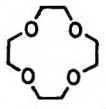
VOLUME 42 AUGUST 19, 1977 NUMBER 17 JOCEAH

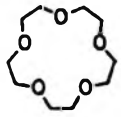
THE JOURNAL OF Organic Chemistry

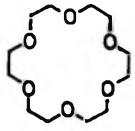
PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

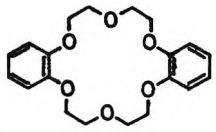
CROWN ETHERS FOR GENERATING "NAKED" ANIONS 8.8.77

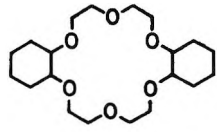
FAVOURABLY PRICED AND WITH QUALITY SPECIFICATIONS

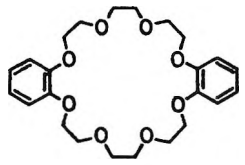

28122

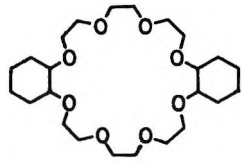

28123


28125


33531


36665/6


33539


36668

28122	**12-Crown-4 purum** >98%(GLC); $BP_{0.1}$ 68-70°; n_D^{20} 1.462	1 lt ≈ 1.11 kg	5 ml	sFr. 32.—	US$ 12.80
	$C_8H_{16}O_4$ MW 176.22		25 ml	sFr. 135.—	US$ 54.00
28123	**15-Crown-5 purum** >98%(GLC); $BP_{0.1}$ 93-95°; n_D^{20} 1.465	1 lt ≈ 1.11 kg	5 ml	sFr. 29.—	US$ 11.60
	$C_{10}H_{20}O_5$ MW 220.27		25 ml	sFr. 120.—	US$ 48.00
28125	**18-Crown-6 purum** >98%(GLC); MP 37-39°		5 g	sFr. 20.—	US$ 8.00
	$C_{12}H_{24}O_6$ MW 264.32		25 g	sFr. 85.—	US$ 34.00
33531	**Dibenzo-18-crown-6 purum** >98%(GLC); MP 161-163°		5 g	sFr. 20.—	US$ 8.00
	$C_{20}H_{24}O_6$ MW 360.41		25 g	sFr. 85.—	US$ 34.00
33539	**Dibenzo-24-crown-8 pract.** >98%(GLC); MP 102-107°		1 g	sFr. 18.—	US$ 7.20
	$C_{24}H_{32}O_8$ MW 448.52		5 g	sFr. 75.—	US$ 30.00
36665	**Dicyclohexyl-18-crown-6 cryst. purum** >98%(GLC); MP 48-58°		5 g	sFr. 29.—	US$ 11.60
	$C_{20}H_{36}O_6$ MW 372.51		25 g	sFr. 120.—	US$ 48.00
36666	**Dicyclohexyl-18-crown-6 techn.** >70%(GLC); contains less than 2% Dibenzo-18-crown-6 (UV)		10 g	sFr. 28.—	US$ 11.20
	$C_{20}H_{36}O_6$ MW 372.51		50 g	sFr. 120.—	US$ 48.00
36668	**Dicyclohexyl-24-crown-8 pract.** >96%(GLC); contains less than 2% Dibenzo-24-crown-8 (UV); MP −23-+27°; n_D^{20} 1.488	1 lt ≈ 1.10 kg	1 ml	sFr. 25.—	US$ 10.00
	$C_{24}H_{44}O_8$ MW 460.61		5 ml	sFr. 105.—	US$ 42.00

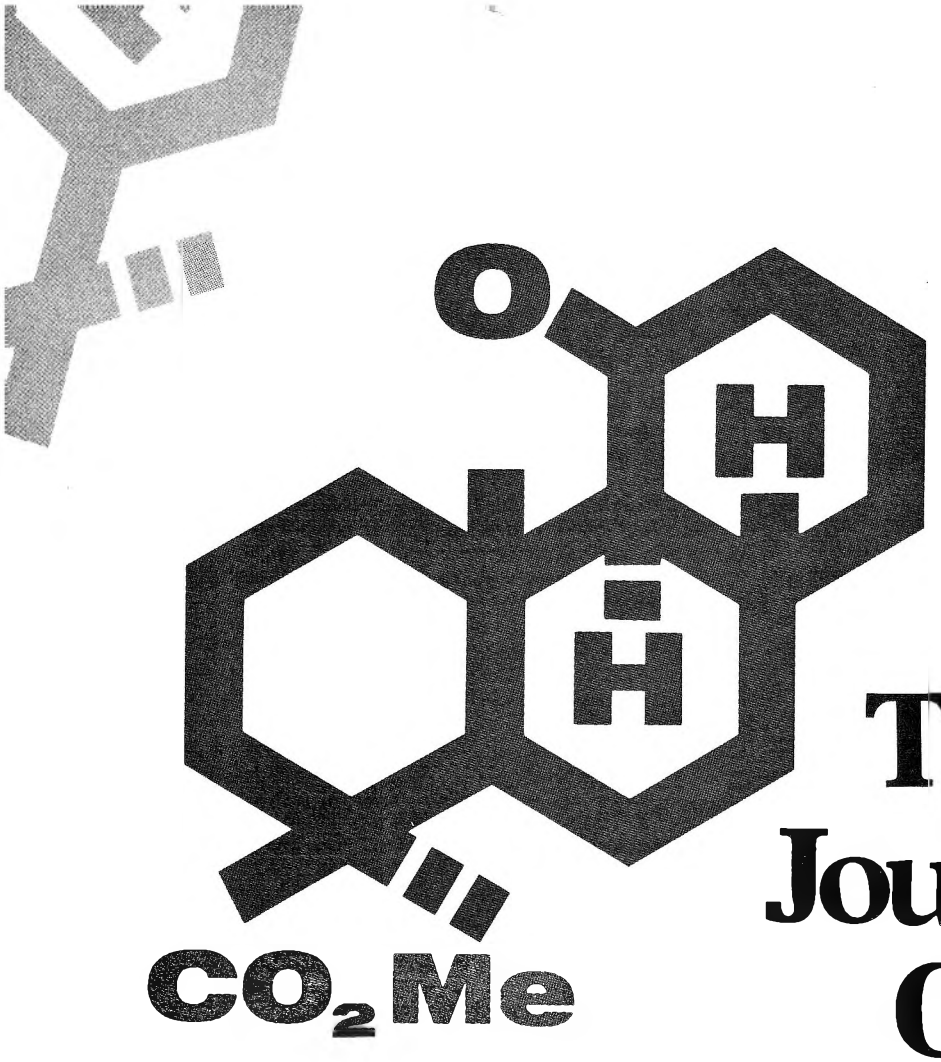
For prices outside of North America and Switzerland please contact the local agent of Fluka AG, CH-9470 Buchs

REVIEWS ON CROWN ETHERS

C.J. Pedersen, H.K. Frensdorff, "Makrocyclische Polyaether und ihre Komplexe", Angew. Chem. **1972**, *84*, 16–26; Angew. Chem. Int. Ed. **1972**, *11*, 16–26
J.J. Christensen, D.J. Eatough, R.M. Izatt, "The Synthesis and Ion Binding of Synthetic Multidentate Macrocyclic Compounds", Chem. Rev. **1974**, *74*, 351-384
G.W. Gokel, H.D. Durst, "Principles and Synthetic Applications in Crown Ether Chemistry", Synthesis **1976**, 168–184

ON REQUEST WE WILL BE PLEASED TO SEND YOU THE FLUKA BROCHURE "NEW REAGENTS FOR ORGANIC SYNTHESIS WITH 'NAKED' ANIONS X^-"

Tridom Chemical Inc. 255 Oser Avenue, Hauppauge, New York 11787, Phone (516) 273-0110
Exclusive North American Representative of Fluka AG, CH-9470 Buchs, Switzerland



Reactions, natural products, mechanisms, theory and spectroscopy covered comprehensively in

The Journal of Organic Chemistry

Recognized by many organic chemists as the leading American journal in the field, this biweekly publication brings subscribers over 1,000 articles, notes and communications each year—over 4,000 pages including original contributions on fundamental researches in all branches of the theory and practice of organic chemistry. Improved procedures, accounts of novel observations or compounds of special interest are also noted. Complete and mail the coupon NOW to join the thousands of organic chemists who find this journal vital in keeping current in the field.

AVAILABLE IN HARD COPY OR MICROFICHE.

The Journal of Organic Chemistry
American Chemical Society **1977**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

Yes, I would like to receive THE JOURNAL OF ORGANIC CHEMISTRY at the one-year rate checked below:

	U.S.	Foreign and Canada	Latin America
ACS Member*	☐ $26.00	☐ $36.00	☐ $35.00
Nonmember	☐ $104.00	☐ $114.00	☐ $113.00

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start in January '77.
Allow 60 days for your first copy to be mailed.
*NOTE: Subscriptions at ACS member rates are for personal use only.

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

BOOKS AND JOURNALS DIVISION

D. H. Michael Bowen, *Director;* Marjorie Laflin, *Assistant to the Director*

Editorial Department: Charles R. Bertsch, Head; Marianne C. Brogan, Associate Head; Eileen B. Segal, Production Editor; Fern S. Jackson, Assistant Editor; Andrew J. D'Amelio, Editorial Assistant

Magazine and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 25 Silvan Road South, Westport, Conn. 06880.

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second class postage paid at Washington, D.C., and at additional mailing offices.

Editorial Information

Instructions for authors are printed in the first issue of each volume. Please conform to these instructions when submitting manuscripts.

Manuscripts for publication should be submitted to the Editor, Frederick D. Greene, at his Cambridge, Mass., address.

Correspondence regarding **accepted papers and proofs** should be directed to the Editorial Department at the address below.

Page charges of $70.00 per page may be paid for papers published in this journal. Payment does not affect acceptance or scheduling of papers.

Bulk reprints or photocopies of individual articles are available. For information write to Business Operations, Books and Journals Division, at the ACS Washington address. Requests for **permission to reprint** should be directed to Permissions, Books and Journals Division, at the ACS Washington address.

The American Chemical Society and its Editors assume no responsibility for the statements and opinions advanced by contributors.

Subscription and Business Information

1977 subscription rates—including surface postage:

	Domestic	PUAS	Canada, Foreign
Member	$26.00	$35.00	$36.00
Nonmember	104.00	113.00	114.00
Supplementary material	15.00	19.00	20.00

Air mail and Air freight rates are available from Membership & Subscription Services, at the address below.

New and renewal subscriptions should be sent with payment to the Office of the Controller at the ACS Washington address. **Changes of address** must include both old and new addresses with ZIP code and a recent mailing label. Send all address changes to the Membership and Subscription Services. Please allow 6 weeks for change to become effective. **Claims for missing numbers** will not be allowed if loss was due to failure of notice of change of address to be received in the time specified; if claim is dated, (a) North America, more than 90 days beyond issue date, (b) all other foreign, more than one year beyond issue date; or if the reason given is "missing from files". Hard copy claims are handled by Membership and Subscription Services.

Microfiche subscriptions are available at the same rates but are mailed first class to U.S. subscribers, air mail to the rest of the world. Direct all inquiries to Special Issue Sales at the ACS Washington address or call (202) 872-4554.

Single issues in hard copy and/or microfiche are available from Special Issues Sales at the ACS Washington address. Current year $5.00. Back issue rates available from Special Issues Sales. **Back volumes** are available in hard copy and/or microform. Write to Special Issues Sales at the ACS Washington address for further information. **Microfilm** editions of ACS periodical publications are available from volume 1 to the present. For further information, contact Special Issues Sales at the ACS Washington address.

Supplementary material mentioned in the journal appears in the microfilm edition. Single copies may be ordered directly from Business Operations, Books and Journals Division, at the ACS Washington address.

	U.S.	PUAS, Canada	Other Foreign
Microfiche	$2.50	$3.00	$3.50
Photocopy			
1–7 pages	4.00	5.50	7.00
8–20 pages	5.00	6.50	8.00

Orders over 20 pages are available only on microfiche, 4 × 6 in., 24× negative, silver halide. Orders must state photocopy or microfiche if both are available. Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

American Chemical Society
1155 16th St., N.W.
Washington, D.C. 20036
(202) 872-4600

Editorial Department
American Chemical Society
P.O. Box 3330
Columbus, Ohio 43210
(614) 421-6940, Ext. 3171

Membership & Subscription Services
American Chemical Society
P.O. Box 3337
Columbus, Ohio 43210
(614) 421-7230

Notice to Authors last printed in the issue of January 7, 1977

JOCEAH 42(17) 2799–2952 (1977)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 17 AUGUST 19, 1977

AUTHOR INDEX

■ Supplementary material for this paper is available separately (consult the masthead page for ordering information); it will also appear following the paper in the microfilm edition of this journal.

* In papers with more than one author, the asterisk indicates the name of the author to whom inquires about the paper should be addressed.

THE JOURNAL OF Organic Chemistry®

VOLUME 42, NUMBER 17

AUGUST 19, 1977

Mass Spectrometry in Structural and Stereochemical Problems. 250.[1] Characteristic Fragmentations of Cholesterol Acetate[2]

L. G. Partridge[3] and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Received February 28, 1977

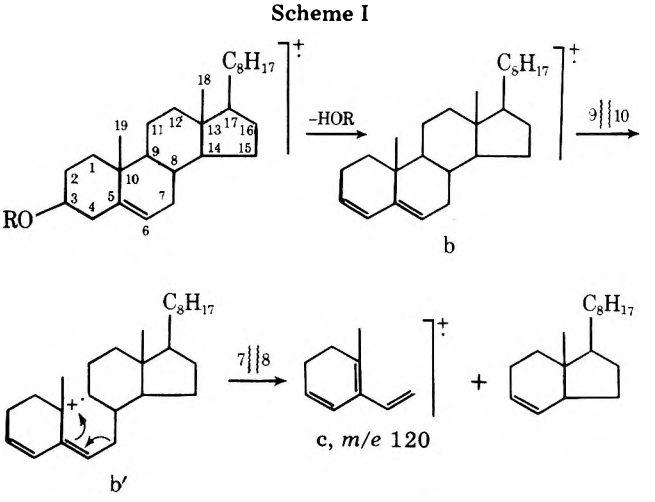
Through the use of extensive deuterium labeling, the structure and origin of the diagnostic fragments of cholesterol acetate have been clarified. Deuterium labels at carbon atoms 9, 11, 12, 14, and 19 which have not previously been reported for cholesterol itself provide information on the genesis of the characteristic $M^+ - 168$ (*m/e* 260) and $M^+ - 181$ (*m/e* 247) fragments of the acetate as well as on the more common loss of acetic acid (*m/e* 368), ring D fragmentation (*m/e* 213), and the proposed retro-Diels–Alder fragment (*m/e* 120). The mass spectra of cholesterol acetate and the free sterol are compared, and further information is provided on the fragments of mass 247, 231, and 213 in cholesterol.

The Δ^5-steroidal olefins and especially those with 3β-hydroxyl substituents and their esters are among the most common naturally occurring steroids. It is not surprising, therefore, that sterols have been the subject of numerous studies attempting to identify them by their characteristic electron impact induced fragmentation. The mass spectrum of cholesterol acetate (Figure 1) is quite different from that of cholesterol (Figure 2) but surprisingly has hardly been examined critically even though sterol acetates are frequently derivatives which are employed in separation schemes of naturally occurring sterol mixtures (e.g., from marine sources). The origins of the major electron impact induced fragments of cholesterol have been established in two recent papers,[4,5] and we have now utilized a number of new labeled cholesterols synthesized in this laboratory during our recent study[1] of the ring D fragmentation of some steroidal olefins to provide information on the acetate.

The characteristic $M^+ - 85$ (*m/e* 301) and $M^+ - 111$ (*m/e* 275) peaks in the mass spectrum of cholesterol (Figure 2) have no analogue in that (Figure 1) of the acetate. A fragment of mass 260 is unique to the latter while *m/e* 247 is present in both spectra as is a small peak at *m/e* 120. Zaretskii[6a] suggested that perhaps the most characteristic peak of the Δ^5-steroids is *m/e* 247, which is present in both cholesterol acetate and the free sterol. Friedland et al.[7] proposed the structure for this fragment shown in (a) which was examined by Knights[8] in his study of Δ^5-3β-hydroxyl sterols who also proposed (a) as the most likely cleavage. However, Budzikiewicz and Ockels[4] found that in their androst-5-en-3β-ols, labels at C-15 and C-16 which would be completely retained in structure (a) were retained only to the extent of 70% in *m/e* 135 (analogous to *m/e* 247 in a steroid with no C-17 substituent). The authors pointed out that while (a) could be established as the major source of *m/e* 135, there must be other contributing fragments. Consistent with this, metastable defocusing showed a number of progenitor ions for that peak in their androstenols. Budzikiewicz and Ockels[4] did note a large apparent transfer from C-8 and C-9 indicating that these sites are the origin of the shifted protons.

A peak at *m/e* 120 was reported in $\Delta^{3,5}$-cholestadiene and cholesterol acetate by Galli and Maroni[9] who proposed its formation in the thermally disallowed retro-Diels–Alder fragmentation of the 3,5-dienyl system (Scheme I). These

Scheme I



authors suggested that this fragment (c) or its analogue should be present in the mass spectrum of a Δ^5-steroid and might be the most characteristic type of fragmentation for such an olefin. This proposal has been questioned by Zaretskii,[6a] who pointed out that since the actual origin of *m/e* 120 was not known and since a wide range of steroidal olefins show a group of peaks of similar intensity in that mass range, more careful study of the origin of this peak would be necessary before it

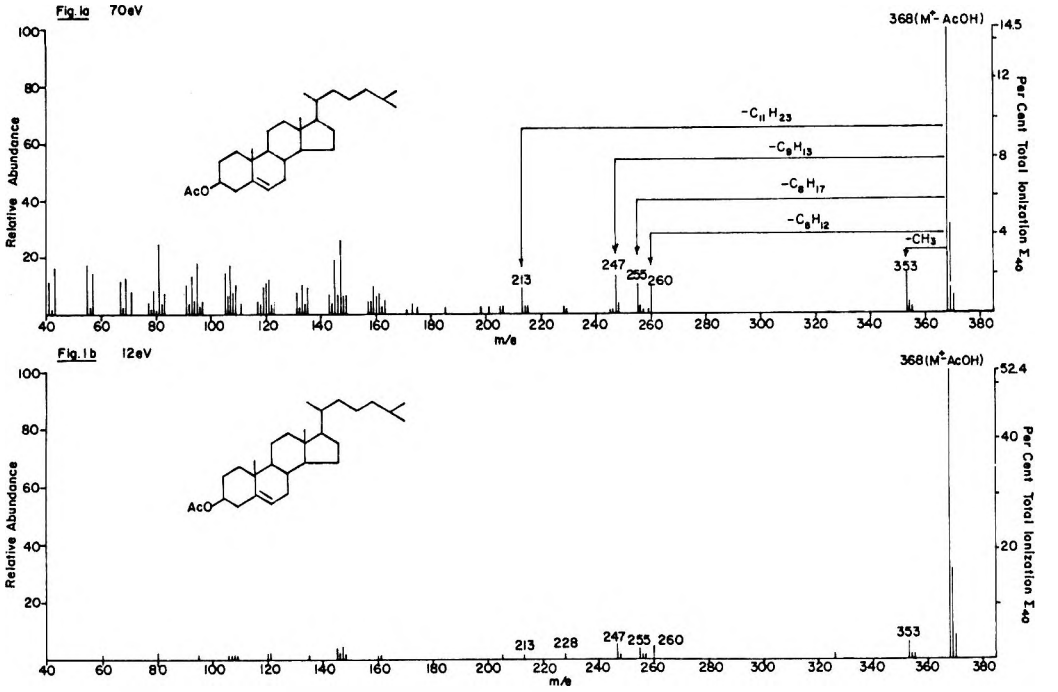


Figure 1. Mass spectra of cholesterol acetate (**1b**): (a) 70 eV; (b) 12 eV.

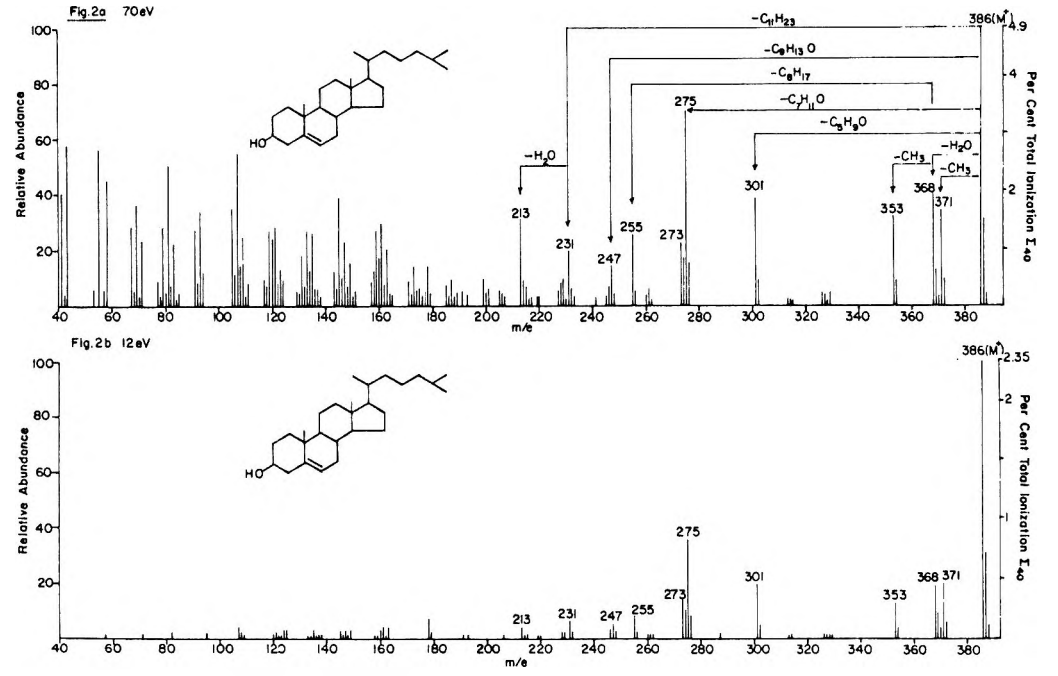
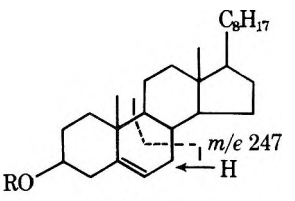


Figure 2. Mass spectra of cholesterol (**1a**): (a) 70 eV; (b) 12 eV.

could be considered characteristic of any particular class of steroids.



a, *m/e* 247
(M − 181)

Results and Discussion

Since the mass spectrum of cholesterol-2,2,4,4-d_4 acetate (**11b**) (Table I) shows no more than three deuterium labels in the $M^+ - 60$ peak, virtually all of the acetic acid loss must involve adjacent carbon atoms, presumably the allylically activated C-4. Consistent with this observation is the fact that no detectable transfer was observed (Table I) from the other labeled acetates. Zaretskii[6b] has speculated that the absence of a molecular ion peak in the mass spectra of the Δ^5-steroidal 3β-acetates reported by Galli and Maroni[9] could have been due to the high temperatures used in that study. However, we have found that no molecular ion is visible in the mass spectrum of the acetate even if the samples are run using a direct insertion probe. Because of this facile 1,2-elimination of acetic acid, the mass spectrum of cholesterol acetate is quite different from that of cholesterol and must be explained in terms of fragmentation of a $\Delta^{3,5}$-cholestadiene (or isomeric diene) species (*m/e* 368, $M^+ - 60$) which is the largest fragment in the spectrum.

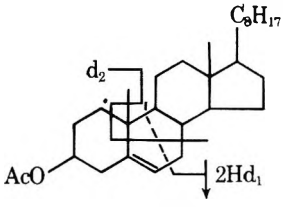
Table I. Shifts[a] of Mass Spectral Peaks of Deuterated Cholesterol Acetates

Registry no.	Compd	Label	Isotope composition, %	$M^+ - AcOH$	$M^+ - CH_3 - AcOH$	$M^+ - C_8H_{12} - AcOH$	$M^+ - C_8H_{17} - AcOH$	$M^+ - C_9H_{13} - AcOH$	$M^+ - C_{11}H_{23} - AcOH$
604-35-3	**1b**		Cholesterol acetate	368	353	260	255	247	213
62743-51-5	**12b**	3α-d_1	2 d_0 98 d_1	369	354	260	256	247	214
62743-52-6	**10b**	1β-d_1	23 d_0 73 d_1 4 d_2	369	354	260	256	247	214
62743-53-7	**11b**	2,2,4,4-d_1	3 d_0 3 d_1 8 d_2 29 d_3 54 d_4 3 d_5	371	356	260	258	247	216
62743-54-8	**13b**	7,7-d_2	4 d_0 6 d_1 90 d_2	370	355	260 (26%) 261 (62%) 262 (12%)	257	247	214 (26%) 215 (74%)
62743-55-9	**14b**	8β-d_1	3 d_0 96 d_1 1 d_2	269	354	261	256	247 (47%) 248 (53%)	213 (11%) 214 (89%)
62743-56-0	**2b**	9α-d_1	12 d_0 88 d_1	369	354	260 (6%) 261 (94%)	256	247 (9%) 248 (91%)	213 (25%) 214 (75%)
62743-57-1	**3b**	11,11-d_2	4 d_1 96 d_2	370	355	261 (4%) 262 (96%)	257	249	215
62743-58-2	**4b**	12,12-d_2	28 d_1 72 d_2	370	355	262	257	249	215
62743-59-3	**9b**	14α-d_1	4 d 96 d_1	369	354	260 (45%) 261 (55%)	256	247 (26%) 248 (74%)	213 (25%) 214 (75%)
62743-60-6	**5b**	19-d_1	9 d_0 91 d_1	369	353 (67%) 354 (33%)	260	256	247	213 (9%) 214 (91%)
62743-61-7	**15b**	26,26,26,-27,27,27-d_6	2 d_2 4 d_3 9 d_4 24 d_5 61 d_6	374	359	266	255	253	213

[a] The shift values have been corrected for ^{13}C contributions and effects due to isotope composition. The spectra were measured at 70 eV.

Loss of a methyl group from $M^+ - 60$ in cholesterol acetate or from M^+ in the free sterol results in both cases in a 67% loss of the C-19 label (Tables I and II). These figures are in fair agreement with those of the 19-labeled pregnenediol analogue used by Wyllie et al.[5] which showed a 58% loss of C-19 in the $M^+ - 15$ peak. The quantitative differences are probably due to the different steroid models rather than to the different instruments used to measure the mass spectra. For instance, in Δ^7-steroids considerable variation in the ratio of loss of the C-18 and C-19 angular methyl groups with variation of the length of the C-17 side chain has been observed.[1] Loss of water and methyl radical in the spectrum of cholesterol to give *m/e* 353 resulted in 77% loss of C-19, and the presence of metastable peaks at *m/e* 336 (371 → 353) and *m/e* 339 (368 → 353) shows that either loss of H_2O from M^+ (*m/e* 368) or loss of methyl from M^+ (371) can precede the formation of *m/e* 353. It is evident that initial loss of water from M^+ in cholesterol must have a significant effect on the expulsion of C-19 over C-18 whereas the loss of acetic acid from cholesterol acetate does not. This is in good agreement with the proposal[5] that loss of water from M^+ in cholesterol is preceded to a large extent by skeletal cleavages.

The data in Table I indicate complete loss of the label on carbon atoms 1, 2, 3, 4, and 19 and retention at positions 8, 12, 26, and 27 for the ion of mass 260. The retention of C-7 which would differentiate between fragments d_1 and d_2 cannot be established directly from the mass spectrum of the C-7 labeled cholesterol acetate (**13b**) since one of the C-7 labels is lost cleanly while the second is retained to the extent of 74%. This could be due to contribution by a species arising from complete loss of C-7 after proton exchange with the charge retaining fragment (d_2) or to stepwise transfer of one or both of the C-7 protons to the portion of the molecule lost in d_1.



d, *m/e* 260
(M − 168)

Partial retention of the label at C-7 in d_2 would most likely involve abstraction of one of the allylic C-7 protons by a radical somewhere in the charge retaining portion of the molecule followed by abstraction of another proton by the radical at C-7 which the data in Table I indicate would originate mostly from C-14. Since transfer to the hypothetical radical at C-7 would proceed through a 1,3 shift from C-14 rather than a 1,2 shift from C-8, a rationalization of d_2 would have to include activation of the C-14 proton for transfer as well as removal of the availability of the C-8 proton. Furthermore, since both the angular methyl group (C-19) and the skeletal fragment are lost, metastable defocusing would be expected to show cleavage d_2 to proceed through a stepwise loss of these unconnected fragments; however, this is not the case. The only parent seen (Table III) for *m/e* 260 (in the first field-free re-

Table II. Shifts[a] of Mass Spectral Peaks of Deuterated Cholesterols

Registry no.	Compd	Label	Isotope composition, %	M^+	$M^+ - CH_3$	$M^+ - H_2O$	$M^+ - CH_3 - H_2O$	$M^+ - C_5H_9O$	$M^+ - C_7H_{11}O$	$M^+ - C_8H_{17}$	$M^+ - C_8H_{17} - H_2O$	$M^+ - C_9H_{15}O$	$M^+ - C_{11}H_{23}$	$M^+ - C_{11}H_{23} - H_2O$
57-88-5	1a	Cholesterol		386	371	368	353	301	275	273	255	247	231	213
7604-91-3	11a	2,2,4,4-d_4	3 d_0	390	375	372	357	301	275	277	259	247	235	217
			3 d_1											
			8 d_2											
			29 d_3											
			54 d_4											
			3 d_5											
62743-62-8	2a	9α-d_1	12 d_0	387	372	368 (19%)	353 (12%)	301 (11%)	276	274	255 (14%)	247 (25%)	231 (8%)	213 (29%)
			88 d_1			369 (81%)	354 (88%)	302 (89%)			256 (86%)	248 (75%)	232 (92%)	214 (71%)
62743-63-9	3a	11,11-d_2	4 d_1	388	372	370	355	303	277	275	257	248 (5%)	232 (3%)	215
			96 d_2									249 (95%)	233 (97%)	
62743-64-0	4a	12,12-d_2	28 d_1	388	373	370	355	303	277	275	257	248 (5%)	232 (2%)	214 (1%)
			72 d_2									249 (95%)	233 (98%)	215 (99%)
62743-65-1	9a	14α-d_1	4 d_0	387	372	369	354	301 (22%)	276	274	256	247 (26%)	231 (37%)	213 (26%)
			96 d_1					302 (78%)				248 (74%)	232 (63%)	214 (74%)
62743-66-2	5a	19-d_1	9 d_0	387	371 (67%)	369	353 (77%)	302	276	274	256	247	231 (17%)	213 (28%)
			91 d_1		372 (33%)		354 (23%)						232 (83%)	214 (72%)

[a] The shift values have been corrected for ^{13}C contributions and effects due to isotopic composition. The spectra were measured at 70 eV.

gion) is *m/e* 368 ($M^+ - 60$); therefore, any rationalization of this cleavage would also necessarily include migration of the C-19 angular methyl group to the expelled portion of the molecule. Because of these requirements any mechanistic rationalization of d_2 becomes unfavorably long and complex.

Absolute differentiation between d_1 and d_2 would require ^{13}C labeling. However, since d_1 can be rationalized most believably using standard techniques, it would seem to be the most favorable possibility. The formal vinylic cleavage and additional loss of both protons from C-7 required in d_1 necessitate a mechanism which would include isomerization of the double bond and several successive proton shifts; because of the complex nature of these processes, any rationalization should be considered highly speculative.

In contrast to the multiple progenitor ions reported by Budzikiewicz and Ockels[4] in their discussion of the peak analogous to *m/e* 247 in the study of Δ^5-androstenols, metastable defocusing work done in this study (Table III) on cholesterol acetate shows that the expected parent *m/e* 368 ($M^+ - 60$) is virtually the only source of this peak. It is notable that since the model compounds used by Budzikiewicz and Ockels[4] possessed no side chain, the corresponding fragment was of significantly lower mass and therefore appeared in a portion of the mass spectrum which is much more likely to contain fragments from a multitude of different pathways.

The deuterium labeling data in Table I show that the fragment at mass 247 in cholesterol acetate has the schematic structure shown in (a), the same as established by Wyllie et al.[5] for the free sterol. The transferred deuterium originates at C-8 (47%) and C-14 (26%) with some transfer from C-9 (9%). Wyllie et al.[5] established that in cholesterol major portions (55%) of the transferred hydrogen originate at C-8. Using a Δ^5-cholen-3β-ol model compound labeled at C-9 they reported that transfer from this position appeared to be of equal importance. However, neither of the previous studies[4,5] included sterols labeled at C-14, and our work (Table II) indicates that in cholesterol transfer from C-9 and C-14 are of approximately equal importance (25 and 26%, respectively). A mechanism which would provide a route to the desired fragment is shown in Scheme II (b → e → f) for the ionized diene species b presumed to be the major constituent of *m/e* 368 in cholesterol acetate. This mechanism allows access by the C-7 carbonium to positions 8 and 9 as well as 14 as does the mechanism proposed by Wyllie et al.[5] for the free sterol, and either of these

Scheme II

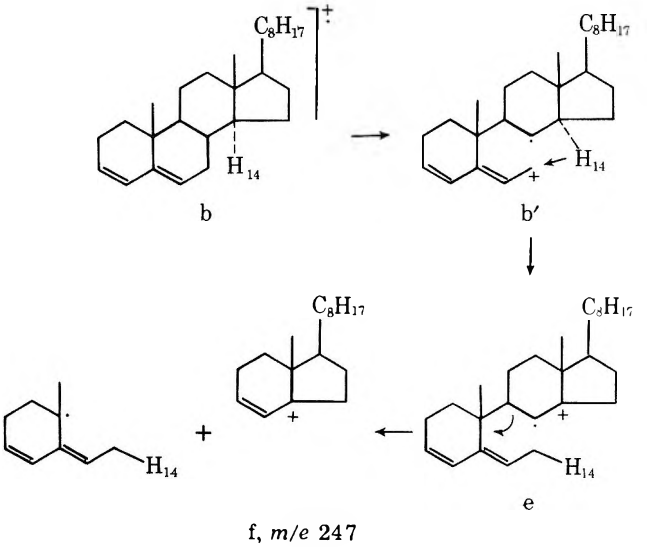


Table III. Cholesterol Acetate Metastable Defocusing[a] Data

Daughter ion	Parent ion	% area
260	368 (M^+ − AcOH)	100
247	368	>95
	354	<5
246	368	>95
	261	<5
213	368	35
	353	<5
	326	<5
	255	<5
	228	55
121	368	30
	247	20
	206	20
	191	<5
	177	10
	163	5
	149	5
	136	5
120	368	50
	260	10
	228	5
	214	5
	202	5
	176	<5
	162	5
	148	5
	135	5
119	368	5
	353	10
	255	5
	215	5
	201	5
	187	<5
	175	5
	161	15
	147	25
	134	20

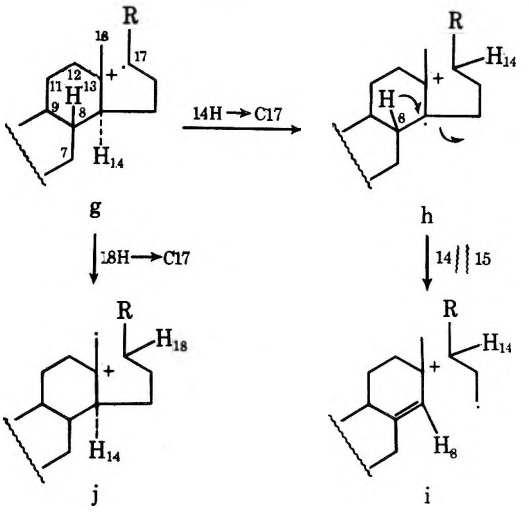
[a] Values are given in terms of relative percent area of the parent peak in the defocused spectrum and are accurate to ±5%. Measurements were made on an AEI MS-9 double focusing mass spectrometer.

Table IV. Deuterium Transfer (%)[a] in the Ring D Cleavage of Labeled Cholesterols and Cholesterol Acetates

	Labeled position						Total,
	14	12	11	9	8	7	%
			Cholesterols				
m/e 231	45	2	4	10	20[b]	8[b]	89
m/e 213	36	1	0	40	7	14	98
			Cholesterol acetates				
m/e 213	27	0	0	27	12	29	95

[a] These values have been corrected for ^{13}C contributions, isotopic composition, and the presence of fragments originating from other cleavage patterns involving loss of C-19 as described in the text. [b] Data from ref 13.

Scheme III



rationalizations is equally valid for cholesterol or the acetate.

The ion of mass 213 in cholesterol acetate can be seen to occur via the usual ring D cleavage involving loss of carbon atoms 15, 16, and 17 together with their substituents and one additional hydrogen atom.[1,10] The proton transferred to this fragment originates (Table IV) from positions 7, 9, and 14 (29, 27, and 27%, respectively) in approximately equal amounts with some transfer also from C-8 (12%). These values have been corrected for the existence of an unrelated fragment at *m/e* 213 which is the product of loss of carbons 16 and 17 and their substituents followed by expulsion of C-19 (Tables I and III) as described previously for the unsaturated steroids and steroidal olefins.[1,10]

In cholesterol the ring D fragmentation with or without loss of the 3β substituent occurs with hydrogen transfer originating much more specifically from C-14 (45% in the formation of *m/e* 231 and 36% in 213), the second largest site of transferred hydrogen being C-8 in the formation of *m/e* 231 (20%) with most of the remaining transfer from carbon atoms 7 and 9. The ion of mass 213 shows considerably more transfer from C-9 (40%) although some of this [19% in the case of *m/e* 368 (M^+ − 18), Table II] is due to loss of the label at C-9 in the expulsion of the 3β-hydroxyl substituent. The fragmentation pathway (g → h → i) would be expected to be exactly analogous to the one proposed for the corresponding cleavage in saturated steroids[10] and steroidal olefins[1] and is discussed in greater detail in those papers. In the Δ^5-steroids as established for the other steroidal olefins,[1] abstraction from C-18 to form a primary radical j is expected to be much less favorable than in the saturated steroids[10] due to the availability of allylically activated C-7 protons.

The labeling data presented in Table V indicate that the *m/e* 120 peak of cholesterol and cholesterol acetate is shifted by the presence of deuterium on carbons 1–7 and on C-19, supporting the proposal of Galli and Maroni[9] that some or all of this peak is due to a retro-Diels–Alder type fragmentation of the presumed $\Delta^{3,5}$-dienyl system resulting from the loss of the 3β substituent (Scheme I). The fragment represented by structure c is then probably a major contributor to *m/e* 120; however, Table V also shows that the peaks at *m/e* 119 and 121 are not shifted cleanly by the deuterium labels and are therefore the result of multiple fragmentation pathways. This is as expected since these peaks are visible in the mass spectra of a wide variety of steroids; their presence makes the exact total composition of *m/e* 120 difficult to elucidate and virtually eliminates the diagnostic utility of the *m/e* 120 peak. The metastable defocusing data of Table III show that in the first field-free region the largest portion of the peak at *m/e* 120 originates directly from *m/e* 368 as would be expected for the RDA fragment c. Both *m/e* 119 and 121 show three major progenitor ions and numerous minor ones supporting the idea that these peaks are composed of a variety of fragments.

In summary, due to the facile 1,2-elimination of acetic acid, the mass spectrum of cholesterol acetate exhibits no molecular ion and the most characteristic peaks in the spectrum, *m/e* 260

Table V. Mass Spectral Peaks[a] of Labeled Cholesterols and Cholesterol Acetates in the Region of *m/e* 120

Labeled position	Peak 117	118	119	120	121	122	123	124	125
				Cholesterols					
(d_0)	39	23	100	87	97	23	45	26	32
9(d_1)	26	20	74	100	67	50	41	37	21
11(d_2)	18	16	51	100	95	48	64	40	47
12(d_2)	33	29	82	100	45	40	53	36	41
14(d_1)	38	39	80	100	65	41	27	31	26
19(d_1)	25	17	57	60	100	58	32	15	27
				Cholesterol Acetates					
(d_0)	39	23	80	90	100	28	40	0	0
1(d_1)	31	20	54	31	100	50	45	13	0
2,2,4,4(d_4)[b]	19	18	53	19	71	21	100	39	16
3(d_1)	31	29	65	49	100	45	27	2	0
7(d_2)	25	33	89	66	100	85	25	19	1
8(d_1)	39	36	60	100	55	57	28	15	8
9(d_1)	29	35	54	100	86	49	32	25	0
11(d_2)	19	17	45	100	85	28	43	14	26
12(d_2)	29	26	55	100	71	30	34	21	23
14(d_1)	31	28	58	100	66	28	22	18	0
19(d_1)	22	13	44	48	100	64	30	10	0
26,27(d_6)	41	23	82	100	98	25	47	0	0

[a] See footnote *a*, Table I. [b] After loss of AcOD, this compound is labeled with three remaining deuterium atoms.

