The mixture was poured into a beaker and the solvent allowed to evaporate. The white powder was thick-layer chromatographed to give 0.150 g (100%) of lower melting **17b**, mp 98–100 °C. A sample prepared for analysis (EtOH) had mp 101.5–102 °C: IR (KBr) 6.0, 14.4 μm; UV (EtOH) λ_{max} 256 nm (log ε 4.37); NMR ($CDCl_3$) δ 7.9–8.3 (2 H, m, H ortho on PhC=O) 6.8–7.7 ppm (13 H, m, all other Ph); mass spectrum, parent peaks m/e 362, 364.

Anal. Calcd for $C_{21}H_{15}BrO$: C, 69.42; H, 4.13; Br, 22.03. Found: C, 69.30; H, 4.29; Br, 21.69.

Succinimide was also obtained from the TLC: 0.0260 g (64%), mp 123–125 °C [lit.[47] mp 125–126 °C]; IR identical to Sadtler Infrared No. 482.[48]

Isolation of Chlorovinyl Ketones 17a. Reactions in which the isomeric **17a** were found used 0.150 g of **1** and an equivalent of ferric chloride in acetonitrile–water at room temperature for 0.5 h. The workup by thick-layer chromatography gave a chlorovinyl ketone band (average yield, 0.015 g) practically contiguous with the indenone band even after several elutions; fractions from several runs were mixed. After standing in benzene–hexane for several months in the freezer, the crude chlorovinyl ketone mixture crystallized and one pure isomer, the higher melting isomer, could be obtained. It was identical to the higher melting isomer obtained from chlorination of **1** with $CuCl_2$ in acetonitrile. The presence of the other isomer could be detected by NMR in the region for the ortho hydrogens of the benzoyl group.

Preparation of 3-Ethoxy-1,2-diphenylindene (21). A mixture of 0.118 g (0.375 mmol) of **1**, 0.056 g (0.375 mmol) of CuBr, and 15 mL of absolute EtOH was refluxed for 12 h, yielding a very pale green clear solution with a trace of cream-colored solid. Thick-layer chromatography gave five fractions (plus a non-benzene-soluble component); the major fraction was a white solid (0.100 g, 85%): white feathers (EtOH); mp 130.5–132 °C; IR (KBr) 6.25, 7.45, 9.35, 9.8 μm; UV (EtOH) λ_{max} 313 (log ε 4.35), sh 302 (log ε 4.34), 242 (log ε 4.10), 235 nm (log ε 4.15); NMR ($CDCl_3$) δ 1.4 (3 H, t, J = 7 Hz, Me), 4.2 (2 H, q, J = 7 Hz, CH_2), 4.9 (1 H, s, >CH–), 7.1–7.8 ppm (14 H, m, Ph).

Anal. Calcd for $C_{23}H_{20}O$: C, 88.43; H, 6.45. Found: C, 88.68; H, 6.65.

Further evidence for the structure of **21** is that refluxing in EtOH–$AgNO_3$ for 20 h gives 39% 2,3-diphenylindanone[4] (hydrolysis product) as well as 58% recovered starting material.

Preparation of 1-Ethoxy-2,3-diphenylindene (26) and 1-Ethoxy-1,2-diphenylindene (22). To a stirred solution of 0.150 g (0.5 mmol) of 1-chloro-2,3-diphenylindene[34] in 25 mL of EtOH was added 0.255 g (0.5 mmol) of $AgNO_3$. All the $AgNO_3$ finally dissolved after heating for 15 min on a steam bath, and a whitish precipitate formed, which was collected and not analyzed. Evaporation of the filtrate in vacuo left an orange-green oil which was thick-layer chromatographed. Two distinct fractions were collected, the first exhibiting weak blue fluorescing and the second pronounced blue fluorescing under short-wavelength UV.

Fraction 1 (0.020 g 13%) was identified as **22**: white needles (EtOH–H_2O); mp 93–96 °C; IR (KBr) 9.0, 9.25, 9.3, 13.0, 13.35, 14.25 μm; UV (EtOH) λ_{max} 314 (log ε 4.31), 327 (log ε 4.32), 342 (log ε 4.10), sh 243 (log ε 4.38), 251 mm (log ε 4.35); NMR ($CDCl_3$) δ 1.1 (3 H, t, J = 7 Hz, Me), 3.2 (2 H, m, CH_2), 7.25 ppm (15 H, m, vinylic + Ph).

Fraction 2 (0.052 g, 33%) was identified as **26**: white tiny needles (EtOH–H_2O); mp 101–102.5 °C; IR (KBr) 8.95, 9.05, 9.25, 12.85, 13.1, 13.3, 14.1, 14.3 μm; UV (EtOH) λ_{max} 315 (log ε 4.11), 242 (log ε 4.45) nm; NMR ($CDCl_3$) δ 1.0 (3 H, t, J = 7 Hz, Me), 3.3 (2 H, q, J = 7 Hz, CH_2), 5.7 (1 H, s, –CHO–), 7.4 ppm (14 H, m, Ph).

Anal. Calcd for $C_{23}H_{20}O$: C, 88.43; H, 6.45. Found for **22**: C, 88.65; H, 6.69. Found for **26**: C, 88.55; H, 6.60.

Preparation of 1-Hydroxy-1,2-diphenylindene (23). To a solution of 0.151 g (0.5 mmol) of 1-chloro-2,3-diphenylindene[34] in 6 mL of acetone was added 0.234 g of $AgNO_3$ dissolved in 3.5 mL of water. The cloudy mixture was refluxed on a steam bath for 2 h, then poured into water, and extracted three times with ether which was washed, dried ($MgSO_4$), and removed in vacuo to give an orange oil which was thick-layer chromatographed. Isolation of the first fraction gave 0.026 g (18%) of **23**, mp 132–135 °C. Recrystallization (benzene–hexane) gave mp 135–137 °C (lit.[35] mp 138.7–139.5 °C), NMR ($CDCl_3$) δ 2.1 (1 H, s, OH), 7.0–7.7 ppm (15 H, m, vinylic + Ph). The second fraction gave 0.075 g (53%) of 1-hydroxy-2,3-diphenylindene, mp 114–117 °C, after recrystallization (benzene–hexane). If heated very slowly this material softens at 118 °C and melts 134.5–135 °C [lit.[34] mp 132–135 °C). The infrared spectrum of this compound was identical to the infrared of the product of reduction of 2,3-diphenylindenone with sodium borohydride.

Reaction of 29 with Potassium Nitrite. A 500-mL flask was charged with 2.024 g (5.7 mmol) of 1,2,3-triphenylcyclopropenyl tetrafluoroborate–hydroxyfluoroborate[11] (**29**) and 115 mL of dry CH_3CN. The mixture was magnetically stirred at room temperature for 10 min to dissolve the salt. A solution of 5.21 g (57 mmol) of KNO_2 in 7.5 mL of distilled water was then added in one portion with good stirring followed by an additional 90 mL of CH_3CN. The bright orange mixture was stirred for 3.5 h. Dry benzene (45 mL) was then added, the mixture was filtered, and the solvent was evaporated in vacuo. The residue had a strong odor of bitter almonds. Gas chromatography of an ethereal wash of the residue confirmed the presence of benzonitrile as indicated by an identical retention time with an authentic sample. A collected sample had mass spectrum, calcd for C_7H_5N: mol wt 103.0422; found: 103.0420; IR identical to that of an authentic sample except for a weak extraneous peak at 1724 cm^{-1}.

In a separate experiment, the material after evaporation of the benzene was partitioned between ether and water, and the aqueous layer (pH 6) was extracted with five 75-mL portions of ether. The organic extracts were washed with five 25-mL portions of fresh ether. The alkaline solution was saturated with NaCl, acidified to pH 2 with 6 N HCl, and extracted with ether. After drying ($MgSO_4$), the solvent was removed in vacuo to give 68 mg (10%) of benzoic acid, mp 117–119 °C, identical (IR, mixture mp) with an authentic sample.

The ethereal solution of nonacidic material was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residual red oil was chromatographed on 200 g of Woelm silica gel. Five fractions were collected. Fraction one was eluted with 250 mL of hexane and consisted of 2 mg of an unidentified yellow solid. Fraction two, a red-orange band, eluted with 250 mL of 1% ether–hexane and 375 mL of 3% ether–hexane, contained in addition to benzonitrile 260 mg (22%) of benzil, mp 93–95 °C (mixture mp 93.5–94 °C) and <1% 2,3-diphenylindenone (IR).

Fraction three, eluted with 250 mL of 3% ether–hexane and 250 mL of 5% ether–hexane, gave only small amounts of intractable oils after preparative thick-layer chromatography.

Fraction four, a red-orange band, was eluted with 350 mL of 5% ether–hexane. The red solid, purified by preparative layer chromatography and recrystallization (ether), was 2-phenylisatogen (70 mg, 11%), mp 189–191 °C [lit.[49] mp 185–186 °C]; mass spectrum, calcd for $C_{14}H_{19}NO_2$: mol wt 223.0634. Found: 223.0635; IR (nujol) identical to lit.[48]

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 75.37; H, 4.08; N, 6.28. Found: C, 75.02; H, 4.38; N, 6.25.

Fraction five was eluted with 600 mL of ether. TLC showed the presence of at least four compounds. Preparative thick-layer chromatography produced only intractable glasses.

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Registry No.—**1**, 13668-0306; **2**, 64163-62-8; **3**, 16510-49-9; **4**, 1801-42-9; **15**, 4919-51-1; **6a**, 64163-17-3; **6b**, 64163-18-4; *cis*-**16**, 7512-67-6; *trans*-**16**, 7474-65-9; *cis*-**17a**, 64163-19-5; *trans*-**17a**, 64163-20-8; *cis*-**17b**, 64163-21-9; *trans*-**17b**, 64163-22-0; **18**, 4888-39-5; **21**, 27331-18-6; **22**, 64163-23-1; **23**, 64163-24-2; **24**, 7474-64-8; **26**, 64163-25-3; **27**, 64163-26-4; **28**, 64163-27-5; **29**, 741-16-2; **30**, 38395-

70-9; ferric chloride, 7705-08-0; EtOH, 64-17-5; *i*-PrOH, 67-63-0; (*E*)-1,2,3-triphenylprop-2-en-1-ol, 57015-16-4; phenyl bromide, 108-86-1; 3-chloro-2,3-diphenylpropenal, 14063-81-1; 3-bromo-2,3-diphenylpropenal, 36998-45-5; *N*-bromosuccinimide, 128-08-5; 1-chloro-2,3-diphenylindene, 4023-85-2; 1-hydroxy-2,3-diphenylindene, 53347-50-5; benzil, 134-81-6; 2-phenylisatogen, 1969-74-0; MeOH, 67-56-1; *t*-BuOH, 75-65-0; $FeBr_3$, 10031-26-2; 3-bromo-2,3-diphenylpropanol, 64163-28-6.

Supplementary Material Available: Table V entitled "Reactions of 1 and 2 and Control Experiments" (7 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented in part by A. Monahan, J. D. Freilich, and J.-J. Fong, Abstracts, 164th National Meeting of the American Chemical Society, New York, N.Y., Aug. 1972, ORGN 62, and by A. Monahan and D. Kronenthal, Abstracts, 172nd National Meeting of the American Chemical Society, San Francisco, Calif., Sept. 1976, ORGN, 157.

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Nitromethylation of Aromatics with Nitromethane–Manganese(III) Acetate[1]

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Manganese(III) acetate was found to effect aromatic substitution by a nitromethyl group when reacted with an aromatic and nitromethane in acetic acid. Based on similarities to previously studied maganese(III) acetate systems, a mechanism involving the generation of and substitution by nitromethyl radicals is proposed. The partial rate factors, ρ value (vs. σ^+) of -1.1, and the failure to substitute on nitrobenzene suggest that the nitromethyl radical exhibits appreciable electrophilic character. This reaction, which proceeds in a clean, reasonably high-yield manner, might well provide an alternate route to synthesizing certain aryl nitromethanes, which are currently made through multistep, side-chain substitutions involving α-halo- or α-cyanotoluenes.

Though metal salts have been used extensively to aid in aromatic substitutions by oxy radicals,[2-4] there are only a few cases of metal salt promoted homolytic aromatic alkylations. For example, the interaction of manganese(III) acetate with toluene and acetic acid at reflux has been shown to produce carboxymethyl radicals which react with the aromatic by side-chain hydrogen abstraction or ring addition leading subsequently to benzyl acetate and methylphenylacetic acids, respectively.[5] Further reaction of the latter in the system generates a xylyl radical which is converted to isomeric xylyl acetates. The reaction of toluene or benzene with acetone in refluxing acetic acid containing manganese(III) acetate was recently reported to lead to aromatic substitution by an α-oxyalkyl radical (**1**, eq 1 and 2).[6]

$$CH_3COCH_3 + Mn(OAc)_3 \rightarrow \underset{\mathbf{1}}{CH_3COCH_2\cdot} + Mn(OAc)_2 + HOAc \quad (1)$$

$$\mathbf{1} + ArH \xrightarrow[-Mn(II)]{Mn(III)} CH_3COCH_2Ar \quad (2)$$

In view of our interest in homolytic substitutions promoted by metal salts,[2,3] we set out to see if manganese(III) acetate could be utilized to generate and substitute other types of radicals onto aromatics. Specifically, we studied the interaction of nitroalkanes and aromatics with manganese(III) acetate in the hope of producing arylnitroalkanes by way of homolytic aromatic substitution involving nitroalkyl radicals.

Results and Discussion

Manganese(III) acetate[7] was allowed to react with toluene in refluxing gacial acetic acid according to the method described by Heiba and Dessau.[5] After workup, product analysis indicated that benzyl acetate (15%), methylbenzyl acetate (40%), and tolylacetic acid (10%) were formed as reported earlier.[5]

Inclusion of nitromethane in the above system led to striking results. Instead of observing products due to carboxymethyl radicals, the only aromatic products formed were nitromethylated toluenes (isomeric α-nitroxylenes). Various ratios of nitromethane, toluene, and acetic acid, all present in 7–70 molar excess to the managnese(III) limiting reagent, caused minor fluctuations (41–61%) in substitution product yield. However, equal volumes of toluene, nitromethane, and glacial acetic acid seemed to give the best substitution yields for this system, and these amounts (25 mL each of aromatic, nitromethane, and acetic acid and 10 mmol of manganese(III) acetate) were adopted as our standard procedure.

Other aromatics were reacted with the nitromethane–manganese(III) acetate system in the same manner, though different reflux conditions pertained in each case (Table I). As with toluene, the only aromatic products observed were $-CH_2NO_2$ adducts in moderate to good yields. Better yields were obtained with the more electron-rich aromatics (e.g., anisole, or toluene); on the other hand, no substitution was noted with nitrobenzene. Removal of salt by washing and the evaporation of excess solvent and reactants yielded the pure aryl nitromethane directly (Table I, isolated yield).

Table I reveals that the higher the reflux temperature, the shorter the reaction time (e.g., the nitrobenzene case). The reaction time is the same for the anisole and chlorobenzene cases which reflux at the same temperature despite the wide variance in aromatic reactivity. This suggested that the rate-determining step does not involve the aromatic, but rather the manganese(III) salt and nitromethane common to all the reactions.

Based on analogy to previously studied manganese(III) acetate systems,[5,6] a free radical mechanism is proposed for aromatic nitromethylation (eq 3–5). Nitromethyl radicals, **2**, are generated by the oxidation of nitromethane by manganese(III) acetate (eq 3) and substituted onto the aromatic ring to give a cyclohexadienyl radical, **3** (eq 4). This in turn is oxidized by another manganese(III) acetate to give $-CH_2NO_2$ adducts (eq 5). The overall stoichiometry is shown in eq 6.

$$CH_3NO_2 + Mn(OAc)_3 \rightarrow \underset{\mathbf{2}}{\cdot CH_2NO_2} + Mn(OAc)_2 + HOAc \quad (3)$$

$$\mathbf{2} + ArH \rightarrow \underset{\mathbf{3}}{Ar(H)CH_2NO_2} \quad (4)$$

$$\mathbf{3} + Mn(OAc)_3 \rightarrow ArCH_2NO_2 + Mn(OAc)_2 + HOAc \quad (5)$$

$$CH_3NO_2 + ArH + 2Mn(OAc)_3 \rightarrow ArCH_2NO_2 + 2Mn(OAc)_2 + 2HOAc \quad (6)$$

Previously, Heiba[5] had demonstrated that small amounts of cupric acetate inhibited the carboxymethylation process (eq 4) and attributed this to the efficient oxidation of the carbon radical by cupric[8] preventing its attack on the aromatic. Introduction of cupric acetate to our system had no effect on the nitromethylation process. We attribute this to the higher expected ionization potential of the nitromethyl radical which makes it resistant to the usual cupric-facilitated oxidation.[9]

To get a better idea of the influence of temperature on this substitution process, the nitromethylation of anisole was studied at different temperatures (Table II). Though the reaction time varied as expected, not much difference was noted in the yields, with the exception of the slightly lower result at

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Table I. Nitromethylation of Aromatics with Nitromethane[d]–Manganese(III) Acetate[e] at Reflux[a]

Aromatic	Registry no.	Temp, °C	Time,[b] min	% $ArCH_2NO_2$[c] By GC	Isolated
Benzene	71-43-2	87	110	46	31
Toluene	108-88-3	97	40	78	66
Anisole	100-66-3	106	30	72	62
Chlorobenzene	108-70-7	107	30	27	
Nitrobenzene	98-95-3	112	25		

[a] Equal volumes (25 mL) of aromatic, nitromethane, and acetic acid and manganese(III) acetate (10 mmol) were refluxed under a nitrogen gas atmosphere. [b] Time at reflux until the brown manganese(III) color changed to light yellow with white manganese(II) acetate precipitate. [c] Yield is based on the stoichiometry of 2 mol of manganese(III) acetate/mol of product formed (eq 6). [d] Registry no.: 75-52-5. [e] Registry no.: 993-02-2.

Table II. Effect of Temperature on Anisole–Nitromethane–Manganic Acetate Reaction

Temp, °C	Time, min	Yield, %
69	1380	55
83	140	77
93	75	67
106	30	72

Table III. Nitromethylation of Aromatics at 83 °C

Aromatic	Yield	Isomer distribution ortho	meta	para
Benzene	78			
Toluene	77	52	27	21
Anisole	77	71	5	24
Chlorobenzene	20	52	48[a]	

[a] The meta and para isomer could not be separated.

Table IV. Nitromethylation Competition Reactions[a]

Molar Ratio C_6H_5X/C_6H_5Y	–X	–Y	Molar ratio[b] $XC_6H_4CH_2NO_2/YC_6H_4CH_2NO_2$	Rel rate $K_{C_6H_5X}/K_{C_6H_5Y}$
0.84	$-CH_3$	–H	3.65	4.34
0.27	$-OCH_3$	–H	4.00	14.84
0.88	–Cl	–H	0.33	0.37
0.98	$-OCH_3$	$-CH_3$	3.34	3.41

[a] Total aromatics:manganic acetate:nitromethane = 20:1:40. [b] Average of at least duplicate reactions in good agreement.

Table V. Partial Rate Factors for Nitromethylation

Partial rate factor[a]	σ^+ [b]
$P_f^{-CH_3} = 5.47$	−0.31
$M_f^{-CH_3} = 3.52$	−0.07
$P_f^{-OCH_3} = 21.37$	−0.78
$M_f^{-OCH_3} = 2.23$	+0.12

[a] P_f is for para isomer, M_f for meta isomer. [b] See ref 12.

Table VI. Comparison of ρ Values for Alkyl Radical–Arene Reactions

Radical	π	Method, reference: Arene substit	Hydrogen abstract. from subst toluene
C_6H_{11}	1.1	14	
i-C_3H_7	0.9		15
3-n-C_7H_{15}	0.7		16
n-$C_{11}H_{23}$	0.5		17, 18
CH_3	0.1, −0.2	11	19
CH_2CO_2H	−0.6	5	
CH_2NO_2	−1.1	this study	
CCl_3	−1.5		20
$C_6H_5CO_2$	−1.6	3	
p-$O_2NC_6H_4C$-O_2	−2.5	3	

69 °C. The optimum yield was obtained at 83 °C, the temperature which was chosen to more carefully study the nitromethylation product distribution.

Yields and isomer distributions for aromatics under these conditions are listed (Table III) and, except in the chlorobenzene case, were improved at this temperature. The reaction time was 140 min for all reactions. The isomer distributions were obtained by a combination of NMR and GC comparative analyses of the product mixtures to those of authentic isomers synthesized by alternate routes (see Experimental Section).

The isomer distribution resulting from attack of the nitromethyl species onto toluene resembles that observed from toluene methylations ($o/m/p$ = 56/27/17[10] or 52/32/15[11]). However, with anisole, which is more susceptible to the polar nature of the substituting entity, the pattern of nitromethylation is actually more similar to that found from substitution of anisole by a carboxymethyl radical ($o/m/p$ = 78/5/17)[5] than by a methyl radical ($o/m/p$ = 74/15/11).[10]

Competition reactions between pairs of aromatics, both present in large molar excess, were carried out with the nitromethane–manganese(III) acetate system (Table IV). The relative reactivities so observed were in the usual order observed for electrophilic substitutions (anisole > toluene > benzene > chlorobenzene). A good check for the apparent validity of the relative rates was the excellent agreement between $K_{C_6H_5OCH_3}/K_{C_6H_6}$ obtained directly and obtained as the product of $(K_{C_6H_5OCH_3}/K_{C_6H_5CH_3})(K_{C_6H_5CH_3}/K_{C_6H_6})$ = 14.80.

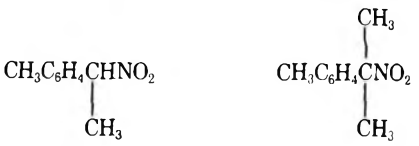
Partial rate factors (Table V) were determined using the relative rates and isomer distributions for toluene and anisole. Failure to separate the m- and p-chloro-α-nitrotoluenes prevented us from calculating these partial rate factors. A plot of the log of the partial rate factor vs. σ^+ values[12] gave a good straight line from which a ρ value of −1.08 was obtained (correlation coefficient = 0.994; least-squares treatment). A better fit was observed using σ^+ substituent values rather than σ values, a situation noted previously for more electrophilic radicals.[3,13] The negative ρ value suggested appreciable positive change buildup in the transition state and indicates that the nitromethyl-substituting entry possesses a good deal of electrophilic character.

The ρ value for nitromethylation is compared to those obtained for other radical-aromatic processes either by way of radical substitution onto arenes or side-chain hydrogen abstraction from substituted toluenes (Table VI). Table entries are mostly limited to radicals derived from carbons of sp^3 hybridization. Most unsubstituted alkyl radicals, with the exception of methyl, exhibit nucleophilic tendencies. However, those substituted with electron-withdrawing substituents take on electrophilic properties. As anticipated from common substituent effects, nitromethyl is more electrophilic than carboxymethyl, yet less so than trichloromethyl (Table VI). Most oxy radicals, for comparison, are still more electrophilic in their reactivity with arenes (Table VI).

It is interesting to note that the nitromethyl radical preferentially attacks the aromatic ring of toluene rather than abstracting an α-carbon hydrogen. No products indicative of side-chain abstraction were noted throughout this study. Such

behavior is consistent with an electrophilic radical species.[2]

In order to determine the scope of this reaction, nitroalkylations of toluene were attempted with nitroethane and 2-nitropropane. In the former case, small amounts of the expected nitroethyl adducts **4** were obtained; however, the expected product **5** was not found in the 2-nitropropane reaction.



4 **5**

These findings suggest that the aci form of the nitroalkane is the species actually undergoing oxidation to produce the radical. Tautomerization is much more rapid for nitromethane than for the other two nitroalkanes.[21]

Other compounds possessing labile α-carbon hydrogens (acetonitrile, ethyl acetate, and malononitrile) were also reacted with manganese(III) acetate and toluene, but in these cases no substitution product was observed.

Previous substitutions by α-substituted radicals[5,6] gave rather low yields due to competing side reactions. The reasonable yields, absence of side products, and ease of workup suggest possible synthetic utility for the nitromethylation reaction. Examination of the literature indicates two general synthetic methods for making aryl nitromethanes. One involves the reaction of silver nitrite with the corresponding benzyl bromide (eq 7).[22] The other (eq 8) utilizes the action

$$ArCH_2Br + AgNO_2 \longrightarrow ArCH_2NO_2 + AgBr \quad (7)$$

$$ArCH_2CN + CH_3ONO_2 \xrightarrow{NaOEt} ArC(CN)=NO_2Na \xrightarrow[-CO_2]{H_3O^+} ArCH_2NO_2 \quad (8)$$

of freshly prepared methyl nitrate on the appropriate aryl nitrile, followed by a rather lengthy workup procedure.[23] In both cases, the starting material is already an α-substituted arene, whereas in our case simple, commonly available aromatics are utilized. One drawback with the nitromethylation reaction is the occurrence of isomeric product mixtures with many simple aromatics (Table III). However, with benzene and certain other para-disubstituted aromatics from which only one substitution product is possible, this method looks promising.[24]

Experimental Section

The aromatics and nitroalkanes were shown to be of greater than 99% purity by GC and were used directly. All inorganic reagents and aralkyl bromides and cyanides were analyzed commercial products and used as supplied. Many of the expected products of nitromethylation were synthesized by alternate literature methods. Thus, α-nitrotoluene (70% GC purity), α-nitro-*p*-xylene (50% GC purity), and α-nitro-*m*-xylene (60% GC purity) were prepared from the corresponding α-bromo compound by the method of Kornblum et al.[22] α-Nitro-*m*-chlorotoluene, α-nitro-*p*-chlorotoluene, α-nitro-*o*-methoxytoluene, and α-nitro-*p*-methoxytoluene were synthesized from the corresponding benzyl cyanide, methyl nitrate, and sodium ethoxide.[23] Manganese(III) acetate was prepared according to a literature procedure[7] and found to be 97% pure by iodometric titration.

Mass spectral analyses were carried out out on a Finnegan Model 3000 GC peak identifier with a quadrupole mass filter. Mass spectra were obtained at 70 eV of the organic products from the ethereal extracts of reaction mixtures eluted from a 6.0 ft × 0.125 in. stainless-steel, 10% SE-30/Chrom-W column.

Infrared spectra were recorded on Perkin-Elmer Models 700 and 710B infrared spectrophotometers, while NMR spectra were run on a Varian EM-300X NMR spectrophotometer.

GC analyses were made on a Hewlett-Packard Model 5830A gas chromatograph or a Varian Model 1400 equipped with hydrogen flame-ionization detectors. Products were determined on the following columns: 1.67 ft × 0.125-in. stainless-steel UCW-982/Chrom-W, 6.0 ft × 0.125 in. stainless-steel OV-225/Chrom-W, and 6.0 ft × 0.125 in. glass 10% SP 1000/Chrom-W.

Reaction of Nitromethane–Manganese(III) Acetate with Aromatics. General Procedure. Manganese(III) acetate (0.01 mol) was dissolved in glacial acetic acid (25 mL) at 70 °C, and an excess amount of aromatic (25 mL) and nitromethane (25 mL) was added through an addition funnel. The mixture was then refluxed under nitrogen atmosphere with continuous magnetic stirring until the brown color changed to a light yellow (a white manganese(II) acetate precipitate formed continuously during the reaction). For quantitative GC determinations, an internal standard, *p*-nitrotoluene (2 mmol), was added to the cooled reaction mixture. Workup involved washing the reaction mixture with water (2 × 50 mL) (the white precipitate was dissolved by water) and drying the organic portion over anhydrous sodium sulfate. After stripping off the solvent on a rotatory evaporator, the residue was then analyzed by GC, GC–MS, and in some cases IR and NMR.

For reactions performed at temperatures other than reflux, the reactants were heated in a jacketed vessel containing specific refluxing solvents (dichloroethane, 83 °C; hexane, 69 °C; and methyl isopropyl ketone, 93 °C), and allowing for continuous stirring. The same general procedure was followed using either nitroethane or 2-nitropropane instead of nitromethane. Workup and analysis was done as before.

For copper salt effects, the reaction was carried out under the same conditions but in the presence of a small amount (~ 0.1 g) of cupric acetate. For the concentration-effect studies, the reactions are carried out under the same conditions, except for changes in the composition of the solutions.

A number of experimental variations were performed in an effort to regenerate manganese(III) from that salt which was reduced during the course of the reaction. In one case, oxygen was continually bubbled through the refluxing reaction mixture (with benzene as the aromatic). Upon workup only a small amount of α-nitrotoluene was detected by GC. Controls in which manganese(II) acetate in refluxing acetic acid was treated with a stream of oxygen or ozone in oxygen gave rise to salt mixtures which contained manganese(IV) dioxide (iodometry and liberation of chlorine from aqueous HCl[25]) in small and large amounts, respectively. In aother reaction, portions of $KMnO_4$ (1.4 molar equiv to the original manganese salt) were added to the reaction mixtures after the dark color of the manganese(III) species lightened up. This process was repeated with additional increments of $KMnO_4$ (six additions overall). The usual workup led to a complex product mixture with only a trace of the desired arylnitromethanes. A similar procedure was used to try to generate manganese(III) acetate in situ from manganese(II) acetate, nitromethane, and either toluene or benzene in acetic acid. In these cases, complex product mixtures resulted. Benzoic acid was detected in the toluene run and aldehydic products were detected in the benzene reaction.

The reaction of toluene and manganese(III) acetate in acetic acid was carried out as reported in the literature.[5] The attempted reaction of acetonitrile with toluene in the presence of manganese(III) acetate was carried out in the same manner using acetonitrile instead of nitromethane. A similar product pattern as for the reactions without acetronitrile was noted.[5]

Competition Reaction for Two Aromatics in Nitromethane–Manganese(III) Acetate. General Procedure. Manganese(III) acetate (0.01 mol) was dissolved in glacial acetic acid (20 mL) in a constant-temperature reactor with refluxing ethylene dichloride as jacket liquid. Equal volumes of two different aromatic (10 mL of each) and nitromethane (20 mL) were added through the condenser. The reaction was heated at 83 °C under nitrogen for 140 min and then cooled, and the reaction mixture was washed twice with water (50 mL) and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was analyzed by GC and the peak area ratios of the respective aromatic substitution products were used to determine relative reactivities.

Qualitative Analysis of Organic Products. In all cases where authentics were available, products were identified by comparison of their GC retention times and their MS and NMR spectra with those of the authentics. In this manner, α-nitrotoluene [MS peak at *m/e* 119, base peak at *m/e* 77; NMR singlet (5 H) at 7.2 ppm, singlet (2 H), at 5.2], α-nitroxylenes [MS parent peak at *m/e* 151, base peak at *m/e* 105; NMR singlet (4 H) at 7.0 ppm, isomeric singlets (2 H) at 5.2 ppm, singlet (3 H) at 2.2 ppm], methoxy-α-nitrotoluenes [MS peak at *m/e* 135, base peak at *m/e* 121; NMR multiplet (4 H), at 7.2 ppm, isomeric singlets (2 H) at 5.5 ppm, singlet (3 H) at 4.0 ppm], and chloro-α-nitrotoluenes [MS peak at *m/e* 155, base peak at *m/e* 111; NMR weak signals at 7.3 and 5.6 ppm] were identified. No authentics were available for the 1-tolyl-1-nitroethanes and 2-tolyl-2-nitropropanes.

However, the mass spectra of the aromatic products (apparently isomers) from the nitroethane–toluene (MS parent peak at *m/e* 165, base peak at *m/e* 119, others at *m/e* 91, 104) were consistent with the expected product structures.

For quantitative yield determinations, an internal standard, *p*-nitrotoluene, was added in known amount to the reaction mixture before workup. After workup, the solutions were analyzed by GC and yields were obtained by comparing the relative peak areas of the products and internal standard (internal standard program of the automatic integrator). Percent yield was based on the stoichiometry of 0.5 mol of product per mol of manganese(III) as the limiting reagent. The average yield of at least duplicate reactions in good agreement are reported in the tables.

Registry No.—**2,** 16787-85-2; α-nitrotoluene, 622-42-4; α-nitroxylene, 64147-35-9; methoxy-α-nitrotoluene, 64147-36-0; chloro-α-nitrotoluene, 64147-37-1.

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A Study of the Capacity of Group 4 Substituents for Directing the Course of Silver(I)-Catalyzed Tricyclo[4.1.0.0^{2,7}]heptane Rearrangement into the Elusive Type δ Manifold[1]

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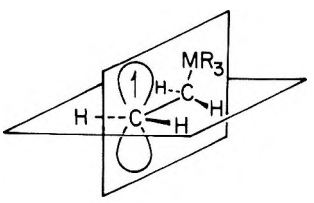
The effect of 1-trimethylsilyl and 1-trimethylgermyl substitution on the course of Ag^+- and H^+-catalyzed rearrangement reactions of the tricyclo[4.1.0.0^{2,7}]heptane ring system has been investigated. When no other substituents are present, as in the case of **12a** and **12b,** exposure to Ag^+ causes ring opening according to the type α mechanism with formation of 2-Me_3M-1,3-cycloheptadienes. When treated with acids or anhydrous ethereal magnesium bromide, these strained molecules were efficiently converted to 2-norcarene **16** and/or its positional isomer **17.** An additional methyl substituent at C_2 resulted in 2-norcarene production irrespective of the catalyst. However, the use of Ag^+ led chiefly to **21,** whereas *p*-TosOH afforded predominantly **22.** By attaching a deuterium atom at C_7 as in **25,** it could be shown that C_2–C_7 bond cleavage proceeded with overall retention of configuration at C_7. The 7-methyl derivatives **28a** and **28b** underwent polymerization in the presence of Ag^+ but smoothly isomerized to **29a** and **29b,** respectively, under conditions of *p*-TosOH catalysis. These results can be fitted to a mechanistic profile in which electrophilic attack at a given edge bicyclobutane bond is dependent upon the locus of the alkyl substituent, the timing of the transition state, and, most importantly, the ability of certain cationic intermediates to become stabilized by virtue of exalted C–Si and C–Ge hyperconjugative and homoconjugative interaction.

The exceptional stabilization provided by group 4 β-(metallomethyl) substituents to neighboring free-radical[3] and carbonium ion centers[4] is a subject which has been accorded considerable attention. Electron spin resonance studies performed on intermediates of type **1** (M = Si, Ge, and Sn) have revealed the sizable hyperconjugative delocalization of the odd electron to the C–M σ bond to be roughly comparable in magnitude to its p–d homoconjugative delocalization onto the metal p orbitals.[5] To permit maximum interaction in **1** (the level of which can approach 5 kcal/mol),[6] that conformational orientation is adopted where the β C–M bond eclipses the half-filled carbon p orbital. In the structurally related carbocations **2,** there is again no doubt that the substituent effect



1 **2**

is likewise very sensitive to the relative orientation of the β C–M linkage and the plane of the electron-deficient p orbital. Furthermore, substantial chemical[4,7] and spectroscopic evi-

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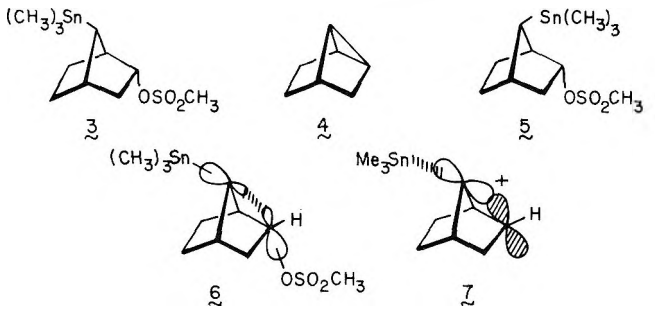
dence[8] is now available to show that the driving force underlying the high reactivity of $R_3MCH_2CH_2X$ compounds in S_N1 solvolysis is derived from vertical σ–π conjugation and not neighboring nucleophilic participation. Since the term "vertical" is intended to have a Franck–Condon connotation, the observed kinetic acceleration has been interpreted as due to σ–π conjugation which operates without significant change in the geometry of the antiplanar β-oriented organometallic center. The observed stereochemical consequences of nucleophilic capture, viz., high levels of configurational retention, are likewise satisfied by this interpretation on microscopic reversibility grounds. As might be expected, such highly exalted hyperconjugative release is also dependent upon the electronegativity of M or, perhaps more appropriately, the C–M bond polarity.

Studies of the solvolytic chemistry of γ-trimethyltin substituted alcohols and sulfonate esters[9] have also played an important role in the development of our understanding of yet more remote C–M interactions with developing cationic centers. These acetolysis experiments involving the conformationally rigid mesylates **3** and **5** have, to this time, provided the greatest level of stereoelectronic insight.[10] Rate measurements and activation parameters reveal that the C–Sn

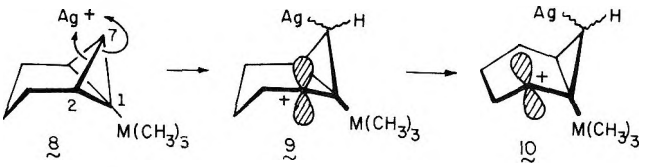


3 4 5 6 7

bond in **3** participates strongly to give **4** as the sole product. The syn–endo isomer also gives some **4** but is not accelerated. The importance of W-plan geometry in providing homoconjugative interaction for concerted 1,3-elimination (**6**) or homoconjugative stabilization to the derived cationic intermediate (**7**) is thereby revealed.

Previous investigations in this laboratory of the varied rearrangement reactions experienced by highly strained molecules under conditions of Ag^+ catalysis have established the principal role of the transition metal ion to be that of a modified Lewis acid.[11] The simplest conceptualization of the mechanistic events which follow upon preliminary substrate–Ag^+ complexation[12] involves the generation of novel covalently bonded Ag-substituted carbocationic structures which generally proceed on to one or more products under the partial control of the metal. It is presently recognized that molecular strain and the attendant exothermicity anticipated upon the release of such energy, although of paramount significance, are not the exclusive controlling factors in determining the directionality and mechanism of ring cleavage. There also exists a striking dependence upon the nature and position of ring substitution, an effect which is perhaps reflected most clearly in the reactivity of the tricyclo[4.1.0.0^{2,7}]heptane ring system.[12a,b,13] These endo,endo-2,4-bridged bicyclobutanes are known to undergo four general types of structural rearrangement. The pathway involving isomerization to 1,3-cycloheptadienes, termed the type α rearrangement,[13c] is believed to proceed by electrophilic Ag^+ attack at one edge bond with subsequent rupture of the diametrically opposite edge bond. This reaction course is followed exclusively by the parent hydrocarbon and is little affected either by "wing" alkyl groups (although kinetic acceleration is evident)[12b] or by a "bridgehead" carbomethoxy substituent (kinetically decelerated).[13a] However, when the bridgehead carbons carry alkyl groups, the type β rearrangement[13c] which defines conversion to alkylidenecyclohexenes gains importance.[12b,13e,f] This mechanistic changeover reflects a facilitation of concurrent (or nearly so) cleavage both of one edge and the central C–C bonds to generate a stabilized (usually secondary) argento carbonium ion. An increase in the effective steric bulk of the 1-substituent simultaneously decreases the tendency for α and β isomerization while promoting bicyclo[3.2.0]hept-6-ene formation (type γ rearrangement).[13a,b,14] This outcome appears to be the necessary consequence of electrophilic edge bond cleavage followed by stereospecific cyclopropylcarbinyl–cyclopropylcarbinyl bond relocation prior to ejection of Ag^+ back to the medium. The fourth (type δ) process which is associated with 2-norcarene production is rarely encountered and its minor role has heretofore not accorded it adequate mechanistic attention. Consequently, it is little understood.

Although a multiplicity of reaction manifolds obviously does exist, it seemingly shares the common parameter of being triggered by Ag^+ attack at one of the four available edge bonds. To the extent that a group 4 metal substituent at C_1 as in **8** might find it possible to direct the approach of Ag^+ to



8 9 10

the opposite surface because of steric and electronic factors, and also to substantially stabilize the resultant cyclopropylcarbinyl cation by hyperconjugative interaction, one would expect the subsequent steps leading to product(s) to be appreciably modified from some established norm (the *tert*-butyl derivative,[13c] for example).

We have discussed elsewhere the substantial alteration in hybridization, electronic character, and relative molecular position which can be perceived at C_7 as it becomes covalently bonded to Ag^+.[13a] The present study demands that we now focus attention on the events which occur at C_2. Molecular models of **8** reveal clearly that the strained C_2–C_7 edge bond which is likely to be subject to electrophilic attack by Ag^+ is aligned orthogonally to the C–M bond emanating from C_1. One notes further that ring opening to give **9** does diminish the size of this angle somewhat but decidedly not to the extent required to align the vacant p orbital and the C–M bond sufficiently to permit reasonable σ–π delocalization. In actuality, that degree of eclipsing necessary to achieve full interaction appears attainable uniquely in that boat conformation depicted in **10**. Because movement of the entire structural framework is required to arrive at **10**, the $-M(CH_3)_3$ substituent cannot be expected to provide vertical stabilization to the rate-determining bond rupture. At the experimental level, this particular feature could likely be reflected merely in small deviations in overall kinetic behavior relative to the 1-*tert*-butyltricycloheptane model.

The question at issue is how sensitive the ensuing product-forming steps are to the possibility of substantial energy minimization later in the reaction profile. If we assume, for example, that conformer **10** cannot be arrived at prior to rapid bond cleavage or alternative electronic shift elsewhere within **9**, then the $-M(CH_3)_3$ group should play a less than direct role in the determination of which rearrangement mode is followed. However, under circumstances where the inherent stability of **9** is enhanced to the level such that conformational ring inversion does have time to operate, then the effects of the resultant exalted hyperconjugation available to **10** could prove limiting. Optimistically, if a little observed rearrangement pathway such as the type δ process were to dominate as

Table I. ^{13}C NMR Chemical Shifts of Selected Tricyclo[4.1.0.0^{2,7}]heptanes[a]

Carbon atom	Compd[b] 11[c]	12a	12b	12c	13
1	5.34	3.26	6.26	2.60	28.49[d]
2	39.98	41.38	41.54	42.55	37.66
3	20.53	20.93	21.07	21.06	20.91
4	21.07	21.12	21.07	21.26	21.34
7	5.34	13.46	11.68	11.54	8.71
CH_3		−1.20	−2.72	−10.30	28.79
					26.68[d,e]

[a] $CDCl_3$, 22.625 MHz, ppm vs. Me_4Si. [b] Registry no.: **11**, 287-13-8; **12a**, 64036-08-4; **12b**, 64036-09-5; **12c**, 64036-10-8; **13**, 51284-17-4. [c] This spectrum has independently been reported by M. Christl, *Chem. Ber.*, **108**, 2781 (1975). [d] Interchangeable assignments. [e] The quaternary carbon of the *tert*-butyl substituent.

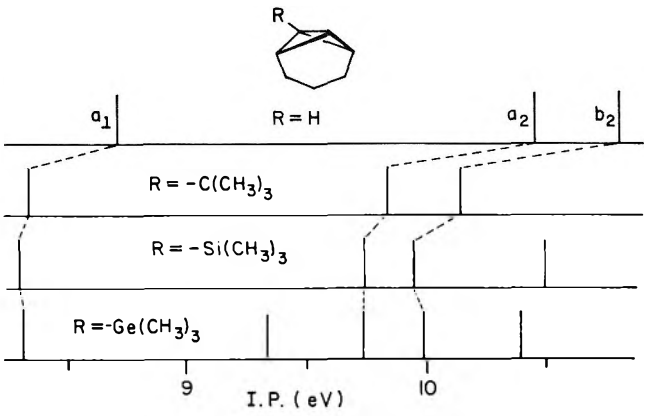
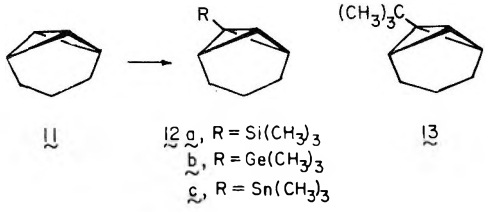


Figure 1. Schematic bar graph of the PE bands of selected 1-substituted tricyclo[4.1.0.0^{2,7}]heptanes.

a result, then an experimental probe for σ–π hyperconjugation might be at hand.

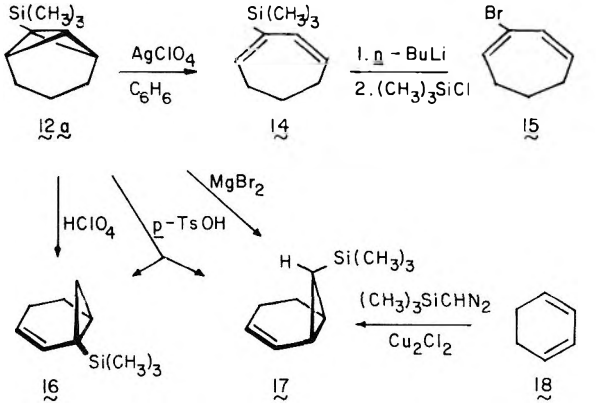
Synthesis and Spectral Properties of the 1-Substituted Derivatives. The desired substrates **12a–c**, conveniently prepared by reaction of 1-lithiotricyclo[4.1.0.0^{2,7}]heptane[15] with $(CH_3)_3MX$, were obtained as colorless stable liquids. Their ^{13}C NMR spectra, the data from which are recorded in Table I together with those for **11** and **13**, reveal certain in-



teresting trends. Although the relative effects of the Si, Ge, and Sn atoms on the attached methyl groups follow the anticipated order of enhanced nuclear shielding with increasing atomic number, the immediately adjacent bridgehead bicyclobutane carbon atom (C_1) appears subject to the fascinating, albeit incompletely understood, irregular variability intrinsic to the chemical behavior of silanes, germanes, and stannanes.[16] The trends reflected in the neighboring bridgehead (C_7) and wing (C_2) carbon shifts are again smoothly progressive but in opposite directions. In both situations, the overall effect is one of deshielding relative to **13**. Inductive polarization is seemingly not uniquely responsible since the shifts differ little, although the electronegativities of Si, Ge, and Sn vary widely. We conclude that yet other undefined factors make substantial contributions as well.

The PE spectra of **11**,[17] **12a**, **12b**, and **13** have also been measured (Figure 1).[18] It is seen that the 1-trimethylsilyl and 1-trimethylgermyl groups, like *tert*-butyl, destabilize the a_1, a_2, and b_2 orbitals of the bicyclobutane ring. This is as expected since PE spectroscopy measures only the energy differences between electronic states. Through application of Koopmans' theorem,[19] these energies can then be associated with factorized molecular orbitals. The perturbation of the latter may be further partitioned into inductive contributions, conjugative interactions, and the like. Qualitatively, the trends observed in Figure 1 are most simply explained on the basis of the donor–acceptor influences of the C_1 substituent.

Rearrangements of the 1-Substituted Derivatives. When **12a** was treated with an anhydrous benzene solution of $AgClO_4$ in the temperature range 40–50 °C, rearrangement proceeded quite slowly with initial formation only of the 1,3-cycloheptadiene **14**, the structure of which was established conclusively by independent synthesis from bromide **15**. At longer reaction times, there appeared a subsidiary product whose ^1H NMR spectrum (see Experimental Section) gave a concrete indication[20] that it was the 1-substituted 2-norcarene **16**. Since rigid control experiments proved beyond doubt that **16** was a transition metal promoted rearrangement product neither of **12a** nor of **14**, our suspicions were aroused

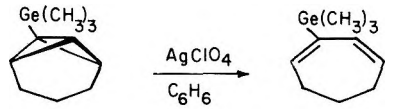


that its formation might result from the presence of perchloric acid which is gradually produced[21] during the extended periods required to achieve complete consumption of **12a**. Indeed, when a solution of **12a** in benzene was treated with a drop of 70% aqueous perchloric acid, an instantaneous rearrangement leading exclusively to **16** was observed.

A brief investigation of the reactivity of **12a** toward other Brønsted and Lewis acids revealed some fascinating alterations in product distribution. For example, exposure to catalytic quantities of *p*-toluenesulfonic acid led to a mixture of **16** and **17**, while ethereal solutions of anhydrous magnesium bromide provided **17** exclusively. Although the ^1H NMR spectrum provided diagnostic structural information on **17**, this silane was prepared in an alternative manner by cuprous ion-catalyzed decomposition of trimethylsilyldiazomethane in 1,3-cyclohexadiene.

These observations indicate that the response of **12a** to Ag^+ attack (exclusive type α isomerization) parallels that observed for parent hydrocarbon **11** rather than the sterically more related congener **13** (4% α; 92% γ; 2% δ).[13c] Furthermore, the behavior of **12a** toward other catalysts is more widely divergent than that exhibited by these other tricycloheptanes. Such relevant points will be discussed later.

Following the same procedure, $AgClO_4$-promoted rearrangement of **12b** proceeded smoothly and quantitatively to give **19**. Upon comparable treatment of the trimethylstannyl derivative **12c**, however, a silver mirror was observed to form rapidly, and ^1H NMR analysis of the supernatant solution revealed the formation of a very complex mixture. Since this behavior was traced to the high susceptibility of the Sn–C



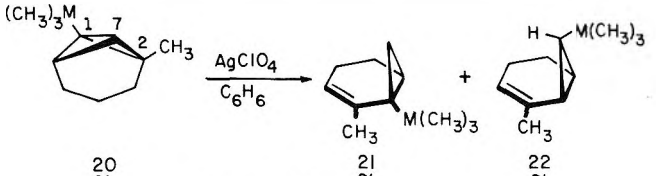
12b 19

bond for cleavage under such conditions, the further study of stannyl compounds was not pursued.

The initial rates of disappearance of **12a** and **12b** at 40.0 °C were determined to proceed with catalytic constants (k_{Ag}) of 1.17 (±0.13) × 10^{-5} and 2.82 (±0.27) × 10^{-5} M^{-1} s^{-1}, respectively. Although the overall isomerization of the *tert*-butyl derivative **13** at the same temperature proceeds with a tenfold faster pseudo-first-order rate constant (1.31 × 10^{-4} M^{-1} s^{-1}),[13c] factoring of this value to exclude all but the type-α pathway gives evidence of a slower kinetic profile for this hydrocarbon (k_α = 3.93 × 10^{-6} M^{-1} s^{-1}) in this specific reaction channel. As a group, this trio of tricycloheptanes is seen to uniformly rearrange more slowly than **11** (k_{Ag} = 2.27 × 10^{-3} M^{-1} s^{-1}).

Impact of 2-Methyl Substitution. With recognition of the fact that **12a** and **12b** undergo type α rearrangement when exposed to Ag^+, attention was next turned to enhancing the stability of the hypothetical cationic intermediates **9** and **10** by positioning a methyl group at C_2. Should cleavage of the C_2–C_7 bond in **20** not be sterically impeded, then the electron-deficient center in the resultant cation would now be tertiary in nature. Should greater levels of C–M bond hyperconjugation now be made possible, we remained optimistic that unprecedented reactivity patterns would be seen.

To test this idea, the preparation of **20a** and **20b** was effected by functionalization of 2-methyltricyclo[4.1.0.0^{2,7}]heptane as before. The results of their $AgClO_4$-promoted rearrangement gave immediate recognition of the fact that the type α pathway was no longer followed. During reaction periods of 1.5–2 h at 40 °C, **20a** was transformed into an inseparable mixture of **21a** and **22a** in the approximate relative



20 21 22

a, M = Si ; b, M = Ge

proportions of 90:10. As the time of reaction was extended, the concentrations of these silanes were seen to decay (^{1}H NMR) as three further transformation products made their appearance. One of these was 1-methyl-1,3-cycloheptadiene (**23**).[12b] Since **21a** and **22a** were converted to the identical three products under the original reaction conditions, it is obvious that the latter are not primary products.

The germane **20b** likewise underwent isomerization initially to a 90:10 mixture of **21b** and **22b**, respectively. These 2-norcarenes are similarly unstable to the reaction medium and experience further chemical change to **23** and other unidentified products.

Silane **20a** also underwent rearrangement in the presence of *p*-toluenesulfonic acid, but the product distribution was now heavily in favor of **22a** (85%) rather than **21a** (15%). When **20b** was treated with an anhydrous ethereal solution of magnesium bromide, somewhat slower rearrangement occurred to give predominantly **22b** (95%). The second product proved to be **21b** (5%).

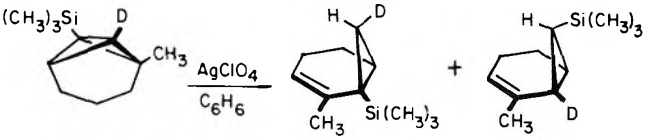
The gross structures of the four 2-norcarenes are consistent with the spectral evidence and their formation upon alternative ring opening of **20.** Compounds **21a** and **21b,** for example, are characterized by an olefinic proton resonance of area 1 in the δ 5.60–5.35 region, an sp^2-bound methyl group at 1.85–1.87, and three individually well-resolved cyclopropyl absorptions. For **22a** and **22b,** the olefinic and methyl signals were again in evidence, but because the exo group 4 substituent at C_7 induces a shielding effect on $H_{7(endo)}$ while deshielding H_1 and H_6 the cyclopropyl protons now appear as a pair of multiplets at δ 1.50–0.70 (2 H) and 0.50–0.00 (1 H) (compare **17**).

The particularly striking aspects of these findings are the total dominance by type δ processes and the particular efficacy of Ag^+ in promoting high levels of C_2–C_7 bond cleavage contrary to the other catalysts. It should be recognized that the exclusivity of 2-norcarene production constitutes an unprecedented mechanistic changeover which proceeds when a silicon or germanium atom is present at C_1. In the case of 1,2-dimethyltricyclo[4.1.0.0^{2,7}]heptane (**24**), for example,

23 24

exposure to catalytic amounts of Ag^+ leads to the following partitioning: 12% α, 28% β, 52% γ, and only 8% δ. In view of the quite small δ fractionation factor shown by this hydrocarbon, C_1–C_2 disubstitution alone is not a sufficient condition for incursion of this isomerization route.

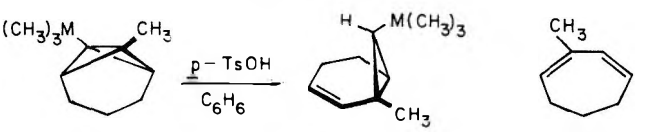
A further stereochemical aspect of the **20a** → **21a** reaction was investigated by the incorporation of a deuterium atom at C_7. Treatment of **25** with the identical silver perchlorate–benzene solution under comparable conditions resulted again in conversion to a 90:10 mixture of 2-norcarenes, in this case **26** and **27.** Since the ^{1}H NMR spectrum of **26** showed loss of



25 26 27

the δ 0.90 multiplet and simplification of the former triplet at 0.40 to a doublet, the deuterium atom must be exo oriented at C_7. The difference in chemical shift between $H_{7(exo)}$ and $H_{7(endo)}$ in **21a** and **21b** appears to be due chiefly to anisotropic shielding by the C–M single bond. If it is recognized that the diamagnetic susceptibility of C–M bonds should be greatest in a transverse direction,[22] then the deshielding zone which extends out along the bond direction will cause $H_{7(endo)}$ to shift upfield of $H_{7(exo)}$. In this context, it is interesting that a comparable effect has been encountered earlier in 1-*tert*-butyl-2-methyl-2-norcarene.[13c] However, 1,2-dimethyl-2-norcarene which possesses an identical substitution plan exhibits overlapping signals for this pair of protons at δ 0.60.[20] Although a change in molecular geometry may be responsible for a portion of this effect, we are inclined to believe that the electron-donating capabilities of the three methyl groups attached to the atom bonded to C_1 also make an important anisotropy contribution.

Consequence of Bridgehead Methyl Substitution. Prepared by trimethylsilylation of the 1-methyltricyclo[4.1.0.0^{2,7}]heptyl anion, **28a** was found to be isomerized exceedingly slowly by Ag^+. This lack of reactivity is perhaps best reflected in our finding that considerable amounts of **28a**



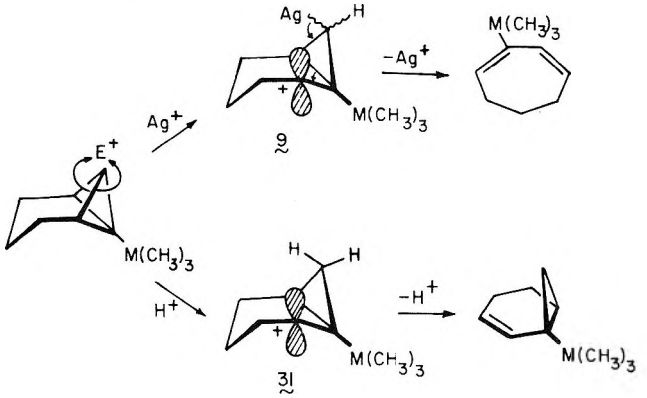
28a, M = Si 29a, M = Si 30
b, M = Ge b, M = Ge

could be recovered after heating with silver perchlorate in benzene at 40 °C for 14 days! As expected, the small quantities of adventitious acid produced during such prolonged treatment did cause partial decomposition of the silane. Although the majority of these by-products appeared to be polymeric, the one volatile constituent was identified as 2-methyl-1,3-cycloheptadiene (**30**).[12b]

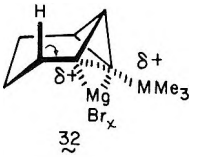
Methyl-substituted germane **28b** was conveniently synthesized by methylation of the anion generated upon treatment of **12b** with *n*-butyllithium and EDA. This substance also demonstrated a low reactivity toward Ag^+ and a comparable susceptibility for conversion to polymer and **30**. Independent treatment of **28b** in benzene with a drop of 70% aqueous perchloric acid caused entirely similar degradation. This was not the case with *p*-toluenesulfonic acid in benzene where efficient ring opening to **29b** was observed. The conversion of **28a** to **29a** was satisfactorily accomplished in a comparable manner.

Discussion

Our results indicate that **12a** and **12b** react with Ag^+ and H^+ (as $HClO_4$) by initial C_2C_7 bond cleavage. According to Wiberg and Szeimies,[23] approach of an electrophile along the bisector of the $C_1C_2C_7$ angle is the minimum energy pathway for the ring opening of bicyclobutanes, particularly when retention of configuration occurs. If inversion of configuration at C_7 is operational, then that working hypothesis featuring approach of the electrophile unsymmetrically from above the flap is most likely.[13a] Irrespective of which assumption is made, the first formed 2-norcaranyl cations will be **9** and **31**. Despite the obvious structural similarity of these intermediates, **9** proceeds to deliver 1,3-cycloheptadiene products (e.g., **14** and **19**) while **32** gives rise to 2-norcarenes (e.g., **16**). This mechanistic dichotomy must be intimately tied to the nature of the C_7 substituent just introduced and can best be understood in the following terms. As a consequence of the weakness of C–Ag bonds, molecules containing such entities manifest a particular sensitivity to those homolytic or heterolytic processes which cause loss of the transition metal.[24] In **9**, the existing positive charge at C_2 will certainly cause the silver atom to be ejected as Ag^+ and there apparently exists an overwhelming preference for that particular electronic change within this cation which introduces the diene unit (see arrows) to occur more rapidly and effectively than other possible conformational or chemical changes. In **31**, the proton just appended is not as likely a leaving group and this cation possesses no intrinsic driving force to do other than the chemistry customarily associated with 2-norcaranyl cations. Under the conditions of the present experiments, this would appear to be simple proton loss from C_3.



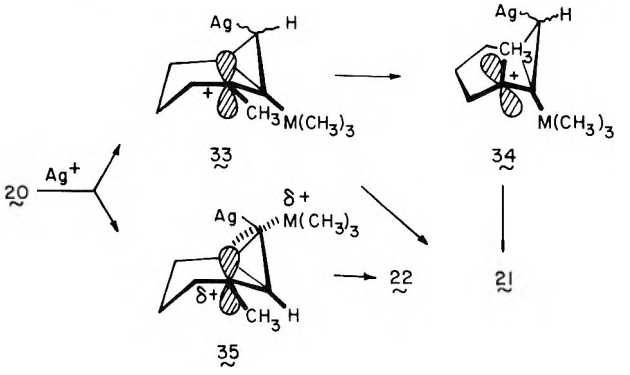
Anhydrous magnesium bromide, in contrast, is found to attack the C_1–C_2 bond of **12a** exclusively. The ability of this catalyst to promote 2-norcarene formation has previously been recognized.[25] Free cyclopropylcarbinyl cations have not been implicated as intermediates in these isomerizations. Rather, the main pathway is believed to involve proton transfer to a bicyclobutane edge bond within a complex, followed by proton loss from C_3 to an external base such as bromide ion.[25] We do not wish to address mechanistic issues in this particular instance but emphasize only the uniqueness of site selectivity for $MgBr_2$ attack. It is particularly tempting to invoke the possible involvement of long-range contributions by the C–M bond as in **32**, despite the fact that little evidence is available to substantiate this hypothesis.[26]



32

A further significant comparison emerges from analysis of the product distributions which arise from the $HClO_4$- and *p*-TosOH-promoted rearrangements of **12a**. The production of **17** under the latter conditions is the likely result of the differing acid strengths of these catalysts and the dissimilarities in solvent polarity. In the case of *p*-TosOH, catalytic quantities of the hydrated form were added to an otherwise anhydrous benzene solution of the silane. On the other hand, the $HClO_4$ was dissolved in water (commercial 70% solution). These apparently small changes are not negligible and exert a pronounced effect on the kinetically controlled bond cleavages in **12a**. It may well be that yet different acids or solvent systems could promote higher levels of C_1–C_2 attack than observed with *p*-TosOH.

The response of **20a** and **20b** to isomerization provides an interesting contrast to the above. Under conditions of Ag^+ catalysis, the product distribution reveals that C_1–C_2 and C_2–C_7 bond cleavages have now become competitive. The latter process still does remain dominant, however, being favored by a factor of 9:1. In either event, 2-norcarene formation (type δ rearrangement) is the ultimate result. The findings that "wing" methyl substitution causes total inoperability of the type α isomerization favored by the parent systems suggest that the enhanced stability of the 2-norcaranyl cation intermediates is very much a key factor in these reactions. To the extent that the tertiary nature of **33** and **35** reflects an enhanced degree of charge localization at C_2 and lesser intimate interaction with the adjoining cyclopropane ring, kinetically controlled proton loss from C_3 appears to gain kinetic importance. Although there exists no direct evidence that **33** experiences conformational inversion to boat form **34** prior to conversion to **21**, the exceptional chemical behavior of **33** provides some measure of support for this theory. It should be recognized that this structural modification, the energetics of which remain unknown, necessitates that the thermodynamically favored bisected alignment of the vacant p–π orbit with the three-membered ring[27] be substantially altered to enjoy C–M hyperconjugative effects. The prevailing dihedral angle relationships are such that these two stabilizing influ-



ences cannot be operative to their maximum level at the same time. Under normal circumstances, therefore, the ring inversion leading from **33** to **34** would have little reason to operate. We have previously found that 1,2-dimethyltricyclo[4.1.0.0^{2,7}]heptane reacts with Ag^+ to give a transient cation related to **33** but with $M(CH_3)_3$ equal to CH_3.[12b] In the absence of an opportunity for exalted hyperconjugative interaction, this species experiences only 8% conversion to type δ (2-norcarene) product. Consequently, the possibility exists that the availability of stabilizing C–M interaction in **34** facilitates passage to this conformer.

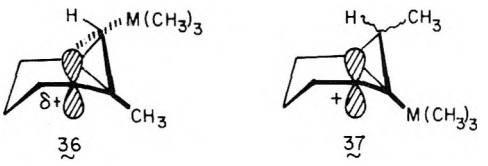
Perhaps a more revealing aspect of this study is the finding that attack by Ag^+ at the most highly substituted edge bond (C_1–C_2) in **20** has gained a certain amount of kinetic importance. The additional experimental evidence indicates that interaction with *p*-TosOH causes cleavage of this same bond with a still higher preference than observed earlier with **12a.** We view this contrasting behavior to be a possible reflection of the timing at which the rate-determining transition states are reached. Qualitative rate measurements have shown that these tricycloheptane rearrangements proceed more rapidly under conditions of acid (*p*-TosOH) catalysis than with Ag^+. Logically, those reactions promoted by H^+ could pass through earlier transition states relative to when Ag^+ is the electrophile, their structures resembling starting material more closely than intermediate. Those pathways involving the highest attainable levels of internal stabilization will therefore be especially favored kinetically under acidic conditions.

We might on this basis ascribe the preference for *p*-TosOH-promoted cleavage in **12a, 20a,** and **20b** to the involvement of long-range homoconjugative interaction (cf. **35** with and without the 2-methyl substituent) of the same type encountered during the solvolysis of **3.** Molecular models reveal that rupture of the C_1–C_2 bond with retention of configuration progresses through an intermediate stage (possibly that of maximum σ-bond stretching) where the C–M bond and the developing p orbital at C_2 adopt a well-defined W-plan orientation.

Such contributions need not be of comparable importance when Ag^+ is involved not only for the reasons discussed above but also because an endo-oriented silver atom in **9, 31,** or **33** could further stabilize the cation by d orbital interactions of its own (not illustrated). Also, if the methyl group in **33** and **35** does provide enough added stability to the electron-deficient center to relieve it of a strong dependency on the proximate cyclopropane ring, then the dominant role which cyclopropylcarbinyl interaction plays in **31** could be diminished sufficiently to allow for observation of other usually less influential stabilizing effects. Although such "secondary" influences as C–M hyperconjugative interaction are likely to have their greatest impact on early transition states (see above), they appear to be capable of influencing Ag^+-promoted isomerizations as well (10% **22a;** 10% **22b**).

Our approach to determining whether the C–Ag bond in **33** is oriented exo or endo at C_7 was to examine the stereochemical outcome of the $AgClO_4$-catalyzed rearrangement of **25.** Although **26** was shown to be the exo-7-*d* isomer, it has remained unclear whether protonolysis of the C–Ag bond occurs with retention or inversion of configuration, and alternative attempts to establish this point have not yielded positive information. This particular question remains unsolved. The locus of the deuterium atom in **26** and **27** does, however, unequivocally define the isomerization as the result of C_2–C_7 cleavage.

The pair of molecules **28a** and **28b** likewise is converted to 2-norcarenes upon treatment with *p*-TosOH. Both of these rearrangements are strikingly regiospecific, giving rise uniquely to 2-methyl-*exo*-7-trimethylsilyl- and -germyl-2-norcarenes (**29a** and **29b**). The intermediacy of **36** but not **37**



36 **37**

is thereby implicated in agreement with the preceding mechanistic analysis. Both **28a** and **28b** polymerized when treated with catalytic quantities of $HClO_4$, thus pointing up again the rather different nature of this proton source.

In summary, it is our conclusion that the ability of certain cationic intermediates to gain stabilization by means of hyperconjugative interaction with C–M bonds is the major determinant underlying the propensity for several of the 1-trimethylsilyl- and 1-trimethylgermyl-substituted tricycloheptanes studied herein to undergo clean type δ rearrangement.

Experimental Section

All boiling points are uncorrected. Melting points were obtained on a Thomas-Hoover capillary apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 467 instrument. ^1H NMR spectra were recorded on Varian A-60A, T-60, and HA-100 instruments as well as a Joelco MH-100 spectrometer. Fourier spectra (both carbon and proton) were obtained on a Bruker HX-90 instrument. Apparent splittings are given. Combustion analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Preparative VPC work was carried out with the aid of a Varian Aerograph A-90P3 chromatograph equipped with a thermal conductivity detector, while analytical determinations were performed on a Hewlett-Packard HP5750 research gas chromatograph equipped with a flame ionization detector and Model HP3370A electronic integrator.

1-Trimethylsilyltricyclo[4.1.0.0^{2,7}]heptane (12a). To a solution containing 10 mL of 2.4 M *n*-butyllithium in hexane, 2.3 mL of tetramethylethylenediamine (TMEDA), and 10 mL of pentane was added under nitrogen 2.0 g (0.02 mol) of tricyclo[4.1.0.0^{2,7}]heptane (**11**) at 5 °C. The yellow solution was diluted with 15 mL of pentane, allowed to warm to room temperature, and stirred for 12 h prior to treatment at 5 °C with 2.40 g (0.022 mol) of trimethylchlorosilane dissolved in 5 mL of pentane. The resultant mixture was stirred for 1 h and 15 mL of water was slowly added. The organic layer was washed with saturated curpic sulfate solution (2 × 50 mL), dried, and concentrated. Flash distillation afforded 1.19 g (34%) of an oil which VPC analysis (2 ft × 0.25 in. 5% SE-30 on Chromosorb W, 80 °C) indicated was uncontaminated: $\delta_{Me_4Si}^{C_6D_6}$ 2.22 (m, 2), 1.68–1.20 (m, 7), and 0.14 (s, 9); *m/e* 166.1179 (calcd 166.1178). Anal. Calcd for $C_{10}H_{18}Si$: C, 72.22; H, 10.93. Found: C, 72.22; H, 11.11.

1-Trimethylgermyltricyclo[4.1.0.0^{2,7}]heptane (12b). In the predescribed manner, 940 mg (10 mmol) of **11** dissolved in 20 mL of pentane was treated with 6 mL of 2.2 M *n*-butyllithium in hexane and 1.8 mL of TMEDA. After 12 h the anion was similarly treated with 2.0 g (10 mmol) of bromotrimethylgermane. The usual workup afforded 1.05 g (49%) of **12b,** further purification of which was accomplished by VPC methods (5.5 ft × 0.25 in. 12% OV-11 on Chromosorb W, 100 °C): $\delta_{Me_4Si}^{C_6D_6}$ 2.30–2.05 (m, 2), 1.65–1.30 (m, 7), and 0.14 (s, 9); *m/e* 212.0624 (calcd 212.0620). Anal. Calcd for $C_{10}H_{18}Ge$: C, 56.95; H, 8.62. Found: C, 56.90; H, 8.91.

1-Trimethylstannyltricyclo[4.1.0.0^{2,7}]heptane (12c). In the same manner, 940 mg (10 mmol) of **11** was lithiated by addition to a pentane solution (50 mL) containing 6 mL of 2.2 M *n*-butyllithium and 1.8 mL of TMEDA. Subsequent to addition of chlorotrimethylstannane (2.0 g. 10 mmol) and the usual workup, there was isolated 2.13 g (80%) of **12c.** Isolation by VPC (5.5 ft × 0.25 in. 12% OV-11, 115 °C) afforded an analytically pure sample: $\delta_{Me_4Si}^{C_6D_6}$ 2.17 (m, 2), 1.78 (m, 1), 1.45 (m, 6), and 0.10 (s, 9); *m/e* 258.0435 (calcd 258.0429). Anal. Calcd for $C_{10}H_{18}Sn$: C, 46.73; H, 7.07. Found: C, 47.14; H, 7.10.

Ag(I)-Catalyzed Rearrangement of 12a. Into a thin-walled NMR tube was dissolved 152.5 mg of **12a** in 3 mL of a 0.2204 M solution of silver perchlorate in benzene. The tube was sealed and heated in a constant temperature bath at 40.0 °C. The ^1H NMR spectrum of the solution no longer contained starting material. The tube was opened and the solution was added to saturated brine. VPC analysis (5.5 ft × 0.25 in. 12% OV-11, 100 °C) indicated the presence of two components which proved to be 1-trimethylsilylbicyclo[4.1.0]hept-2-ene (**16**) and 2-trimethylsilyl-1,3-cycloheptadiene (**14**). Quantitative analysis of several runs of this reaction revealed the ratio of these two

products to vary from 80:20 to 30:70, respectively. Careful NMR observation and VPC examination of the solutions employed in the kinetic experiments (vide infra) at various time intervals showed **14** to be the only product formed initially. In contrast, the 2-norcarene **16** arose very rapidly at longer reaction times, usually coinciding with the formation of a dark, finely divided precipitate.

2-Trimethylsilyl-1,3-cycloheptadiene (14). A stirred solution of 2.73 g (0.016 mol) of 2-bromo-1,3-cycloheptadiene (**15**)[28] in 20 mL of dry ether was cooled to 5 °C under a nitrogen atmosphere. *n*-Butyllithium in hexane (10 mL of 2.2 M) was added. The resulting solution was stirred at room temperature for 12 h, recooled to 5 °C, and treated with 2.50 g (0.023 mmol) of chlorotrimethylsilane. After 60 min at room temperature, water (50 mL) was introduced and the separated organic layer was washed with water, dried, and concentrated. VPC analysis (5.5 ft × 0.25 in. 12% OV-11, 100 °C) yielded a single product which was identical in all respects with **14** isolated earlier: $\delta_{Me_4Si}^{C_6D_6}$ 6.35–5.90 (m, 3), 2.40–2.00 (m, 4), 2.00–1.70 (m, 2), and 0.16 (s, 9); *m/e* 166.1179 (calcd 166.1178). Anal. Calcd for $C_{10}H_{18}Si$: C, 72.22; H, 10.93. Found: C, 72.19; H, 10.93.

Perchloric Acid Catalyzed Rearrangement of 12a. 1-Trimethylsilylbicyclo[4.1.0]hept-2-ene (16). Into a solution of 30 mg of **12a** in 110 μL of C_6D_6 was added 1 drop of 70% aqueous perchloric acid. ^1H NMR analysis indicated an instantaneous reaction. The solution was extracted with dilute sodium bicarbonate solution. VPC analysis (12 ft × 0.25 in. 5% XF-1150, 90 °C) indicated quantitative isomerization to a single product whose isolation afforded pure **16**: $\delta_{Me_4Si}^{C_6D_6}$ 6.04–5.92 (d, ½ of AB, J = 13 Hz, 1), 5.60–5.40 (m, 1), 1.96–1.60 (m, 4), 1.30–1.00 (m, 1), 0.88–0.60 (m, 2), and 0.40 (s, 9); *m/e* 166.1179 (calcd 166.1178). Anal. Calcd for $C_{10}H_{18}Si$: C, 72.22; H, 10.93. Found: C, 72.34; H, 10.93.

Magnesium Bromide Promoted Rearrangement of 12a. *exo*-7-Trimethylsilylbicyclo[4.1.0]hept-2-ene (17). Into 1.0 mL of 1.0 M magnesium bromide in anhydrous ether was injected 45 μL of **12a** via syringe. The solution was shaken in a 2-dram vial and kept at room temperature for 24 h. Water (1.0 mL) was added. VPC ANALYSIS (12 ft × 0.25 in 5% XF-1150, 90 °C) of the organic layer indicated quantitative conversion to **17**: $\delta_{Me_4Si}^{C_6D_6}$ 6.10 (m, 1), 5.50 (m, 1), 1.75 (m, 4), 1.16 (m, 2), 0.13 (t, J = 6 Hz, 1), and 0.00 (s, 9); *m/e* 166.1179 (calcd 166.1178). Anal. Calcd for $C_{10}H_{18}Si$: C, 72.22; H, 10.93. Found: C, 72.55; H, 11.02.

***p*-Toluenesulfonic Acid Catalyzed Rearrangement of 12a.** A few crystals of *p*-toluenesulfonic acid monohydrate were added to a solution containing 20 g of **12a** in 300 μL of C_6D_6. After heating at 40.0 °C for 24 h, the solution was added to water. VPC analysis (12 ft 5% XF-1150, 90 °C, 60 mL/min) of the organic phase showed a single broad peak, which ^1H NMR analysis indicated to consist of an approximately 50:50 mixture of **16** and **17** (from careful integration of the olefinic region).

Independent Synthesis of 17. To a solution of 1,3-cyclohexadiene (300 mg, 3.75 mmol) in 3 mL of benzene was added 100 mg of cuprous chloride and 570 mg (5.0 mmol) of trimethylsilyldiazomethane.[29] The slurry was stirred at room temperature for 2 h and added to 10 mL of water. The organic layer was washed with brine, dried, and concentrated. Preparative VPC isolation (5.5 ft × 0.25 in. 10% OV-11, 125 °C) afforded 50 mL (~10%) of **17** as the only observable adduct. Its spectral properties proved identical with those of the silane isolated above.

Kinetic Study of the Ag(I)-Catalyzed Rearrangement of 12a. Into each of 18 dry previously base-washed ampules was added 100 μL of 0.1898 M silver perchlorate in benzene and 3 μL of **12a**. The ampules were heated in a constant temperature bath at 40.0 ± 0.1 °C. As aliquots were periodically removed, the progress of reaction was arrested by addition to saturated brine and determined quantitatively by VPC analysis of the organic phases (18 ft × 0.125 in. UC-W-98, 120 °C). Measurements were made for periods up to 48 h. Only those ampules in which rearrangement to the diene was the exclusive reaction were included in the analysis. Six ampules in which some amount of the norcarene **16** was observed were discarded. A plot of ln [([**12a**] + [**14**])/[**12a**]] vs. time was linear. Least-squares regression analysis gave a pseudo-first-order rate constant, division of which by the concentration of silver perchlorate yielded k_{Ag} = 1.17 ± 0.13 × 10^{-5} M^{-1} s^{-1}.

Ag(I)-Catalyzed Rearrangement of 12b. Into an NMR tube was placed 30 mg of **12b** and 100 μL of a 0.2204 M solution of silver perchlorate in benzene. The tube was sealed and heated at 40.0 °C while the extent of rearrangement was monitored. After 90 h, less than 10% of the starting material remained, while conversion to a single rearrangement product had occurred. The solution was treated with brine and the organic layer was subjected to VPC analysis (5.5 ft × 0.25 in. 12% OV-11, 100 °C). Quantitative rearrangement to a single component identified as 2-trimethylgermyl-1,3-cycloheptadiene (**19**) was observed: $\delta_{Me_4Si}^{C_6D_6}$ 6.16–5.64 (m, 3), 2.28–1.96 (m, 4), 1.88–1.60 (m, 2), and 0.24 (s, 9); *m/e* 212.0624 (calcd 212.0620). Anal. Calcd for $C_{10}H_{18}Ge$: C, 56.95; H, 8.62. Found: C, 57.06; H, 8.71.

Kinetics of the Ag(I)-Catalyzed Rearrangement of 12b. As before, 15 ampules containing 100 μL of 0.1898 M silver perchlorate in benzene and 2.5 μL of **12b** were sealed and heated at 40.0 ± 0.1 °C. The ampules were periodically removed, treated with brine, and analyzed by VPC (18 ft × 0.125 in. UC-W-98, 120 °C). A plot of ln [([**12b**] + [**19**])/[**12b**]] vs. time was linear and least-squares analysis produced the pseudo-first-order rate constant. When divided by [$AgClO_4$], the k_{Ag} value of 2.82 ± 0.27 × 10^{-5} M^{-1} s^{-1} was obtained.

Ag(I)-Promoted Decomposition of 12c. To 100 μL of 0.1898 M silver perchlorate in benzene was added 20 μL of **12c**. Within minutes, the solution darkened and a silver mirror was formed. After addition to brine, the organic layer was analyzed by VPC (5.5 ft × 0.25 in. 12% OV-11, 115 °C). The disappearance of starting material and total absence of any volatile products were thereby indicated.

1-Trimethylsilyl-2-methyltricyclo[4.1.0.0^{2,7}]heptane (20a). In the predescribed manner, 430 mg (4.0 mmol) of 2-methyltricyclo[4.1.0.0^{2,7}]heptane was subjected to the action of 2.0 mL of 2.4 M *n*-butyllithium and 0.5 mL of TMEDA dissolved in 10 mL of pentane. The anion was treated with 0.5 g (4.6 mmol) of chlorotrimethylsilane and the product isolated by preparative VPC (12 ft × 0.125 in. 5% XF-1150, 105 °C). There was obtained 200 mg (28%) of **20a**: $\delta_{Me_4Si}^{C_6D_6}$ 2.02 (m, 1), 1.70 (m, 1), 1.32 (m, 6), 1.00 (s, 3), and 0.07 (s, 9); *m/e* 180.1336 (calcd 180.1334). Anal. Calcd for $C_{11}H_{20}Si$: C, 73.25; H, 11.18. Found: C, 73.04; H, 11.31.

1-Trimethylgermyl-2-methyltricyclo[4.1.0.0^{2,7}]heptane (20b). In an identical manner, 430 mg (4.0 mmol) of 2-methyltricyclo[4.1.0.0^{2,7}]heptane was lithiated by addition to 2.0 mL of 2.4 M *n*-butyllithium and 0.5 mL of TMEDA in 10 mL of pentane. The resulting anion was treated with 900 mg (4.5 mmol) of bromotrimethylgermane. After the usual workup, VPC isolation (5.5 ft × 0.25 in. 12% OV-11, 120 °C) afforded 300 mg (30%) of **20b**: $\delta_{Me_4Si}^{C_6D_6}$ 2.05 (m, 1), 1.65 (m, 1), 1.40 (m, 6), 1.00 (s, 3), and 0.22 (s, 9); *m/e* 226.0781 (calcd 226.0777). Anal. Calcd for $C_{11}H_{20}Ge$: C, 58.75; H, 8.97. Found: C, 58.85; H, 9.10.

Ag(I)-Catalyzed Rearrangement of 20a. Into an NMR tube was placed 300 μL of a 0.1898 M solution of silver perchlorate in anhydrous benzene. A 60-μL sample of **20a** was injected and the solution was heated to 40.0 ± 0.1 °C with constant monitoring of the ^1H NMR spectrum. As reaction proceeded, one product was seen to predominate but proved in turn to be subject to further rearrangement leading to several other products. After 1.5 h when the integral associated with the first formed isomer was at a maximum, the solution was poured into saturated brine. VPC analysis (12 ft × 0.25 in. 5% XF-1150, 100 °C) revealed the presence of several peaks, one of which did predominate. Collection of this component permitted its identification as 1-trimethylsilyl-2-methylbicyclo[4.1.0]hept-2-ene (**21a**): $\delta_{Me_4Si}^{C_6D_6}$ 5.50 (m, 1), 1.88 (pseudo s, 7), 1.60–1.00 (m, 1), 0.90 (m, 1), 0.40 (t, J = 3 Hz, 1), and 0.07 (s, 9); *m/e* 180.1336 (calcd 180.1334). Anal. Calcd for $C_{11}H_{20}Si$: C, 73.25; H, 11.18. Found: C, 73.17; H, 11.45.

Careful analysis of the ^1H NMR spectrum of this norcarene indicated the presence of ca. 10% of **22a** as prepared below.

Resubmission of **21a** to the original reaction conditions or extension of the isomerization of **20a** to 12 h gave rise to identical product mixtures. VPC analysis (12 ft × 0.25 in. 5% XF-1150, 100 °C) of these solutions showed three components to be present in the ratio of 1:3.3:4.

The smallest constituent proved identical with authentic 1-methyl-1,3-cycloheptadiene (**23**).[12b]

The middle peak remains as yet unidentified: $\delta_{Me_4Si}^{C_6D_6}$ 6.40–5.90 (m, 2), 2.40–1.85 (m, 5), 1.80 (br s, 4), and 0.16 (s, 9); *m/e* 180.1336 (calcd for $C_{11}H_{20}Si$ 180.1334).

The largest peak has likewise eluded positive structural assignment: $\delta_{Me_4Si}^{C_6D_6}$ 6.12 (m, 1), 5.50 (m, 1), 2.90 (m, 2), 2.28 (m, 4), 1.80 (br s, 3), and 0.20 (s, 9); *m/e* 180.1336 (calcd for $C_{11}H_{20}Si$ 180.1334).

Acid-Promoted Rearrangement of 20a. exo-7-Trimethylsilyl-2-methylbicyclo[4.1.0]hept-2-ene (22a). Into a solution containing 45 mg of **20a** in 300 μL of C_6D_6 was added a few crystals of *p*-toluenesulfonic acid monohydrate. After being heated at 40 °C for 3 h, the solution was added to water. Preparative VPC purification of the product contained in the organic layer afforded 20 mg (45%) of **22a**: $\delta_{Me_4Si}^{C_6D_6}$ 5.20 (m, 1), 1.83 (br s, 7), 1.50–0.80 (m, 2), 0.30–0.00 (m, 1), and 0.00 (s, 9); *m/e* 180.1336 (calcd 180.1334). Anal. Calcd for $C_{11}H_{20}Si$: C, 73.25; H, 11.18. Found: C, 73.48; H, 11.60.

Careful integration of the ^1H NMR spectrum indicated the presence of ca. 15% of **21a**.

Ag(I)-Catalyzed Rearrangement of 20b. In the previously de-

scribed manner, a solution of **20b** (80 mg) in 250 μL of 0.1898 M silver perchlorate in anhydrous benzene was heated at 40.0 °C for 2 h and then added to saturated brine. VPC isolation of the predominant peak (12 ft × 0.25 in. 5% XF-1150, 100 °C) afforded 30 mg (38%) of 1-trimethylgermyl-2-methylbicyclo[4.1.0]hept-2-ene (**21b**): $\delta_{Me_4Si}^{C_6D_6}$ 5.60–5.35 (m, 1), 1.85 (pseudo s, 7), 1.00–0.80 (m, 1), 0.80–0.50 (m, 1), 0.50–0.20 (m, 1), and 0.15 (s, 9); *m/e* 226.0781 (calcd 226.0777). Anal. Calcd for $C_{11}H_{20}Ge$: C, 58.75; H, 8.97. Found: C, 59.06; H, 9.08.

Careful ^{1}H NMR analysis indicated the presence of ca. 10% of **22b** (as prepared below) to be present.

Further reaction of **20b** or **21b** with the silver perchlorate solution for 12 h produced identical reaction mixtures, VPC analysis of which (12 ft × 0.25 in. 5% XF-1150, 100 °C) showed three components to be present in the ratio of 1:3:3.

The minor constituent was again identical with an authentic sample of 1-methyl-1,3-cycloheptadiene (**23**).[12b]

The first of the larger peaks was not identified: $\delta_{Me_4Si}^{C_6D_6}$ 6.20–5.80 (m, 2), 2.40–1.80 (m, 6), 1.70 (br s, 3), and 0.24 (s, 9); *m/e* 226.0781 (calcd for $C_{11}H_{20}Ge$ 226.0787).

The final component likewise remains unidentified: $\delta_{Me_4Si}^{C_6D_6}$ 6.00 (m, 1), 5.50 (m, 1), 2.92 (m, 2), 2.25 (m, 4), 1.72 (br s, 3), and 0.24 (s, 9); *m/e* 226.0781 (calcd for $C_{11}H_{20}Ge$ 226.0787).

***exo*-7-Trimethylgermyl-2-methylbicyclo[4.1.0]hept-2-ene (22b).** To 450 μL of a 1.0 M ethereal solution of magnesium bromide was added 15 mg of **20b.** The solution was sealed in an ampule and heated at 40.0 °C for 14 h and then added to water. VPC isolation of the volatile product afforded 8 mg (53%) (12 ft × 0.25 in. 5% XF-1150, 100 °C) of **22b:** $\delta_{Me_4Si}^{C_6D_6}$ 5.24 (m, 1), 1.90 (br s, 7), 1.40–0.70 (m, 2), 0.50–0.20 (m, 1), and 0.14 (s, 9).

Careful integration of the ^{1}H NMR spectrum indicated contamination by approximately 5% of **21b.**

1-Trimethylsilyl-2-methyltricyclo[4.1.0.0^{2,7}]heptane-*7-d* (25). Into a solution containing 3 mL of 2.5 M *n*-butyllithium in hexane, 1.0 mL of TMEDA, and 10 mL of pentane was added 168 mg (0.9 mmol) of **20a** at 0 °C under nitrogen. After being stirred at room temperature for 12 h, the solution was cooled and 1.0 mL of 99.8% deuterium oxide was added. After the usual workup, the organic phase was concentrated and then flash distilled. The oil thus obtained was resubmitted to the above conditions and the process repeated for a total of four lithiations. Preparative VPC purification (12 ft × 0.25 in. 5% XF-1150, 100 °C) yielded 50 mg (30%) of **25;** *m/e* 181.1400 (calcd 181.1397). Deuterium incorporation was calculated to be 97%. The ^{1}H NMR spectrum showed loss of the signal at δ 1.70.

Ag(I)-Catalyzed Rearrangement of 25. Into a solution of 150 μL of 0.1898 M silver perchlorate in anhydrous benzene was added 40 mg of **25.** Following 12 h of heating at 40.0 °C, the solution was added to saturated brine. VPC purification on the XF-1150 column allowed isolation of the major peak, which was identified as *exo*-7-deuterio-1-trimethylsilyl-2-methylbicyclo[4.1.0]hept-2-ene (**26**) (20 mg, 50%): *m/e* 181.1400 (calcd 181.1397). Deuterium incorporation was estimated at 97%. The ^{1}H NMR spectrum indicated loss of the signal at δ 0.90 and simplification of the triplet at δ 0.40 to a doublet (J = 4 Hz). Careful integration of this spectrum showed approximately 10% of **27** to also be present.

1-Trimethylsilyl-7-methyltricyclo[4.1.0.0^{2,7}]heptane (28a). In the usual manner, 200 mg (1.85 mmol) of 1-methyltricyclo[4.1.0.0^{2,7}]heptane was added to 1.0 mL of 2.5 M *n*-butyllithium and 0.2 mL of TMEDA in 10 mL of pentane. The resulting anion was silylated with 220 mg (2.0 mmol) of chloromethylsilane and the reaction mixture processed in the usual manner. Preparative VPC isolation (12 ft × 0.25 in. 5% XF-1150, 90 °C) provided 300 mg (70%) of **28a:** $\delta_{Me_4Si}^{C_6D_6}$ 2.03 (m, 2), 1.53 (s, 3), 1.40 (m, 6), and 0.13 (s, 9); *m/e* 180.1336 (calcd 180.1334). Anal. Calcd for $C_{11}H_{20}Si$: C, 73.25; H, 11.18. Found: C, 73.14; H, 11.34.

1-Trimethylgermyl-7-methyltricyclo[4.1.0.0^{2,7}]heptane (28b). To a solution of 2 mL of 2.2 M *n*-butyllithium and 0.5 mL of TMEDA in 20 mL of pentane was added 533 mg (3.2 mmol) of **12b.** The resulting anion was methylated through addition of 570 mg (4.0 mmol) of methyl iodide. The usual workup and preparative VPC purification (5.5 ft × 0.25 in. 12% OV-11, 120 °C) afforded a nearly quantitative yield of **28b:** $\delta_{Me_4Si}^{C_6D_6}$ 2.00 (m, 2), 1.45 (s, 3), 1.35 (m, 6), and 0.17 (s, 9); *m/e* 226.0781 (calcd 226.0777). Anal. Calcd for $C_{11}H_{20}Ge$: C, 58.75; H, 8.97. Found: C, 58.55; H, 9.19.

***exo*-7-Trimethylsilyl-1-methylbicyclo[4.1.0]hept-2-ene (29a).** To a solution of 30 mg of **28a** in 300 μL of C_6D_6 was added a few crystals of *p*-toluenesulfonic acid monohydrate. The solution was heated at 40.0 °C for 5 h at which time ^{1}H NMR analysis showed nearly quantitative conversion to a single product. The solution was added to water. VPC isolation (12 ft × 0.25 in. 5% XF-1150, 100 °C) afforded 15 mg (50%) of **29a;** $\delta_{Me_4Si}^{C_6D_6}$ 5.90 (d, ½ of AB, J = 10 Hz, 1), 5.70–5.10 (m, 1), 1.80 (m, 4), 1.30 (s, 3), 1.29–1.00 (m, 1), 0.20–0.10 (m, 1), and 0.10 (s, 9); *m/e* 180.1336 (calcd 180.1334).

***exo*-7-Trimethylgermyl-1-methylbicyclo[4.1.0]hept-2-ene (29b).** In the same manner, 40 mg of **28b** in 300 μL of C_6D_6 was admixed with *p*-toluenesulfonic acid and heated at 40.0 °C for 2 h, at which time ^{1}H NMR analysis revealed total reaction. After the usual workup, VPC isolation (12 ft × 0.25 in. 5% XF-1150, 110 °C) afforded 30 mg (75%) of **29b:** $\delta_{Me_4Si}^{C_6D_6}$ 6.00 (d, ½ of AB, J = 10 Hz, 1), 5.40 (m, 1), 1.80 (m, 4), 1.20 (s, 3), 1.10 (m, 1), 0.40 (d, J = 7 Hz, 1), and 0.20 (s, 9); *m/e* 222.0781 (calcd 222.0777). Anal. Calcd for $C_{11}H_{20}Ge$: C, 58.75; H, 8.97. Found: C, 58.54; H, 9.40.

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Registry No.—**14,** 64036-11-9; **15,** 3045-85-0; **16,** 64036-12-0; **17,** 64036-13-1; **19,** 64036-14-2; **20a,** 64036-15-3; **20b,** 64036-16-4; **21a,** 64036-17-5; **21b,** 64036-18-6; **22a,** 64036-19-7; **22b,** 64036-20-0; **25,** 64036-21-1; **28a,** 64036-22-2; **28b,** 64036-23-3; **29a,** 64036-24-4; **29b,** 64036-25-5; trimethylchlorosilane, 75-77-4; bromotrimethylgermane, 1066-37-1; chlorotrimethylstannane, 1066-45-1; 2-methyltricyclo[4.1.0.0^{2,7}]heptane, 40391-49-9; 1-methyltricyclo[4.1.0.0^{2,7}]heptane, 32348-63-3; methyl iodide, 74-884.

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Reaction of Thiophenoxides with Nitro- and Halo-Substituted Phthalimide Derivatives

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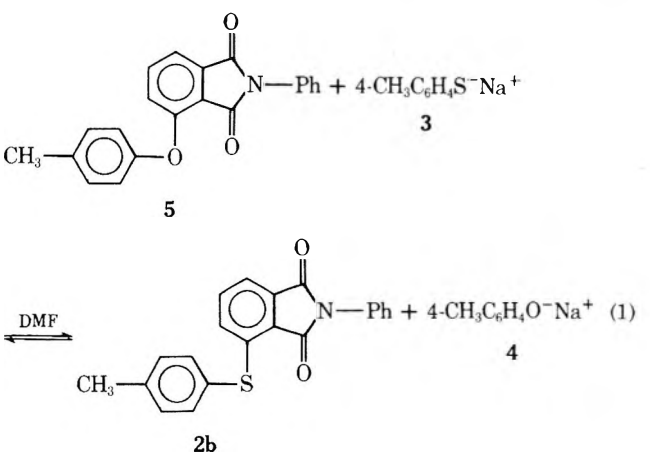
The reaction of thiophenoxides **3** with nitro- and halo-substituted phthalimide derivatives **1** was studied. In contrast to the reaction of **1** with phenoxides, a variety of inorganic bases, organic amines, and solvents such as THF, EtOH, and CH_2Cl_2 were used successfully in the thiophenol reactions. Using these procedures, a series of previously unknown thioether imides **2** were synthesized and identified with the assistance of ^{13}C NMR analysis. The relative rates of reaction of the different imides with thiophenoxide were measured and the differences in rate between the thiophenoxide and phenoxide nucleophiles are discussed in detail. The 3-substituted nitro derivatives were much more reactive toward thiophenoxide than any of the other systems which were studied. An examination of the formation of disulfides as side products was also made.

Recent studies by these authors have dealt with the reaction of phenoxide nucleophiles with nitro and halo groups activated by derivatives of phthalic acid. These studies have covered reactions with N-substituted phthalimides,[1] phthalate esters,[2] and phthalic anhydrides.[3] The tremendous nucleophilicity of sulfur in aromatic nucleophilic displacement reactions is well documented.[4] According to Parker,[5] "the thiophenoxide ion is the most powerful nucleophile which has been thoroughly studied in bimolecular SnAr reactions".

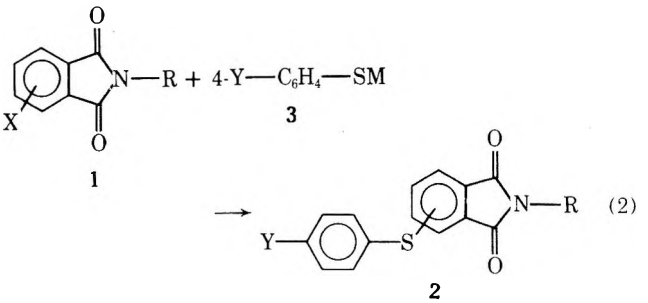
Preliminary work[1] has demonstrated that, indeed, in displacement reactions involving the phthalimide moiety as an activating group, thiophenoxide is vastly superior to phenoxide as a nucleophile. For example, in the displacement of the nitro group from 3-nitro-*N*-phenylphthalimide (**1**, X = 3-NO_2; R = Ph) in DMF, sodium 4-methylthiophenoxide (**3**) was found to react >100 times faster than sodium 4-methylphenoxide (**4**). In addition, if a mixture of **3** and 3-(4-methylphenoxy)-*N*-phenylphthalimide (**5**) or **4** and 3-(4-methylthiophenoxy)-*N*-phenylphthalimide (**2b**) was allowed to react in DMF at 120 °C for 1 h, the ratio of **2b** to **5** from either starting mixture was 97 to 3 (eq 1). These experiments suggested that the enhanced reactivity of sulfur might allow us to explore new base and solvent systems with thiophenol derivatives in these displacements.



(1)

Results and Discussion[6]

Studies of Base System. Initial work was carried out with the preformed sodium salt of thiophenol (**3**, Y = H; M = Na) or 4-methylthiophenol (**3**, Y = CH_3; M = Na). Reaction of these salts with 3- or 4-substituted nitro, chloro, or fluoro derivatives of **1** (R = alkyl or aryl) in DMF gave essentially quantitative yields of **2** (eq 2). Reactions involving an in situ



(2)

formation of the anion of 4-methylthiophenol using potassium carbonate or sodium hydroxide as a base gave good yields of **2**. Apparently, the displacement is so rapid with the sulfur nucleophile that the reaction is complete before the base can enter into the hydrolysis reactions with **1** that are seen in the phenol derivatives.[7]

Amine bases were also used in these reactions of **1** where X = NO_2, and essentially quantitative yields of **2** were obtained. These results are in direct contrast to reactions involving 4-methylphenol in which amine bases gave no displacement with any derivatives of **1**. Particularly interesting was the reaction of 4-hydroxythiophenol (**3**, Y = OH; M = H) in which only displacement by sulfur was seen. If amine bases were used with fluoro and chloro derivatives of **1**, only 50% yields of **2** were obtained, even at temperatures of 80 °C. In addition to

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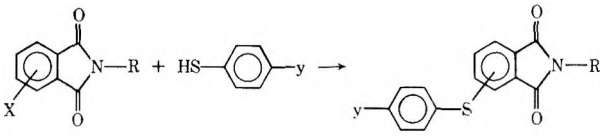
Table I. Displacement Reactions in DMF[a]

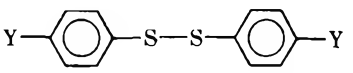


1 2

Compd	Registry no.	R	Isomer-X	y	Registry no.	Base (temp. °C)	% yield (isolated)	mp (ethanol)
2a	58045-34-4	Ph	3-NO_2	H	108-98-5	NaOH[e] (25)	91[b]	146-148
2b	58045-38-8	Ph	3-F	CH_3	106-45-6	$NaOCH_3$[e] (25)	99	204-205
2g	58045-39-9	Ph	4-NO_2	CH_3		$NaOCH_3$[e] (60)	96	165-167
2g		Ph	4-Cl	CH_3		$NaOCH_3$[e] (25)	98	
2l	64146-71-0	CH_3	4-NO_2	CH_3		$NaOCH_3$[e] (25)	92	135-137
2n	64146-70-9	CH_3	3-NO_2	CH_3		$NaOCH_3$[e] (25)	99	147-148
2b		Ph	3-NO_2	CH_3		K_2CO_3[f] (25)	96[c]	
2l		CH_3	4-F	CH_3		K_2CO_3[f] (25)	81[d]	
2l		CH_3	4-NO_2	CH_3		NaOH[g] (25)	57[d]	
2a		Ph	3-NO_2	H		Et_3N (25)	98	
2c	58045-36-6	Ph	3-NO_2	OH	637-89-8	Et_3N (25)	96	193-195
2b		Ph	3-NO_2	CH_3		Et_3N (25)	99	
2d	58045-35-5	*n*-Bu	3-NO_2	H		Et_3N (25)	92	83-85
2e	64146-09-6	H	3-NO_2	CH_3		Et_3N (25)	93	260-262
2f	64146-68-5	Ph	4-NO_2	H		Et_3N (25)	99	157-159
2g		Ph	4-NO_2	CH_3		Et_3N (60)	98	
2h	64146-67-4	Ph	4-NO_2	Br	106-53-6	Et_3N (60)	87	184-185
2i	64146-66-3	Ph	4-NO_2	OCH_3	696-63-9	Et_3N (60)	98	145-146
2j	64146-65-2	Ph	4-NO_2	Cl	106-54-7	Et_3N (60)	91	177-178
2k		Ph	4-NO_2	F	371-42-6	Et_3N (60)	97	161-163
2l		CH_3	4-NO_2	CH_3		Et_3N (25)	97	
2m		H	4-NO_2	CH_3		Et_3N (25)	86	194-195
2a		Ph	3-NO_2	H		$NaNO_2$[h] (25)	99[c]	
2b		Ph	3-NO_2	CH_3		$NaNO_2$[h] (25)	98	
2a	64146-64-1	Ph	3-NO_2	H		None (25)	51[c]	
2b	64146-72-1	Ph	3-NO_2	CH_3		None (25)	32	

[a] Satisfactory analytical data (±0.4 for C, H, N, S) were reported for all new compounds listed in the table. [b] Reaction run by D. R. Heath in Me_2SO. The displacement was apparently so fast that very little 6 was formed even in this solvent. [c] VPC yield. [d] Yield was low due to samples removed for analysis. [e] Preformed salt—either H_2O or MeOH removed before addition of 1. [f] Used 1 equiv of granular anhydrous K_2CO_3/1 equiv of thiophenol. [g] Used 1 equiv of sodium hydroxide pellets (97%)/1 equiv of thiophenol. [h] Used 0.02 equiv of anhydrous $NaNO_2$/1 equiv of thiophenol.

unreacted 1, a considerable amount of the disulfide 6 (Y = CH_3) was found in these reactions.



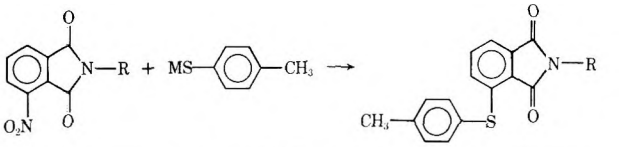
6

The addition of a small amount (~2 mol %) of sodium nitrite to a DMF solution of 4-methylthiophenol (3, Y = CH_3; M = H) and 1 (R = Ph; X = 3-NO_2) resulted in a rapid reaction at room temperature, and after 1 h a 98% yield of 2 (R = Ph; Y = CH_3) was obtained. A catalytic amount of any number of bases should effect this reaction with the nitrite generated from the displacement functioning as the actual base. Surprisingly, we also found that the displacement could be carried out in DMF with no base present; however, the reaction did not proceed to completion. It is possible that there are traces of dimethylamine in the DMF which function as the base or that perhaps the DMF acts as the base itself. However, in either case the nitrite which is generated apparently does not effectively function as a base, since the reaction does not proceed to completion. This indicates that the cation associated with the base has a definite influence on whether the nitrite generated from displacement can function as a base itself to complete the reaction.[8] The results of these base studies are summarized in Table I. ^{13}C NMR assignments for the compounds 2 are contained in Table VI in the supplementary material.

Studies of Solvent Systems. The yields of 2 from the reactions of phenoxides with 1 in nondipolar aprotic solvents were generally poor.[1] The exception occurred in the 3-nitro system in which displacements involving 1 (R = Ph; X = 3-NO_2) could be carried out in THF. Thiophenoxides react with 3-nitro derivatives in a variety of solvents such as THF, methylene chloride, acetone, acetonitrile, and ethanol to give excellent yields of 2 (see Table II). Unexpectedly, the 4-nitro isomers of 1 did not react well in these solvents.

The successul use of methylene chloride as a solvent allowed a two-phase reaction to be carried out. Using Adogen 464

Table II. Nitro Displacements in New Solvent Systems at 25 °C



R	M	Base	Solvent	Time, h	% yield (isolated)[a]
Ph	H	K_2CO_3	THF	16[b]	98
Ph	H	Et_3N	THF	3	88
Ph	Na	Preformed	CH_2Cl_2	3	95
Ph	Na	Preformed	CH_3CN	1	90
Ph	Na	Preformed	Acetone	1	90
Ph	Na	Preformed	EtOH	3	98
CH_3	H	Et_3N	THF	3	93
CH_3	Na	Preformed	THF	1	87
CH_3	Na	Preformed	CH_2Cl_2	3	97

[a] No attempt was made to maximize the yields. [b] This reaction was carried out at reflux.

Table III. Relative Rates of Reactivity of 1 in Me_2SO at 25 °C[a]

Relative Rates with $4\text{-}CH_3C_6H_4S^-Na^+$ [c]	Compound	Registry no.	Relative Rates with $C_6H_5O^-Na^+$ [d]
1	**1j** (R = CH_3; X = 4-Cl)	63197-17-1	1
6	**1a** (R = Ph; X = 3-Cl)	42899-83-2	*b*
8	**1b** (R = CH_3; X = 4-F)	63196-44-1	4
8	**1c** (R = Ph; X = 4-Cl)	26491-49-6	*b*
38	**1d** (R = Ph; X = 4-F)	63197-16-0	20
190	**1e** (R = Ph; X = 3-F)	42899-84-3	65
250	**1f** (R = CH_3; X = 4-NO_2)	41663-84-7	37
750	**1g** (R = Ph; X = 4-NO_2)	40392-27-6	130
9 400	**1h** (R = CH_3; X = 3-NO_2)	2593-81-9	170
16 000	**1i** (R = Ph; X = 3-NO_2)	19065-85-1	520

[a] Each series was determined independent of the other and thus the relative value of one in the sulfur series *does not equal* the relative value of one in the oxygen series. Thus, no direct comparison of the rates between the two series should be made. [b] An accurate value for this compound could not be obtained due to the formation of side products. [c] Registry no.: 10486-08-5. [d] Registry no.: 139-02-6.

[methyltrialkyl (C_8–C_{10}) ammonium chloride] as a phase-transfer catalyst, an 80% yield of **2n** was obtained from **1** (R = CH_3; X = 3-NO_2) and **3** (Y = CH_3; M = H).

Relative Rates of Reaction. A series of competition reactions was carried out between the various halo- and nitroimides, **1**, with sodium 4-methylthiophenoxide, **3** (Y = CH_3; M = Na), in Me_2SO at 25 °C. The results of these experiments are presented in Table III along with the relative rates of reactivity for each of these compounds with sodium phenoxide in Me_2SO at 25 °C. Table IV contains a comparison of pairs of leaving groups with respect to displacement by sulfur or oxygen and a comparison of the relative rates of displacement of the 3- and 4-isomer for each leaving group with sulfur or oxygen. From the data in Tables III and IV several trends can be seen: (1) For both sulfur and oxygen nucleophiles, the relative leaving group ability is $NO_2 > F > Cl$. (2) The relative difference between the rate of displacement of nitro and halo is much greater for sulfur than oxygen. (3) Displacements are favored when the leaving group is substituted in the 3-position with both sulfur and oxygen nucleophiles. The exception is for the chloro group with the sulfur nucleophile. (4) When sulfur is the nucleophile, the ratio of rates of displacement of the 3- to 4-nitro group is much greater than when oxygen is the nucleophile. (5) The relative rate of displacement of a 3-substituted nitro group with the sulfur nucleophile is much larger than for any other system studied.

As previously stated,[1] the nitro group can be either a better or worse leaving group than fluorine depending upon the system studied. As evidenced in Table IV, nitro is a better leaving group than fluorine in these systems regardless of whether the nucleophile is sulfur or oxygen. The more highly polarizable and "softer" sulfur nucleophile should prefer attack at a center which is closer to a polarizable group (nitro), and thus the nitro to halo differences should be enhanced with the sulfur nucleophile relative to the less polarizable oxygen nucleophile which favors attack at centers containing "harder", less polarizable groups such as fluoro and chloro. This is in fact the case as illustrated in Tabel IV, where, for example, with compounds **1j** and **1f** the NO_2 vs. Cl difference for sulfur is 250 vs. 37 for the oxygen nucleophile.

The strong inductive effect of the *o*-carbonyl in the 3-isomer

Table IV

(A) Relative Rate Ratios for Various Leaving Groups for N-Substituted Phthalimide Derivatives **1**

Nucleophile	N-R	Isomer	NO_2/Cl	NO_2/F	F/Cl
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	3	2600	84	32
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	4	94	20	5
$4\text{-}CH_3C_6H_4S^-Na^+$	N-CH_3	4	250	31	8
$C_6H_5O^-Na^+$	N-Ph	3		8	
$C_6H_5O^-Na^+$	N-Ph	4		6	
$C_6H_5O^-Na^+$	N-CH_3	4	37	9	4

(B) Relative Rate Differences for **3/4** Isomers

Nucleophile	N-R	Ratio of **3/4** Isomers NO_2	F	Cl
$4\text{-}CH_3C_6H_4S^-Na^+$	N-Ph	21	5	0.75
$4\text{-}CH_3C_6H_4S^-Na^+$	N-CH_3	38		
$C_6H_5O^-Na^+$	N-Ph	4	3	
$C_6H_5O^-Na^+$	N-CH_3	5		

(which is not possible in the 4-isomer) should favor displacement in the 3-position over the 4-position. In terms of steric interactions, however, the 3-isomer may be less favored, since approach of the nucleophile is hindered. Thus, the actual rate difference between the 3- and 4-isomers should be lower than if just the electronic effects were important. However, since sulfur is sufficiently polarizable to supply electrons and form bonds with carbon at relatively large separations,[9] there is potentially less chance for steric interaction with the sulfur nucleophile. This polarizability may be very important when the carbon center is attached to a strongly polarizable group such as nitro, and may be further enhanced by the adjacent electron-withdrawing carbonyl group. Thus, when nitro is the leaving group, it is reasonable that the 3-isomer reacts extremely rapidly with the sulfur nucleophile and the resulting **3/4** rate ratio is high (21 for **1j/1g**; 38 for **1h/1f**). It should be noted that the 3-nitro isomer may behave much differently from the 4-isomer, since there is considerable interaction between the 3-nitro oxygen atoms and the carbonyl group which prevents the nitro group from being coplanar with the imide ring. The effect of this change in nitro group configuration on the rate of reactions of the 3- and 4-isomers is unknown.

With the substitution of less polarizable halogen groups, the steric interactions at the 3-position become more important for sulfur and the **3/4** ratio more closely resembles the oxygen ratio (for **1d/1e** the ratio is 5 for sulfur and 3 for oxygen). It is interesting to note that with the sulfur nucleophile the 3-chloro derivative is even slower than the 4-isomer (**1a/1c** = 0.75). Again the lower polarizability of chlorine may enhance the steric effect and, since chlorine is larger than fluorine, this increased steric interaction in the 3-isomer now results in the 4-isomer being slightly more reactive.

We also compared the relative rates of reaction of **1h** (R = Me; X = 3-NO_2) vs. **1f** (R = Me; X = 4-NO_2) and **1b** (R = Me; X = 4-F) vs. **1f** (R = Me; X = 4-NO_2) when the sulfur nucleophile was generated by reacting 4-methylthiophenol with triethylamine. The nucleophile generated in this fashion behaved very similarly to sodium 4-methylthiophenoxide (**3**, Y = CH_3; X = Na) in that the 3-nitro isomer reacted much faster than the 4-nitro isomer and that the nitro derivative was much faster than the fluoro derivative. Likewise, if the nucleophile generated from triethylamine and 4-methylthiophenol was allowed to react with a mixture of **1b** (R = Me; X = 4-F) and **1c** (R = Ph; X = 4-Cl), it was found that **1c** was 1.1 times faster than **1b** vs. a difference of 1.3 when sodium 4-methylthio-

phenoxide was used as the nucleophile. Thus, at least for these two methods the manner in which the nucleophile is generated has little influence on the reactivity differences between pairs of imide derivatives.

An attempt was made to determine the relative nucleophilicities of sodium phenoxide and sodium 4-methylthiophenoxide vs. a given phthalimide derivative. If this could be achieved, we could then compare the values for sulfur in Table III directly with those for oxygen. As reported previously,[1] reaction of equal molar quantities of sodium 4-methylphenoxide (**4**) and sodium 4-methylthiophenoxide (**3**, Y = CH_3; M = Na) with **1i** (R = Ph; X = 3-NO_2) in DMF showed only reaction of the sulfur nucleophile. Similar reaction of equal molar amounts of **3** and **4** with **1j** (R = CH_3; X = 4-Cl), **1b** (R = CH_3; X = 4-F), **1f** (R = CH_3; X = 4-NO_2), **1e** (R = Ph; X = 3-F), and **1d** (R = Ph; X = 4-F) always produced >95% of the product from sulfur displacement. Thus, it is impossible, by our methods, to determine accurately the relative reactivity of **4** to **3** and we can only say that **3** is at least 100 times more reactive than **4** toward displacement in these systems.

Formation of Disulfide Derivatives. During some of our displacement studies we found appreciable amounts of disulfides **6**, and thus we attempted to learn more about their formation. It is well known that thiophenols are very air sensitive and can easily be oxidized to give disulfides. Likewise, reactions carried out with thiophenols in Me_2SO[10] can produce high yields of disulfides. We had noticed that more disulfide was produced in nitro rather than halo displacements and thus we studied the effect of sodium nitrite and unreacted nitro compound[11] on the disulfide formations. These results are summarized in Table V (section A) and indicate that nitrite by itself causes little oxidation of **3** (Y = CH_3; M = H), but when it is allowed to react with 1.2 N HCl (as in the workup of the displacement reaction) to form nitrous acid considerable coupling occurs to give **6**. In addition, the results also indicate that unreacted nitroimide may be responsible for the formation of **6**.

Reactions carried out between **3** (Y = CH_3; M = Na) and **1h** (R = CH_3; X = 3-NO_2) and **1b** (R = CH_3; X = 4-F) demonstrated that if the reactions are carried out under nitrogen using a neutral workup no **6** is produced (Table V, section B). Likewise, it was discovered that when the displacement is slower (as with the halo derivatives) and triethylamine is present considerable coupling takes place[12] (Table V, section B). This side reaction with triethylamine or impurities in the amine is serious enough that in the halo systems the displacement reaction cannot proceed to completion even if a 20% excess of thiophenol is used. This explains the low yields of **2** which are formed from these displacements.

Summary. The reactions of thiophenols with nitro- and halo-substituted phthalimides were found to be much different than similar reactions using phenols. The increased reactivity of the thiophenols permitted the use of inorganic and amine bases as well as many nondipolar aprotic solvents. The thiophenols were found to be extremely reactive with the 3-nitro isomers in comparison to the other nitro- and halo-substituted derivatives. We have extended our studies of thiophenols to nitro and halo derivatives of phthalic anhydride, and these results are presented in a separate paper.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were determined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6-ft 10% UC-W98 on 80/100 Chromosorb W column with temperature programming. A variety of different programs were used depending upon the compounds studied. The thioether phthalimides had long retention times and generally required temperatures around 300 °C to be eluded from the column. Melting points were determined on a Thomas-Hoover instrument and are uncorrected. C, H, N analyses were determined on a Perkin-Elmer 240 C, H, N analyzer, and sulfur analyses were determined by conventional analytical techniques either in house or by Galbraith.

Table V

(A) Coupling of Thiophenol Derivatives **3** (Y = CH_3; M = H)

Reactants	Time, h	Workup	% 3	% 6 (Y = CH_3)
DMF	1	1.2 N HCl	93	4
	23.5	1.2 N HCl	70	22
DMF, $NaNO_2$	1	1.2 N HCl	0	87
	4	H_2O	83	9
	4	1.2 N HCl	0	78
	23.5	H_2O	59	31
DMF, Nitrobenzene-	1	H_2O	87	11
	4	H_2O	38	50
	23.5	H_2O	0	91

(B) Disulfide Formation during Displacement Reactions

$$1 + 3\ (Y = CH_3) \xrightarrow{DMF} 2 + 6\ (Y = CH_3)$$

Imide	M	Time (h)	Workup	% 6
1h (R = CH_3; X = 3-NO_2)	Na	1	H_2O	0
		1	1.2 N HCl	5
1b (R = CH_3; X = 4-F)	Na	0.5	H_2O	0
		0.5	1.2 N HCl	0
1h (R = CH_3; X = 3-NO_2)	H/Et_3N	1	1.2 N HCl	<2
		1	H_2O	<2
1b (R = CH_3; X = 4-F)	H/Et_3N	4.5	H_2O	46
1c (R = Ph; X = 4-Cl)	H/Et_3N	16	H_2O	37

Anhydrous DMF or Me_2SO were purchased from Burdick and Jackson Laboratories. The acetone, acetonitrile, and ethanol used were reagent grades. The THF used was freshly distilled from sodium benzophenone ketyl. The triethylamine was used as purchased from Eastman. A sample of di-*p*-tolyl disulfide was also purchased from Eastman. The thiophenol derivatives were obtained from commercial sources.

Preparation of Nitro- and Halophthalimides. The majority of nitro- and halophthalimides were prepared as has previously been described[1] by reacting the substituted phthalic anhydride with the desired amine derivatives. The 4-nitro-*N*-methylphthalimide derivative was prepared by nitration of *N*-methylphthalimide.[13] The 3- and 4-nitrophthalimides were purchased from Eastman.

Displacement Reactions—Different Base Systems. In general, the displacements were run by stirring the desired thiophenol and base (or performed thiophenoxide) with 1 and solvent under nitrogen. The reactions were followed by VPC analysis and the products were isolated by addition of the reaction mixture to a 1.2 N HCl/ice mixture followed by filtration. The crude products were recrystallized from ethanol. Analytical data for the compounds **2** are contained in Table I, and ^{13}C NMR shifts are in Table VI (see supplementary material). Specific details for the various methods are given below as well as one detailed example.

(A) Sodium Hydroxide Azeotrope. A mixture of the thiophenol, 50% aqueous sodium hydroxide, Me_2SO, and benzene was heated at reflux under nitrogen while the water was azeotropically removed with the aid of a Dean–Stark trap. After 8 h of reflux, the benzene was removed by distillation and the reaction mixture was cooled to 25 °C. To this mixture was then added the desired imide 1.

(B) Sodium Methoxide Preformed. The preformed salt of 4-methylthiophenol (Aldrich) was prepared exactly as has been described for 4-methylphenol.[1]

(C) Triethylamine. A mixture of 1.26 g of *p*-hydroxythiophenol (Crown Zellerbach), 2.68 g of 3-nitro-*N*-phenylphthalimide, and 25 mL of DMF was stirred under a nitrogen atmosphere at 25 °C. To this mixture was added 1.40 mL of triethylamine with the aid of a syringe. The color of the solution immediately changed from light yellow to red and then slowly it changed back to light yellow. After 15 min the

reaction mixture was added to 1.2 N HCl/ice and **2c** was collected to give 3.35 g (96%) after drying. A sample was recrystallized from ethanol for analytical purposes. In addition to the analytical data presented in Tables II and III, an infrared spectra showed an absorption at 3500 cm^{-1} characteristic of a phenol.

Displacement Reactions—Different Solvents. Besides DMF and Me_2SO, displacement reactions were also run in THF, EtOH, CH_3CN, acetone, and methylene chloride. All of these reaction mixtures were worked up by addition to water followed by filtration of the product, except for methylene chlroide. When methylene chloride was the solvent, the reaction mixture was washed with water and the methylene chloride layer was dried and concentrated to give the desired product. A typical reaction procedure is presented below.

THF 4-NO_2 Isomer. A mixture of 1.34 g of 4-nitro-*N*-phenylphthalimide, 0.80 g of sodium 4-methylthiophenoxide, and 15 mL of THF was heated at reflux under a nitrogen atmosphere for 43 h. Aliquots were removed at 3, 19, and 43 h and analysis indicated an ca. 50% yield of **2**. There was little difference in analysis of the 3- and 43-h point. The VPC analysis indicated large amounts of the disulfide and unreacted nitroimide.

Two-Phase Reaction. A mixture of 2.06 g of 3-nitro-*N*-methylphtahlimide, 1.24 g of 4-methylthiophenol, 0.80 g of 50% aqueous sodium hydroxide, 50 mL of H_2O, 50 mL of methylene chloride, and 0.50 g of Adogen 464 (phase-transfer catalyst from Aldrich) was stirred using a Vibro Mix stirrer. The mixture was kept at room temperature but was not blanketed with a nitrogen atmosphere. After 2 h the stirrer was stopped and an aliquot was removed from the methylene chloride layer. In addition, another aliquot was removed from both the methylene chloride and aqueous layers. Workup of both aliquots and analysis by VPC showed ~80% of 3-*p*-methylthiophenoxy-*N*-methylphthalimide, ~10% of the nitroimide, and ~10% of the disulfide **6**. Extraction of the methylene chloride solutions with aqueous sodium bicarbonate did not alter the product composition, indicating that indeed the materials present were imides and not amide acids which ring closed upon analysis. Further reaction time up to 10 h did not alter the product composition.

Competition Experiments: Reactivity of Nitro or Halo Derivatives toward Displacements by Sodium *p*-methylthiophenoxide. An arbitrary amount of anhydrous sodium 4-methylthiophenoxide was accurately weighed into a flask under nitrogen. An equivalent molar amount of each of the two compounds being studied and an internal standard (o-terphenyl) were then dissolved in enough Me_2SO to make a solution containing 10% solids. An aliquot was removed from this solution and added to a mixture of 1.2 N HCl and methylene chloride. After vigorous shaking, the methylene chloride layer was removed and dried, and this solution was then used to determine the composition of the starting mixture. The Me_2SO solution was then added to the sodium 4-methylthiophenoxide and this mixture was stirred under a nitrogen atmosphere at room temperature. After 1 h, an aliquot was removed and worked up as described above. The solutions were then subjected to VPC analysis, and the peak area for each compound was determined. From these measurements and the analysis of the starting mixture, the percentage of reaction for each material was determined and then, using the equation presented by Huisgen,[14] the relative rates of reactivity were calculated. Similar reactions were run in which 4-methylthiophenol/triethylamine were used in place of sodium 4-methylthiophenoxide.

Reactivity of Sodium Phenoxide and Sodium 4-Methylthiophenoxide (3) with Substituted Phthalimide Derivatives. Equal molar amounts of **3** and sodium phenoxide were weighed out under nitrogen and were dissolved in enough DMF (Me_2SO does not give a homogeneous solution) to make a solution containing 10% solids. To this solution was then added an equal molar amount of the desired imide **1** and the reaction was run at 25 °C under nitrogen for 1 h. An aliquot was removed and analyzed as described above. The areas of each product peak were determined and corrected for response differences. From these measurements the relative rates of reactivity were calculated.[13]

Formation of Disulfides. Response factors were determined for di-*p*-tolyl disulfide, and the silylated product of 4-methylthiophenol and BSA. VPC analysis was done using a 150 to 300 °C at 20 °C/min program. In a typical run, a mixture of 0.68 g of 4-methylthiophenol, 0.8357 g of *o*-terphenyl, 0.35 g of sodium nitrite, and 15 mL of DMF was stirred at room temperature under a nitrogen atmosphere. Aliquots were removed at timed intervals and worked up by addition to a CH_2Cl_2/1.2 N HCl or CH_2Cl_2/H_2O mixture. The organic phases were dried and BSA (Aldrich) was added. The resulting solution was analyzed by VPC.

Acknowledgments. We thank H. M. Relles for his many helpful discussions concerning this work and E. A. Williams and J. D. Cargioli for their help in obtaining and interpreting the ^{13}C spectra.

Registry No.—**1**, R = H; X = 4-NO_2, 89-40-7; **1**, R = H; X = 3-NO_2, 603-62-3.

Supplementary Material Available. ^{13}C NMR assignments for all new thiophenoxy-substituted phthalimides (2) (3 pages). Ordering information is given on any current masthead page.

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(6) Some of this work is contained in D. R. Heath and F. J. Williams, U.S. Patent 3 922 284, Nov. 25, 1975.
(7) The ease with which the displacement reaction between 4-methylthiophenol and the phthalimide derivatives (1) occurred when carbonate was used as the base suggested that the reaction might also be effected by passing reactants over a basic support contained in a column, providing that the contact time was of sufficient length. A mixture of **1** (R = CH_3; X = 3-NO_2) and 4-methylthiophenol was dissolved in DMF and the solution was passed through a column packed with potassium carbonate. Addition of this DMF solution to water resulted in the isolation of an 89% yield of the desired product **2** (R = CH_3; Y = CH_3). In a similar fashion, a mixture of **1** (R = CH_3; X = 3-NO_2), 4-methylthiophenol, and DMF was passed through a column of Woelm Basic Alumina to give an 85% yield of **2**.
(8) The reaction in which nitrite functions as a base and the reaction with no added base may be specific for derivatives of **1** where X = 3-NO_2. The 4-NO_2 derivatives are much slower toward displacement than the 3-isomers and may not be reactive under these conditions.
(9) See Reference 4a, page 103.
(10) See Reference 4d, G. Capozzi and G. Modena, Chapter 17, p 795.
(11) The oxidation of thiols by nitrobenzene is known. See Reference 4d, Chapter 17, page 800.
(12) The oxidation of thiols is reported to be catalyzed by amines. See Reference 4d, Chapter 17, page 816.
(13) J. Tirouflet and R. Dabard, *C. R. Uebd. Seances Acad. Sci.*, 916 (1956); R. Dabard and J. Tlrouflet, *Bull. Soc. Chim. Fr.*, 565 (1957). See also F. J. Williams and P. E. Donahue, submitted for publication in *J. Org. Chem.*
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Reaction of Thiophenoxides with Nitro- and Halo-Substituted Phthalic Anhydrides

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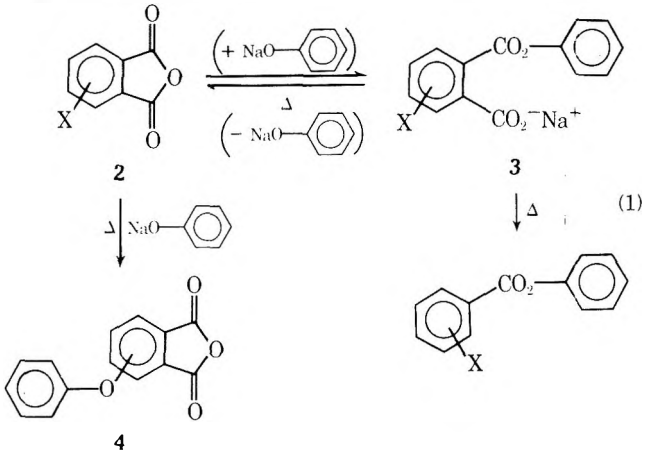
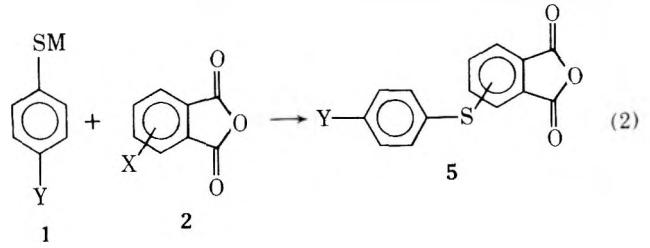
A wide variety of thioether-substituted phthalic anhydride derivatives **5** have been synthesized from the reaction of thiophenoxides with nitro- or halo-substituted phthalic anhydrides **2**. These reactions were carried out at room temperature and gave no indication of attack by the sulfur nucleophile at the carbonyl groups of the anhydride. This is in direct contrast with the room-temperature reactions of **2** with phenoxide nucleophiles, in which the nucleophile attacks only the carbonyl groups. The reaction involving the sulfur nucleophile works well using either preformed salts of the thiophenols or by generating the nucleophile in situ with amine or inorganic salts used as bases. The choice of the base system determines the speed of the reaction, which can vary from <5 min to 3 h at 25 °C. The halo derivatives are preferred over the nitro derivatives to minimize side reactions.

We have recently studied the reaction of thiophenoxide nucleophiles **1** with nitro- and halo-substituted phthalimides.[1] Of particular interest was the comparison between the two different types of nucleophiles, thiophenoxide and phenoxide, and the differences in reactivity that were observed. The reactions of phenoxide derivatives with nitro- and halo-substituted phthalic anhydrides **2** have also been studied,[2] and the course of each reaction was found to be very dependent upon the conditions employed and the identity of the leaving group. In all three systems (X = nitro, chloro, or fluoro), reaction with sodium phenoxide at room temperature resulted in opening of the anhydride ring to produce a mixture of acid ester salts **3**. Upon heating, these salts either decarboxylated (X = NO_2) or ring closed to varying degrees (X = F > Cl ≫ NO_2) to regenerate starting material. This starting material

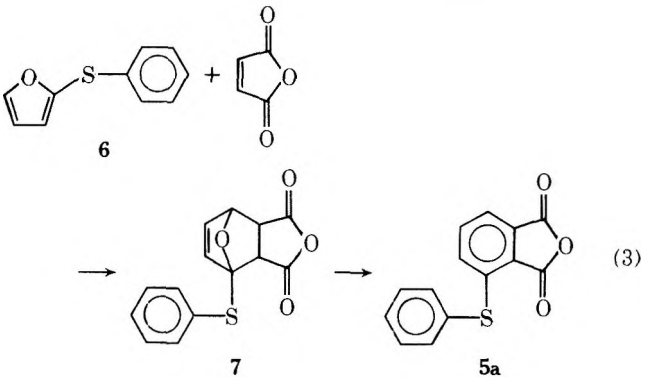


then underwent a displacement reaction with phenoxide to give the desired product **4** with varied success (F > Cl > NO_2) (see eq 1). If the reactions were carried out at 25 °C, *no displacement was observed.*

Successful reaction of the sulfur nucleophiles **1** with the substituted phthalic anhydrides **2** offers a facile synthesis of a variety of 3- and 4-substituted aromatic thioether derivatives of **5** (eq 2). The synthesis of only one derivative of **5** (3-isomer; Y = H) has been previously reported.[3] This material was prepared by the reaction of maleic anhydride with a 2-furyl



thioether (**6**) to give the adduct **7** which was dehydrated to give **5a** in 40% overall yield (eq 3). This route necessitates the



synthesis of derivatives of **6** and, in addition, is limited to only the synthesis of 3-isomers of **5**.[4]

Results and Discussion[5]

Reaction of sodium 4-methylthiophenoxide (**1**, M = Na; Y = CH_3) with 3-fluorophthalic anhydride (**2e**) in DMF at 25 °C proceeded to completion in less than 5 min and gave a 94% yield of the desired product **5c** (3-isomer; Y = 4-CH_3). The product was isolated by adding the reaction to an ice/water mixture and collecting the product by filtration. The reaction worked equally well for the other halo-substituted derivatives and the results of these reactions are summarized in Table I, section A. All the reactions were extremely clean with less than 2% of the disulfide **8** formed.[6] It is likely that this 2% is present as an impurity in the starting material **1**. No attempts were made to maximize the yields of **5**. In examples where the yield of isolated product is lower, some hydrolysis of the product has taken place during workup. Extraction of the aqueous filtrate permits the recovery of **5** as the corresponding diacid. For example, examination of the reaction of **1** (M = Na; Y = CH_3) with 4-fluorophthalic anhydride (**2d**) by ^{13}C NMR confirmed the exclusive formation of **5d** and showed no trace of hydrolyzed product.

The reaction of **1** (M = Na; Y = CH_3) with 3- or 4-nitrophthalic anhydride was not as straightforward (eq 4). As shown in Table I (section A) not only were the yields of displacement product **5** much lower (42–43%), but a large amount of the disulfide **8** (55–57%) was produced. We feel that the lower yield of **5** is a result of two factors. First, as has been demonstrated previously,[2,7] once the sodium nitrite is produced from the displacement reaction, it can initiate a very fast ring-opening reaction with the starting nitro anhydride to produce **9**. This reaction deactivates the molecule toward further nitro (nitrite) displacement, and if it is competitive

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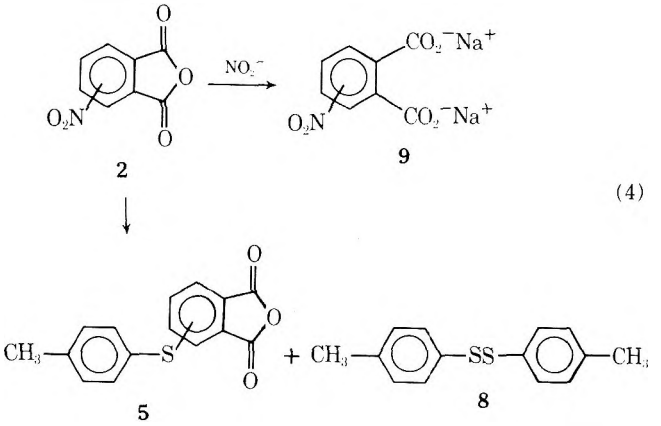
Table I. The Use of Different Base Systems
1 + 2 → 5 + 8

Group X	Group Y	Isolated % yield of 5	VPC % yield of 5	VPC % yield of 8
		A. Preformed Sodium Salt		
4-F	CH_3	83	99	~2
3-F	CH_3	94		
4-Cl	CH_3	87	99	~2
3-Cl	CH_3	93		
4-NO_2	CH_3		42	55
3-NO_2	CH_3		43	57
4-Br	CH_3		97	~2
		B. Triethylamine		
4-F	CH_3	93	93	4
4-F	Cl	88		
4-F	H	93		
3-F	OH	74		
3-F	H	94		
3-F	Cl	91		
4-Cl	CH_3		94	6
4-Cl	CH_3O	88		
3-Cl	CH_3	92		
4-NO_2	CH_3		40	60
3-NO_2	CH_3		51	46
		C. Other Bases		
K_2CO_3 4-F	CH_3		98	2
$KHCO_3$ 4-F	CH_3		91	~4
Na_2CO_3 4-F	CH_3		99	
NaOH 4-F	CH_3		92	5
K_2CO_3 4-NO_2	CH_3		40	60

with the rate of displacement by the sulfur nucleophile a lower yield of the product **5** results. In addition, much coupling of the nucleophile **1** is seen.[8] Control experiments have shown that there is not enough moisture present to form the diacid derivative of **2** and thus the lower yields are not a function of the ring opening of the anhydride by water.



Experiments designed to improve the yield of nitro (nitrite) displacement were not very successful. Reactions in which the anhydride **2** was added to a homogeneous solution of the nucleophile in DMF or in which cosolvents were used to precipitate the sodium nitrite did not improve the yield. If 2 equiv of **1** was used, the yield of **5d** could be increased to 74%. It is interesting to note that ^{13}C NMR analysis of the reaction mixture indicated that the product **5** was present exclusively in the anhydride form, which demonstrates the preference of nitrite attack for the nitro anhydride **2**.

The relative rates of reaction of a series of nitro- and halo-substituted phthalimides with the nucleophile **1** (M = Na; Y = CH_3) have been obtained.[1] We felt that it would also be of interest to determine the relative rates of reactivity of the halo- and nitro-substituted phthalic anhydride derivatives with **1** under similar conditions. The results of these experiments are presented in Table II. The general order of halo displacement was F > Br > Cl, although there was not a very large difference between any of the halogens. As in the phthalimide system,[1] the 3-isomer was faster than the 4-isomer for fluoro displacement, but the order was reversed for chloro displacement. It appears that nitro (nitrite) displacement is again much faster than halo displacement, but the side reactions due to the sodium nitrite and the disulfide production from **1** made it impossible to obtain accurate values for the competition reactions involving the nitro derivatives. It is interesting to note that the anhydride linkage appears to be a better activating group than the phthalimide linkage for these displacements with the thiophenoxide nucleophile. A competition reaction between 3-chlorophthalic anhydride (**2a**) and 3-chloro-*N*-phenylphthalimide with **1** in DMF showed **2a** to be ca. 20 times more reactive than the imide.

Table II. Relative Rates of Reaction of Sodium 4-Methylthiophenoxide with 2 in DMF at 25 °C

Compound	Relative rate
2a (X = 3-Cl)	1
2b (X = 4-Cl)	1.5
2c (X = 4-Br)	4
2d (X = 4-F)	10
2e (X = 3-F)	20
2f (X = 4-NO_2)	(100)[a]
2g (X = 3-NO_2)	(1400)[a]

[a] May be in error due to side reactions of nitrite.

If a mixture of the desired thiophenol **1** (M = H), phthalic anhydride derivative **2**, and DMF was stirred at 25 °C, then an equivalent amount of triethylamine could be added to effect the displacement reaction. The reaction was slower than if the free anion **1** (M = Na) was used, but proceeded very well for a variety of substituted thiophenols. The results of these experiments are summarized in Table I, section B. Again it can be seen that the use of halo-substituted phthalic anhydrides is favored over the nitro derivatives. As was the case when the free anion **1** (M = Na) was used, the reaction with the nitro anhydrides led to lower yields of the desired products **5** and the formation of the disulfide **8**. In addition to using an amine system as the base, several reactions were carried out in which inorganic bases were used in situ with the thiophenol and phthalic anhydride derivative. The results of these experiments are summarized in Table I, section C. Generally, the rates of reactions using the inorganic bases were about the same as when the amine bases were used. All reactions were complete within 3 h at 25 °C. Control experiments were run to show that the displacement of the group X from **2** would not occur if the anhydride ring were opened to give either the diacid, disalt **9**, or monosalt–monoacid. Thus, if any ring opening does take place when the inorganic bases are used, it must take place after the displacement reaction. A summary of the analytical data for the new compounds synthesized from these displacements is contained in Table III and the chemical shifts from the ^{13}C NMR spectra of these compounds are presented in Table IV (see supplementary material).

Brief attempts were made to carry out the displacement reaction in solvents other than those classified as dipolar aprotic. Reaction of 4-fluorophthalic anhydride (**2d**) with **1** (M = Na; Y = CH_3) in methylene chloride or THF was unsuccessful. However, reaction of **2d** with **1** in acetone gave a 92% yield of **5d** (4-isomer; Y = CH_3). Reactions were also attempted in methylene chloride between **2g** and **1** and between **2d** and 4-methylthiophenol/Et_3N, but they also were not successful.

In summary, a wide variety of thioether-substituted phthalic anhydride derivatives **5** have been synthesized from the facile reaction of thiophenols with nitro- and halo-sub-

stituted anhydrides **2**. These reactions, carried out at room temperature, showed no attack by the sulfur nucleophile at the carbonyl groups of the anhydride. These results are in contrast to the reaction of **2** with phenoxide nucleophiles at 25 °C in which attack occurs exclusively at the carbonyl groups.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 457 grating infrared spectrophotometer in chloroform solution or as a KBr pellet. Mass spectra were determined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor-phase chromatography (VPC) was carried out on a Hewlett Packard 5750 research chromatograph using a 6-ft 10% *UCW-98* on 80/100 Chromosorb W column with temperature programming from 150 to 300 °C at 15 °C/min. Melting points were determined on a Thomas-Hoover Instrument and are uncorrected. C, H, N analyses were determined on a Perkin-Elmer 240 C, H, N analyzer, and sulfur analyses were determined by conventional analytical techniques either in house or by Galbraith.

Anhydrous DMF was purchased from Burdick and Jackson Laboratories. The THF used was freshly distilled from sodium benzophenone ketyl. The acetone, methylene chloride, and toluene used were reagent grades. The triethylamine was purchased from Eastman. A sample of di-*p*-tolyl disulfide was also purchased from Eastman. The thiophenol derivatives were obtained from commercial sources.

Phthalic Anhydride Derivatives. The starting phthalic anhydride derivatives 2 were obtained as has been described previously.[9] A sample of 4-bromophthalic anhydride (**2c**) was prepared from the bromination of phthalic anhydride followed by separation of the isomer mixture. We thank C. B. Quinn for a sample of this material.

Displacement Reactions. In general, the displacement reactions were run as has been described previously.[1] Conditions which are specific for the anhydride system are described below.

(A) Sodium Methoxide—Preformed (Isolated Yield). The reactions were run for 5 min to 2 h at 25 °C. All crude samples were examined by infrared analysis to ensure that the anhydride ring was intact. Several of the crude samples were also submitted for ^{13}C NMR analysis to verify the anhydride structure.

(B) Sodium Methoxide—Preformed (VPC Yield). Mixtures of the starting materials and internal standard (o-terphenyl) were stirred at 25 °C under nitrogen. Aliquots were removed at timed intervals and were worked up by shaking them with a 1.2 N HCl/Et_2O mixture. The organic layer was dried and analyzed by VPC. The peak area was determined for the standard and for each of the products, **5** and **8**. VPC yields were then obtained for each compound by using standard procedures, correcting for detector response differences. The results are presented in Table I, section A.

(C) Inorganic Salt. In general, the anhydride and thiophenol derivative were dissolved in DMF, the desired inorganic salt was added, and the reactions were stirred at 25 °C for 1 to 3 h. The salts were standard A.C.S. grade materials and were used as purchased.

(D) Triethylamine. The anhydride and thiophenol were dissolved in the desired solvent and the triethylamine was added by syringe. Reactions were generally run for 3 h at 25 °C or 1 h at 60 °C. All products were again examined by IR to ensure that the anhydride ring was intact. A specific example follows: A mixture of 1.66 g of **2e**, 1.59 g of *p*-chlorothiophenol (Aldrich), and 17 mL of DMF was stirred at 25 °C under nitrogen. To this solution was added 1.52 mL of triethylamine. The reaction mixture was stirred at 60 °C for 1 h to ensure complete reaction and then added to 1.2 N HCl/ice, and the resulting precipitate was collected and dried to give 2.77 g (91%) of **5f**. Analysis by infrared spectroscopy indicated that the anhydride ring was still intact. Analytical data for this compound is contained in Tables III and IV (see supplementary material).

Competition Experiments: Reactivity of Nitro or Halo Derivatives toward Displacement by Sodium 4-Methylthiophenoxide (1, M = Na; Y = CH_3). An arbitrary amount of anhydrous sodium 4-methylthiophenoxide (1) was accurately weighed into a flask under nitrogen. An equivalent molar amount of each of the two compounds being studied and an internal standard (o-terphenyl) were then dissolved in enough DMF to make a solution containing 10% solids. The solution was then added to the salt and the reaction mixture was stirred for 2 h at 25 °C. After 2 h, an aliquot was removed and worked up with 1.2 N HCl/CH_2Cl_2. The organic layer was dried and analyzed by VPC. The percent yield for each product was determined, and using the equation presented by Huisgen[10] the relative rates of reactivity were calculated. Similar experiments were run to determine the relative rates of reactivity of 3-chloro-*N*-phenylphthalimide and 3-chlorophthalic anhydride.

Attempts to Run Reactions in Other Solvents. Reactions were run between 1 (M = Na, Y = CH_3) and **2d** exactly as described for "displacement reactions: (B) Sodium Methoxide—Preformed." However, in place of DMF, reactions were run with methylene chloride, THF, acetone, and toluene. In the reactions using methylene chloride or THF, no product was obtained after 68 h. However, in acetone an 85% yield of product was obtained after 45 min at 25 °C.

Attempts to Run Reactions on 4-Fluorophthalic Acid. A mixture of 2.0 g **2d** was stirred with 50 mL of 25% aqueous sodium hydroxide. The basic solution was extracted with ether and the aqueous solution was then acidified with HCl and again extracted with ether. The combined ether extracts were then dried over anhydrous magnesium sulfate and concentrated to give 1.83 g of 4-fluorophthalic acid (**10**). The structure was verified from its ^{13}C NMR spectrum.

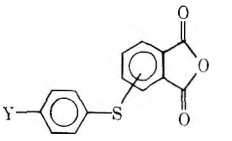
A mixture of 0.1752 g of **10**, 0.1390 g of **1** (M = Na; Y = CH_3), 0.0860 g of o-terphenyl, and 6 mL of DMF was stirred at 25 °C under nitrogen. After 16 h of stirring, analysis of an aliquot by VPC showed no reaction had taken place. Two equivalents of **1** (0.278 g) was added and the reaction was stirred for 2 h (no further reaction). The reaction mixture was heated at 140 °C for 16 h, but still no displacement reaction was seen.

A mixture of 0.23 g of **10**, 0.172 g of K_2CO_3, 0.150 g of 4-methylthiophenol, and 0.1142 g of o-terphenyl was stirred at 25 °C under nitrogen with 6 mL of DMF. An aliquot, removed after 16 h, indicated that no reaction had taken place. Two additional equivalents of K_2CO_3 (0.344 g) was added, but after 6 h at 25 °C no further reaction was seen.

^{13}C NMR of Reaction Mixtures. (A) A mixture of 0.7505 g of sodium 4-methylthiophenoxide, 0.8433 g of 4-fluorophthalic anhydride, and 4 mL of DMF was stirred at 25 °C under a nitrogen atmosphere. After 0.5 h, the light-yellow homogeneous solution was transferred to an NMR tube. Analysis by ^{13}C NMR indicated the absence of 4-fluorophthalic anhydride, a trace of the disulfide 8, and the formation of the desired product 4-(4-methylthiophenoxy)-phthalic anhydride.

(B) A mixture of 0.6960 g of sodium 4-methylthiophenoxide, 0.920 g of 4-nitrophthalic anhydride, and 8 mL of DMF was stirred at 25 °C under nitrogen. After 2 h, the thick yellow solution was filtered and the filtrate analyzed by ^{13}C NMR. The NMR showed that all the displacement product was present in the form of the anhydride and that the disulfide 8 was present. The ratio of 8 to **5d** was 42 to 58 by NMR. The NMR also indicated the presence of 4-nitrophthalic acid or salts of this acid. The difference between these materials could not be distinguished by this spectrum. The solid, which was removed by filtration, was dissolved in 1.2 N HCl and extracted with ether. Analysis by VPC of these extracts indicated the presence of only 4-nitrophthalic anhydride (most likely ring closed upon analysis).

Table III. Thiophenoxy-Substituted Phthalic Anhydrides[a]



5

Compound	Registry no.	mp,[b] °C	*m/e*
5a (3-isomer; Y = H)	18241-49-1	147.5–149[c]	256
5b (4-isomer; Y = H)	64163-01-5	137–138	256
5c (3-isomer; Y = CH_3)	64163-02-6	136.5–138	270
5d (4-isomer; Y = CH_3)	64163-03-7	129–130	270
5e (4-isomer; Y = OCH_3)	64163-04-8	137.5–138.5	286
5f (3-isomer; Y = Cl)	64163-06-0	159–160	290
5g (4-isomer; Y = Cl)	64163-05-9	132.5–133.5	290
5h (3-isomer; Y = OH)	64163-07-1	166–168	272

[a] Satisfactory analytical data (±0.4% for C, H, S) were reported for all new compounds listed in the table. [b] All samples were recrystallized from toluene. [c] Lit. mp 148.5–149.5 (see ref 4).

Acknowledgments. We thank H. M. Relles for many helpful discussions concerning this work, and the analytical section of the Materials Characterization Branch for their assistance in obtainind the necessary analytical data.

Registry No.—**1** (M = Na; Y = CH_3), 10486-08-5; **1** (M = H; Y = CH_3), 106-45-6; **1** (M = H; Y = Cl), 106-54-7; **1** (M = H, Y = H), 108-98-5; **1** (M = H; Y = OH), 637-89-8; **1** (M = H; Y = OCH_3), 696-63-9; **2** (X = 4-F), 319-03-9; **2** (X = 3-F), 652-39-1; **2** (X = 4-Cl), 118-45-6; **2** (X = 3-Cl), 117-21-5; **2** (X = 4-NO_2), 5466-84-2; **2** (X = 3-NO_2), 641-70-3; **2** (X = 4-Br), 86-90-8; **8**, 103-19-5.

Supplementary Material Available. ^{13}C NMR assignments for the thiophenoxyphthalic anhydrides **5** (1 page). Ordering information is given on any current masthead page.

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Effect of Monoalkyl Phosphates upon Micellar-Catalyzed Dephosphorylation and Deacylation[1]

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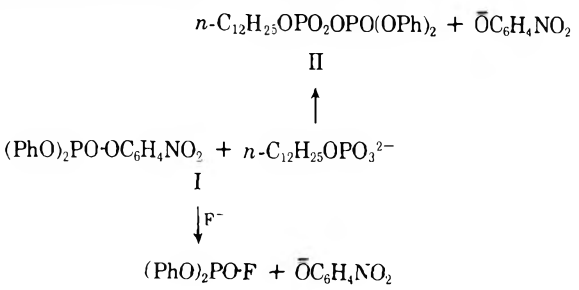
Disodium *n*-dodecyl phosphate (NaDodP) and to a lesser extent *n*-butyl phosphate are nucleophilic catalysts for the decomposition of *p*-nitrophenyl diphenyl phosphate (I) in cationic micelles, with up to 100-fold rate enhancement over the rate in water. Micelles of NaDodP are poor catalysts, even though they incorporate the substrate, suggesting a role for micellar charge in these reactions. Although *n*-butyl phosphate dianion weakly catalyzes deacylation of 2,4-dinitrophenyl 3-phenylpropionate, it and NaDodP inhibit the reaction in cationic micelles of cetyltrimethylammonium bromide by excluding hydroxide ion.

Micellar catalysis of bimolecular reactions involves concentration of the reagents at the micelle–water interface, in the so-called Stern layer.[3-6] Estimation of the rate constants at the interface depends on the volume element used in measuring concentration, but for a number of such reactions the second-order rate constants are apparently no larger at the interface than in water.[6,7] Functional micelles are often very effective catalysts because concentration of reagents minimizes the unfavorable entropy changes in forming a transition state from two or more reactants.[3-5,8] Many functional micelles are cationic or zwitterionic, and the role of the positive charge is not always obvious. For example, comicelles of acylhistidines and quaternary ammonium ions are excellent deacylating agents, whereas the acylhistidines alone are relatively ineffective,[9] but nonionic micelles of *n*-alkylamines and *n*-alkylimidazoles are often effective.[10]

The reaction of *p*-nitrophenyldiphenyl phosphate (I) with hydroxide ion is catalyzed by micelles of cetyltrimethylammonium bromide (CTABr).[11] At high pH this catalysis is reduced by phosphate and aryl phosphate ions, although at lower pH the nucleophilic attack by these ions becomes important.[12]

In order to obtain evidence on the role of micellar charge, we used micelles of disodium *n*-dodecyl phosphate (NaDodP) and examined its reactions with I giving initially II and its effect on dephosphorylation by fluoride ion.[11]



Although most work with nucleophilic micelles has been on deacylation, functional cationic micelles having hydroxyl or imidazole head groups are effective catalysts of dephosphorylation.[13] For purposes of comparison, we also examined the effect of NaDodP on the deacylation of 2,4-dinitrophenyl 3-phenylpropionate (III) in CTABr.

Experimental Section

Materials. *n*-Dodecyl- and *n*-butylphosphoric acid were prepared from the alcohols and $POCl_3$ by standard methods.[14] The phosphates were analyzed quantitatively for phosphorus and *n*-dodecylphosphoric acid had mp 58–60 °C (lit.[15] 58 °C). The preparation and purification of the other materials has been described.[11-15]

Kinetics. Reactions were followed spectrophotometrically at 403 and 358 nm for the *p*-nitrophenyl and 2,4-dinitrophenyl compounds, respectively, using a Gilford spectrophotometer with a water-jacketed cell compartment at 25.0 °C.[11-13] The first-order rate constants, k_ψ, are in s^{-1}. The pH of the reaction solution was measured in the presence of the surfactant, and the substrate concentrations were 1–2 $\times 10^{-5}$ M.

Critical Micelle Concentration. The critical micelle concentration (cmc) of disodium *n*-dodecyl phosphate (NaDodP) is 1.6×10^{-2} M at 22 °C in 0.02 M borate buffer, determined by surface-tension measurement. The cmc is considerably higher than that of sodium dodecyl sulfate (NaDodSO$_4$) of ca. 8×10^{-3} M,[16] because of the dianionic phosphate head group.

Products. The products of reaction of I with 2×10^{-3} M NaDodP in 4×10^{-3} M CTABr at pH 9.1 were separated by thin-layer chromatography using Eastman Kodak 6060 Si gel plates. After complete reaction, the pH was brought to 4 and the chromatogram was developed using MeOH–$CHCl_3$ (15:85, v/v). The surfactants did not move, and spots were observed at R_f 0.11 (of diphenyl phosphate) and 0.54 (of *p*-nitrophenol) plus a third spot with R_f 0.17 which we assume was that of the diphenyl *n*-dodecyl pyrophosphate (II). When reaction was done in the absence of NaDodP and it was added after complete reaction, this spot with R_f 0.17 was absent. The formation of diphenyl phosphate could have been due to reaction of OH^- with the substrate or to subsequent hydrolysis of the pyrophosphate (cf. ref 12).

We attempted to use the hydroxamic acid test in the detection of an acyl phosphate[17] as an intermediate in the reaction of *n*-dodecyl

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Table I. Reaction of *p*-Nitrophenyldiphenyl Phosphate with a Monoalkyl Phosphate Dianion[a]

10^2 [$ROPO_3^{2-}$], M	R	
	n-Bu	*n*-$C_{12}H_{25}$
0.18		5.25
1.35		5.64 (3.0)
1.80		5.60 (3.36)
2.70		10.90 (8.16)
4.50	5.85	
5.00	6.6	
7.50	7.1	
10.0	7.7	

[a] Values of $10^5 k_\psi$, s^{-1} in 0.01 M borate buffer at pH 9.1 and 25.0 °C. The values in parentheses are k_M.

Table II. Inhibition of the Reaction of *p*-Nitrophenyldiphenyl Phosphate with Fluoride Ion[a]

10^2 [NaDodP], M	$10^4 k_\psi$, s^{-1}
	9.65
0.40	7.14
0.75	6.35
1.00	5.75
1.50	5.60
2.00	4.48

[a] At 25.0 °C with 0.01 M NaF and borate buffer at pH 9.13.

phosphate dianion with III. The test was positive, but we can draw no conclusions from this observation because it was also positive with III under our experimental conditions, but in the absence of NaDodP.

Results

Reaction of *p*-Nitrophenyldiphenyl Phosphate (I). Reaction of nucleophiles with I in the absence of cationic micelles is considered first. *n*-Butyl phosphate has a small effect upon the rate constant of decomposition of I which is ca. 5×10^{-5} s^{-1} in the absence of added reagent, showing that the alkyl phosphate dianion is a relatively ineffective nucleophile in water (Table I). (In this table, k_M is the first-order rate constant for reaction of NaDodP.) There is a linear relation between k_ψ and the concentration of *n*-butyl phosphate, and the second-order rate constant is 4×10^{-4} M^{-1} s^{-1}, which is similar to the value for inorganic and phenyl phosphate.[12] Micelles of NaDodP (Table I) have two effects, (1) they inhibit reaction with hydroxide ion and (ii) they may speed reaction by attacking the substrate nucleophilically, and to separate these two effects we need to know how much substrate is incorporated into micelles of NaDodP.

We cannot examine incorporation directly, but the reaction with fluoride ion is inhibited by NaDodP (cf. ref. 11), which must therefore be incorporating the substrate (Table II). The reaction with fluoride ion is much faster than the other reactions, and we will neglect them.

Assuming that fluoride ion does not react with substrate in the dianionic micelles of NaDodP, we estimate the binding constant K in terms of micellized NaDodP[11] in Scheme I, where subscript m denotes micellized material and k_W is the rate constant in the absence of the micelle. (In earlier formulations, K was written as a binding constant to the micelle.) Scheme I gives eq 1.[11]

$$(k_W - k_\psi) - 1 = K([\text{NaDodP}] - \text{cmc}) \quad (1)$$

This treatment gives $K = 55$, which is very much smaller than the binding constants in CTABr or sodium lauryl sulfate.[11] It may be too low to the extent that we neglect reaction of NaDodP with the substrate, which would increase the value of k_ψ. The kinetically estimated cmc is 4×10^{-3} M, which is much smaller than in water, showing that the hydrophobic substrate markedly reduces the cmc.[11]

Scheme I

$$(\text{NaDodP})_m + I \rightleftharpoons I_m$$

$$I_m \xrightarrow{F^-} \text{products}, \quad I \xrightarrow{k_w, F^-} \text{products}$$

We use this binding constant to separate the inhibiting and catalyzing effects of micelles of NaDodP, by assuming that micellar incorporated substrate will not react with hydroxide ion. The observed first-order rate constant is given by:

$$k_\psi = k_W(1 - \alpha) + k_M\alpha \quad (2)$$

where α is the fraction of substrate in the micelle and k_W and k_M are the first-order rate constants for reactions in the water and the micelle, respectively. The values of α are calculated using the binding constant of 55 and the cmc is determined from inhibition of the fluoride ion reaction, and we obtain the corrected values of the first-order rate constant, k_M, for reaction in micelles of NaDodP (Table I). These rate constants are approximate, but they show that micelles of NaDodP are not effective nucleophiles even though they incorporate the substrate. It is unfortunate that we were unable to use higher concentrations of NaDodP, but it readily forms liquid crystals under the reaction conditions.

The situation is different for reaction in the presence of CTABr or dodecyltrimethylammonium bromide (DodTABr), where there is considerable rate enhancement for attack of 0.002 M NaDodP or *n*-butyl phosphate. These phosphates have two effects: (i) as nucleophiles they attack the substrate and (ii) they inhibit the attack of hydroxide ion. This second effect is less important than the first, but our estimates of the rate enhancements by the alkyl phosphate dianions are low because of neglect of this inhibition.

The rate enhancements on addition of 0.002 M NaDodP are by factors of approximately 40 for DodTABr and 9 for CTABr, at pH 8.5, as compared with the maximum rate constants in the cationic micelles. These rate enhancements are similar to but larger than those obtained on addition of aryl phosphate dianions to CTABr.[12] For reactions with NaDodP the rate maxima are observed when the concentration of cationic surfactant is approximately twice that of NaDodP, i.e., when the charge of the ammonium ion approximately neutralizes that of the alkyl phosphate dianion. Earlier work shows that a hydrophobic substrate such as I should be almost completely micellar bound in $2–3 \times 10^{-3}$ M CTABr,[11] so that under these conditions both the substrate and the alkyl phosphate should be in the micellar pseudophase.

For lower concentrations of cationic surfactant the micelle will have a net negative charge, and the results in Table I suggest that the rate constant should decrease as the micelle becomes anionic, but at concentrations of cationic surfactant greater than 4×10^{-3} M addition of further surfactant merely decreases the concentration of NaDodP in the micelle, so that the rate constant decreases (cf. ref 6 and 7).

This explanation presupposes that the hydrophobic *p*-nitrophenyldiphenyl phosphate is almost completely micellar bound at ca. 2×10^{-3} M cationic surfactant, but if NaDodP decreases the substrate binding this effect would contribute to the decrease of k_ψ as the concentration of cationic surfactant (CD) is reduced below the optimum (Figure 1).

The binding constant of I to micellized CTABr is not known, but binding constants of greater than 10^4 have been estimated toward sodium lauryl sulfate,[11] so that it is probable that the bulk of the substrate is micellar bound under our reaction conditions.

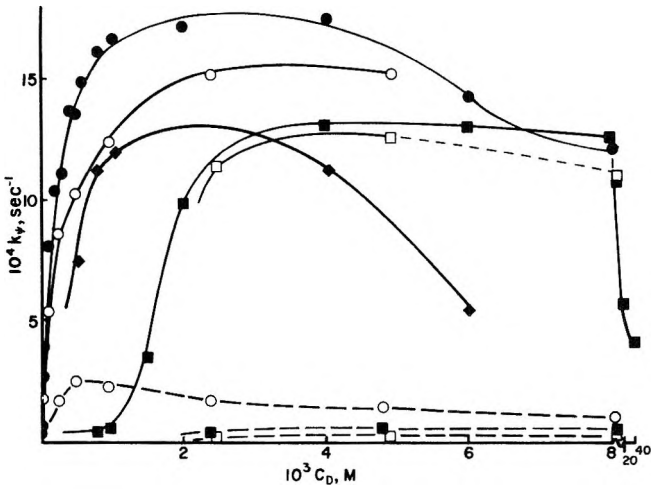


Figure 1. Micellar effects on the dephosphorylation of *p*-nitrophenyldiphenyl phosphate (I). The solid points are at pH 9.1 and the open points are at pH 8.5. The dashed lines denote reactions in the absence of alkyl phosphate. (●, ○) CTABr; (■, □) DDTABr; (♦) CTABr + 2×10^{-3} M *n*-$BuOPO_3Na_2$.

Table III. Reaction of 2,4-Dinitrophenyl 3-Phenylpropionate in Alkyl Phosphate Dianion[a]

	R	
10^2 [$ROPO_3^{2-}$], M	*n*-Bu	*n*-$C_{12}H_{25}$
0.5		1.26
0.8		1.28
0.9		1.30
1.8	4.21	
3.7		1.06
4.5	4.91	
10.0	5.71	

[a] Values of $10^3 k_\psi$, s^{-1} at 25.0 °C in 0.01 M borate buffer, pH 9.13; in the absence of added alkyl phosphate, $k_\psi = 1.7 \times 10^{-3}$ s^{-1}.

n-Butyl phosphate dianion is also an effective reagent when incorporated into micelles of CTABr, and its behavior is very similar to that of aryl phosphate dianions. It is not as effective a reagent as NaDodP, and the maximum rate is obtained with a lower concentration of CTABr than that required for NaDodP, which is understandable if the rate maximum is reached with an electrically neutral micelle, because *n*-butyl phosphate should bind less strongly than NaDodP.

Deacylation of 2,4-Dinitrophenyl 3-Phenylpropionate. The deacylation of 2,4-dinitrophenyl 3-phenylpropionate (III) is speeded up by added *n*-butyl phosphate (Table III), but the effect is small, as expected from the relatively low nucleophilicity of inorganic phosphate in deacylation.[18] However, added NaDodP slightly inhibits the reaction (Table III), suggesting that the substrate is being taken up into the anionic micelles which block attack by hydroxide ion, and this inhibition overcomes any catalysis by nucleophilic attack of the phosphate dianion.

Cationic micelles of CTABr effectively catalyze the deacylation (Table IV), and the 50-fold rate enhancement is similar to those found using *p*-nitrophenyl esters of hydrophobic alkane carboxylic acids,[3-5] and there is a rate maximum at 10^{-3} M CTABr which can be interpreted in terms of a distribution of reagents between water and micelle. This catalysis is reduced by both *n*-butyl and *n*-dodecyl phosphate dianion, with the latter being much more effective. Thus, in deacylation the phosphate dianions are such poor nucleophiles, relative to the hydroxide ion, that any nucleophilic contribution by them is more than offset by their inhibition of the reaction of hydroxide ion. In 10^{-2} M CTABr the value of k_ψ decreases sharply on the addition of a small amount of NaDodP and then remains approximately constant, suggesting that reaction with hydroxide ion has been largely suppressed and that we are following deacylation by the dodecyl phosphate dianion. If this hypothesis is correct, the nucleophilicity of NaDodP is enhanced by micellization (cf. Tables III and IV). However, in these buffered systems the micelles may introduce complications due to changes in buffer equilibria.

Other examples of inhibition of deacylation by micelles of weakly nucleophilic anions are reactions of *p*-nitrophenyl esters in the presence of *n*-alkyl carboxylate and bile salt micelles.[19] (Carboxylate ions are poorer nucleophiles than phosphates in deacylation.[18])

Discussion

Micellar Charge and Catalysis. Although phosphate dianions are effective nucleophiles toward phosphoryl groups, micelles and NaDodP are not particularly effective dephosphorylating agents. For example, under conditions in which I is over 50% micellar incorporated the first-order rate constant for dephosphorylation in the micelle is only 8×10^{-5} s^{-1} (Table I), but in comicelles of CTABr and NaDodP we observe an approximately 100-fold rate enhancement at pH 9.1 over the rate in water, and the rate constant is ca. 170×10^{-5} s^{-1} (Figure 1). This difference seems too large to be explained in terms of substrate incorporation in the micelles, suggesting that it is due in part to transition-state interactions.

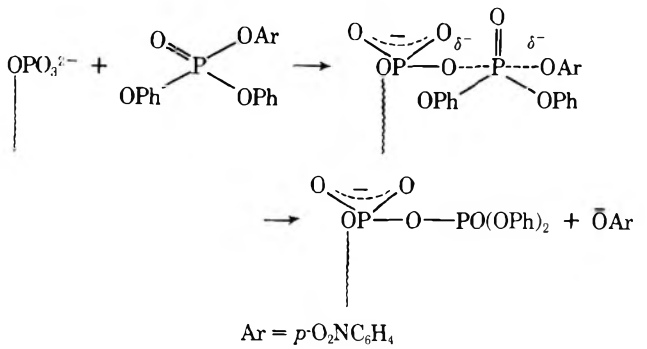
The transition state for dephosphorylation of *p*-nitrophenyldiphenyl phosphate is anionic, and because of its dispersed charge there should be strong coulombic attractions with the quaternary ammonium head groups in a cationic micelle, but the interactions will be unfavorable for reaction carried out in an anionic micelle of NaDodP (Scheme II).

Table IV. Reaction of 2,4-Dinitrophenyl 3-Phenylpropionate in CTABr and Monoalkyl Phosphate Dianion[a]

		10^3 [$ROPO_3^{2-}$], M				
10^3 [CTACBr], M		5.0[b]	2.5[c]	5.0[c]	7.5[c]	10.0[c]
0.5	60.5	28.1				
0.75		39.7				
1.0	89.5	48.3		5.90		
1.5	82.7					
3.0				7.36		
5.0	53.7	33.4		9.64		
6.67				11.5		
10.0	43.2		11.9	12.0	11.3	11.2
15.0	43.1					
30.0				13.7		

[a] Values of $10^3 k_\psi$, s^{-1}, in 0.01 M borate buffer, pH 9.1; in the absence of CTABr, $k_\psi = 1.7 \times 10^{-3}$ s^{-1}. [b] *n*-$BuOPO_3^{2-}$. [c] *n*-$C_{12}H_{25}OPO_3^{2-}$.

Scheme II



Ar = p-$O_2NC_6H_4$

The situation is different for deacylation in a micellized amine.[10] Reactions with nonmicellized amines are general base catalyzed, and both water- and amine-catalyzed reactions have been identified in reactions of micellized n-alkylamines with carboxylic esters, suggesting that a proton is transferred from nitrogen in the transition state and a micellized alkylamine could function very effectively as the base.

These observations suggest that micellar catalysis of bimolceular reactions depends on the bringing together of the reactants at the micellar surface prior to reaction, but that unfavorable coulombic interactions between the head groups and the transition state can prevent reaction, even though the reactants are taken up by the micelle. This conclusion should apply to reactions in both chemically inert and functional micelles, and it is consistent with the treatment of micelles as if they behave as a separate phase with their own solvent properties. We also note that micellar effects upon unimolecular reactions are wholly due to free-energy differences between initial and transition states.[20]

Registry No.—I, 10359-36-1; n-$BuOPO_3Na_2$, 64114-42-7; NaDodP, 7423-32-7; NaF, 7681-49-4; 2,4-dinitrophenyl-3-phenylpropionate, 23522-80-7; CTABr, 57-09-0; DodTABr, 1119-94-4.

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Photoinduced Decomposition of Peracetic Acid in Toluene

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A mixture of peracetic acid and toluene has been photolyzed at room temperature. The main products with 2537-Å light were carbon dioxide, methane, ethane, methanol, ethylbenzene, o-, m-, and p-xylenes, and bibenzyl together with smaller amounts of benzyl alcohol and o-, m-, and p-cresols. On the other hand, with light over 2900 Å, different yields of benzyl alcohol (a main product) and cresols (undetectably small) were observed. The effects of concentration of peracid on yields were studied, and the mechanism and reactivities of methyl and hydroxyl radicals were discussed.

The photolysis of a mixture of peracetic acid and toluene is of particular interest because of the possibility of reaction both with aliphatic and aromatic parts of the toluene molecule. The vapor-phase pyrolysis of peracetic acid in a stream of toluene was reported to involve both radical and wall reactions,[1b] while the thermolysis in liquid phase involves the two simultaneous reactions.[2] The photolysis of peracetic acid in cyclohexane gives cyclohexanol.[3]

As to the reaction of methyl radical with toluene both in the liquid and gas phases, evidences were presented for both addition to the ring and abstraction of hydrogen atom to form methane.[4-7] But there is little information on the yields of the other products besides gaseous products. The reaction of a hydroxyl radical with toluene gives cresols and bibenzyl.[8]

The present paper reports on the photolysis of peracetic acid in toluene. The mechanism of decomposition and the behavior of the produced radicals, i.e., CH_3· and HO· were discussed on the basis of the products analysis.

Results

The photolysis products from peracetic acid in toluene were carbon dioxide, methane, ethane, methanol, methyl acetate, ethylbenzene, xylenes, benzyl alochol, benzaldehyde, cresols, bibenzyl, and a trace of benzoic acid with quartz filter (2537-Å light). An almost similar distribution of products was also obtained with Pyrex-filtered light (>2900 Å), except for a marked decrease in the yield of cresols and an increase of the yield of benzyl alcohol.

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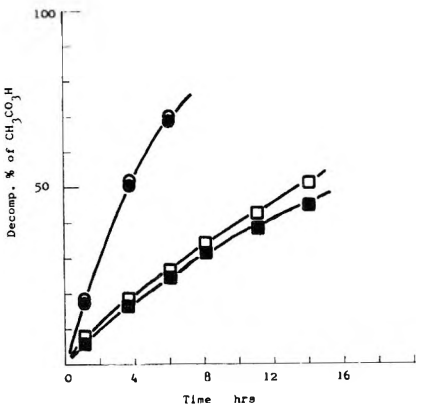


Figure 1. Time dependence of decomposition % estimated by evolved CO_2: (○) measured by iodometry with 2537-Å light, (●) by CO_2 evolution with 2537-Å light, (□) by iodometry with >2900-Å light, and (■) by CO_2 evolution with >2900-Å light. Initial concentration of peracid = 5.00 mmol/25 mL.

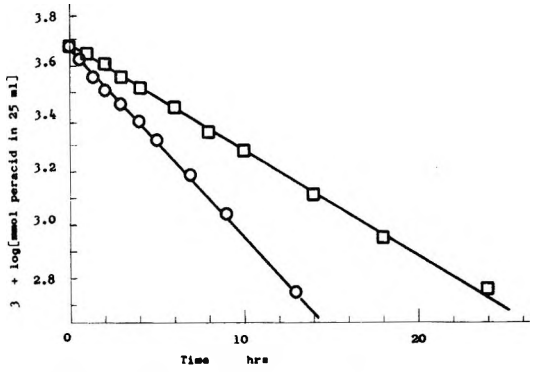


Figure 2. Kinetics of the overall decomposition of peracetic acid: (○) 2537-Å light irradiation, (□) >2900-Å light irradiation. Initial concentration of peracid = 4.58 mmol/25 mL.

Relation between Peracetic Acid Decomposition and CO_2 Evolution. The yield of CO_2 from peracetic acid was measured to see the mode of photolysis. As shown in Figure 1, the photolysis with 2537-Å light is only a radical decomposition giving CO_2, CH_3·, and HO·, while with >2900-Å light the photolysis proceeds 90% via the radical but 10% via the other mode of decomposition.

The rate of the overall decomposition was first order in peracetic acid (Figure 2), and, hence, [CH_3CO_3H decomposed] = [CO_2 formed] with 2537-Å light, while [CH_3CO_3H decomposed] = [CO_2 formed] + [CH_3CO_2H formed] with >2900-Å light, where [ ] means the molar amount of each compound.

Time Dependence of the Product Yields. The time dependence of product yield and the possibility of further reactions were studied and the yields which vary little with time except for methanol and benzyl alcohol are shown in Figures 3 (2537 Å) and 4 (>2900 Å). Methanol initially formed is partially esterified to methyl acetate with acetic acid originally present, while benzyl alcohol is partially oxidized to benzaldehyde.

The 2537-Å photolysis products with a methyl radical, i.e., ethylbenzene and xylenes, have a higher yield than the products with a hydroxyl radical, i.e., benzyl alcohol and cresols. A remarkable difference between 2537- and >2900-Å light photolysates is the higher yields of benzyl alcohol and bibenzyl and the lower yields of cresols with >2900-Å light.

Effect of Initial Concentration of Peracetic Acid on Product Yield. The effects of the concentrations of peracetic acid and produced radicals on the yield were measured to

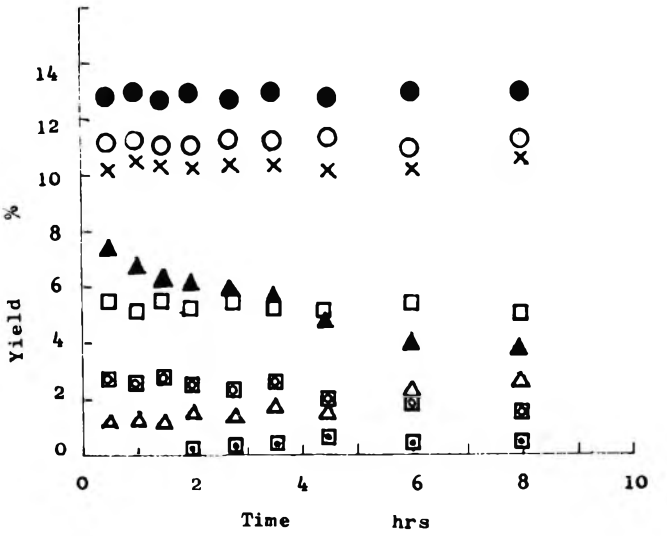


Figure 3. Time dependence of product yields with 2537-Å light decomposition. The yield means the value of the mole of formed compound vs. the mole of decomposed peracid. Initial concentration of peracid = 5.13 mmol/25 mL, decomposition (8 h) = 80%: (▲) methanol, (△) methyl acetate, (○) ethylbenzene, (●) xylenes, (×) bibenzyl, (□) benzyl alcohol, (⊡) benzaldehyde, (□) cresols.

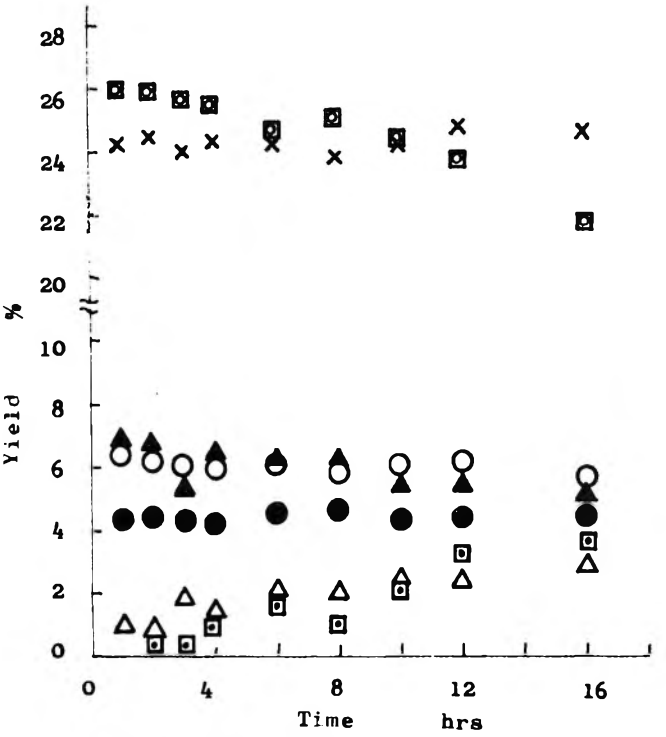


Figure 4. Time dependence of product yields with 2900-Å light decomposition. The yield means the value of the mole of formed compound vs. the mole of decomposed peracid. Initial concentration of peracid = 4.69 mmol/25 mL, decomposition (16 h) = 72%: (▲) methanol, (△) methyl acetate, (○) ethylbenzene, (●) xylenes, (×) bibenzyl, (□) benzyl alcohol, (⊡) benzaldehyde.

study the reactivities of methyl and hydroxyl radicals and are shown in Tables I (2537 Å) and II (>2900 Å). Table I leads to eq 1, where [CO_2 evolved] ≈ [methyl radical], i.e.

$$[CH_4 + 2C_2H_6 + CH_3OH + CH_3CO_2CH_3 + PhEt + xylenes] \approx [CO_2] \text{ or } [CH_3\cdot] \quad (1)$$

The yield of methane is 35–45% and that of ethane is ca. 32% per methyl radical, and the yields of methanol and methyl acetate increase with an increase of initial concentration of

Table I. Effect of Peracetic Acid Concentration on the Yield of Products with 2537-Å Light

$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	Product × 10^4 mol (%)[b]									
		CH_4	C_2H_6	CH_3OH	$CH_3CO_2CH_3$	PhEt	Xylene[c]	$PhCH_2OH$	PhCHO	Cresol[c]	$(PhCH_2)_2$
3.51	54.4	18.5	8.61	3.16	2.65	7.04	7.49	1.77	0.39	1.64	1.90
		(34.5)	(31.6)	(5.8)	(4.9)	(12.9)	(13.7)	(3.3)	(0.7)	(3.0)	(7.0)
2.00	43.7	16.0	7.31	1.69	1.57	4.69	5.99	0.75	0.24	2.10	2.37
		(36.0)	(33.5)	(3.9)	(3.6)	(10.7)	(13.7)	(1.7)	(0.5)	(4.8)	(10.8)
1.81	30.5	11.3	5.00	1.03	0.76	3.31	3.70	0.44	0.09	1.47	1.64
		(37.0)	(32.3)	(3.8)	(2.1)	(10.9)	(12.1)	(1.4)	(0.3)	(4.8)	(10.7)
0.65	13.8	5.62	2.20	0.34	0.20	1.23	1.71	0.31	0.04	0.76	1.11
		(40.8)	(31.9)	(2.5)	(1.4)	(8.9)	(12.5)	(2.2)	(0.3)	(5.5)	(16.0)
0.37	7.23	3.25	1.19	0.13	0.06	0.63	0.75	0.16	trace	0.45	0.53
		(45.0)	(33.0)	(1.8)	(0.8)	(8.9)	(10.8)	(2.2)	(trace)	(6.1)	(14.6)

[a] Amount of sample is 25 mL. [b] (Moles of product/moles of decomposed peroxide) × 100, except for ethane and bibenzyl where this number is doubled. [c] The total amounts of ortho, meta, and para isomers.

Table II. Effect of Peracetic Acid Concentration on the Yields of Products with >2900-Å Light

$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	Product × 10^4 mol (%)[b]									
		CH_4	C_2H_6	CH_3OH	$CH_3CO_2CH_3$	PhEt	Xylene[c]	$PhCH_2OH$	PhCHO	Cresol	$(PhCH_2)_2$
4.71	51.3	30.4	3.27	2.74	1.64	2.06	2.39	11.3	1.93		2.76
		(59.3)	(12.8)	(5.3)	(3.2)	(4.0)	(4.7)	(22.9)	(3.8)		(10.8)
3.77	45.0	29.0	2.27	2.45	1.90	1.75	1.66	10.1	1.70		2.75
		(64.5)	(10.0)	(5.4)	(4.2)	(3.9)	(4.2)	(22.4)	(3.8)		(12.2)
2.74	34.2	21.2	2.24	0.97	0.67	1.63	1.40	7.60	2.02		2.97
		(62.1)	(13.0)	(2.8)	(2.0)	(4.8)	(4.6)	(22.2)	(5.9)		(17.4)
1.87	23.2	14.0	1.30	1.06	0.43	1.38	1.02	5.83	1.40		2.82
		(59.9)	(11.6)	(4.5)	(1.9)	(5.9)	(4.4)	(24.9)	(6.0)		(24.1)
1.06	11.6	7.19	0.66	0.44	0.10	0.92	0.70	2.77	0.53		1.60
		(61.7)	(11.4)	(3.8)	(0.9)	(7.9)	(6.0)	(23.7)	(4.6)		(28.7)
0.68	8.90	5.26	0.46	0.39	0.11	0.65	0.65	1.82	0.29		1.17
		(59.4)	(10.4)	(4.4)	(1.2)	(6.7)	(6.7)	(20.5)	(3.3)		(26.4)

[a] Amount of sample is 25 mL. [b] (Moles of product/moles of decomposed peroxide) × 100, except for ethane and bibenzyl where this number is doubled. [c] The total amounts of ortho, meta, and para isomers.

Table III. Effect of Peracetic Acid Concentration on the Yield

	2537-Å light		>2900-Å light	
$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	H_2O × 10^4 mol (%)	$[CH_3CO_3H$ decomposed] × 10^4 mol	H_2O × 10^4 mol (%)
5.08	85.9	25.5 (29.7)	73.1	9.14 (12.5)
2.86	59.0	16.3 (27.6)	48.1	7.94 (16.5)
2.13	45.4	13.8 (30.3)	36.3	6.82 (18.8)
0.94	20.4	5.00 (24.5)	16.5	2.57 (15.6)
0.39	7.80	2.06 (26.4)	7.10	1.58 (22.2)

[a] Initial concentration.

peracid, where methyl acetate is derived from direct photolysis and/or esterification of methanol, whereas the yields of ethylbenzene and xylenes are almost constant and isomer composition of xylenes decreases in the order: meta > ortho > para. In contrast, the yields of hydroxylation products are lower than those of methylation, the isomer composition of cresols being in the order: ortho > para > meta.

Equation 1 is valid with >2900-Å light, but, based on the amount of decomposed peracid, eq 2 is more appropriate.

$$[CH_4 + 2C_2H_6 + CH_3OH + CH_3CO_2CH_3 + PhEt + \text{xylenes}] \approx 0.9[CH_3CO_3H \text{ decomposed}] \quad (2)$$

The yields of methane and ethane per decomposed peracid are ca. 60 and 11%, respectively; the yields of ethylbenzene and xylenes decrease only by ca. 2–3% with increasing concentration of peracid. The isomer distribution of xylenes decreases in the order ortho > meta > para at a higher concentration of peracid. The yield of benzyl alcohol based on the decomposed peracid is 20–25% and that of benzaldehyde is 3–6%; the yields of cresols are very low.

A similar effect of peracid concentration on the yield of bibenzyl was observed; i.e., an increase of peracid concentration caused a decrease in the yield, especially with >2900-Å light.

Analysis of Water Produced by Photolysis. A hydroxyl radical formed by direct photolysis of peracid may also abstract a H atom from both toluene and peracetic acid to give water and it may couple with each other to H_2O_2 which then decomposes thermally to H_2O and O_2.

The analysis of water was done by means of GLC with a thermal-conductivity detector (TCD) under similar experimental conditions, and the results are shown in Table III, although the analysis by TCD is less accurate than that by FID. The yields of water per decomposed peracid were 25–30% at 2537 Å and 15–20% at >2900 Å. The observed difference of yields at 2537 and >2900 Å may be due to the difference of HO· radical concentration.

Discussion

Initial Process of Decomposition. In view of the extinction coefficients of toluene and peracetic acid shown in Table IV, the 2537-Å light should be absorbed predominantly by

Table IV. Extinction Coefficient at Various Wavelengths

Compd	ϵ_{240}, nm	ϵ_{254}, nm	ϵ_{290}, nm	ϵ_{300}, nm	ϵ_{360}, nm
$PhCH_3$		170	0.025		
CH_3CO_3H	25[a]		2.40[b]	1.23[b]	0.046[b]

[a] Data by O. H. Wheeler and L. A. Kaplan, "Organic Electron Spectral Data", Vol. 3, Interscience, New York, N.Y., 1966. [b] The value obtained in CH_3OH containing a small amount of acetic acid whose extinction coefficient is negligible at over 290 nm.

toluene, since its extinction coefficient is ca. ten times as large as that of peracid and toluene is in large excess. Then excited toluene transfers energy to peracid, producing two radicals (eq 3–5).

$$PhCH_3 \xrightarrow{h\nu\ (2537\ Å)} [PhCH_3]^* \quad (3)$$

$$[PhCH_3]^* + CH_3CO_3H \rightarrow PhCH_3 + [CH_3CO_3H]^* \quad (4)$$

$$[CH_3CO_3H]^* \rightarrow CH_3CO_2\cdot + \cdot OH \rightarrow CH_3\cdot + CO_2 + \cdot OH \quad (5)$$

$$CH_3CO_3H \xrightarrow{h\nu\ (>2900\ Å)} CH_3CO_2\cdot + \cdot OH \rightarrow CH_3\cdot + CO_2 + \cdot OH \quad (6)$$

In fact, Stern–Volmer plots in quenching fluorescence of toluene by peracetic acid are shown in Figure 5, in which a fairly good linearity was observed. The rate constant for quenching (k_q) was $1.71 \times 10^{10}\ M^{-1}\ s^{-1}$. Therefore, the excited (singlet) toluene may transfer energy to peracid at the diffusion-controlled rate.

On the other hand, the >2900-Å irradiation excites mainly peracetic acid, resulting in the O–O cleavage (eq 6) because the extinction coefficient of peracid is much higher than that of toluene at >2900 Å.

The radical concentration of eq 3–5 may be greater than that of eq 6, since the O–O cleavage via eq 3–5 should be faster, because the decomposition rate by eq 3–5 is much faster than that by eq 6, as shown in Figure 2. This faster rate is due to the higher extinction coefficient of toluene than that of peracetic acid and is also due to the presence of a large excess of toluene.

Induced Decomposition of Peracid by Radicals. Two sorts of radicals ($CH_3\cdot$ and HO·) formed initially in eq 5 and 6 may induce following propagation (eq 7–9):

$$PhCH_3 + R\cdot \rightarrow PhCH_2\cdot + RH \quad (7)$$

$$CH_3CO_3\text{-}H + R\cdot \rightarrow CH_3CO_3\cdot + RH \quad (8)$$

$$CH_3CO_2\text{-}OH + CH_3\cdot \rightarrow CH_3CO_2\cdot + CH_3OH \quad (9)$$

(R· = $CH_3\cdot$ and HO·)

The benzyl radical formed in eq 7 may take part in eq 8 and 9. When R· is $CH_3\cdot$, eq 7 and 8 give methane and eq 9 gives methanol. When R· is HO·, water is produced by eq 7 and 8; H_2O_2 may also be formed by coupling of HO· (eq 10). The H_2O_2 formed may decompose to water and oxygen (eq 11).

$$2HO\cdot \rightarrow H_2O_2 \quad (10)$$

$$H_2O_2 \rightarrow H_2O + 0.5O_2 \quad (11)$$

Therefore, water may be produced from one or two HO· radicals, and hence the total moles of HO· radicals yielding water is larger than the total moles of produced water.

In the 2537-Å photolysis, total yields of methane and water (from Tables I and III) are 60–70% per decomposed peracid,

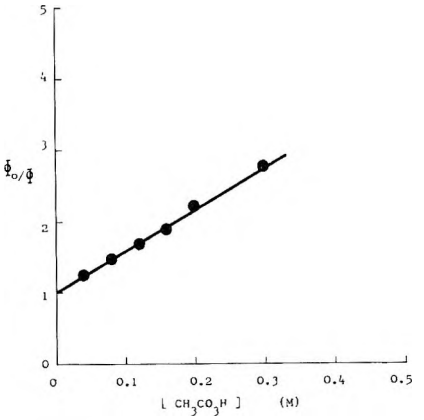


Figure 5. Stern–Volmer plot for quenching of the singlet state of toluene by peracetic acid. Slope ($k_q\tau$) = 5.83, $k_q = 1.71 \times 10^{10}\ M^{-1}\ s^{-1}$, where k_q is the quenching rate constant and τ is the lifetime of lowest singlet state. The value of τ (3.4×10^{10} s) was quoted from S. L. Murov, "Handbook of Photochemistry", Marcel Dekker, New York, N.Y., 1973.

and total yields of products from toluene are ca. 40%. The results suggest that $CH_3\cdot$ and HO· radicals must abstract a H atom from peracid as *tert*-butoxy radical does,[9] because the quantity of H atoms from toluene is insufficient for total yields of methane and water.

This assumption is further confirmed in the >2900-Å photolysis; i.e., even the yield of methane alone (ca. 60%) is greater than total yields of products from toluene (45–60%). In view of the yields of water (ca. 15%), eq 8 must contribute to the extent of 15–30% for decomposition of peracid. Therefore, assuming an occurence of a dark reaction of ca. 10% and a benzyl radical-induced reaction (eq 9) of ca. 20% (see below), the contribution of eq 6 for total decomposition of peracid may be below 50% at >2900 Å.

Acetylperoxy radical ($CH_3CO_3\cdot$) in eq 8 should decompose to give $CH_3\cdot$, CO_2, and O_2, and also reacts with $CH_3OO\cdot$ to give CH_3CO_2H and HCHO via various known termination steps.[9] Unfortunately, we have no estimation of formed O_2 and CH_3CO_2H yet, since the original solution contains CH_3CO_2H in a large excess (see Experimental Section).

Formation of Methane and Ethane. Ethane may be formed by radical coupling shown in eq 12 and 13. In view of the faster decomposition rate of acetoxy radical ($1.6 \times 10^{-9}\ s^{-1}$ at 60 °C),[10] ethane may mainly be formed via eq 12.

$$2CH_3\cdot \rightarrow C_2H_6 \quad (12)$$

$$2CH_3CO_2\cdot \rightarrow C_2H_6 + 2CO_2 \quad (13)$$

Table V reveals that $[C_2H_6]/[CO_2]$ (≈0.16 with 2537 Å and ≈0.065 with >2900 Å light) is little affected by peracid concentration, which indicates that the rate of radical formation is in a steady state. The higher yield at 2537 Å may be due to the higher radical concentration. The thermolysis of peracetic acid in toluene gave no ethane, since the reaction gives acetic acid preferentially, and thus methyl radical concentration is lower.[2] The photolysis proceeds via radical reactions because $[CO_2]$/[decomposed peracid] is close to unity. This decomposition is similar to thermolysis of diacetyl peroxide in toluene[6] with $[CH_4]/[CO_2]$ = 0.65–0.78 and $[C_2H_6]/[CO_2]$ = 0.02–0.047 on the basis of a comparable value of $[CH_4]/[CO_2]$ = 0.65–0.74 and $[C_2H_6]/[CO_2]$ = 0.057–0.072 for our reaction at >2900 Å. But the values at 2537 Å are different, which is attributed to either a higher concentration of methyl radical or the effect of an energy transfer from excited toluene.

Hydrogen Abstraction and Addition of Methyl Radical. A methyl radical in the gas phase does not add to the ring, but the addition to the ring is more important in the liquid

Table V. Decomposition of Peracetic Acid in Toluene

Temp °C	$[CH_3CO_3H]^a$ × 10 M	$\frac{CO_2}{[CH_3CO_3H \text{ decomposed}]}$	$\frac{CH_4}{CO_2}$	$\frac{C_2H_6}{CO_2}$	$\frac{CH_4 + C_2H_6}{CO_2}$
Rt[b]	3.51	1.02	0.33	0.16	0.65
Rt[b]	2.00	0.98	0.37	0.17	0.71
Rt[b]	1.81	0.98	0.38	0.17	0.72
Rt[b]	0.65	1.01	0.40	0.16	0.72
Rt[b]	0.37	1.02	0.44	0.16	0.76
Rt[c]	4.71	0.89	0.66	0.072	0.80
Rt[c]	3.77	0.87	0.74	0.058	0.86
Rt[c]	2.74	0.92	0.67	0.071	0.81
Rt[c]	1.87	0.86	0.70	0.068	0.84
Rt[c]	1.06	0.89	0.70	0.064	0.83
Rt[c]	0.68	0.91	0.65	0.057	0.76
74.9[d]	0.14		0.88		
85.0[d]	0.23	0.07	0.72		
94.8[d]	0.14		0.76		
64.9[e]	0.068	0.86	0.78	0.047	0.87
64.9[e]	0.081	0.87	0.66	0.040	0.74
64.9[e]	0.663	1.01	0.67	0.020	0.71
64.9[e]	0.675	0.93	0.65	0.034	0.72

[a] Initial concentration. [b] At room temperature, with 2537-Å light irradiation. [c] At room temperature, with >2900-Å light irradiation. [d] Data summarized for thermal decomposition of peracetic acid by F. W. Evans and A. H. Sehon, *Can. J. Chem.*, **41**, 1826 (1963). [e] Data summarized for thermal decomposition of diacetyl peroxide in toluene by M. Levy and M. Szwarc, *J. Am. Chem. Soc.*, **76**, 5981 (1954).

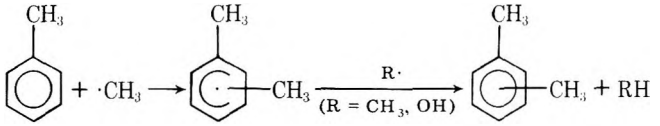
phase.[11] The yields of xylenes (10–14%) increase slightly with an increase of peracid concentration (Table I). The formation of methane is suppressed as the peracid concentration increases; hence, the addition of a methyl radical to the ring and the coupling of a methyl radical with other radicals become important. The yield of CH_3· radical addition at >2900 Å is smaller than that at 2537 Å, and the yields of H abstraction are the reverse order. This difference may be due to the difference in rate of CH_3· radical formation.

A probable mechanism for the formation of methane, ethylbenzene, and xylene is shown in eq 14–17.

$$PhCH_3 + \cdot CH_3 \rightarrow PhCH_2\cdot + CH_4 \quad (14)$$

$$CH_3CO_3\text{-}H + \cdot CH_3 \rightarrow CH_3CO_3\cdot + CH_4 \quad (15)$$

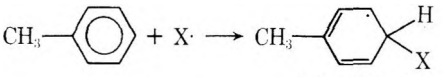
$$CH_3\cdot + PhCH_2\cdot \rightarrow PhCH_2CH_3 \quad (16)$$



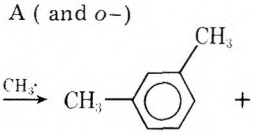
(*o*-, *m*-, *p*-) (17)

In view of the strong aromatic C–H bond as compared to a benzylic C–H bond, the formation of methane via direct abstraction of a ring H atom by a CH_3· radical is unlikely. As stated above, the total yields of methane and water are larger than those of products obtained from toluene. Hence, H abstraction of peracid by CH_3· may occur considerably (eq 15). Ethylbenzene is obtained in yields of 9–13 and 4–8% at 2537 and >2900 Å, respectively, though the photolysis of azomethane in toluene is reported to give enthybenzene in a lower yield than that of *o*-xylene.[11] The observed high yield of ethylbenzene in the liquid phase is explained by the longer life of the benzyl radical and the higher concentration of the CH_3· radical in comparison with the above report.[11]

The formation of xylene may involve addition of a CH_3· radical to the ring followed by H abstraction by other radicals (CH_3· and HC·) (eq 17). The isomer content of xylenes is in the order: meta > ortho > para at 2537 Å and ortho > meta > para at >2900 Å (Table VI). The electrophilic addition to the ground-state toluene (>2900 Å) predicts the order ortho > meta, para, and the order agrees at least with the higher yield of ortho isomer at >2900 Å, which is also in accord with the result of the photolysis of azomethane in toluene[11] and of the thermolysis of diacetyl peroxide[12] with the order ortho > meta > para. On the other hand, the frontier electron density in the excited toluene calculated by the CI method predicts the order meta > para,[13] which is in accord with our observation at 2537 Å. Another explanation of *m*-xylene formation is shown in eq 18.



A (and *o*–)



(18)

m-xylene

(X = CH_3CO_2, HO, and/or $PhCH_2$)

The release of a radical by the attack of another radical in the transition state (A) is reported when the attacking radical is a benzoyloxy radical.[14–16] But no evidence for the presence of A and its derivatives was obtained now in these photolyses.

The Reaction of Hydroxyl Radical with Toluene. There are four possible mechanisms for the formation of benzyl alcohol, i.e., coupling (eq 19), the "induced reaction" (eq 20), a toluene–peracid complex decomposition (eq 21), and a toluene–molecular oxygen complex (eq 22).

$$PhCH_2\cdot + \cdot OH \rightarrow PhCH_2OH \quad (19)$$

$$PhCH_2\cdot + CH_3CO_2\text{-}OH \rightarrow PhCH_2OH + CH_3CO_2\cdot \quad (20)$$

$$[PhCH_3 \cdot CH_3CO_3H]^*_{complex} \rightarrow PhCH_2OH + CH_3CO_2H \quad (21)$$

$$[PhCH_3 \cdot O_2]^*_{complex} \rightarrow PhCH_2OH + PhCHO + PhCH_2OOH[17] \quad (22)$$

Equation 22 is negligible because neither PhCHO nor $PhCH_2OH$ is detectable in the absence of peracid and the ratio $[PhCH_2OH]/[PhCHO]$ is over 3; in contrast to the literature value (below 1),[17] the yield of PhCHO increases with time. Equation 21 can also be eliminated, because eq 21 evolves no CO_2.

In spite of the lower concentration of HO·, the yield of $PhCH_2OH$ at >2900 Å is considerably larger than that at 2537 Å. Hence, the major process for formation of $PhCH_2OH$ at >2900 Å may be a reaction induced by $PhCH_2$· (eq 20), as exemplified by the photolysis of peracetic acid in cyclohexane leading to cyclohexanol,[3] where the participation of eq 19 is small. The yield of $PhCH_2OH$ is only a few percent, though the concentration of HO· is high at 2537 Å. Therefore, at low radical concentration, the longer-lived $PhCH_2$· compared with CH_3· and HO· plays an important role for the formation of $PhCH_2OH$.

In the 2537-Å photolysis, eq 19 becomes more important in comparison with >2900-Å photolysis, since [HO·] is higher at 2537 Å.

Cresols, which may be produced via an attack of HO· on toluene (eq 23), were favored at 2537 Å. The trace formation of cresols at >2900 Å is attributable to low HO· concentration (eq 6) on account of the consumption of peracid in eq 7–9 and 20 as stated above. The less formation of hydroxyl compounds ($PhCH_2OH$ and cresols) compared with methyl compounds

Table VI. The Isomer Distribution of Xylene

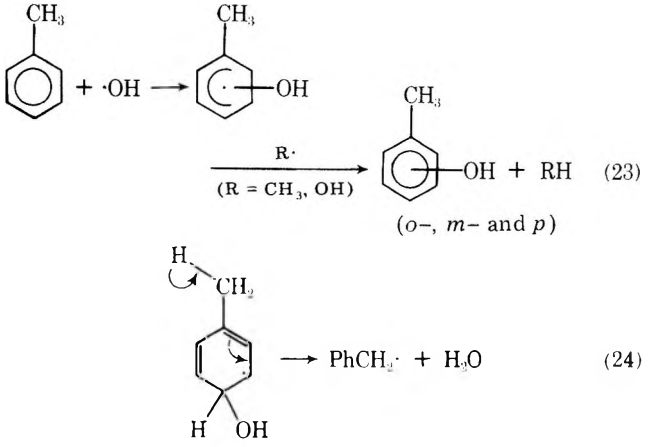
$[CH_3CO_3H]^a$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	Xylene × 10^4 mol (orientation %) o-	m-	p-	$[CH_3CO_3H]^b$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	Xylene × 10^4 mol (orientation %) o-	m-	p-
3.51	54.4	2.64	4.19	0.66	4.71	51.3	1.36	0.78	0.25
		(35)	(56)	(9)			(57)	(32)	(11)
2.00	43.7	1.95	3.34	0.70	3.77	45.0	0.95	0.53	0.18
		(33)	(56)	(11)			(57)	(32)	(11)
1.81	30.5	1.15	2.08	0.47	2.74	34.2	0.84	0.38	0.18
		(31)	(56)	(13)			(60)	(27)	(13)
0.65	13.8	0.53	0.94	0.24	1.87	23.4	0.56	0.32	0.14
		(31)	(55)	(14)			(55)	(31)	(14)
0.37	7.23	0.27	0.40	0.08	1.06	11.6	0.34	0.24	0.12
		(36)	(53)	(11)			(49)	(34)	(17)

[a] Irradiation with 2537-Å light. [b] Irradiation with >2900-Å light.

Table VII. The Isomer Distribution of Cresols in the Photolysis with 2537-Å Light

$[CH_3CO_3H]$ × 10 M	$[CH_3CO_3H$ decomposed] × 10^4 mol	Cresol × 10^4 mol (orientation %) o-	m-	p-
3.54	54.4	0.97	0.17	0.50
		(59)	(10)	(31)
2.00	43.7	1.23	0.12	0.75
		(59)	(6)	(35)
1.81	30.5	0.85	0.09	0.53
		(58)	(6)	(36)
0.65	13.8	0.45	0.05	0.26
		(59)	(7)	(34)
0.37	7.23	0.30	trace	0.15
		(67)		(33)

(PhEt and xylenes) at 2537 Å is attributable to its more effective radical abstraction from peracetic acid (eq 8 and 9) and from toluene by HO· than by CH_3· leading to the lower concentration of HO· than CH_3·. Further, cresols may give a benzyl radical (eq 24)[8] by acid-catalyzed elimination of water.



The yields of cresols were low (ca. 3–6%) with 2537 Å light, though a high concentration of HO· is expected. Their isomer distribution (o- > p- > m-) (Table VII) is consistent with the electrophilic nature of the HO· radical.[18] The observed difference between xylenes and cresols in their isomer distributions is attributable to the more random attack of the reactive HO· radical, which favors ortho and meta attack in a factor of 2. In fact, the photolysis of H_2O_2 in toluene affords also cresols in the similar distribution of ortho > para > meta.[8]

The Small Cage Reaction of the Formation of Methanol. Methanol may be formed by coupling in or out of a cage (eq 25 and 26, respectively) and/or by the reaction of a CH_3· radical with peracid (eq 27).

$$[CH_3\cdot + CO_2 + \cdot OH]_{cage} \rightarrow CH_3OH + CO_2 \quad (25)$$

$$CH_3\cdot + \cdot OH\ (free) \rightarrow CH_3OH \quad (26)$$

$$CH_3\cdot + CH_3CO_2\text{-}OH \rightarrow CH_3OH + CH_3CO_2\cdot \quad (27)$$

The fact that yield increases with increasing peracid concentration indicates that eq 26 and 27 may be major pathways, though the cage reaction (eq 25) is not eliminated. Equation 26 is less important at >2900 Å because of the low [HO·].

Methyl acetate may be formed by eq 28, 29, and/or 30, but actually reaction 28 and 29 are negligible at 2537 Å because $[CO_2]$/[decomposed peracid] is almost at unity; hence,

$$CH_3CO_2\cdot + \cdot CH_3 \rightarrow CH_3CO_2CH_3 \quad (28)$$

$$CH_3CO_2\text{-}OH + \cdot CH_3 \rightarrow CH_3CO_2CH_3 + \cdot OH \quad (29)$$

$$CH_3OH + CH_3CO_2H \rightarrow CH_3CO_2CH_3 + H_2O \quad (30)$$

esterification with acetic acid present in the starting material (eq 30) is the most probable pathway for methyl acetate. The ratio $[CO_2]$/[decomposed peracid] for >2900 Å is ca. 0.9 and, therefore, ca. 10% of peracid decomposition proceeds via no evolution of CO_2. But a CH_3CO_2· radical should decompose rapidly to form a CH_3· radical and CO_2 rather than eq 28. A similar yield of methanol at >2900 and 2537 Å (Table I and II) may be due to the participation of eq 29 and 30 which also afford methyl acetate.

Finally, an increase of bibenzyl formation with a decrease of peracid concentration may be due to the stability of a $PhCH_2$· radical relative to CH_3· and HO· radicals. Thus, coupling between $PhCH_2$· radicals is preferred to coupling of a $PhCH_2$· radical with the other radicals at lower peracid concentration.

Our results on peracetic acid photolysis show that both CH_3· and HO· may abstract both H of RCO_3-H and HO of RCO_2-OH and that their abstraction reactions compete with toluene-induced photolysis or direct photolysis (eq 3–5 and 6). The induced decomposition of peracid by CH_3· or HO· becomes predominant at >2900 Å, and the direct photolysis is suppressed to below 50% per decomposed peracid.

Experimental Section

Materials. Peracetic acid was prepared by the reaction of $(CH_3CO)_2O$ (205 g) with 60% aqueous H_2O_2 added with concentrated H_2SO_4 (0.5 mL) at 35–40 °C.[19] Toluene was purified by distillation over P_2O_5. A water-free peracetic acid–toluene solution was prepared by the method of Hormer;[20] i.e., 40–50 g of P_2O_5 was suspended in 200 mL of dried toluene and 20–50 mL of 3.0–3.5 M peracetic acid was added slowly under cooling and stirring. After 10–15 min, the solution was filtered and then the mixture of a water-free peracetic acid and toluene was immediately irradiated after the estimation of peracid concentration.

Apparatus. UV spectra were measured by a Hitachi 124 spectrophotometer. GLC analyses were performed on a Yanagimoto gas chromatograph with FID, Model GCG-550F, and on a Yanagimoto gas chromatograph with FID and TCD, Model G 180. A Hitachi RMS-4 gas chromatograph–mass spectrometer was used to determine gaseous products. A Halos low-pressure 30-W Hg lamp and a Halos high-pressure 300-W Hg lamp were used as light sources. All experiments were carried out in a cylindrical quartz vessel (2 × 12 cm) or a cylindrical Pyrex vessel (2 × 12 cm).

Analyses of Gaseous Products. The gaseous products evolved by photolysis were collected in a gas burette (300 mL volume) connected with a capillary tube to the photolysis system. Analysis of CO_2 in the gas, carried out by the measurement of the volume absorbed in 33% aqueous KOH, and then analysis of O_2 were done by measurement with an alkaline pyrogallol solution[21] or a Fieser's solution,[22] in which a little of O_2 was evolved with both 2537- (quartz vessel) and >2900-Å light (Pyrex vessel), but the reproducibility of the analysis of O_2 was poor because of insufficient exclusion of the present O_2 in the initial solution and/or considerable solubility of O_2 in this solution. Gaseous products which remained in the gas burette were analyzed by GC–MS and GLC with two sorts of columns packed with Porapak Type T (80–100 mesh, 2.5 mm × 2 m) and Porapak Type QS (80–100 mesh, 2.5 mm × 2 m), and analyses of mass peaks of CH_4 and C_2H_6 were carried out by the comparison of standard samples.[23] The other CO_2 estimation was carried out by acidimetry of aqueous $Ba(OH)_2$ which had been bubbled by the gas together with N_2 as a carrier gas.

Photolysis of a Mixture of Peracetic Acid and Toluene. A mixture of peracetic acid and toluene was photolyzed in a quartz cell with a 30-W low-pressure Hg lamp or in a Pyrex cell with a 300-W high-pressure Hg lamp through a water-cooling jacket. Gaseous products evolved were analyzed by the above method and the products in the solutions were analyzed by GLC with four sorts of columns (Porapak Type QS, Bentone 34-DIDP, PEG 20M Chamelite CS, and Apiezon Grease L). All peracid which remained in photolyzed solutions were decomposed with $Na_2S_2O_3$ or Na_2SO_3 under cooling (−15 to −20 °C) to remove peracid and then analyzed by GLC. This method gave always reproducible data within experimental error.

Analysis of water was carried out alternatively. After estimation of peracid remained in the solution, a constant amount of Me_2SO–toluene was added to the photolysate to avoid the formation of water by GLC thermolysis, and this solution was analyzed by GLC with TCD (Porapak QS column) in triplicate runs.

Quenching of the Singlet State of Toluene. A toluene–peracetic acid solution diluted with isopentane 100-fold was used because of the strong self-quenching ability of toluene. Fluorescence spectra of toluene were measured with a Hitachi fluorescence spectrophotometer, Model MPF-2A, at room temperature and appeared at λ_{max} 284 nm, the optimum excitation wavelength was 240 nm, and the red shift was observed by an increase of peracetic acid concentration. No fluorescence of peracetic acid was observed, and no quenching fluorescence of toluene by acetic acid was observed. Stern–Volmer plots for quenching of excited toluene showed a good linearity within 0–0.3 M peracetic acid concentration.

Registry No.—peracetic acid, 79-21-0; toluene, 108-88-3; methyl radical, 2229-07-4; hydroxyl radical, 3352-57-6.

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Fluorescence Yields of Isatoic Anhydride from the Reaction of *N*-Glyoxyloylanthranilic Acid 2-Oxime with Electrophiles

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N-Glyoxyloylanthranilic acid 2-oxime (1) was converted to isatoic anhydride (2) and cyanide ion by reaction with methanesulfonyl fluoride and chloride, isopropyl methylphosphonofluoridate (Sarin), acetic anhydride, Parathion, and Meta-Systox R in 1:1 organic solvent–aqueous borate buffer and in 98% organic solvent containing tetrabutylammonium hydroxide. The borate buffer catalyzed the hydrolysis of the electrophiles agents and reduced the yield of **2**. A stoichiometric yield of **2** was obtained in 98% nonhydroxylic solvents, in which **2** was stable. The anion of **1** quenched the fluorescence of **2** anion and caused a shift in excitation wavelength for maximum fluorescence without a shift in the emission wavelength. These facts were ascribed to an inner filter effect of **1** anion. The quenching could be represented by a Stern–Volmer relationship with slopes of 620 M^{-1} in 50% aqueous acetonitrile, 330 M^{-1} in 73:25:2 acetonitrile–acetone–water, and 690 M^{-1} in 73:25:2 *tert*-butyl alcohol–acetone–water. The excitation and emission wavelengths and relative fluorescence intensities were measured for various substituted isatoic anhydrides: **2**, 350, 430, 1.00; 5-Cl-**2**, 360, 440, 1.68; 5-sulfo-*N*-Me-**2**, 330, 395, 0.92; 5-aza-**2** (2,3-pyrido-3,1-oxazine-2,4-dione), 350, 435, 3.55; 5-NO_2-**2**, 335, 435, 0.016; *N*-Me-**2**, 328, 398, 1.61; 5-Cl-*N*-Me-**2**, 338, 405, 1.21.

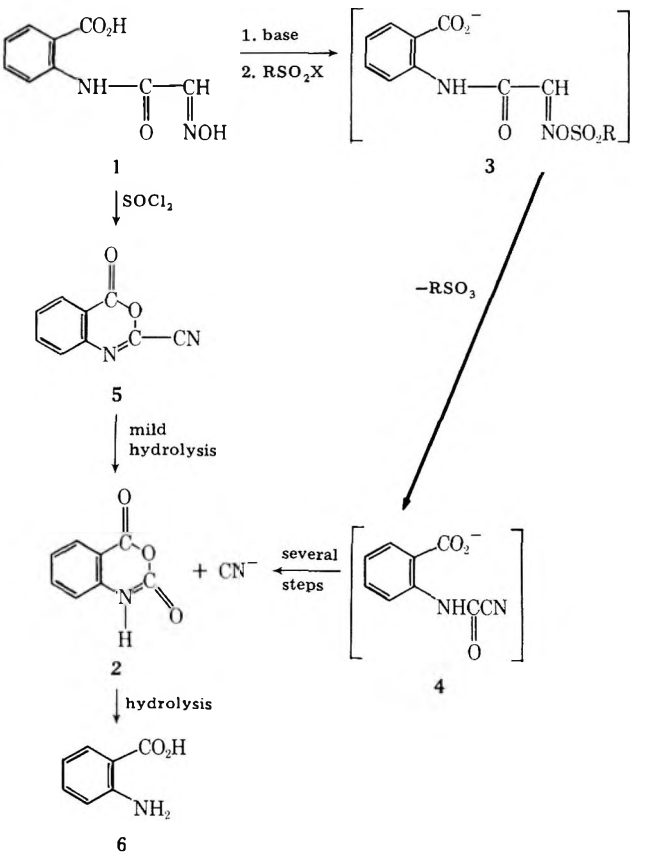
Dziomko, Ivanov, and Kremenskaya[1] have reported a sensitive, quantitative fluorometric method for the determination of acid chlorides and anhydrides, sulfonyl chlorides, and phosphorus oxychloride based on the reaction with *N*-glyoxyloylanthranilic acid 2-oxime (2-carboxyisonitrosoacetanilide, **1**) in an alkaline, buffered 25% aqueous acetone medium. Because we were unable to achieve the reported sensitivity in the 5×10^{-9} to 10^{-10} M range (perhaps due to the absence of experimental details), we initiated a study to maximize the yield of the fluorescent species, the anion of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride, **2**).[2] The anion of **1** was shown to quench the fluorescence of **2** anion. Conditions were developed for the reactions of methanesulfonyl fluoride (MSF) and isopropyl methylphosphonofluoridate (Sarin) with **1** anion to yield **2** anion quantitatively with a minimum of quenching. Using these conditions the sensitivity of the detection of Sarin was 0.002 μg/mL, which approaches that of the enzymatic methods (0.001 μg/mL).[3]

Results and Discussion

Identification of the Fluorescent Species. When oxime **1** in 1:3 acetone–water buffered at pH 9.0 by 0.05 M borate was allowed to react with methanesulfonyl chloride, the resulting solution exhibited fluorescence, λ_{ex} 365 nm, λ_{em} 435 nm. The only isolable solid was anthranilic acid (λ_{ex} 330 nm, λ_{em} 400 nm, in basic solution). However, reaction of **1** with benzenesulfonyl chloride in pyridine afforded **2**. The fluorescence of an authentic sample of **2** in 25% aqueous acetone, buffered at pH 9.0 (λ_{ex} 350 nm, λ_{em} 435 nm), was similar to the fluorescence of the reaction solution. Furthermore, the pH dependence of the fluorescence intensity produced in the reaction of **1** with methanesulfonyl fluoride over the pH range 8.0–10.5 paralleled that of authentic **2** in the presence of **1**. The fluorescence excitation and emission spectra of a mixture of **2** and **1** at pH 9.0 were identical with the spectra obtained in the reaction of **1** anion with MSF. Variations in solvent affected the fluorescence of **2** and that of the reaction mixture in a similar manner.

A reasonable sequence for the conversion of **1** to **2** by sulfonyl halides via **3** and **4** is shown in Scheme I. A similar sequence has been proposed by Guinullina et al.[2] for **1** with acetic anhydride in aqueous solution. In support of this abnormal Beckmann type mechanism, it was shown that cyanide ion accompanied the formation of the fluorescent **2**. Karrer, Diechmann, and Haebler[4] heated **1** with excess thionyl chloride to obtain **5**, which was rapidly converted to **2** under mild hydrolytic conditions. We considered compound **5** an unlikely intermediate in the conversion of **3** to **2**, since strong dehydrating conditions seem necessary for the formation of **5**. The reaction of **1** with acetic anhydride in pyridine did not give the nitrile **5** (Scheme I), but yielded **7**. The structure of **7** was established by IR, NMR, elemental, and mass spectral analyses. Hurd and Bethune[5] showed that o-carboxyarylhydroxamic acids, when subjected to the Lossen rearrangement in an inert

Scheme I



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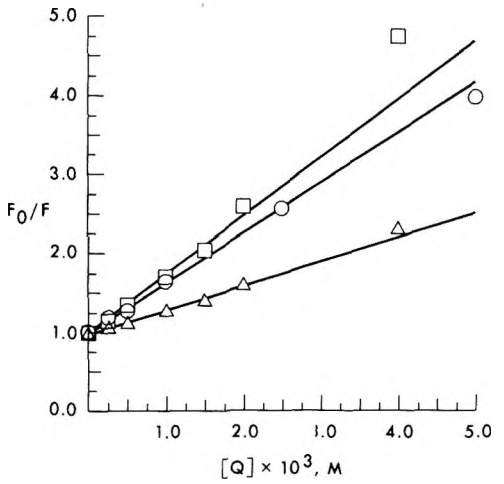
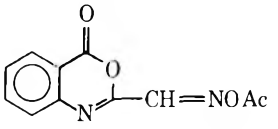


Figure 1. Stern–Volmer plots for solvent dependence of quenching of isatoic anhydride (2) fluorescence by *N*-glyoxyloylanthranilic acid 2-oxime (Q): ○, 1 × 10^{-5} M 2 in acetonitrile–water (1:1), pH 9.7 borate; △, 5 × 10^{-7} M 2 in acetonitrile–acetone–water (73:25:2), Bu_4NOH; □, 5 × 10^{-7} M 2 in tert-butyl alcohol–acetone–water (73:25:2), Bu_4NOH.

medium, gave the corresponding isatoic anhydrides presumably via isocyanates. The above reactions of 1 are in accord with its conversion to 2 via 3 and 4 (Scheme I).



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Reduction of the Fluorescence of 2 by 1. The reduction of the fluorescence of 2 anion by 1 anion could be characterized by the Stern–Volmer equation.[6] The plots (Figure 1) were linear, with the same slope for the two concentrations of 2 anion (5 × 10^{-7} and 1 × 10^{-5} M) over the concentration range of 1 anion from 2.5 × 10^{-4} to 5.0 × 10^{-3} M. The slope was 620 M^{-1} in 50% aqueous acetonitrile, 330 M^{-1} in 73:25:2 acetonitrile–acetone–water, and 690 M^{-1} in 73:25:2 *tert*-butyl alcohol–acetone–water.

The quenching of the fluorescence was due largely to an inner-filter effect.[6] This conclusion was based on the following observations: (1) 1 anion and 2 anion had overlapping absorptions; (2) 1 anion did not absorb in the region of the fluorescence emission; (3) the excitation wavelength for maximum fluorescence shifted to longer wavelengths as the concentration of 1 anion increased; and (4) the fluorescence emission wavelength was independent of the concentration of 1 anion.

The overlapping absorption spectra of 2 anion and 1 anion each at 1.25 × 10^{-4} M in acetonitrile–pH 9.7 borate buffer (1:1) are shown in Figure 2. Compound 2 anion had λ_{max} 350 nm, ϵ 3.93 × 10^3, while 1 anion had λ_{max} 298, 310 nm (s), ϵ 1.25 × 10^4. At 345 nm, 1 anion showed an overlapping absorbance about one-third that of 2 anion. An equimolar mixture of 1 anion and 2 anion obeyed Beer's law over the 300–700-nm range. We could not examine Beer's law behavior of 2 anion at 5 × 10^{-7} and 1 × 10^{-5} M because of the negligible contribution of 2 anion to the total absorbance.

The excitation wavelength for maximum emission of 2 increased with increasing concentrations of 1 anion. The reduction of fluorescence by collisional energy transfer should not alter the excitation wavelength for maximum fluorescence.[6] We conclude that the variation of the excitation wavelength for maximum emission must result from the absorption by 1 anion (A = 1.3 at 1 × 10^{-3} M) at the expense of

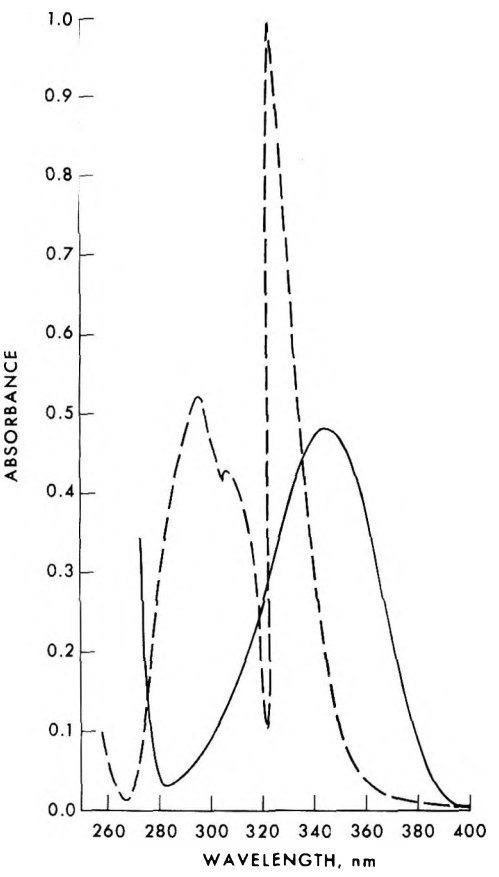

Figure 2. Absorption spectra of isatoic anhydride anion (—) and 2-carboxyisonitrosoacetanilide anion (- - -); 1.25 × 10^{-4} M in 1:1 acetonitrile–pH 9.8 borate buffer.

2 anion (A = 0.002 at 5 × 10^{-7} M). These facts, together with the observation that 1 anion was not fluorescent, are in accord with a significant inner-filter effect.

Necessary conditions for maximum fluorescence intensity are the quantitative reaction of MSF with 1 anion to form 2 anion and the minimization of the hydrolysis of 2 anion. The yield of 2 anion was assessed by determining the fluorescence yield (FY) defined by

$$FY = (FI_1 \times 100)/FI_2 \quad (1)$$

where FI_1 is the fluorescence intensity generated in the reaction of MSF with excess 1 anion and FI_2 is the intensity measured for 2 anion in the presence of the same large excess of 1 anion. The concentration of 2 used to measure FI_2 was equal to the initial concentration of MSF in each case. The excitation and emission wavelengths were the same for FI_1 and FI_2.

Compound 2 has been shown to undergo pH-independent hydrolysis with a rate constant of 9.4 × 10^{-4} s^{-1} ($t_{1/2}$ = 12 min, 25 °C).[7] The hydroxide-catalyzed hydrolysis is negligible at pH 10. We have found that this hydrolysis (pH 9.75, borate buffer) was slower by more than tenfold in 25% acetone and negligibly slow in 50% acetone. Moreover, since the fluorescence yield of the reaction of 1 anion and MSF at pH 9.75 decreased as the buffer concentration increased, we concluded that MSF must be subject to general-base-catalyzed hydrolysis. These results suggested the use of a reaction medium containing a minimum of water and no borate buffer. A fluorescence yield of 100% was realized for the reaction of MSF with 1 by employing 73% acetonitrile–25% acetone–2% water (solvent A) containing 2 equiv of tetrabutylammonium hydroxide relative to 1.

Table I compares fluorescence intensities of 5 × 10^{-7} M solutions of 2 in the presence of various excess concentrations

Table I. Effects of Solvent and 1 Anion Concentration on Fluorescence Intensity and Yield of 2 in the Conversion of 1 to 2 by MSF

[1] × 10^4, M	FI, 2[a]	FI, MSF[b]	Yield, %[c]
	Solvent A[d]		
None	55.5	0	0
2.5	52.0	25.5[e]	49.5[e]
5.0	50.0	50.0	103
10.0	43.5	45.5	104
20.0	34.5	36.0	106
40.0	23.0	23.0	100
	Solvent B[f]		
None	74.0	0	0
2.5×10^{-4}	64.0	35.0[e]	55.5[e]
5.0×10^{-4}	55.0	43.0	78.0
1.0×10^{-3}	44.0	37.5	86.0
2.0×10^{-3}	28.5	27.0	90.0
4.0×10^{-3}	15.5	14.0	90.5

[a] Reading for a mixture of 5×10^{-7} M 2 and the indicated concentration of 1 after 4 min. [b] Reading for a mixture of 5×10^{-7} M MSF and the indicated concentration of 1, after 4 min unless otherwise noted. [c] Fluorescence yield: (column 3/column 2) × 100. [d] Acetonitrile–acetone–water (73:25:2) and 2 equiv of Bu_4NOH/equiv of 1. [e] Values after 10 min; the fluorescence intensity was still increasing. [f] *tert*-Butyl alcohol–acetone–water (73:25:2) and 2 equiv of Bu_4NOH/equiv of 1.

of 1 (column 2) with the fluorescence intensities produced by the reaction of 5×10^{-7} M solutions of MSF with the same excess concentrations of 1 (column 3). The fluorescence yields (column 4) of the MSF–oxime reactions were quantitative after 4 min in solvent A for oxime concentrations $>5 \times 10^{-4}$ M. The fluorescence yields were not quantitative in 73% *tert*-butyl alcohol–25% acetone–2% water (solvent B), presumably due to competing solvolysis of MSF. In solvent A at 2.5×10^{-4} M 1, the fluorescence yield of 2 was about 50% in 10 min, while at 5×10^{-4} M 1 the fluorescence yield was 100% in 4 min, and at 1×10^{-3} M 1 the yield was 100% in 2 min. In solvent B the maximum fluorescence yield was 90% and the rate of attainment of that maximum was slower.

Dziomko[1] reported that the maximum fluorescence intensity was achieved in 4 min when the concentration of 1 was 2.5×10^{-2} M, whereas the maximum fluorescence intensity in our solvent A was achieved in 2 min at 1×10^{-3} 1 anion, i.e., with a 25-fold lower concentration of quencher. Therefore, the fluorescence intensity is much greater in solvent A than in 25% acetone-containing buffer. Furthermore, the hydrolyses of MSF and 2 were eliminated in solvent A, as shown by the quantitative fluorescence yield. Finally, the rate of formation of 2 is significantly faster in solvent A than in 25% acetone, demonstrating the superiority of a nonaqueous, nonhydroxylic solvent system.

Several solvents (1:1, organic solvent–water; acetone, acetonitrile, tetrahydrofuran, *tert*-butyl alcohol, *p*-dioxane, and 2-butanol) were tested for their effects on the quenching of 2 anion by 1 anion. No significant effects were found. However, MSF and 2 anion were found to solvolyze in hydroxylic solvents, e.g., methanol, ethanol, and isopropyl alcohol. The inner-filter effect was less by twofold in 98% organic nonhydroxylic solvent (Figure 1).

The fluorescence properties of several substituted isatoic anhydrides were examined for advantages over 2. The relative fluorescence intensities of 10^{-6} M solutions (50% acetonitrile, pH 9.85) were 0.016 for 5-NO_2-2, 1.00 for 2, 1.68 for 5-chloro-2, and 3.35 for 5-aza-2 (2,3-pyrido-3,1-oxazine-2,4-dione). The last compound was over three times more fluorescent than 2, but the corresponding isonitroso precursor could not be prepared. It was also noted that the fluorescence intensity of *N*-Me-2 was greater than that of 2, although it cannot ionize in base (see Experimental Section).

Quantitative studies were made on several electrophiles with 1 anion (1×10^{-3} M) using as solvent acetonitrile–acetone–water (92:2:1) with 2×10^{-3} M tetrabutylammonium hydroxide. Sarin and MSF were readily determined in 3 min in the range 0.01 μg/mL (7.14×10^{-8} M Sarin) to 2.0 μg/mL (1.45×10^{-5} M Sarin). Sarin gave a 100% yield within 10 min. Acetic anhydride was detected at a concentration of 1×10^{-7} M. Parathion was detected in 3 min at 3 μg/mL (1×10^{-5} M). Meta-Systox R was not detected at this level.

Using Barney's[8] definition of minimum detectable difference, namely,

$$I_s - I_b = KS_b\sqrt{2}$$

where I_s = sample fluorescence, I_b = blank fluorescence, S_b = standard deviation of blank fluorescence, and $K = 2\sqrt{2}$ for a 99% confidence limit, we found the minimum detectable limit for Sarin to be 1.43×10^{-8} M or 0.002 μg/mL. We have exceeded the minimum detectable limit (0.026 fluorescence unit) after 3 min and in 10 min the reading less blank ($I_s - I_b$) was 0.038. The sensitivity of the reagent to Sarin approached that of the enzymatic detection methods, which have been reported to be 0.001 μg/mL.[3]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 521 spectrophotometers. The ultraviolet absorption spectra were obtained using a Cary 14 instrument with the cell compartment at 25 ± 0.1 °C and matched 1-cm cells. Proton NMR spectra were determined on a Varian A-60D spectrometer using methanol-d_4 and Me_4Si as the internal standard. Mass spectra were run on a Perkin-Elmer Hitachi Model RMU-6E at 70 eV. Fluorescence spectra and intensities were measured with an Aminco-Bowman Model 4-8202 spectrophotofluorometer (SPF) equipped with a 200-W xenon–mercury lamp and with the cell compartment maintained at 25 ± 0.5 °C. The SPF was calibrated and adjusted daily against a 1-μg/mL solution of quinine sulfate dihydrate in 0.1 N sulfuric acid at an emission wavelength of 450 nm and excitation at 350 nm. The excitation and emission wavelengths reported in this paper are uncorrected.

Reagents. Solvents were spectroquality and showed no significant fluorescence at 430 nm when excited at 360 nm. Borate buffers, pH 8.0–10.2, 0.05 M with respect to H_3BO_3 and KCl (buffer values of 2.0–5.8), were prepared by established procedures.[9] Aqueous 1 M tetrabutylammonium hydroxide (Bu_4NOH) (Beckman Electrometric Reagent) was appropriately diluted with water or organic solvent; the diluted solution could be used for 1 week if stored in a refrigerator. Methanesulfonyl chloride and fluoride, obtained from Eastman Kodak Company, Rochester, N.Y., and *O,O*-diethyl *O*-(*p*-nitrophenyl)phosphorothioate (Parathion) and *O,O*-dimethyl *S*-2-(ethylsulfinyl)ethylphosphorothioate (Meta-Systox R) from Kit No. 52AX, Polyscience Corp., Evanston, Ill., were used without further purification to prepare stock 0.01 M solutions in acetone. Isatoic anhydride and variously substituted isatoic anhydrides were recrystallized from acetonitrile and the purity verified by elemental analysis. Standard solutions of Sarin in acetone, 100 and 1 μg/mL, were furnished by the Detection and Alarms Branch, Development and Engineering Directorate, Edgewood Arsenal, APG, MD, and further diluted with acetonitrile.

Warning! Sarin is an extremely toxic cholinesterase inhibitor. Sarin, methanesulfonyl fluoride, and the pesticides should be handled in a well-ventilated fume hood and precautions taken to prevent inhalation or skin contamination. Concentrated NaOH solution should be used to decontaminate material and glassware.

2-Carboxyisonitrosoacetanilide (1) was prepared by the method of Sandmeyer and obtained as a light tan powder, mp 206–208 °C (lit.[10] 208 °C). Repeated recrystallization from hot water with Darco treatment yielded a white powder: mp 230–231 °C; IR (Nujol) 3300 (–NH), broad absorption 2500–2600 (OH of CO_2H), 1695 (CO_2H), 1665 (–CONH), 1590, and 1540 cm^{-1} (C=N); NMR δ 4.9 (3 H, exchangeable), 7.55 (1 H, CH=NO), 8.7–7.0 (4 H, br aromatic CH); mass spectrum *m/e* 208 (parent peak).

Anal. Calcd for $C_9H_8N_2O_4$: C, 51.9; H, 3.9; N, 13.6; O, 30.7. Found: C, 51.7; H, 4.0; N, 13.6; O, 30.6.

Reaction of 1 with Methanesulfonyl Chloride. Methanesulfonyl chloride (0.6 g, 5.5 mmol) in 12 mL of acetone was added to a solution of 1 (1.0 g, 4.8 mmol) in 50 mL of 0.02 N NaOH. The solution was adjusted to pH 9.5 with a few drops of 2.5 N NaOH. The resulting solution exhibited a strong blue fluorescence (λ_{ex} 365, λ_{em} 430 nm). The presence of cyanide in the reaction mixture was established by three methods: (a) by a colorimetric test with *o*-dinitrobenzene and *p*-nitrobenzaldehyde;[11] (b) by a cyanide specific electrode (Orion Research, Inc.); and (c) by an HCN detector tube test of the gas evolved from the solution upon acidification.[12] The reaction mixture was acidified with glacial acetic acid and extracted with ether. The ether extract was washed with water and dried over sodium sulfate. Evaporation of the solvent left a cream-colored powder which was identified as anthranilic acid by comparison of its IR spectrum and fluorescence spectra in 3:1 pH 10 buffer–acetone, λ_{ex} 330, λ_{em} 400 nm, with the spectra of an authentic sample.

Conversion of 2-Carboxyisonitrosoacetanilide (1) to Isatoic Anhydride (2). Compound 1 (1 g, 4.8 mmol) was dissolved in 10 mL of pyridine containing benzenesulfonyl chloride (0.94 g, 5.3 mmol). The solution turned red-purple and became slightly warm. The solution was refluxed for 20 min and then poured into 30 mL of ice–water slurry and the mixture stirred for 15 min. A pale green-yellow solid formed. Recrystallization of the product from 95% ethanol yielded 0.104 g of a powder, mp 239–240 °C dec. The IR spectrum (Nujol mull) was comparable to that reported by Sadtler[13] (spectrum 10 143) for isatoic anhydride (mp 243 °C).[14]

4-Oxo-4*H*-3,1-benzoxazine-2-carboxaldehyde 2-(*O*-Acetyloxime) (7). A mixture of 1 (4.8 g, 24 mmol) with 20 mL of acetic anhydride and 5.0 mL of pyridine was stirred at room temperature for 30 min. The precipitate was collected by filtration, washed with cold ethanol, and recrystallized from hot ethanol to give 4.2 g of white crystals: mp 179–180 °C; IR (KBr) 1775, 1755, 1720 sh (br, C=O), 1600 cm^{-1} (strong, C=N); mass spectra *m/e* 232 (parent peak). The NMR spectrum was in accord with the assigned structure.

Anal. Calcd for $C_{11}H_8N_2O_4$: C, 56.90; H, 3.47; N, 12.07; O, 27.56. Found: C, 57.1; H, 3.2; N, 12.0; O, 27.6.

Treatment of 7 with Methanolic KOH. To a suspension of 7 (1.0 g, 4.3 mmol) in 25 mL of methanol was added 5 mL of 1 M methanolic KOH, and the mixture was stirred at ambient temperature until the solid had dissolved (about 10 min). The solution was diluted with 60 mL of distilled water and then acidified with dilute HCl. The resulting white crystalline precipitate was collected and washed with water. Recrystallization from chloroform gave 0.5 g of methyl isonitrosoacetoanthranilate[15] (8): mp 175–180.5 °C (lit.[16] 180 °C); IR (Nujol) 3200 (br, NH, OH), 1705 (-CO_2Me), 1670 (NHCO–), 1595 cm^{-1} (-CH=NOH); NMR (CD_3OD) δ 3.95 (3 H, OCH_3), 4.6 (2 H, NH, OH), 6.7 (1 H, CH=N–), 8.8–7.0 (4 H, broad aromatic absorption); mass spectrum *m/e* 222 (parent peak).

Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.6; O, 28.8. Found: C, 54.4; H, 4.6, N, 12.7; O, 28.1.

Cooling the filtrate from the reaction mixture after isolation of 8 gave shiny plates (0.17 g), mp 53–54 °C, identified by NMR and mass spectra as a mixture of 78% *N*-carboxyanthranilic acid dimethyl ester 9 and 22% 8.

pK_a of Isatoic Anhydride in Mixed Aqueous-Organic Solvents. Solutions of isatoic anhydride (0.01 M) in mixed solvents (50% organic solvent–50% water) were titrated potentiometrically at 25 °C with 0.1 N KOH using a Radiometer pH stat (TTT/C Titrator fitted with an SBU-1a syringe buret and an SBR-2C Titragraph). The apparent pK_as were: acetonitrile, 8.87; acetone, 8.61; isopropyl alcohol, 8.40; *tert*-butyl alcohol, 8.37; 2-methyl-2,4-pentanediol, 7.86; tetrahydrofuran, 8.56; dimethylformamide, 8.63; dimethylacetamide, 8.36.[17]

General Procedure for the Fluorescence Studies. The effects of parameters such as pH, solvent, and reagent concentration on fluorescence intensities, fluorescence stability, and rates of reaction were studied. Reaction solutions were made by mixing in a glass-stoppered test tube the organic solvent (or solution of 1) and buffer or Bu_4NOH. At zero time, a solution of the test compound was added, mixed rapidly, and about 2 mL of the mixture was transferred to a Teflon-stoppered quartz fluorometer cell. Volumes and concentrations of the solutions were chosen to give the desired final concentration of reagents, solvents, and test sample. At the same time, a reagent blank was prepared similarly. The change in fluorescence intensity, $\Delta F/\Delta t$, was measured at 1-min intervals. The blank was subtracted from the sample reading to obtain the net fluorescence. The blank was determined for the same time intervals as for the sample.

Spectral Properties of Isatoic Anhydride (2) in the Presence of 2-Carboxyisonitrosoacetanilide (1). Stock solutions (5×10^{-3} M) of 1 and 2 were prepared in acetonitrile. Addition of 0.1 mL of stock solution to a mixture of 1.0 mL of acetonitrile and 2.0 mL of aqueous pH 9.7 borate buffer was used to prepare 1.25×10^{-4} M solutions. The UV absorption spectra were recorded for solutions of 1 and 2 separately (Figure 2) and as equimolar mixtures. Scans were repeated at 10-min intervals to check solution stability. In separate experiments, methanol, ethanol, and isopropyl alcohol were substituted for acetonitrile.

The excitation and emission spectra were recorded for solutions of 2 (5×10^{-7} M, in 1:1 acetone–aqueous pH 9.7 borate buffer) in the absence of 1 and in the presence of measured amounts of 1 (5×10^{-4} to 5×10^{-3} M final concentration). The excitation wavelength for maximum emission shifted from 350 nm in the absence of 1 to 370 nm in the presence of 5×10^{-3} M 1. The wavelength of the emission maximum remained constant at 430 nm, but the emission intensity decreased with increasing concentrations of 1.

Fluorescence intensity ratios (F^0/F) were established for 5×10^{-7} M solutions of 2 in 1:1 acetonitrile–water (pH 9.7 borate buffer), in the absence of 1 (F^0), and after the addition of measured amounts of 1 (F) over the concentration range 5×10^{-4} to 5×10^{-3} M. The quenching experiments were repeated for the following: (1) 1×10^{-5} M 2 in 50% aqueous acetone with borate buffer; (2) 5×10^{-7} M 2 in 73% acetonitrile–25% acetone–2% water (solvent A) with Bu_4NOH at double the concentration of 1 (in the absence of 1, 2.5×10^{-4} M Bu_4NOH was used to ionize compound 2); (3) 5×10^{-7} M 2 in 73% *tert*-butyl alcohol–25% acetone–2% water (solvent B) with Bu_4NOH as given above. All fluorescence intensity measurements were made 1 min after mixing, using λ_{ex} 360, λ_{em} 430 nm. Stern–Volmer quenching plots were made of F^0/F vs. [Q], where [Q] is the concentration of 1.

Fluorogenic Reaction of 1-Anion with Electrophilic Agents. A. Reaction in Aqueous Organic Solvent. In a representative experiment, the reagent solution was prepared by mixing in a glass-stoppered Erlenmeyer flask 2.0 mL of 0.02 M, pH 9.75 borate buffer and 1.0 mL of 4×10^{-3} M 1 in acetone. Then 1.0 mL of MSF solution (4×10^{-8}–4×10^{-5} M) in acetone was added rapidly. An aliquot of the reaction mixture was transferred to a 1-cm Teflon-stoppered quartz cell, and fluorescence readings were made at 2-min intervals using λ_{ex} 360 and λ_{em} 430 nm. A reagent blank was made by mixing 2.0 mL of the aqueous buffer, 1.0 mL of 4×10^{-3} M 1 in acetone, and 1.0 mL of acetone. Net fluorescence intensities were calculated by subtracting the blank from the sample readings.

B. Reaction in 98% Organic Solvent. Stock solutions of 1 and of the electrophiles were prepared in acetone. Further dilutions were made in the selected organic solvent, usually acetonitrile or *tert*-butyl alcohol. Reagent concentrations were adjusted to give 2 mmol of Bu_4NOH for each millimole of 1 in the reaction mixture.

In a typical experiment, the effect of the concentration of 1 on the rate and yield of the reaction with 5×10^{-7} M MSF was studied by comparing the fluorescence intensity produced in the reaction mixture, with the fluorescence of 5×10^{-7} M 2 in the presence of the same concentration of 1. The reaction was studied first in solvent A and then repeated in solvent B. Fluorescence yields for the MSF–oxime reactions were calculated using the fluorescence intensity reading of 2 as 100%.

Procedure for Quantitative Estimation of Electrophiles. Stock 0.04 M solutions of the electrophilic agents were prepared in dry acetone and stored in a refrigerator; dilutions with acetonitrile were prepared immediately before use. Solutions of 1 were prepared daily by dissolving 8.32 mg of 1 in 0.50 mL of acetone and then diluting to 10.0 mL with acetonitrile. The reaction medium was prepared by mixing 2.0 mL of 4×10^{-3} M Bu_4NOH and 1.0 mL of 4×10^{-3} M 1 in a stoppered test tube. Electrophile solution (1 mL) was added rapidly, and the mixture was quickly shaken. A reagent blank was prepared for each set of tests by mixing 1.0 mL of acetonitrile, 2.0 mL of 4×10^{-3} M Bu_4NOH, and 1.0 mL of 4×10^{-3} M 1. Aliquots (ca. 2 mL) of the reaction mixture and blank solutions were transferred to matched 1-cm quartz cuvettes. At a standard reaction time (e.g., 10 min) readings were made using λ_{ex} 360, λ_{em} 430 nm, and slits and sensitivity settings were adjusted to give a reading of 5.0 with a 1 μg/mL solution of quinine sulfate dihydrate.

Fluorescence Properties of Substituted Isatoic Anhydrides. The excitation and emission spectra and the relative fluorescence intensities at the emission maxima were measured for various substituted isatoic anhydrides at 2×10^{-6} M in 1:1 acetonitrile–water (pH 9.8 borate buffer); this pH was in the range for maximum emission for each of the tested compounds. The λ_{ex} (nm), λ_{em} (nm), and relative fluorescence intensity for each compound were: isatoic anhydride, 350, 430, 1.00; 5-chloroisatoic anhydride, 360, 440, 1.68; 5-nitroisatoic anhydride; 355, 435, 0.016; *N*-methylisatoic anhydride, 328, 398, 1.61;

5-chloro-*N*-methylisatoic anhydride, 338, 405, 1.21; 5-sulfo-*N*-methylisatoic anhydride, 330, 395, 0.92; 3-azaisatoic anhydride, 350, 435, 3.55.

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Registry No.—**1**, 6579-46-0; **2**, 118-48-9; 5-Cl-**2**, 20829-96-3; 5-NO_2-**2**, 20829-97-4; *N*-Me-**2**, 10328-92-4; 5-Cl-*N*-Me-**2**, 40707-01-5; 5-sulfo-*N*-Me-**2**, 63016-84-2; 5-aza-**2**, 63016-85-3; **7**, 63016-86-4; **8**, 630160-87-5; anthranibic acid, 118-92-3.

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Stereochemistry of Valerenane Sesquiterpenoids. Crystal Structure of Valerenolic Acid[1]

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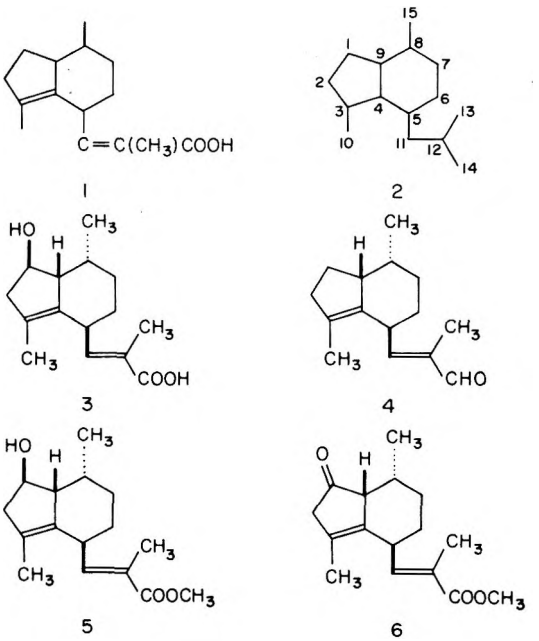
The three-dimensional structure of valerenolic acid, $C_{15}H_{22}O_3$, was determined by x-ray crystallography. The substance crystallizes in the orthorhombic space group $P2_12_12_1$ and the unit-cell dimensions are a = 12.705 (2), b = 14.476 (3), c = 15.477 (1) Å. Intensity data were measured with Cu radiation on a four-circle diffractometer. The structure was solved by direct methods and refined to R = 3.6% for 2543 reflections. The hydroxyl group attached to the five-membered ring is cis to the hydrogen atom at the adjacent ring junction, and both are trans to the axial methyl substituent on the six-membered ring. The latter is trans to the methacrylic acid side chain, in which the methyl group is cis to the ring carbon atom. Chemical and spectroscopic data indicate that the same stereochemistry also occurs in valerenic acid and in valerenal. The absolute configuration was established on the basis of the CD spectrum of methyl 1-ketovalerenate.

Valeriana officinalis L. has been used for centuries in popular medicine as a mild sedative or tranquilizing agent in the form of aqueous or alcoholic extracts of its roots and rhizomes, and it has been included in pharmacopeias of many countries.[3] The search for its active principle took more than a century and it was shown relatively recently that, while the main active principles are undoubtedly esters and glucosides of terpenoids possessing an iridoid skeleton,[4,5] some of its sesquiterpenoid constituents such as valeranone[6] (a mild sedative) and valerenic acid[7] (a spasmolytic) may well contribute to the overall effect of the drug.

Valerenic acid and the closely related acetylvalerenolic acid were first isolated from the drug in Sandoz laboratories,[7] where their pharmacological profiles were investigated as well. It was Büchi and co-workers[8] who showed that valerenic acid possesses the unique structure **1**. It represents the first example of a quite unusual skeletal type **2** (valerenane) in terpenoid chemistry, and since its discovery only valerenolic acid (**3**)[9] and valerenal (**4**)[10] have been confirmed as belonging to the same family. However, the stereochemistry of all chiral centers and the geometry around the double bond in the side chain have remained unknown.



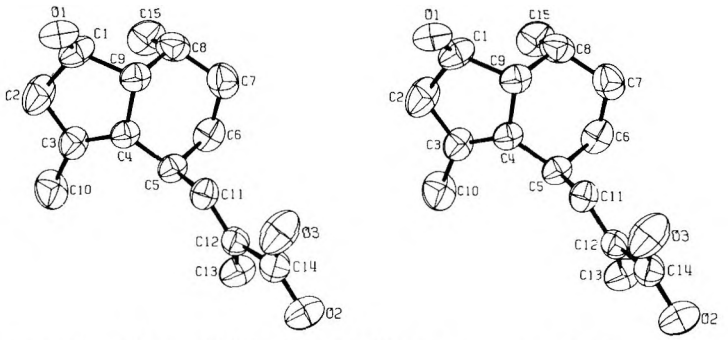


Figure 1. Stereoscopic view of valerenolic acid (mol. A). The thermal ellipsoids correspond to 50% probability.

Table I. Torsion Angles (in Degrees)

	mol. A	mol. B
C(9)–C(1)–C(2)–C(3)	6.6	15.9
C(1)–C(2)–C(3)–C(4)	−3.5	−10.9
C(2)–C(3)–C(4)–C(9)	−1.2	1.1
C(3)–C(4)–C(9)–C(1)	5.4	9.1
C(4)–C(9)–C(1)–C(2)	−7.1	−15.2
C(9)–C(4)–C(5)–C(6)	−48.7	−51.3
C(4)–C(5)–C(6)–C(7)	48.4	49.6
C(5)–C(6)–C(7)–C(8)	−57.1	−57.1
C(6)–C(7)–C(8)–C(9)	58.8	57.4
C(7)–C(8)–C(9)–C(4)	−54.9	−53.8
C(8)–C(9)–C(4)–C(5)	53.8	55.5
C(11)–C(12)–C(14)–O(3)	−3.8	2.1
C(13)–C(12)–C(14)–O(2)	−5.2	2.5

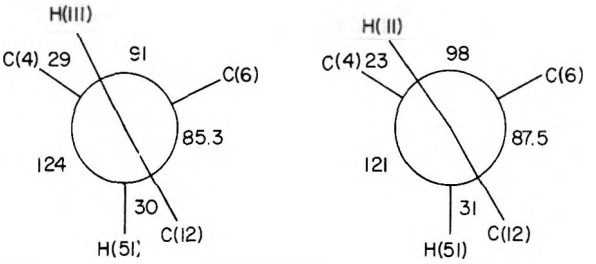


Figure 2. Newman projection along the C(11)–C(5) bond for molecules A (left) and B (right).

Because of the uniqueness of the structure and the physiological activity of at least one of these three compounds, we considered the determination of the relative and absolute stereochemistry of this group of compounds to be desirable. An x-ray analysis appeared worthwhile and valerenolic acid (3) was the best candidate, as it contains one additional chiral center at C-1.

Results and Discussion

X-Ray Analysis. A stereoscopic view of valerenolic acid is shown in Figure 1. The x-ray analysis revealed the configuration at the four chiral centers as well as the isomerism of the exocyclic double bond. The hydroxyl group is cis to the hydrogen atom at the adjacent ring junction and both are trans to the methyl substituent on the six-membered ring; the latter is trans to the methacrylic acid side chain. Both of these substituents are in axial orientation. The six-membered ring is chair shaped and the torsion angles (Table I) indicate that the conformation in the two crystallographically independent molecules is very similar. The exocyclic double bond and the axial substituents[11] cause the torsion angles to deviate from the normal values of ±55.9° in a cyclohexane chair.[12] The decreased average torsion angle (54°) expresses the expected flattening of the ring. Very similar torsion angles were observed in capsidiol[13] in which there also is a double bond exocyclic to a six-membered chair with axial substituents. These distortions are also manifested by bond angles: the angles are smaller at the carbon atoms bearing the axial substituents than the normal value of 111.1° [12] and larger at C-6 and C-7. The same pattern was observed in capsidiol.[13]

The presence of two trigonal atoms in a five-membered ring normally causes that ring to adopt a flattened envelope conformation.[14] A calculation of Δ, the phase angle of pseudorotation,[15] reveals that in molecule B its value deviates by only 7° from that in a perfect envelope. However, in molecule A the conformation is just halfway between an envelope and half-chair. The maximum torsion angle, ϕ_m, is 7.5° in molecule A and 16.7° in molecule B. The decreased pucker (in cyclopentene the angle of pucker was found to be 29° [16]) is presumably caused by the fusion to the six-membered ring. Small deviations of C-1 from the mean plane through the four other atoms in the ring, 0.114 and 0.257 Å in molecules A and B, respectively, are additional indications of the ring's unusual flatness.

The Newman projections in Figure 2 show the attachment of the methacrylic acid side chain to the six-membered ring. From the remarkable similarity between the conformations in the two independent molecules one may conclude that this conformation represents an energy minimum. It is also of interest to examine the isomerism and conformation within the side chain. Firstly, it should be pointed out that, contrary to previous publications,[8,9] the carboxyl group is trans to C-5. Secondly, the C=C—O—H groups were found to be in the more stable synplanar conformation[17] in both independent molecules. Finally, the conformation of the C=C—C=O groups is antiplanar; this conformation is rather rare and requires some comment.

A recent review of carboxylic acids[18] reveals that in saturated acids the C—C—C=O group is invariably synplanar. Leiserowitz and Schmidt[19] attributed this phenomenon to nonbonded interactions. In unsaturated carboxylic acids the effect of such interactions is reduced. On the other hand, a bent-bond description of carbonyl double bonds favors an antiplanar conformation of C=C—C=O because it corresponds to the energetically preferable staggering of bonds about the central single bond.[20] Einspahr and Donohue predicted that in α,β-unsaturated acids for which nonbonded interactions are ambivalent, the antiplanar conformation should be preferred; they found their prediction confirmed in the structure of dimethyl *trans,trans*-2,5-dichloromuconate.[21] Bulky substituents in the α position are likely to cause a reversal in the conformational preference attributable to nonbonded interactions; i.e., they reinforce the preference for an antiplanar conformation due to bond staggering. With the α substituent in our structure being bulkier than Cl, it is not surprising to find an antiplanar conformation and the C(13)–C(12)–C(14) bond angle (115.9°) over 2° larger than the corresponding angle in the chloromuconate.[21]

All bond lengths, including those involving hydrogen atoms,

Table II. Distances and Angles for Hydrogen Bonds

	Distances, Å		Angles, deg	
	O···O	O···H	OH···O	HO···O
O(3A)–H··· O(1A)[a]	2.645	1.89	162	13
O(3B)–H··· O(1B)[b]	2.577	1.76	168	8
O(1A)–H··· O(2B)[c]	2.797	1.96	171	6
O(1B)–H··· O(2A)[d]	2.777	1.90	179	1

[a] At $\bar{x}$, $-1/2 + y$, $1/2 - z$. [b] At $1 - x$, $-1/2 + y$, $3/2 - z$. [c] At $1/2 - x$, $1 - y$, $-1/2 + z$, [d] At $1/2 - x$, $1 - y$, $1/2 + z$.

Table III. Carbon Chemical Shifts (in ppm) in the NMR Spectra of Valerenic (1) and Valerenolic (3) Acids

Carbon	1	3
1	24.6	73.4
2	37.5	47.8
3	131.3	128.6
4	133.2	131.7
5	34.7	34.7
6	25.4	25.4
7	28.8	28.8
8	33.1	31.4
9	47.5	57.7
10	12.0[a]	12.9[a]
11	146.2	145.0
12	125.4	125.9
13	13.5	13.4
14	174.3	172.8
15	12.1[a]	12.1[a]

[a] The assignments can be interchanged, even if the slight downfield shift of C-10 can be expected from the homoannular hydroxyl effect.

were found to have expected values and require no further comment. The highly satisfactory agreement between equivalent bonds in molecules A and B, in most cases within 2σ, indicates that the relatively low estimated standard deviations (0.003–0.004 Å, 0.2°) are realistic.

All A molecules in the crystal are joined by a strong hydrogen bond in which the carboxyl group donates its proton to the hydroxyl group in a symmetry-related molecule. The same scheme, with an even stronger hydrogen bond, join all the B molecules. The two chains are cross-linked by hydrogen bonds in which the hydroxyl groups in one chain act as proton donors and the C=O portions of the carboxyl in the other chain act as acceptors. Geometrical details are given in Table II.

Correlation of 3 with 1 and 4. Having determined the structure of **3**, we wished to correlate its stereochemistry with that in **1** and **4**. On the basis of chemical and spectroscopic data, we can demonstrate that the steric relationships of all chiral centers and the geometry of the double bond in the side chain are identical in all three compounds. Valerenic acid (**1**) was transformed unambiguously into **4**,[10] and **3** gave the saturated hydrocarbon **2**, identical with that prepared from **1**.[9] The identity of configurations at C-5, -8, and -9 is further confirmed by the ^{1}H NMR spectra of **1** and **3** which exhibit signals of principal proton groupings with the same chemical shifts and coupling constants.[9]

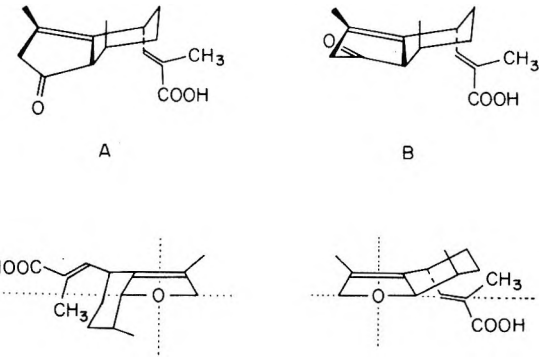
It is well known[22] that carbon chemical shifts are influenced by chiral centers to such an extent that, even if such a center is removed by four bonds from the carbons considered, the shielding differences reflected in differences in chemical shifts for various configurations are significant. As these configurational differences are reflected more strongly on carbons than on protons, we expected that, should the configurations of chiral centers of **1** and **3** be different, the ^{13}C NMR spectra would show considerable differences in carbon chemical shifts, while similar effects in the ^{1}H NMR spectrum might be overlooked. Table III indicates, however, that most carbons exhibit the same chemical shifts. The carbons forming the five-membered ring are an exception, as the hydroxyl located on C-1 in **3** causes, as expected, a profound difference in shielding of these carbons. As can be seen, the actual values of chemical shifts of carbons[23] in both **1** and **3** agree well with the assumption that **3** is a hydroxylated derivative of **1** (with conservation of configuration at all chiral centers). C-1 is shifted to considerably lower fields in **3** because of the α-effect of the hydroxyl substitution, and similarly both C-2 and C-9 experience a strong β-effect (deshielded by 10 ppm), while both C-3 and C-4 are shielded by 2.7 and 1.5 ppm, respectively, and C-8 by 1.7 ppm (expected γ-effects) relative to the values for **1**. Otherwise, all remaining signals retain their chemical shifts in both **1** and **3**.

Table IV. Circular Dichroism Data (in Methanol) for Valerenic and Valerenolic Acids

Valerenic acid λ, nm (Δε)	Valerenolic acid λ, nm (Δε)
	272 (−0.81)
263 (−1.89)	260 (−1.75)
237 (+4.03)	236 (+3.7)
217 (−11.1)	216 (−9.9)
	198 (+7.2)

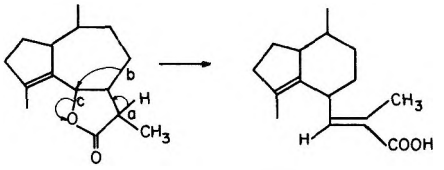
These comparisons show convincingly enough that relative configurations at all chiral centers in **1**, **3**, and **4** are the same, but they do not exclude the possibility that we are dealing with antipodes. In order to prove that the absolute configurations of all three compounds are also identical, we compared the results of two chiroptical methods, i.e., optical rotatory dispersion and circular dichroism. As CD curves have a less complex appearance than ORD curves when several Cotton effects are superimposed to shape the resulting curve, we felt that CD might support earlier reports, based on ORD, on configurational identity of chromophores in **1** and **3**.[9,24] In fact, the overall similarity of the CD curves over the whole spectral range[25] (Table IV) makes this identity practically certain.

Absolute Configuration. We expected the determination of the absolute configuration of the valerenane group to be possible by measurement of the Cotton effect of the carbonyl group resulting from an oxidation of the C-1 hydroxyl in methyl valerenolate. The presence of the Δ^3 double bond forces the five-membered ring to adopt a conformation in which C-2, -3, -4, -9 are approximately coplanar with C-1 displaced from that plane (Table II). This displacement can be either below (A) or above (B) the plane. Both conformations, however, have the same contribution to the Cotton effect (cf. the projections with right-handed Cartesian coordi-



nates), i.e., octant consignate. While recent literature[26-30] deals with six-membered ring systems containing carbonyls, there is a lack of comparative material for five-membered rings. Consequently, we felt at the beginning that any assignment of absolute configuration on this basis would not be devoid of certain ambiguity. We prepared methyl valerenolate (**5**) by treatment of **3** with diazomethane, and it was subsequently transformed to a mixture of oxidation products from which methyl 1-ketovalerenate (**6**) was isolated by chromatography on a silica gel column. It showed only a weak Cotton effect in its CD spectrum at 325 nm ($\Delta\epsilon$ −0.49) in addition to the absorption at 238 nm ($\Delta\epsilon$ +3.20), comparable with similar values in both **1** and **3**. The absolute configuration of valerenolic acid should be therefore as it is portrayed in **3**, since the antipodal structure would exhibit a positive sign of the Cotton effect. The correct absolute configuration was used in the refinement of atomic parameters and is shown in Figure 2.

Biosynthesis. A working hypothesis which helped Büchi and co-workers[8] to determine the structure of **1** was based on



its possible origin from a guaianolide via a rearrangement. Considering that an elimination reaction can proceed only if bonds a and b are coplanar, it is clear that CH_3 and H must eventually appear on the same side of the double bond. However, the configuration determined by the x-ray analysis is the opposite one. On the grounds that the oxidation of an aldehyde to the corresponding acid is more likely than the reverse process, Bates and Paknikar[10] suggested that the immediate precursor of **1** is **4**, which, in turn, may be derived from a guaiane. They also postulated that the valerenanes are biogenetically related to α-gurjunene. Accordingly, Scheme I may now be proposed.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are not corrected. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer at 70 eV. The ^1H NMR spectra were recorded in $CDCl_3$ solutions with a Varian T-60 instrument using Me_4Si as an internal standard. The infrared spectra were recorded with a Perkin-Elmer 457 grating infrared spectrophotometer in $CHCl_3$ solutions. The ^{13}C NMR spectra were recorded on a Varian XL-100-15 spectrometer at 25.2 MHz in the Fourier transform mode of operation in $CDCl_3$ solutions using Me_4Si as internal standard through the courtesy of Dr. J. B. Stothers. Assignments were made by comparison of proton noise decoupled and off-resonance decoupled spectra. CD spectra were run on a Jouan Dichrographe in methanol solutions through the courtesy of Dr. W. Klyne.

Valerenolic Acid (3). Prepared as described previously[7] and crystallized from an ether solution by very slow cooling to room temperature, mp 169.0–169.5 °C. Valerenic acid (**1**), mp 136–137 °C, was crystallized similarly from an ether solution.

Methyl Valerenolate (5). A solution of **3** (16 mg) in 1 mL of purified ether was treated with an excess of ethereal CH_2N_2 for 5 min. The solution was evaporated to dryness and yielded a colorless thick oil: IR ν_{max} 1708 (CO), 1636 (C=C), 3550 cm^{-1} (OH); MS *m/e* 264 (calcd 264). It was used without purification in the following step.

Methyl 1-Ketovalerenate (6). Chromic acid[31] (0.15 mL) was added with stirring to a 17-mg sample of **5** dissolved in dry ether (purified by distillation with $KMnO_4$) and cooled by an ice–water bath. The course of oxidation was monitored by TLC on silica gel and the reaction was stopped when no more **5** was detectable. After a customary workup,[31] the mixture was subjected to chromatography on a column of 15 g of silica gel (Merck, G) in CH_2Cl_2–1 to 5% ether mixtures, and the fractions exhibiting absorptions at 1638, 1708, and 1739 cm^{-1}, but no OH bands, were collected. The solvent was evaporated to give an oily product (5 mg) which showed *m/e* 262 (calcd 262); it was used for CD measurement without further purification.

X-Ray Analysis of Valerenolic Acid (3). Precession photographs indicated orthohombic symmetry with systematic absences of reflections $h00$ for h odd, $0k0$ for k odd, and $00l$ for l odd. The space group was thus uniquely determined to be $P2_12_12_1$. A crystal fragment with dimensions 0.25 × 0.35 × 0.50 mm was mounted along the b axis on a card-controlled Picker four-circle diffractometer equipped with a Cu target. Cell dimensions were determined from angular settings of ten high-angle reflections and both Cu $K\alpha_1$ (λ 1.54051 Å) and Cu $K\alpha_2$ (λ 1.54433 Å) radiations were used. The following crystal data were obtained: a = 12.705 (2), b = 14.476 (3), c = 15.477 (1) Å; V = 2846.5 $Å^3$; D_x = 1.17, D_m = 1.18 (1) g cm^{-3} (flotation in chlorobenzene/bromobenzene); Z = 8; $F(000)$ = 1088; μ (Cu $K\alpha$) = 6.1 cm^{-1}.

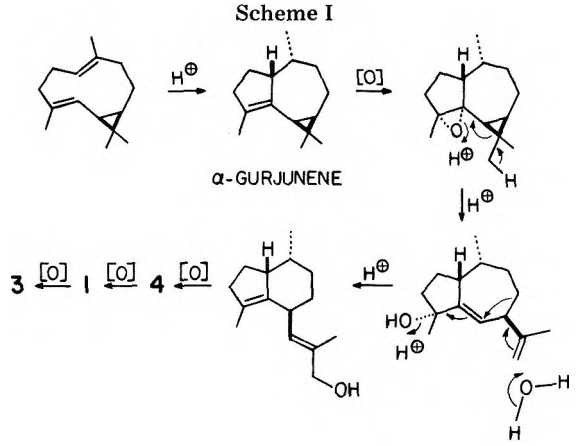
The moving-crystal/moving-counter technique (θ–2θ scan) was used to collect the intensity data, and monochromatization was achieved by the use of a nickel filter and a pulse-height analyzer. A net count of 70 or 10% of the background, whichever was higher, was determined as threshold intensity below which reflections were considered unobserved. There were 2726 unique reflections accessible to the diffractometer ($2\theta \leq 130°$) of which 2506 (92%) had intensities above threshold values. The intensities were corrected for Lorentz and polarization factors. Absorption effects were considered insignificant and corrections were not applied.

The structure was determined by direct methods with a multisolution method similar to that described by Kennard et al.[32] With α_{min} = 2.33 and t_{min} = 0.3, one of the 32 permutations yielded R_E = 0.22 for 381 reflections with $E \geq 1.40$ after a tangent refinement carried out in four steps. The E map revealed the positions of all 36 nonhydrogen atoms (two independent molecules) in the asymmetric unit. Atomic parameters were refined by block-diagonal least squares. All scattering factors were taken from the "International Tables for X-Ray Crystallography"[33] and the oxygen curve was corrected for anomalous dispersion ($\Delta f'' = 0.032$). However, the anomalous scattering power of oxygen was not sufficient for a reliable determination of the absolute configuration.[34] The absolute configuration indicated by the CD spectrum is the one reported here. All hydrogen atoms were located on difference Fourier maps and their parameters were refined isotropically. Throughout the refinement, the function $\Sigma w(|F_o| - |F_c|)^2$ was minimized and a factor of 0.8 was applied to all shifts. The following weighting scheme was used during the final stages: $w = w_1w_2$, where $w_1 = 1$ for $|F_o| \leq 10.0$, $w_1 = 10.0/|F_o|$ for $|F_o| > 10.0$; and $w_2 = \sin^2\theta/0.40$ for $\sin^2\theta < 0.40$, $w_2 = 1$ for $\sin^2\theta \geq 0.40$. After the final cycle, the average parameter shift equaled 0.1 σ, and the largest one equaled 0.8 σ. The agreement index $R(\Sigma|\Delta F|/\Sigma|F_o|)$ is 0.036 and the weighted index $R'(\Sigma w\Delta F^2/\Sigma wF_o^2)$ is 0.042 for 2543 reflections, including 40 unobserved ones for which $|F_o| < |F_c|$. Three strong reflections appeared to suffer from extinction effects and were given zero weights. A final difference Fourier map was featureless. A listing of observed and calculated structure factors may be obtained from G.I.B.

Registry No.—**1**, 64130-69-4; **3**, 1619-16-5; **5**, 64130-70-7; **6**, 64130-71-8.

Supplementary Material Available. Atomic coordinates and temperature factors, bond lengths, bond angles, and mean planes (6 pages). Ordering information is given on any current masthead page.