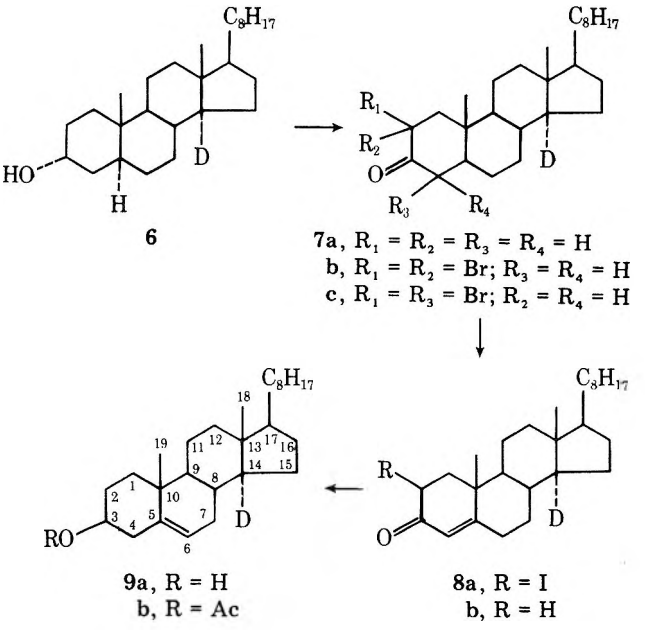
($M^+ - 168$) and 247 ($M^+ - 181$), appear to originate from *m/e* 368 ($M^+ - 60$). Elimination of the 3β substituent in the free sterol proceeds through an entirely different route[5] and the major peaks in its spectrum, *m/e* 301 ($M^+ - 85$) and 275 ($M^+ - 111$), are absent from that of the acetate. These characteristic peaks are of great diagnostic utility and the mechanistic origins of them have proven extraordinarily complicated and virtually unprecedented. This affords another example of the importance of deuterium labeling in unraveling fragmentation mechanisms.

Synthesis

The benzoate esters of cholesterol (**1a**) labeled at carbon atoms 9, 11, 12, and 19 were intermediates in the recently reported[1] synthesis of the correspondingly labeled Δ^7-cholestenes, and hydrolysis provided cholesterol-*9α-d*$_1$ (**2a**), cholesterol-*11,11-d*$_2$ (**3a**), cholesterol-*12,12-d*$_2$ (**4a**), and cholesterol-*19-d*$_1$ (**5a**). Cholesterol-*14α-d*$_1$ (**9a**) was accessible through the known cholestan-3α-ol-*14α-d*$_1$ (**6**)[1] which was oxidized to the ketone (**7a**) and converted to cholest-4-en-3-one-*14α-d*$_1$ (**8b**) (Scheme IV) by successive dibromination[11] to **7b**, rearrangement to **7c**, sodium iodide treatment to **8a**, and chromous chloride reduction.[12] Conversion of the Δ^4-3-ketone **8b** to cholesterol-*14α-d*$_1$ (**9a**) was effected by the method of Dauben and Eastham.[13] The syntheses of the remaining compounds [cholesterol-*1β-d*$_1$ (**10a**),[5] cholesterol-*2,2,4,4-d*$_4$ (**11a**),[14] cholesterol-*3α-d*$_1$ (**12a**),[5] cholesterol-*7,7-d*$_2$ (**13a**),[15] cholesterol-*8β-d*$_1$ (**14a**),[5] and cholesterol-*26,26,-26,27,27,27-d*$_6$ (**15a**)][5] have been reported in the literature and their respective acetates **1b, 2b, 3b, 4b, 9b, 10b, 11b, 12b, 13b, 14b,** and **15b** were available by acetic anhydride treatment.

Cholest-4-en-3-one-*14α-d*$_1$ (8b). Cholestan-3α-ol-*14α-d*$_1$[1] (**6**, 400 mg) was oxidized in acetone (40 mL) using an excess of Jones reagent. Extraction into ether and evaporation of the combined extracts provided cholestan-3-one-*14α-d*$_1$ (**7a**), mp 127–129 °C (lit.[11] 128–130 °C), which was converted to **8b** in the same way as described for the unlabeled compound.[11] Successive dibromination, rearrangement in acetic acid, and dehydrobromination with sodium iodide followed by chromous chloride reduction[12] gave **8b** contaminated with some starting material **7a** which was removed by chromatography on silica. Elution with 30% ether/hexane gave 230 mg of **8b**: mp 82–83.5 °C (lit.[11] 79–81 °C); δ 5.59 (s, 1 H, vinyl), 1.19 (s, 3 H, C-19 calcd[16] 1.19), 0.72 (s, 3 H, C-18 calcd. 0.72); M^+ *m/e* 385.

Scheme IV



Cholesterol-*14α-d*$_1$ (9a). Cholest-4-en-3-one-*14α-d*$_1$ (**8b**, 48 mg) was stirred at room temperature under N_2 in 10 mL of dry dimethylformamide until dissolved. Potassium *tert*-butoxide (90 mg) was added and the reaction mixture was stirred under N_2 for 2 h and poured into a briskly stirred solution of 500 mg of $NaBH_4$ in 20 mL of 10% aqueous methanol.[13] The mixture was stirred for another 15 min, then extracted into ether, evaporated, and recrystallized from methanol to produce pure cholesterol-*14α-d*$_1$ (**9a**): 27 mg; mp 145 °C (lit.[1] 145 °C); NMR identical with that of unlabeled material; M^+ *m/e* 387.

Acknowledgment. We wish to thank Dr. L. Tökés of Syntex Research for his generous donation of the labeled cholesterols **10a, 12a, 14a,** and **15a** and for a preprint of ref 5

as well as Professor K. H. Overton of the University of Glasgow for the generous donation of 13a. We are also grateful to Dr. M. Ratcliff of Zoecon Corp. for running several spectra on a Hewlett-Packard 5984A GC/MS system.

Registry No.—6, 62777-57-5; 7a, 62743-67-3; 8b, 62743-68-4.

References and Notes

(1) For part 248 see L. Partridge, I. Midgley, and C. Djerassi, *J. Am. Chem. Soc.*, in press.
(2) Taken in part from the Ph.D. Dissertation of L. G. Partridge, 1977.
(3) We are grateful to the National Institutes of Health for financial support (Grants AM 04257 and GM 06840) of this work.
(4) H. Budzikiewicz and W. Ockels, *Tetrahedron*, **32**, 143 (1976).
(5) S. Wyllie, B. Amos, and L. Tökés, *J. Org. Chem.*, **42**, 725 (1977).
(6) (a) Z. V. Zaretskii, "Mass Spectrometry of Steroids", Wiley, New York, N.Y., 1976, p 106; (b) *ibid.*, p 103.
(7) S. S. Friedland, G. H. Lane, Jr., R. T. Longman, K. E. Train, and M. J. O'Neal, Jr., *Anal. Chem.*, **31**, 169 (1959).
(8) B. A. Knights, *J. Gas Chromatogr.*, **5**, 273 (1967).
(9) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).
(10) L. Tökés, G. Jones, and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 5466 (1968).
(11) (a) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); (b) E. S. Rothman and M. E. Wall, *ibid.*, **78**, 1744 (1956).
(12) G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).
(13) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, **73**, 4463 (1951).
(14) J. Diekman and C. Djerassi, *J. Org. Chem.*, **32**, 1005 (1967).
(15) I. M. Cunningham and K. H. Overton, *J. Chem. Soc., Perkin Trans. 1*, 2458 (1974).
(16) (a) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964.

Reactions of New Organocuprates. 2.[1] Substitution Reactions of Alkyl, Cycloalkyl, and Aryl Halides with $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$

Eugene C. Ashby* and J. J. Lin

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received February 18, 1977

The new cuprates $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$ in Et_2O and THF have been compared to $LiCu(CH_3)_2$ and CH_3Li in their reaction toward alkyl, cycloalkyl, and aryl halides (where halogen = I, Br, Cl, F). In most cases the new cuprate $Li_2Cu(CH_3)_3$ was superior to all other reagents and in some cases the superiority was substantial.

We have recently obtained evidence for the existence of the new organocuprate species, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O.[2] We have also reported the reactions of these new organocuprates with enones in order to compare their regioselectivity and reaction rate with $LiCu(CH_3)_2$.[1] Owing to the current interest in substitution reactions using organocopper reagents,[3] we have now evaluated these new cuprates in their reaction with alkyl, cycloalkyl, and aryl halides and have noted some interesting and important observations.

Results and Discussion

The organic halides were allowed to react with the new organocuprates and $LiCu(CH_3)_2$ in THF and Et_2O in order to compare the reactivity of the new cuprates and the yields of the reactions. Since $Li_2Cu(CH_3)_3$ is in equilibrium with $LiCu(CH_3)_2$ and CH_3Li, the reaction of CH_3Li in each case is also compared. Each reaction was carried out using excess reagent (10:1 molar ratio of active methyl:halide), room temperature, and two solvents (THF and Et_2O). Since $LiCu_2(CH_3)_3$ is insoluble in Et_2O and $Li_2Cu_3(CH_3)_5$ is insoluble in THF, studies of these cuprates were not involved in these particular solvents. The results of these reactions are shown in Table I.

In the reactions of 1-iododecane (expt 1–7), each organocuprate reagent reacted similarly to produce the substitution product, *n*-undecane, in high yield. The earlier reaction time (10 min) indicated that $Li_2Cu(CH_3)_3$ in THF reacted more rapidly than any other reagent. The metal–halogen exchange to form 50% *n*-decane in the reaction of CH_3Li with 1-iododecane suggests that in reactions involving $Li_2Cu(CH_3)_3$, the reactive species is $Li_2Cu(CH_3)_3$ and not one of its equilibrium components (e.g., CH_3Li). Our previous studies have shown that $Li_2Cu(CH_3)_3$ forms an equilibrium mixture in THF and Et_2O as described by eq 1.

$$Li_2Cu(CH_3)_3 \rightleftharpoons CH_3Li + LiCu(CH_3)_2 \quad (1)$$

Methyllithium as well as the cuprates also reacted with 1-bromodecane to form undecane. The yields in THF were quantitative after just 1 h reaction time (expt 8–14), although the yields were considerably lower (42–61%) in ether solvent. The reactione of1-chlorodecane (expt 15–21) illustrate the superiority of $Li_2Cu(CH_3)_3$ over $LiCu(CH_3)_2$ or $LiCu_2(CH_3)_3$ in THF or Et_2O in the substitution of chlorine for methyl. A quantitative yield was obtained with $Li_2Cu(CH_3)_3$, whereas with $LiCu(CH_3)_2$ in THF only 22% yield was observed and in the case of CH_3Li in THF, no reaction at all was observed under the same conditions. Although yields are low in all other cases studied involving reaction of the new cuprates and CH_3Li with 1-fluorodecane, a quantitative yield of *n*-undecane was observed when $Li_2Cu(CH_3)_3$ in ether was the reagent. It is interesting to note that whereas $Li_2Cu(CH_3)_3$ in THF is a superior reagent for chlorine displacement, the same reagent in Et_2O is superior for fluorine displacement (expt 22–28).

The reactions of 6-bromo-1-hexene and 6-chloro-1-hexene behaved similarly to 1-bromodecane and 1-chlorodecane (expt 29–40). In general, THF solvent is more suitable than Et_2O for organocuprate substitution reactions of alkyl iodides, bromides, and chlorides and the relative reactivity of the cuprates is $Li_2Cu(CH_3)_3 > LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$, although $Li_2Cu(CH_3)_3$ in Et_2O was superior to THF in its reaction with 1-fluorodecane (expt 26, 96%). Although CH_3Li also produced good yields of substitution products with the iodides and bromides, no reaction took place between CH_3Li and the chlorides and fluorides. In most cases the yield of substitution products is better using the new cu-

Table I. Substitution Reactions of Halides with $LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$, $Li_2Cu_3(CH_3)_5$, and CH_3Li at Room Temperature

Expt	Cuprate reagent	Halide substrate	Reaction time and solvent	Product(s) (yield(s), %)
1	$LiCu(CH_3)_2$	1-Iododecane	10 min, THF	*n*-Undecane (57)
			1 h, THF	*n*-Undecane (100)
2	$LiCu_2(CH_3)_3$	1-Iododecane	10 min, THF	*n*-Undecane (65)
			1 h, THF	*n*-Undecane (104)
3	$Li_2Cu(CH_3)_3$	1-Iododecane	10 min, THF	*n*-Undecane (92)
			1 h, THF	*n*-Undecane (98)
4	$LiCu(CH_3)_2$	1-Iododecane	1 h, Et_2O	*n*-Undecane (106)
5	$Li_2Cu(CH_3)_3$	1-Iododecane	1 h, Et_2O	*n*-Undecane (76)
			3 h, Et_2O	*n*-Undecane (101)
6	$Li_2Cu_3(CH_3)_5$	1-Iododecane	1 h, Et_2O	*n*-Undecane (59)
7	CH_3Li	1-Iododecane	1 h, Et_2O	*n*-Undecane (30)
				n-Decane (50)
8	$LiCu(CH_3)_2$	1-Bromodecane	1 h, THF	*n*-Undecane (98)
9	$LiCu_2(CH_3)_3$	1-Bromodecane	1 h, THF	*n*-Undecane (96)
10	$Li_2Cu(CH_3)_3$	1-Bromodecane	1 h, THF	*n*-Undecane (96)
11	$LiCu(CH_3)_2$	1-Bromodecane	1 h, Et_2O	*n*-Undecane (42)
12	$Li_2Cu(CH_3)_3$	1-Bromodecane	1 h, Et_2O	*n*-Undecane (44)
13	$Li_2Cu_3(CH_3)_5$	1-Bromodecane	1 h, Et_2O	*n*-Undecane (61)
14	CH_3Li	1-Bromodecane	1 h, Et_2O	*n*-Undecane (95)
15	$LiCu(CH_3)_2$	1-Chlorodecane	12 h, THF	*n*-Undecane (22)
16	$LiCu_2(CH_3)_3$	1-Chlorodecane	12 h, THF	*n*-Undecane (60)
17	$Li_2Cu(CH_3)_3$	1-Chlorodecane	12 h, THF	*n*-Undecane (102)
18	$LiCu(CH_3)_2$	1-Chlorodecane	12 h, Et_2O	*n*-Undecane (14)
19	$Li_2Cu(CH_3)_3$	1-Chlorodecane	12 h, Et_2O	*n*-Undecane (37)
20	$Li_2Cu_3(CH_3)_5$	1-Chlorodecane	12 h, Et_2O	*n*-Undecane (30)
21	CH_3Li	1-Chlorodecane	12 h, Et_2O	*n*-Undecane (0)
22	$LiCu(CH_3)_2$	1-Fluorodecane	48 h, THF	*n*-Undecane (2)
23	$LiCu_2(CH_3)_3$	1-Fluorodecane	48 h, THF	*n*-Undecane (2)
24	$Li_2Cu(CH_3)_3$	1-Fluorodecane	48 h, THF	*n*-Undecane (8)
25	$LiCu(CH_3)_2$	1-Fluorodecane	24 h, Et_2O	*n*-Undecane (24)
26	$Li_2Cu(CH_3)_3$	1-Fluorodecane	24 h, Et_2O	*n*-Undecane (96)
27	$Li_2Cu_3(CH_3)_5$	1-Fluorodecane	24 h, Et_2O	*n*-Undecane (13)
28	CH_3Li	1-Fluorodecane	24 h, Et_2O	*n*-Undecane (0)
29	$LiCu(CH_3)_2$	6-Bromohexene	1 h, THF	1-Heptene (95)
30	$LiCu_2(CH_3)_3$	6-Bromohexene	1 h, THF	1-Heptene (105)
31	$Li_2Cu(CH_3)_3$	6-Bromohexene	1 h, THF	1-Heptene (108)
32	$LiCu(CH_3)_2$	6-Bromohexene	3 h, Et_2O	1-Heptene (88)
33	$Li_2Cu(CH_3)_3$	6-Bromohexene	3 h, Et_2O	1-Heptene (86)
34	CH_3Li	6-Bromohexene	1 h, THF	1-Heptene (93)
35	$LiCu(CH_3)_2$	6-Chloro-1-hexene	24 h, THF	1-Heptene (84)
36	$LiCu_2(CH_3)_3$	6-Chloro-1-hexene	24 h, THF	1-Heptene (75)
37	$Li_2Cu(CH_3)_3$	6-Chloro-1-hexene	24 h, THF	1-Heptene (95)
38	$LiCu(CH_3)_2$	6-Chloro-1-hexene	24 h, Et_2O	1-Heptene (68)
39	$Li_2Cu(CH_3)_3$	6-Chloro-1-hexene	24 h, Et_2O	1-Heptene (92)
40	CH_3Li	6-Chloro-1-hexene	24 h, Et_2O	1-Heptene (0)
41	$LiCu(CH_3)_2$	Iodocyclohexane	48 h, THF	Methylcyclohexane (21), cyclohexane (14)
42	$LiCu_2(CH_3)_3$	Iodocyclohexane	48 h, THF	Methylcyclohexane (5), cyclohexane (15)
43	$Li_2Cu(CH_3)_3$	Iodocyclohexane	48 h, THF	Methylcyclohexane (93), cyclohexane (5)
44	$LiCu(CH_3)_2$	Iodocyclohexane	48 h, Et_2O	Methylcyclohexane (68), cyclohexane (20)
45	$Li_2Cu(CH_3)_3$	Iodocyclohexane	48 h, Et_2O	Methylcyclohexane (53), cyclohexane (32)
46	CH_3Li	Iodocyclohexane	5 h, Et_2O	Methylcyclohexane (0), cyclohexane (97)
47	CH_3Li	Iodocyclohexane	48 h, THF	Methylcyclohexane (26), cyclohexane (10)
48	$LiCu(CH_3)_2$	Bromocyclohexane	48 h, THF	Methylcyclohexane (0), cyclohexane (0)
49	$LiCu_2(CH_3)_3$	Bromocyclohexane	48 h, THF	Methylcyclohexane (3), cyclohexane (0)
50	$Li_2Cu(CH_3)_3$	Bromocyclohexane	48 h, THF	Methylcyclohexane (3), cyclohexane (0)
51	$LiCu(CH_3)_2$	Bromocyclohexane	48 h, Et_2O	Methylcyclohexane (12), cyclohexane (0)
52	$Li_2Cu(CH_3)_3$	Bromocyclohexane	48 h, Et_2O	Methylcyclohexane (12), cyclohexane (4)
53	CH_3Li	Bromocyclohexane	48 h, Et_2O	Methylcyclohexane (0), cyclohexane (27)
54	$LiCu(CH_3)_2$	Chlorocyclohexane	48 h, THF	Methylcyclohexane (0), cyclohexane (0)
55	$LiCu_2(CH_3)_3$	Chlorocyclohexane	48 h, THF	Methylcyclohexane (0), cyclohexane (0)
56	$Li_2Cu(CH_3)_3$	Chlorocyclohexane	48 h, THF	Methylcyclohexane (0), cyclohexane (0)
57	$LiCu(CH_3)_2$	Chlorocyclohexane	48 h, Et_2O	Methylcyclohexane (0), cyclohexane (0)
58	$Li_2Cu(CH_3)_3$	Chlorocyclohexane	48 h, Et_2O	Methylcyclohexane (0), cyclohexane (0)
59	$LiCu(CH_3)_2$	Iodobenzene	14 h, THF	Toluene (91)
60	$LiCu_2(CH_3)_3$	Iodobenzene	14 h, THF	Toluene (91)
61	$Li_2Cu(CH_3)_3$	Iodobenzene	14 h, THF	Toluene (96)
62	$LiCu(CH_3)_2$	Iodobenzene	14 h, Et_2O	Toluene (82)
63	$Li_2Cu(CH_3)_3$	Iodobenzene	14 h, Et_2O	Toluene (92)
64	CH_3Li	Iodobenzene	14 h, Et_2O	Toluene (95)
65	$LiCu(CH_3)_2$	Bromobenzene	24 h, THF	Toluene (45)

Table I (Continued)

Expt	Cuprate reagent	Halide substrate	Reaction time and solvent	Products(s) (yield(s), %)
66	$LiCu_2(CH_3)_3$	Bromobenzene	24 h, THF	Toluene (0)
67	$Li_2Cu(CH_3)_3$	Bromobenzene	24 h, THF	Toluene (102)
68	$LiCu(CH_3)_2$	Bromobenzene	24 h, Et_2O	Toluene (59)
69	$Li_2Cu(CH_3)_3$	Bromobenzene	24 h, Et_2O	Toluene (61)
70	CH_3Li	Bromobenzene	24 h, Et_2O	Toluene (115)
71	$LiCu(CH_3)_2$	Chlorobenzene	24 h, THF	Toluene (65)
72	$LiCu_2(CH_3)_3$	Chlorobenzene	24 h, THF	Toluene (0)
73	$Li_2Cu(CH_3)_3$	Chlorobenzene	24 h, THF	Toluene (42)
74	$LiCu(CH_3)_2$	Chlorobenzene	24 h, Et_2O	Toluene (0)
75	$Li_2Cu(CH_3)_3$	Chlorobenzene	24 h, Et_2O	Toluene (47)
76	CH_3Li	Chlorobenzene	24 h, Et_2O	Toluene (33)
77	$LiCu(CH_3)_2$	Fluorobenzene	24 h, THF	Toluene (24)
78	$LiCu_2(CH_3)_3$	Fluorobenzene	24 h, THF	Toluene (0)
79	$Li_2Cu(CH_3)_3$	Fluorobenzene	24 h, THF	Toluene (49)
80	$LiCu(CH_3)_2$	Fluorobenzene	24 h, Et_2O	Toluene (0)
81	$Li_2Cu(CH_3)_3$	Fluorobenzene	24 h, Et_2O	Toluene (50)
82	CH_3Li	Fluorobenzene	24 h, THF	Toluene (21)
83	$LiCu(CH_3)_2$	*p*-Chloroanisole	48 h, THF	*p*-Methylanisole (0)
84	$LiCu_2(CH_3)_5$	*p*-Chloroanisole	48 h, THF	*p*-Methylanisole (0)
85	$Li_2Cu(CH_3)_3$	*p*-Chloroanisole	48 h, THF	*p*-Methylanisole (0)
86	$LiCu(CH_3)_2$	*p*-Chloroanisole	48 h, Et_2O	*p*-Methylanisole (0)
87	$Li_2Cu(CH_3)_3$	*p*-Chloroanisole	48 h, Et_2O	*p*-Methylanisole (21)
88	CH_3Li	*p*-Chloroanisole	48 h, Et_2O	*p*-Methylanisole (11) Anisole (8)
89	$LiCu(CH_3)_2$	*p*-Fluoroanisole	48 h, THF	*p*-Methylanisole (0)
90	$LiCu_2(CH_3)_2$	*p*-Fluoroanisole	48 h, THF	*p*-Methylanisole (0)
91	$Li_2Cu(CH_3)_3$	*p*-Fluoroanisole	48 h, THF	*p*-Methylanisole (83)
92	$LiCu(CH_3)_2$	*p*-Fluoroanisole	48 h, Et_2O	*p*-Methylanisole (3)
93	$Li_2Cu(CH_3)_3$	*p*-Fluoroanisole	48 h, Et_2O	*p*-Methylanisole (101)
94	CH_3Li	*p*-Fluoroanisole	48 h, Et_2O	*p*-Methylanisole (82)
95	$LiCu(CH_3)_2$	1-Chlorocyclohexene	48 h, THF	1-Methylcyclohexene (0)
96	$LiCu_2(CH_3)_3$	1-Chlorocyclohexene	48 h, THF	1-Methylcyclohexene (0)
97	$Li_2Cu(CH_3)_3$	1-Chlorocyclohexene	48 h, THF	1-Methylcyclohexene (0)
98	$LiCu(CH_3)_2$	1-Chlorocyclohexene	48 h, Et_2O	1-Methylcyclohexene (0)
99	$Li_2Cu(CH_3)_3$	1-Chlorocyclohexene	48 h, Et_2O	1-Methylcyclohexene (71)
100	CH_3Li	1-Chlorocyclohexene	48 h, Et_2O	1-Methylcyclohexene (0)
101	$LiCu(CH_3)_2$	3-Chlorocyclohexene	48 h, THF	3-Methylcyclohexene (57)
102	$LiCu_2(CH_3)_3$	3-Chlorocyclohexene	48 h, THF	3-Methylcyclohexene (33)
103	$Li_2Cu(CH_3)_3$	3-Chlorocyclohexene	48 h, THF	3-Methylcyclohexene (83)
104	$LiCu(CH_3)_2$	3-Chlorocyclohexene	48 h, Et_2O	3-Methylcyclohexene (58)
105	$Li_2Cu(CH_3)_3$	3-Chlorocyclohexene	48 h, Et_2O	3-Methylcyclohexene (62)
106	CH_3Li	3-Chlorocyclohexene	48 h, Et_2O	3-Methylcyclohexene (8)

prate $Li_2Cu(CH_3)_3$ than $LiCu(CH_3)_2$ and in many cases the difference in yield is substantial.

The reactions of iodocyclohexane (expt 41–47) are much slower than the reactions observed earlier with the primary alkyl iodides and in addition considerable metal–halogen interchange is observed. Once again the best substitution reaction was achieved in the reaction of iodocyclohexane with $Li_2Cu(CH_3)_3$ in THF (93% yield with 5% cyclohexane by-product). Reaction of iodocyclohexane with other cuprates and CH_3Li produced substantial amounts of the metal–halogen interchange product, cyclohexane. Under the best conditions, bromocyclohexane (expt 48–53) gave only 12% yield in its reaction with $Li_2Cu(CH_3)_3$ whereas chlorocyclohexane (expt 54–58) showed no reaction with any of the reagents after 48 h. The halogen reactivity decreased in the order I > Br > Cl which is the same trend observed for primary halides.

Experiments 59–82 describe the results of the reactions of various cuprates with the halogenobenzenes in ether and THF. The substitution reactions of iodobenzene can be effected in good yields by each organocuprate studied or methyllithium itself. In the case of bromobenzene, both CH_3Li in ether and $Li_2Cu(CH_3)_3$ in THF caused quantitative substitution whereas the other cuprates were much less effective. The results involving chlorobenzene and fluorobenzene show moderate yields when $LiCu(CH_3)_2$, $Li_2Cu(CH_3)_3$ in THF, and $Li_2Cu(CH_3)_3$ in Et_2O are allowed to react. In each case CH_3Li gives significantly lower yields. Although it was not possible to determine the relative rate of reaction between $Li_2Cu(CH_3)_3$ and $LiCu(CH_3)_2$ in order to see if CH_3Li affects the substitution reaction as well as $LiCu(CH_3)_2$, the reactions of fluorobenzene, *p*-chloroanisole, and *p*-fluoroanisole (expt 83–94) show that $Li_2Cu(CH_3)_3$ is more reactive than $LiCu(CH_3)_2$ in THF or Et_2O in aryl halide substitution reactions. It is interesting that in the case of *p*-chloroanisole only $Li_2Cu(CH_3)_3$ and CH_3Li in ether produced any product at all and that was in very modest yield whereas *p*-fluoroanisole, when allowed to react with $Li_2Cu(CH_3)_3$ in ether, formed *p*-methylanisole in quantitative yield.

It is important to note that $Li_2Cu(CH_3)_3$ in Et_2O reacted with 1-chlorocyclohexene to yield 71% 1-methylcyclohexene whereas all other reagents had no effect on this alkenyl halide (expt 95–100). When the chlorine atom was placed in the allylic position (3-chlorocyclohexene) $Li_2Cu(CH_3)_3$ in THF had a significantly higher reactivity than the other cuprates (expt 101–106).

In conclusion, it has been shown that, in general, $Li_2Cu(CH_3)_3$ exhibits a higher reactivity than other cuprates in halide substitution reactions involving alkyl, cycloalkyl, and aryl halides. Also, $LiCu_2(CH_3)_3$ in THF and $Li_2Cu_3(CH_3)_5$ in Et_2O were considerably less effective than $LiCu(CH_3)_2$ or $Li_2Cu(CH_3)_3$ in the same reactions in most cases. Most often THF was the superior solvent, although in some cases ether was decidedly better. The superiority of $Li_2Cu(CH_3)_3$ over $LiCu(CH_3)_3$ and the other cuprates in most cases reported here indicates a potential for this reagent in other reactions not heretofore explored.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[4] Other manipulations were carried out in a glove box equipped with a recirculating system using manganese oxide columns to remove oxygen and dry ice–acetone to remove solents vapors.[5-7] ^1H NMR spectra were obtained at 60 MHz using a Varian A-60 NMR spectrometer.

Analytical. Active CH_3 group analysis was carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the evolved methane with a Toepler pump.[5] Lithium was determined by flame photometry. Iodide was determined by the Volhard procedure. Copper was determined by electrolytic deposition on a Pt electrode.

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 precipitation from an aqueous KI–CuI solution.[6] The precipitated solid was washed with water, ethanol, and diethyl ether and then dried at room temperature under reduced pressure.

Preparation of Reagents in THF. $LiCu_2(CH_3)_3$. Cuprous iodide (1.53 g, 8.05 mmol) was weighed into a 50-mL round-bottom flask in the drybox, then the flask fitted with a rubber septum. The flask was removed from the drybox and connected by means of a needle to a nitrogen bubbler, and 15 mL of THF was added in order to slurry the solid. The slurry was cooled to −78 °C and 15.1 mL of a 0.802 M solution of CH_3Li (12.1 mmol) in THF was added to the flask. Within 5 min all of the solid had dissolved and a clear, brown solution was present. ^1H NMR at −96 °C showed the solution to contain only $LiCu_2(CH_3)_3$.[2] Analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 1.49:1.00:1.50:1.02.

$LiCu(CH_3)_2$. Cuprous iodide (1.26 g, 6.62 mmol) was allowed to react with 16.5 mL of 0.802 M CH_3Li (13.2 mmol) in THF using the same procedure as was used to prepare $LiCu_2(CH_3)_3$ (see above). All the solid dissolved within 1 min to yield a clear, light-brown solution. ^1H NMR at −96 °C showed only one signal at δ 15.7, which corresponds to $LiCu(CH_3)_2$. An analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 2.00:1.00:2.12:0.98.

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.80 g, 4.32 mmol) was allowed to react with 19.0 mL of 0.802 M CH_3Li (16.9 mmol) in THF using the above procedure for making $LiCu_2(CH_3)_3$. All the solid dissolved within 1 min to yield a clear, colorless solution. ^1H NMR at −96 °C showed the presence of $Li_2Cu(CH_3)_3$ in equilibrium with $LiCu(CH_3)_2$, and CH_3Li (four signals at δ −1.40, −1.57, −1.73, and −2.08 are observed; signals at δ −1.57 and −2.08 are due to $LiCu(CH_3)_2$ and CH_3Li, respectively, while those at δ −1.40 and −1.73 are due to $Li_2Cu(CH_4)_3$). An analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 3.82:1.00:3.62:0.94.

Preparation of Reagents in Et_2O. $LiCu(CH_3)_2$. Cuprous iodide (0.53 g, 2.79 mmol) was weighed into a 50-mL round-bottom flask in the drybox, then the flask fitted with a rubber septum. The flask was removed from the drybox and connected by means of a needle to a nitrogen bubbler, and 5 mL of Et_2O was added in order to slurry the solid. The slurry was cooled to −78 °C and 4.4 mL of 1.27 M solution of CH_3Li (5.58 mmol) in Et_2O was added to the flask. All the solid dissolved immediately and a clear, colorless solution formed. ^1H NMR at −96 °C showed only $LiCu(CH_3)_2$ to be present. An analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 1.97:1.00:0.96:0.95.

$Li_2Cu_3(CH_3)_5$. Cuprous iodide (0.380 g, 2.0 mmol) was allowed to react with 3.5 mL of a 0.95 M solution of CH_3Li (3.3 mmol) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). Most of the solid dissolved immediately to give a clear, light pink solution, but a small amount of a yellow solid (methylcopper) remained. An analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 5.21:3.00:5.09:3.03. If all of the iodide is assumed to be present as LiI, then the organocopper species would have a Li:Cu:CH_3 ratio of 2.18:3.00:5.09. This indicates the presence of the complex $Li_2Cu_3(CH_3)_5$. This compound was indeed shown to be present by NMR spectroscopy.[2]

$Li_2Cu(CH_3)_3$. Cuprous iodide (0.57 g, 2.97 mmol) was allowed to react with 9.36 mL of a 1.27 M solution of CH_3Li (11.9 mmol) in Et_2O using the same procedure as was used to prepare $LiCu(CH_3)_2$ (see above). All the solid dissolved immediately and a clear, colorless solution remained. ^1H NMR at −96 °C showed $Li_2Cu(CH_3)_3$, $LiCu(CH_3)_2$, and CH_3Li to be present.[2] An analysis of the solution showed Li, Cu, CH_3, and I to be present in the ratio 3.82:1.00:3.88:1.02.

General Reactions of Halides. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen, then sealed with a rubber septum and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. The cuprate reagent (ca. 0.1–0.5 mmol) was syringed into the flask and the calculated amount of halide substrate (in THF or Et_2O solvent with internal standard, n-$C_{12}H_{26}$ for n-decyl halides, n-C_8H_{18} for 6-bromo-1-hexene, 6-chloro-1-hexene, cyclohexyl halides, 1-chlorocyclohexene, and 3-chlorocyclohexene, p-xylene for benzyl halides) added to the stirred reagent. After the designated reaction time, the reaction mixture was quenched with H_2O slowly and dried over $MgSO_4$. A 10-ft column (5% Carbowax 20M on Chromosorb W) was used to separate the product of n-decyl halides (110 °C). A 6-ft column (10% Apiezon L 60-80S) was used to separate the products of 6-bromo-1-hexene, 6-chloro-1-hexene, cyclohexyl halides, 1-chlorocyclohexene, 3-chlorocyclohexene (55 °C), and benzyl halides (105 °C). Halide substrates and authentic samples of products were purchased commercially and the percent yield reported in Table I is the absolute yield based on halide substrate.

Acknowledgment. We are indebted to the National Science Foundation for partial support of this work.

Registry No.—$LiCu(CH_3)_2$, 15681-48-8; $LiCu_2(CH_3)_3$, 61303-82-0; $Li_2Cu(CH_3)_3$, 61278-42-0; $Li_2Cu_3(CH_3)_5$, 61701-36-8; CH_3Li, 917-54-4; 1-iododecane, 2050-77-3; 1-bromodecane, 112-29-8; 1-chlorodecane, 1002-69-3; 1-fluorodecane, 334-56-5; 6-bromohexene, 2695-47-8; 6-chloro-1-hexene, 928-89-2; iodocyclohexane, 626-62-0; bromocyclohexane, 108-85-0; chlorocyclohexane, 542-18-7; iodobenzene, 591-50-4; bromobenzene, 108-86-1; chlorobenzene, 108-90-7; fluorobenzene, 462-06-6; p-chloroanisole, 623-12-1; p-fluoroanisole, 459-60-9; 1-chlorocyclohexene, 930-66-5; 3-chlorocyclohexene, 2441-97-6.

References and Notes

(1) Part 1: E. C. Ashby, J. J. Lin, and J. J. Watkins, *J. Org. Chem.*, in press.
(2) E. C. Ashby and J. J. Watkins, *J. Chem. Soc., Chem. Commun.*, 784 (1976).
(3) G. H. Posner, *Org. React.*, **22**, 253 (1975).
(4) D. F. Shriver, "The Manipulation of Air Sensitive Compounds", McGraw-Hill, New York, N.Y., 1969.
(5) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, **51**, 65 (1974).
(6) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).

Studies on Biologically Active Nucleosides and Nucleotides. 2. A Convenient One-Step Synthesis of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)pyrimidines from Pyrimidine Ribonucleosides

Kazuhiko Kondo and Ichizo Inoue*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

Received January 25, 1977

Treatment of cytidine with a number of aliphatic and aromatic carboxylic acid anhydrides in the presence of boron trifluoride etherate in refluxing acetonitrile afforded 3′,5′-diesters (**5a**) of 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine hydrotetrafluoroborate in yields of 42–79%. Carboxylic acid chlorides and carboxylic acids gave similar results when used in place of carboxylic anhydrides. Application of the reaction to uridine was attempted with acetic anhydride to afford 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)uracil in a moderate yield.

The antileukemic,[1] immunosuppressive,[2] and anti-DNA viral activities[3] of 1-(β-D-arabinofuranosyl)cytosine (araC) are well known. In attempts to find derivatives of greater activity and selectivity various modifications of the cytosine ring and the sugar moiety have been made. Among compounds recently investigated 2,2′-anhydro-1-(β-D-arabinofuranosyl)cytosine (anhydro-ara-C)[4] and its 3′,5′-di-O-acyl derivatives[5] are particularly interesting because of their high antitumor potency and resistance to cytidine deaminase.

In a previous report[6] from this laboratory, the reaction of tetraacetoxysilane with pyrimidine ribonucleosides in the presence of acid catalyst was shown to yield 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)pyrimidine nucleosides. The reaction mechanism was interpreted to involve monoacetylation of one of the vicinal hydroxyls as a result of participation by the silyl group, followed by the formation of a 2′,3′-acetoxonium ion. The 2′,3′-acetoxonium ion then reacts intramolecularly with the C_2-carbonyl oxygen to afford the 2,2′-anhydronucleoside.

From these mechanistic considerations it was envisaged that it might be possible to accelerate acetoxonium ion formation at the expense of acetylation of the remaining hydroxyl, provided a suitable catalyst was employed. If this were possible even unselective acylating reagents might be used successfully. Accordingly, we attempted the reaction of a pyrimidine ribonucleoside with various acylating reagents in the presence of a Lewis acid catalyst with the hope of developing a convenient method for the preparation of 2,2′-anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)pyrimidine nucleoside.

Reactions with Carboxylic Acid Anhydrides. A preliminary reaction was run by mixing cytidine (**1**) with acetic anhydride (3 molar equiv) and boron trifluoride etherate (3 molar equiv) as a catalyst in acetonitrile, and then heating the resulting solution gradually to reflux. The reaction could be conveniently monitored by ultraviolet (UV) spectroscopy in acidic media. As it proceeds the UV maximum of **1** at 280 nm should be changed to double maxima at approximately 231 and 263 nm, the characteristic maxima of the anhydro-ara-C chromophore.[7] The UV spectrum of the reaction mixture after 15 min heating showed a maximum at 275 nm. Examination of the crude product by NMR indicated it to be roughly a 2:1 mixture of 2′,3′,5′-tri-O-acetylcytidine[8] (**6**, R = CH_3) and 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)-cytosine hydrotetrafluoroborate (**5a**, R = CH_3). It seemed likely that the competing peracetylation predominated at the expense of 2′,3′-acetoxonium ion formation under these reaction conditions. This result reminded us of our previous observation[6] where formation of 3′,5′-di-O-acetyl anhydro-ara-C from cytidine and tetraacetoxysilane in the presence of boron trifluoride etherate was found to be very slow below 50 °C. Therefore, it was presumed that the rate of 2′,3′-acetoxonium ion formation could surpass the rate of peracetylation, if the reaction was kept at reflux throughout. Thus, the reaction was conducted by adding acetic anhydride to a boiling solution of cytidine and boron trifluoride etherate in acetonitrile. Within 5 min the reaction was essentially complete. The UV spectrum exhibited double maxima at 232 and 265 nm, indicating predominant formation of **5a** (R = CH_3). The presence of a negligible amount of 2′,3′,5′-tri-O-acetylcytidine was observed on TLC. Evaporation of the solvent followed by crystallization by trituration with ether gave crude product, which upon recrystallization from ethanol afforded pure **5a** (R = CH_3) in 67% yield. Other Lewis acids such as ferric chloride and antimony pentachloride could also be used as catalyst but were not as effective as boron trifluoride etherate. The fairly good yield and simplicity of the isolation method prompted us to extend this reaction to the preparation of homologous 3′,5′-di-O-acyl anhydro-ara-C derivatives. The reactions were performed under the same conditions, and isolation of the crude product was readily achieved by concentrating the reaction mixture, followed by crystallization of the residue from an appropriate solvent. Recrystallization of the crude product from an appropriate solvent gave **5a** in yields of 42–79%. In general the lower acyl derivatives could be readily isolated in pure form in higher yields than the longer acyl derivatives. The rather low yields of the long chain esters were mainly due to the difficulty in the separation of the esters from the liberated carboxylic acids. The structures of the representative compounds listed in Table I were confirmed by their elemental analyses and by NMR spectra. In addition, all of the diesters other than those containing a conjugated double bond system in the acyl moiety gave UV spectra characteristic of anhydro-ara-C. The spectral features of 3′,5′-di-O-acyl anhydro-ara-C and related compounds prepared by the acylation of anhydro-ara-C in dimethylacetamide have recently been described by Moffatt et al.[5] The 3′,5′-di-O-acyl anhydro-ara-C hydrotetrafluoroborate salt could be converted to the hydrochlorides (**5b**) by passing them (in aqueous methanol or aqueous tetrahydrofuran) through a column of anion-exchange resin (Cl^- form). A distinct spectral difference between **5a** and **5b** was observed with regard to the NH stretching vibration band in the infrared (IR) spectrum. Thus, the IR spectrum of **5a** shows sharp bands (generally three peaks) between 3200 and 3440 cm^{-1}, while **5b** shows a broad unsolved band which overlaps the CH stretching band of Nujol in the region of 3050–3280 cm^{-1}.

The mechanism of the conversion of cytidine to 3′,5′-di-

Table I. 3′,5′-Diacyl Derivatives of 2,2′-Anhydro-1-(β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a)

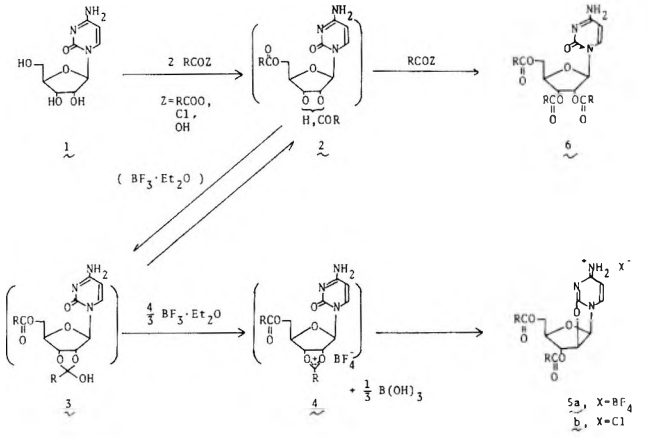
Registry no.	Acyl group	Composition[a]	Mp, °C	Method[b]	Yield,[c] %	Recrystn solvent	UV (MeOH), λ_{max} (ε)
62840-04-4	Acetyl	$C_{13}H_{16}N_3O_6BF_4 \cdot H_2O$	150–151	A	67	EtOH	235 (10 400)
				B	61		264 (11 800)
62757-81-7	*n*-Valeryl	$C_{19}H_{28}N_3O_6BF_4 \cdot 0.5H_2O$	171–173	A	71	EtOH	236 (10 000)
							264 (11 600)
62757-83-9	Isovaleryl	$C_{19}H_{28}N_3O_6BF_4 \cdot H_2O$	210–212	A	55	EtOH	235 (10 500)
							264 (12 000)
62757-85-1	*sec*-Valeryl	$C_{19}H_{28}N_3O_6BF_4 \cdot 0.5H_2O$	183–185	B	63	EtOH	236 (10 800)
							264 (12 700)
62757-87-3	Pivaloyl	$C_{19}H_{28}N_3O_6BF_4$	243–244	A	79	H_2O	237 (10 300)[d]
				B	56		264 (12 200)
				C	52		
62840-06-6	Decanoyl	$C_{29}H_{48}N_3O_6BF_4 \cdot 0.5H_2O$	75–92	B	64	MeOH	235 (10 200)[d]
							264 (11 400)
62757-89-5	Margaroyl	$C_{43}H_{76}N_3O_6BF_4 \cdot 0.5H_2O$	137–138	B	78	EtOH	235 (10 000)
				C	64		264 (11 600)
62757-91-9	Lignoceroyl	$C_{57}H_{104}N_3O_6BF_4$	204	B	61	THF	235 (10 000)
							264 (11 500)
62757-93-1	Cyclopropane-carbonyl	$C_{17}H_{20}N_3O_6BF_4 \cdot H_2O$	221–223	A	42	EtOH	235 (10 200)
							264 (11 600)
62757-95-3	1-Adamantoyl	$C_{31}H_{40}N_3O_6BF_4$	285–286	A	64	MeOH	236 (11 500)
				B	76		264 (13 400)
62757-97-5	Crotonoyl	$C_{17}H_{20}N_3O_6BF_4$	189–191	A	43	*i*-PrOH	264 (11 000)
62840-07-7	Benzoyl	$C_{23}H_{20}N_3O_6BF_4 \cdot 0.5H_2O$	280–283	A	63	MeOH	233 (35 700)
				B	57		265 (13 200)
				C	60		
62757-99-7	γ-Phenyl-butyryl	$C_{29}H_{32}N_3O_6BF_4$	103–105	A	42	*i*-PrOH	237 (9300)[d]
							264 (10 700)
62758-01-4	Cinnamoyl	$C_{27}H_{24}N_3O_6BF_4$	255	A	46	MeOH	217 (37 500)
							223 (30 800)
							278 (49 600)

[a] All compounds analyzed correctly for C, H, and N. In the case of the diacetyl ester, F was also analyzed: calcd, 18.31; found, 18.22. [b] A, acid anhydride; B, acid chloride; C, carboxylic acid. [c] The yields are all calculated on the isolated pure product. [d] Measured in EtOH.

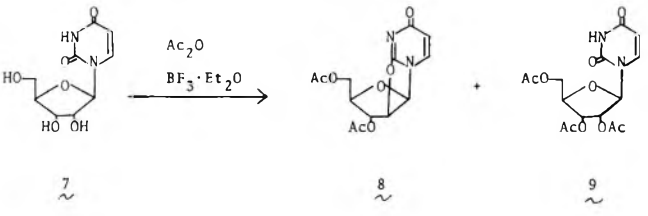
O-acyl anhydro-ara-C most likely involves formation of 2′,3′-acyloxonium ion **4** as an intermediate. Subsequent intramolecular attack at C-2′ by the C-2 carbonyl oxygen would then give 3′,5′-di-*O*-acyl anhydro-ara-C. The 2′,3′-acyloxonium ion **4** can be envisaged to have formed via ring closure of the 2′(3′),5′-di-*O*-acylated nucleoside. Attack of the 2′(3′)-hydroxyl on the adjacent acyl group could be facilitated through coordination to boron trifluoride.[9] The reaction should proceed competitively in two directions: one to the 2′,3′-acyloxonium ion and another to 2′,3′,5′-tri-*O*-acylcytidine (**6**). However, the result of the experiment indicated that the 2′,3′-acyloxonium ion formation proceeded much faster than the peracylation at a temperature around 80 °C, whereas at low temperature peracylation predominated. In addition to its role as a catalyst for formation of intermediate **3**, boron trifluoride etherate could function as a dehydroxylating agent in the conversion of **3** to **4**. In this respect the equilibrium between diacylated intermediate **2** and ortho ester **3** would be shifted to the right by removal of hydroxyl (Scheme I). The formation of acyloxonium ion from ortho esters using boron trifluoride[10a] or its ether complex[10b] has been demonstrated.

A similar result was obtained when the reaction was applied to uridine (**7**). Treatment of **7** with acetic anhydride in the presence of boron trifluoride etherate in refluxing acetonitrile gave 2,2′-anhydro-1-(3′,5′-di-*O*-acetyl-β-D-arabinofuranosyl)uracil[6] (**8**) and 2′,3′,5′-tri-*O*-acetyluridine[6] (**9**) in 65 and 4% yield, respectively (Scheme II). It may be noted that the cleavage of the anhydro bond has been reported by Holý[11] via treatment of 2,2′-anhydro-3′,5′-di-*O*-acyluridine with boron trifluoride etherate in refluxing methanol. We have observed the same phenomenon[6] in the treatment of **8** with zinc chloride in acetic acid. However, cleavage of the anhydro bond would not occur in acetonitrile because of the low nucleophilicity of acetonitrile, and reaction with the liberated carboxylic acid would be minimized because of its low concentration in the aprotic reaction solvent.

Scheme I



Scheme II



Reactions with Carboxylic Acid Chlorides. The facile preparation of 3′,5′-di-*O*-acyl anhydro-ara-C's by the anhy-

dride method described above prompted us to examine this reaction with the corresponding carboxylic acid chlorides. It may be noted that the preparation of 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)cytosine hydrobromide via reaction of cytidine with acetyl bromide in refluxing acetonitrile (40% yield) has recently been described by Marumoto and Honjo.[12] However, it seems difficult to extend their method to higher homologues of 3′,5′-di-O-acetyl anhydro-ara-C.[5]

As expected treatment of cytidine with different carboxylic acid chlorides (3 molar equiv) in the presence of boron trifluoride etherate (3 molar equiv) in refluxing acetonitrile resulted in the formation of **5a** in yields of 56–78% (see Table I). Once again the reactions took place quite rapidly and the products were isolated by the simple workup as described in the anhydride method. Somewhat lower yields were obtained in the case of short-chain esters compared to the anhydride method. However, relatively better yields were obtained in a series of longer chain esters, since the difficulty in separating the product from the carboxylic acid liberated was eliminated in this case. In the case of benzoyl chloride, a small amount of a by-product which corresponds to a faster moving spot on TLC (silica gel) was isolated in crystalline form by chromatographic separation on silica gel. This compound was identified as 2′,3′,5′-tri-O-benzoylcytidine (**6**, R = C_6H_5) by its NMR spectrum.

Reactions with Carboxylic Acids. It is well known that boron trifluoride etherate functions as an effective reagent in a direct esterification of carboxylic acids.[13] In view of the mechanim of the present reaction, it was quite natural to consider that the reaction of cytidine with carboxylic acid in the presence of boron trifluoride etherate should also afford **5a** following subsequent steps. After some experimentation it was found that the reactions with carboxylic acids were slow, and required longer refluxing time (1–3 h) and larger excess amount of the reagents (3–9 molar equiv, depending on the nature of the carboxylic acid used). As shown in Table I, the 3′,5′-diesters of anhydro-ara-C were prepared in moderate yields by this method.

The work presented in this paper provides a convenient method for the synthesis of a wide range of 3′,5′-di-O-acyl anhydro-ara-C's by a single-step reaction from cytidine.

Experimental Section

Infrared spectra were obtained on a Shimadzu IR-27G spectrophotometer. ^1H NMR spectra were obtained with a Hitachi Perkin-Elmer R-20A spectrometer; chemical shifts are reported in δ units using tetramethylsilane as an internal reference. UV spectra were measured on a Hitachi EPS-3T spectrometer. Column chromatography was done using Merck silica gel (0.05–0.20 mm particle size).

Materials. Boron trifluoride etherate was purified by distillation according to the method of Zweifel and Brown.[14] Acetonitrile was dried over magnesium sulfate and distilled after being refluxed with phosphorus pentoxide.

General Procedure for the Preparation of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a). 2,2′-Anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)cytosine Hydrotetrafluoroborate (5a, R = CH_3). By Anhydride Method (Method A). A solution of acetic anhydride (6.3 g, 61.8 mmol) in acetonitrile (50 mL) was added dropwise to a stirred refluxing solution of cytidine (5.0 g, 20.6 mmol) and boron trifluoride etherate (7.8 mL, 61.8 mmol) in acetonitrile (150 mL) at such a rate (ca. 10 min) as to maintain refluxing. After the addition was completed, the reaction mixture was maintained at the reflux temperature for 5 min and then cooled immediately. The mixture was concentrated to dryness in vacuo below 40 °C. The residue was triturated with ether (200 mL) and then with 2-propanol (20 mL). 2-Propanol (20 mL) was added to the triturated residue, and the mixture was allowed to stand overnight in a refrigerator. The resulting crystals were recrystallized from EtOH to give 5.7 g (67%) of **5a** (R = CH_3) with mp 148–150 °C. An analytical sample had mp 150–151 °C: NMR (Me_2SO-d_6) δ 1.90 (s, 3, OAc), 2.14 (s, 3, OAc), 3.9–4.5 (m, 2, $C_{5'}H_2$), 4.6–4.9 (m, 1, $C_{4'}H$), 5.3–5.6 (m, 1, $C_{3'}H$), 5.77 (d, 1, J = 6 Hz, $C_{2'}H$), 6.58 (d, 1, J = 7.5 Hz, C_5H), 6.64 (d, 1, J = 6 Hz, $C_{1'}H$), 8.36 (d, 1, J = 7.5 Hz, C_6H), 9.2–9.6 (br s, 2, NH_2); IR ν_{max} (Nujol) 3280–3440, 1756, 1748, 1668 cm^{-1}. The UV spectrum is described in Table I. Anal. Calcd for $C_{13}H_{16}N_3O_6BF_4 \cdot H_2O$ (415.13): C, 37.61; H, 4.36; N, 10.12; F, 18.31. Found: C, 37.27; H, 4.22; N, 10.11; F, 18.22.

2,2′-Anhydro-1-(3′,5′-di-O-benzoyl-β-D-arabinofuranosyl)-cytosine Hydrotetrafluoroborate (5a, R = C_6H_5). A. By Method B. A solution of benzoyl chloride (7 g, 49.6 mmol) in acetonitrile (40 mL) was added dropwise to a stirred refluxing solution of cytidine (4.0 g, 16.5 mmol) and boron trifluoride etherate (6.2 mL, 49.6 mmol) in acetonitrile (120 mL) over a period of 10 min. After the addition was completed, the mixture was kept at the reflux temperature for 5 min and then concentrated to dryness in vacuo. The residue was triturated with ether (70 mL) and the resulting crystals were collected by filtration. The crystals were washed with EtOH (50 mL) and recrystallized from MeOH to give 5.0 g (57%) of **5a** (R = C_6H_5) with mp 280–283 °C dec: NMR (Me_2SO-d_6) δ 4.4–4.7 (m, 2, $C_{5'}H_2$), 4.8–5.2 (m, 1, $C_{4'}H$), 5.7–5.9 (m, 1, $C_{3'}H$), 6.04 (d, 1, J = 6 Hz, $C_{2'}H$), 6.53 (d, 1, J = 7.5 Hz, C_5H), 6.69 (d, 1, J = 6 Hz, $C_{1'}H$), 7.3–8.2 (m, 10, 2 Ar), 8.37 (d, 1, J = 7.5 Hz, C_6H), 9.1–9.5 (br s, 2, NH_2). Anal. Calcd for $C_{23}H_{20}N_3O_6BF_4 \cdot 0.5H_2O$ (530.26): C, 52.10; H, 3.99; N, 7.92. Found: C, 51.73; H, 4.02; N, 7.84.

A portion (¼) of the EtOH washings was concentrated to dryness, and the residue (0.7 g) was chromatographed on a column of silicic acid using $CHCl_3$–MeOH (95:5). Evaporation of the fractions which contained less polar substance (monitored by TLC) followed by crystallization of the residue from 2-propanol gave 0.15 g of 2′,3′,5′-tri-O-benzoylcytidine with mp 186–187 °C: NMR ($CDCl_3$) δ 4.6–4.9 (m, 3, $C_{5'}H_2$, $C_{4'}H$), 5.8–6.3 (m, 4, $C_{3'}H$, $C_{2'}H$, $C_{1'}H$, C_5H), 7.2–8.3 (m, 18, 3 Ar, NH_2, C_6H); UV λ_{max} (MeOH) 232 nm (ε 43 600), 272 (10 600). Anal. Calcd for $C_{30}H_{25}N_3O_8 \cdot 0.5H_2O$ (564.56): C, 63.82; H, 4.64; N, 7.44. Found: C, 64.29; H, 4.71; N, 7.46.

B. By Carboxylic Acid Method (Method C). Benzoic acid (6.0 g, 49.2 mmol) was added portionwise to a stirred refluxing solution of cytidine (2.0 g, 8.2 mmol) and boron trifluoride etherate (9.4 mL, 74.5 mmol) in acetonitrile (60 mL) over a period of 5 min. The mixture was kept at the reflux temperature for 3 h and then concentrated to dryness in vacuo. The residue was triturated with ether (150 mL), and the resulting crystals were collected by filtration. The crystals were washed with EtOH (20 mL) and recrystallized from MeOH, giving 2.6 g (60%) of 5a (R = C_6H_5) with mp 279–280 °C dec. The compound was identified with the sample prepared by method B.

Preparation of 2,2′-Anhydro-1-(3′,5′-di-O-acyl-β-D-arabinofuranosyl)cytosine Hydrochloride (5b) from 5a. A Typical Example. A solution of **5a** (R = CH_3) (2 g, 4.8 mmol) in H_2O (10 mL) was passed through a column of Diaion SA-11B (Cl^-, 50 mL), and the column was washed with H_2O (100 mL). The combined eluate and washings were concentrated to dryness in vacuo, giving 1.6 g (92%) of **5b** (R = CH_3) with mp 218–219 °C dec: IR ν_{max} (Nujol) 3120–3280, 1765, 1743, 1678, 1649 cm^{-1}. This was identical with an authentic sample[6] by the criteria of IR and NMR spectra.

In the cases of hydrotetrafluoroborate salts with poor solubility in H_2O, the salts were dissolved in aqueous organic solvents (50–70% MeOH or 50–60% tetrahydrofuran), and passed through a column of Diaion SA-11B (Cl^-).

Reaction of Uridine with Acetic Anhydride in the Presence of Boron Trifluoride Etherate. A solution of acetic anhydride (6.3 g, 61.8 mmol) in acetontrile (50 mL) was added dorpwise to a stirred refluxing solution of uridine (5 g, 20.5 mmol) and boron trifluoride etherate (8 mL, 63.4 mmol) in acetontrile (100 mL) at such a rate (5 min) as to maintain refluxing. After the addition was completed, the mixture was cooled and concentrated to dryness in vacuo. The residue was poured into saturated aqueous sodium bicarbonate (150 mL), and the solution was applied to a column of activated charcoal (50 g). The column was washed with H_2O (500 mL) and eluted with EtOH–pyridine (4:1). The eluate (800 mL) was concentrated to dryness in vacuo, and the residue was crystallized from EtOH, giving 4.1 g (65%) of 2,2′-anhydro-1-(3′,5′-di-O-acetyl-β-D-arabinofuranosyl)uracil (**8**) with mp 184–186 °C. Identity was established by comparison of the IR and UV spectra with those obtained from an authentic sample,[6] mp 185–186 °C. Storage of the mother liquor from the recrystallization in a refrigerator gave 0.3 g (4%) of 2′,3′,5′-tri-O-acetyluridine (**9**) with mp 129–130 °C which was identical with an authentic sample.[6]

Acknowledgment. The authors wish to express their thanks to Drs. Ichiro Chibata and Muneji Miyoshi for their encouragement in this study. They are also indebted to Professor D. E. Bergstrom (University of California, Davis, Calif.) for his helpful suggestions in preparing the manuscript.

Registry No.—**5b** (R = Me), 50896-84-9; **8**, 28309-53-7; **9**, 4105-38-8; acetyl chloride, 75-36-5; valeric anhydride, 2082-59-9; isovaleric anhydride, 1468-39-9; *sec*-valeryl chloride, 5856-79-1; pivaloyl chloride, 3282-30-2; pivalic anhydride, 1538-75-6; pivalic acid, 75-98-9; decanoyl chloride, 112-13-0; margaroyl chloride, 40480-10-2; margaric acid, 506-12-7; lignoceroyl chloride, 58576-73-1; cyclopropanecarboxylic anhydride, 33993-24-7; 1-adamantanecarboxylic anhydride, 42601-02-5; 1-adamantoyl chloride, 2094-72-6; crotonic anhydride, 623-68-7; benzoic anhydride, 93-97-0; γ-phenylbutyric anhydride, 1940-02-9; cinnamic anhydride, 538-56-7; acetic anhydride, 108-24-7; cytidine, 65-46-3; boron trifluoride, 7637-07-2; benzoyl chloride, 98-88-4; 2′,3′,5′-tri-*O*-benzoylcytidine, 31652-74-1; benzoic acid, 65-85-0; uridine, 58-96-8.

References and Notes

(1) See, e.g., (a) R. B. Livingston and S. K. Carter, *Cancer Chemother. Rep., Part 3*, **1**, 179 (1968); (b) J. J. Wang, O. S. Selawry, T. J. Vietti, and G. P. Bodey, *Cancer*, **25**, 1 (1970); (c) R. R. Ellison et al., *Blood*, **32**, 507 (1968); (d) E. Frei, J. N. Bickers, J. S. Hewlett, M. Lane, W. V. Leary, and R. W. Talley, *Cancer Res.*, **29**, 1325 (1969); (e) R. L. Momparler, *ibid.*, **34**, 1775 (1974).

(2) See, e.g., (a) G. D. Gray, M. M. Mickelson, and J. A. Crim, *Transplantation*, **6**, 805 (1968); (b) R. O. Gordon, M. E. Wade, and M. S. Mitchell, *J. Immunol.*, **103**, 233 (1969).

(3) See, e.g., (a) D. A. Buthala, *Proc. Soc. Exp. Biol. Med.*, **115**, 69 (1964); (b) H. N. Prince, E. Grunberg, M. Buck, and R. Cleeland, *ibid.*, **130**, 180 (1969).

(4) See, e.g., (a) A. Hoshi, F. Kanzawa, and K. Kuretani, *Gann*, **63**, 353 (1972); (b) J. M. Venditti, M. C. Baratta, N. H. Greenberg, B. J. Abott, and I. Kline, *Cancer Chemother. Rep., Part 1*, **56**, 483 (1972).

(5) E. K. Hamamura, M. Prystasz, J. P. Verheyden, J. G. Moffatt, K. Yamaguchi, N. Uchida, K. Sato, A. Nomura, O. Shiratori, S. Takase, and K. Katagiri, *J. Med. Chem.*, **19**, 663 (1976).

(6) K. Kondo, T. Adachi, and I. Inoue, *J. Org. Chem.*, **41**, 2955 (1976).

(7) See, e.g., (a) E. R. Walwick, W. K. Roberts, and C. A. Dekker, *Proc. Chem. Soc., London*, 84 (1959); (b) I. L. Doerr and J. J. Fox, *J. Org. Chem.*, **32**, 1462 (1967).

(8) J. Beránek and J. Pitha, *Collect. Czech. Chem. Commun.*, **29**, 625 (1964).

(9) See, e.g., H. S. Booth and D. R. Martin, "Boron Trifluoride and Its Derivatives", Wiley, New York, N.Y., 1949, p 72.

(10) (a) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Justus Liebigs Ann. Chem.*, **632**, 38 (1960); (b) T. C. Jain, I. D. Jenkins, A. F. Russell, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **39**, 30 (1974).

(11) A. Holý, *Collect. Czech. Chem. Commun.*, **38**, 423 (1973).

(12) R. Marumoto and M. Honjo, *Chem. Pharm. Bull.*, **22**, 128 (1974).

(13) (a) P. K. Kadaba, M. Carr, M. Tribo, J. Triplett, and A. C. Glasser, *J. Pharm. Sci.*, **58**, 1422 (1969); (b) J. L. Marshall, K. C. Erickson, and T. K. Folsom, *Tetrahedron Lett.*, 4011 (1970); (c) P. K. Kadaba, *Synthesis*, 317 (1971); *J. Pharm. Sci.*, **63**, 1333 (1974).

(14) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 28 (1963).

Acyclic Polyhalogenated Monoterpenes from the Red Alga *Plocamium violaceum*

Phillip Crews* and Ernest Kho-Wiseman

Thimann Laboratories, University of California, Santa Cruz, California 95064

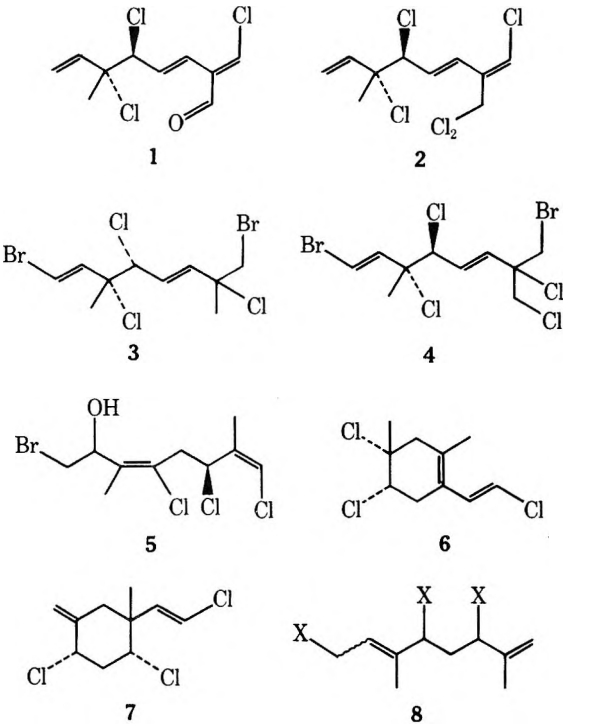
Received January 24, 1977

Several new acyclic 1,4,6-trichloro-3,7-dimethyl-2,7-octadiene monoterpenes are reported from the red marine alga *Plocamium violaceum* (Dixon) collected along a narrow coastal region of Monterey County, Calif. Both the gross structures and all of the stereochemical features of these halocarbons were established by extensive analysis of their ^1H and ^{13}C NMR data in comparison to data from numerous model compounds.

Our recent study of the natural products from the marine algae of the Plocamiaceae has revealed a fascinating array of halogenated monoterpenes. Without exception, every Plocamiaceae species that we have examined has been rich in one or more of these natural products.[1] For example, *Plocamium cartilagineum* (Dixon) contains several 2,7-dimethyl-1,5,7-octatrienes such as cartilagineal **1**[2] or **2**.[3] Other unusual acyclic monoterpenes including **3** and **4** can be isolated from *Plocamium oregonum* (Doty),[4] and costatol (**5**) is found in *Plocamium costatum* (C. Ag.).[5] By contrast, *Plocamium violaceum* (Farlow) has been a source for a number of alicyclic monoterpenes[6,7] such as plocamene B (**6**) and plocamene D (**7**).

Our past work upon the monocyclic constituents from *P. violaceum* has involved specimens toxic to both fish and insects which are collected from a broad area north of Santa Cruz, Calif. (Santa Cruz and San Mateo Counties). Concurrent work by others has shown that *P. violaceum* from San Diego County, Calif., contains additional examples of cyclic monoterpenes.[8] Not long ago we had occasion to collect samples of *P. violaceum* from a narrow coastal region of Monterey County just south of Santa Cruz, Calif. These seaweeds displayed no alicyclic monoterpenes and instead yielded several new acyclic monoterpenes. Reported below are the structures of these interesting new compounds.

Collections of *P. violaceum* from Pescadero Point, Point Joe, and Asilomar Beach (all in Monterey County, Calif.) gave crude oils, from $CHCl_3$ extraction of fresh plants, having fairly



a, X = $ClBr_2$

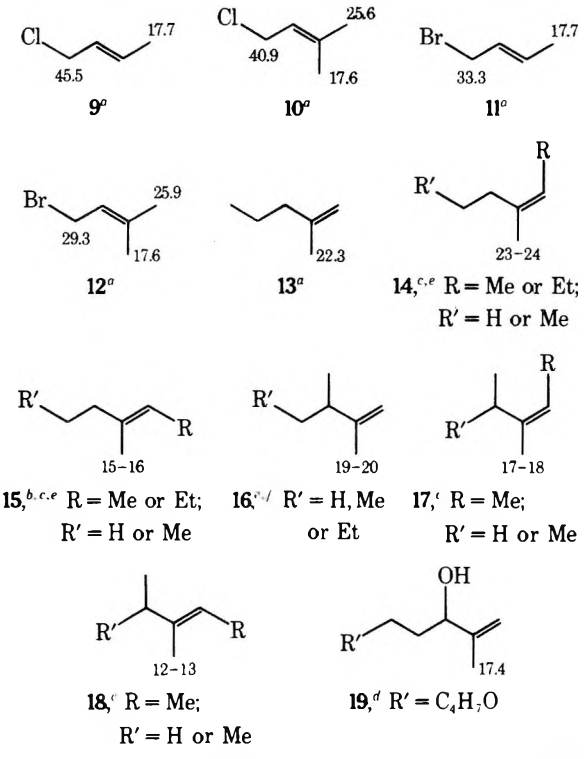
b, c, X = Cl_2

different GC/MS profiles. The Point Joe oil contained a single major component, which was easily purified, of molecular formula $C_{10}H_{15}ClBr_2$ to which we assigned a gross structure **8a**. While its UV was blank above 200 nm and the IR showed only halocarbon functionality, both the mass spectrum (weak M^+ cluster at *m/e* 328/330/332) and the ^{13}C NMR spectrum (Table I) provided information about the total formula. In addition, the ^{13}C NMR exhibited two double bonds thereby revealing, in combination with the molecular formula, an acyclic constitution. The relative atom connectivities were solved from the ^1H NMR spectra ($CDCl_3$, 100 MHz). The 15 H's were distributed among six multiplet clusters divisible into four subgroups: (a) two vinyl CH_3's δ 1.87 (A = 6) singlet (as two singlets δ 1.67 and 1.77 in 1:1 $CDCl_3$–Bz-d_6); (b) $XCHCH_2CHX$ δ 2.42 (A = 2) triplet (J = 7.2 Hz), δ 4.66 and 4.69 (A = 1, 1) overlapping triplets (J = 7.2 Hz), collapsible to a single triplet at δ 4.61 (A = 2) in 1:1 $CDCl_3$–Bz-d_6 or collapsible to two singlets by irradiation at δ 2.42; (c) $>C{=}CH_2$ δ 4.95 and 5.11 (A = 1, 1) br singlets; and (d) $XCH_2CH{=}C<$ δ 4.07 (A = 2) doublet (J = 7.4 Hz), δ 5.80 (A = 1) br triplet (J = 7.4 Hz). These four fragments could be pieced together in only one way as shown by structure **8a**.

The remaining details unsolved for the total structure of **8a** included the geometry about the C_2–C_3 trisubstituted double bond, the absolute halogen regiochemistry, and the relative stereochemistry of the halogens at C_4 and C_6. Each of these assignments was unambiguously established below by employing several types of NMR data.

The ^{13}C shift assignments for **8a** (Table I) were made based upon the J_{CH} data[6] and reference to chemical shift data for several model compounds (Scheme I). That ^{13}C shifts for

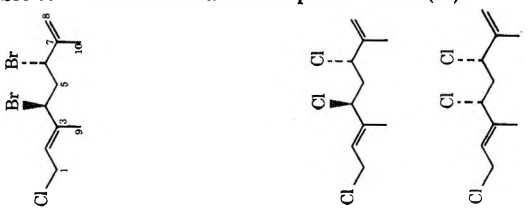
Scheme I. ^{13}C NMR Chemical Shifts of Model Compounds



[a] This work. [b] Reference 9. [c] Reference 10. [d] Reference 11. [e] Reference 12. [f] Reference 13.

halogenated carbons in an isostructural environment are quite dependent upon the type of halogen substituent is illustrated in Scheme I. Thus, a $-CH_2Br$ appears 12 ppm higher than a $-CH_2Cl$ in models **9** and **10** vs. **11** and **12**. Of the three halogenated carbons in **8a** which occur at δ 39.8, 56.5, and 57.9, it

Table I. ^{13}C NMR Data for Preplocamenes (8)



8a **8b** **8c**

Carbon	δ	Mult	J_{CH}	δ	δ
1	39.7	t	151	39.5	40.4
2	124.6	d	156	125.3	124.7
3	139.9[a]	s		142.7	
4	56.2[b]	d	159	62.8[b]	63.1[b]
5	43.4	t	131	42.7	43.0
6	57.6[b]	d	159	63.9[b]	64.4[b]
7	143.7	s		142.7	
8	114.8	t	156	115.5	114.8
9	12.7	q	127	11.5	11.9
10	18.4	q	127	16.9	17.7

[a,b] The assignments of these close-lying peaks could be reversed.

was possible to assign the Cl to the peak at δ 39.8 attached at C_1 because of the similarity in shift between that carbon and the $-CH_2Cl$ in **10** (δ 41.3). The remaining two Br's could then be placed at C_4 and C_6 which was consistent with closeness of their δ's.

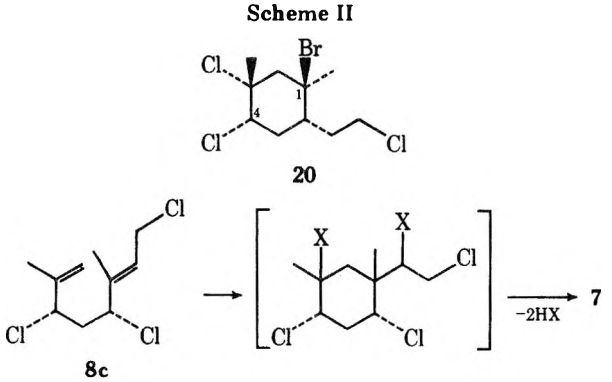
Turning to the vinyl methyl carbons, by comparison to Scheme I, it was possible to assign the **8a** C_7 CH_3 to the peak at 18.4 ppm and the 12.7 ppm absorption to the C_3 CH_3. In addition arguments which follow indicated that this latter methyl must be oriented cis to the $-CH_2Cl$ unit. The pattern of methyl shifts from the trisubstituted olefins in Scheme I reveals, in agreement with past observations,[14] that the chemical shift of a methyl cis to an alkyl chain is shielded by about 5–8 ppm relative to a trans methyl. The base shift value for a methyl which is geminal to a straight alkyl chain and either on a 1,1-disubstituted alkene or trans to another alkyl appears at δ 22–24 (i.e., **13** and **14**) while the base value for a methyl which is geminal to an alkyl chain and cis to another alkyl appears upfield at δ 15–16 (i.e., **15**). Comparison of the data for compound sets **13** and **16**, **14** and **17**, and **15** and **18** shows that a γ-alkyl substituent on the alkyl chain imparts a 3–6 ppm upfield shift upon the geminal methyl.[15] The methyl shifts for the series, **13**, **16**, and **19** are also informative and indicate that the γ shift of a polar group is about 2 ppm larger than for a γ-alkyl substituent. Applying these collective insights to the data of **8a** led to the methyl shift and double bond geometry assignments shown in Table I.

The seven-carbon constellation in **8a** from C_2 to C_8 has a symmetry element at C_5. Within this fragment the Br's at C_4 and C_6 can adopt either a relative C_s or C_2 type arrangement, which will then impart a distereotopic or homotopic relationship, respectively, for the protons on C_5. An extension of this analysis to the mildly unsymmetrical C_1–C_8 piece is enticing and a relative C_2-like Br stereochemistry is indicated based upon the observation that the methylene protons appear as a sharp triplet and maintain their chemical shift equivalence even at 360 MHz in both benzene-d_6 and $CDCl_3$.

Mixtures of two isomers **8b** and **8c** of formula $C_{10}H_{15}Cl_3$ (*m/e* 240/242/244) were isolated from *P. violaceum* from Pescadero Point and Asilomar Beach Calif., but they could not be separated by either normal or reverse phase preparative HPLC or by preparative GLC. However, the purified isomer mixtures were found to be enriched in **8b** (70%) or **8c** (60%) from the collections at these different sites. A comparison of

the GC/MS and magnetic resonance data for these enriched mixtures enabled specific NMR peak assignments for each isomer. Most of the ^1H NMR signals (100 MHz, $CDCl_3$) of these two components had identical chemical shifts which were similar to that of **8a** for the peaks at δ 1.79 (A = 6), singlet; 4.98 and 5.09 (A = 1, 1), br singlets; 4.08 (A = 2), doublet, J = 7.4 Hz; and 5.74 (A = 1), br triplets, J = 7.4 Hz; but different than **8a** for the resonances due to the $XCHCH_2CHX$ unit at δ 2.22 (A = 2), overlapping triplet and multiplet, and 4.41 and 4.61 (A = 2), br triplet, J = 7.3 Hz. These data along with the molecular formula indicated that gross structure 8 was also appropriate for **8b** and **8c**. This was further supported by the vinyl carbons observable in the ^{13}C spectra of the **8b** and **8c** mixtures. The specific assignments shown in Table I for **8b** and **8c** were made by comparison to the data for **8a** and the model compounds in Scheme I. In agreement with arguments above, the ^{13}C shifts of C_1 in **8b** and **8c** of 39.7 and 40.6 ppm were ascribable to a $-CH_2Cl$ cis to another alkyl chain or methyl. As expected the shift positions for C_4 and C_6 in both isomers were quite similar. The diagnostic shift positions of the C_3 methyl peaks (**8b** δ 11.5, **8c** δ 11.9) were consistent only with a cis geometry of the methyl and $-CH_2Cl$ unit. Having the C_2–C_3 double bond of identical geometry for **8b** and **8c** then required the halogens at C_4 and C_6 to be respectively C_s-like and C_2-like for the two diastereomers. This could be further confirmed by analogy to the case for **8a** in that the ^1H NMR at 360 MHz of the isomer mixture showed a triplet resonance (J = 7.3 Hz) ascribable to the C_5 methylene protons of isomer **8b** and two sets of ddd (J = 14.5, 8, 6 Hz) for the C_5 methylene protons of the isomer assigned as **8c**.

Scheme II



Several pairs of erimeric acyclic distereomers have been isolated from both *Plocamium cartilagineum*[3] and *Plocamium oregonum*[4] and they all have adjacent chiral centers. In contrast, the epimeric diastereomers **8b** and **8c** contain chiral centers which are separated by two bonds. This same structural feature is also present in a few of the monocyclic terpenes from *Plocamium*. Thus, structural frame 8 provides a logical biogenetic relay to the cyclic series of *Plocamium* compounds. For example, addition of X_2 to **8c** accompanied by olefin-assisted cyclization followed by loss of 2HX could produce a 1,1,5-trialkylcyclohexane ring skeleton such as **7**. In view of this potential relationship we have given the trivial name of preplocamene to the skeleton of **8**. Recently, the x-ray structure of **20** was reported by Mynderse et al.[16] Owing to the striking relationship between the S–C_4 in **20** and C_6 in **8c**,[17] it is tempting to propose an S stereochemistry for this latter center, and in view of the relative C_6 and C_4 (**8c**) symmetry deduced above, an R arrangement at C_4 in **8c**.

Experimental Section

The NMR spectra were recorded on a JEOL PS 100 pulsed FT spectrometer operating at 100 MHz for ^1H and 25.1 MHz for ^{13}C. The 360-MHz ^1H spectra were recorded at the Stanford Magnetic Resonance Laboratory. Optical rotations were measured on a Perkin-Elmer 141 polarimeter with a 1-dm cell (5 mL). GC/MS data were recorded on a Finnigan 4000 system equipped with a 6 ft × 0.125 in. glass column packed with 3% OV-17 on Chromosorb G and temperature programmed 115–225 °C at 5 °C/min. Routine low-resolution mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer and UV data were recorded on a Cary 14 spectrometer. Infrared data were recorded on a Perkin-Elmer 237 B spectrophotometer. High-performance liquid chromatography (HPLC) was done on a Waters ALC 201 instrument fitted with Porasil columns (8 ft × 0.375 in.) for normal phase and C-18 Corasil columns (4 ft × 0.375 in.) for reverse phase. All solvents were reagent grade and distilled prior to HPLC use. Spectral grade solvents were used for NMR (Me_4Si standard), UV, and optical rotation measurements. Low-boiling petroleum ether was used in all instances.