Scheme I



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Steroid Conformations in Solid and Solution: Stereoselectivity of Grignard Addition to 20-Keto Steroids

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Stereoselectivity of the Grignard addition to pregnenolone was studied by use of regiospecific isotope labeling in order to reconcile conflicting concepts for the conformational isomerism of the steroid side chain. (20*S*)- and (20*R*)-[20-methyl-labeled]-20-methyl-5-pregnene-3β,20-diols (**4a** and **4b**) were synthesized by addition of (a) CD_3MgI to pregnenolone acetate, (b) CH_3MgI to pregnenolone-*17*α,*21,21,21-d*$_4$, and (c) $^{13}CH_3MgI$ to pregnenolone acetate. Stereoselectivity of the Grignard addition was analyzed by proton NMR at 60 MHz in $CDCl_3$ [20(*pro-S*)-CH_3 at 72 Hz, 20(*pro-R*)-CH_3 at 79 Hz, $J_{^{13}C-H}$ = 126 Hz], and the ratio of 20*S* to 20*R* was observed in all cases to be 9:1. Ethyl-Grignard addition to pregnenolone also gave ca. 9:1 for the 20*S*/20*R* ratio. The results indicate that the rotational isomerism around the C(17)–C(20) bond of pregnenolone in solution highly favors the above-*D*-ring conformation of the carbonyl group, opposing the recent claim that pregnenolone exists in a 6:4 equilibrium of "cis" and "trans" conformers. The assignment of the 20*S* configuration to the major product of the Grignard addition to pregnenolone was confirmed by x-ray crystallography for the first time.

Conformational isomerism in steroid chemistry still remains enigmatic. Nes and Varkey[2] recently reported that pregnenolone exists in benzene/ether as a 6:4 equilibrium of cis and trans conformers, directly based on their observed ratio of 20-hydroxycholesterol to 20-hydroxyisocholesterol which was obtained by isohexyl-Grignard addition to pregnenolone acetate. The same reaction has been previously reported by Petrow and Stuart-Webb[3] and Mijares et al.[4] as giving only one product which was assigned to be 20*S*.[4,5] These two groups reported that in no case was there any evidence for the formation of more than one C(20) stereoisomer,[3] and the isolated compound was the only product formed during the condensation, although a careful search was made to isolate the 20*R* epimer.[4] The hypothesis of Rakhit and Engel[6] that there exists four preferred conformations of 20-keto steroids, A_1, A_2, B_1, and B_2 as designated, has been used[2,5] for rationalization of their conclusions, but without specific evidence.

We have recently found[7] a high stereoselectivity for methyl-Grignard addition to 17α-hydroxypregnenolone (99% 20*S* addition) and 16α,17α-epoxypregnenolone (93% 20*R* addition), which indicates that these 20-keto steroids exist in solution highly selectively in the preferred conformation found in the solid state, as determined by x-ray crystallography. Therefore, in this paper we decided to measure the stereoselectivity of methyl-Grignard addition to pregnenolone in order to clarify the conformational preference of 20-keto steroids in solution. Examination of the side-chain conformation in the solid state of 35 steroid structures[8] shows that the carbonyl oxygen is located above the D ring as depicted in **1a** (Figure 1) whether or not the structure has a hydroxy substituent at the neighboring 17α and/or 21 positions. An unusual 20-carbonyl conformation eclipsed with the C(13)–C(17) bond (**1b**) has been observed in 16β-bromo,[9] 16α,17α-epoxy,[10] and 16β-methyl[11] substituted structures. The preferred *si*-face attack by the Grignard reagent on conformation **1a** and the *re*-face attack on conformation **1b** are predicted to occur for steric reasons,[7] therefore giving a 20*S* configuration (**2a**, Figure 1, the incoming alkyl (R) being C(17) > R > C(21)) for the major product from the pregnenolone reaction. To distinguish and quantitatively assess the chemically like, paired methyl groups at C(20) of the methyl-Grignard reaction product, we have chosen three regiospecific labeling sets, (a) deuterated Grignard reagent and pregnenolone acetate, (b) Grignard reagent and deuterated pregnenolone, and (c) ^{13}C-labeled Grignard reagent and pregnenolone acetate, and ^1H NMR at 60 MHz for analysis of the stereoselectivity of the reaction. Ethyl-Grignard addition to pregnenolone was also analyzed.

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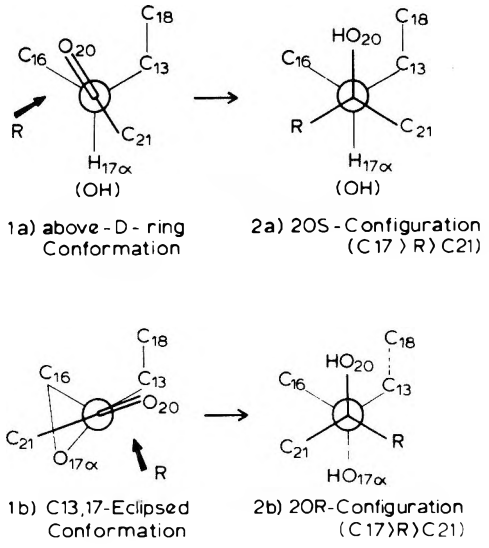


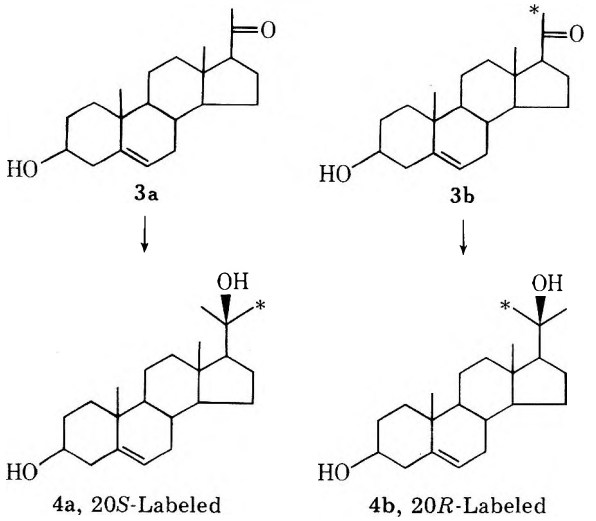
Figure 1. Conformations projected through C(20)–C(17). Preferred *si*-face attack by the Grignard reagent (R) is indicated for the conformation 1a and *re*-face attack for **1b**.

Results and Discussion

20-Methyl-5-pregnene-3β,20-diol (**4**), mp 195–197 °C, was synthesized by addition of excess methylmagnesium bromide in ether to a benzene solution of pregnenolone (**3a**; Scheme I). The reaction was practically quantitative, and the purified product was isolated in 91% yield. ^{1}H NMR (Figure 2a) of **4** 3-acetate, mp 149–150 °C, showed two signals of equal intensity for the chemically like, paired methyl groups at 1.20 and 1.32 ppm. Deuterated methyl-Grignard reagent (99.5 atom % d_3) in 2 equiv was reacted with pregnenolone acetate (**3a** 3-acetate), and the product was isolated in a similar manner. ^{1}H NMR of (20*S*)-[20-C^{2}H$_3$]-**4a** 3-acetate showed a diminished peak for the 1.20-ppm signal while maintaining a nearly quantitative methyl signal at 1.32 ppm, as shown in Figure 2b. Quantitative analysis by the weight method in the expanded scan showed 88:12 for the 20*S*/20*R* ratio. If this analysis of the relative peak areas, which lie in the high-background area of skeletal protons, is reasonably accurate, the reversed deuterium labeling should show an inversed ratio for the 20*S*/20*R*. Therefore, pregnenolone-17α,21,21,21-d_4 (**3b**, Scheme I) was prepared by enolization in deuterated water with perchloric acid. ^{1}H NMR showed a disappearance of the C(21)–methyl signal, and **3b** was oxidized with Jones' reagent followed by an alkaline treatment to give progesterone-17α,21,21,21-d_4. Mass spectrometry of the product showed the labels to be 88 atom % at each position (Figure 3). After Grignard addition and acetylation, ^{1}H NMR of (20*R*)-[20-C^{2}H$_3$,17α-^{2}H]-**4b** 3-acetate showed, as expected, only a small peak at 1.32 ppm while maintaining approximately the full scale of methyl signal at 1.20 ppm (Figure 2c). Quantitative analysis by the weight method showed 13:87 for the 20*S*/20*R* ratio.

Even though it is evident from the deuterium-label study that methyl-Grignard addition is highly stereoselective, quantitative assessment of the selectivity is not very reliable in this area due to the unresolved high-background protons of the steroid skeleton. Thus, we have carried out a further ^{13}C-labeled Grignard reaction. We have previously applied[7] this to obtain a more accurate ratio by taking advantage of the large ^{13}C–^{1}H coupling constant of 126 Hz. In addition, tritium tracer was added to the reagent for two reasons: first, further to support our evidence[12] that there is no separation among rotational isomers around the C(17)–C(20) bond due to purification procedures; second, to use the radioisotopically labeled product as a substrate to study the stereomechanism of steroid biosynthesis. The methyl-Grignard reaction gave a mixture of labeled products which showed only one radioisotopic spot on TLC, and the radioactive mixture showed no indication of separation through the purification proce-

Scheme I



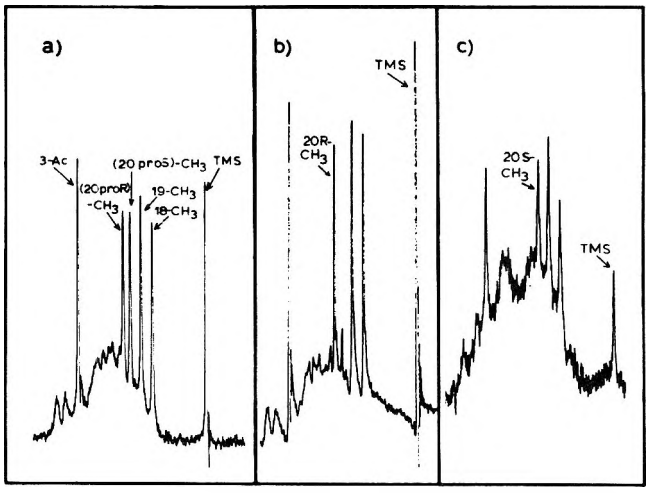


Figure 2. ^{1}H NMR spectra: (a) 20-methyl-5-pregnene-3β,20-diol 3-acetate (**4** 3-Ac), (b) (20*S*)-[^{2}H-labeled]**4a** 3-Ac, and (c) (20*R*)-[^{2}H-labeled]**4b** 3-Ac. All spectra were measured in deuteriochloroform at 60 MHz using tetramethysilane (Me_4Si) as internal standard.

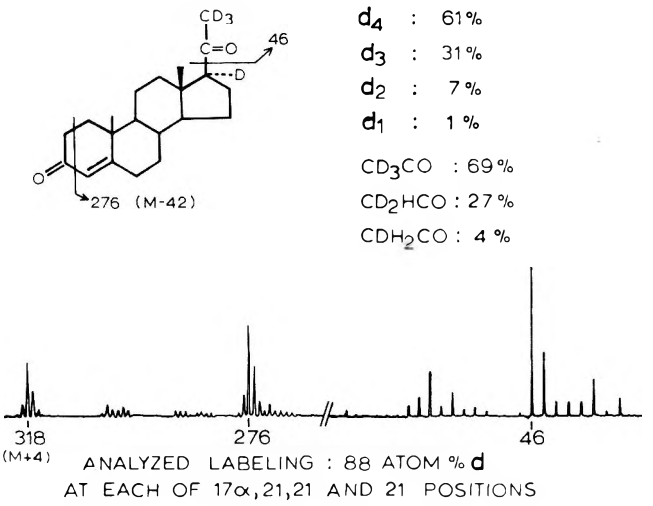


Figure 3. Mass spectrum of progesterone-17,21,21,21-d_4.

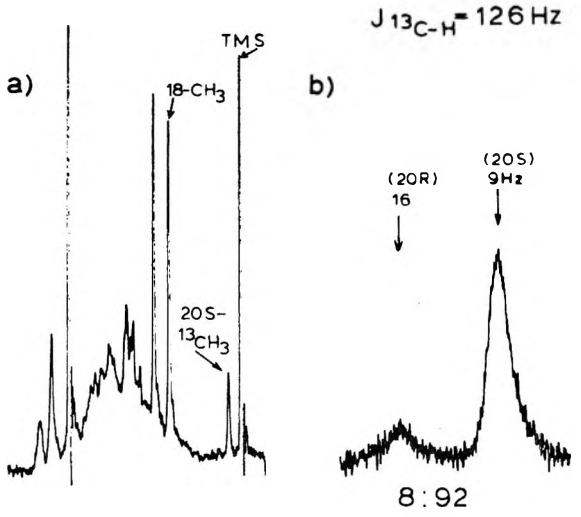


Figure 4. ^1H NMR spectra: (a) (20*S*)-[20-$^{13}CH_3$]-20-methyl-5-pregnene-3β,20-diol 3-acetate and (b) an expanded spectra (1 ppm full scale) of the same compound.

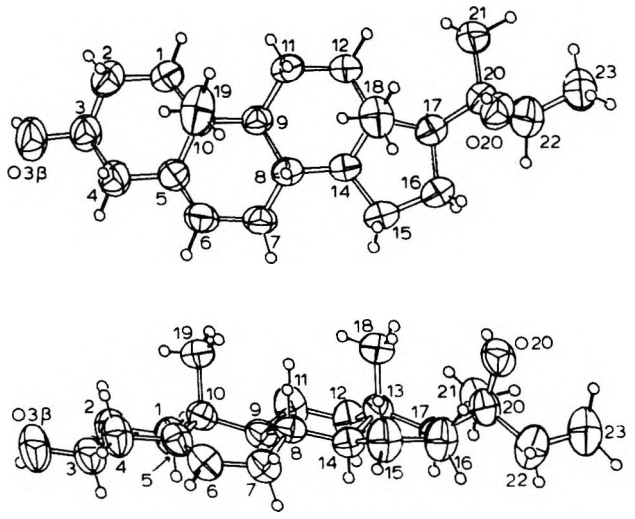


Figure 5. Observed conformation of (20*S*)-20-ethyl-5-pregnene-3β,20-diol. The thermal ellipsoids are scaled to a 50% probability level, and the hydrogens are shown as circles.

dures. ^1H NMR of (20*S*)-[20-$^{13}CH_3$–C^3H_3]-**4a** 3-acetate showed (Figure 4a) a predominant peak (approximately 1.5 H) at 0.15 ppm compared to an almost negligible signal at 0.27 ppm. In the expanded scan (Figure 4b), the stereoselectivity was analyzed to be 92:8 for the 20*S*/20*R* ratio. (20*S*)-[20-$^{13}CH_3$–C^3H_3]-20-Methyl-5-pregnene-3β,20-diol (92% 20*S*, 8% 20*R*) with a specific activity of 4.12 mCi of ^3H/mmol was obtained.

It is clear through the three sets of analyses that methyl-Grignard addition to pregnenolone has a 9:1 stereoselectivity. We had previously observed[13] 9:1 for 19*S*/19*R* in the sodium borodeuteride reduction of the 19-aldehyde of 17-benzoyloxy-3-oxo-4-androsten-19-al, where the "over A-ring" attack is clearly preferable to the "over C-ring" attack by the reagent and 2:1 for 19*S*/19*R* in the same reaction for 3β-hydroxy-17-oxo-5-androsten-19-al, where the steric preference of attack is not conspicuous when analyzed on the conformations determined[14,15] by x-ray crystallography. The stereoselectivity as measured by the product ratio depends not only on the equilibrium of the conformational isomers but also on the "α-side/β-side" attack ratio which is affected by each reagent–carbonyl conformer relationship. One cannot, therefore, attribute a priori an observed stereoselectivity to either or

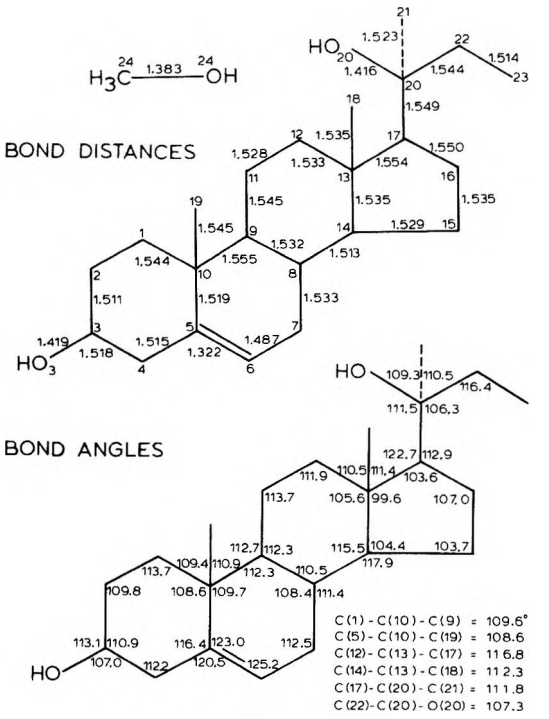


Figure 6. Observed bond lengths and angles in (20*S*)-20-ethyl-5-pregnene-3β,20-diol.

both of the factors quantitatively. However, in view of the facts that the methyl-Grignard reaction to 17α-hydroxypregnenolone and 16α,17α-epoxypregnenolone showed such highly selective addition to the opposite chirality and that the addition to pregnenolone showed again a high stereoselectivity, it is reasonable to assume that the steroid conformation in solution highly favors the same preferred conformation as found in the solid state.

The ethyl-Grignard reaction with pregnenolone was also carried out to assess the stereoselectivity of addition and to confirm the absolute configuration at C(20) by x-ray crystallography. The product showed characteristics similar to those previously reported.[16] The ratio of the 21-methyl signals at 1.25 ppm (20*S*) and 1.11 ppm (20*R*) of 20-ethyl-5-pregnene-3β,20-diol 3-acetate was 9:1.

The assignment of 20*S* for the absolute configuration of 20-alkyl-20-hydroxy steroids formed by the Grignard addition to pregnenolone has been made on the basis of the α-side attack and supported by a series of chemical modifications where steric control approach is assumed.[4,5] However, in view of our experience[13,17] for the necessary reassignment of the absolute configuration at C(19) of 19-alkyl-19-hydroxy steroids in spite of "the well-founded" chemical modification method,[18] we undertook the single-crystal growth and the total structural determination by diffraction methods of 20-ethyl-5-pregnene-3β,20-diol.

X-ray crystallographic analysis of the major diastereoisomeric product obtained from the ethyl-Grignard reaction shows conclusively that the configuration of C(20) is *S* (Figure 5). The crystals of (20*S*)-20-ethyl-5-pregnene-3β,20-diol were obtained from a methanol solution and contain one molecule of methanol per steroid molecule. The bond distances and bond angles shown in Figure 6 are within the range of values normally found in other 5-pregnene molecules.[19] The flexible B ring in this structure has nearly ideal C(8)/C(9) half-chair conformation as indicated by the $\Delta C_2^{5,6}$ asymmetry parameter[20] value of 1.0°. The A and C rings both have chair conformations, and the D ring has a distorted conformation nearly midway between a C(13) β-envelope (ΔC_s^{13} = 11.0°) and a C(13)/C(14) half-chair (ΔC_2^{16} = 9.4°).

The pertinent parts of the molecular structure of the major diastereoisomer are the *S* configuration of C(20) and the conformation of the C(20) substituents relative to the D ring. Figure 7 shows the conformation of the C(17)–C(20) bond with O(20) + gauche to C(13) and the ethyl substituent trans to C(13). Thus, the previous configurational assignment of 20-alkyl-20-hydroxy steroids is confirmed while that for 20-alkyl-17α,20-dihydroxy steroids still remains controversial.[5,7,21]

Shimizu in 1964 postulated[21] the 20*S* configuration for the isolated product of isohexyl-Grignard addition to 17α-hydroxypregnenolone acetate by simple assumption of the α-side attack, thus assigning the product to be 17α,20-dihydroxycholesterol. Chaudhuri et al. in 1969 reversed[5] the assignment to be 20*R* by chemical derivatization methods and thereby corrected the structure to be 17α,20-dihydroxyisocholesterol. We have in 1976 assigned[7] the 20*S* configuration for the isotope-labeled methyl-Grignard addition product of 17α-hydroxypregnenolone acetate by a correlation approach[13] of steroid conformations in solid and solution. If the stereochemical courses of the methyl- and isohexyl-Grignard reactions are assumed to be similar, it would indicate that the initial designation by Shimizu was correct, and the latter reassignment should be reversed. On the other hand, a large variance in stereoselectivity due to alkyl radicals of the Grignard reagents has been reported[5] to occur to a 20-keto steroid, 16α,17-epoxypregnenolone acetate. Therefore, a more decisive study is required in order to reconcile the controversy on the absolute configuration at C(20).

The high stereoselectivity observed in this study and the structure determination by x-ray crystallography support the concept that the rotational isomerism of the pregnenolone side chain in solution lies highly selectively (≥90%) toward the above D-ring conformation.

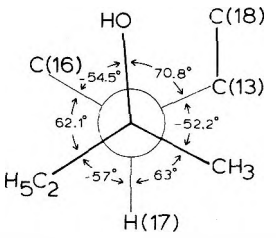


Figure 7. Observed conformation around the C(20)–C(17) bond of (20*S*)-20-ethyl-5-pregnene-3β,20-diol.

Experimental Section

Materials and General Methods. Methyl-d_3 iodide (99.5 atom %) was purchased from ICN, methyl-^{13}C iodide (90 atom %) from Bio-Rad Lab, [^{3}H]methyl iodide (80 mCi/mmol) from NEN Corp., and deuterium oxide (99.8%) from Mallinckrodt Chem. Methyl- and ethylmagnesium bromide in ether were purchased from Ventron Corp., and precoated silica gel GF plates (Uniplates, Analteck, Inc.) were used for TLC. Melting points were measured on a Fischer-Jones melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 267 spectrophotometer in KBr pellets. Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Varian EM-360 spectrometer at 60 MHz using tetramethylsilane (Me_4Si) as an internal standard. The 20*S*-CH_3/20*R*-CH_3 ratios were measured by the weight method. The area of corresponding signals on Xerox copies of the expanded spectra (0–1 ppm full scale, five repeated scans) was cut off and weighed on a Metler H20T balance. Mass spectra were recorded using a Dupont (CEC) 21-21-491 double-focusing mass spectrometer. Radioisotope scanning of TLC plates was made by a Packard 7201 radiochromatogram scanner.

20-Methyl-5-pregnene-3β,20-diol 3-Acetate (4 3-Acetate). To a stirred solution of 316 mg (1 mmol) of pregnenolone (**3a**) in 80 mL of benzene was added 14 mL (40 mmol) of 2.86 M methylmagnesium bromide in ether. The reaction mixture was stirred at room temperature for 18 h and then refluxed for 2 h. The reaction mixture was decomposed by dropwise addition of 60 mL of 20% ammonium chloride in an ice bath, and the product was extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to give 342 mg of crude product, mp 182–185 °C. TLC analysis showed only one spot (R_f 0.41, $CHCl_3$/acetone 8:2) with no sign of residual starting material. The crude product was recrystallized from chloroform/methanol to give 302 mg of 20-methyl-5-pregnene-3β,20-diol (**4**): mp 195–197 °C (187 °C,[3] 194–195 °C[22]); IR 3320, 1445, 1373, 1025 cm^{-1}.

A 129-mg portion of diol **4** was dissolved in 2 mL of pyridine and 0.4 mL of acetic anhydride. The mixture was left at room temperature for 16 h and then poured into ice water. The precipitates were collected by filtration and dried in vacuo to give 132 mg of the 3-acetate, mp 142–151 °C. The crude acetate was recrystallized from ethanol, giving 79 mg of **4** 3-acetate: mp 149–150 °C (151–152 °C[23]); IR 3320, 1720, 1465, 1360, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, Figure 2a) δ 0.85 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 1.20 (3H, s, 20(*pro-S*)-CH_3), 1.32 (3H, s, 20(*pro-R*)-CH_3), 2.04 (3H, s, 3-OAc), 5.40 (1H, m, 6-H).

(20*S*)-[20-C^2H_3]-20-Methyl-5-pregnene-3β,20-diol 3-Acetate (4a 3-Acetate). An ethereal solution of methyl-d_3-magnesium iodide was prepared from 4 mmol of methyl-d_3 iodide and 4.25 mmol of magnesium turnings in 4 mL of anhydrous ether. The prepared reagent was added to 714 mg (2 mmol) of **3a** acetate in 20 mL of anhydrous benzene, and the mixture was stirred at room temperature for 16 h and then refluxed for 2 h. The mixture was decomposed by addition of 10 mL of 20% ammonium chloride solution, and the product was extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to give 722 mg of crude material, mp 122–137 °C. ^{1}H NMR of the crude material showed a signal ratio of 91:9 for δ 1.32 and 1.20 (20*S*/20*R*). A 621-mg portion of the product was recrystallized from benzene/hexane to give 449 mg of (20*S*)-[20-C^2H_3]-20-methyl-5-pregnene-3β,20-diol 3-acetate (**4a** 3-acetate): mp 141–145 °C; ^{1}H NMR ($CDCl_3$, Figure 2b) δ 0.85 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 1.32 (ca. 3H, s, 20*R*-CH_3), 2.04 (3H, s, 3-OAc), 5.40 (1H, m, 6-H). The signal ratio for δ 1.32 and 1.20 was 88:12 (20*S*/20*R*).

Pregnenolone-*17,21,21,21-d*$_4$ (3b). To a solution of 620 mg (1.96 mmol) of pregnenolone (**3a**) in 10 mL of dioxane was added 2 mL (100 mmol) of deuterated water and 0.11 mL of 70% perchloric acid, and the mixture was kept at 65 °C for 3 days. The solvent was evaporated under a nitrogen stream, and the residue was recrystallized from methanol to give 169 mg of **3b**, mp 192–193 °C. The nearly quantitative labeling at C(21) was shown by the disappearance of the methyl signal at 2.1 ppm. A 120-mg portion of **3b** in 20 mL of acetone was treated with Jones' reagent (0.1 mL of standard solution[24]), and the resultant unconjugated ketone was treated with 0.03 mL of 5% NaOH in 15 mL of methanol. The product was purified through preparative TLC and recrystallizations to give 32 mg of progesterone. The deuterium labeling at C(21) was shown by ^{1}H NMR to again be extensive, and it was quantitatively analyzed by mass spectrometry. The areas of *m/e* 318 (M + 4), 276 (M + 4 − 42), and 46 (C^2H_3CO) are shown in Figure 3, and the labeling is calculated to be 88 atom % at each of the 17α,21,21, and 21 positions.

(20*R*)-[20-C^2H_3, 17α-^{2}H]-20-Methyl-5-pregnene-3β,20-diol 3-Acetate, (4b 3-Acetate). To a solution of 16 mg (0.05 mmol) of pregnenolone-*17α,21,21,21-d*$_4$ (**3b**) in 20 mL of benzene was added 10 mmol of methylmagnesium bromide (2.86 M in ether). The mixture was stirred at room temperature for 16 h and then decomposed with 15 mL of 20% ammonium chloride solution. The product was extracted with methylene chloride, and the extract was washed with water, dried with anhydrous sodium sulfate, and evaporated to dryness. The residue was acetylated with 1.0 mL of pyridine and 0.2 mL of acetic anhydride at room temperature for 16 h. Pouring into ice water and separation by filtration gave 15 mg of **4b** 3-acetate. The total crude material was used for ^{1}H NMR measurements; ($CDCl_3$, Figure 2c) δ 0.85 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 1.20 (ca. 3H, s, 20*S*-CH_3), 2.04 (3H. s, 3-OAc), 5.40 (1H, m, 6-H). The signal ratio for δ 1.32 and 1.20 was 13:87 (20*S*/20*R*).

(20*S*)-[20-$^{13}CH_3$-C^3H_3]-20-Methyl-5-pregnene-3β,20-diol 3-Acetate (4a 3-Acetate). An ethereal solution of 1.75 mmol of methyl-^{13}C iodide traced with [^{3}H]methyl iodide (12.5 mCi) was added to 48 mg (1.9 mmol) of ether-washed magnesium turnings. After a vigorous reaction subsided, the mixture was refluxed for 15 min. To a solution of 360 mg (1 mmol) of **3a** acetate in 8 mL of benzene was added 1 mmol of the methylmagnesium iodide solution (0.4 mL) prepared above. The mixture was stirred at room temperature for 16 h, refluxed for 1 h, and decomposed with 5 mL of 20% ammonium chloride solution. The product was extracted with methylene chloride, and the extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to give 376 mg of crude material. The crude product showed 99% of the total radioisotope in a single

peak at R_f 0.60 (chloroform/acetone 8:2) superimposed with authentic 20-methyl-5-pregene-3β,20-diol 3-acetate in the radioisotope scanning of the TLC plate. Some amount of unreacted pregnenolone acetate was detected in the crude material by TLC, IR, and ^{1}H NMR. Half of the product (188 mg) was subjected to preparative TLC (chloroform/acetone 8:2 followed by chloroform/acetone 95:5), and the radioactivity was detected by exposure to an x-ray film (Kodak RP/R2) which showed only one band. The radioisotopic band was eluted with ethanol/ether (2:8) and evaporation of the eluent gave 74 mg of (20*S*)-[20-$^{13}CH_3$-C^3H_3]-20-methyl-5-pregnene-3β,20-diol 3-acetate (**4a** acetate): mp 146–151 °C; ^{1}H NMR ($CDCl_3$, Figure 4) δ 0.15 and 2.25 (ca. 1.5 H each, d, (20*S*)-20-$^{13}CH_3$, $J_{H-^{13}C}$ = 126 Hz), 0.27 (ca. 0.1H, (20*R*)-20-$^{13}CH_3$, $J_{H-^{13}C}$ = 126 Hz), 0.87 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.05 (3H, s, 3-OAc), 5.45 (1H, m, 6-H). The signal ratio for δ 0.15 and 0.27 was 92:8 (20*S*/20*R*).

(20*S*)-[20-$^{13}CH_3$-C^3H_3]-20-Methyl-5-pregnene-3β,20-diol (4a). A solution of 22 mg of **4a** 3-acetate in 2 mL of ether was added to a suspension of 168 mg of lithium aluminum hydride in 25 mL of ether, and the mixture was stirred at room temperature for 30 min and then refluxed for 1 h. Water (12 mL) and 1 N H_2SO_4 (12 mL) was added, and the product was extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness to give 24 mg of residue. The crude product was recrystallized from chloroform/methanol to give 12 mg of **4a**: mp 196–197 °C; specific activity, 4.12 mCi of ^{3}H/mmol.

20-Ethyl-5-pregnene-3β,20-diol 3-Acetate. To a solution of 1 g (3.18 mmol) of **3a** in 170 mL of benzene was added 26 mL (78 mmol) of 3 M ethylmagnesium bromide in ether. The mixture was stirred at room temperature for 17 h and then refluxed for 1 h. After treating with 120 mL of 20% ammonium chloride solution, the product was extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from methylene chloride/methanol to give 903 mg of 20-ethyl-5-pregene-3β,20-diol: mp 159–165 °C; IR 3350, 1460, 1375, 1190, 1060, 1025 cm^{-1}. A 208-mg portion of the diol was acetylated with 2 mL of pyridine and 0.4 mL of acetic anhydride at room temperature for 16 h. The mixture was poured into ice water, and the precipitates were collected by filtration, washed with water, and dried in vacuo, giving 208 mg of crude material, mp 165–169 °C. The product was recrystallized from methanol to give 126 mg of 20-ethyl-5-pregnene-3β,20-diol 3-acetate: mp 171–175 °C (178–181 °C);[16] IR 3500, 1720, 1460, 1370, 1250, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, s, 18-CH_3), 1.03 (3 H, s, 19-CH_3), 1.11[16] (ca. 0.3H, s, (20*R*)-20-CH_3), 1.25 (ca. 3 H, s, (20*S*)-21-CH_3), 2.04 (3 H, s, 3-OAc), 5.38 (1 H, m, 6-H). The relative intensity of the signals at δ 1.25 and 1.11 was 9:1 (20*S*/20*R*).

X-Ray Crystallography. X-ray crystallographic analysis of (20*S*)-20-ethyl-5-pregnene-3β,20-diol/methanol (1:1) was carried out using a crystal with dimensions 0.36 × 0.40 × 0.41 mm obtained by evaporation of an acetone/methanol solution. The crystal data are as follows: $C_{23}H_{38}O_2 + CH_3OH$, formula wt 378.60 g; monoclinic; a = 13.7409 (7), b = 7.5992 (7), c = 11.0979 (8) Å, β = 104.857 (5)°; V = 1120.10 Å^3; Z = 2; ρ_{obsd} = 1.129 g cm^{-3}, ρ_{calcd} = 1.123 g cm^{-3}; space group $P2_1$.

The data were measured on a Nonius CAD-4 automatic diffractometer using Ni-filtered Cu Kα radiation (λ = 1.54178 Å) to a maximum θ of 75° at room temperature. A total of 2496 independent data were measured, of which 2124 had net intensities of at least twice the estimated standard deviation and were considered observed. The structure was solved by the multisolution direct methods program MULTAN[25] and refined by a full-matrix least-squares procedure to a final R value $(\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ of 4.6% for the observed data and 5.6% for all data. The positional and thermal parameters for all atoms except the y coordinate of C(9) were allowed to vary in the final cycles of refinement. The final fractional coordinates are given in Table I (Supplementary Material). Listings of F_o and F_c may be obtained from the authors.

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Registry No.—**3a**, 145-13-1; **3a** acetate, 1778-02-5; **3b**, 61574-54-7; **4**, 20976-92-5; **4** 3-acetate, 64070-60-6; [20-$^{13}CH_3$-C^3H_3]-**4a**, 64070-55-9; [20-$^{13}CH_3$]-**4a** 3-acetate, 64070-61-7; [20-C^2H_3]-**4a** 3-acetate, 64070-57-1; [20-C^2H_3,17α-^{2}H]-**4a** 3-acetate, 64070-59-3; [20-$^{13}CH_3$-C^3H_3]-**4a** 3-acetate, 64082-21-9; [20-C^2H_3,17α-^{2}H]-**4b** 3-acetate, 64082-22-0; [20-^{2}H]-**4b** 3-acetate, 64070-58-2; [20-$^{13}CH_3$-C^3H_3]-**4b** 3-acetate, 64070-56-0; methyl bromide, 74-83-9; deuterated water, 7789-20-0; [^{3}H]methyl iodide, 50630-93-8; (20*S*)-ethyl-5-pregnene-3β,20-diol 3-acetate, 21902-59-0; (20*R*)-ethyl-5-pregnene-3β,20-diol 3-acetate, 21902-60-3; (20*S*)-ethyl-5-pregnene-3β,20-diol, 54082-55-2; 20*R*-ethyl-5-pregnene-3β,20-diol, 23071-01-4; acetic anhydride, 108-24-7; (20*S*)-ethyl-5-pregnene-3β-20-diol: methanol (1:1), 64070-54-8; progesterone-17α,*21,21,21-d*$_4$, 64070-62-8; methyl-^{13}C iodide, 4227-956.

Supplementary Material Available: A listing of the atomic and fractional coordinates with the thermal parameters (2 pages). Ordering information is given on any current masthead page.

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Methyl 10-Epipheophorbide a: an Unusual Epimeric Stability Relative to Chlorophyll a or a'[1]

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Methyl 10-epipheophorbide a has been isolated from the equilibrium mixture of 1 and 2 by column chromatography on powdered cellulose (Whatman CF-1) using 10% ethylene dichloride in hexane as the eluting solvent. The equilibrium mixture of 1 and 2 contains 13–15% 2 compared to 15–20% chlorophyll a' present in the equilibrium mixture of chlorophyll a and a'. The rate of epimerization of 2 to 1 is much slower than the rate of chlorophyll a' to a conversion.

We report the isolation of methyl 10-epipheophorbide a (2) and its slow rate of epimerization relative to either chlorophyll a or a'. The stability of a pheophorbide analogue that is epimeric at the chiral C-10 position is particularly interesting since this chiral center may play an important role in both the synthesis and the photosynthetic activity of chlorophyll.[2] Several models have been proposed for the structure of the photosynthetic reaction center involving a chlorophyll dimer,[3] and the integrity of C-10 has been demonstrated as a structural requirement for the biological activity of chlorophyllase.[4]

Reaction-center chlorophyll makes up only a small fraction of the total leaf chlorophyll,[5] and until recently it has been very difficult to determine with reliability whether a minor component found in a plant leaf workup was an artifact or an important natural product occurring in trace amounts. Recent advances in instrumental studies have aided in the structural identification of these reactive species present in small amounts.[6,7] In bacterial systems capable of undergoing photosynthesis, a metal-free form of bacteriochlorophyll has been accepted as being part of the bacterial photosynthetic reaction center.[8] Evidence for or against the involvement of a metal-free chlorin in green plant photosynthesis is still forthcoming.

Results and Discussion

When a sample of 1 (Figure 1), isolated as described in the Experimental Section, was chromatographed on powdered cellulose, thin layer chromatography of the early fractions clearly showed two closely related constituents. The 220-MHz ^{1}H NMR spectrum of the early fractions (Figure 2) also showed the presence of two very similar chlorins. The α, β, and δ-methine proton resonances which are singlets in the ^{1}H NMR spectrum of pure 1[9] appear as six peaks between 8.4 and 9.5 ppm. Examination of the low-field methyl region between 3.0 and 4.7 ppm further corroborated this conclusion. Instead of the 5 singlet resonances expected, 9 peaks are observed.

Further examination of the ^{1}H NMR spectrum eliminated several plausible contaminants. The AB lines from the vinyl ABX system together with the C-10 proton resonances (at 6 ppm) integrated for three protons, ruling out both a mesopheophorbide contaminant as well as any compound resulting from the loss of the active hydrogen at C-10. The integrity of the low-field methyl groups and the methine bridge protons eliminated a variety of other possible contaminants.

The small difference in chemical shift observed for the protons affected suggested the subtle differences that would be expected from diasteriomers. Compound 1 has three chiral centers at C-7, C-8, and C-10. When ring V is cleaved with methylamine,[10] as in Scheme I, isochlorin e_4-6-carboxymethylamide dimethyl ester (3, Figure 3), in which C-10 is no longer chiral, is formed. If the mixture were epimeric at either C-7 or C-8 one would expect to see continued evidence in subsequent ^{1}H NMR spectra. When Scheme I was performed

Scheme I

$$1 + 2 + CH_3NH_2 \rightarrow 3$$

with a quantitative workup, the resulting ^{1}H NMR spectrum demonstrated the presence of only one chlorin. A similar multiplicity of peaks in the ^{1}H NMR spectra of a mixture of chlorophyll a and a' has been previously reported.[11]

Once the composition of the chlorin mixture was established the unexpected stability of 2 became a point of interest. Katz et al.[11] have studied the epimerization of chlorophylls at C-10 in a variety of solvents. They determined that an equilibrium mixture contained 15–20% chlorophyll a' (10-epichlorophyll a), and that this equilibrium mixture was temperature independent over a temperature range of 30 to 70 °C. The half-life for the epimerization of chlorophyll a at C-10 in either pyridine or tetrahydrofuran was estimated to be about 2 h.[11] It has further been cited that chlorophyll a' epimerizes "quickly" at 10 °C in tetrahydrofuran.[11]

We have observed that 2, a metal-free analogue of chlorophyll a, is stable indefinitely in $CDCl_3$ at room temperature. In the presence of 0.58 M deuteriopyridine, the half-life for epimerization is 45 h at 25 °C. When 2 was held at 56.5 °C in the presence of deuteriopyridine, it epimerized slowly to an equilibrium mixture containing 13–15% 2. The half-life for this process at 56.5 °C is 2.5 h.[12]

We believe that the origin of the large difference in the rate of epimerization at the C-10 position is the result of a considerable conformational difference between the chlorophyll and pheophorbide. Although ring V in the chlorophyll introduces considerable distortion and the magnesium is not in the plane of the chlorin ring, the central metal ion does serve to keep the four porphyrin nitrogens more or less coplanar.[13] Proton NMR evidence suggests that ring III in the pheophorbides is tipped upward at quite a sharp angle with N–H 1.4 Å above the plane of the porphyrin ring.[14] This is a sufficient enough distortion to stop internal movement of the N–H protons and move the ring III N–H from δ −1.7 to 0.90.[14] This distortion would also be expected to lead to considerable relief

Table I. 220-MHz ^{1}H NMR of 1 and 2 at Infinite Dilution in $CDCl_3$

Proton	Chemical shift, ppm 1	2
β-Methine	9.49	9.45
α-Methine	9.34	9.30
δ-Methine	8.57	8.51
OCH_3 (C-10)	3.91	3.85
(C-7)	3.70	3.66
CH_3 (C-5)	3.60	3.60
(C-1)	3.40	3.39
(C-3)	3.20	3.18
N-H (pyrrole)	0.90	0.90
	1.52	1.73

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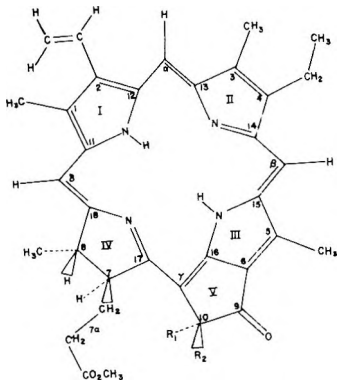

Figure 1. Structure of methyl pheophorbide a (**1**, $R_1 = CO_2CH_3$, $R_2 = H$) and methyl 10-epipheophorbide a (**2**, $R_1 = H$, $R_2 = CO_2CH$).

of strain at the C-10 position and is reflected in the slower rate of epimerization at that position.

The conformational differences between chlorophyll a and a′ and **1** and **2** are only reflected to a small degree in the equilibrium constant for the epimerization. The 15–20% chlorophyll a′ reported at equilibrium[11] compares favorably to the 13–15% **2** we observe at equilibrium. The mechanism for the epimerization most likely involves either the C-10 anion or the enol of the carbonyl group at C-9. The steric deformations imposed on the chlorophyll molecule by the incorporation of the Mg(II) ion affects the transition-state energy leading through these intermediates more than the ground-state energies reflected in the equilibrium constant and results in the more rapid epimerization of **2**. Chlorophyll a, **1**, and pheophytin a all exchange the C-10 proton under mild conditions. A careful study of the rate of C-10 proton exchange in each species as compared to the rate of epimerization in each species would be useful in understanding the mechanism of reaction.

It may also be noted that the chemical shift of protons in **2** on the outside of the porphyrin ring are to high field of **1**, while the N–H of **2** is to low field of **1** (Table I). This is also consistent with a distortion of the basic chlorin system, leading to a lower net ring-current effect in **2** than in **1**.

Experimental Section

Methyl Pheophorbide a (1). The procedure of Strain[15] was used to prepare chlorophyll a from fresh spinach leaves. The final sucrose column was replaced by Willstatter's procedures for the preparation[16a] and purification[16b] of methyl pheophorbide a. A final purification by column chromatography (described below) was added to remove any last traces of methyl pheophorbide b or allomerized methyl pheophorbide a. Inadvertently it also provided a fraction of **1** that was highly enriched in **2**.

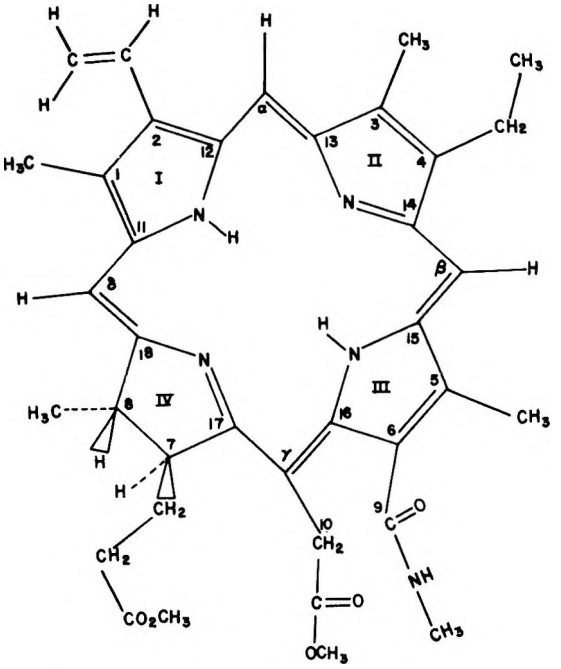

Figure 3. Structure of isochlorin e_4-6-carboxymethylamide dimethyl ester (**3**).

Methyl 10-Epipheophorbide a (2). A solution of **1** containing 0.546 g in a minimal amount of ethylene dichloride (EDC) was absorbed on 6 g of powdered cellulose (Whatman CF-1) and the EDC removed under vacuum, followed by a gentle stream of N_2 until the odor of EDC was no longer detectible. The chlorin sample was placed on a cellulose column (5.0 × 24.5 cm) packed in hexane, and the column was developed with 10% ethylene dichloride in hexane. The initial 25% of the total chlorin eluted from the column was enriched in **2** with individual fractions containing 80% **2**. TLC on Eastman Chromagram silica gel sheets, using 6% acetone in CCl_4 separated the epimers for analytical determination (R_f: **1**, 0.20; **2**, 0.23).

Isochlorin e_4-6-Carboxymethylamide Dimethyl Ester (3). The following procedure was found to be superior to those described by Fischer[17] and Pennington.[10] To a suspension of **1** (1.20 g, 1.98 mmol) in 10 mL of peroxide-free[18] tetrahydrofuran a solution containing 2 mL of 40% aqueous CH_3NH_2 (23.1 mmol) and 8 mL of THF was added dropwise with rapid stirring. After 2 h under N_2, the green

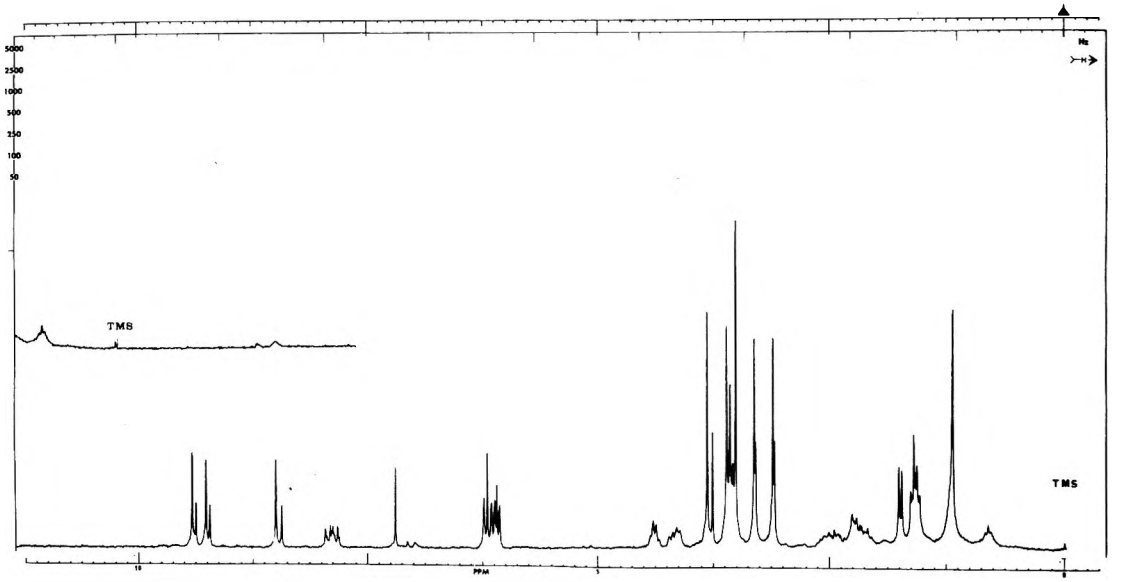

Figure 2. The 220-MHz ^1H NMR spectrum of a sample containing 67% **1** and 33% **2**.

solution was transferred to Et_2O (150 mL), washed with H_2O (100 mL × 4), and extracted with cold 5% HCl (50 mL × 6). The acid extract was washed with Et_2O (100 mL × 2) and extracted with CH_2Cl_2 (50 mL × 4). The CH_2Cl_2 extract was washed with H_2O and the solvent removed; yield after vacuum drying, 1.07 g (85%). Workup of the ether phases yielded 0.131 g (10.4%) of impure **2**. The major fraction was chromatographed on a silicic acid column (2.5 × 32 cm) with methanol/acetone/CCl_4 1:20:79 and twice crystalized from methylene chloride/pentane. Anal. Calcd for $C_{37}H_{43}O_5N_5$: C, 69.67; H, 6.81; N, 10.98. Found: C, 69.31; H, 6.73; N, 11.11.

To verify the structure of **2** the procedure was modified to employ a quantitative workup. $CHCl_3$ was added directly to the reaction flask, and the organic phase was washed with successive portions of cold water, removing the excess CH_3NH_2 but no chlorin. After solvent removal and vacuum drying, the entire reaction was analyzed by ^1H NMR, demonstrating the presence of only one chlorin.

Determination of the Epimer Ratio. In addition to the C-10 carbomethoxymethyl group used by Katz et al.,[11] the resonances for the β- and δ-methine protons were selected on the basis of minimum signal interference and maximum epimer chemical-shift difference. Either multiple scans were averaged on a Varian A-60 spectrometer and integrated, or in the case of very dilute samples the FT 220-MHz ^1H NMR spectrum was obtained and the peaks were integrated to determine the epimer ratio.

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Registry No.—**1**, 5594-30-9; **2**, 64070-09-3; **3**, 64045-79-0.

References and Notes

(1) This investigation was supported by research grants from the donors of The Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health (GM 16969). C.B.S. is the recipient of Public Health Service Research Career Development Award GM-70586 from the National Institute of General Medical Sciences.
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An Improved Chemical Synthesis of Racemic Phycocyanobilin Dimethyl Ester[1]

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The title compound, a bile pigment-like product isolated from the photosynthetically active chromoproteins of the blue-green and red algae, has been synthesized chemically in 32% overall yield from readily accessible starting materials. The key reaction of the synthesis consists of the preparation of the 3,4-dihydro-5(1*H*)-pyrromethenone **11a** by condensation of the monothiosuccinimide **8** with the pyrrole derivative **10**. This reaction represents a new type of formation of C=C bonds using resonance-stabilized phosphorus ylides.

Phycocyanobilin is the blue pigment released by boiling methanol from the photosynthetically active chromoproteins R and C phycocyanin and allophycocyanin of the blue-green and red algae.[2,3] The structure of phycocyanobilin has been elucidated by means of spectroscopic[4,5] as well as degradation studies.[6]

Three years ago a convergent chemical synthesis of racemic phycocyanobilin dimethyl ester (***rac*-15**) was achieved for the first time in our laboratory by condensation of methyl 5′-formylisoneoxanthobilirubinate (**13b**) with the 5(1*H*)-pyrromethenone derivative **11b**. The latter was obtained by reaction of the substituted monothiosuccinimide **8** with the brominated pyrrole derivative **9** under the conditions of Eschenmoser's sulfide contraction method.[7] However, the overall yield of this synthesis amounted only to 0.6% when referred to 3-ethylidene-4-methylpyrrolidine-2,5-dione which was used as a precursor of the ring I of the bile pigment. This unsatisfactory result was attributable to the occurence of several critical steps in the synthesis, namely: (i) the nonregiospecific transformation of the 3-ethylidene-4-methylpyrrolidine-2,5-dione into the corresponding 2-monothio derivative **8**, (ii) the moderate yield of the sulfide contraction reaction of **8** with **9** even though it could be improved from 18 to 49% by carrying out the reaction at −78 °C, and (iii) the relatively low reactivity of the *tert*-butyl ester **11b** toward the aldehyde **13b**.

We have now improved considerably the overall yield of the synthesis of phycocyanobilin dimethyl ester by introducing some substantial modifications into our earlier approach. Thus, monothioimide **8** was prepared regiospecifically as follows: alkylation of diethyl cyanomethylphosphonate (**1**)[8]

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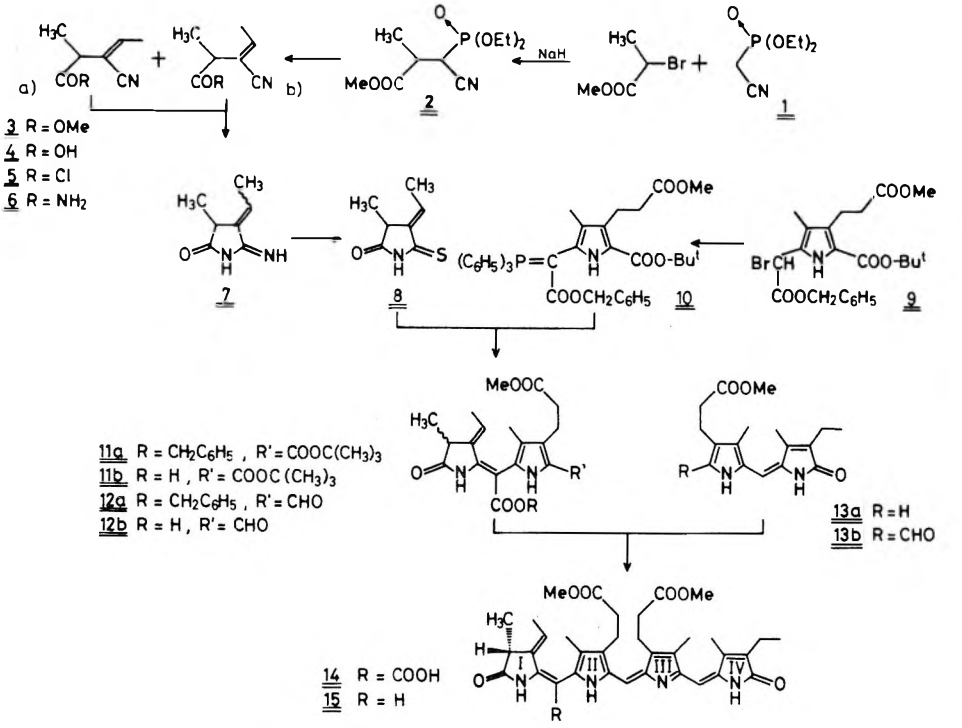

with methyl α-bromopropionate and subsequent Horner reaction of the obtained phosphonic acid ester **2** with acetaldehyde led to the monomethyl ester **3** (as a mixture of *Z* and *E* isomers) which was selectively hydrolyzed to the corresponding carboxylic acids **4** and subsequently transformed into the chlorides **5** and the amides **6**. The latter were cyclized in the presence of sodium ethoxide, yielding the succinimidines **7** which on treatment with hydrogen sulfide in pyridine afforded pure (*E*)-ethylidenemethylmonothiosuccinimide (**8**) in 38% overall yield (referred to **3**). As only the *E* isomer of **8** is obtained from a mixture of *Z*- and *E*-configurated **7**, no attempt was made to separate the stereoisomers of the intermediates **4** to **7**. Reaction of **8** with the phosphorus ylide **10**, which is readily accessible from the brominated pyrrole derivative **9**[7] by treatment with triphenylphosphine, afforded the 3,4-dihydro-5(1*H*)-pyrromethenone derivative **11a** in 79% yield. This kind of reaction, whose mechanism is presumably analogous to that of the Wittig reaction involving the C=S bond, represents a new general method for the synthesis of alkylidene lactams from monothioimides and resonance-stabilized phosphorus ylides.

Formylation of **11a** with triethyl orthoformate in trifluoroacetic acid (see ref 10) afforded the corresponding aldehyde **12a** whose benzylic ester group was cleaved by hydrogenolysis. Acid-catalyzed condensation of **12b** with the already known[11] methyl isoneoxanthobilirubinate **13a** yielded 5-hydroxycarbonylphycocyanobilin dimethyl ester ***rac*-14** which was finally decarboxylated by treatment with trifluoracetic acid at room temperature.

The overall yield of the thus obtained phycocyanobilin dimethyl ester (***rac*-15**) amounted to 32% (referred to **8**); its analytical and spectroscopic data, including IR, UV/vis, and ^{1}H NMR, agree with those of the pigment isolated from C phycocyanin by treatment with boiling methanol as well as of the synthetic material prepared earlier by us.[7]

Experimental Section

Melting points were determined with a Kofler hot-stage melting-point apparatus (Reichert) and are uncorrected. UV and visible spectra were recorded on a Leitz-Unicam SP 800 B spectrophotometer using methanol solutions unless otherwise specified. Infrared spectra (IR) were run on a Perkin-Elmer Model 157 G spectrometer in KBr disks. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Associates Models T-60 and XL 100 and a Bruker Model HFX-90 instruments using deuteriochloroform solutions. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane and coupling constants (*J* values) in hertz. Spin multiplicities are indicated by symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra (MS) data were obtained at an ionizing voltage of 70 eV on AEI MS 9 and MS 30 instruments as well as on a Varian-Mat Model CH 4 mass spectrometer. Metastable peaks are given as m*. Elemental analyses were performed by I. Beetz Microanalytical Laboratories, D-8640 Kronach. Preparative layer chromatography of colorless products or pigments made use of 2-mm-thick plates measuring 100 × 20 cm precoated with silica gel $PF_{254+366}$ or silica gel H (both from E. Merck, Darmstadt), respectively.

(*Z*)- and (*E*)-Methyl 3-Cyano-2-methyl-3-pentenoate (3a and 3b). A cooled suspension of sodium hydride (3 g as 80% dispersion in mineral oil) in ethylene glycol dimethyl ether (250 mL) was treated dropwise with diethyl cyanomethylphosphonate[8] (17.7 g), and the mixture was stirred until the evolution of hydrogen was complete. Thereafter, methyl 2-bromopropionate (16.7 g) was added at once and the mixture was allowed to stand at room temperature overnight. Then, sodium hydride (3 g as 80% dispersion in mineral oil) was added, the suspension was stirred for 5 h at room temperature before it was cooled to 0 °C and acetaldehyde (4.4 g) was added dropwise. The mixture was stirred overnight at room temperature, thereupon water (200 mL) was added and the reaction mixture was extracted repeatedly with ether (4 × 100 mL). The organic phases were dried (Na_2SO_4) and the solvent was removed on the rotary evaporator. The oily residue was then fractionated in a spinning-band column to give 10 g (63%) of the *E* isomer **3b**: $bp_{0.1}$ 48 °C; IR (neat) 2800, 2170, 1710, 1620, 1420, 1190, 1080, 1050, 980, 840 cm^{-1}; ^{1}H NMR δ 1.33 (d, 3, J = 7.5 Hz, CH_3), 1.90 (d, 3, J = 7 Hz, vinylic CH_3), 3.40 (9, 1, J = 7.5 Hz, 2-H), 3.72 (s, 3, OCH_3), 6.53 ppm (q, 1, J = 7 Hz, vinylic H); MS *m/e* (rel intensity) 153 (52, M$^+$), 138 (20), 122 (10), 94 (78), 67 (55), 59 (100); m* 124.4 (153 → 138), 47.7 (94 → 67).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.76; H, 7.90; N, 9.14. Found: C, 62.80; H, 7.95; N, 9.14.

A second fraction ($bp_{0.1}$ 51 °C) contained the *Z*-isomer 3a (2 g; 15%): IR (neat) 2800, 2170, 1710, 1625, 1420, 1190, 1110, 1050, 980, 840 cm^{-1}; ^{1}H NMR δ 1.33 (d, 3, J = 7.5 Hz, CH_3) 2.03 (d, 3, J = 7 Hz, vinyl CH_3), 3.41 (q, 1, J = 7.5 Hz, H-2), 3.72 (s, 3, OCH_3), 6.54 ppm (q, 1, J = 7 Hz, vinylic H); MS *m/e* (rel intensity) 153 (53, M$^+$), 138 (20), 122 (10), 94 (78), 67 (55), 59 (100); m* 124.4 (153 → 138), 47.7 (94 → 67).

(*Z*)- and (*E*)-3-Cyano-2-methyl-3-pentenoic Acid Amide (6). Both *Z* and *E* isomers **3a** and **3b** were suspended together in 2 N KOH (100 mL), and the mixture was stirred for 40 min at room temperature. The obtained solution was extracted repeatedly with ether (4 × 50 mL), then acidified with 2 N H_2SO_4, and extracted with ethyl acetate (5 × 100 mL). The organic phases were dried (Na_2SO_4), the solvent was removed on a rotary evaporator, and the oily residue (10 g) was dissolved without further purification in dry benzene (50 mL). The solution was cooled to 0 °C and $SOCl_2$ (10 mL) was added. After the evolution of gas had ceased, the mixture was stirred for 30 min at 40

°C and thereafter the solvent was removed in vacuo. The oily residue was dissolved in dry tetrahydrofuran (20 mL) and the solution was dropped slowly into a chilled (−78 °C) solution of liquid ammonia (20 mL) in tetrahydrofuran (100 mL). The mixture was allowed to warm to room temperature, the solvent was removed in vacuo, the residue was extracted with boiling acetone, and the remaining NH_4Cl was filtered off. The filtrate was concentrated in vacuo, and the oily residue was purified by column chromatography on alumina (activity grade II) eluting successively with ethyl acetate and ethyl acetate/methanol (8:2). The product obtained after evaporation of the solvent (5.5 g, 55%) was further purified by crystallization from ethyl acetate/ether, yielding a white solid which consisted of a mixture of both stereoisomeric amides **6**: MS *m/e* (rel intensity) 138 (20, M^+), 123 (20), 94 (78), 79 (25), 67 (100), 66 (95), 44 (75); m* 47.8 (94 → 67), 32.5 (138 → 66).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.83; H, 7.29; N, 20.27. Found: C, 60.72; H, 7.15; N, 20.20.

(*Z*)- and (*E*)-2-Ethylidene-5-imino-3-methylpyrrolidine-2-one (7). A solution of the amides **6** (5 g) in dry ethanol (100 mL) was treated with 2 N sodium ethoxide in ethanol (100 mL), and the mixture was allowed to stand for 1 h at room temperature. The solvent was removed on a rotary evaporator and the remaining oily residue was purified by column chromatography on silica gel (300 g) with ethyl acetate as eluent. After removal of the solvent, a white solid (4.8 g; 96%) was obtained: mp 189–190 °C; UV λ_{max} (log ϵ) 218 (3.95), 265 nm (4.10); MS *m/e* (rel intensity) 138 (80, M^+), 123 (30), 111 (60), 96 (35), 68 (45), 44 (100); m* 109.6 (138 → 123), 89.3 (138 → 111), 81.3 (111 → 96).

(*E*)-2-Ethylidene-3-methyl-1-thiosuccinimide (8). Gaseous hydrogen sulfide (dried over Al_2S_3) was bubbled for 1 h into a solution of the iminopyrrolidinones **7** (4 g) in dry pyridine (25 mL). Thereafter a stream of nitrogen was passed for 10 min through the boiling reaction mixture. After evaporation of the solvent, the remaining pyridine was removed by repeated addition of toluene and evaporation to dryness on the rotary evaporator. Recrystallization of the residue from ether/*n*-hexane yielded 3.5 g (78%) of the product as a pale-yellow solid, mp 115 °C (Lit.[7] mp 113–115 °C).

Benzyl α-Triphenylphosphoranylidene-α-[5-*tert*-butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methylpyrrol-2-yl)-acetate (10). A solution of triphenylphosphine (262 mg) in ether (10 mL) was added dropwise to a solution of **9**[7] (493 mg) in anhydrous ether (50 mL) and the mixture was allowed to stand overnight at room temperature. The formed phosphonium salt was separated by filtration, washed with ether (200 mL) and suspended in the same solvent (50 mL). The suspension was shaken in a separatory funnel with saturated aqueous Na_2CO_3 solution (50 mL) until two clear layers appeared. The organic phase was separated and the aqueous layer extracted once with ether (50 mL). The organic phases were dried (Na_2SO_4) and evaporated in vacuo to afford the product (641 mg; 95%) as a while solid: mp 65 °C; UV λ_{max} (log ϵ) 267 (4.29), 275 (4,31), 294 nm (4.44); IR 3470, 2980, 2920, 1730, 1640, 1620, 1430, 740, 697 cm^{-1}; ^1H NMR δ 1.50 (s, 9, $C(CH_3)_3$), 1.62 (s, 3, CH_3), 2.3 (m, 2, α-methylene of propionic ester), 2.8 (m, 2, β-methylene of propionic ester), 3.65 (s, 3, OCH_3), 5.10 (br s, 2, benzylic H), 7.3–7.6 (m, 20, phenyl H), 8.2 ppm (br s, 1, NH); MS m/e (rel intensity) 675 (10, M^+), 619 (10), 262 (12), 247 (30), 166 (100), 91 (55).

Anal. Calcd for $C_{41}H_{42}NO_6P$: C, 72.88; H, 6.27; N, 2.07; P, 4.58. Found: C, 73.04; H, 6.40; N, 2.10; P, 4.50.

3-Ethylidene-*ms*-benzyloxycarbonyl-5′-*tert*-butoxycarbonyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-4′-propionic Acid Methyl Ester (11a). A solution of **10** (641 mg) and **8** (221 mg) in dry toluene (20 mL) was refluxed for 18 h under argon. After evaporation of the solvent in vacuo, the desired product was separated from the formed triphenylphosphine sulfide by preparative TLC eluting with ether/*n*-hexane (6:4). Besides **11a** (420 mg; 79%), small quantities of the starting materials **8** (55 mg) and **10** (14 mg) were recovered, corresponding to two minor components of the reaction mixture with a higher and a lower R_f value than the main product, respectively. Crystallization of the latter from ether/*n*-hexane yielded yellow prisms, mp 138 °C, (lit.[7] 137–138 °C).

3-Ethylidene-*ms*-benzyloxycarbonyl-5′-formyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-4′-propionic Acid Methyl Ester (12a). A solution of **11a** (400 mg) in trifluoroacetic acid (8 mL) was allowed to stand under argon for 5 min at room temperature. Trimethyl orthoformate (4 mL) was added, and after 4 min the mixture was poured into water (50 mL). The obtained solution was extracted several times with CH_2Cl_2, the organic phases were dried (Na_2SO_4), and the solvent was removed on the rotary evaporator. Crystallization of the residue from ether/*n*-hexane yielded **12a** (300 mg; 93%): mp 142–143 °C; UV λ_{max} (log ϵ) 234 (4.57), 309 (4.74), 350 nm (4.22); IR 3480, 3330, 2950, 1780, 1665, 1640, 1250, 1150, 1025, 740 cm^{-1}; ^1H NMR δ 1.35 (d, 3, J = 7 Hz, 4-CH_3), 1.66 (dd, 3, ^3J = 7 Hz, ^5J = 1.5 Hz, ethylidene CH_3), 1.80 (s, 3, 3′-CH_3), 2.55 (m, 2, α-methylene of propionic ester), 3.08 (m, 3, β-methylene of propionic ester overlapped by 4-H), 3.63 (s, 3, OCH_3), 5.16 (s, 2, benzylic H), 5.24 (dq, 1, ^3J = 7 Hz, ^4J = 2 Hz, vinylic H), 7.24 (s, 5, phenyl H), 8.9 (br s, 1, NH), 9.61 (s, 1, CHO), 10.7 ppm (br s, 1, NH); MS *m/e* (rel intensity) 464 (10, M^+), 329 (20), 148 (15), 91 (100).

Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.24; H, 6.08; N, 6.03. Found: C, 67.24; H, 6.21; N, 6.06.

3-Ethylidene-4′-(2-methoxycarbonylethyl)-5′-formyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-*ms*-carboxylic Acid (12b). A solution of **12a** (300 mg) in tetrahydrofuran (30 mL) was hydrogenated on 10% palladized charcoal (100 mg) at atmospheric pressure for 10 min. The catalyst was removed by filtration and the solvent evaporated in vacuo. Crystallization of the residue from ether/*n*-hexane yielded the product (215 mg; 89%): mp 163 °C; UV λ_{max} (log ϵ) 234 (4.61), 311 (4.77), 349 nm (4.36); IR 3480, 3260, 2980, 1760, 1660, 1590, 1248 cm^{-1}; ^1H NMR δ 1.36 (d, 3, J = 7 Hz, 4-CH_3), 1.68 (d, 3, J = 7 Hz, ethylidene CH_3), 1.92 (s, 3, 3′-CH_3), 2.6 (m, 2, α-methylene of propionic ester), 3.1 (m, 3, β-methylene of propionic ester overlapped by 4-H), 3.73 (s, 3, OCH_3), 5.33 (q, 1, J = 7 Hz, vinylic H), 9.46 (s, 1, CHO), 10.3 (br s, 1, NH), 10.7 ppm (br s, 1, NH); MS *m/e* (rel intensity) 374 (<1, M^+), 330 (100), 315 (10); m* 291.2 (374 → 330).

18-Ethyl-3-ethylidene-2,7,13,17-tetramethyl-1,2,3,19,21,24-hexahydro-1,19-dioxo-22*H*-biline-8,12-dipropionic Acid Dimethyl Ester (Racemic Phycocyanobilin Dimethyl Ester) (*rac*-15). A solution of the aldehyde **12b** (33 mg) and methyl isoneoxanthobilirubinate (**13a**)[11] (33 mg) in methanol (10 mL) to which 2 drops of 40% HBr in glacial acetic acid had been added was refluxed under nitrogen for 30 min. The deep-blue reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in CH_2Cl_2 and shaken with dilute aqueous $NaHCO_3$. The organic phase was evaporated to dryness, and the residue was purified by preparative TLC on silica gel eluting with CH_2Cl_2/methanol (98:2). The obtained 5-hydroxycarbonylphycocyanobilin dimethyl ester (***rac*-14**) was dissolved in trifluoroacetic acid (2 mL) and the mixture was allowed to stand at room temperature for 5 min. The solvent was evaporated in a stream of dry nitrogen, and the residue was dissolved in CH_2Cl_2 and shaken with dilute aqueous $NaHCO_3$ solution. The organic phase was evaporated and the residue purified by preparative TLC on silica gel eluting with CH_2Cl_2/methanol (98:2). Recrystallization from CH_2Cl_2/*n*-hexane yielded 28 mg (46%) of phycocyanobilin dimethyl ester (***rac*-15**), mp 194 °C (Lit.[7] mp 194–195 °C), whose UV/vis, IR, and ^1H NMR spectra were identical with those reported earlier.[7]

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Registry No.—**1**, 2537-48-6; **3a**, 64056-66-2; **3b**, 64056-67-3; (*2*)-**6**, 64056-70-8; (*E*)-**6**, 64056-71-9; (*E*)-**7**, 64056-68-4; (*2*)-**7**, 64056-69-5; **8**, 64056-72-0; **9**, 43155-00-6; **10**, 64056-73-1; **11a**, 64091-58-3; **12a**, 64056-74-2; **12b**, 64056-75-3; **13a**, 64056-76-4; **14**, 64056-77-5; **15**, 43155-04-0; methyl 2-homopropionate, 5445-17-0; triphenyl phosphine, 603-35-0; trimethyl orthoformate, 149-73-5.

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Total Synthesis of Nitidine Chloride

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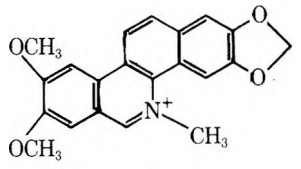
A new approach to the total synthesis of benzophenanthridine alkaloids is presented in the context of a preparation of the antileukemic agent nitidine chloride (**11**). The route proceeds from a diastereomeric mixture of isoquinolones **4** and **5** obtained in high yield by the addition of 4,5-dimethoxyhomophthalic anhydride (**2**) to 3,4-methylenedioxybenzylidenemethylamine (**3**). The pure trans isomer **5** is produced on heating the diastereomeric mixture in acetic acid. A classical Arndt–Eistert synthesis, followed by an intramolecular Friedel–Crafts acylation, affords intermediate **8**, which on $LiAlH_4$ reduction, dehydration, and dehydrogenation yields nitidine, isolated as the chloride **11**.

The benzo[*c*]phenanthridine alkaloid nitidine was first isolated from the root bark and root wood of *Zanthoxylum nitidum*, a woody climber which grows in most areas of Hong Kong.[1,2] The structure **1** of nitidine was established by its



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conversion to known compounds[2] and by synthesis of dihydronitidine.[3,4] Nitidine has since been isolated from a variety of *Zanthoxylum* and *Fagara* species in yields ranging from 0.003 to 0.07%.[5–13] Initial pharmacological testing of nitidine chloride uncovered high cytotoxicity, antileukemic activity in L1210 and P388 systems in mice, and inhibition of Lewis lung carcinoma.[14,15] However, interest in nitidine chloride as a potential chemotherapeutic agent has now waned owing to its acute toxicity.[16] Many of the reported syntheses[3,4,17] are based on the method established by Bailey and Worthing in their synthesis of chelerythrine,[18] which involves many steps and gives low overall yields. Recently we,[19] as well as Haimova et al.,[20] have been interested in synthetic applications of the condensation of Schiff bases with homophthalic anhydrides, and as a result of this work we now wish to report a new total synthesis of nitidine chloride.

The addition of 4,5-dimethoxyhomophthalic anhydride (**2**) to a solution of 3,4-methylenedioxybenzylidenemethylamine (**3**) in chloroform resulted in a rapid exothermic reaction which afforded a diastereomeric mixture of cis and trans isoquinolones **4** and **5** (Chart I). The cis isomer **4** (J_{AB} = 6 Hz) was insoluble in the reaction mixture and could be isolated in 49% yield by filtration, while the trans diastereomer **5** (J_{AB} = 0) could be isolated from the filtrate as a crystalline solid in 39% yield. On heating in refluxing acetic acid for 16 h the cis diastereomer **4** epimerized to the thermodynamically more stable trans isomer **5**. In practice, the mixture of **4** and **5** obtained by evaporation of chloroform from the reaction mixture was heated in acetic acid, which afforded the trans diastereomer **5** in 92% overall yield.

The low coupling constant (J_{AB} = 0) observed for the trans diastereomer **5** is in agreement with a preferred conformation in which the carboxyl and aromatic substituents occupy the expected pseudoaxial orientations.[19] By analogy to the effect of A strain in cyclohexenes,[21] the vicinal nonbonded interaction between the *N*-methyl substituent and the aromatic ring is expected to force the latter into the pseudoaxial conformation.

Treatment of the acid chloride of **5** with an alcohol-free ethereal solution of diazomethane gave the crystalline diazoketone **6**. Wolff rearrangement of **6** dissolved in methanol and tetrahydrofuran was performed by addition of a silver benzoate suspension in triethylamine.[22] The resulting methyl ester was hydrolyzed with potassium hydroxide in ethanol to the homologous acid **7**. Intramolecular Friedel–Crafts acylation of **7** with poly(phosphoric acid) yielded the tetracyclic ketone **8**. The conversion of **7**, in which the aromatic and carboxymethyl substituents are pseudoaxial, to the conformationally rigid tetracyclic system **8** was accompanied by a change in the NMR coupling constant between protons H_A and H_B from J_{AB} = 0 to J_{AB} = 11 Hz, thus confirming the trans disposition of protons H_A and H_B.[23] Lithium aluminum hydride reduction of **8** proceeded in 90% yield to a diastereomeric mixture of amino alcohols **9** and **10** in a 9:1 ratio as estimated by integration of the *N*-methyl signals in the NMR spectrum. The major diastereomer **9** was isolated by fractional crystallization and shown to possess the expected[24] pseudoequatorial alcohol by the appearance of the methine proton α to the alcohol as a doublet of doublets with coupling constants 5 and 12 Hz in its NMR spectrum.[23a,d] Examination of Dreiding models reveals that in the conformationally rigid system **9** a pseudoequatorial alcohol at C-12 and the 10b methine proton are trans. The minor diastereomer **10** was also isolated by fractional crystallization, and the alcohol was shown to be pseudoaxial and therefore cis to the 10b methine proton by the appearance of the methine proton α to the alcohol as an unresolved multiplet having a width at half height of 6 Hz.[23a,d] Dehydration and dehydrogenation of the diastereomeric mixture of amino alcohols **9** and **10** with palladium on charcoal in refluxing acetic acid afforded nitidine, isolated as the chloride **11** in 47% yield, accompanied by a 24% yield of the hydrogenolysis product **12**.

Experimental Section

All reactions were performed under a nitrogen atmosphere unless otherwise noted and solvents were removed on a rotary evaporator under reduced pressure. Melting points were taken on a Thomas Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument or JEOL PFT-100 spectrometer, and, except where noted, in $CDCl_3$ solvent. Chemical shifts are reported in ppm relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Dupont 21-492B double-focusing spectrometer using an ion source temperature of 200–280 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA. Microanalyses were performed by Dr. C. S. Yeh and associates of Purdue University.

***cis*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (4).** 4,5-Dimethoxyhomophthalic anhydride (**2**,[25] 2.22 g, 10 mmol) was added to a stirred solution of 3,4-methylenedioxybenzylidenemethylamine (**3**, 1.63 g, 10 mmol) in chloroform (10 mL) at 25 °C. An exothermic reaction occurred as the anhydride dissolved. After 20 min the precipitate was filtered and washed with chloroform to give a pale-yellow solid (1.88 g, 49%): mp 227–230 °C (dec). An analytical sample was obtained by recrystallization from acetic acid: mp 229–230 °C (dec);

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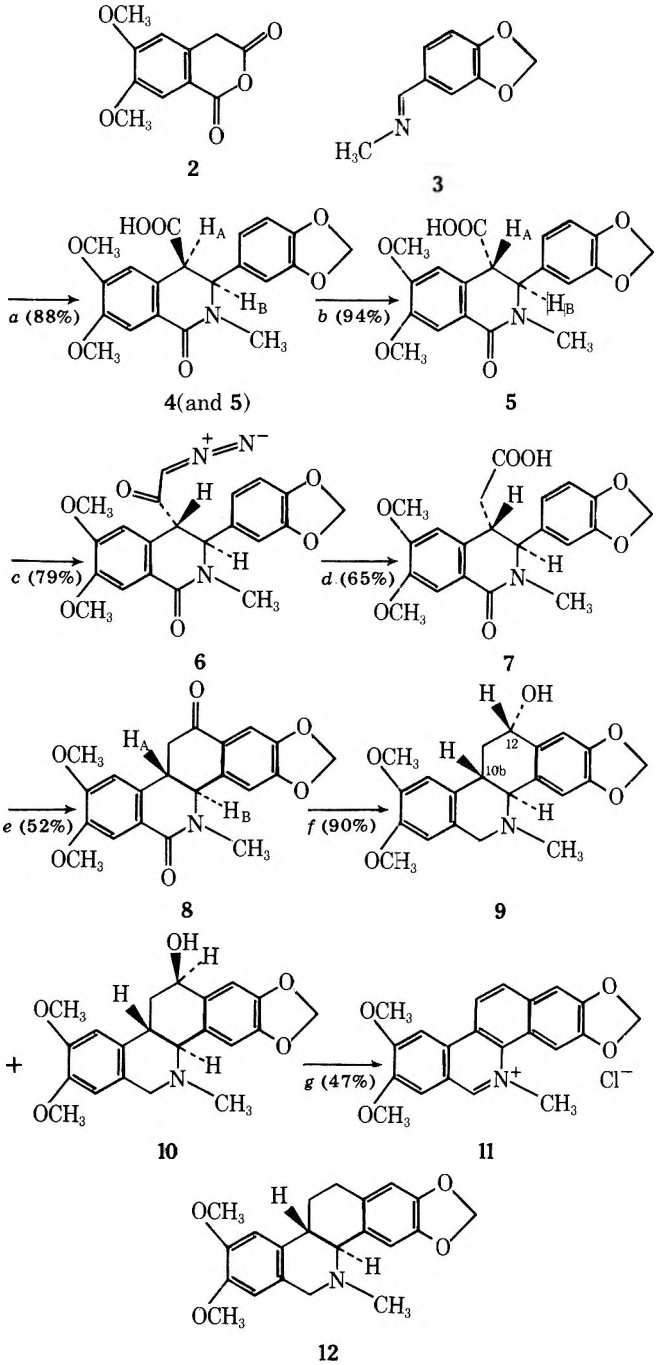
Chart I



[a] $CHCl_3$, 25 °C (30 min). [b] CH_3COOH, reflux (16 h). [c] (1) $SOCl_2$, C_6H_6, reflux (15 min), 25 °C (60 min); (2) CH_2N_2, 0 °C (5 min), then 25 °C (20 min). [d] (1) Silver benzoate, CH_3OH, THF, 25 °C (3 h); (2) KOH, 95% EtOH, reflux (1.5 h). [e] PPA, steam bath (35 min). [f] $LiAlH_4$, THF, reflux (16 h). [g] (1) CH_3COOH, 5% Pd/C, reflux (18 h); (2) aq NaCl.

IR (KBr) 3300–2800, 1740, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 8.37 (s, 1 H, exchangeable with D_2O), 7.57 (s, 1 H), 7.13 (s, 1 H), 7.00–6.50 (m, 3 H), 5.97 (s, 2 H), 5.03 (d, 1 H, J = 6 Hz), 4.63 (d, 1 H, J = 6 Hz), 3.87 (s, 3 H), 3.80 (s, 3 H), 2.90 (s, 3 H); mass spectrum m/e (rel intensity) 385 (M^+, 17), 339 (67), 222 (53), 178 (47), 164 (100), 163 (60), 162 (73).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.23; H, 5.12; N, 3.80.

***trans*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (5).** The filtrate from the previous experiment was concentrated and the residue recrystallized from ethyl acetate to give a colorless solid (1.52 g, 39%): mp 208–209 °C; IR (KBr) 3400–2400, 1735, 1625, 1605 cm^{-1}; NMR (Me_2SO-d_6) δ 13.00 (br s, 1 H, exchangeable with D_2O), 7.50 (s, 1 H), 7.00–6.33 (m, 4 H), 5.97 (s, 2 H), 5.18 (br s, 1 H), 4.00 (s, 1 H), 3.83 (s, 3 H), 3.77 (s, 3 H), 2.98 (s, 3 H); mass spectrum m/e (rel intensity) 385 (M^+, 21), 341 (10), 222 (34), 194 (35), 165 (10), 164 (100), 162 (10).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.10; H, 5.03; N, 3.47.

Epimerization of *cis*- to *trans*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxy-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (5). A solution of cis acid **4** (3.00 g, 7.78 mmol) in glacial acetic acid (150 mL) was heated at reflux for 16 h. The acetic acid was evaporated under reduced pressure and the resulting yellow powder was triturated with hot benzene (100 mL). Filtration gave a very pale yellow solid (2.82 g, 94%): mp 208–210 °C.

In later experiments, the cis acid **4** was not isolated but epimerized immediately to the trans acid **5**. Thus, 4,5-dimethoxyhomophthalic anhydride (**2**, 26.85 g, 121 mmol) was added to a stirred solution of 3,4-methylenedioxybenzylidenemethylamine (**3**, 19.72 g, 121 mmol) in chloroform (450 mL) at 25 °C. At the end of 30 min the chloroform was removed under reduced pressure. To the residue was added glacial acetic acid (1200 mL) and the resulting mixture was heated at reflux for 16 h. Removal of acetic acid followed by trituration with benzene gave a pale-yellow solid (42.85 g, 92%): mp 206–209 °C.

***trans*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-diazomethylcarbonyl-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (6).** A mixture of trans acid **5** (21.00 g, 54.5 mmol) and thionyl chloride (21 mL, 272 mmol) in benzene (150 mL) was heated at reflux for 15 min and then stirred at 25 °C for 1 h. Excess thionyl chloride and benzene were removed by distillation under reduced pressure. The resulting tan residue, dissolved in benzene (150 mL), was added to an ethereal solution of alcohol-free diazomethane (ca. 142 mmol) at 0 °C. After stirring at 25 °C for 20 min, the precipitate (17.69 g, 79%) was collected: mp 163.5 °C (dec). An analytical sample was obtained by recrystallization from hexane–ethyl acetate (1:1): mp 164 °C (dec); IR (KBr) 2120, 1650, 1610 cm^{-1}; NMR δ 7.77 (s, 1 H), 6.40–6.80 (m, 4 H), 5.93 (s, 2 H), 5.18 (d, 1 H, J = 1 Hz), 4.90 (s, 1 H), 4.00 (s, 3 H), 3.90 (s, 3 H), 3.62 (d, 1 H, J = 1 Hz), 3.07 (s, 3 H); mass spectrum m/e (rel intensity) 409 (M^+, 16), 381 (68), 340 (29), 339 (25), 190 (100), 164 (26), 162 (24).

Anal. Calcd for $C_{21}H_{19}N_3O_6$: C, 61.61; H, 4.68; N, 10.26. Found: C, 61.74; H, 4.80; N, 10.41.

***trans*-*N*-Methyl-3-(3′,4′-methylenedioxyphenyl)-4-carboxymethyl-6,7-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (7).** To a solution of diazoketone **6** (17.59 g, 43.0 mmol) in methanol (300 mL) and tetrahydrofuran (400 mL) was added a suspension of silver benzoate (2.29 g, 10 mmol) in triethylamine (60 mL) over a period of 25 min at 25 °C. Rapid gas evolution occurred after introduction of the silver benzoate–triethylamine suspension and the pink reaction mixture gradually darkened. At the end of 3 h, activated charcoal (Darco, 3 g) was added and the resulting mixture was heated on a steam bath. Hot filtration through Celite and concentration gave an orange oil. The orange oil was immediately hydrolyzed with potassium hydroxide (85%, 4.25 g, 64.5 mmol) in 95% ethanol (160 mL) at reflux for 1.5 h. Most of the ethanol was removed under reduced pressure, and water (150 mL) was added to the residue. The solution was acidified with concentrated hydrochloric acid. The aqueous phase was extracted with chloroform (150 mL) and the organic phase was backwashed with 5% aqueous sodium bicarbonate (ca. 900 mL). The combined aqueous extracts were acidified and extracted with chloroform (250 mL). The chloroform was evaporated and the residue recrystallized from methanol, yielding a pale-yellow solid (11.16 g, 65%): mp 203–206 °C. The analytical sample was prepared by recrystallization from methanol: mp 206–207 °C; IR (KBr) 3400–2800, 1725, 1635, 1610 cm^{-1}; NMR δ 10.60 (s, 1 H, exchangeable with D_2O), 7.63 (s, 1 H), 6.80–6.35 (m, 4 H), 5.83 (s, 2 H), 4.76 (s, 1 H), 3.90 (s, 3 H), 3.73 (s, 3 H), 3.60–3.23 (m, 1 H), 3.10 (s, 3 H), 2.92–2.62 (m, 2 H); mass spectrum m/e (rel intensity) 399 (M^+, 100), 340 (17), 339 (25), 208 (73), 191 (35), 164 (40).

Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.30; H, 5.46; N, 3.36.

***trans*-*N*-Methyl-2,3-methylenedioxy-6,12-dioxo-8,9-dimethoxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (8).** The acid **7** (3.60 g, 9 mmol) was stirred with poly(phosphoric acid) (36 g) exposed to air on a steam bath for 35 min during which time it changed from pale yellow through orange, then ruby, and finally to dark brown. The reaction mixture was hydrolyzed with water (400 mL) and extracted with chloroform (300 mL). The chloroform extract was backwashed with 5% sodium carbonate (200 mL) and then water (400 mL). After drying over anhydrous magnesium sulfate, removal of chloroform and trituration of the pale tan residue with hot methanol (30 mL) gave felt crystals (1.77 g, 52%): mp 272 °C (dec). An

analytical sample was prepared by column chromatography on silica gel (98:2 $CHCl_3/CH_3OH$ as eluent): mp 274 °C (dec); IR (KBr) 1680, 1650, 1605 cm^{-1}; NMR δ 7.73 (s, 1 H), 7.53 (s, 1 H), 7.00 (s, 1 H), 6.73 (s, 1 H), 6.13 (s, 2 H), 4.95 (d, 1 H, J = 11 Hz), 4.00 (s, 6 H), 3.70–3.20 (m, 2 H), 3.20 (s, 3 H), 2.77 (d, 1 H, J = 14 Hz); mass spectrum m/e (rel intensity) 381 (M^+, 75), 352 (12), 232 (14), 191 (34), 165 (100), 147 (18).

Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.34; H, 5.16; N, 3.69.

***N*-Methyl-2,3-methylenedioxy-8,9-dimethoxy-12α-hydroxy-4bβ,5,6,10bβ,11,12-hexahydrobenzo[*c*]phenanthridine (9).** A mixture of keto amide 8 (778 mg, 2.04 mmol) and lithium aluminum hydride (95%, 163 mg, 4.08 mmol) in THF (100 mL) was heated at reflux for 16 h. The reaction mixture was decomposed by addition of water (1 mL), 15% sodium hydroxide (1 mL), and water (3 mL) at 0 °C. The residue was filtered and washed with chloroform (75 mL), and the combined filtrates were dried over anhydrous magnesium sulfate. Removal of solvent and column chromatography on silica gel afforded colorless crystals (680 mg, 90%), mp 180–193 °C, which by NMR is a diastereomeric mixture as evidenced by the presence of two $N-CH_3$ peaks at δ 2.23 and 2.16 in the ratio of 1 to 9. Two recrystallizations from benzene gave a colorless soft solid (437 mg, 58%): mp 211–212 °C; IR (KBr) 3600–3100 cm^{-1}; NMR δ 7.22 (s, 1 H), 7.10 (s, 1 H), 6.90 (s, 1 H), 6.60 (s, 1 H), 5.95 (br s, 2 H), 4.90 (d of d, 1 H, J = 5, 12 Hz), 4.47 (d, 1 H, J = 16 Hz), 4.10–3.50 (m, 2 H), 3.90 (br s, 6 H), 3.27–2.50 (m, 2 H), 2.16 (s, 3 H), 2.00–1.20 (m, 2 H, one exchangeable with D_2O); mass spectrum m/e (rel intensity) 369 (M^+, 36), 351 (82), 350 (36), 338 (100), 192 (45).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.64; H, 6.26; N, 3.51.

***N*-Methyl-2,3-methylenedioxy-8,9-dimethoxy-12β-hydroxy-4bα,5,6,10bβ,11,12-hexahydrobenzo[*c*]phenanthridine (10).** The mother liquors from above were combined and evaporated to dryness, and the residue was subjected to fractional crystallization from benzene to give colorless crystals (19 mg, 2.5%): mp 193–195 °C; NMR δ 7.30 (s, 1 H), 6.90 (s, 1 H), 6.87 (s, 1 H), 6.60 (s, 1 H), 5.93 (s, 2 H), 4.87 (m, 1 H, $W_{1/2}$ = 6 Hz), 4.47 (d, 1 H, J = 16 Hz), 3.90 (s, 6 H), 3.80–2.52 (m, 4 H), 2.22 (s, 3 H), 2.13–1.50 (m, 2 H, one exchangeable with D_2O); mass spectrum m/e (rel intensity) 369 (M^+, 100), 351 (63), 338 (33), 336 (29), 320 (40), 192 (45).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.27; H, 6.27; N, 3.79. Found: C, 68.06; H, 6.43; N, 3.51.

Nitidine Chloride (11). A 9:1 mixture of amino alcohols **9** and **10** (0.52 g, 1.41 mmol) and 5% palladium on charcoal (180 mg) in glacial acetic acid (100 mL) was heated at reflux for 18 h. After cooling, the catalyst was removed by filtration through a pad of Celite. Evaporation of the yellow filtrate gave a green-yellow residue which was then dissolved in water (50 mL) and ethanol (10 mL). To the resulting yellow solution was added 10 mL of 15% sodium chloride solution. An immediate precipitation of flocculent material was observed. This was filtered, washed with water (25 mL), and dried over phosphorus pentoxide at 25 °C under vacuum. In this manner, a greenish-yellow residue (278 mg, 47%), mp 274–278 °C (dec, lit.[17] mp 275–277 °C), was obtained. The infrared spectrum (KBr) was identical with that of an authentic sample of nitidine chloride obtained from the National Cancer Institute. Recrystallization from methanol (50 mL) gave yellow needles (242 mg, 41%): mp 284–286 °C (dec), mixture mp 281–286 °C (dec). An authentic sample melted at 281–286 °C (dec): NMR (Me_2SO-d_6) δ 9.86 (s, 1 H), 8.95 (d, 1 H, J = 8 Hz), 8.40 (s, 1 H), 8.32 (s, 1 H), 8.30 (d, 1 H, J = 8 Hz), 7.92 (s, 1 H), 7.80 (s, 1 H), 6.36 (s, 2 H), 4.90 (s, 3 H), 4.24 (s, 3 H), 4.05 (s, 3 H); mass spectrum m/e (rel intensity) 333 ($M^+ - CH_3Cl - 2H_2O$, 100), 52 (18), 50 (CH_3Cl, 60).

Anal. Calcd for $C_{21}H_{18}NClO_4 \cdot 2H_2O$: C, 60.07; H, 5.28; N, 3.34; Cl, 8.46. Found: C, 59.95; H, 5.44; N, 3.14; Cl, 8.60.

***trans*-*N*-methyl-2,3-methylenedioxy-8,9-dimethoxy-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (12).** The filtrate from above was extracted with chloroform (75 mL), and the extracts were combined and washed once with water (100 mL). After drying over anhydrous magnesium sulfate, the chloroform was removed under reduced pressure. The residue, upon chromatography on silica gel (chloroform as eluent), gave a pale yellow solid (120 mg, 24%): mp 190–196 °C. One recrystallization from methanol afforded colorless plates: mp 198–200 °C; IR (KBr) 3100–2700, 1600, 1500, 1465 cm^{-1}; NMR δ 7.30 (s, 1 H), 6.93 (s, 1 H), 6.63 (s, 2 H), 5.93 (s, 2 H), 4.47 (d, 1 H, J = 16 Hz), 4.13–3.30 (m, 8 H), 3.30–2.37 (m, 3 H), 2.22 (s, 3 H), 2.10–1.33 (m, 2 H); mass spectrum m/e (rel intensity) 353 (M^+, 35), 352 (24), 323 (24), 322 (100), 84 (16).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.12; H, 6.51; N, 4.01.

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Synthesis of 7- and 9-β-D-Ribofuranosides of 3-Deaza-6-thioguanine and 3-Deaza-2,6-diaminopurine by a Novel Ring Closure of 4(5)-Cyano-5(4)-cyanomethylimidazole β-D-Ribofuranosides

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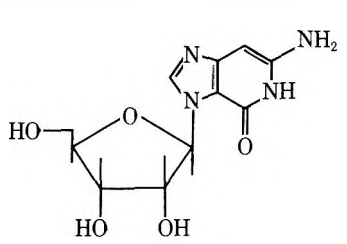
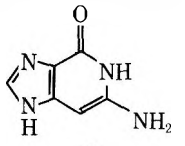
3-Deaza-7-β-D-ribofuranosyl-6-thioguanine [6-amino-3-β-D-ribofuranosylimidazo[4,5-c]pyridine-4(5*H*)-thione (**11**)] and 3-deaza-6-thioguanosine [6-amino-1-β-D-ribofuranosylimidazao[4,5-c]pyridine-4(5*H*)-thione (**16**)] were synthesized by the novel cyclization (and subsequent deblocking) of 5-cyano-4-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**6**) and 4-cyano-5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**9**), respectively, with hydrogen sulfide and triethylamine. 3-Deaza-2,6-diamino-7-β-D-ribofuranosylpurine [4,6-diamino-3-β-D-ribofuranosylimidazo[4,5-c]pyridine (**18**)] and 3-deaza-2,6-diamino-9-β-D-ribofuranosylpurine [4,6-diamino-1-β-D-ribofuranosylimidazo[4,5-c]pyridine (**19**)] were synthesized directly by the novel cyclization of blocked imidazole nucleosides **6** and **9**, respectively, with ammonia. Blocked imidazole nucleosides **6** and **9** were prepared from the stannic chloride catalyzed condensation of 4(5)-cyano-5(4)-cyanomethyl-1-trimethylsilylimidazole (**4**) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**). 6-Amino-3-β-D-ribofuranosylimidazo[4,5-c]pyridine (**12**) and 6-amino-1-β-D-ribofuranosylimidazo[4,5-c]pyridine (**17**) were obtained from the Raney nickel desulfurization of imidazo[4,5-c]pyridine nucleosides **18** and **19**, respectively. Debromination and deblocking of 6-amino-4-bromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine (**20**) (obtained by the cyclization of blocked imidazole nucleoside **9** with anhydrous hydrogen bromide) also led to imidazo[4,5-c]pyridine nucleoside **17**. The structures of the nucleosides were established by the use of proton NMR. Mechanistic implications of these cyclizations are discussed.

The synthesis[2] and antibacterial activity[3] of 3-deaza-7-β-D-ribofuranosylguanine [(6-amino-3-β-D-ribofuranosylimidazo[4,5-c]pyridin-4(5*H*)-one (**1**)] was recently described. Since it is likely that **1** acts as a prodrug of 3-deazaguanine (**2**),



1



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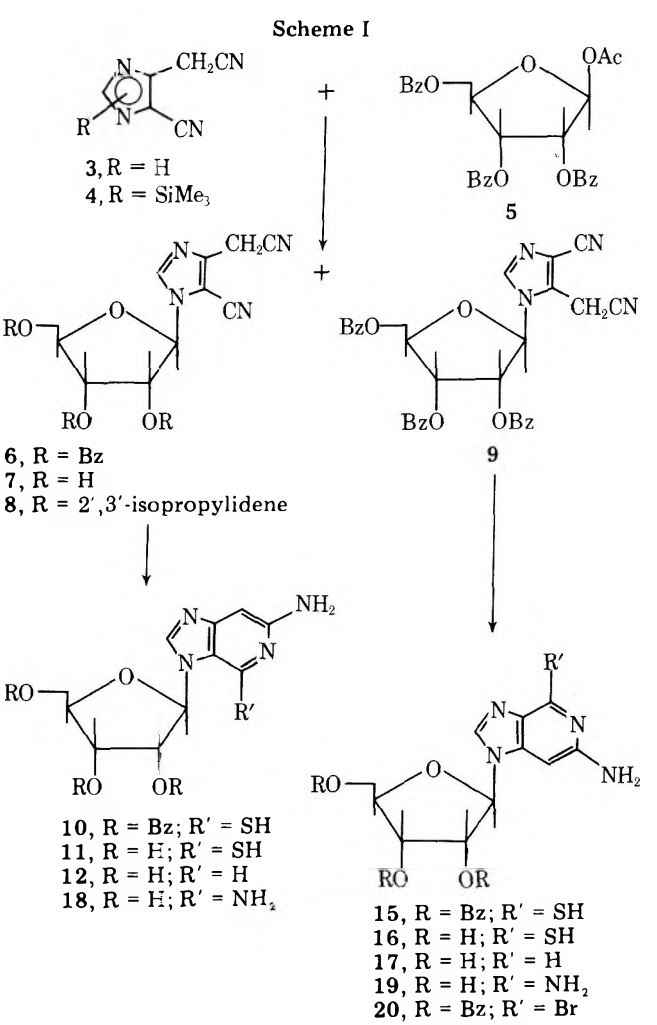
a potent guanine antimetabolite with anticancer,[4] antiviral,[5] and antibacterial activity,[6] the synthesis of the 3-deaza-7-β-D-ribofuranosyl modifications of 6-thioguanine and 2,6-diaminopurine, both known antimetabolites with anticancer activity,[7] was considered. Furthermore, the 9-β-D-ribofuranosyl derivative of 3-deaza-6-thioguanine and 3-deaza-2,6-diaminoguanine was considered an equally interesting synthetic goal.

Previous studies by Robins, Townsend, and their coworkers which led to the synthesis of certain 3-deazapurines,[8a,b] 3-deazaguanosine, and **1**[2] indicated that the ribosides of 4(5)-cyano-5(4)-cyanomethylimidazole (**3**) could be cyclized with various reagents directly into the desired 4,6-disubstituted imidazo[4,5-c]pyridine nucleosides.[9] Imidazole **3** has previously been cyclized with anhydrous hydrogen bromide to provide 6-amino-4-bromoimidazo[4,5-c]pyridine.[8b] This bicyclic intermediate, its 9-riboside,[12] and 4,6-dichloro-1-β-D-ribofuranosyl imidazol[4,5-c]pyridine[12b] do not lead to 4,6-disubstituted imidazo[4,5-c]pyridines and their ribosides due to lack of reactivity of the halogen atoms.[8b,12] Furthermore, in an attempt to circumvent the resistance to nucelophilic substitution of the chlorine atoms in imidazo[4,5-c]-pyridines, Kroon et al. recently prepared the fluoro analogue, 4,6-difluoroimidazo[4,5-c]pyridine for substitution studies.[14] Brief investigations of this intermediate revealed a reactivity similar to 4,6-dichloroimidazo[4,5-c]pyridine and, consequently, not a suitable intermediate to 4,6-disubstituted imidazo[4,5-c]pyridines. Thus, imidazole **3** was considered for ribosylation and subsequent cyclization procedures.

The stannic chloride catalyzed condensation of trimethylsilylated imidazoles with fully acylated ribofuranoses[15] has been found to be an excellent procedure for preparing the

Scheme I



3, R = H
4, R = $SiMe_3$
5
6, R = Bz
7, R = H
8, R = 2′,3′-isopropylidene
9
10, R = Bz; R′ = SH
11, R = H; R′ = SH
12, R = H; R′ = H
18, R = H; R′ = NH_2
15, R = Bz; R′ = SH
16, R = H; R′ = SH
17, R = H; R′ = H
19, R = H; R′ = NH_2
20, R = Bz; R′ = Br

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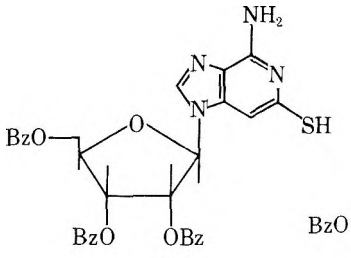
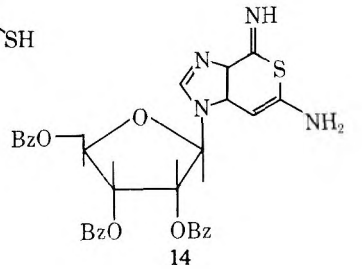
requisite imidazole nucleosides for conversion into 7- and 9-ribosides of 3-deazaguanine[2] and imidazo[4,5-*d*]pyridazine ribosides.[10] Thus, treatment of 4(5)-cyano-5(**4**)-cyanomethyl-1-trimethylsilyimidazole (**4**) in 1,2-dichloroethane with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**) and 1.44 molar equiv of anhydrous stannic chloride provided two blocked imidazole nucleosides, 5-cyano-4-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**6**, 72%) and 4-cyano-5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (**9**, 18%), tentatively assigned the structures as shown in Scheme I. Reduction of the amount of anhydrous stannic chloride in this ribosylation procedure to 0.72 molar equiv significantly affected the ratio of positional isomers (50% of **6**, 25% of **9**). This corresponds to the stannic chloride catalyzed ribosylation of methyl 4(5)-cyanomethyl-1-trimethylsilyimidazole-5(4)-carboxylate,[2] although not to such a marked extent.[16]

Reaction of nucleoside **6** with ethanolic hydrogen sulfide and triethylamine at room temperature for 72 h followed by 0.45 h of reflux provided only one product in 94% yield. Proton NMR and UV absorption studies indicated a bicyclic product, and elemental analysis indicated only one sulfur atom. Of the numberous possibilities, only six reasonable structures are consistent with this data: tribenzoyl-blocked 7- and 9-ribosides of 3-deaza-6-thioguanine (the desired products), 3-deaza-2-mercaptoadenine (**13**), and 6-amino-4-iminoimidazo[4,5-*c*]thiine (**14**). Hydrogenolysis of the deblocked



13



14

thiated nucleoside with Raney nickel provided an aromatic, bicyclic nucleoside without a sulfur atom, as determined by proton NMR, UV absorption, and elemental analysis. The lack of an AX coupling system in the proton NMR spectrum confirmed the structure of the aglycones **10**, **11**, and **12**. Dethiation of **11** to afford **12** has also provided some indication as to the location of the ribofuranosyl moiety in nucleosides **6**–**12**, since a large upfield shift of the anomeric proton ($H_{1'}$) was observed for **12** (ΔH from **11** to **12** was 1.62 ppm). This results from removing the anisotropic effect of a thione group in close proximity to the anomeric proton ($H_{1'}$) in nucleoside **11**.[17] Therefore, 3-deazapurine nucleosides **11** and **12** are 7-ribosides and, hence, the position of the blocked ribofuranosyl moiety in imidazole nucleosides **6** and **9** are correct as shown in Scheme I. Furthermore, the dissimilarity of the UV absorption spectra of nucleosides **11** and **12** to 3-deaza-6-thioguanosine and 6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine, respectively, both recently prepared by May and Townsend,[12] provide conclusive proof that deazapurines **11** and **12** are not the 9-ribosides.

The β-configuration was expected for nucleosides **6**–**12** due to the propensity of the stannic chloride catalyzed ribosylations of silylated heterocycles to form exclusively β-anomers.[2,15] Proof that the nucleosides **6**–**8** and **10**–**12** were of the β-configuration was obtained by considering the difference in the chemical shift of the methyl groups of 5-cyano-4-cyanomethyl-1-(2,3-isopropylidene-β-D-ribofuranosyl)imidazole (**8**), obtained from deblocking nucleoside **6** and subsequent isopropylidenation of the resulting imidazole **7**. A difference of 0.19 ppm was found which is a reliable indicator for the β-configuration according to Imbach and workers.[18]

Treatment of nucleoside **9** with hydrogen sulfide and triethylamine at ambient temperature provided 6-amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine-4(5*H*)-thione (**15**) in near quantitative yield. Deblocking of **15** with sodium methoxide in methanol provided 3-deaza-6-thioguanosine (**16**) in an excellent yield. The anomeric proton ($H_{1'}$) in **16** is considerably upfield compared to the isomeric compound 3-deaza-7-β-D-ribofuranosyl-6-thioguanine (**11**) (δ 5.63 compared to 7.47). This is due to the lack of a magnetic anisotropy effect of a closely positioned thione group as found in nucleoside **11**. Dethiation of nucleoside **16** with Raney nickel provided 6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (**17**). The chemical shift of the anomeric proton ($H_{1'}$) in nucleoside **17** is, as expected, only slightly removed from the chemical shift of $H_{1'}$ in the isomeric dethiated nucleoside **12** and 3-deaza-6-thioguanosine (**16**) (δ 5.85 compared to 5.76 and 5.63, respectively). Nucleosides **16** and **17** are, respectively, spectroscopically identical to 3-deaza-6-thioguanosine and 6-amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine, which were prepared by May and Townsend's procedure.[12] Thus, as usual,[2,10,15] the stannic chloride catalyzed ribosylation of silylated heterocycles has provided an excellent yield of blocked nucleosides in the β-configuration.

4,6-Diamino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (**18**), another interesting modification of 3-deaza-7-β-D-ribofuranosylguanine (**1**), was obtained in 75% yield from treatment of blocked imidazole **6** with methanolic ammonia (130 °C) for 16 h. The corresponding isomer, 4,6-diamino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (**19**) was also obtained in excellent yield from imidazole **9** and methanolic ammonia at ambient temperature. Proof that nucleosides **18** and **19** were indeed the diaminobicyclic structures rather than a mono- or diamidine imidazole nucleoside was evident from elemental analysis; UV absorption, which exhibits the characteristic bathochromic shifts due to the annelation of the pyridine ring to the imidazole ring;[19] lack of a nitrile absorption band at 2220 cm^{-1}, which was present in nucleosides **6** and **9**; and proton NMR, which indicated an additional aromatic proton (C_7H) in comparison with **6** and **9**, the lack of a methylene group, and two aromatic amino groups.

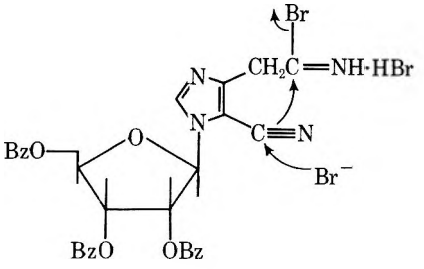
Attempts to cyclize nucleoside **6** with anhydrous hydrogen bromide in methylene chloride provided, according to thin-layer chromatography, unreacted starting material and several trace products. However, treatment of imidazole **9** under the same conditions provided a moderate yield of a slightly impure 6-amino-4-bromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-*c*]pyridine (**20**). Structure proof of nucleoside **20** was obtained by subjecting it to deblocking and subsequent hydrogenolysis procedures to form **17**.

Acid-catalyzed intramolecular cyclizations between a cyanomethyl group and an adjacent cyano group located on a benzene,[20] pyridine,[21] or imidazole ring[8b] to form isoquinolines, pyrido[*c*]pyridines, or imidazo[4,5-*c*]pyridines, respectively, have been reported. Furthermore, Alhaique et al.,[22] in the most recent report concerning cyclizations of dinitriles, describes the synthesis of aminoalkoxynaphthyridines (pyrido[*c*]pyridines) via sodium alkoxides.

In the present work, the use of hydrogen sulfide or ammonia to affect this type of cylization does not appear to have been described in the literature.[23] Since our cyclizations with hydrogen sulfide and ammonia were carried out in a basic medium, just as Alhaique et al.'s, the same direction of cyclization would be expected. However, our basic cyclization with hydrogen sulfide proceeded in the "reverse" manner to provide 6-aminoimidazo[4,5-*c*]pyridine-4(5*H*)-thione ribosides **10** and **15** rather than the 4-aminoimidazo[4,5-*c*]pyridine-6(5*H*)-

thione ribosides (e.g., **13**). As to speculations concerning a mechanism for these cyclizations, one might assume an attack of hydrogen sulfide–triethylamine or ammonia at the carbon atom of the aromatic nitrile first, followed by nucleophilic cyclization of the imino group and the cyanomethyl group, but the possibility of bis(thiocarboxamide) or bis(amidine) formation would complicate the problem.

Anhydrous hydrogen bromide cyclizations of aromatic nitriles with an adjacent cyanomethyl group have all proceeded in the same direction;[8b,20,21] that is, the nitrogen of the aromatic nitrile becomes the ring nitrogen of the pyridine moiety. Our cyclization of nucleoside **9** with anhydrous hydrogen bromide, although proceeding poorly, did afford the expected product. The greater reactivity of aliphatic nitriles to acid as compared to aromatic nitriles might account for this in that the aliphatic imino hydrogen bromide is preferentially formed (**21** and **22**) and then nucleophilic attack by the aromatic ni-



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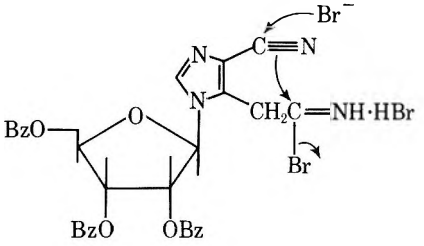

22

trile takes place. This mechanism might also account for the failure of nucleoside **6** to react with hydrogen bromide, since the approach of the bromide for attack on the carbon atom of the aromatic nitrile **21** would encounter considerable steric hinderance as compared with the isomeric aliphatic imino hydrogen bromide **22**. More strenuous conditions were required in all cyclizations described in this paper which led to the 7-ribosides as compared with the 9-ribosides. This was also evident in the cyclization of the ribosides of methyl 4-cyanomethylimidazole-5-carboxylate to 7- and 9-ribosides of 3-deazaguanine.[2] The tribenzoyl-blocked ribose and the cyanomethyl (or addition product thereof, such as imino hydrogen bromide) located on the nitrogen in the 1 position and the carbon atom in the 4 position of nucleoside **6**, respectively, provide considerable steric hinderance to a nitrile or carbomethoxy group in the 5 position of the imidazole ring system according to space-filling models (CPK). We suspect that steric hinderance is the main reason for the reduced reactivity of imidazole nucleosides in cyclization leading to 7-ribosides of 3-deazapurines as compared to the corresponding isomer which lacks this steric hinderance and leads to 9-riboside of 3-deazapurines.

The biological evaluation of these modifications of 3-deaza-7-β-D-ribofuranosylguanine (**1**) and 3-deazaguanosine will be reported elsewhere.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Proton magnetic resonance (^{1}H NMR) spectra were obtained on a Varian A-60 spectrometer and a Perkin-Elmer R-20A spectrometer in Me_2SO-d_6 using DSS as an internal reference. Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer and infrared spectra on a Perkin-Elmer 257 spectrophotometer (KBr pellets). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Evaporations were carried out under reduced pressure with bath temperature below 40 °C unless otherwise noted. Detection of components on silica gel (ICN Life Sciences Group, Woelm F254) was by ultraviolet light and with anisaldehyde, methanol, sulfuric acid (1:10:100) spray followed by heating. ICN Life Sciences Group Woelm silica gel (0.063–0.2 mm) was used for column chromatography.

5-Cyano-4-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (6) and 4-Cyano-5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazole (9). 4(5)-Cyano-5(4)-cyanomethylimidazole[8b] (**3**) (15.0 g, 113.6 mmol) was refluxed under anhydrous conditions for 8–24 h with hexamethyldisilazane (200 mL) and ammonium sulfate (250 mg). The excess hexamethyldisilazane was removed by distillation under reduced pressure providing the trimethylsilyl derivative as a tan oil. The oil was dissolved in dry 1,2-dichloroethane (500 mL). 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**5**) (57.25 g, 113.6 mmol) was added to the solution followed by direct addition of anhydrous stannic chloride (19 mL, 163.6 mmol) in one portion. TLC (silica gel, benzene–ethyl acetate, 4:1) of an ethanolized aliquot indicated almost complete conversion of the sugar and base to products after 15 min of stirring at ambient temperature. The reaction solution was stirred further for 5 h and then poured slowly into a vigorously stirred 5% sodium hydrogen carbonate solution (2 L). Chloroform (2 L) was added and stirring continued for 0.5 h. The mixture was filtered through Celite and the organic layer was removed. The aqueous layer was extracted with chloroform (300 mL). The combined, dried ($MgSO_4$) extracts were evaporated in vacuo (50 °C) to a light-beige foam (64.4 g, 98%). The foam was dissolved in benzene and placed on a column of silica gel (1800 g, packed in benzene). Elution with benzene–ethyl acetate (5:1) provided **9** (11.7 g of colorless foam, 18%) as the first isomer off the column. Recrystallization from methanol afforded **9** as colorless crystals: mp 145–146 °C; IR (KBr) 2220 (w) (C≡N) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.55 (d, 1, J = 4 Hz, $H_{1'}$), 8.51 (s, 1, C_2H).

Anal. Calcd for $C_{32}H_{24}N_4O_7$ (576.54): C, 66.66; H, 4.20; N, 9.72. Found: C, 66.55; H, 4.30; N, 9.67.

Further elution of the column with benzene–ethyl acetate (5:1) afforded **6** as a colorless foam (46.8 g, 72%): IR (KBr) 2220 (w) (C≡N) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.54 (d, 1, J = 4 Hz, $H_{1'}$), 8.50 (s, 1, C_2H).

Anal. Calcd for $C_{32}H_{24}N_4O_7$ (576.54): C, 66.66; H, 4.20; N, 9.72. Found: C, 66.45; H, 4.22; N, 9.60.

Utilizing the same conditions, except that the amount of anhydrous stannic chloride was decreased to 0.72 molar equiv (9.5 mL, 81.8 mmol), provided **9** and **6** in 25 and 50% yields, respectively.

5-Cyano-4-cyanomethyl-1-(2,3-isopropylidene-β-D-ribofuranosyl)imidazole (8). Nucleoside **6** (10 g, 17.4 mmol) and liquid ammonia (70 mL) were placed in a steel bomb (140 mL) and heated at 100 °C for 3 h. The ammonia was allowed to evaporate at room temperature, and the residue was subjected to a vacuum overnight to remove the last traces of ammonia. The brown residue was dissolved in methanol, absorbed on silica gel (40 g), and placed on a column of silica gel (300 g, packed in chloroform). Elution with chloroform–methanol (5:1) provided 5-cyano-4-cyanomethyl-1-β-D-ribofuranosylimidazole (**7**, 3.5 g, 76%) as a colorless foam. This foam was dissolved in a solution of dry acetone (50 mL), 2,2-dimethoxypropane (25 mL), and 70% perchloric acid (700 mg) and stirred at ambient temperature for 10 min. Saturated sodium carbonate solution (1 mL) was added, and the mixture was absorbed on silica gel (10 g) with the aid of methanol and placed on a column of silica gel (100 g, packed in chloroform). Elution with chloroform–methanol (10:1) provided the isopropylidene **8** as a colorless foam (3.2 g, 79%); ^{1}H NMR (Me_2SO-d_6) δ 1.39 (s, 3, CH_3), 1.58 (s, 3, CH_3), 4.20 (s, 2, C_4-CH_2), 5.99 (d, 1, J = 2 Hz, $H_{1'}$), 8.36 (s, 1, C_2H).

Anal. Calcd for $C_{14}H_{16}N_4O_4$ (304.3): C, 35.87; H, 5.30; N, 18.41. Found: C, 35.81; H, 5.28; N, 18.23.

6-Amino-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo[4,5-c]pyridine-4(5*H*)-thione (10). A mixture of **6** (7.0 g, 12.2 mmol), ethanol saturated at −10 °C with hydrogen sulfide (250 mL), and triethylamine (1.8 mmol) was kept in a steel bomb (300 mL) for 3 days at ambient temperature. TLC (silica gel, chloroform–methanol, 10:1) indicated two products in approximately equal amounts. The yellow suspension was refluxed for 0.45 h (complete dissolution obtained at start of reflux). This cleanly converts the higher R_f valued product into the lower R_f valued product. The solvents were removed

by evaporation in vacuo, and the yellow residue was dissolved in chloroform and placed on a column of silica gel (100 g, packed in chloroform). Elution with methylene chloride–methanol (10:1) provided pure **10** as a yellow foam (7.0 g, 94%). A sample of the foam was crystallized from ethyl ether to afford light yellow crystals: mp 223–224 °C dec (after drying at 100 °C for 5 h); ^{1}H NMR (Me_2SO-d_6) δ 6.08 (s, 2, NH_2), 6.17 (s, 1, C_7H), 8.73 (s, 1, C_2H), 12.11 (s, 1, NH).

Anal. Calcd for $C_{32}H_{26}N_4O_7S$ (610.66): C, 62.94; H, 4.29; N, 9.18; S, 5.25. Found: C, 63.02; H, 4.18; N, 9.01; S, 5.34.

6-Amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridine-4(5*H*)-thione [3-Deaza-7-β-D-ribofuranosyl-6-thioguanine (11)]. Nucleoside **10** (2.5 g, 4.09 mmol) was dissolved in dry methanol (175 mL) containing sodium methoxide (from 5 mg of sodium) and kept at ambient temperature for 24 h. The yellow solution was refluxed 5 min, cooled, and treated with Amberlite IRC-50 (H^+) (10 mL). The resin was filtered and washed with hot ethanol. The filtrate was evaporated in vacuo in the presence of silica gel (5 g). The residue was slurried with chloroform and placed on a column of silica gel (45 g). Elution with chloroform–methanol (4:1) and evaporation of the product containing fractions provided the pure nucleoside as a yellow foam (1.05 g, 86%). Recrystallization from ethanol–water afforded yellow rosettes: mp grad dec >155 °C (after drying at 100 °C for 5 h); $[\alpha]^{25}_D$ +202° (*c* 1.0, DMF); UV λ_{max} (pH 1) 227 (ϵ 15 830), 255 (5000), 283 (6380), 378 nm (13 880); λ_{max} (pH 7) 231 (20 000), 264 (8610), 373 nm (13 880); λ_{max} (pH 11) 227 (17 500), 261 (6110), 343 nm (8330); ^{1}H NMR (Me_2SO_4-d_6) δ 5.96 (s, 2, NH_2), 6.10 (s, 1, C_1H), 7.48 (d, 2, J = 3.5, $H_{1'}$), 8.63 (s, 1, C_2H), 11.95 (s, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$ (298.32): C, 44.29; H, 4.73; N, 18.78; S, 10.75. Found: C, 44.10; H, 4.91; N, 18.57; S, 10.59.

6-Amino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (12). A mixture of **11** (100 mg, 0.335 mmol), Raney nickel (ca. 500 mg), and ethanol (20 mL) was stirred and refluxed for 10 min and then filtered hot. The filtrate was concentrated in vacuo to a small volume and cooled overnight to afford **12** as colorless needles (63 mg, 70%): mp 226–227 °C dec (after drying at 100 °C for 2 h); UV λ_{max} (pH 1) 222 (ϵ 34 990), 224 (4700), 339 nm (6000); λ_{max} (H_2O) 215 (30 550), 253 (sh) (2870), 314 nm (3390); λ_{max} (pH 11) 221 (16 710), 253 (sh) (2870), 312 nm (3655); ^{1}H NMR (Me_2SO-d_6) δ 5.41 (s, 2, NH_2), 5.82 (d, 1, J = 6 Hz, $H_{1'}$), 6.69 (s, 1, C_7H), 8.40 (s, 1, C_2H or C_4H), 8.55 (s, 1, C_2H or C_4H).

Anal. Calcd for $C_{11}H_{14}N_4O_4$ (266.27): C, 49.62; H, 5.30; N, 21.04. Found: C, 49.53; H, 5.26; N, 21.34.

6-Amino-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazo-[4,5-*c*]pyridine-4(5*H*)-thione (15). A mixture of nucleoside **9** (8.0 g, 13.88 mmol), ethanol saturated at 0 °C with hydrogen sulfide (250 mL), and triethylamine (2.5 g, 24.7 mmol) was kept in a steel bomb (300 mL) for 48 h at ambient temperature. The reaction solution was evaporated in vacuo to a yellow foam which was coevaporated with ethanol several times. TLC (silica gel, chloroform–methanol, 10:1) indicated one major product and several small products from partially deblocked material. This material was sufficiently pure for the next reaction.

6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine-4-(5*H*)-thione [3-Deaza-6-thioguanosine (16)]. Nucleoside **15** (8.0 g, 13.0 mmol) was dissolved in dry methanol (200 mL) containing sodium methoxide (from 460 mg of sodium) and refluxed 15 min. The cooled solution was treated with Amberlite IRC-50 (H^+ (20 mL) and stirred for 0.5 h. The resin was filtered and washed with hot water. The combined filtrates were evaporated in vacuo to dryness and the resulting residue was triturated with methanol to afford quite pure **16** (3.5, 90%). Recrystallization from water provided large yellow chunks of **16**: mp 226–227 °C dec (after drying at 100 °C for 2 h) (lit. mp 185 °C dec as dihydrate);[10] $[\alpha]^{25}_D$ −55.7° (*c* 0.945, DMF); UV λ_{max} (pH 1) 223 (sh) (ϵ 16 870), 245 (sh) (6630), 291 (7230), 374 nm (16 870); λ_{max} (pH 7) 228 (17 770), 253 (6630), 283 (8430), 353 nm (18 370); λ_{max} (pH 11) 226 (15 360), 245 (sh) (9640), 283 (6630), 323 nm (13 550); ^{1}H NMR (Me_2SO-d_6) δ 5.62 (d, 1, J = 5 Hz, $H_{1'}$), 6.13 (s, 2, NH_2), 6.12 (s, 1, C_7H), 8.18 (s, 1, C_2H), 11.95 (s, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_4O_4S$ (298.32): C, 44.29; H, 4.73; N, 18.78; S, 10.75. Found: C, 43.99; H, 4.84; N, 18.59; S, 10.44.

6-Amino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (17). A mixture of **16** (500 mg, 1.67 mmol), Raney nickel (ca. 2.5 g), ethanol (100 mL), and water (20 mL) was refluxed with stirring for 10 min and then filtered hot through celite. The filtrate was concentrated in vacuo to a small volumn and cooled overnight to provide **17** as beige needles (325 mg, 73%); mp 219–220 (after drying at 100 °C for 2 h) (lit. 221–223 °C dec);[10] $[\alpha]^{25}_D$ −44.2° (*c* 0.96, H_2O); UV λ_{max} (pH 1) 226 (ϵ 43 970), 254 (sh) (3921), 261 (4761), 268 (3921), 320 nm (3641); λ_{max} (pH 7) 218 (31 092), 256 (5042), 298 nm (3081); λ_{max} (pH 11) 222 (48 739), 255 (5602), 297 nm (3641); ^{1}H NMR (Me_2SO-d_6) δ 5.63 (s, 2, NH_2), 5.76 (d, 1, J = 6 Hz, $H_{1'}$), 5.62 (s, 1, C_7H), 8.26 (s, 1, C_2H or C_4H), 8.40 (s, 1, C_2H or C_4H).

Anal. Calcd for $C_{11}H_{14}N_4O_4$·0.5H_2O (275.27): C, 47.99; H, 5.49; N, 20.35. Found: C, 47.99; H, 5.35; N, 20.24.

4,6-Diamino-3-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (18). A mixture of nucleoside **6** (5 g, 8.68 mmol), liquid ammonia (10 mL), and methanol (10 mL) was heated in a steel bomb (40 mL) at 125–135 °C for 16 h. The reaction solution was evaporated in vacuo and the residue triturated several times with ethyl ether–methanol (3:1). The residue was absorbed on silica gel (5 g) with the aid of methanol and placed on a column of silica gel (150 g, packed in chloroform). Elution with chloroform–methanol (1:1) provided benzamide and a small amount of pure 5-cyano-4-cyanomethyl-1-β-D-ribofuranosylimidazole (**7**) (0.26 g, 11%). Elution with chloroform–methanol (1:1) removed the desired nucleoside. Evaporation of the product containing fractions and recrystallization of the residue from methanol afforded **18** as beige crystals (1.44 g in 2 crops, 60%): mp 130–132°C dec (after drying at 100 °C for 2 h); UV λ_{max} (pH 1) 214 (ϵ 20 057), 273 (6857), 338 nm (6571); λ_{max} (pH 7) 218 (2286), 248 (4286), 318 (4857); λ_{max} (pH 11) 222 (15 428), 248 (4857), 313 nm (5143); ^{1}H NMR (Me_2SO-d_6) δ 5.90 (d, 2, J = 5 Hz, $H_{1'}$), 6.18 (s, 1, C_7H), 5.30–7.00 (br s, 2, NH_2), 7.20 (s, 2, NH_2), 8.58 (s, 1, C_2H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$ (281.27): C, 46.97; H, 5.38; N, 24.90. Found: C, 47.22: H, 5.24; N, 24.99.

4,6-Diamino-1-β-D-ribofuranosylimidazo[4,5-*c*]pyridine (19). A mixture of nucleoside **9** (3.0 g, 5.2 mmol) and dry methanol saturated at 0 °C with ammonia (150 mL) was kept in a steel bomb at ambient temperature for 24 h and then evaporated in vacuo to dryness. The residue was triturated with ether, dissolved in methanol, absorbed on silica gel (10 g), and placed on a column of silica gel (60 g, packed in chloroform). Elution with chloroform–methanol (1:1) removed the product from the column. The product containing fractions were combined and concentrated in vacuo to a small volumn. Addition of ether until the cloud point was obtained and cooling provided **19** as colorless cyrstals (780 mg). An additional 430 mg of **19** was obtained in a second crop (1.21 g total, 83%): mp 210–212 °C dec (after drying at 100 °C, 3 h); $[\alpha]^{25}_D$ −41.8° (*c* 0.99, DMF); UV λ_{max} (pH 1) 217 (ϵ 29 539), 271 (11 382), 315 nm (8943); λ_{max} (pH 7) 217 (29 539), 272 (11 110), 295 nm (sh) (7046); λ_{max} (pH 14) 218 (18 690), 273 (10 570), 288 nm (sh) (8940); ^{1}H NMR (Me_2SO-d_6) δ 5.14 (br s, 2, NH_2), 5.65 (d, 1, J = 2 Hz, $H_{1'}$), 5.82 (s, 1, C_7H), 5.83 (s, 2, NH_2), 7.98 (s, 1, C_2H).

Anal. Calcd for $C_{11}H_{15}N_5O_4$ (281.27): C, 46.97; H, 5.38; N, 24.90. Found: C, 47.0; H, 5.29; N, 25.08.

6-Amino-4-bromo-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofurano-syl)imidazo[4,5-*c*]pyridine (20). A solution of nucleoside **9** (6.4 g, 11.1 mmol) and dry chloroform (300 mL) was cooled to −30 °C and saturated with anhydrous hydrogen bromide at −30 °C. The cooling bath was removed and the reaction solution stirred 6 h at ambient temperature. The residue, obtained from removal of the chloroform in vacuo at 20 °C, was dissolved in chloroform and washed with sodium hydrogen carbonate solution. TLC of the dried ($MGSO_4$) chloroform solution (silica gel, chloroform–methanol, 10:1) indicated one major spot which turns yellow with anisaldehyde–methanol–sulfuric acid spray (1:10:100) and then chars, on heating, some starting material and several other small spots. The solution was evaporated in vacuo to a small volumn and placed on a column of silical gel (250 g, packed in chloroform). Elution with chloroform–methanol (20:1) provided **20** as a slighlty impure light yellow foam (3.6 g, 49%) as determined by TLC. Structure proof of this material was obtained by deblocking with methanolic sodium methoxide and subsequent hydrogenolysis with palladium on charcoal to provide nucleoside **17**.

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Registry No.—**3**, 52605-83-1; **4**, 64082-24-2; **5**, 6974-32-9; **6**, 64070-67-3; **7**, 64070-68-4; **8**, 64070-69-5; **9**, 64070-8; **10**, 64070-71-9; **11**, 64070-72-0; **12**, 64070-73-1; **15**, 64070-66-2; **16**, 57873-01-5; **17**, 60431-94-9; **18**, 64070-65-1; **19**, 64070-64-0; **20**, 64070-63-9; hexamethyldisilazane, 999-97-3; 2,2-dimethoxypropane, 77-76-9; hydrogen sulfide, 7783-06-4.

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(9) In principle, an approach to 3-deazapurine nucleosides and, in general, to other modified purine nucleosides in which glycosylation is performed on an appropriate imidazole intermediate rather than on a bicyclic intermediate appears advantageous because only two ring nitrogens are available for reaction in the imidazole rather than three (or more) in the bicyclic intermediate, and the substituents on the imidazole base, if different, may provide a directive effect and thus a preponderance of one of the two possible positional isomers. Ribosylation and subsequent cyclization of methyl 4(5)-cyanomethylimidazole-5(4)-carboxylate[2] and dimethyl imidazole-4,5-dicarboxylate[10] are successful examples of this approach. Experimentally, imidazoles are more easily silylated as our procedure requires, but also, if needed, other glycosylation procedures such as acid-catalyzed fusions are possible.[2,11,12] Finally, and possibly most important, imidazole nucleosides are potentially chemotherapeutically useful agents themselves.[5a,13]
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(16) We have previously suggested the possibility of a stannic chloride–silylated heterocycle complex which may provide regiospecific ribosylation.[2] Complex formation in the ribosylation of silylated imidazole **4** either does not take place or if so then a much less stable complex is formed, since variance of the molar equiv of stannic chloride does not provide the marked effect as in the ribosylation of methyl 4(5)-cyanomethyl-1-trimethylsilylimidazole-5(4)-carboxylate.[2] U. Niedballa and H. Vorbruggen [*J. Org. Chem.*, **41**, 2084 (1976)] have also recently discussed the possibility that complexes between silylated uracils and stannic chloride may account for rate differences as well as isomer distribution in glycosylations of substituted uracils.
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Synthesis of a Cyclic Charge Transfer Labeled Analogue of the Luteinizing Hormone-Releasing Factor[1]

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The synthesis of

p-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Nva(Nic$^+$Cl$^-$)-Pro-Gly-NH_2

a cyclic analogue of the luteinizing hormone-releasing factor carrying a charge-transfer label, is described. The linear peptide *p*-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Orn(TFA)-Pro-Gly-NH_2 was synthesized by the solid-phase method in a 32% overall yield. The side-chain cyclization was carried out in pyridine at high dilution in 65% yield by using 30 equiv of dicyclohexylcarbodiimide and 2 equiv of *N*-hydroxysuccinimide as coupling reagents. Selectivity in the side-chain deprotection of the two ornithine residues was provided by using the benzyloxycarbonyl and the trifluoroacetyl protecting groups.