Collections and Extractions. *Plocamium violaceum* was collected intertidally from three locations (wet weight and yield of extract) including the following: Point Joe, Dec 3, 1975 and Dec 20, 1975 (2.38 kg, 3.65 g, 0.15%); Pescadero Point, June 29, 1976 and July 27, 1976 (3.65 kg, 4.23 g, 0.12%); and Asilomar Beach, July 15, 1976 (0.34 kg, 0.43 g, 0.13%), all within a 10-mile range in Monterey County, Calif.

The freshly collected algae were either directly extracted or frozen until extraction. All samples were extracted first with $CHCl_3$ for ca. 3 days and then with EtOH for ca. 3 days in a Soxhlet apparatus. The combined extracts were then chromatographed through silica gel (Grace Co. grade 62, 60–200 mesh, activated) using petroleum ether. The resulting semipurified oil was then subjected to HPLC using petroleum ether–benzene (95:5).

Isolations. Following the procedure above, compounds **8a** and mixtures of **8b** and **8c** were isolated.

1-Chloro-4,6-dibromo-3,7-dimethyl-2,7-octadiene (8a) was isolated as a clear, mobile oil, HPLC fractions 10–14 (20-mL fractions, 116 mg oil) from the collections made at Point Joe. Its ^1H and ^{13}C NMR are described in the text and in Table I and at 360 MHz (benzene-d_6), H_{5a} and H_{5b} are seen as a dt at δ 2.40 (J = 7.5, 2.3 Hz) and H_{1a} as dd at δ 3.65 and 3.75 (J = 11.3, 7.5 Hz). It displayed an $[\alpha]^{20}_D$ −35° (c 1.43, $CHCl_3$); IR 1430, 1380, 1260, 910 cm^{-1}; MS m/e 328, 330, 332 (M^+); 293, 295, 297 ($M^+ - Cl$); 249, 251, 253 ($M^+ - Br$); 213, 215 ($M^+ - HBr, Cl$); 169, 171 ($M^+ - HBr, Br$); 133 base ($C_{10}H_{13}$).

Ozonolysis of 8a. Several attempts were made to ozonize **8a** (10 mg) in CH_2Cl_2 at −78 °C with a stream of ozone generated by a Welsbach T-408 apparatus. The crude ozonide from above was worked up with several reagents including $(Ph)_3P$ and $(CH_3)_2S$ and in each case an unstable product was obtained whose spectral properties indicated oxygen formation (i.e., IR peak at 1720 cm^{-1}). Attempts to purify this material (i.e., distillation, chromatography, or DNPH formation) yielded only intractable material.

Hydride Reduction of 8a. Attempts to displace a bromine in **8a** by $Li(Et)_3BH$ were also unsuccessful. Following a good literature analogy,[18] **8a** (10 mg) in 2 mL of HF (anhydrous) was reacted with 1 equiv of $Li(Et)_3BH$ in THF solution (1 M) at 0 °C for 15 min which resulted in only recovery of starting material. Prolonged reaction at higher temperatures yielded only decomposed products.

1,4,6-Trichloro-3,7-dimethyl-2,7-octadienes (8b and 8c) were isolated as a mixture of diastereomers in varying relative percents from two locations. Neither preparative HPLC (Porasil A or Corasil C_{18}) or preparative GC afforded separation of the mixture. Analytical GLC did show two separate peaks for **8b** and **8c**, t_r 18.3 and 19.0 min. The collections made at Pescadero Point yielded pure **8b** and **8c** (180 mg) as an oil after reverse phase HPLC (CH_3CN–H_2O solvent, 60:40), ten recycles. The ratio of **8b**:**8c**, 69:31, was determined by integration of the –CHCl– region in the ^1H NMR (100 MHz, $CDCl_3$) where **8b** signals (δ 4.41, triplet, J = 7.3 Hz) were clearly separable from **8c** signals (δ 4.61, triplet, J = 7.3 Hz) and by rough intensity comparisons to the C_5 methylene region in which a triplet at δ 2.28 (J = 7.3 Hz) (**8b**) and multiplet at δ 2.32 (J = 14.5 and 7.3 Hz) (**8c**) were observed. These upfield resonances along with the added detail observable at 360 MHz added strength to our specific ^1H NMR assignments of **8b** and **8c** (Table I). At 360 MHz in benzene-d_6 **8b** displayed –CH(Cl)– δ 4.23 (t), J = 7.3 Hz, and 4.36 (t), J = 7.3 Hz; H_5 δ 1.98 (t), J = 7.3 Hz, while **8c** displayed –CH(Cl)– δ 4.49 (dd), J = 8.4, 5.7 Hz, and 4.58 (dd), J = 8.4, 5.7 Hz; H_{5a} δ 1.97 (ddd), J = 14.5, 8, 6 Hz, and H_{5b} 2.26 (ddd), J = 14.5, 8, 6 Hz. The ratio of **8b**:**8c** was also determined by GC/MS and ^{13}C NMR data as 70:30 and 71:29, respectively. Another collection from Asilomar Beach (22 mg) afforded the opposite enrichment as determined by GC/MS (**8b**:**8c** 40:60). The mixture of **8b** and **8c** displayed IR 1430, 1260, 910, 800 cm^{-1}, and MS at each GC peak m/e 240, 242, 244 (M^+); 225, 227, 229 ($M^+ - CH_3$); 205, 207, 209 ($M^+ - Cl$); 170, 172 ($M^+ - Cl_2$); 81 base (C_6H_4).

^{13}C NMR of Model Compounds. Compounds **9**, **11**, and **13** were

purchased from Aldrich Chemical Co. and **10** and **12** were prepared according to the literature.[19] ^{13}C NMR data were obtained with 50% solutions in $CDCl_3$. ^{13}C NMR data (Me_4Si standard) not in Scheme I; 1-chloro-*trans*-2-butene (**9**), C_2 127.5, C_3 130.7; 1-chloro-3-methyl-2-butene (**10**), C_2 121.0, C_3 139.0; 1-bromo-*trans*-2-butene (**11**), C_2 127.8, C_3 131.0; 1-bromo-3-methyl-2-butene (**12**), C_2 121.0, C_3 139.5; 2-methyl-1-pentene (**13**), C_1 110.1 (t), C_2 145.7 (s), C_3 40.6 (t), C_4 21.2 (t), C_5 13.9 ppm (q).

Acknowledgment. We thank Professor I. A. Abbott (Hopkins Marine Station) for guidance in alga identification. We also thank the NOAA office of Sea Grant and UCSC Committee on Research for support of this research, and the NSF Chemical Instrumentation Program for their financial assistance in the purchase of a GC/MS apparatus.

Registry No.—**8a**, 62743-07-1; **8b**, 62743-08-2; **8c**, 62743-09-3; **9**, 4894-61-5; **10**, 503-60-6; **11**, 29576-14-5; **12**, 870-63-3; **13**, 763-29-1.

References and Notes

(1) P. Crews in "NATO Conference on Marine Natural Products", D. J. Faulkner and W. Fenical, Ed., Plenum Press, New York, N.Y., 1977, pp 211–223.
(2) P. Crews and E. Kho, *J. Org. Chem.* **39**, 3303 (1974).
(3) J. S. Mynderse and D. J. Faulkner, *Tetrahedron*, **31**, 1963 (1975).
(4) P. Crews, *J. Org. Chem.*, in press.
(5) R. Kazlauskas, P. T. Murphy, R. J. Quinn, and R. J. Wells, *Tetrahedron Lett.*, 4451 (1976).
(6) P. Crews and E. Kho, *J. Org. Chem.*, **40**, 2568 (1975).
(7) P. Crews and E. Kho-Wiseman, Abstracts, 31st Northwest Regional Meeting of the American Chemical Society, June 1976, No. G122.
(8) J. S. Mynderse and D. J. Faulkner, *J. Am. Chem. Soc.*, **96**, 6771 (1974).
(9) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971).
(10) J. W. de Haan, and L. J. M. van de Ven, *Org. Magn. Reson.*, **5**, 147 (1973).
(11) F. Bohlmann, R. Zeisberg, and E. Klein, *Org. Magn. Reson.*, **7**, 426 (1975).
(12) P. A. Couperus, A. D. H. Clague, and J. P. C. M. van Dongen, *Org. Magn. Reson.*, **8**, 426 (1976).
(13) J. W. de Haan, L. J. M. van de Ven, A. R. N. Wilson, A. E. van der Hout-Ludder, C. Altona, and D. H. Faber, *Org. Magn. Reson.*, **8** 477 (1976).
(14) J. W. de Haan and L. J. M. van de Ven, *Tetrahedron Lett.*, 3965 (1971).
(15) For a discussion of ^{13}C NMR γ effects in acyclic systems see (a) G. C. Levy and G. R. Nelson, "Carbon-13 Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972, Chapter 3; (b) G. J. Martin, M. L. Martin, and S. Odiot, *Org. Magn. Reson.*, 7, 2 (1975), and references cited therein.
(16) J. S. Mynderse, D. J. Faulkner, J. Finer, and J. Clardy, *Tetrahedron Lett.*, 2175 (1975).
(17) See Scheme II and the discussion in ref 6.
(18) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973).
(19) S. Julia, M. Julia, and G. Linsturmelle, *Bull. Soc. Chim. Fr.*, 3499 (1966).

Majusculamides A and B, Two Epimeric Lipodipeptides from *Lyngbya majuscula* Gomont

Franz-Josef Marner and Richard E. Moore*

Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822

Ken Hirotsu and Jon Clardy*[1]

Ames Laboratory, USERDA, and Department of Chemistry, Iowa State University, Ames, Iowa 50011

Received March 15, 1977

Majusculamides A and B are major lipophilic constituents of the blue-green alga *Lyngbya majuscula* Gomont. Detailed spectral analysis, chemcial degradation, and x-ray crystallographic studies show that majusculamide A is *N*-[(2*R*)-2-methyl-3-oxodecanoyl]-D-*N*,*O*-dimethyltyrosyl-L-*N*-methylvalinamide (**6a**) and that majusculamide B is *N*-[(2*S*)-2-methyl-3-oxodecanoyl]-D-*N*,O-dimethyltyrosyl-L-*N*-methylvalinamide (**6b**). Majusculamide B is epimerized into a mixture of majusculamides A and B and then degraded into D-*N*,O-dimethyltyrosyl-L-*N*-methylvaline lactam (**2**) and racemic 2-methyl-3-oxodecanoic amide (**1**) at 140 °C in anhydrous dimethyl sulfoxide.

The blue-green alga *Lyngbya majuscula* Gomont is responsible for sporadic outbreaks of a contact dermatitis known in Hawaii as "swimmers' itch".[2] Not all varieties of this seaweed show dermonecrotic activity. *L. majuscula* from Laie Bay, Oahu, however, is frequently dermatitis-producing during the summer months. The causative agent, which is found in the lipid extract of the seaweed, may be debromoaplysiatoxin,[3] a poisonous substance that was first isolated from the digestive tract of the gastropod mollusk *Stylocheilus longicauda*.[4]

We have found that *L. majuscula* is characterized chemotaxonomically by the presence of two major lipophilic constituents which we have named majusculamides A and B. Majusculamides A and B are constituents of both the dermatitis- and nondermatitis-producing varities, but are not found in *L. gracilis*.[5a] In this report we describe the structure determination of these two nontoxic[5b] compounds.

Isolation. The alga was collected in shallow water (0.5–2 m) from several points around the island of Oahu, but mainly from Kahala Beach for the structure work. Extraction of the wet seaweed with methanol and chloroform or the freeze-dried seaweed with chloroform gave an oily extract which after chromatography and gel filtration resulted in a crystalline mixture of majusculamides A and B. Separation of the two epimeric compounds was readily achieved by high-pressure liquid chromatography.

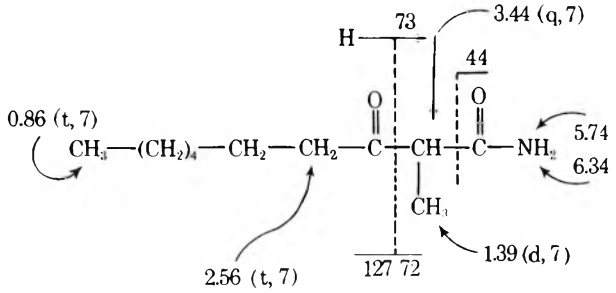
Structure Determination. Majusculamides A and B both crystallized from aqueous methanol and analyzed for $C_{28}H_{45}N_3O_5 \cdot H_2O$. Molecular ions could not be observed in their electron-impact (EI) mass spectra, but fragment ions appeared at *m/e* 486 and 487 for loss of NH_3 and NH_2 from the molecular ions and high-resolution mass measurements gave elemental compositions of $C_{28}H_{42}N_2O_5$ for the *m/e* 486 peaks. Molecular ions, however, were easily seen at *m/e* 503 in the field desorption (FD) mass spectra. The loss of NH_3 and NH_2 from the molecular ions in the EI mass spectra suggested that the majusculamides were primary amides and this was confirmed by IR and ^1H NMR.

The ^1H NMR spectra of majusculamides A and B in chloroform-*d* and dimethyl-d_6 sulfoxide at room temperature were rather complex due to the presence of two slowly interconverting conformers for each compound. At 140 °C in anhydrous dimethyl-d_6 sulfoxide, however, the ^1H NMR spectra were greatly simplified and each one clearly showed the presence of a para-substituted anisole ring, two *N*-methyl groups, three secondary methyl groups, two adjacent methine

groups with one bearing two of the secondary methyl groups, a methylene attached to a methine group, and an n-alkyl group attached to a carbonyl group.

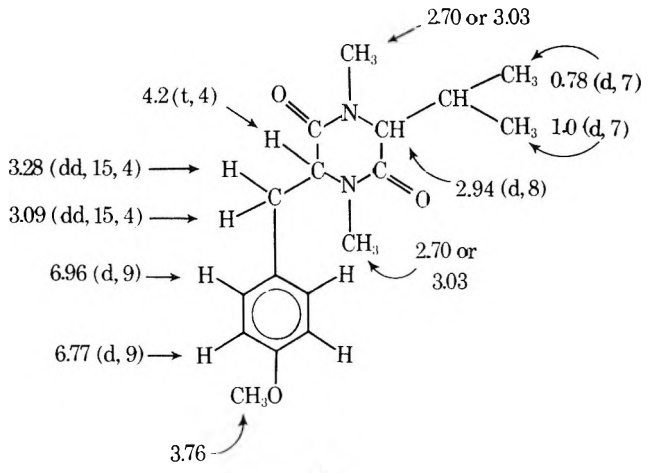
Similarly the ^{13}C NMR spectra were also complex at room temperature. The 28 carbon atoms of majusculamide B, however, could be easily distinguished by determining the spectrum in anhydrous dimethyl-d_6 sulfoxide at 140 °C. One carbon was a ketone carbonyl and three carbons were amide carbonyls, in agreement with IR data and the neutrality of the compound. During the ^{13}C NMR experiments, which required over 15 h of continuous heating, appreciable darkening of the sample occurred. Gel filtration resulted in only a 50% recovery of majusculamide, which proved to be a mixture of the two epimers rather than the pure majusculamide B, and two new substances **1** and **2**, apparently products of a pyrolysis that had ensued during the heating period.

Compound **1** was optically inactive, had the molecular composition $C_{11}H_{21}NO_2$ as shown by combustion analysis and high-resolution mass spectrometry, and was easily deduced to be 2-methyl-3-oxodecanoic amide from spectral data.



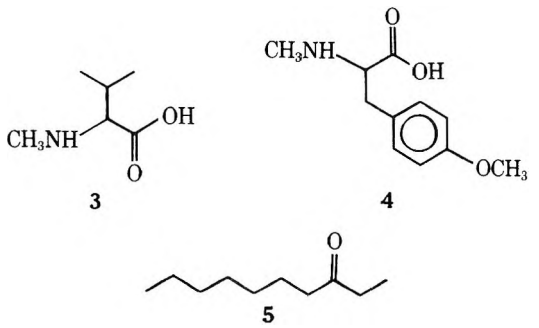
1

Compound **2** was optically active and analyzed for $C_{17}H_{24}N_2O_3$. Its structure was also readily elucidated from



2

spectral data as a cyclic dipeptide. Acid hydrolysis of the majusculamides to N-methylvaline (**3**) and N,O-dimethyltyrosine (**4**) confirmed the amino acid composition of **2**.

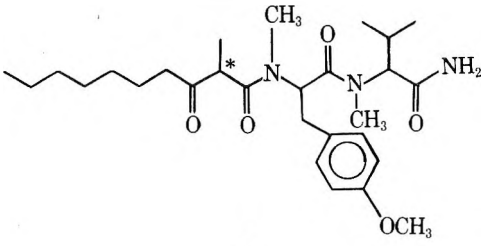


3 **4**

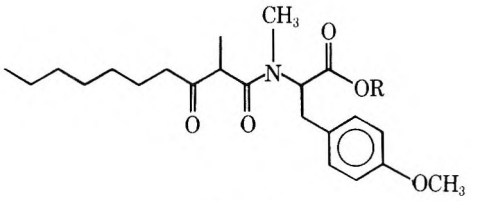
5

When the pyrolysis was repeated in wet dimethyl sulfoxide, only the dipeptide **2** was formed. Compound **1** could not be detected at all. Instead a volatile substance, having the same fruity odor as the acid hydrolysate of the majusculamides, was produced. The odoriferous compound, which formed a crystalline 2,4-dinitrophenylhydrazone, was shown to be 3-decanone (**5**).

Two possible skeletal structures could be written for the majusculamides and an unequivocal choice of **6** was made when partial acid hydrolysis of the majusculamides in aqueous methanol resulted in N-methylvaline and a mixture of **7** and the corresponding methyl ester **8**. N,O-Dimethyltyrosyl-N-methylvaline was not detected.

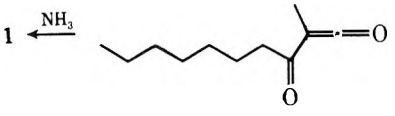


6

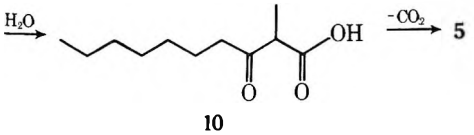


7, R = H
8, R = CH_3

To rationalize the pyrolysis in dimethyl sulfoxide, however, majusculamide B had to decompose to the cyclic dipeptide **2**, an intermediate ketene **9**, and ammonia. Combination of **9** and ammonia in the anhydrous solvent resulted in **1** whereas addition of water to the ketene in the wet solvent yielded the β-keto acid **10** which then decarboxylated to 3-decanone (**5**). Hydrolysis of majusculamide to **10** directly in the wet solvent appeared to be a less likely pathway.



9



10

Majusculamides A and B had to be α and β isomers involving the asymmetric carbon in the 3-oxodecyl side chain (* in **6**). When either majusculamide A or B was heated in dimethyl sulfoxide at 140 °C for several hours, tautomeric epimerization of this carbon occurred. The epimerization process was somewhat slow as the ^1H NMR spectra of the pure amides in Me_2SO-d_6 at 140 °C, which required about 10 min of heating, showed no visible amounts of the epimeric counterparts.

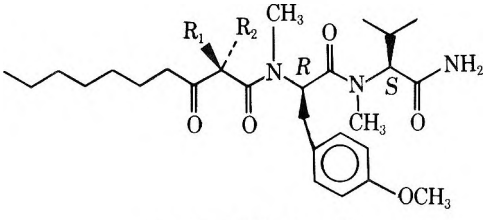
Relative Stereochemistry and X-Ray Crystallographic Studies. Crystals of majusculamide B suitable for single-crystal x-ray analysis were obtained by slow evaporation of MeOH–H_2O solutions at 0 °C. The crystal that was selected was 0.40 × 0.19 × 0.14 mm. Preliminary x-ray photographs showed orthorhombic symmetry and accurate cell constants were determined by a least-squares fit of 15 high angle re-

flections, where a = 9.027 (3), b = 12.102 (3), and c = 26.512 (9) Å. The systematic extinctions conformed to the common chiral space group $P2_12_12_1$. A density of ~1.16 g/cm^3 (flotation in aqueous zinc iodide solution) indicated one molecule per asymmetric unit.

Intensity data were collected at −100 °C with graphite monochromated Cu Kα radiation (1.54178 Å) and using an ω-scan technique and a nitrogen cold stream. All crystal data were recorded at −100 °C. A total of 2183 unique diffraction maxima with $2\theta \leq 114°$ were recorded and after correction for Lorentz, polarization, and background effects 1823 (84%) were judged observed [$I \geq 3\sigma(I)$]. The structure was solved by direct methods using a multisolution weighted tangent formula approach.[6] Full-matrix least-squares refinement with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for hydrogen atoms have converged to a standard crystallographic residual of 0.031 for the observed reflections.[7] The weight of each observation is based on estimated error using counting statistics with a 2% instrumental instability factor. Figure 1 is a perspective drawing of the final x-ray model less hydrogen atoms. The single-crystal x-ray diffraction experiment could not resolve the question of absolute configuration. Further crystallographic details are available in the supplementary material.

In general all bond distances and angles agree well with generally accepted values for given bond types. The chiralities of the two amino acid α carbons [C(2) and C(7)] are opposite. The torsional angles of C(1)–C(2)–N(2)–C(6), N(2)–C(6)–C(7)–N(3), and C(6)–C(7)–N(3)–C(15) are 134.1, 61.7, and −127.8°, respectively. Therefore, C(2)-H is trans to N(2)–C(26); C(6)–O(2) is cis to C(7)–C(8); and C(7)-H is trans to N(3)–C(28). The torsional angle of C(6)–C(7)–C(8)–C(9) is −179°. There are two intermolecular hydrogen bonds between N(1)···O(1) of 2.840 Å and N(1)···O(2) of 2.890 Å. All other intermolecular approaches correspond to van der Waals interactions.

Absolute Configuration. Hydrolysis of a mixture of majusculamides A and B with refluxing 0.7 N hydrochloric acid in 30% aqueous methanol produced (+)-*N*-methylvaline and (−)-*N,O*-dimethyltyrosine. The *N*-methylvaline had an optical rotation that was identical with that reported in the literature for the L enantiomer.[8] The *N,O*-dimethyltyrosine, on the other hand, had an optical rotation that was equal in magnitude but opposite in sign to that of synthetic *N,O*-dimethyl-L-tyrosine.[9] Majusculamides A and B therefore had to have structures **6a** and **6b**, respectively.



6a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$

It is noteworthy to mention that when the hydrolysis of the majusculamides was carried out in stronger acid (3 N HCl), considerable racemization of the *N,O*-dimethyltyrosine, but not of the *N*-methylvaline, occurred.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-100 spectrometer equipped with a Digilab Fourier transform system; chemical shifts are reported in δ units (ppm) relative to Me_4Si (δ 0). Electron impact (EI) mass spectra were determined at 70 eV on a Varian MAT 311 high-resolution mass spectrometer; field desorption (FD) mass spectra were measured by Dr. D. Brent at the Wellcome Research Laboratories, Burroughs-Wellcome Co., Research Triangle Park, N.C. High-performance liquid chromatography was carried out on a Du Pont 830 liquid chromatograph equipped with a UV monitor and a Waters Associates R401 differential refractometer. Optical rotations were determined on a ETL-NPL (Ericsson Telephone Unlimited) automatic polarimeter. UV spectra were measured on a Cary 14 spectrophotometer and IR spectra on a Beckman IR-10 spectrophotometer.

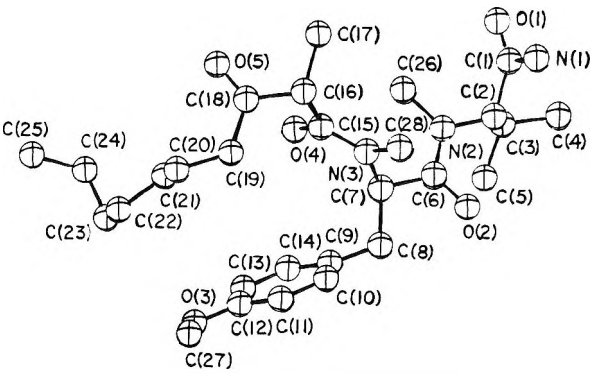


Figure 1. A computer-generated drawing of majusculamide B. Hydrogen atoms are omitted.

Isolation. *Lyngbya majuscula* was collected at Kahala Beach, Oahu, in Jan 1976 and dried at 50 °C for 20 h. The dried seaweed (915 g) was extracted twice with chloroform and twice with methanol. After evaporation of the solvents, both extracts were combined and partitioned between chloroform and water. The chloroform-soluble material, a viscous brown oil, amounted to 22.8 g.

Twenty grams of the crude extract was applied to a 5 × 55 cm column of Florisil and chromatographed with a hexane/chloroform/methanol gradient. The fraction eluted with 90% chloroform/10% methanol (6.41 g) was rechromatographed on a 3.5 × 45 cm column of silica gel using a chloroform/methanol gradient. Elution with 60% methanol/40% chloroform removed a 2.57-g fraction, 1.1 g of which was subjected to gel filtration on a 2 × 120 cm column of Sephadex LH-20 with 1:1 chloroform/methanol to give 510 mg of a black oil. This fraction was further chromatographed on neutral alumina (60 g, chloroform/methanol gradient) and finally on silica gel G (10 g, TLC grade, chloroform/methanol gradient) to yield 140 mg of a crystalline mixture of majusculamides A and B. Final separation of the two epimers was achieved by HPLC on a 1-ft column of μ-Porasil using chloroform/methanol (99.5/0.5) as eluent at a pressure of 500 psi.

Majusculamide A (**6a**) crystallized from aqueous methanol as white needles (36 mg): mp 96–97 °C; $[\alpha]^{26}D$ +19.3° (EtOH, c 1.14); IR (KBr) ν_{max} 3360, 3190, 1720, 1620 cm^{-1}; UV (EtOH) λ_{max} 224 nm (ϵ 7400), 277 (900), 283 (720); EI mass spectrum *m/e* 486 ($M^+ - NH_3$), 374, 290, 246, 183, 164 (base peak, $C_{10}H_{14}NO^+$), 161 ($C_{10}H_9O_2^+$), 121 ($C_8H_9O^+$); high-resolution mass measurement *m/e* 486.307978 ($C_{28}H_{42}N_2O_5$ requires 486.309381); FD mass spectrum *m/e* 503 (M^+); ^{1}H NMR (Me_2SO-d_6, 142 °C) δ 7.16 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.50 (b, 1 H), 5.65 (t, J = 7.5 Hz, 1 H), 4.45 (d, J = 10.5 Hz, 1 H), 3.79 (quartet, J = 7.0 Hz, 1 H), 3.76 (s, 3 H), 3.15 (dd, J = 14 and 7.5 Hz, 1 H), 2.99 (s, 3 H), 2.94 (s, 3 H), 2.84 (dd, J = 14 and 7.5 Hz, 1 H), 2.39 (t, J = 7.0 Hz, 2 H), 2.20 (m, 1 H), 1.50 (m, 2 H), 1.28 (m, 8 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H), 0.72 (d, J = 6.5 Hz, 3 H).

Anal. Calcd for $C_{28}H_{45}N_3O_5 \cdot H_2O$: C, 64.5; H, 9.1; N, 8.1. Found: C, 64.1; H, 8.9; N, 8.4.

Majusculamide B (**6b**) crystallized from aqueous methanol as white needles (84 mg): mp (102–103 °C; $[\alpha]^{26}D$ +14.6° (EtOH, c 0.82); IR (KBr) ν_{max} 3380, 3210, 1725, 1620 cm^{-1}; UV (EtOH) λ_{max} 223 nm (ϵ 8100), 276 (840), 283 (760); EI mass spectrum identical with that of majusculamide A; ^{1}H NMR (Me_2SO-d_6, 140 °C) δ 7.16 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.50 (b, 1 H), 5.71 (t, J = 7.5 Hz, 1 H), 4.43 (d, J = 10.5 Hz, 1 H), 3.79 (quartet, J = 7.0 Hz, 1 H), 3.76 (s, 3 H), 3.17 (dd, J = 14 and 7.5 Hz, 1 H), 3.02 (s, 3 H), 2.90 (s, 3 H), 2.86 (dd, J = 14 and 7.5 Hz, 1 H), 2.21 (t, J = 7.0 Hz, 2 H), 2.19 (m, 1 H), 1.45 (m, 2 H), 1.29 (m, 8 H), 1.18 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 6.5 Hz, 3 H), 0.90 (t, J = 7 Hz, 3 H), 0.71 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (Me_2SO-d_6, (140 °C) δ 205.3 (C), 171.2 (C), 171.0 (C), 170.5 (C), 158.3 (C), 130.0 (2 CH), 129.6 (C), 114.1 (2 CH), 63.2 (CH), 55.4 (CH_3), 54.6 (CH), 50.2 (CH), 39.6 (CH_2), 34.5 (CH_2), 31.0 (CH_3), 30.9 (CH_3), 30.2 (CH), 28.6 (2 CH_2), 26.3 (CH), 23.4 (CH_2), 22.0 (CH_2), 19.5 (CH_3), 18.6 (CH_3), 13.6 (CH_3), 13.0 (CH_3).

Anal. Calcd for $C_{28}H_{45}N_3O_5 \cdot H_2O$: C, 64.5; H, 9.1; N, 8.1. Found: C, 64.0; H, 8.9; N, 8.3.

Pyrolysis of the Majusculamides. A solution of 350 mg of majusculamide B in 2 mL of anhydrous Me_2SO-d_6 (100 atom %) was heated at 140 °C for 15 h to obtain a simplified ^{13}C NMR spectrum that was free of complexity due to two slowly interconverting conformers. Evaporation of the solvent gave a brown gum that was separated on a 2 × 120 cm column of Sephadex LH-20 with 1:1 $CHCl_3$/MeOH into three main fractions (monitored by UV).

Fraction 1 contained 190 mg of a crystalline mixture of majusculamides A and B.

Fraction 2 contained 90 mg of an oil, compound **2**, which slowly crystallized on standing at room temperature: mp 74–76 °C (recrystallization attempts were unsuccessful); $[\alpha]^{25}D$ −8.1° (EtOH, c 1.4); IR (thin film) ν_{max} 1650 cm^{-1}; UV (EtOH) λ_{max} 200 nm (ε 18 700), 225 (12 500), 275 (1700), 282 (1600); EI mass spectrum *m/e* 304 (M^+), 183 ($C_9H_{15}N_2O_2^+$), 121 ($C_8H_9O^+$, base peak); ^1H NMR ($CDCl_3$) δ 6.96 (d, *J* = 9 Hz, 2 H), 6.77 (d, *J* = 9 Hz, 2 H), 4.20 (t, *J* = 4 Hz, 1 H), 3.76 (s, 3 H), 3.28 (dd, *J* = 15 and 4 Hz, 1 H), 3.09 (dd, *J* = 15 and 4 Hz, 1H), 3.03 (s, 3 H), 2.94 (d, *J* = 8 Hz, 1 H), 2.70 (s, 3 H), 2.14 (m, 1 H), 1.00 (d, *J* = 7 Hz, 3 H), 0.78 (d, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.2 (C), 165.0 (C), 158.7 (C), 130.5 (2 CH), 126.3 (C), 113.6 (2 CH), 66.0 (CH), 62.3 (CH), 55.1 (CH_3), 36.4 (CH_2), 33.2 (CH_3), 32.4 (CH_3), 31.7 (CH), 19.1 (CH_3), 16.6 (CH_3).

Fraction 3 contained 60 mg of racemic 2-methyl-3-oxodecanoic amide (**1**) which crystallized from aqueous methanol as white needles: mp 100–101 °C; no $[\alpha]_D$ observed; IR (KBr) ν_{max} 3370, 3180, 1705, 1645 cm^{-1}; UV (EtOH) λ_{max} 199 nm (ε 3500), 222 sh (1100), 285 (280); EI mass spectrum *m/e* 200, 199 (M^+), 181 ($M^+ - H_2O$), 127 ($C_8H_{15}O^+$), 73 ($C_3H_7NO^+$, base peak), 72, 44 ($CONH_2^+$); high-resolution mass measurement *m/e* 199.1577 ($C_{11}H_{21}NO_2$ requires 199.1572); ^1H NMR ($CDCl_3$) δ 6.34 (b, 1 H), 5.74 (b, 1 H), 3.44 (quartet, *J* = 7 Hz, 1 H), 2.56 (t, *J* = 7 Hz, 2 H), 1.6 (bm, 2 H), 1.39 (d, *J* = 7 Hz, 3 H), 1.25 (bs, 8 H), 0.86 (t, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.4 (C), 172.0 (C), 54.0 (CH), 41.7 (CH_2), 31.6 (CH_2), 29.0 (2 CH_2), 23.4 (CH_2), 22.5 (CH_2), 15.1 (CH_3), 14.1 (CH_3).

Anal. Calcd for $C_{11}H_{21}NO_2 \cdot H_2O$: C, 60.6; H, 10.6; N, 6.3. Found: C, 60.8; H, 10.7; N, 6.5.

The pyrolysis was repeated by heating a solution of a 190-mg mixture of majusculamides A and B in 5 mL of wet dimethyl sulfoxide at 140 °C for 84 h. Fractionation of the reaction mixture on Sephadex LH-20 as described above gave 80 mg of impure **2**. Starting material and **1**, however, were not found. In a later fraction was found 18 mg of *p*-methoxybenzoic acid.

Hydrolysis. A. With 1 N Hydrochloric Acid. A 230-mg sample of majusculamides A and B was dissolved in 5 mL of methanol, 12 mL of 1 N HCl was added, and the solution was refluxed for 14 h. Extraction of the reaction mixture, which possessed a fruity odor, with CH_2Cl_2 yielded, after evaporation of the solvent, 80 mg of an odorless oil which was chromatographed on a column of Sephadex LH-20 (2 × 120 cm, 1:1 $CHCl_3$/MeOH) to give 18 mg of a crystalline acid **7** and 43 mg of a colorless, oily ester **8**. The odorless aqueous layer was evaporated to give 100 mg of crystalline material which was separated on a column of Sephadex G-15 (2 × 105 cm, 0.2 N acetic acid[10]) into 30 mg of *N*-methyl-L-valine (**3**) and 40 mg of *N,O*-dimethyl-D-tyrosine (**4**).

The acid, *N*-(2-methyl-3-oxodecanoyl)-*N,O*-dimethyl-D-tyrosine (a mixture of epimers), was recrystallized three times from $CHCl_3$/hexane to give white crystals: mp 93–103 °C; ^1H NMR ($CDCl_3$) δ 7.2–6.7 (m, 4 H), 5.4–4.9 (bs, 1 H), 5.38–5.14 (m, 1 H), 3.67 (s, 3 H), 3.6–2.9 (m, 3 H), 2.82 (s, 3 H), 2.5–1.8 (m, 2 H), 1.60–0.99 (bm, 13 H), 0.83 (t, 3 H); IR (KBr) ν_{max} 3300–2400 (broad), 1725, 1585 cm^{-1}; UV (EtOH) λ_{max} 225 nm (ε 9400), 276 (1250), 283 (1100); EI mass spectrum *m/e* 391 (M^+), 347 ($M^+ - CO_2$), 178 ($C_{10}H_{10}O_3^+$, base peak), 121 ($C_8H_9O^+$).

N-(2-Methyl-3-oxodecanoyl)-(*N,O*-dimethyl)-D-tyrosine methyl ester was a colorless oil and analysis by HPLC (1-ft μ-Porasil, 1:1 hexane/$CHCl_3$, 400 psi) showed the presence of two epimers: ^1H NMR ($CDCl_3$) δ 7.2–6.7 (m, 4 H), 5.48–5.18 (m, 1 H), 3.76 (s, 3 H), 3.72 (s, 3 H), 3.60–2.87 (m, 3 H), 2.83 (s, 3 H), 2.50–1.70 (m, 2 H), 1.6–0.99 (bm, 10 H), 1.07 (d, *J* = 7 Hz, 3 H), 0.84 (t, 3 H); IR (KBr) ν_{max} 1725 (broad), 1635 cm^{-1}; UV (EtOH) λ_{max} 225 nm (ε 11 000), 277 (1700), 284 (1600); EI mass spectrum *m/e* 405 (M^+), 346 ($M^+ - CO_2CH_3$), 192 ($C_{11}H_{12}O_3^+$, base peak), 121 ($C_8H_9O^+$).

The *N*-methyl-L-valine (**3**) had the following properties: $[\alpha]^{27}D$ +16° (H_2O, *c* 1.0) [reported[8] $[\alpha]^{15}D$ +17.5° (H_2O)]; ^1H NMR (D_2O) δ 3.15 (d, *J* = 5 Hz, 1 H), 2.71 (s, 3 H), 2.22 (m, 1 H), 1.03 (d, *J* = 6 Hz, 3 H), 1.00 (d, *J* = 6 Hz, 3 H); EI mass spectrum *m/e* 132 (M + 1), 131 (M^+), 88 ($C_5H_{14}N^+$), 86 ($C_5H_{12}N^+$, base peak).

The *N,O*-dimethyl-D-tyrosine (**4**) had the following properties: $[\alpha]^{25}D$ −17.1° (1 N HCl, c 0.82); ^1H NMR (D_2O + HCl) δ 7.25 (d, *J* = 9 Hz, 2 H), 6.99 (d, *J* = 9 Hz, 2 H), 4.27 (t, *J* = 7 Hz, 1 H), 3.80 (s, 3 H), 3.27 (d, *J* = 7 Hz, 2 H), 2.74 (s, 3 H); EI mass spectrum *m/e* 209 (M^+), 164 ($M - CO_2$), 121 ($C_8H_9O^+$, base peak), 88 ($C_3H_6NO_2^+$).

B. With 3 N Hydrochloric Acid. A 250-mg mixture of majusculamides A and B was hydrolyzed in 5 mL of refluxing 3 N HCl for 20 h. The hydrolysate was extracted with ether and the dried ethereal layer was carefully evaporated in the cold. The residual oil was treated with 2,4-dinitrophenylhydrazine to give an orange semicrystalline solid. Gel filtration on Sephadex LH-20 with 1:1 methanol/chloroform yielded 17 mg of 3-decanone 2,4-dinitrophenylhydrazone: orange needles from aqueous methanol, mp 53–54 °C (reported[11] 55.5–56.5 °C); EI mass spectrum[12] *m/e* (rel intensity) 336 (31), 301 (13), 252 (15), 178 (22), 83 (100); high-resolution mass measurement *m/e* 336.1789 ($C_{16}H_{24}N_4O_4$ requires 336.1797; ^1H NMR ($CDCl_3$) δ 11.2 (b, 1 H), 9.13 (d, *J* = 3 Hz, 1 H), 8.31 (dd, *J* = 10 and 3 Hz, 1 H), 7.95 (dd, *J* = 10 and 1.5 Hz, 1 H), 2.45 (q, *J* = 7 Hz, 2 H), 2.41 (t, *J* = 7 Hz, 2 H), 1.8–1.2 (b, 10 H), 1.22 (t, *J* = 7 Hz, 3 H), 0.88 (bt, *J* = 7 Hz, 3 H).

The aqueous phase was evaporated, redissolved in water, and reevaporated to remove excess HCl. The crystalline residue was applied to a column of Sephadex G-15 (2 × 105 cm) and eluted with 0.2 N acetic acid to give 20 mg of *N*-methyl-L-valine, $[\alpha]^{25}D$ +16° (H_2O, c 1.0), and 28 mg of partially racemized *N,O*-dimethyl-D-tyrosine, $[\alpha]^{25}D$ −8.1° (1 N HCl, *c* 2.7).

When the hydrolysis of majusculamide was carried out in refluxing 6 N HCl for 12 h, a small amount of *p*-hydroxybenzaldehyde, an orange solid that was identified by its ^1H NMR spectrum, was identified in the reaction mixture. Chromatography on silica gel G achieved the separation of the amino acids from the *p*-hydroxybenzaldehyde.

Synthesis of *N,O*-Dimethyl-L-tyrosine. L-Tyrosine was acetylated[13] and the *N*-acetyl-L-tyrosine was converted to *N*-acetyl-*O*-methyl-L-tyrosine with dimethyl sulfate[14] using previously described procedures. The *N*-acetyl protecting group was removed[14] and the resulting *O*-methyl-L-tyrosine was methylated to *N,O*-dimethyl-L-tyrosine following the procedure of Corti.[15] After purification on Sephadex G-15 as described above, it showed an optical rotation of $[\alpha]^{25}D$ +17.5° (1 N HCl, *c* 4.85).[9]

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE74-01950) and Public Health Service (CA-12623). We thank Dr. Mitchell D. Hoyle, Department of Botany, University of Hawaii, and Dr. Roy Tsuda, The Marine Laboratory, University of Guam, for identifying our algal specimens.