Introduction

We have undertaken a systematic investigation of the conformation of the luteinizing hormone-releasing factor by using charge-transfer labels[2,3] in order to visualize side chain–side chain interactions. In an attempt to obtain quantitative intramolecular charge-transfer effects, we have prepared a nicotinamidium-labeled cyclic analogue in which the folding of the peptide backbone at the central tetrapeptide sequence is forced by a covalent bond between the side chains of residues at positions 4 and 7. In this paper, we describe the synthesis of [*cyclo*(Glu^4,D-Ala^6,Orn^7),Nva^8(Nic$^+$)]LRF·Cl$^-$. The conformational studies of this and similarly labeled LRF analogues will be reported in a subsequent paper.[4]

Results and Discussion

A combination of the solid phase and the classical peptide synthesis methodologies has been applied to prepare the desired LRF analogues. Schemes I and II outline these syntheses. Selectivity in deprotection of the δ-amino side chains of the two ornithine residues in positions 7 and 8 was provided through the use of the benzyloxycarbonyl group and the trifluoroacetyl group, the latter of which is stable to the hydrogen fluoride treatment employed to cleave the peptide from the resin. This procedure results in a linear peptide in which the ornithine side chain in position 7 is deprotected in preparation for ring closure with the γ-carboxyl side chain of the glutamic acid in position 4. Selective N$^\delta$-trifluoroacetylation of orni-

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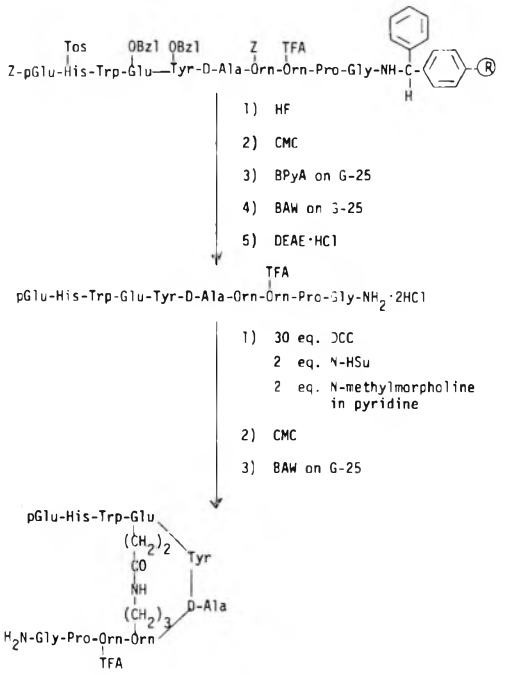
Scheme I. Synthesis of [*cyclo*(Glu⁴,D-Ala⁶,Orn⁷)-Orn⁸(TFA)]LRF

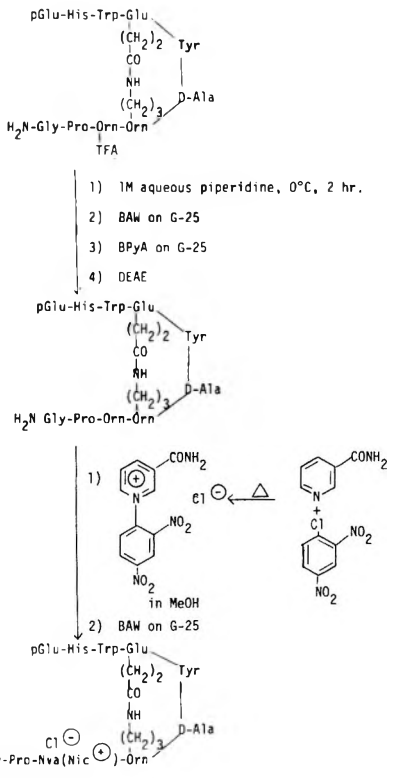


thine was achieved by following the procedure of Schallenberg and Calvin[5] using *S*-ethylthiol trifluoroacetate as the acylating agent. These authors have shown that the trifluoroacetyl group in monoacetylated D,L-lysine and D,L-ornithine was exclusively located on the side chain amino group, and not on the α-amino group. A further confirmation of these results was obtained from the NMR spectrum of the N^{α}-*tert*-butyloxycarbonyl-N^{δ}-trifluoroacetylornithine, which we have prepared. This compound exhibits the characteristic doublet for the α-NH proton signal (Me_2SO-d_6 as solvent) which completely disappears after selective removal of the Boc protecting group with trifluoroacetic acid, while the triplet signal of the δ-NH proton remains unchanged after this treatment.

The N^{α} protection of the N^{δ}-trifluoroacetylornithine with the *tert*-butyloxycarbonyl group was preferentially carried out in dimethyl sulfoxide using triethylamine as base instead of applying the conditions reported by Anfinsen et al.[6] for the synthesis of N^{ϵ}-*tert*-butyloxycarbonyl-*N*-trifluoroacetyllysine. The linear peptide *p*-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Orn(TFA)-Pro-Gly-NH_2 (Scheme I) was obtained in 32% overall yield after cleavage from the resin with hydrogen fluoride and extensive purifications with ion exchange and successive partition chromatography using basic and acidic eluent mixtures.

The synthesis of the first cyclic LRF analogue for structure–activity relationship studies was carried out in our laboratories.[7] We have further optimized the cyclization conditions. The high dilution method described by Schwyzer et al.[8] and Wieland and Birr[9] was applied and different coupling reagents were tested. With carbonyldiimidazole (30 equiv) in dimethylformamide, we failed to isolate and characterize any cyclic product. Using dicyclohexylcarbodiimide (30 equiv) in dimethylformamide or pyridine, it was shown by thin-layer chromatography (ninhydrin positive spot) and confirmed by NMR that the *N*-acylurea derivative was the main product (3:1 ratio as compared to the desired cyclic compound). However, with 30 equiv of dicyclohexylcarbodiimide and 2 equiv of *N*-hydroxysuccinimide, the *N*-acylurea formation was completely suppressed and a 65% yield of pure cyclic product was obtained. By increasing the *N*-hydroxysuccinimide concentration, we observed a decrease in the yield of cyclization.

Scheme II. Synthesis of [*cyclo*(Glu⁴,D-Ala⁶,Orn⁷))Nva⁸(Nic⁺Cl⁻)]LRF



Cleavage of the trifluoroacetyl group with aqueous piperidine at 0 °C was followed by thin-layer chromatography; the appearance of a single new spot confirms the homogeneity of the cyclic compound. Furthermore, molecular weight determination by sedimentation equilibrium is consistent with the monomeric nature of the product.

The unprotected cyclic compound was purified by partition chromatography, neutralized on a diethylaminoethylcellulose column (basic form), and treated with 2,4-dinitrophenylnicotinamidium chloride to give the desired charge transfer labeled compound.[3,11]

In a combined in vitro biological assay carried out by Dr. W. Vale at the Salk Institute, La Jolla, Calif.,[12] using LRF as standard (100%), the cyclic compounds described in this paper, together with [(Glu⁴,D-Ala⁶,Orn⁷)]LRF and [Gln⁴,D-Ala⁶,Orn⁷(Ac)]LRF described earlier, exhibit potencies of about 0.1% or less. As we have stated above, we prepared these compounds to analyze the conformational characteristics of LRF and related molecules. It is not surprising that the changes we have made in the LRF sequence lead to inactive compounds.

Experimental Section

The N^{α}-*tert*-butyloxycarbonyl amino acid derivatives were obtained from Bachem Fine Chemicals, Inc. Solvents were purchased from Mallinckrodt and were of AR grade. The reagents *N*,*N*-dicyclohexylcarbodiimide, *N*-hydroxysuccinimide, trifluoroacetic acid, diisopropylethylamine, and 1,2-ethanedithiol were purchased from Aldrich and were used without further purification. Anisole and piperidine were obtained from Matheson, Coleman and Bell and *S*-ethylthiol trifluoroacetate from the Pierce Chemical Co. *N*-methylmorpholine (Aldrich) was distilled over sodium and stored over molecular sieves. Dimethylformamide was dried over sodium hydroxide and distilled under vacuum over ninhydrin (1 g of ninhydrin per liter of dimethylformamide). Pyridine was dried over barium oxide. Thin-layer chromatography was carried out on precoated silica gel plates (Kodak) using the following solvent systems: 1-butanol/acetic

acid/water (4:1:5 v/v, upper phase) (A), 1-butanol/pyridine/0.1% acetic acid in water (5:3:11 v/v, upper phase) (B), 1-butanol/acetic acid/water (3:1:1 v/v) (C), methyl ethyl ketone/pyridine/water/acetic acid (70:15:18:2 v/v) (D), and chloroform/methanol (1:1 v/v) (E). All intermediates and end products were characterized by NMR spectroscopy. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Amino acid analyses and the testing of the biological activity of the LRF analogues were carried out in Dr. Guillemin's laboratory at the Salk Institute, La Jolla, Calif.

N^{α}-Trifluoroacetyl-L-ornithine. This compound was synthesized according to the procedure of Schallenberg and Calvin:[5] to a solution of L-ornithine monohydrochloride (0.337 g, 2 mmol) in 1 N sodium hydroxide (2 mL) *S*-ethylthiol trifluoroacetate (0.4 mL) was added. The heterogeneous mixture was vigorously stirred for 6 h. A precipitate slowly separated. The reaction mixture was cooled to 0 °C and the solid was collected by filtration and washed with ether. After recrystallization from a water/ethanol mixture (1:1) 250 mg (55%) was obtained: mp 247–249 °C; $[\alpha]^{25}D$ +13.3° (c 0.2, 3 N hydrochloride acid), $[\alpha]^{25}D$ +18.9° (c 1, dichloroacetic acid) R_f^C 0.42, R_f^D 0.58, R_f^E 0.44 (lit.[13] mp 250–251 °C).

Studies on the Stability of the N^{δ}-Trifluoroacetyl Protecting Group. (A) To HF treatment. Liquid hydrogen fluoride was distilled in a sample of N^{δ}-trifluoroacetylornithine suspended in a little anisole and the mixture was kept at 0 °C for 1 hour, when the hydrogen fluoride was removed under vacuum and ether was added into the residue. The solid material was then filtered and subjected to thin-layer chromatography in systems C, D, and E when no traces of ornithine could be detected.

(B) To Partition Chromatography Solvent Systems. A solution of N^{δ}-trifluoroacetylornithine in the upper phase of 1-butanol/pyridine/0.1% acetic acid in water (5:3:11) was kept at room temperature for 24 h. No decomposition was detected by thin-layer chromatography after this treatment.

(C) To Boc Deprotection Conditions during Solid-Phase Synthesis. A solution of N^{α}-*tert*-butyloxycarbonyl-N^{δ}-trifluoroacetyl-L-ornithine in trifluoroacetic acid was kept at room temperature for 30 min. Thin-layer chromatography of this solution in systems C and D showed only the presence of N^{δ}-trifluoroacetylornithine, which assured the stability of the trifluoroacetyl group during solid-phase synthesis.

N^{α}-*tert*-Butyloxycarbonyl-N^{δ}-trifluoroacetyl-L-ornithine. N^{δ}-Trifluoroacetylornithine (0.23 g, 1 mmol) was dissolved in dimethyl sulfoxide (5 mL) containing triethylamine (0.28 mL, 2 mmol) and *tert*-butyloxycarbonyl azide (0.2 mL, 1.3 mmol). A further 0.1 mL of *tert*-butyloxycarbonyl azide was added after 8 h and the solution stirred for a total of 24 h at room temperature. The solution was finally diluted with three volumes of water and extracted twice with ether to remove the unreacted *tert*-butyloxycarbonyl azide. The aqueous phase was acidified (pH 2–3) with 1 N sulfuric acid and extracted with ethyl acetate (three times). The combined ethyl acetate extracts were washed to neutral pH with water, dried over magnesium sulfate, and evaporated to dryness. The residue (0.25 g, 76.5% viscous oil) was homogeneous by thin-layer chromatography (R_f^C 0.81, R_f^D 0.82, and R_f^E 0.82) and characterized by NMR spectroscopy (the characteristic α-NH doublet at 7.015 ppm (J = 7.5 Hz, Me_2SO-d_6 as solvent, hexamethyldisiloxane as reference) completely disappears after quantitative cleavage of the N^{α}-*tert*-butyloxycarbonyl protecting group with trifluoroacetic acid).

p-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Orn(TFA)-Pro-Gly-NH_2·CH_3COOH. The linear compound was synthesized by the solid-phase method using a benzhydrylamine resin[14-15] (18.2 g, 0.16 mequiv/g substitution, 3 mmol) as support. All the amino acids were coupled as the N^{α}-*tert*-butyloxycarbonyl derivatives except pyroglutamic acid, where N^{α}-benzyloxycarbonylpyroglutamic acid was used. The side chains were protected as follows: imidazolyltosylhistidine, glutamic acid γ-benzyl ester, tyrosyl *O*-benzyl ether, and N^{δ}-benzyloxycarbonylornithine for position 7 and N^{δ}-trifluoroacetylornithine for position 8. Dicyclohexylcarbodiimide was used as the coupling reagent in dichloromethane or dimethylformamide/dichloromethane mixture. Completion of the coupling reactions was ensured by use of the ninhydrin test. Cleavage of the N^{α}-*tert*-butyloxycarbonyl group was carried out with a 40% solution of trifluoroacetic acid in dichloromethane containing 1,2-ethanedithiol (2%) and anisole (8%), followed by neutralization with a 10% solution of diisopropylethylamine in dichloromethane. The protected decapeptide was cleaved from the resin by the action of doubly distilled hydrogen fluoride in the presence of anisole for 1 h at 0 °C. The crude peptide (3.3 g) was purified by ion-exchange chromatography on carboxymethylcellulose eluting with an ammonium acetate gradient (0–0.3 M) and by two successive partition chromatographies on Sephadex G-25 in two different systems: 1-butanol/pyridine/0.1% acetic acid in water (5:3:11 v/v) and 1-butanol/acetic acid/water (4:1:5 v/v). The white product (1.24 g, 32%) was homogeneous by thin-layer chromatography in acidic and basic systems (R_f^A 0.23 and R_f^B 0.58) and was characterized by NMR spectroscopy and by quantitative amino acid analyses (hydrolyzates of the final material gave 100% peptide with the ratio: Orn, 2.05; His, 0.94; Trp, 0.96; Glu, 2.07; Pro, 0.96; Gly, 1.00; Ala, 0.99; Tyr, 0.98).

Anal. Calcd for $C_{58}H_{75}N_{16}O_{15}F_3$·$CH_3COOH$·$4H_2O$: C, 50.56; H, 6.15; N, 15.72. Found: C, 50.71; H, 6.13; N, 15.82.

p-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Orn(TFA)-Pro-Gly-NH_2·CH_3COOH. The linear decapeptide (197.8 mg) was converted to the hydrochloride salt on a cellex-D diethylaminoethylcellulose (HCl form) column. After lyophilization, the peptide (191 mg, 0.14 mmol) was dissolved in a dimethylformamide/pyridine mixture (20 mL, 1:1 v/v) containing *N*-hydroxysuccinimide (32 mg, 0.28 mmol) and *N*-methylmorpholine (36.2 μL, 0.28 mmol). The solution was added into a solution of dicyclohexylcarbodiimide (880 mg, 4.2 mmol) in pyridine (200 mL) over a period of 5 days at room temperature. The reaction mixture was further kept at 40 °C for an additional 4 days. After evaporation of the pyridine under reduced pressure, the product was precipitated with peroxide-free ether. Trituration of the solid material three times with ether removed the unreacted dicyclohexylcarbodiimide. The crude compound (183 mg, 96%) was purified by partition chromatography on Sephadex G-25 in 1-butanol/acetic acid/water (4:1:5 v/v), by ion-exchange chromatography on carboxymethylcellulose eluting with an ammonium acetate gradient (0–0.1 M), and once more by partition chromatography using the same solvent system. The white cyclic product (120.5 mg, 65%) showed a single, ninhydrin negative, spot on thin-layer chromatography (R_f^A 0.32 and R_f^B 0.75) and gave the correct amino acid analysis with the ratio: Orn, 2.06; His, 1.04; Trp, 1.09; Glu, 2.06; Pro, 1.14; Gly, 1.00; Ala, 1.01; Tyr, 0.95.

Anal. Calcd for $C_{58}H_{73}N_{16}O_{14}F_3$·$\frac{1}{2}CH_3COOH$·$4H_2O$: C, 51.45; H, 6.08; N, 16.27; F, 4.14. Found: C, 51.49; H, 6.06; N, 16.29; F, 4.14.

A few milligrams of the final material were dissolved in 1 M aqueous piperidine at 0 °C and the cleavage of the TFA group was followed each minute by thin-layer chromatography (systems A, B, C, D, E). A single new spot appeared up to the point of the full deprotection.

Molecular Weight Determination. The molecular weight of the cyclic compound was determined by sedimentation equilibrium using a Spinco Model R analytical centrifuge equipped with a TRLC temperature unit. Centrifugation was carried out at 20 °C at an angular velocity of 60 000 rpm for 50 h, when we confirmed that equilibrium had been reached. The cyclic peptide was dissolved in 0.1 M KCl (10^{-3} M concentration of the peptide). A 12-mm double-sector cell with sapphire windows and Kel-F double-sector centerpiece was used. The partial specific volume (0.732 mL/g) was estimated from the amino acid composition.[16] The molecular weight was found to be 951, compared with a value of 1275 calculated from the primary structure of the cyclic monomer.

p-Glu-His-Trp-*cyclo*(Glu-Tyr-D-Ala-Orn)-Orn-Pro-Gly-NH_2. p-Glu-His-Trp-cyclo(Glu-Tyr-D-Ala-Orn)-Orn(TFA)-Pro-Gly-NH_2 (146 mg) dissolved in 1 M aqueous piperidine (7 mL) was maintained at 0 °C for 2 h. Acetic acid was added to stop the reaction and the solution was then lyophilized. The crude, completely deprotected peptide was purified by partition chromatography on Sephadex G-25 on 1-butanol/pyridine/0.1% acetic acid in water (5:3:11 v/v) to give 136.3 mg (96%) of pure, white compound: R_f^A 0.08 and R_f^B 0.47. Amino acid analysis gave the ratio: Orn, 1.93; His, 0.95; Trp, 0.90; Glu, 1.96; Pro, 0.93; Gly, 1.00; Ala, 1.01; Tyr, 0.96.

p-Glu-His-Trp-*cyclo*(Glu-Tyr-D-Ala-Orn)-Nva(Nic$^+CH_3$-COO^-)-Pro-Gly-NH_2·CH_3COOH. The acetate salt of p-Glu-His-Trp-cyclo(Glu-Tyr-D-Ala-Orn)-Orn-Pro-Gly-NH_2 (136.3 mg) was neutralized through a DEAE-cellulose (cellex-D) column. After lyophilization, the decapeptide free base (121 mg, 0.1026 mmol) was dissolved in absolute, distilled methanol (6 mL) and treated with a solution of 2,4-dinitrophenylnicotinamidium chloride (33.8 mg, 0.1041 mmol) in methanol (1.5 mL) slowly over 5–6 h at room temperature. The reaction mixture was stirred overnight, the methanol evaporated to a small volume, and the product precipitated with ether. The solid material was triturated three times with ether and purified by two successive partition chromatographies on Sephadex G-25 in 1-butanol/acetic acid/water (4:1:5 v/v) to give a pure yellow compound (114.9 mg, 81%), which was homogeneous by thin-layer chromatography in acidic and basic systems (R_f^A 0.00 and R_f^B 0.36) and was characterized by NMR spectroscopy and by quantitative amino acid analysis which gave the ratio: Orn, 1.02; His, 1.00; Trp, 0.86; Glu, 1.96; Pro, 0.97; Gly, 1.00; Ala, 1.01; Tyr, 0.92. The product was converted to its bisacetate salt by neutralization on a DEAE-cellulose column and acidification

with acetic acid.

Anal. Calcd for $C_{62}H_{78}N_{17}O_{14}\cdot CH_3COO^-\cdot CH_3COOH\cdot 6H_2O$: C, 52.41; H, 6.47; N, 15.74. Found: C, 52.57; H, 6.63; N, 15.72.

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Registry No.—N^{α}-Trifluoroacetyl-L-ornithine, 5123-49-9; N^{α}-*t*-Boc-N^{α}-trifluoroacetyl-L-ornithine, 63865-89-4; *tert*-butyloxycarbonyl azide, 1070-19-5; *p*-Glu-His-Trp-Glu-Tyr-D-Ala-Orn-Orn(TFA)-Pro-Gly-$NH_2\cdot CH_3CO_2H$, 63865-91-8; *p*-Glu-His-Trp-*cyclo*(Glu-Tyr-D-Ala-Orn)-Orn(TFA)-Pro-Gly-$NH_2\cdot CH_3CO_2H$, 63904-16-5; *p*-Glu-His-Trp-*cyclo*(Glu-Tyr-D-Ala-Orn)-Orn(TFA)--Pro-Gly-$NH_2\cdot 2HCl$, 63865-92-9; *p*-Glu-His-Trp-*cyclo*(Glu-Tyr-D-Ala-Orn)-Orn-Pro-Gly-NH_2, 63865-93-0; *p*-Glu-His-*cyclo*(Trp-Glu-Tyr-D-Ala-Orn)-Nva($Nic^+CH_3COO^-$)-Pro-Gly-$NH_2\cdot CH_3CO$-OH, 63904-76-7; *p*-Glu-His-*cyclo*(Trp-Glu-Tyr-D-Ala-Orn)-Nva(Nic^+Cl^-)-Pro-Gly-NH_2, 63865-97-4; Z-*p*-Glu-His(Tos)-Trp-Glu(OBzl)-Tyr(OBzl)-D-Ala-Orn(Z)-Orn(TFA)-Pro-Gly-NH_2, 63915-17-3; 2,4-dinitrophenylnicotinamidium chloride, 53406-00-1.

References and Notes

(1) Abbreviations used in the text are: LRF, luteinizing hormone-releasing factor (also called luliberin); Z, benzyloxycarbonyl; TFA, trifluoroacetyl; Bzl, benzyl; Tos, toluenesulfonyl; HF, hydrogen fluoride; CMC, carboxymethylcellulose; BPyA, 1-butanol/pyridine/0.1% acetic acid in water (5:3:11); BAW, 1-butanol/acetic acid/water (4:1:5); G-25, Sephadex G-25 fine; DEAE-cellulose, diethylaminoethylcellulose; DCC, dicyclohexylcarbodiimide; *N*-HSu, *N*-hydroxysuccinimide; Nic^+, nicotinamidium; Ac, acetyl; Me_2SO, dimethyl sulfoxide; Boc, *tert*-butyloxycarbonyl.
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Synthesis of Tentoxin and Related Dehydro Cyclic Tetrapeptides[1,2]

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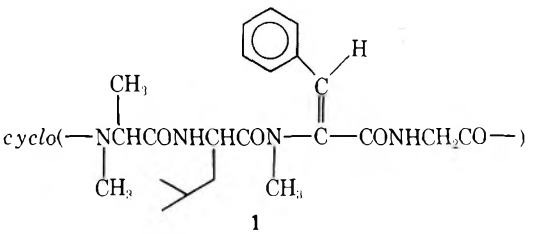
Three methods are reported for synthesizing the dehydro cyclic tetrapeptide tentoxin, *cyclo*(-L-MeAla-L-Leu-MePhe[(*Z*)Δ]-Gly-), a plant toxin that inhibits chloroplast coupling factor 1. Boc-MeAla-Leu-Phe(3-SBzl)-Gly-OMe was prepared by solid-phase synthesis, oxidized to the sulfoxide, dehydrosulfenylated, and *N*-methylated to give Boc-MeAla-Leu-MePhe[(*Z*)Δ]-Gly-OMe. Boc-MeAla-Leu-MePhe(3-SBzl)-Gly-OMe was prepared stepwise in solution from *erythro*-Boc-MePhe(3-SBzl) and converted by dehydrosulfenylation to the dehydro tetrapeptide which was also prepared in good yield by coupling Boc-MeAla with H-Leu-MePhe[(*Z*)Δ]-Gly-OMe. The synthesis of the cyclic tetrapeptides (-X-Leu-MePhe[(*Z*)Δ]-Gly-), where X = L-MeAla, D-MeAla, L-Pro, D-Pro, L-Me[2,3-^{3}H]Ala, L-*N*-[^{13}C-Me]MeAla, and D-*N*-[^{13}C-Me]MeAla, was achieved using the trichlorophenyl ester method. Saponification of Boc-*N*-methyldehydrophenylalanyl peptides led to hydantoin formation with loss of *tert*-butyl alcohol.

The cyclic tetrapeptide, tentoxin, *cyclo*(*N*-methyl-L-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycyl) (**1**) is a phytotoxin produced by the plant pathogenic fungus *Alternaria tenuis*.[3] When applied to germinating seedlings tentoxin causes chlorosis in some species but has little apparent effect on others.[3,4] This selectivity has been linked to the presence of a single tentoxin binding site on chloroplast coupling factor 1 (CF_1), a key protein involved in ATP synthesis.[5] CF_1 from sensitive species bind tentoxin strongly ($K_{assn} = 10^8$), while CF_1 from insensitive species binds tentoxin weakly ($K_{assn} \leq 10^4$). Tentoxin is the only inhibitor of CF_1 reported to exhibit such species specificity.

Tentoxin contains two structural features not commonly found in peptides, the 12-membered cyclic tetrapeptide ring system and the α,β-unsaturated amino acid, *N*-methyldehydrophenylalanine, MePhe[(*Z*)Δ].[2,6] Although several naturally occurring biologically active cyclic tetrapeptides have been identified in nature recently,[7] and a number of peptides containing dehydro residues have been reported,[8] tentoxin



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remains the only peptide isolated that contains both structural features. We report here methods to synthesize tentoxin and several tentoxin analogues that are required for biochemical and conformational studies in progress.

Results and Discussion

(I) Synthesis of Linear Tetrapeptides. The synthesis of peptides containing dehydro amino acid residues may be complicated by the chemical reactivity of the double bond. The simplest unit, dehydroalanine, rapidly adds anhydrous

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Scheme I

Boc-Gly-O polymer
solid-phase synthesis with
1. Boc-Phe(3-SBzl) (7)
2. Boc-Leu
3. Boc-MeAla
4. MeOH/TEA
→ Boc-MeAla-Leu-Phe(3-SBzl)-Gly-OMe (12)

$NaIO_4$, $MeOH/H_2O$ → Boc-MeAla-Leu-Phe[3-S(O)Bzl]-Gly-OMe (13)

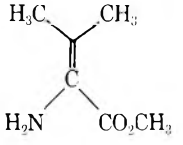
xylene, reflux → Boc-MeAla-Leu-Phe (Δ)-Gly-OMe (14a [(Z)Δ]-, 14b [(E)Δ]-)

K_2CO_3, CH_3I, DMF → Boc-MeAla-Leu-MePhe[(Z)Δ]-Gly-OR (15a)

1. 1 N KOH/EtOH
2. Tcp/DCC
3. pyridine
→ Boc-MeAla-Leu-MePhe[(Z)Δ]-Gly-OR (16a, R = H; 16b, R = Tcp)

1. 1 N HCl/HOAc
2. Pyridine (18%)
→ cyclo(-L-MeAla-L-Leu-MePhe[(Z)Δ]-Gly-) (1)

hydrobromic acid, hydrochloric acid,[9] or water. This reactivity has been exploited to effect specific cleavages of protein chains[10] and removal of peptides from polystyrene resins,[11] but the acid lability severely limits the methods that can be used to synthesize dehydro peptides. Substitution at the β position of a dehydro amino acid increases its stability toward electrophilic reagents, and two analogues, dehydrovaline methyl ester **2**[12] and dehydrophenylalanine anilide **3**,[13] are sufficiently stable to have been isolated.



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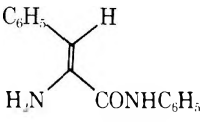

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Dehydro amino acids also may be difficult to couple using standard peptide-coupling procedures. While testing several routes to the synthesis of tetoxin precursors, we found that the C-terminal carboxyl group of Boc-leucyldehydrophenylalanine (**4**) was hard to activate. Dipeptide **4** did not couple with glycine ethyl ester when dicyclohexylcarbodiimide (DCC) was used. When **4** was converted to the acid chloride **5** by reaction with triphenylphosphine–carbon tetrachloride,[14] only low yields of tripeptide, Boc-Leu-MePhe(Δ)-GlyOMe (**6**), could be obtained. These results, and those reported for the reaction of electrophilic and nucleophilic reagents with dehydro peptides,[9-11] suggested that the synthesis of tentoxin precursors, e.g., **15a**, should be designed so that the α,β-double bond would be introduced into the molecule as late as possible in the synthesis.

A synthesis[15] of the protected linear tetrapeptide **15a** was carried out first using the solid-phase method[16] (Scheme I). The nonmethylated, 3-benzylthiophenylalanine derivative **7** was chosen for this synthesis, rather than the *N*-methyl derivative **8**, because it avoided the possible formation of *cyclo*[Leu-MePhe(3-*S*-benzyl)]. Diketopiperazine formation is a side reaction which occasionally occurs with *N*-methyl- or prolylamides,[17,18] and which appeared to be particularly troublesome in preliminary studies of related model systems. For example, attempts to synthesize Boc-MeAla-Leu-MePhe-GlyOMe from **9**, either in solution or on the solid phase,[16] gave, predominantly, the dipeptide **10** and the diketopiperazine **11**.[19] The use of amino acid **7** also made possible the assignment by ultraviolet spectroscopy of the

Boc-MeAla + H-Leu-MePhe-Gly-OR (9)
↓ DCC or the *p*-nitrophenyl ester
Boc-MeAla-Gly-OR (10) + *cyclo*-(-Leu-MePhe-) (11)

stereochemistry of the *E* and *Z*[20] isomers of tetrapeptides **14a** and **14b**, and this information could be used to confirm the *Z* configuration proposed[6] for the double bond in tentoxin.

Tetrapeptide **12** was prepared by solid-phase synthesis[16] and removed from the resin by methanolysis. Oxidation with sodium metaperiodate gave the sulfoxide **13** which undergoes thermolytic dehydrosulfenylation[21] at 140 °C to give the dehydrophenylalanine isomers **14a,b**. These could be separated by chromatography on silica gel.

Peptide **14a** (λ_{max} 284, ϵ 18 400) was assigned the *Z* configuration and peptide **14b** (λ_{max} 282, ϵ 9080) assigned the *E* configuration on the basis of the greater intensity of absorbance observed for the trans isomers of cinnamic acids.[23]

Peptide **14a** was converted to the MePhe[(*Z*)Δ] tetrapeptide **15a** by treatment with methyl iodide and anhydrous potassium carbonate in DMF or acetonitrile,[24] which methylates only the dehydrophenylalanine nitrogen without isomerizing the double bond. Complete methylation of the dehydrophenylalanine nitrogen is difficult to achieve consistently and requires that these reagents be dried carefully. However, when 18-crown-6-ethers[25] are added to the reaction mixture (0.05 equiv), the methylation proceeds in spite of small amounts of contaminating moisture. When cesium carbonate was used instead of potassium carbonate, acyl–glycine bonds were methylated at about the same rate as the dehydroamide bond, and the remaining amide nitrogens were methylated more slowly. Thus, cesium carbonate in DMF is not suitable for methylating dehydro residues selectively. The potassium carbonate–methyl iodide reagent did not methylate the *E* isomer of dehydropeptide **14b**.

Peptide **15a** was converted to the acid **16a** and then to the trichlorophenyl ester **16b**, deprotected with 1 N hydrochloric acid in acetic acid, and cyclized in pyridine to tentoxin (**1**) in 18% yield overall. The NMR, IR, UV, and mass spectral properties of synthetic **1** were identical with those of natural tentoxin and the biological potencies on germinating lettuce seedlings were indistinguishable. Thus, the proposed structure of tentoxin[6] is correct insofar as sequence and olefin configuration are concerned.

Several labeled analogues of tentoxin were required for our biological and conformational studies. The synthesis described in Scheme I is not efficient for preparing labeled derivatives because an excess of each protected amino acid is required for each solid-phase coupling reaction, and because dehydrosulfenylation of sulfoxide **13** produces 20–30% of the *E* isomer which can't be used to prepare **15a** and which must be discarded. For these reasons, a more economical route for the synthesis of labeled derivatives of **15a** was developed.

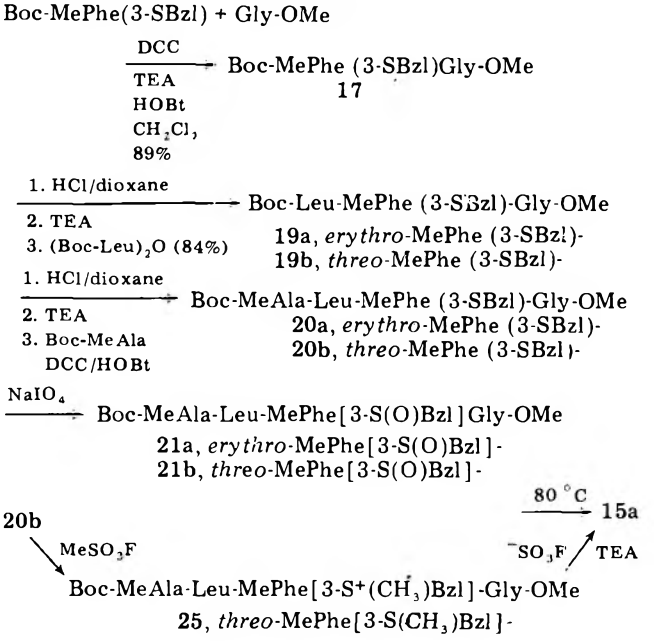
Tetrapeptide **15a** was prepared stepwise in solution starting with the N-methylated amino acid, Boc-MePhe(3-SBzl) (**8**) (Scheme II). Using DCC/1-hydroxybenzotriazole (HOBt),[26] **8a** was coupled with glycine methyl ester to give dipeptide **17** in 89% yield. When HOBt was omitted from the reaction solution a 60% yield of *N*-acylurea was obtained. Following deprotection and neutralization, the free dipeptide, MePhe(3-SBzl)-Gly-OMe (**18**), was coupled with Boc-Leu using the symmetrical anhydride method.[27] The tripeptide **19a** was obtained in 84% yield. We have found that the symmetrical anhydride method gives higher yields of product than use of either DCC or DCC with HOBt for acylation of secondary amino acids (e.g., *N*-methyl-, prolyl-, or thiazolidinecarboxylic

Table I

Compd	Boc-X-L-Leu-MePhe[(*Z*)Δ]-Gly-OMe (X =)	Compd	*cyclo*(-X-L-Leu-MePhe[(*Z*)Δ]-Gly-) (X =)	Cyclization % yield
15a	L-MeAla	**1**	L-MeAla	26–32
27	D-MeAla	**41**	D-MeAla	44–46
28	L-Pro	**42**	L-Pro	30
29	D-Pro	**43**	D-Pro	48
30	L-Me[2,3-^{3}H]Ala	**44**	L-Me[2,3-^{3}H]Ala[a]	26
31	L-*N*-[Me-^{13}C]MeAla	**45**	L-*N*-[Me-^{13}C]MeAla	32
32	D-*N*-[Me-^{13}C]MeAla	**46**	D-*N*-[Me-^{13}C]MeAla	46

[a] Data for this compound has been reported in reference 5.

Scheme II



acid derivatives). In the present case, inclusion of HOBt in the reaction led to products formed by elimination of the thiobenzyl group.

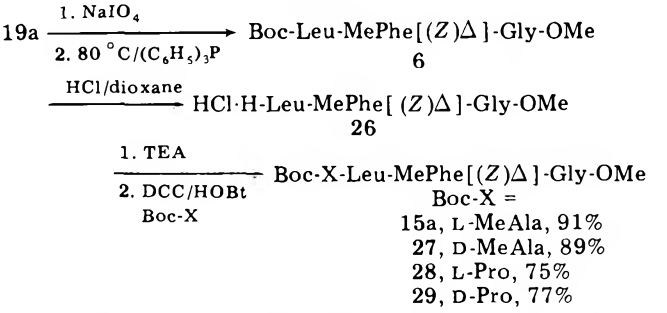
Tripeptide **19a** was deprotected, neutralized, and coupled with *tert*-butyloxycarbonyl-*N*-methylalanine using DCC/HOBt to give tetrapeptide **20a** in 85% yield. The tetrapeptide sulfide **20a** was oxidized with sodium metaperiodate to the sulfoxide **21a** which eliminated sulfenic acid slowly at 25 °C and rapidly at 80 °C. Unsaturated tetrapeptide **15a** was isolated in 70% yield.

The stereochemistry of the product obtained from dehydrosulfenylation of **21a** was predominantly *Z*. Since dehydrosulfenylation of β-alkylsulfinyl amino acids is stereospecific,[22] the MePhe(3-SBzl) precursor employed was predominantly the erythro isomer **8a**. The diastereomers **8a,b** were prepared by addition of benzyl mercaptan to *N*-acetyl-*N*-methyldehydrophenylalanine methyl ester. The adduct was hydrolyzed and the free amino acids were converted to the mixture of diastereomeric Boc derivatives by reaction with *tert*-butyl azidoformate. The diastereomers could be separated by precipitation of **8a** from hexane.

By changing the method used to generate the double bond, diastereomer **8b** also could be used to prepare **15a** and the corresponding threo linear peptides **20b** and **21b**. Dehydrosulfenylation of sulfoxide **21b** gave, as expected, the *E* isomer **15b**. However, when the *threo*-sulfide **20b** was converted to the sulfonium salt **25** by reaction with methyl fluorosulfonate, and then subjected to β elimination using triethylamine,[28] the *Z* isomer **15a** was obtained in 40% yield (Scheme II). No attempt was made to optimize the yield of this reaction.

The successful conversion of dehydro tetrapeptide **15a** into

Scheme III



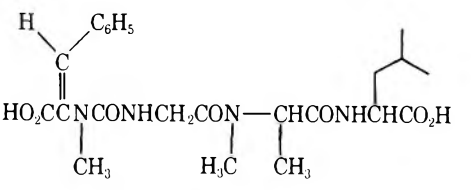
tentoxin (Scheme I) established that the *N*-methyldehydrophenylalanine residue was not destroyed by the acidic conditions needed to remove the Boc group nor by the basic conditions used for saponification or cyclization. As a result, tetrapeptide **15a** could be synthesized from tripeptide **26** which contained a preformed *N*-methyldehydrophenylalanyl residue (Scheme III). Oxidation of tripeptide **19a** followed by dehydrosulfenylation gave the *Z* dehydro peptide **6** in 61% yield. The *E* isomer, when present, could be removed by chromatography but neither the *E* nor the *Z* isomer could be crystallized. However, after removal of the Boc group, the tripeptide hydrochloride salt **26** could be crystallized from chloroform–hexane mixtures.

Condensation of Boc-MeAla or Boc-Pro with tripeptide **26** using DCC/HOBt gave good yields of the protected tetrapeptides **15a** and **27–32** (75–91%) (Scheme III). No formation of the diketopiperazine, *cyclo*(-Leu-MePhe[(*Z*)Δ]-), was detected. Thus, peptide **26** is an excellent intermediate for the synthesis of analogues of **15a** substituted in the 1 position. Using this intermediate, analogues **27–32** (Table I) were synthesized by replacing Boc-L-MeAla with the appropriate Boc amino acid.

The conformational and biological properties of cyclic tetrapeptides **41–46** will be reported separately. However, attention should be drawn to the analogue, [1-D-methylalanine[1] tentoxin (**41**)] which is a mixture of two conformers at room temperature. Our recent results have established that these conformers are in equilibrium with each other at 25 °c but can be separated and isolated at 4 °C. This work plus assignment of their conformations and biological activities will be reported in another communication.[37]

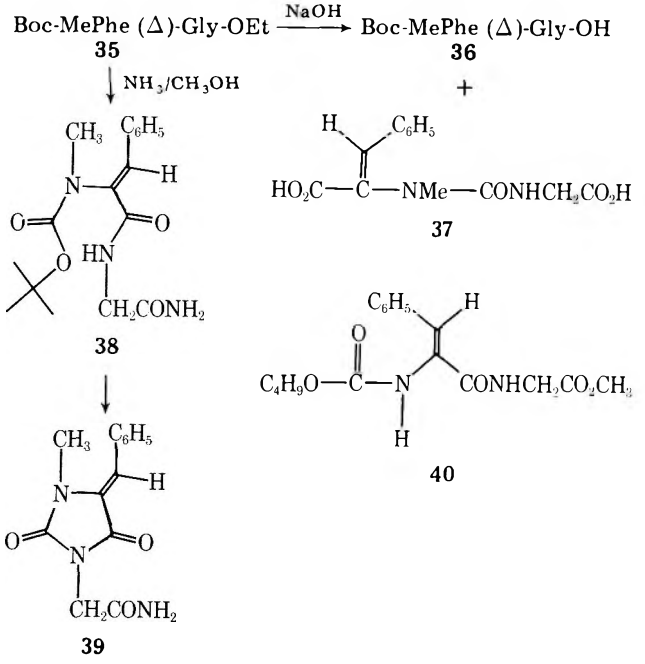
Not all *N*-methyldehydrophenylalanyl peptides are stable to the conditions used to saponify peptide esters. During the

Boc-MePhe[(*Z*)Δ]-Gly-MeAla-Leu-OMe
33



34

Scheme IV



synthesis of other linear sequences of tentoxin, an unusual side reaction was encountered when Boc-MePhe(Δ) was at the N-terminus of the chain. Saponification of the N-terminal Boc-*N*-methyldehydrophenylalanyl peptide **33** with alcoholic sodium hydroxide gave, exclusively, a ninhydrin-negative product, which did not contain a *tert*-butyl group. The product, identified as diacid **34**, probably was formed by hydrolysis of an intermediate hydantoin. Although N-terminal carbamates, e.g., the benzyloxycarbonyl group, are known to undergo hydantoin formation under basic conditions,[29] the more hindered Boc group does not. Thus, we decided to study this reaction more closely using Boc-MePhe(Δ)-Gly-OEt (**35**) (Scheme IV) to determine the parameters affecting hydantoin formation.

Saponification of dipeptide ester **35** gave the Boc acid **36** in 80% yield along with a small amount of diacid **37**. Because abstraction of the glycyl amide proton would be less likely to occur when the glycyl nitrogen is adjacent to a carboxylate anion (as it is in **36**) than to an amide group (as it is in **33**), an attempt was made to convert dipeptide ester **35** to the amide **38**. However, ammonolysis of **35** led rapidly to the formation of hydantoin **39**, which was isolated in 75% yield. In contrast, no hydantoin was formed when the non-N-methylated dehydrophenylalanyl peptide **40** was treated with either sodium hydroxide or methanolic ammonia. These results suggest that the dehydrophenylalanyl nitrogen must be methylated for hydantion formation or occur. No attempt has been made to determine if peptides containing other *N*-methyl dehydro amino acids will undergo hydantoin formation as readily as the *N*-methyldehydrophenylalanyl peptides. The unusual lability of this system, in comparison with normal N-terminal Boc peptides, probably is caused by the five adjacent trigonal centers which place the glycyl nitrogen adjacent to the Boc carbonyl group when the phenylalanine nitrogen is methylated and can assume the *cis*-amide conformation shown in structure **38**. The *cis*-amide conformation is less likely to occur in **40** because secondary amide bonds are predominantly trans.

The results reported here for linear, *N*-methyldehydrophenylalanine-containing peptides indicate that tripeptides, such as **6**, are the smallest *N*-methyldehydrophenylalanyl unit which can be used conveniently to prepare larger peptides using standard synthetic procedures. The linear peptides we studied that contained N-terminal Boc-MePhe[(*Z*)Δ] residues, e.g., **33**, **35**, **38**, are suceptible to base-catalyzed hydantoin formation, and peptides containing C-terminal MePhe[(*Z*)Δ]-OR residues, e.g., Boc-Leu-MePhe(Δ)-OH (**4**) or the acid chloride **5**, did not react well with glycine ethyl ester and may be difficult to couple. Once in the center of a tripeptide, e.g., **6**, the *N*-methyldehydrophenylalanyl residue is stable toward the acidic and basic conditions used for the synthesis of the linear and cyclic tetrapeptides reported here. However, the successful use of tripeptides containing dehydro residues may be limited to more stable dehydro residues, e.g., dehydrophenylalanine, which are much more stable to acid than aliphatic dehydro amino acids.[9,13]

Cyclization of Linear Tetrapeptides (Scheme I). Tetrapeptide **15a** was saponified and converted to the 2,4,5-trichlorophenyl ester **16** by reaction with Tcp and DCC in pyridine. After precipitation from hexane to remove DCU and Tcp, the Boc group was removed using HCl/dioxane. We obtained better yields using the hydrochloride salt of the linear tetrapeptide during the cyclization reaction than the trifluoroacetate salt. The hydrochloride was carefully dried, dissolved in DME, and added slowly to preheated pyridine to effect cyclization under dilute conditions (10^{-4} M). Systematic variation of the reaction temperature established that the highest yields were obtained at temperatures near 90 °C. A similar temperature was reported to be optimal for the synthesis of *cyclo*(ProGly)$_2$.[30] No cyclic tetrapeptides were detected from cyclizations run at temperatures below 50 °C. No attempt was made to isolate or characterize other products of the reaction. Slow addition of the peptide in DMF to the pyridine solution also was important, and this was accomplished using a motor-driven syringe. The use of other active esters, e.g., *p*-nitrophenyl ester or 2-thiopyridyl ester, did not lead to increased yields. Using the general cyclization procedure, cyclic tetrapeptides **1** and **41–46** were synthesized from the linear peptides in 26–48% yield (Table I). Linear peptides containing a D-amino acid in position 1 (e.g., **27**, **29**, **32**) gave better yields of cyclic tetrapeptide (44–48%) than the corresponding peptides containing an L-amino acid in this position (26–32%).

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

The ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer or a Bruker HX-90E-pulse Fourier transform NMR spectrometer interfaced with a Nicolet 1080 computer and disk unit. The mass spectrometer employed was Finnigan 1015. Ultraviolet data were taken with a Cary-14 ultraviolet spectrometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin-layer chromatography (TLC) was performed on silica gel G plates using the following solvent sysetms: (1) 6% methyl in benzene; (2) 20% ethyl acetate in benzene; (3) 35% ethyl acetate in benzene; (4) 50% ethyl acetate in benzene; (5) 5% ethanol in ethyl acetate; (6) 10% ethanol in ethyl acetate.

General Workup Procedure for Boc Amino Acids and Peptides. After removal of reaction solvent by evaporation, the organic residue was dissolved in ethyl acetate and washed three times with 1 N citric acid. The organic layer was separated, washed three times with saturated sodium chloride solution, dried ($MgSO_4$), and evaporated in vacuo.

Methyl *N*-Acetyl-2-*N*-methylaminocinnamate. Following the procedure developed for methylating carbamyl amino acids,[31] reaction of *N*-acetyldehydrophenylalanine (12.4 g) in 200 mL of DMF with sodium hydride (7.34 g, 57% dispersion) and methyl iodide (56.5 mL) for 30 min gave, after distillation (bp 159–163 °C, 10 mm), 13.57 g (94%) of the *N*-methyl ester: R_f (1) 0.375; NMR δ 1.98 (3 H, s), 3.068 (3 H, s), 3.86 (3 H, s), 7.46 (5 H, s), 7.63 (1 H, s).

***N*-Acetyl-*N*-methyl-3-benzylthiophenylalanine Methyl Ester (47).** To a solution of ester **46** (12.77 g) in anhydrous methanol (50 mL) were added benzyl mercaptan (9.63 mL) and sodium methoxide (100 mg). The solution was stirred at 25 °C for 7 days. Disappearance of **46** was followed by TLC. The solvent was evaporated in vacuo, and the ester **47**, after purification by chromatography over silica gel

eluting with ethyl acetate–benzene (1:9), was isolated in 80% yield (12.6 g): R_f (1) 0.47. Anal. ($C_{20}H_{23}NO_3S$): C, H, N.

***N*-Methyl-3-*S*-benzylthiophenylalanine (48).** A solution of **47** (7.15 g) in 240 mL of hydrochloric acid, 80% formic acid, and water (1:1:1) was refluxed for 6 h. The solution was cooled, diluted with water (200 mL), neutralized with ammonium hydroxide, and cooled. The product which crystallized was collected, washed with water and acetone, and dried. Recrystallization from refluxing acetic acid gave 3.74 g (67%) of **48**: mp 216–218 °C. Anal. ($C_{17}H_{19}NO_2S$): C, H, N.

***N*-*tert*-Butyloxycarbonyl-*N*-methyl-3-*S*-benzylthiophenylalanine (8a,b).** Finely powdered acid **48** (3.0 g) was suspended in DMF (30 mL), and tetramethylguanidine[32] (4.6 g, 4 equiv) was added followed by *tert*-butyloxycarbonyl azide (5.72 g, 4 equiv). The solution was stirred for 3 days. Precipitated starting material was collected and resubjected to the carbamylating conditions until free amino acid no longer precipitated. The solutions were kept at 4 °C for an additional 72 h, and then evaporated in vacuo. The residue was suspended in ethyl acetate (50 mL) and acidified with 1 N citric acid. The organic layer was separated, washed three times with 1 N citric acid (50 mL) and three times with saturated sodium chloride solution (30 mL), dried ($MgSO_4$), and evaporated. The residue was suspended in petroleum ether (50 mL) at room temperature for 24 h and then filtered to give erythro diastereomer **8a** (2.24 g, 56%): mp 133–136 °C; NMR δ 1.45 (s, 9 H), 2.6–2.7 (3 H, m), 3.65 (s, 2 H), 4.3 (1 H, m), 5.1 (1 H, m), 7.2 (10 H), 9.7 (NH); mass spectrum *m/e*, M^+ 401. Anal. ($C_{22}H_{27}NO_4S$): C, H, N, S.

Evaporation of the filtrate from **8a** gave the threo diastereomer **8b**: NMR δ 1.47 (9 H, d), 2.6–2.7 (3 H, m), 3.2 (2 H, d), 4.1 (1 H, m), 4.7 (1 H, m), 7.0 (10 H, d), 9.7 (1 H, s); mass spectrum *m/e*, M^+ 401. Anal. ($C_{22}H_{27}NO_4S$): C, H, N, S.

***N*-*tert*-Butyloxycarbonyl-*N*-methyl[2,3-^{3}H]alanine (49).** L-[2,3-^{3}H]Alanine (2.5 mCi, sp act. 31 Ci/mmol) was added to L-alanine (4.6 mg) in water (85 μL). Triethylamine (32 μL) and *tert*-butyl azidoformate (10 μL) in dioxane (85 μL) were added. The mixture was stirred for 16 h. The solvent was removed by evaporation and the residue dissolved in ether. Standard workup gave Boc-L-[2,3-^{3}H]Ala (80% yield), which was dissolved in THF (1 mL) and treated at −78 °C with sodium hydride (20 mg, 50% dispersion) and methyl iodide (300 μL) under nitrogen. The mixture was warmed to room temperature with stirring and worked up in the usual manner to give **49** (88% yield).

***N*-*tert*-Butyloxycarbonyl-L-*N*-[Me-^{13}C]methylalanine (50).** Boc-L-Ala (570 mg) and [^{13}C]methyl iodide (99% ^{13}C, 0.86 g) in 5 mL of tetrahydrofuran at 0 °C were treated with sodium hydride (84 mg, 50% dispersion). The mixture was stirred for 18 h (it gels). Solvent was added (5 mL) along with 0.5 mL of methyl iodide. The mixture was stirred for 5 days and then worked up in the normal manner to give 558 mg (91%) of **50**: $[\alpha]_D$ (MeOH) −30.0° (lit.[33], −29°). Analysis by NMR and mass spectrometry showed that L-MeAla was 80 atom-% ^{13}C: NMR δ 1.35 (3 H, d, J = 5 Hz), 1.54 (9 H, s), 2.85 (2.4 H, d, J = 135 Hz, and 0.6 H, s, unlabeled N-CH_3), 4.7 (1 H, m), and 11.3 (1 H); mass spectrum M^+ 204/203 = 4.

***N*-*tert*-Butyloxycarbonyl-D-*N*-[Me-^{13}C]methylalanine (51).** This compound was synthesized in 90% yield and 75 atom-% ^{13}C following the procedure described for the L isomer.

Methyl *N*-*tert*-Butyloxycarbonyl-*N*-methyl-3-*S*-benzylthiophenylalanylglycinate (17). To a solution of Boc-MePhe(3-SBzl) **8a** (2 g), glycine methyl ester hydrochloride (0.625 g), 1-hydroxybenzotriazole (76 mg) in 5 mL methylene chloride at 4 °C were added triethylamine (0.632 mL) and dichclohexylcarbodiimide (1.03 g) and 5 mL of CH_2Cl_2. The mixture was stirred at 4 °C for 8 h. The solvent was evaporated in vacuo. The residue was worked up normally to give a white solid, shown by TLC to be essentially one product. Crystallization from EtOAc/hexane gave pure **17** (2.2 g, 89%): R_f (2) 0.48; NMR δ 1.5 (9 H, s), 2.8 (3 H, s), 3.36 (2 H, d, J = 10.5 Hz), 3.7 (3 H, s), 3.7–3.9 (2 H, m), 4.3 (1 H, d, J = 11.5 Hz), 5.05 (1 H, d, 11.5 Hz), 6.45 (1 H, br s), 7.15–7.5 (10 H, m); mass spectrum M^+ 472. Anal. ($C_{25}H_{32}N_2O_5S$): C, H, N.

Methyl *N*-*tert*-Butyloxycarbonyl-L-leucyl-*N*-methyl-3-*S*-benzylthiophenylalanylglycinate (19). The dipeptide **17** (1.828 g) was dissolved in 5 mL of 4 N HCl–dioxane, and the solution was stirred for 30 min. The solvent was evaporated in vacuo and the residue was dried in vacuo over KOH. The dried hydrochloride was dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C. The symmetrical anhydride of Boc-L-Leu (1.9 g) (prepared by reaction of 1.99 g of Boc-Leu with 2.47 g of DCC for 7 h at 5 °C in CH_2Cl_2) was added followed by 0.556 mL of triethylamine. The solution was stirred at 4 °C for 12 h. Workup in the usual manner gave **19** as an uncrystallizable semisolid (1.96 g, 84%) which was homogeneous by TLC: R_f (3) 0.45; NMR δ 0.65–1.1 (6 H, m), 1.2–2 (15 H, m), 2.8 (3 H, s), 3.65 (2 H, s), 3.7 (3 H, s), 3.8–5.7 (5 H, m), 7.1–7.4 (12 H, m). This material was used in the next step without further purification.

Methyl *N*-*tert*-Butyloxycarbonyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (6). To the tripeptide **19** (1.9 g) in methanol (5 mL) was added sodium metaperiodate (852 mg) in 3 mL of water at 4 °C. The oxidation was followed by TLC and was complete within 12 h. The solvent was evaporated and the residue extracted with ether. The ether layer was washed, dried, and evaporated. The residue was heated in refluxing toluene for 8 h. Solvent was evaporated and the residue chromatographed on silica gel eluting with a gradient of 20 to 50% ethyl acetate in benzene. Tripeptide **6** (1.22 g, 64%) was isolated as a noncrystalline solid: R_f (4) 0.4; NMR δ 0.5–0.7 (6 H, m), 0.9–1.55 (12 H, contains nine proton singlet for Boc and β and γ protons of Leu), 3.2 (3 H, s), 3.75 (3 H, s), 4.2 (2 H, d, J = 6 Hz), 6.7 (1 H, br s), 7.25 (5 H, s), 7.75 (1 H, S, vinyl proton).

Hydrochloride of L-Leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycine Methyl Ester (26). Dehydrotripeptide **6** (1.6 g) was treated with 4 N HCl/dioxane for 30 min and the solvent was evaporated. The residue was dried in vacuo and crystallized from chloroform–hexane to give pure **6** (885 mg, 86%). Anal. ($C_{19}H_{27}N_3O_4$·HCl): C, H, N.

Methyl *N*-*tert*-Butyloxycarbonyl-*N*-methyl-L-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (15a). Boc-MeAla (102 mg) was added to a solution of the tripeptide **6** (200 mg) in CH_2Cl_2 (3 mL). The solution was cooled (4 °C), DCC (105 mg), triethylamine (50.5 mg), and 1-hydroxybenzotriazole (10 mg) were added, and the solution was stirred for 8 h. After the normal workup, the tetrapeptide **15a** was isolated (246 mg, 91%): R_f (4) 0.36; NMR δ 0.5–0.7 (6 H, d, J = 9 Hz), 1.49 (9 H, s), 1.35 (3 H, d, J = 6.6 Hz), 0.9–1.2 (3 H, m), 2.82 (3 H), 3.2 (3 H, s), 3.7 (3 H, s), 4.15 (2 H, d, J = 6 Hz), 6.4 (1 H, br s), 7.38 (5 H, s), 7.7 (1 H, s) and 8.5 (1 H, br s); UV ($CHCl_3$) λ_{max} 277 (ϵ 18 400); IR 3400, 3300, 2960, 1680–1650, 1525 cm^{-1}. Anal. ($C_{28}H_{42}N_4O_7$): C, H, N.

Methyl *N*-*tert*-Butyloxycarbonyl-*N*-methyl-D-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (27). Tetrapeptide **27** was prepared in 89% yield from **6** using Boc-D-MeAla: R_f (3) 0.50; NMR ($CDCl_3$) δ 0.60 (6 H, d, J = 6 Hz), 1.28 (3 H, d, J = 7 Hz), 1.2–1.7 (3 H, m), 1.48 (9 H, s), 2.83 (3 H, s), 3.2 (3 H, s), 3.73 (3 H, s), 4.15 (2 H, d, J = 6.5 Hz), 4.5 (1 H, m), 4.7 (1 H, m), 6.5 (NH, br s), 7.4 (5 H, s), 7.7 (1 H, s), 8.5 (NH, m); mass spectrum, *m/e*, M^+ 547, 485, 458, 384, 346, 248 (58), 132 (32), 116 (12), 102 (48), 86 (75), 57 (100).

Methyl *N*-*tert*-Butyloxycarbonyl-L-prolyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (28). Following the procedure developed for the analogue **15a**, tetrapeptide **28** was prepared in 75% yield using Boc-L-Pro: R_f (3) 0.44; NMR ($CDCl_3$) δ 0.55 (6 H, d, J = 6 Hz), 1.30 (3 H, d, J = 7 Hz), 1.41 (9 H, s), 1.2–1.7 (3 H, m), 1.7–2.2 (4 H, m), 3.21 (3 H, s), 3.05–3.55 (2 H, m), 3.72 (3 H, s), 4.0–4.35 (4 H, m), 7.2–7.4 (2 NH, m), 7.44 (5 H, s), and 7.74 (1 H, s); mass spectrum, *m/e*, M^+ 559, 459, 458, 414, 297, 298, 248, 132 (33), 131 (22), 116 (12), 114 (35), 86 (49), **70** (100), 56 (40).

Methyl *N*-*tert*-Butyloxycarbonyl-D-prolyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (29). Following the procedure developed for the synthesis of analogue **15a**, the tetrapeptide **29** was prepared using Boc-D-Pro in 77% yield: R_f (3) 0.43; NMR ($CDCl_3$) δ 0.55, 0.63 (6 H, dd, J = 3.5 Hz), 1.40 9 H, s), 0.8–1.4 (3 H, m), 1.7–2.2 (4 H, m), 3.2 (3 H, s), 3.35–3.55 (2 H, m), 3.62 (3 H, s), 4.0–4.45 (4 H, m), 7.38 (5 H, s), 7.71 (1 H, s); mass spectrum, *m/e*, M^+ 559, 459, 458, 414, 299, 298, 248, 132 (30), 131 (26), 116 (15), 114 (39), 86 (52), **70** (100), 56 (43).

Ethyl *N*-*tert*-Butyloxycarbonyl-*N*-methyl-L-[2,3-$^3H_2$]-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (30). For this tetrapeptide, the ethyl ester was used. Following the general procedure described, Boc-L-Me[2,3-$^3H_2$]Ala **49** in 600 μL of CH_2Cl_2, tripeptide **6** (21.2 mg), triethylamine (7.2 mg), and dicyclohexylcarbodiimide (10.5 mg) at 0 °C for 15 h gave a 50% yield of tetrapeptide **30** which was purified by preparative TLC on silica gel and identified by direct comparison with unlabeled analogue **15a**.

Methyl *N*-*tert*-Butyloxycarbonyl-L-*N*-[Me-^{13}C]methylalanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (31). Starting with 100 mg of ^{13}C-labeled Boc-MeAla **50**, the tetrapeptide was synthesized in 91% yield. Analytical data for **31** are the same as for **15a**, except for the NMR of the *N*-methyl group: δ 2.82 (2.4 H, d, J = 138 Hz, and 0.6 H, s), 80 atom-% ^{13}C.

Methyl *N*-*tert*-Butyloxycarbonyl-D-*N*-[Me-^{13}C]methylalanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate (32). Labeled tetrapeptide **32** was prepared in 89% yield from **6** and Boc-D-*N*-[Me-^{13}C]MeAla **51**: R_f (3) 0.50. Analytical data for **32** are the same as for the unlabeled compound **27** except for the NMR of the alanyl *N*-methyl group: δ 2.81 (2.4 H, d, J = 138 Hz, and 0.6 H, s),

80 atom-% ^{13}C.

General Procedure for Saponification. *N-tert*-Butyloxycarbonyl-*N*-methyl-L-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycine (16a). The tetrapeptide **15a** was dissolved in 95% ethanol and 1.5 equiv of ethanolic potassium hydroxide solution was added. The reaction mixture was stirred at 25 °C for 30–45 min and the saponification monitored by TLC. The solvent was evaporated, suspended in ether, and acidified with 1 N citric acid solution. The ether layer was removed, and the aqueous layer washed with ethyl acetate. The organic layers were combined, dried, and evaporated. The NMR of **16a** was essentially the same as that of **15a**, except the methyl signal at 3.7 ppm was absent.

General Procedure for Cyclization of Tetrapeptides. A solution of Boc tetrapeptide acid **16a** (0.3 mmol) and 2,4,5-trichlorophenol (0.36 mmol) in pyridine (3–4 mL) was stirred at 4 °C under nitrogen. DCC (0.36 mmol) was added and the reaction was allowed to proceed for 12 h at 4 °C. The pyridine was removed in vacuo and the residue dissolved in ethyl acetate. The solution was cooled (−78 °C) and filtered to remove DCU. Solvent was removed and the residue treated with 4 N HCl in dioxane for 30 min at 25 °C. The solvent was evaporated in vacuo. The hydrochloride was dissolved in DMF (1–2 mL) and this solution was added dropwise, using a motor-driven syringe, to pyridine (1 L) preheated to 90 °C. After 8 h, the solvent was evaporated at 40 °C and the residue was dissolved in ethyl acetate. The solution was washed three times with cold water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel eluting with a gradient of 0 to 30% ethanol in ethyl acetate. Fractions containing product **1** were pooled, concentrated, and crystallized from chloroform–ether or, occasionally, further purified by preparative TLC on silica gel eluting with 5% ethanol in ethyl acetate. Using this method, the tentoxin analogues **40–45** were prepared in 25–40% yield.

Tentoxin. *cyclo*(*N*-Methyl-L-alanyl-L-leucyl-*N*-methyldehydrophenylalanylglycyl) (1). Applying the general saponification and cyclization procedures, tentoxin **1** was prepared in 26% yield from tetrapeptide **15a**: mp 173–175 °C (lit.[6], 172–175 °C); R_f (5) 0.356, (6) 0.52; UV λ_{max} (CH_3OH), 282 (ϵ 20 700); NMR ($CDCl_3$) δ 0.52, 0.71 (6 H, m), 1.15–1.25 (3 H, m), 1.52 (3 H, d, J = 8 Hz), 2.77 (3 H, s), 3.24 (3 H, s), 3.52 (1 H, dd, J = 2, 15 Hz), 4.16 (1 H, m), 4.30 (H, q), 5.07 (1 H, dd, J = 10.1, 15 Hz), 7.2 (1 H, d, 8.9 Hz), 7.27 (5 H, s), 7.74 (H, s), and 7.97 (1 H, d, 10.1 Hz); mass spectrum, *m/e*, 414. Anal. ($C_{22}H_{30}N_4O_4$): C, H, N.

***cyclo*(*N*-Methyl-D-alanyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycyl). D-MeAla[1]-tentoxin (41).** Following the standard saponification and cyclization procedures, D-MeAla[1]-tentoxin was prepared in 44% yield: mp 158–162 °C; UV λ_{max} (CH_3OH) 278 (ϵ 19 700); NMR ($CDCl_3$) shows signals for two conformers: conformer A δ 0.77–0.53 (6 H, m), 1.55–1.15 (3 H, m), 1.52 (3 H, d, J = 8 Hz), 3.04 (3 H, s), 3.18 (3 H, s), 3.7 (1 H, d, J = 16 Hz), 4.17 (1 H, m), 4.48 (1 H, q, J = 8 Hz), 5.19 (1 H, dd, J = 10, 16 Hz), 6.94 (1 H, d, J = 10 Hz), 6.0 (1 H, d, J = 6 Hz), 7.4 (5 H, s); conformer B: δ 0.67–0.53 (6 H, m), 1.4–1.1 (3 H, m), 1.54 (3 H, d, J = 7 Hz), 3.07 (3 H, s), 3.26 (3 H, s), 3.5 (1 H, m), 4.24 (1 H, q, J = 7 Hz), 4.52 (1 H, m), 4.9 (1 H, br s), 7.25 (1 H), 6.34 (1 H, s), and 7.4 (5 H, s). Mass spectrum *m/e* (% base peak) 414 (5), 301 (3), 216 (3), 215 (3), 214 (3), 132 (12), 131 (15), 116 (19), 114 (12), 86 (11), 81 (10), 58 (100). Anal. ($C_{22}H_{30}N_4O_4$): C, H, N.

***cyclo*(L-Prolyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycyl). L-Pro[1]-tentoxin (42).** Starting with tetrapeptide **28** and following standard procedure for saponification and cyclization, L-Pro-tentoxin **42** was obtained in 30% yield: mp 173–175 °C; R_f (5) 0.153, R_f (6) 0.29; UV λ_{max} (CH_3OH) 282 (19 100); NMR ($CDCl_3$) δ 0.63–0.51 (6 H, m), 1.25–1.11 (3 H, m), 1.98–1.59 (3 H, m), 2.41 (1 H, 3.19 (3 H, s), 3.54 (1 H, d, 14.8 Hz), 3.54 (2 H, m), 4.40 (1 H, dd, 7 and 6 Hz), 4.49 (1 H, m), 5.12 (1 H, dd, 8 and 14.8 Hz), 7.41 (5 H, s), 7.93 (1 H, d, J = 8 Hz), 7.3 (1 H, d, J = 7 Hz), 7.76 (1 H, s); mass spectrum *m/e* (% of base) 427 (1.2), 426 (1.5), 216 (1), 189 (1), 188 (4), 187 (3.5), 132 (7), 131 (8), 130 (3), 117 (5), 116 (10), 91 (5), 89 (5), 86 (5), 82 (5), 70 (100). Anal. ($C_{23}H_{30}N_4O_4$): C, H, N.

***cyclo*(D-Prolyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycyl). D-Pro[1]-Tentoxin (43).** Following the procedure for the L isomer, D-Pro[1]-tentoxin **43** was prepared in 48% yield: mp >300 °C (sublimes); UV λ_{max} (CH_3OH) 282 (19 100); NMR ($CDCl_3$) δ 0.77–0.54 (6 H, m), 1.53–1.08 (3 H, m), 1.93 (3 H, m), 2.2 (1 H, m), 3.2 (3 H, s), 3.6 (2 H, m), 3.72 (1 H, d, J = 16 Hz), 4.34 (1 H, d), 4.48 (1 H, m), 5.06 (1 H, dd, 10 and 16 Hz), 6.42 (1 H, d, J = 6.8 Hz), 7.17 (1 H, s), 7.2 (1 H, d, J = 10 Hz), 7.35 (5 H, s), 7.74 (1 H, s); mass spectrum *m/e* (% of base), 427 (2.5), 426 (2.5), 216 (2.5), 189 (1), 188 (2), 187 (2), 132 (10), 131 (12), 130 (3), 117 (5), 116 (12), 91 (6), 89 (4), 86 (4), 83 (6), 70 (100). Anal. ($C_{23}H_{30}N_4O_4$): C, H, N.

***cyclo*(*N*-[Me-^{13}C]Methyl-L-alanyl-L-leucyl-*N*-methyldehydrophenylalanylglycyl-) (45).** Compound **45** was prepared in 32% yield from linear tetrapeptide **31** following the procedures developed for the unlabeled compound. Compound **45** was 80 atom-% in ^{13}C in the methyl group of *N*-methylalanyl residue in position one: mass spectrum *m/e* (% of base), M^+ 415 (7), 414 (6.3), 302 (2), 301 (1), 217 (1.6), 216 (2.4), 215 (2.0), 214 (2.2), **58** (100).

***cyclo*(*N*-[Me-^{13}C]Methyl-D-alanyl-L-leucyl-*N*-methyldehydrophenylalanylglycyl) (46).** Compound **46** was prepared in 46% yield from the tetrapeptide **32** following the procedures developed for the unlabeled compound. Compound **46** was 75 atom-% ^{13}C in the *N*-methyl-D-alanine residue: mass spectrum *m/e* (% of base), M^+ 415 (7), 414 (6.5), 302 (3), 301 (1), 217 (1.5), 216 (2.2), 215 (2.1), 214 (2.2), 58 (100).

Saponification of Methyl *tert*-Butyloxycarbonyl-*N*-methyldehydrophenylalanylglycyl-*N*-methylalanylleucinate. Compound **33** (12.5 mg, 0.023 mmol) was dissolved in methanol (1 mL), and 1 N sodium hydroxide (0.025 mL, 0.025 mmol) was added and the solution was stirred at 25 °C for 30 min. The methanol was removed by evaporation and the solution was acidified to pH 3 and washed three times with ethyl acetate. The organic layer was dried ($MgSO_4$) and evaporated to give the diacid **34** (9 mg, 83%): R_f (EtOAc) 0.55; UV λ_{max} 277.5 (ϵ 14 400); NMR δ 0.93 (6 H, dd), 1.35 (3 H, d, J = 7 Hz), 1.63 (3 H, m), 3.0 (3 H. s), 3.04 (3 H, s), 4.14 (1 H, m), 4.60 (2 H, m), 5.1 (1 H, m), 7.45, 7.68 (6 H, m). Anal. ($C_{23}H_{32}N_4O_7$): C, H, N.

Ethyl *tert*-Butyloxycarbonyl-*N*-methyldehydrophenylalanylglycinate (35). Ethyl *tert*-butyloxycarbonyl-*N*-methyl-3-benzylthiophenylalanylglycinate (mp 86–87 °C, 470 mg, 0.96 mmol) was oxidized in methanol (25 mL) and water (10 mL) with sodium periodate (226 mg, 1.05 mmol) to the sulfoxide. After the usual workup, the residue was dissolved in benzene and heated at reflux for 1 h. Workup, followed by chromatography on silica gel eluting with 40% ethyl acetate in benzene, gave pure **35** (300 mg, 87%): R_f (3) 0.22; NMR δ 1.3 (9 H, s), 1.3 (3 H, t, J = 7 Hz), 3.0 (3 H, s), 4.4 (4 H, m, q), 7.25 (1 H, s), 7.32 (5 H, s), 6.7 (NH). Anal. ($C_{19}H_{26}N_2O_5$): C, H, N.

Ammonolysis of 35. Formation of Hydantoin 39. A solution of **35** (100 mg) and 10 mL of methanol was saturated with anhydrous ammonia at 0 °C for 40 min. The solution was stirred for 3.5 h and then the solvent was evaporated. Crystallization from acetone gave pure hydantoin **39** (77%): mp 197–203 °C; IR 5.65, 5.82, 5.95, 6.05, 6.12 μm; NMR (Me_2SO-d_6) 2.88 (3 H, s), 4.07 (2 H, s), 6.84 (1 H, s), and 7.45 (5 H, s). Anal. ($C_{13}H_{13}N_3O_3$): C, H, N.

Solid-Phase Synthesis of *N-tert*-Butyloxycarbonyl-L-*N*-methylalanyl-L-leucyl-3-*S*-benzylthiophenylalaninylglycine Methyl Ester (12). The solid-phase synthesis was carried out on a Beckman Model 990 peptide synthesizer. Removal of the *N*-Boc protecting group, neutralization of the peptide resin salt, and addition of the next amino acid followed a program previously reported[34,35] for the synthesis of oxytocin. The resin (1% divinyl benzene) contained 0.6 mmol of Gly/g. The protected peptide was cleaved from the peptide resin (5.9 g) by stirring in freshly prepared anhydrous methanol (60 mL) and dimethoxyethane (60 mL) containing triethylamine (15 mL).[36] The flask was wired shut and stirred at room temperature for 24 h. The suspension was filtered and the resin resuspended in identical amounts of the above solvent for an additional 24 h. After filtration, the filtrates were combined and rotary evaporated to give a crude product which was dissolved in ethyl acetate and washed with water, citric acid, water, and sodium bicarbonate, and dried ($MgSO_4$). The residue was chromatographed on silica gel eluting with a gradient of benzene to 50% ethyl acetate in benzene. This material was further purified by gel filtration through LH-20 in methanol to give 1.48 g (64%) of pure **12**: R_f (4) 0.38; NMR ($CDCl_3$) δ 0.85 (6 H, m), 1.0–1.40 (3 H, m), 1.18 (3 H, d, J = 7 Hz), 1.36 (9 H, s), 2.76 and 2.69 (3 H, two s), 3.58 (2 H, d), 3.70 (3 H, s), 3.94 (3 H, m), 4.2 (1 H, m), 4.41 (1 H, m), 4.85 (1 H, m), 6.52 (3 H, m), 7.27 (5 H, s), 7.29 (5 H, s). Anal. ($C_{34}H_{48}N_4O_7S$): C, H, N, S.

***N-tert*-Butyloxycarbonyl-L-*N*-methylalanyl-L-leucyldehydrophenylalanylglycine Methyl Ester (14a,b).** The sulfide **12** (176 mg) was dissolved in methanol (5 mL), and sodium periodate (60 mg) and water (3 mL) were added. The reaction mixture was stirred at 0–5 °C for 24 h. The solvent was removed under reduced pressure. Ethyl acetate and water were added to the residue, and the aqueous layer was separated and washed with ethyl acetate. The organic extracts were combined, washed with water, and dried ($MgSO_4$), and solvent was removed to give sulfoxide **13** (180 mg, 94%) which was used without further purification.

Sulfoxide **13** (180 mg) was refluxed in xylene (18 mL) under nitrogen for 30 h. The solvent was removed in vacuo and the residue chromatographed on LH-20 in methanol to give a mixture of *E* and *Z* isomers in 60% yield.

The isomers were separated by chromatography on a column of silica gel packed in 30% ethyl acetate–benzene, eluting with a gradient to 50% ethyl acetate.

Boc-L-MeAla-L-Leu-Phe[(*Z*)Δ]-Gly-OMe (**14a**): R_f (EtOAc) 0.62; UV λ_{max} 276 (ϵ 18 400); NMR ($CDCl_3$) δ 0.91 (6 H, m), 1.27 (3 H, d, J = 7 Hz), 1.42 (9 H, s), 1.1–1.3 (3 H, m), 2.77 (3 H, s), 3.71 (3 H, s), 4.05 (2 H, d, J = 6 Hz), 4.4 (1 H, m), 4.5 (1 H, m), 6.73 (1 H, br s), 7.37 (5 H, m), 8.3 (1 H, br s). Anal. ($C_{28}H_{42}N_4O_7$): C, H, N.

Boc-L-MeAla-L-Leu-Phe[(*E*)Δ]-Gly-OMe (**14b**): R_f (EtOAc) 0.81; UV λ_{max} 282 (ϵ 9080); NMR ($CDCl_3$) δ 0.92 (6 H, m), 1.36 (3 H, d, J = 7 Hz), 1.2–1.4 (3 H, m), 1.48 (9 H, s), 2.79 (3 H, s), 3.64 (3 H, s), 3.91 (2 H, d, J = 6 Hz), 4.50 (1 H, m), 4.56 (1 H, m), 6.29 (1 H, m), 6.67 (1 H, m), 7.34 (5 H, m), 7.90 (1 H, s). Anal. ($C_{28}H_{42}N_4O_7$): C, H, N.

N-Methylation of Ester 14a to Give 15a. The procedure reported earlier[24] gave **15a** in 89% yield. Traces of moisture retard the methylation. However, addition of 18-crown-6-ether (0.05 equiv) to potassium carbonate in either dimethylformamide or acetonitrile gave reproducible and comparable yields of product.

Registry No.—**1**, 28540-82-1; **6**, 64044-93-5; **8a**, 64044-94-6; **8b**, 64044-95-7; **12**, 64070-04-8; **13**, 64091-06-1; **14a**, 55478-19-8; **14b**, 55528-34-2; **15a**, 55478-20-1; **16a**, 55478-21-2; **17**, 64044-96-8; **19**, 64044-98-0; **26**, 64044-97-9; **27**, 64070-05-9; **28**, 64044-99-1; **29**, 64070-06-0; **30**, 64045-00-7; **31**, 64045-01-8; **22**, 64070-07-1; **33**, 55477-73-1; **34**, 64044-92-4; **35**, 64044-81-1; **39**, 64044-82-2; **41**, 64070-01-5; **42**, 64044-83-3; **43**, 64070-02-6; **45**, 64044-84-4; **46**, 64070-03-7; **47**, 64044-85-5; 48, 64044-86-6; **49**, 64070-50-4; **50**, 64044-87-7; **51**, 64044-88-8; methyl-*N*-acetyl-2-*N*-methylamino cinnamate, 64044-89-9; *N*-acetyldehydrophenylalanine, 5469-45-4; methyl iodide, 74-88-4; benzyl mercaptan, 100-53-8; *tert*-butyloxycarbonyl azide, 1070-19-5; L-[2,3-^{3}H]alanine, 56877-49-7; Boc-L-[2,3-^{3}H]Ala, 64044-90-2; Boc-L-Ala, 15761-38-3; [^{13}C]methyl iodide, 4227-95-6; Boc-D-Ala, 7764-95-6; glycine methyl ester hydrochloride, 5680-79-5; Boc-L-Leu anhydride, 51499-91-3; Boc-Leu, 13139-15-6; Boc-MeAla, 16948-16-6; Boc-D-MeAla, 19914-38-6; Boc-L-Pro, 15761-39-4; Boc-D-Pro, 37784-17-1; ethyl *tert*-butyloxycarbonyl-*N*-methyl-3-benzylthiophenylalanylglycinate, 64044-91-3; ethyl *N*-*tert*-butyloxycarbonyl-L-leucyl-*N*-methyl-(*Z*)-dehydrophenylalanylglycinate, 64044-80-0.

References and Notes

(1) Taken in part from the Ph.D. Theses of Jim P. Tam, University of Wisconsin, 1976, and Pradip K. Bhatnagar, University of Wisconsin, 1977. Financial support from the National Institutes of General Medical Sciences (GM 19311) is gratefully acknowledged.

(2) All amino acids except glycine are of the L configuration unless noted. Standard abbreviations for amino acids, protecting groups, and peptides as recommended by the IUPAC–IUB Commission on Biochemical Nomenclature [*J. Biol. Chem.*, **247**, p 977 (1972)] are used. Additional abbreviations are: MePhe(*ZΔ*), *N*-methyl-(*Z*)-dehydrophenylalanine; MeAla, *N*-methylalanine; Boc, *tert*-butoxycarbonyl; MePhe(3-SBzl), *N*-methyl-3-*S*-benzylthiophenylalanine; MePhe[3-S(O)Bzl], *N*-methyl-3-benzylsulfinylphenylalanine; DCC, dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; TEA, triethylamine; TMG, tetramethylguanidine; Tcp, trichlorophenyl; DCU, dicyclohexylurea.

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Photochemistry of the Chroman and 3-Chromanone Ring Systems. An Example of Tautomeric Control of Excited-State Chemistry[1]

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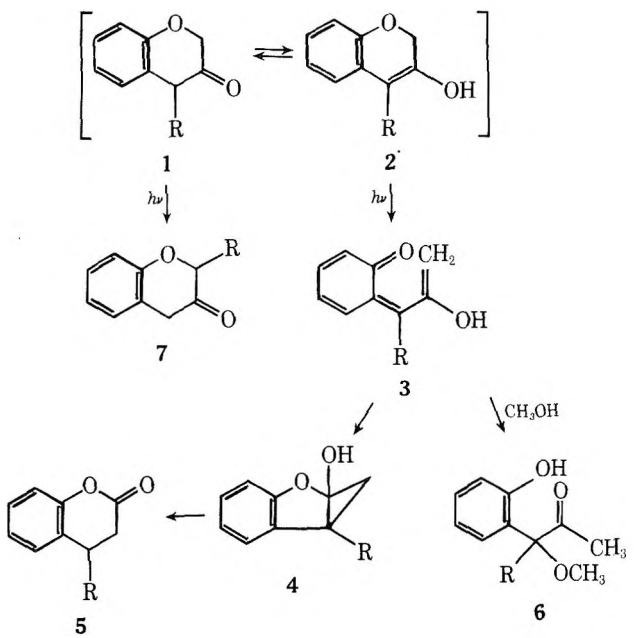
Photorearrangement reactions are described for 4-phenyl-3-chromanone (1) and 4,7-dimethyl-3-chromanone (10). Irradiation of these compounds in nonprotic solvents gives a 2-substituted 3-chromanone as the only photoproduct. The mechanism proposed involves β scission of the C–O bond and recoupling of the zwitterion through the aromatic ring to give a transient spirocyclohexadienone which gives the product by a [1,3]sigmatropic shift. Irradiation of the 3-chromanone system in methanol, however, proceeds via the small amount of enol present in tautomeric equilibrium with the keto form. The solvent effect noted can best be rationalized in terms of the enol content in each solvent. In alcoholic solvents there is a significant amount of the enol form present, which can be selectively excited with long wavelength light. In benzene or acetonitrile, insignificant quantities of the enol tautomer are present in solution and consequently the photoreaction is due to excitation of the keto form of the chromanone system. The excited-state behavior of the closely related chroman ring was also studied. The results obtained indicate that the reaction proceeds by homolytic cleavage of the C–O bond to give a diradical intermediate, which undergoes a subsequent fragmentation or internal hydrogen abstraction reaction.

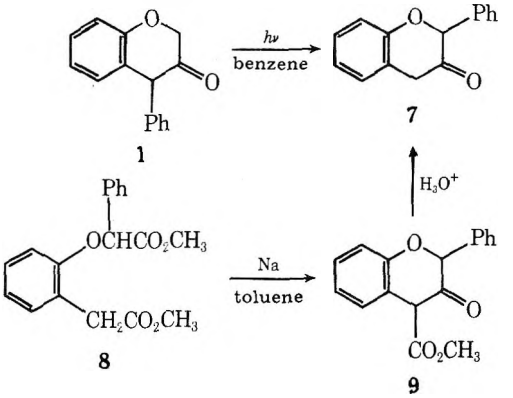
Previous papers from this laboratory have demonstrated the variety of transformations which ensue on electronic excitation of 4-substituted 3-chromanones.[2-5] The kinds of reactions which have been observed in alcoholic media have led to the suggestion that the photochemistry of this system involves the prior enolization of **1** into its enol tautomer (**2**) which subsequently undergoes photochemical ring opening to *o*-quinoneallide **3**. The conversion of enol **2** to o-quinoneallide **3** is analogous to the well known ring openings of pyrans, chromenes, isochromenes, and other related benzoheterocyclic olefins.[6-14] The initially produced o-quinoneallide **3** was suggested to have two competitive pathways open to it. One path involves the ring closure of **3** to give a 1-hydroxy-5-substituted-2-oxabenzobicyclo[3.1.0]hex-3-ene (**4**) which is rapidly converted to a 4-substituted dihydrocoumarin (**5**). The other competing pathway consists of 1,4-addition of methanol across the C–C double bond of **3** to give a phenolic ketone.[5]



As part of our continuing studies dealing with carbonyl group photochemistry through the enol form, we became interested in determining whether the enol content can contribute in controlling the photochemical behavior of the carbonyl chromophore. This interest led us to examine the photochemistry of **1** in a nonprotic solvent where the concentration of the enol form (**2**) was negligible. In an earlier communication[4] we reported that the photochemistry of 4-phenyl-3-chromanone (**1**; R = Ph) could be completely diverted from dihydrocoumarin (**5**) formation to formation of a rearranged 3-chromanone (i.e., **7**) when benzene was used as the solvent.[4] We now wish to report additional studies on the photochemistry of several 4-substituted 3-chromanones in nonprotic solvents which extend our previous observations and afford important information on the mechanism of this novel rearrangement. The present paper also describes the photochemical behavior of the closely related chroman system.

Results and Discussion

Irradiation of 4-phenyl-3-chromanone **1** (R = Ph) in benzene for 15 h resulted in the formation of a single photoproduct. This material was easily separable from the starting ketone which remained (15%) by preparative GLC. The photoproduct was an isomer of **1**, having the same molecular weight (224) by mass spectral analysis. The assignment of 2-phenyl-3-chromanone (**7**; R = Ph) as the structure of the photoproduct was based on its spectroscopic properties (IR 5.80 μm; UV (methanol) 305 nm (ϵ 650); NMR ($CDCl_3$) τ 6.38 (s, 2 H), 4.80 (s, 1 H), 2.4–3.3 (m, 9 H)) and was further confirmed by comparison with an authentic sample prepared by treating 2-phenyl-4-carbomethoxy-3-chromanone (**8**) with aqueous acid. β-Keto ester **8** was synthesized, in turn, from a Dieckmann condensation of methyl α-phenyl(o-carbomethoxymethyl)phenoxyacetate (**9**) with sodium in refluxing toluene. Extended irradiation of **1** did not enhance the degree of conversion but only increased the amount of polymer formed. The possibility that the unreacted starting material present in the crude photolysate was derived by photoisom-



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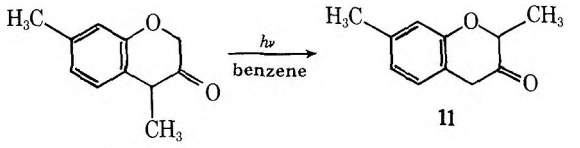
erization of the final photoproduct was eliminated by the finding that **7** did not give **1** on extended irradiation in benzene.

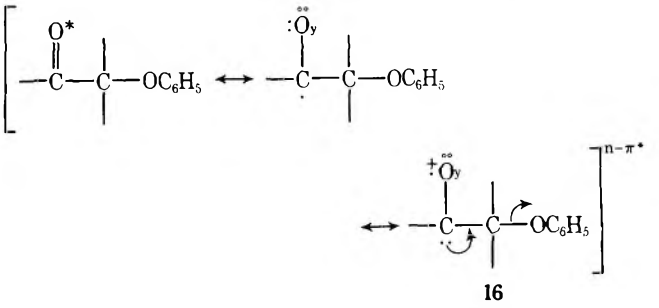
The photochemistry of the closely related 4,7-dimethyl-3-chromanone (**10**) system was also studied in order to assess the generality of the rearrangement. Photolysis of **10** in benzene resulted in the formation of a single photoproduct. The photoproduct, isolated by preparative GLC, was an isomeric ketone whose structure was assigned as 2,7-dimethyl-3-chromanone (**11**) on the basis of its spectral data (IR 5.78 μm; UV (methanol) 305 nm (ϵ 740); *m/e* 176 (M^+)). The NMR preperties of this compound ((CDCl$_3$), τ 8.54 (d, 2 H, J = 7.0 Hz), 7,70 (s, 3 H), 6.47 (s, 3 H), 5.73 (q, 1 H, J = 7.0 Hz), and 3.0–3.4 (m, 3 H)) were identical with those of an authentic sample of 2-methyl-3-chromanone except for the absence of the benzylic methyl group.



10 **11**

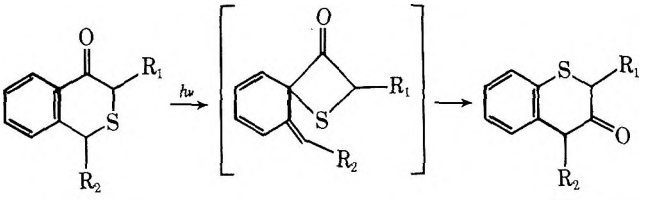
In the interest of understanding the mechanism of the rearrangement more fully, the photolytic behavior of 4-methyl-4-phenyl-3-chromanone (**12**) was also investigated. When a benzene solution of **12** was irradiated for 10 h in Pyrex with a 3130-Å source, a single product was formed. The spectral data obtained (see Experimental Section for details) indicate the product to be 3-methyl-3-phenyl-2,3-dihydrobenzofuran (**13**). This assignment was confirmed by an independent *synthesis* which is outlined in Scheme I.

The photochemical rearrangement of chromanones **1** and **10** in benzene can be rationalized according to the mechanism outlined in Scheme II. Initial n–π^* excitation followed by C–O bond cleavage and recoupling through the aromatic ring leads to spirocyclohexadienone **15**. This transient species can either revert back to starting material or proceed on to the final product by a [1,3]sigmatropic shift. The first step of the proposed mechanism is not unprecedented as related β-scission reactions of n–π^* excited ketones have appeared in the literature.[15-17] Zimmerman has explained these reactions by utilizing a simple atomic orbital resonance model for the excited carbonyl group.[18] In his description, the n–π^* excited state was suggested to have the dual capacity of ejecting a group in the α-position either as a radical or as an anion. A polar route for fragmentation of the C–O bond of **1** is particularly attractive, considering the relatively high electron density on the carbonyl carbon of the n–π^* excited ketone and the stability of the resulting phenoxide anion. In terms of resonance reasoning, canonical form **16** is quite important[18] (i.e., the

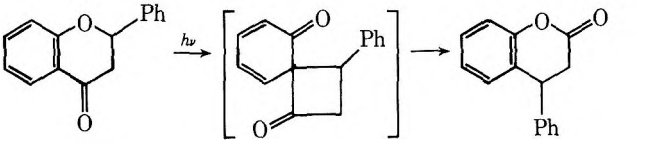


16

excited carbonyl is a good electron-donating group). This facile heterolysis is a manifestation of π^* assisted cleavage, of which there are a growing number of examples.[19-21] The conversion of **1** to **7** is also analogous to the light-induced rearrangements of isothiochroman-4-ones (**17**) to thiochroman-3-ones (**18**)[22-24] and flavone (**19**) to 4-phenyldihydrocoumarin (**20**)[25] where intermediates similar to **15** have been suggested. Related intermediates have also been postulated in abnormal Claisen rearrangements.[26-28]



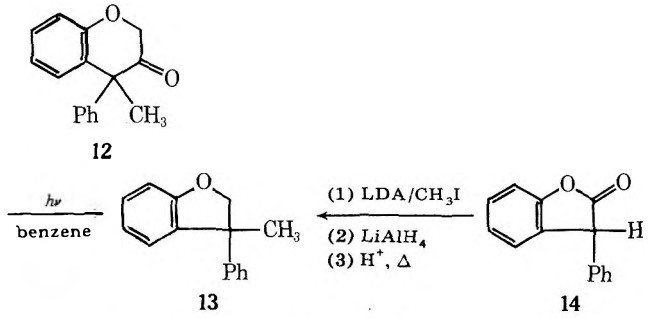
17 **18**



19 **20**

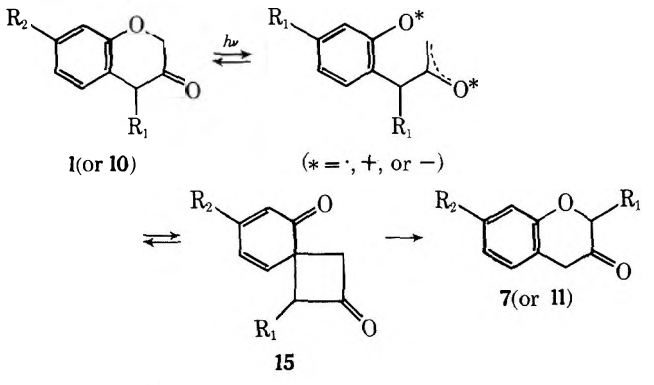
The transformations of chromanone **1** is especially interesting in view of the fact that the photolysis of this system is solvent dependent. As was pointed out in previous papers,[2-5] irradiation of **1** in a protic solvent such as methanol led to the formation of dihydrocoumarin **5**. A number of factors could account for this solvent perturbation, including the adjustment of ground- and excited-state energy levels, excited-state configurations and barriers, as well as the multiplicity of the electronically reactive state. We suggest, however, that the solvent effect noted can best be rationalized on the basis of the enol content present in each solvent. We have previously shown that the conversion of **1** to **5** proceeds via the small amount of enol present in tautomeric equilibrium with the keto form. In alcoholic solvents there is a significant (ca. 1–2%) amount of the enol form present in solution which can be selectively excited with long wavelength light. Electronic excitation of the enol tautomer results in a photochemical ring opening to give an *o*-quinoneallide intermediate (**3**) which is ultimately converted to dihydrocoumarin **5**. In benzene or acetonitrile, insignificant quantities of the enol tautomer are present in solution and consequently the photoreaction encountered in these solvents is due to excitation of the keto form of chromanone **1**. This conclusion was reached by ex-

Scheme I



12 **13** **14**

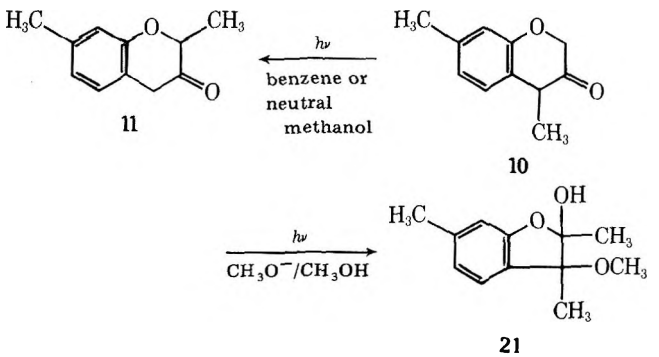
Scheme II



1(or **10**) (* = ·, +, or −) **15**

amination of the UV spectrum of 1 in various solvents. This technique provides a convenient method of estimating the amount of the enol form present in solution. In acetonitrile, chromanone 1 shows three absorption bands with maxima at 298, 280, and 274 nm (ϵ 1500, 3000, and 3300) whereas in methanol solution a new long-wavelength absorption band at 314 nm is also present (ϵ 170). The possibility that the long wavelength absorption band in methanol was due to enol (or enolate) 2 was confirmed when trace amounts of base were added to spectral solutions. Under these conditions, a dramatic enhancement in the intensity of the 314-nm band occurred. Addition of a full equivalent of sodium methoxide to a methanolic solution of 1 resulted in the appearance of two new maxima at 314 and 239 nm. The extinction coefficients of these maxima were on the order of 10^4. Furthermore, the absorption spectrum of the corresponding methyl enol ether, which provides a reasonable model for the enol tautomer 2, also showed a long wavelength maximum at 311 nm (ϵ 4800). Based on the above spectral data, we propose that in methanolic solutions approximately 1–2% of the enol (or enolate) exists in equilibrium with the keto form of 1. In benzene or acetonitrile solutions, however, concentrations of less than 0.1% of enol 2 exist in equilibrium with the keto tautomer. It is this difference in enol concentration which we believe is responsible for the dramatic solvent effect encountered with this system.

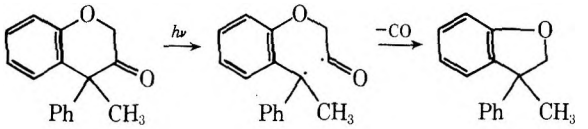
In contrast to 4-phenyl-3-chromanone (1), the photochemistry of the closely related 4,7-dimethyl-3-chromanone (10) system was not significantly altered upon changing the solvent from benzene to neutral methanol. Brief irradiation of 10 in methanol resulted in a moderate yield of chromanone 11, whereas prolonged photolysis gave rise to a complex mixture of photoproducts. The absence of a dramatic solvent effect with this system is also understandable in terms of the enol content present in solution. With this system, the concentration of the enol form is significantly less than that present in the phenylchromanone system. In addition, the absorption characteristics of the enol derived from 10 would be expected to be hypsochromically shifted relative to the enol derived from the phenyl system. Thus, it will not be possible to selectively excite this tautomer as was the case with chromanone 1. It should be pointed out that when a basic methanolic solution of 10 was subjected to UV irradiation the only product obtained was 2-hydroxy-3-methoxy-2,3,6-trimethyl-2,3-dihydrobenzofuran (21).[5] The formation of 21 is



readily explicable in terms of a photoinduced ring opening of the enolate anion of 10 to give an *o*-quinoneallide intermediate which subsequently adds methanol across the C–C double bond. Under these conditions, the enolate anion derived from 10 absorbs almost all of the incident light whereas in neutral methanol the keto tautomer is the major light absorbing species.

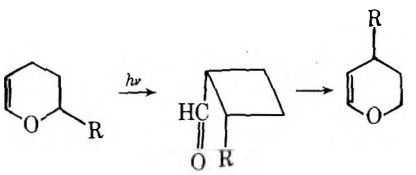
Several experiments were also carried out with the intent of identifying the excited state responsible for the rearrangement of 1 and 10. The data obtained suggest that the above transformations (i.e., 1 → 7) proceed from a n–π^* excited singlet state. As expected for a singlet reaction, we have found that the photochemical rearrangement of chromanones 1 and 10 were not quenched by piperylene or cyclohexadiene. When the triplet state was generated artificially by acetone sensitization, the rearrangement did not proceed. Quantum yields for product formation were determined in acetonitrile using cyclopentanone as the chemical actinometer.[29] The calculated values indicated the efficiency of the rearrangement to be about 0.02. The low efficiency of the rearrangement can be attributed, in part, to the fact that spirocyclohexadienone 15 can revert back to starting material in competition with rearrangement to the observed product. Alternatively, it is quite possible that the n–π^* singlet state undergoes a facile Norrish Type I cleavage to give a diradical which recombines to regenerate starting material. The two rationales are operationally indistinguishable with the present information, but both lead to the same conclusion that reorganization of the 4-substituted 3-chromanone system is an inefficient process. We thought that it might be possible to demonstrate the occurrence of the Norrish Type I cleavage with chromanones 1 and 10 by synthesizing optically pure starting material and demonstrating that it undergoes racemization prior to rearrangement. However, our attempts to prepare an optically active chromanone by conversion of the ketone to a pyrrolidine iminium *d*-camphor-10-sulfonate salt[30] failed, and consequently we abandoned this approach.

It should be pointed out that the formation of 3-methyl-3-phenyl-2,3-dihydrobenzofuran (13) from the irradiation of chromanone 12 does establish the credibility of the Norrish Type I cleavage with this ring system. The isolation of 13 from 12 is most simply viewed as proceeding via the loss of carbon

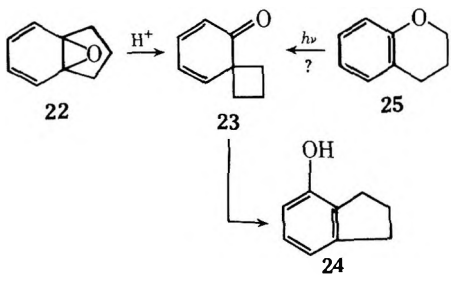


monoxide from an initially generated diradical. Similar decarbonylations of cyclic ketones have been reported in the literature[31–33] and provide reasonable chemical analogy for this reaction. Irradiation of 12 in benzene did not produce a rearranged chromanone, and it therefore seems that the incorporation of an additional methyl group in the 4-position of the chromanone ring facilitates the rate of Norrish Type I scission relative to C–O bond cleavage.

Srinivasan[34] had previously suggested that the photoisomerization of 3,4-dihydro-2*H*-pyrans to cyclobutane carboxaldehydes is a general process[35] which is analogous to the photochemical ring contraction that is known to occur with

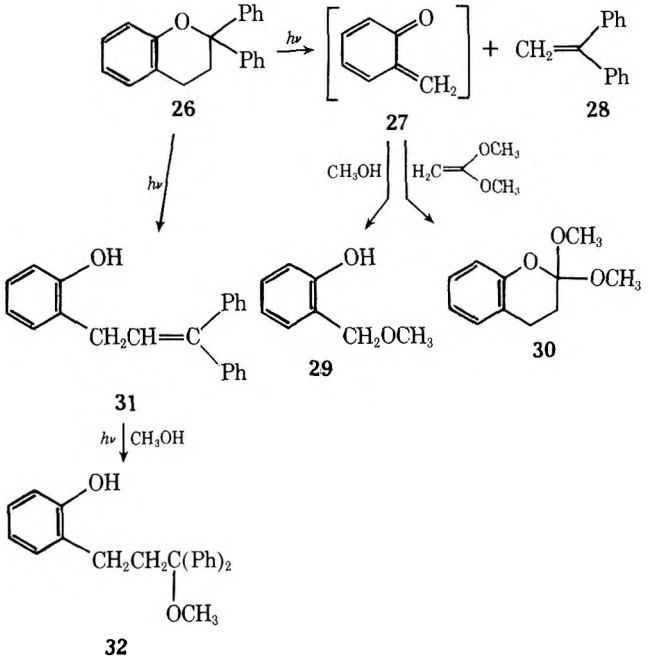


2,3-dihydrofurans[36,37] and furans.[36,38] The rearrangements that we have uncovered upon irradiation of 3-chromanones 1 and 10 in benzene may be viewed as specific examples of this general process. As part of a broader study dealing with enol ether photochemistry,[2–5] we thought it of considerable interest to determine whether a comparable rearrangement would occur with the related chroman system. In addition, a number of reports dealing with the aromatization of arene oxides (22) to 4-indanols (24) have shown that these reactions proceed via a spiroketone (23) intermediate.[39–42] These reports suggested that a related rearrangement might also occur upon irradiation



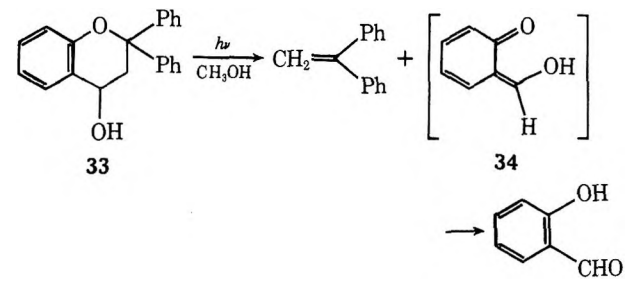
of the chroman ring (**25**). In order to test for this possibility, we investigated the photochemical behavior of several substituted chromans.

The first system we studied was 2,2-diphenylchroman (**26**). Irradiation of **26** in methanol through Corex using a 450-W Hanovia lamp gave a mixture of four products. On the basis of their spectral properties (see Experimental Section) these compounds were identified as 1,1-diphenylethylene (**28**), o-hydroxybenzyl methyl ether (**29**), 1,1-diphenyl-3-(*o*-hydroxyphenyl)-1-propene (**31**), and 1-methoxy-1,1-diphenyl-3-(o-hydroxyphenyl)propane (**32**). Photoproduct **32** was



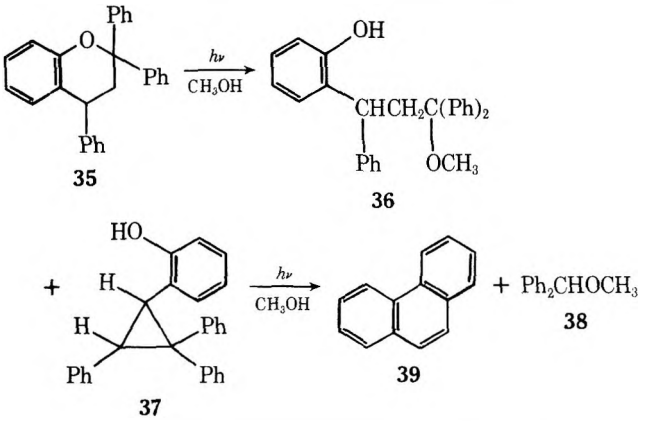
shown to be a secondary product resulting from further irradiation of **31**. No detectable quantities of a rearranged 4-indanol or chroman could be observed in the crude photolysate. The formation of **28** and **29** is readily explicable in terms of a photoinduced fragmentation of **26** to diphenylethylene and *o*-quinonemethide **27**. This transient species is rapidly trapped with methanol to give ether **29**. Additional support for the intermediacy of **27** comes from carrying out the irradiation of **26** in benzene in the presence of 1,1-dimethoxyethylene. Under these conditions, a high yield of chroman **30** could be isolated.[43]

The photochemical ring opening reaction of 2,2-diphenyl-4-chromanol (**33**) was also studied. Irradiation of **33** in

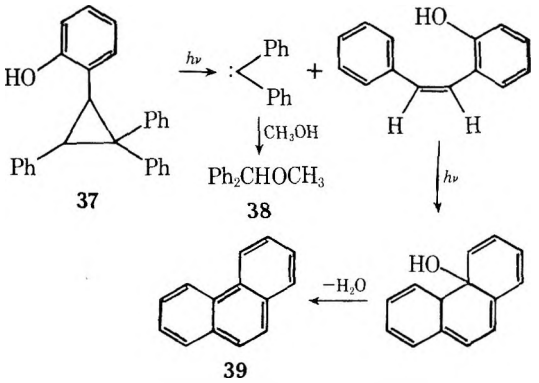


methanol produced a mixture of 1,1-diphenylethylene and salicylaldehyde. In this case, the initially produced *o*-quinonemethide **34** prefers to undergo a 1,5-sigmatropic hydrogen shift rather than reaction with the solvent.

The last system which was studied involved the photochemistry of 2,2,4-triphenylchroman (**35**). Irradiation of **35** in methanol with a 450-W Hanovia lamp through Corex led to the formation of four products (**36–39**) whose relative yields varied as a function of the reaction conditions. On prolonged irradiation the major products were benzhydryl methyl ether (**38**) and phenanthrene (**39**). With short exposure to UV light, the major photoproducts were identified as 3-(*o*-hydroxyphenyl)-3-phenyl-1-methoxy-1,1-diphenylpropane (**36**) and 3-(*o*-hydroxyphenyl)-1,1,2-triphenylcyclopropane (**37**). Structures **38** and **39** were shown to be secondary photo-



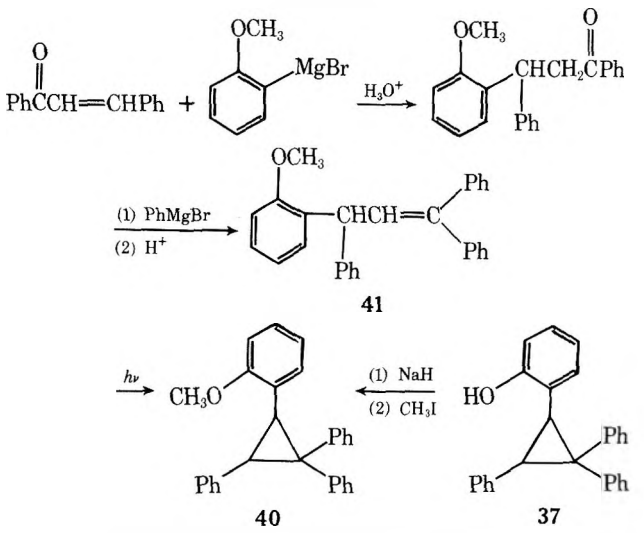
products resulting from the irradiation of cyclopropane **37**. This secondary photoreaction corresponds to a "Griffin type fragmentation".[44] The initially generated diphenylcarbene inserts into the O–H bond of methanol to give benzhydryl methyl ether **38**. The corresponding olefin produced from this [3 → 2 + 1] cycloelimination apparently undergoes a *cis*-stilbene–phenanthrene type cyclization[45] followed by loss of water to give phenanthrene (**39**).



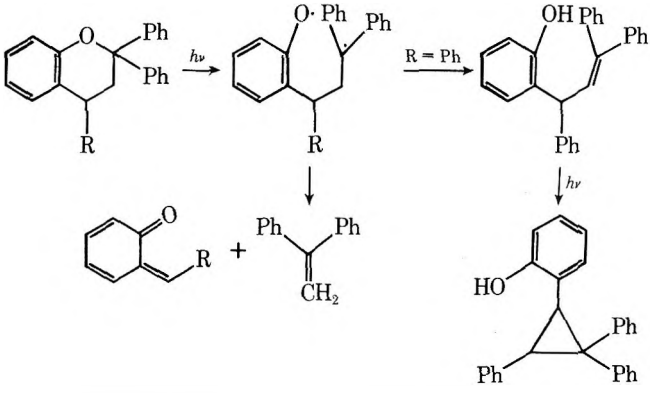
The identity of structure **37** was determined from its straightforward spectral properties (NMR (60 MHz) τ 6.32–6.40 (AB q, 2 H, J = 7.2 Hz), 4.95 (s, 1 H, exchanged with D_2O), 2.6–3.6 (m, 19 H)) as well as its conversion to the corresponding methyl ether **40**. The structure of **40** was established by comparison with an independently synthesized sample as shown in Scheme III. The key step in this independent synthesis involves a photochemical di-π-methane[46] rearrangement of **41** to **40**.

The photochemical cleavage reaction encountered upon irradiation of chromans **26** and **35** does not follow the same pattern as had been observed with the 3-chromanone system. Electronic excitation of the chromanone ring results in the formation of a spirocyclohexadienone whereas irradiation of chromans **26** and **35** produces a diradical intermediate which undergoes a subsequent cleavage or internal hydrogen ab-

Scheme III



straction. The initially produced olefin derived from internal hydrogen abstraction absorbs another photon of light and undergoes a di-π-methane reaction. The fact that we were able to independently synthesize **40** by a di-π-methane route clearly establishes the validity of this step. It should also be noted that Griffin and co-workers have previously shown that various substituted 3-arylpropenes undergo aryl migration on direct irradiation to yield cyclopropane products,[47,48] thereby providing excellent analogy for the above transformation.



Finally, the difference in photochemical reactivity between the chroman and chromanone systems should be briefly discussed. Possibly this difference is due to a polar route for C–O bond cleavage in the 3-chromanone system. This heterolysis is not unreasonable considering the relatively high electron density on the carbonyl carbon of the n–π^* excited ketone. In the chroman system, C–O bond cleavage proceeds via a homolytic fragmentation to give a diradical intermediate which prefers to undergo internal hydrogen abstraction or bond cleavage rather than recombination to a spirocyclohexadienone intermediate.

In conclusion, we have shown that the tautomeric forms of certain carbonyl derivatives undergo diverse and interesting photochemistry. Electronic excitation of the enol tautomer of the 3-chromanone system results in a photochemical ring opening to give an o-quinoneallide intermediate. In nonprotic solvents, insignificant quantities of the enol tautomer are present in solution and consequently the photoreaction is due to excitation of the keto form. We are continuing to examine wavelength and solvent effects in enol photochemistry and will report additional findings at a later date.

Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 100 MHz using a XL-100 and JEOL MH-100 spectrometer and at 60 MHz with a Varian T-60 spectrometer.

Irradiation of 4-Phenyl-3-chromanone (1) in Benzene. A solution containing 250 mg of 4-phenyl-3-chromanone[49] (1) in 80 mL of benzene was irradiated under an argon atmosphere using a Rayonet reactor equipped with 15 3000-Å lamps. After 15 h, the reaction mixture was concentrated under reduced pressure to leave a brown oil. This oil was found to decompose slowly at room temperature in the presence of air. The oil contained a band at 5.80 μm in its infrared spectrum. The NMR spectrum also indicated the presence of a new product along with 15% of unreacted starting material. All attempts to separate this mixture by distillation, sublimation, liquid and/or thick-layer chromatography were unsuccessful. Separation of the mixture was achieved, however, by gas chromatography using a 0.25 in. × 6-ft SF 1265 column at 200 °C. Under these conditions, 29.5 mg of a pale yellow liquid was obtained from 45 mg of the crude oil. This material was assigned the structure of 2-phenyl-3-chromanone (7) on the basis of its physical and chemical properties and by an independent synthesis: IR (CCl_4) 5.80 μm; UV (methanol) 305 nm (ϵ 650); NMR ($CDCl_3$, 100 MHz) τ 6.38 (s, 2 H), 4.8 (s, 1 H), and 2.4–3.3 (m, 9 H); *m/e* 224 (M^+), 210, 36, 181 (base), 152, 144, 91, 77, and 43.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.81. Found: C, 80.24; H, 5.76.

extended irradiation of 4-phenyl-3-chromanone did not simplify the separation procedure but only increased the amount of polymer formed. It should be noted that 2-phenyl-3-chromanone (7) was thermally stable and did not give 4-phenyl-3-chromanone (1) when stirred overnight with silica gel in acetone.

Independent Synthesis of 2-Phenyl-3-chromanone (7). To a solution containing 0.84 g of methyl *o*-hydroxyacetate and 50 mg of tetra-*n*-butylammonium chloride in 50 mL of methylene chloride was added 150 mg of sodium hydride followed by 1.14 g of methyl α-bromophenylacetate. After stirring overnight, the mixture was washed with several portions of water, followed by a saturated ammonium chloride solution. The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude oil obtained was purified by thick-layer chromatography using 10% acetone–cyclohexane and then benzene as the eluents. The major band obtained (0.82 g, 52%) was identified as methyl α-phenyl(o-carbomethoxymethyl)phenoxyacetate (9): IR (neat) 5.70 and 5.75 μm; NMR τ 6.47 (s, 3 H), 6.39 (s, 3 H), 6.26 (AB q, 2 H, J = 16 Hz), 4.44 (s, 1 H), and 3.4–2.4 (m, 9 H).

A mixture containing 30 mg of metallic sodium and 80 mg of the above diester (9) in 30 mL of dry toluene was refluxed under a nitrogen atmosphere for 7 h. After cooling, the yellow mixture was poured onto 10 mL of a 10% hydrochloric acid solution and was then extracted with ether. The ethereal extracts were washed with a saturated sodium bicarbonate solution and then dried over magnesium sulfate and concentrated under reduced pressure. The crude oil obtained was chromatographed on a thick-layer plate using a 10% acetone–cyclohexane mixture as the eluent. The major band contained 33 mg (57%) of 2-phenyl-4-carbomethoxy-3-chromanone (8): IR (neat) 5.76, 6,08, and 6.20; NMR (100 MHz, $CDCl_3$) 6.08 (s, 3 H), 4.30 (s, 1 H), 3.2–2.2 (m, 9 H), and −3.0 (s, 1 H, exchangeable); *m/e* 281, 224, 196, 135, 92, 77, and 44.

A sample of 106 mg of the above β-keto ester (8) was heated at reflux with a mixture containing 1 mL of concentrated sulfuric acid, 3 mL of water, and 5 mL of acetic acid for 7 h. After cooling, the solution was extracted with ether and the ether extracts were washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated under reduced pressure to an oil. When this oil was chromatographed on a thick-layer plate using 7% acetone–cyclohexane as the eluent, 42 mg (49%) of the desired 2-phenyl-3-chromanone (7) was obtained. This material is identical in every respect with the compound obtained from the photolysis of 4-phenyl-3-chromanone (1) in benzene.

Irradiation of 4,7-Dimethylchroman-3-one (10) in Benzene. A solution containing 200 mg of 4,7-dimethylchroman-3-one[50] (10) in 150 mL of benzene was irradiated under an argon atmosphere using a 450-W Hanovia lamp equipped with a Corex filter sleeve. The photolysis was followed by gas chromatography using a 3-ft 10% Ucon on Chromosorb W column at 185 °C. After 35 min of irradiation, the gas chromatogram showed the presence of unreacted starting ketone (20%) and a major photoproduct (80%). Longer irradiation times resulted in decomposition of this material. Separation of the product

from starting material was achieved by preparative gas chromatography. The major component was assigned the structure of 2,7-dimethylchroman-3-one (11) on the basis of its spectral data and by comparison with a model system: IR (neat) 5.78 μm; NMR ($CDCl_3$, 60 MHz) τ 8.54 (d, 3 H, J = 7.0 Hz), 7.70 (s, 3 H), 6.47 (s, 2 H), 5.73 (q, 1 H, J = 7.0 Hz), and 3.4–3.0 (m, 3 H); UV (methanol) 305 and 227 nm (ε 740 and 2200); m/e 176 (M^+, base), 148, 133, 105, 91, 77, 51, and 44.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.13; H, 6.84.

It should be noted that the NMR spectra of 2-methyl-3-chromanone and 2,7-dimethyl-3-chromanone (11) were superimposable except for the tolyl methyl and aromatic protons.

Preparation of 4-Methyl-4-phenyl-3-chromanone (12). A solution containing 6 mL of freshly distilled dimethoxyethane and 6 mL of a 1.7 M methyllithium solution was cooled to 0 °C and 2.0 g of 3-acetoxy-4-phenylchromene[49] in 10 mL of dimethoxyethane was added dropwise. The resulting yellow solution was allowed to warm to room temperature and was stirred for an additional 10 min at 25 °C. To this mixture was added 3.0 mL of iodomethane and the solution was allowed to stir at room temperature for 10 h. At the end of this time, water was added and the mixture was extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The oily solid that remained was sublimed at 40 °C (0.01 mm) to give 1.05 g (59%) of 4-methyl-4-phenyl-3-chromanone (12): mp 64–65 °C; IR (KBr) 5.78, 6.23, 6.32, 6.74, 8.11, 9.52, 13.13, and 14.33 μm; NMR ($CDCl_3$, 100 MHz) τ 8.20 (s, 3 H), 5.80–5.32 (AB q, 2 H, J_{AB} = 18.0 Hz), and 3.2–2.6 (m, 9 H); UV (methanol) 305 (shoulder) and 278 nm (ε 490 and 2070); m/e 238 (M^+), 210, 195 (base), 178, 167, 165, 115, 105, 91, and 77.

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.59; H, 5.93.

Irradiation of 4-Methyl-4-phenyl-3-chromanone (12) in Benzene. A 100-mg sample of 4-methyl-4-phenyl-3-chromanone (12) in 40 mL of benzene was distributed among five Pyrex test tubes which were then purged with argon for 5 min. The tubes were irradiated with 16 3000-Å low-pressure ultraviolet lamps using a Rayonet reactor. After 10.5 h, the solvent was removed under reduced pressure and the residual oil was purified by thick-layer chromatography using a 10% ether–pentane mixture as the eluent. The major component obtained contained 52 mg (59%) of 3-methyl-3-phenyl-2,3-dihydrobenzofuran (13) whose structure was assigned on the basis of its spectral data and by an independent synthesis: IR (neat) 6.24, 6.79, 8.13, 9.86, 10.21, 13.32, and 14.33 μm; NMR ($CDCl_3$, 60 MHz) τ 8.27 (s, 3 H), 5.68–5.34 (AB q, 2 H, J_{AB} = 9.0 Hz), and 3.2–2.6 (m, 9 H); m/e 210 (M^+), 195 (base), 167, 165, 152, 91, and 77.

Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.72; H, 6.74.

Independent Synthesis of 3-Methyl-3-phenyl-2,3-dihydrobenzofuran (13). A mixture containing 0.16 mL of diisopropylamine in 7 mL of dry tetrahydrofuran was cooled to 0 °C and 0.5 mL of a 2.1 M solution of n-butyllithium was added dropwise. After stirring for 15 min at 0 °C, 210 mg of 3-phenylbenzofuran-2-one[51] (14) in 5 mL of dry tetrahydrofuran was added dropwise over a 5-min interval. The resulting yellow solution was stirred for 15 min at 0 °C and then 200 mg of methyl iodide was added. The solution was allowed to warm to room temperature and then stirred at 25 °C for 2 h. The reaction mixture was diluted with ether and washed with water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give 206 mg (92%) of 3-methyl-3-phenyl-2-benzofuranone: IR (neat) 5.53, 6.18, 6.24, 6.85, 8.12, 9.67, 11.20, 13.26, and 14.37 μm; NMR ($CDCl_3$, 60 MHz) τ 8.18 (s, 3 H) and 2.9–2.6 (m, 9 H).

A 206-mg sample of 3-methyl-3-phenyl-2-benzofuranone in 5 mL of ether was added to a mixture of 34 mg of lithium aluminum hydride in 10 mL of anhydrous ether. The mixture was stirred for 25 min at room temperature and then 1 drop of water was added followed by 1 drop of a 15% sodium hydroxide solution and 3 additional drops of water. The precipitated salts were filtered, ether was added to the filtrate, and the ethereal solution was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 200 mg (95%) of 2-phenyl-2-(o-hydroxyphenyl)-1-propanol: mp 103–104 °C; IR (KBr) 3.00, 6.22, 6.33, 6.71, 6.92, 8.06, 9.73, 10.93, 11.88, 13.15, and 14.32 μm; NMR ($CDCl_3$, 60 MHz) τ 8.47 (s, 3 H), 6.29–5.68 (AB q, 2 H, J_{AB} = 11.0 Hz), 4.65 (s, 2 H, exchangeable with D_2O), and 3.4–2.6 (m, 9 H).

A mixture containing 100 mg of 2-phenyl-2-(o-hydroxyphenyl)-1-propanol and a grain of p-toluenesulfonic acid in 0.5 mL of deuteriochloroform was heated at 130 °C for 6 h. The NMR and IR spectra of the product were identical with those of 3-methyl-3-phenyl-2,3-dihydrobenzofuran (13) obtained from the irradiation of 4-methyl-4-phenyl-3-chromanone (12).

Irradiation of 2,2-Diphenylchroman (26) in Methanol. A solution containing 500 mg of 2,2-diphenylchroman[52] (26) in 450 mL of methanol was purged with argon and irradiated with a 450-W Hanovia lamp equipped with a Corex filter sleeve for 2 h. The solvent was removed under reduced pressure and the crude oil was subjected to thick-layer chromatography using a 10% ether–pentane mixture as the eluent. The top band contained 50 mg (18%) of 1,1-diphenylethylene (28): IR (neat) 6.22, 6.71, 6.93, 7.54, 9.71, 11.04, 12.89, and 14.35 μm; NMR ($CDCl_3$, 60 MHz) τ 4.57 (s, 1 H), and 2.70 (s, 5 H). This material was identified by comparison with an authentic sample. The middle band contained 88 mg of starting material. The bottom band contained 320 mg of an oil which proved to be a mixture of three phenols which could be separated further by extraction with a 10% sodium hydroxide solution. The base soluble component amounted to 60 mg (25%) and was identified as o-hydroxybenzylmethyl ether (29) on the basis of its spectral data and by comparison with an authentic sample: IR (neat) 3.04, 6.26, 6.73, 6.91, 8.04, 9.23, and 13.29 μm; NMR ($CDCl_3$, 60 MHz) τ 6.60 (s, 3 H), 5.40 (s, 2 H), 4.80 (s, 1 H, exchangeable with D_2O), and 3.4–2.6 (m, 4 H). The base insoluble fraction contained two components in a 3:1 ratio. The major component was identified as 1-methoxy-1,1-diphenyl-3-(o-hydroxyphenyl)propane (32): IR (neat) 3.03 μm; NMR ($CDCl_3$, 60 MHz) τ 7.6–7.4 (m, 4 H), 6.90 (s, 3 H), 4.69 (s, 1 H, exchangeable with D_2O), and 3.4–2.5 (m, 14 H). The minor component was identified as 1,1-diphenyl-3-(o-hydroxyphenyl)-1-propene (31): IR (neat) 2.90 μm; NMR ($CDCl_3$, 60 MHz) τ 6.60 (d, 2 H, J = 7.0 Hz), 5.30 (s, 1 H, exchangeable with D_2O), 3.83 (t, 1 H, J = 7 Hz), and 3.5–2.7 (m, 14 H).

The structure of the two insoluble phenols was established by the following chemical reactions. A 50-mg sample of 1-methoxy-1,1-diphenyl-3-(o-hydroxyphenyl)propane (32) was dissolved in 60 mL of methanol which was saturated with hydrogen chloride gas. The resulting solution was stirred at room temperature for 10 h and the methanol was removed under reduced pressure. Ether was added to the residual oil and the ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 37 mg (82%) of 2,2-diphenylchroman (26).

An authentic sample of phenol 31 was prepared from 2,2-diphenylchroman by treatment with acidic methanol. A solution containing 2.0 g of 2,2-diphenylchroman (26) in 75 mL of methanol was treated with 3 mL of concentrated hydrochloric acid. The resulting solution was heated at reflux for 6 h, cooled, and concentrated under reduced pressure. Ether was added and the ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The oil obtained proved to be a mixture containing 63% of unreacted 2,2-diphenylchroman and 37% of 1,1-diphenyl-3-(o-hydroxyphenyl)-1-propene (31). These two components were separated by dry column chromatography using a 10% ether–pentane mixture as the eluent to give 520 mg of 1,1-diphenyl-3-(o-hydroxyphenyl)-1-propene (31), which was identical with one of the insoluble phenols isolated from the irradiation of 2,2-diphenylchroman.

Irradiation of 2,2-Diphenylchroman (26) in Benzene Containing 1,1-Dimethoxyethylene. A solution containing 200 mg of 2,2-diphenylchroman (26) and 1.0 g of 1,1-dimethoxyethylene in 175 mL of benzene was purged with nitrogen and irradiated with a 450-W Hanovia lamp equipped with a Corex filter sleeve for 2 h. Removal of the solvent under reduced pressure gave a mixture of three components which were separated by thick-layer chromatography using a 10% ether–pentane solution as the eluent. The top band contained 65 mg (51%) of 1,1-diphenylethylene. The middle band contained 61 mg (45%) of 2,2-dimethoxychroman (30): IR (neat) 3.41, 6.30, 6.74, 6.95, 8.18, 9.13, 10.94, and 13.15 μm; NMR ($CDCl_3$, 60 MHz) τ 7.96 (t, 2 H, J = 7.0 Hz), 7.16 (t, 2 H, J = 7.0 Hz), 6.63 (s, 6 H), and 3.3–2.7 (m, 4 H). The bottom band contained 80 mg (40%) of 1,1-diphenyl-3-(o-hydroxyphenyl)-1-propene (31). The structure of 2,2-dimethoxychroman was verified by hydrolysis to dihydrocoumarin.

Irradiation of 2,2-Diphenyl-4-chromanol (33) in Methanol. A solution containing 100 mg of 2,2-diphenyl-4-chromanol[53] (33) in 170 mL of methanol was irradiated with a 450-W Hanovia lamp equipped with a Corex filter sleeve for 3 h. The solvent was removed under reduced pressure and the residial oil was subjected to thick-layer chromatography using a 10% acetone–hexane mixture as the eluent. The upper band contained 45 mg (75%) of 1,1-diphenylethylene (28), while the lower band contained 28 mg (70%) of salicylaldehyde which was identified by comparison with an authentic sample.

Preparation of 2,2,4-Triphenylchroman (35). To a solution containing 2.24 g of 4-phenyldihydrocourmarin[54] under nitrogen was added 11 mL of a 2.3 M ethereal solution of phenylmagnesium bro-

mide. The resulting solution was stirred at room temperature for 30 min followed by heating at reflux for 4 h. The ethereal solution was cooled, hydrolyzed using a 10% hydrochloric acid solution, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 3.6 g (94%) of 3-(*o*-hydroxyphenyl-1,1-diphenyl-1-propanol: mp 109–110 °C; IR (KBr) 3.03, 6.32, 6.89, 8.19, 9.84, 13.06, and 14.24 μm; NMR (DCl_3, 60 MHz) τ 6.88 (d, 2 H, J = 5 Hz), 5.67 (t, 1 H, J = 5 Hz), and 3.6–2.6 (m, 19 H).

A solution containing 3.6 g of 3-(*o*-hydroxyphenyl-3-phenyl-1,1-diphenyl-1-propanol in 175 mL of benzene containing a catalytic amount of *p*-toluenesulfonic acid was heated at reflux for 1.3 h. The reaction mixture was cooled and the solvent was removed under reduced pressure to give an oil which was crystallized from 95% ethanol to give 2.7 g (75%) of 2,2,4-triphenylchroman (**35**): mp 158–160 °C (lit.[55] mp 162–163 °C); IR (KBr) 6.22, 6.32, 6.73, 6.91, 8.11, 9.83, 10.87, 12.70, 13.09, and 14.28 μm; NMR ($CDCl_3$, 60 MHz) τ 7.43 (d of d, 1 H, J_{AB} = 14 Hz, J_{BX} = 13 Hz), 6.90 (d of d, 1 H, J_{AB} = 14 Hz, J_{AX} = 5 Hz), 6.13 (d, of d, 1 H, J_{BX} = 13 Hz, J_{AX} = 5 Hz), and 3.4–2.4 (m, 19 H); UV (methanol) 284 and 277 nm (ε 2800 and 2800); *m/e* 362 (M^+), 284, 271, 268, 255, 181 (base), 167, 165, 152, 91, and 77.

Irradiation of 2,2,4-Triphenylchroman (35) in Methanol. A solution containing 300 mg of 2,2,4-triphenylchroman (**35**) in 475 mL of methanol was purged with nitrogen and irradiated with a 450-W Hanovia lamp equipped with a Corex filter sleeve for 1.75 h. The solvent was removed under reduced pressure and the resulting oil was purified by preparative thick-layer chromatography using a 10% acetone–hexane mixture as the eluent. After several elutions, four bands were obtained. The top two bands contained 60 mg (36%) of benzhydryl methyl ether (**38**) (identified by spectral data and comparison with an authentic sample prepared by the method of Rutherford)[56] and phenanthrene. The third band contained 24 mg of a material whose structure is assigned as 3-(*o*-hydroxyphenyl)-3-phenyl-1-methoxy-1,1-diphenylpropane (**36**) on the basis of its characteristic spectra: IR (CCl_4) 2.94, 6.23, 6.68, and 6.85 μm; NMR ($CDCl_3$, 60 MHz) τ 7.14 (s, 3 H), 6.81 (d, 2 H, J = 5 Hz), 5.75 (t, 1 H, J = 5 Hz), and 3.4–2.6 (m, 20 H). The bottom band contained 110 mg (37%) of 3-(*o*-hydroxyphenyl)-1,1,2-triphenylcyclopropane (**37**): mp 133–135 °C; IR (KBr) 2.83, 6.24, 6.70, 6.90, 7.56, 7.91, 8.30, 8.55, 9.12, 9.71, 13.35, and 14.31 μm; NMR ($CDCl_3$, 60 MHz) τ 6.40–6.32 (AB q, 2 H, J_{AB} = 7.2 Hz), 4.95 (s, 1 H, exchangeable with D_2O), and 3.6–2.6 (m, 19 H); UV (methanol) 283 (shoulder) and 277 nm (ε 3650 and 4000); *m/e* 362 (M^+), 284, 271, 268, 255, 195, 165, 121, 115, 105 (base), 91, and 77.

Anal. Calcd for $C_{27}H_{22}O$: C, 89.47; H, 6.12. Found: C, 89.53; H, 6.17.

Irradiation of cyclopropane **37** in methanol with Corex filtered light gave phenanthrene and benzhydryl methyl ether in good yield.

Independent Synthesis of 3-(*o*-Anisyl)-1,1,2-triphenylcyclopropane (40). The structure of **37** was further verified by conversion to the corresponding methyl ether which was, in turn, independently synthesized. To a stirred solution containing 180 mg of 3-(*o*-hydroxyphenyl)-1,1,3-triphenylcyclopropane (**37**) in 5 mL of methanol was added 20 mg of sodium hydride (99%) in 2 mL of methanol. The resulting solution was stirred under nitrogen for 30 min and then 1.0 mL of methyl iodide was added. After stirring at room temperature for 3 h, the reaction mixture was diluted with ether and washed with water. The ethereal layer was dried over magnesium sulfate and concentrated under reduced pressure to give 104 mg (55%) of 3-(*o*-anisyl)-1,1,2-triphenylcyclopropane (**40**): mp 111–112 °C; IR (KBr) 3.30, 6.22, 6.69, 8.06, 9.69, 12.90, and 14.37 μm; NMR ($CDCl_3$, 60 MHz) τ 6.60–6.27 (AB q, 2 H, J_{AB} = 7.0 Hz), 6.09 (s, 3 H), and 3.4–2.6 (m, 19 H); UV (methanol) 281 and 274 nm (ε 3100 and 3600); *m/e* 376 (M^+), 298, 285, 268 (base), 255, 239, 194, 191, 165, 91, and 77.

Anal. Calcd for $C_{28}H_{24}O$: C, 89.32; H, 6.43. Found: C, 89.35; H, 6.54.

This same material could be independently synthesized according to the procedure outlined below. To a Grignard solution prepared from 1.3 g of magnesium and 9.3 g of *o*-bromoanisole in 100 mL of ether was added 6.24 g of chalcone in 100 mL of ether. The resulting solution was stirred at room temperature for 1 h and then hydrolyzed using a 10% hydrochloric acid solution. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The oil obtained was crystallized from 95% ethanol to give 8.6 g (90%) of 3-(*o*-anisyl)-1,3-diphenyl-1-propanone: mp 117–118 °C; IR (KBr) 3.31, 5.90, 6.24, 6.69, 8.01, 9.70, 13.35, and 14.24 μm; NMR ($CDCl_3$, 60 MHz) τ 6.34 (d, 2 H, J = 8.0 Hz), 6.30 (s, 3 H), 4.85 (t, 1 H, J = 8.0 Hz), 3.3–2.6 (m, 12 H), and 2.3–2.0 (m, 2 H).

To a solution containing 3.6 g of 3-(*o*-anisyl)-1,3-diphenyl-1-propanone in 60 mL of ether was added 5 mL of a 2.5 M solution of phenylmagnesium bromide in ether. After stirring the resulting solution at room temperature for 1.5 h, 40 mL of a 10% hydrochloric acid solution was added. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 3.98 g (88%) of 3-(*o*-anisyl)-1,1,3-triphenyl-1-propanol: IR (neat) 2.83, 3.35, 6.24, 6.72, 8.04, 8.96, 9.68, 13.29, and 14.32 μm; NMR ($CDCl_3$, 60 MHz) τ 7.45 (s, 1 H, exchangeable with D_2O), 6.90 (d, 2 H, J = 7.0 Hz), 6.4[illegible] (s, 3 H), 5.46 (t, 1 H, J = 7.0 Hz), and 3.4–2.6 (m, 19 H).