Registry No.—**1**, 62758-03-6; **2**, 62758-04-7; **3**, 2480-23-1; **4**, 62758-05-8; **6a**, 62758-06-9; **6b**, 62840-08-8; **7** epimer 1, 62796-01-4; **7** epimer 2, 62796-02-5; **8** epimer 1, 62758-07-0; **8** epimer 2, 62758-08-1; 2,4-dinitrophenylhydrazine, 119-26-6; 3-decanone DNP, 62758-09-2; L-tyrosine, 60-18-4; *N*-acetyl-L-tyrosine, 537-55-3; *N*-acetyl-*O*-methyl-L-tyrosine, 28047-05-4; *N,O*-dimethyl-L-tyrosine, 52939-33-0.

Supplementary Material Available. The fractional coordinates (for unnatural enantiomer) and temperature factors (Table I), bond distances (Table II), and bond angles (Table III) for majusculamide B and the 100-MHz ^1H NMR spectra of majusculamides A and B in chloroform-*d* at 30 °C (Figure 2, A and B) and in dimethyl-d_6 sulfoxide at 140 °C (Figure 2, C and D) (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Camille and Henry Dreyfus Foundation Teacher-Scholar Grant Awardee, 1972–1977.
(2) (a) F. H. Grauer, *Hawaii Med. J.*, **19**, 32 (1959); (b) A. H. Banner, *ibid.*, **19**, 35 (1959); (c) A. H. Banner, P. J. Scheuer, S. Sasaki, P. Helfrich, and C. B. Alender, *Ann. N.Y. Acad. Sci.*, **90**, 770 (1960); (d) S. N. Moikeha, C. W. Chu, and L. R. Berger, *J. Phycol.*, **7**, 4 (1971).
(3) J. S. Mynderse, R. E. Moore, M. Kashiwagi, and T. R. Norton, *Science*, **196**, 538 (1977).
(4) (a) Y. Kato and P. J. Scheuer, *J. Am. Chem. Soc.*, **96**, 2245 (1974); (b) Y. Kato and P. J. Scheuer, *Pure Appl. Chem.*, **41**, 1 (1975); (c) Y. Kato and P. J. Scheuer, *ibid.*, **48**, 29 (1976).
(5) (a) J. S. Mynderse and R. E. Moore, unpublished work; (b) M. Kashiwagi and T. R. Norton, unpublished work.
(6) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect A*, **27**, 368 (1971).
(7) The following library of crystallographic programs was used: C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "The Fast Fourier Algorithm and the Programs ALFF, ALFFDP, ALFFT and FRIEDEL", USAEC Report IS-2625, Iowa State University, Institute for Atomic Research, Ames, Iowa, 1971;

W. R. Busing, K. O. Martin, and H. A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965.
(8) P. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 665, 2192 (1948).
(9) T-s. Tō, *Hoppe-Seylers Z. Physiol. Chem.*, **260**, 175 (1939), reports the isolation of levorotatory *N,O*-dimethyltyrosine from the urine of rabbits which had been injected with racemic *N,O*-dimethyltyrosine. He assigns the D configuration to the excreted amino acid, but a plus sign appears to have been erroneously placed in front of the optical rotation, $[\alpha]^{20}D$ +21.9° (solvent and concentration not indicated).
(10) D. Eaker and J. Porath, *Sep. Sci.*, **2**, 518 (1967).
(11) H. Bertsch and H. Reinheckel, *Fette, Seifen, Anstrichm.*, **64**, 881 (1962).
(12) R. J. C. Kleipool and J. T. Heins, *Nature (London)*, **203**, 1280 (1964).
(13) V. du Vigneaud and C. E. Meyer, *J. Biol. Chem.*, **93**, 295 (1932).
(14) P. Karrer, M. Gisler, E. Horlacher, F. Locher, W. Mäder, and H. Thomann, *Helv. Chim. Acta*, **5**, 469 (1922).
(15) U. S. Corti, *Helv. Chim. Acta*, **22**, 681 (1949).

1,2-Diphenylmaleyl, a Protecting Group for Amino Functions

Uri Zehavi†

Chemistry Department, Imperial College, London SW7 2AY, United Kingdom

Received December 29, 1976

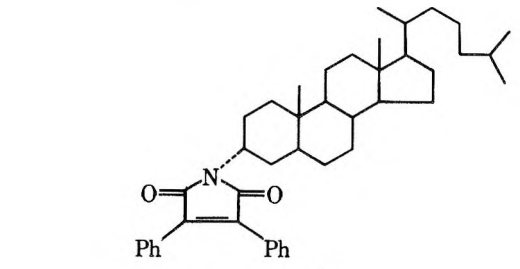
1,2-Diphenylmaleyl (DPM) is described as a protecting group for amino functions and was applied to carbohydrates and steroids. DPM derivatives are prepared through the condensation of the corresponding amines with 1,2-diphenylmaleic anhydride and removed by ethanolic hydrazine. DPM proves to be compatible with and a useful protecting group in glycoside synthesis.

Phthaloyl has been a particularly advantageous protecting group for amino functions in peptide chemistry,[1] penicillin chemistry,[2] and in many areas of natural product chemistry. Diphenylmaleyl (DPM) derivatives, introduced here as a protecting group for amino functions, bear many similarities to the corresponding phthaloyl derivatives, including, to some extent, the protection and deprotection steps; DPM derivatives differ, however, in that they are yellow and fluorescent and thus can be easily determined quantitatively and followed chromatographically; their increased volume compared to many other protecting groups for amino functions can affect adjacent functional groups and they can be conveniently modified into reactive protecting groups as will be described in the subsequent paper.

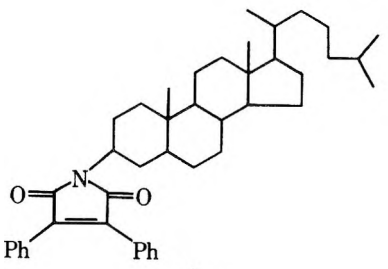
Compounds **1**, **2**, and **3** were conveniently prepared by heating 1,2-diphenylmaleic anhydride[3] and the corresponding amine in dimethylformamide or in dimethylformamide–toluene. Compound **3** in turn was acetylated in pyridine to give compound **4** ($J_{1,2}$ = 8 Hz) in a very good yield. The selective formation of the β-tetraacetate **4** could be explained by the possibility that compound **3**, owing to the steric effect of the DPM group, could be mostly the β anomer (this is supported by the low optical rotation) and by the less hindered approach of the acetylating reagent from the β (e) side. In the Fischer glycoside synthesis both the α and the β anomers (compounds **5**, and **6**, respectively) are formed, the β being the more abundant. It is pertinent to note that in this case the α anomer moves faster in TLC and is less polar than the β anomer. In addition, the NMR spectrum of compound **5** suggests that it might be present in chloroform solution as an equilibrium mixture of conformers rather than the $^4C_1$ chair conformer.

Compound **4** was treated with hydrobromic acid in acetic acid to yield the intermediate 1-bromo derivative (the DPM group appears to be unaffected even after 48 h under these conditions). Subsequent condensation of the bromo intermediate with methanol in the presence of mercuric cyanide afforded the β-glycoside **7** ($J_{1,2}$ = 9 Hz). A number of factors could govern the anomeric nature of compound **7**. At present, the anomeric composition of the bromo intermediate is not known and also it is not clear whether neighboring group participation of the DPM groups could take place; obviously, the easier approach for a nucleophile would be from the β side.

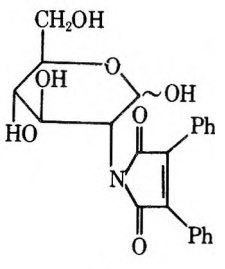
Compound **7** was correlated with compound **6** by deacetylation and by acetylation of compound **6**.



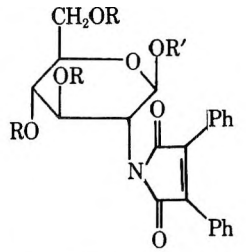
1



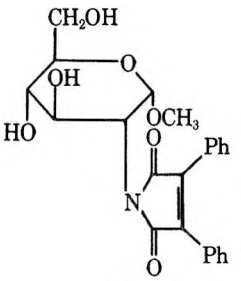
2



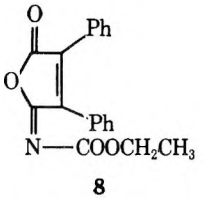
3



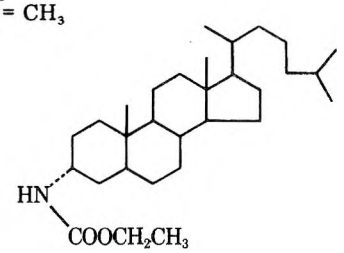
4, R = R′ = CH_3CO
6, R = H; R′ = CH_3
7, R = CH_3CO; R′ = CH_3



5



8



9

† Dr. Uri Zehavi, Research and Development Authority, Ben-Gurion University of the Negev, Beer-Sheva 84110, P.O. Box 1025, Israel.

A few methods designed to facilitate and improve the yields of formation of phthalimido derivatives are reported in the literature. Usually they aim at circumventing or activating the intermediate phthalamic acids. A useful reagent for phthaloylation is reported to be *N*-ethyloxycarbonyl phthalimide.[4] Since the author's early preparations gave rise to yields much lower than those reported here (33–87%) for DPM derivatives, a similar approach was tried in this series. Attempted preparation of *N*-ethyloxy-1,2-diphenylmaleimide gave rise, however, to the isoimide 8 (as apparent from the IR spectrum) that reacted with 3α-aminocholestane[5] to give some of the desired imide 1 but more significantly the ethyloxycarbonyl derivative 9. Hence employing compound 8 proved to be much inferior to the use of 1,2-diphenylmaleic anhydride in the preparation of DPM derivatives.

Removal of the DPM protecting groups and regeneration of the parent amines is effected by ethanolic hydrazine. Thus, compound 1 yielded, following hydrazine treatment and acetylation, 3α-acetamidocholestane[6,5] in 65% yield and compound 7, following the same treatment, gave methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside[7] in 71% yield.

The yields of protection and deprotection employing DPM derivatives are thus similar to those reported for phthaloyl derivatives. The utility of the DPM protecting group in glycoside synthesis is particularly established for the Königs–Knorr synthesis where very conveniently a pure β-glycoside was formed (compound 7).

Experimental Section

Melting points were determined on a Reichert apparatus and are not corrected. ^{1}H NMR spectra were determined in deuteriochloroform with tetramethylsilane as an internal standard at 60 MHz, unless otherwise mentioned. IR, visible, and UV spectra and optical rotations are taken in chloroform, unless otherwise mentioned. TLC and preparative layer chromatography (PLC) were carried out with chloroform (unless otherwise mentioned) on silica gel GF (Merck) and all compounds described (unless otherwise mentioned) were pure by TLC. Column chromatography was performed on silica gel 60 (70–230 mesh, Merck). Evaporations were carried out with a rotary evaporator and in vacuo.

3α-(1,2-Diphenylmaleylimido)cholestane (1). Crude 3α-aminocholestane (0.787 g) and 1,2-diphenylmaleic anhydride (0.560 g) were refluxed in a mixture of dimethylformamide (10 mL) and toluene (2 mL) for 1 h. The reaction mixture was then evaporated, extracted with ether, washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate, dried over sodium sulfate, evaporated, and purified on a "dry" silica gel column (20 g, eluted with benzene–petroleum ether, 1:1). Compound 1 was isolated as a yellow glass (0.412 g, 33%) that was crystallized from acetone: mp 157–162 °C; $[\alpha]^{21}_D$ +43.3° (c 0.09); ν_{max} 3400, 3350, 1698, and 1345 cm^{-1}; λ_{max} 278 nm (ϵ 1.04 × 10^4) and 357 (3.84 × 10^3); ^{1}H NMR τ 2.68 (m, 10, narrow, aromatic), 5.60 (m, 1, H-3e, half-height width 15 Hz), 7.9–9.5 (steroid "envelope" including CH_3 signals at 9.12, 9.13, and 9.37).

Anal. Calcd for $C_{43}H_{57}NO_2$: C, 83.31; H, 9.27; N, 2.26. Found: C, 83.18; H, 9.30; N, 2.22.

3α-(1,2-Diphenylmaleylimido)cholestane (1) and 3β-(1,2-Diphenylmaleylimido)cholestane (2). A mixture of 3α- and 3β-aminocholestane[5] (326 mg) and 1,2-diphenylmaleic anhydride (413 mg) in dimethylformamide (6 mL) was kept in a 160 °C bath for 6 h. The reaction mixture was then evaporated and applied to a "dry" silica gel column (20 g, 1 cm in diameter). Fractions (8 mL each) were collected as soon as the yellow color started to emerge. Fractions 9–13 contained compound 1 (124 mg, 24%) and fractions 2–6 contained compound 2 (155 mg, 30%). Compound 2 was recrystallized from acetone to give yellow needles: mp 238–239 °C, $[\alpha]^{21}_D$ +14.6° (c 0.26); ν_{max} 2900, 2850, 1690, 1600, and 1330 cm^{-1}; λ_{max} 277 nm (ϵ 1.10 × 10^4) and 357 (3.75 × 10^3); ^{1}H NMR τ 2.53 (narrow m, 10, aromatic), 5.95 (38 Hz half-height width m, H-3a, measured at 100 MHz), 7.5–9.4 (steroid "envelope" including CH_3 signals at 9.02, 9.06, 9.17, 9.33).

Anal. Calcd for $C_{43}H_{57}NO_2$: C, 83.31; H, 9.27; N, 2.26. Found: C, 83.27; H, 9.31; N, 2.31.

2-Deoxy-2-(1,2-diphenylmaleylimido)-D-glucose (3). 2-Amino-2-deoxy-D-glucose hydrochloride (1.5 g) was dissolved in methanol (20 mL) and treated with sodium methoxide in methanol (40 mL, 0.15 M). The methanol was subsequently evaporated at 30 °C, 1,2-diphenylmaleic anhydride (1 g), dimethylformamide (35 mL), and toluene (15 mL) were added, and the reaction mixture was kept at reflux for 2 h. Considerable decomposition was apparent (browning). The reaction mixture was evaporated, extracted with chloroform, and washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate, dried over sodium sulfate, evaporated, and applied to a column of silica gel (30 g, 2 cm in diameter and eluting with ethyl acetate at 10 mL per fraction). Collection started when the yellow color began to emerge. Compound 3 (fractions 6–16) was isolated as a yellow glass: mp 85–95 °C (0.265 g); $[\alpha]^{19}_D$ +23.4° (3 min) → 18.3° (18 h, final, c 0.21); ν_{max} 3430 (wide), 1695, 1600, 1350 cm^{-1}.

2-Deoxy-2-(1,2-diphenylmaleylimido)-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (4). The compound was prepared under conditions that caused less browning from 2-amino-2-deoxy-D-glucose without the intermediate isolation of compound 3. 2-Amino-2-deoxy-D-glucose hydrochloride (108 mg) and 1,2-diphenylmaleic anhydride (125 mg) were stirred in dimethylformamide and triethylamine (0.1 mL) was added. The reaction mixture was then placed in a bath of 105 °C for 15 min whereby it was transformed to a clear yellow solution. The solution was evaporated, dissolved in a mixture of pyridine (1 mL) and acetic anhydride (0.5 mL), and kept at room temperature overnight. Ice was added to the reaction mixture and after 1 h it was evaporated, extracted with ether, washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate, dried over sodium sulfate, evaporated, and purified by PLC. Compound 4 was isolated as a yellow oil (197 mg, 87%) or glass: mp 88–93 °C; $[\alpha]^{30}_D$ +46.7° (c 0.66); ν_{max} 1770, 1730, 1700 (shoulder), and 1400 cm^{-1}; λ_{max} 274 nm (ϵ 7.44 × 10^3), 370 (4.02 × 10^3); 100-MHz ^{1}H NMR τ 2.46 (narrow m, 10 aromatic), 3.39 (d, 1, H-1, $J_{1,2}$ = 9.0 Hz, and no sign of a narrow d), 4.05 (q, 1, J = 11, 9.5 Hz), 4.70 (t, 1, J = 9.5 Hz), 5.4–6.1 (multiplets, 4), 7.90 (s, 3, $COCH_3$), 7.93 (s, 3, $COCH_3$), 7.96 (s, 3, $COCH_3$), and 8.08 (s, 3, $COCH_3$).

Anal. Calcd for $C_{30}H_{29}NO_{11}$: N, 2.42. Found: N, 2.57.

Methyl 2-Deoxy-2-(1,2-diphenylmaleylimido)-α-D-glucopyranoside (5) and Methyl 2-Deoxy-2-(1,2-diphenylmaleylimido)-β-D-glucopyranoside (6). **A.** Compound 3 (0.252 g) and Amberlite IR 120 (H^+ form) were refluxed in methanol (20 mL) for 18 h, by which time compound 3 was partially converted, as evidenced by TLC (chloroform–ethyl acetate, 1:1), into compound 5 and the slower moving compound 6. The two products were greatly purified by PLC (in the same solvent). Compound 5 (46 mg) was isolated as a yellow oil, crystallized from ethanol–water as elongated leaflets: mp 128 °C $[\alpha]^{30}_D$ +51.2° (c 0.65); λ_{max} 278 nm (9.22 × 10^3) and 370 (5.43 × 10^3); 100-MHz ^{1}H NMR [same for a sample isolated from the mother liquor, $[\alpha]^{18}_D$ +46.6° (c 0.7)] τ 2.68 (m, 10), 4.67 (d, 0.6, H-1, $J_{1,2}$ = 5 Hz), 4.82 (d, 0.4, H-1, $J_{1,2}$ = 3.5 Hz), 5.10 (m, 1), 5.3–6.5 (multiplets), 6.58 (s, 1.8, OCH_3), 6.68 (s, 1.2, OCH_3), 6.58 (s, 1.8, OCH_3), and 6.68 (s, 1.2, OCH_3).

Anal. Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.74; H, 5.34; N, 3.16.

Attempted crystallization of compound 6 (97 mg, yellow oil) from the same solvent yielded a very small amount of solid, mp 107 °C, $[\alpha]^{30}_D$ +63.5 (c 0.6). Compound 6 was isolated from the mother liquor following PLC as a yellow oil: $[\alpha]^{18}_D$ +21.2° (c 0.8); ^{1}H NMR τ 2.48 (m, 10, aromatic), 4.8 (d, 1, H-1, $J_{1,2}$ = 8 Hz), 4.9–6.7 (multiplets), 6.54 (s, 3, OCH_3).

B. Compound 7 was dissolved in ethanolic ammonia (2%) and left at room temperature overnight. The product moved in TLC (chloroform–ethyl acetate, 1:1) like compound 6.

Methyl 2-Deoxy-(1,2-diphenylmaleylimido)-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (7). **A.** Compound 4 (3.0 g) was dissolved in 1,2-ethylene dichloride and hydrobromic acid in acetic acid (3 mL, 45%) was added. The reaction mixture was kept for 2 h at room temperature, evaporated from a bath of 30 °C, and extracted with ether and the intermediate 1-bromo derivative separated as an oil upon the addition of petroleum ether (faster moving than compound 4 and relatively clean by TLC): ν_{max} 1770, 1730, 1700 (shoulder), 1605, 1450, 1400, and 1250 cm^{-1}. The oily intermediate, mercuric cyanide (2.0 g), and crushed calcium sulfate (2.0 g) were stirred in chloroform (30 mL), washed with water, and dried. Methanol (3 mL) was added and the reaction mixture was refluxed overnight. Subsequently, it was filtered through a Celite filter, washed with water, dried over sodium sulfate, evaporated, and applied to a "dry" silica gel column (40 g, 2.0 cm in diameter, eluted with chloroform–ethyl acetate, 1:1, 5-mL fractions). Pure compound 7 (2.34 g, yellow glass) was present in fractions 11–32. It was crystallized from ethanol as yellow, elongated prisms: mp 194–195 °C; $[\alpha]^{20}_D$ +40.4° (c 0.2); ν_{max} 275 nm (ϵ 9.12 × 10^3) and 362 (4.83 × 10^3); ^{1}H NMR (100 MHz) τ 2.68 (m, 10, aro-

matic), 4.31 (q, 1, H-3, $J_{2,3}$ = 11, $J_{3,4}$ = 9 Hz), 4.77 (d, 1, H-1, $J_{1,2}$ = 9 Hz), 4.86 (t, 1, H-4, $J_{4,5}$ = 9 Hz), 5.5–5.9 (multiplets, 3), 6.20 (wide m, ca. 20 Hz, 1, H-5), 6.54 (s, 3, OCH_3), 7.92 (s, 3, $COCH_3$), 8.00 (s, 3, $COCH_3$), 8.12 (s, 3, $COCH_3$). Irradiation at τ 4.31 changes the signal at τ 4.86 into a doublet. Irradiation at τ 4.86 changes the signal at τ 6.20 to a triplet (J = ca. 8 Hz) and affects the signal at τ 4.31.

Anal. Calcd for $C_{29}H_{29}NO_{10}$: C, 63.15; H, 5.30; N, 2.54. Found: C, 63.08; H, 5.12; N, 2.48.

B. Compound **6** (12 mg) was dissolved in a mixture of pyridine (2 mL) and acetic anhydride was kept at room temperature overnight. Ice was added to the reaction mixture and after 1 h it was evaporated. The product was crystallized as yellow prisms from ethanol (10 mg), mp 191–192 °C, and was identical by TLC (chloroform) and gave no depression in a mixture melting point with a sample prepared according to procedure A.

***N*-Ethyloxycarbonyl-1,2-diphenylmaleylisoimide (8).** 1,2-Diphenylmaleic anhydride (5 g) and ammonium hydroxide (4 mL, 35%) in dimethylformamide (5 mL) were refluxed for 1 h. The reaction mixture was cooled, another identical portion of ammonium hydroxide was added, and heating was continued after the condenser was removed, to let most of the water evaporate. The starting material was converted predominantly (TLC) into 1,2-diphenylmaleimide. The stirred reaction mixture was then cooled in an ice bath, and triethylamine (2.8 mL) in dimethylformamide was added following by ethyl chloroformate (2 mL). The reaction mixture was brought to room temperature for 1 h, poured into ether, dried over sodium sulfate, evaporated, and applied to a column of "dry" silica gel (100 g, 3 cm in diameter and eluted with chloroform at 15 mL per fraction). Fractions 3–7 contained 1,2-diphenylmaleic anhydride (0.482 g). Fractions 8–23 contained the slightly contaminated compound **9** (2.536 g) that was recrystallized from chloroform–petroleum ether as yellow prisms: mp 108 °C; ν_{max} 1800, 1755, 1715, and 1315 cm^{-1}.

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.92; H, 4.72; N, 4.26. Compound **8** could be also crystallized from ethanol as yellow needles: mp 95 °C identical IR spectrum; ^1H NMR τ 2.58 (s, 10, aromatic), 5.52 (q, 2, J = 7 Hz), 8.59 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 71.22; H, 4.57; N, 4.20.

Reaction of Compound 8 with 3α-Aminocholestane. 3α-Aminocholestane hydrochloride (27.3 mg) and compound **8** were stirred in dimethylformamide at 0 °C, triethylamine (0.25 mL) was added, and the stirring was continued for 1 h. The reaction mixture was evaporated and separated by PLC. Compounds identified (in order of increased migration) were ethylurethane (TLC); 1,2-diphenylmaleimide (15.5 mg, TLC, IR, NMR); compound **8** (8.3 mg, TLC, IR); 3α-ethyloxycarbonylaminocholestane (**9**, 19.3 mg), recrystallized from ethanol as very thin needles [mp 125–126 °C $[\alpha]^{21}_D$ +29.5° (c 0.11); ^1H NMR τ 5.18 (1, NH), 5.90 (q, 2, J = 7.0 Hz, CH_2O), 6.16 (m, 1, H-3), 8–9.4 (steroid "envelope" containing CH_3 signals at 9.10, 9.20, and 9.38)].

Anal. Calcd for $C_{30}H_{53}NO_2$: C, 78.37; H, 11.62; N, 3.05. Found: C, 78.30; H, 11.46; N, 3.05.

Compound **1** (3.9 mg, TLC).

Removal of the 1,2-Diphenylmaleyl Protecting Groups. A. Compound **1** (106 mg) was left at reflux in a solution of hydrazine hydrate (0.2 mL) in ethanol (5 mL) whereby it gradually dissolved. After 4 h the reaction mixture was evaporated and the residue was dissolved in pyridine (2 mL) and acetic anhydride (1 mL) and left at room temperature overnight. Ice was added and after 1 h the reaction mixture was extracted with ether, washed with dilute hydrochloric acid, water, and sodium hydrogen carbonate, dried over sodium sulfate, evaporated, and purified by PLC to give 3α-acetamidocholestane (42.8 mg, 65%), mp 193–205 °C. The product recrystallized as needles from ethanol: mp 218 °C; $[\alpha]^{23}_D$ +35.3° (c 0.31) (lit.[6] mp 216 °C, $[\alpha]_D$ +33°); ν_{max} 3440, 2910, 2850, and 1660 cm^{-1}.

B. Compound **7** was refluxed for 1 h in an ethanolic hydrazine solution and then acetylated as above. TLC (ethyl acetate) showed only one compound that was charred by sulfuric acid. Methyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside was isolated from PLC (ethyl acetate, 46.1 mg, 71%). It was recrystallized as needles from ethanol, mp 162 °C (ethyl acetate–petroleum ether, mp 156 °C), $[\alpha]^{21}_D$ −20.9° (c 0.12, methanol) (lit.[7] mp 163 °C, $[\alpha]^{21}_D$ −22.2° in methanol).

Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.52; H, 6.17; N, 3.81.

Acknowledgment. The author is grateful to Professor Sir D. H. R. Barton, F.R.S., for his discussions and encouragement and would like to thank Dr. W. Motherwell for a gift of 3α-aminocholestane and Dr. S. Narang for a gift of a mixture of 3α- and 3β-aminocholestane.

Registry No.—**1**, 62460-40-6; **2**, 62493-02-1; **3**, 62461-73-8; **4**, 62461-74-9; **4** 1-bromo derivative, 62461-78-3; **5**, 62461-75-0; **6**, 62461-76-1; **7**, 62448-72-0; **8**, 62461-77-2; **9**, 62493-03-2; 3α-aminocholestane, 62560-52-5; 1,2-diphenylmaleic anhydride, 4808-48-4; 3β-aminocholestane, 62532-40-5; 2-amino-2-deoxy-D-glucose HCl, 66-84-2; ethyl chloroformate, 541-41-3; 3α-aminocholestane HCl, 62532-41-6; 1,2-diphenylmaleimide, 31295-36-0; 3-acetamidocholestane, 16356-49-3; methyl 2-acetamido-2-deoxy-3,4,6-triacetyl-β-D-glucopyranoside, 2771-48-4.

References and Notes

(1) R. A. Boissonnas, *Adv. Org. Chem.*, **3**, 159 (1963).
(2) B. G. Ramsay and R. J. Stoodley, *J. Chem. Soc. C.*, 1319 (1969); S. Kukolja and S. R. Lammert, *J. Am. Chem. Soc.*, **97**, 5582 (1975).
(3) C. F. Koelsch and S. Wawzonek, *J. Org. Chem.*, **6**, 684 (1941).
(4) G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **79**, 688 (1960).
(5) C. W. Shoppe, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).
(6) R. D. Haworth, L. H. C. Lunts, and J. McKenna, *J. Chem. Soc.*, 986 (1955).
(7) P. G. Walker, *J. Chem. Soc.*, 4754 (1957).

Photochemical Reactions of Phenylglyoxalyl Amides

Uri Zehavi†

Chemistry Department, Imperial College, London SW7 2AY, United Kingdom

Received December 29, 1976

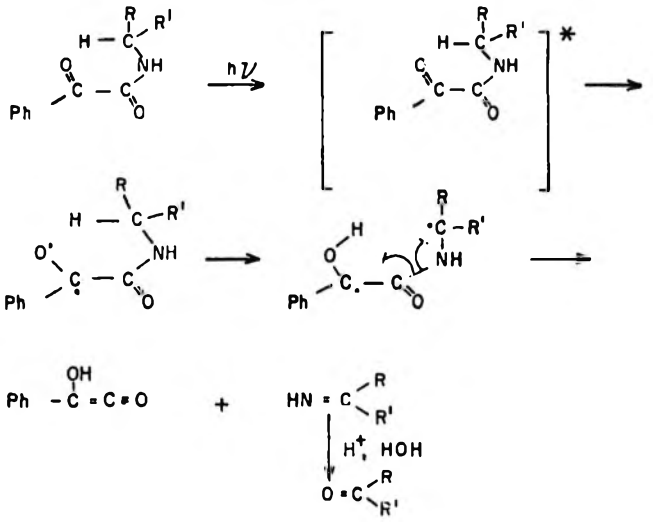
Phenylglyoxalyl amides undergo a photochemical oxidation–reduction that, after acid hydrolysis, converts the amino residues of the amides to the corresponding carbonyl derivatives. The procedure is applied to the conversion of cyclohexylamine, amino sugars, and steroidal amines to the corresponding carbonyl compounds. A convenient synthesis of phenylglyoxalyl amides is through the ozonolysis and partial trans acylation of 1,2-diphenylmaleimides. This presents an example of utilizing the 1,2-diphenylmaleyl (DPM) derivative as a *reactive protecting group*.

Phenylglyoxalic acid esters undergo an intramolecular photochemical redox reaction in which the alcohol moiety of the ester is oxidized.[1,2] Phenylglyoxalic acid amides could be expected to undergo an analogous reaction, possibly through a similar n → π* excited state as indicated in Scheme I.

This reaction could prove to be useful in polyfunctional molecules where acylation (and thus the formation of the corresponding phenylglyoxylic acid amide) may be directed

† Address correspondence to Dr. Uri Zehavi, Research and Development Authority, Ben Gurion University of the Negev, Beer-Sheva 84110, P.O. Box 1025, Israel.

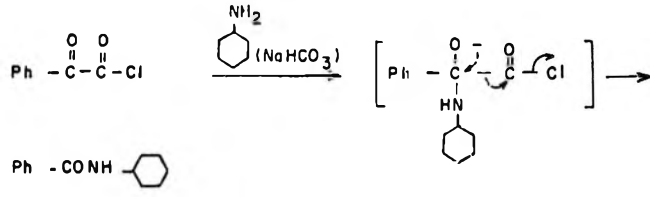
Scheme I



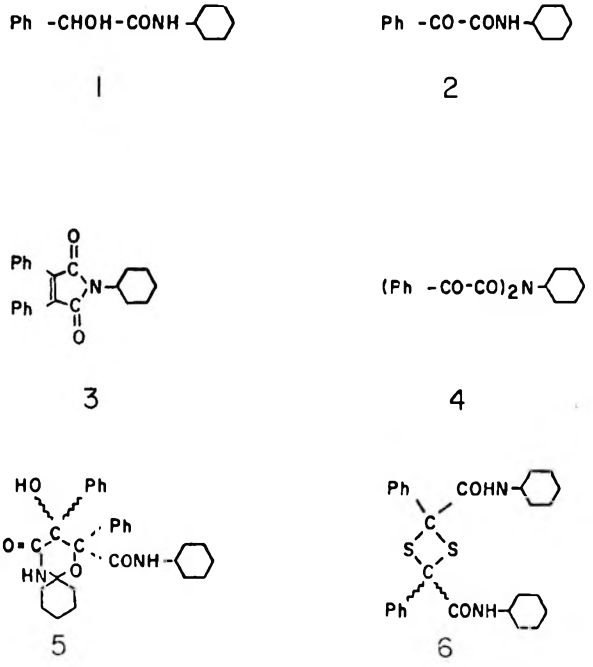
selectively to nitrogen. The net result would be the synthetic operation of converting primary amines to the corresponding carbonyl derivatives.[3]

In our first attempt to prepare phenylglyoxalyl-*N*-cyclohexylamide, starting from phenylglyoxalyl chloride[4] and cyclohexylamine under Schotten–Baumann conditions, decarbonylation took place and benzoyl-*N*-cyclohexylamide was isolated (Scheme II). Alternative routes to phenylglyoxalic

Scheme II



acid amides were sought and they have been prepared through (a) the oxidation of the mandelic acid amide (thus compound 1 was oxidized with permanganate[5] to compound 2); or (b)



through the ozonolysis[6] of 1,2-diphenylmaleyl imides and via bisphenylglyoxalylimides. Thus compound 3 was ozonolyzed to yield compound 4 which, in turn, could be selectively deacylated to give compound 2.

Table I. Irradiation of Compound 2 (0.066 M, Ambient Temperature) in Different Solvents

Solvent	Yield of cyclohexanone, %[a]	Solvent	Yield of cyclohexanone, %[a]
Acetone	25	*tert*-Butyl alcohol	10
Acetonitrile	14	Ethanol	25–46[c]
Benzene	16[b]	Ether	18

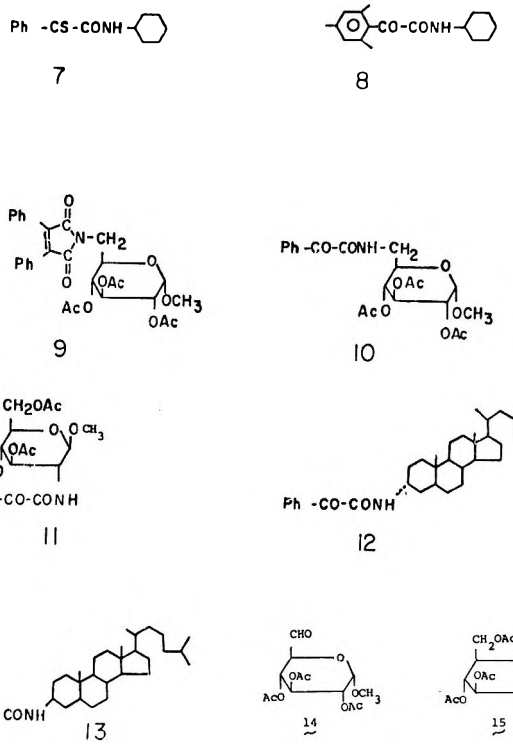
[a] Irradiation times were 100 or 120 min, longer than necessary for the disappearance of compound 2 (TLC) and with no noticeable difference. The solution was subsequently acidified with a drop of 3 N hydrochloric acid and cyclohexanone was determined a few minutes later by GC. [b] Benzaldehyde (3%) was also determined. [c] Irradiation at reflux temperature did not improve the yield; irradiation without the exclusion of air or even with bubbling oxygen did not alter the yield.

Irradiation of compound 2 in a variety of solvents provided cyclohexanone in low yields with ethanol being the choice solvent for the reaction (Table I). Examination of the nonvolatile products from a reaction in ethanol resulted in the isolation of three of them: compound 1 and two products (B and C) to which structure 5 is tentatively assigned.

In an attempt to obtain similar results but employing lower energy irradiations, compound 7 was made alongside the dimer 6 from the corresponding Bunte salt $PhCH(CONHC_6H_{11})S{-}SO_3Na$, by a procedure similar to the one described for thiobenzoylcarboxylic acid ethyl ester.[7] In distinction from the ester, compound 7 is stable in the solid state for months. In chloroform solution, however, it tends to dimerize to compound 6 (TLC). Irradiation of compound 7 with a tungsten lamp failed to yield more than traces of cyclohexanone and mostly led to dimerization.

Several routes were tried in order to improve the cyclohexanone yield from the irradiation of compound 2. Thus, compound 8 was designed to inhibit the extent of dimerization through steric hindrance. It was synthesized by a Friedel–Crafts reaction with mesitylene using (presumably) $(ClCOCO)_2NC_6H_{11}$ as an intermediate. Unfortunately, the substitution on the benzene ring inhibited also the photochemical reaction—no reaction was obtained. It was then considered that since, in the proposed mechanism for the photochemical reaction (Scheme I) a crucial step is the homolytic cleavage of the amide C–N bond and since, in distinction from the ester case, this should have had a partial double bond character that could be expected to retard such a homolytic cleavage, an appropriate electron-withdrawing substitution on the nitrogen could improve the yield. Compound 4 was an obvious choice where an additional (electron-withdrawing) phenylglyoxalyl group is situated on nitrogen and could also increase the probability of the required hydrogen abstraction in the photochemical reaction. This compound, however, presented no advantage over compound 2. An alternative approach was to include aqueous mineral acids in the irradiation mixture; this, in addition, should have hydrolyzed the intermediate imine to the desired ketone. In fact, including mineral acids proved to be very satisfactory and compound 2 was converted into cyclohexanone in 77% yield.

Encouraged by these results, we have prepared a few phenylglyoxalic acid amides, compounds 10–13, through the ozonolysis of the corresponding DPM derivatives and selective deacylation. Compound 10 was transformed in low yield to the 6-aldehydo intermediate 14 and identified (compare ref 8) after sodium borohydride reduction and acetylation as methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranoside or as the *p*-ni-



trophenylhydrazone. Compound **11** was converted by irradiation to the 2-keto derivative **15** that was not isolated (compare ref 9) but reduced and hydrolyzed to a mixture of D-glucose and mannose. More suitable conditions designed to circumvent side reactions and to isolate the carbonyl product are being considered.

Compounds **12** and **13** yielded, upon irradiation, 51 and 59% of 3-cholestanone demonstrating the synthetic usefulness of the photolysis of phenylglyoxalyamides in converting primary amines to carbonyl derivatives (at least in cases where complication is not expected).

Phenylglyoxalyl itself could serve as a protecting group for amines in certain synthetic operations. The DPM group, however, is much more suited for this purpose.[10] At the appropriate stage of synthesis it can be made reactive by converting it to phenylglyoxalyl, whose photochemistry is the subject of this paper.

Experimental Section

Experimental details are as described in the preceding paper.[10] In addition, GC was carried out employing a Perkin-Elmer F 11 instrument and a column of 8% Carbowax 1540 on Chromosorb W AW DMCS, 80–100 mesh, 0.125 in. in diameter and 2 m long. All irradiations, unless otherwise mentioned, were carried out at room temperature, under argon with a 250-W high-pressure mercury lamp through a Pyrex filter and irradiation times were longer than necessary for the complete conversion (TLC) of the starting material. Descending paper chromatography was carried out on Whatman No. 1 paper developed with 1-butanol–ethanol–water (4:1:1, I) or with 1-butanol–acetic acid–water (25:6:25, upper phase, II) and chromatographs were sprayed with an *m*-phenylenediamine reagent.[11]

Benzoyl-*N*-cyclohexylamide. A solution of cyclohexylamine (2.5 mL) and of sodium hydrogen carbonate (3.0 g) in water (50 mL) was stirred in an ice bath. Phenylglyoxalyl chloride[4] (3.0 g) was added slowly and the stirring was continued at room temperature overnight. The white, amorphous product was collected by filtration (4.4 g, mp 147–151 °C) and recrystallized from ethyl acetate to yield prisms, mp 151 °C (lit.[12] mp 153 °C).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.59; H, 8.22; N, 6.85.

α-Hydroxy-α-phenylacetyl-*N*-cyclohexylamide (1). This was prepared according to the general procedure of Shapiro, Rose, and Freedman[13] starting from mandelic acid ethyl ester (10 g) and cyclohexylamine (5.8 mL). The title compound **1** was crystallized from a mixture of ethanol and water to give leaflets: mp 95 °C (7.0 g); ν_{max} 1665 cm^{-1} (C=O); ^1H NMR τ 2.66 (narrow m, 5, aromatic), 5.01 (d, 1, benzylic, J = 4 Hz), 6.20 (d, 1, NH, J = 4 Hz), 6.28 (m, 1, cyclohexyl H), 7.8–9.2 (m, 10). The signal at τ 6.20 disappears upon the addition of D_2O and the one at τ 5.01 collapses to a singlet.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.20; N, 6.00. Found: C, 72.11; H, 8.11; N, 5.90.