A mixture containing 5 mL of concentrated sulfuric acid and 45 mL of glacial acetic acid was added to 3.98 g of 3-(*o*-anisyl)-1,1,3-triphenyl-1-propanol. The resulting solution was stirred at room temperature for 5 min and was then diluted with water and extracted with ether. The ethereal extracts were washed with a 5% sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated under reduced pressure. The crude oil obtained was purified by medium pressure column chromatography using a 3% acetone–hexane mixture as the eluent to give 2.9 g (76%) of 3-(*o*-anisyl)-1,1,3-triphenyl-1-propene (**1**): mp 88–90 °C; IR (KBr) 6.25, 6.72, 8.0, 9.71, 13.24, and 14.35 μm; NMR ($CDCl_3$, 60 MHz) τ 6.46 (s, 3 H), 4.86 (d, 1 H, J = 10 Hz), 3.46 (d, 1 H, J = 10 Hz), and 3.1–2.6 (m, 19 H); UV (methanol) 256 nm (ε 18 200); *m/e* 376 (M^+), 299, 285, 268 (base), 255, 191, 181, 165, 105, 91, and 77.

A solution containing 500 mg of 3-(*o*-anisyl)-1,1,3-triphenyl-1-propene (**41**) in 475 mL of methanol was irradiated for 1 h using a 450-W Hanovia lamp equipped with a Corex filter. The solvent was removed under reduced pressure and the resulting oil was purified by thick-layer chromatography using a 10% acetone–hexane mixture as the eluent. The oil obtained was crystallized from 95% ethanol to give 350 mg (70%) of 3-(*o*-anisyl)-1,1,2-triphenylcyclopropane (**40**) which was identical with that obtained from treating phenol **37** with methyl iodide.

Further irradiation of **40** in methanol with Corex-filtered light gave phenanthrene and benzhydryl methyl ether in high yield.

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Registry No.–**1,** 17698-43-0; **7,** 20760-17-2; **8,** 55842,26-7; **9,** 55842-25-6; **10,** 24454,30-6; **11,** 64024-50-6; **12,** 64024-51-7; **13,** 64024-52-8; **14,** 3117-37-1; **26,** 10419-28-0; **28,** 530-48-3; **29,** 5635-98-3; **30,** 32524-84-8; **31,** 17398-02-6; **32,** 64024-53-9; **33,** 4222-15-5; **35,** 5655-25-4; **36,** 64024-54-0; **37,** 64024-55-1; **40,** 64024-56-2; 3-acetoxy-4-phenylchromen, 22788-34-7; 3-methyl-3-phenyl-2-benzofuranone, 4355-42-4; 2-phenyl-2-(*o*-hydroxyphenyl)-1-propanol, 64024-57-3; 4-phenyldehydrocoumarin, 51737-00-9; 3-(*o*-hydroxyphenyl)-1,1-diphenyl-1-propanol, 64024-58-4; 3-(*o*-anisyl)-1,3-diphenyl-1-propanone, 64024-59-5; 3-(*o*-anisyl)-1,1,3-triphenyl-1-propanol, 64024-60-8.

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Photochemical Reaction of 2,3-Dihydro-2,3-methano-1,4-naphthoquinone Derivatives. Three Different Types of Reaction

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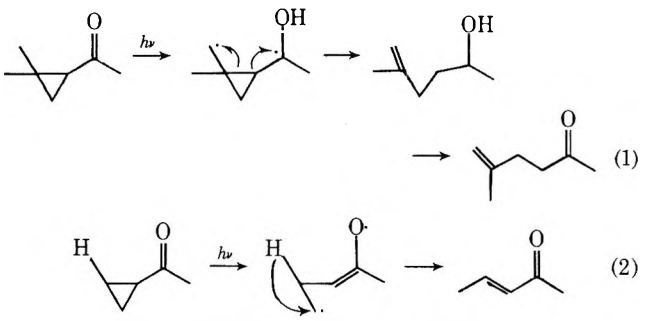
Photochemical reactions of 2,3-dihydro-2,3-methano-1,4-naphthoquinone derivatives in the presence or absence of a hydrogen donor were investigated. The modes of the photochemically induced reactions are dependent on the substituents on the cyclopropane ring, and the reactions can be classified as three different types: isomerization, hydrogen abstraction, and degradation.

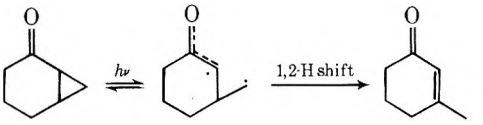
The photochemistry of conjugated cyclopropyl ketones has been studied by W. G. Dauben et al. systematically.[1] Photoisomerization of the conjugated cyclopropyl ketones can occur via at least two different mechanistic sequences. The first is the well-known type II reaction (eq 1).[1] The second, found when the δ hydrogen is absent or its abstraction by the carbonyl oxygen atom is sterically impossible, is the cleavage of the bond of the cyclopropane ring adjacent to the carbonyl group. This reaction is accompanied with subsequent 1,2-hydrogen migration (eq 2).



(1)

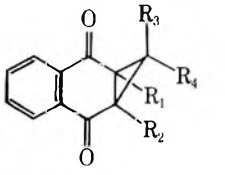
(2)

In the bicyclo[4.1.0]heptan-2-one series,[2] the two adjacent cyclopropyl bonds are in a different geometry with respect to the carbonyl group, and in these cases the C_1–C_7 bond cleaves to give cyclohexenones (eq 3). The irradiation of bicyclo[4.1.0]heptan-2-ones in 2-propanol gives cyclohexanones, resulting from the rupture of the outer bond.



(3)

In the present study, eight methanonaphthoquinones(**1a–h**) were prepared, and their photochemical behaviors were examined in both the presence and absence of xanthene, known as a highly reactive hydrogen donor.



1a	$R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
b	$R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
c	$R_1 = R_2 = R_3 = R_4 = H$
d	$R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
e	$R_1 = R_2 = COOEt$; $R_3 = R_4 = H$
f	$R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = Ph$
g	$R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = Ph$
h	$R_1 = CH_3$; $R_2 = H$; R_3,R_4 = fluorenyl

Results and Discussion

Photoisomerization of 2,3-Diethoxycarbonyl-2,3-dihydro-2,3-methano-1,4-naphthoquinone (1e). A solution of **1e** was irradiated under deaerated conditions in a Pyrex

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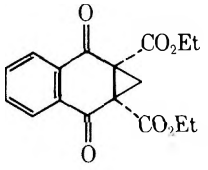
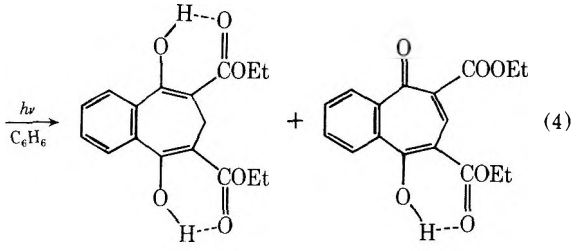
vessel for 12 h with light from a high-pressure Hg-arc lamp at room temperature. After workup, separation by column chromatography gave the two major photoproducts **2** and **3** in yields of 24 and 42%, respectively (eq 4). The structure of



1e

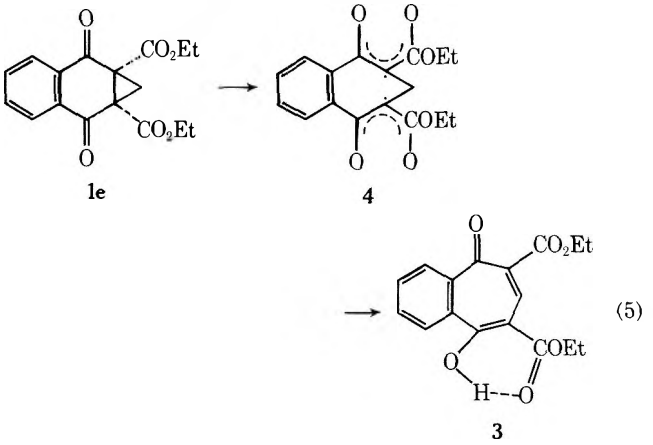


(4)

2 **3**

the first was identified as 6,8-diethoxycarbonyl-7*H*-5,9-dihydroxybenzocycloheptene (**2**) by comparison of its melting point and IR and NMR spectra with those of an authentic sample.[3] The second photoproduct was assigned as 6,8-diethoxycarbonyl-9-hydroxybenzocycloheptene-5-one (**3**) by comparison of its melting point IR and NMR spectra with those of an authentic sample.[3] In the presence of xanthene in a benzene solution, a higher yield (45%) of **2** was obtained upon irradiation of **1e**, but no appreciable change in the yield of **3** (42%) was noted. The result indicates that product **2** is the reduction product formed by intermolecular hydrogen abstraction; the photoexcited species of **1e** abstracts hydrogen atoms from another molecule of **1e** when a hydrogen donor such as xanthene is absent from the reacting solution. The mechanism for intermolecular hydrogen atom abstraction by methanonaphthoquinones, including **1e**, will be discussed in detail below.

For the formation of photoproduct **3**, the mechanism shown in eq 5 is highly probable. The initial photoexcitation of **1e** is



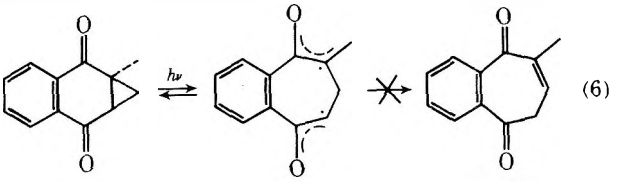
(5)

1e **4** **3**

followed by the opening of the inner cyclopropane bond to form biradical **4**. Through subsequent 1,4-hydrogen atom migration, photoisomerization product **3** may be formed.

The present results are quite interesting when compared with the photoisomerization of bicyclo[4.1.0]heptan-2-ones, in which the outer cyclopropane bond cleaves. The preferred rupture of the inner bond of **1e** is probably due to the fact that the developing biradical **4** could be stabilized by the delocalization of the two unpaired electrons over the two separated ethoxycarbonyl groups and the two carbonyl groups. The inner dipole–dipole repulsive force due to the ethoxycarbonyl groups could also be responsible for the easier C_2–C_3 bond cleavage.

On the contrary, irradiation of the other methanonaphthoquinones (**1a–d** and **1f–g**) in benzene under comparable conditions gave none of the photoproducts corresponding to **2** and **3**. The extreme reluctance of these methanonaphthoquinones to photoisomerize is dramatic. As for methanonaphthoquinone **1a**, for example, biradical **5**, if it once was formed, would not be as stable as biradical **4**. **5** may simply undergo ring closure to give the starting material (eq 6).

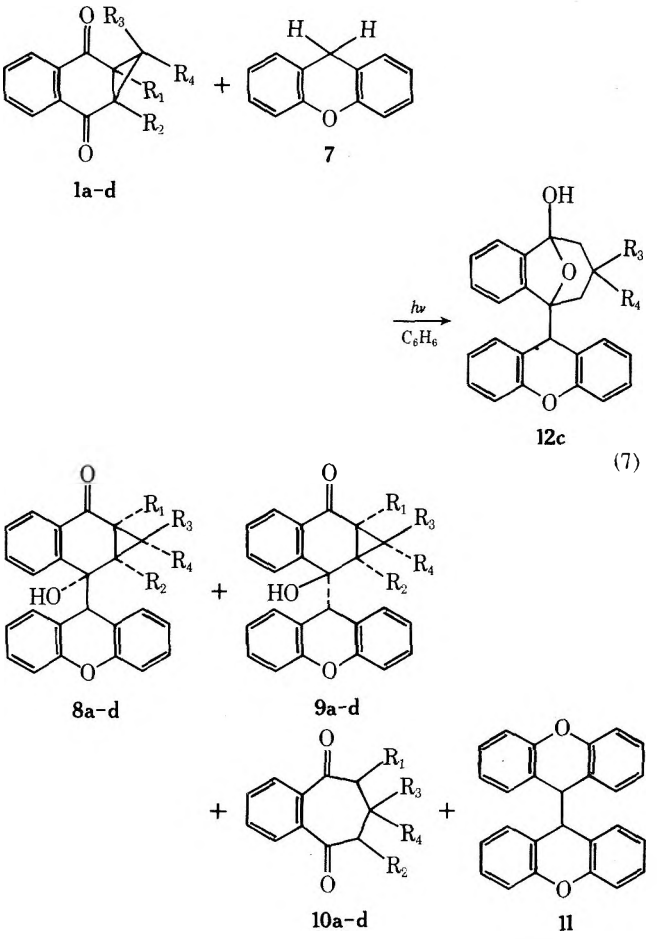


(6)

1a **5** **6**

Photoreduction of Alkyl-Substituted 2,3-Dihydro-2,3-methano-1,4-naphthoquinones (1a–d). We previously published a note on the photochemical reactions of **1a–b**.[4] Products and the cause of the reactions were briefly discussed in it. Further details and extensions of the reaction will be given below.

Respective solutions of **1a–d** in benzene are photostable when they are irradiated by light from a 300-W high-pressure Hg-arc lamp. However, in the presence of xanthene (**7**), they reacted fairly fast to afford **8a–d**, **9a–d**, and **10a–d** as the main products together with 9,9′-bixanthenyl (**11**). These results are summarized in eq 7 and Table I.



(7)

1a–d **7** **12c** **8a–d** **9a–d** **10a–d** **11**

The photoproducts **8a** and **9a**, for example, result from the addition of xanthene to C_4-carbonyl group, and they are configurational isomers of each other. The basis for structural assignment of **8a**, **9a**, and **10a** was described in the previous

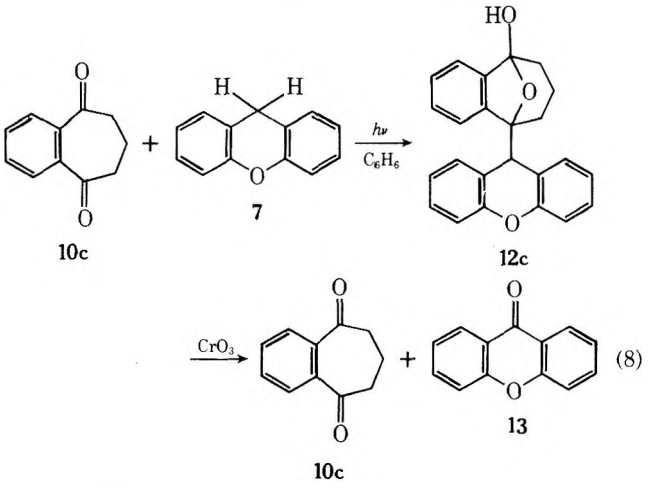
Table I. Yields of Products in the Photochemical Reactions of Methanonaphthoquinones 1a-d with Xanthene[a]

Methanonaphthoquinones	Irradiation time, h	Isolated yields,[b] %			
		8a-d	9a-d	10a-d	12c
1a	6	35	21	19	*c*
b	18	45	14	Trace	*c*
c	4	20	8	30	14
d	6	29	10	15	*c*

[a] The solution of methanonaphthoquinones and 2 equiv of xanthene was irradiated in benzene using a 300-W high-pressure Hg-Arc lamp. [b] Yield was based on the amounts of methanonaphthoquinones used. [c] Not determined.

paper.[4] Similarly, the structures of **8b-d, 9b-d,** and **10b-d** were determined on the basis of their IR, NMR, and mass spectral data. Elemental analyses of these compounds were all compatible with their structures. Chromic acid oxidation and sodium borohydride reduction were used as the major weapons for the structural differentiation between two configurational isomers (**8** and **9**).

The structure of **12c** was assigned on the basis of the following: IR spectrum showed the absence of a carbonyl group and the presence of a hydroxyl group (3400 cm^{-1}) and ether bonding (1000 cm^{-1}); chromic acid oxidation gave **10c** and xanthone; **12c** was formed on irradiation of a benzene solution of **10c** and xanthene (**7**) (eq 8).



(8)

Furthermore, the rate of disappearance of methanonaphthoquinones **1a-d** in the presence of xanthene was measured in order to estimate the relative reactivities of **1a-d.** The results are summarized in Table II. It is noticeable that the reactivity of **1b** was extremely low compared with that of other methanonaphthoquinones. The reason for the low reactivity is probably due to the two carbonyl groups on C_1 and C_4 being hindered sterically by two methyl groups. Such a steric effect of methyl groups explains the photochemical behavior of **1a,** i.e., the exclusive addition of xanthene moiety to the sterically less-hindered C_4-carbonyl group. On the same basis, the low reactivity of **1f** will be explainable; **1f** was recovered unchanged even after irradiation for 80 h in the presence of xanthene.

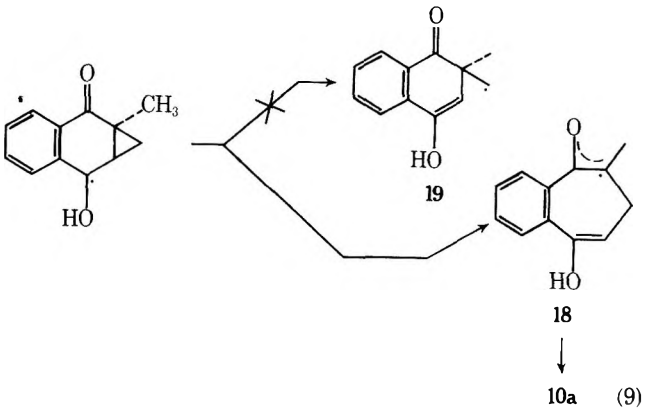
As was described in the previous paper,[4] ^1H CIDNP examination of the reactions revealed that **8a** and **9a** are recombination products via an initial triplet radical pair. Considering that the methine proton on C_3 of **1a** showed an emission polarized signal, we concluded that the starting material, **1a,** was reproduced again as the escape product from the triplet radical pair (**16**).[5]

Table II. Relative Reactivities of Methanonaphthoquinones 1a-d[a]

Methanonaphthoquinones	Recovery, %	Conversion %
1a	31	69
b	95	5
c	58	42
d	67	33

[a] Irradiation of a benzene solution of methanonaphthoquinone (5×10^{-4} M) and xanthene (1×10^{-3} M) was carried out under deaerated conditions for 1.5 h (20 mL of benzene used).

For the photochemical reaction of methanonaphthoquinone **1a** with xanthene, the mechanism shown in Scheme I may be postulated. The photochemical reaction of **1b-d** with xanthene is recognized on the same line. Isomerization of ketyl radical **17** to possible alternative **19** seems to be excluded because the derivative of the latter could not be found in the reaction mixture (eq 9).

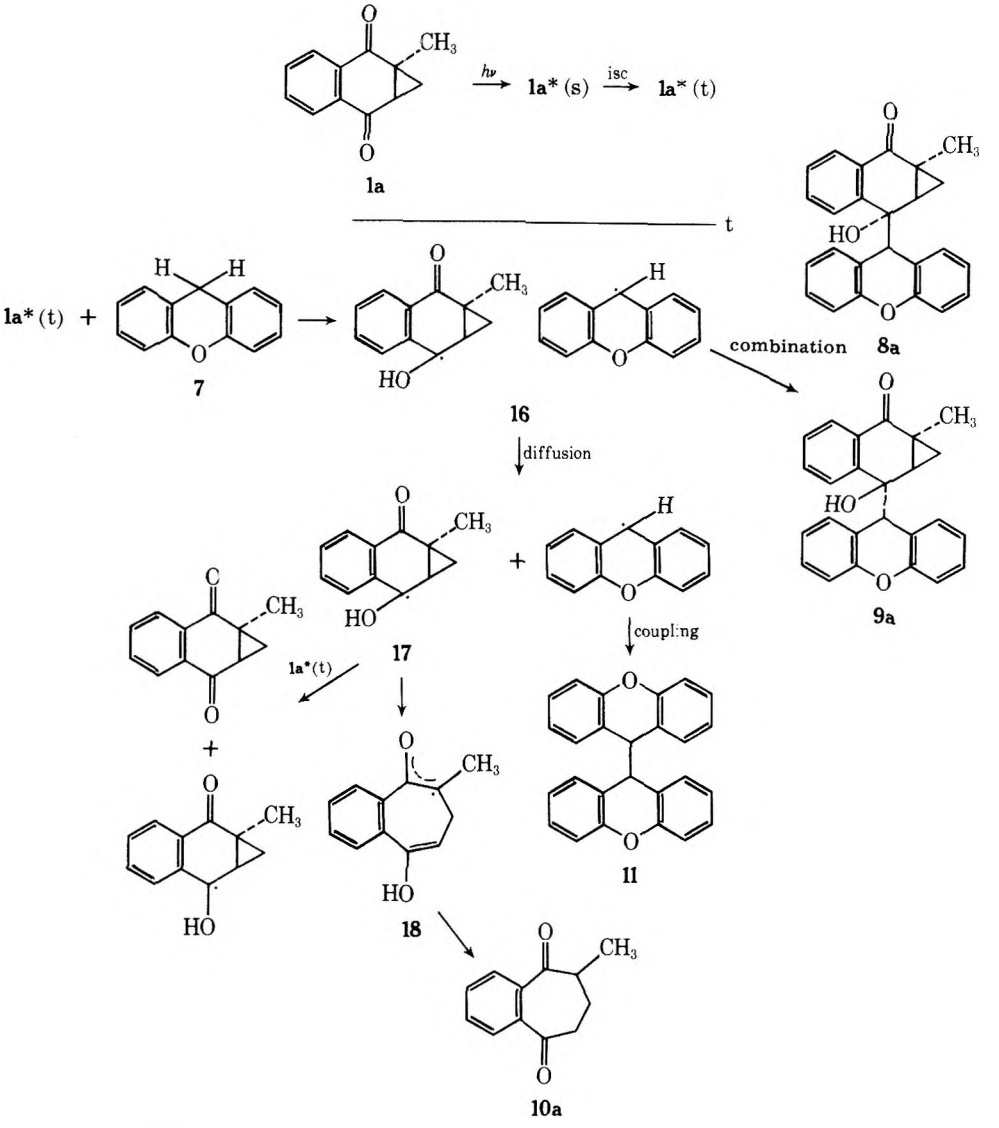


(9)

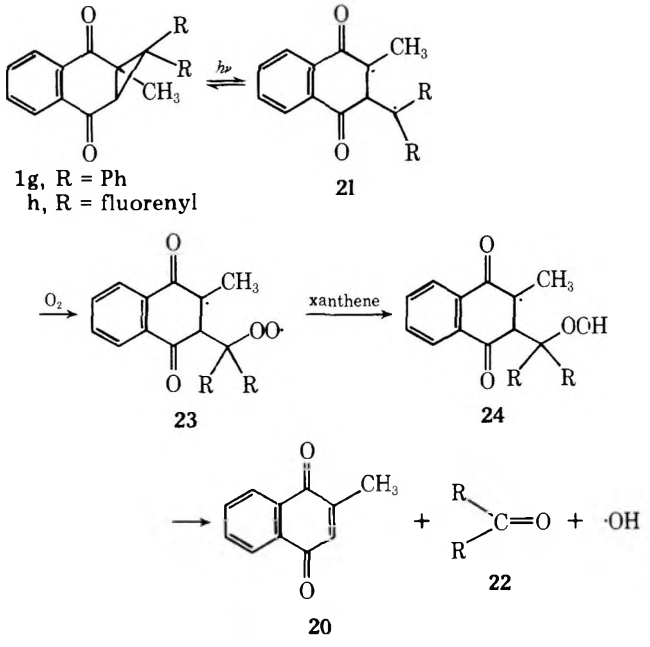
Photodecomposition of Aryl-Substituted 2,3-Dihydro-2,3-methano-1,4-naphthoquinones (1g and 1h). Whereas **1f** is quite stable upon irradiation as described above, under aerated conditions a benzene solution of **1g** or **1h** degradated fairly fast in the presence of xanthene. On the other hand, when under complete deaerated conditions a benzene solution of **1g** or **1h** irradiated in the presence or absence of xanthene in a Pyrex vessel using a 300-W high-pressure Hg-arc lamp showed no reaction even after prolonged exposure (50 h). Thus, 7,7-diaryl-substituted 2,3-dihydro-2,3-methano-1,4-naphthoquinones, **1g-h,** are photostable even in the presence of a good hydrogen donor, contrary to the reaction of **1a-d.** However, oxygen dissolved in the solution brought about a drastic change in the feature of the reactions. As described above, under the aerated conditions, **1g** and xanthene dissolved in benzene reacted fairly fast upon irradiation and disappeared completely after exposure for 40 h, giving 2-methyl-1,4-naphthoquinone (**20,** 49%), benzophenone (**22g,** 32%), and 9,9′-bixanthenyl. The other products were composed of intractable brown materials. Dissolved oxygen in solution has a similar effect on the reaction of **1h.** The result was comparable to that of **1g,** yielding 2-methyl-1,4-naphthoquinone (67%), fluorenone (45%), and 9,9′-bixanthenyl.

At first sight, the mechanism involving the formation of diarylcarbene might be postulated for this type of photochemical reaction. In fact, such a mechanism has already been proposed for the gas-phase photolysis of benzylcyclopropane.[6] However, the route via carbene as a reactive intermediate was ruled out for our reactions by the following experimental data. Irradiation of a benzene solution of **1g** or **1h** in the absence of xanthene afforded no photoproduct. In addition, when a so-

Scheme I



Scheme II



lution of **1g** and xanthene in benzene/methanol was irradiated, no photoproduct resulting from the insertion of diphenylcarbene into methanol was isolated.[7] The above results are likely to suggest that photodegradation of **1g** or **1h** under aerated conditions did not proceed via diarylcarbene but via diradical **21**, which is probably soon stabilized to **1g** or **1h**. The lifetime of diradical **21** will be elongated by the presence of *substituents, aryls and methyl, at radical centers in an appreciable degree.*[7] It is reasonable to consider that diradical **21** can uptake an oxygen molecule but not abstract a hydrogen atom from xanthene. Thus, the reaction of **1g** and **1h** under aerated conditions will be tentatively formularized as shown in Scheme II.

Experimental Section

Infrared spectra were recorded on a JASCO IR-G spectrometer using a KBr disk or a liquid film. ^1H NMR spectra were obtained on a JEOL PS-100 MHz instrument with Me_4Si as internal standard in a suitable solvent. Ultraviolet spectra were recorded on a Shimadzu UV-200 spectrometer. Mass spectra were taken on a Hitachi M-52 mass spectrometer. All melting points were taken on a Yanagimoto *micro-melting-point apparatus and are uncorrected.*

1. Preparation of 2,3-Dihydro-2,3-methano-1,4-naphthoquinones (1a–h). The methanonaphthoquinones used were prepared by denitrogenation of the corresponding indazoles.[8] The indazoles were synthesized from appropriate diazo compounds and 1,4-naphthoquinone derivatives. Methanonaphthoquinones **1c** and **1e**, however, were prepared as described by G. L. Buchanan.[3,9] If not otherwise stated, denitrogenation of indazoles was performed by treating them with 72% perchloric acid. Physical constants and spectral data of the prepared 2,3-dihydro-2,3-methano-1,4-naphthoquinones, **1a–h**, are tabulated in Table III. The UV absorption spectrum of **1a** in cyclohexane exhibited three characteristic bands at 245.5 (log ε 3.84), 293.5 (3.24), and 331 nm (2.4). The other methanonaphthoquinones showed similar bands to those of **1a**.

Table III. Physical Constants of 2,3-Dihydro-2,3-methano-1,4-naphthoquinones

Compound	Registry no.	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H	*m/e* (M^+)	^{1}H NMR, ppm
1a	16650-34-3	68–69	77.38	5.41	77.41	5.40	186	1.50 (s, 3 H), 1.58 (m, 2 H), 2.50 (d ofd, 1 H), 7.5–8.0 (m, 4 H)
b	36225-17-9	80–81	77.96	6.04	77.95	6.03	200	1.40 (AB q, 2 H), 1.80 (s, 6 H), 7.60–8.0 (m, 4 H)
c	29200-97-3	68–69	76.71	4.68	76.70	4.73	172	1.42–1.90 (m, 2 H), 2.60–2.8 (m, 2 H), 7.6–8.1 (m, 4 H)
d	64044-71-9	59–61	77.96	6.04	78.00	6.02	200	1.30 (d, 3 H), 1.50 (s, 3 H), 2.0 (m, 1 H), 2.30 (d, 1 H), 7.60–8.10 (m, 4 H)
e	64044-72-0	118–119	69.83	5.51	69.81	5.55	292	2.50 (AB q, 2 H), 3.20 (t, 6 H), 4.28 (q, 4 H), 7.7–8.2 (m, 4 H)
f	64044-73-1	132–134	84.99	4.59	85.02	4.55	307	1.25 (s, 3 H), 3.12 (AB q, 1 H), 7.2–7.4 (m, 5 H), 7.6–8.2 (m, 4 H)
g	13599-29-6	216–218	85.18	5.36	85.16	5.34	172 (M^+ − 166	1.40 (s, 3 H), 3.30 (s, 1 H), 6.8–8.0 (m, 14 H)
h[10]	64070-49-1	219–220	85.69	4.79	85.70	4.71	172 (M^+ − 164)	1.82 (s, 3 H), 3.55 (s, 1 H), 6.2–8.4(m, 12 H)

2. Isomerization of 2,3-Diethoxycarbonyl-2,3-dihydro-2,3-methano-1,4-naphthoquinone (1e). A solution of **1e** (500 mg) in benzene was irradiated in a Pyrex vessel by light from a 300-W high-pressure Hg-arc lamp for 12 h at room temperature. Isolation of the photoproducts by column chromatography on silica gel gave 6,8-diethoxycarbonyl-7*H*-5,9-dihydroxybenzocycloheptene (**2**, 48 mg, 24%) and 6,8-diethoxycarbonyl-9-hydroxybenzocycloheptene-5-one (**3**, 86 mg, 46%) together with the recovered starting material **1e** (297 mg). The structures of photoproducts **2** and **3** were determined by comparison with the corresponding authentic samples.[9]

6,8-Diethoxycarbonyl-7*H*-5,9-dihydroxybenzocycloheptene (**2**): colorless needles from ethanol; mp 86–87 °C; IR (KBr) 2900 (H-bonding OH), 1620, 1250, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4 (t, 6 H, ethyl CH_3), 3.00 (broad s, 2 H, CH_2), 4.34 (q, 4 H, ethyl CH_2), 7.64 (m, 2 H, aromatic H), 12.5 (s, 2 H, bonding OH).

6,8-Diethoxycarbonyl-9-hydroxybenzocyclohepten-5-one (**3**): pale yellow needles from ethanol; mp 76–76.5 °C; IR (KBr) 2900 (H-bonding OH), 1710 (C=O), 1650 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 3 H, ethyl CH_3), 4.32 (q, 4 H, ethyl CH_2), 7.76 (m, 2 H, aromatic H), 7.92 (m, 1 H, aromatic H), 8.36 (m, 1 H, aromatic H), 8.44 (s, 1 H, CH), 14.8 (s, 1 H, H-bonding OH).

3. Photoreduction of Alkyl-substituted 2,3-Dihydro-2,3-methano-1,4-naphthoquinones (1a–d). General Procedure. With some exceptions where it is noted, irradiations were conducted in a Pyrex vessel using a 300-W high-pressure Hg-arc lamp through a 5-cm thick water layer at room temperature. During irradiation, the reacting mixture was monitored by thin layer chromatography. Evaporation of solvent gave semisolids which were crystallized on the addition of methanol. Filtration of the semisolid and recrystallization from benzene/methanol gave 9,9′-bixanthenyl as colorless needles: mp 212–213 °C; IR (KBr) 1480, 1450, 1250, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.2 (s, 2 H, CH), 6.6–7.4 (m, 16 H, aromatic H). 9,9′-Bixanthenyl was obtained in all cases for the reactions examined and isolated as the first eluent on column chromatography of the products.

Photoreduction of 1a,b with Xanthene. The structures and spectral data of photoreduction products of **1a** and **1b** with xanthene were described already in a previous paper.[4,5]

Photoreduction of 1c with Xanthene. Irradiation of a solution of **1c** (200 mg) and xanthene (400 mg) in benzene (30 mL) gave *cis*-4-xanthenyl-2,3-methano-3,4-dihydro-4-hydroxynaphthalene-1(2*H*)-one (**8c**, 70 mg, 20%), *trans*-4-xanthenyl-2,3-methano-3,4-dihydro-4-hydroxynaphthalene-1(2*H*)-one (**9c**, 28 mg, 8%), 6,7,8,9-tetrahydrobenzocycloheptene-5,9-dione (**10c**, 52 mg, 30%), and 9-xanthenyl-5,9-epoxy-6,7,8,9-tetrahydrobenzocycloheptene-5-ol (**12c**, 49 mg, 14−) together with recovered starting material **1c** (25.1 mg).

Photoproduct **8c**: colorless needles from benzene/hexane; mp 157–158 °C; IR (KBr) 3400 (OH), 1650 (C=O), 1480, 1430, 1240, 750 cm^{-1}; ^{1}H NMR $CDCl_3$) δ 0.64 (m, 1 H, CH_2), 1.00 (m, 1 H, CH_2), 1.90 (m, 2 H, CH), 2.4 (s, 1 H, OH), 4.24 (s, 1 H, CH), 6.2–7.68 (m, 12 H, aromatic H); MS *m/e* 172 (M^+ − 181), 181, 182. Anal. Calcd for $C_{24}H_{13}O_3$: C, 81.34; H, 5.12. Found: C, 81.12; H, 5.30.

Photoproduct **9c**: colorless needles from benzene/hexane; mp 206–208.5 °C; IR (KBr) 3400 (OH), 1650 (C=O), 1470, 1240, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.00 (m, 2 H, CH_2), 1.6–2.0 (m, 2 H, CH), 2.6 (s, 1 H, CH), 6.7–8.3 (m, 12 H, aromatic H); MS *m/e* 172 (M^+ − 181), 181, 182. Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.55; H, 5.02.

Photoproduct **12c**: colorless needles from benzene/hexane; mp 203–205 °C; IR (KBr) 3320 (OH), 1470, 1450, 1250, 1000, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4–2.0 (m, 6 H), 3.32 (s, 1 H, OH), 4.52 (s, 1 H, CH), 6.9–7.5 (m, 12 H, aromatic H); MS *m/e* 356 (M^+), 185 (M^+ − 181), 182, 181.

The structure of **10c** was identified by comparison with an authentic sample obtained by Zn–CH_3COOH reduction of **1c**. Photoproduct **10c**: colorless needles from hexane; mp 39–40 °C; IR (KBr) 1685 (C=O), 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.92–2.29 (m, 2 H, CH_2), 2.80 (t, 4 H, CH_2), 7.4–7.72 (m, 4 H, aromatic H).

Photoreduction of 1d with Xanthene. Irradiation of a solution of **1d** (200 mg) and xanthene (400 mg) in benzene (30 mL) gave cis-2,9-dimethyl-4-xanthenyl-2,3-methano-3,4-dihydro-4-hydroxynaphthalen-1(2H)-one (**8d**, 98.6 mg, 29%), trans-2,9-dimethyl-4-xanthenyl-2,3-methano-3,4-dihydro-4-hydroxynaphthalen-1(2*H*)-one (**9d**, 34.1 mg, 10%), and 6,7-dimethyl-6,7,8,9-tetrahydrobenzocycloheptene-5,9-dione (**10d**, 25.5 mg, 15%) together with recovered starting material **1d** (30.2 mg).

Photoproduct **8d**: colorless needles from benzene/hexane; mp 188–189 °C; IR (KBr) 3320 (OH), 1650 (C=O), 1475, 1450, 1245, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91–1.16 (m, 1 H, *endo*-H), 1.00 (s, 3 H, *exo*-CH_3), 1.10 (s. 3 H, CH_3), 1.28 (d, 1 H, CH), 2.22 (s, 1 H, OH), 4.16 (s, 1 H, CH), 5.8–7.7 (m, 12 H, aromatic H); MS *m/e* 201 (M^+ − 181), 182, 181. Anal. calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.44; H, 5.68.

Photoproduct **9d**: colorless needles from benzene/hexane; mp 220–222 °C; IR (KBr) 3480 (OH), 1650 (C=O), 1475, 1450, 1245, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.44 (m, 1 H, *endo*-H), 0.8 (d, 3 H, *exo*-CH_3), 1.16 (s, 3 H, CH_3), 1.24 (d, 1 H, CH), 2.2 (s, 1 H, OH), 5.16 (s, 1 H, CH), 6.7–8.1 (m, aromatic H); MS *m/e* 201 (M^+ − 181), 182, 181. Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.68; H, 5.69.

The assignment of **10d** was made by comparison with an authentic sample prepared by Zn–CH_3COOH reduction of **1d**. Photoproduct **10d**: oil; IR (liquid film) 1695 (C=O), 1590 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.04 (d, 3 H, CH_3), 1.16 (d, 3 H, CH_3), 2.2–3.3 (m, 4 H), 7.48–7.80 (m, 4 H, aromatic H).

Oxidation of 12c with Chromic Acid. Oxidation of photoproduct **12c** (52 mg) with chromic acid (300 mg) under the same conditions used for that of **8a** gave 6,7,8,9-tetrahydrobenzocycloheptene-5,9-dione (**10c**) (12 mg, 50%) and xanthone (15 mg, 52%).

4. Photodegradation of Aryl-Substituted 2,3-Dihydro-2,3-methano-1,4-naphthoquinones (1f–h). Reaction of 1f with Xanthene. Irradiation of a solution of **1f** (100 mg) and xanthene (200 mg) in benzene (20 mL) for 80 h gave no photoproduct, and the starting material was recovered quantitatively. Even under deaerated conditions the feature of the reaction was quite similar.

Reaction of 1g with Xanthene. Under deaerated conditions, a solution of **1g** (480 mg) and xanthene (800 mg) in benzene (60 mL) was irradiated for 50–60 h in a Pyrex vessel. After the solvent was removed, we recovered only a mixture composed of **1g** and xanthene. However, under aerated conditions, irradiation of a solution of **1g** (480 mg) and xanthene (800 mg) in benzene (60 mL) for 40 h by light from

a 300-W high-pressure Hg-arc lamp gave reaction products. After removal of the solvent, isolation of the residue by column chromatography on silica gel gave 2-methyl-1,4-naphthoquinone (**20**, 85 mg, 49%) and benzophenone (**22g**, 62 ng 32%) together with 9,9′-bixanthenyl.

Photoproduct **20**: yellow needles from ethanol; mp 107 °C; IR (KBr) 1650 (C=O), 1618 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.2 (d, 3 H, CH_3), 6.84 (d, 1 H, CH), 7.64–7.84 (m, 2 H, aromatic H), 7.96–8.16 (m, 2 H, aromatic H).

Photoproduct **22 g**: colorless crystals; mp 49–50 °C, confirmed by mixture-melting-point method compared with an authentic sample.

Reaction of 1h with Xanthene. Under completely deaerated conditions, irradiation of a mixture of **1h** and xanthene dissolved in benzene gave no photoproduct. However, under aerated conditions, irradiation of **1h** (200 mg) and xanthene (400 mg) dissolved in benzene (30 ml) for 40 h gave 2-methyl-1,4-naphthoquinone (**20**, 63 mg, 67%) and fluorenone (**22h**, 4 mg, 45%). Photoproduct **22n** was assigned to fluorenone by comparing with an authentic sample.

Registry No.—**2**, 64044-74-2; **3**, 64044-75-3; **8c**, 64044-76-4; **8d**, 64044-77-5; **9c**, 64069-99-4; **9d**, 64070-00-4; **10c**, 54034-10-5; **10d**, 64044-78-6; **12c**, 64044-79-7; **20**, 58-27-5; **22g**, 119-61-9; 9,9′-bixanthenyl, 4381-14-0; xanthene, 92-83-1.

References and Notes

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Pericyclic Synthesis and Exploratory Photochemistry of Potentially Direct Progenitors of the Unrestricted Hetero[11]annulene System

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The procedure of α-pyrone C_4H_4 homologation was applied to the synthesis of the heterotricycles shown in **5**, **6**, **9**, and **18**, which were judged to be useful, potentially direct, synthetic precursors for the construction of "unrestricted" hetero[11]annulenes. Compounds **6**, **9**, and **18** readily fragment under the influence of heat or light to produce benzene and the corresponding five-membered heterocycle. On the other hand, exploratory photochemical work with **5** has revealed the system's propensity to undergo dimerization on sensitized illumination and multidirectional bond relocation, to **20** and **21** and **22**, on direct irradiation.

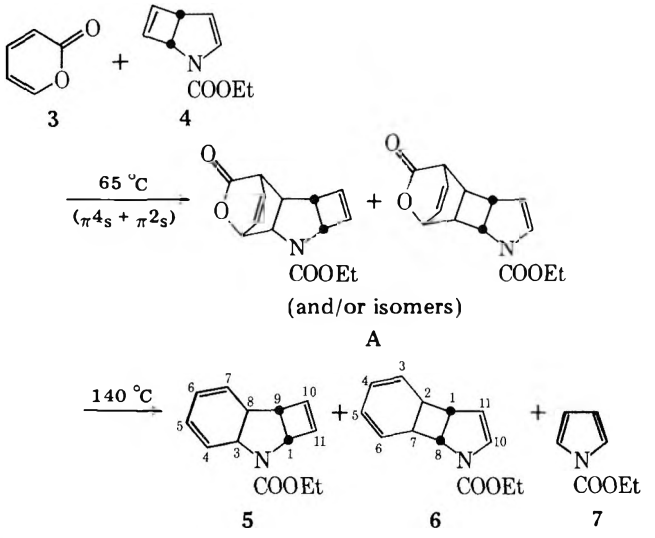
The tactical use of pericyclic transformations offers a unique means of gaining entry into potentially labile unrestricted[1] π-excessive frames such as the hetero[9]-,[2] hetero[13]-,[2b,3] and hetero[17]annulenes.[3] One notable common characteristic of these monocyclic substances is that they were all prepared by synthetic procedures utilizing cyclooctatetraene as the basic synthon and are thus associated with a $(4n + 1)$-membered periphery containing a total of $(4n + 2)$ π electrons. In other words, the pericyclic synthetic schemes developed here[2] and elsewhere[3] are strictly designed for the construction of potentially aromatic heterocycles. In theory, extension of this useful procedure to the preparation of potentially antiaromatic π-excessive heterocycles, i.e., molecules incorporating a $(4n - 1)$-membered periphery and a total of $4n$ π electrons, may be realized simply by changing the basic hydrocarbon building unit from cyclooctatetraene to benzene. We have examined the practical aspects of such a modification to the original synthetic design and wish to present in this report a description of our experiences in this connection, relating to the construction of a variety of potentially direct synthetic progenitors of the unrestricted hetero[11]annulene system.

Multicyclic Valence Tautomers of the Aza[11]annulene System

Since N-substituted azepines are known to undergo thermal cycloaddition[4–6] with a variety of reactive dienes yielding symmetrically bridged 1:1 adducts of general structure **1**, our initial attempts in this project concentrated on the possible application of the α-pyrone-induced C_4H_4 homologation procedure we previously devised[7,8] for converting an aza[9]annulene (azonine) to the 13-membered counterpart. All effort along these lines, however, was effectively frustrated by the failure of the azepine **2**[9] to react with α-pyrone (**3**) on prolonged contact and over a wide temperature range (70–110 °C). Our failure to effect cycloadditive coupling between **2** and **3** was not entirely unexpected insofar as the homologation process as initially designed calls for cycloadditive trapping of a skeletally uncomfortable trans double bond, i.e., a reactive functionality not present in **2**. Therefore, it became necessary to utilize in the basic homologation scheme a C_6H_6NR synthon with more reactive double bonds than are present in **2**. With this in mind we directed our attention to the readily available [3.2.0] photoisomer of **2**, shown as **4**[10] in Scheme I. This molecule does indeed react with a benzene solution of **3** at 65 °C to produce a mixture of cycloadducts (A, Scheme I) in ca. 62% yield. A, in turn, readily extrudes CO_2 upon heating at 140–145 °C in vacuo (ca. 0.05 mm) to yield a thermolysate consisting of the three nonvolatiles **5** (^1H NMR, IR, UV, MS), **6** (^1H NMR, IR, UV, MS), and **7** (^1H NMR, IR) in a molar ratio of 1:1.2:1.8 (60% yield). The assignment of anti stereochemistry to **5** follows from the small value of $J_{8,9}$ (2 Hz) which is more consistently accommodated by the dihedral angle estimated (Dreiding models) for a trans H–H disposition (~100°) than

0022-3263/78/1943-0315$01.00/0

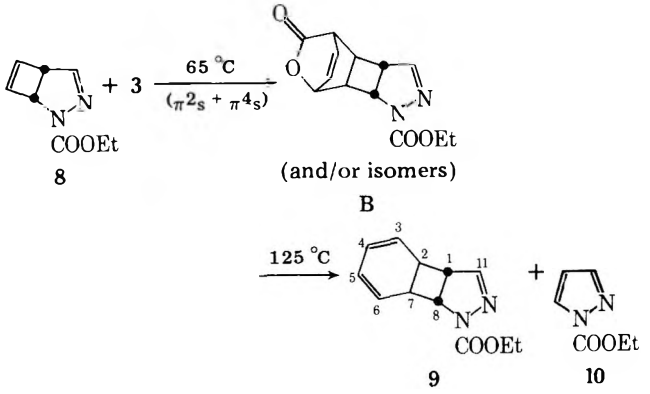
Scheme I



for the cis alternative (~0°) (cf. ^{1}H NMR of **22** (vide infra)). Similar reasoning allows one to assign an anti disposition to **6** ($J_{1,2}$ = 3.5 Hz) as well.

In related experiments designed for the preparation of one or more multicyclic isomers of an aza[11]annulene incorporating a nitrogen in place of an sp^2 C–H unit, the diazabicycle depicted in **8** (reaction 1) was exposed to **3** at 65 °C, leading to cycloadduct(s) B in ca. 64% yield. Thermally induced (125 °C, 0.05 mm) loss of CO_2 produced a two-component mixture of nonvolatiles consisting of **9** (^{1}H NMR, IR, UV, MS) ($J_{7,8}$ = 3.5 Hz) and pyrazole **10**[12] (^{1}H NMR, MS) in a molar ratio of 1:1.5 (55% yield).[13]

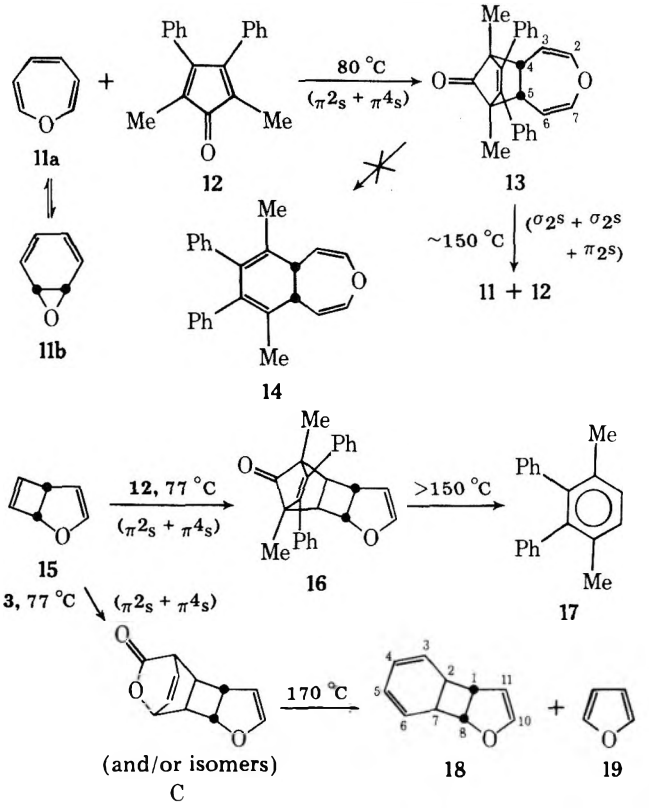
The presence of pyrrole **7** and pyrazole **10** in the pyrolysates of A and B is best accounted for by the respective fragmentation of **6** (and/or its syn isomer) and **9** (and/or its syn counterpart) via a retro-($_\pi 2_s + {}_\pi 2_s$) process whose formal "forbiddenness" is largely lifted because of the developing aromaticity of its six-membered moiety, i.e., as a result of benzene extrusion. Gratifyingly, one finds tricycles **6** and **9** to fragment to **7** + benzene ($k_{109.6°}$ = 3.29 ± 0.23 × 10^{-4} s^{-1}, $\Delta G^{\ddagger}$ = 28.7 kcal/mol) and **10** + benzene ($k_{109.7°C}$ = 3.69 ± 0.20 × 10^{-4} s^{-1}, $\Delta G^{\ddagger}$ = 28.6 kcal/mol), respectively.



Multicyclic Valence Tautomers of the Oxa[11]annulene System

A survey of prior art relating to the response of oxepin (**11**, Scheme II) to thermal cycloaddition[14] reveals it to be strictly limited to dienophilic reagents which invariably single out the

Scheme II



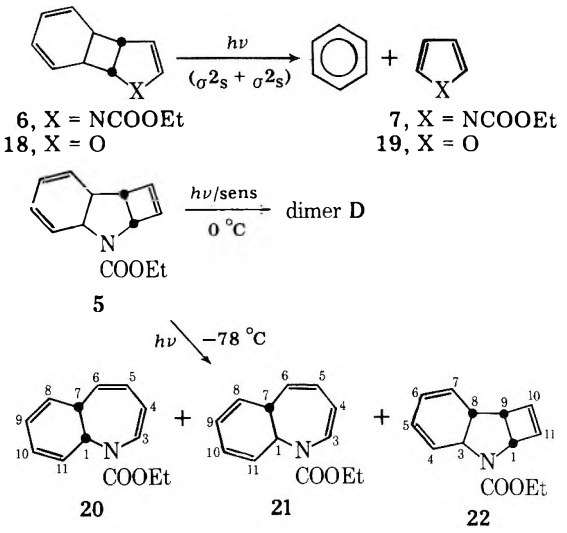
bicyclic oxanorcaradiene form of the molecule, i.e., **11b**, for cycloadditive union.[15] Consequently, it was encouraging to discover that dienone **12** adds cleanly to the remote double bond of oxepin itself, i.e., **11a**. Specifically, we find that prolonged (48 h) exposure of oxepin to **12** in boiling benzene leads to the formation of oxatricycle **13** (mp 164–165 °C; ^{1}H NMR, IR, UV, MS) in 65% yield. The proposed structure clearly follows from the spectroscopic data which require that the molecule possess a pair of magnetically equivalent enol ether functions ($\Delta\tau_{\alpha,\beta}$ = 1.66 ppm) and a highly strained ketonic bridge (ν_{CO} = 1760 cm^{-1}) flanked by a pair of symmetrically disposed methyl groups (6H singlet of τ 8.60). Disappointingly, all attempts at thermally decarbonylating **13** to the desired oxabicycle **14** were frustrated by the molecule's readiness to undergo thermal cycloreversion to **12** and oxepin in benzene solution (110–192 °C) or in the molten state.

Contrasting the rather sluggish response of **11** to cycloaddition with **12**, its bicyclic photoisomer **15**[14,16] undergoes rapid cycloadditive coupling with **12** in hot benzene (77 °C) to produce adduct **16** (mp 142–143 °C; ^{1}H NMR, IR, UV, MS) in essentially quantitative yield. Our preference for an anti-disposition of the two rings flanking the cyclobutane unit of **16** follows from the large observed difference between $J_{1,7}$ (2.0 Hz) and $J_{1,5}$ (7.0 Hz), which requires that dihedral angles H^1–H^7 and H^1–H^5 also be widely different; cursory examination of Dreiding models reveals that the key dihedral angles are equal in the syn counterpart of **16** and, as required by the observed coupling constants, distinctly different ($H_{1,5}$ ~5°, $H_{1,7}$ ~110°) in **16**.

Cycloadduct **16** does undergo overall thermal decarbonylation when heated above 150 °C in benzene, but the molecule's basic skeleton is labile at these elevated temperatures so that the only nonvolatile product one isolates under these conditions is the tetrasubstituted benzene **17**. The overall fragmentation of **16** to **17** was monitored by ^{1}H NMR at 163 °C ($t_{1/2}$ ~4.5 h) and 192 °C ($t_{1/2}$ ~18 min) without indication of any intermediates.

Exposure of **15** to α-pyrone (**3**) instead of dienone **12** produced cycloadduct(s) C which, in turn, readily extrudes CO_2

Scheme III



upon heating at 170 °C in vacuo (ca. 0.05 mm) to afford oxatricycle **18** (^{1}H NMR, IR, UV, MS) in 21% overall yield. The assignment of anti stereochemistry to this substance follows from the distinctly different magnitudes of key coupling constants $J_{1,8}$ (7.5 Hz) and $J_{7,8}$ (4.0 Hz) and is further supported by its unquestionable dissimilarity (IR, ^{1}H NMR) from the recently described product of photoinduced coupling between benzene and furan formulated as the syn counterpart of **18**.[17]

Chemically, the general structural features depicted in **18** are supported by the compound's affinity to undergo thermally induced fragmentation ($k_{110.4°C} = 4.49 \pm 0.39 \times 10^{-4}$ s^{-1}, $\Delta G^{\ddagger} = 28.5$ kcal/mol) to benzene and furan.

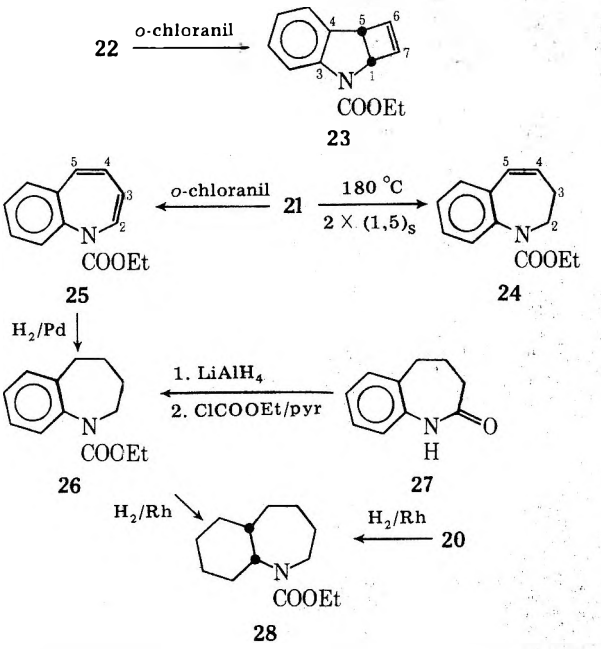
Exploratory Photochemistry

Once the various substances described earlier became available, we turned our attention to exploring their possible usefulness as photoprogenitors of the hitherto unknown hetero[11]annulene frame.

To begin with, we examined the structurally related molecules **6, 9,** and **18** and were disappointed to discover that exposure of this general tricyclic skeleton to either direct or sensitized illumination readily triggers fragmentation to benzene and the expected π-excessive heterocycle (Scheme III). This, of course, is not an unexpected result for it is difficult to conceive of a process such as valence isomerization or dimerization which would effectively compete energetically with the symmetry-allowed genesis of benzene.

Next we turned our attention to the alternate tricyclic arrangement prepared in this study, i.e., **5,** which is structurally incapable of readily extruding an aromatically stabilized fragment. While this is in fact the case, i.e., **5** does effectively resist photofragmentation, exposure of this substance to the type of sensitized irradiation and subsequent workup conditions which proved successful in our recent generation and isolation of an aza[13]annulene[8] resulted in the formation of a dimer (mp 134–137 °C; ^{1}H NMR, IR, UV, MS) as the only tractable product (16% yield). Since this dimeric product is of no direct use to the primary goal set by this study, no serious effort was expended toward its characterization, although it is evident from certain key spectroscopic characteristics that the substance possesses twofold symmetry (^{1}H NMR) and, further, that it lacks a conjugated diene chromophore (UV). Sharply contrasting its response to sensitized irradiation, brief unfiltered exposure of **5** to direct illumination with a low-pressure mercury coil at ca. −78 °C effected clean 50% conversion to three photoisomers characterized as **20** (^{1}H NMR, IR, UV, MS), **21** (^{1}H NMR, IR, UV, MS), and **22** (^{1}H NMR, IR, UV, MS) and isolated in the respective ratio of 2:1:1.

Scheme IV



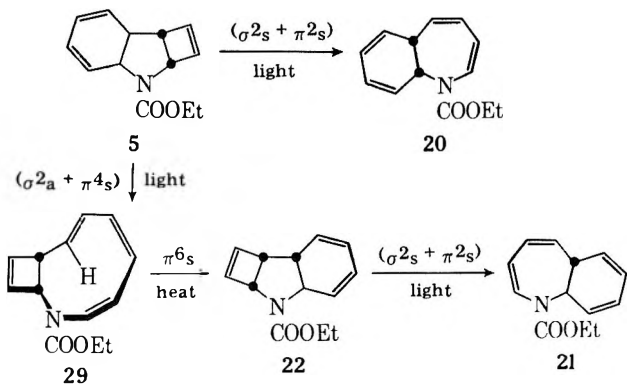
Ring-juncture stereochemical assignments follow in each case from an assessment of pertinent coupling constants. Specifically, one measures $J_{1,7} \sim 7$ Hz for **20,** $J_{1,7} = 17$ Hz for **21,** and $J_{1,9} = 3.5$, $J_{8,9} = 7.5$, and $J_{3,8} = 18.0$ Hz for **22.**

Chemically, the structural assignments of **20, 21,** and **22** received added confirmation from the following transformations: compound **22** was oxidized to **23** (^{1}H NMR, IR, UV, MS) on exposure to *o*-chloranil, and **21** was (i) thermolyzed (GLC injection port, 180 °C) to **24** (^{1}H NMR, IR, UV, MS) and (ii) oxidized to the rare[18,19] 2,3-benzazepine frame depicted in **25** (^{1}H NMR, IR, UV, MS) on treatment with *o*-chloranil. Further, the presence of the same basic [5.4.0] frame in **20** and **21** was securely established through partial hydrogenation (Pd/C) of **25** to **26** (^{1}H NMR, IR, UV, MS), followed by exhaustive saturation (Rh/C) of this substance to **28** (^{1}H NMR, IR, UV, MS), which was shown to be spectroscopically (^{1}H NMR, IR) indistinguishable from a synthetic sample prepared from catalytic hydrogenation (Rh/C) of **20.**

As already stressed in this section's title, the photoinduced transformations described here are largely exploratory, our primary emphasis being directed at deciding whether any of the available tricyclic isomers of the hetero[11]annulene system might be considered synthetically promising. For obvious operational reasons, tricycles **6, 9,** and **18** do not hold much promise in this regard. On the other hand, the multidirectional response of **5** to direct illumination is deemed synthetically encouraging insofar as it may be considered implicative of one or more monocyclic intermediates. It must be remembered, of course, that the overall photoisomerization of **5** to **20, 21,** and **22** may be accounted for equally well via sequential bond relocation as exemplified by the combination of symmetry-permitted steps collected in Scheme V.

To conclude, it might be noted that given the current state of preparative development of **5,** any studies directed at assessing its synthetic utility in relation to the desired monocyclic analogue would undoubtedly be hampered by the molecule's limited availability (ca. 10% yield from **4**). As a result of this complication, it now appears necessary to concentrate one's immediate effort chiefly to the development of such conditions as are required to maximize the source of **5** in the mixture of cycloadducts (A) in Scheme I. It is hoped that, once realized, the increased availability of **5** would allow one to conduct a methodical study aimed at the possible detection and eventual isolation of the desired heteroannulene.

Scheme V



Experimental Section

Preparation of *N*-Carbethoxy-2-azabicyclo[3.2.0]hepta-2,4-diene (4).[21] A solution of *N*-carbethoxyazepine (2)[9] (4 g, 0.024 mol) in deaerated (N_2) ethyl ether (650 mL) was irradiated at ambient temperature under a nitrogen atmosphere through a Pyrex filter with a Hanovia 450-W lamp for a period of 20 h. The solution was then concentrated at the water aspirator at ambient temperature, and the resulting crude yellow oil was distilled at a head temperature of 40–45 °C and 0.05 mm to afford pure *N*-carbethoxy-2-azabicyclo[3.2.0]-hepta-2,4-diene (4) (3.4 g, 85%) as a colorless oil (^{1}H NMR, IR).

Reaction of *N*-Carbethoxy-2-azabicyclo[3.2.0]hepta-2,4-diene (4) with α-Pyrone (3): Formation of A. A deaerated (N_2) solution of *N*-carbethoxy-2-azabicyclo[3.2.0]hepta-2,4-diene (4) (3.4 g, 0.021 mol) and α-pyrone (3) (17.0 g, 0.21 mol) in benzene (20 mL) was heated at 60–65 °C under nitrogen for 40 h. The solution was concentrated at the water aspirator, and unreacted α-pyrone was then removed at a bath temperature of 50–55 °C and 0.1 mm to yield a dark residue. This residue was dissolved in a minimum amount of ethyl ether and the resulting solution placed on a 630 × 15 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (55 g) and maintained at ca. −15 °C. Elution with petroleum ether/ethyl ether (1:1 v/v, 300 mL) removed the impurities so that subsequent elution with petroleum ether/ethyl ether (1:3 v/v, 300 mL) afforded A (3.4 g, 62%) as a white foamy residue.

Pyrolysis of A: Formation of *N*-Carbethoxy-2-aza-*cis*^{1,9},*trans*^{8,9},*cis*^{3,8}-tricyclo[7.2.0.0^{3,8}]undeca-4,6,10-triene (5), *N*-Carbethoxy-9-aza-*cis*^{1,8},*trans*^{1,2},*cis*^{2,7},*trans*^{7,8}-tricyclo-[6.3.0.0^{2,7}]undeca-3,5,10-triene (6), and *N*-Carbethoxypyrrole (7). A sample of A (3.4 g, 0.013 mol) was pyrolyzed dry under vacuum (0.05 mm) at a bath temperature of 150–165 °C in a short-path distillation unit. Gas evolution was observed, and the distillate was collected in a flask immersed in dry ice/acetone (ca. −70 °C). The resulting colorless oil was then placed on a 760 × 15 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (60 g) and maintained at ca. −15 °C. Elution with petroleum ether/ethyl ether (49:1 v/v, 200 mL) afforded *N*-carbethoxypyrrole (7) (488 mg, 27%): ^{1}H NMR (60 MHz, $CDCl_3$) τ 2.70 (2H, t, J = 2 Hz), 3.76 (2H, t, J = 2 Hz), 5.60 (2H, q, ethyl), 8.60 (3H, t, ethyl); IR (neat), prominent maxima at 2980, 1750, 1460, 1400 cm^{-1}. Continued elution with petroleum ether/ethyl ether (9:1 v/v, 100 mL) afforded **6** (508 mg, 18%). Distillation at a bath temperature of 45–50 °C and 0.025 mm produced a pure sample of **6** as a colorless oil: IR (neat) prominent maxima at 1710, 1610, 1420, 1335, 1130, 905. 765, 720, 685 cm^{-1}; UV (C_6H_{14}) max 282 (ε 1740), 238 nm (18 900); ^{1}H NMR (100 MHz, $CDCl_3$, +55 °C)[22] τ 3.33 (1H, d, H^{10}, J = 4.25 Hz), 4.1–4.5 (4H, m, H^3 + H^4 + H^5 + H^6), 4.72 (1H, dd, H^{11}, J = 4.25, 3 Hz), 5.39 (1H, dd, H^8, $J_{8,1}$ = 8.5, $J_{8,7}$ = 4 Hz), 5.80 (2H, q, CH_2, J = 7 Hz), 6.4 (1H, m, H^1), 6.71 (1H, ddd, H^7, $J_{7,2}$ = 12, $J_{7,8}$ = 4, $J_{7,6}$ = 3.5 Hz), 6.98 (1H, ddd, H^2, $J_{2,7}$ = 12, $J_{2,1}$ = 3.5, $J_{2,3}$ ~ 4 Hz), 8.71 (3H, t, CH_3, J = 7 Hz); MS *m/e* 139 (P$^+$ − C_6H_6, 38), 78 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.80; H, 6.98; N, 6.47.

Further elution with the same solvent mixture (150 mL) afforded **5** (423 mg, 15%). Distillation at an oil bath temperature of ca. 45 °C and 0.025 mm afforded a pure sample of **5** as a colorless oil: IR (neat) prominent maxima at 1700, 1400, 1370, 1340, 1310, 1270, 1110, 782 cm^{-1}; UV (C_6H_{14}) max 271 (sh) (ε 2644), 261 (sh) (3830), 251 (4250), 244 nm (4360); ^{1}H NMR (100 MHz, $CDCl_3$)[22] τ 3.68 (1H, dd, H^{11}, $J_{11,10}$ ~ 2, $J_{11,1}$ ~ 2 Hz), 3.7–4.6 (5H, m, H^{10} + H^4 + H^5 + H^6 + H^7), 5.46 (1H, dd, H^1, $J_{1,9}$ = 3.5, $J_{1,11}$ ~ 2 Hz), 5.55 (1H, dd, H^3, $J_{3,8}$ = 9.5, $J_{3,4}$ = 5 Hz), 5.94 (2H, q, CH_2, J = 7 Hz), 6.66 (1H, dd, H^9, $J_{9,1}$ = 3.5, $J_{9,8}$ ~ 2 Hz), 7.21 (1H, dm, H^8, $J_{8,3}$ = 9.5 Hz), 8.83 (3H, t, CH_3, J = 7 Hz); MS *m/e* 217 (P$^+$, 61), 144 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.70; H, 6.97; N, 6.55.

Thermolysis of 6: Formation of *N*-Carbethoxypyrrole (7) and Benzene. A vacuum-sealed (ca. 0.005 mm) medium-wall NMR tube containing a degassed solution of **6** (75 mg, 0.346 mmol) in acetonitrile-d_3 (ca. 0.4 mL) was heated in a bath of boiling toluene (109.6 °C), and the consumption of the reactant was quantitatively monitored by ^{1}H NMR spectroscopy at ambient temperature to yield k = 3.29 ± 0.23 × 10^{-4} s^{-1} ($\Delta G^{\ddagger}$ = 28.7 kcal/mol). Heating was continued for a total of 7 h, at which time ^{1}H NMR analysis showed only **7** and benzene. Evaporation of all volatiles at the water aspirator afforded *N*-carbethoxypyrrole (7) (45 mg, 93.5%) (IR, ^{1}H NMR).

Direct Irradiation of 6 at −78 °C: Formation of *N*-Carbethoxypyrrole. A solution of **6** (100 mg, 0.46 mmol) in deaerated (N_2) petroleum ether (45 mL) was irradiated under nitrogen with a Hanovia low-pressure mercury lamp at −78 °C (dry ice/acetone) for 1 h. The solution was then, in turn, filtered and concentrated at ca. 0 °C at the water aspirator, and the resulting residue was placed on a 300 × 12 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g) and maintained at ca. −15 °C. Elution with petroleum ether/ethyl ether (49:1 v/v, 100 mL) afforded *N*-carbethoxypyrrole (7) (32 mg, 50%), and continued elution with petroleum ether/ethyl ether (8:2 v/v, 100 mL) produced what is believed to be 3-carbethoxypyrrole (26.5 mg, 41%), which was purified by recrystallization from petroleum ether (white solid): mp 38–39 °C; IR (KBr) prominent maxima at 3300, 1695, 1410, 1310, 1180, 1160, 955, 745 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) τ 3.12 (2H, m), 3.78 (1H, m), 5.74 (2H, q, ethyl), 8.73 (3H, t, ethyl); MS *m/e* 139 (P$^+$, 63.9), 94 (100).

Direct and Sensitized Irradiation of 6: Formation of *N*-Carbethoxypyrrole (7). A 125 × 15 mm quartz test tube containing a solution of **6** (100 mg, 0.46 mmol) in deaerated (N_2) ethyl ether (12 mL) was capped tightly under nitrogen and placed in an ice bath and its contents irradiated with a 450-W Hanovia mercury arc along the external surface of a quartz immersion well fitted with a Vycor filter and containing the lamp. After a total irradiation time of 80 min, the ether was removed at the water aspirator and the residue separated into *N*-carbethoxypyrrole (7) (^{1}H NMR, IR) (60%) and 3-carbethoxypyrrole (^{1}H NMR, IR) (30%) by column chromatography on activity III Woelm neutral alumina at ca. −15 °C (vide supra). Under similar conditions, Pyrex-filtered irradiation of **6** for 1 h in ethyl ether or 80 min in acetone containing Michler's ketone yielded a photolysate consisting (^{1}H NMR, IR) primarily (95%) of *N*-carbethoxypyrrole (7).

Irradiation of *N*-Carbethoxypyrrole: Formation of 3-Carbethoxypyrrole. Into each of two quartz test tubes (125 × 15 mm) was placed a solution of *N*-carbethoxypyrrole (7) (200 mg, 1.44 mmol) in deaerated (N_2) ethyl ether (12 mL). The tubes were then capped under nitrogen, suspended along the outside surface of a photochemical immersion well fitted with a Vycor filter, and irradiated with a Hanovia 450-W mercury lamp at ca. 0 °C (ice bath) for 2 h. The contents of the tubes were then combined and concentrated at the water aspirator at ca. 0 °C to yield a crude oil which was placed on a 300 × 12 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g) and maintained at ca. −15 °C. Elution with petroleum ether/ethyl ether (49:1 v/v, 100 mL) afforded unreacted *N*-carbethoxypyrrole (140 mg, 70%), and subsequent elution with petroleum ether/ethyl ether (8:2 v/v, 100 mL) produced 3-carbethoxypyrrole (50 mg, 25%), which was purified by recrystallization from petroleum ether (IR, ^{1}H NMR).

Sensitized Irradiation of 5: Formation of Dimer D. A solution of **5** (100 mg, 0.46 mmol) and Michler's ketone (100 mg) in deaerated (N_2) acetone (125 mL) was transferred to a photochemical reaction flask fitted with a photochemical immersion well and irradiated through a Pyrex filter with a Hanovia 450-W mercury arc under nitrogen at ca. 0 °C for 1 h. The contents were then concentrated at the water aspirator at ca. 0 °C, and the yellow residue was treated with ethyl ether (25 mL). The resulting precipitate (Michler's ketone) was removed by pressure filtration under nitrogen, and the filtrate was concentrated at the water aspirator at ca. 0 °C to afford a yellow oil which was placed on a 300 × 12 mm jacketed column maintained at ca. −15 °C and wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g). Elution with petroleum ether/ethyl ether (9:1 v/v, 200 mL) removed the impurities so that subsequent elution with petroleum ether/ethyl ether (3:1 v/v, 75 mL) yielded D (32 mg, 16%). Recrystallization from ethyl ether provided a pure sample of this substance: mp 134–138 °C; IR prominent maxima at 1690, 1380, 1275, 1120, 680 cm^{-1}; UV (C_6H_{14}) end absorption; ^{1}H NMR (100 MHz,

$CDCl_3$) τ 3.73 (2H, dd, J = 3.2 Hz), 3.93 (2H, d, J = 3 Hz), 4.10 (2H, dm, J = 10 Hz), 4.62 (2H, broad d, J = 10 Hz), 5.23 (2H, dd, J = 3.5, 2 Hz), 5.7–6.1 (6H, m), 6.35 (2H, broad d J = 6 Hz), 6.81 (2H, d, J = 3.5 Hz), 7.16 (2H, m), 7.67 (2H, broad s), 8.78 (3H, t); MS m/e 434 (P^+, 5.2), 217 (100).

Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.75; H, 7.00; N, 6.39.

Direct Irradiation of 5 at −78 °C: Formation of *N*-Carbethoxy-2-aza-*cis*-bicyclo[5.4.0]undeca-3,5,8,10-tetraene (20), *N*-Carbethoxy-2-aza-*trans*-bicyclo[5.4.0]undeca-3,5,8,10-tetraene (21), and *N*-Carbethoxy-2-aza-*cis*^{1,9},*trans*^{3,8},*cis*^{8,9}-[7.2.0.0^{3,8}]undeca-4,6,10-triene (22). A solution of **5** (480 mg, 2.21 mmol) in deaerated (N_2) petroleum ether (45 mL) was irradiated under nitrogen with a Hanovia low-pressure coil at ca. −78 °C (dry ice/acetone) for 1.5 h. The solution was then filtered and concentrated at ca. 0 °C and 0.1 mm, yielding a yellow oil which was placed on a 760 × 15 mm jacketed column maintained at ca. −15 °C and wet packed (petroleum ether) with activity III Woelm neutral alumina (60 g). Elution with petroleum ether (100 mL) and then petroleum ether/ethyl ether (19:1 v/v, 150 mL) afforded **20** (75.8 mg, 16%) as a colorless oil. Vacuum distillation (0.025 mm) at a bath temperature of 35–40 °C afforded pure **20** as a colorless liquid: IR (neat) prominent maxima at 1715, 1260, 770, 675 cm^{-1}; UV (C_6H_{14}) max 267 (sh) (ϵ 16 380), 248 nm (20 340); ^1H NMR (100 MHz, $CDCl_3$)[22] τ 3.29 (1H, d, H^3, $J_{3,4}$ = 9 Hz), 3.8–4.4 (5H, m), 4.4–5.1 (3H, m), 5.74 (2H, d, ethyl), 6.89 (1H, broad d, H^7, $J_{1,7} \sim 7$ Hz), 8.67 (3H, t, ethyl); MS m/e 217 (P^+ 59.2), 144 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.85; H, 6.93; N, 6.50.

Continued elution with the same solvent mixture (200 mL) afforded a mixture of products (105 mg) consisting of **20** (25%), **21** (35%), and **22** (40%). Continued elution with petroleum ether/ethyl ether (9:1 v/v, 200 mL) produced unreacted **5** (270 mg, 56%) (^1H NMR).

The three-component fraction was placed on a 760 × 15 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (60 g) and maintained at ca. −15 °C. Elution with petroleum ether/ethyl ether (19:1 v/v, 100 mL) followed by the same solvent mixture (50 mL) afforded **20** (25 mg) (^1H NMR, IR). Continued elution with this solvent mixture (100 mL) afforded **21** (30 mg). Vacuum distillation (0.005 mm) at an oil bath temperature of 40–45 °C produced pure **21** as a colorless oil: IR (neat) prominent maxima at 1710, 1255, 710 cm^{-1}; UV (C_6H_{14}) max 270 (sh) (ϵ 7700), 258 nm (17 000); ^1H NMR (100 MHz, acetone-d_6) τ 3.23 (1H, d, H^3, $J_{3,4}$ = 8.5 Hz), 4.0–4.4 (6H, m), 4.5–4.7 (1H, m, H^4), 5.7–6.0 (3H, m, H^1 + ethyl), 6.38 (1H, broad d, H^7, $J_{7,1}$ = 17 Hz), 8.75 (3H, t, ethyl); MS m/e 217 (P^+, 100).

Further elution with petroleum ether/ethyl ether (19:1 v/v, 50 mL) yielded an equimolar mixture (20 mg) of **21** and **22**, and final elution with this solvent mixture (50 mL) produced **22** (30 mg). Vacuum distillation (0.005 mm) at an oil bath temperature of 40–45 °C yielded pure **22** as a colorless oil: IR (neat) prominent maxima at 1700, 1275, 685 cm^{-1}; UV (C_6H_{14}) max 254 (ϵ 2450), 227 nm (2480); ^1H NMR[22] (100 MHz, $CDCl_3$) τ 2.98 (1H, broad d, H^4, $J_{4,5}$ = 9.0 Hz), 3.4–4.2 (5H, m), 5.18 (1H, dd, H^1, $J_{1,11}$ = 2.5, $J_{1,9}$ = 3.5 Hz), 5.6–6.1 (3H, m, H^3 + ethyl), 6.47 (1H, dd, H^9, $J_{9,1}$ = 3.5, $J_{8,9}$ = 7.5 Hz), 7.54 (1H, dd, H^8, $J_{8,3}$ = 18, $J_{8,9}$ = 7.5 Hz), 8.70 (3H, t, ethyl); MS m/e 217 (P^+, 42), 144 (100).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.83; H, 6.89; N, 6.48.

Preparation of *N*-Carbethoxy-2,3,4,5-tetrahydro-1-benzazepine (26). To a cold (ca. 0 °C) deaerated (N_2) solution of 2,3,4,5-tetrahydro-1-benzazepine[23] (809 mg, 5.5 mmol) and pyridine (632 mg, 8 mmol) in dry ethyl ether (20 mL) was rapidly added, under nitrogen, ethyl chloroformate (756 mg, 7 mmol) in dry ethyl ether (10 mL), and the resulting suspension was allowed to stir under these conditions for an additional hour. The mixture was then pressure-filtered under nitrogen, and the resulting filtrate was concentrated at ca. 0 °C, first at water aspirator pressure and then at ca. 0.05 mm and a bath temperature of 70–75 °C, to yield pure *N*-carbethoxy-2,3,4,5-tetrahydro-1-benzazepine (**26**) (638 mg, 53%) as a colorless oil; GLPC analysis (conditions A[20]) indicated the presence of a single component (11 min, 30 s). Preparative GLPC furnished a pure sample of **26** as a colorless oil: IR (neat) prominent maxima at 2870, 1700, 1410, 1310, 1280, 1262, 1182, 1050, 1038, 772, 765 cm^{-1}; UV (C_6H_{14}) max 261 (ϵ 327), 229 (3860), 204 nm (14 910); ^1H NMR (60 MHz, $CDCl_3$) τ 2.9 (4H, s), 5.6–6.7 (4H, m), 7.1–7.4 (2H, m), 7.9–9.2 (7H, m); MS m/e 219 (P^+, 74.3), 146 (100).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.01; H, 7.91; N, 6.27.

Catalytic Hydrogenation of *N*-Carbethoxy-2,3,4,5-tetrahydro-1-benzazepine (26) to *N*-Carbethoxy-2-aza-*cis*-bicyclo[5.4.0]undecane (28). A mixture of *N*-carbethoxy-2,3,4,5-tetrahydro-1-benzazepine (**26**) (100 mg, 0.46 mmol) and 5% rhodium-on-charcoal catalyst (300 mg) in dry, freshly distilled tetrahydrofuran (20 mL) was treated with hydrogen at ca. 0 °C and atmospheric pressure. Uptake was complete after 24 h. The mixture was then pressure-filtered (N_2) and the filtrate concentrated at the water aspirator to a colorless oil (113 mg, ~ 100%). GLPC analysis (conditions A) revealed the presence of two components, A (80%, 17 min, 20 s) and B (20%, 13 min, 20 s). Collection of the major component (A) yielded a pure sample of *N*-carbethoxy-2-aza-*cis*-bicyclo[5.4.0]undecane (**28**) as a colorless oil: IR (neat) prominent maxima at 2850, 1670, 1410, 1110, 1081 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) τ 5.6–6.6 (4H, m), 6.7–7.3 (1H, m), 7.8–9.1 (18H, m); MS m/e 225 (P^+, 36.6), 182 (100).

Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.49; H, 10.30; N, 6.41.

Catalytic Hydrogenation of 20 to *N*-Carbethoxy-2-aza-*cis*-bicyclo[5.4.0]undecane (28). A mixture of **20** (128 mg, 0.59 mmol) and 5% rhodium-on-charcoal catalyst (300 mg) in dry, freshly distilled tetrahydrofuran (200 mL) was treated with hydrogen at ca. 0 °C and atmospheric pressure. Uptake was complete after 24 h. The suspension was then pressure-filtered (N_2) and the resulting filtrate concentrated at the water aspirator to a colorless oil (132 mg, 99%). GLPC analysis (conditions A) revealed the presence of a single component (17 min, 20 s) which was collected to yield a pure sample of *N*-carbethoxy-2-aza-*cis*-bicyclo[5.4.0]undecane (**28**) (IR, ^1H NMR).

Dehydrogenation of 21 to *N*-Carbethoxy-1-benzazepine (25). To a stirring solution of **21** (43 mg, 0.198 mmol) in benzene (5 mL) maintained under nitrogen was added at ambient temperature a solution of o-chloranil (49.2 mg, 0.198 mmol) in benzene (2 mL), and the ensuing red solution was allowed to stir under these conditions for an additional 12 h. The resulting orange solution was then concentrated at the water aspirator, the ensuing red-brown residue was dissolved in a minimum amount of ethyl ether, and the solution was placed on a 300 × 12 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g) and maintained at ca. −15 °C. Elution with petroleum ether (100 mL) removed all the impurities so that subsequent elution with petroleum ether/ethyl ether (3:1 v/v, 100 mL) afforded *N*-carbethoxy-1-benzazepine (**25**) (27.2 mg, 64%) as a colorless oil. GLPC analysis (conditions B[20]) revealed the presence of a single component (21 min, 45 s) which was collected to yield a pure sample of **25** as a colorless oil: IR (neat) prominent maxima at 1700, 1380, 1330, 1295, 1060, 1040, 770, 760, 710 cm^{-1}; UV (C_6H_{14}) max 306 (sh) (ϵ 1540), 289 (1720), 245 (sh) (9370), 241 (10 570), 228 (11 800), 204 nm (23 500); ^1H NMR (100 MHz, $CDCl_3$) τ 2.5–2.9 (4H, m), 3.14 (1H, d, J = 11.0 Hz), 3.64 (1H, d, J = 7.0 Hz), 3.76 (1H, dd, J = 11.0, 6.0 Hz), 4.19 (1H, dd, $J \sim 7,6$ Hz), 5.77 (2H, q), 8.74 (3H, t); MS m/e 215 (P^+, 29.7), 142 (100).

Catalytic Hydrogenation of *N*-Carbethoxy-1-benzazepine (25) to *N*-Carbethoxy-2,3,4,5-tetrahydro-1-benzazepine (26). A mixture of **25** (25 mg, 0.12 mmol) and 5% palladium-on-charcoal catalyst (100 mg) in dry, freshly distilled tetrahydrofuran (20 mL) was treated with hydrogen at ca. 0 °C and atmospheric pressure. After uptake was complete (~24 h), the suspension was pressure-filtered (N_2) and the resulting filtrate concentrated at the water aspirator to a colorless oil (~40 mg). GLPC analysis (conditions A) revealed the presence of a single component (11 min, 30 s) which was collected and shown to be *N*-carbethoxy-2,3,4,5-tetrahydrobenzazepine (**26**), identical (IR, ^1H NMR, GLC) with a synthetic specimen (vide supra).

Thermolysis of *N*-Carbethoxy-2-aza-*trans*-bicyclo[5.4.0]-3,5,8,10-tetraene (21): Formation of Dihydrobenzazepine 24. A sample of **21** (15 mg, 0.07 mmol) was dissolved in ethyl ether (0.5 mL), and the resulting solution was injected into a gas chromatograph (conditions B) in 50-μL portions. The single component observed (21 min, 5 s) was collected at 0 °C as a colorless oil, shown to be the dihydrobenzazepine **24**: IR (neat) prominent maxima at 1705, 1400, 1310, 782, 760 cm^{-1}; UV (C_6H_{14}) max 294 (sh) (ϵ 680), 285 (930), 252 (9070), 227 nm (22 700); ^1H NMR (100 MHz, $CDCl_3$) τ 2.6–2.9 (4H, *m*), 3.60 (1H, d, H^5, $J_{5,4}$ = 12.5 Hz), 4.05 (1H, dm, H^4, $J_{4,5}$ = 12.5 Hz), 5.81 (2H, q, ethyl), 6.3 (2H, broad m, H^2), 7.4 (2H, broad m, H^3), 8.76 (3H, t, ethyl); MS m/e 217 (P^+, 100).

Dehydrogenation of *N*-Carbethoxy-2-aza-*cis*^{1,9},*trans*^{3,8},-*cis*^{8,9}-tricyclo[7.2.0.0^{3,8}]undeca-4,6,10-triene (22) to 23. To a stirring solution of **22** (135 mg, 0.62 mmol) in benzene (5 mL) maintained under nitrogen was added at ambient temperature a solution of o-chloranil (152 mg, 0.62 mmol) in benzene (3 mL), and the resulting red solution was allowed to stir under these conditions for ca. 12 h. The ensuing orange solution was then concentrated at the water

aspirator, and the red-orange residue thus obtained was dissolved in a minimum amount of ethyl ether and the solution placed on a 300 × 12 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g). Elution with petroleum ether (100 mL) removed the impurities so that subsequent elution with petroleum ether/ethyl ether (3:1 v/v, 100 mL) produced **23** (81 mg, 53%). GLPC analysis (conditions A) indicated the presence of a single component (16 min, 15 s) which was collected to furnish a pure sample of **23** as a colorless oil: IR (neat) prominent maxima at 1700, 1480, 1405, 1380, 1280, 1200, 1150, 1070, 770, 760 cm^{-1}; UV (C_6H_{14}) max 292 (ϵ 2710), 283 (2540), 278 (sh) (2018), 255 (sh) (9660), 247 (11 970), 243 (sh) (11 240), 212 (sh) (26 820), 208 nm (31 150); ^1H NMR (100 MHz, $CDCl_3$) τ 2.15 (1H, broad s), 2.7–3.2 (3H, m), 3.58 (1H, dd, H^7, $J_{7,6}$ = 3, $J_{7,1}$ = 1.5 Hz), 3.82 (1H, d, H^6, $J_{6,7}$ = 3Hz), 4.82 (1H, dd, H^1, $J_{1,5}$ = 4, $J_{1,7}$ = 1.5 Hz), 5.5–5.9 (3H, m, H^6 + ethyl), 8.64 (3H, t, ethyl); MS *m/e* 215 (P^+, 39.7), 142 (100).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.52; H, 6.09; N, 6.51. Found: C, 72.64; H, 6.20; N, 6.69.

Preparation of *N*-Carbethoxy-2,3-diazabicyclo[3.2.0]hepta-3,6-diene (8).[24] A solution of *N*-carbethoxy-1,2-diazepine[25] (1.0 g, 0.006 mol) in deaerated (N_2) ethyl ether (200 mL) was irradiated at ambient temperature under a nitrogen atmosphere through a Pyrex filter with a Hanovia 450-W lamp for a period of 6 days. The solution was then concentrated at the water aspirator at ambient temperature and the resulting yellow oil placed on a 400 × 20 mm column wet packed (petroleum ether) with activity III Woelm neutral alumina (40 g). Elution with petroleum ether (100 mL) removed residual reactant so that subsequent elution with petroleum ether (150 mL) produced pure *N*-carbethoxy-2,3-diazabicyclo[3.2.0]hepta-3,6-diene (8) (0.9 g, 90%) as a pale yellow liquid (^1H NMR, IR).[11]

Reaction of *N*-Carbethoxy-2,3-diazabicyclo[3.2.0]hepta-3,6-diene (8) with α-Pyrone (3): Formation of B. A deaerated (N_2) solution of *N*-carbethoxy-2,3-diazabicyclo[3.2.0]hepta-3,6-diene (8) (2.0 g, 0.012 mol) and α-pyrone (3) (6.0 g, 0.063 mol) in benzene (6 mL) was heated at 65 °C under nitrogen for 40 h. The solution was concentrated at the water aspirator, and unreacted α-pyrone was then removed at a bath temperature of 50–55 °C and 0.1 mm to yield a dark residue. This residue was dissolved in a minimum amount of ethyl ether and the resulting solution placed on a 300 × 12 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (20 g) and maintained at ca. −10 °C. Elution with ethyl ether (300 mL) removed the impurities so that subsequent elution with chloroform (200 mL) afforded B (2.1 g, 64%) as a colorless oil.

Pyrolysis of B: Formation of 9-Carbethoxy-9,10-diaza-*cis*^{1,9},*cis*^{2,7},*trans*^{1,2},*trans*^{7,8}-tricyclo[6.3.0.0^{2,7}]undeca-3,5,10-triene (9), 9-Carbethoxy-9,10-diaza-*cis*^{1,8},*cis*^{2,7},*cis*^{1,2},*cis*^{7,8}-tricyclo[6.3.0.0^{2,7}]undeca-3,5,10-triene (9),[13] and *N*-Carbethoxypyrazole (10). A sample of 8 (2.0 g, 0.008 mol) was pyrolyzed dry under vacuum (0.05 mm) at a bath temperature of 125 °C in a short-path distillation unit in four equal portions. Gas evolution was observed, and the distillate was collected in a flask maintained at −78 °C (dry ice/acetone). The resulting colorless oil was then placed on a 600 × 17 mm jacketed column wet packed (petroleum ether) with activity III Woelm neutral alumina (60 g) and maintained at ca. −15 °C. Elution with petroleum either/ethyl ether (1:5 v/v, 150 mL) afforded *N*-carbethoxypyrazole (**10**)[12] (340 mg, 32%); ^1H NMR (60 MHz, $CDCl_3$) τ 1.82 (1H, d, H^5, $J_{5,4}$ = 3.0 Hz), 2.23 (1H, m, H^3), 3.56 (1H, dd, H^4, $J_{4,3}$ = 1, $J_{4,5}$ = 3.0 Hz), 5.45 (2H, q), 8.54 (3H, t); MS *m/e* 140 (P^+, 16). Continued elution with the same solvent mixture (120 mL) afforded **9** (370 mg, 22.5%). Distillation of this material at a bath temperature of 60–65 °C and 0.02 mm produced a pure sample of **9** as a colorless oil: IR (neat) prominent maxima at 2900, 1730, 1700, 1580, 1420 cm^{-1}; UV (CH_3CN) max 280 (sh) (ϵ 1940), 246 nm (10 140); ^1H NMR (60 MHz, $CDCl_3$) τ 2.93 (1H, d, H^{11}, $J_{11,1}$ = 2.0 Hz), 4.0–4.7 (4H, m, H^3 + H^4 + H^5 + H^6), 5.38 (1H, dd, H^8, $J_{8,1}$ = 8.5, $J_{8,7}$ = 3 Hz), 5.71 (2H, q, ethyl), 6.18 (1H, ddd, H^1, $J_{1,8}$ = 8.5, $J_{1,11}$ = 2.0, $J_{1,2}$ = 3.3 Hz), 6.6–6.9 (2H, m, H^2 + H^7), 8.67 (3H, t, ethyl); MS *m/e* 140 (pyrazole **10**, 12), 78 (100).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.84. Found: C, 65.97; H, 6.36; N, 12.98.

Further elution with the same solvent combination (50 mL) afforded an equimolar mixture of **9** and what is presumed to be the syn isomer **9′**[13] (40 mg), while final elution with petroleum ether/ethyl ether (1:5 v/v, 100 mL) afforded a pure sample of the presumed isomer **9′** (58 mg, 3.5%) as a colorless liquid: ^1H NMR (60 MHz, $CDCl_3$) τ 3.10 (1H, d, H^{11}, $J_{11,1}$ = 2.0 Hz), 4.0–4.8 (4H, m, H^3 + H^4 + H^5 + H^6), 4.8–5.2 (1H, m, H^8), 5.73 (2H, q, ethyl), 5.7–6.6 (3H, m, H^1 + H^2 + H^7), 8.66 (3H, t, ethyl).

Thermolysis of 9: Formation of *N*-Carbethoxypyrazole (10) and Benzene. A vacuum-sealed (ca. 0.005 mm) medium-wall NMR tube containing a degassed solution of **9** (75 mg, 0.344 mmol) in acetonitrile-d_3 (ca. 0.4 mL) was heated in a bath of boiling toluene (109.7 °C), and the consumption of the reactant was quantitatively monitored by ^1H NMR spectroscopy at ambient temperature to yield k = $3.69 \pm 0.20 \times 10^{-4}$ s^{-1} ($\Delta G^{\ddagger}$ = 28.6 kcal/mol). Heating was continued for a total of 7 h, at which time ^1H NMR analysis showed only **10** and benzene.

Under a similar set of thermolysis conditions, a sample of what is presumed to be **9′** produced a clean two-component mixture consisting (^1H NMR) of benzene and **10.**

Direct Irradiation of 9 at −78 °C: Formation of *N*-Carbethoxypyrazole (10). A solution of **9** (50 mg, 0.229 mmol) in deaerated (N_2) ethyl ether/petroleum ether (1:5 v/v, 50 mL) was irradiated under nitrogen with a Hanovia low-pressure mercury lamp at −78 °C (dry ice/acetone) for 1 h. Concentration at ca. 0 °C at the water aspirator afforded *N*-carbethoxypyrazole (**10**) (30 mg, 93.5%) (^1H NMR).

Under similar conditions of irradiation, an equimolar mixture of **9** and the presumed syn isomer **9′**[13] also produced **10** (^1H NMR) as the only nonvolatile product.

Reaction of Oxepin (11) with 2,4-Dimethyl-3,4-diphenylcyclopentadienone (12): Formation of 13. A solution of oxepin (**11**)[26] (470 mg, 5.0 mmol) and 2,5-dimethyl-3,4-diphenylcyclopentadienone (**12**) (1.3 g, 2.5 mmol) in deaerated (N_2) benzene (10 mL) was maintained at the reflux temperature under nitrogen for 48 h. Removal of the solvent at the water aspirator afforded a pale yellow solid which was dissolved in the minimum amount of chloroform and placed on a 300 × 12 mm jacketed column maintained at ca. −15 °C and wet-packed (petroleum ether) with activity III Woelm neutral alumina (20 g). Elution with petroleum ether (100 mL) and then petroleum ether/ethyl ether (9:1 v/v, 200 mL) gave **13** as a foamy solid which was recrystallized from hot ethanol to produce a pure specimen of white needles: mp 164–165 (dec); IR (KBr) prominent maxima at 2900, 1760, 1660, 1440, 1350, 1140, 970, 910, 820, 810, 780, 740, 730, 700 cm^{-1}; UV (hexane) max 257 (ϵ 9100), 222 nm (18 700); ^1H NMR (60 MHz, $CDCl_3$) τ 2.9 (10H, m, phenyls), 3.55 (2H, d, H^2(H^7), $J_{2,3}$ = 8.0 Hz), 5.20 (2H, ddd, H^3(H^6), $J_{3,2}$ = 8.0, $J_{3,4}$ = 2.5, $J_{3,5}$ = 1.5 Hz), 7.08 (2H, m, H^4(H^5)), 8.60 (6H, s, methyls); MS *m/e* 354 (P^+, 24.4), 260 (100).

Anal. Calcd: C, 84.72; H, 6.25; O, 9.08. Found: C, 84.63; H, 6.40; O, 9.03.

Thermolysis of Cycloadduct 13. A vacuum-sealed (ca. 0.005 mm) Pyrex tube (3 mm × 25 cm) containing a solution of **13** (354 mg, 1 mmol) in deaerated (N_2) benzene (10 mL) was immersed in a bath of boiling ethylene glycol (ca. 192 °C) for 10 min. The tube was then cooled to −78 °C (dry ice/acetone) and filed open, and the bright red solution was concentrated at the water aspirator to yield a dark semisolid residue which we dissolved in the minimum amount of chloroform and placed on a 500 × 15 mm jacketed column maintained at ca. −15 °C and wet packed (petroleum ether) with activity III Woelm neutral alumina (40 g). Elution with petroleum ether (100 mL) afforded a pure specimen of **11** (50 mg) (^1H NMR, IR). Continued elution with petroleum ether/ethyl ether (9:1 v/v, 200 mL) afforded pure **12** (200 mg) as a white solid: mp 182 °C (IR).

Similar results were obtained on conducting the thermolysis of **13** at 163 °C (boiling mesitylene).

Preparation of 2-Oxabicyclo[3.2.0]hepta-3,6-diene (15).[27] A solution of oxepin (2.2 g, 0.023 mol) in freshly distilled, deaerated (N_2) ethyl ether was equally distributed in eight 125 × 15 mm Pyrex test tubes. The test tubes were tightly capped under nitrogen and irradiated for 2 days at ambient temperature in a Rayonet photochemical reactor with a bank of 16 3500-Å lamps, leading to slow decoloration of the initially yellow ether solution. The contents of the test tubes were combined, and the colorless photosylate was concentrated at atmospheric pressure and ca. 31 °C to yield a colorless mobile liquid which was vacuum distilled at the water aspirator and ambient temperature to produce a pure sample of 2-oxabicyclo[3.2.0]hepta-3,6-diene (**15**) (2.0 g, 95%): ^1H NMR (60 MHz, $CDCl_3$) τ 3.33 (1H, pseudo-t, J = 3.0 Hz), 3.70 (1H, d, J = 3.0 Hz), 4.00 (1H, dd, J = 1.5, 3.0 Hz), 4.80 (1H, m), 6.25 (2H, m).

Reaction of 2-Oxabicyclo[3.2.0]hepta-3,6-diene (15) with 2,5-Dimethyl-3,4-diphenylcyclopentadienone (12): Formation of 16. A vacuum-sealed (ca. 0.005 mm) Pyrex tube (3 mm × 25 cm) containing a solution of 2-oxabicyclo[3.2.0]hepta-3,6-diene (850 mg, 8 mmol) and **12** (1.4 g, 4 mmol) in deaerated benzene (6 mL) was maintained at ca. 77 °C (boiling ethyl acetate) for 2 h. The tube was then cooled to −78 °C (dry ice/acetone) and filed open, and the colorless solution concentrated at the water aspirator to produce a white foamy residue (2.2 g, ~ 100%). Two recrystallizations of this material from ethanol afforded analytically pure **16** as white needles: mp

142–143 °C; IR ($CHCl_3$) prominent maxima at 2900, 1760, 1610, 1605, 1480, 1440, 1380, 1140, 1050, 950, 705 cm^{-1}; UV (C_6H_{14}) max 258 (ϵ 10 000) and 222 nm (20 000); ^1H NMR (100 MHz, $CDCl_3$)[22] τ 2.80 (5H, m, phenyl), 2.96 (5H, m, phenyl), 3.54 (1H, dd, H^3, $J_{3,4}$ = 2.5 H, $J_{3,5}$ = 1.0 Hz), 4.88 (1H, pseudo-t, H^4, $J_{3,4} = J_{4,5}$ = 2.5 Hz), 5.38 (1H, dd, H^1, $J_{1,5}$ = 7.0, $J_{1,7}$ = 2.0 Hz), 6.85 (1H, m, H^5), 7.18 (1H, broad d, H^7, $J_{7,6}$ = 8.5 Hz), 7.48 (1H, dd, H^6, $J_{6,7}$ = 8.5, $J_{5,6}$ = 2.0 Hz), 8.70 (3H, s, methyl), 8.74 (3H, s, methyl); MS *m/e* 354 (P^+, 4.3), 94 (100).

Anal. Calcd for $C_{23}H_{22}O_2$: C, 84.71; H, 6.27; O, 9.01. Found: C, 84.52; H, 6.34; O, 8.79.

Thermal Fragmentation of 16. A vacuum-sealed (ca. 0.005 mm) NMR tube containing a solution of **16** (100 mg, 0.685 mmol) in benzene-d_6 (ca. 0.4 mL) was maintained in a bath of boiling ethylene glycol (ca. 192 °C), and the contents were periodically monitored by ^1H NMR, revealing the presence of furan and 1,4-dimethyl-2,3-diphenylbenzene (**17**). After a total in-bath time of 4 h, the tube was cooled to −78 °C (dry ice/acetone) and filed open, and its contents concentrated at the water aspirator to yield **17** (65 mg, 95%) as a white solid. One recrystallization of this material from ethanol afforded a pure specimen as white needles: mp 106–107 °C; MS *m/e* 258 (P^+, 100); identical in all respects (mp, IR) with authentic material.[28] Similar results were obtained when the thermolysis of **16** was conducted at 163 °C (boiling mesitylene).

The ^1H NMR-determined thermal half-life of **16** is 18 min at 192 °C and 4 h at 163 °C.

Reaction of Oxabicyclo[3.2.0]hepta-3,6-diene (15) with α-Pyrone (3): Formation of C. A vacuum-sealed (three freeze–thaw cycles) Pyrex tube (3 mm × 25 cm) containing a solution of oxabicyclo[3.2.0]hepta-3,6-diene (**15**) (1.5 g, 16 mmol) and α-pyrone (**3**),[29] (9.6 g, 0.1 mol) in benzene (5 mL) was maintained in a bath of boiling ethyl acetate (77 °C) for 3 days. The tube was then cooled to −78 °C (dry ice/acetone) and filed open, and its contents concentrated at the water aspirator to yield a yellow oil consisting of C and unreacted α-pyrone (^1H NMR). The α-pyrone (6.7 g) was removed by vacuum distillation (ca. 0.01 mm) at a bath temperature of ca. 50 °C, the residue was dissolved in ethyl ether (50 ml), and the resulting solution was pressure-filtered (N_2) through a layer of Florisil (30 g) to remove polymer. The filtrate was concentrated at the water aspirator, and the resulting yellow mobile liquid was heated at ca. 50 °C under vacuum (ca. 0.01 mm) to remove any residual α-pyrone, yielding C (2.0 g) as the residue.

Pyrolysis of C: Formation of 9-Oxa-*cis*^{1,8},*cis*^{2,7},*trans*^{7,8}-tricyclo[6.3.0.0^{2,7}]undeca-3,5,10-triene (18). A sample of C (2.0 g, ~10.5 mmol) was pyrolyzed dry under vacuum (0.05 mm) at a bath temperature of 170 °C in a short-path distillation unit. Gas evolution was observed, the yellow distillate was collected in a flask maintained at −78 °C (dry ice/acetone) and dissolved in the minimum amount of ethyl ether, and the resulting solution was placed on a 760 × 15 mm jacketed column wet packed (petroleum ether) with activity II Woelm neutral alumina (60 g) and maintained at ca. −15 °C. Elution with petroleum ether (300 mL) afforded **18** (490 mg, 21%) as an air-sensitive colorless oil. An analytical sample of **18** was obtained by vacuum distillation (0.01 mm) at a bath temperature of ca. 30 °C: IR (neat) prominent maxima at 2900, 1600, 1400, 1380, 1300, 1270, 1250, 1170, 1130, 1050, 1010, 1000, 980, 870, 760, 700 cm^{-1}; UV (C_6H_{14}) max 283 (ϵ 1750), 220 nm (6250); ^1H NMR (60 MHz, $CDCl_3$) τ 3.65 (1H, dd, H^3, $J_{3,4}$ = 3.0, $J_{3,5}$ = 1.5 Hz), 4.28 (4H, m, $H^3 + H^4 + H^5 + H^6$), 4.80 (1H, pseudo-t, H^4, $J_{3,4} = J_{4,5}$ = 3.0 Hz), 5.08 (1H, dd, H^1, $J_{1,5}$ = 7.5, $J_{1,11}$ = 4.0 Hz), 6.50 (1H, m, H^5), 6.90 (1H, dt, H^{11}, $J_{11,6}$ = 12.0, $J_{1,11} = J_{10,11}$ = 3.0 Hz), 7.08 (1H, dt, H^6, $J_{6,11}$ = 12.0, $J_{6,5} = J_{6,7}$ = 3.0 Hz); MS *m/e* 146 (P^+, 1), 78 (100).

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.88; O, 10.94. Found: C, 82.10; H, 6.96; O, 11.05.

Continued elution with petroleum ether/ethyl ether (9:1 v/v, 400 mL) produced a colorless viscous oil (ca. 400 mg) believed to be a C_4H_4 homologue of **18**. GLPC analysis of this oil (conditions C[20]) revealed the presence of a single component (~35 min) which was collected: IR (neat) prominent maxima at 2800, 2500, 1600, 1390, 1340, 1315, 1290, 1150, 1125, 1050, 1010, 985, 945, 930, 865, 835, 800, 760, 720, 690 cm^{-1}; UV (C_6H_{14}) max 266 (sh) (ϵ 1680), 258 (3860), 249 (sh) (1840); ^1H NMR (100 MHz, $CDCl_3$) τ 3.55 (1H, dd, J = 1.5, 3.0 Hz), 4.10 (4H, m), 4.65 (2H, broad d, J = 10.0 Hz), 4.82 (1H, pseudo-t, J = 3.0 Hz), 5.18 (2H, dd, J = 4.0, 7.0 Hz), 6.8–7.2 (4H, m); MS *m/e* 198 (P^+, <1), 78 (100).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.66; H, 7.16.

Thermolysis of 18: Formation of Furan (19) and Benzene. A vacuum-sealed medium-wall NMR tube containing a degassed solution of **18** (80 mg, 0.578 mmol) in acetonitrile-d_3 (ca. 0.4 mL) was heated in a bath of boiling toluene (110.4 °C), and the consumption of reactant **18** was quantitatively monitored by ^1H NMR spectroscopy at ambient temperature to yield $k = 4.49 \pm 0.39 \times 10^{-4}$ s^{-1} ($\Delta G^{\ddagger}$ = 28.5 kcal/mol). Heating was continued for a total of 6 h, at which time ^1H NMR analysis showed only furan and benzene.

Direct Irradiation of 18 at 0 °C: Formation of Furan (19) and Benzene. An NMR tube containing a deaerated (N_2) solution of **18** (50 mg, 0.342 mmol) in acetone-d_6 (ca. 0.4 mL) was placed in an ice bath, and its contents were irradiated with a 450-W Hanovia mercury arc along the external surface of a quartz immersion well for 10 h. ^1H NMR analysis of the resulting photolysate showed the presence of only furan and benzene.

Acknowledgment. We thank the National Science Foundation (CHE76-06462 A01) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support and Mr. Larry McCandless for the determination of the 100-MHz ^1H NMR spectra.

Registry No.—**2,** 2955-79-5; **3,** 504-31-4; **4,** 64056-59-3; **5,** 64045-80-3; **6,** 64082-14-0; **7,** 4277-64-9; **8,** 42068-20-2; **9,** 34056-60-6; **8′,** 64090-69-3; **10,** 10199-59-4; **11,** 291-70-3; **12,** 26307-17-5; **13,** 64056-61-7; **15,** 13920-54-2; **16,** 64082-13-9; **17,** 13102-23-3; **18,** 64090-70-6; **20,** 64056-63-9; **21,** 64056-65-1; **22,** 64090-68-2; **23,** 64056-52-6; **24,** 64056-53-7; **25,** 64056-54-8; **26,** 64056-55-9; **28,** 64082-15-1; A isomer I, 64056-64-0; A isomer II, 64056-58-2; B, 64056-56-0; C, 64056-57-1; 3-carbethoxypyrrole, 37964-17-3; D, 64045-81-4; 2,3,4,5-tetrahydro-1-benzazepine, 1701-57-1; ethyl chloroformate, 541-41-3; *N*-carbethoxy-1,2-diazepine, 17377-08-1.

References and Notes

(1) The term is used here to distinguish from annelated, dehydro, and bridged members of the family.
(2) For reviews on the subject see: (a) A. G. Anastassiou, *Acc. Chem. Res.*, **5,** 281 (1972); (b) A. G. Anastassiou, *Pure Appl. Chem.*, **44,** 691 (1975).
(3) For a review on the subject see: G. Schroder, *Pure Appl. Chem.*, **44,** 925 (1975).
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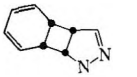
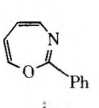
(13) Upon careful chromatographic processing of the photolysate one also

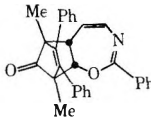


9′

isolates small quantities (ca. 3.5% yield) of a third component tentatively formulated as **9′** (see Experimental Section).
(14) E. Vogel and H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **6,** 385 (1967).
(15) It is notable in this connection that the azoxepin shown in i was recently[6]

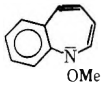


i



ii

shown to yield tricyclic cycloadduct ii on thermal exposure to dienone **12**.
(16) J. M. Holovka and P. D. Gardner, *J. Am. Chem. Soc.*, **89,** 6390 (1967).
(17) The syn counterpart of **18** was recently prepared photochemically from benzene and furan: J. C. Berridge, D. Bryce-Smith, A. Gilbert, and T. S. Cantrell, *J. Chem. Soc., Chem. Commun.*, 611 (1975), and references cited therein. We are grateful to Professor A. Gilbert for kindly supplying us with detailed information relating to the preparation and characterization of this substance.
(18) As far as we can ascertain, the compound tentatively formulated as iii (V.



iii

Rantenstrauch, *Chem. Commun.*, 1122 (1969)) constitutes the sole published reference to an "unrestricted" 1-benzazepine.

(19) A substance believed to be the *N*-cyano counterpart of **25** was prepared in these laboratories by H. Yamamoto (Ph.D. Dissertation, 1973).

(20) All melting points and boiling points are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 137B spectrophotometer, NMR spectra were recorded on a Varian A-60 or XL-100 spectophotometer, ultraviolet spectra were determined on a Cary 18 spectrophotometer, and mass spectra were obtained with a Hitachi Perkin-Elmer Model RMU-6E single-focusing spectrometer. Gas chromatographic analyses were performed on a Varian Aerograph A90-P3 instrument operating under the following conditions: (A) 7 ft × 0.25 in aluminum column packed with SE-30 on Chromosorb W at 188 °C with the vaporizer at 205 °C, the detector at 210 °C, and a helium flow of 100 cm^3/min; (B) same as in (A) except the column temperature was 177 °C; (C) 6 ft × 0.25 in aluminum column packed with SF-96 on Chromosorb W at 140 °C with the vaporizer at 150 °C, the detector at 170 °C, and a helium flow of 85 cm^3/min. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All solvents were ACS Reagent Grade and were used without further purification, except for ethyl ether and tetrahydrofuran which were freshly distilled from lithium aluminum hydride.

(21) This procedure constitutes a modification of that described in ref 10.

(22) Proper analysis of this spectrum required the use of double irradiation.

(23) B. D. Astill and V. Boekelheide, *J. Am. Chem. Soc.*, **77**, 4079 (1955).

(24) This procedure represents a modification of that described in ref 11.

(25) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.*, **35**, 433 (1970); T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *ibid.*, **35**, 426 (1970).

(26) E. Vogel, W. A. Boll, and H. Günther, *Tetrahedron Lett.*, 609 (1965).

(27) This procedure was developed on the basis of brief descriptions given in ref 16.

(28) C. F. Allen, R. W. Ryan, and J. A. Van Allen, *J. Org. Chem.*, **27**, 778 (1962), and references cited therein.

(29) It is essential that the α-pyrone employed in this reaction be freshly distilled from potassium carbonate. Failure to do so results in the exothermic rearrangement of **15** to phenol.

Benzo- and Indoloquinolizine Derivatives. 13.[1] Conformation of the Perhydrobenzo[*c*]quinolizines

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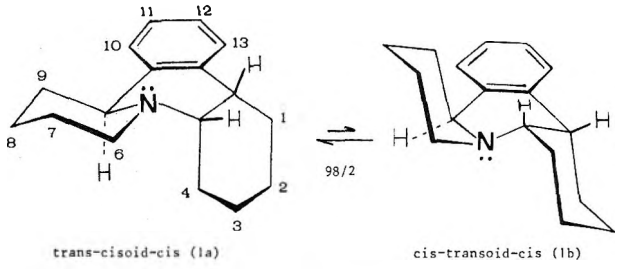
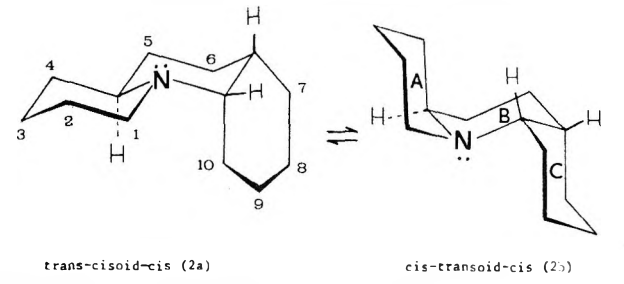
The conformation of three isomers of perhydrobenzo[c]quinolizine is determined by the study of their ^{13}C and 270-MHz ^1H NMR spectra. The previous cis-transoid-cis conformation assignment for one of the isomers is shown to be erroneous. The proposed trans-cisoid-cis conformation is further corroborated by molecular-mechanics calculations.

We recently were able to show by variable-temperature ^{13}C NMR that in the *rel*-(4aβ,9aα,13bβ) isomer (**1**) of 1,2,3,4,4a,6,7,8,9,13b-decahydro-9a*H*-pyrido[1,2-*f*]phenanthridine the trans-cisoid-cis conformation (**1a**) is strongly



favored over the cis-transoid-cis one (**1b**)[1] ($\Delta G°_{243}$ = 7.5 kJ/mol (1.8 kcal/mol)).

On the other hand, Ohki[2] reported the cis-transoid-cis isomer (**2b**)[3] as the preferred conformation for the analogous isomer of perhydrobenzo[*c*]quinolizine (**2**). This result seemed

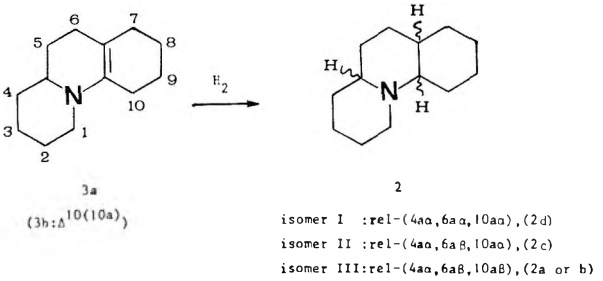


improbable to us since the trans-cisoid-cis conformation **2a** does not experience the destabilizing allylic strain[6] which occurs between the C-9 and C-10 protons and between the C-1 and C-13 protons in **1a**. Therefore, we expected the trans-cisoid-cis conformation to be even more favored in **2** than **1**.

In the carbocyclic analogues, the trans-cisoid-cis conformation of perhydrophenanthrene has been calculated to be more stable than the cis-transoid-cis isomer by 6.7–7.5 kJ/mol (1.6–1.8 kcal/mol).[7,8] We parametrized the molecular-mechanics calculations for the introduction of a nitrogen atom,[9] taking into account the lone-pair influence as described by Allinger[10] for oxygen compounds. These calculations indicate a net preference for **2a** over **2b** by 5.4–6.7 kJ/mol (1.3–1.6 kcal/mol), depending on the importance of the lone-pair interaction parameters.

In order to solve the ambiguity, we reinvestigated the conformational equilibrium in **2**, mainly by the use of ^{13}C NMR.

Synthesis of Compounds. Three isomers (I–III) of **2** were



obtained by the reduction of the enamine **3**[2] or its perchlorate salt (Table I). The fourth isomer, which was present in a very minute amount, could not be isolated.

The excellent agreement in the isomeric composition for the catalytic and the sodium borohydride reductions, along with the gas liquid chromatographic data, established the identity of the isomers as those reported by Ohki.[2]

Conformational Analysis. Infrared Spectroscopy. As already observed by Ohki,[2] isomers I and II show strong Bohlmann bands in the 2700–2800-cm^{-1} region of their in-

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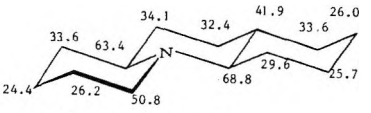
Table I. Reduction Results of 3

Compd	Catalyst	Isomer ratio[a] I	II	III	IV
3	PtO_2/H_2	63	30	5	2
	$NaBH_4/AcOH$	40	42	10	8
3·$HClO_4$	$LiAlH_4$	40	57	3	
	K-selectride (−50 °C)	47	11	42	

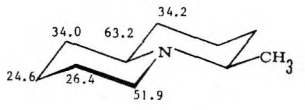
[a] The relative ratios were determined by GLC. The isomer numbers (I–IV) correspond to the order of elution from the column.[2]

frared spectra, whereas the spectrum of isomer III shows only very weak absorptions in this region. This, however, does not allow the conclusion that the quinolizidine conformation of isomer III is cis, as was done previously.[2] A *trans*-quinolizidine with an axial substituent on the carbon α to the nitrogen, as is the case in the trans-cisoid-cis conformation (**2a**) of isomer III, is expected to absorb weakly in the Bohlmann region.[11,12]

4 [13]



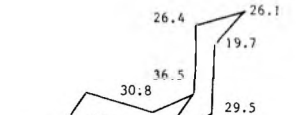
trans-transoid-trans (2c) isomer II



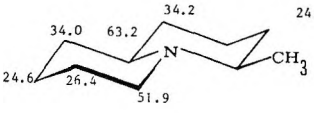
5 [14]

^{13}C NMR. The signals of the three methine carbons were distinguished on the basis of their multiplicity in the gated decoupled spectra, while the lowest field triplet signal was assigned to C-1.

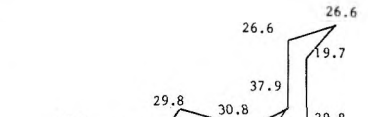
The spectrum of isomer II, which was assigned the *rel*-(4aα,6aβ,10aα) configuration by Ohki,[2] was interpreted with the aid of the published chemical shifts for *N*-methyl-*trans*-perhydroquinoline (**4**)[13] and for *cis*-4-methylquinolizidine (**5**).[14] Excellent agreement with the experimental values is obtained, thus confirming trans-transoid-trans conformation



6 [15]



5 [14]



trans-transoid-cis (2d) isomer I

2c for this compound.

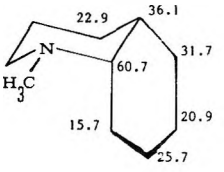
In the same way, the signals of isomer I were assigned and the trans-transoid-cis conformation **2d** could be confirmed.

The good agreement between the models and the experimental values for these two isomers prove the reliability of these comparisons. This method can therefore be used to determine the preferred conformation of isomer III (**2a** or **2b**). The ^{13}C spectrum of this latter isomer is temperature independent over a range from +50 to −50 °C, except for a general −0.3-ppm shift. This indicates that the compound is even more conformationally homogeneous than **1**. The chemical shifts are in close agreement with those of *cis*-4-methylqui-

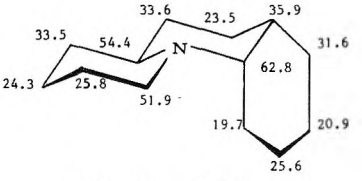
Table II. 270-MHz ^{1}H NMR Parameters for Isomer III

Shift, δ	Assignment	Multiplicity (*J*, Hz)[a]
2.86	H-10a	d (12.4) of t (4.4)
2.71	H-1_{eq}	Broad d (11.5)
2.59	H-1_{ax}	t (11.5) of d (3.1)
2.40	H-4a	t (10.6) of t (2.7)
2.18	H-10_{eq}	Multiplet

[a] The spacings were read directly from the spectrum.



7 [15,16]



trans-cisoid-cis (2a) isomer III

nolizidine (**5**)[14] and the *N*-methyl-*cis*-perhydroquinoline conformer (**7**, Figure 6).[15]

As models for the cis-transoid-cis conformation (**2b**) of isomer III, the ring C values of **2d** were taken, together with the ring A values of the *rel*-(4aα,9aβ,13bβ) isomer of **1**, which has the cis-transoid-trans conformation.[1] The C-10a value of **2d** has to be corrected then for a double γ interaction.[17] In no way, however, can these model shifts be matched to the experimental ones without giving at least two or three strongly deviating values. Therefore, this conformer can be excluded.

A comparison of the chemical shifts of isomers I and II with those of their carboxcyclic analogues[17] reveals the presence of the shielding effect of the nitrogen atom on antiperiplanar γ carbons.[18] As also noted by Eliel,[13,15] the antiperiplanar lone-pair shifts C-10 in **2a** upfield by 3.9 ppm, compared to the perhydrophenanthrene value.[17] No indication was found, however, for a deshielding of the syn-axial carbons by the lone pair[19] in **2d**. The approximate equality of a nitrogen lone pair and a carbon–hydrogen γ effect was also observed by Wenkert.[20]

270-MHz ^{1}H NMR. The ^{1}H NMR spectra of isomers I and II are very uninformative. In both cases, the only signal which can be assigned is the H-1 equatorial signal at δ 3.10 and 3.35, respectively. This agrees with the chemical shift of the equivalent proton in the isomers of **1**.[11] For isomer II, another equatorial proton signal at δ 2.15 is separated from the broad hump between 1 and 2 ppm. For isomer I, a three-proton signal resonates between δ 1.95 and 2.15. The spectrum of isomer III, however, shows several well-separated signals which were assigned by double-resonance experiments (Table II).

The chemical shift of H-10a is almost exactly the same as in **1a**.[11] The multiplicity indicates its axial position in the C ring and thus also confirms the trans-cisoid-cis conformation for this isomer. The small chemical-shift difference between the H-1_{eq} and H-1_{ax} signals, which is also observed in the trans-cisoid-cis conformation (**1a**),[11] is exceptional for a *trans*-quinolizidine. The geminal coupling of 11 Hz is, however, in agreement with the trans conformation.[11,21] The angular quinolizidine proton H-4a is deshielded from the normal quinolizidine value (1.7–2.0 ppm[22]) by the C10–C10a bond.[23]

In summary, the study of the ^{13}C and ^{1}H NMR spectra of the perhydrobenzo[c]quinolizines (2) has enabled us to show that in this compound, as in the benzo-substituted analogue (1), the preferred conformation is the trans-cisoid-cis one. This is in agreement with the energies obtained by molecular-mechanics calculations. Once more,[24] it has been shown that an assignment of a *cis*-quinolizidine conformation, based upon the absence of strong Bohlmann absorptions in the infrared spectrum, should be made with due caution.

Experimental Section

The NMR spectra were recorded on Bruker HX 270 (^{1}H) and Bruker WH 90(^{13}C) pulsed-Fourier-transform spectrometers in $CDCl_3$ solutions as described previously.[1] The infrared spectra were recorded on a Perkin-Elmer 257 spectrometer as dispersions in KBr.

2-(2-Pyridylethyl)cyclohexanone Ethylene Ketal (8) was prepared as described by Ohki[2] using ~0.33 equiv of *p*-toluenesulfonic acid; yield 60%.

2-(2-Piperidylethyl)cyclohexanone Ethylene Ketal (9). To a solution of 10 g of 8 in 100 mL of absolute ethanol, 15 g of sodium was added in portions. This required about 2 h. Water was then added, and most of the ethanol was evaporated under vacuum. Extraction with benzene, drying over $MgSO_4$, and distillation gave 7.8 g (76%) of a colorless oil; bp 132 °C (0.8 mm).

Δ^{6a}- and $\Delta^{10(10a)}$-Dehydroperhydrobenzo[*c*]quinolizine (3a, b) was prepared as described by Ohki[2] by refluxing 9 in 20% HCl for 2 h. Distillation of the enamine at 70 °C (0.5 mm) yielded 71% of a colorless oil. The ^{1}H NMR (270 MHz, $CDCl_3$) indicated the vinylic proton of the $\Delta^{10(10a)}$ isomer at δ 4.6, integrating for about 10% of a proton. The ^{13}C spectrum (22.63 MHz, $CDCl_3$) showed two sets of signals in a 90:10 proportion. The literature[2,25] reports a 4:1 composition of the isomeric mixture.

Perhydrobenzo[*c*]quinolizine (Perhydropyrido[1,2-*a*]quinoline) (2). Method 1. Catalytic and $NaBH_4$ reductions of **3a** or **3b** were carried out under the previously described conditions.[2] The composition of the reaction mixture was determined on a Varian 1520 B gas chromatograph (5% SE 30 Chromosorb W, 160 °C column, 290 °C detector, and N_2 and H_2 flow rates of 25 mL/min).

Method 2. $LiAlH_4$ reduction of 500 mg of the perchlorate salt of **3a** or **3b** was carried out in 200 mL of dry tetrahydrofuran. After a 4-h reflux, water was added and most of the tetrahydrofuran was evaporated. After extraction with ether, drying over $MgSO_4$, and evaporation of the solvent, the residue was examined by GLC (Table I). The isomers were separated by column chromatography over Al_2O_3 (Fluka, Type 507 C, Activity I) with ether elution.

Method 3. Reduction with K-selectride (5 equiv of a 0.5 M solution in THF, Aldrich) of 1 g of the perchlorate salt of **3a** or **3b** in 50 mL of dry THF was carried out at −50 °C for 15 h. The reaction was worked up as described for the $LiAlH_4$ reduction, followed by an acid–base extraction.

About 20% unreduced enamine was further reduced by the PtO_2/H_2 procedure.

Acknowledgment. We wish to thank the Fonds voor Fundamenteel Kollektief Onderzoek and the Nationale Raad voor Wetenschapsbeleid for their contribution to the equipment of our laboratory.

Registry No.—**2**, isomer I, 64161-72-4; **2**, isomer II, 64161-73-5; **2**, isomer III, 64161-74-6; **3a**, 944-68-3; **3a**·$HClO_4$, 64114-15-4; **3b**, 944-67-2; **3b**·$HClO_4$, 64114-16-5; **8**, 1023-99-0; **9**, 1444-15-1.

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(1) G. Van Binst, G. Laus, and D. Tourwé, *Org. Magn. Reson.*, in press.
(2) S. Ohki, M. Akiba, H. Shimada, and K. Kunihiro, *Chem. Pharm. Bull.*, **16**, 1889 (1968).
(3) The nomenclature of the stereoisomers is identical with that used in our previous publications[1,4] and is made to conform with IUPAC recommendations.[5] Ohki[2] uses the reverse order of the ring-fusion indication.
(4) G. Van Binst and D. Tourwé, *Org. Magn. Reson.*, **6**, 590 (1974).
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Use of α-Cyano Amines for the Regiospecific Synthesis of Multisubstituted Pyridines. Preparation of Nicotine Analogues[1]

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A general synthesis of 2-alkyl-3-acylpyridines and 2-alkyl-3-formylpyridines via [2,3] sigmatropic rearrangements of α-pyrrolidinyl-2-alkylpyridines is described. The initially obtained α-cyano amine can be hydrolyzed to an aldehyde, reductively cleaved to an amine, or alkylated and hydrolyzed to a ketone. These procedures are applied toward the synthesis of pyridine-substituted nicotine, nornicotine, and anabasine derivatives. In certain cases, the Stevens rearrangement product was observed along with the desired Sommelet–Hauser product, and studies indicated that sodium amide/NH_3 gave the largest preference for the latter rearrangement pathway.

The importance of the pharmacology of nicotine (1) and the nicotiana alkaloids is demonstrated by the intensive study they have received over the past century.[2] Some time ago Haglid reported that 6-methylnicotine (3) retained virtually full nicotinic activity, whereas 4-methylnicotine (2) displayed no activity on isolated muscle preparations.[3] This finding was rationalized by assuming that the 4-methyl group prevented the compound from adopting the conformation necessary for interaction with the receptor. As part of our interest in the structure, chemistry, and pharmacology of nicotine,[4,5] we

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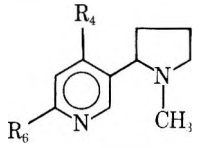
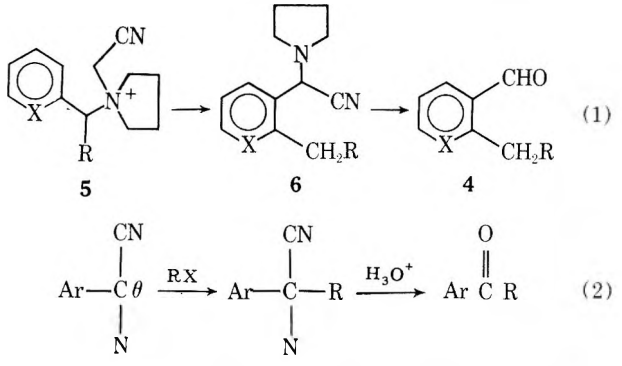
initiated a study directed toward the synthesis of 2-alkylnicotinoids so as to better assess the effect of substituents ortho to the pyrrolidine ring of nicotine.



1, $R_4 = R_6 = H$
2, $R_4 = CH_3$; $R_6 = H$
3, $R_4 = H$; $R_6 = CH_3$

The most commonly used approach toward the regiospecific synthesis of polysubstituted pyridines involves the formation of the pyridine ring from appropriately substituted acyclic precursors.[6] However, the requirements of our desired pharmacological studies suggested that a synthetic strategy should involve a general route to 2-alkyl-3-acylpyridines. We now report a sequence of reactions leading to 4 (X = N) from readily available 2-picolyl halides involving α-cyano amines in which the α-cyano amines (1) serve as the migrating moiety in a Sommelet–Hauser rearrangement,[7] and (2) are utilized



(1)

(2)

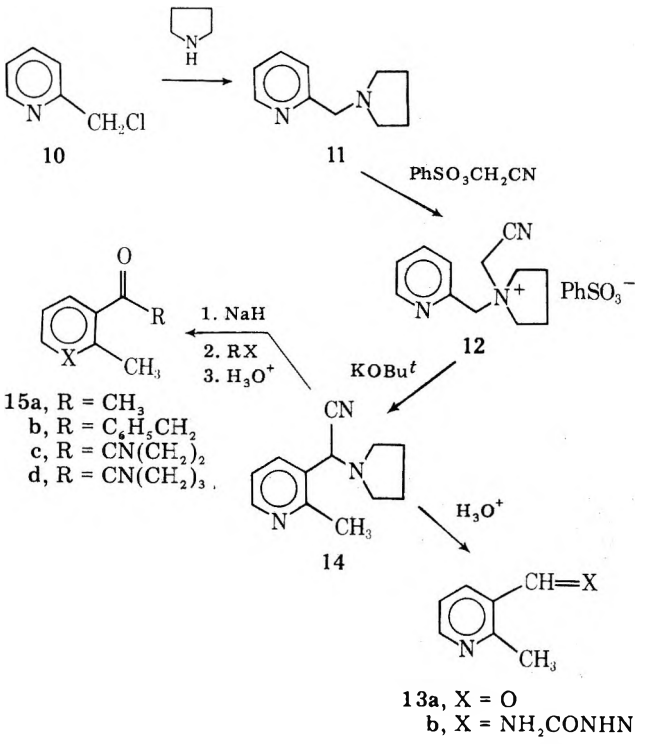
as acyl carbanion equivalents to effect alkylations. We also report the direct synthesis of the 1-methyl-2-(2-alkyl-3-pyridyl)pyrrolidine ring system using these procedures (cf. Scheme 8).

Results and Discussion

The only successful use of the Sommelet–Hauser rearrangement in pyridine chemistry is the formation of 4-dimethylaminomethyl-3-picoline (7) from trimethyl-3-picolylammonium chloride (**8b**).[7a] Under similar conditions, trimethyl-4-picolylammonium chloride (**8c**) gave no rearranged product and trimethyl-2-picolylammonium chloride (**8a**) gave 2-(1-dimethylaminoethyl)pyridine (9), the Stevens rearrangement product, in 12% yield.[7a] The existence of more than one acidic proton in **8a–c** results in the opportunity for competitive reaction pathways. Recently, Mander and Turner[8] described the [2,3] sigmatropic rearrangement of a variety of ylides derived from α-cyano amines, e.g., **5** → **4** (X = CH). This reaction appeared particularly attractive for use in the pyridine series, since the strongly electron-withdrawing cyano group should direct ylide formation away from the acidic picolyl position. Indeed, such a consideration is important for compounds having two sites bearing abstractable α-hydrogens, as is the case at hand.

Treatment of 2-chloromethylpyridine (**10**) with pyrrolidine gave 1-(2-picolyl)pyrrolidine (**11**) (93%) which could be converted to quaternary salt **12** (86%) with cyanomethyl benzenesulfonate in acetonitrile.[9] Reaction of **12** with either NaH or KOBu^t in THF–Me_2SO at −10 °C followed by acid hydrolysis gave (50%) 2-methylpyridine-3-carboxaldehyde (**13a**) isolated as its semicarbazone **13b**. Cyano amine **14**, the initial rearrangement product, was not isolated, but its formation was confirmed by the ^1H NMR spectrum of the crude reaction

Scheme I



product which exhibited three well-resolved pyridyl protons and a three-proton singlet at δ 2.65 in addition to the eight pyrrolidine protons.

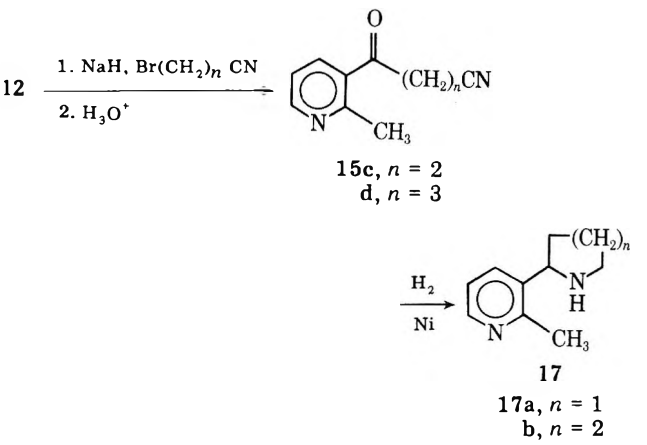
The flexibility of this reaction sequence was extended by utilizing the α-cyano amine moiety of **14** as an acyl carbanion equivalent.[10,11] Pyrrolidinium salt **12** was treated with 1 equiv of KOBu^t to bring about rearrangement as before. After the rearrangement was complete, as judged by TLC and ^1H NMR, 1 equiv of NaH or KH was added followed by 1 equiv of methyl iodide. Acid hydrolysis gave (78%) 2-methyl-3-acetylpyridine (**15a**). The corresponding benzyl ketone **15b** was obtained (87%) via alkylation with benzyl bromide (Scheme I). No evidence was obtained for pyridine nitrogen alkylation, although we have previously shown that nicotine itself is alkylated on both nitrogens when treated with methyl iodide.[5a]

Further investigation showed that the ylide formation–rearrangement–alkylation procedure could be simplified by using NaH in THF–Me_2SO to effect both rearrangement and alkylation. Thus, the pyrrolidine salt **12** was treated with 2 equiv of NaH and, after ylide formation, rearrangement, and anion formation, 3-bromopropionitrile was added. The crude reaction product after mild acid hydrolysis afforded the crystalline cyano ketone **15c** in 48% yield.