Phenylglyoxalyl-*N*-cyclohexylamide (2). A. Compound **1** (9.2 g) in ether (300 mL) was stirred mechanically together with a solution of dihydrogen phosphate (dihydrate, 76 g) in a saturated aqueous solution of magnesium sulfate (48 mL) in an ice bath. Potassium permanganate (5.3 g) was added and the reaction mixture was allowed to reach room temperature. Following the disappearance of the purple permanganate color (checked by applying a drop to a filter paper), water (40 mL) and another portion of potassium permanganate were added. TLC indicated a partial reaction. The ether solution was separated, washed with water, dried over sodium sulfate, and evaporated. The residue was applied to a column of silica gel (100 g, 2.5 cm in diameter) and the crystalline product, pure by TLC (chloroform), was eluted with ethyl acetate–chloroform (3:2, 1.4 g), mp 75–80 °C. The title compound **2**, needles from chloroform–petroleum ether, had mp 112 °C; ν_{max} (carbon tetrachloride) 1670 and 1695 cm^{-1}; λ_{max} 253 nm (ϵ 1.10 × 10^4); ^1H NMR τ 1.2–1.9 (m, 2), 2.2–2.9 (m, 3), 6.18 (m, 1 cyclohexyl H), 7.6–9.1 (m, 10).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.41; N, 6.06. Found: C, 72.79; H, 7.33; N, 5.96.

Further fractions from the column chromatography contained a mixture of compounds **1** and **2** (0.3 g) and pure compound **1** (5.9 g).

B. Sodium methoxide (10 mL, 0.15 M in methanol) was added to a methanolic solution (10 mL) of compound **4** (91 mg) at 0 °C. The reaction was stopped after 10 min by stirring and neutralizing with excess Amberlite IR 120 (H^+ form). The resin was removed, the solution was evaporated, and the residue was purified by PLC and the product crystallized as needles (49 mg, 84%), mp 111–112 °C (Found: C, 72.49; H, 7.50; N, 5.79). Compound **2** was alternatively prepared from compound **4** by dissolving the later in pyridine–water (5:1) and keeping it overnight at room temperature.

1,2-Diphenylmaleyl-*N*-cyclohexylimide (3). 1,2-Diphenylmaleic anhydride[14] (0.5 g) in toluene–dimethylformamide (3:1, 40 mL) and cyclohexylamine (0.2 mL) were left for reflux under nitrogen for 3 h. The solvents were evaporated and the residue was crystallized from ethanol to give the title compound as yellow, fluorescent needles: mp 160–161 °C (0.48 g, 72%); λ_{max} 278 nm (ϵ 9.80 × 10^3) and 365 (3.76 × 10^3); ^1H NMR τ 2.47 (narrow m, 10, aromatic), 8.20 (m, 11, cyclohexane).

Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.52; H, 6.15; N, 4.10.

Bisphenylglyoxalyl-*N*-cyclohexylimide (4). Compound **3** (0.55 g) was dissolved in acetone (20 mL) and propionaldehyde was added (5 mL). Ozone in oxygen was bubbled through the solution at −78 °C until the disappearance of the yellow color. The solution was then evaporated at room temperature and the title compound was crystallized as prisms (0.46 g, 77%) from ethanol: mp 98 °C; ν_{max} 2900, 2850, 1755 (low), and 1700 cm^{-1} (high); λ_{max} 260 nm (shoulder, ϵ 1.90 × 10^3) and 266 (shoulder, ϵ 1.56 × 10^3) increasing absorbance 240–200 nm; ^1H NMR τ 2.48 (m, 10, aromatic), 7.4–9.2 (m, 11).

Anal. Calcd for $C_{22}H_{21}NO_4$: N, 3.85. Found: N, 3.77.

Nonvolatile Products from the Irradiation of Compound 2. Compound **2** (186 mg) in ethanol (15 mL) was irradiated for 2 h. The reaction mixture was evaporated and separated by PLC (benzene) and three bands, in order of decreased polarity, were isolated: A, oil, 78 mg, impure component containing compound **1** (TLC and IR); B, oil, 38 mg (21%), that could be crystallized from methanol–water [mp 129–130 °C; ν_{max} 3500 (wide, OH), 3390 (sharp, NH), 3250 (CH), 1650 (CO), 1600, 1550 cm^{-1}; the ^1H NMR had no benzylic proton, τ 2.2–2.8 (m, aromatic), 2.81 (apparent s, aromatic), 6–7 (multiplets), 7.9–9.0 (cyclohexyl envelope)]; C, 31.4 mg (17%), elongated prisms [mp 189–190 °C; IR very similar to that of B with variation in the "fingerprint" area; the ^1H NMR had no benzylic proton, τ 1.9–2.8 (m, aromatic), 2.81 and 2.82 (apparent singlets, aromatic), 3.91 (wide m), 6.23 (wide m), 7.7–9.0 (cyclohexyl envelope)].

Anal. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.69; E, 7.41; N, 6.06. Found: C, 72.70; H, 7.45; N, 5.97.

The mass spectra of compounds B and C were very similar: *m/e* 463 (M + 1), 462 (M), 338, 336 ($C_{21}H_{22}NO_3^+$·, M − $C_6H_{11}NHCO$), 233 (PhCHOH − $CONHC_6H_{11}$+·), 105 ($PhCO^+$), 98 and 77 (Ph^+·). Compounds B and C were stable in ethanol solution. Upon acidification and GC (as described in Table I) cyclohexanone was released at 25 and 28% yield, respectively (theory 50%).

2,4-Di(*N*-cyclohexyl)carbamyl-2,4-diphenyldithietane (6) and Thiobenzoylcarboxylic Acid *N*-Cyclohexylamide (7). Sodium

thiosulfate (pentahydrate, 3 g) was dissolved in water (30 mL). Dimethylformamide (100 mL) and α-phenyl-α-chloroacetyl-*N*-cyclohexylamide (2.51 g) were added to form a homogenous solution. The reaction mixture was left at reflux for 3 h. The solution was evaporated and the residue dissolved in water (300 mL) and washed with ether. Chloroform (300 mL) and sodium hydroxide solution (10%, 150 mL) were then added, the mixture was vigorously shaken, and the blue chloroform solution quickly separated. It was washed with water, dried over sodium sulfate, and evaporated at room temperature. The residue was extracted with benzene (15 mL) and a white precipitate (compound **6**, 0.125 g) formed upon the addition of petroleum ether (10 mL). Recrystallized from chloroform the amide **6** formed needles: mp 236 °C; ν_{max} 3300 (NH), 2910 and 2850 (CH), and 1660 cm^{-1} (CO); λ_{max} 315 nm (ϵ 3.58 × 10^2) and 250 (shoulder, 6.02 × 10^3); mol wt 446 (osmometry in chloroform) (required 494.70).

Anal. Calcd for $C_{28}H_{34}N_2O_2S_2$: C, 67.97; H, 6.93; N, 5.66; S, 12.96. Found: C, 67.76; H, 6.67; N, 5.57; S, 13.04. This compound is many times accompanied by a slower moving component that could represent a trimer. The benzene–petroleum ether solution described above was concentrated and compound **7** was allowed to crystallize as blue, elongated prisms: mp 106 °C (loses the color); ν_{max} (carbon tetrachloride) 3400 (NH), 2930 and 2850 (CH), 1670 (CO), 1500 (NH), and 1130 cm^{-1} (C=S, the only significant absorbance that does not have its equivalent in compound **2**); λ_{max} 615 nm (ϵ 45.5), 330 (6.29 × 10^3), and 264 (5.54 × 10^3).

Anal. Calcd for $C_{14}H_{17}NOS$: C, 67.97; H, 6.97; N, 5.66. Found: C, 67.66; H, 6.80; N, 5.33. Only part of compound **7** crystallized as described. Most of it stayed in the mother liquor. Attempted fractionation on silica gel, using benzene for elution, brought about the partial conversion to compound **2**. Yield 0.375 g (15%, compounds **7** and **2**).

A solution of compound **7** (λ_{max} 615 nm, A = 0.3) was left at room temperature for 18 h. As the result the absorbance went down by 35% and the formation of the dimer **6** was evident (TLC).

Irradiation of Compounds 6 and 7. Compound **6** (6.6 mmol) in chloroform was irradiated for 2 h with a 750-W tungsten lamp. No reaction was observed (TLC and GC). Similar irradiation (4 h) was carried out on a chloroform solution of compound **7** (λ_{max} 615 nm, A = 0.1). Only a trace amount of cyclohexanone was formed and compound **7** dimerized and produced also a slower moving compound that could be a trimer (TLC).

2,4,6-Trimethylphenylglyoxalyl-*N*-cyclohexylamide (8). Cyclohexylamine (2.88 mL) in carbon tetrachloride (20 mL) was added slowly to a stirred solution of oxalyl chloride (5 mL) in carbon tetrachloride (20 mL) at −10 °C. After the initial exothermic reaction, the reaction mixture was refluxed for a few hours and evaporated. Mesitylene (8.4 mL) and dichloromethane (50 mL) were added and the stirred solution was cooled in a salt–ice bath. Stannic chloride (5 mL) was added dropwise for 30 min and the reaction mixture was stirred for an additional 2 h at 0 °C. It was then poured into dilute hydrochloric acid, extracted with ether, washed with water, and dried over sodium sulfate. Following evaporation, the residue was applied to a column of silica gel (100 g, 2.5 cm in diameter) and eluted with benzene–chloroform (1:1). The title compound **8** (0.556 g) emerged after 450 mL and was further purified by PLC (benzene–chloroform, 1:1). Recrystallization from chloroform–petroleum ether gave elongated prisms (0.153 g): mp 173–174 °C; ν_{max} 3380 (NH), 2920 and 2850 (CH), 1710 and 1670 (CO), and 1600 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.47; N, 5.12. Found: C, 74.63; H, 8.36; N, 5.30.

Irradiation of Compound 8. The irradiation was carried out in ethanol under the conditions specified in Table I and up to 16 h. No reaction was observed by TLC or by GC.

Irradiation of Compound 4 and the Irradiation of Compound 2 in the Presence of Mineral Acids. The irradiations were carried out as specified in Table I; compound **4** in ethanol and compound **2** in ethanol–aqueous 3 M hydrochloric acid (5:1) or in ethanol–aqueous 10% sulfuric acid (4:1). Yields of cyclohexanone were 25–30, 61, and 77%, respectively.

Methyl 6-deoxy-6-(1,2-diphenylmaleylimido)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (9) was prepared as described for 2-deoxy-2-(1,2-diphenylmaleylimido)-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[10] but starting from crude methyl 6-amino-6-deoxy-α-D-glucopyranoside[15] (0.634 g). The product was purified by chromatography on a column of "dry" silica gel (20 g, 1 cm in diameter and eluted with chloroform at 6 mL per fraction). Collection started when a yellow color emerged and fractions 9–21 contained compound **9**: yellow glass (0.954 g, 52%); $[\alpha]^{20}_D$ +114.5° (c 0.13); ν_{max} 1745, 1705, 1600 (weak), 1360, 1105, and 1005 cm^{-1}; λ_{max} 273 nm (ϵ 9.19 × 10^3) and 365 (4.26 × 10^3); ^{1}H NMR τ 2.62 (m, 10, aromatic), 4.57, 5.84, and 6.17 (multiplets, 5), 5.03 (narrow m, 2), 6.66 (s, 3, OCH_3), 7.95 (s, 6, $COCH_3$), 8.00 (s, 3, $COCH_3$).

Anal. Calcd for $C_{29}H_{29}NO_{10}$: N, 2.57. Found: N, 2.30.

Methyl 6-Deoxy-6-phenylglyoxalamido-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (10). Compound **9** (0.771 g) was ozonolyzed as described in the preparation of compound **4** and the residue was dissolved in pyridine (7 mL)–water (4 mL). The reaction mixture was kept at room temperature overnight, evaporated from a 30 °C bath, and purified on a column as described for compound **9**. The product (0.630 g, quantitative yield) was a slightly contaminated oil. The title compound **10** crystallized as needles from ethyl acetate–petroleum ether: mp 119 °C; $[\alpha]^{20}_D$ +140.0° (c 0.23); ν_{max} 3400 (weak), 1740, 1670, 1600 (weak), and 1370 cm^{-1}; λ_{max} 266 nm (ϵ 1.24 × 10^4); ^{1}H NMR τ 1.79 (m, 2, aromatic), 2.60 (m, 3, aromatic), 4.63, 5.10, 5.17, 6.08, and 6.40 (multiplets, 8, including a 2 H narrow m at 5.10), 6.62 (s, 3, OCH_3), 7.92 (s, 3, $COCH_3$), 7.95 (s, 3, $COCH_3$), 8.03 (s, 3, $COCH_3$).

Anal. Calcd for $C_{21}H_{25}NO_{10}$: C, 55.87; H, 5.58; N, 3.10. Found: C, 55.81; H, 5.56; N, 3.07.

Methyl 2-Deoxy-2-phenylglyoxalylamido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (11). This compound was prepared by ozonolysis and deacylation of methyl 2-deoxy-2-(1,2-diphenylmaleylimido)-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside[10] as described for compound **10**. Evaporation of the pyridine solution and recrystallization from ethyl acetate–petroleum ether afforded the title compound as needles: mp 194 °C; $[\alpha]^{30}_D$ −2.6° (c 0.15); ν_{max} 3390 (wide), 1745, 1670, 1690 (shoulder), 1595, and 1365 cm^{-1}; λ_{max} 262 nm (ϵ 1.19 × 10^4); 100-MHz ^{1}H NMR τ 1.74 (m, 2, aromatic), 2.56 (m, 3, aromatic), 4.56 (q, 1, H-3, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 9 Hz), 4.91 (t, 1, H-4, $J_{4,5}$ = 9 Hz), 5.29 (d, 1, H-1, $J_{1,2}$ = 8.5 Hz), 5.6–6.3 (4 H, multiplets), 6.50 (s, 3, OCH_3), 7.93 (3 H, s, $COCH_3$), 8.00 (3 H, s, $COCH_3$), 8.04 (3 H, s, $COCH_3$). Assignments were made in analogy to the ones in the starting material.

Anal. Calcd for $C_{21}H_{25}NO_{10}$: C, 55.87; H, 5.58; N, 3.10. Found: C, 55.74; H, 5.55; N, 3.05.

3α-Phenylglyoxalylamidocholestane (12). 3α-(1,2-diphenylmaleimido)cholestane[10] (0.335 g) and propionaldehyde (10 mL) were dissolved in acetone (40 mL) and ozone in oxygen was bubbled through the solution at −78 °C. Since some of the starting material crystallized out the bubbling was stopped, the solution was brought to room temperature, the precipitate was dissolved, the reaction mixture was cooled again to −78 °C, and the bubbling was continued. This procedure had to be repeated four times before the yellow color disappeared. The solution was then evaporated at room temperature, and the residue was dissolved in pyridine (15 mL)–water (4 mL) and was kept overnight at room temperature. The reaction mixture was evaporated, extracted with ether, washed with dilute hydrochloric acid, water, and sodium hydrogen carbonate, dried over sodium sulfate, and evaporated. The oily residue (0.258 g, 92%) contained only traces of impurities and was crystallized to give the title compound **12** as an amorphous solid from ethanol–ethyl acetate: mp 163 °C; $[\alpha]^{21}_D$ + 35.9° (c 0.17); ν_{max} 3400, 2900, 2850, 1665, 1600, 1450 cm^{-1}; λ_{max} 260 nm (ϵ 1.44 × 10^4); ^{1}H NMR τ 1.68 (m, 2, aromatic), 2.60 (m, 3, aromatic), 5.67 (m, 1, H-3, 100 MHz, half-height width 18 Hz), 7.8–9.4 (steroid "envelope" containing CH_3 signals at 9.10, 4.17, and 9.37).

Anal. Calcd for $C_{35}H_{53}NO_2$: C, 80.87; H, 10.27; N, 2.69. Found: C, 81.08; H, 10.32; N, 2.60.

3β-Phenylglyoxalylamidocholestane (13). 3β-(1,2-Diphenylmaleylimido)cholestane[10] (59 mg) and propionaldehyde (2.0 mL) were dissolved in carbon tetrachloride (20 mL) and ozone in oxygen was bubbled through at 0 °C till the yellow color disappeared. The solution was evaporated and treated as described for compound **12**. The product was further purified by PLC (benzene–petroleum ether, 1:2) and was crystallized from ethanol–ethyl acetate to give the title compound as prisms (23.5 mg, 46%): mp 145–146 °C; $[\alpha]^{20}_D$ +27.2° (c 0.05); ν_{max} 3395, 2910, 2850, 1665, and 1600 cm^{-1}; λ_{max} 269 nm (ϵ 1.54 × 10^4); ^{1}H NMR τ 1.5–1.74 (m, aromatic), 2.2–2.64 (m, aromatic), 6.22 (m, H-3), 7.8–9.5 (steroid "envelope" including CH_3 signals at 9.10, 9.16, 9.35).

Anal. Calcd for $C_{35}H_{53}NO_2$: C, 80.87; H, 10.27; N, 2.69. Found: C, 80.92; H, 10.22; N, 2.59.

Irradiation of Compound 10. Compound **10** (63 mg) in ethanol (30 mL) containing aqueous hydrochloric acid (3 mL, 3 N) was irradiated for 2 h resulting in the complete disappearance of the starting material (TLC). The reaction mixture was neutralized with lead carbonate and filtered through a Celite filter and the filter washed with additional ethanol (total ca. 100 mL).

A. Sodium borohydride (250 mg) was added to the reaction mixture and kept at 4 °C overnight. It was then neturalized with acetic acid, evaporated, and dissolved in pyridine (30 mL)–acetic anhydride (10

mL) and kept overnight at room temperature. Ice was added to the mixture and after 2 h the solution was evaporated. The residue was dissolved in chloroform, washed with water, and purified by PLC. Methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (1.5 mg, 3%) was isolated, identical in TLC and IR with an authentic sample.[16] Two slower moving components (acetate signals but no *O*-methyl) were also isolated from the same PLC.

B. The solution was evaporated, and methyl 2,3,4-tri-*O*-acetyl-α-D-gluco-1,6-dialdohexo-1,5-pyranoside *p*-nitrophenylhydrazone was prepared[17] and purified by PLC (chloroform–methanol, 9.8:0.2) to give a yellow, crystalline product (6.4 mg, 10%), possessing the expected ^{1}H NMR, mp 126 °C (lit.[17] mp 126–128 °C).

Irradiation of Compound 11. Compound **11** was irradiated as described for compound **10.** Water (15 mL) and platinum oxide (40 mg) were added to the solution and the mixture was shaken overnight under hydrogen at room temperature and atmospheric pressure. The solution was neutralized with calcium carbonate, filtered, and evaporated. Barium methoxide (0.1 M, 25 mL in methanol) was added to the residue and the solution was left for 7 h at room temperature. It was then neutralized with carbon dioxide, filtered, and evaporated. Following this, the residue was extracted with water (10 mL), hydrochloric acid was added (3 N, 10 mL), and the acid solution was left under reflux overnight. It was then neutralized with a mixture of Amberlite IR 120 (H^+ form) and IR 4B (OH^- form), evaporated, and dissolved in water (3 mL). The solution gave a positive reaction with Clinistix (Ames laboratories, a glucose oxidase–peroxidase strip). Glucose and mannose were detected by paper chromatography (solvent systems I and II); they were isolated from preparative paper chromatography (solvent I and solvent II) and determined by the phenol–sulfuric acid test. Average yields follow: glucose, 6.9%; mannose, 4.0%.

Irradiation of Compound 12. Compound **12** (46 mg) was dissolved in benzene (4 mL)–ethanol (6 mL) and sulfuric acid (10%, 1 mL) was added. Irradiation was carried out for 3 h. The solution was diluted with ether (300 mL), washed with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate, dried over sodium sulfate, and evaporated. The product, 3-cholestanone, 17.2 mg (51%), a white solid, was isolated from PLC (chloroform) following detection with iodine. It was recrystallized from ethanol, mp 131–132 °C, $[\alpha]^{30}_D$ +41.0° (*c* 0.13) (lit.[18] mp 128–129 °C, $[\alpha]^{20}_D$ +43.7°). The product was identical with an authentic sample in TLC (chloroform), IR, and a mixture melting point.

Anal. Calcd for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.99; H, 12.11.

Irradiation of Compound 13. Compound **13** (46 mg) was treated as described for compound **12** yielding 3-cholestanone (20.3 mg, 59%) as prisms, mp 127–128 °C, $[\alpha]^{20}_D$ +40.5° (c 0.26), identical with an authentic sample by TLC, which gave no depression of a mixture melting point (Found: C, 83.98; H, 11.96).

Acknowledgment. The author is most grateful to Professor Sir D. H. R. Barton, F.R.S., for his suggestions, encouragement, and support.

Registry No.—1, 62448-60-6; **2,** 724-92-5; **3,** 62448-61-7; **4,** 62448-62-8; **5,** 62448-63-9; **6,** 62448-64-0; **7,** 62448-65-1; **8,** 62448-66-2; **9,** 62448-67-3; **10,** 62448-68-4; **11,** 62448-69-5; **12,** 62448-70-8; **13,** 62448-71-9; benzoyl-*N*-cyclohexylamide, 1759-68-8; cyclohexylamine, 108-91-8; phenylglyoxalyl chloride, 25726-04-9; mandelic acid ethyl ester, 774-40-3; 1,2-diphenylmaleic anhydride, 4808-48-4; α-phenyl-α-chloroacetyl-*N*-cyclohexylamide, 40934-39-2; oxalyl chloride, 79-37-8; mesitylene, 10867-8; methyl 6-amino-6-deoxy-α-D-glucopyranoside, 5155-47-5; methyl 2-deoxy-2-(1,2-diphenylmaleylimido)-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside, 62448-72-0; 3α-(1,2-diphenylmaleimido)cholestane, 62460-40-6; propionaldehyde, 123-38-6; 3-cholestanone, 15600-08-5.

References and Notes

(1) E. S. Huyser and D. C. Neckers, *J. Org. Chem.*, **29,** 276 (1964); P. A. Leermakers and G. F. Vesley, *J. Am. Chem. Soc.*, **85,** 3776 (1963); P. A. Leermakers, P. C. Warren, and G. F. Vesley, *ibid.*, **86,** 1768 (1964).
(2) Compare also R. W. Binkley, *J. Org. Chem.*, **41,** 3030 (1976).
(3) Examples of some related procedures include E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91,** 1421 (1969); V. Caló, L. Lopez, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1,* 1652 (1972); J. A. Hyatt, *J. Org. Chem.*, **37,** 1254 (1972); U. Zehavi, unpublished results; T. L. Nagabhushan, unpublished results. In particular, *N*-phenacyl amines are reported by Hyatt to be photolyzed to the corresponding carbonyl derivatives. *N*-Phenacyl derivatives of primary amines, however, are unstable and the reaction requires long irradiation times and effects low conversions.
(4) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **64,** 329 (1942).
(5) Analogous to J. W. Cornforth, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 467.
(6) P. R. Story, J. A. Alford, J. R. Burgess, and W. C. Ray, *J. Am. Chem. Soc.*, **93,** 3024 (1971).
(7) K. Thimm and J. Voss, *Tetrahedron Lett.*, 537 (1975).
(8) D. Horton, A. E. Luetzow, and J. C. Wease, *Carbohydr. Res.*, **8,** 366 (1968); D. Gagnaire, D. Horton, and F. R. Travel, *ibid.*, **27,** 363 (1973).
(9) P. M. Collins, W. G. Overend, and B. A. Rayner, *Carbohydr. Res.*, **31,** 1 (1973).
(10) U. Zehavi, *J. Org. Chem.*, preceding paper in this issue.
(11) S. S. Chennick, I. L. Chaikoff, and S. Abraham, *J. Biol. Chem.*, **193,** 793 (1951).
(12) A. Mailhe and (Mme) Bellegarde, *Cautchouc et Guttapercha,* **16,** 9947 (1919); *Chem. Abstr.*, **14,** 3651 (1920).
(13) S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Am. Chem. Soc.*, **81,** 6322 (1959).
(14) C. F. Koelsch and S. Wawzonek, *J. Org. Chem.*, **6,** 684 (1941).
(15) F. D. Cramer, H. Otterbach, and H. Springer, *Chem. Ber.*, **92,** 384 (1959).
(16) G. N. Bollenback, *Methods Carbohydr. Chem.*, **2,** 326 (1963).
(17) B. A. Dmitriev, A. A. Kost, and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 903 (1969).
(18) R. Willstatter and E. W. Mayer, *Chem. Ber.*, **41,** 2199 (1908).

Reaction of Dimethyl 3-Ketoglutarate with 1,2-Dicarbonyl Compounds. 5.[1] Simple Synthesis of Derivatives of 2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indene from Dimethyl 3-Ketoglutarate and Glyoxal

Kenner C. Rice and Ulrich Weiss*

Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20014

J. V. Silverton and G. John Shaw

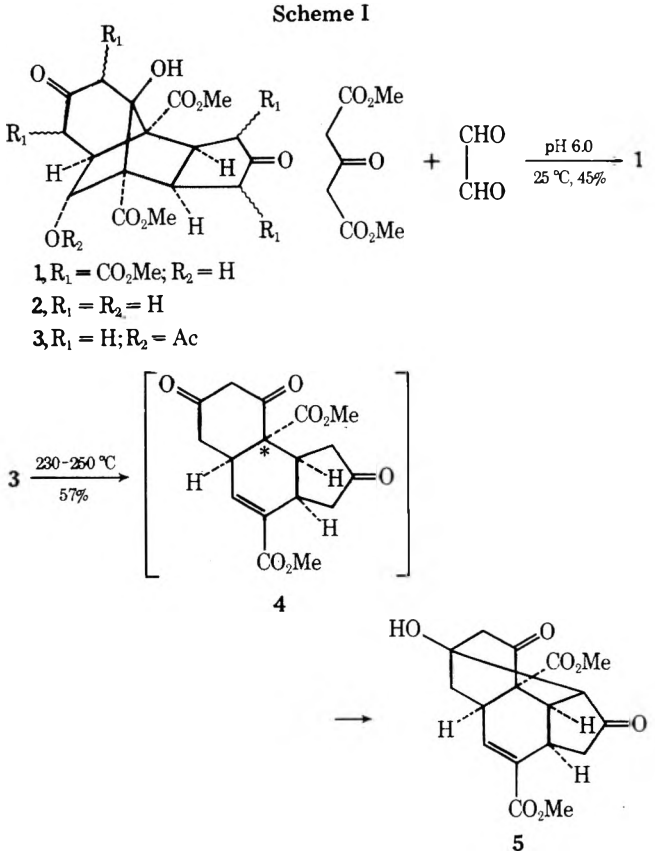
Laboratory of Chemistry, National Heart, Lung and Blood Institute, Bethesda, Maryland 20014

Received September 24, 1976

Treatment of either of the tetracyclic aldols **3** or **5** (themselves readily available in three simple steps from dimethyl 3-ketoglutarate and glyoxal) with excess sodium methoxide in boiling methanol gives the 2,3,3a,4,5,9b-hexahydro-1*H*-benz[e]indene derivative **6a** in good yield. The structure of this compound was assigned on the basis of spectral data; the resulting assignment was confirmed by x-ray crystallographic analysis of the dimethyl ether **8** of **6a**. The unexpected aromatization involved in the formation of **6a** seems to proceed with a 1,3 shift of a quaternary carbomethoxy group, presumably by way of an intermediate cyclobutanone. Further transformations of **6a** are described.

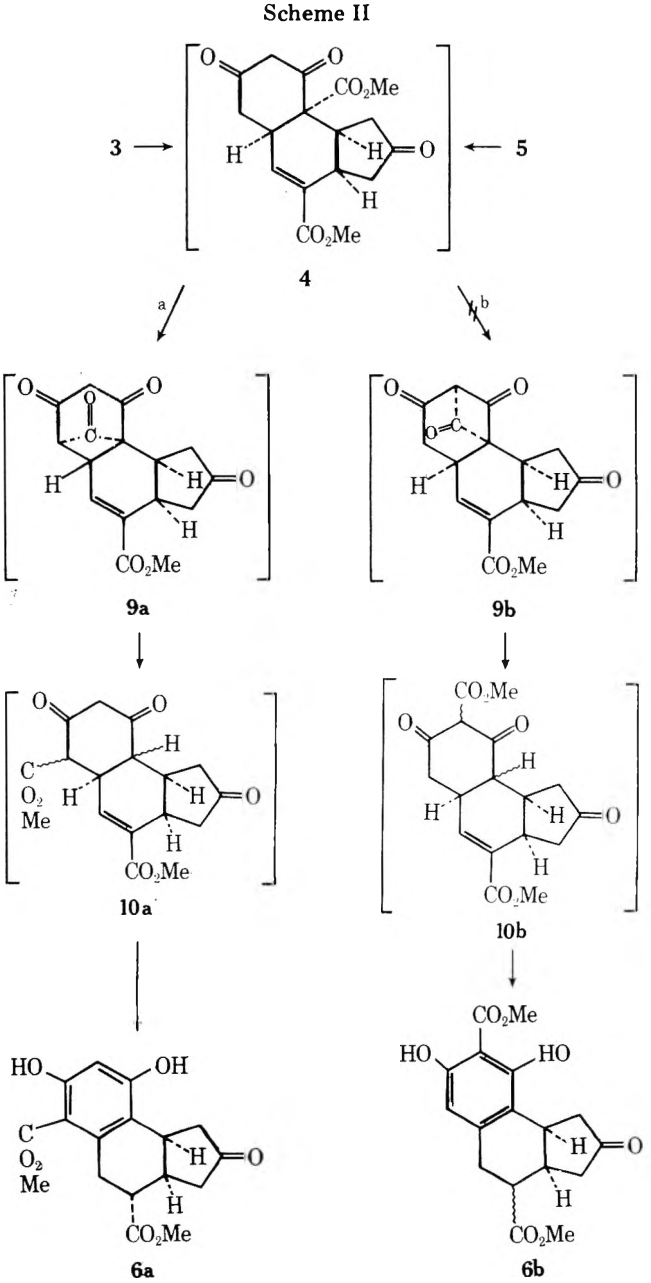
In the preceding communication[1] of our series concerning certain biomimetic-type reactions, we have described (Scheme I)[2] the ready formation of the tetracyclic aldol (**2**) by partial

Scheme I

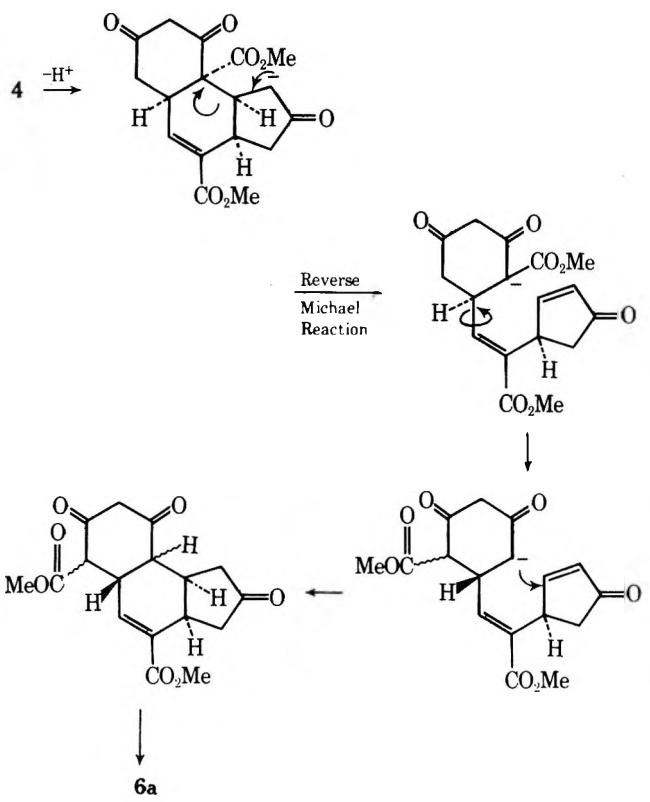


acid hydrolysis and decarboxylation of the corresponding hexacarbomethoxy derivative (**1**), which itself is formed in 45% yield by simply stirring a solution of dimethyl 3-ketoglutarate and glyoxal at room temperature in aqueous solution buffered to pH 6.0. Pyrolysis of **3**, the monoacetate of **2**, was shown to give **5**, obviously arising through intramolecular aldolization of a primary thermolysis product **4**. We now wish to describe the facile synthesis of derivatives of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indene through an unexpected base-catalyzed aromatization of **3** or **5** which involves an apparent 1,3 shift of a carbomethoxy group.

Scheme II



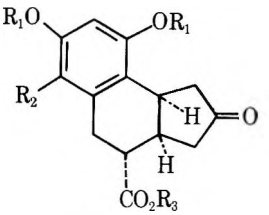
Scheme III



Action of sodium methoxide (10 equiv) in refluxing methanol upon either **3** or **5** converted both compounds, in about 60% yield, into a new substance, **6a**, isomeric with **5**, which gave a diacetate **7** and a dimethyl ether **8**. The formation of these two derivatives, a singlet, 1 H, at δ 6.38 in the NMR spectrum of **6a**, and other spectral data suggested a diphenolic structure with a single free position on the aromatic ring. Conversion of **3**, **4**, or **5** to a benzenoid compound *isomeric* with **5** can obviously take place only if the quaternary nature of the carbon marked by an asterisk is altered. A priori, two possibilities for such a change can be formulated. The one which we prefer is illustrated in Scheme II. As shown there, it could yield either one of two isomeric aromatic compounds, **6a** and **6b**; it will be shown below that **6a** is the one actually obtained. In both cases, dealdolization of **5** to **4** by the NaOMe is assumed. Internal, base-promoted acylation of **4** can next produce two different cyclobutanone intermediates, **9a** or **9b**. The four-membered rings in these intermediates would then undergo cleavage as indicated, to give **10a** or **10b**, respectively. Their conversion to the aromatic structures, **6a** and **6b**, by enolization, extraction of the doubly allylic proton at the ring juncture by the base,[3] and shift of the double bond into the ring seems reasonable; the aromaticity of the resulting structure provides a powerful driving force. The apparent shift of the carbomethoxy group[4] by way of an intermediate cyclobutanone has its exact precedent in the sequence[5] generally accepted[4] to occur in the so-called "abnormal Michael reactions", e.g., the addition of diethyl ethylmalonate to ethyl crotonate,[6] which takes place in the presence of excess NaOMe under conditions very similar to ours.

This mechanism of the aromatization reaction provides a satisfactory interpretation of the observed facts, and it is based on well-established precedent. However, an alternative possibility has been pointed out to us by Professor R. Morrin Acheson, Oxford, after completion of this work; it is shown in Scheme III. Evidently, this sequence can only yield **6a**. We are not aware of a practicable way of deciding conclusively between the mechanisms given in Schemes II and III. We prefer the former on account of its similarity to the anomalous Michael reaction, and because of the negative outcome of a test of the alternative, which was suggested by Professor W. B. Whalley, London, and kindly carried out in his laboratory. It is based on the assumption that the ionic intermediate involved in this sequence might become stabilized not only by the intramolecular Michael reaction shown, but also by Michael addition of an active external nucleophile added in excess. However, addition of nitromethane, dimethyl malonate, or thiophenol had no detectable influence upon the course of the reaction or the yield of the aromatization product.

Except for the ^{1}H NMR spectrum, the spectroscopic properties of the aromatic compound are compatible with either structure **6a** or **6b**. Decision in favor of the former is



6a, $R_1 = H$; $R_2 = CO_2Me$; $R_3 = Me$
7, $R_1 = Ac$; $R_2 = CO_2Me$; $R_3 = Me$
8, $R_1 = R_3 = Me$; $R_2 = CO_2Me$
11, $R_1 = R_3 = H$; $R_2 = CO_2H$
12, $R_1 = R_2 = R_3 = H$
13, $R_1 = R_3 = Me$; $R_2 = H$

based on the presence, in the ^{1}H NMR spectrum, of two signals from the phenolic hydroxyls (D_2O-exchangeable singlets, 1 H each) with widely different chemical shifts: δ 6.79 and 11.60, respectively. These δ values prove that only *one* of the two hydroxyls, the one giving rise to the signal at δ 11.60, is adjacent to the aromatic carbomethoxy group and hydrogen-bonded to it. This situation prevails in **6a**, while in **6b** both hydroxyls would be bonded, and should produce coinciding or closely adjacent signals at much lower field than δ 6.79. Our findings on model compounds prove the correctness of this interpretation: methyl 2,6-dihydroxybenzoate, δ 9.78 (D_2O-exchangeable singlet, 2 H); methyl 2,4-dihydroxybenzoate, δ 6.55 and 11.28 (D_2O-exchangeable singlets, 1 H each).

The free acid (**11**) corresponding to **6a** should lose CO_2 with great ease to give the resorcinol (**12**), readily recognizable as such by the characteristic NMR signals for two aromatic protons in meta relationship. Saponification of **6a** with aqueous sodium hydroxide, followed by acidification of the warm solution with hydrochloric acid, gave **12** directly. The compound showed the expected AB system, with the signals centered at δ 6.18 and 6.30, J = 2.3 Hz. Treatment of **12** with dimethyl sulfate and K_2CO_3 in acetone gave **13**.

The structural assignment for each new compound reported in this work was strongly confirmed by the corresponding ^{13}C NMR spectrum; all spectra were fully consistent with the assignments formulated. These spectra, together with those of a number of closely related compounds previously described,[1,7-9] will be discussed elsewhere.

The NMR spectra of **6a**, **7**, **8**, **12**, and **13** were too complex for complete analysis and provided no evidence concerning the configuration of the carbomethoxy group on the alicyclic ring in **6a**, **7**, **8**, and **13**, or the carboxyl group in **12**. In order to settle this point, and to provide unequivocal confirmation of the structure of **6a**, an x-ray crystallographic analysis of the well-crystallized dimethyl ether **8** was undertaken. This analysis proves that **6a** has indeed the structure assigned by us, and that the orientation of the carbomethoxy group is cis to the hydrogens at the ring juncture.

The x-ray crystallographic data are summarized in Table I. The molecule in its crystal conformation is shown in Figure

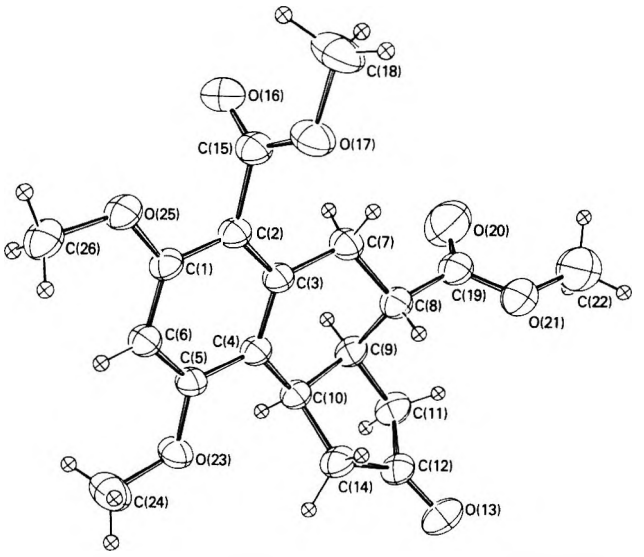


Figure 1. The molecule 8 in its crystal conformation. The heavier atoms are drawn with 40% probability ellipsoids and the hydrogen atoms are arbitrary spheres.

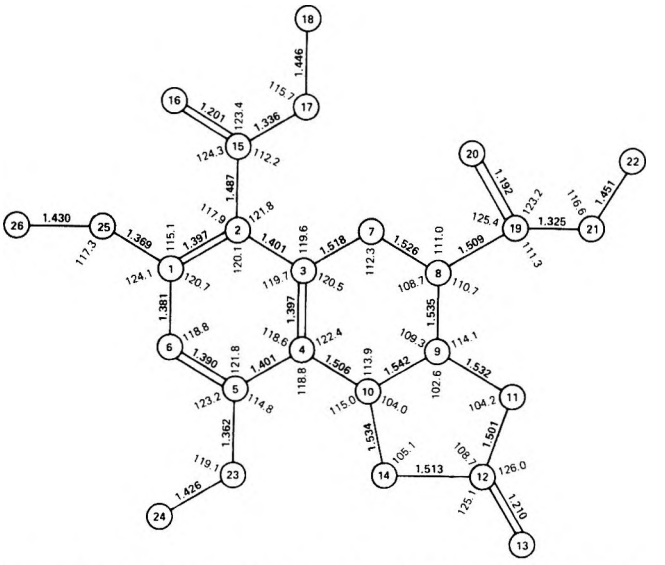


Figure 2. The bond lengths and angles of 8. Esd's of bond lengths range from 0.002 to 0.003 Å for atoms in the nucleus and are less than or equal to 0.005 Å for substituted atoms. Esd's of angles are less than or equal to 0.2°.

Table I. Crystal and Refinement Data

Mol formula	$C_{19}H_{22}O_7$	Space group	$P\bar{1}$ (no. 2)
Formula weight	362.38	Habit	Prismatic
		Crystal size	0.4 × 0.25 × 0.18 mm³
Cell parameters[a]		X-radiation	Cu Kα[b]
		λ	1.5418 Å
		Diffractometer	Nonius CAD-4
a	9.558 (1) Å	Reflections	3584 (793 unobsd 1σ)
b	10.336 (2) Å		
c	10.662 (1) Å	Max sin θ/λ	0.616 Å^{-1}
α	109.78 (1)°	Function minimized	$\Sigma w\Delta^2$
β	106.28 (1)°		
γ	98.76 (1)°	Weighting	Peterson and Levy[13]
V	915.11 Å³	R-factor (obsd refs. only)	0.045
Z	2		
D_x	1.315 g cm^{-3}		
D_m	1.32 (1) g cm^{-3}		

[a] From LS refinement of $\pm\theta$ data. [b] Graphite monochromator.

1 (ORTEP[10] drawing); the bond lengths and angles are given in Figure 2. Molecular dimensions do not present any surprises, and the intermolecular distances are all consistent with van der Waals contacts. The ring junctions are all cis, as may be seen from the pattern of torsion angles.[11] A full table of torsion angles has been deposited as supplementary material. The conformation of the substituted cyclopentanone ring has Altona, Geise, and Romers[12] parameters $\Delta = 44.8°$ and $\varphi_m = 39.2°$. This conformation therefore lies between the half-chair ($\Delta = 36°$) and the envelope ($\Delta = 72°$) and, as might be expected for a cyclopentanone ring, it is somewhat flatter than that of a cyclopentane ring in a steroid ($\varphi_m \approx 45°$).

Experimental Section

Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Md. Melting points are uncorrected and were taken on a Kofler hot stage. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer; infrared spectra were obtained with a Perkin-Elmer 257 instrument. The ^{1}H NMR spectra were recorded using a Varian HR-220 instrument with tetramethylsilane as the internal reference. Ultraviolet spectra were measured using a Cary 14 or Beckman DB-G spectrophotometer.

Reaction of 3 with NaOMe. Preparation of 6a. To a solution of Na (6.9 g, 300 mmol) in MeOH (450 mL) was added **3**[1] (12.0 g, 30 mmol). The solution was heated under reflux for 3 h (N_2), cooled, acidified with HCl gas, and filtered. The filtrate was evaporated in vacuo, and the residue was dissolved in hot dioxane (200 mL), treated with Norite, filtered, and evaporated. The residue was crystallized from MeOH–H_2O (90:10) to give **6a** (6.4 g, 64%), mp 206–209 °C. Recrystallization from 95% EtOH gave pure material: mp 210–212 °C; M$^+$ *m/e* 334; IR (KBr), 3370, 1730, 1650, and 1600 cm^{-1}; UV λ_{max}(EtOH) 304 nm (ϵ 5100), 263 (10 300), 215 (16 600); NMR ($DCCl_3$) δ 1.92–2.12 (m, 1 H), 2.27–2.84 (m, 4 H), 3.01–3.23 (m, 2 H), 3.42–3.56 (m, 1 H), 3.57–3.74 (m, 1 H), 3.78 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.38 (s, 1 H, ArH), 6.79 (s, 1 H, exchanges with D_2O, OH), and 11.60 (s, 1 H, exchanges with D_2O, OH).

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 60.88; H, 5.23.

Diacetate of 6a (7). Acetylation of **6a** with excess Ac_2O in pyridine at 25 °C (24 h) gave, after workup and recrystallization from 2-propanol, pure **7** (83%): mp 147–149 °C; M$^+$ *m/e* 418; IR (KBr) 1720, 1660, and 1600 cm^{-1}; UV λ_{max}(EtOH) 275 nm (ϵ 930), 225 (5900, shoulder), and 210 (16 500); NMR ($DCCl_3$) δ 2.09 (dd, 1 H, J = 18.0 and 11.0 Hz), 2.26 (s, 3 H, CH_3CO), 2.32 (s, 3 H, CH_3CO), 2.30–2.67 (m, 3 H), 2.71–2.88 (m, 2 H), 3.05–3.14 (m, 2 H), 3.50–3.66 (m, 1 H), 3.74 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), and 6.97 (s, 1 H, ArH).

Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.19; H, 5.49.

Dimethyl Ether of 6a (8). A mixture of **6a** (300 mg, 0.9 mmol), anhydrous K_2CO_3 (1.0 g, 7.24 mmol), Me_2SO_4 (504 mg, 4.0 mmol), and dry acetone (25 mL) was refluxed while stirring for 3.5 h. The inorganic material was filtered off and washed with acetone, and the filtrate was evaporated. The residue was dissolved in $HCCl_3$ (30 mL) and the solution washed with water, dried, and evaporated to give 8 (334 mg, 100%), mp 175–177 °C. Recrystallization from 2-propanol gave pure 8: mp 176–178 °C; M$^+$ *m/e* 362; IR ($HCCl_3$) 1736, 1718 (shoulder), and 1600 cm^{-1}; UV λ_{max}(EtOH) 286 nm (ϵ 3400), 250 (5150, shoulder), 213 (16 500); NMR ($DCCl_3$) δ 1.76–2.02 (1 H, 5 lines), 2.21 and 2.34 (1 H, 2 lines), 2.45–2.80 (3 H, complex), 2.86–3.02 (3 H, complex), 3.59–3.70 (1 H, complex), 3.73 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), and 6.39 (s, 1 H, ArH).

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 63.19; H, 5.96.

Alkaline Hydrolysis of 6a and Decarboxylation to 12. To a refluxing solution of NaOH (3.0 g, 75 mmol) in H_2O (30 mL), which had been purged with N_2 for 0.5 h, was added 6 (2.5 g, 7.48 mmol). Reflux under N_2 was continued for 2.5 h; the solution was then cooled to 50 °C and acidified to pH 1.0 with 37% HCl (CO_2 evolution). After cooling to 5 °C, the solution was filtered and the solid washed with H_2O and dried in air to give the monohydrate of 12, mp 277–278 °C dec. Recrystallization was carried out by dissolving the solid in the minimum amount of 95% EtOH, treating with Norite, filtering, and adding two volumes of H_2O. Air drying gave pure 12 H_2O: mp 282–284 °C; M^+ *m/e* 262; IR (KBr) 3255, 1735, 1710, 1615, and 1600 cm^{-1}; UV λ_{max}(EtOH) 280 nm (ϵ 2200), 223 (8500, shoulder), and 210 (14 000). The NMR spectrum (acetone-d_6) of a sample that had been dried under high vacuum overnight (100 °C) showed absorptions at δ 1.95 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.18–3.05 (m, 7 H), 3.52–3.82 (m, 1 H), 5.55 (s, broad, 1 H), 6.18 and 6.30 (AB system, J_{AB} = 2.3 Hz, meta ArH), and 3.46 (s, broad, 2 H).

Anal. Calcd for $C_{14}H_{14}O_5 \cdot H_2O$: C, 62.66; H, 6.02. Found: C, 62.60; H, 5.70.

Methylation of 12 to 13. To a solution of dimethyl sulfate (1.52 g, 12.0 mmol) in acetone (20 mL) were added 12 (800 mg, 3.05 mmol) and anhydrous K_2CO_3 (1.66 g, 12.0 mmol). The solution was refluxed during 5 h with stirring, cooled, filtered, and evaporated to give 13. Two recrystallizations from 2-propanol gave pure material: mp 107–109 °C; M^+ *m/e* 304; IR ($HCCl_3$) 1740, 1730, 1610, and 1590 cm^{-1}; UV λ_{max}(EtOH) 280 nm (ϵ 2100), 224 (8460, shoulder), and 209 nm (14 300); NMR ($DCCl_3$) δ 1.91 (dd, 1 H, J = 17.5 and 12.0 Hz), 2.29 (d, 1 H, J = 17.5 Hz), 2.45–3.07 (m, 6 H), 3.50–3.68 (m, 1 H), 3.75 (s, 3 H, OCH_3), 3.78 (s, 6 H, 2 OCH_3), 6.26 and 6.32 (AB system, J_{AB} = 2.4 Hz, meta ArH).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.14; H, 6.72.

X-Ray Crystallography. Preliminary experimental techniques and data collection methods were standard for this laboratory and have been described previously.[14] Details are given in Table I. As the crystal system was triclinic, there was a possible ambiguity as to the space group, but since the compound is racemic and there were two molecules in the unit cell, $P\bar{1}$ was assumed and appears confirmed by the successful refinement. Programs used for most computations were from the XRAY72 system,[15] but the structure was solved using MULTAN.[16]

All but two of the heavier atoms were visible in the E map. The missing atoms, including hydrogen, were found by a sequence of least-squares refinements and difference maps and the structure was finally refined using a partitioned full-matrix least squares approach with anisotropic thermal parameters for the heavier atoms, to an R factor of 4.5%. Final parameters are given in Tables II and III. (See paragraph at end of paper concerning supplementary material.)

Acknowledgments. The authors wish to thank Dr. Robert J. Highet for helpful discussions concerning this work, and for determination of the ^{13}C NMR spectra. We also thank Mrs. Alice Wong and Mr. William R. Landis for elemental analyses and mass spectra, respectively. The award of an NIH Visiting Fellowship to G.J.S. is acknowledged.

Registry No.—**3,** 58648-32-1; **6a,** 62562-54-3; **7,** 62562-55-4; **8,** 62562-56-5; **12,** 62562-57-6; **13,** 62562-58-7; dimethyl 3-ketoglutarate, 1830-54-2; glyoxal, 107-22-2.

Supplementary Material Available. Tables of final parameters and torsion angles (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Part 4: K. C. Rice, U. Weiss, T. Akiyama, R. J. Highet, T. Lee, and J. V. Silverton, *Tetrahedron Lett.*, 3767 (1975).
(2) All compounds described are racemic; for the formulas, one antipode has been chosen arbitrarily.
(3) For a recent example of a closely analogous reaction, see A. Gerhard, R. Muntwyler, and W. Keller-Schierlein, *Helv. Chim. Acta*, **58,** 1323 (1975). In the case described there, the need for activation of the proton by the double bonds was proven: hydrogenation yielded an alkali-stable compound.
(4) For a recent review of such processes, see R. Morrin Acheson, *Acc. Chem. Res.*, **4,** 177 (1971).
(5) N. E. Holden and A. Lapworth, *J. Chem. Soc.*, 2368 (1931).
(6) A. Michael and J. Ross, *J. Am. Chem. Soc.*, **52,** 4598 (1930).
(7) J. M. Edwards, I. H. Qureshi, U. Weiss, T. Akiyama, and J. V. Silverton, *J. Org. Chem.*, **38,** 2919 (1973).
(8) U. Weiss and J. M. Edwards, *Tetrahedron Lett.*, 4885 (1968).
(9) K. C. Rice, N. E. Sharpless, U. Weiss, and R. J. Highet, *Tetrahedron Lett.*, 3763 (1975).
(10) C. K. Johnson (1965), ORTEP, Oak Ridge National Laboratory, Report ORNL-3794.
(11) R. Bucourt, *Top. Stereochem.*, **8,** 159 (1974).
(12) C. Altona, H. L. Geise, and C. Romers, *Tetrahedron*, **24,** 13 (1968).
(13) S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10,** 70 (1957). The correction factor used was $0.0004\beta^2$.
(14) J. V. Silverton and H. A. Lloyd, *Acta Crystallogr., Sect. B*, **31,** 1576 (1975).
(15) J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, "The X-Ray System", Technical Report TR-192, Computer Center, University of Maryland, 1972.
(16) P. Main, M. M. Woolfson, and G. Germain, "MULTAN. A Computer Program for the Automatic Solution of CRYSTAL Structures", Universities of York and Louvain, 1971.

1,3-Butadiene-2,3-dicarboxylic Acid Derivatives from Cyclohexene-1,2-dicarboxylic Acid Analogues

R. Lynn Cobb* and John E. Mahan

Phillips Petroleum Company, Bartlesville, Oklahoma 74004

Received October 14, 1976

Vapor-phase pyrolysis of dimethyl cyclohexene-1,2-dicarboxylate (1), and of cyclohexene-1,2-dicarbonitrile (3), at 700–800 °C and a few hundredths of a second contact time gave dimethyl 1,3-butadiene-2,3-dicarboxylate (4) and 1,3-butadiene-2,3-dicarbonitrile (12) in about 50 and 90% (ultimate) yields, respectively. Similar pyrolysis of *N*-methylcyclohexene-1,2-dicarboximide (2) gave a polymeric product, apparently arising from (labile) *N*-methyl-1,3-butadiene-2,3-dicarboximide (8). Evidence for the formation of 8 was obtained by isolation of its dimer *N,N'*-dimethyl-4-vinylcyclohexene-α,1,2,4-tetracarboxdiimide (9), and by trapping it with *N*-methylmaleimide, producing *N,N'*-dimethylcyclohexene-1,2,4,5-tetracarboxdiimide (10).

Derivatives of 1,3-butadiene-2,3-dicarboxylic acid are difficult to prepare; consequently, their chemistry has not been well studied. Esters of this type have been prepared by pyrolysis of dimethyl cyclohexene-1,2-dicarboxylate (1),[1] dimethyl 2,3-diacetoxy-2,3-dimethylsuccinate,[2] and diethyl 2,3-bis(1-piperidinomethyl)succinate dihydrochloride,[3] while the dinitrile has been prepared by pyrolysis of 2,3-diacetoxy-2,3-dimethylsuccinonitrile.[2,4,5] Because the method has not been well documented, and because of the potential value of these compounds, we have reinvestigated some of these pyrolytic syntheses. Very recently, the thermal rearrangement of derivatives of cyclobutene-1,2-dicarbonitrile has been shown to provide ready access to dienes of this type.[6,7]

Although the retro-Diels–Alder cleavage of cyclohexenes

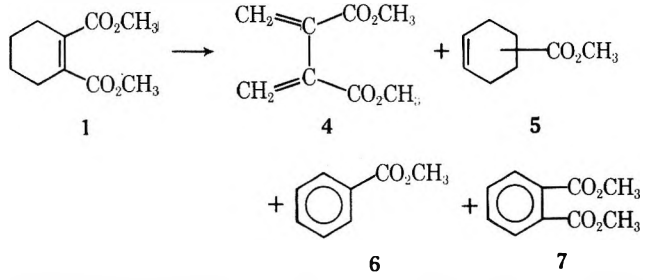
Table I. Pyrolysis of Dimethyl Cyclohexene-1,2-dicarboxylate (1)[a]

Temp, °C	Pressure, mmHg	Contact time, ms	% conversion (by VPC)[b]	VPC[b] % selectivity 4	5	6	7
600	~150[c]	50–60	4	23	32	5	
700	~150[c]	50–60	17	48	15	15	
750	~150[c]	50–60	22	38	9	21	
800	~150[c]	50–60	41	15	2	18	
900	~150[c]	50–60	60	10	0	10	
1000	~150[c]	50–60	87	11	0	3	
700	~12	25–30	17	47	21	9	2
750	~12	25–30	33	47	5	21	5
800	~12	25–30	60	40	1	42	

[a] Added neat to the system described in the Experimental Section. [b] Analysis on a 5 ft × 0.25 in. column packed with 5% Carbowax M on 40/60 mesh Chromosorb T. [c] Added as a 10 wt % solution in benzene; biphenyl formation interfered with VPC determination of 7.

such as 1 is a relatively high energy process,[8] the ready availability of the necessary precursors (by isomerization of the Diels–Alder adduct of, e.g., butadiene and maleic anhydride) makes this at least potentially an attractive route to butadiene-2,3-dicarboxylic acid derivatives. We wish to report here the results of our work with 1, *N*-methylcyclohexene-1,2-dicarboximide (2), and cyclohexene-1,2-dicarbonitrile (3) as sources of dimethyl butadiene-2,3-dicarboxylate (4), *N*-methylbutadiene-2,3-dicarboximide (8), and butadiene-2,3-dicarbonitrile (12), respectively.

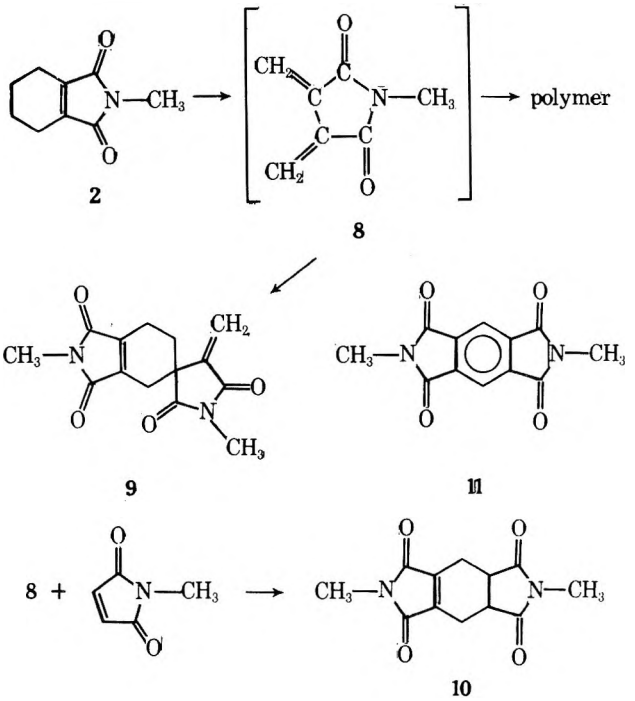
Gas-phase pyrolysis of 1 using very short contact times (Table I) gave 4 in about 50% (ultimate) yields. The retrograde Diels–Alder process occurred at temperatures somewhat above 600 °C. Competing processes seriously affected the desired reaction route, i.e., production of diene 4 and ethylene; these other major processes yielded, inter alia, methyl cyclohexenecarboxylate (5), methyl benzoate (6), dimethyl



phthalate (7), and small amounts of dimethyl maleate and fumarate. For comparison, the thermal stabilities of materials related to 1 and some of the observed by-products were noted under the same conditions. Thus, at 700 °C and a contact time of 30–40 ms, 1 underwent ca. 30% conversion, 6 and 7 were essentially inert, dimethyl maleate isomerized to dimethyl fumarate but was otherwise unchanged, and dimethyl cyclohexane-1,2-dicarboxylate underwent ca. 7% conversion (at 150 ms contact time, to undetermined products). The relative instability of 1 may be a consequence of its ability to undergo a cycloreversion process, a reaction path unavailable to these other materials.

Pyrolysis of imide 2 occurred at temperatures above ca. 650–700 °C. Although VPC conversions were high at, e.g., ca. 800 °C and 15–20 ms contact time, diene 8 could not be isolated. Disproportionation of 2 giving *N*-methylphthalimide and its saturated derivative, and a degradation yielding hydrogen cyanide at higher temperatures, were noted. These two processes, however, contributed to no more than perhaps 10% of the total product.

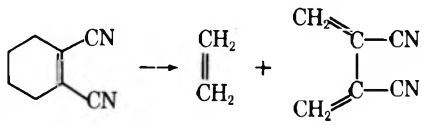
All attempts to isolate monomeric diene 8 were futile. That it had been formed was demonstrated conclusively by the isolation of its dimer, *N,N'*-dimethyl-4-vinylcyclohexene-α,1,2,4-tetracarboxdiimide (9), although the major product was polymeric. Further, the diene 8 was "trapped" as the expected Diels–Alder adduct *N,N'*-dimethyl-1-cyclohexene-1,2,4,5-tetracarboxdiimide (10) when the pyrolysis was carried out in the presence of *N*-methylmaleimide (no 10 was noted in the absence of the latter). Although polymer formation and attendant separation difficulties prevented good yield data from being obtained, both the total (VPC) yield of 9 and 10 and the yield of 10 relative to 9 increased as the *N*-methylmaleimide concentration was increased. Thus, from VPC data, by assigning a value of 1.0 to the relative yield of 9 with no added maleimide, the total relative yield of 9 and 10 increased from 3.3 to 7.1 and the product ratio of 10 to 9 increased from 0.22 to 1.14 as the molar ratio of *N*-methylmaleimide to 2 was increased from 1.5 to 6.0. Another pyrolysis product of 2, isolated in very low yield in the absence of the maleimide, was *N,N'*-dimethylpyromellitdiimide (11).



The reasons for the instability of the exocyclic diene 8 are not clear. An earlier attempt to prepare the anhydride related to 8 by pyrolysis of 2,3-diacetoxy-2,3-dimethylsuccinic anhydride gave 2,3-dimethylmaleic anhydride.[2] Similarly, dehydration of 1,3-butadiene-2,3-dicarboxylic acid, even under mild conditions, gave only the dianhydride dimer related to 9.[3] Further unsuccessful attempts to isolate anhydrides of this type have been made.[9] In this connection, it may be noted that cyclobutane- and 3-cyclobutene-1,2-dicarboxylic anhydrides are known, while 1-cyclobutene-1,2-dicarboxylic anhydride (a valence tautomer of the anhydride analogous to 8) has never

been reported and may be incapable of existence in a free state.[10]

Pyrolysis of the dinitrile **3** occurred smoothly at 750–800 °C and a 15-ms contact time to give 85–90% (VPC) yields of the diene **12**. Hydrogen cyanide was never detected in the gaseous by-products; indeed, there were no significant by-products formed in this remarkably clean process. In some large-scale runs utilizing recycling of recovered cyclohexene **3**, isolated yields of recrystallized diene **12** were 72–83%.



3 **12**

Another theoretically possible, although energetically unfavorable,[8] mode of decomposition of the cyclohexene system is the formation of two molecules of ethylene and a molecule of acetylene. With cyclohexene **3**, such a process would yield dicyanoacetylene. This latter material (stable under the reaction conditions) could be detected in no more than trace amounts (if any at all, by VPC) among the pyrolysis products from **3**; it is thus doubtful[11] that this mode of degradation plays more than a minute role in the retro-Diels–Alder reaction of cyclohexenes of this type.

Because of isolation and analytical problems, a direct comparison of the relative stabilities of the cyclohexenes **1**, **2**, and **3** toward a retro-Diels–Alder cycloreversion may not be entirely practical. However, from some representative runs at 750 °C and a contact time of ca. 40 ms, these cyclohexenes underwent conversions of 38, 72, and 95%, respectively, suggesting that the order of thermal stability is ester **1** > imide **2** > nitrile **3**.

Experimental Section[13]

Dimethyl cyclohexene-1,2-dicarboxylate (1) was prepared by esterification of cyclohexene-1,2-dicarboxylic anhydride with methanol in the presence of TsOH at 125 °C (autoclave): ^{1}H NMR ($CDCl_3$) δ 3.74 (s, CH_3, 6), 2.32 and 1.65 (m, CH_2, 4 each). The anhydride was prepared by the P_2O_5-catalyzed isomerization[14] of readily available 4-cyclohexene-1,2-dicarboxylic anhydride.

***N*-Methylcyclohexene-1,2-dicarboximide (2).** A solution of 304 g (2 mol) of cyclohexene-1,2-dicarboxylic anhydride in 500 mL of ethanol was stirred while 62 g (2 mol) of gaseous methylamine was added below the liquid level under a dry ice–acetone condensor. Complete solution occurred shortly with a mildly exothermic reaction. The solution was heated under reflux overnight. After removal of the ethanol in vacuo, the residual syrup was taken up in ether. Chilling the ether at −70 °C gave the imide **2** in several crops[15] (total yield of 320 g, 96%) as white crystals: mp 51–52 °C (from ether); IR (KBr) 1730, 1785 cm^{-1} (s and w, C=O); ^{1}H NMR ($CDCl_3$) δ 2.96 (s, CH_3, 3), 2.34 and 1.77 (m, CH_2, 4 each). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.47. Found: C, 65.38; H, 6.63; N, 8.56.

Cyclohexene-1,2-dicarbonitrile (3) was prepared in a multistep synthesis[16] from cyclohexene-1,2-dicarboxylic anhydride via the imide [by treatment with urea in refluxing xylene, removing water azeotropically; mp 172–174 °C; IR (KBr) 3330 (NH), 1755 and 1725 cm^{-1} (w and vs, C=O)] and the diamide [by treating the imide with aqueous ammonium hydroxide and ammonia at 0 °C; mp 230–231 °C; IR (KBr) 3360 and 3170 (NH_2), 1640 and 1610 cm^{-1} (C=O)]. Reaction of the diamide with phosgene in pyridine at 80 °C on a large scale (1–2 mol) gave a reaction mixture that was worked up by the published procedure[16b] with great difficulty. The following modification allowed a much easier isolation of **3**. The pyridine reaction mixture, after addition of phosgene, was dissolved in a mixture of chloroform and toluene. After addition of cyclohexane, the solution was heated at 100 °C to remove the chloroform. This gave pyridine hydrochloride as a granular solid that was easily removed. The solution was then washed successively several times with hot water, hot aqueous potassium hydroxide, and hot water. After drying over magnesium sulfate, the solvents were removed to give the solid dinitrile **3** (50–75% yields): mp 95–96 °C (from cyclohexane and tetrahydrofuran); IR (KBr) 2210 (CN), 1580 cm^{-1} (C=C); UV (acetonitrile) λ_{max} 232 nm (ϵ 12 200); ^{1}H NMR ($CDCl_3$) δ 2.45 (m, CH_2, 4), 1.84 (m, CH_2, 4).

General Pyrolysis Procedures. The reactor consisted of a 1 × 12 in. quartz tube packed with quartz chips, and was held at an angle of ca. 30° from the horizontal. Heating was by a two-element electrical tube furnace controlled by Thermo Electric 400 controllers. The cyclohexene to be pyrolyzed was vaporized neat or in a solvent by dropping via a pressure-equalized dropping funnel into a pot packed with glass beads held at about 250 °C; the vaporization pot was connected to the upper end of the pyrolysis tube by an adaptor heated with a heating tape. Provision was also made for addition of nitrogen, controlled via a flow meter, through the vaporization pot into the system. Effluent from the furnace was collected in suitable traps.

Typically, the system was evacuated to the desired pressure, with the furnace and vaporization system preheated to the desired temperature. The reactant was then added dropwise at a rate such as to give the desired contact time. This was calculated by the expression

$$\text{contact time (ms)} = \frac{1000 \times \text{reactor void space (mL)} \times \text{addition time (s)}}{\text{volume of gas added (mL)}}$$

with the gas volume described as

$$\frac{760}{\text{mm pressure}} \frac{\text{T (K)}}{273} \left[22\,400 \left(\frac{\text{g reactant}}{\text{mol wt}} + \frac{\text{g diluent}}{\text{mol wt}} \right) \right]$$

and the reactor void space calculated as the volume of the reactor less the "net" volume of the quartz chip packing (by measurement of the displaced liquid in a graduate cylinder). After addition of reactant was completed, and a few (10–15) minutes had elapsed, the reactor was opened in a stream of nitrogen. The reactor system was cleaned as desired by burning out in a stream of air.

Pyrolysis of Diester 1. The ester **1** (150 g) was added dropwise to the reactor system at 700 °C and 10 mm pressure over a period of 105 min (the reactor was packed with 50 mL of quartz chips; contact time was ca. 40 ms). The effluent was passed through two traps, cooled in ice and dry ice–acetone, respectively, to give a total of 114.5 g of product. This material was rapidly distilled through a 6-in. Vigreux column from a steam bath under high vacuum, removing 18.4 g of a distillate (VPC analysis on the column described in the footnote to Table I indicated about 12% diester **1**, 3% dimethyl fumarate, 18–19% **5**, 22% **6**, and 34% diene **4**), leaving 87 g of residual oil (analyzing 91–92% diester **1**, 4% diene **4**, and 4% dimethyl phthalate **7**). The latter was recycled through the reactor. Material distilled in this manner from several runs was combined (ca. 40 g), diluted with an equal volume of ether, and chilled at −70 °C to give a crystalline solid. Filtering gave 12.6 g of diene **4** (low melting, purity about 90% by VPC). This was distilled under high vacuum, after addition of a little hydroquinone, to give pure (99.7% by VPC) diene **4**: bp 62 °C (0.3 mm); mp 17–18 °C; IR (neat) 1725 (C=O), 1620 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ 6.26 and 5.83 (CH_2=, J_{gem} = 1.5 Hz), 3.75 (s, CH_3); mass spectrum *m/e* (rel intensity) 170 (55, M^+). Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.45; H, 5.95.

Pyrolysis of Imide 2. A 50% solution of **2** in dimethyl phthalate was pyrolyzed at 750 °C and 10 mm pressure. The effluent, a viscous and sticky liquid (similar in consistency to a heavy rubber cement), was collected in the manner described for the pyrolysis of **1**. Combined product from several runs was distilled under high vacuum through a short-path column, removing solvent and small amounts of easily volatilized products. The residue, from a mixture of tetrahydrofuran and ether, gave a tarry solid that was removed. Further standing allowed slow deposition of the diene dimer **9** as almost white crystals: mp 139–140 °C (from tetrahydrofuran); IR (KBr) 1690 and 1760 cm^{-1} (s and w, imide C=O); ^{1}H NMR (DMF-d_6) δ 6.23 and 5.81 (2 s, CH_2=, 2), 3.01 and 2.93 (2 s, CH_3, 6), 2.67 (m, CH_2, 4), 2.09 (m, CH_2, 2); ^{13}C NMR (Me_2SO-d_6) δ 177.9, 169.8, and 167.6 (C=O), 142.4, 140.1, and 138.4 (C=), 119.2 (H_2C=), 43.2 (quaternary C), 28.7, 26.9, and 17.2 (CH_2), 24.5 and 23.2 (CH_3); mass spectrum *m/e* (rel intensity) 274 (100, M^+), 259 (15), 245 (10), 217 (17), 189 (28), 132 (29), 104 (20). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.30; H, 5.15; N, 10.21. Found: C, 61.42; H, 5.27; N, 10.93.

In a run utilizing no solvent, imide **2** at 700 °C, 25 mm pressure, and a contact time of about 120 ms, gave a dark-colored effluent oil that deposited a crystalline solid upon standing. This product was collected and recrystallized from tetrahydrofuran to give *N,N'*-dimethylpyromellitdiimide (**11**) as large, hard plates: mp 375–378 °C (sealed tube); IR (KBr) 1690 and 1750 cm^{-1} (imide C=O); mass spectrum *m/e* 244 (M^+). Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.12; H, 3.39; N, 11.59.

Representative of the runs utilizing *N*-methylmaleimide, a solution of 5 g of imide 2, 5 g of *N*-methylmaleimide, and 25 g of dimethyl phthalate was vaporized into the furnace at 750 °C, 2.5 mm pressure, and a contact time of ca. 10 ms. Effluent[17] from the traps was poured slowly into 600 mL of ether, giving several crops of crystalline solid upon standing. These were combined and recrystallized twice from tetrahydrofuran to give the Diels–Alder adduct **10** as flocculent, cream-colored crystals: mp 202–203 °C; IR (KBr) 1695 and 1760 cm^{-1} (s and w, imide C=O); ^1H NMR (DMF-d_6) δ 3.4–3.7 (m, CH, 2), overlapping resonances at 2.90 and 2.87 (2 s, CH_3), and 2.7–3.1 (m, CH_2) (total of 10 H); mass spectrum *m/e* (rel intensity) 248 (40, M^+), 244 (26), 200 (15), 191 (23), 163 (36), 106 (100), 105 (65). Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.09; H 4.90; N, 12.05.

Pyrolysis of Dinitrile 3. In a typical run, a solution of 25 g of dinitrile **3** and 25 g of benzonitrile was vaporized into the pyrolysis apparatus at 775 °C, 10 mm pressure, and a contact time of ca. 21 ms. The effluent (ca. 29 g) from a series of traps at −70 °C was taken up in 30 mL of tetrahydrofuran. Chilling at −20 °C gave 4.4 g of diene **12**, which, from ether, gave almost white needles of the pure (by VPC on a 5 ft × 0.25 in. Apiezon on Chromosorb T column) diene, mp 126–127 °C (by placing the capillary in the apparatus preheated to ca. 125 °C) (lit.[4] mp 125–127 °C). Dilution of the tetrahydrofuran mother liquor with ether gave an additional 1.44 g of the diene **12**: IR (KBr) 2220 (CN), 1570 (C=C), 950 cm^{-1} (=CH_2, overtone at 1900); ^1H NMR ($CDCl_3$) δ 6.45 and 6.33 (2 s, J_{gem} = 0 Hz); mass spectrum *m/e* (rel intensity) 104 (26, M^+), 77 (95), 64 (48), 52 (100). Anal. Calcd for $C_6H_4N_2$: C, 69.22; H, 3.87; N, 26.91. Found: C, 69.2; H, 4.0; N, 27.1.

Registry No.—**1**, 4336-19-0; **2**, 28839-49-8; **3**, 52477-67-5; **4**, 38818-30-3; **9**, 59082-62-1; **10**, 59120-88-6; **11**, 26011-79-0; **12**, 19652-57-4; cyclohexene-1,2-dicarboxylic anhydride, 4720-86-9; cyclohexene-1,2-dicarboxamide, 62601-01-8.

References and Notes

(1) A. L. Barney and H. B. Stevenson, U.S. Patent 2 870 196 (E. I. du Pont de Nemours and Co.) (Jan 20, 1959).
(2) W. J. Bailey. R. L. Hudson, and E. T. Yates, *J. Org. Chem.*, **28**, 828 (1963).
(3) U.-I. Zähorszky and H. Musso, *Justus Liebigs Ann. Chem.*, 1777 (1973).
(4) P. O. Tawney, U.S. Patent 2 444 882 (U.S. Rubber Co.), (July 6, 1945).
(5) E. J. Prill, U.S. Patent 2 480 961 (U.S. Rubber Co.), (Sept 6, 1949).
(6) D. Belluš, K. von Bredow, H. Sauter, and C. D. Weis, *Helv. Chim. Acta*, **56**, 3004 (1973).
(7) We independently confirmed the facile synthesis of dienes of this type from the cyclobutene derivatives.
(8) H. Kwart and K. King, *Chem. Rev.*, **68**, 416 (1968).
(9) R. K. Huff, C. E. Moppett, and J. K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, 2584 (1972).
(10) F. B. Kipping and J. J. Wren, *J. Chem. Soc.*, 1773 (1957).
(11) The reactivity of dicyanoacetylene with diene **12**, which could account for its absence, was not assessed. However, diene **12** reacts only extremely slowly with the related dimethyl acetyienedicarboxylate.[12]
(12) R. L. Cobb and J. E. Mahan, to be published.
(13) Melting points, determined in a Mel-Temp apparatus, are uncorrected; IR spectra were determined on a Perkin-Elmer Model 137 Infracord; NMR spectra were determined vs. internal Me_4Si on Varian T60 or XL100 instruments.
(14) M. E. Bailey and E. D. Amstutz, *J. Am. Chem. Soc.*, **78**, 3828 (1956).
(15) Recrystallization of the first product crop, 269 g, from ether gave a small amount of insoluble *N*-methylcyclohexene-1,2-dicarboxamic acid: mp 178–179 °C (from isopropyl alcohol–ether); IR (KBr) 3280 (sharp, strong, NH), 1630, 1540, and 1290 (amide), 1670 and 930 cm^{-1} (acid). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.11; H, 7.19; N, 7.13.
(16) (a) G. E. Ficken and R. P. Linstead, *J. Chem. Soc.*, 4846 (1952); (b) G. E. Ficken, H. France, and R. P. Linstead, *ibid.*, 3730 (1954).
(17) VPC analyses for 9 and **10** were made utilizing the Carbowax column described in footnote *b* of Table I and a similar silicone rubber column.

Organoboranes. 21. Facile Syntheses of *cis*-Bicyclo[3.3.0]oct-1-yl Derivatives from Lithium Dialkyl-9-borabicyclo[3.3.1]nonane "Ate" Complexes[1]

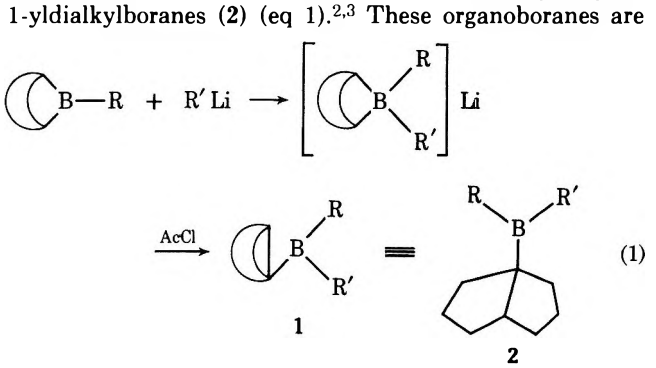
Gary W. Kramer and Herbert C. Brown*

The Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

Received March 1, 1977

Lithium dialkyl-9-borabicyclo[3.3.1]nonane "ate" complexes react with acetyl chloride via hydride transfer to form *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes. These organoboranes are valuable intermediates for the preparation of a variety of 1-substituted *cis*-bicyclo[3.3.0]octanes. Many of these derivatives have heretofore been difficult to prepare. However, the ready availability of the organoborane precursor now permits their convenient preparation in high yield.

We recently reported that lithium "ate" complexes (**1**), derived from the addition of alkyllithiums to *B*-alkyl-9-borabicyclo[3.3.1]nonanes (*B*-alkyl-9-BBN), react with acetyl chloride via hydride transfer to form *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes (**2**) (eq 1).[2,3] These organoboranes are valuable intermediates for the preparation of a variety of 1-substituted *cis*-bicyclo[3.3.0]octanes. Since many of these derivatives have heretofore been difficult to prepare, we explored the synthetic utility of these organoboranes (**2**).[4] Employing several common reaction sequences from the organoborane arsenal, we prepared and isolated in high yield several representative 1-substituted *cis*-bicyclo[3.3.0]octanes (**3–7**).



1 2 (1)

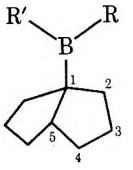
The preparations of compounds **5–7** deserve further discussion. These synthetic procedures are known to proceed via free-radical reaction paths.[6–9] Accordingly, we felt that the proper choice of the other alkyl groups (R and R′ in **2**) would be important to the overall success in effecting preferential transfer of the bicyclic moiety. To demonstrate this point, we carried out 1,4-additions to methyl vinyl ketone with several derivatives of **2** with varying alkyl substituents. The results (Table I) clearly show, as anticipated, that selective migration

Table I. Reaction of *cis*-Bicyclo[3.3.0]oct-1-yldialkylboranes with Methyl Vinyl Ketone

Registry no.	2	R	R′	5,[a] %	$RCH_2CH_2COCH_3$,[a] %	$R'CH_2CH_2COCH_3$,[a] %
59322-84-8	2a	Methyl	Methyl	90	Tr	
62726-59-4	2b	Methyl	Ethyl	86	*b*	13
62726-60-7	2c	Methyl	Isopropyl	47	*b*	42
62726-61-8	2d	Methyl	*tert*-Butyl	32	*b*	66
62726-62-9	2e	Methyl	*n*-Butyl	98	*b*	4
59322-87-1	2f	*n*-Butyl	*n*-Butyl	96	7	

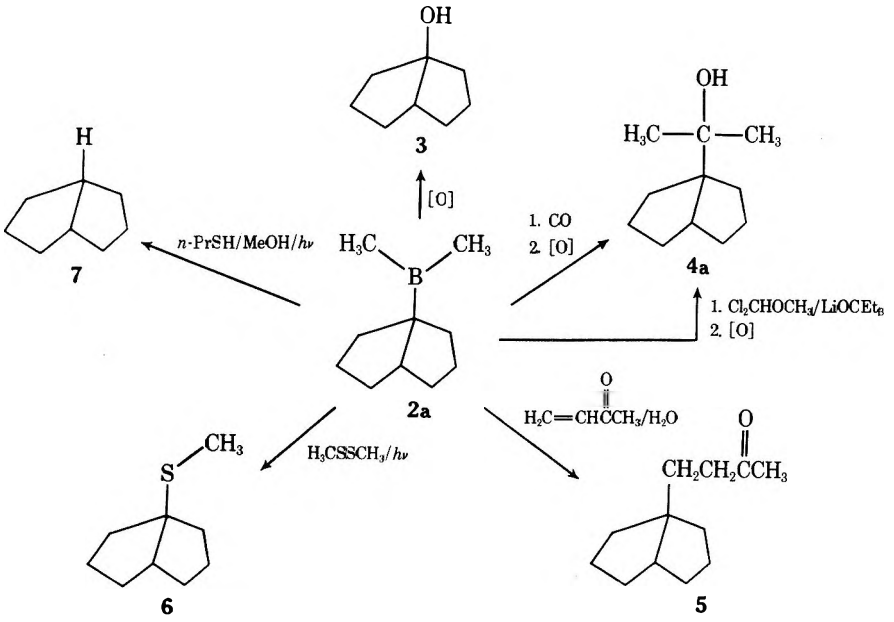
[a] GLC yields. [b] Amount of methyl transfer product not determined.