Cyano ketone **15c** is a key intermediate in the synthesis of pyridine-substituted nicotinoids, since the reductive cyclization of 3-pyridyl 2-cyanoethyl ketone (**16**) has been shown to yield myosmine and nornicotine, depending on reaction conditions.[10] Thus, hydrogenation of **15c** over Raney nickel in ethanol saturated with ammonia (Scheme II) led to a single product which was purified by distillation. This material, obtained in 36% overall yield from **11**, was identified as 2-methylnornicotine (**17a**) on the basis of spectroscopic and elemental analyses. The synthesis of 2-methylanabasine (**17b**) was accomplished in a similar fashion by the reductive cyclization of 2-methyl-3-pyridyl 3-cyanopropyl ketone (**15d**) obtained via alkylation of the rearranged cyanoamine **14** with 4-bromobutyronitrile.

Synthesis of 2-Ethyl 3-Substituted Pyridines. Pyridine-2-carboxaldehyde (**19**) was converted to α-cyano-α-(1-pyrrolidinyl)-2-picoline (**20**) (58%) by treatment with po-

Scheme II

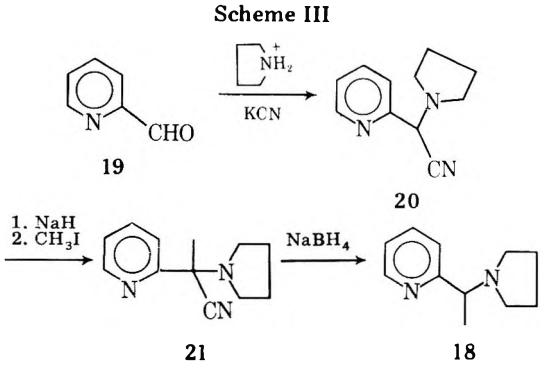


tassium cyanide and pyrrolidinium perchlorate. Methylation of **20** using NaH and methyl iodide gave **21**, which was converted to α-methyl-α-(1-pyrrolidinyl)-2-picoline **18** by reduction with $NaBH_4$ in ethanol (Scheme III).[12] The ^1H NMR spectrum of **18** exhibited a complex pair of multiplets for the pyrrolidine ring, a doublet and a quartet for the methyl and methine protons, and the normal splitting pattern of a 2-substituted pyridine.

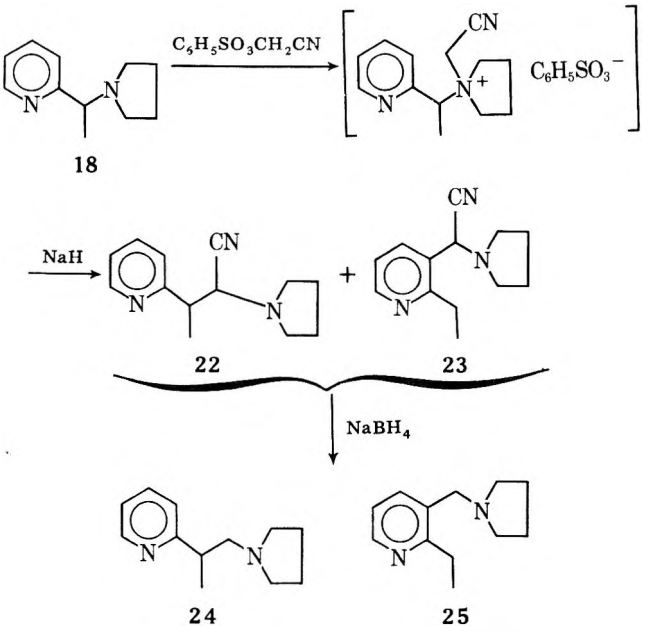
In contrast to the cyanomethylation of **11**, treatment of **18** with cyanomethyl benzenesulfonate did not give a crystalline product. Quaternization in Me_2SO or CH_3CN was followed by ^1H NMR. After salt formation was complete, the reaction mixture was exhaustively extracted with ether and the resulting product treated with NaH in THF–Me_2SO. The rearrangement was monitored by following the disappearance of the pyrrolidinium salt by TLC. Instead of obtaining a single product, however, two products were observed. Trituration of the crude reaction mixture with ether allowed the isolation of one of these as a crystalline material. A ^1H NMR spectrum of this substance eliminated the possibility that it was the [2,3] sigmatropic rearrangement product, in that four pyridyl protons were observed in a pattern consistent only with a 2-picoline derivative. The spectrum indicated that this material was 2-(1-pyrrolidinyl)-3-(2-pyridyl)butyronitrile (**22**), the Stevens rearrangement product. This assignment was confirmed by the remainder of the ^1H NMR spectrum which consisted of a doublet at δ 1.42 for the methyl group, a doublet at δ 4.32 for the β-hydrogen, and a doublet of quartets at δ 3.20 for the α-hydrogen. Infrared and elemental analyses and its subsequent conversion to amine **24** (see below) supported the assignment of **22**.

Identification of the second product, **23**, was accomplished subsequent to reductive decyanation of the crude product mixture with $NaBH_4$. GLC analysis of the total reduced material showed two products in about equal amounts. These two compounds were isolated by GLC and analyzed by ^1H NMR. The product of shorter retention time was found to be 1-(1-pyrrolidinyl)-2-(2-pyridyl)propane (**24**) derived via decyanation of **22**. The ^1H NMR resonances for the pyridyl protons of the longer retention-time product established it to be a 2,3-disubstituted pyridine, while the aliphatic region exhibited a triplet at δ 1.28, a quartet at δ 2.91, and a singlet at δ 3.68. This spectrum was consistent with 1-(2-ethyl-3-picolyl)pyrrolidine (**25**), the compound derived from Sommelet–Hauser rearrangement and reductive cleavage of the cyanide moiety. Identification of **25** allowed the assignment of **23** as the second rearrangement product. Thus, treatment of the quaternary salt derived from **18** with NaH led to a ca. 1:1 mixture of [2,3] sigmatropic rearrangement and [1,2] shift products (Scheme IV).

Scheme III



Scheme IV

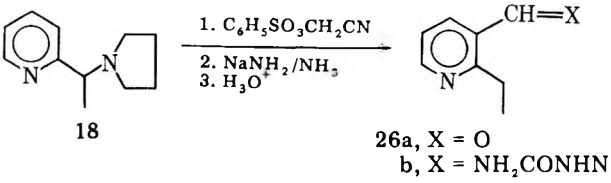


It has been shown that, where Stevens and Sommelet–Hauser rearrangements occur competitively, the use of sodium amide in liquid ammonia generally favors the latter reaction.[13] The reaction sequence **18** → **22** + **23** was repeated using sodium amide/NH_3, and the crude product was reduced with $NaBH_4$ as before. Analysis of the reduced product indicated the ratio of **25** to **24** had increased to 2:1. Other attempts to increase this ratio in favor of Sommelet–Hauser product were unsuccessful. It is worthy of note that Mander and Turner[8] observed ca. 10% phenylacetaldehyde, the Stevens reaction product, in the isomerization of **5** (X = CH, R = H), using $KOBu^t$ as the base.

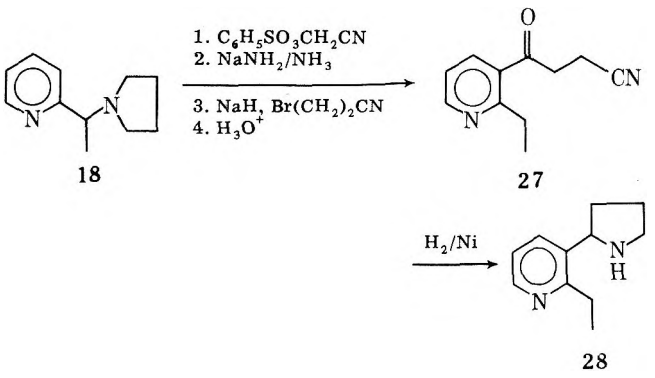
We next attempted to prepare 2-ethylpyridine-3-carboxaldehyde (**26a**). Treatment of **18** with cyanomethyl benzenesulfonate was carried out in acetonitrile. The derived salt was treated with sodium amide in liquid ammonia and the product hydrolyzed with aqueous acetic acid. The resulting crude product, which possessed an aldehyde group as shown by ^1H NMR, was treated with semicarbazide hydrochloride to give 2-ethylpyridine-3-carboxaldehyde semicarbazone (**26b**) (Scheme V). The derivative was isolated by preparative TLC and recrystallized to give a low yield (10%) of a crystalline solid which had spectral data consistent with **26b**.

The cyanomethylation of **18** was repeated, and the resulting salt was treated with sodium amide in liquid ammonia to ef-

Scheme V

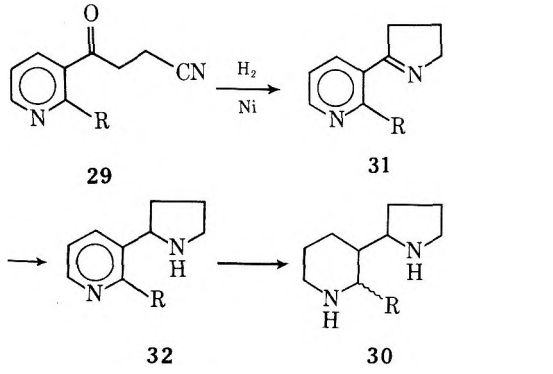


Scheme VI



18 27 28

Scheme VII



29 31 32 30

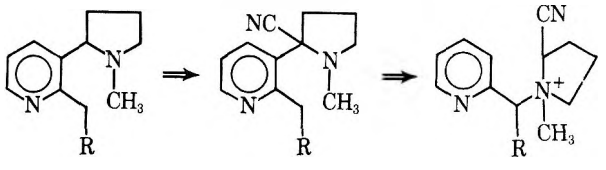
fect rearrangement, alkylated with 3-bromopropionitrile utilizing sodium hydride as the base, and hydrolyzed with aqueous acetic acid. The crude product was distilled giving a 21% yield (based on **18**) of the desired product, 2-ethyl-3-pyridyl 2-cyanoethyl ketone (**27**), as an oil of about 90% purity. The ^1H NMR spectrum exhibited a typical pattern for a 2,3-disubstituted pyridine, a pair of triplets at δ 3.23 and 2.78, and a quartet and triplet at δ 3.02 and 1.27. Hydrogenation of distilled **27** over Raney nickel gave 2-ethylnornicotine (**28**) (Scheme VI).

The reductive cyclization of **29** (R = H) must be performed with care as we have observed overreduction of the desired nornicotines to the corresponding piperidine derivatives **30**. Indeed, this sequence is somewhat problematical in that underreduction of **29** leads to mixtures of myosmine **31** (R = H) and nornicotine **32** (R = H),[10] while overreduction leads to **30** (R = H). However, we have found that for cyano ketones having substituents at C-2 of the pyridine ring (**29**, R = methyl or ethyl) the tendency for competitive pyridine reduction is not observed, presumably due to steric reasons. (Scheme VII).

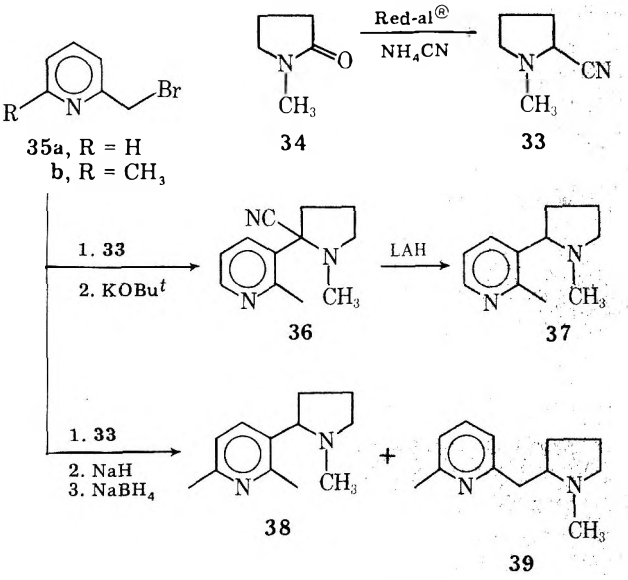
Direct Synthesis of Nicotinoids via [2,3] Pyrrolidine Rearrangement. With the now established utility of α-cyano amines as migrating moieties in the Sommelet–Hauser rearrangement and as acyl anion equivalents, an antithetical analysis for 2-alkylnicotines reveals an intriguing synthetic sequence as shown in Scheme VIII.

The required 1-methyl-2-cyanopyrrolidine (**33**) was prepared by treatment of 1-methyl-2-pyrrolidinone (**34**) with sodium bis(2-methoxyethoxy)aluminum hydride (Red-al®)

Scheme VIII



Scheme IX



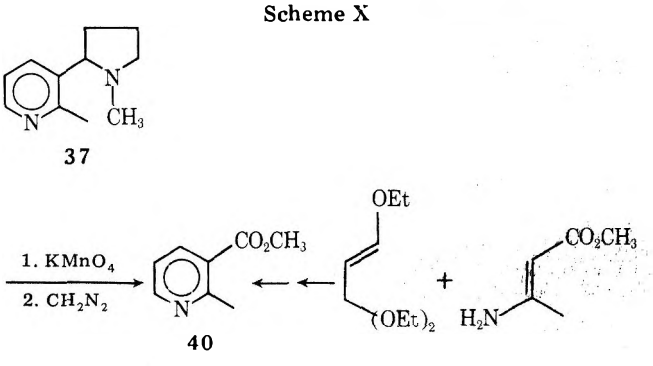
35a, R = H
b, R = CH_3
34 33 36 37 38 39

followed by aqueous ammonium cyanide (46%) (Scheme IX).[14] Reaction of **33** with 2-bromomethylpyridine (**35a**) in Me_2SO was followed by ^1H NMR until salt formation was complete. The Me_2SO solution was cooled, diluted with THF, and treated with $KOBu^t$. Rearrangement was monitored by TLC until no further salt remained. Isolation of the intermediate, 2-methyl-2′-cyanonicotine (**36**) was not pursued because of its observed lability.[14] Consequently, LAH reduction was carried out directly on the crude product after removal of Me_2SO. Distillation of the reduced product gave (20%) 2-methylnicotine (**37**). Spectral data and elemental analyses were consistent with the assigned structure. Synthesis of 2,6-dimethylnicotine (**38**) was carried out by the same procedure starting with 2-bromomethyl-6-methylpyridine (**35b**) (Scheme IX). In this case, a significant amount (~20%) of competitive Stevens rearrangement occurred to give α-(1-methyl-2-pyrrolidinyl)-2,6-dimethylpyridine (**39**).

Oxidation of 2-methylnicotine (**37**) was carried out as a further proof of its structure. Treatment of **37** with neutral aqueous $KMnO_4$ at 80 °C followed by esterification with diazomethane gave a product identical in all respects with methyl 2-methyl-3-nicotinate (**40**), prepared following a literature procedure[15] (Scheme X).

Conclusions. These procedures represent a synthetically useful methodology for the regiospecific formylation and acylation of 2-methylpyridines. The process has been extended to prepare 2-methylnicotinoids expeditiously. Of particular interest is the modification of the sequence such that the pyrrolidine ring functions initially as the amino portion of the cyano amine and ultimately as the pyrrolidine ring of the nicotinoid. Although we have thus far confined our studies to the pyrrolidine ring due to our interest in the synthesis of nicotine analogues, the reaction should also be applicable to systems containing heteroatoms other than nitrogen, such as

Scheme X



37 40

sulfur and phosphorus. The significant percentage of product due to Stevens rearrangement in the case of the acylation of 2-ethylpyridine is interesting and unfortunately detracts considerably from the reaction's synthetic utility. In that 2-picolines can be directly alkylated,[16] however, elaboration of the 2-methyl substituent can be performed at some stage following rearrangement. We have found this, in fact, to be a valid alternative, and details on this work will appear subsequently.

Experimental Section

^{1}H NMR spectra were recorded on a Varian XL-100 spectrophotometer operating at 100 MHz in the Fourier transform mode. Infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. THF was distilled from LAH prior to use, and Me_2SO was distilled from CaH_2. Both solvents were stored over 4-Å molecular sieves. $KOBu^t$ was freshly sublimed. All reactions were run under a dry N_2 atmosphere. Gas chromatography was carried out on a Bendix 2300 instrument using 5-ft 5% SE-30 on chromosorb G-HP columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-(2-Picolyl)pyrrolidine (11). To a solution of 5.0 g (0.03 mol) of 2-chloromethylpyridine hydrochloride in 10 mL of Me_2SO was added 10 mL of pyrrolidine. The resulting solution was stirred for 3 h at 50 °C and then for 16 h at room temperature. The solution was diluted with ether and washed once with 50% KOH and three portions of saturated brine. The ether solution was dried (KOH) and filtered, and the solvent was removed. The residue was distilled, yielding 4.60 g (93%) of a light yellow oil: bp 57–59 °C/0.1 mm; lit.,[17] 106–8 °C/9 mm; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 4, 3′,4′-H), 2.57 (m, 4, 2′,5′-H), 3.62 (s, CH_2), 7.45 (m, 3, 3,4,5-PyH), 8.62 (m, 1, 6-PyH).

1-Cyanomethyl-1-(2-picolyl)pyrrolidinium Benzenesulfonate (12). To 20.0 g (0.124 mol) of **11** in 100 mL of acetonitrile was added 1 equiv of cyanomethyl benzenesulfonate in 50 mL of acetonitrile at 25 °C with cooling. The reaction was stirred at room temperature for 18 h, and the acetonitrile was removed under reduced pressure. THF was added, and the product was collected by filtration and washed with THF and ether. After air drying, 38.5 g (86%) of colorless crystals was obtained: mp 118.5–120 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.17 (m, 4, pyrrolidine), 3.82 (m, 4, pyrrolidine), 4.82 (s, 2, $ArCH_2N$), 4.95 (s, 2, NCH_2CN), 6.59 (m, 8, aromatic), 7.59 (m, 1, pyridine).

Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.14; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.40; H, 5.89; N, 11.72; S, 8.82.

2-Methylpyridine-3-carboxaldehyde Semicarbazone (13b). A solution of 718 mg (2 mmol) of 12 in 6 mL of Me_2SO and 30 mL of THF was cooled to −10 °C and treated with 280 mg (2.5 mmol) of $KOBu^t$. The reaction mixture was stirred for 3 h and the bulk of the THF removed at the water pump at about 40 °C under reduced pressure. The residue was diluted with ice water and CH_2Cl_2, and 2.3 g of KOH was added. The basic solution was extracted with three portions of CH_2Cl_2. The organic extracts were combined, washed with saturated brine and dried (Na_2SO_4). Filtration followed by removal of the solvent gave 746 mg of a tan oil which was dissolved in 16 mL of THF and treated with an equal volume of 30% aqueous oxalic acid at reflux for 15 min. The THF was removed under reduced pressure and the aqueous solution neutralized with a slurry of 11 g of $NaHCO_3$ in ice water. The solution was extracted with two portions of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4). Filtration of the solution and evaporation of the solvent gave 231 mg of a dark brown oil. The major product was identified as **13a** from the ^{1}H NMR spectrum of the crude product. The product was dissolved in EtOH and treated with an aqueous solution of NaOAc and semicarbazide hydrochloride. Filtration of the solution gave 142 mg (31%) of **13b** as colorless crystals, mp 218–219 °C, lit.[15] 209 °C.

2-Methyl-3-acetylpyridine (15a). A solution of 1.48 g (4.15 mmol) **12** in 10 mL of Me_2SO was cooled to −10 °C and treated with 580 mg (5.2 mmol) of $KOBu^t$. The reaction mixture was stirred for 30 min at −10 °C and for an additional 30 min at room temperature. The mixture was cooled to −10 °C, and 740 mg (4.6 mmol) of a 25% dispersion of KH was added. The cooling bath was removed and the reaction mixture was stirred for 15 min and for an additional 15 min under reflux to ensure complete anion formation. The solution was then cooled to −10 °C and treated with 705 mg (5.0 mmol) of MeI. After addition of MeI was complete, the mixture was stirred at room temperature for 1 h and under reflux for 30 min. The reaction mixture was cooled and distributed between ether and a mixture of 50% KOH and saturated brine. The aqueous phase was extracted with ether, and the ether extracts were combined and washed once with saturated brine. The ether solution was dried ($CaSO_4$) and filtered, and the solvent was removed. The residual oil was treated with 6 mL of acetic acid, 3 mL of water, and 1 mL of THF. The solution was heated at 53 °C for 24 h, cooled, and treated with 10 g of K_2CO_3. Water was added to the basic slurry and the excess solids were removed by filtration. The filtrate was extracted with $CHCl_3$ and the $CHCl_3$ phase in turn extracted with 2 N HCl. The acidic phase was basified with solid K_2CO_3 and again extracted with $CHCl_3$. The crude product after solvent removal was distilled to give 400 mg (78.5%) of a clear liquid: bp 55–65 °C/0.05 mm; IR (neat) 1690 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.59 (s, 3, $PyCH_3$), 2.74 (s, 3, $COCH_3$), 7.27 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.00 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.61 (dd, 1, J = 5, 2 Hz, 6-PyH). A sample of the product was treated with picric acid to give a crystalline dipicrate, mp 174–176 °C, lit. 174 °C.[18]

2-Methyl-3-phenylacetylpyridine (15b). The preparation of **15b** was accomplished using the same procedure described for the preparation of **15a**, except that NaH was used as the base and benzyl bromide served as the alkylating agent. The crude product, isolated as a crystalline solid (87%), was estimated to be 95% pure. Two recrystallizations from *n*-hexane gave a 37% yield of colorless crystals: mp 66–67 °C, lit.[19] 61–63 °C; IR (nm) 1695 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3, CH_3), 4.21 (s, 2, CH_2), 7.28 (m, 6, phenyl + 5-PyH), 7.99 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.61 (dd, 1, J = 5, 2, Hz, 6-PyH).

2-Methyl-2-pyridyl 2-Cyanoethyl Ketone (15c). A solution of 12.32 g (34.6 mmol) of **12** in 125 mL of Me_2SO was prepared and 290 mL of THF added. The solution was cooled to −10 °C, and 1.84 g (38.1 mmol) of a 50% NaH dispersion was added. The mixture was stirred at −5 to −10 °C for 30 min and allowed to warm to room temperature over 1.5 h. An additional 1.84 g (38.1 mmol) of NaH was added, and the mixture was heated under reflux for 30 min and then cooled to −10 °C. A solution of 5.1 g (38 mmol) of 3-bromopropionitrile in 25 mL of THF was added over a 30-min period, and the reaction was stirred for an additional 30 min, filtered, and concentrated under reduced pressure. The residue was dissolved in ether and washed three times with a saturated NaCl–K_2CO_3 solution. The organic phase was filtered, dried (Na_2SO_4), and concentrated to give 8.17 g of a brown oil. The crude product was hydrolyzed and isolated as described for **15a** above. Distillation (147 °C/0.1 mm) gave a yellow oil which crystallized on trituration with ether. The colorless crystals were collected and dried, giving 3.2 g (53%): mp 82–83.5 °C; IR (nm) 1675 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 2.73 (s, 3, CH_3), 2.76 (t, 2, CH_2CH_2CN), 3.32 (t, 2, J = 8 Hz, CH_2CH_2CN), 7.28 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.00 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.65 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.13; H, 5.80; N, 16.13.

2-Methylnornicotine (17a). To a solution of 3.15 g (18 mmol) of **15c** in 180 mL of ethanol saturated with ammonia was added 10 g of freshly prepared Raney nickel W-2.[20] The mixture was hydrogenated in a Parr apparatus at ca. 50 psi for 15 h. The reaction mixture was filtered and concentrated under reduced pressure. The residue was taken up in hexane and dried ($CaSO_4$), filtered, concentrated, and distilled. The fraction boiling at 100–105 °C/0.175 mm was collected, giving 2.1 g (75%) of **17a:** IR (neat) 3295 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$) δ 1.68 (m, 4, 3′, 4′-H), 2.53 (s, 3, CH_3), 3.10 (m, 2, 5′-H), 4.30 (t, 1, J = 7 Hz, 2′-H), 7.07 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.88 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.35 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.93; H, 8.75; N, 16.99.

2-Methylanabasine (17b). The preparation of 2-methyl-3-pyridyl 3-cyanopropyl ketone (**15d**) was carried out exactly as described for the preparation of **15c,** except that 4-bromobutyronitrile was used as the alkylating agent. The crude product was distilled (bp 140–144 °C/0.05 mm), giving (65%) a light yellow oil (**15d**) which resisted crystallization: ^{1}H NMR ($CDCl_3$) δ 2.08 (m, 2, $CH_2CH_2CH_2$), 2.54 (t, 2, J = 6 Hz, CH_2CN), 2.68 (s, 3, CH_3), 3.12 (t, 2, J = 7 Hz, $COCH_2$), 7.25 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.95 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.58 (dd, 1, J = 5, 2 Hz, 6-PyH).

A solution of 2.8 g (15 mmol) of **15d** in 150 mL of ethanol saturated with ammonia was prepared, and 10 g of freshly prepared Raney nickel W-2 was added. The mixture was hydrogenated for 20 h in a Parr apparatus at 67 psi. The reaction was worked up using the procedure outlined for **17a.** The product was isolated by distillation (108–112 °C/0.2 mm), giving 2.2 g (89%) of **17b:** IR (neat) 3290 cm^{-1} (NH); ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 5, piperidine), 2.38 (m, 3, piperidine), 3.79 (m, 2, piperidine), 2.54 (s, 3, CH_3), 7.08 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.47 (dd, 1. J = 8, 2 Hz, 4-PyH), 8.43 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.04; H, 8.96; N, 15.81.

α-Methyl-α-(1-pyrrolidinyl)-2-picoline (18). To 25.0 g (133.5 mmol) of α-cyano-α-(1-pyrrolidinyl)-2-picoline (**20**), prepared by the reaction of pyridine-2-carboxaldehyde (**19**) with KCN and pyrrolidinium perchlorate,[21] in 75 mL of Me_2SO and 200 mL of THF was added 7.75 g (161 mmol) of NaH dispersion at −10 °C. The reaction mixture was stirred until no further gas evolution was noted, at which time 22.84 g (161 mmol) of MeI in 10 mL of THF was added over 10 min. After addition was complete, the reaction mixture was filtered and the precipitate washed with CH_2Cl_2. The filtrates were combined, washed with brine, dried (Na_2SO_4), filtered, and concentrated to give 24.75 g (92%) of crude product, α-cyano-α-methyl-α-(1-pyrrolidinyl)-2-picoline (**21**). The total crude nitrile was dissolved in 500 mL of 95% ethanol, cooled to 5 °C, and treated with 9.3 g (245 mmol) of $NaBH_4$. The reaction mixture was stirred at room temperature for 20 h, filtered, and rotary evaporated, giving a tan oil which was dissolved in hexane and dried (Na_2SO_4). The crude product was distilled (78–80 °C/0.2 mm), yielding 20.77 g (88%) of **18**: ^1H NMR ($CDCl_3$) δ 1.43 (d, 3, J = 6.5 Hz, CH_3), 1.77 (m, 4, 3′,4′-H), 2.50 (m, 4, 2′,5′-H), 3.44 (q, 1, J = 6.5 Hz, CH), 7.33 (m, 3, 3,4,5-PyH), 8.55 (m, 1, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.93; H, 9.23; N, 15.81.

Attempted Rearrangement of 18. A solution of 1.76 g (10 mmol) of **18** and 2.17 g (10.3 mmol) of cyanomethyl toluenesulfonate in 25 mL of Me_2SO was stirred overnight at room temperature and then at 45 °C for 2.5 h. The solution was cooled to −10 °C and 75 mL of THF and 602 mg (12.5 mmol) of 50% NaH dispersion were added. The reaction mixture was stirred at −10 °C for 2.5 h and then at room temperature overnight. Ether was added to precipitate the salts, the mixture was filtered, and solvent was removed in vacuo. A TLC of the crude product showed two major products. The residue was dissolved in ether and extracted into 2 N HCl, the acid solution was basified, and the aqueous solution was extracted with CH_2Cl_2. The organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated to give a brown oil which crystallized on trituration with ether. The solid was collected by filtration to give 135 mg (5%) of product, mp 109–112 °C, showing a single spot on TLC, corresponding to one of the major products in the reaction mixture. This product was identified as 2-(1-pyrrolidinyl)-3-(2-pyridyl)butyronitrile (**22**) on the basis of its spectral data: IR (nm) 2220 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 1.44 (d, 3, J = 7 Hz, CH_3), 1.65 (m, 4, 3′,4′-H), 2.60 (m, 4, 2′,5′-H), 3.12 (m, 1, CH_3CH), 4.32 (d, 1, J = 10 Hz, CNCH), 7.11 (m, 2, 3,5-PyH), 7.55 (m, 1,4-PyH), 8.52 (m, 1, 6-PyH).

Anal. Calcd for $C_{13}H_{17}N_3$: C, 72.52; H, 7.96; N, 19.52. Found: C, 72.43; H, 8.06; N, 19.41.

Treatment of **18** with cyanomethyl toluenesulfonate followed by reaction with NaH was repeated as above. The crude product was isolated, dissolved in 35 mL of 95% EtOH, treated with an excess of $NaBH_4$, and stirred overnight. The mixture was filtered and concentrated. The residue was dissolved in ether and extracted with 2 N HCl. The acid solution was washed with ether, basified, and extracted with ether. The ether extracts were combined, dried (Na_2SO_4), and filtered, and the solvent was removed. Distillation of the residue gave 1.02 g of a colorless oil which was shown to be a 1:1 mixture of two components by GLC. The substance with shorter retention time was identified as 1-(1-pyrrolidinyl)-2-(2-pyridyl)propane (**24**): ^1H NMR ($CDCl_3$) δ 1.33 (d, 3, J = 7 Hz, CH_3), 1.74 (m, 4, 3′,4′-H), 2.52 (m, 4, 2′,5′-H), 2.80 (d, 2, J = 7 Hz, CH_2), 3.14 (m, 1, CH), 7.14 (m, 2, 3,5-PyH), 7.60 (m, 1, 4-PyH), 8.56 (m, 1, 6-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.69; H, 9.45; N, 15.02.

The second substance was identified as 1-(2-ethyl-3-picolyl)pyrrolidine (**25**): ^1H NMR ($CDCl_3$) δ 1.29 (t, 3, J = 8 Hz, CH_3), 2.72 (m, 4, 3′,4′-H), 2.59 (m, 4, 2′,5′-H), 2.92 (q, 2 H, J = 8 Hz, CH_3CH_2), 3.59 (s, 2, NCH_2), 7.10 (dd, 1, J = 8, 6 Hz, 5-PyH), 7.73 (dd, 1, J = 8, 1 Hz, 4-PyH), 8.46 (dd, 1, J = 6, 1 Hz, 6-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54, N, 14.72. Found: C, 75.91; H, 9.67; N, 14.59.

2-Ethylpyridine-3-carboxaldehyde Semicarbazone (26b). A solution of 1.00 g (5.67 mmol) of **18** in 3 mL of MeCN was cooled to 0 °C and treated with 1.12 g (5.67 mmol) of cyanomethyl benzenesulfonate in 3 mL of MeCN. The solution was stirred for 1 h at 0 °C and then for 11 days at room temperature. The solution was transferred to a 100-mL three-necked flask, and the solvent was removed in vacuo. About 50 mL of ammonia was condensed into the flask, the temperature was adjusted to −40 °C, and the mixture was stirred until a homogeneous solution resulted. The solution was treated with 280 mg (7.18 mmol) of $NaNH_2$, and the reaction mixture was stirred under reflux for 3 h. The ammonia was evaporated and the residue treated with a mixture of water and ether. The aqueous phase was further extracted with ether, and the ether extracts were combined, washed with aqueous KOH, and water, and dried (Na_2SO_4). The solution was filtered and concentrated, and the resulting crude product was hydrolyzed as before, using 6 mL of acetic acid, 3 mL of water, and 1 mL of THF to give a dark brown oil which showed two major components on TLC. An NMR spectrum of the crude product established the presence of an aldehyde. Treatment of the crude product with an aqueous solution of semicarbazide hydrochloride and NaOAc followed by preparative TLC ($CHCl_3$/EtOH/NH_4OH, 85:14:1) gave the crystalline semicarbazone. Recrystallization (H_2O) gave 110 mg (10%) of colorless **26b**: mp 176–177 °C; IR (nm) 1700 cm^{-1} (C=O); ^1H NMR (Acetone-d_6, 50 °C) δ 1.21 (t, 3, J = 7 Hz, CH_3), 2.07 (q, 2 H, J = 7 Hz, CH_2), 6.83 (s, 2, NH_2), 7.13 (dd, 1, J = 8, 5 Hz, 5-PyH), 8.17 (s, 1, CH), 8.27 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.42 (dd, 1, J = 5, 2 Hz, 6-PyH), 10.17 (s, 1, NH).

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.23, H, 6.29; N, 29.15. Found: C, 56.54; H, 6.33; N, 29.07.

2-Ethylnornicotine (28). To 5.0 g (28.4 mmol) of **18** in 30 mL of MeCN was added 5.6 g (28.4 mmol) of cyanomethyl benzenesulfonate. The mixture was allowed to stand 3 days at room temperature, the solvent was removed, and the residue was subjected to continuous ether extraction. The resulting ether-insoluble material after drying was dissolved in 250 mL of anhydrous ammonia, the temperature was adjusted to −40 °C, and the mixture was stirred until homogeneous. The reaction mixture was treated with 1.45 g (37.2 mmol) of $NaNH_2$, stirred for 4 h at −40 °C, and allowed to warm to room temperature. Ether was added to the residue, and the resulting solution was washed with saturated brine, dried (Na_2SO_4), and concentrated to give 4.88 g of a tan oil. The oil was dissolved in 70 mL of Me_2SO and 300 mL of THF to which 1.48 g (30.8 mmol) of 50% NaH dispersion was added. The mixture was heated under reflux for 30 min and then cooled to −10 °C. A solution of 3.64 g (27.2 mmol) of 3-bromopropionitrile in 10 mL of THF was added over a 15-min period. After stirring for 1 h at room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in ether, washed with 10% K_2CO_3 and saturated brine, dried (Na_2SO_4), and concentrated to give 3.78 g of a tan oil. Hydrolysis as before using 30 mL of acetic acid, 15 mL of water, and 5 mL of THF followed by distillation (150–5 °C/0.05 mm) gave 1.1 g (21%) of **27**: ^1H NMR ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 3.05 (m, 6), 7.25 (dd, 1, J = 8, 5 Hz, 5-PyH), 7.95 (dd, 1, J = 8, 2 Hz, 4-PyH), 8.63 (dd, 1, J = 5, 2 Hz, 6-PyH). A 500-mg (2.6 mmol) sample of **27** and 10 g of Raney nickel in 100 mL of EtOH saturated with ammonia was hydrogenated in a Parr apparatus at about 60 psi for 20 h and worked up as before. Isolation by preparative TLC ($CHCl_3$/EtOH/NH_4OH, 85:14:1) gave 125 mg (28%) of **28** as a light yellow oil. An analytical sample was obtained by preparative GLC: IR (neat) 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3, J = 8 Hz, CH_2CH_3), 1.94 (m, 5, NH, 3′,4′-H), 2.88 (q, 2, J = 8 Hz, CH_2CH_3), 3.08 (m, 2, 5′-H), 4.37 (t, 1, J = 7 Hz, 2′-H), 7.40 (dd, 1, J = 6, 5 Hz, 5-PyH), 7.88 (dd, 1, J = 6, 2 Hz, 4-PyH), 8.12 (dd, 1, J = 5, 2 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.07; H, 9.25; N, 16.01.

1-Methyl-2-cyanopyrrolidine (33). A solution of 75 g (0.76 mol) of 1-methyl-2-pyrrolidinone (**34**) in 900 mL of THF was cooled to 0 °C, and 117 mL (0.404 mol) of 70% Red-Al® solution was added over a 1-h period maintaining the temperature between −10 and 0 °C. After stirring for an additional hour at 0 °C and 1.5 h at room temperature, the solution was cooled to 10 °C and an ice-cold solution of 74.5 g (1.52 mol) of NaCN and 80.7 g (1.52 mol) of NH_4Cl in 625 mL of water was added. The mixture was stirred overnight at room temperature and heated under reflux for 30 min, and the organic phase was separated. The aqueous phase was filtered and extracted with two 200-mL portions of ether, and the combined organic extracts were washed with base. The ether solution was chilled and extracted with 1 equiv of ice-cold dilute HCl in two portions. The acidic phase, after washing with ether, was basified at <5 °C by addition to a 50% KOH solution, and the basic solution was extracted with ether. The ether extract was washed with saturated brine, dried (Na_2SO_4), concentrated, and distilled to give 38.26 g (46%) of a colorless oil: bp 79–82 °C/12 mm; lit.[22] 68–71 °C/12 mm; IR ($CHCl_3$) 2230, 2250 cm^{-1} (CN); ^1H NMR ($CDCl_3$) δ 2.07 (m, 4, 3,4-H), 2.48 (s, 3, CH_3(= 2/75 (m, 2, NCH_2), 3.68 (t, 1, J = 5 Hz, CHCN).

2-Methylnicotine (37). An ethereal solution of 2-bromomethylpyridine (**35a**), obtained by treating 9.0 g (35.6 mmol) of 2-bromomethylpyridine hydrobromide with aqueous $NaHCO_3$, was added to 4.30 g (39 mmol) of 1-methyl-2-cyanopyrrolidine (**33**) in 100 mL of Me_2SO. The ether was removed at reduced pressure, and the solution was stirred at room temperature for 24 h. To the resulting solution was added 500 mL of THF and, after cooling to 20 °C, 4.0 g (35.8

mmol) of KOBu^t. The reaction mixture was stirred for 5 h at −20 °C, after which the solvents were removed under high vacuum at <50 °C. The residue was distributed between ether and ice water and the aqueous phase further extracted with ether. The combined extracts were washed with saturated brine and base, and dried (Na_2SO_4). The ethereal solution containing 3.74 g of a brown oil was adjusted to a volume of 60 mL and added to a slurry of 1.41 g (37 mmol) of LAH in 120 mL of ether maintained at 0 °C. The solution was stirred at 0 °C for 30 min, heated under reflux for 3 h, cooled to 0 °C, treated dropwise with 15 mL of saturated K_2CO_3, and again heated under reflux for 30 min. The mixture was filtered and the filtrate extracted with two 10-mL portions of 20% aqueous acetic acid. The combined acid extracts were basified and extracted with ether, and the combined ether extracts were washed with saturated brine and dried (Na_2SO_4). The solvent was removed and the residue was distilled (56–59 °C/0.1 mm), giving 1.22 g (19.5%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3, NCH_3), 2.58 (s, 3, $PyCH_3$), 3.32 (m, 2, 2′,5′$_{cis}$-H), 7.16 (dd, 1, J = 8, 6 Hz, 5-PyH), 7.87 (dd, 1, J = 8, 1 Hz, 4-PyH), 8.39 (dd, 1, J = 6, 1 Hz, 6-PyH).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 75.04; H, 9.06; N, 15.68.

Oxidation of 2-Methylnicotine (37). A suspension of 55.6 mg (0.312 mmol) of 2-methylnicotine (**37**) in 55 mL of water was treated with small portions of $KMnO_4$ at 80 °C until no further oxidation was evident. The suspension was filtered, and the filtrate was acidified (HCl) and concentrated to dryness in vacuo. The residue was dissolved in a minimum amount of methanol, ten drops of diethylamine was added, and the solution was added to an etheral solution containing a slight excess of diazomethane. The solvent was removed, the residue was taken up in ether, and the solution was filtered and dried (Na_2SO_4). The resulting solution contained a single major product as shown by both GLC and TLC, which was identical in all respects to a sample of methyl 2-methylnicotinate (**40**) prepared by the method of Dornow and Bormann.[15]

2,6-Dimethylnicotine (38). To a solution of 22.09 g (82.7 mmol) of 2-bromomethyl-6-methylpyridine hydrobromide (**35b**) in 40 mL of water was added 40 mL of CH_2Cl_2 and 6.95 g (82.7 mmol) of $NaHCO_3$ at 0 °C. The organic portion was separated and the aqueous solution extracted with three portions of CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated to ca. 35 mL, diluted with 50 mL of THF, again concentrated to ca. 35 mL, and then treated with a solution of 10 g (91 mmol) of 1-methyl-2-cyanopyrrolidine (**33**) in 100 mL of Me_2SO. After stirring overnight at room temperature, the Me_2SO was removed in vacuo to give a viscous yellow oil which was dissolved in 100 mL of Me_2SO and 500 mL of THF, cooled to −10 °C, and treated with 4.5 g (94 mmol) of a 50% NaH dispersion. The reaction mixture was stirred for 3.5 h at 0 °C, 16 h at room temperature, filtered, and concentrated in vacuo. The resulting oil was dissolved in ether, filtered to clarify, washed with basic saturated brine, and dried (Na_2SO_4). Removal of solvent gave 14.96 g of crude product which was dissolved in 300 mL of 95% EtOH and 4.7 g (124 mmol) of $NaBH_4$ was added. After stirring at 0 °C for 1 h and at room temperature for 2 h, the mixture was filtered, and the insolubles were washed with ethanol and ether. The combined filtrates were concentrated, and the residue was taken up in ether and filtered. The ether solution was extracted with 20% acetic acid, and the acid solution after washing with ether was treated with 11 mL of concentrated HCl and rotary evaporated. The residue was treated with base and extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 12.88 g of a crude product which was distilled. The fraction boiling from 88–135 °C/0.25 mm was collected, giving 6.2 g of a colorless oil which was chromatographed on 200 g of basic alumina, activity grade I. Elution with 2% ethyl acetate in hexane gave 4.6 g of an oil which was distilled (63–64 °C/0.05 mm), yielding 3.8 g (25%) of pure **38**: ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 5, 3′,4′,5′$_{trans}$-H), 2.15 (s, 3, NCH_3), 2.48 (s, 3, $PyCH_3$), 2.51 (s, 3, $PyCH_3$), 3.28 (t, 2, J = 8 Hz, 2′,5′$_{cis}$-H), 6.99 (d, 1, J = 9 Hz, 5-PyH), 7.81 (d, 1, J = 9 Hz, 4-PyH).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.54; N, 14.72. Found: C, 75.61; H, 9.62; N, 14.64.

Further elution of the column with 10–50% ethyl acetate in hexane gave 560 mg (~4%) of a light yellow oil which was essentially a single product. Analytical data obtained on a GLC trapped sample were consistent with α-(1-methyl-2-pyrrolidinyl)-2,6-dimethylpyridine (**39**): ^{1}H NMR ($CDCl_3$) δ 1.67 (m, 4, 3′,4′-H), 2.39 (s, 3, NCH_3), 2.52 (s, 3, $PyCH_3$), 2.65 (m, 2, CH_2), 3.14 (m, 2, 2′,5′$_{cis}$-H), 6.97 (m, 2, 3,5-PyH), 7.57 (AB q, 1, J = 8, 8 Hz, 4-PyH).

The compound was converted to the dipicrate in EtOH and recrystallized from water, mp 193–194 °C.

Anal. Calcd. for $C_{24}H_{24}N_8O_{14}$: C, 44.45; H, 3.73; N, 17.28. Found: C, 44.54; H, 3.58; N, 17.43.

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Registry No.—**10** HCl, 6959-47-3; **11**, 60032-62-4; **12**, 60032-56-6; **13a**, 60032-57-7; **13b**, 60032-58-8; **14**, 64114-17-6; **15a**, 1721-12-6; **15b**, 31251-53-3; **15c**, 60032-59-9; **15d**, 64114-18-7; **17a**, 64114-19-8; **17b**, 64114-20-1; **18**, 60032-60-2; **19**, 1121-60-4; **20**, 56752-65-9; **21**, 64114-21-2; **22**, 64114-22-3; **23**, 64114-23-4; **24**, 64114-24-5; **25**, 64114-25-6; **26a**, 64114-26-7; **26b**, 60032-61-3; **27**, 64114-27-8; **28**, 64114-28-9; **33**, 20297-37-4; **34**, 872-50-4; **35a**, 55401-97-3; **35a** HBr, 31106-82-8; **35b** HBr, 64114-29-0; **36**, 64114-30-3; **37**, 64114-31-4; **38**, 64114-12-1; **39**, 64114-13-2; **39**, dipricrate, 64114-14-3; pyrrolidine, 123-75-1; cyanomethyl benzenesulfonate, 10531-13-2; methyl iodide, 74-88-4; benzyl bromide, 100-39-0; 3-bromopropionitrile, 2417-90-5, 4-bromobutyronitrile, 5332-06-9; pyrrolidinium perchlorate, 22401-44-1; cyanomethyl toluenesulfonate, 14562-04-0.

References and Notes

(1) (a) A preliminary account of this work has appeared; cf.: E. B. Sanders, H. V. Secor, and J. I. Seeman, *J. Org. Chem.*, **41**, 2658 (1976); (b) For the previous paper in this series, see: J. I. Seeman and W. A. Farone, *J. Org. Chem.*, in press.
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Photochemistry of Some Heterocyclic Analogues of 3,3,5,5-Tetramethylcyclohexanone

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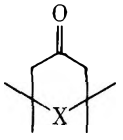
The photolysis of tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-one (**1**), 2,2,6,6-tetramethyl-4-piperidone (**2**), tetrahydro-2,2,6,6-tetramethyl-4*H*-thiopyran-4-one (**3**), and 3,3,5,5-tetramethylcyclohexanone (**4**) was investigated in methanol and 2-propanol. The main products formed in the irradiation of **1** and **2** were the pinacol dimers octahydro-2,2,2′,2′,6,6,6′,6′-octamethyl[4,4′-bi-4*H*-pyran]-4,4′-diol (**5**) and 2,2,2′,2′,6,6,6′,6′-octamethyl[4,4′-bipiperidine]-4,4′-diol (**9**), respectively, while **3** gave primarily the photoreduced product, tetrahydro-2,2,6,6-tetramethyl-2*H*-thiopyran-4-ol (**12**). The principal reaction of compound **4** on irradiation in methanol was a Norrish type I cleavage to yield methyl 3,3,5,5-tetramethylhexanoate (**14**).

The photolysis of tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-3-one in methanol has been shown to yield 2,2-dimethyl-5-methoxytetrahydrofuran.[1] The formation of this ring contraction product was postulated to arise via an oxacarbene intermediate, although it could also be explained by direct cleavage of the starting material into acetone and 2,2-dimethylcyclobutanone from which 2,2-dimethyl-5-methoxytetrahydrofuran is known to form on photolysis.[2]

To determine the scope of this reaction we examined the photolysis of the related heterocyclic systems **1**, **2**, and **3** and their carbocyclic analogue **4** in methanol and 2-propanol. After

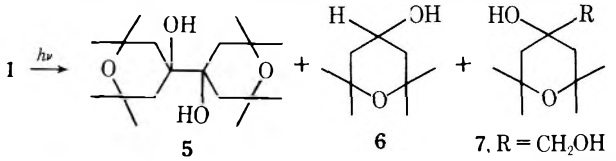


1, X = O
2, X = NH
3, X = S
4, X = CH_2

each photolysis, the reaction mixture was examined by gas chromatography and combined gas chromatography–mass spectrometry in order to obtain quantitative and qualitative information on the products formed.

Results

The irradiation of **1** in methanol afforded octahydro-2,2,2′,2′,6,6,6′,6′-octamethyl[4,4′-bi-4*H*-pyran]-4,4′-diol (**5**) as the major product. The remaining products were tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-ol (**6**) and tetrahydro-

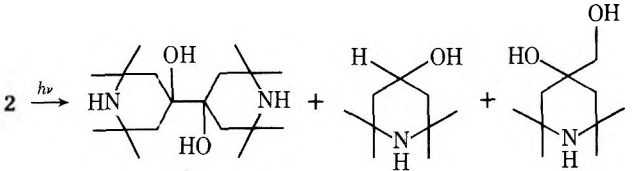


5 **6** **7**, R = CH_2OH **8**, R = $(CH_3)_2COH$

4-hydroxy-2,2,6,6-tetramethyl-4*H*-pyran-4-methanol (**7**). The structure of **5** was supported by its analytical data and its infrared, nuclear magnetic resonance, and high-resolution mass spectra. Compound **6** was identified by comparison of its properties and spectra with those of an authentic sample prepared by lithium aluminum hydride reduction of **1**. The structure of **7** was obtained from spectral data.

The photolysis of **1** in 2-propanol also gave **5** and **6** in addition to the mixed pinacol tetrahydro-4-hydroxy-α,α,2,2,6,6,-hexamethyl-4*H*-pyran-4-methanol (**8**), which was identified from its spectral data.

When **2** was irradiated in methanol, 2,2,2′,2′,6,6,6′,6′-octamethyl[4,4-bipiperidine]-4,4′-diol (**9**), 4-hydroxy-2,2,6,6-tetramethylpiperidine (**10**), and 4-hydroxy-2.2,6,6-tetramethyl-4-piperidinemethanol (**11**) were obtained. Compounds **9** and **11** were identified from their spectral data, and the



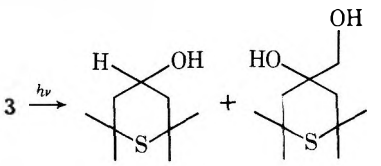
9 **10** **11**

structure of **10** was established by comparison of its physical and spectral properties with those of an authentic sample.

The irradiation of **2** in 2-propanol gave results similar to those obtained in the irradiation of **1**.

When **3** was irradiated in methanol, tetrahydro-2,2,6,6-tetramethyl-2*H*-thiopyran-4-ol (**12**) and tetrahydro-4-hydroxy-2,2,6,6-tetramethyl-2*H*-thiopyran-4-methanol (**13**) were the only products isolated by preparative gas chromatography. Compound **12** was identified by comparison of its physical properties with those of an authentic sample prepared by lithium aluminum hydride reduction of **3**. The structure of **13** was established from its spectral data. Ring contraction products had been previously reported[3] for the photolysis of **3** and other tetrahydrothiopyranones in *tert*-butyl alcohol, but no such products could be detected under our experimental conditions.

The photolysis of **3** in 2-propanol afforded compound **12** (84%) as the main product.



12 **13**

Although the photolysis of **4** in methanol had previously been investigated by Hagens,[4] we repeated the experiment and confirmed the products reported by Hagens: methyl 3,3,5,5-tetramethylhexanoate (**14**), 2,2,4,4,10,10,12,12-octamethyl-7,14-dioxadispiro[5.1:5.2]pentadecane (**15**), 1-hydroxy-3,3,5,5-tetramethylcyclohexanemethanol (**16**), and 3,3,5,5-tetramethylcyclohexanol (**17**).

Hagens[4] suggested that **15** could arise via the condensation of **4** with the mixed pinacol 1-hydroxy-3,3,5,5-tetramethylcyclohexanemethanol (**16**) in a ground-state acid-catalyzed reaction. We found that compounds **14** and **15** were the major

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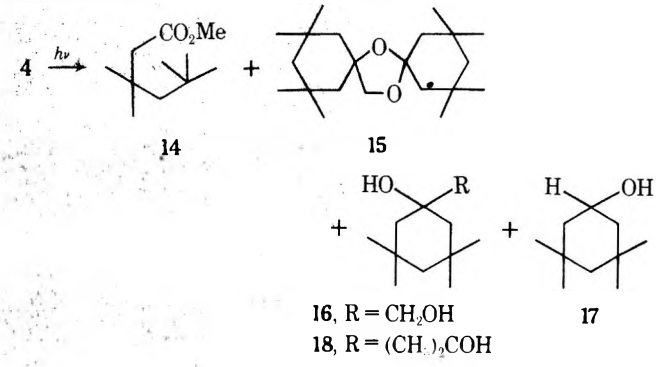
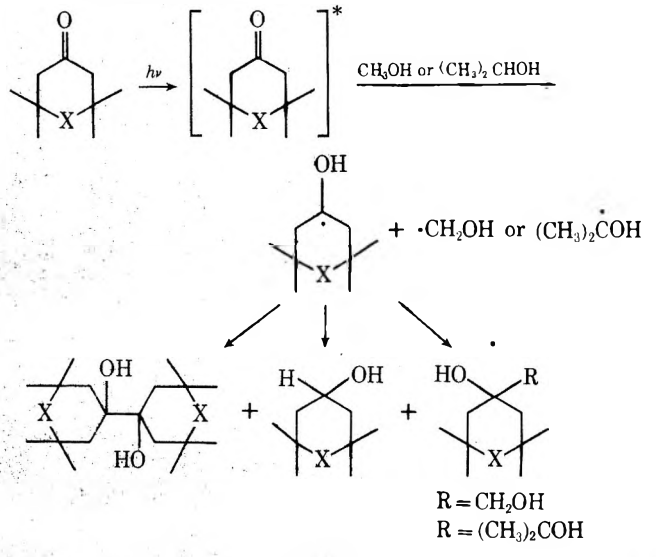
products formed along with smaller amounts of 1-hydroxy-3,3,5,5-tetramethylcyclohexanemethanol (**16**). Compound **15** precipitated from solution and was identified via its mass spectral fragmentation data as well as by comparing its physical and spectral properties to the literature values reported by Hagens.[4] The filtrate was resolved by preparative gas chromatography. Compounds **14, 16,** and **17** were identified from their spectral data and by comparison of their physical properties to the literature values of the products obtained by Hagens.[4]

In 2-propanol, the major photolysis product was **17.** A small amount of 1-hydroxy-$\alpha,\alpha,3,3,5,5$-hexamethyl-1-cyclohexanemethanol (**18**) was also observed.

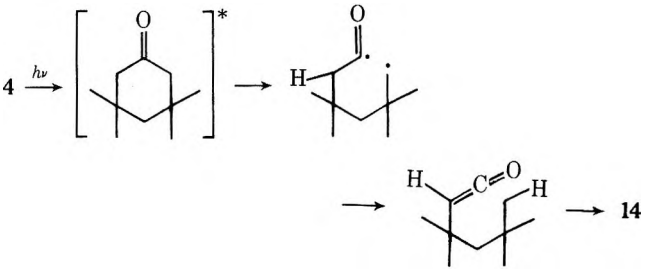


Discussion

The photolysis of either tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-one (**1**) or its piperidone analogue (**2**) in methanol or 2-propanol resulted in the formation of the corresponding pinacols **5** and **9** as the major reaction products. Conversely, the photolysis of **3** and **4** under similar conditions gave the respective pinacols, but as minor products which could only be detected by combined gas chromatograhpy–mass spectrometry. These products were tentatively identified from their mass spectral fragmentation patterns which were similar to those of **5** and **9.** The principal products from the irradiation of **3** in either methanol or 2-propanol or **4** in 2-propanol were the corresponding alcohols **12** and **16,** respectively, suggesting that photoreduction was the predominant reaction pathway in these photolyses. Only compound **4** underwent a Norrish type I cleavage to afford ester products, this process being the major decomposition pathway in methanol. No evidence of ring contraction or of a Norrish type I cleavage could be detected in the photolysis of any of the six-membered heterocyclic ketones studied (**1, 2,** and **3**). These observations are in direct contrast with the behavior of tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-3-one, which exhibited both processes upon photolysis.[1]



All of the products formed upon irradiation of heterocyclic ketones **1–3** were the result of a hydrogen transfer process between the solvents, methanol or 2-propanol, and the excited state of the ketone to yield a ketyl radical.[5] The ketyl radical, in turn, could abstract another hydrogen atom from the solvent to give the photoreduced products (**6, 10,** and **12**) or could couple to afford the corresponding pinacol dimers as major reaction products (**5** and **9**). Finally, the ketyl radical could react with solvent-based radicals to give mixed pinacols (**7, 8, 11, 13, 16,** and **18**). The mixed pinacols, 4-hydroxy-$\alpha,\alpha,2,2,6,6$-hexamethylpiperidone-4-methanol and tetrahydro-4-hydroxy-$\alpha,\alpha,2,2,6,6$-hexamethyl-2*H*-thiopyran-4-methanol, were also found to occur in trace amounts and were tentatively identified by comparison of their mass spectral fragmentation patterns to those of **8** and **18.**[6]



Although **4** underwent reduction and dimerization reactions similar to those of its heterocyclic analogues **1, 2,** and **3,** it also decomposed via a Norrish type I cleavage.

The fact that the heterocyclic analogues of **4** (**1, 2,** and **3**) did not undergo a Norrish type I cleavage is of some interest. This behavior is not only in contrast with that of **4** but also with that of other heterocyclic ketones such as 2,2,4,4-tetramethyl-3-oxetanone,[7] 2,2,5,5-tetramethyldihydro-3-furanone,[8] and tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-3-one,[1] which predominantly undergo Norrish type I cleavage on irradiation under similar conditions. The nature of the solvent appears to be of great importance in these reactions since irradiation of **3** in *tert*-butyl alcohol yielded products which resulted primarily from a Norrish type I cleavage.[3] In a nonprotic solvent such as acetonitrile, no reaction occurred.[9]

The Norrish type I cleavage of compounds **1–4,** in contrast with those of oxaheterocyclic ketones previously investigated,[1,7,8] would yield a primary radical which, although possessing some stability in the carbocyclic analogue **4,** could be further destabilized by the heteroatoms present in **1, 2,** and **3.** Therefore, α cleavage in these compounds should be highly reversible and should allow hydrogen abstraction to compete successfully.[10] However, other factors may be involved. It is also plausible that the 4-heteroatoms stabilize the excited state in such a way that compounds **1–3** react from the excited state before cleavage can occur.

Experimental Section

Melting points were taken on a Mel-Temp or Thomas Hoover Unimelt apparatus and are uncorrected. Preparative VPC separations were carried out on an Aerograph 700 chromatograph equipped with 12 ft × 0.25 in stainless steel columns containing Carbowax 20M (15%) and/or a column containing SE-30 (15%) on 45–60 mesh Chromosorb W. Yields are based on gas chromatographic analysis with the balance of the mixture consisting of unreacted starting material. ^{1}H NMR spectra were recorded on Varian A-60A, Varian HA-100, or Varian HR-220 spectrometers using Me_4Si as an internal standard. Combined gas chromatography–mass spectrometry was carried out using a Perkin-Elmer 990 gas chromatograph interfaced to a Hitachi RMU-6L mass spectrometer via a Watson-Biemann separator.[11] The gas chromatograph was equipped with a flame ionization detector and a 10 ft × 2 mm (i.d.) 3% XE-60 glass column to separate the reaction mixtures. Chromatographic conditions were as follows: He flow rate, 30 mL/min; temperature program, 60 °C (4 min) to 230 °C at 6 °C/min; injector 290 °C and detector 250 °C. Conditions for the mass

spectrometer were as follows: 70-eV ionizing potential; ion source temperature 200 °C and interface temperature, 250 °C. High-resolution spectra are recorded on a CEC-110B mass spectrometer using photoplate recording. The spectra were run at the Mass Spectrometry Laboratory at Massachusetts Institute of Technology, Professor Klaus Biemann, director. Ultraviolet spectra were obtained on a Beckman DBG spectrophotometer. Infrared spectra were taken on a Perkin-Elmer 137 Infracord or a Perkin-Elmer 521 spectrophotometer. Microanalyses were performed by Midwest Microlabs, Ltd., Indianapolis, Ind.

Starting Materials. 2,2,6,6-Tetramethyl-4-piperidone (**2**) and 3,3,5,5-tetramethylcyclohexanone (**4**) were commercially available. Compound **4** was used without further purification, and **2** was purified by sublimation. The procedure of Korobitsyna and Pivnitskii,[12] as modified by Wasacz,[13] was used to prepare **1**, and a similar procedure by Naylor[14] was used to prepare **3**, both in low yields. Preparative gas chromatography yielded **1** and **3** in greater than 99.9% purity.

Tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-one (1). 2,6-Dimethyl-2,5-heptadien-4-one (Phorone) (20 g, 0.195 mol) was placed in a 100-mL, two-necked, round-bottomed flask equipped with a condenser, a magnetic stirring bar, and a gas inlet tube. The flask was cooled in an ice bath, and hydrogen chloride was bubbled through the stirred ketone for 2 h. The reaction mixture was allowed to stand overnight and was then washed with water. The oil that separated was treated with 100 mL of water, saturated with sodium chloride, and extracted three times with 30 mL of diethyl ether. The ether extracts were dried with anhydrous magnesium sulfate, filtered, and distilled at atmospheric pressure to remove the solvent. The residue was combined with an equal volume of saturated sodium bisulfite solution, and the mixture was stirred magnetically overnight. The white crystalline solid that formed was collected by filtration, washed with ether, air-dried, and then treated with sufficient 20% aqueous sodium hydroxide solution to dissolve the solid. The oil that separated was chromatographically pure tetra-2,2,6,6-tetramethyl-4*H*-pyran-4-one (**1**): 3.39 g, 15% yield; lit.[12] bp 62.5–63.5 °C (11 mm); IR (CCl_4) 3000, 1720, 1380, 1365, 1295, 1225 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 6 H,), 1.38 (s, 6 H), 2.49 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 156 (M^+, 3), 141 (95), 98 (52), 85 (79), 83 (100), 70 (52), 56 (84).

2,2,6,6-Tetramethyl-4-piperidone (2). This compound was sublimed at its melting point: mp 56 °C (lit.[15] mp 58–59 °C); IR (KBr) 3320, 2960, 1687, 1450, 1285, 1210 cm^{-1}; NMR (CCl_4) δ 1.23 (s, 12 H), 1.52 (br s, 1 H), 2.25 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 155 (M^+, 18). 140 (100), 112 (20), 98 (67), and 83 (99); UV λ_{max} 245 nm (ϵ 14).

Tetrahydro-2,2,6,6-tetramethyl-4*H*-thiopyran-4-one (3). In a 125-mL, two-necked, round-bottomed flask equipped with a condenser, a gas inlet tube, and a gas outlet adapter attached to the top of the condenser leading to a trap containing a potassium hydroxide solution was placed 20 g (0.145 mol) of 2,6-dimethyl-2,5-heptadien-4-one (Phorone), 80 mL of 95% ethanol, and 0.4 g (0.007 mol) of potassium hydroxide. The solution was heated to reflux, and hydrogen sulfide was bubbled through it for 7 h. The resulting mixture was then cooled, diluted with an equal volume of water to give a two-phase system, and extracted with three 40-mL portions of diethyl ether. The combined ether extracts were dried with anhydrous magnesium sulfate, filtered, and evaporated. The residue was distilled in vacuo to give 15.5 g of product (62.1% yield), bp 90–95 °C (13 mm) [lit.[3] bp 96 °C (8 mm)]. Treatment of the product with 15.5 g of semicarbazide hydrochloride afforded 17.9 g of the corresponding semicarbazone (86.9% yield). The semicarbazone (12.5 g, 0.0545 mol) was hydrolyzed by refluxing it in 125 mL of 2 N hydrochloric acid for 30 min. The oil that separated was extracted with ether (3 × 20 mL). The extracts were dried with anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to yield 7.1 g of the chromatographically pure ketone (56.7% yield): lit.[3] bp 92 °C (14 mm); IR (neat) 2910, 1705, 1440, 1380, 1290, 1210 cm^{-1}; NMR ($CDCl_3$) δ 1.40 (s, 12 H), 2.55 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 172 (M^+, 91), 157 (76), 129 (9), 117 (65), 101 (61), 89 (54), 83 (100), 75 (81), 74 (93); UV λ_{max} 253 nm (ϵ 3.3).

3,3,5,5-Tetramethylcyclohexanone (4). This compound was commercially available: lit.[16] bp 79 °C (12 mm); IR (neat) 2950, 2910, 1705, 1450, 1380, 1360, 1340, 1275, 1220 cm^{-1}; NMR ($CDCl_3$) δ 1.03 (s, 12 H), 1.58 (s, 2 H), 2.15 (s, 4 H); mass spectrum (70 eV), *m/e* (relative intensity) 154 (M^+, 56), 139 (58), 126 (8), 111 (6), 97 (56), 83 (100), 56 (57), 55 (65); UV λ_{max} 288, 243 nm [lit.[16] λ_{max} 286 (ϵ 20)].

Photochemical Studies. The photolysis of **1** was carried out using a Hanovia 450-W, type L, high-pressure, mercury-arc lamp in a water-cooled, unfiltered quartz immension well. Special grade solvents were used for all photolyses and analyzed by VPC prior to use. All solutions were irradiated with stirring in a nitrogen atmosphere. Compounds **2**, **3**, and **4** were irradiated in a quartz cell positioned at the center of a helical Hanovia, low-pressure, mercury-arc lamp.

A. Irradiation of Tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-one (1) in Methanol. When compound **1** (3.0 g, 0.0192 mol) was irradiated in 10 mL of methanol for 48 h, compound **5** (41%) precipitated from solution and was removed by filtration. The remaining products, **6** (11%) and **7** (5%), were isolated by preparative gas chromatography. An additional compound detected in the chromatogram was tentatively identified as octahydro-2,2,4,4,10,10,12,12-octamethyl-3,7,11,14-tetraoxadispiro[5.1:5.2]pentadecane, the pyran analogue of **15.** This tentative identification is based on the similarity of its mass spectral fragmentation pattern with that of **15.**[6]

B. Irradiation of 1 in 2-Propanol. Compound **1** (2.0 g, 0.0128 mol) in 6 mL of 2-propanol was irradiated as in A to give **5** (38%), **6** (13%), and **8** (6%).

C. Irradiation of 2,2,6,6-Tetramethyl-4-piperidone (2) in Methanol. Compound **2** (2.0 g, 0.0129 mol) was irradiated in 10 mL of methanol for 72 h to give **9** (36%), which precipitated from solution and was removed by filtration. Compounds **10** (18%) and **11** (5%) were isolated by preparative gas chromatography.

D. Irradiation of 2 in 2-Propanol. Compound **2** (3.0 g, 0.0193 mol) in 15 mL of 2-propanol was irradiated as in C to give **9** (25%). An additional compound detected in the chromatogram was tentatively identified as 4-hydroxy-α,α,2,2,6,6-hexamethylpiperidinemethanol, the nitrogen analogue of **8.** This tentative identification is based on the similarity of its mass spectral fragmentation pattern with that of **8.**[6]

E. Irradiation of Tetrahydro-2,2,6,6-tetramethyl-4*H*-thiopyran-4-one (3) in Methanol. Compound **3** (1.5 g, 0.0087 mol) in 10 mL of methanol was irradiated for 48 h to give **12** (27%) and **13** (4%).

F. Irradiation of 3 in 2-Propanol. Compound **3** (1.5 g, 0.0087 mol) in 10 mL of 2-propanol was irradiated as in E to give **12** (85%) and **13** (1%), and two additional compounds detected in the chromatogram were tentatively identified as tetrahydro-α,α,2,2,6,6-hexamethyl-2*H*-thiopyran-4-methanol and octahydro-2,2,2′,2′,6,6,6′,6′,-octamethyl[4,4′-bi-2*H*-thiopyran]-4,4′-diol, the sulfur analogues of **8** and **5.** This tentative identification is based on the similarity of their mass spectral fragmentation patterns to those of **8** and **5.**[6]

G. Irradiation of 3,3,5,5-Tetramethylcyclohexanone (4) in Methanol. Compound **4** (5 g, 0.032 mol) in 15 mL of methanol was irradiated for 72 h to afford **14** (29%), **15** (24%), **16** (14%), and **17** (7%). Very small amounts of two additional products detected in the chromatogram were tentatively identified as 3′,3′,5′,5′-tetramethylcyclohexyl-3,3,5,5-tetramethylhexanoate and 3,3,3′,3′,5,5,5′,5′-octamethyl[1,1′-bicyclohexane]-1,1′-diol. This tentative identification is based on the similarity of their mass spectral fragmentation patterns to the products isolated in the photolyses of **1** and **2.**[6]

H. Irradiation of 4 in 2-Propanol. Compound **4** (5 g, 0.032 mol) in 15 mL of 2-propanol was irradiated as in G to give **17** (24%) and **18** (5%). Small amounts of the two products tentatively identified in G were also noted. Only a trace of the expected 2-propyl-3,3,5,5-tetramethylhexanoate, tentatively identified from its mass spectral fragmentation pattern, was observed in the photolysis mixture.[6]

Authentic samples of alcohols **6**, **10**, **12**, and **17** were prepared by lithium aluminum hydride reduction of the starting ketones **1** and **4.** The general procedure is illustrated with the preparation of tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-ol (**6**).

Tetrahydro-2,2,6,6-tetramethyl-4*H*-pyran-4-ol (6). Lithium aluminum hydride (1 g, 0.026 mol) was stirred in 15 mL of ether in a 50-mL, two-necked flask equipped with a dry ice condenser and a pressure-equalizing dropping funnel. Compound **1** (0.5 g, 0.0032 mol) in 10 mL of ether was added through the dropping funnel over a period of 5 min. The mixture was refluxed for 30 min, allowed to cool to room temperature (~15 minutes), and then slowly hydrolyzed with water (20 mL). The solution was filtered, and the filtrate was separated. The aqueous layer was extracted with ether (3 × 10 mL). The ether extracts were combined with the separated ether layer. The ether was dried with $MgSO_4$ and filtered and the ether evaporated to yield **6** as white crystals (0.494 g, 97.5% yield): mp 82–83 °C; IR (KBr) 3225, 2900, 1450, 1360, 1165 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 6 H), 1.29 (s, 6 H), 1.41 (d, J = 9 Hz, 2 H), 2.58 (s, 1 H), 4.09 (m, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 143 (82), 125 (96), 107 (56), 87 (88), 59 (100). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 68.11; H, 11.59.

4-Hydroxy-2,2,6,6-tetramethyl-4-piperidine (10): mp 127–128 °C (lit.[15] mp 128–128.5 °C); IR (KBr) 3335, 3195, 2875, 1370, 1355, 1050 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (s, 6 H), 1.21 (s, 6 H), 1.32 (dd, $\Delta\nu$ = 6 Hz, J = 4 Hz, 4 H), 2.26 (s, 1 H), 4.05 (m, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 157 (M^+, 3), 142 (99), 124 (39), 107 (19),

98 (67), 86 (58), 83 (62), 59 (100).

Tetrahydro-2,2,6,6-tetramethyl-2*H*-thiopyran-4-ol (12): mp 65–66 °C (lit.[5] mp 67 °C); IR (KBr) 3250, 2940, 2880, 1460, 1140, 1040 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (s, 6 H), 1.43 (s, 6 H), 1.81 (s, 1 H), 2.00 (dd, $\Delta\nu$ = 6 Hz, J = 2 Hz, 4 H), 3.98 (m, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 174 (M^+, 89), 159 (84), 141 (21), 140 (19), 125 (57), 99 (38), 98 (19), 85 (79), 75 (74), 69 (100).

3,3,5,5-Tetramethylcyclohexanol (17): mp 83–84 °C (lit.[4] mp 82–84 °C); IR (CCl_4) 3610, 3335, 2920, 1475, 1460, 1385, 1360, 1050 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (d, J = 10 Hz, 12 H), 1.03–1.24 (complex), 1.73 (d, J = 6 Hz, 4 H), 3.91 (m, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 155 (3), 154 (6), 141 (7), 138 (32), 123 (100), 97 (64), 95 (57), 85 (72), 83 (57), 82 (52), 81 (82), 67 (55).

Octahydro-2,2,2',2',6,6,6',6'-octamethyl[4,4'-bi-4*H*-pyran]-4,4'-diol (5): mp 154–155 °C; IR (KBr) 3520, 3360, 2970, 2925, 1450, 1370, 1360, 1120 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 12 H), 1.44 (s, 12 H), 1.45 (d, J = 6 Hz, 4 H), 1.69 (d, J = 6 Hz, 4 H), 2.26 (s, 2 H); mass spectrum (Figure 1, Supplementary Material) (70 eV), *m/e* relative intensity) 299 (4; elemental composition $C_{17}H_{31}O_4$), 281 (39), 263 (22), 207 (25), 205 (22), 158 (56), 140 (63), 125 (78), 99 (100). Anal. Calcd for $C_{18}H_{34}O_4$: C, 69.24; H, 11.04. Found: C, 69.25; H, 11.01.

Tetrahydro-4-hydroxy-2,2,6,6-tetramethyl-4*H*-pyran-4-methanol (7): IR (KBr) 3475, 2985, 2890, 1385, 1370, 1235, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, J = 8 Hz, 12 H), 1.44 (s, 2 H), 1.65 (br s, 4 H), 1.99 (br s, 1 H), 3.75 (s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 173 (70), 157 (11), 155 (89), 137 (75), 99 (100), 95 (95). Anal. Calcd for $C_{10}H_{20}O_3$: C, 64.48; H, 9.74. Found: C, 64.33; H, 9.96.

Tetrahydro-4-hydroxy-α,α,2,2,6,6-hexamethyl-4*H*-pyran-4-methanol (8): IR (KBr) 3450, 3335, 1460, 1375, 1360, 1155 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (s, 12 H), 1.45 (s, 6 H), 1.71 (br s, 4 H), 3.42 (br s, 1 H), 3.68 (br s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 201 (29), 183 (24), 165 (25), 157 (51), 145 (20), 127 (56), 99 (100), 59 (89).

2,2,2',2',6,6,6',6'-Octamethyl[4,4'-bipiperidine]-4,4'-diol (9): mp 170–172 °C; IR (KBr) 3525, 2960, 2925, 1440, 1370, 1360, 1350, 1110 cm^{-1}; NMR (acetic acid-d_4) δ 1.46–1.50 (br d, 6 H), 1.70 (br s, 6 H), 1.96 (br s, 4 H), 2.16 (s, 1 H); mass spectrum (Figure 2, Supplementary Material) (70 eV) *m/e* (relative intensity) 297 (14; elemental composition $C_{18}H_{36}N_2O_2$), 279 (72), 261 (46), 246 (9), 156 (51), 142 (11), 138 (25), 124 (24), 98 (82), 58 (100).

4-Hydroxy-2,2,6,6-tetramethyl-4-piperidinemethanol (11): IR (CCl_4) 3330, 2900, 2860, 1440, 1365, 1350 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (s, 6 H), 1.19 (s, 6 H), 1.43 (s, 4 H), 2.25 (br s, 1 H), 3.35 (s, 1 H), 3.64 (s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 187 (M^+, 9), 172 (100), 156 (56), 154 (82), 140 (11), 136 (25), 112 (42), 98 (88).

Tetrahydro-4-hydroxy-2,2,6,6-tetramethyl-2*H*-thiopyran-4-methanol (13): IR (CCl_4) 3400, 2940, 2900, 1460, 1440, 1365, 1070 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.46 (s, 6 H), 1.59 (br s, 2 H), 2.04 (dd, $\Delta\nu$ = 12 Hz, J = 4 Hz, 2 H), 2.60 (s, 1 H), 2.73 (s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 204 (M^+, 53), 189 (37), 173 (47), 171 (90), 153 (28), 143 (53), 130 (38), 115 (93), 83 (96), 75 (100).

Methyl 3,3,5,5-Tetramethylhexanoate (14). The spectral properties of this compound agreed with those reported by Hagens:[4] IR (CCl_4) 2980, 2955, 1735, 1470, 1435, 1365, 1230, 1150, 1115 cm^{-1}; NMR ($CDCl_3$) δ 0.98 (s, 9 H), 1.08 (s, 6 H), 1.40 (s, 2 H), 2.25 (s, 2 H), 3.60 (s, 3 H). The structure of this compound was further supported by its mass spectral data: mass spectrum (70 eV), *m/e* (relative intensity) 186 (M^+, 2), 171 (21), 155 (25), 153 (31), 139 (38), 131 (44), 130 (48), 129 (42), 115 (68), 113 (72), 97 (74), 57 (100).

2,2,4,4,10,10,12,12-Octamethyl-7,14-dioxadispiro[5.1:5.2]-pentadecane (15). This compound precipitated during photolysis. It was removed by filtration and recrystallized from 95% ethanol: mp 96–97 °C (lit.[4] mp 96–99 °C); IR (CCl_4) 3015, 2945, 1480, 1455, 1390, 1370, 1350 cm^{-1}; NMR ($CDCl_3$) δ 0.92 (s, 6 H), 1.02 (s, 6 H), 1.13 (s, 2 H), 1.45 (s, 2 H), 3.68 (s, 2 H); mass spectrum (Figure 3, Supplementary Material) (70 eV), *m/e* (relative intensity) 322 (M^+, 1), 307 (6), 251 (85), 197 (3), 195 (2), 168 (13), 151 (81), 109 (58), 83 (100).

1-Hydroxy-3,3,5,5-tetramethylcyclohexanemethanol (16). The spectral properties of this compound agreed with those reported by Hagens:[4] IR (CCl_4) 3500, 3330, 1385, 1365, 1045 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (s, 12 H), 1.21 (s, 6 H), 2.42 (br s, 2 H), 3.26 (m, 2 H); mass spectrum (70 ev), *m/e* (relative intensity) 171 (1), 168 (16), 155 (10), 153 (36), 150 (25), 137 (56), 135 (97), 125 (36), 83 (100).

1-Hydroxy-α,α,3,3,5,5-hexamethyl-1-cyclohexanemethanol (18): IR (CCl_4) 3460, 2865, 1450, 1375, 1360 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (s, 6 H), 1.23 (s, 12 H), 1.36–1.47 (complex), 1.69 (br s, 1 H); mass spectrum (70 eV), *m/e* (relative intensity) 196 (1), 181 (11), 178 (14), 163 (42), 155 (100), 137 (60), 121 (41), 107 (42), 97 (85), 83 (61).

Registry No.—**1**, 1197-66-6; **2**, 826-36-8; **3**, 22842-41-7; **4**, 14376-79-5; **5**, 64113-64-0; **6**, 20931-50-4; **7**, 64113-65-1; **8**, 64113-66-2; **9**, 55196-74-2; **10**, 2403-88-5; **11**, 64113-67-3; **12**, 20931-54-8; **13**, 64113-68-4; **14**, 64113-69-5; **15**, 64113-70-8; **16**, 64113-71-9; **17**, 2650-40-0; **18**, 64113-72-0; 2,6-dimethyl-2,5-heptadien-4-one, 504-20-1.

Supplementary Material Available: Mass spectra of compounds **5**, **9**, and **15** (3 pages). Ordering information is given on any current masthead page.

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Notes

Electrochemical Synthesis Of *N*-Acetyl-2,3-substituted Pyrroles[1]

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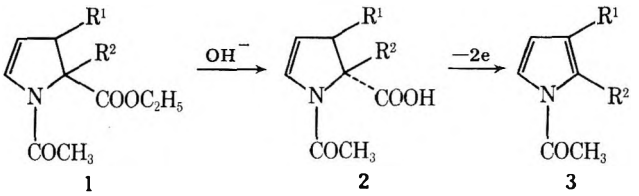
2,3-Substituted pyrroles are of physiological interest.[2] These pyrroles have been synthesized mainly by Knorr condensation of aminocarbonyl compounds or their precursors and carbonyl or dicarbonyl compounds;[3,4] the carbonyl compounds, however, are available with difficulty. Although a synthetic route to these pyrroles from aminonitrile and cinnamaldehyde, a so-called Miller–Plöchl condensation, has also been reported,[5] drastic conditions are required in the elimination step to the pyrroles. We now wish to report a convenient synthesis of *N*-acetyl-2,3-substituted pyrroles by anodic decarboxylation of *N*-acetyl-2,3-substituted-Δ^4-pyrroline-2-carboxylic acids, which are readily available. In previous reports from this laboratory, anodic oxidation, especially the abnormal Kolbe reaction,[6–8] has been investigated and shown to be of great preparative significance in the replacement of carboxylic acids by methoxy[9] or acetoxy[1] groups.

A synthesis of the pyrroles was carried out according to Scheme I. *N*-Acetyl-2,3-substituted-2-ethoxycarbonyl-Δ^4-pyrrolines **1a–d** were easily prepared by the reported methods;[10–12] diethyl acetamidomalonate and α,β-unsaturated aldehydes were condensed in ethanol in the presence of a catalytic amount of sodium ethoxide, followed by dehydration with *p*-toluenesulfonic acid. Saponification of the compounds (**1a–d**) gave the corresponding *N*-acetyl-2,3-substituted-Δ^4-pyrroline-2-carboxylic acids **2a–d** in good yields; the NMR spectra[11,12] of the compounds obtained herein showed that 2-carboxylic acids are trans to 3-substituents.

Anodic oxidation of compounds **2a–d** was carried out at 5–10 °C in a nondivided cell by the use of a graphite anode–graphite cathode. On electrolysis of compounds **2a–d** in water–tetrahydrofuran (3:1) using 0.05 molar equiv of potassium hydroxide, pyrroles **3a–d** were obtained in 86–94% yield. The products due to thermal decarboxylation of compounds **2a–d** were not observed under the electrolysis conditions. The use of a platinum anode gave almost the same result as that of the graphite anode. The current efficiencies of these electrode reactions were approximately 100%. The yields and electrolysis conditions are summarized in Table I. The *N*-acetylpyrroles **3a–d** thus obtained were easily hydrolyzed with aqueous ethanol containing sodium bicarbonate to give the deacetylated pyrroles.

Scheme I



1 2 3

a, R^1 = Ph; R^2 = $COOC_2H_5$
b, R^1 = Ph; R^2 = H
c, R^1 = CH_3; R^2 = $COOC_2H_5$
d, R^1 = CH_3; R^2 = H

Simultaneous oxidation of the electrolysis products is frequently encountered in anodic oxidation of organic compounds. It has been well documented that pyrroles are anodically oxidized at a relatively low potential to show a complicated product distribution; the products are usually 2,5-substituted-Δ^3-pyrrolines,[13] 2-*H*-pyrroles,[14] etc. Although a variety of solvent–electrolyte systems have been examined to avoid further oxidation of the products in these electrolyses, only the water–tetrahydrofuran system employed here enabled the reactions to proceed smoothly without any side reactions, even with 1.5 times a theoretical amount of current. When, for example, the oxidation was carried out in water–acetonitrile or acetonitrile, the electrolyzed solution became dark brown presumably because of the concurrent oxidation of the products. Furthermore, the addition of an inorganic salt such as sodium sulfate or sodium perchlorate made the product distribution more complex.

Although the stabilization of the carbonium ion by an acylamino group is responsible for the formation of only substitution products in the anodic oxidation of substituted acylaminomalonic acid monoester,[1,9] the electrolysis of *N*-

Table I. Electrolyses Conditions and Product Yields[a]

Run	Substrated (mmol)	Anode material[b]	Electrolyte[c]	Current density, mA/cm^2	Amount of electricity, F/mol	Product (yield %)
1	**2a** (10)	C	A	100	2.0	**3a** (91)
2	(10)	C	B	100	3.0	(91)
3	(10)	Pt	A	100	2.0	(94)
4	(100)	C	A	100	2.0	(90)
5	**2b** (10)	C	A	50	2.0	**3b** (86)
6	(10)	C	B	50	3.0	(41)[d]
7	**2c** (10)	C	A	100	2.0	**3c** (92)
8	(10)	C	B	100	3.0	(80)
9	**2d** (10)	C	A	100	2.0	**3d** (93)
10	**4** (3)	C	B	100	2.0	**5** (98)[e]

[a] The electrolysis was carried out at 5–10 °C in a nondivided cell. [b] C, carbon electrode and Pt, platinum electrode. [c] A, water–tetrahydrofuran (3:1) containing 0.05 molar equiv of potassium hydroxide to that of the substrate (**2a–d**); B, methanol containing 0.05 molar equiv of sodium methoxide to that of the substrate (**2a–c, 4**). [d] Compound **6** as well as the main product **3b** was isolated in 4.5% yield. [e] Mixture of *cis*-**5a** and *trans*-**5b** isomers.

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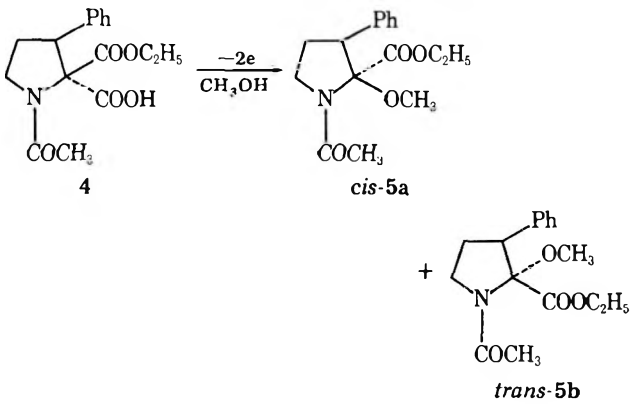
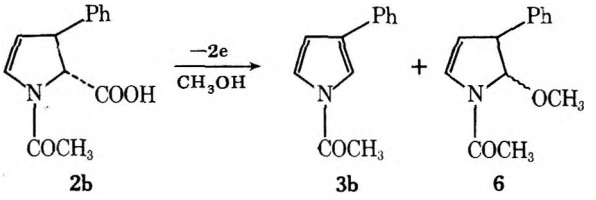
Scheme II



Scheme III



acetyl-Δ^4-pyrroline-2-carboxylic acids in this system gave no substitution products but only elimination products, pyrroles. However, even if *N*-acetyl-2-hydroxy-Δ^4-pyrroline, which is considered to be a substitution product, was formed in this electrolysis, this compound would be transformed spontaneously into the pyrrole by elimination of water. Accordingly, in order to examine the real electrode reaction, the electrolysis was carried out in methanol; the methoxylated products would be stable and isolated by the workup procedure employed here. Compound **2a** was electrolyzed in methanol containing 0.05 molar equiv of sodium methoxide, and the corresponding pyrrole **3a** was obtained in 91% yield. Careful analysis of the electrolysis product showed that the substitution product did not form. This result indicates that the lifetime of the carbonium ion generated by anodic oxidation of **2a** in a methanol or water–tetrahydrofuran (3:1) system is too short to enable solvent capture to compete with elimination; the driving force for elimination is aromatization. In fact, the products in the electrolysis of *cis*-*N*-acetyl-2-ethoxycarbonyl-3-phenylpyrrolidine-2-carboxylic acid (**4**) were those by substitution, which are a mixture of *cis*- and *trans*-*N*-acetyl-2-ethoxycarbonyl-2-methoxy-3-phenylpyrrolidines (Scheme II); these two isomers were assigned based on NMR spectra in which the chemical shift of the ester group CH_2CH_3 of compound **5a** (cis form) falls at a considerable lower field than that of compound **5b** (trans form). Furthermore, in the electrolysis of compound **2b** in which the reaction would proceed via the carbonium ion possessing a longer lifetime than that of **2a**, a small amount of substitution product **6** (4.5%) was formed, although the predominant formation of pyrrole **3b** was also observed (Scheme III); methoxy compound **6** was stable to the reaction and workup conditions.

In the electrolysis in water–tetrahydrofuran or methanol, the electrode reaction is initiated by an electron transfer from the carboxylate of compounds **2a–d** to the anode; the products due to oxidation of the allylic[15,16] or benzylic positions[17,18] of compounds **2a–d** were not observed.

Experimental Section

Equipment. Melting points were measured using the Yamato melting point apparatus and were uncorrected. IR spectra were recorded on a Schimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained using a Hitachi Perkin-Elmer R-20 high-resolution NMR spectrometer with tetramethylsilane as an internal standard. Electrolysis was carried out by use of a Hokuto HA 104 (1 A–55 V) potentio–galvanostatt attached to a Hokuto HA 108A coulomb meter.

Preparation of *N*-Acetyl-Δ^4-pyrroline-2-carboxylic Acids 2a–d. Compounds **2a** and **2c** were prepared as follows. Diester **1a** or **1c**[11,12] (0.1 mol) was dissolved in 70 mL of ethanol. To this was added dropwise a solution of potassium hydroxide (0.11 mol) dissolved in 20 mL of ethanol containing 6 mL of water at 20–25 °C under vigorous stirring. The reaction mixture was allowed to stand at ambient temperature for 3 days, and then the solvent was evaporated under reduced pressure below 30 °C. The residue was dissolved in 10–30 mL of water, and the solution was washed with ethyl acetate. The aqueous layer was acidified to Congo red with 12 N hydrochloric acid at 0 °C. The acidified solution was shaken with three 100-mL portions of ethyl acetate, and the combined ethyl acetate layer was washed twice with 20 mL of water, dried over magnesium sulfate, and then evaporated to dryness in vacuo below 30 °C. The resulting crystals were recrystallized with ethyl acetate–*n*-hexane. This procedure led to the saponification of only the ester group trans to the 3-substituents.

Compound **2a** (mp 106–107 °C) was obtained in 98% yield. The spectral and analytical data are as follows: IR (Nujol) 1745, 1735, 1590 cm^{-1}; NMR ($CDCl_3$ + Me_2SO-d_6) δ 0.85 (t, 3 H), 2.30 (s, 3 H), 3.54 (q, 2 H), 5.10 (t, 1 H, J = 2 Hz), 5.36 (dd, 1 H, J = 2, 5 Hz), 6.82 (dd, 1 H, J = 2, 5 Hz), 7.28 (s, 5 H). Anal. Calcd for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.25; H, 5.61; N, 4.55.

Saponification of compound **1c** afforded mono ester **2c** (mp 62–63 °C) in 78% yield: IR (Nujol) 1745, 1730, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (d, 3 H), 1.28 (t, 3 H), 2.24 (s, 3 H), 3.6–4.1 (m, 1 H), 4.28 (q, 2 H), 5.22 (dd, 1 H, J = 3, 5 Hz), 6.50 (dd, 1 H, J = 3, 5 Hz), 12.0 (broad s, 1 H). Anal. Calcd for $C_{11}H_{15}O_5N$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.71; H, 6.29; N, 5.80.

Saponification of compound **1b**[12] under the same conditions as above gave *trans*-**2b** (78%), mp 184–186 °C (lit.[12] mp 187–189 °C); *trans*-**2d** was similarly prepared from compound **1d** in 82% yield: mp 120–121 °C; IR (Nujol) 3120, 1740, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, 3 H), 2.20 (s, 3 H), 2.9–3.4 (m, 1 H), 4.38 (m, 1 H), 5.20 (dd, 1 H, J = 3, 5 Hz), 6.48 (dd, 1 H, J = 3, 5 Hz), 10.05 (broad s, 1 H). Anal. Calcd for $C_8H_{11}O_3N$: C, 56.79; H, 6.55; N, 8.38. Found: C, 56.88; H, 6.66; N, 8.23.

General Electrolysis Procedure. The electrolysis cell used was an ordinary beaker as reported previously.[1] The compound (**2a–d**) (0.01 mol) was dissolved in a mixture of 15 mL of tetrahydrofuran and 5 mL of water containing 0.15 mL of 1 N potassium hydroxide. The solution was put in the electrolysis cell and electrolyzed under the conditions described in Table I. When a theoretical amount of electricity was passed, the starting material was completely consumed. The electrolyzed solution was concentrated to dryness in vacuo below 30 °C. The residue was extracted with ethyl acetate. The extract was washed once with water, dried over magnesium sulfate, and then concentrated to dryness in vacuo. Compounds **2a** and **2b** were recrystallized from ethyl acetate–*n*-hexane. Compounds **2c** and **2d** were purified by distillation under reduced pressure.

Electrolysis in methanol was carried out under the same conditions described above, except that sodium methoxide was used as an electrolyte instead of potassium hydroxide.

Compound 3a. Compound **2a** was electrolyzed in water–tetrahydrofuran (3:1) or methanol to afford the titled compound: mp 52–53 °C; IR (Nujol) 1730, 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.52 (s, 3 H), 4.29 (q, 2 H), 6.38 (d, 1 H), 7.14 (d, 1 H), 7.2–7.7 (m, 5 H); MS *m/e* 257 (M^+). Anal. Calcd for $C_{15}H_{15}O_3N$: C, 69.98; H, 5.82; N, 5.53. Found: C, 70.02; H, 5.88; N, 5.44.

Compound **2a** was also oxidized using a platinum anode to afford compound **3a**, the physical constants being identical with those described above.

Compound **3a** (0.92 g) obtained above was suspended in 10 mL of water saturated with sodium bicarbonate, and the suspension was vigorously stirred at room temperature for 3 days. The reaction mixture was shaken with ethyl acetate, and the ethyl acetate layer was dried over magnesium sulfate. The solvent was evaporated to dryness in vacuo. The resulting crystals were recrystallized with ethyl acetate–*n*-hexane. This procedure allowed the quantitative formation of the deacetylated compound 2-ethoxycarbonyl-5-phenylpyrrole, mp 67–68 °C (lit.[19] mp 66–67 °C). Anal. Calcd for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.15; H, 6.17; N, 6.31.

Compound 3b. Compound **2b** was decarboxylated anodically in water–tetrahydrofuran (3:1) to afford compound **3b**: mp 87–89 °C; IR (Nujol) 1710, 1610, 1510 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (s, 3 H), 6.5–6.7 (m, 1 H), 7.1–7.7 (m, 7 H); MS (intensity) *m/e* 185 (M^+, 41), 143 (base peak), 115 (36), 43 (23). Anal. Calcd for $C_{12}H_{11}ON$: C, 77.81; H, 5.99; N, 7.59. Found: C, 77.61; H, 5.99; N, 7.43.

When compound **2b** was electrolyzed in methanol, the electrolyzed solution became dark brown. The solution showed several spots on TLC. The main products were isolated by silica gel chromatography using chloroform–ethyl acetate (9:1) as eluate. These were compounds **3b** (41%) and **6** (4.5%). The physical constants of compound **3b** obtained here were in complete agreement with those described above. Compound **6** (syrup) was a mixture of cis and trans isomers: NMR ($CDCl_3$) δ 2.14 and 2.24 (s and s, 3 H), 3.55 and 3.52 (s and s, 3 H), 3.8–4.0 and 4.0–4.2 (m and m, 1 H), 5.1–5.5 (m, 2 H), 6.6–7.6 (m, 6 H). The ratio of these isomers is 7:6 (cis/trans).

Compound 3c. Electrolysis of compound **2c** gave the titled compound: bp 99–100 °C (1 mm); IR (film) 3150, 1740–1710 (broad) cm^{-1}; NMR ($CDCl_3$) δ 1.34 (t, 3 H), 2.22 (s, 3 H), 2.48 (s, 3 H), 4.33 (q, 2 H), 6.05 (d, 1 H), 7, 12 (d, 1 H); MS (intensity) 185 (M^+, 41), 143 (base peak), 115 (36), 43 (23). Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.33; H, 6.43; N, 7.01.

Compound 3d. Anodic oxidation of compound **2d** afforded the titled compound: bp 41–42 °C (2 mm); IR (film) 3050, 1715 cm^{-1}; NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.45 (s, 3 H), 6.0–6.2 (m, 1 H), 6.9–7.1 (m, 1 H), 7.1–7.3 (m, 1 H); MS (intensity) 123 (M^+, 26), 97 (10), 81 (43), 80 (base peak), 53 (18), 43 (48). Anal. Calcd for C_7H_9ON: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.31; H, 7.32; N, 11.31.

Preparation of *cis*-4. *N*-Acetyl-2,2-diethoxycarbonyl-3-phenylpyrrolidine[12] was saponified with potassium hydroxide under the same conditions as described above to afford the title compound in 49% yield; this was recrystallized from ethyl acetate–*n*-hexane: mp 97–99 °C; IR (Nujol) 1740, 1720, 1620, 1560 cm^{-1}; NMR ($CDCl_3$) δ 1.01 (t, 3 H), 2.22 (s, 3 H), 2.0–2.9 (m, 2 H), 3.5–4.5 (m, 3 H), 3.88 (q, 2 H), 7.35 (s, 5 H). Anal. Calcd for $C_{16}H_{19}O_5N$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.94; H, 6.23; N, 4.56.

Electrolysis of *cis*-4. After compound **4** (910 mg) was electrolyzed under the conditions as shown in Table I, the electrolyzed solution was neutralized by the addition of acetic acid, and the solvent was evaporated to dryness in vacuo. The resulting residue was extracted with ethyl acetate, and the solution was washed with water, dried over magnesium sulfate, and then evaporated to dryness in vacuo. The residue was treated with silica gel chromatography using chloroform–ethyl acetate (5:4) as eluate to afford 460 mg of *cis*-**5a** and 420 mg of *trans*-**5b.**

Compound 5a: mp 130–131 °C; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 2.10 (s, 3 H), 2.0–3.0 (m, 2 H), 3.35 (s, 3 H), 3.5–3.8 (m, 3 H), 4.22 and 4.24 (q, 2 H), 7.25 (s, 5 H). Anal. Calcd for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.74; H, 7.14; N, 4.76.

Compound **5b** (syrup): NMR ($CDCl_3$) δ 0.81 and 0.89 (t and t, 3 H), 1.98 and 2.15 (s and s, 3 H), 2.0–3.0 (m, 2 H), 3.46 (s, 3 H), 3.72 and 3.79 (q and q, 2 H), 3.4–4.5 (m, 3 H), 7.1–7.4 (m, 5 H). Anal. Calcd for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.89; H, 7.31; N, 4.93.

The separation of the NMR signals of each group observed above is attributed to the rotational barrier about the C–N bond.[20]

Acknowledgment. We thank Drs. I. Chibata and M. Matsuoka for their encouragement.

Registry No.—**2a,** 64163-63-9; **2b,** 51212-32-9; **2c,** 64163-64-0; **2d,** 64163-65-1; **4,** 64163-66-2; **3a,** 64163-67-3; **3b,** 64163-68-4; **3c,** 64163-69-5; **3d,** 823-75-6; **1a,** 51212-30-7; **1b,** 64163-70-8; **1c,** 5846-04-8; **1d,** 64163-71-9; **5a,** 64175-43-5; **5b,** 64163-72-0; *cis*-**6,** 64163-73-1; *trans*-**6,** 64163-74-2; 2-ethoxycarbonyl-5-phenylpyrrole, 13355-43-6; *N*-acetyl-2,2-diethoxycarbonyl-3-phenylpyrrolidine, 51212-36-3.

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Thiocarbonyl Transfer Reagents[1]

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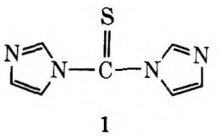
Heterocyclic thiocarbonyl transfer reagents, first prepared by Staab and co-workers,[3] have in the recent years found several important applications in the synthesis of new compounds.[4,5] Among these reagents mainly 1,1′-thiocarbonyldiimidazole (**1**) has been used, though reactions involving the



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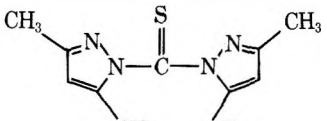

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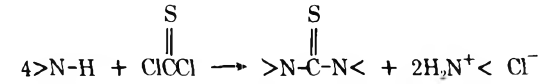
use of 1,1′-thiocarbonylbis(3,5-dimethylpyrazole) (**2**) also have been reported.[6]

Very little attention has been paid to the other members of this series, including 1,1′-thiocarbonyldibenzimidazole (**3**), 1,1′-thiocarbonyldibenzotriazole (**4**), and thiocarbonyldiindazole (**5**). Compounds **1** and **2** have been prepared in excellent yield[3,6] according to the following reaction. Compounds



3 and **5** have been synthesized by this reaction, but yields were uncertain.[7] For **4** the use of the free base is reported to be precluded, as this method results in the formation of 1-(2-benzothiazolyl)benzotriazole.[8] However, using the sodium salt of the heterocycle, compound **4** is formed, though no yield is reported.[7,8]

A more general approach to the preparation of these compounds requiring only 2 mol of the heterocycle involves the reaction between its silylated derivative and thiophosgene. In this way we have synthesized not only **1, 3,** and **4** but also

1,1′-thiocarbonyldipyrazole (**6**), for which the known methods have been reported to fail.[7] In addition, a new reagent, 1,1′-thiocarbonyldi-1,2,4-triazole (**7**), was also made (Table I). In all cases, the yields are excellent (90–100%) and the purity of the crude product very high.[9] The silylated precursors were prepared from the heterocycle and hexamethyldisilazane (HMDS) according to the method of Birkofer.[10]

Although **3, 4,** and **6** are generally less reactive (compared to **1**) with compounds having labile hydrogen atoms (amines, alcohols, and thiols), the properties of the reagents (stability toward moisture) and the low solubility of the heterocycle formed by the reaction may in certain situations give these reagents advantages superior to **1.** In the case of **7,** we found

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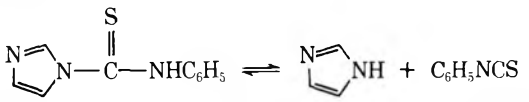
Table I. Thiocarbonyl Transfer Reagents

Compd	S = CR_2, R =	Registry no.	Mp, °C	Lit. Mp, °C	Yield, %	(C, H, N: calcd/found)
1	Imidazolyl	6160-65-2	105–106	105–106[3]	99	47.17, 3.39, 31.44/46.90, 3.87, 31.44
3	Benzimidazolyl	4314-17-4	137–138	149–150[7]	100	64.73, 3.62, 20.13/64.40, 3.52, 20.25
4	Benzotriazolyl	4314-19-6	170–171	176–178[7]	90	55.70, 2.88, 29.99/55.95, 2.80, 29.97
6	Pyrazolyl	21578-37-0	50–51		92	47.17, 3.39, 31.44/47.17, 3.22, 31.66
7	1,2,4-Triazolyl	63976-76-1	99–100		93	33.32, 2.24, 46.65/32.89, 2.80, 46.27

that it was more reactive than 1 in some reactions. For instance, 7 reacts with 2 mol of phenol to give diphenylthionocarbonate; the reaction is very fast at room temperature, while 1 requires heating to 90 °C for 6 h.

While 1 normally reacts well with 2 mol of aliphatic or aromatic primary amines, forming 1,3-disubstituted thioureas, the corresponding reaction with 1 mol of amine results in the formation of an isothiocyanate, due to dissociation of the unstable 1-(alkylthiocarbamoyl)imidazole.[3,11] However, 7 reacts instantaneously with 1 mol of amine to produce 1-(alkylthiocarbamoyl)-1,2,4-triazole. The reaction has been carried out with both aliphatic and aromatic amines, and the reaction products show no tendency to dissociate in chloroform solution, neither on prolonged standing nor on heating to 60 °C. If, however, more amine is added to the solution, 1,3-disubstituted thioureas are formed. This provides an advantage over 1 as it is possible to produce unsymmetrically



substituted thioureas directly. The orange color of reagent 7 is discharged after treatment with 1 mol of base, thus providing an added convenience for its use.

When 7 is reacted with diethylamine at room temperature, 1-(diethylcarbamoyl)-1,2,4-triazole was obtained, and even when an excess of the amine was used no tetraethylthiourea was obtained. This is in accord with the finding by Staab[3b] using 1 and diethylamine.

Reactions of 3 and 4 with aniline both gave 1,3-diphenylthiourea in good yields, but the use of these latter reagents has no advantages (compared to the use of 1 and 7) except in cases where the desired product has different properties of solubility than that of the displaced azole.

Experimental Section[12]

1,1'-Thiocarbonyldiimidazole (1). To a stirred solution of 1-trimethylsilylimidazole (0.169 mol, 23.6 g) in CCl_4 (150 mL) a solution of thiophosgene (0.085 mol, 9.73 g) in CCl_4 (25 mL) was added dropwise over a 90-min period. When ca. two-thirds of the thiophosgene solution had been added, yellow crystals of 1 began to precipitate. To ensure complete reaction, stirring was continued for 8 h. After cooling the reaction mixture in an ice–water bath, the crystals were collected, giving 13.10 g of analytically pure 1, mp 105–106 °C (lit.[3] 105–106 °C). Upon flash evaporation of the filtrate, an additional 1.95 g of slightly impure 1 was obtained; total yield 15.05 g (99%).

1,1'-Thiocarbonyldibenzimidazole (3), 1,1'-Thiocarbonyldibenzotriazole (4), and 1,1'-Thiocarbonyldi-1,2,4-triazole (7) were all prepared according to the method described for 1. In all cases, the crude products were analytically pure. The reaction product 6 from thiophosgene and silylated pyrazole remained in solution. Flash evaporation of the solvent and chlorotrimethylsilane left a brown oil which crystallized after seeding with crystals obtained by cooling a few drops of the oil in liquid nitrogen and subsequent addition of hexane. The crystals were recrystallized from an ether/hexane mixture to give analytically pure **1,1'-thiocarbonyldipyrazole (6).**

Diphenyl Thiocarbonate. Phenol (5.0 mmol, 470 mg) was added to a solution of 7 (2.5 mmol, 450 mg) in acetone (25 mL). Upon addition of one drop of triethylamine, the colored solution immediately turned colorless, and the subsequent addition of water afforded crystals which after recrystallization from ethanol/water gave a melting point of 106–107 °C (lit.[3b] 106 °C); yield 480 mg (83%).

1-(Phenylthiocarbamoyl)-1,2,4-triazole. To a solution of 7 (1.25 mmol, 225 mg) in acetone (25 mL) aniline (1.25 mmol, 116 mg) was added. The orange color of the solution disappeared immediately. Addition of water and subsequent cooling afforded a slightly yellow precipitate which was filtered off. The crystals (230 mg, 90%) had a melting point of 80–81 °C. Recrystallization from a benzene/hexane mixture did not increase the melting point.

Anal. Calcd for $C_9H_8N_4S$: C, 52.92; H, 3.95; N, 27.44. Found: C, 52.64; H, 3.72; N, 27.73.

1-Benzyl-3-phenylthiourea. To a solution of 1-(phenylthiocarbamoyl)-1,2,4-triazole (0.93 mmol, 190 mg) in 10 mL of CH_2Cl_2 was added benzylamine (0.93 mmol, 100 mg). The solution was left overnight and then cooled to −20 °C whereupon colorless crystals were formed. Filtration gave 190 mg (84%) of the target compound (mp 153–154 °C lit.[13] 153–154 °C).

1-(Cyclohexylthiocarbamoyl)-1,2,4-triazole. This compound was prepared as above. The crude product (92% yield of colorless crystals with a melting point of 78–79 °C) was submitted for analysis without any purification.

Anal. Calcd for $C_9H_{14}N_4S$: C, 51.40; H, 6.71; N, 26.65. Found: C, 51.45; H, 6.77; N, 26.85.

1-(Benzylthiocarbamoyl)-1,2,4-traizole. Using the same method as above, a 81% yield of colorless crystals was obtained. After recrystallization from a benzene/hexane mixture, the crystals had a melting point of 130–131 °C.

Anal. Calcd for $C_{10}H_{10}N_4S$: C, 55.02; H, 4.62; N, 25.67. Found: C, 55.05; H, 4.60; N, 25.84.

1-(Diethylthiocarbamoyl)-1,2,4-triazole. *In the same way as* above, a 91% yield of colorless crystals (mp 53–53.5 °C) was obtained. The crystals were submitted for analysis without any purification.

Anal. Calcd for $C_7H_{12}N_4S$: C, 45.62; H, 6.56; N, 30.41. Found: C, 45.50; H, 6.30; N, 30.40.

1,3-Diphenylthiourea. To a solution of 7 (2.5 mmol, 450 mg) in CH_2Cl_2 (10 mL) aniline (5 mmol, 465 mg) was added. The orange color of the solution disappeared, and at the same time a precipitate was formed. Filtration and evaporation of the solvent and recrystallization from ethanol/water gave 540 mg (95%) of 1,3-diphenylthiourea (mp 154–155 °C, lit.[14] 155 °C).

Acknowledgment. We thank the National Research Council of Canada, Imperial Oil of Canada, and the Danish Natural Science Research Council for financial support of this work.

Registry No.—1-Trimethylsilylimidazole, 18156-74-6; thiophosgene, 463-71-8; 1-(trimethylsilyl)benzimidazole, 13435-08-0; 1-(trimethylsilyl)benzotriazole, 43183-36-4; 1-(trimethylsilyl)-1,2,4-triazole, 18293-54-4; 1-(trimethylsilyl)pyrazole, 18156-75-7; 1-(phenylthiocarbanoyl)-1,2,4-triazole, 63976-77-2; anilene, 62-53-3; 1-benzyl-3-phenylthiourea, 726-25-0; benzylamine, 100-46-9; 1-(cyclohexylthiocarbanoyl)-1,2,4-triazole, 63976-78-3; cyclohexylamine, 108-91-8; 1-(benzylthiocarbanoyl)-1,2,4-triazole, 13101-79-2; 1-(diethylthiocarbanoyl)-1,2,4-triazole, 63976-79-4; diethylanine, 109-89-7; 1,3-diphenylurea, 102-08-9.

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(9) Except for the preparation of **6**, all the crude products were analytically pure. This is usually not found when the free base is used, and as the

thiocarbonyldiazoles in general are difficult to recrystallize (e.g., analytically pure **1** is obtained by sublimation in high vacuum[3b]), the synthesis via silylated precursors is to be preferred when pure products are needed. It is also our experience that the pure products are more "nonperishable" compared to compounds having a lesser purity.

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A New Tetrahydropyran Synthesis. Acid-Catalyzed Cyclization of δ-Substituted Aldehydes

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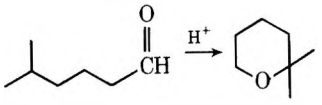
In preparing 1,1-diarylalkanes via acid-catalyzed condensation of aldehydes with alkylbenzenes, a novel rearrangement was discovered involving hydrogen exchange. While the scope of this rearrangement has not been defined, this reaction appears useful for a one-step synthesis of certain tetrahydropyran derivatives.[1] To function in this cyclization, the al-



(1)

dehydes must have at least seven carbon atoms and an alkyl substituent in the δ position.

Experiments were carried out using a C_8 aldehyde fraction, bp 148–150 °C, containing over 90% of 3,5-dimethylhexanal. This aldehyde was obtained from hydroformylation of mixed heptenes, bp 76–100 °C, synthesized in our laboratory by phosphoric acid dimerization of propylene with butenes. The novel cyclization product was isolated by distillation and characterized (Table I). Data were consistent for either 2,2,4-trimethyltetrahydropyran or 2-isopropyl-3-methyltetrahydrofuran, both unreported in the literature. For further elucidation, we prepared a simpler aldehyde, 5-methylhexanal, which on treatment with sulfuric acid gave 2,2-dimethyltetrahydropyran, a known compound.[2] Its structure was additionally verified by NMR.

Table I. Cyclization of 3,5-Dimethylhexanal[a]

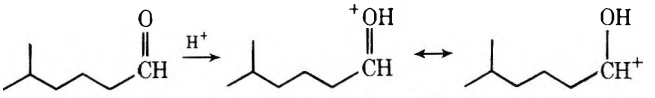
Run no.	Acid concn, wt %	Molar ratio, acid/RCHO	%yield of 2,2,4-trimethyl tetrahydropyran	Remarks
1	96% H_2SO_4	6:1	60	
2	96% H_2SO_4	9:1	74	
3	80% H_2SO_4	6:1	3	
4	100% H_2SO_4	6:1	65	
5	BF_3-H_2O	3:1	90	BF_3/H_2O ratio, 1:1
6	BF_3-H_2O	3:1	75	BF_3/H_2O ratio, 1:1.5
7	85% H_3PO_4	6:1	~0	Two-phase system.
8	100% H_3PO_4	6:1	25	
9	BF_3-H_2O-H_3PO_4	6:1	80	$BF_3/H_2O/H_3PO_4$, 1:0.23:1.27

[a] Reaction temperature 0 °C. [b] By distillation; bp 134–136 °C. Anal. Calcd for $C_8H_{16}O$: C, 74.94; H, 12.58; O, 12.48 (diff); $[M_R]_D$ 38.6 mL/mol. Found: C, 74.5; H, 12.4; O, 13.1 (diff). mol wt (*m/e*) 128; IR 1100 cm^{-1} (s, cyclic ether); sp gr (15°) 0.8493; $n^{20}D$ 1.4250; $[M_R]_D$ 38.6 mL/mol.

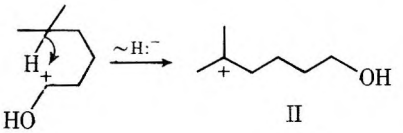
Cyclization competes with condensation and oxidation, but was favored by adding aldehyde slowly to acid. In cases where the addition sequence was reversed, cyclic ethers were not detected, and only resinous product was obtained.

The driving force for cyclization of δ-substituted aldehydes appears to be the generation of a relatively stable tertiary carbonium ion at the δ position when the hydride ion transfers. With *n*-hexanal and *n*-heptanal consequently, only condensation, but no cyclization, is observed as there is no incentive to form the less stable secondary carbonium ion. An attempt to prepare 2-phenyltetrahydropyran from 5-phenylpentanal failed, as intermolecular alkylation of the benzene ring was considerably faster than the expected benzylic carbonium ion formation.

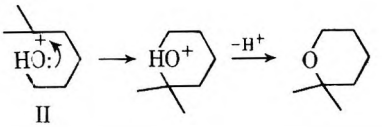
Products are rationalized by an ionic mechanism. In the first step, aldehyde is protonated to give carbonium ion I, which then undergoes intramolecular exchange to form carbonium ion II, followed by cyclization.



I (2)

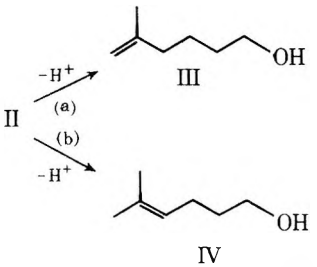


I II (3)



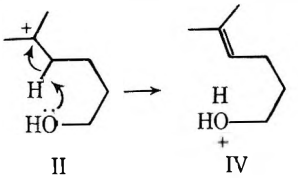
II (4)

In view of the similarity of products and also the reaction conditions between the present work and that of the Prins reaction,[3-5] it is also possible for the tetrahydropyran ring to form by a mechanism involving olefinic intermediates. Ion II can undergo deprotonation in two directions to give alcohols which are derivatives of vinylidene III or internal olefin IV, respectively.



II III IV (5)

Since typical El elimination reactions afford the more highly substituted olefins as major products (Saytzeff rule),[6] the dominant pathway in our work would involve route b. Formation of IV can be assisted by a quasi-six-membered transition state. To form III, this process would require an eight-membered ring transition state which is energetically not fa-



II IV (6)

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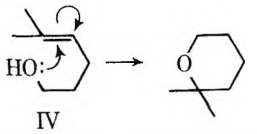
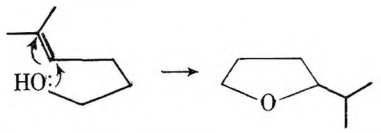
vored. The last step involves cyclization of IV to the tetrahydropyran ring.



(7)

IV

In fact, acid-catalyzed cyclizations of unsaturated alcohols to give either tetrahydropyrans[7,8] or tetrahydrofurans[8,9] are known, and in at least one case unsaturated alcohol has been isolated as an intermediate in the Prins reaction.[4] If unsaturated alcohols are involved, some cyclization is expected to



(8)

occur via a five-membered transition state to give tetrahydrofuran derivatives. The key compound in the case of 5-methylhexanal cyclization would be the presence of 2-isopropyltetrahydrofuran. We found no evidence for this ether among the reaction products. Cyclization appears therefore not to involve olefinic intermediates, and the reaction proceeds mostly via eq 4, analogous to acid-promoted cyclization of 1,5-pentanediol or pentamethylene chlorohydrin which form a tetrahydropyran ring via a cyclic oxonium ion intermediate.[10]

Experimental Section

Preparation of 5-Methylhexanal. About 100 g of 4-methyl-1-pentene (Phillips Petroleum) was carbonylated in benzene solvent (437 g) over 1.0 g of $RhH(CO)(Ph_3P)_3$ catalyst (100 °C, 60 atm, 30 min, $2H_2/CO$) to give 17 g of 5-methylhexanal: bp 80–85 °C (100 mm.Hg) (lit.[11] bp 84 °C at 100 mm); NMR (CCl_4, Me_4Si) 9.5 (s, 1 H, CHO), 2.3 (t, 2 H, CH_2CO, $J \approx 7$ Hz), 1.0–1.8 (m, 5 H, CH_2, CH), and 0.95 (d, 6 H, CH_3, $J \approx 7$ Hz) ppm. The spectrum, however, contained several peaks in the 9.5-ppm region, indicating a purity of only 70%. This is consistent with compositions carried out with $(Co_2(CO)_4)_2$ catalysts.[12,13]

Cyclization of 5-Methylhexanal. In a typical experiment, 9.0 g (0.08 mol) of the above aldehyde was added dropwise, while stirring, to 184 g of 96% sulfuric acid (1.8 mol), maintaining a temperature between 0 and −5 °C. After the addition was completed, the reaction mixture was stirred for 30 min and poured over 500 g of cracked ice. Extraction with ether, followed by washing with water, drying ($MgSO_4$), and distillation gave 3.5 g (39%) of 2,2-dimethyltetrahydropyran: bp 58–60 °C (100 mmHg), $n^{24.5}D$ 1.4245 [lit.[2] bp 119–120 °C (atm), $n^{18}D$ 1.4272]; NMR (CCl_4, Me_4Si) 3.5 (m, 2 H, CH_2O), 1.5 (m, 6 H, CH_2), and 1.1 (s, 6 H, CH_3) ppm, identical to the spectrum of the authentic sample. Aldehydes which did not have a methyl substituent in the δ position were converted to high-boiling resinous materials.

Acknowledgment. We thank Dr. R. C. Williamson for a gift of rhodium carbonylation catalyst.

Registry No.—3,5-Dimethylhexanal, 19796-88-4; 2,2,4-trimethyltetrahydropyran, 7379-08-0; 4-methyl-1-pentene, 691-37-2; 5-methylhexanal, 1860-39-5; 2,2-dimethyltetrahydropyran, 35270-87-2.

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Studies on Pyrazines. 2.[1] Structural Assignment of the Reaction of α-Amino-α-phenylacetonitrile with Chloral or Bromal to *N*-(2,2-Dihaloethenyl)-1-imino-1-phenylacetonitriles

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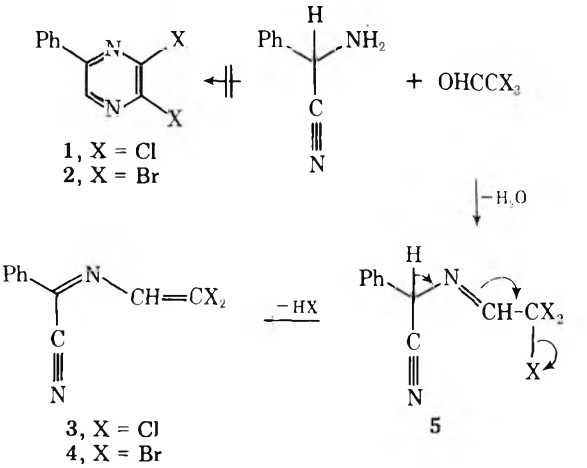
In a previous paper,[1] we reported a preparation of 2,3-dichloro-5-phenylpyrazine (1) by chlorination of 2,3-dihydroxy-5-phenylpyrazine with phosphoryl chloride. In 1915, Minovici and Bente[2] also described compound **1** and its bromo homologue **2** as reaction products of α-amino-α-phenylacetonitrile with chloral and bromal, respectively. We have now found that the dichloro product obtained in this reaction is entirely different (spectra, mixture melting point) from our earlier preparation and have assigned the structures of the Minovici–Bente products as *N*-(2,2-dihaloethenyl)-1-imino-1-phenylacetonitriles **3** and **4**.

The NMR spectra contain 1 H singlets at δ 7.78 in **3** and 8.11 in **4**. These signals can not be assigned to the ring protons of authentic 2,5-[3] and 2,6-dihalo-3-phenylpyrazines,[4] the latter of which were prepared by halogenation of 2-hydroxy-6-chloro-5-phenylpyrazine. The presence of a conjugated cyano group in the IR spectra at 2210 cm^{-1} in **3** and 2205 cm^{-1} in **4** indicates that **3** and **4** are not dihalopyrazines but acyclic compounds formed on dehydrohalogenation of Schiff base **5**



prior to the cyclization of dihalopyrazines. The presence of a Ph–C–CN group in **3** and **4** was further confirmed by hydrolytic degradations with concentrated hydrochloric acid to give phenylglyoxalic acid (90–93%) and with 5% ethanolic potassium hydroxide to give benzoic acid (70–75%). Additional evidence for the structure of **3** and **4** was obtained from mass spectra, e.g., for the formation of β,β-dihaloethenium ion, *m/e* 95 and 183, respectively.

The formation of **5**, in contrast to the reaction of α-aminoacetonitrile and chloral which forms an adduct and not a Schiff base,[5] is clearly due to the phenyl group. Similarly,

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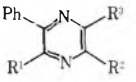
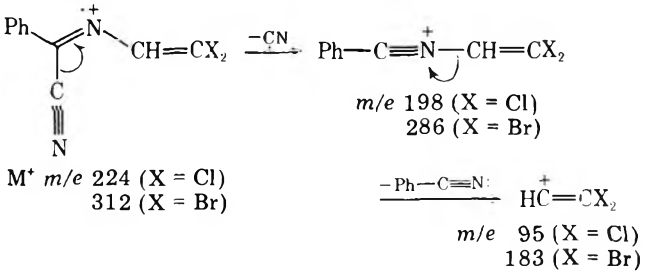
Table I. Preparation and NMR Spectral Data of Dihalopyrazines



	R¹	R²	R³	Registry no.	Type of starting material	Yield, %	Mp, °C (lit. mp, °C)	NMR (ring proton), δ
1	H	Cl	Cl	32493-80-4			(106-107)[1]	8.67
2	H	Br	Br	64163-08-02	Dihydroxy[1]	85[f]	115[a]	8.81
	Cl	H	Cl	64163-09-3	Bromohydroxy[3]	96[g]	58-59[d] (59-60)[3]	8.31
	Br	H	Br	64163-10-6	Bromohydroxy[3]	89[g]	83-84[b] (71-72)[3]	8.39
	Cl	Cl	H	64163-11-7	Chlorohydroxy	93	57-58[e,h]	8.54
	Br	Br	H	64163-12-8	Dichloro	84[g]	66-67[c]	8.65

[a] Anal. Calcd for $C_{10}H_6N_2Br_2$: C, 38.25; H, 1.93; N, 8.92; Br, 50.90. Found: C, 38.45; H, 2.08; N, 9.01; Br, 50.92. [b] Found: C, 38.33; H, 1.87; N, 8.95; Br, 51.09. [c] Found: C, 38.38; H, 1.94; N, 8.95; Br, 50.48. [d] Anal. Calcd for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45; Cl, 31.15. Found: C, 53.30; H, 2.27; N, 12.34; Cl, 31.34. [e] Found: C, 53.58; H, 2.59; N, 12.44; Cl, 31.56. [f] Recrystallized from *n*-hexane. [g] Recrystallized from ethanol. [h] Bp 122-123 °C (0.1 mm).



3-bromo-4-methylphenylhydrazine reacts with chloral to form the hydrazone,[6] whereas hydrazine gives the adduct *N*-(1-hydroxy-2,2,2-trichloroethyl)hydrazine.[7] This halohydrazone was dehydrochlorinated to form 3-bromo-4-methylbenzeneazo-β,β-dichloroethylene,[6] supporting the transformation of Schiff base **5** to **3** or **4**.

Experimental Section

Melting points were determined in a capillary and are corrected. IR spectra (KBr) were recorded on a Hitachi Model EPI-G3 spectrometer. NMR spectra ($CDCl_3$) were recorded on a JEOL Model JNM-MH-100 instrument with tetramethylsilane as an internal standard. Mass spectra were measured on a Hitachi Model RMU-6L instrument at 70 eV.

General Procedure for Preparation of Dihalopyrazines. These results are summarized in Table I.

A mixture of the starting material indicated in Table I (0.01 mol) and phosphoryl chloride or phosphorus tribromide (20 mL) in a sealed tube was heated at 180–200 °C for 5–40 h and then poured into ice water. The precipitate which formed was collected by filtration, and the mother liquor was extracted with ether. The extract was combined with the precipitate, and undissolved matter was removed by filtration. The filtrate was washed with water, dried over magnesium sulfate, evaporated, and recrystallized to afford dihalopyrazine.

Preparation of 2-hydroxy-6-chloro-5-phenylpyrazine is as follows. A mixture of 1-hydroxy-2-keto-5-phenyl-1,2-dihydropyrazine[8] (7.21 g, 0.038 mol) in 30 mL of phosphoryl chloride was refluxed with stirring for 30 min and then poured into ice water. The precipitate which formed was collected by filtration, sublimed at 180–185 °C (0.01 mm), and recrystallized from ethanol to give colorless prisms (4.57 g, 58%): mp 235–236 °C; IR 3050–2550 (br), 1656, 1590, 846 cm^{-1}; NMR δ 12.5 (br s, 1), 8.20 (s, 1), 7.75–7.6 (m, 2), 7.55–7.4 (m, 3).

Anal. Calcd for $C_{10}H_7N_2OCl$: C, 58.13; H, 3.41; N, 13.56; Cl, 17.16. Found: C, 57.92; H, 3.51; N, 13.40; Cl, 17.00.

***N*-(2,2-Dichloroethenyl)-1-imino-1-phenylacetonitrile (3)** was prepared according to the procedure of Minovici and Bente:[2] mp 102 °C from ethanol (lit.[2] mp 102 °C); IR 2210, 1596, 1572, 1448, 1302, 1279, 952, 855 cm^{-1}; NMR δ 7.78 (s, 1), 8.2–8.0 (m, 2), 7.7–7.3 (m, 3); mass spectrum *m/e* 224 (M^+, 64), 228 (8), 226 (42), 200 (6), 198 (9), 191 (36), 189 (100), 183 (9), 182 (7), 164 (7), 162 (20), 154 (7), 153 (31), 129 (10), 115 (19), 114 (11), 113 (14), 112 (14), 111 (10), 104 (21), 103 (20), 102 (10), 99 (10), 97 (13), 95 (14), 88 (14), 85 (28), 83 (16), 81 (18), 77 (24).

Anal. Calcd for $C_{10}H_6N_2Cl_2$: C, 53.36; H, 2.69; N, 12.45; Cl, 31.51. Found: C, 53.44; H, 2.66; N, 12.54; Cl, 31.49.

***N*-(2,2-Dibromoethenyl)-1-imino-1-phenylacetonitrile (4)** was similarly prepared: mp 120 °C from ethanol (lit.[2] mp 120 °C); IR 2205, 1592, 1566, 1442, 1294, 1272, 879, 852 cm^{-1}; NMR δ 8.11 (s, 1), 8.3–8.1 (m, 2), 7.7–7.3 (m, 3); mass spectrum *m/e* 312 (M^+, 44), 314 (88), 316 (44), 290 (2), 288 (4), 286 (2), 235 (38), 233 (38), 208 (3), 206 (9), 187 (5), 185 (10), 183 (5), 155 (13), 154 (100), 152 (35), 127 (20), 115 (14), 114 (12), 104 (31), 103 (21), 102 (24), 88 (16), 77 (24).

Anal. Calcd for $C_{10}H_6N_2Br_2$: C, 38.25; H, 1.93; N, 8.92; Br, 50.90. Found: C, 38.33; H, 2.05; N, 8.84; Br, 50.85.

Acknowledgment. The authors wish to thank Dr. T. Nakagawa for his helpful suggestions.

Registry No.—**3**, 64201-59-8; **4**, 64201-60-1; α-amino-α-phenylacetonitrile, 16750-42-8; chloral, 75-87-6; bromal, 115-17-3; phosphorus tribromide, 7789-60-8; 1-hydroxy-2-keto-5-phenyl-1,2-dihydropyrazine, 64163-13-9; 2-hydroxy-6-chloro-5-phenylpyrazine, 64163-14-0; phosphoryl chloride, 10025-87-3; 2,3-dihydroxy-5-phenylpyrazine, 32493-63-3; 2-bromo-3-phenyl-5-hydroxypyrazine, 64163-15-1; 2-chloro-3-phenyl-5-hydroxypyrazine, 64163-16-2; 2,5-dichloro-3-phenylpyrazine, 64163-09-3.

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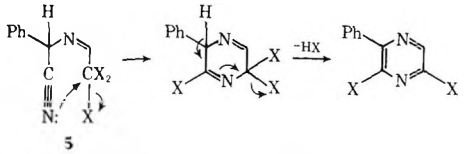

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Studies on Pyrazines. 3.[1] A Facile Synthetic Method for 2,3-Diaminopyrazines

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Methods for the preparation of 2,3-diaminopyrazines **1** have hitherto involved amination of 2,3-dihalopyrazines or 2-amino-3-halopyrazines, whose synthesis requires several steps.[2-5] We have found a more direct synthetic method for

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Table I. Preparation of Furazanopyrazines 5d–f

Compd	Registry no.	Method	Yield, %	Mp,[c] °C
5d[a]	64163-29-7	A	92	145–146
e[b]	64163-30-0	A	79	110–111
f	24294-88-0	B	98	195–196 (lit.[d] 195–196)

[a] Anal. Calcd for $C_{10}H_6N_4O$: C, 60.60; H, 3.05; N, 28.27. Found: C, 60.70; H, 3.33; N, 28.32. [b] Anal. Calcd for $C_{11}H_8N_4O$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.47; H, 3.79; N, 26.56. [c] Recrystallized from ethanol. [d] A. Gasco, G. Rua, E. Menziani, G. M. Nano, and G. Tappi, *J. Heterocycl. Chem.*, **6**, 769 (1969).

Table II. Preparation of Triazolopyrazines 6a–f

Compd	Registry no.	Method	Yield, %	Mp, °C
6a[a]	64163-31-1	C	89	179–180[f]
b[b]	64163-32-2	C	91	140–142[f]
c[c]	64163-33-3	A	88	208–209[g]
d[d]	64163-34-4	A	92	184–185[g]
e[e]	64163-35-5	A	86	153[g]
f	64163-36-6	A	90	224[h] (lit.[11] 217)

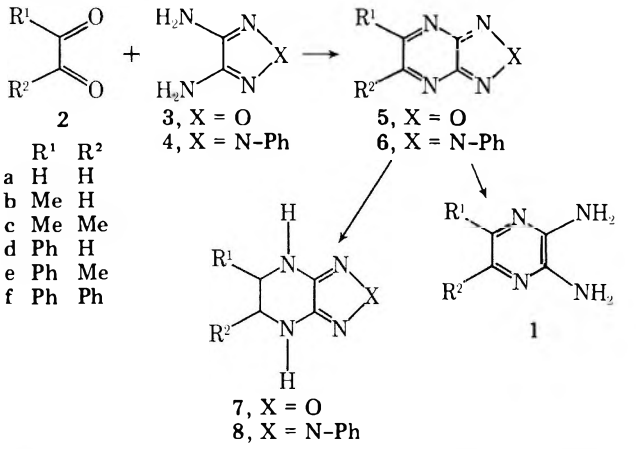
[a] Anal. Calcd for $C_{10}H_7N_5$: C, 60.90; H, 3.58; N, 35.52. Found: C, 61.18; H, 3.64; N, 35.79. [b] Anal. Calcd for $C_{11}H_9N_5$: C, 62.55; H, 4.30; N, 33.16. Found: C, 62.48; H, 4.20; N, 32.90. [c] Anal. Calcd for $C_{12}H_{11}N_5$: C, 63.98; H, 4.92; N, 31.09. Found: C, 63.69; H, 5.08; N, 30.81. [d] Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.31; H, 4.06; N, 25.63. Found: C, 70.43; H, 3.90; N, 25.77. [e] Anal. Calcd for $C_{17}H_{13}N_5$: C, 71.06; H, 4.56; N, 24.38. Found: C, 71.18; H, 4.36; N, 24.23. [f] Recrystallized from methanol. [g] Recrystallized from ethanol. [h] Recrystallized from acetic acid.

Table III. Preparation of 2,3-Diaminopyrazines 1d–f

Compd	Registry no.	Yield, %	Mp,[a] °C	Lit. mp, °C
1d	32493-83-7	97	172–173[b]	172[1]
e	32493-84-8	67	169–170[b]	167–168[1]
f[c]	64163-37-7	65	282–283	275–285[5]

[a] Recrystallized from benzene. [b] This compound was also identified with an authentic sample[1] by IR spectrum. [c] Anal. Calcd for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.30; H, 5.25; N, 21.12.

diaminopyrazines **1d–f** in the catalytic hydrogenation of furazanopyrazines **5d–f**, readily obtained by condensation of 3,4-diaminofurazan **3** with the corresponding 1,2-dicarbonyl compounds **2d–f**, with palladium on carbon.[6] Condensations of **3** with **2a–c** to give **5a–c** were unsuccessful under various



conditions so far examined and resulted in the recovery of **3** on using acidic solvent as a condensing agent or in the formation of a small amount of unidentified byproducts in basic solvent.

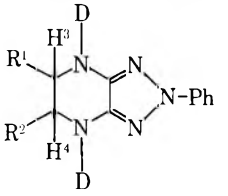
With palladium on carbon, platinum black, or Raney nickel, triazolopyrazines **6a–f**, easily prepared by the condensation of 4,5-diaminotriazole **4** with the corresponding **2a–f**, were converted to triazolopiperazines **8a–f** in excellent yields instead of diaminopyrazine **1**. The structure of **8** was confirmed by elemental and NMR spectral analyses. Coupling constants of the protons in **8** (in Me_2SO-d_6 and D_2O) are approximately consistent with those (in aqueous solution) of *trans*-2,5-dimethylpiperazine,[7] which exists in the chair conformation and whose coupling constants[8] $J_{3,4}$, $J_{2,3}$, $J_{2,4}$, and $J_{Me,H}$[3] are 2.9, 10.8, 12.5, and 6.4 Hz, respectively. A slight difference of the coupling constants between **8** and dimethylpiperazine, particularly $J_{2,3}$, may be caused by a distorted chair conformation of the piperazine ring of **8** fused with the triazolopiperazine ring.

Triazolopiperazines **8** were also prepared by the reduction

Table IV. Preparation and NMR Spectral Data of Triazolopiperazines 8a–f

				NMR[k] (Me_2SO-d_6 + D_2O)							
				Chemical shift, δ				Coupling constant, Hz			
Compd	Registry no.	Yield,[g] %	Mp, °C	R^1	R^2	H^3	H^4	$J_{3,4}$	$J_{2,3}$	$J_{2,4}$	$J_{Me,H_3\ (H_4)}$
8a[a]	64163-38-8	96	190–191[h]			3.27		0	0	0	
b[b]	64163-39-9	97	145–146[h]	1.15	2.87	3.42	3.27	3.0	8.4	11.4	6.2
c[c]	64163-40-2	98	125–126[i]	1.07		3.44		0			6.8
d[d]	64163-41-3	84	155–156[i]	*l*	3.19	4.50	3.42	3.5	7.8	12.0	
e[e]	64163-42-4	95	66–67[h]	*l*	0.87	4.53	*m*	3.0			7.0
f[f]	64163-43-5	98	236[j]	*l*	*l*	4.77		0			

[a] Anal. Calcd for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81. Found: C, 59.84; H, 5.29; N, 34.78. [b] Anal. Calcd for $C_{11}H_{13}N_5$: C, 61.37; H, 6.09; N, 32.54. Found: C, 61.47; H, 5.95; N, 32.53. [c] Anal. Calcd for $C_{12}H_{15}N_5$: C, 62.87; H, 6.62; N, 30.55. Found: C, 62.87; H, 6.66; N, 30.66. [d] Anal. Calcd for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45; N, 25.26. Found: C, 69.59; H, 5.53; N, 24.92. [e] Anal. Calcd for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 69.73; H, 6.02; N, 23.85. [f] Anal. Calcd for $C_{22}H_{19}N_5$: C, 74.76; H, 5.42; N, 19.82. Found: C, 74.82; H, 5.36; N, 19.83. [g] These yields result from hydrogenation of **6** with 10% palladium on carbon. [h] Recrystallized from *n*-hexane. [i] Recrystallized from cyclohexane. [j] Recrystallized from benzene/petroleum ether. [k] Structure.

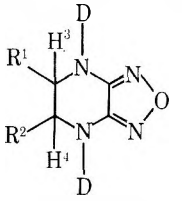


[l] This peak can not be determined because of overlap with one of the phenyl groups situated in the triazolo ring. [m] This peak can not be determined because of overlap with one of water.

Table V. Preparation and NMR Spectral Data of Furazanopyrazines 7d-f

Compd	Registry no.	Yield,[d] %	Mp, °C	NMR[g] (Me_2SO-d_6 + D_2O) Chemical shift, δ R¹	R²	H³	H⁴	Coupling constant, Hz $J_{3,4}$	$J_{2,3}$	$J_{2,4}$	J_{Me,H^4}
7d[a]	64163-44-6	84	189-190[e]	7.37	3.16	4.53	3.40	3.5	8.0	12.0	
e[b]	64163-45-7	87	203[f]	7.2-7.4	0.84	4.52	*h*	3.5			6.5
f[c]	64163-46-8	84	234-235[e]	7.0-7.2		4.80		0			

[a] Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.33; H, 5.22; N, 27.38. [b] Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.90. Found: C, 61.02; H, 5.52; N, 25.70. [c] Anal. Calcd for $C_{16}H_{14}N_4O$: C, 69.05; H, 5.07; N, 20.13. Found: C, 68.91; H, 4.83; N, 20.13. [d] These result from the reduction of 5 with sodium borohydride. [e] Recrystallized from benzene. [f] Recrystallized from benzene/petroleum ether. [g] Structure



[h] This peak can not be determined because of overlap with one of water.

of **6** with sodium borohydride, but compounds **6** were inert to lithium aluminum hydride. On the other hand, furazanopyrazines **5** were reduced with lithium aluminum hydride, as well as sodium borohydride, to yield furazanopiperazines **7**. The NMR spectra of **7** give the same results as those of **8**.

Recently, syntheses of 3,4-diamino-1,2,5-thiadiazole and 1,2,5-thiadiazolo[3,4-*b*]pyrazines were reported,[9] and the latter would be expected to give diaminopyrazines **1** under reductive conditions.

Experimental Section

All melting points were determined in a capillary and are corrected. NMR spectra were measured on a JEOL Model JNM-MH-100 instrument with tetramethylsilane as an internal standard.

Condensation of 3,4-Diaminofurazan (3)[10] or 4,5-Diamino-2-phenyl-1,2,3-triazole (4)[11] with 1,2-Dicarbonyl Compounds 2. The results are summarized in Tables I and II, respectively.

Method A. A solution of **3** or **4** (0.01 mol) and **2** (0.011 mol) in 20 mL of acetic acid/ethanol (1:3 v/v) was refluxed for 2 h. After cooling to room temperature, the precipitate which formed was collected by filtration and recrystallized to afford **5** or **6**, respectively.

Method B. A mixture of **3** (0.01 mol), **2f** (0.01 mol), and boron trifluoride etherate (1 mL) was heated at 120–130 °C for 10 min. The precipitate that formed after cooling to room temperature was collected by filtration, washed with water, and recrystallized from ethanol to provide **5f**.

Method C. A warm (~80 °C) solution of **2** (bisulfite salt, 0.011 mol) in 20 mL of water was added to a stirred solution (at 80 °C) of **4** in 50 mL of water. The resulting solution was maintained at 80 °C for 1 h. Sodium carbonate (0.011 mol) was added to the cooled solution, and the precipitates were collected by filtration. The filtrate was extracted with three 10-mL portions of ether, and the extracts were washed with water, dried over magnesium sulfate, and evaporated. The combined products were recrystallized to give **6**.

Hydrogenation of 5 or 6 in the Presence of Palladium Catalyst. A solution of **5** or **6** (0.01 mol) in 30–200 mL of ethyl acetate, except for **6c** where tetrahydrofuran was used, was hydrogenated in the presence of 10% palladium on carbon (~2g) under atmospheric pressure until the uptake of hydrogen ceased (~20 h) and then was filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue was recrystallized to give **1** or **8**, respectively. These results are summarized in Tables III and IV, respectively.

Reduction of 5 or 6 with Sodium Borohydride. A mixture of **5** or **6** (3 mmol) and sodium borohydride (6 mmol) in 50 mL of ethanol was refluxed for 1 h. A small amount of acetic acid was added to the cooled mixture to decompose excess sodium borohydride, and the mixture was then evaporated to dryness under reduced pressure. The residual solid was triturated with diluted aqueous sodium hydroxide, filtered, and recrystallized to provide **7** or **8**, respectively. The results of **7** are summarized in Table V.

Reduction of 5 with Lithium Aluminum Hydride. A solution of lithium aluminum hydride (6 mmol) in 20 mL of dry tetrahydrofuran was added dropwise to a solution of **5** (3 mmol) in 10 mL of the same solvent, and the mixture was refluxed for 2 h. Excess lithium aluminum hydride was decomposed by the addition of water and diluted aqueous sodium hydroxide. The resulting solution was evaporated to dryness under reduced pressure, and the residue was extracted with hot chloroform. The solution was evaporated, and the residue was recrystallized to afford **7**.

The procedure for reaction of **6** with lithium aluminum hydride is as follows. A mixture of **6** (3 mmol) and lithium aluminum hydride (15 mmol) in 100 mL of dry dioxane was refluxed for 5 h under nitrogen atmosphere and then treated in the predescribed manner to recover a 95–97% yield of **6**.

Acknowledgment. The authors are grateful to Dr. T. Nakagawa for his helpful suggestions.

Registry No.—**2a**, 107-22-2; **2b**, 78-98-8; **2c**, 431-03-8; **2d**, 1074-12-0; **2e**, 579-07-7; **2f**, 134-81-6; **3**, 17220-38-1; **4**, 53543-28-5; **2a** bisulfite salt, 18381-20-9; **2b** bisulfite salt, 64163-47-9.

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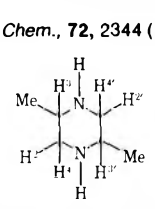

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Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones Related to Epimaalienone[1]

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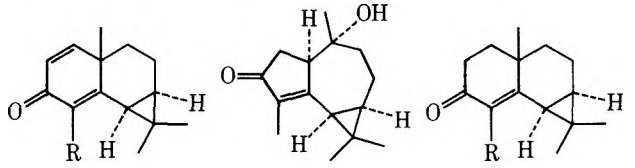
Recently, we reported that the tricyclic cross-conjugated cyclohexadienone **1a**, derived from epimaalienone, was pho-

tochemically converted into the tricyclic hydroxyenone **2** on irradition in aqueous acetic acid.[2] Compound **2** was utilized in a synthesis of (−)-4-epiglobulol and (+)-4-epiaromadendrene.[2] Since examples of successful photochemical rearrangements of cross-conjugated cyclohexadienones containing a conjugated cyclopropane ring are rare,[3,4] further investigation of the photochemistry of compounds of type **1** appeared to be of interest. In this paper we wish to report the results of irradiation of **1a** in the aprotic solvent dioxane and of the related ring-A unsubstituted dienone **1b** in both dioxane and glacial acetic acid.

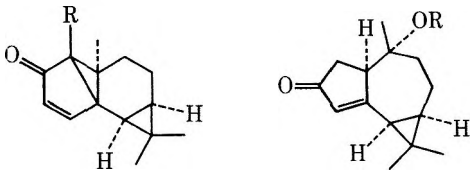


1a, R = CH_3
b, R = H

2 **3**

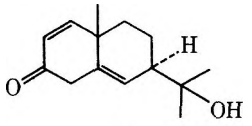
The synthetic route employed for the preparation of **1b** was similar to that used for the synthesis of **1a**,[2,5] except that the phenylselenenylation–selenoxide elimination procedure,[6] involving the conversion of enone **3** to the homoannular lithium dienolate with lithium diisopropylamide (LDA) in THF at −70 °C,[7] was used instead of oxidation with DDQ (dichlorodicyanoquinone) in dioxane.

Irradiation of a dilute solution of **1a** in anhydrous dioxane using a 2537-Å light source for 2.7 h at room temperature led to the formation of a single photoproduct which was isolated in 52% yield after column chromatography on silica gel. The spectral properties of this compound (see Experimental Section) were completely consistent with the tetracyclic enone structure **4a.** Under similar conditions irradiation of dienone **1b** for 9.0 h produced a single photoproduct having spectral properties consistent with structure **4b** in 60% yield (based upon unrecovered starting material).[8]



4a, R = CH_3
b, R = H

5a, R = H
b, R = $COCH_3$



6

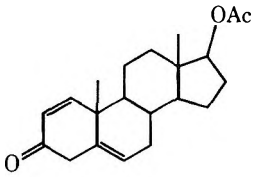
Irradiation of **1b** in 45% aqueous acetic acid gave erratic results. A compound having spectral properties consistent with hydroxyenone **5a** was apparently formed in low yield in some runs, but in others the NMR and IR spectral properties of the photolysis mixture indicated that the major component had the ring-opened structure **6.** Compound **6** was isolated by chromatography when a dilute solution of **1b** was allowed to stand in 45% aqueous acetic acid in the dark for 1.0 h. Apparently, in aqueous acetic acid, 1,6 addition of water to the vinylogous cyclopropyl ketone system in **1b** is an especially favorable process which largely prevents photochemical rearrangement of the dienone. The inconsistent results obtained during irradiation of **1b** were presumably related to variations in time between dissolution of the sample and the start of the irradiation period.

The structural assignment for **6** is based upon its NMR spectral and chemical properties (see Experimental Section). The absorption pattern for the methylene protons at C-4 was similar to that observed for the deconjugated steroidal dienone **7.**[9] The lower field absorption at δ 3.18 was expected to be due to the axial (4β) proton, and this was strongly supported by a deuterium-exchange experiment. Thus, when **6** was mixed with 0.01 equiv of NaOD in acetone-d_6/D_2O, the peak at δ 3.18 rapidly disappeared, whereas the absorption at δ 2.82 simply changed from a doublet to a broad singlet. Axial protons α to ketones generally exchange much faster than equatorial protons.[10]

The deconjugated dienone **6** was converted to conjugated dienone **8** on treatment with methanolic sodium hydroxide. The structural assignment for **8** followed readily from the close similarity of its NMR and IR spectral properties to those of related cross-conjugated dienones, e.g., **1b.**

When dienone **1a** was treated with aqueous acetic acid under conditions similar to those described for **1b,** its slow conversion into a product apparently related to **6** was observed. However, the rate of this reaction was much too slow to be competitive with the normal dienone photochemical rearrangement.

Photochemical rearrangement of **1b** could readily be accomplished using glacial rather than aqueous acetic acid as the solvent. Thus the acetoxyenone **5b** was produced in 71% yield when a dilute solution of **1b** in glacial acetic acid was irradiated for 0.75 h using ultraviolet light with a wavelength greater than 3000 Å. No other products were isolated from the photolysis.



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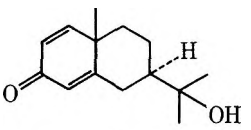


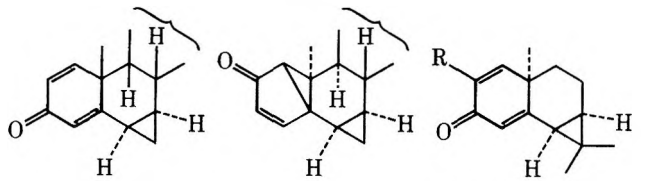
8

These results show that the predominate modes of photochemical rearrangement of dienones of type **1** parallel those which are commonly observed for related systems in which the cyclopropane ring is absent.[11] The steroid derivative *O*-acetyl-1-dehydro-6β,7β-methylenetestosterone (**9**), which like **1** has a cis relationship between the cyclopropane ring and the angular methyl group, has been reported to be readily converted into the bicyclohexenone derivative **10** on irradiation in dioxane at 2537 Å.[4] The photolability of dienones of types **1** and **9** is in marked contrast to that of the isomeric systems **11** and **12,** respectively, which have a trans relationship between the cyclopropane ring and the angular methyl substituent. For example, dienone **11a** has been found to be stable on direct irradiation in aprotic[12] and protic media,[3,13] while **12** was shown to be unchanged on irradiation in dioxane.[4]

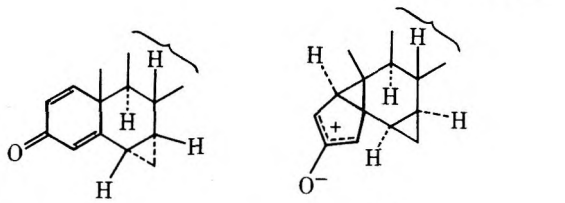
It has been suggested[11c] that the conversion of **9** into **10** proceeds via the generally accepted zwitterionic intermediate **13,** which would have a trans relationship between the adjacent cyclopropane rings on the six-membered B RING/ The failure of **12** to undergo an analogous rearrangement was attributed to the fact that the zwitterionic intermediate corresponding to **13** would be highly strained because the two adjacent cyclopropane rings on the six-membered B ring would have a cis relationship to each other. A similar explanation could account for the photostability of **11a.** However, it is not obvious that the strain associated with adjacent cis cyclopropane rings would be of such magnitude as to preclude the formation of an intermediate related to **13.** We have shown that the 2-carboxydienone **11b** undergoes rearrangement to 5/7-fused products having the cyclopropane ring intact on irradiation in dioxane and aqueous acetic acid.[3,14] However, whether the presence of the carboxyl group in some way pro-

vides stabilization of the zwitterionic intermediate derived from **11b** or allows an alternative rearrangement pathway to intervene is not clear.

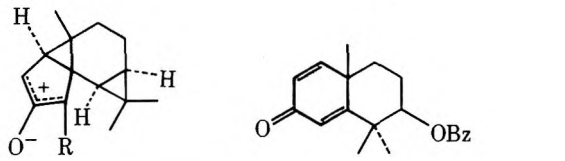
The photochemical behavior of **1a** and **1b** may be explained in terms of the zwitterionic intermediate **14** which is analogous to **13** derived from the steroidal system.[15] In dioxane the usual symmetry-allowed 1,4-sigmatropic rearrangement can lead to products of type **4**, while in aqueous or glacial acetic acid protonation of **14** on oxygen followed by solvolytic cleavage



9 **10** **11a**, R = H; **b**, R = CO_2H



12 **13**



14a, R = CH_3; **b**, R = H **15**

of the 5,10 bond would lead to fused-ring products such as **2** or **5**. Normally, ring-A unsubstituted dienones yield mixtures of fused-ring and spirocyclic products because solvolytic cleavage of both bonds of the cyclopropane ring of the mesoionic intermediate derived from protonation of **14** is possible. However, in the case of **14**, the topside attack of solvent at C-10, which would lead to a spirocyclic hydroxy ketone, is hindered by the dimethylcyclopropane ring.[16] A similar steric argument has been used to account for the fact that a spirocyclic hydroxy ketone was not produced on irradiation of the ring-A unsubstituted dienone **15**.[17]

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were determined using a Perkin-Elmer Model 457 instrument, NMR spectra (Me_4Si internal standard) were obtained using a Varian Model T-60 spectrometer, and ultraviolet spectra were measured using a Beckman Model 25 instrument. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-7 or a Varian Model M-66 spectrometer. Combustion analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga.

For column chromatography either Florisil (Fisher Scientific Co.) or silica gel (Grace, 60–200 mesh; deactivated with acetone before use) were employed as adsorbants.

A Hanovia 450-W high-pressure mercury lamp housed in a Pyrex probe was used for irradiation in acetic acid. A Hanau NK 20 7-W low-pressure mercury lamp was used for all irradiations in dioxane. When either solvent was used, dry nitrogen was bubbled through the reaction vessel for a few minutes preceeding and during the period of irradiation.

Preparation of 4-Normethyl-1,2-dehydroepimaalienone (1b). (−)-2-Carone was reacted with methyl vinyl ketone according to the procedure of Caine and Gupton.[5] (−)-3-(2-Oxobutan-4-yl)-2-carone (bp 100–135 °C) (0.30 °C (0.30 mm)) was obtained in 64% yield and showed the following properties: UV λ_{max} (95% EtOH) 220 nm (ϵ 3540); IR (CCl_4) 1720, 1690 cm^{-1}; NMR δ (CCl_4) 0.85 (s, 3 H), 1.05 (s, 3 H), 1.15 (s, 3 H), 2.10 (s, 3 H); MS *m/e* (70 eV) 222.161 (EMC = 222.162).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.96.

The product of the previous reaction (23.25 g, 0.105 mol) was added dropwise to 200 mL of anhydrous saturated ethanolic hydrogen chloride at 5 °C. After warming to room temperature and stirring for 30 min, the reaction mixture was poured into 200 mL of ice water and extracted with $CHCl_3$. Removal of the solvent gave 24.0 g (95%) of *cis*-6-(2-chloropropan-2-yl)-3-oxo-9-methyl-Δ^4-octahydronaphthalene: mp 106–107 °C (from hexane); IR (CCl_4) 1675, 1620 cm^{-1}; NMR δ (CCl_4) 1.25 (s, 3 H), 1.60 (s, 6 H), 5.65 (broad s, 1 H); MS *m/e* (70 eV) 204 ($M^+ - HCl$).

Anal. Calcd for $C_{14}H_{21}OCl$: C, 69.84; H, 8.79. Found: C, 69.72; H, 8.80.

To a suspension of 10.7 g (ca. 0.25 mol) of sodium hydride in 50 mL of dry dimethoxyethane (DME) was added 20.4 g (0.085 mol) of the above chloroenone in 500 mL of dry DME. The mixture was heated at reflux overnight, and 25 mL of ethanol was added. Removal of the solvents and partitioning between ether and water followed by distillation yielded 11.8 g (68%) of an amber oil, **3**: bp 109–119 °C (0.08 mm); UV λ_{max} (95% EtOH) 277 nm (ϵ 18 200); IR (CCl_4) 1663, 1592 cm^{-1}; NMR δ (CCl_4) 1.10 (s, 3 H), 1.16 (s, 3 H), 1.20 (s, 3 H), 5.86 (s, 1 H); MS *m/e* (70 eV) 204.151 (EMC = 204.151). Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.10; H, 9.88.

Although compound **3** could be converted to **1b** by DDQ oxidation, as reported for **1a**,[2] the yields were erratic and low. In the preferred method, 5.00 g (0.0245 mol) of **3** in 25 mL of dry THF was added slowly to 1.2 equiv of lithium diisopropylamide (LDA) in 100 mL of THF in a dry ice–acetone bath. After stirring for an additional 30 min at this temperature, a solution prepared from 4.59 g (0.0147 mol, 1.2 equiv) of diphenyl diselenide and 0.76 mL (2.35 g, 0.0147 mol) of bromine in 25 mL of THF was added quickly, and the reaction mixture was allowed to warm to room temperature. The crude phenyl selenide was isolated and dissolved in 75 mL of methylene chloride. To this solution was added, over a 20-min period, 6.66 g (0.0588 mol, 2.4 equiv) of 30% aqueous hydrogen peroxide dissolved in 20 mL of water. Slight external cooling was necessary to maintain the temperature at 25 °C. Extraction of the methylene chloride layer with aqueous $NaHCO_3$ and removal of the solvent yielded 5.1 g of yellow oil. Chromatography on Florisil (20% ether in hexane) afforded 3.00 g (60%) of crystalline dienone **1b**: mp 87–88 °C (from pentane); UV λ_{max} (95% EtOH) 243 (ϵ 10 000), 303 nm (8600); IR (CCl_4) 1660, 1622, 1588 cm^{-1}; NMR δ (CCl_4) 1.18 (s, 6 H), 1.25 (s, 3 H), 5.95 (q, J = 1.5, 10 Hz, 1 H), 6.13 (broad, $J \sim 1.5$ Hz, 1 H), 6.72 (d, J = 10 Hz, 1 H); MS *m/e* (70 eV) 202.139 (EMC = 202.136).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.02; H, 8.99.

Irradiation of 1b in Dioxane. A 375-mg sample of dienone **1b** was dissolved in 100 mL of dry dioxane and irradiated for 9.0 h. The solvent was removed under reduced pressure and the crude material chromatographed on Florisil. Elution with 10% ether in hexane afforded 133 mg (60%, based on unrecovered starting material) of **4b**: mp 58–60 °C (from pentane); IR (CCl_4) 1700 cm^{-1}; NMR δ (CCl_4) 1.07 (s, 6 H), 1.20 (s, 3 H), 5.78 (d, J = 6 Hz, 1 H), 7.37 (d, J = 6 Hz, 1 H).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.09; H, 8.97.

Further elution with 50% ether in hexane afforded 149 mg of starting material.

Irradiation of 1a in Dioxane. A solution of 516 mg of **1a** was irradiated for 2.7 h in 100 mL of dry dioxane. After removal of solvent, the residue was chromatographed on silica gel. Elution with hexane yielded 267 mg (52%) of **4a**: bp 78–105 °C (bath temperature), 0.05 mm; UV λ_{max} (95% EtOH) 220 (ϵ 5450), 280 nm (2490), IR (CCl_4) 1695, 1651 cm^{-1}; NMR δ (CCl_4) 0.98 (s, 3 H), 1.03 (s, 3 H), 1.12 (s, 3 H), 1.38 (s, 3 H), 5.84 (d, J = 6 Hz, 1 H), 7.34 (d, J = 6 Hz, 1 H); MS *m/e* (70 eV) 216.155 (EMC = 216.151).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.09; H, 9.40.

Reaction of 1b with Aqueous Acetic Acid. A solution of 100 mg (0.495 mm) of **1b** in 10 mL of 45% aqueous acetic acid was allowed to stand for 1.0 h. The reaction mixture was poured into excess aqueous sodium bicarbonate and extracted with 50 mL of ether. After drying and solvent removal, approximately 110 mg (101%) of yellow oil was isolated. After chromatography on Florisil (60% ether in hexane), 100 mg (92%) of **6** was isolated and showed the following properties: mp 75–76 °C (from ether/pentane); IR (CCl_4) 3310, 2970, 2920, 2860, 1678, 1615 cm^{-1}; NMR δ (CCl_4) 1.02 (s, 3 H), 1.10 (s, 3 H), 1.21 (s, 3 H), 2.82 (d, J = 17 Hz, 1 H), 3.18 (d, each member split into a triplet, J = 17,

2.5 Hz, 1 H), 5.50 (broad s, 1 H), 5.70 (d, J = 10 Hz, 1 H), 6.50 (d, J = 10 Hz, 1 H).

Anal. Calcd for $C_{14}h_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.30; H, 9.17.

Irradiation of the signal at δ 5.50 changed the absorption at δ 3.18 into a doublet, each member of which was split into a doublet (J = 17 and 2.5 Hz). Irradiation at δ 2.25 produced the same effect on the signal at δ 3.18 as did irradiation at 5.50.

When a solution of ca. 100 mg of **6** in 0.5 mL of acetone-d_6 containing 0.01 equiv of NaOD and 0.10 mL of D_2O was allowed to stand for ca. 15 min, the following changes in the NMR spectrum were observed: the signal at δ 3.18 disappeared, whereas the signal at δ 2.82 changed from a doublet to a broad singlet; the signal at δ 5.50 became much sharper and appeared as a doublet ($J \sim 2$ Hz). When ca. 100 mg of **6** was treated with excess NaOH in methanol, a mixture of compounds (77 mg) could be isolated. Chromatography on Florisil (75% ether in hexane) yielded 40 mg of a pale yellow oil, tentatively identified as **8**: IR (CCl_4) 3420, 2960, 2860, 1662, 1622, 1607 cm^{-1}; NMR δ (CCl_4) 1.20 (s, 6 H), 1.27 (s, 3 H), 3.03 (s, 1 H), 6.00 (s, 1 H), 6.08 (d, J = 10 Hz, 1 H), 6.73 (d, J = 10 Hz, 1 H).

Irradiation of 1b in Glacial Acetic Acid. A solution of 1.00 g (0.00495 mol) of **1b** in 250 mL of freshly distilled glacial acetic acid was irradiated for 0.75 h. The excess solvent was removed at reduced pressure and the resulting yellow oil taken up in ether/water. Extraction of the ether with saturated aqueous sodium bicarbonate followed by drying and removal of solvent yielded 1.31 g (101%) of a yellow oil. This material was carefully chromatographed on Florisil, with each fraction being monitored by TLC. The only identifiable material that was isolated was eluted with 25% ether in hexane. This fraction yielded 0.920 g (71%) of **5b**: mp 64–66 °C (from hexane); IR (CCl_4) 2990, 2920, 2870, 1737, 1718, 1610 cm^{-1}; NMR δ (CCl_4) 1.05 (s, 3 H), 1.12 (s, 3 H), 1.17 (s, 3H), 1.93 (s, 3 H), 3.73 (t, J = 3 Hz, 1 H), 5.97 (t, J = 1.6 Hz, 1 H); UV λ_{max} (95% EtOH) 241 nm (ϵ 11 800).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.39; H, 8.43.

Registry No.—**1a**, 55659-72-8; **1b**, 64057-42-7; **3**, 64090-80-8; **4a**, 64057-43-8; **4b**, 64057-44-9; **5b**, 64057-45-0; **6**, 64070-26-4; **8**, 64057-46-1; (−)-2-carone, 5561-14-8; methyl vinyl ketone, 78-94-4; (−)-3-(2-oxobutan-4-yl)-2-carone, 64057-41-6; *cis*-6-(2-chloropropan-2-yl)-3-oxo-9-methyl-Δ^4-octahydronaphthalene, 64057-47-2.

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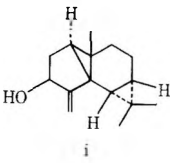

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(16) Examination of models of **14** indicates that it is more sterically crowded than **13** because of the β-methyl group on the dimethylcyclopropane ring. Steric crowding is particularly severe in **14a** where a methyl substituent is present at C-4.
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A Convenient Preparation of Methyl 2,5-Dihydro-2-oxo-3-furancarboxylate

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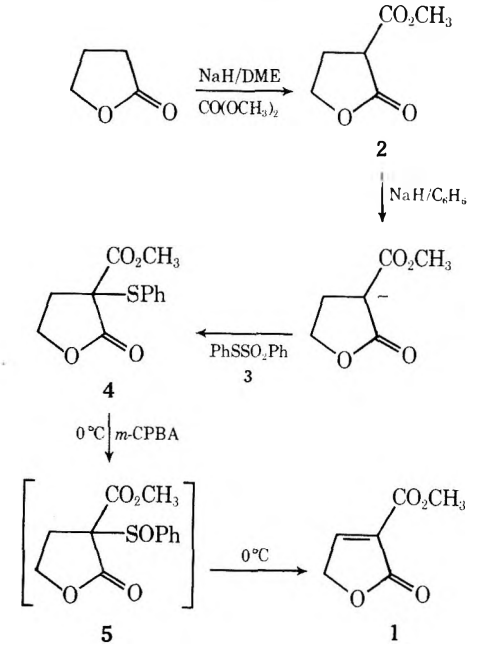
We have recently had need for the C-5 synthon methyl 2,5-dihydro-2-oxo-3-furancarboxylate (**1**) within the context of several total synthetic efforts. Compound **1** can serve as an electron-deficient olefin both in the Michael addition reaction and the Diels–Alder reaction, thus providing a convenient entry into a variety of complex molecular systems. Careful search of the literature revealed that, while several closely related systems were known,[1] compound **1** itself was unknown. The previously described syntheses of compounds related to **1** proved not to be synthetically applicable to the preparation of **1** itself.[1] As a result, we have developed a new approach to the synthesis of **1** (Scheme I) which, in principle, should be general for the synthesis of a variety of systems related to **1**.

Butyrolactone, on treatment with diethyl carbonate and sodium hydride in dimethoxyethane (DME), affords the corresponding carbomethoxy lactone **2** in 72% yield. Treatment of **2** with sodium hydride gives rise to the corresponding β-dicarbonyl anion which, on reaction with the sulfide sulfone **3**, undergoes thiophenylation to compound **4** in 55% yield. Reaction of the β-dicarbonyl anion derived from **2** with diphenyl disulfide does not yield compound **4** as the starting materials are recovered unreacted, even after prolonged reaction times. Thus, for unreactive anions such as those derived from β-dicarbonyl systems the sulfide sulfone **3** is a clearly superior thiophenylating agent.[2]

Scheme I



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Conversion of compound **4** into compound **1** was accomplished by oxidation with *m*-chloroperbenzoic acid in methylene chloride and *tert*-butyl alcohol at 0 °C. This oxidation reaction, even at 0 °C, leads directly to the unsaturated lactone **1**. Presumably the transformation of **4** into **1** involves the intermediacy of the sulfoxide **5**, which undergoes elimination of the elements of PhSOH at unusually low temperatures.[3] The low temperature for this elimination-type reaction is clearly reminiscent of the behavior exhibited by organoselenium compounds[4] and the thermal lability of **5** is most probably due to the β-dicarbonyl residue present in the molecule.

Experimental Section

Infrared spectra were taken on a 467 Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were obtained on a Joel MH-100 spectrometer in the solvent indicated with tetramethylsilane as the internal reference and are expressed as δ values, with the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were taken on a Dupont 21-490B instrument.

Preparation of 2. To a 2-L Morton flask equipped with mechanical stirrer, addition funnel, and condenser was added sodium hydride (28 g, 50% dispersion in mineral oil). The sodium hydride was washed five times with hexane, dried under a stream of nitrogen, and then covered with DME (300 mL). Dimethyl carbonate (73.5 mL) was added followed by butyrolactone (25 g, 0.29 mol, 21 mL) and the resulting mixture was then stirred and warmed to 45 °C. After 15 min, a vigorous evolution of gas occurred and the reaction solidified. Heating was discontinued and the reaction was allowed to stand for 2 h at room temperature. Sufficient ice water was added to permit stirring, whereupon 6 N HCl (150 mL) was added. The resulting mixture was extracted with $CHCl_3$ (3 × 75 mL), dried by vacuum filtration through $MgSO_4$, and then evaporated to give an orange oil. Distillation of this oil gave 29 g of **2** (72% yield): bp 110 °C (0.5 mm); IR ($CHCl_3$) 1778 and 1740 cm^{-1}; NMR ($CDCl_3$) δ 2.55 (m, 2 H), 3.5 (m, 1 H), 3.7 (s, 3 H), 4.28 (m, 2 H); MS parent *m/e* 144.

Preparation of 3. To a solution of diphenyl disulfide (50 g, 0.229 mol, 1 M in ether) contained in a 1-L three-necked flask equipped with magnetic stirrer, addition funnel, and condenser was added 40% peracetic acid (100 mL) dropwise (1 drop/s) at 0–5 °C. The reaction mixture was allowed to slowly warm to room temperature, stirred for 12 h, treated with more 40% peracetic acid (10 mL), and stirred an additional 4 h at room temperature. The reaction was poured into a 2-L Erlenmeyer flask and celite then added followed by the slow addition of K_2CO_3 (120 g). The resulting mixture was stirred for 20 min at room temperature and filtered under vacuum, and the filtrate was evaporated to dryness to yield 45 g of **3** as a white crystalline solid, mp 35–37 °C (lit.[5] mp 37.5–38.5 °C).

Preparation of 4. Sodium hydride (2.06 g, 50% dispersion in mineral oil) was placed in a three-neck flask equipped with reflux condenser. After washing five times with hexane and drying over nitrogen, the sodium hydride was covered with 70 mL of benzene, whereupon the lactone ester **2** (5 g, 35.7 mm) was added. Compound **3** (10.7 g) was then added (as a solid) and the resulting mixture was heated at 100 °C for 2.5 h. After cooling to room temperature, ice followed by water was added to the reaction mixture and the resulting two-phase system was then extracted with $CHCl_3$ (3 × 50 mL) and dried by filtration through $MgSO_4$, and the filtrate was evaporated to dryness to yield 8.8 g of crude material which, by NMR analysis, contained 74% of the desired product **4**. Of this crude mixture 5.1 g was filtered (under vacuum) through 30 g of silica gel G (10–40 μm), eluted first with 520 mL of hexane:ether (4:1), followed by 350 mL of hexane:ether (1:1). Evaporation of the latter eluent gave 2.8 g (55% yield) of compound **4** suitable for conversion into the lactone **1**. Spectral properties of compound **4** obtained in this manner are as follows: IR ($CHCl_3$) 1775 and 1735 cm^{-1}; NMR ($CDCl_3$) δ 2.85 (m, 2 H), 3.8 (s, 3 H), 4.22 (m, 2 H), 7.5 (m, 5 H); MS parent *m/e* 252.

Preparation of 1. Compound **4** (2 g, 8.06 mm), 1 M in CH_2Cl_2, was treated dropwise at 0 °C with *m*-chloroperbenzoic acid (1.8 g) dissolved in a mixture of CH_2Cl_2 (6 mL) and *t*-BuOH (2 mL). After addition of the peracid was complete, the reaction was stirred for 2 h at 0 °C. Saturated sodium bicarbonate was added and the mixture was extracted with $CHCl_3$ (3 × 20 mL), dried over anhydrous sodium sulfate for 2 h, filtered under vacuum, and evaporated to dryness to yield a white solid which on crystallization from Et_2O:$CHCl_3$ gave 0.87 g (79% yield) of white crystals: mp 103–105 °C; IR ($CHCl_3$) 1820 (shoulder), 1785, and 1733 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 3 H), 5.05 (d, 2 H), 6.42 (m, 1 H); MS parent *m/e* 142. Anal. Calcd for $C_6H_6O_4$: C, 50.70; H, 4.23; O, 45.07. Found: C, 50.61; H, 4.32.

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Registry No.—**1**, 63731-11-3; **2**, 19406-00-9; **3**, 1212-08-4; **4**, 63731-12-4; dimethyl carbonate, 616-38-6; butyrolactone, 96-48-0; diphenyl disulfide, 882-33-7.

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Chiroptical Properties of Pelletierine and Anaferine

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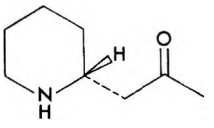
The alkaloid (−)-pelletierine **1** [1-(2-piperidyl)propan-2-one] has been shown to have the D configuration (= *R*) by the isolation of L-(−)-pipecolic acid on chromic acid oxidation of (+)-pelletierine,[1] while the closely related natural anaferine[2] [1,3-bis(2-piperidyl)propan-2-one] appears to be the meso isomer.[3] However, since it has been reported[4] that the resolved enantiomers of anaferine racemize readily, and that under the same conditions the racemate is converted into the meso form[5] in aqueous solution, it remains possible that natural anaferine



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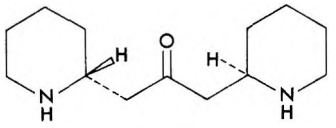

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is one of the optically active forms and undergoes isomerization during the isolation procedure. Since resolved (−)-1,3-bis(2-piperidyl)propan-2-one yielded D-(+)-pipecolic acid on chromic acid oxidation,[6] resolved (−)-anaferine possesses the D,D configuration (= *R*,*R*) **2**.

From recent work on the ORD and CD spectra of 2-alkylpiperidines[7] it is clear that the negative plain curve below 225 nm found (in addition to a negative Cotton effect at 280 nm for the n → π* transition of the ketone) in an earlier ORD spectrum of (−)-pelletierine sulfate[8] is due to the π → π* absorption of the ketone and cannot be used for configurational assignments by comparison with 2-alkylpiperidines. However, such a comparison can be made if the rotational contribution of the ketone chromophore is removed by chemical means which do not interfere with the asymmetric center.

The keto group in (−)-pelletierine sulfate was converted to the dimethyl ketal by reaction with methanolic hydrogen chloride[9] at room temperature. The resulting solution then

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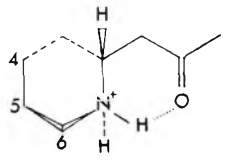
Table I. ORD and CD Spectra

Compd	Registry no.	Solvent	Molecular ellipticity $[\theta]_{max}$ (nm)	Molecular rotation [Φ] (nm) Peak	Trough
D-(−)-Pelletierine sulfate	2133-57-5	95% EtOH	−365 (281)	+180 (264)	−314 (298)
		H_2O	−290 (272)	−760 (258)	−930 (282)
D-(−)-Pelletierine base	2858-66-4	95% EtOH	−127 (285)	−25 (260)	−238 (295)
		H_2O	+140 (292)	−9.5 (305)	−162 (280)
D-(−)-Pelletierine dimethyl ketal·HCl	63731-39-5	MeOH	0 (208–300)		
D-(−)-Pelletierine dimethyl ketal base	63731-40-8	MeOH	−158 (208!)	+284 (210!)	
D-(−)-Anaferine·2HCl	19519-54-1	95% EtOH	+276 (287)[a]		
Reduced anaferine·2HCl	63783-46-0	MeOH	0 (203–300)		
Reduced anaferine base	63783-47-1	MeOH	−4700 (203!)[a]	+9800 (198!)	−690 (217)
D-(+)-Coniine[b]	458-88-8	95% EtOH	−630 (205)	+1900 (200!)	
D-(+)-Allo-Sedridine	26171-47-1	95% EtOH	−915 (205)		
D-(−)-Sedridine	5320-51-4	95% EtOH	−518 (205)		

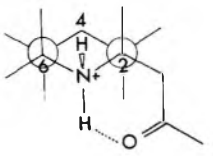
[a] Corrected for optical purity. [b] $[\alpha]_D$ +5.0° (c 2.95% EtOH).

showed a negative plain ORD curve below 230 nm (Table I) and no CD between 200 and 300 nm because the n → σ* transition of nitrogen does not exist in acidic solution. After the solution was made alkaline, it had a positive plain ORD curve, and a negative CD maximum below 208 nm,[10] in agreement with the chiroptical properties of D-(+)-coniine (Table I) and with the chemically established D configuration[1] for natural (−)-pelletierine.

The sensitivity of pelletierine to conformational changes is shown by its chiroptical properties (Table I). Assuming the piperidine ring to be in the more stable chair form[11] and equatorially substituted at C-2,[12] pelletierine sulfate can form two six-membered pseudoring structures through H bonding with the carbonyl oxygen: a trans-fused conformation **3a** (C-5 and C-6 in the front upper left octant) associated by the octant rule[13] with a negative Cotton effect, and a cis-fused structure **3b** (C-4, -5 and, -6 in the front lower left octant) corresponding



3a



3b

to a positive Cotton effect. The observed negative CE in both 95% ethanol and in water (Table I) suggests that the former structure (**3a**) predominates at room temperature.[14] The CD and ORD of (−)-pelletierine base in 95% ethanol, measured immediately after basification of the salt, showed essentially the same features as the salt (Table I).[17]

However in water the sign of the n → π* Cotton effect for (−)-pelletierine base was reversed[18] (Table I) suggesting a conformational change such as might occur by solvation of the equatorial electron pair of nitrogen, causing the carbonyl oxygen to form a cis-fused pseudoring structure resembling **3b**, with a positive Cotton effect.[13]

Unlike (−)-pelletierine, (−)-anaferine (**2**) resisted attempts to form the dimethyl ketal, probably due to steric factors. However, reduction proceeded rapidly by catalytic hydrogenation and gave a product which (as the dihydrochloride salt) showed no CD in the range 200–300 nm, indicating complete disappearance of the carbonyl chromophore (Table I). On making the solution alkaline, the base displayed a strong negative CE in its ORD spectrum (Table I). These observations resemble the CD and ORD findings for D-(+)-coniine and D-(+)-allosedridine (Table I), and agree with the chemically established configuration[6] of (−)-anaferine (**2**) as D,D (= *R*,*R*). The greater intensity of the ellipticity (as compared to coniine) may be due to the reduced conformational freedom of this diamino alcohol through intramolecular H bonding.[19]

The CD spectrum of (−)-anaferine dihydrochloride (**2**·2HCl) shows a positive ellipticity for the n → π* carbonyl transition (Table I) of about the same magnitude as for (−)-pelletierine sulfate but of opposite sign, indicating major conformational changes of an unknown nature.

Experimental Section

ORD and CD curves were measured at 25 °C on a JASCO ORD-CD 5 spectropolarimeter and on a JOUAN 185 Mark II dichrograph.

Pelletierine Dimethyl Acetal. A solution of 5.6 mg of natural (−)-pelletierine sulfate, $[\alpha]_D$ −29.5° (c 1, H_2O), in 3 mL of methanol was treated with 1 drop of 10 N HCl. After standing at 25 °C for 20 h, the CD signal at 280 nm had essentially disappeared. The solution was then cooled to 0 °C (ice) and made alkaline with sodium methoxide to liberate the free base. After removal of precipitated sodium chloride, the solution was immediately used for CD measurement.

Reduction of Anaferine. A solution of 23.4 mg of (−)-anaferine dihydrochloride, $[\alpha]_D$ −22.1° (c 0.8 EtOH), in 3 mL of 95% ethanol was reduced with Adams' catalyst (PtO_2) and hydrogen. The solution was filtered and cooled to 0 °C (ice), and the filtrate was made alkaline with 10% aqueous KOH and used immediately for CD measurement.

Acknowledgment. We are grateful to Dr. L. Marion for a sample of natural pelletierine and to Drs. H. Beyerman and L. Maat for a sample of resolved anaferine.

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(19) The alternate suggestion that the greater intensity of the CD of reduced anaferine could be due to the effect of the newly generated asymmetric center does not seem valid since (a) the prochiral ketone **2** (C_2 symmetry) represents a trigonal system Yk_1k_2i in which the two faces of the carbonyl carbon are indistinguishable[20] as k_1 and k_2 are chemically and configurationally identical, (b) k_1 and k_2 are also identical in the reduced compound.
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Total Synthesis of Steroids. 12.[1] Final Evidence of the Configuration of the C-14 Hydroxyl Group in 3-Methoxy-14β-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione

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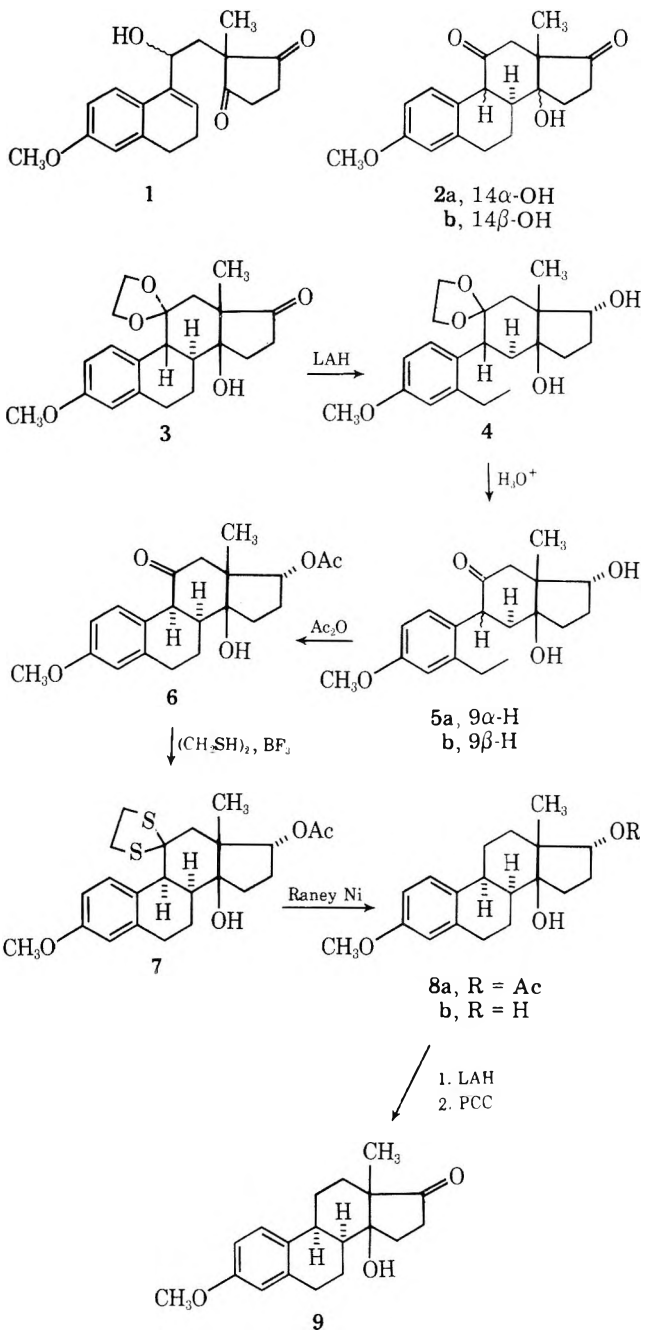
In one of the previous papers[2] of this series we described the synthesis of *rac*-3-methoxy-14α-hydroxy-8α,9ξ-estra-1,3,5(10)-triene-11,17-dione (**2a**) from the allylic alcohol **1** by cyclization with Meerwein reagents. The stereochemistry of compound **2a** at chiral carbon atoms 8, 9 and 13 was proved beyond any doubt. The configuration at C-14 was assumed to be α, on the basis of Sondheimer's observation[3] that either epoxidation or hydrogenation of the C-14 (15) double bond in nonaromatic steroids takes place from the β side of the molecule.

However, this assumption does not hold true for ring A aromatic steroids, and in fact the configuration of the 14-OH group in the cyclization product should be β, as in **2b**. This was demonstrated by the sequence of reactions shown in Scheme I.

The cyclization product **2b** was transformed into **3** as reported previously.[2] Reduction of the C-17 carbonyl group with lithium aluminum hydride led solely to the 17α-OH compound **4**. The configuration of the 17-OH group was proved to be α, because the hydrolysis products **5a** and **5b** and the acetyl derivative **6** obtained from **5a** were different in all respects from their epimers prepared previously[1] from optically active Torgov's secolone (with 17β-OH). Subsequently, compound **6** was converted by standard methods into *rac*-3-methoxy-14β-hydroxy-8α-estra-1,3,5(10)-trien-17-one (**9**). The latter compound had a MS spectrum identical with that reported by Wulfson et al.[4] Direct comparison of our sample **9** with the compound prepared by Zakharychev et al.[5] confirmed their identity.

Thus, the position of the C-14 hydroxyl group in compound **2** obtained by cyclization of **1** was proved to be β (as in **2b**) but not α (compound **2a**), contrary to the previous report.[2] This means that epoxidation of the C-14 (15) double bond in ring A aromatic 8-isosteroids takes place in a manner opposite, i.e., from the α side, to that observed during hydrogenation of the same double bond.

Scheme I



Consequently, the configuration at C-14 of all compounds with the 14-OH group described in our previous papers,[1,2,6] as well as in compounds **15, 16, 22,** and **24–28** reported in Part 7 of this series,[7] should be reversed.

If we assume that the π orbitals must overlap in the transition state for the cyclization **1** → **2**, reexamination of Dreiding models indicates that the preferred geometry of the product at C-8 and C-14 should be trans with a cis C/D ring junction.

Experimental Section[8]

3-Methoxy-11,11-ethylenedioxy-8α,9β-estra-1,3,5(10)-triene-14β,17α-diol (4). To a solution of **3** (1.0 g, 2.79 mmol) in THF (100 mL) was added 0.2 g of LAH, and the mixture was stirred at room temperature for ca. 10 min. The reaction was quenched with aqueous $(NH_4)_2SO_4$ and after standard workup a quantitative yield of **4** was obtained: mp 185–186.5 °C (from C_6H_6); IR no CO band, 3450 cm^{-1}; ^1H NMR δ 1.28 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 4.18 (t, 1, H-17), 6.58–6.73 (m, 2, H-2 and H-4), 7.32 ppm (d, 1, H-1).

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Anal. Calcd for $C_{21}H_{28}O_5$: C, 70.00; H, 7.78. Found: C, 70.08; H, 7.71.

3-Methoxy-14β,17α-dihydroxy-8α-estra-1,3,5(10)-trien-11-one (5a) and 3-Methoxy-14β,17α-dihydroxy-8α,9β-estra-1,3,5(10)-trien-11-one (5b). The solution of **4** (1.0 g, 2.77 mmol) in 100 mL of MeOH and 10 mL of 10% aqueous HCl was left at room temperature for 2 h. Methanol was evaporated in vacuo and the residue was extracted with $CHCl_3$. The extracts were washed with saturated aqueous $NaHCO_3$ and dried with anhydrous $MgSO_4$. Chromatography on 30 g of silica gel using hexane–ethyl acetate (95:5) as eluent afforded **5a** (0.71 g, 81%) and **5b** (0.04 g, 4.6%). The second run of the same reaction gave only compound **5a.**

5a: mp 109–112 °C (from C_6H_6); IR 1710 cm^{-1}; ^1H NMR δ 1.11 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 6.25 Hz, H-9), 4.22 (t, 1, H-17), 6.58–6.80 (m, 2, H-2 and H-4), 6.82 ppm (d, 1, H-1).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.15; H, 7.59. Found: C, 72.10; H, 7.52.

5b: ^1H NMR δ 1.08 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 3.98 (d, 1, $J_{9,8}$ = 12.5 Hz. H-9), 4.35 (q, 1, H-17), 6.58–6.88 (m, 2, H-2 and H-4), 7.25 ppm (d, 1, H-1).

However, the regeneration of **5b** from the ^1H NMR sample gave a mixture of both epimers **5a** and **5b;** therefore, we are not giving further analytical data of **5b.**

3-Methoxy-14β-hydroxy-17α-acetoxy-8α-estra-1,3,5(10)-trien-11-one (6). The solution of **5a** (0.60 g, 1.89 mmol) in acetic anhydride (2 mL) and pyridine (4 mL) was left at room temperature for 12 h. Evaporation of pyridine and of excess of Ac_2O in vacuo followed by crystallization from methanol afforded **6** (0.62 g, 92%): mp 207–211 °C (from MeOH): IR 1710 and 1725 cm^{-1}; ^1H NMR δ 1.12 (s, 3, CH_3), 2.08 (s, 3, CH_3COO), 3.80 (s, 3, OCH_3), 3.95 (d, 1, $J_{9,8}$ = 6.25 Hz, H-9), 5.15 (t, 1, H-17), 6.68–6.80 (m, 2, H-2 and H-4), 6.85 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.39; H, 7.26. Found: C, 70.20; H, 7.25.

11-Thioketal of 3-Methoxy-14β-hydroxy-17α-acetoxy-8α-estra-1,3,5(10)-trien-11-one (7). To the solution of **6** (0.50 g, 1.39 mmol) in ethanedithiol (2 mL), $BF_3{\cdot}Et_2O$ (0.1 mL) was added and the mixture was stirred at room temperature for ca. 20 min until a clear solution was obtained. The reaction was then diluted with 10 mL of aqueous $NaHCO_3$ and extracted with benzene. Further standard workup gave the crude product **7,** which after recrystallization from Et_2O yielded pure **7** (0.48 g, 80%): mp 213–217 °C (from Et_2O): IR 1715 cm^{-1}; ^1H NMR δ 1.42 (s, 3, CH_3), 2.12 (s, 3, CH_3COO), 3.50 (d, 1, $J_{9,8}$ = 5 Hz, H-9), 3.85 (s, 3, OCH_3), 5.12 (t, 1, H-17), 6.55–6.72 (m, 2, H-2 and H-4), 7.80 ppm (d, 1, H-1).

Anal. Calcd for $C_{23}H_{30}O_4S_2$: C, 63.60; H, 6.92. Found: C, 63.65; H, 6.91.

3-Methoxy-8α-estra-1,3,5(10)-trien-14β,17α-diol 17-Acetate (8a). Freshly prepared Raney nickel (from 5 g of alloy) was added to the solution of the thioketal **7** (0.35 g, 0.80 mmol) in a mixture of methanol and benzene (1:1, 50 mL) and it was stirred at room temperature for ca. 3 h. Nickel was then filtered off and the solvent was evaporated in vacuo. The residue was crystallized from methanol giving **8a** (0.25 g, 91%): mp 178–188 °C (from MeOH): IR 1720 cm^{-1}; ^1H NMR δ 1.10 (s, 3, CH_3), 2.10 (s, 3, CH_3COO), 3.82 (s, 3, OCH_3), 5.20 (t, 1, H-17), 6.58–6.85 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.25; H, 8.13. Found: C, 73.26; H, 8.20.

3-Methoxy-14β-hydroxy-8α-estra-1,3,5(10)-trien-17-one (9). To a solution of **8a** (0.20 g, 0.58 mmol) in THF (10 mL) was added 0.05 g of LAH, and the mixture was stirred at room temperature for ca. 10 min. The reaction was quenched with aqueous $(NH_4)_2SO_4$, and after standard workup the oily diol **8b** (0.15 g, 91%) was obtained. It was dissolved in dry methylene chloride (25 mL) and oxidized with pyridinium chlorochromate (PCC)[9] (0.20 g). The compound **9** was isolated by short-column chromatography and crystallized from hexane–acetone (2:1) solution yielding pure **9** (0.13 g, 86%): mp 174–176 °C (from hexane–acetone): IR 1730 cm^{-1}; ^1H NMR δ 1.18 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 6.62–6.85 (m, 2, H-2 and H-4), 7.05 ppm (d, 1, H-1); MS *m/e* 300.

Registry No.—**3,** 64069-77-8; **4,** 64035-53-6; **5a,** 64069-78-9; **5b,** 64069-79-0; **6,** 64069-80-3; **7,** 64035-54-7; **8a,** 64069-81-4; **9,** 10003-00-6; acetic anhydide, 108-24-7; ethanedithiol, 540-63-6.

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Base-Catalyzed Disproportionation Reactions of 3′,5′-Di-*O*-aroyl Derivatives of 1-β-D-Arabinofuranosyluracil

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In a recent publication,[1] we reported that 1-(2′,3′,5′-tri-*O*-benzoyl-β-D-arabinofuranosyl)uracil (iii) forms as a by-product in the synthesis of 1-(3′,5′-di-*O*-benzoyl-β-D-arabinofuranosyl)uracil (ii) from 1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (i) and sodium benzoate in hot DMF and that the immediate precursor of iii is compound ii. The unusual formation of iii has posed the question of whether the 2′-*O*-benzoyl group in iii originates from the external benzoate anion of benzoic acid, or if iii forms by an intramolecular disproportionation reaction of ii. Another possibility that it results by an intramolocular benzoyl rearrangement with concomitant introduction of a second benzoyl unit from outside can not be ruled out immediately. To solve this problem, we designed a synthetic study using analogues of i and ii with different aroyl groups and sodium salts of substituted benzoic acids as basic catalysts. This report deals with some mechanistic evidences to support a disproportionation reaction in the formation of iii, the first observed example of such reactions in the nucleoside field.

Treatment of 2′,3′,5′-tri-*O*-mesyluridine (**1**)[2] with sodium *p*-chlorobenzoate by the known method[2] gave 2,2′-anhydro-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-uracil (**2**) in an excellent yield. Acidic hydrolysis of **2** yielded the desired substance, 1-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**3**). The structures of **2** and **3** were based on the analysis and spectroscopic data described in the Experimental Section.

The first reaction of sodium *p*-methylbenzoate on **3** was focused on the separation of two possible isomers, 1-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)uracil (**4a**) and 1-(5′-*O*-*p*-chlorobenzoyl-2′-*O*-*p*-methylbenzoyl-β-D-xylofuranosyl)uracil (**5**), to evaluate the approximate yields of these isomers, reducing the formations of other products as far as possible. Thus, a short-time reaction using a rather more dilute mixture of the reactants (method A) permitted isolation of **4a** and **5** in 44 and 8% yield, respectively. TLC on the reaction mixture also revealed the formation of a trace amount of a faster running substance corresponding to a triaroyl derivative like iii, but it was neglected. The structures of **4a** and **5** could be easily assigned largely on the basis of NMR data (Table I): in the spectrum of **4a,** the anomeric proton signal appeared at 6.28 ppm as a

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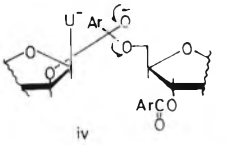
Table I. NMR Resonances of Uridine Derivatives at 60 MHz

Compd	Registry no.	$C_{5'}H$	$C_{4'}H$	$C_{3'}H$	$C_{2'}H$	$C_{1'}H$	C_5H^h	NH
4a[a]	64114-32-5	4.48 (m)	4.72 (m)	5.35 (s)	*d*	6.28 (d) $J_{1',2'}$ = 3.3 Hz	5.58 (d)	10.70 (br s)
4b[c]	64114-33-6	4.3–4.6 (m)	4.6–4.9 (br s)	5.35 (s)	*d*	6.15 (d) $J_{1',2'}$ = 3.2 Hz	6.32 (d)	12.50 (br s)
5[b]	64114-34-7	4.45 (m)	4.72 (m)		5.42 (s)	5.98 (s)	5.68 (d)	10.55 (br s)
6a[a]	64114-35-8	4.85 (d) J = 4.5 Hz	4.58 (m)	5.60 (m)	5.80 (dd) $J_{1',2'}$ = 3.75 Hz $J_{2',3'}$ = 1.6 Hz	6.45 (d) $J_{1',2'}$ = 3.75 Hz	5.58 (d)	10.90 (br s)
6b	64114-36-9	4.79–5.0 (m)	4.60 (m)	5.60 (m)	5.85 (d) $J_{1',2'}$ = 3.9 Hz	6.40 (d) $J_{1',2'}$ = 3.9 Hz	6.33 (d)	*e*
7[c]	64114-79-6	3.95 (d) J = 3.4 Hz	4.32 (m)	5.32 (dd)	*d* $J_{2',3'}$ = $J_{3',4'}$ = 1.6 Hz	6.19 (d) $J_{1',2'}$ = 3.2 Hz	5.62 (d)	10.68 (br s)
8[c]	64114-37-0	4.1–4.3 (m)			4.5–4.7 (m)	6.19 (d) $J_{1',2'}$ = 3.3 Hz	5.53 (d)	10.70 (br s)
9[b]	64114-38-1	4.1–4.9 (m)		5.35 (m)	*f*	6.28 (d) $J_{1',2'}$ = 3.3 Hz	5.61 (d)	
10[b]	64114-39-2	4.85 (d) J = 4.5 Hz	4.52 (m)	5.60 (m)	5.7–5.9 (m)	6.45 (d) $J_{1',2'}$ = 3.75 Hz	*g*	

[a] In $CDCl_3/Me_2SO$-d_6(5:1). [b] In $CDCl_3$. [c] $CDCl_3/Me_2SO$-d_6(3:1). [d] In $H_{4'}$ envelope. [e] Did not appear clearly. [f] In $H_{4'}$–$H_{5'}$ envelope. [g] In $H_{2'}$ envelope. [h] All the coupling constants were 8.0 Hz.

doublet ($J_{1',2'}$ = 3.3 Hz) and the aroyloxy-deshielded $C_{3'}$ proton signal at 5.35 ppm as a singlet. On the other hand, in the spectrum of **5** the signals of both the anomeric and aroyloxy deshielded $C_{2'}$ proton appeared as singlets at 5.98 and 5.42 ppm, respectively. These spectral patterns are consistent with the structure of **4a** with a cis $H_{1'}$–$H_{2'}$ relationship and that of **5** with a trans $H_{1'}$–$H_{2'}$ relationship, respectively.[3] Furthermore, it has been well established that 1-(2′,3′-anhydro-β-D-lyxofuranosyl)uracil and its 5′-*O*-substituted analogues undergo nucleophilic attacks predominantly at the $C_{3'}$ position.[4,1] Thus, the formation of the xylo isomer proved to be trivial and hence neglected in the subsequent synthetic reactions.

Reaction of **3** with the same reagent under more vigorous conditions (3.5 h at 125 °C) gave **4a,** 1-(2′,5′-di-*O*-*p*-chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)uracil (**6a**), 1-(3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)uracil (**7**), and 1-(5′-*O*-*p*-chlorobenzoyl-β-D-arabinofuranosyl)uracil (**8**) in 37.2, 11.8, 7.3, and 2.93% yield, respectively. Compounds **6a–8** exhibited uridine absorptions (sh) in the region of 260 nm and NMR resonances of $H_{1'}$ as doublets ($J_{1',2'}$ = 3.2–3.75 Hz) indicative of their arabino configurations. In the spectrum of the monoaroyl derivative (**7**), the ester-deshielded signal at 5.32 ppm did not interact with $H_{1'}$ and hence should be assigned to $H_{3'}$. Moreover, the 5′-methylene signal appeared at a significantly higher field (3.95 ppm). In contrast, the spectrum of the halogen-containing product **8** showed the 5′-methylene signal at a lower field (4.1–4.3 ppm) and the signals of $H_{2'}$ and $H_{3'}$ at the same, relatively higher field (4.5–4.7 ppm). These findings are consistent with the proposed structures **7**, and **8**. The structure of **6a** was further confirmed by an alternative synthesis (see Experimental Section). Similar treatment of **4a** with basic catalysts[5] gave **6a** in similar yields. The isolation of **6a** and its counterpart **7** let us directly conclude that there was involved a base-catalyzed disproportionation reaction of **4a** as visualized in formula iv, also supported by separate experiments using basic catalysts other than *p*-methylbenzoate salts.[5] It must be noted here that combinations of **4a** with free aromatic acids gave only the starting materials under similar reaction conditions. The formation of the far minor product **8** could be explained in terms of hydrolysis caused by the presence of a trace of moisture, since we did not detect any trace of another counterpart (triaroyl compound) for **8**. The selective formation of

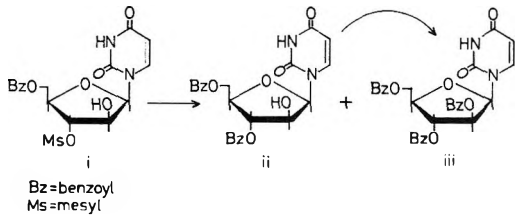


iv

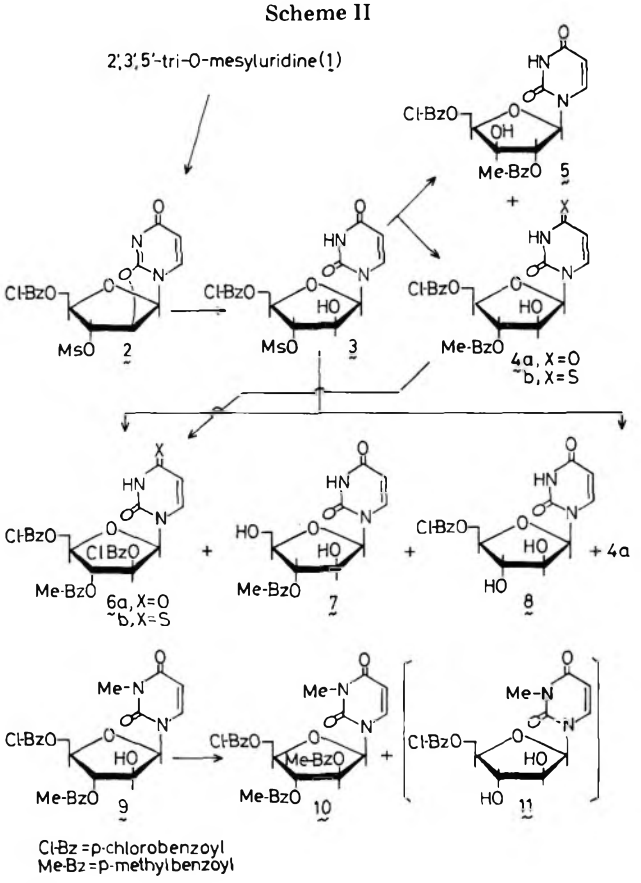
6a and **7** was interesting in view of the synthetically useful transacetylation between adenosine and its 2′,3′,5′-tri-*O*-acetyl derivative,[6] but all the attempts to improve their yields have been unsuccessful.[7] **4a** was converted to 1-(5′-*O*-*p*-chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)-4-thiouracil (**4b**), which also gave 1-(2′,5′-di-*O*-*p*-chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)-4-thiouracil (**6b**) as the sole triaroyl product by the action of sodium benzoate.

It seemed to be interesting to examine the effect of the ionized base moiety in the disproportionation reaction.[8] For this purpose, compound **4a** was selectively methylated at N^3 using *N,N*-dimethylformamide dimethylacetal[9] to give 1-(5′-*O*-*p*-chlorobenzoyl-β-D-arabinofuranosyl)-3-methyluracil (**9**). The structure of **9** was evident on the basis of analysis and general spectroscopic data. **9** was first treated with sodium *p*-methylbenzoate under similar conditions. The product distribution was quite similar to the reactions between **4a,b** and basic catalysts, suggesting a similar disproportionation reaction (see Experimental Section). This time only the faster moving product was isolated, and the other slower moving substance, probably **11**, was discarded because of its paucity. The triaroyl component separated in 13% yield was, surprisingly, 1-(5′-*O*-*p*-chlorobenzoyl-2′,3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)-3-methyluracil (**10**) as shown by its analysis and spectroscopic data. Treatment of **9** with sodium benzoate also afforded exclusively **10** in a similar yield (12%),

Scheme I



Scheme II



thus precluding the possibility that the source of the introduced aroyl group is exogeneous. Thus, the protection at N^3 completely altered the direction of the disproportionation reaction, the 3'-*O*-aroyl group having been transported to the 2'-hydroxyl of another molecule of **9**. At the present stage, no obvious explanation can be given for this intriguing phenomenon even from a molecular model study.

Although we have not succeeded in raising the yields of the two main products, the triaroyl and monoaroyl compounds, and thus in raising the synthetic value of the disproportionation reactions for obtaining selectively protected monoaroyl compounds, this sequence of reactions has disclosed a new aspect of the behavior of protected arabinosides.

Experimental Section[10]

2,2'-Anhydro-1-(5'-*O*-*p*-chlorobenzoyl-3'-*O*-mesyl-β-D-arabinofuranosyl)uracil (2). A mixture of 2',3',5'-tri-*O*-mesyluridine (**1**) (1.0 g, 2.09 mmol) and sodium *p*-chlorobenzoate (1.12 g, 6.27 mmol) in *N*,*N*-dimethylformamide (DMF) (15 mL) was stirred at 110–115 °C for 2 h. After cooling, the mixture was poured into ice water (150 mL) under vigorous stirring. The precipitate was collected by suction, dried by pressing on a porous plate, and recrystallized from acetonitrile to give 880 mg (95%) of **2** as colorless needles: mp 223–225 °C; UV λ_{max}^{MeOH} 242 nm (ε 23 000).

Anal. Calcd for $C_{17}H_{15}N_2O_8SCl$: C, 46.07; H, 3.39; N, 6.32. Found: C, 46.11; H, 3.41; N, 6.32.

1-(5'-*O*-*p*-Chlorobenzoyl-3'-*O*-mesyl-β-D-arabinofuranosyl)uracil (3). To a stirred suspension of **2** (0.65 g, 1.45 mmol) in acetone–water (1:1) (200 mL) was added 12 N hydrochloric acid (3 mL). The mixture was stirred at room temperature for 20 h. The resulting solution was evaporated below 35 °C to remove acetone, and the separating crystals were collected by suction. Recrystallization from a mixture of acetone and water gave 0.59 g (86%) of colorless needles (**3**): mp 169–171 °C; UV λ_{max}^{MeOH} 243 (ε 28 000) and 263 nm (ε 13 200, sh).

Anal. Calcd for $C_{17}H_{17}N_2O_9SCl$: C, 44.31; H, 3.72; N, 6.08. Found: C, 44.23; H, 3.69; N, 5.94.

Reaction of 1-(5'-*O*-*p*-Chlorobenzoyl-3'-*O*-mesyl-β-D-arabinofuranosyl)uracil (3) with Sodium *p*-Methylbenzoate. Method A. Separation of 4a and 5. A mixture of **3** (0.92 g, 2 mmol) and sodium *p*-methylbenzoate (0.95 g, 6 mmol) in DMF (50 mL) was stirred at 120 °C for 70 min and cooled. TLC with an aliquot of the reaction mixture using chloroform/ethyl acetate (7:1) showed tightly running, two main spots with a tiny amount of a much faster moving substance. The consumption of the starting material was also indicated. The mixture was evaporated and the residue partitioned between chloroform (100 mL) and water (30 mL). The organic layer was dried over sodium sulfate and evaporated to a gum, which was triturated with ca. 10 mL of a solvent mixture, $CHCl_3$ (7)/ETOAc (1), to give **4a** as homogeneous crystals (154 mg). The mother liquor separated from the crystals was applied on a silica gel column (2.5 × 32 cm) and eluted with the same solvent to effect separation of the closely running components, **4a** and **5**. The slightly faster moving fraction was rechromatographed on a silica gel plate (10 × 20 cm) using the same solvent mixture (twice developed) to give 83 mg (8.3%) of **5** as a homogeneous foam: UV λ_{max}^{MeOH} 240 (ε 45 800) and 262 nm (ε 19 200).

Anal. Calcd for $C_{24}H_{21}N_2O_8Cl$: C, 57.55; H, 4.43; N, 5.59. Found: C, 57.25; H, 4.28; N, 5.39.

The second crystalline fraction was combined with the above obtained crystals and recrystallized from acetone to give 442 mg (44%) of **4a** as needles: mp 216–218 °C; UV λ_{max}^{MeOH} 240 (ε 40 000) and 261 nm (ε 16 400, sh).

Anal. Calcd for $C_{24}H_{21}N_2O_8Cl$: C, 57.55; H, 4.43; N, 5.59. Found: C, 57.60; H, 4.37; N, 4.40.

Method B. Isolation of 6a, 7, 8, and 4a. A mixture of **3** (2.235 g, 4.55 mmol) and sodium *p*-methylbenzoate (2.15 g, 13.65 mmol) in DMF (48 mL) was stirred at 125 °C for 3.5 h. After cooling, the solvent was evaporated off and the residue partitioned between ethyl acetate (100 mL) and ice water (30 mL). The organic layer was worked up as usual, charged on a silica gel column (3 × 24 cm), and eluted first with chloroform/ethyl acetate (5:1). The first fraction gave 343 mg (11.8%) of **6** as needles of mp 245–246 °C after one crystallization from a mixture of acetone and ethanol: UV λ_{max}^{MeOH} 241 (ε 70 700) and 267 nm (ε 9080, sh).

Anal. Calcd for $C_{31}H_{24}N_2O_9Cl_2$: C, 58.23; H, 3.78; N, 4.38. Found: C, 58.15; H, 3.99; N, 4.26.

The second fraction gave a semisolid mixture of **4a** and **5**, from which 847 mg (37.2%) of **4a** was obtained as crystals after crystallization from acetone and rechromatography of the overlapped fraction on a silica gel column using the same solvent mixture. The finally obtained, small amount of mixture of **4a** and **5** was neglected. The identity of **4a** with an authentic sample prepared by method A was confirmed by infrared and NMR spectroscopy.

The column was then thoroughly eluted with ethyl acetate to give a small amount of a paste, which was shown by TLC [chloroform/methanol (9:1) and ethyl acetate/chloroform (2:1)] to be a mixture of two closely running products. The mixture was charged on a silica gel plate (15 × 20 cm) and developed twice with ethyl acetate/chloroform (2:1). Elution of the slightly faster moving band with acetone and recrystallization of the obtained solid from a mixture of ethyl acetate and acetone gave 59 mg (7.3%) of **7** as needles, mp 226–229 °C; UV λ_{max}^{MeOH} 242 (ε 25 600) and 265 nm (ε 15 400, sh).

Anal. Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.06; H, 5.03; N, 7.53.

The slower moving band was similarly worked up to give 25 mg (2.93%) of **8**, mp 193–196 °C (from ethyl acetate); UV λ_{max}^{MeOH} 241 (ε 22 600) and 262 nm (ε 12 000, sh).

Anal. Calcd for $C_{16}H_{15}N_2O_7Cl$: C, 50.21; H, 3.95; N, 7.32. Found: C, 50.48; H, 4.08; N, 7.30.

Reaction of 1-(5'-*O*-*p*-Chlorobenzoyl-3'-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)uracil (4a) with Sodium *p*-Methylbenzoate. A mixture of **4a** (100 mg, 0.205 mmol) and sodium *p*-methylbenzoate (130 mg, 0.82 mmol, 4 molar excess) in DMF (2.5 mL) was stirred at 125–130 °C for 19 h and worked up as in the reactions of **3**. The finally obtained ethyl acetate extract, TLC of which showed a product distribution quite similar with the reaction of **3** (method B), was submitted to preparative TLC [5 × 20 cm, chloroform/ethyl acetate (3:1)] to give 16 mg (12.5%) of **6a**, identical in all respects with an authentic specimen obtained above. The starting material and other products were discarded.

Reaction of 4a with Potassium *p*-Methylbenzoate. A mixture of **4a** (442 mg, 0.88 mmol) and potassium *p*-methylbenzoate (612 mg, 3.52 mmol, 4 molar excess) in DMF (22 mL) was stirred at 125–130 °C for 3.5 h. TLC at this stage showed a product distribution similar with the above reaction of **4a** with the same reagent. The mixture was worked up as usual and chromatographed on silica gel (32 × 2 cm) using chloroform/ethyl acetate (6:1) to give 75 mg (13.3%) of **6a** after one recrystallization. Recovery of the starting material was 36.7% (160 mg).

Alternative Synthesis of 6a. To an ice-cold stirred solution of **4a**

(100 mg, 0.2 mmol) in pyridine (2 mL) was added *p*-chlorobenzoyl chloride (0.03 mL, 0.23 mmol). The mixture was then left at room temperature for 6 h, treated with water (0.3 mL) for 5 min, and evaporated. The residue was partitioned between ethyl acetate (20 mL) and water (5 mL). TLC showed the presence of a small amount of another faster moving substance (most probably N^3-*p*-chlorobenzoyl derivative of **6a**). The ethyl acetate extract was heated in 95% pyridine at 110 °C for 2 h and cooled. The mixture was evaporated and repeatedly coevaporated with ethanol, and the residue was recrystallized from a mixture of ethanol and acetone to give 93 mg of needles of mp 245–247 °C, identical with the above-obtained sample of **6a** in all respects.

1-(5′-*O*-*p*-Chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)4-thiouracil (4b). A mixture of **4a** (800 mg, 1.595 mmol) and phosphorus pentasulfide (710 mg, 3.19 mmol) in pyridine (25 mL) was stirred at 105 °C for 2 h and 20 min. Further phosphorus pentasulfide (300 mg) was added and the reaction continued for an additional 2 h. After cooling, the reaction mixture was partitioned between ethyl acetate (100 mL) and water (30 mL). The separated ethyl acetate layer was evaporated, the residual gum heated in water (50 mL) at 90–95 °C for 10–15 min, and the water decanted off. This procedure was repeated four times. The finally obtained solid residue was crushed with hot water, collected by suction, and recrystallized from acetonitrile to give 550 mg (67%) of **4b,** mp 254–256 °C; UV λ_{max}^{MeOH} 238 (ε 48 600) and 328 nm (ε 25 100).

Anal. Calcd for $C_{24}H_{21}N_2O_7SCl$: C, 55.77; H, 4.10; N, 5.42. Found: C, 55.64; H, 4.08; N, 5.67.

1-(2′,5′-di-*O*-*p*-Chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)-4-thiouracil (6b). A mixture of **4b** (200 mg, 0.388 mmol) and sodium benzoate (224 mg, 1.55 mmol) in DMF (4.8 mL) was stirred at 115–120 °C for 3.5 h. After evaporation of the solvent, the residue was partitioned between ethyl acetate (50 mL) and water (10 mL). The separated organic phase was dried and evaporated, and the residue was triturated with chloroform to give 44 mg of the starting material. TLC with the filtrate using chloroform/ethyl acetate (3:1) showed the presence of a main (starting material) and two minor spots, one of which was faster moving and the other slower moving than the starting material. The filtrate was concentrated, charged on a silica gel plate (5 × 20 cm), and developed with chloroform. After usual workup, 20 mg (7.7%) of **6b,** mp 179–181 °C (from acetone + MeOH), was obtained: UV λ_{max}^{MeOH} 238 (ε 59 400) and 327 nm (ε 19 100).

Anal. Calcd for $C_{31}H_{24}N_2O_9SCl$: C, 55.45; H, 3.60; N, 4.17. Found: C, 55.21; H, 3.85; N, 4.15.

Additional starting material (56 mg) was recovered. The slower moving product was neglected.

1-(5′-*O*-*p*-Chlorobenzoyl-3′-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)3-methyluracil (9). A mixture of **4a** (300 mg, 0.615 mmol) and *N,N*-dimethylformamide dimethylacetal (0.3 mL, 3 mmol) in chloroform (10 mL) was heated to a reflux for 4 h and cooled. The mixture was evaporated, charged on a silica gel plate (20 × 20 cm), and developed twice with chloroform/ethyl acetate (3:1). Elution of the main band with acetone gave 173 mg of a homogeneous solid, which was recrystallized from methanol to give 163 mg (52.7%) of **9** as needles of mp 173–175 °C: UV λ_{max}^{MeOH} 240 (ε 46 100) and 262 nm (ε 17 100).

Anal. Calcd for $C_{25}H_{23}N_2O_8Cl$: C, 58.31; H, 4.50; N, 5.44. Found: C, 58.54; H, 4.77; N, 5.43.

1-(5′-*O*-*p*-Chlorobenzoyl-2′,3′-di-*O*-*p*-methylbenzoyl-β-D-arabinofuranosyl)-3-methyluracil (10). Method A. A mixture of **9** (163 mg, 0.318 mmol) and sodium *p*-methylbenzoate (202 mg, 1.27 mmol, 4 molar excess) in DMF (4 mL) was stirred at 125–130 °C for 3.5 hr. TLC with an aliquot of the reaction mixture revealed the starting material as the major component with two minor products, one of which was faster moving and the other slower moving. Thus, the general pattern was similar with the case of the reactions between **4a,b** and the basic catalysts. The mixture was evaporated and the residue partitioned between ethyl acetate (30 mL) and water (7 mL). The obtained ethyl acetate extract was charged on a silica gel plate (20 × 20 cm) and developed with chloroform/ethyl acetate (3:1). The most mobile band gave 26 mg (12.9%) of **10** as needles of mp 182–184 °C after crystallization from a mixture of methanol and acetone: UV λ_{max}^{MeOH} 242 (ε 65 400) and 262 nm (ε 17 600).

Anal. Calcd for $C_{33}H_{29}N_2O_9Cl$: C, 62.61; H, 4.62; N, 4.43. Found: C, 62.43; H, 4.58; N, 4.53.

The major fraction gave 85 mg (51%) of the starting material. The other minor product was neglected.

Method B. A mixture of **9** (0.142 g, 0.277 mmol) and sodium benzoate (160 mg, 1.11 mmol, 4 molar excess) in DMF (4.5 mL) was stirred at 125–130 °C for 3.5 h. The reaction was worked up as described in method A to give 21 mg (12%) of **10,** identical with the product obtained above in terms of infrared and ultraviolet spectroscopy and mixef fusion. The other components were neglected.

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Registry No.—**1,** 59211-02-8; **2,** 64114-40-5; **3,** 64114-41-6; sodium *p*-methylbenzoate, 17264-54-9; potassium *p*-methylbenzoate, 16518-25-5; *p*-chlorobenzoylchloride, 122-01-0; phosphorus pentasulfide, 1314-80-3; sodium benzoate, 532-32-1; *N,N*-dimethylformamidedimethylacetal, 4637-24-5.

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(7) Elongation of time to 19 h did not improve the yields of **6a** significantly (see Experimental Section). Elongated reactions using stronger base like sodium azide revealed gradual dearoylation of the resulting **6a.**
(8) Evidences for ionization of the uracil part under the used conditions can be drawn from some literatures. For example, see: (a) ref 2; (b) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29,** 558 (1964).
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Cyclocarbonylation of 2-*exo*-Ethynyl-7-*syn*-norbornanol to an α-Methylene δ-Lactone

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Although α-methylene butyrolactones are much more prevalent in natural products and have thus received more synthetic attention,[2] naturally occurring α-methylene valerolactones are also known, e.g., in vernolepin and vernomenin.[3] We have thus investigated the usefulness of our $PdCl_2$/thiourea catalyst system[4] in the synthesis of α-methylene valerolactones from carbon monoxide and appropriately substituted 4-pentynols.[5]

Only traces of α-methylene δ-valerolactone (1) were obtained by this method from 4-pentyn-1-ol itself, either under catalytic conditions or in the presence of 1 equiv of $PdCl_2$; most of the starting ethynyl alcohol remained unreacted even after 60 h. However, better results seemed likely with a fused-ring system where the ethynyl and hydroxyl groups were fixed in the appropriate geometry for lactone ring formation. A suitable substrate, **2a,** proved available from the treatment

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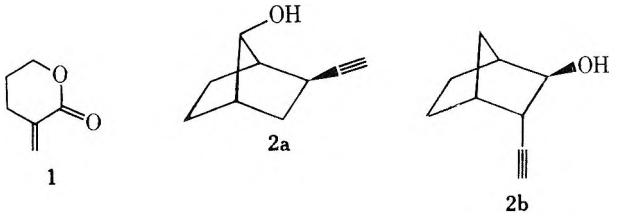
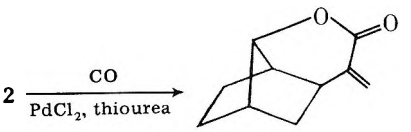


1 2a 2b

of *exo*-norbornene oxide (**3**) with dimethylethynylaluminum etherate.[6]

Results and Discussion

On the basis of decoupling experiments revealing an NMR coupling constant of about 3 Hz between the hydroxyl-substituted methine proton and the ethynyl-substituted methine proton, the product **2** of ethynylaluminum treatment of *exo*-norbornene oxide had originally been assigned the structure **2b**. However, **2b** would not be expected to form a lactone



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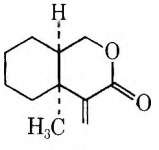
readily, whereas carbonylation of **2** in the presence of $PdCl_2$/thiourea gives a methylene lactone (**4**) in good yield.

The spectroscopic properties of **4** clearly show that it is an α-methylene δ-lactone and not an α-methylene γ-lactone. For example, the ν_{CO} of **4** (1722 cm^{-1}) is well below the range (1770–1750 cm^{-1}) typical of the latter,[2,7] while within the range (1730–1710 cm^{-1}) typical of the former.[5]

The ^1H NMR spectrum of **4** confirms the δ-lactone structure. The *exo*-methylene group appears as a pair of doublets (each with J = 1.3 Hz) at δ 5.94 and 5.28. Spin-decoupling shows that this J is a *geminal* coupling constant; no coupling to other, e.g., allylic, protons is resolvable. While geminal couplings are typically negligible in α-methylene γ-lactones[2,7,8] (e.g., <0.2 Hz in a case analyzed in detail in reference 7a), they are frequently observed with a value of about 1 Hz in α-methylene γ-lactones (e.g., in **5**[5c] and **1**[5d]). On the other



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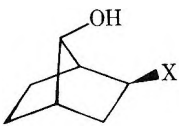
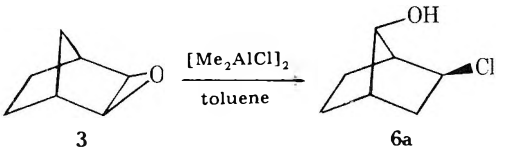
hand, allylic couplings decrease from the 2.0–3.5-Hz range found in most α-methylene γ-lactones[2,7,8] to values of 1 Hz or less in most α-methylene δ-lactones.[5,9]

In light of the above generalizations, a methylene doublet with a *geminal* splitting of 1.3 Hz, as in **4**, must be assigned



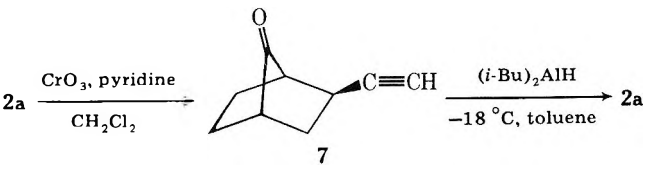
6a, X = Cl
b, X = Br



3 **6a**

to a methylene group in the α position on a δ-lactone. A plausible structure for **2** is thus **2a**,[10] obviously an excellent precursor for the δ-lactone **4**. The ethynylation of **3** by dimethylethynylaluminum etherate must then be proceeding by rearrangement under the influence of this Lewis acid reagent. Such substitution patterns (**6**) are well known as the products of the reaction of **3** with protic acids such as HBr and HCl.[11] The implication that they can also be formed with Lewis acid reagents[12] can be verified by noting that **3** gives **6a** when treated with $[(CH_3)_2AlCl]_2$.

Confirmation of structure **2a** is afforded by its oxidation to the ketone **7**. The IR spectrum of **7** shows split carbonyl bands



7

centered at high frequency (1775 cm^{-1}) characteristic of the strained bicyclo[2.2.1]heptan-7-one system.[13] Reduction of **7** by diisobutylaluminum hydride gives **2a** again, proving that the apical ketone arises from an apical hydroxyl in **2a** and not from rearrangement during oxidation.

The sequence **3** → **2a** → **4** thus represents a facile two-step synthesis of an unusual fused-ring α-methylene δ-lactone from commercially available starting materials.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 283 and NMR spectra were recorded on Varian A-60 and XL-100 instruments using tetramethylsilane as internal standard. Mass spectra were obtained on an AEI MS-9. Gas chromatographic analyses were carried out on a Perkin-Elmer 3920.

Preparation of *exo*-2-Ethynylbicyclo[2.2.1]heptan-*syn*-7-ol (2a). To a solution of dimethylethynylaluminum etherate[5] in toluene (1 M, 45 mL) was added under nitrogen, while stirring, a solution of *exo*-2,3-epoxybicyclo[2.2.1]heptane (**3**) (2.2 g, 20 mmol, in 20 mL of toluene) at room temperature. After 2 h, the reaction mixture was hydrolyzed by the slow addition of a minimum amount of water. The solution was then dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by TLC on silica gel plates (development with 4:1 C_6H_6/EtOAc) to give **2a** (0.9 g, 35%) as a low-melting solid, homogeneous by VPC (5% carbowax 20 M, 180 °C): IR (neat) 3400 (s), 3300 (s), and 2110 (m) cm^{-1}; NMR ($CDCl_3$) δ 3.98 (m, 1 H), 2.3–2.58 (m, 1 H), 2.18 (d, $J \approx 2$ Hz, 1 H), 0.9–2.1 (m, 8 H).

Anal. Calcd for $C_9H_{12}O$: *m/e* 136.08881. Found: 136.08876.

Preparation of Hexahydro-3-methylene-4,7-methanocyclopenta[*b*]pyran-2(3*H*)-one (4). To a mixture of palladium chloride (0.18 g, 1 mmol) and thiourea (0.07 g, 1 mmol), in acetone (5 mL) under 50 psi of carbon monoxide at 50 °C, was added a solution of **2a** (0.14 g, 1 mmol, in 3 mL of acetone), and the mixture was stirred for 48 h at that temperature. It was then filtered through a bed of celite and evaporated in vacuo. The residue was digested with water and was extracted with ether (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was then distilled at 0.1 mm pressure, and the fraction boiling at 62–65 °C was purified by TLC (4:1 C_6H_6/EtOAc) on silica gel plates to yield **4** as an oil (0.07 g, 47%); it was homogeneous by VPC (5% DEGS, 160 °C): IR (neat) 1722 (s), 1647 (m), and 1633 (w) cm^{-1}; NMR ($CDCl_3$) δ 5.94 (d, J = 1.3 Hz, 1 H), 5.28 (d, J = 1.3 Hz, 1 H), 4.50 (m, 1 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.17; H, 7.32. Found: C, 72.67; H, 7.39.

Formation of *exo*-2-Chlorobicyclo[2.2.1]heptan-*syn*-7-ol (6a) from 3. To a stirred solution of dimethylaluminum chloride (5.5 mL, 11 mmol) (Texas Alkyls) in toluene, under nitrogen at room temperature, was added a solution of *exo*-2,3-epoxybicyclo[2.2.1]heptane (**3**) (1.1 g, 10 mmol) in toluene (6 mL) and stirred for 1 h. The mixture was then hydrolyzed with a minimum amount of water, dried ($MgSO_4$), filtered, and evaporated in vacuo. The product was purified by TLC (4:1 C_6H_6/EtOAc) on silica gel plates to give **6a** (1.2 g, 80%). Recrystallization from hexane gave crystals with mp 52–54 °C (lit.[11b]

52–53.2 °C). The IR and NMR spectra were identical with those reported for **6a**.[11b]

Preparation of *exo*-2-Ethynylbicyclo[2.2.1]heptan-7-one (7). Chromium trioxide (1 g, 10 mmol) was added to a stirred solution of pyridine (1.6 g, 20 mmol) in 25 mL of methylene chloride.[14] After 15 min at room temperature, 0.15 g (1.5 mmol) of **2** in 2 mL of methylene chloride was added, and the suspension was stirred at room temperature for 18 h, after which it was poured into water (20 mL) and filtered through a bed of celite. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layers were then washed with cold dilute hydrochloric acid and water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give a yellow oil. This was distilled to give **7** (0.08 g, 50%), bp 50 °C (0.08 mm). It was homogeneous by VPC (5% carbowax 20 M, 160 °C): IR (neat) 3300 (s), 1830 (m), 1775 (s), and 1742 (m) cm^{-1}; NMR ($CDCl_3$) δ 2.86–2.43 (m, 1 H), 2.2 (d, J = 2 Hz, 1 H), 1.36–2.18 (m, 8 H). The 2,4-dinitrophenylhydrazone of **7** melted at 110–111 °C.

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.27; H, 4.47; N, 17.73.

Reduction of 7 with Diisobutylaluminum Hydride to 2a. To a stirred solution of **7** (0.095 g, 0.8 mmol) in 1 mL of toluene at −18 °C was added a toluene solution of diisobutylaluminum hydride (1 mL, 2 M). Stirring was continued for 1 h at −18 °C. The reaction mixture was then hydrolyzed with a minimum amount of water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give **2a** (0.09 g, 32%), which showed IR and NMR spectra identical with that of **2a** prepared earlier.

Acknowledgments. We thank Professor B. Snider for helpful discussions, Hoffmann-La Roche, Inc., for microanalytical services, and Matthey-Bishop, Inc., for a generous loan of $PdCl_2$. This investigation was supported by Grant CA 18546 and by training grants (to T.M. and V.V.) awarded by the National Cancer Institute, DHEW.

Registry No.—**2a**, 64130-75-2; **3**, 3146-39-2; **4**, 64130-76-3; **6a**, 16709-78-7; **7**, 64130-77-4; **7** DNP, 64130-78-5.

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Synthesis and Circular Dichroism Spectral Studies of Arylamides of *trans*-2-Phenylcyclohexanecarboxylic Acid and *trans*-1-Amino-2-phenylcyclohexane[1,2]

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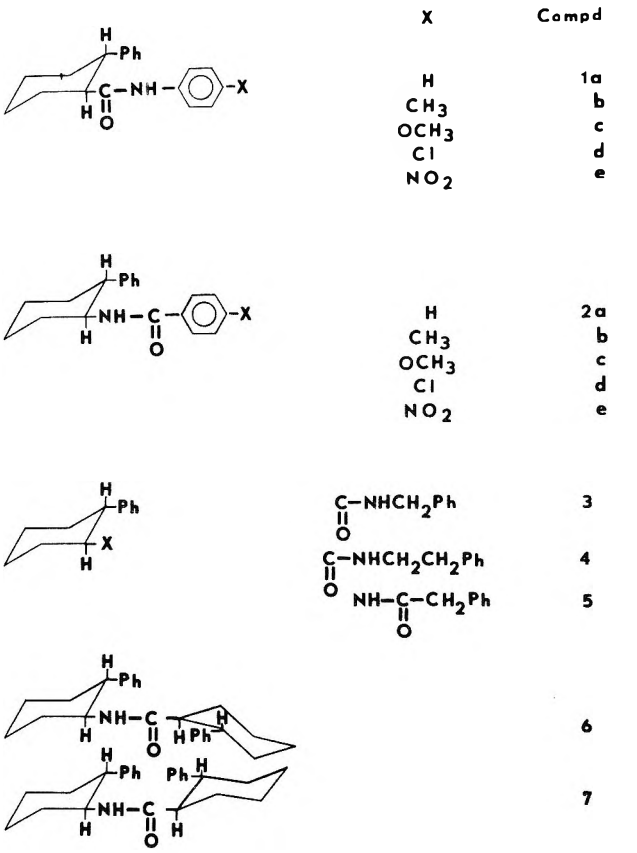
Although the chiroptical phenomena exhibited by aromatic compounds have been studied extensively,[3] papers on benzamides are few,[4–6] and a systematic study of anilides has not been reported. We report the CD and isotropic UV spectra of a series of aromatic amides (Scheme I) derived from *trans*-2-phenylcyclohexanecarboxylic acid (A) and *trans*-1-amino-2-phenylcyclohexane (B).

These amides are of interest because they have structural features in common with amides of the amino acid phenylalanine. The C-1 and C-2 substituents in these amides form a fixed dihedral angle of approximately 60°, resulting in a chromophoric system which resembles a staggered conformer of the analogous phenylalanine amides. Absolute configurational assignments and conformational analysis are available from previously reported studies on the precursors, A and B.[7,8] Finally, the CD spectra of these amides show *separately* the effects of changing the para substituent on an anilide or benzamide, inverting the amide chromophore, or changing the proximity (number of intervening carbons) of the amide and benzene chromophores.

Experimental Section

CD and ORD measurements were made at 25 °C in methanol on a Jasco Model ORD/UV/CD-5 instrument under conditions described by Verbit et al.[7,9] Isotropic UV measurements were made on a Cary Model 11 instrument. For CD, ORD, and isotropic UV measurements, solution concentrations were 2.5–3.0 × 10^{-4} M, except that the $[\alpha]_D$'s of all compounds and the ^1L_b bands (CD and UV) of compounds **3–7**

Scheme I



0022-3263/78/1943-0355$01.00/0

Table I. Experimental Data for Amides of +A and +B [a]

Compd	Mp	$[\alpha]_D$	IR, ν(C=O)	Registry no.
1a	135–138	+105	1651	64163-48-0
b	182–186	+136	1650	64163-49-1
c	217–221	+183	1648	64163-50-4
d	182–185	+124	1655	64163-51-5
e	175–179	+84	1670	64163-52-6
2a	210–212	+105	1634	64200-03-0
b	219–221	+88	1633	64163-53-7
c	232–233	+75	1630	64163-54-8
d	230–231	+79	1637	64163-55-9
e	202–203	+65	1639	64163-56-0
3	121–125	+36	1636	64163-57-1
4	109–112	+11	1632	64163-58-2
5	145–146	−43	1634	64163-59-3
6	258–259	+71	1633	64163-60-6
7	255–256	−65	1633	64200-04-0

[a] The melting points are corrected. Specific rotations were obtained in methanol at 25 °C. The carbonyl stretching IR band (in cm^{-1}) was obtained as a Nujol mull. Additional details are in the experimental Section of the text.

were obtained at 6.0–7.0 × 10^{-3} M. IR spectra were obtained as Nujol mulls between NaCl plates on a Perkin-Elmer Model 467 instrument. Compound melting points were obtained on a Fisher-Johns melting point apparatus and are corrected. Organic solvents were anhydrous unless otherwise stated. Elemental analyses were conducted by Galbraith Laboratories, Knoxville, Tenn.

Synthesis of Acid Chlorides. Acid chlorides were obtained from their corresponding carboxylic acids. The synthesis and resolution of *trans*-2-phenylcyclohexanecarboxylic acid was described in ref 7. The conversion of acids to acid chlorides was as follows. A 1-g amount of the acid was refluxed for 1 h with 5 mL of $SOCl_2$. Most of the excess $SOCl_2$ was evaporated under a stream of nitrogen at 40–45 °C. The remaining $SOCl_2$ was removed by the addition and evaporation of two portions of benzene, yielding the acid chloride.

Synthesis of Amines. The synthesis and resolution of *trans*-1-amino-2-phenylcyclohexane was as described in ref 7. Other amines were reagent grade and were recrystallized or vacuum distilled prior to use.

Synthesis of Amides. The acid chloride (0.0015 mol) dissolved in 5 mL of benzene was added to a solution of the amine (0.0015 mol) in 5 mL of benzene and 2 mL of pyridine. The reaction mixtures were allowed to stand in the dark at 25–30 °C for 3 days. The reaction mixture was taken up in 50 mL of diethyl ether. The ether solution was washed with 50-mL portions of the following aqueous solutions: 5% Na_2CO_3 (twice), saturated NaCl, 1 M HCl (twice), and saturated NaCl. The ether solution was then washed with two 30-mL portions of water and dried over anhydrous Na_2SO_4. The ether was driven off under a stream of N_2, and the amides were recrystallized from benzene or benzene–hexane solutions, except compounds **3** and **5** were recrystallized from CCl_4 and compound **4** from ethanol. Yields of recrystallized amides (based on chiral acid or amine) were 60–78%, except **1a**, **1e**, and **2d** were 40–50%. Silica gel G TLC of the amides gave single spots in the two developing solvents, 2:1 benzene/$CHCl_3$ and 10:2:1 cyclohexane/acetone/CH_3OH. The IR spectra of the amides were characterized by secondary amide NH bands between 3270 and 3340 cm^{-1} and carbonyl bands between 1630 and 1670 cm^{-1}. The melting points, $[\alpha]_D$'s, and carbonyl IR bands for the amides are summarized in Table I.

Results and Discussion

This discussion, as well as spectral and other experimental data, is presented for amides having absolute configurations as shown in Scheme I (although the amide actually synthesized may be the enantiomer). Thus, compounds **1a–e, 2a–e, 3, 4,** and **5** all have the same absolute configuration and are derived from (+)-(1*S*,2*S*)-*trans*-2-phenylcyclohexanecarboxylic acid (+A) or (+)-(1*S*,2*R*)-*trans*-1-amino-2-phenylcyclohexane (+B). Compound **6** is derived from +A and +B and compound **7** from −A and +B.

For the aromatic amides, **1a–d** and **2a–d,** two bands predominate in the CD spectra: the charge transfer (CT)[10] amide band appearing between 225 and 250 nm and the aromatic ^1L_a band (Platt's notation)[11] between 210 and 220 nm. (See Figures 1 and 2 and Table II.)

The aromatic ^1L_b band is largely obscured by the CT band in these compounds but is partially observable in **1a, 2a, 2b,** and **2d.** The nitro CT transition gives rise to a broad CD band around 300 nm for **1e** and **2e.** Thus, the *p*-nitroanilide **1e** shows three positive CD bands: ^1L_a (210 nm), amide CT (229 nm), and nitro CT (317 nm). For the *p*-nitrobenzamide **2e,** however, only two bands (both positive) are observed: the nitro CT band at 289 nm and a weak band at 218 nm. We assign the positive 218-nm band primarily to the amide CT transition, probably superimposed on a weaker negative ^1L_a Cotton effect. This assignment is consistent with trends in the CD spectra of the benzamide series (**2a–d**) where amide CT bands are all positive, an electron-withdrawing parasubstituent producing a hypsochromic shift, and a lessened ellipticity

Table II. CD and Isotropic UV Extrema for Anilides, Benzamides, and Homologues [a]

Compd	205–220 nm bands, [$\lambda(\epsilon)$, $\lambda([\pm\theta])$]	CT and ^1L_b bands, [$\lambda(\epsilon)$, $\lambda([\pm\theta])$]
1a	206 (24 800), 210 (+26 300)	242 (13 300), 240 (+24 400)
b	206 (26 600), 210 (+27 500)	245 (14 100), 243 (+27 800)
c	206 (28 200), 210 (+34 300)	249 (18 600), 245 (+34 500)
d	206 (27 500), 210 (+34 800)	249 (17 800), 247 (+31 300)
e	206 (19 700), 210 (+16 000)	, 229 (+8200); 316 (13 800), 317 (+9700)
2a	206 (16 600), 216 (−7900)	, 227 (+11 300)
b	206 (23 600), 216 (−12 900)	234 (13 200), 234 (+19 500)
c	206 (29 800), 213 (−35 900)	250 (16 600), 251 (+24 600)
d	206 (22 600), 215 (−9 300)	234 (13 400), 237 (+15 300)
e	206 (19 400), [218 (+7800)]	, 218 (+7800); 261 (11 750), 289 (+6300)
3	208 (17 400), 212 (−9000)	252 (320), 254 (+150); 258 (380), 261 (+265) 264 (290), 268 (+250
4	208 (19 300), 212 (+15 500)	252 (448), 254 (+25); 258 (504), 259 (+75) 264 (398), 266 (+73)
5	206 (19 400), 211 (−35 500)	252 (520), 253 (+154); 258 (570), 260 (+255) 264 (452), 267 (+256)
6	208 (18 900), 220 s (−12 300) 210 n (−21 000)	252 (330), 257 (−216); 258 (406), 263 (−265) 264 (308), 269 (−141)
7	208 (19 600), 217 s (−24 800) 209 (−49 000)	252 (363), 255 (−226); 258 (435), 262 (−253) 264 (338), 268 (−155)

[a] s = shoulder and n = extrema not reached. For several amides shoulders were evident in the high-wavelength side of the 206–208 nm isotropic UV band. Isotropic UV amide CT bands of **1e, 2a,** and **2e** are obscured by the ^1L_a band. The 218-nm CD band of **2e** is assigned primarily to the amide CT transition. (See the Results and Discussion Section.)

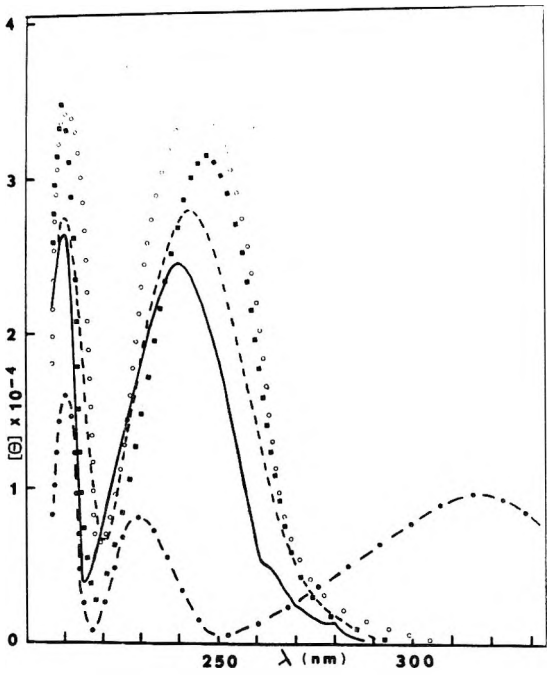


Figure 1. Circular dichroism spectra of anilides of (+)-(1*S*,2*S*)-*trans*-2-phenylcyclohexanecarboxylic acid in methanol; **1a** (—), **1b** (- - -), **1c** (○), **1d** (■), **1e** (●–●).

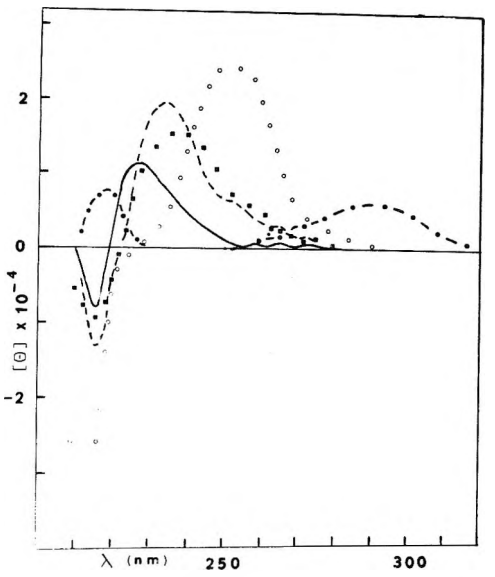


Figure 2. Circular dichroism spectra of benzamides of (+)-(1*S*,2*R*)-*trans*-1-amino-2-phenylcyclohexane in methanol; **2a** (—), **2b** (- - -), **2c** (○), **2d** (■), **2e** (●–●).

in the amide CT band; the ^1L_a bands are negative and, with the exception of **2c**, of lower intensity than the amide CT bands.

In general, an increased electron-donating capability in the parasubstituent increases the intensity of the ^1L_a *Cotton effect and isotropic absorption in both aromatic amide series,* **1a–e** *and* **2a–e.** The shifts in λ_{max} are small and measurable only for the benzamide series (**2a–e**). The amide CT bands (both UV and CD) of both series are markedly influenced by the para substituent: bands generally increasing in intensity and undergoing a bathochromic shift as the electron-donating capacity of the substituent increases. The more-pronounced changes in the amide CT band are observed for the benzamide series (**2a–e**). In contrast, a *p*-nitro substituent shifts the carbonyl IR stretching frequency more in the anilide series (1a–e). (See Table I.)

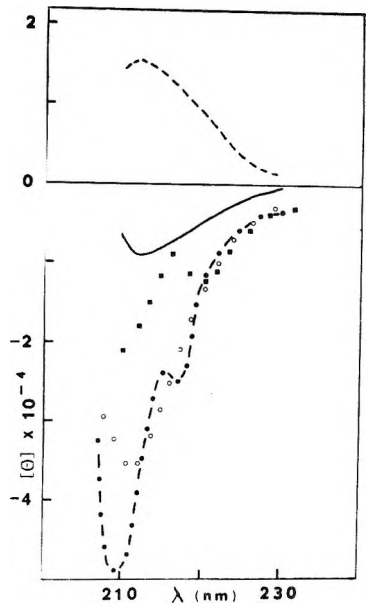


Figure 3. Circular dichroism spectra of compounds 3 (—), 4 (- - -), 5 (○), 6 (■), and 7 (●–●) in methanol.

The sign of the ^1L_a *Cotton effect changes when the amide chromophore is inverted in the aromatic amide series (cf. any anilide with its corresponding benzamide) or when the amide nitrogen is increasingly separated from the benzene ring as in the series* **1a, 3,** *and* **4,** where the ^1L_a Cotton effects are (+), (−), and (+), respectively. (See Figure 3 and Table II.)

The ellipticity of the ^1L_a Cotton effect in the *p*-methoxybenzamide **2c** is triple that of *p*-chlorobenzamide **2d,** whereas in the corresponding anilides, the bands of **1c** and **1d** are of nearly equal intensity. The unique electronic effects of a *p*-methoxy group on a benzamide CD spectra have been noted by Krueger et al,[4] but as yet no adequate explanation is available.

All amides derived from +B (*including* **6** *and* **7**) *exhibit negative* ^1L_a *Cotton effects.* (The amine, +B itself, exhibits a positive ^1L_a band.)[7] The CD spectra of diastereomers **6** and **7** show ^1L_a bands that are interpreted as two overlapping bands. (See Figure 3.) The ORD spectra of these compounds (not shown) are consistent with this interpretation. One can approximate the ellipticity of the ^1L_a bands of **6** and **7** by considering them to be the sum of (1) a strong negative Cotton effect (such as that observed for **5**) contributed by the +B component and (2) a contribution from the A component. The contribution from the A component for **6** (derived from +A and +B) would be a positive Cotton effect similar to that of **4**; for **7** (derived from −A and +B) it would be a negative Cotton effect, the inverse of that observed for **4.**

For compounds **3, 4,** and **5,** no amide CT bands are present, and the ^1L_b bands, with their characteristic vibronic fine structure, are clearly observed in the CD and isotropic UV spectra. (See Table II.) Enough of the ^1L_b Cotton effect can be discerned in the spectra of **1a, 2a, 2b,** and **2d** so that the sign can be reliably determined. *All seven of these compounds exhibit positive* ^1L_b *Cotton effects. Thus, unlike the* ^1L_a *Cotton effect, the* ^1L_b *effect does not change sign in the series* **1a, 3,** *and* **4;** *nor does it change upon inversion of the amide chromophore* (*cf.* **1a** *and* **2a**). As has been pointed out for a series of 2-substituted phenylcyclohexanes,[7,8] conformational mobility apparently obviates sign/chirality correlations for the ^1L_b Cotton effects for these series of amides as well. Consequently, there is no obvious rationale for the interesting feature that the ^1L_b Cotton effects exhibited by diastereomers **6** and **7** are virtually identical. (See Table II.)

We anticipate the further study of related anilides and benzamides with the intent of testing further the generality of the correlations of chirality with amide CT and aromatic ^1L_a bands. Of particular interest are amides derived from the cis isomers of A and B and isomers of the phenylalanine analogue 1-amino-2-phenylcyclohexanecarboxylic acid.

Registry No.–H_2NCH_2Ph, 100-46-9; $H_2N(CH_2)_2Ph$, 64-04-6; $ClCOCH_2Ph$, 103-80-0; H_2NPh, 62-53-3; $H_2NC_6H_4$-*p*-CH_3, 106-49-0; $H_2NC_6H_4$-*p*-OCH_3, 104-94-9; $H_2NC_6H_4$-*p*-Cl, 106-47-8; $H_2NC_6H_4$-*p*-NO_2, 100-01-6; ClCOPh, 98-88-4; $ClCOC_6H_4$-*p*-CH_3, 874-60-2; $ClCOC_6H_4$-*p*-OCH_3, 100-07-2; $ClCOC_6H_4$-*p*-Cl, 122-01-0; $ClCOC_6H_4$-*p*-NO_2, 122-04-3; 2-phenylcyclohexane-1-carbonyl chloride, 34713-97-8; 1-amino-2-phenylcyclohexene, 37982-23-3.

References and Notes

(1) This work was supported by a Faculty Summer Research Grant from Marshall University to H.C.P. The authors wish to thank Dr. Lawrence Verbit of the Department of Chemistry, State University of New York at Binghamton, Binghamton, N.Y., for his assistance and for access to the Jasco ORD/UV/CD-5 instrument.
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A General Synthesis of Terminal and Internal Arylalkynes by the Palladium-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides

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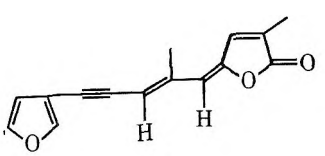
Arylalkynes represent a number of natural products such as freelingyne[1] (1) and junipal[2] (2). They have been most commonly prepared by Cu-promoted aryl–alkynyl coupling,[3] which involves either the reaction of alkynylcoppers with aryl halides[3a] or that of arylcoppers with alkynyl halides.[3b] More recently, an alternate approach consisting of the Pd-catalyzed



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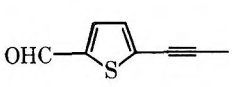

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reaction of alkynes with aryl halides in the presence of suitable bases has been developed.[4] While these known procedures are satisfactory in many cases, none of them appears to provide a satisfactory direct procedure for the synthesis of terminal arylalkynes which does not require any protection–deprotection sequence.[5] The difficulty largely stems from the fact that, under the reaction conditions, the required ethynyl reagents, such as ethynylcopper[6] and ethynylalkali metals,[7] are unstable with respect to disproportionation.

We have recently found that organozinc compounds react rapidly with various aryl and alkenyl halides to produce cross-coupled products even at room temperature in the presence of a catalytic amount of a Pd or Ni catalyst, whereas the corresponding reactions of organoalkali metals and Grignard reagents are not only slower but generally less satisfactory.[8] We have also noted that ethynylzinc chloride can be conveniently prepared by the reaction of either ethynyllithium[7] or its ethylenediamine complex[9] with anhydrous zinc chloride as a reagent stable at room temperature.[10]

We now report that these findings can be exploited in developing a procedure for aryl–alkynyl coupling applicable even to the direct and selective synthesis of terminal arylalkynes (eq 1).

$$RC{\equiv}CZnCl + ArX \xrightarrow{\text{cat Pd complex}} RC{\equiv}CAr \qquad (1)$$

R = H, alkyl, or aryl; X = I or Br

The aryl–alkynyl coupling reaction reported here is essentially complete within several hours at room temperature when either aryl iodides or activated aryl bromides such as *p*-cyanobromobenzene are used. In such cases, the formation of arylalkynes proceeds cleanly without producing any other byproducts in significant amounts (<5%). On the other hand, unactivated aryl bromides such as bromobenzene are quite inert at room temperature. Thus, while the formation of tolan from 2-phenylethynylzinc chloride and iodobenzene is complete within 0.5 h at room temperature, the corresponding reaction of bromobenzene does not give any more than a trace of tolan even after 4 days under comparable conditions. Similar difficulties have also been observed with *p*-methoxybromobenzene and *p*-chlorobromobenzene. No aryl fluorides have been tested.

The present study corroborates our earlier finding that organozinc reagents are superior to the corresponding Grignard and organoalkali metal reagents in Pd or Ni-catalyzed cross-coupling.[8] Thus, for example, the reaction of 1-heptynylmagnesium bromide with *o*-iodotoluene gives only a 49% yield of 1-(*o*-tolyl)-1-heptyne after 24 h, and the corresponding reaction of 1-heptynyllithium does not produce the desired product in any more than a trace amount under comparable conditions. For the preparation of terminal alkynes, both ethynyllithium generated at −78 °C and its ethylenediamine complex serve as satisfactory sources of ethynylzinc chloride, although the latter appears to give somewhat cleaner results. In some experiments, 5 mol % of a Pd catalyst has been used. However, the subsequent studies have indicated that even 1 mol % of the catalyst gives entirely satisfactory results. Both $Pd(PPh_3)_4$ and a Pd catalyst generated in situ from $Cl_2Pd(PPh_3)_2$ and diisobutylaluminum hydride seem almost equally satisfactory. The use of $Pd(PPh_3)_4$, which does not require any additional treatment, is operationally simpler than that of the latter catalyst. On the other hand, the shelf-life of the former appears considerably shorter than that of the latter, although we have not yet determined how long $Pd(PPh_3)_4$ can be kept without a significant loss of its catalytic activity. Nickel–phosphine complexes, such as $Ni(PPh_3)_4$, do induce the desired cross-coupling reaction. However, the product yields have been low (<50%), and no complete consumption of aryl halides has been observed when the amount of the Ni catalyst is 5 mol %.[11] Unlike certain alkynylcoppers and related organotransition metals, which tend to be explosive, the Pd-catalyzed reaction of alkynylzinc derivatives does

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Table I. Preparation of Arylalkynes by the Pd-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides[a]

RC≡CZnCl R	Registry no.	Aryl halide (ArX) Ar	X	Registry no.	Catalyst,[b] (mol %)	Time, h	Yield of ArC≡CR,[c] % GLC	Isolated	Registry no.
H[d]	37008-61-0	*o*-Tolyl	I	615-37-2	A (5)	3	71		766-47-2
H[e]		*p*-Anisyl	I	696-62-8	A (5)	1	66	56	768-60-5
		Phenyl	I	591-50-4	A (1)	1	67		536-74-3
Methyl	64146-56-1	2-Thienyl	I	3437-95-4	A (1)	1	92	82	23229-66-5
n-Pentyl	64146-57-2	2-Thienyl	I		B (1)	2	85	70[f]	64146-58-3
		2-Thienyl	Br	1003-09-4	A (5)	48	75		
		p-Cyanophenyl	Br	623-00-7	A (1)	4	93		64146-59-4
		p-Cyanophenyl	Br		B (1)	4	82	*g*	
		p-Nitrophenyl	I	636-98-6	B (1)	3	94	64[h]	64146-60-7
		p-Anisyl	I		A (1)	0.5	92	70[i]	64146-61-8
		m-Tolyl	I	625-95-6	B (5)	1	89	79[j]	64146-62-9
		o-Tolyl	I		B (5)	1	88		64146-63-0
Phenyl	13984-49-1	*m*-Tolyl	I		B (5)	1.5	87	80[k]	14635-91-7
		Phenyl	I		A (1)	0.5	93	74[l]	501-65-5

[a] All reactions were run at room temperature in THF. The ratio of RC≡CZnCl/ArX is 2 for the cases where R = H and 1 for R ≠ H. [b] A = $Pd(PPh_3)_4$ and B = $Cl_2Pd(PPh_3)_2$ + *i*-Bu_2AlH. [c] All isolated products were identified by ^1H NMR, IR, and mass spectrometry. [d] Prepared from ethynyllithium generated at −78 °C in THF. [e] Prepared from ethynyllithium–ethylenediamine. [f] bp 74–76 °C (0.3 mm); $n^{28}D$ 1.5482. [g] Isolated by GLC; $n^{25}D$ 1.5500. [h] bp 105–110 °C (0.3 mm); $n^{23}D$ 1.6676. [i] bp 114–115 °C (1.1 mm) [lit.[17] bp 92–93 °C (0.1 mm)]; $n^{25}D$ 1.5409. [j] Isolated and purified by column chromatography; $n^{22}D$ 1.5286. [k] mp 29–30 °C [lit.[18] mp 30–31 °C]. [l] mp 63 °C [lit.[19] mp 63.5 °C].

not appear to be associated with explosiveness, although this point is yet to be clearly established.

The synthetic usefulness of the new aryl–alkynyl coupling procedure may be demonstrated by the preparation in 81% yield (92% by GLC) of 1-(2′-thienyl)-1-propyne, which has previously been converted to junipal (2) via formylation.[12]

Experimental Section

All experiments were carried out under nitrogen atmosphere. All aryl halides and alkynes except acetylene were commercial reagents and used without further purification. Acetylene was purified by passing it through a dry ice–acetone trap, concentrated sulfuric acid, and potassium hydroxide pellets. THF was distilled over lithium aluminum hydride and stored over molecular sieves. Zinc chloride (Fisher Scientific Co.) was dried in an oven at 110 °C overnight before use. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer, and ^1H NMR spectra were recorded on a Varian T-60A spectrometer. GLC analyses were performed on a Hewlett-Packard 5750 gas chromatograph using a 6 ft × 0.125 in 5% SE-30 column on Chromosorb W. The GLC yields were determined using suitable hydrocarbon internal standards such as *n*-decane.

Palladium(0)–Phosphine Complexes. One of the palladium(0)–phosphine complexes was prepared from dichlorobis(triphenylphosphine)palladium(II) and diisobutylaluminum hydride.[8] The palladium(II) salt was in turn prepared from palladium chloride (25 mmol) and triphenylphosphine (60 mmol) by dissolving both of the compounds in DMF (160 mL) at 140 to 150 °C. On cooling, dichlorobis(triphenylphosphine)palladium(II) crystallized out of the solution. After filtration, the crystals were rinsed with ether and dried at reduced pressure.

Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure reported by Coulson.[13]

Preparation of 1-Heptynylzinc Chloride. To a solution of 1-heptyne (20 mmol) in THF (10 mL) at 0 °C was added 20 mmol of *n*-butyllithium in hexane. The solution was stirred for 5 min followed by the addition of anhydrous zinc chloride (20 mmol) dissolved in THF (20 mL). The mixture was stirred for an additional 15 min at room temperature.

Preparation of Ethynylzinc Chloride from Ethynyllithium. THF (50 mL) was saturated with acetylene at −78 °C. *n*-Butyllithium (50 mmol) in hexane was diluted with THF (50 mL) and added dropwise to the acetylene solution at −78 °C. Maintaining the temperature at −78 °C, a solution of anhydrous zinc chloride (50 mmol) in THF (50 mL) was also added dropwise. The resulting mixture was then slowly warmed to room temperature.

Preparation of Ethynylzinc Chloride from Ethynyllithium–Ethylenediamine Complex. A suspension of 3.68 g (40 mmol) of ethynyllithium–ethylenediamine complex[6] in 40 mL of THF at 0 °C was charged with 5.46 g (40 mmol) of anhydrous zinc chloride dissolved in 40 mL of THF. The resulting slurry was warmed to room temperature and stirred for an additional 30 min.

Preparation of *p*-Methoxyphenylethyne. Ethynylzinc chloride was prepared as described above. To this were added sequentially at 0 °C 4.68 g (20 mmol) of *p*-iodoanisole dissolved in 20 mL of THF and 1.15 g (1.0 mmol) of $Pd(PPh_3)_4$ in THF (20 mL). The reaction mixture was stirred for 1 h at room temperature. GLC examination of an aliquot of the reaction mixture after quenching indicated the formation of the title compound essentially as the only volatile product. The remainder of the reaction mixture was quenched with 50 mL of 2 N HCl. After adding 50 mL of petroleum ether, the two layers were separated and the aqueous layer was extracted with petroleum ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered through a short alumina column to remove any trace of Pd-containing compound, and distilled under vacuum to give 1.48 g (56%) of *p*-methoxyphenylethyne (99% pure by GLC): bp 39–41 °C (0.7 mm) [lit.[14] bp 90–95 °C (10 mm)]; ^1H NMR (CCl_4, Me_4Si) δ 2.85 (s, 1 H), 3.72 (s, 3 H), 6.78 (d, *J* = 8 Hz, 2 H), 7.37 (d, *J* = 8 Hz, 2 H); IR (neat) 3250 (s), 2100 (m), 1600 (s), 1580 (s), 1450 (m), 1200 (s), 1240 (s), 1165 (s), 1025 (s), 830 (s) cm^{-1}.

Preparation of 1-(2′-Thienyl)-1-propyne. 1-Propynylzinc chloride was prepared by treating 1.10 g (24 mmol) of 1-propynyllithium[15] with 3.27 g (24 mmol) of anhydrous zinc chloride as described above. To a 250-mL flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler were introduced 0.23 g (0.2 mmol) of $Pd(PPh_3)_4$ and 20 mL of THF. To this were added sequentially at 0 °C 5.04 g (3.06 mL, 24 mmol) of 2-iodothiophene and the above-prepared 1-propynylzinc chloride suspended in THF. The reaction mixture was stirred for 3 h at room temperature. GLC examination of a 1-mmol aliquot, after quenching with 5 mL of 2 N HCl, indicated the formation of the title substance in 92% yield. Neither the starting aryl iodide nor any other byproduct was observed in any more than a trace amount. The remainder of the reaction mixture (23 mmol) was quenched with 50 mL of 2 N HCl. After adding 50 mL of ethyl ether, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and distilled to give 2.30 g (82%) of 1-(2′-thienyl)-1-propyne (>99% pure by GLC): bp 73–75 °C (8 mm), $n^{23}D$ 1.5919 [lit.[16] bp 65–66 °C (7 mm), $n^{17}D$ 1.5950]; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.99 (s, 3 H) 6.7–7.2 (m, 3 H); IR (neat) 2230 (w), 1430 (s), 1245 (s), 1195 (s), 1045 (s), 845 (s), 830 (s), 700 (s) cm^{-1}.

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Registry No.—1-Heptyne, 628-71-7; zinc chloride, 7646-85-7;

acetylene, 74-86-2; ethynyllithium–ethylenediamine complex, 50475-76-8; 1-propynyllithium, 4529-04-8.

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Heats of Hydrogenation of the Cis and Trans Isomers of Cyclooctene[1]

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Strain in organic molecules has long been of interest, and there are diverse ways of measuring its effect upon physical and chemical properties. With the advent of the powerful force field method for determining molecular structures and energies,[3] strained molecules have become a testing ground for those interested in this area of chemistry. The largest and most complete body of data available on the energies of molecules is to be found in the heats of formation of hydrocarbons.[4] These are ordinarily determined by measurement of heats of combustion. Since heats of combustion are large numbers and are measured relative to the elements, for which the heats of combustion are also large numbers, the experimental determination of the heat of formation of a compound involves a relatively small difference between two large numbers, and the experimental measurements must be of very high accuracy in order to secure heat of formation data which are of only moderate accuracy. This problem has long been recognized, and one solution is to measure the energy difference between two species in which one is interested, which is usually a much smaller quantity. In the case of unsaturated hydrocarbons, this is in principle easy. Heats of hydrogenation can be measured for alkenes and related compounds, and the heats of formation of the corresponding alkanes are usually known. Hence, the heat of hydrogenation can be determined directly to rather high accuracy, and the heat of formation can usually be obtained for the alkene with an accuracy approaching that which is available for the alkane. In practice there are some problems with experimental heats of hydrogenation. These can be determined in the gas phase, and this was the method used by Kistiakowsky in his classical investigations.[5] For experimental convenience, subsequent measurements have usually been made in acetic acid solution. This presents some interpretive difficulty. The experimental technique used by Turner[6] in his extensive studies on the heats of hydrogenation of alkenes is such that in order to convert his data to gas-phase numbers, one needs to know the heats of solvation of the alkanes obtained in acetic acid solution. These numbers are positive and often quite sizable since solvation of the hydrocarbon disrupts the liquid structure of the acetic acid. The heats of solvation are not usually known.

Recently, a technique for measuring heats of hydrogenation of unsaturated hydrocarbons in hexane solution at room temperature was developed.[7,8] The experimental technique is such that the directly measured number differs from the gas phase value only to the extent that the thermodynamic states of the reactant and product in very dilute hexane solution differ from the thermodynamic states of the gaseous product and reactant. We argue that the absence of differential intermolecular interactive forces makes this difference negligibly small. Hence, the values obtained pertain (to a very good approximation) to the actual molecular quantity desired, uncomplicated by solvation effects.

The cyclooctenes are a case of special interest in several ways. First, the heat of hydrogenation of *cis*-cyclooctene itself is known in the gas phase[5] and in acetic acid solution,[6] and these values can be compared with the value in hexane. More importantly, the trans isomer is a highly strained molecule, in which there is a bending (or rehybridization) deformation about the double bond.[9-11] Molecules with this deformation are scarce, hence the heat of hydrogenation of this compound is of interest. Since the heat of formation of cyclooctane is accurately known,[4] the heats of hydrogenation give us the heats of formation for these compounds.

Finally, there has been some question as to the structure of *trans*-cyclooctene.[9-12] The initial independently proposed structures arrived at from electron diffraction[11] and by molecular mechanics calculations[10] differed with respect to the stable conformation. More recent electron diffraction results[12] have borne out the calculations rather than the original electron diffraction results. We feel it is especially important that the energy of this molecule, as well as its structure, be accurately calculated by any force field which is going to be useful for strained alkenes.

We recently reported[13] a new force field (MM2) which utilized low-order torsional terms as a key feature and which was shown to work extremely well for calculation of the structures and energies of saturated hydrocarbons.[13,14] In extending this force field to alkenes, we noticed that we were not able to reproduce very well the heat of formation of *trans*-cyclooctene, as estimated from the heat of hydrogenation in acetic acid by Turner.[6] Our calculated structure was 2–3 kcal/mol more strained than Turner's heat of hydrogenation indicated.

It was concluded that it would be worthwhile to remeasure the heats of hydrogenation of the cyclooctenes in a hexane solvent so as to avoid the solvation problem. In addition, we now have available better criteria for determining the purity of the compounds than were available to Turner, and finally, we are now aware of the fact that *trans*-cyclooctene polymerizes to some extent upon distillation, and presumably also upon simply standing at room temperature. The purity of the samples was established by gas chromatography.

The heats of hydrogenation were determined, and the data are summarized in Table I. Indeed, the *cis*-cyclooctene value

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Table I. Heats of Hydrogenation ($-\Delta H_{H_2}$, kcal/mol)[a] for the Cyclooctenes

Cis	*Trans*	Solvent	Ref
22.98 ± 0.10	32.24 ± 0.21	Acetic acid	6
23.53 ± 0.04	–	Gas phase	5
23.04 ± 0.17	34.41 ± 0.43	Hexane	This work

[a] Under Turner's conditions in acetic acid, the magnitude of the heat of hydrogenation will be smaller than the gas-phase value by the heat of solvation of cyclooctane in acetic acid (about 0.4 kcal/mol). Kistiakowsky's measurements were at 82 °C, and heats of hydrogenation are generally slightly greater in magnitude at elevated temperatures.

is quite comparable with earlier values, as anticipated. The *trans*-cyclooctene value is approximately 2 kcal greater in magnitude than that reported by Turner. The difference is attributed in part to solvation but mainly to sample purity, as discussed above. The predictive value of the force field calculations is again borne out. From the heat of hydrogenation obtained herein, we can estimate the heats of formation and strain energies of the cyclooctenes. Taking the heat of formation of cyclooctane[4a] as -29.73 ± 0.28, we obtain $H_f°$ values for the gas phase at 25 °C, as: trans, $+4.68 \pm 0.71$ kcal/mol, and cis, -6.69 ± 0.45 kcal/mol. An independent literature value[4a] gives: cis, -6.45 ± 0.30 kcal/mol.

The calculated inherent strain energies[3a] for cyclooctane, and *cis*- and *trans*-cyclooctene are respectively 14.15, 10.36, and 21.99 kcal/mol.[13] While these numbers are quantitatively different from earlier values, the interpretation is the same, namely that cyclooctane contains considerable strain from van der Waals repulsion and unfavorable torsion, which is partly relieved in *cis*-cyclooctene. The *trans*-cyclooctene, on the other hand, contains a large amount of bending and twisting strain about the double bond.

Experimental Section

The apparatus and technique used for the heat of hydrogenation measurements has been previously described.[8] 1-Hexane was used as the standard ($H_{H_2} = -30.00$[4b] kcal/mol). Samples of compound, 0.15–0.30 g, were weighed to ±0.01 mg and made up to volume with hexane. Forty-microliter aliquots were added to the hydrogenation vessel, which contained the Pd/C catalyst suspended in hexane.

cis-Cyclooctene was purchased from Columbia Carbon Co., Princeton, N.J., and was distilled. GLC showed it to be quite pure (SE 30 capillary column). The trans isomer was furnished by Dr. R. Bach, and had been prepared by elimination from the 1,2-diol. It was shipped in pentane. The pentane was removed by distillation and the *trans*-cyclooctene was distilled. A polymeric residue remained. This sample of *trans*-cyclooctene was shown by GLC not to contain any detectable amount of the cis isomer. It did contain 1.8 ± 0.5% pentane, which was allowed for in calculation of the heat of hydrogenation.

The *trans*-cyclooctene sample described above was both used as described and partly redistilled (to give a second sample), which now was found by GLC to contain 0.45 ± 0.15% pentane. The heat of hydrogenation was also measured with this sample. Uncertainties in Table I are 95% confidence limits on nine replicate samples plus an estimated uncertainty on the correction due to pentane in the trans sample.

Acknowledgment. The authors are grateful to Dr. Robert D. Bach, Wayne State University, for furnishing them with the *trans*-cyclooctene sample used in this work.

Registry No.—*cis*-Cyclooctene, 931-87-3; *trans*-cyclooctene, 931-89-5.

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Reaction of Methyl and *tert*-Butyl Hypochlorite with Cyclopentadiene

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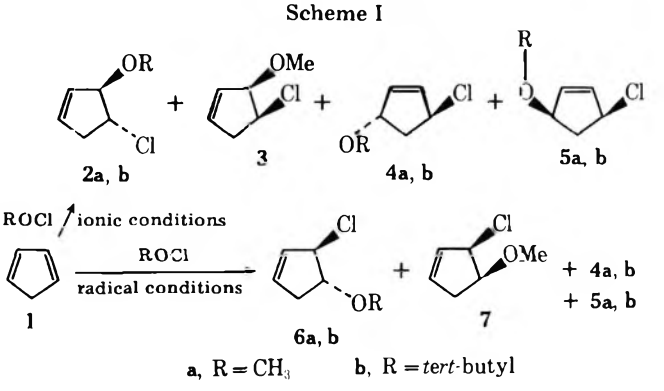
Recently, we reported studies on the ionic and radical addition of methyl hypochlorite to acyclic, conjugated dienes.[1] In order to examine the stereochemistry of this reaction, we decided to explore the addition of alkyl hypochlorites to cyclopentadiene (1). The reaction of 1 with *tert*-butyl hypochlorite has been reported[2] but without identification of the stereoisomers and without a discrimination between ionic and radical addition mechanisms.

The products obtained from 1 and methyl and *tert*-butyl hypochlorite are identified in Scheme I. The ratios of products obtained under ionic and radical conditions are listed in Tables I and II, respectively. Both of the hypochlorites give a rapid radical reaction (molecule-induced homolysis) with the

Scheme I



a, R = CH_3 b, R = *tert*-butyl

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Table I. Reactions of Cyclopentadiene with Methyl and *tert*-Butyl Hypochlorite under Ionic Conditions

Expt no.	Conditions[b,c]	Products, %[a] 1,2 addn (Markownikoff) 2a,b	3	1,4 addn 4a,b	5a,b	Yield of alkoxy chlorides, %	Yield of dichlorides, %
1	MeOCl, MeOH (98%)	36	7	26	31	72	
2	Cl_2, MeOH (98%)	34	6	27	33	60	16[d]
3	Cl_2, MeOH (98%), 0.1 M LiCl	36	8	25	31	55	17[d]
4	Cl_2, *t*-BuOH (98%)	66		10	24	14	28[d]
5	MeOCl, MeOH (98%), BF_3	26	9	30	35	82	
6	MeOCl, HOAc (98%)	14	28	4	54	5	
7	MeOCl, HOAc (2%), CH_2Cl_2 (96%)	24	39	10	32	16	
8	MeOCl, $PhCO_2H$ (2%), CH_2Cl_2 (96%)	27	42	9	22	18	
9	MeOCl, $ClCH_2CO_2H$ (2%), CH_2Cl_2 (96%)	24	37	10	29	21	
10	MeOCl, CH_2Cl_2 (98%), BF_3	30	27	16	27	47	

[a] Percentages of alkoxy chloride products are normalized to 100%. [b] Reactions were carried out by saturating the reaction mixtures with oxygen gas before addition of the hypochlorite. [c] Percentages in parentheses refer to the mole percentage of that reagent before addition of the hypochlorite solution. The concentration of **1** was always 0.02 mole fraction. [d] The dichlorides[7] are *trans*-3,4-dichlorocyclopentene (**8**), *cis*-3,4-dichlorocyclopentene (**9**), *trans*-3,5-dichlorocyclopentene (**10**), and *cis*-3,5-dichlorocyclopentene (**11**); the percentage of each of the dichlorides is, respectively in expt 2: 43, 13, 22, 22; in expt 3: 42, 14, 22, 22; and in expt 4: 27, 27, 15, 31.

Table II. Reactions of Cyclopentadiene with Halogenating Reagents under Radical Conditions

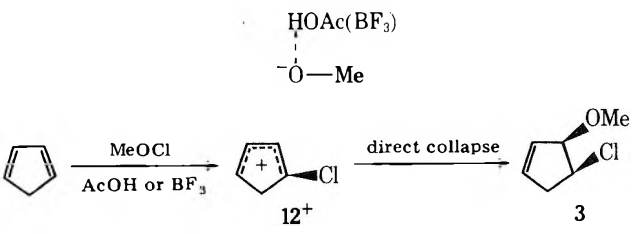
Reagent[a]	Yield	Products, % 1,2-Addition[b] trans	cis	1,4-Addition trans	cis
CH_3OCl	97	28[b]	5[b]	50	17
t-BuOCl	100	39[b]	0	52	9
NCl_3[c]	55	38	12	25	25
$PhICl_2$[c]	88	41	0	29	30

[a] Reactions were carried out by adding the reagent in methylene chloride to neat **1** which was saturated with nitrogen before addition. The reaction mixture was illuminated with ultraviolet light from a 275-W sunlamp. [b] The 1,2-alkoxy products are anti-Markownikoff. [c] Data from ref 11.

neat diene, affording near-quantitative yields of the alkoxy chloride adducts (Table II). Ionic addition to **1** was achieved under a variety of conditions. In line with our previous observations with acyclic dienes,[1] **1** did not react with the hypochlorites in dilute methylene chloride solution under oxygen as a radical inhibitor.[3] In dilute methanol a complete reaction was observed in 30 min (Table I, expt 1). A more rapid reaction occurs when BF_3 is present in the methanol (expt 5).[4] The reaction between **1** and *tert*-butyl hypochlorite in *tert*-butyl alcohol was much slower and, since the product ratios showed some variation over this long time period, the results are not reported in Table I.[5] The products from the chlorination of **1** in methanol and *tert*-butyl alcohol are also reported in Table I (expts 2 and 4).[5]

We designed experiments in which the addition of methyl hypochlorite to **1** occurred in the absence of methanol, thus avoiding the complication of methoxide incorporation from the solvent. For example, reaction between **1** and methyl hypochlorite in glacial acetic acid (expt 6) gave a 5% yield[6] of methoxy chlorides. The yield was increased to 16% by using only 2% acetic acid in methylene chloride (expt 7). Benzoic acid (expt 8) and chloroacetic acid (expt 9) under the same conditions gave methoxy chlorides in yields of 18 and 21%, respectively. The highest yield (47%) under these conditions was obtained by adding a few drops of boron trifluoride etherate (expt 10) to the mixture of **1** and methyl hypochlorite in methylene chloride.

Scheme II



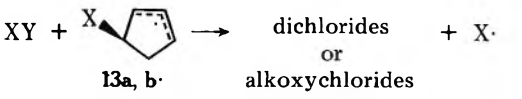
Turning to the mechanistic significance of our results, we wish to make several observations. First, concerning the 1,2 addition under ionic conditions, we note that, while some syn 1,2 addition was observed with methyl hypochlorite,[5] the amount of syn addition is greatly increased when methanol is not the solvent. Apparently, the carboxylic acids or BF_3 catalyze formation of the ion pair **12** by stabilizing the methoxide ion as shown in Scheme II. The methoxide ion can then collapse directly to give the cis product **3**. Reactions in methanol give mainly the trans-1,2-product evidently because solvent collapse happens very rapidly from the back-side.

It is interesting that the four reactions (expts 1, 2, 3, and 5) employing methanol solvent all give very similar product ratios. Apparently, chlorine and methyl hypochlorite produce essentially identical carbonium ion intermediates, a conclusion previously reported.[1] The addition of excess chloride ion (expt 3) did not increase the percentage of dichlorides formed in chlorination, suggesting as previously reported in the chlorination of styrenes[8a] and pentenes[8b] that the dichlorides are formed from the collapse of an intimate ion pair.

The data show that the stereochemical results from 1,4 addition are similar to those of 1,2 addition. For example, much more syn 1,4 addition is obtained when methanol is not the solvent. However, in contrast to the 1,2 addition, the 1,4 addition is slightly more syn than anti, even for the reaction in methanol of **1** with methyl hypochlorite or chlorine. This may be due to the lower degree of steric hindrance which would be encountered for syn 1,4 addition of methoxide (or methanol) compared to syn 1,2 addition.

Under radical conditions (molecule-induced homolysis) the *trans*-1,4-adduct predominates[9] and the 1,2-adduct is the anti-Markownikoff product. A steric effect is observed in the chain-propagating step for the formation of cis-1,2-adducts.[10] The steric effect is indicated by the absence of cis-1,2-products

when *tert*-butyl hypochlorite or iodobenzene dichloride[11] react with radical intermediate **13a** or **13b** (Table II).



13a, X = OBu^t; Y = Cl
13b, X = Cl; Y = PhICl

Experimental Section

General. Cyclopentadiene was obtained from its dimer and distilled just prior to use. The hypochlorites were prepared by a modification of the method used by Jenner to prepare *n*-butyl hypochlorite.[12] NMR spectra were obtained on a Varian T-60A spectrometer and IR spectra on Beckman IR-10 or Perkin-Elmer 337 spectrophotometers. VPC analysis was done with a Hewlett-Packard 5750 flame-ionization chromatograph.

Reaction Conditions. Reactions in methanol and radical reactions were done under the same conditions as described previously.[1] In expt 5 (Table I) two drops of boron trifluoride etherate were added to 30 mL of methanol, and in expt 10 six drops of boron trifluoride were added last to a solution of 1.2 mL of **1** and 2.5 mL of 1.5 M methyl hypochlorite in 47 mL of methylene chloride.

Analysis and Identification of Products. Methoxy chlorides and dichlorides were analyzed by VPC as follows: 2.5% β,β-oxydipropionitrile on 80–100 mesh Chromosorb W(AW-DMCS), 70 °C, 4 ft × 0.25 in. SS. Retention times were 2.2, 2.5, 2.5, 3.6, 4.2, 7.4, 8.4, 8.4, 9.6, and 10.2 min for **8, 2a, 6a, 10, 4a, 5a, 3, 7, 9,** and **11**, respectively.

tert-Butyl chloride products were analyzed as follows: 6% SE-30 on 80–100 mesh Chromosorb W(AW-DMCS), 65 °C, 8 ft × 0.25 in. SS. Retention times were 33, 33, 41, and 47 min for **2b, 6b, 4b,** and **5b**, respectively.

Products were isolated by preparative VPC or spinning-band distillation and structures assigned mainly on the basis of the NMR spectra reported below. The compound assigned structure **7** was not isolated. The structure is tentatively assigned on the basis that this VPC peak had the same retention time as **3** and that the peak was removed by methanol solvolysis described below.

The most suitable column for VPC collection of the methoxy chloride products was 5% DC-550 silicone in 8 ft × 10 mm glass. *tert*-Butoxy chloride products were collected by VPC on the same column as was used for analysis. The *tert*-butoxy chloride **6b** was isolated in large amounts by spinning-band distillation, bp 64 °C (14 mm).

Additional evidence for the structure of the methoxy chloride product was obtained by solvolysis to dimethoxycyclopentenes in methanol, thus producing diethers. Three of the expected dimethoxy products were isolated by VPC collection: *trans*-3,4-dimethoxycyclopentene (**12**), *trans*-3,5-dimethoxycyclopentene (**13**), and *cis*-3,5-dimethoxycyclopentene (**14**). The VPC retention times of **12, 13,** and **14** on the propionitrile column (70 °C) described above are 3.0, 4.9, and 6.8 min, respectively. The allylic methoxy chlorides **2a, 3, 4a,** and **5a** were distinguished from the nonallylic (anti-Markownikoff adducts) methoxy chlorides **6a** and **7** by subjecting each to solvolysis in methanol at 50 °C. After 24 h, peaks corresponding to **2a, 3, 4a,** and **5a** had essentially disappeared, whereas **6a** and **7** were unaffected.

NMR Spectra. Structures were assigned on the basis of NMR. The spectra of the cyclopentadiene dibromides and dichlorides where spectra had been assigned previously served as important models.[1,7,13] Spectra were obtained in carbon tetrachloride (reported in parts per million downfield from Me_4Si).

Chloromethoxy Cyclopentenes. 2a: NMR δ 2.48 (dd, 1, *trans*-CH(H)CH, $J_{55'}$ = 17.6, J_{45} = 4.4 Hz, other fine coupling), 3.08 (dd, 1, *cis*-CH(**H**)–CH, $J_{55'}$ = 17.6, J_{45} = 7.0 Hz, other fine coupling), 3.40 (s, 3, CH_3O), 4.12 (ddd, 1, CHCl, J_{45} = 4.4, $J_{45'}$ = 7.0, J = 3.2 Hz), 4.32–4.52 [m (narrow), 1, C**H**OCH_3], 5.73–5.92 (m, 2, Ch=CH); **3:** NMR δ 2.72 (d, 2, CH_2, J_{45} = 5.2 Hz), 3.37 (s, 3, CH_3O), 4.20 (br d, 1, C**H**OCH_3, J_{34} = 5.2 Hz), 4.37 (dt, 1, CHCl, J_{45} = 5.2, J_{34} = 5.2 Hz), 5.87 (m, 2, CH=CH); NMR δ **4a;** 2.23–2.47 (m, 2, CH_2), 3.28 (s, 3, CH_3O), 4.47–4.77 (m, 1, C**H**OCH_3), 4.83–5.12 (m, 1, CHCl), 6.02 (s, 2, CH=CH); **5a:** NMR δ 1.93 [dt, 1, *trans*-C**H**(H)CH, $J_{44'}$ = 13.8, $J_{4'3(5)}$ = 4.4 Hz], 2.83 [dt, 1, *cis*-CH(**H**)CH, $J_{44'}$ = 13.8, $J_{4'3(5)}$ = 7.0 Hz], 3.27 (s, 3, CH_3O), 4.35 (dd with fine structure, 1, C**H**OCH_3, J_{45} = 7.0, $J_{4'5}$ = 4.4 Hz), 4.72 (dd with fine structure, 1, CHCl, J_{34} = 7.0, $J_{34'}$ = 4.4 Hz), 5.97 [m (narrow), 2, CH=CH]; **6a:** NMR δ 2.32 [br d, 1, *trans*-CH(H)-CH, $J_{45'}$ = 17.0 Hz], 2.85 [dd with fine structure, 1, *cis*-CH(**H**)–CH, J_{55} = 17.0, J_{45} = 7.0 Hz], 3.40 (s, 1, CH_3O), 3.95–4.23. (m, 1, C**H**OCH_3), 4.65–4.87 (m, 1, CHCl), 5.58–6.10 (m, 2, CH=CH).

Dimethoxycyclopentenes. 12: NMR δ 2.15 (dd with fine splitting, *trans*-C**H**(H)CH, $J_{5'5}$ = 16, $J_{5'4}$ = 4.5 Hz), 2.72 (dd with fine splitting, 1, *cis*-CH(**H**)CH, $J_{55'}$ = 16, J_{54} = 6.8 Hz), 3.32 (s, 6, CH_3O), 3.78 (ddd, 1, C**H**CH_2, J_{45} = 6.8, $J_{45'}$ = 4.5, J_{43} = 3.3 Hz), 4.12–4.33 (m, 1, C**H**CH=CH), 5.75 [m (narrow), 2, CH=CH]; **13:** NMR δ 1.92 (t, 2, CH_2, $J_{43(5)}$ = 4.8 Hz), 3.23 (s, 6, CH_3O), 4.48 (dt, 2, C**H**CH_2, $J_{3(5)4}$ = 4.8, $J_{13(5)}$ = 0.9 Hz), 6.02 (dd, 2, CH=CH, $J_{13(5)}$ = 0.9 Hz); **14:** NMR δ 1.50 [dt, 1, *trans*-C**H**(H)CH, $J_{4'4}$ = 13.2, $J_{4'3}$ = 4.8 Hz], 2.50 [dt, 1, *cis*-CH(**H**)CH, $J_{44'}$ = 13.2, J_{45} = 7.0 Hz], 3.25 (s, 6, CH_3O), 4.20 (dd, 2, C**H**OCH_3, $J_{3(5)4'}$ = 4.8, $J_{3(5)4}$ = 7.0 Hz), 5.95 (s, 2, CH=CH).

Chloro-*tert*-butoxycyclopentenes. 2b: NMR δ 1.20 (s, 9, Bu^tO), 2.43 [m, 1, *trans*-C**H**(H)CH], 3.07 [m, 1, *cis*-CH(**H**)CH], 4.03 (ddd, 1, CHCl, J = 7.0, J = 4.0, J = 3.5 Hz), 4.50–4.73 (m, 1, CH-OBu^t), 5.57–5.93 (m, 2, CH=CH); **4b:** NMR δ 1.18 (s, 9, Bu^tO), 2.15–2.45 (m, 2, CH_2), 4.72–5.05 (m, 2, CHCl and **H**C-OBu^t), 5.90 [m (narrow), 2, CH=CH]; **5b:** NMR δ 1.18 (s, 9, Bu^tO), 1.88 [dt, 1, *trans*-C**H**(H)CH, $J_{4'4}$ = 13.2, $J_{4'3(5)}$ = 5.0 Hz], 2.85 [dt, 1, *cis*-CH(**H**)CH, $J_{44'}$ = 13.2, $J_{43(5)}$ = 6.8 Hz], 4.38–4.80 (m, 2, CHCl and **H**COBu^t), 5.82 [m (narrow), 2, CH=CH]; **6b:** NMR δ 1.22 (s, 9, Bu^tO), 2.17 [m, 1, *trans*-C**H**(H)CH, $J_{5'5}$ = 16, $J_{5'4}$ = 3.4 Hz, other coupling], 2.83 [m, 1, *cis*-CH(**H**)CH, $J_{55'}$ = 16, J_{54} = 7.2 Hz, other coupling], 4.30 (ddd, 1, C**H**OBu^t, J_{45} = 7.2, $J_{45'}$ = 3.4, J_{43} = 2.8), 4.53–4.70 (m, 1, CHCl), 5.67–5.97 (m, 2, CH=CH).

Acknowledgment. Support for this work was provided by the Research Corporation and by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1,** 542-92-7; **2a,** 63866-22-8; **2b,** 63866-23-9; **3,** 63866-24-0; **4a,** 63866-25-1; **4b,** 63866-26-2; **5a,** 63866-27-3; **5b,** 63855-28-4; **6a,** 63966-29-5; **6b,** 63866-30-8; **8,** 31572-43-7; **9,** 51502-28-4; **10,** 31572-44-8; **11,** 31572-45-9; **12,** 59415-73-5; **13,** 59415-71-3; **14,** 59415-72-4; methyl hypochlorite, 593-78-2; *tert*-butyl hypochlorite, 507,40-4.

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(4) The ionic addition of *tert*-butyl hypochlorite to olefins catalyzed by boron trifluoride has been reported. See C. Walling and R. T. Clark, *J. Org. Chem.*, **39,** 1962 (1974).
(5) The *tert*-butoxy chloride cis-1,2-adduct was not detected under ionic conditions when *tert*-butyl hypochlorite or chlorine was added to **1** in *tert*-butyl alcohol. Apparently, steric effects preclude the formation of this product.
(6) The main product formed in the presence of carboxylic acids is undoubtedly a mixture of chloro esters. Riemschneider and Nehring[2] isolated chloroacetates from the reaction of **1** with *tert*-butyl hypochlorite in acetic acid. We observe several large VPC peaks of long retention time in the product from **1,** methyl hypochlorite, and acetic acid, but these peaks were not identified.
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(10) We make the same assumption we made in a previous paper,[11] that the cis/trans 1,2- and 1,4-product ratios are a consequence of steric approach in the chain-propagating step and not the result of steric crowding in the developing product.
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Unsaturated Carbenes from Primary Vinyl Triflates. 9. Intramolecular Rearrangement via Free Carbenes[1]

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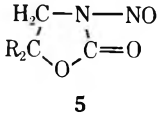
The Fritsch–Buttenberg–Wiechell (FBW) rearrangement of diarylhaloethylenes to diarylacetylenes upon treatment with strong bases has been known since the 1890's.[2,3] Although this rearrangement was recognized as an α-elimination involving a sextet rearrangement by the original discoverers, the exact mechanism and the nature of the intermediate was not firmly established until some 60 years later. By means of elegant C-14 labeling studies, Bothner-By[4] and Curtin and co-workers[5] have shown a strong trans stereochemical requirement for aryl migration and thereby clearly established that the rearrangement proceeds via an organometallic intermediate and carbenoid and not the free unsaturated carbene. Subsequently, Köbrich and co-workers[6] were able to demonstrate the existence and unambiguous involvement of organolithium **1** in these rearrangements in THF at low temperatures (eq 1). Similarly, 1-halo-2-phenylpropene has been

$$(Ar)_2C{=}CHCl \xrightarrow[THF,\,-100\,^\circ C]{n\text{-BuLi}} (Ar)_2C{=}C(Li)Cl \quad \mathbf{1}$$
$$\xrightarrow{-LiCl} ArC{\equiv}CAr \qquad (1)$$

shown to give only 1-phenylpropyne upon treatment with strong base.[7] Once again, Köbrich and co-workers[3,8] unambiguously established the carbenoid nature and the involvement of an organolithium compound in this reaction as well.

Recently there has been considerable interest in unsaturated carbenes[9] **2** generated via base-promoted α-elimination from primary vinyl halides **3** or vinyl triflates **4** and base-promoted decomposition of *N*-nitrosooxazolidones **5**. Moreover, it has been established that the vinyl halide-derived species is a carbenoid whereas the triflate **4** derived intermediate is in fact the free carbene.[10,11] Furthermore, analogous

$(R)_2C{=}C:$ **2** $\quad (R)_2C{=}CHX$ **3** $\quad (R)_2C{=}CHOSO_2CF_3$ **4**



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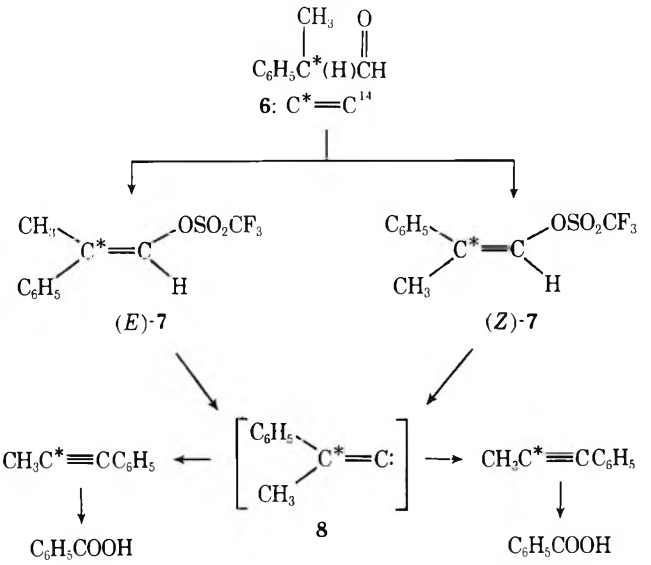
to the FBW reaction, arylvinyl triflates[12] as well as aryloxazolidones[13] give arylacetylenes as sole products. Hence, it was of interest to examine the mechanism and exact nature of the intermediates in the base-initiated rearrangement of arylvinyl triflates and specifically to ascertain if the reaction proceeds via a carbenoid, analogous to the FBW reaction, or the unencumbered carbene, similar to the behavior of the dialkyl species **2**.[10]

In order to investigate and answer this question, we prepared C-14 labeled (*E*)- and (*Z*)-2-phenylpropenyl triflates **7**. Vinyl triflates (*E*)- and (*Z*)-**7** were prepared from the corresponding labeled 2-phenylpropanal **6** by known methods

Scheme I



and separated by gas chromatography.[12] Labeled 2-phenylpropanal was prepared from the known[14] carbonyl-labeled acetophenone-^{14}C via the procedure of Allen.[15]

Reaction of each pure (*E*)- and (*Z*)- triflate with 50% excess *t*-BuOK in a mixture of dry pentane and glyme for 24 h at −20 °C gave phenylpropyne[16] as the sole product collected by preparative gas chromatography, respectively. In order to determine the location of the C-14 label, and hence the stereochemical requirements of this rearrangement, the product phenylpropyne from each reaction was oxidized[17] to benzoic acid by $KMnO_4$ as shown in Scheme I. The resultant benzoic acids were assayed along with the respective precursor acetylenes and triflates.[18] The complete lack of activity in *both* acids indicates that the alkyne products had to arise via a nonstereoselective process and hence a common intermediate derived from the two isomeric starting triflates. Since prior control experiments[12] had established that the starting isomeric vinyl triflates do not interconvert, these results are only compatible with a free carbene intermediate, **8**, rather than a carbenoid. Either a carbenoid or some type of organometallic intermediate would have been expected to show a stereochemical preference for migration and hence an unequal distribution of labels in the resulting alkynes as has been observed by Bothner-By[4] and Curtin[5] in the FBW reaction.

Hence, analogous to the behavior of the alkylidene carbenes as a function of progenitors,[10] there is a clear-cut difference in the intramolecular rearrangement of aryl-substituted unsaturated carbenes; with the reaction proceeding via a carbenoid in the case of arylvinyl halides and most likely the free carbene in the case of arylvinyl triflates.[20]

Experimental Section

Preparation of ^{14}C Labeled 2-Phenylpropanal (6). Carbonyl-labeled acetophenone-^{14}C,[14] 27.7 g (231 mm), was converted to phenylmethylglycidic ester in 62% yield and used in the preparation of **6** to give 12.5 g (65%) of product[16] according to Allen.[15]

Preparation of (*E*)- and (*Z*)-7 Vinyl Triflates. Carbon-14 labeled 2-phenylpropanal, (**6**) 11.8 g (88 mm), was converted to a mixture of the isomeric (*E*)- and (*Z*)-vinyl triflates **7** via their silyl enol ethers in 50% overall yield according to procedures previously reported.[12] The *E* and *Z* isomers were separated by preparative GC on a 15 ft by 0.375 in. 15% QF-1 column at 130 °C and identified by spectral means.[12,16]

Reaction of (*E*)- and (*Z*)-7 Vinyl Triflates. Each pure isomer was reacted according to the following general procedure. To a 5-mL round-bottom flask, equipped with a magnetic stirring bar and a serum cap, were added 0.269 g (2.4 mm) of sublimed *t*-BuOK and 1.5 mL of an 80:20 mixture of dry pentane and glyme. The reaction mixture was cooled in a dry ice–acetone bath and 0.425 g (1.6 mm) of the pure triflate, dissolved in 1.0 mL of the above pentane–glyme

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mixture, was added over a 15-min period. The mixture was allowed to warm to −20 °C and stirred for 24 h. At the end of this period, the dark-orange reaction mixture was poured into 10 mL of pentane and washed with four 1-mL portions of H_2O, the aqueous layer back-extracted with 10 mL of pentane, and the combined pentane solution was dried over $MgSO_4$. The pentane was distilled and the product phenylpropyne[16] was collected by preparative GC on the above column in 56% yield (104 mg).

Oxidation of Phenylpropyne to Benzoic Acid. The product phenylpropyne from each pure isomeric vinyl triflate was oxidized according to the following general procedure.[17] Into a 25-mL round-bottom flask equipped with a magnetic stirring bar and reflux condenser was added 4 mL of H_2O, 0.41 g (2.6 mmol) of $KMnO_4$, and 38 mg of Na_2CO_3 followed by 75 mg (0.65 mmol) of the phenylpropyne. The entire mixture was stirred for 1 h at room temperature and then refluxed for about 3 h until the purple color had completely vanished. After cooling, 0.5 mL of 50% H_2SO_4 was slowly added, the mixture was refluxed for 0.5 h and then cooled, and the brown MnO_2 was decomposed with $NaHSO_3$. The solution was made strongly acidic by the addition of 0.5 mL of 50% H_2SO_4 and after cooling in an ice bath the white precipitate was filtered. The filtrate was washed with cold water and the crystals allowed to air dry. The resulting benzoic acid was doubly sublimed to yield 35 mg (44%) of product which was assayed[18] for radioactivity along with each precursor phenylpropyne and vinyl triflate.

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Registry No.—6, 64188-89-2; (*E*)-7, 64162-87-4; (*Z*)-7, 64162-86-3; phenylpropyne-^{14}C, 64162-88-5; acetophenone-^{14}C, 5821-66-9; ethyl phenylmethylglyudate, 64162-89-6.

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(19) Fluorine interferes with this method of assay, hence, the lower precision and activity of the triflates.
(20) The possible rapid equilibration of (*E*)- and (*Z*)-carbenoids prior to rearrangement can not be ruled out, nor easily probed experimentally. The possibility of a *large* difference in migratory aptitude (in favor of phenyl) overwhelming any tendency toward stereochemical selectivity can be ruled out by the observation of alkyl migration and acetylene formation in certain dialkylvinyl triflates $R(CH_3)C=CHOTf$ under similar conditions.[21]
(21) Unpublished observations, D. P. Fox.

Reaction of Pentafluorosulfur Bromide with *cis*- and *trans*-1,2-Difluoroethylene

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The incorporation of pentafluorosulfur groups into hydrocarbons was first accomplished by Case et al. in reactions of pentafluorosulfur chloride with olefins and chloroolefins under free-radical conditions.[1] Similar results were later obtained by Gard and coworkers in reactions with pentafluorosulfur bromide with olefins, but under more facile conditions.[2] In some recent work in this laboratory, we have also noted a distinct difference in the reactivity of SF_5Cl and SF_5Br toward olefins,[3] as well as in the ability of SF_5Br itself to add to various substituted olefins.[4] Such behavior has prompted an investigation into the mechanism by which SF_5Br adds to unsaturated systems.

We have found that pentafluorosulfur bromide reacts with *cis*- and *trans*-1,2-difluoroethylene to give the erythro and threo forms of the addition product $SF_5CHFCHFBr$. The relative amounts of conformers produced are very similar for each olefin and are essentially identical for reactions carried out in the presence or absence of light as shown in Table I. This indicates that the reactions are not stereospecific and suggests that they are occurring via the same radical intermediate in all systems. Dehydrobromination of the addition products yields a mixture of *cis*- and *trans*-$SF_5CF=CFH$.

Structural assignments of the erythro and threo diastereomers have been made on the basis of a comparison of vicinal fluorine coupling constants obtained from proton-decoupling experiments in the C–F region of the fluorine NMR spectra. In one compound, a multiplet was found to collapse to two overlapping pentets arising from coupling between the vicinal fluorine atoms and between one of these fluorines and the SF_4 group. The second multiplet in the same spectrum collapsed to two doublets that were formed from coupling between vicinal fluorines and between one of the fluorine atoms and the axial fluorine in the SF_5 group. From these data, the vicinal fluorine coupling constant in this compound was determined to be 37 Hz. Similar proton decoupling in the second compound resulted in a vicinal fluorine coupling of 13 Hz. The larger coupling constant was assigned to the trans arrangement of the fluorine atoms found in the erythro structure **1a**, in accordance with the Karplus rule that relates the size of the coupling constant to the dihedral angle between coupled species.[5] Similarly, the smaller F–F coupling constant was assigned to the gauche arrangement of fluorine atoms in the threo compound in **1b**. Additional fluorine and proton NMR data are contained in Table II.

Dehydrobromination of the *erythro*- and *threo*-$SF_5CHFCHFBr$ diastereomers yielded mixtures of *cis*- and *trans*-$SF_5CF=CFH$. The predominant formation of the cis isomer from the erythro compound and the trans isomer from the threo compound is consistent with an antiperiplanar arrangement of the hydrogen and bromine atoms to be eliminated. The presence of a second isomer in each reaction, as indicated by a cis–trans ratio of 4:1 for erythro and 0.4:1.0 for threo, suggested that some syn elimination was occurring as well. The trans olefin underwent isomerization to the more stable cis form in good yields (77%) at 125 °C. This isomerization is consistent with previous work that has shown the *cis*-1-fluoro-2-haloolefins to be more stable than the trans isomer.[6] Structural assignments of the olefins are based on the greater intensity of the olefin-stretching vibration in the infrared spectrum, as expected, for the less symmetrical cis

Table I. Results of SF_5Br[a] Addition to Difluoroethylenes

	Registry no.	Threo:erythro	Conversion, %	Yield, %
cis-$C_2F_2H_2$, dark	1630-77-9	2.17 (2.24)	86	60
cis-$C_2F_2H_2$, $h\nu$		2.15	100	74
trans-$C_2F_2H_2$, dark	1630-78-0	1.83 (1.76)	87	66
trans-$C_2F_2H_2$, $h\nu$		1.94	100	75

[a] Registry no.: 15607-89-3.

Table II. ^1H and ^{19}F Nuclear Magnetic Resonance Data

Compound	Registry no.	Chemical shift[a]	Coupling constant,[b] J	
erythro-$FSF_4CHFCHFBr$	64282-18-4	A −70.9	A–B = 145	C–D = 37
A B C D		B −49.5	A–C = 1	C–X = 38
X Y		C +152.1	A–D = 1	C–Y = 5
		D +145.0	A–X = 4.6	D–X = 5
		X −5.49	B–D = 11	D–Y = 47
		Y −6.67	B–X = 4.5	X–Y = 5
threo-$FSF_4CHFCHFBr$	64235-94-5	A −70.6	A–B = 144	C–D = 11
A B C D		B −49.4	A–C = –	C–X = 43
X Y		C +171.7	A–D = –	C–Y = 19
		D +158.5	A–X = –	D–X = 18
		X −5.50	B–D = 11	D–Y = 46
		Y −6.77	B–X = 6	X–Y = 0
cis-$FSF_4CF{=}CHF$	64282-17-3	A −72.1	A–B = 145	C–D = 12
A B C D		B −59.5	B–C = 4	C–X = 13.5
X		C +128.2	B–D = 12	D–X = 69.3
		D +158.7		
		X −7.10		
Trans-$FSF_4CF{=}CHF$	64282-16-2	A −69.6	A–B = 146	C–D = 133
A B C D		B −56.3	B–D = 19	C–X = 4.3
X		C +153.5	B–X = 22	D–X = 69.0
		D +160.7		
		X −7.04		

[a] Proton chemical shifts in ppm relative to Me_4Si. Fluorine shifts in ppm relative to CCl_3F. [b] In Hz.

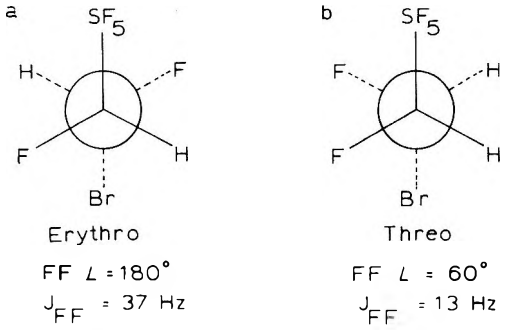


Figure 1. (a) *erythro*-$SF_5CHFCHFBr$; (b) *threo*-$SF_5CHFCHFBr$.

isomer and on proton-decoupling experiments of the C–F resonance in the fluorine NMR spectrum. The larger F–F coupling constant was assigned to the trans isomer, as in the parent compound.

From the results of the addition experiments, it is apparent that SF_5Br does not add stereospecifically to the difluoroethylenes, since only one product would have formed in each of the addition reactions. This would appear to rule out a trans addition via a configuration-holding cyclic bromonium ion, which would have resulted in stereospecificity. The possibility of this bridging bond uncoupling to form an open-chain carbonium ion, or of the direct formation of such a carbonium ion, cannot be ruled out entirely. However, the similarity of product ratios for the reactions carried out both in the presence and in the absence of light mitigates against this possibility. Furthermore, this similarity in product ratios implies that the additions in all cases are occurring via the same intermediate. The behavior of the reactions carried out in the presence of light suggests a radical mechanism and a radical intermediate species. The addition reactions are essentially complete after exposure to ambient lighting for 30 min and can be stopped effectively at partial conversion by removing them from the light, as observed in NMR measurements. The fact that the same product ratios are obtained for reactions carried out in the absence of light suggests that a radical mechanism is operating under these conditions as well, but it is initiated at a slower rate in the dark. The addition of an inhibitor to these systems in the form of hydroquinone led to inconclusive results with the recovery of SiF_4, SO_2, CF_3CFBrH, and unreacted $C_2F_2H_2$. No SF_5Br was recovered nor any addition product isolated.

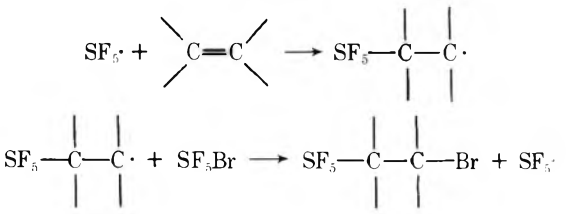
With regard to the mechanism for both reaction systems, a referee has suggested the sequence in Scheme I which is similar to that proposed by Case et al.[1] and others.[7] This route would apparently be preferred over one involving bromine atom addition to the olefin in the first propagation step, since it utilizes the more common atom transfer instead of a radical displacement in the second step. Furthermore, as pointed out in the case of SF_5Cl additions to olefins,[1] attack of a radical species on SF_5Br as shown in the propagation step would be

Scheme I

Initiation

$$SF_5Br \longrightarrow SF_5 + Br\cdot$$

Propagation



more likely to occur at the bromine atom than at the sulfur, which is highly protected by fluorine atoms.

Experimental Section

All reactant manipulations were conducted in a Pyrex system equipped with greaseless Kontes glass/Teflon valves. Infrared spectra were recorded on a Perkin-Elmer Model 567 spectrophotometer using a 10-cm cell equipped with KBr windows. NMR spectra were recorded on a JEOL PS-100 spectrometer operating at 100 MHz for proton and 94.1 MHz for fluorine resonances. Chromatographic separations were carried out using a Gow-Mac Model 69-550 gas chromatograph equipped with an 8 ft × ¼ in. SS column packed with 20% DC-QF-1 45/60 Chromosorb P, operating at 90 °C for the addition products and ambient temperatures for the olefins with a flow rate of 40 cm³/min. Liquid injections were made at an injection port temperature of 120 °C. Analyses were performed by PCR, Inc., Gainesville, Fla.

2-Bromo-1,2-difluoroethylsulfur Pentafluoride. In a typical reaction, SF_5Br (0.207 g, 1 mmol) and $C_2F_2H_2$ (0.0649 g, 1 mmol) were condensed into a 3-mL Pyrex cell equipped with a glass/Teflon valve. Depending upon the nature of the experiment to be conducted, the reaction mixture was stored either in the dark or left under ambient lighting conditions for 1 week. The volatile materials were then transferred to a vacuum system, and a preliminary separation was made by fractional condensation through a series of traps at −78, −116, and −196 °C. Any unreacted difluoroethylene was collected at −196 °C, with the SF_5Br and small amounts of S_2F_{10} being isolated at −116 °C. The material that was not volatile at −78 °C was separated by GLC. No attempt was made to identify minor products that were formed.

***erythro*-$SF_5CHFCHFBr$:** IR 3030 (vw), 3000 (sh), 1480 (vw), 1360 (vw), 1310 (vw), 1285 (vw), 1240 (vw), 1210 (w), 1175 (w), 1150 (m), 1105 (m), 1085 (w), 1060 (w), 910 (s), 885 (vs), 770 (w), 695 (w), 665 (m), 615 (m), 575 (w), 520 (vw) cm^{-1}.

Anal. Calcd for $C_2H_2F_7SBr$: C, 8.86; H, 0.74; F, 49.07; S, 11.8. Found: C, 9.01; H, 0.90; F, 49.5; S, 12.41.

***threo*-$SF_5CHFCHFBr$:** IR 3025 (vw), 3010 (vw), 1480 (vw), 1365 (vw), 1295 (vw), 1235 (vw), 1180 (m), 1135 (w), 1095 (m), 1055 (vw), 945 (m), 885 (vs), 785 (w), 745 (w), 695 (w) 660 (m), 610 (m), 575 (w) cm^{-1}.

Anal. Found: C, 9.03; H, 0.90; F, 42.91; S, 12.58.

1-Pentafluorosulfur-1,2-difluoroethylene. *threo*-SF_5CH-FCFHBr (0.147 g, 0.541 mmol) was condensed into a Pyrex reactor containing powdered KOH (0.168 g, 2.98 mmol) and left at ambient temperature for 5 min. The volatile material (0.539 mmol) was dried over P_2O_5 and separated by GLC using gas injections.

***cis*-$SF_5CF{=}CFH$:** mol wt 189.6 (calcd, 190.08); IR 3150 (vw), 2900 (vvw), 1715 (w), 1355 (w), 1190 (m), 1140 (w), 900 (vs), 810 (m), 695 (w), 625 (w), 585 (vw), 550 (vw) cm^{-1}.

***trans*-$SF_5CF{=}CFH$:** mol wt 189.8 (calcd, 190.08); IR 3110 (vw), 1705 (w), 1230 (m), 1200 (m), 900 (vs), 890 (s), 835 (w), 710 (vw), 630 (w), 575 (vw), 540 (w) cm^{-1}.

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Acetylenic Nucleosides. 1. Synthesis of 1-(5,6-Dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil and 1-(2,5,6-Trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil

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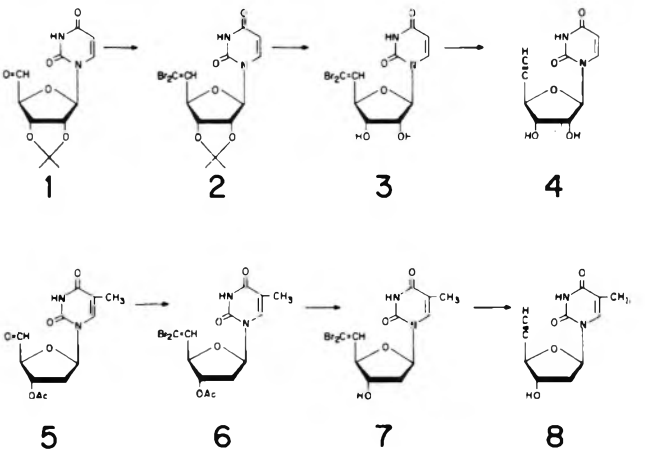
We have recently synthesized 5-ethynyluridine[1] and 5-ethynyl-2′-deoxyuridine,[2] which showed significant (50% at 2×10^{-8} M) growth inhibitory activity against L-1210 cells in vitro. This finding, and the fact that various drugs incorporating the acetylenic function can behave as specific inhibitors[3] for certain enzymatic systems, suggested that nucleosides bearing the acetylenic function at various positions in the carbohydrate moiety of pyrimidines and purines are of interest as potential antimetabolites. In this paper, we describe the synthesis of 1-(5,6-dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil (**4**) and 1-(2,5,6-trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil (**8**).

Introduction of unsaturated groups in the sugar moiety of the pyrimidine nucleosides using the Wittig reaction has not been very useful, presumably due to the instability of the aldehyde or the product under the experimental conditions used.[4] Recently, a modified Wittig-type method for the transformation of aldehydes to dibromo olefins and their subsequent conversion to acetylenes has been developed.[5-7] We have used this procedure effectively in our previous[2] work and now explored its potential for the preparation of nucleosides modified in the carbohydrate portion.

The crude 2′,3′-*O*-isopropylideneuridine-5′-aldehyde[4] (**1**) was condensed with (dibromomethylene)triphenylphosphorane,[7] yielding 1-(5,6-dideoxy-6,6-dibromo-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)uracil (**2**). Treatment of



2 with formic acid at room temperature removed the isopropylidene group and provided 1-(5,6-dideoxy-6,6-dibromo-β-D-*ribo*-hex-5-enofuranosyl)uracil (**3**) in excellent yield. The transformation of **3** to acetylenic derivative **4** was achieved by stirring with *n*-butyllithium in tetrahydrofuran in a dry ice–acetone bath, followed by neutralization with acetic acid.

Utilizing similar experimental conditions, 3′-*O*-acetylthymidine-5′-aldehyde[8] (**5**) was condensed with (dibromomethylene)triphenylphosphorane in methylene chloride to afford 1-(2,5,6-trideoxy-6,6-dibromo-3-*O*-acetyl-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (**6**).

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Compound **6** is somewhat unstable and decomposes in solid form as well as in solution. One of the products of decomposition was the deblocked nucleoside **7**, as identified by TLC. Since compound **7** is quite stable as compared to **6**, the instability of **6** is presumably due to the interaction of the 3′-acetyl function and 5′-dibromovinyl group.

Treatment of **6** with sodium methoxide in methanol for 30 min, followed by neutralization with Dowex 50 (H^+) resin, gave 1-(2,5,5,-trideoxy-6,6-dibromo-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (**7**) in good yield. Unlike **6**, the deblocked compound **7** was quite stable. Compound **7** on treatment with *n*-butyllithium in tetrahydrofuran gave product **8**.

The structural elucidation for all the compounds was made by mass and NMR spectrometry and by elemental analyses, In the NMR spectra, the C≡CH proton integrated to less than 1 proton. This fact and the downfield shift of the acetylenic proton may be due to the interaction of the ethynyl function with the carbonyl group of the pyrimidine ring. After the completion of this work, a preliminary account of the preparation of some acetylenic nucleosides from nucleoside 5′-aldehydes was given by Moffatt and co-workers.[9]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. UV spectra were measured on a Cary Model 14 spectrophotometer and NMR spectra were measured on a Varian XL-100 spectrometer using Me_4Si as an internal standard. The mass spectra were recorded on a CEC 21-491 double-focusing spectrometer using an ionization voltage of 70 eV. TLC was performed on silica gel N-HR/UV254 precoated plastic sheets (Brinkman), and column chromatography was performed on silica gel (60–200 mesh), J. T. Baker No. 3405. Elemental analyses were performed by Robertson Laboratory, Florham Park, N.J.

1-(5,6-Dideoxy-6,6-dibromo-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)uracil (2). A mixture containing triphenylphosphine (22.14 g, 0.0844 mol), carbon tetrabromide (27.98 g, 0.0844 mol), and zinc dust (5.52 g, 0.0844 mol) in 200 mL of dry methylene chloride was stirred at room temperature for 24 h.[7] To the resulting (dibromomethylene)triphenylphosphorane a solution of aldehyde **1** (prepared from 13.79 g, 0.0485 mol of 2′,3′-*O*-isopropylideneuridine) in 150 mL of anhydrous methylene chloride was added dropwise, and the mixture was stirred for 24 h at room temperature. TLC of the mixture in benzene/ethyl acetate (7:3) showed only one major product containing a sugar moiety. The mixture was evaporated to dryness, suspended in chloroform, and extracted with water. The chloroform layer was dried on anhydrous sodium sulfate, evaporated to a small volume, and poured on a dry silica gel column. The column was washed with 500 mL of benzene and then with benzene/ethyl acetate (7:3). The fractions containing the carbohydrate moiety were combined and passed again through a dry silica gel column using benzene/ethyl acetate (7:3) as eluant. The appropriate fractions were mixed together, evaporated, and triturated with acetone, yielding a colorless crystalline material. The acetone-soluble material was chromatographed again using the above solvent system. The fractions were combined, evaporated, and triturated with acetone. Thus, the yield of TLC-pure **2** was 12.29 g (56%, based on 2′,3′-*O*-isopropylideneuridine used).

Recrystallization from methanol gave an analytically pure sample: mp 230–231 °C; NMR (Me_2SO-d_6) δ 1.30 1.50 (2 s, 6, isopropylidene group), 5.65 (d, 1, $J_{5,6}$ = 8 Hz, H-5), 5.78 (d with small coupling constant, 1, H-1′), 6.85 (d, 1, $J_{4',5'}$ = 8 Hz, 5′-CH=CBr_2), 7.77 (d, 1, $J_{6,5}$ = 8 Hz, H-6), 11.52 (b, 1, NH).

Anal. Calcd for $C_{13}H_{14}N_2Br_2O_5$: C, 35.61; H, 3.19; N, 6.39; Br, 36.53. Found: C, 35.56; H, 3.30; N, 6.24; Br, 36.80.

1-(5,6-Dideoxy-6,6-dibromo-β-D-*ribo*-hex-5-enofuranosyl)-uracil (3). A solution of 1.1 g of **2** in 200 mL of 90% formic acid was stirred at room temperature for 4 h, when TLC showed no starting material present. The mixture was evaporated and coevaporated with ethanol to afford 1 g (94%) of **3**. The material was recrystallized from methanol, furnishing an analytical sample: mp 197–198 °C; NMR (Me_2SO-d_6) δ 5.68 (d, 1 H, $J_{5,6}$ = 8 Hz, H-5), 5.80 (d, 1 H, $J_{1',2'}$ = 5.5 Hz, H-1′), 7.04 (d, $J_{4',5'}$ = 9 Hz, 5′-CH=CBr_2), 7.74 (d, 1 H, $J_{6,5}$ = 8 Hz, H-6), 11.38 (brd s, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}Br_2N_2O_5$: C, 30.15; H, 2.51; N, 7.04; Br, 40.20. Found: C, 30.29; H, 2.67; N, 7.04; Br, 39.97.

1-(5,6-Dideoxy-β-D-*ribo*-hex-5-ynofuranosyl)uracil (4). A solution of **3** (1.22 g, 0.0030 mol) in 350 mL of anhydrous THF was cooled in a dry ice–acetone bath, and to this solution *n*-BuLi (20 mL, 0.032 mol; 1.6 M solution in hexane) was added. The mixture was stirred for 4 h, neutralized with acetic acid, evaporated, and coevaporated with ethanol. The crude material was dissolved in a small amount of methanol, poured on a dry silica gel column, and eluted with ethyl acetate and then with ethyl acetate/methanol (9:1). The fractions were combined, evaporated, and crystallized from a methanol/ethanol mixture, furnishing an analytically pure sample (0.415 g, 57%) of **4**: mp 209–211 °C; λ_{max}(MeOH) 260 (ε 10 637), λ_{min} 229 nm (1992); mass spectrum, *m/e* 238 (M^+), 112 (B + H), 113 (B + 2H); NMR (Me_2SO-d_6) δ 3.83 (d, 1 H, $J_{4',5'}$ = 2.2 Hz, 5′-C≡CH), 5.78 (d, 1 H, $J_{5,6}$ = 8 Hz, H-5), 5.86 (d, 1 H, $J_{1',2'}$ = 5 Hz, H-1′), 7.60 (d, 1 H, $J_{6,5}$ = 8 Hz, H-6), 11.42 (brd, 1 H, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.20 N, 11.76. Found: C, 50.22; H, 4.29; N, 11.68.

1-(2,5,6-Trideoxy-6,6-dibromo-3-*O*-acetyl-β-D-erythro-hex-5-enofuranosyl)-5-methyluracil (6). 3′-*O*-Acetylthymidine-5′-aldehyde[8] (**5**, prepared from 8g, 0.0281 mol of 3′-*O*-acetylthymidine) was reacted with (dibromomethylene)triphenylphosphorane (prepared from 14.76 g (0.0562 mol) of triphenylphosphine, 18.65 g (0.0562 mol) of carbon tetrabromide, and 3.68 g (0.0562 mol) of zinc dust) as described for the preparation of **2**. TLC of the reaction mixture showed one major and another very minor charring spot. The mixture was evaporated to a small volume and chromatographed twice on a dry silica gel column, eluting with benzene/ethyl acetate (7:3) and then with benzene/ethyl acetate (1:1). The combined fractions, after evaporation, were dissolved in methanol, where the product crystallized within 30 min for a 2.4-g yield. The filtrate was chromatographed again on silica gel using the above solvent system, furnishing 4.2 g of the TLC (95%)-pure material. Thus, the total yield of product **6** was 6.6 g (53%). Recrystallization from methanol gave **6** as a colorless, crystalline material: mp 123–125 °C dec; NMR ($CDCl_3$) δ 1.97 (d, 3, $J_{5\text{-}CH_3,6}$ = 1 Hz, 5-CH_3), 2.14 (s, 3, 3′-OAc), 2.45 (m, 2, H-2′), 4.72, 5.27 (m, 2, H-3′, 4′), 6.18 (t, 1, $J_{1',2'}$ = 6.5 Hz, H-1′), 6.62 (d, 1, $J_{5',4'}$ = 8.5 Hz, 5′-CH=CBr_2), 7.14 (d, 1 $J_{6,5\text{-}CH_3}$ = 1 Hz, H-6), 8.96 (brd, 1, NH).

1-(2,5,6-Trideoxy-6,6-dibromo-β-D-*erythro*-hex-5-enofuranosyl)-5-methyluracil (7). A solution of **6** (3 g, 0.0068 mol) in excess of sodium methoxide in methanol was stirred at room temperature for 30 min. It was then neutralized with Dowex 50 (H+) resin and filtered. The resin was washed with methanol, combined, and evaporated to a small volume, where product **7** crystallized for a 2.43-g (90%) yield. An analytical sample was prepared by crystallization from ethanol with mp 203–204 °C; NMR (Me_2SO-d_6) δ 1.82 (s, 3 H, 5-CH_3), 6.20 (t, 1 H, $J_{1',2'}$ = 7 Hz, H-1′), 6.98 (d, 1 H, $J_{4',5'}$ = 8 Hz, 5′-CH=CBr_2), 7.53 (s, 1 H, H-6), 11.33 (s, 1 H, NH).

Anal. Calcd for $C_{11}H_{12}Br_2N_2O_4$: C, 33.33; H, 3.06; N, 7.07; Br, 40.40. Found: C, 33.60; H, 3.16; N, 7.10; Br, 40.12.

1-(2,5,6-Trideoxy-β-D-*erythro*-hex-5-ynofuranosyl)-5-methyluracil (8). A solution of **7** (0.558 g, 0.0014 mol) in dry THF was treated with *n*-BuLi (8 mL, 0.0128 mol; 1.6 M solution in hexane) as described for **4**. The crude material was chromatographed on a dry silica gel column using ethyl acetate as eluent. After evaporation and crystallization from ethanol, the desired product **8** was obtained in a 0.22-g (66%) yield. Recrystallization from ethanol gave an analytical sample: mp 228–230 °C; λ_{max}(MeOH) 265 (ε 12 272), λ_{min} 233 (2265); mass spectrum, *m/e* 236 (M^+), 237 (M^+ + 1), 126 (B + H), 127 (B + 2 H); NMR (Me_2SO-d_6) δ 1.81 (low coupling constant doublet, 3,5-CH_3), 2.14 (m, 2, H-2′), 3.85 (d, 1, $J_{4',5'}$ = 2 Hz, 5′-C≡CH), 4.40 (m, 2, H-3′, 4′), 5.72 (d, 1, 3′-OH), 6.30 (t, 1, $J_{1',2'}$ = 7 Hz, H-1′), 7.54 (d, 1, $J_{6,5\text{-}CH_3}$ = 1 Hz, H-6), 11.35 (s, 1, NH).

Anal. Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.64; H, 5.30; N, 11.69.

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Registry No.—1, 27999-65-1; **2**, 64189-19-1; **3**, 64189-20-4; **4**, 64189-21-5; **5**, 5983-15-3; **6**, 64189-22-6; **7**, 64189-23-7; **8**, 64189-24-8; (dibromomethylene)triphenylphosphorane, 42867-45-8; 3′-*O*-acetylthymidine, 21090-30-2.

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Communications

Organic Metals: a General Synthesis of Unsymmetrical Tetrathiafulvalenes

Summary: A number of unsymmetrical tetrathiafulvalenes have been prepared by the use of a new and general synthesis. This synthesis, which involves a phosphorane intermediate, allows the overall specific coupling of two different 1,3-dithiolium salts.

Sir: Tetrathiafulvalene (TTF) and its derivatives are heterocycles of great current interest in view of their ability to act as π donors in the preparation of organic charge-transfer salts having metallic properties.[1] Almost all known TTF derivatives are symmetrical about the central double bond, due to the fact that general methods for their synthesis have involved the coupling or condensation of two identical S_2 containing moieties, usually a 1,3-dithiol-2-thione (or selone) or a 1,3-dithiolium ion.[2] With the exception of monoethyl- and monocarboxytetrathiofulvalene (prepared from lithiated TTF),[3] the few known unsymmetrical TTF derivatives have been prepared by random coupling or condensation; their separation from symmetrical co-products was the result of fortuitous crystallization properties in two cases,[4] and sufficient polarity differences to allow chromatographic separation[5] in a third case. We now report the discovery of a fundamentally new TTF synthesis which allows the preparation of a wide range of unsymmetrical TTF derivatives from two different 1,3-dithiolium cations without the concomitant formation of symmetrical byproducts.

A recent report has described the reaction of 1,3-benzodithiolium fluoborate (1) with triphenylphosphine to give the phosphonium salt 2 (Scheme I); deprotonation of the latter with *n*-butyllithium at −78 °C and reaction of the resulting unstable phosphorane 3 with various aldehydes afforded 1,4-benzodithiafulvalenes (4) in good yield.[6,7] Our attempts to couple phosphorane 3 with various 1,3-dithiol-2-thiones (or selones) were unsuccessful. However, the red color of 3 was discharged at −78 °C upon addition of the 1,3-dithiolium salts

Scheme I

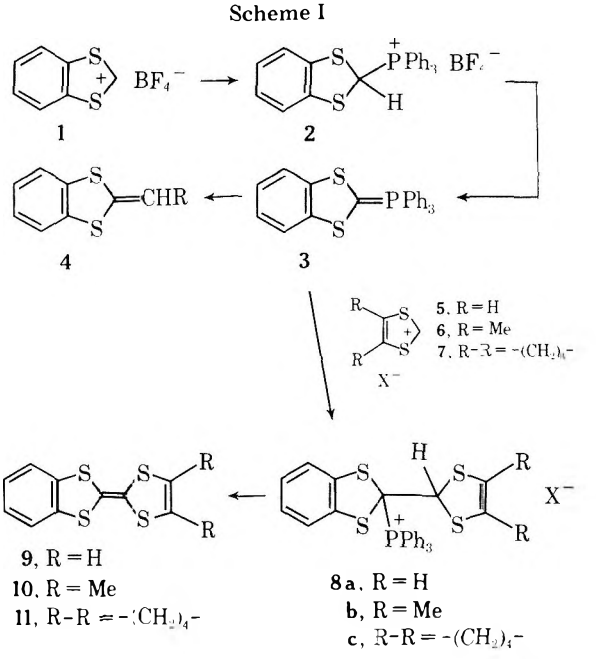

Table I

TTF derivative	Mp, °C (uncorr)	Yield,[a] %	NMR[e] ($CDCl_3$), δ	UV–visible, nm (log ϵ)
9	135–136 (lit.[5] 138.5–140)	40	*d*	
10	190–191	30	1.9 (s, 6 H) 7.1–7.2 (m, 4 H)	247 (3.84), 253 (3.94), 259.5 (4.00), 292 (4.15), 319 (4.11), 454 (2.5)
11	207–208	31	1.7–2.4 (m, 8 H) 7.1–7.3 (m, 4 H)	258 (3.83), 265 (3.89), 271 (3.91), 281 (3.98), 293 (4.04), 307 (4.00), 319 (3.99), 456 (2.28)
14	105–106	18[b] 41[c]	1.6–2.5 (m, 8 H) 6.25 (s, 2 H)	274 (3.84), 299 (4.02), 310 (3.99), 322 (3.98), 364 (3.18), 460 (2.41)
15	174–175	43	1.5–2.4 (m, 8 H) 1.9 (s, 6 H)	286 (4.01), 298 (4.05), 314 (4.02), 323 (3.98), 478 (2.33)

[a] Isolated, crystallized yield, based on phosphonium salt. [b] Based on **13**. [c] Based on **12**. [d] In accord with ref 5. [e] In units downfield from Me_4Si.

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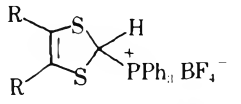
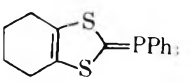
5, 6, or 7, with the formation of an intermediate of the type 8; addition of triethylamine brought about the elimination of triphenylphosphine and the formation of the monobenzotetrathiafulvalenes 9, 10, and 11, respectively. Symmetrical TTFs corresponding to the individual 1,3-dithiole units were not detected, and the products were readily purified.

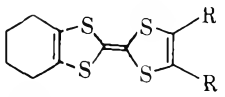
The new procedure is not limited to the synthesis of monobenzotetrathiafulvalene derivatives. Thus, the tetramethylene-1,3-dithiolium fluorophosphate (7) added triphenylphosphine to give the corresponding phosphonium salt 12a; reaction of the latter with *n*-butyllithium at −78 °C and reaction of the intermediate phosphorane 13 with 1,3-di-



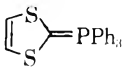
12a, R = $-(CH_2)_4-$
b, R = H



13



15, R = H
16, R = Me



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thiolium fluoborate (5) or 4,5-dimethyl-1,3-dithiolium fluoborate (6)[4b] gave, after triethylamine treatment, the mixed TTF derivatives 15 and 16, respectively. Finally, the same derivative 15 was prepared in the reverse manner from 4,5-tetramethylene-1,3-dithiolium ion (7) and the phosphorane 14 derived from the unsubstituted 1,3-dithiolium phosphonium salt 12b.

In a typical procedure, phosphonium salt 2 (360 mg, 0.72 mmol) was suspended in dry THF (25 mL) at −78 °C, and a solution of *n*-butyllithium (0.72 mmol) in hexane was added, After 2 h at −78 °C, fluoborate 5 (137 mg, 0.72 mmol) was added. After the red solution lightened to yellow, excess triethylamine was introduced and the mixture was stirred for 3 h at −78 °C, and then allowed to come to room temperature. Removal of solvent, followed by silica chromatography (hexane eluant), afforded 9 in 40% yield.

The extension of this method to the synthesis of unsymmetrical selenathiafulvalenes is under investigation in our laboratory.

The physical measurements and preparation of organic conductors based on these donors will be reported separately.

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A New 7,12-Dimethylbenz[*a*]anthracene Synthesis: 9-Methoxy- and 10-Methoxy-7,12-dimethylbenz[a]anthracene

Summary: Hydrolysis of the reaction product of 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline with methyl 2-naphthyl ketone affords 5-methoxy-3-methyl-3-(2-naphthyl)phthalide which is converted by three known steps to 9-methoxy-7,12-dimethylbenz[*a*]anthracene. Similarly, methyl 1-naphthyl ketone affords 10-methoxy-7,12-dimethylbenz[*a*]anthracene.

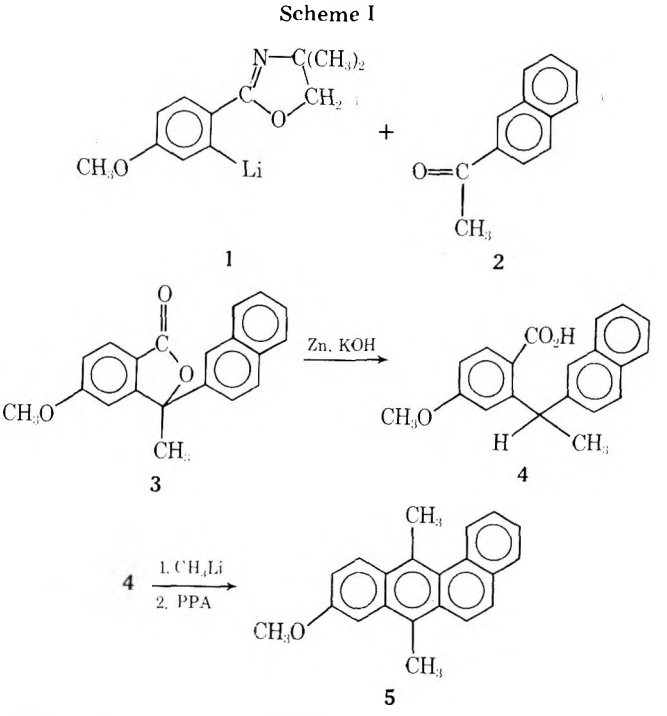
Substituted 7,12-dimethylbenz[*a*]anthracenes are of importance in studies on carcinogenesis. Present synthetic routes involve fundamentally the following condensation reactions: a substituted phenyl organometallic reagent with 1,2-naphthalic anhydride; a phenyl organometallic reagent with a substituted 1,2-naphthalic anhydride; a substituted naphthyl organometallic reagent with phthalic anhydride; or a naphthyl organometallic reagent with a substituted phthalic anhydride. Friedel–Crafts condensations of analogous appropriate compounds have also been used. In three of the above cases difficultly separable mixtures of keto acids of the *o*-benzoylbenzoic acid type are obtained. The two carbons in the anhydride function become the meso carbons in the anthracene moiety of the final compound.

We describe herein a new synthesis in which the two carbons which become the meso carbons are initially present in different reactants. The advantages of the new route are the following: no difficultly separable mixtures of isomeric compounds are formed; fewer steps are required to reach the final benz[*a*]anthracenes; and the reaction components are easier to obtain than the unsymmetrical anhydrides.

The new synthesis is outlined in Scheme I.

The key reagent is 2-(2-lithio-4-methoxyphenyl)-4,4-dimethyl-2-oxazoline (1) prepared by lithiation[3] of 2-(4-methoxyphenyl)-4,4-dimethyl-2-oxazoline.[4] In a typical reaction a solution of 0.1 mol of 1, prepared as described,[3] in 300 mL of dry ether was added dropwise during 5 min to a solution of 0.1 mol of 2 in 100 mL of ether at 0 °C. After 18 h at room temperature and 1 h at reflux, the products of the reaction, isolated in a conventional way, were heated at reflux for 18 h with 8% aqueous ethanolic sulfuric acid[4] to yield 62% of 5-

Scheme I



1 2 3 4 5

methoxy-3-methyl-3-(2-naphthyl)phthalide (**3**) as a colorless oil, IR absorption at 5.7 μm (five-membered lactone carbonyl). Zinc dust in alkali reduction[5] of **3** readily afforded 4-methoxy-2-(α-2-naphthylethyl)benzoic acid* (**4**), mp 176.5–177.5 °C, which by reaction[5] with CH_3Li was converted into the corresponding methyl ketone, in turn cyclized to 9-methoxy-7,12-dimethylbenz[*a*]anthracene* (**5**) mp 204.5–205.5 °C (33% overall yield from **1**), by treating with polyphosphoric acid at room temperature for 3 h.

In a similar sequence starting with **1** and methyl 1-naphthyl ketone there was obtained 10-methoxy-7,12-dimethylbenz[*a*]anthracene,[6] mp 135.0–136.0 °C, in 27% overall yield from **1**. In this case, the PPA cyclization required 40 min at 95 °C.

The application of this new synthesis to the synthesis of other methoxy- and fluoro-substituted benz[*a*]anthracenes is under study.

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N-Bromosuccinimide Oxidation of Silyl Ethers[1]

Summary: *N*-Bromosuccinimide converts the trimethylsilyl (Me_3Si) ethers of primary alcohols into esters and the Me_3Si ethers of secondary alcohols into ketones. An aldehyde and a Me_3Si ether give a "mixed" ester in the presence of NBS.

Sir: Oxidation of alcohols is a fundamental transformation of organic chemistry which is attracting much current interest.[2] Since the hydrogens on a carbon atom attached to oxygen are labile in the free radical sense,[3] we reasoned that conversion of an alcohol into an unsymmetrical ether and treatment with *N*-bromosuccinimide (NBS) would effect the desired oxidation (eq 1).[4] In order to have the proper regiochemistry,

$$RR'CHOH \rightarrow RR'CHOR'' \xrightarrow{NBS} [RR'CBrOR''] \rightarrow RCOR' \quad (1)$$

R″ cannot possess α hydrogens and thus might be *tert*-butyl;[5] however, treating the *tert*-butyl ether of 1-hexanol with NBS under a variety of conditions gives only traces of hexanal and *N*-chlorosuccinimide fails to react at all. In addition, neither bromine nor sulfuryl chloride causes oxidation of *tert*-butyl 1-hexyl ether.

We decided to examine the analogous trimethylsilyl (Me_3Si) ethers[6] readily available in high yield from alcohols by treatment with chlorotrimethylsilane and pyridine or triethylamine.[7a] When a Me_3Si ether is dissolved in CCl_4 and stirred with NBS under the irradiation of an ordinary sun lamp, a reaction occurs. The results with a variety of systems are summarized in Table I. Thus, the trimethylsilyl ether of 1-

Table I. Oxidation of Silyl Ethers

Reactant	Conditions	Product	Yield, g (%)[a]
$CH_3(CH_2)_5OSiMe_3$	*hν*, 0 °C, 5 h	$CH_3(CH_2)_4CO_2(CH_2)_5CH_3$	1.90 (80)
$C_6H_5CH_2OSiMe_3$	*hν*, −20 °C, 2.5 h	C_6H_5CHO	1.06 (48)
$C_6H_5CH(OSiMe_3)CH_3$	*hν*, Pyr, rt, 3.5 h	$C_6H_5COCH_3$	1.37 (76)
$CH_3(CH_2)_5CH(OSiMe_3)CH_3$	*hν*, Pyr, rt, 3.5 h	$CH_3(CH_2)_5COCH_3$	1.05 (55[b])

[a] Refers to pure, isolated products. Yields not optimized. [b] Based on 36% recovery of starting material.

Table II. Oxidation of Silyl Ethers in the Presence of Aldehydes

Aldehyde	Silyl ether (equiv)	Conditions	Product	Yield, g (%)
$CH_3(CH_2)_8CHO$	$CH_3CH_2OSiMe_3$ (2.0)	*hν*, 0 °C, 2.5 h	$CH_3(CH_2)_8CO_2CH_2CH_3$	0.96 (83)
$CH_3(CH_2)_4CHO$	$CH_3CH_2OSiMe_3$ (1.3)	*hν*, 0 °C, 3.5 h	$CH_3(CH_2)_4CO_2CH_2CH_3$	0.81 (58)
C_6H_5CHO	$CH_3CH_2OSiMe_3$ (1.0)	*hν*, 0 °C, 2.5 h	$C_6H_5CO_2CH_2CH_3$	0.90 (45)
C_6H_5CHO	$CH_3CH_2OSiMe_3$ (2.5)	*hν*, 0 °C, 2.5 h	$C_6H_5CO_2CH_2CH_3$	1.78 (89)
CH_3CH_2CHO	c-$C_6H_{11}OSiMe_3$ (1.0)	*hν*, 0 °C, 2.5 h	c-$C_6H_{11}O_2CCH_2CH_3$	2.72 (68)
$CH_3(CH_2)_8CHO$	$(CH_3)_3COSiMe_3$ (2.0)	*hν*, 0 °C, 2.5 h	$CH_3(CH_2)_8CO_2C(CH_3)_3$	1.28 (44)
$CH_3(CH_2)_4CHO$	$(CH_3)_3COSiMe_3$ (3.0)	*hν*, 0 °C, 2.5 h	$CH_3(CH_2)_4CO_2C(CH_3)_3$	0.97 (42)

[a] Refers to pure, isolated products. Yields not optimized.

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hexanol yields the corresponding hexanoate ester in 80% yield after column chromatography.[8] Treatment of the Me_3Si ether of benzyl alcohol with NBS at −20 °C gives a 48% yield of benzaldehyde.

The silyl ethers of secondary alcohols give ketones when reacted with NBS in the presence of pyridine. For example, the Me_3Si ether of α-phenylethanol gives acetophenone in 76% yield. A 55% yield of 2-octanone is isolated from 2-(trimethylsiloxy)octane.

Isolation of an ester from the reaction employing 1-(trimethylsiloxy)hexane is a most striking result. A possible mechanism might involve the corresponding aldehyde, which is then converted to an acetal (eq 2). The failure to isolate the

$$CH_3(CH_2)_5OSiMe_3 \xrightarrow{NBS} [CH_3(CH_2)_4CHO] \xrightarrow[\text{"catalyst"}]{CH_3(CH_2)_5OSiMe_3}$$

$$[CH_3(CH_2)_4\overset{\displaystyle OSiMe_3}{\overset{|}{C}}HO(CH_2)_5CH_3] \xrightarrow{NBS} CH_3(CH_2)_4CO_2(CH_2)_5CH_3 \quad (2)$$

acetal implies that it reacts rapidly with NBS.[9] Furthermore, no hexanal was obtained so that the second step of eq 2 must be faster than the first step.[10,11]

Indeed, the addition of an aldehyde to a silyl ether in the presence of NBS gives the "mixed" ester (eq 3) (see Table II).

$$RCH_2OSiMe_3 + R'CHO \xrightarrow{NBS} R'CO_2CH_2R \quad (3)$$

Thus, decanal, hexanal, and benzaldehyde are each converted by NBS and the Me_3Si ether of ethanol into the corresponding ethyl esters in good yield. In addition, treatment of trimethylsiloxycyclohexane with NBS in the presence of propional gives a 68% yield of cyclohexyl propionate.

Increasing the ratio of Me_3Si ether to aldehyde improves the yield of ester. Benzaldehyde reacts with 1 equiv of trimethylsiloxyethane to give a 45% yield of ethyl benzoate. By using 2.5 equiv of the silyl ether, the yield of ethyl benzoate is improved to 89%.

This most unusual aldehyde to ester conversion can be extended to the preparation of *tert*-butyl esters. For example, decanal is transformed into *tert*-butyl decanoate in 43% yield when stirred with NBS and the Me_3Si ether of *tert*-butyl alcohol. Hexanal similarly yields *tert*-butyl hexanoate in 42% yield.

In a typical procedure, the Me_3Si ether of 1-hexanol (4.14 g, 23.7 mmol) is dissolved in 50 mL of dry CCl_4 under N_2 and cooled in an ice bath. To this is added 4.65 g (26.1 mmol, 1.1 equiv) of NBS and the reaction flask is exposed to a sun lamp for 5 h. The reaction mixture is stirred without irradiation for 3–4 h and filtered. The filtrate is stirred with $NaHCO_3$, dried, and concentrated. A benzene solution is filtered through a column of Fisher A-540 alumina (1.7 × 35 cm) to give 1.91 g (80%) of pure 1-hexyl hexanoate. In most cases, filtration through alumina was an adequate purification; however, in some systems, because of the scale used, distillation proved to be more efficient.

The mixed esterification reactions are conducted in the same way. The aldehyde and silyl ether are dissolved in CCl_4 at 0 °C. The NBS (1.1 equiv) is added and the reaction mixture is exposed to a sun lamp. When the reaction is complete, the reaction mixture is stirred for 3–4 h without light, after which workup is carried out as above.

We attempted to extend this oxidation procedure to more complex substrates; however, the presence of a double bond prevents the desired reaction. For example, the Me_3Si ether of geraniol gives only a trace of citral (not isolated) when stirred with NBS. Similarly, the Me_3Si ether of citronellol and NBS give a dark reaction mixture from which no oxidation product was obtained.

The mixed ester reaction with unsaturated substrates was equally fruitless. Citral, trimethylsiloxyethane, and NBS give a low yield (by NMR) of the corresponding ethyl ester. *trans*-Cinnamaldehyde, trimethylsiloxyethane, and NBS do not react in 4 h and give only a trace of ester after 7 days. In addition, methacrolein fails to react with the Me_3Si ether of 1-hexanol in the presence of NBS. In fact, a catalytic amount of distilled methacrolein retards the formation of 1-hexyl hexanoate in the reaction of NBS with the Me_3Si ether of 1-hexanol.

Thus, the presence of a double bond, a functional group which is known to scavenge free radicals,[12] precludes the oxidation reaction, implying that a free-radical reaction is involved. Furthermore, since a catalytic amount of methacrolein acts as an inhibitor of ester formation, a free-radical chain reaction is suggested. In addition, light is essential for the reaction since the Me_3Si ether of 1-hexanol and NBS give a very slow conversion to ester (~50% in 80 h) without a sun lamp.

It is also of interest to note that pyridine completely inhibits the conversion of primary Me_3Si ethers into esters while promoting the secondary Me_3Si ether to ketone reaction. Much work remains in exploring the mechanism of these new reactions and will be reported in due course.

In addition to its versatility as an oxidation method, this study serves as an illustration that trimethylsilyl ethers are *not inert* to NBS.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for the support of this research.

References and Notes

(1) Presented at the 29th Southeastern Regional Meeting of the American Chemical Society, Tampa, Fla., Nov. 9–11, 1977.
(2) See, for example, R. W. Binkley, *J. Org. Chem.*, **42**, 1216 (1977), and references cited therein.
(3) M. L. Poutsma in "Methods in Free Radical Chemistry", Vol. 1, E. S. Huyser, Ed., Marcel Dekker, New York, N.Y., 1969, p 137.
(4) Indeed, two studies involving oxidation of analogous thiophenyl ethers with *N*-chlorosuccinimide appeared after initiation of the present work: (a) L. A. Paquette, W. D. Klobucar, and R. A. Snow, *Synth. Commun.*, **6**, 575 (1976); (b) P. Bakuzis, M. L. F. Bakuzis, C. C. Fortes, and R. Santos, *J. Org. Chem.*, **41**, 2769 (1976).
(5) Another oxidation scheme using triphenylcarbenium (trityl) cation solved the problems of regiochemistry by using trityl ethers: M. P. Doyle, D. J. DeBruyn, and D. J. Scholten, *J. Org. Chem.*, **38**, 625 (1973).
(6) Trimethylsilyl ethers yield aldehydes and ketones when subjected to "hydride abstraction" by trityl tetrafluoroborate[7a] and by nitrosyl tetrafluoroborate.[7b]
(7) (a) M. E. Jung, *J. Org. Chem.*, **41**, 1479 (1976); (b) G. A. Olah and T.-L. Ho, *Synthesis*, 609 (1976).
(8) Similar results were obtained recently from the NBS oxidation of tributylstannyl ethers: T. Ogawa and M. Matsui, *J. Am. Chem. Soc.*, **98**, 1629 (1976).
(9) NBS is known to oxidize acetals to esters: J. D. Prugh and W. C. McCarthy, *Tetrahedron Lett.*, 1351 (1966); L. C. Anderson and H. W. Pinnick, unpublished results.
(10) (a) In addition, since hexanal and 1-(trimethylsiloxy)hexane do not react, a "catalyst" is apparently necessary for the second step of eq 2. (b) In the case of the Me_3Si ether of benzyl alcohol, initial oxidation to benzaldehyde (presumably via the rather stable benzylic radical) must be faster than the second step so that the aldehyde and not the ester is isolated.
(11) We feel that the present data do not justify a more detailed mechanism at this time. It is of interest, however, to note the following additional observations. (a) The silicon byproduct is bromotrimethylsilane, identified by NMR (0.5 ppm) of the crude reaction mixture. (b) Bromine converts the Me_3Si ether of a primary alcohol into the ester, but is less efficient than NBS (some starting material is recovered). (c) Pyridine inhibits this bromine reaction, but a yellow solid is formed (apparently pyridine perbromide: see L. F. Fieser and M. Fieser, "Reagents For Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 966) so that the significance of this result is in doubt. (d) The Me_3Si ether of 1-hexanol fails to react with propionaldehyde in the presence of HBr so that the "catalyst" of eq 2 is not HBr.
(12) See, for example, M. E. Kuehne and R. E. Damon, *J. Org. Chem.*, **42**, 1825 (1977).

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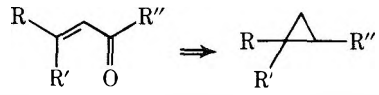
Preparation of Cyclopropanes from α,β-Unsaturated Aldehydes, Esters, and Ketones

Summary: α,β-Unsaturated carbonyl compounds are efficiently transformed into the corresponding cyclopropanes by a sulfone-mediated bond formation.

Sir: In connection with natural product synthesis, we have been concerned with the problem of converting α,β-unsaturated compounds into cyclopropanes (eq 1) and recently developed a method to accomplish this; however, the open chain hydrocarbon was also formed (eq 2).[1] We now report another



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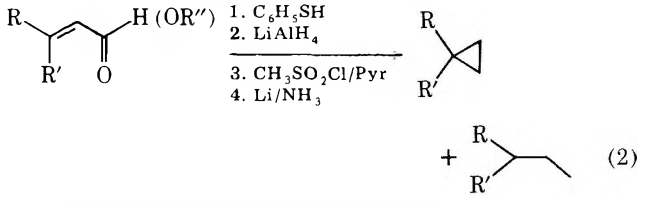

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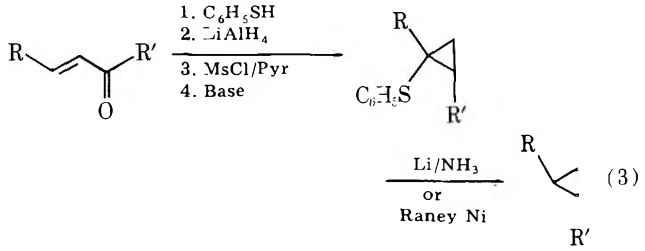
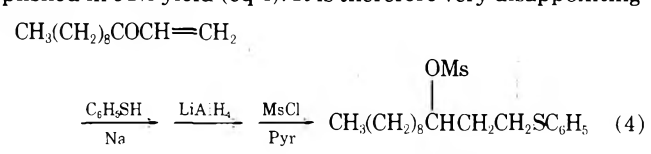
approach which cleanly gives the desired goal.

The new strategy is summarized in eq 3. It was hoped that



(3)

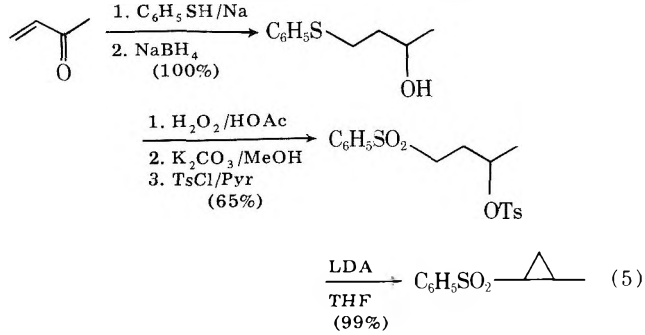
the thiophenyl moiety would stabilize an adjacent carbanion and thus promote cyclopropane formation. In fact, the first three steps in the sequence work well. The conversion of 1-dodecen-3-one into the methanesulfonate ester is accomplished in 91% yield (eq 4). It is therefore very disappointing



(4)

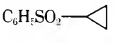
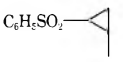
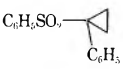
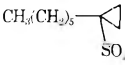
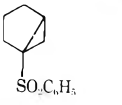
that stirring this ester with lithium diisopropylamide (LDA) in THF between −78 °C and room temperature gives only recovered starting material. The corresponding tosylate also fails to react.[2]

Because a sulfone group is better than a lone sulfur at stabilizing an adjacent carbanion, we decided to explore sulfones.[3,4] Indeed, methyl vinyl ketone is converted into phenyl 3-tosyloxybutyl sulfone in 65% yield and then successfully cyclized with LDA in THF between −78 °C and room temperature to 2-methylcyclopropyl phenyl sulfone in 99% yield (eq 5).[5-7] Table I summarizes the cyclopropyl sulfones prepared in this way. Desulfurization yields the desired cyclopropanes. This was carried out for representative systems with 6% sodium amalgam[8] in refluxing ethanol. For example, cyclopropylbenzene is obtained in 83% yield.



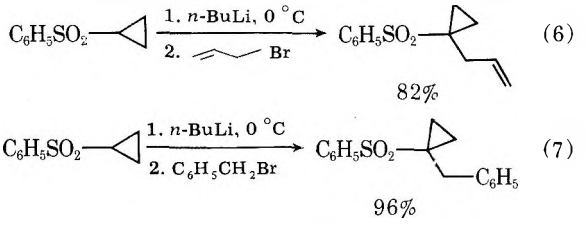
(5)

Table I. Cyclopropyl Sulfones from α, β-Unsaturated Carbonyl Compounds

Carbonyl compd	Sulfone tosylate,[a] % yield	Cyclopropyl sulfone (% yield)
CH_2=CHCHO	78	 (100)
CH_2=CHCOCH_3	65	 (99)
C_6H_5CH=CHCHO	84[b]	 (100)
$CH_3(CH_2)_5$CH=CHCO$_2$Et	86[b]	 (100)
	75	 (100)

[a] Includes addition of thiophenol, reduction of carbonyl, oxidation of sulfide, and tosylate formation. [b] Mesylate ester used instead of tosylate.

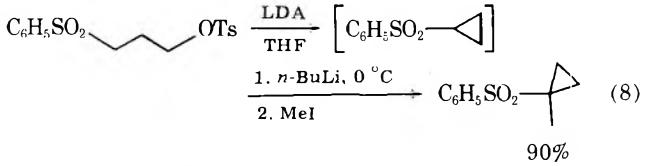
The utility of cyclopropyl sulfones containing an acidic α hydrogen can be extended. For example, cyclopropyl phenyl sulfone can be alkylated to give the allyl derivative in 82% yield (eq 6) and the benzyl analogue in 96% yield (eq 7). Desulfurization of the latter compound with 6% Na(Hg) in refluxing ethanol gives benzylcyclopropane in 75% yield.



(6)

(7)

For added convenience, cyclopropyl phenyl sulfone need not be isolated. A one-pot conversion of phenyl 3-tosyloxypropyl sulfone to 1-methylcyclopropyl phenyl sulfone proceeds in 90% overall yield (eq 8).



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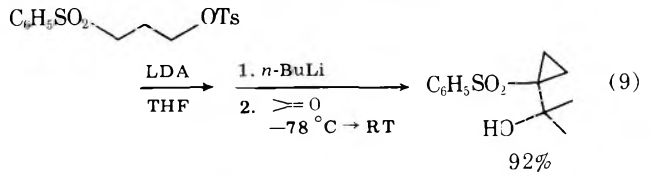
The sulfone anion can be quenched with carbonyl compounds as well. For example, the one-pot sequence of eq 9 gives the tertiary alcohol in 92% overall yield. Hexanal gives the secondary alcohol of eq 10 in 91% yield. Desulfurization



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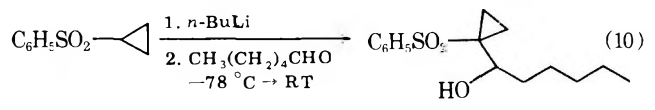

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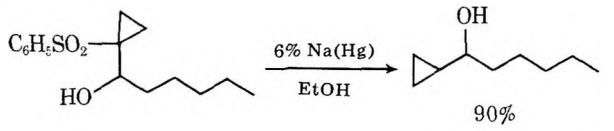
of the latter compound in the usual way gives the cyclopropylcarbinol in 90% yield (eq 11). These compounds can be



(11)

converted stereospecifically into homoallylic bromides by the elegant method developed by Julia[9a] and Johnson.[9b] In addition, cyclopropyl ketones are available by oxidation of the carbinols.

In conclusion, this method allows the synthesis of a wide variety of functionalized cyclopropanes derived from readily available α,β-unsaturated aldehydes, esters, and ketones.

A typical experimental procedure for the conversion of cinnamaldehyde into phenylcyclopropane is described.

Cinnamaldehyde (26.4 g, 200 mmol) in 80 mL of 95% EtOH was added dropwise over 20 min to 0.6 g of sodium in 200 mL of 95% EtOH containing 30.8 g (280 mmol) of thiophenol at room temperature. After 20 h, 3.80 g (100 mmol) of $NaBH_4$ was added and the reaction mixture was stirred for 2 h. Workup gave 48.3 g (100%) of 3-phenyl-3-thiophenylpropanol as a thick oil which solidified upon standing: NMR (CCl_4) δ 2.2 (br s, 1 H), 3.6 (m, 2 H), 4.3 (t, J = 7 Hz, 1 H), 7.2 (m, 10 H). This alcohol (24.2 g, 100 mmol) was dissolved in 32 mL of glacial acetic acid and 32 mL of 30% H_2O_2 was added dropwise over 30 min such that the temperature did not exceed 70 °C (exothermic). When the addition was complete, the reaction mixture was refluxed for 1 h, cooled, and worked up with 10% NaOH. This crude product was stirred with K_2CO_3 in aqueous MeOH overnight to give 24.1 g (88%) of solid sulfone. This sulfone (5.08 g, 18.5 mmol) was dissolved in 20 mL of pyridine and 3.10 g (25.9 mmol) of mesyl chloride was added dropwise over 20 min. After 5 h, the reaction mixture was poured into cold 5% HCl and extracted with CH_2Cl_2 to give 6.2 g (95%) of sulfone mesylate as a white solid: NMR ($CDCl_3$) δ 2.5–2.8 (m, 2 H), 2.9 (s, 3 H), 4.0–4.5 (m, 3 H), 7.1–7.6 (m, 10 H). Diisopropylamine (3.73 g, 37.0 mmol) was dissolved in 130 mL of dry THF (distilled from potassium) at 0 °C and 34 mmol of n-BuLi/hexane was added. After 30 min, the reaction mixture was cooled to −78 °C and 9.30 g (26.4 mmol) of the sulfone mesylate in 200 mL of THF was added dropwise over 40 min. After an additional 90 min at −78 °C, the reaction mixture was allowed to warm to room temperature and stir for 2 h more. The reaction was quenched with water and extracted with CH_2Cl_2 to give 6.8 g (100%) of phenyl 1-phenylcyclopropyl sulfone as a yellow solid: NMR ($CDCl_3$) δ 1.25 (dt, J_d = 2 Hz, J_t = 5 Hz, 2 H), 2.0 (dt, J_d = 2 Hz, J_t = 5 Hz, 2 H), 7.1–7.6 (m, 10 H). This sulfone (5.16 g, 20.0 mmol) was dissolved in 50 mL of absolute EtOH and refluxed with 30 g of 6% Na(Hg) for 12 h. The reaction mixture was poured into 5% HCl and extracted with ether. Careful removal of the solvent and distillation of the residue at atmospheric pressure gave phenylcyclopropane as a colorless liquid (1.95 g, 83%): bp 153–154 °C; NMR (CCl_4) δ 0.6–1.0 (m, 4 H), 1.7–2.1 (m, 1 H), 6.9–7.2 (m, 5 H).

Acknowledgment. We wish to thank the UGA Office of General Research for partial support of this work and Mobil Chemical Company for a generous gift of 2-cyclohexen-1-one.

References and Notes

(1) Y.-H. Chang, D. E. Campbell, and H. W. Pinnick, *Tetrahedron Lett.*, 3337 (1977). The only earlier report of a conversion such as that of eq 1 is that of C. P. Casey, L. D. Albin, and T. J. Burkhardt (*J. Am. Chem. Soc.*, **99**, 2533 (1977)), who prepared 1-methyl-2,3-diphenylcloropane from 1,3-diphenyl-2-buten-1-one. The two cyclopropanes synthesized in this paper each contain two aromatic rings so the method may be severely limited.

(2) (a) This is surprising since Johnson has reported[2b] without experimental detail that 3-chloropropyl phenyl sulfide yields cyclopropyl phenyl sulfide when treated with potassium amide in ether. (b) C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.*, **95**, 7692 (1973).

(3) In fact, phenyl cyclopropyl sulfone has been prepared from the open-chain sulfone by several groups: H. E. Zimmerman and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **82**, 2505 (1960); W. E. Truce and L. B. Lindy, *J. Org. Chem.*, **26**, 1463 (1961); R. Bird and C. J. M. Stirling, *J. Chem. Soc. B*, 111 (1968).

(4) (a) A possible alternative solution to this problem is suggested by the recent work of Bryson,[4b] who has found that alkyl phenyl sulfides can be metalated with *tert*-butyllithium in the presence of hexamethylphosphoramide. This paper appeared as our study was almost complete so we did not investigate bases stronger than LDA. (b) T. M. Dolak and T. A. Bryson, *Tetrahedron Lett.*, 1961 (1977).

(5) The methine adjacent to the sulfone group (2.1–2.4 ppm, multiplet) disappears when the sulfone is treated with LDA and then quenched with D_2O.

(6) The required sulfones could also be prepared by Michael-type addition of a sulfinic acid. For example, 3-oxobutyl *p*-tolyl sulfone has been prepared recently from methyl vinyl ketone and sodium *p*-tolylsulfinate: J. Fayos, J. Clardy, L. J. Dolby, and T. Farnham, *J. Org. Chem.*, **42**, 1349 (1977).

(7) Cyclopropyl sulfones have been prepared by a similar intramolecular epoxide opening: Y. Gaoni, *Tetrahedron Lett.*, 503 (1976).

(8) G. H. Posner and D. J. Brunelle, *Tetrahedron Lett.*, 935 (1973). We thank Dr. Posner for providing experimental details for the preparation of 6% Na(Hg) powder.

(9) (a) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. Fr.*, 1072 (1960); (b) S. F. Brady, M. A. Ilton and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).

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Reduction of Aldehydes and Ketones to Alcohols and Hydrocarbons through Use of the Organosilane–Boron Trifluoride System

Summary: Ketones and many aldehydes are converted directly and rapidly to hydrocarbons by the action of gaseous boron trifluoride and organosilicon hydrides in dichloromethane solution.

Sir: Deoxygenation of aldehydes and ketones to alkanes is a step frequently encountered in organic synthesis. Of the relatively few direct methods available, none appears to be of universal applicability;[1] many require harsh reaction conditions incompatible with the requirements of high selectivity needed when dealing with polyfunctional compounds.[2] We report here a convenient alternative to previously existing methods.

Aldehydes and ketones are reduced by organosilicon hydrides[3] upon addition of Brønsted acids[4] or certain Lewis acids.[5] In general, only aryl ketones and aryl aldehydes with electron-donating ring substituents give synthetically useful yields of completely deoxygenated products.[6] Reductions of other aldehydes and ketones normally stop after 1 equiv of hydride has been transferred, to give a variety of products (e.g., alcohols, esters, silyl ethers, ethers, olefins, or Friedel–Crafts dimers) whose nature depends upon substrate and reaction conditions. Doyle and co-workers have reported similar results using boron trifluoride etherate to promote the reductions.[7]

Recently we reported the unique ability of a system consisting of an organosilicon hydride and gaseous boron trifluoride to effect rapid direct reductions of alcohols to hydrocarbons.[8] With this system, reductions of even simple secondary aliphatic alcohols to hydrocarbons take place in minutes at room temperature or below. We now report that use of this system on aldehydes and ketones results in facile reductions to alcohols and hydrocarbons in synthetically useful yields (Table I). Under the reaction conditions, the organosilicon hydride is converted into an organosilicon fluoride.

The best reaction results were obtained by a method (A) which consisted of initial formation of the carbonyl–boron

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Table I. Reduction of Aldehydes and Ketones with Triethylsilane and BF_3

RCOR′	Et_3SiH, equiv	Method[a]	Reaction time, min	Product yield, % RCH(OH)R′	Product yield, % RCH_2R'
Undecanal	1.5	A	10	92[b]	
Benzaldehyde	18	B	11		52[c]
p-Methylbenzaldehyde	10	A	10		45[c]
p-Chlorobenzaldehyde	10	A	10		68[c]
p-Methoxybenzaldehyde	2	B	10		100[d]
p-Cyanobenzaldehyde	3	B	10	100[e]	
p-Nitrobenzaldehyde	1.5	B	5	100[b]	
2-Undecanone	3.3	A	60		80[b,f]
Cyclohexanone	2	B	1.5	82[c]	
	4	B	30		90[d]
2-Methylcyclohexanone	2.2[g]	A[h]	60		88[c]
Adamantanone	2.2	A	60		100[b]
p-Cyanoacetophenone	3	B	10	100[b]	
p-Nitroacetophenone	4	B	3	100[b]	
	4	B	30		100[b]

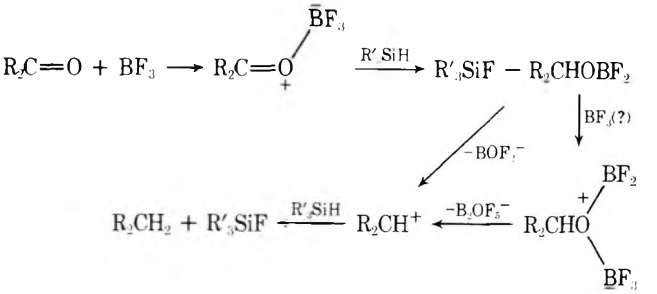
[a] See text. [b] Isolated yield. [c] Yield by VPC, using internal standard. [d] Yield by NMR, using internal standard. [e] Only product by NMR, VPC, and IR analyses. [f] (*E*)-2-Undecene was obtained in 16% yield. [g] Dimethylethylsilane used. [h] Reaction mixture not cooled.

trifluoride adduct by dropwise addition of a concentrated dichloromethane solution of the carbonyl compound into chilled (0 °C) dichloromethane (1–2 mL/mmol) through which a constant flow of scrubbed boron trifluoride was passed.[9] After 2–3 min, neat triethylsilane was rapidly added to the solution of complex. Slow passage of scrubbed boron trifluoride through the solution was maintained at 0 °C for the indicated period, at which time aqueous sodium chloride was added to quench the reaction prior to workup. In an earlier method (B), commercial boron trifluoride gas was passed directly without scrubbing into an uncooled dichloromethane solution of the carbonyl substrate and silane. However, when the boron trifluoride was drawn from different cylinders, this method gave variable yields of reduced product.[10] These problems were alleviated with method A.

It is significant that the present technique leads to toluene from benzaldehyde in light of the reported failure of other acid–silane systems to do so.[4,6,7] However, even with the present technique, failure to provide a large excess of silane (up to eightfold) in the reduction of benzaldehyde and several related aryl aldehydes leads to significant amounts of material of low volatility which seem to be polymers derived from Friedel–Crafts processes.[6]

A mechanistic rationale for the overall success of this reductive technique is offered in Scheme I. Its basis is attributed both to the ability of gaseous boron trifluoride to rapidly coordinate with oxygen and to the formation of the extremely strong (~139 kcal/mol[11]) Si–F bond. It is known that boron trifluoride forms stable complexes with ketones and aryl aldehydes.[12] There is an early report of analogous complexes with aliphatic aldehydes.[13] We have found that the quantitative formation of these aldehyde complexes and their subsequent reduction to what are presumed to be difluoroborate esters[7] upon addition of triethylsilane may easily be observed by NMR.[14] The stepwise nature of the reductions to hydrocarbons is indicated by the isolation of alcohols from some of

Scheme I



the carbonyl compounds. For example, when a dichloromethane solution of the boron trifluoride adduct of adamantanone was stirred with 1.1 equiv of triethylsilane at 0 °C for only 3 min without introduction of additional boron trifluoride, brine quenching yielded quantitatively a 1:1 mixture of 2-adamantanol and recovered adamantanone. These facts, taken together with the known relative ineffectiveness of boron trifluoride etherate[7] or Brønsted acids[4] at mediating complete deoxygenation, suggest that, in the case of substrates which require the intermediacy of a relatively unstable carbenium ion for passage to hydrocarbon, coordination of a second equivalent of boron trifluoride to the oxygen of the proposed difluoroborate intermediate may be beneficial in producing a better leaving group. Experiments are in progress to establish this point.

Acknowledgment. This work was supported in part by a grant from The University of Toledo Faculty Research Awards and Fellowships Program.

References and Notes

(1) R. L. Augustine, Ed., "Reduction", Marcel Dekker, New York, N.Y., 1968.
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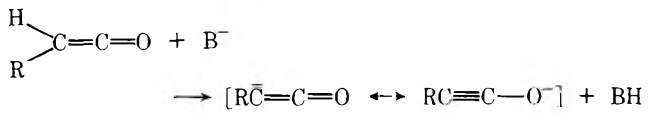
Reaction of Trimethylsilylketene with Strong Base. Evidence for Ketene Enolate Formation

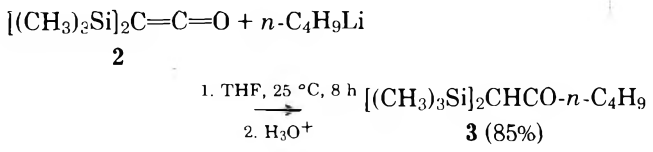
Summary: Evidence for the formation of a ketene enolate of trimethylsilylketene, based on trapping experiments with trimethylchlorosilane, is described.

Sir: The β hydrogens of aldoketenes are potentially acidic and it is possible to conceive of base-promoted ketene enolate formation in a fashion analogous to that for the familiar aldehyde or ketone enolates. Indeed, Bryce-Smith obtained insoluble, presumably polymeric materials on treatment of ketene with copper or silver salts in the presence of weak

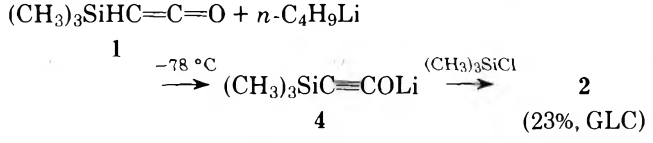


bases.[1] The products were formulated as metal ketenides, $M_2C{=}C{=}O$ ($M = Cu^I, Ag^I$). We present here evidence for the formation of a lithium enolate derived from trimethylsilylketene (**1**).

The reaction of bis(trimethylsilyl)ketene (**2**) with *n*-butyllithium proceeds normally, if somewhat sluggishly, at room temperature. The reaction mixture remains colorless and quenching gives good yields of the expected addition product **3**. In contrast, when *n*-butyllithium was added to **1** under the same conditions, the solution turned black immediately and quenching after periods of 5 min to 24 h gave trimethylsilylcarbinol as the only GLC mobile product of longer retention time than the solvent. The complete absence of the following addition products was established: $(CH_3)_3SiCH_2CO$-*n*-C_4H_9, $(CH_3)_3SiCH_2COH(n\text{-}C_4H_9)_2$, CH_3CO-*n*-C_4H_9, and $CH_3COH(C_4H_9)_2$.

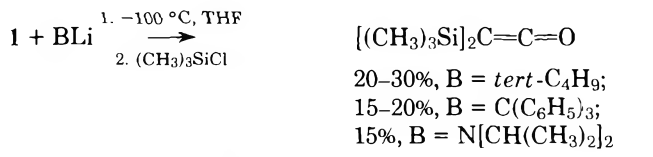


Addition of 1 equiv of **1** to a 0.5 M THF solution of *n*-butyllithium at −78 °C gave a colorless solution. Quenching this solution after 5 min with an equivalent amount of trimethylchlorosilane gave a 23% yield of **2**, presumably by formation of the ketene enolate **4**.



Addition of **1** to solutions of *n*-butyllithium at −100 °C increased the yield of **2** to 60–65%. Finally, addition of **1** to 0.1 M solutions of *n*-butyllithium at −100 °C gave 80–90% yields of **2**. Reaction mixtures obtained by this latter procedure turned black when allowed to warm to 0 °C for 15 min prior to the addition of trimethylchlorosilane and only 15–20% yields of **2** were obtained.

Similar results were obtained using other bases, although somewhat lower yields of **2** were obtained. The red color of



tritylllithium is rapidly discharged by **1** and, though the yield of **2** is small, triphenylmethane was recovered quantitatively. This is additional evidence that the sequence leading to **2** involves a simple acid–base reaction.

Attempts to trap the enolate **4** with other electrophiles, ϵ^+, have so far been unsuccessful. No GLC mobile products were obtained by quenching reaction mixtures of **1** and *n*-butyllithium with methyl iodide, benzyl bromide, acetone, or acetic anhydride. In addition, quenching with a variety of proton acids including water, acetic acid, or methanesulfonic acid returned only trace amounts of **1**. These negative results may simply be due to the instability of **4** or the instability of the product alkynol ethers **5** or ketenes **6**.

The following procedure describes a typical trapping experiment using trimethylchlorosilane. A 50-mL flask equipped with septum inlet, mercury bubbler, and magnetic stirrer was flushed with argon and immersed in a −100 °C cooling bath (liquid nitrogen and ethanol). The flask was charged with 10 mL of THF followed by 0.67 mL (1.0 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 15 min of stirring, 0.114 g (1.0 mmol) of trimethylsilylketene[2] was injected over a 5-min period. The colorless solution was stirred an additional 15 min and then 0.131 g (1.2 mmol) of trimethylchlorosilane was injected all at once. The solution was allowed to reach room temperature and analyzed by GLC (6 ft × 0.25 in. Carbowax 20 M column). The presence of 0.9 mmol (90%) of bis(trimethylsilyl)ketene[3] was established. Evaporation of the solvent at 25 °C gave a residue (0.16 g, 85%) of pure **2** based on either ^1H NMR [δ 0.25 (s)] or IR [2085, 1295 cm^{-1} (lit.[4] 2085, 1295 cm^{-1})] spectral examination.

Acknowledgment is made to the National Science Foundation for partial support of this research.

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An Approach to Cytochalasins: Diels–Alder Addition of α,β-Unsaturated Imides

Summary: Diels–Alder reactions of α,β-unsaturated imides are considerably accelerated relative to the reaction of the parent amides. This activating effect is used for the synthesis of a cytochalasin precursor.

Sir: Weinreb and Auerbach have described an elegant synthetic approach[1] to cytochalasins[2] by internal Diels–Alder addition of the diene ester **3**. This interesting reaction controls the regiochemistry of cycloaddition and defines four asymmetric centers in the adduct **4**. However, the problem of C-3 benzyl stereochemistry and the correct C-3 oxidation level remains unsolved.

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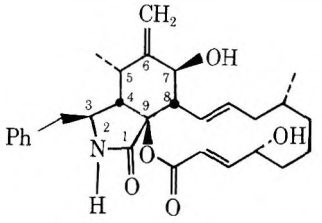
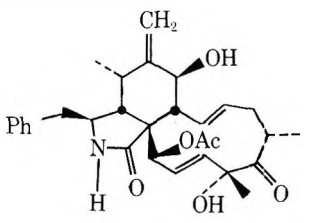
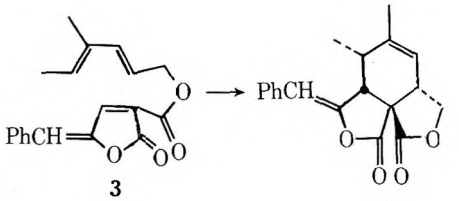
We report here the alternative approach using an intermolecular Diels–Alder reaction. Assuming the usual preference for an endo transition state a diene **5** would be expected to approach α,β-unsaturated lactam dienophiles such as **6** from the side opposite to the C-3 benzyl substituent.[3] A bicyclic adduct **7** would be formed with cytochalasin stereochemistry at C-3, C-4, C-5, and C-8. Subsequent functionalization at C-7 and C-9 should then be feasible from the less-hindered β face of the Diels–Alder product, and would allow entry into the lactone (**1**) or carbocycle (**2**) series.



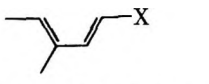
1
cytochalasin B
(phomin)



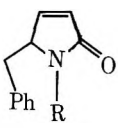
2
cytochalasin D



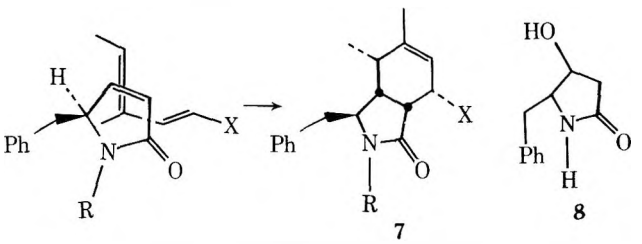
3 **4**



5a, X = $CH_2OCOC_2H_5$
b, X = CH_2CH_2OAc
c, X = CH_2OAc
d, X = CH_2OCH_3
e, X = CO_2CH_3



6a, R = H
b, R = $COCH_2Cl$



7 **8**

The parent dienophile **6a** does not survive the conditions of Diels–Alder addition.[4] Double-bond migration in similar pyrrolinones is well known in the literature,[5] and has been verified in our laboratory with 3-substituted dervatives of **6a**.[6] The double-bond migration presumably involves the formation of a hydroxypyrrole tautomer as the crucial intermediate.

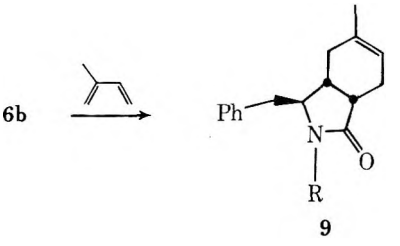
To avoid formation of tautomers from pyrrolinone dienophiles, it is desirable to introduce an electron-withdrawing N substituent which destabilizes the aromatic hydroxypyrrole intermediate. An *N*-chloroacetyl derivative **6b** is ideal in several respects. First, examples of relatively stable *N*-acetylpyrrolinones are already in the literature.[7] Furthermore, we have observed that simple α,β-unsaturated imides are considerably more reactive as dienophiles than the related esters, and much more reactive than the parent amides (Table I). Finally, *N*-acylpyrrolinones are easily cleaved by sodium carbonate in aqueous methanol to give the parent pyrrolinone.[7]

Reaction of **8** (easily available from phenylalanine ethyl ester)[9] with chloroacetic anhydride/lutidine in toluene affords **6b** in 74% isolated yield. The *N*-acylpyrrolinone **6b** is quite stable at 150 °C in hydrocarbon solvents and does not appear

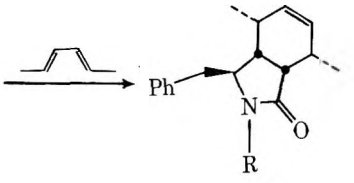
Table I. Diels–Alder Reactivity of α,β-Unsaturated Imides [a] and Related Dienophiles [b]

Dienophile	% isolated yield of adduct
$CH_2{=}CHCO_2CH_3$	7
$CH_2{=}CHCONMe_2$	5
$CH_2{=}CHCONH\,CH_3$	<1
$CH_2{=}CHCON(CH_3)COCH_3$	56
$CH_2{=}CHCON(CH_3)COCH_2Cl$	81
$CH_2{=}CHCON(CH_3)COCHCl_2$	92
$CH_3CH{=}CHCON(CH_3)COCHCl_2$	Trace [c]

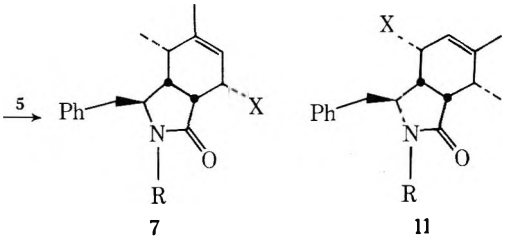
[a] All imides prepared by acylation of the *N*-trimethylsilylamide.[8] [b] Reaction at 60 °C, 24 h, in benzene, with 2,3-dimethylbutadiene in excess. [c] Reaction of α,β-unsaturated imides in the acrylate, crotonate, or tiglate series occurs at 25 °C in the presence of $TiCl_4$ catalyst (2,3-dimethylbutadiene substrate).



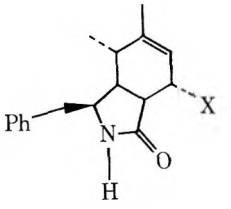
9



10



7 **11**



12a, X = $CH_2OCOC_2H_5$
R = $COCH_2Cl$

to form double-bond isomers. Upon reaction with isoprene or 1,4-dimethylbutadiene at 150 °C, **6b** affords a single adduct in each case. The regiochemistry of **9** follows from 270-MHz decoupling studies, while the stereochemistry of **10** is in accord with observed coupling relationships between adjacent methine protons.[11,12]

The formation of a single adduct **10** from 1,4-dimethylbutadiene is taken as evidence that our assumption of the less hindered endo transition state is correct. Given the strong directive effect of methyl in the condensation between **6b** and isoprene, we expected that directive effects from the terminal substituents in diene **5** would tend to cancel provided that substituent X does not encounter unfavorable steric or dipole interactions with dienophile substituents. In fact, the Diels–

Alder reaction between **5a** or **5b** and dienophile **6b** (120–150 °C) is selective in favor of **7a** and **7b** by a ca. 2:1 ratio relative to the undesired regioisomer **11**. However, dienes **5c** and **5d** afford approximately 1:1 mixtures of both regioisomers, while **5e** reacts slowly to give a 4:1 mixture in favor of the wrong isomer **11e**.

With the proper choice of diene substituents, a synthetically useful ratio of adducts **7** can now be obtained by the intermolecular Diels–Alder route. Furthermore, cleavage of the activating *N*-chloroacetyl group is easily accomplished with methanolic carbonate. Thus, crystalline **12a** can be obtained in ~50% overall yield from **6b**.

Methods for introduction of cytochalasin ring A functionality are under active investigation and will be described in due course.

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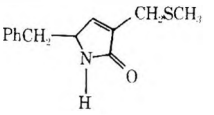
(6) Compound i decomposes within 12 h at 80 °C in toluene, and gives no Diels–Alder adduct with 2,3-dimethylbutadiene.



i

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(9) The sequence involves acylation of phenylalanine ethyl ester with the acid chloride of monoethyl malonate, Dieckmann cyclization[10] (sodium ethoxide, ethanol, room temperature), decarboxylation of the neutralized Dieckmann product (CH_3CN/H_2O, 1.5 h, 70 °C), and reduction (Na $CNBH_3$, $ClCH_2CO_2H$ in MeOH, 1 h, room temperature) to give **8**.
(10) H. Yuki, Y. Tohira, B. Aoki, T. Kano, S. Takama, and T. Yamazaki, *Chem. Pharm. Bull.*, **15**, 1107 (1967).
(11) NMR spectrum of **10** (R = $COCH_2Cl$): 270-MHz NMR ($CDCl_3$) δ 7.32 (5 H, m), 5.64 (1 H, dt, *J* = 9, 3 Hz), 5.56 (1 H, dt, *J* = 9, 3 Hz), 4.65 (2 H, s), 4.32 (1 H, ddd, *J* = 8, 3, 2 Hz), 3.07 (1 H, dd, *J* = 13, 3 Hz), 2.75 (1 H, dd, *J* = 13, 8 Hz), 2.71 (1 H, dd, *J* = 9, 6 Hz), 2.52 (1 H, br t, *J* = 9 Hz), 2.31 (1 H, m), 2.13 (1 H, m), 1.40 (3 H, d, *J* = 7 Hz), 0.83 (3 H, d, *J* = 7 Hz). NMR spectrum of **10** (R = H): 270-MHz NMR ($CDCl_3$) δ 7.22 (5 H, m), 5.77 (1 H, dt, *J* = 9, 3 Hz), 5.65 (1 H, dtd, *J* = 9, 3, 1 Hz), 5.48 (1 H, br s), 3.41 (1 H, ddd, *J* = 10, 5, 4 Hz), 2.96 (1 H, dd, *J* = 14, 4 Hz), 2.76 (1 H, dd, *J* = 10, 7 Hz), 2.57 (1 H, m), 2.52 (1 H, dd, *J* = 14, 10 Hz), 2.34 (2 H, m), 1.36 (3 H, d, *J* = 7 Hz), 1.22 (3 H, d, *J* = 7 Hz).
(12) Compound **10** has been prepared by a different route by G. Stork et al. (personal communication, G. Stork).
(13) NSF Predoctoral Fellow, 1975–1978.

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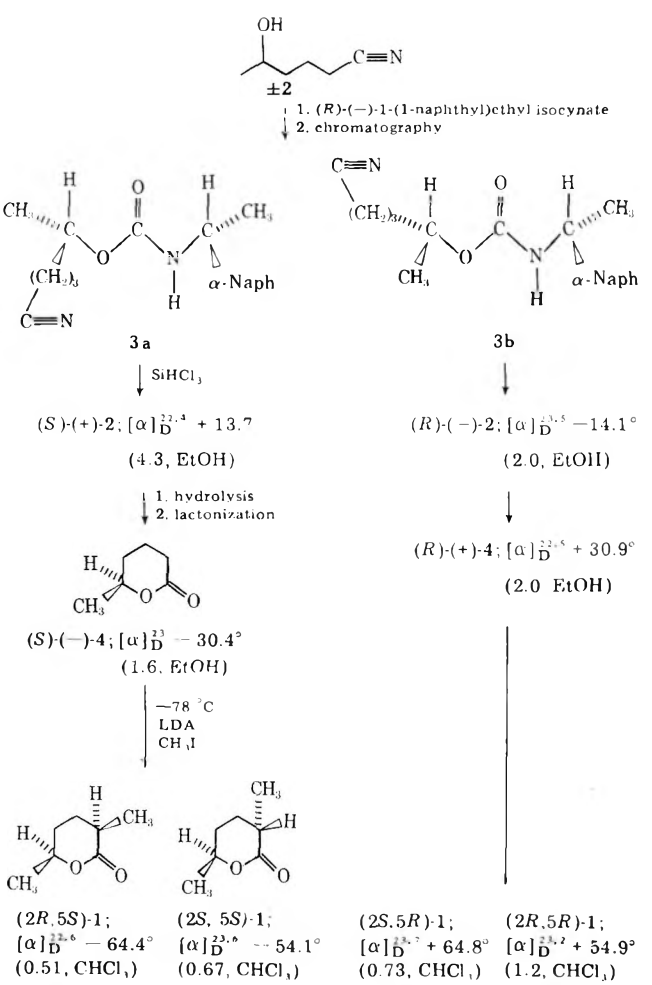
Synthesis of the Carpenter Bee Pheromone. Chiral 2-Methyl-5-hydroxyhexanoic Acid Lactones

Summary: 5-Cyanopentan-2-ol was resolved by chromatographic separation of diastereomeric carbamate derivatives. Hydrolysis and lactonization of each enantiomer afforded optically pure δ-methyl-δ-valerolactone, which was methylated to give cis and trans isomers of 5-hydroxyhexanoic acid lactone. One of the cis enantiomers is the carpenter bee pheromone.

Sir: As a prelude to a future account of a convenient and general synthetic approach to enantiomerically pure γ-substituted γ-lactones or δ-substituted δ-lactones, we describe the synthesis of all four stereoisomers of 2-methyl-5-hydroxyhexanoic acid lactone (**1**). One (presumably)[1] of the enantiomers of the *cis*-lactone is the major volatile component of the carpenter bee sex attractant.[2]

Our synthetic approach was designed to utilize a racemic intermediate that could be predictably and conveniently resolved into its enantiomers using our recently described broad-spectrum chromatographic method.[3] As shown in Scheme I, racemic 5-cyanopentan-2-ol (**2**), prepared by the method of Colonge et al.,[4] was converted to diastereomeric cyanocarbamates **3a** and **3b** by reaction with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate.[5] These diastereomers are easily separable by automated multigram HPLC[6] (acidic alumina; 2:1 $CHCl_3$–hexane) and the enantiomerically pure cyano alcohols were retrieved quantitatively by silanolysis with trichlorosilane.[7] Basic hydrolysis of the enantiomeric cyano alcohols and subsequent lactonization afforded the corresponding enantiomers of δ-methyl-δ-valerolactone **4**. Low-temperature methylation (LDA–methyl iodide) of the enan-

Scheme I



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tiomers of lactone **4** afforded a 1:1 mixture of the GLC-separable (Carbowax, 150 °C) cis and trans isomers of **1**.[8] Since the methylation sequence has no effect upon the stereochemistry of the configurationally known δ carbon of **4**,[9] the absolute configurations of the four stereoisomers of **1** are established. Even had the absolute configuration of **4** not been previously assigned,[9] it could have been assigned from the elution order of the diastereomeric carbamates **3a** and **3b**.[10] Moreover, the absolute configurations of the enantiomers of *cis*-**1** (and hence the *trans*-**1** as well) are assignable from the sense of the (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol induced NMR spectral nonequivalence.[11] This induced NMR nonequivalence allows facile NMR determination of the enantiomeric purity of *cis*-**1** (and thus *trans*-**1** as well); both enantiomers were enantiomerically pure by this criterion. Lactone **4** recovered by GLC from the methylation reaction mixture was of unchanged specific rotation.[12]

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

Supplementary Material Available: the experimental details of this work (4 pages). Ordering information is given on any current masthead.

References and Notes

(1) Although the report[2] of the identification of *cis*-**1** as the major component of the sex attractant contains no chiroptic data, it is reasonable to assume that the natural material is chiral and not racemic. In the absence of such data, we cannot state which enantiomer of *cis*-**1** corresponds to the natural material. Toward this end, samples of the stereoisomers are available for testing.
(2) J. W. Wheeler, S. L. Evans, M. S. Blum, H. H. V. Velthius, and J. M. F. de Camargo, *Tetrahedron Lett.*, 4029 (1976).
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(7) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).
(8) Cis–trans assignments were made originally on the basis of low-temperature NMR studies.[2] In the present instance, assignments are based upon previously reported[2] chemical shifts and GLC elution orders.
(9) (a) R. Kuhn and K. Kum, *Chem. Ber.*, **95**, 2009 (1962); (b) R. Lukes, J. Jary, and J. Nemec, *Chimia*, **13**, 336 (1959); *Collect. Czech. Chem. Commun.*, **27**, 735 (1962).
(10) From the chromatographic separation model advanced for diastereomeric carbamates in ref 3, the known absolute configuration of the resolving agent, and the knowledge that polar groups such as cyano absorb rather strongly upon silica gel or alumina, one expects **3a** to elute before **3b**.
(11) W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, **42**, 384 (1977).
(12) Our specific rotations of the enantiomers of **4** are not in close agreement with prior literature values. Note that the prior values are also in disagreement [i.e., (*R*)-(+)-**4**, $[\alpha]^{20}_D$ +18.4° (1.7, MeOH);[13] (*S*)-(−)-**4**, $[\alpha]^{19}_D$ −51.4° (EtOH)[9a]]. Owing to our use of preparative GLC for purification and subsequent NMR demonstration of enantiomeric purity, we believe our rotational values to be those of the enantiomerically pure enantiomers.
(13) J. MacMillan and T. J. Simpson, *J. Chem. Soc., Perkin Trans. 1*, **14**, 1487 (1973).

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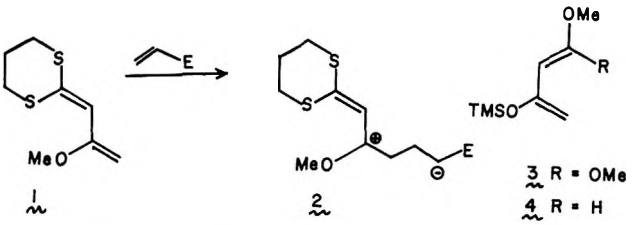
Diels–Alder Reactions of 1,1-Dimethoxy-3-trimethylsilyloxy-1,3-butadiene

Summary: The title compound has been shown to be a powerful diene in Diels–Alder reactions with electron-deficient dienophiles. In these processes, it functions as a directed synthetic equivalent of $^+COCH_2COCH_2^-$. The contrast in behavior between this diene and that of 2-(2-methoxy)allylidene-1,3-dithiane, which has a high tendency to afford Michael addition products with highly electrophilic olefins, is particularly striking.

Sir: Recently we investigated the feasibility of cycloaddition reactions of diene **1** with potential dienophiles.[1] We found that the generality of Diels–Alder cycloadditions of **1** was undermined by its tendency to afford simple Michael addition products with highly electrophilic olefins such as benzoquinone and dimethyl acetylenedicarboxylate. Cycloaddition reactions were observed only with less electrophilic olefins such as methyl vinyl ketone.

It seemed likely that strong electrophiles might react with the powerfully nucleophilic **1** via its "s-trans" conformer, thereby affording an intermediate of the type **2**, wherein cyclyzation would be noncompetitive with proton transfer as a means of charge dissipation.



1 **2** **3** R = OMe **4** R = H

It seemed worthwhile to pursue this line of study. Thus, the general proposition of using heavily functionalized dienes which might endow their Diels–Alder adducts with convenient access points for orderly future elaborations has, potentially, considerable possiblities in the design of synthetic strategy.[2-4] During the course of our studies, addressed to correcting the limitations of diene **1** described above, Brassard and coworkers[5] reported the preparation of diene **3** and homologues thereof by a method similar to that which we used for the preparation of **4**.[6] Of particular interest to us was the finding that compound **3** and its homologues gave cycloaddition products with several naphthoquinones. No other Diels–Alder reactions of **3** were described. Since we had found that reaction of compound **1** with the parent 1,4-benzoquinone afforded a benzofuran which was clearly derived from Michael addition and proton transfer,[1] we have examined the general enophilicity of compound **3**. Below we report that this substance is, in fact, an excellent diene for Diels–Alder reactions and its use allows for the facile elaboration of aromatic and alicyclic systems bearing extensive functionality.

Compound **3** reacted with dimethyl acetylenedicarboxylate in benzene. After 30 min under reflux[7] there was isolated an 89% yield of dimethyl 3-methoxy-5-hydroxyphthalate (**5**), mp 141–143 °C.[8] The unraveling of the presumed adduct **5a** is apparently instantaneous under these conditions. Similarly, compound **3** reacts with 1,4-benzoquinone (C_6H_6; room temperature; 15 min). The crude adduct was treated with pyridine–acetic anhydride (reflux; 12 h), thereby affording a 78% yield of 1-methoxy-3,5,8-triacetoxynaphthalene (**6**),[8] mp 172–173 °C.

It will be recalled that, with these two potential dienophiles, compound **1** gave high yields of products derived from simple 1,4-addition. Diels–Alder reaction of compound **3** with 1,3-dicarbomethoxyallene (C_6H_6; reflux; 1 h) afforded a 72% yield of the differentiated homophthalate derivative, **7**[8] (mp 70–72 °C). Similarly, a 74% yield of methyl 2-methoxy-4-hydroxybenzoate (mp 150–151 °C; lit.[9] 152–153 °C) was obtained after cycloaddition of **3** with methyl propiolate.

Thus, through this methodology, one elaborates in a single step a benzene ring in the form of a resorcinol monomethyl ether. The condition of the process with unsymmetrical dienophiles is that the methoxy group emerges ortho to that function which dominates their regiochemical sense of addition.

Cycloaddition of compound **3** with maleic anhydride occurs essentially instantaneously (neat; 0 °C). Trituration with ether gave a 95% yield of compound **9**,[8] mp 152–153 °C. No acidic

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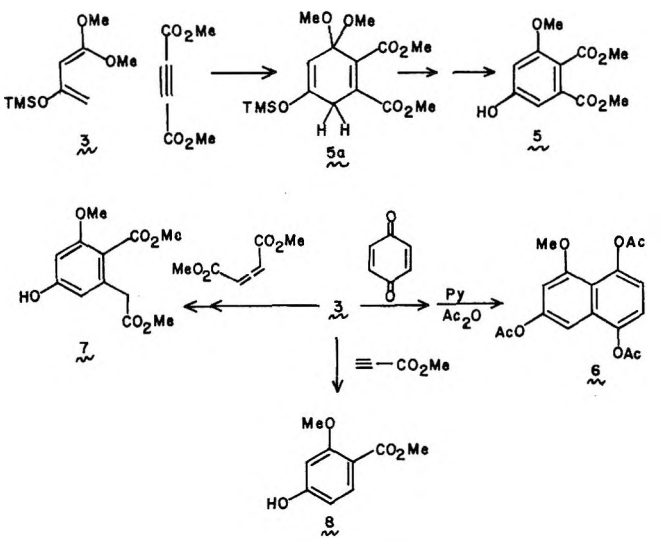
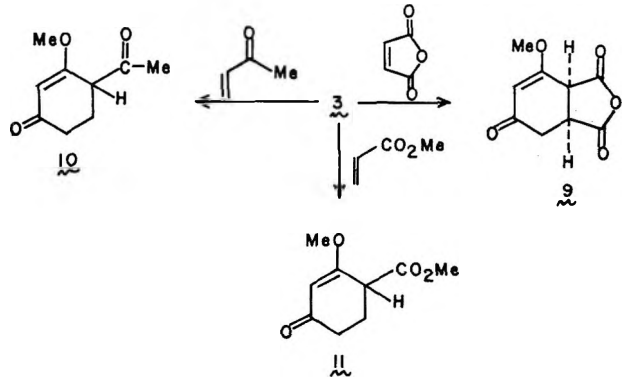


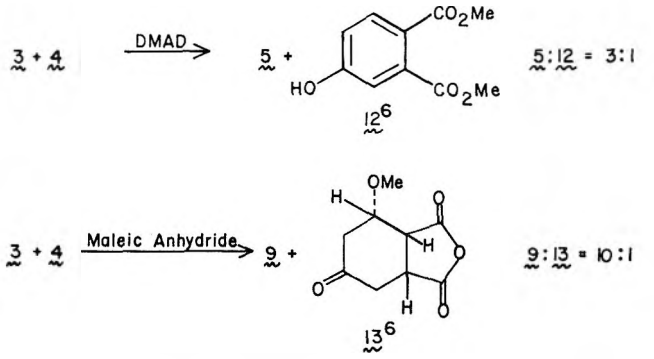
treatment was necessary for unraveling. Cycloaddition of **3** with methyl acrylate (C_6H_6; reflux; 16 h) followed by mild acid hydrolysis afforded a 55% yield of **11**.[8] In a similar way, reaction of **3** with methyl vinyl ketone (C_6H_6; 50 °C; 2 h) afforded **10**,[8] though the isolated yield of homogeneous product was a disappointing 43%.



We were both pleased and surprised at the extremely mild conditions which sufficed for the cycloadditions of **3**, a 1,1-disubstituted butadiene. It was of interest to compare the rate of cycloadditions of **3** with that of parent compound **4**,[6] which lacks the (*Z*)-methoxyl at the 1 position. A direct comparision of these dienes was made as regards their cycloadditions with dimethyl acetylenedicarboxylate and maleic anhydride. In each case, stoichiometric equivalents of **3** and **4** were allowed to compete for 1 equiv of dienophile. The results,[10] described below, indicate that with respect to these dienophiles **3** is a more potent Diels–Alder diene than **4**.

Our findings indicate that Diels–Alder reactions between highly "nucleophilic" dienes and highly "electrophilic" dienophiles may proceed effectively even though the 1 position of the diene is disubstituted. Indeed, the indication from this work is that the enhanced nucleophilic character of the diene may override the steric difficulties associated with an additional (*Z*)-methoxyl function.

In rationalizing the reactivity differences of **1** and **3** with respect to Diels–Alder cyclizations vs. Michael additions, several as yet imponderables await definition. These are: (i) the effect of sulfur (in **1**) vs. oxygen (in **3**) heteroatoms; (ii) the effect of the ring constraint of the 1,1-heteroatoms (in **1**) vs.



the conformationally mobile arrangement in **3**; and (iii) the effect of the 3-OTMS group of **3**[11] relative to the 3-OMe group of **1**. For the moment, one must be content with the phenomenological finding, i.e., that diene **1**, in many of its reactions, is a functional equivalent of $^{-}CH_2COCH_2C(O)H$, while diene **3** is a synthetic equivalent of $^{-}CH_2COCH_2C^{+}(O)$.

Acknowledgments. This research was supported by PHS Grant AI-13939-01 and by a Postdoctral Fellowship to Dr. R. B. Gammill from the American Cancer Society. The assistance of Mr. Glen Herman in obtaining mass spectra is gratefully acknowledged.

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(11) The possibility that the size of the substituent at position 3 is relevant will be studied, since this could well effect the "s-cis" and "s-trans" conformational populations of the dienes.

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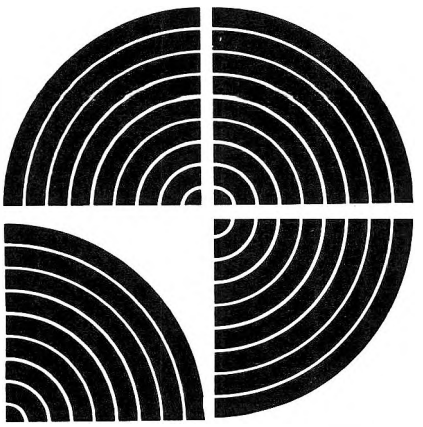

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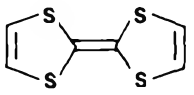
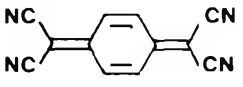
TTF and TCNQ

Components for conductivity

Tetrathiafulvalene (TTF) and several other tetrathioethylenes were originally investigated as possible electron-rich olefins.[1] It was quickly realized that the electrochemistry of **TTF** was by far the most interesting aspect of the compound. Wudl *et al.*[2,3] discovered that **TTF** formed an exceptionally stable radical cation complex with chlorine (TTF•Cl) which exhibited an unusually high electrical conductivity.



TTF

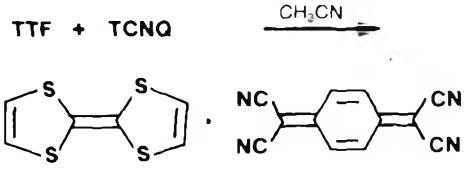


TCNQ

7,7,8,8-Tetracyanoquinodimethane (TCNQ) was first studied for its ability to form radical anions.[4,5,6] Since then, many practical applications have been discovered. For example, **TCNQ** is used in the:

1) colorimetric determination of free radical precursors[7]
2) visualization of certain nitrogen and sulfur compounds on thin-layer and paper chromatograms[7,8]
3) replacement of MnO_2 in aluminum solid electrolytic capacitors[9]
4) construction of heat-sensitive resistors[10]
5) induction of radical polymerizations (in combination with *N,N*-dimethylaniline *N*-oxide)[11]
6) construction of ion-specific electrodes.[12,13]

It was the ability of **TCNQ** to form radical anions that prompted Cowan[14] to combine it with the electron donor **TTF**. The resulting charge-transfer complex was found to contain **TTF** and **TCNQ** in a 1:1 ratio.



This complex behaves electrically and optically like a one-dimensional metal at room temperature. It has one of the highest electrical conductivities known for an organic compound, being highly anisotropic along an axis defined by the colinear stacks of **TTF** and **TCNQ**.[15] Since there was some controversy over the exact value of the conductivity, a study was performed to determine if the chemical purity of the components affected the electrical conductivity of the complex.[16] The workers concluded that crystal perfection rather than chemical purity was the factor chiefly responsible for determining the degree of conductivity. Major research efforts are currently in progress to better understand and find applications for the unusual properties of the **TTF/TCNQ** complex.[17,18,19]

Aldrich has offered **TCNQ** for many years. Now we also offer **TTF**! With the ready availability of these "components for conductivity," the **TTF/TCNQ** complex is more accessible for further studies.

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