Table II. ^{13}C and ^{11}B NMR of Some *cis*-Bicyclo[3.3.0]oct-1-yldialkylboranes



	Compd		^{13}C NMR chemical shift of carbon						^{11}B NMR chemical shift
	R	R′	1[a]	2	3	4	5	Other	
2a	Methyl	Methyl		36.9	26.4	35.0	45.9	~12[b]	−81.9
2b	Methyl	Ethyl		36.8	26.3	35.0	45.7	~19,[b] 8.7[d]	−82.7
2c	Methyl	Isopropyl		36.5	26.3	35.1	45.5	~5,[b] 17.9[d]	−81.3
2d	Methyl	*tert*-Butyl		36.8	26.3	35.0	46.7	~9,[b] 28.0[d]	−80.3
2e	Methyl	*n*-Butyl		37.0	26.0	35.3	45.8	~8.5,[b] 27.2,[c] 13.8,[d] 26.5, 27.6	−82.7
2f	*n*-Butyl	*n*-Butyl		36.7	26.3	35.3	45.5	24.8,[c] 13.8,[d] 24.6, 27.0	−81.8

[a] Bridgehead carbon α to boron not detected. [b] α-Methyl carbon. [c] α-Methylene. [d] Terminal methyl carbon.



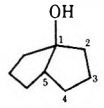
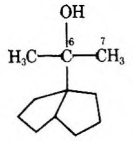
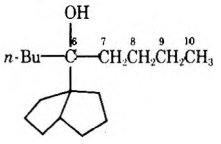
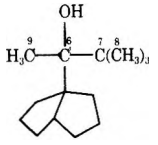
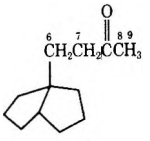
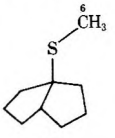
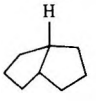
of the bicyclic moiety is enhanced when the other groups are methyls or other primary groups, but decreases seriously with the presence of a secondary or tertiary alkyl substituent. The use of the dimethyl derivative (**2a**) offers the further advantage that the boron-containing by-products of these reactions are volatile and easily removed with the solvent.[10-12]

In our preparations of these bicyclic derivatives (**2–7**), we observed only evidence for the *cis*-bicyclo[3.3.0]octane products. If trans isomers formed, they were present in concentrations below the detectability of ^{13}C NMR (Tables II and III). This may seem surprising in view of the free-radical nature of some of the syntheses. However, examination of molecular models reveals that the *trans*-bicyclo[3.3.0]octyl ring system is greatly strained as compared with the cis-fused isomer. Consequently, it is probable that the bicyclic radical produced in these reactions is constrained into the pyramidal conformation. The complete retention of stereochemistry in these reactions is therefore not unreasonable.

Experimental Section

General Comments. The techniques described in Chapter 9 of ref 6 were used extensively. All glassware was dried at 140 °C for at least 4 h, assembled hot, and allowed to cool under a purge of prepurified nitrogen. The reaction flasks were fitted with side arms capped with rubber septa and were flamed out under a nitrogen purge immediately before use. All reactions were carried out under a static pressure of prepurified nitrogen. The transfer of liquids and solutions of or-

Table III. ^{13}C NMR of Some *cis*-Bicyclo[3.3.0]oct-1-yl Derivatives[a]

Registry no.	Compd	Chemical shift of carbon 1	2	3	4	5	Other				
52318-93-1	3 	90.9	42.2	26.1	33.7	52.0					
62726-63-0	4a 	62.1	38.0	26.2	34.9	45.0	6 75.0	7 26.7			
62726-64-1	4b 	63.7	38.2	26.3	35.1	45.5	6 77.9	23.9	27.1	36.9	10 14.1
62726-65-2	4d 	65.9	40.7	28.4	36.1	49.0	6 80.5	7 36.3	8 29.1	9 23.1	
62726-66-3	5 	53.2	39.2	25.9	34.3	49.9	6 35.6	7 40.9	8 209.0	9 29.9	
62726-67-4	6 	60.9	41.1	26.0	34.1	50.9	6 12.9				
1755-05-1	7 	43.4	34.3	26.4	34.3	43.4					

[a] Spectra recorded of GLC purified samples in $CDCl_3$.

ganometallics were done either with oven-dried, nitrogen-purged hypodermic syringes fitted with stainless steel needles or by the double-ended needle technique.[6] All reactions were stirred magnetically using over-dried, Teflon-coated stirring bars. Photoinduction of reactions was accomplished by placing a Sears 275-W sunlamp about 3 in. from the reaction flask. The rubber septa on the reaction flasks were covered with aluminum foil and positioned away from the lamp to prevent their decomposition. All distillations were carried out using a short path assembly without a column.

Materials. THF and diethyl ether were distilled from lithium aluminum hydride prior to use, degassed with nitrogen, and stored in large ampules with Teflon stopcocks. Technical grade pentane (and hexane) was stirred for 1 day over concentrated sulfuric acid, treated with anhydrous potassium carbonate, distilled from lithium aluminum hydride, degassed with nitrogen, and stored in crown-capped bottles. Acetyl chloride was freshly distilled from calcium hydride. Methanol (Mallinckrodt SpectAR) was dried over 3 Å molecular sieves. The dichloromethyl methyl ether (Aldrich) was freshly distilled prior to use. Lithium triethylcarboxide was prepared by the addition of neat triethylcarbinol (Chemical Samples Co.) to a hexane solution of *n*-butyllithium. Methyl vinyl ketone (Aldrich) was distilled immediately before use to remove any polymerization inhibitor. Dimethyl disulfide and 1-thiopropane (Aldrich) were used as received. The 9-BBN (mp 149–151 °C) and the *B*-alkyl-9-BBN derivatives were prepared as previously described.[13] Methyllithium (from methyl chloride) in diethyl ether (Orgmet) and other organolithium reagents (Alfa) were carefully standardized prior to use by the method of Watson and Eastham.[14] The concentration of the hydrogen peroxide solution was determined by refractive index.[15]

Analyses. ^{11}B NMR spectra were recorded on a Varian XL-100-15 spectrometer (32.1 MHz) using a Nicolet 1080 data system. The spectra were recorded in the CW mode using ^2H internal or ^{19}F external locks; all chemical shifts are relative to BF_3·OEt_2 (δ 0) with the chemical shifts downfield from BF_3·OEt_2 assigned as negative. ^1H NMR spectra were recorded on a Varian T-60 (60 MHz) spectrometer, while the ^{13}C NMR spectra were taken on a Varian CFT-20 (20 MHz, FT) instrument. Both the ^1H and ^{13}C NMR chemical shifts are relative to tetramethylsilane (δ 0). Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. The samples were thin films of neat material held between salt plates.

GLC analyses were carried out on a Hewlett-Packard 5752B chromatograph fitted with a Disc integrator using 6 ft × 0.25 in. stainless steel columns filled with 10% loaded packing on AW-DMCS treated 60/80 Chromosorb W. SE-30 was used for the analyses of the organoboranes, while either XE-60 or XF-1150 were used for the analyses of the non-boron-containing materials. Preparative GLC was carried out on a modified Wilkins A-100 chromatograph using 5 ft × 0.5 in. columns filled with 20% loaded packing on AW-DMCS treated 60/80 Chromosorb W. Either SE-30 or XE-60 liquid phases were employed.

***cis*-Bicyclo[3.3.0]oct-1-yldimethylborane (2a). General Procedure.** To an oven-dried, nitrogen-flushed, 250-mL flask fitted with a magnetic stirring bar, septum inlet, and reflux condenser connected to a mercury bubbler were added 21.77 g (160.1) mmol of *B*-methyl-9-BBN[13,6] and 50 mL of dry, olefin-free pentane. Stirring was begun, and the flask was cooled to −78 °C where 90.5 mL of 1.77 M (160.1 mmol) methyllithium in diethyl ether was added slowly via double-ended needle. After stirring about 10 min at −78 °C, the slurry was allowed to come to room temperature and stir for 2 h. The flask was then immersed in an ice–water bath while 11.4 mL (160.1 mmol) of freshly distilled acetyl chloride was added dropwise from a syringe. A vigorous reaction ensued, and a white precipitate formed. After stirring about 2 h at room temperature, the supernatant liquid was decanted via double-ended needle into an evacuated short-path distillation assembly where the volatiles were flash distilled. The precipitate was washed with pentane (3 × 20 mL) and the washings decanted in like manner into the distillation apparatus. The residual oil was vacuum distilled giving 22.3 g (93% yield) of a clear, colorless

Table IV. 1-Substituted *cis*-Bicyclo[3.3.0]octanes

Compd	Yield, %	Rxn scale, mmol	GLC[a] purity, %	Bp, °C (Torr)	n_D^{20}	IR[c] ν, cm^{-1}				^{1}H NMR ($CDCl_3$),[c] δ ppm
3	75	79.9	91	95–97 (20)	~30[b] (42–43)[b,c]	3375 (s)	1200 (s)	1050 (m)	870 (m)	2.1 (m, 1 H)
						1450 (s)	1170 (m)	1005 (s)	820 (w)	0.9–2.0 (m, 12 H)
						1315 (s)	1125 (m)	980 (s)		~1.2 (s, 1 H)[d]
						1295 (m)	1075 (m)	930 (m)		
4a						3490 (s)	1380 (s)	1070 (m)	810 (m)	2.4 (m, 1 H)
R = methyl	62	4.7	99[c]			1470 (s)	1240 (m)	950 (m)		1.1–2.2 (m, 13 H)
R′ = methyl						1460 (s)	1150 (s)	930 (s)		1.15 (s, ~6 H)
						1390 (s)	1120 (s)	870 (m)		
4b						3500 (m)	1375 (m)	1015 (m)	740 (m)	2.4 (m, 1 H)
R = *n*-butyl	87	20.8	94	97–99 (0.02)	1.4860	1460 (s)	1330 (m)	990 (m)		1.1–2.2 (m, 25 H)
R′ = *n*-butyl						1450 (s)	1120 (m)	920 (m)		0.93 (dist t, ~6 H)
4d						3540 (s)	1365 (s)	1110 (s)	920 (m)	2.75 (m, 1 H)
R = methyl	41	3.8	99[c]		41[b,c]	1470 (s)	1300 (s)	1070 (s)	895 (s)	1.1–2.3 (m, 13 H)
R′ = *tert*-butyl						1400 (s)	1210 (s)	1010 (s)	820 (m)	1.25 (s, ~3 H)
						1380 (s)	1150 (m)	965 (m)		1.05 (s, 9 H)
5	90	42.7	94	72–75 (0.02)	1.4736 (1.4773)[c]	1720 (vs)	1405 (m)	1360 (s)	1160 (s)	2.3–2.6 (m, 3 H)
						1450 (s)	1380 (s)			2.17 (s, 3 H)
										1.1–2.2 (m, ~14 H)
6	91	31.7	87	114–116 (40)	1.5009 (1.5106)[c]	1460 (s)	1290 (m)	1070 (m)	920 (m)	2.05 (s, 3 H)
						1440 (vs)	1220 (m)	1000 (m)	910 (m)	1.2–2.0 (m, ~13 H)
						1430 (s)	1190 (s)	960 (m)	890 (m)	
						1310 (m)	1120 (m)	950 (m)	810 (m)	
7	75	30.3	96	75–78 (95)	1.4609 (1.4620)[c]	2920 (vs)	1480 (m)	1340 (w)	920 (m)	2.4 (m, 2 H)
						2860 (s)	1460 (s)	1240 (w)		1.0–2.0 (m, 12 H)

[a] GLC purity after simple vacuum distillation. [b] Melting point. [c] After further purification by preparative GLC. [d] Concentration dependent chemical shift, exchanges with D_2O.

oil, **2a**, bp 73–76 °C (18 Torr). GLC examination of the distillate showed it to be greater than 94% pure.

***cis*-Bicyclo[3.3.0]octan-1-ol (3). *In Situ* Procedure.** To an oven-dried, nitrogen-flushed, 500-mL flask fitted as described above, there were added 9.75 g (79.9 mmol) of solid 9-BBN and 50 mL of dry, olefin-free pentane. Stirring was begun, and 4.5 g (160 mmol, 100% excess) of ethylene was bubbled into the slurry over 2 h. After stirring for 5 h, the mixture was cooled to −78 °C, and 45.2 mL of 1.77 M (80.0 mmol) methyllithium (from methyl chloride) in diethyl ether was added slowly via double-ended needle. After stirring for 10 min at −78 °C, the slurry was allowed to warm to room temperature and stir for 2 h, at which point the solid completely dissolved. The mixture was cooled with an ice–water bath while 5.70 mL (80.1 mmol) of acetyl chloride (freshly distilled from calcium hydride) was added slowly from a syringe. The reaction mixture was allowed to warm to room temperature and stir for 2 h, and then recooled to 0 °C, where it was oxidized using 28 mL of 3.0 M sodium hydroxide and 28 mL of 30% hydrogen peroxide.[16] To ensure completion of the oxidation, the mixture was maintained at 50 °C for 1 h. After the addition of 56 g of potassium carbonate, the organic layer was separated and the aqueous phase extracted with diethyl ether (3 × 30 mL). The combined extracts were transferred to a distillation assembly where the volatiles were removed in vacuo and the residual oil vacuum distilled. There was collected 7.5 g (75% yield) of a waxy solid, **3** [mp ~30 °C, bp 95–97 °C (20 Torr)].

***cis*-Bicyclo[3.3.0]oct-1-yldi-*n*-butylcarbinol (4b). Carbonylation Method.** A 110-mL high-pressure bomb was thoroughly flushed with nitrogen and then charged with 4.87 g (20.8 mmol) of **2f**, 40 mL of THF, and 1.7 mL (30 mmol, 50% excess) of ethylene glycol. The bomb was pressurized with carbon monoxide (60 atm) and then heated to 150 °C for 16 h. After cooling and depressurization, the contents of the bomb were transferred to a 100-mL flask. The mixture was oxidized using 7.0 mL of 6 M sodium hydroxide, 7.0 mL of ethanol, and 7.0 mL of 30% hydrogen peroxide.[16] After heating to 50 °C for 2 h to ensure complete oxidation, the mixture was saturated with sodium chloride and the organic layer separated. The aqueous phase was extracted with pentane (2 × 15 mL). The combined extracts were decanted into an evacuated distillation assembly where the volatiles were flash distilled. The residual oil was vacuum distilled, and 4.55 g (87% yield) of a colorless oil (**4b**) was collected, bp 97–99 °C (20 Torr).

***cis*-Bicyclo[3.3.0]oct-1-ylbutan-2-one (5).** To a nitrogen-flushed, 100-mL flask fitted with a magnetic stirring bar and septum inlet were added 6.4 g (42.7 mmol) of **2a**, 20 mL of THF, 1.5 mL (85 mmol, 100% excess) of water, and 5.20 mL (64.0 mmol, 50% excess) of freshly distilled methyl vinyl ketone. Stirring was begun, and 10 mL of air was bubbled through the solution. The mixture was allowed to stir for 24 h. The volatiles were removed in vacuo and the residual liquid vacuum distilled to give 6.9 g (90% yield) of product (**5**), bp 72–75 °C (20 mTorr).

***cis*-Bicyclo[3.3.0]oct-1-yl Methyl Sulfide (6).** To an oven-dried, nitrogen-flushed, 100-mL flask fitted with a septum inlet, magnetic stirring bar, and reflux condenser connected to a mercury bubbler were added 4.75 g (31.7 mmol) of **2a**, 25 mL of hexane, and 2.85 mL (31.7 mmol) of dimethyl disulfide. The mixture was irradiated with a Sears 275-W sunlamp. The solvent was allowed to boil. After 2 h, the volatiles were removed in vacuo and the residual oil vacuum distilled to give 4.5 g (91% yield) of a colorless liquid (**6**), bp 114–116 °C (40 Torr).

***cis*-Bicyclo[3.3.0]octane (7).** To an oven-dried, nitrogen-flushed, 50-mL flask fitted with a septum inlet, magnetic stirring bar, and reflux condenser connected to a mercury bubbler were added 4.54 g (30.3 mmol) of **2a**, 2.0 mL of methanol, and 1.0 mL of 1-thiopropane. The mixture was irradiated with a Sears 275-W sunlamp for 1 h. The volatiles were removed in vacuo and the residual liquid vacuum distilled giving 2.5 g (75% yield) of product (**7**), bp 75–78 °C (95 Torr).

Acknowledgment. The authors express appreciation to the National Science Foundation for the support of this work under Grants GP41169X and CHE 76-20846.

Registry No.—*B*-methyl-9-BBN, 23418-81-7; *B*-butyl-9-BBN, 23532-74-3; methyllithium, 917-54-4; ethyllithium, 811-49-4; isopropyllithium, 1888-75-1; *tert*-butyllithium, 594-19-4; butyllithium, 109-72-8; 9-BBN, 280-64-8; dimethyl disulfide, 624-92-0; methyl vinyl ketone, 78-94-4.

References and Notes

(1) Taken in part from the Ph.D. Thesis of G. W. Kramer, Purdue University, 1976.

(2) G. W. Kramer and H. C. Brown, *J. Am. Chem. Soc.*, **98**, 1964 (1976).
(3) G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, **90**, C1 (1975).
(4) For example, the previously reported procedure for the preparation of *cis*-bicyclo[3.3.0]octan-1-ol involves at least seven steps starting with 1,5-cyclooctadiene and going through $\Delta^{1,5}$-bicyclo[3.3.0]octene.[5]
(5) E. J. Corey and E. Block, *J. Org. Chem.*, **34**, 1233 (1969); L. A. Paquette and R. W. Houser, *J. Am. Chem. Soc.*, **91**, 3870 (1969); R. C. Fort, R. E. Hornish, and G. A. Liang, *J. Am. Chem. Soc.*, **92**, 7558 (1970).
(6) H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(7) H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Am. Chem. Soc.*, **89**, 5709 (1967); A. Suzuki et al., *ibid.*, **89**, 5708 (1967).
(8) H. C. Brown and M. M. Midland, *J. Am. Chem. Soc.*, **93**, 3291 (1971).
(9) B. M. Mikhailov and Yu. N. Bubnov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1872 (1960); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1742 (1960); B. M. Mikhailov and Yu. N. Bubnov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2248 (1964); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2154 (1964).
(10) A. B. Burg and R. J. Wagner, *J. Am. Chem. Soc.*, **75**, 3872 (1953).
(11) D. Ulmschneider and J. Gobeau, *Ber.*, **90**, 2733 (1957); G. F. Lanthier and W. A. G. Graham, *Can. J. Chem.*, **47**, 569 (1969).
(12) A. B. Burg and R. J. Wagner, *J. Am. Chem. Soc.*, **76**, 3307 (1954); A. B. Burg and F. M. Graber, *ibid.*, **78**, 1523 (1956).
(13) G. W. Kramer and H. C. Brown, *J. Organomet. Chem.*, **73**, 1 (1974).
(14) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(15) P. A. Giguère and P. Geoffrion, *Can. J. Res., Sect. B*, **27**, 168 (1949).
(16) The hydrogen peroxide should be added dropwise.

Hydroboration. 48. Effect of Structure on Selective Monohydroboration of Representative Nonconjugated Dienes by 9-Borabicyclo[3.3.1]nonane

Ronald Liotta[1] and Herbert C. Brown*

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

Received April 26, 1977

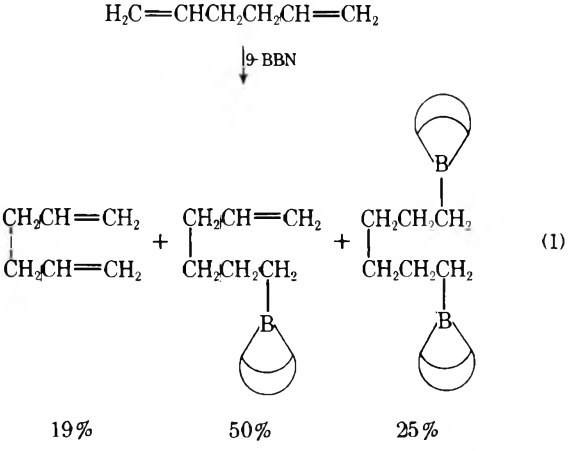
The exceptionally high sensitivity toward structure exhibited by 9-borabicyclo[3.3.1]nonane (9-BBN) in the hydroboration of simple olefins carries over to the hydroboration of nonconjugated dienes. In this way many such dienes can be selectively monohydroborated and thereby converted into synthetically useful intermediates. For example, dienes containing one terminal double bond and one internal double bond can be selectively hydroborated at the terminal position. Whereas 2-methyl-1,4-pentadiene is selectively hydroborated by disiamylborane at the less substituted double bond, the greater reactivity of 9-BBN for the 2-methyl-1-alkene structure permits the preferential hydroboration of the other position. The hydroboration of certain symmetrical cyclic dienes, such as 1,4-cyclohexadiene and 1,5-cyclooctadiene, with 9-BBN (1:1 mole ratio) is readily controlled to produce the monoadducts. The observation that the relative reactivities of simple olefin structures toward hydroboration with 9-BBN can be carried over so reliably to predict the point of hydroboration of nonconjugated dienes greatly facilitates the utilization of such dienes as intermediates in organic synthesis.

9-Borabicyclo[3.3.1]nonane is an interesting hydroborating agent which exhibits unusual regio-[2] and stereospecificities.[3] It also exhibits a remarkable sensitivity to the structure of individual olefins.[4] The question arose as to whether this knowledge could be carried over to predict the course of the monohydroboration of representative dienes. If so, such dienes could be selectively monohydroborated and the products utilized in the many transformations now available for organoboranes.[5] Accordingly, we undertook to study the monohydroboration of a number of representative nonconjugated dienes with this reagent and to compare the results with those realized in an earlier study utilizing disiamylborane.[6]

Results and Discussion

The reaction procedure involved the addition of a standard solution of 9-BBN in tetrahydrofuran (THF) to an equivalent amount of the diene in the same solvent. An internal standard suitable for GC analysis was present. The reaction was allowed to proceed to completion at 25 °C. The reaction product was oxidized by alkaline hydrogen peroxide in the usual manner.[5] GC examination for residual diene established the extent of monohydroboration (0% diene = 100% monohydroboration; 50% diene = 0% monohydroboration). The mono-ol product revealed the point or points of attack.

Symmetrical Acyclic Dienes. The reaction of 9-BBN with symmetrical dienes, such as 1,4-pentadiene and 1,5-hexadiene, would be expected to proceed in an essentially statistical manner, giving 25% residual diene, 50% of the monohydroboration products, and 25% of the dihydroboration product. Indeed, the data for 1,6-hexadiene closely follow this prediction for statistical behavior, with a minor discrepancy in the residual 1,5-hexadiene (eq 1).

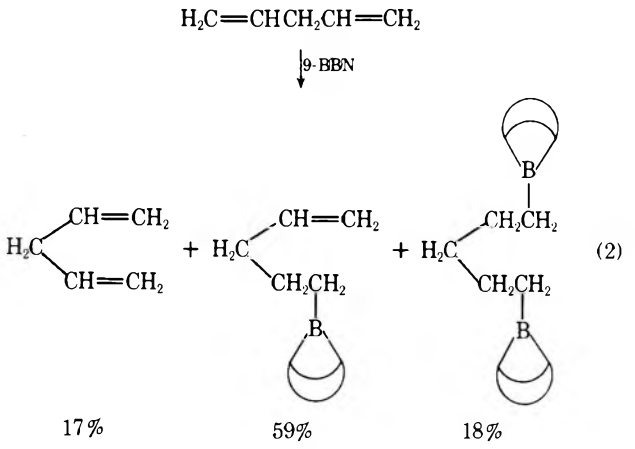


(1)

The results for 1,4-pentadiene are similar, but reveal a moderate displacement from the purely statistical distribution (eq 2). Conceivably there could be a small interaction of the double bond with the boron atom in the monohydroboration product sufficiently significant as to retard slightly its conversion into the dihydroboration product.

Similar results are realized with disiamylborane.[6]

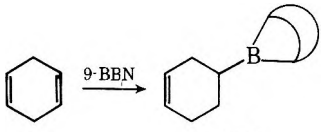
Symmetrical Cyclic and Bicyclic Dienes. In contrast to the behavior of the symmetrical acyclic dienes, the hydroboration of certain symmetrical cyclic dienes with 9-BBN can be controlled to yield the monohydroboration product predominantly. In the case of 1,5-cyclooctadiene, the results differ



(2)

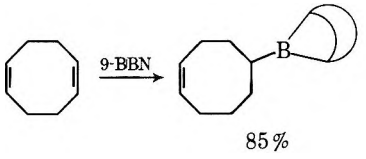
in major respect from those attainable with disiamylborane.[6]

Thus, the treatment of 1,4-cyclohexadiene with 1 equiv of 9-BBN proceeds predominantly to form the monoadduct (eq 3).



(3)

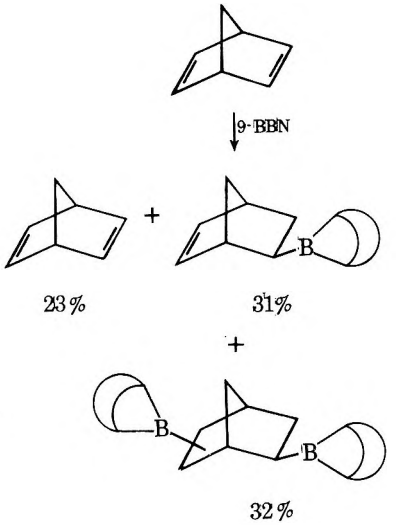
Similarly, the hydroboration of 1,5-cyclooctadiene with 9-BBN in the usual 1:1 molar ratio produces the monoadduct preferentially (eq 4). In sharp contrast, treatment of 2 mol of



(4)

1,5-cyclooctadiene (excess) with 1 mol of disiamylborane gives predominantly (86%) the dihydroboration product.[6] Consequently, the present procedure provides a valuable new synthetic route to 4-cycloocten-1-ol and other 4-cycloocten-1-yl derivatives.[5]

Norbornadiene behaves much more like a simple symmetrical diene, yielding a product distribution approaching that predicted for a statistical reaction (eq 5).

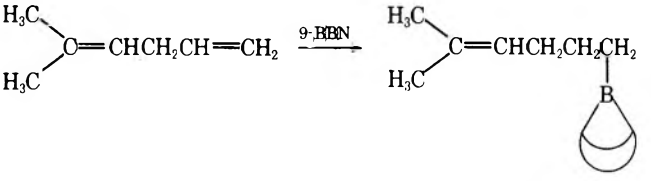


(5)

The monohydroboration product is entirely the exo derivative. GC examination of the alcohol produced via the usual oxidation revealed no trace of the endo isomer. In this respect, the reaction establishes a major advantage over hydroboration with disiamylborane.[6] Here the monohydroboration product yielded *exo*-dehydronorbornenol containing 13% of the endo isomer. The major difficulties in separating such isomers make the present procedure strongly preferable. By utilizing an excess of norbornadiene in the hydroboration stage, a considerably more favorable conversion to the desired *exo*-dehydronorbornenol and other derivatives should be realized.

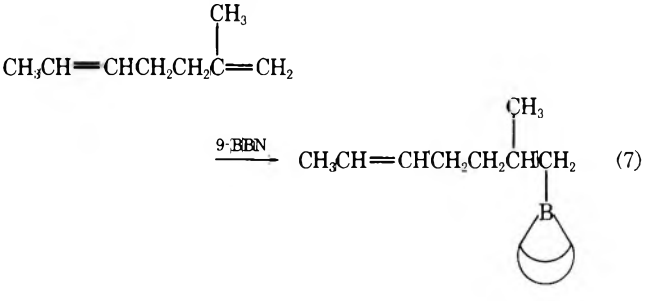
Unsymmetrical Acyclic Dienes. The presence in a diene of two different double bonds, which may differ greatly in reactivity, greatly facilitates monohydroboration.[5] A major question was whether the relative reactivities we had earlier established for the isolated olefin structures[4] could be utilized to predict the behavior of nonconjugated dienes containing related structures.

For example, 1-hexene is 116 times more reactive than 2-methyl-2-butene toward 9-BBN. It appears reasonable to predict that 5-methyl-1,4-hexadiene should undergo hydroboration by 9-BBN predominantly at the 1 position. Indeed, the monohydroboration reaction is remarkably clean—the predicted product is realized essentially isomerically pure (eq 6).



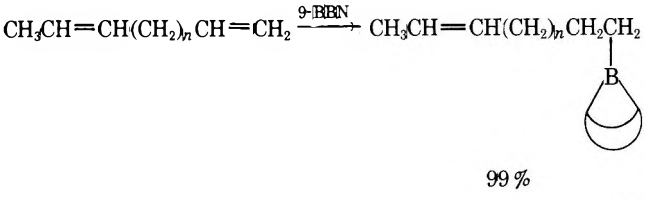
(6)

Similarly, 2-methyl-1-pentene is 194 times more reactive toward 9-BBN than *cis*-2-pentene. Accordingly, 2-methyl-1,5-heptadiene would be predicted to undergo hydroboration predominantly at the 1 position. The observed product is that predicted (eq 7).



(7)

1-Hexene is 100 times more reactive toward 9-BBN than *cis*-2-pentene. Consequently, both 1,4-hexadiene and 1,5-heptadiene would be predicted to undergo monohydroboration cleanly at the 1 position. In fact, the product is cleanly that predicted (eq 8).



(8)

In certain of these cases (eq 6, 8), the direction taken by the monohydroboration process is similar to that predicted for disiamylborane.[6,7] In the case of eq 7, the relative reactivities of the two olefin structures toward disiamylborane are very

similar.[7] Consequently, a selectivity of the kind achieved with 9-BBN cannot be anticipated. In the following case, it appeared from the reactivities of the parent olefins toward disiamylborane[7] and 9-BBN[4] that the regioselectivity of the monohydroboration of certain dienes could be reversed. We undertook to check this possibility.

1-Hexene is preferentially hydroborated by disiamylborane in the presence of 2-methyl-1-pentene. Indeed, the relative reactivity of 1-hexene toward this reagent is some 20 times greater.[7]

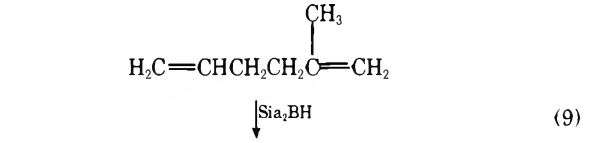
$$\frac{k_{1\text{-hexene}}}{k_{2\text{-methyl-1-pentene}}} = 20.4$$

On the other hand, toward 9-BBN 2-methyl-1-pentene is more reactive than 1-hexene.[4]

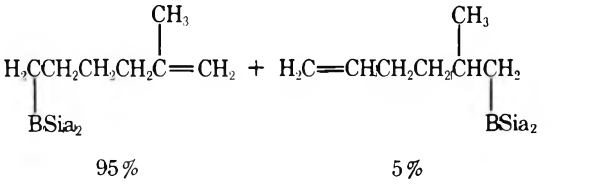
$$\frac{k_{1\text{-hexene}}}{k_{2\text{-methyl-1-pentene}}} = 1.94$$

It is believed that disiamylborane is more sensitive to steric effects than is 9-BBN, whereas the latter is more sensitive to electronic contributions.[4] In the case of disiamylborane, the steric contributions of the 2-methyl substituent dominate the reaction, whereas with 9-BBN, its electronic contributions facilitate the reaction.

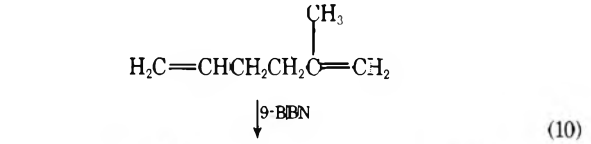
On this basis, it is not unexpected that 2-methyl-1,5-hexadiene is hydroborated by disiamylborane predominantly at the 6 position[6] (eq 9), whereas this diene is hydroborated by 9-BBN preferentially at the 1 position (eq 10).



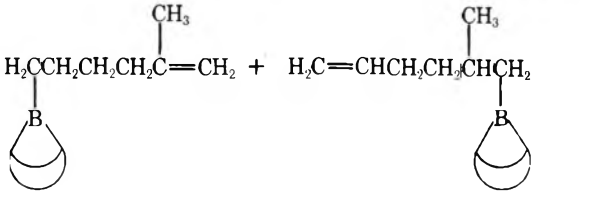
(9)



95% 5%



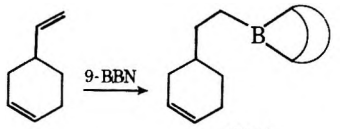
(10)



31% 69%

Consequently, by an appropriate choice of the hydroborating agent, 9-BBN or disiamylborane, it is possible in some cases to achieve a reversal of the particular double bond in a diene which undergoes hydroboration.

Unsymmetrical Alicyclic Dienes. This procedure of predicting the point of attack by 9-BBN in dienes from the reactivity data for the related olefins[4] also works well for "mixed" dienes, such as 4-vinylcyclohexene. 1-Hexene is 1500 times more reactive than cyclohexene toward 9-BBN. With such a large difference in the relative reactivities of the respective double bonds, it would be anticipated that 4-vinylcyclohexene should undergo hydroboration regiospecifically at the vinyl group. That is indeed observed (eq 11).



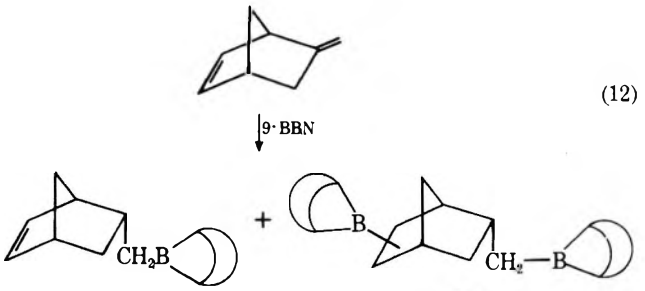
(11)

99%

2-Methylenenorbornane is 3.8 times more reactive than norbornene with respect to 9-BBN hydroboration. This is not a large difference in relative reactivity and considerable competitive attack at the norbornene double bond might have been anticipated. However, 9-BBN adds to the exocyclic double bond preferentially (eq 12).

No detectable amounts of methylenenorbornanols arising from attack at the internal norbornene double bond were observed in the GC examination of the oxidized products. Perhaps the huge strains in this rigid diene cause this minor deviation from the predicted behavior.

In eq 12, the monohydroboration product is indicated to be



(12)

83% 8%

the endo isomer. However, we were unable to separate the exo and endo alcohols on the columns we had available. Consequently, the assignment must be considered tentative, based on the marked preference for exo attack by hydroborating agents in norbornadiene (present study), norbornene,[3] and methylenenorbornane.[8]

The data for the hydroboration of these nonconjugated dienes with the results for the GC examination of the oxidized reaction products are summarized in Table I.

Conclusion

The present study establishes that the data available for the relative reactivities of representative olefins toward 9-BBN[4] can be used with considerable confidence to predict the point of hydroboration of nonconjugated dienes and, possibly, of polyenes. This development makes possible the selective reaction of a particular double bond in a complex structure containing more than one such bond. Moreover, by a judicious choice of disiamylborane[7] or 9-BBN it is on occasion possible to hydroborate one double bond structure in the presence of another or to invert the process. With the large and growing arsenal of organoborane transformations,[5] this development should add to the utility of hydroboration as a synthetic route for synthetic operations.

Experimental Section

General Comments. All glassware, syringes, and needles were oven dried at 150 °C before use. The glassware was assembled hot and cooled under a flow of nitrogen. Syringes were assembled and fitted with needles while hot, then cooled as assembled units. They were flushed out with nitrogen immediately before use.

Materials. The *n*-alkanes (Phillips), employed as internal standards, were used as received. Technical grade pentane was stirred over concentrated sulfuric acid to remove any olefinic impurities, washed with aqueous base, dried over anhydrous magnesium sulfate (Mallinckrodt), and distilled under nitrogen from lithium aluminum hydride. Bicyclo[2.2.1]hepta-2,5-diene and 5-methylene-2-norbornene

Table I. Hydroboration–Oxidation Product Distribution of Nonconjugated Dienes (0.5 M) with 1 Molar Equiv of 9-BBN (0.5 M) in THF at 25 °C

Registry no.	Diene	Residual diene,[a] %	Unsaturated alcohols, %	Diols,[b] %
592-42-7	1,5-Hexadiene	19	5-Hexen-1-ol, 50	1,6-Hexanediol, 25
591-93-5	1,4-Pentadiene	17	4-Penten-1-ol, 59	1,5-Pentanediol, 18
628-41-1	1,4-Cyclohexadiene	Tr	3-Cyclohexen-1-ol, 85	7[c]
111-78-4	1,5-Cyclooctadiene	9	4-Cycloocten-1-ol, 85	8[c]
121-46-0	Norbornadiene	23	exo-Dehydronorborneol,[d] 31	32[c]
763-88-2	5-Methyl-1,4-hexadiene	Tr	5-Methyl-4-hexen-1-ol, 99	0
	2-Methyl-1,5-heptadiene[e]	0	2-Methyl-5-hepten-1-ol,[e] 99	0
	1,4-Hexadiene[e]	Tr	4-Hexen-1-ol,[e] 99	0
	1,5-Heptadiene[e]	0	5-Hepten-1-ol,[e] 99	0
4049-81-4	2-Methyl-1,5-hexadiene	20	2-Methyl-5-hexen-1-ol, 35.8 5-Methyl-5-hexen-1-ol, 15.7	2-Methyl-1,6-hexanediol, 22
100-40-3	4-Vinylcyclohexene	0	2-(4-Cyclohexenyl)ethanol, 99	0
694-91-7	Methylenenorbornene	7	5-(Hydroxymethyl)norbornene,[f] 83	8.2[c]

[a] Analysis after oxidation. [b] % based on diene. [c] Unresolved mixture. [d] None of the endo isomer present. [e] Mixture of cis and trans. [f] Unresolved mixture of epimer.

were obtained from the Aldrich Chemical Co. 1,5-Cyclooctadiene was purchased from Cities Service. All other nonconjugated dienes were purchased from Chemical Samples. These purchased dienes were used after checking ^{1}H NMR, index of refraction, and GC retention time on a Varian Model 1200 gas chromatograph with an appropriate column.

Hydroboration of Nonconjugated Dienes. The following nonconjugated dienes were hydroborated, oxidized, and analyzed in precisely the same manner: 5-methyl-1,4-hexadiene, 2-methyl-1,6-heptadiene (mixture of cis and trans), 1,6-heptadiene, 1,4-hexadiene (mixture of cis and trans), 2-methyl-1,5-hexadiene, 1,5-hexadiene, 5-methylene-2-norbornene, and bicyclo[2.2.1]hepta-2,5-diene.

General Reaction Procedure. A dry 100-mL round-bottom flask equipped with a septum side arm and reflux condenser was connected to a mercury check valve through an adapter. The system was purged of air by nitrogen and the inert atmosphere was maintained until the oxidation stage. Normally, 10.0 mmol of diene was added via syringe along with 3 mmol of a suitable internal standard. 9-BBN (0.5 M in THF), 10.0 mmol, was added to the reaction flask slowly via syringe. After sufficient time for complete reaction, the mixture was oxidized. Sodium hydroxide solution (3 M, 3 mL) was injected into the flask, followed by 3 mL of hydrogen peroxide (30% solution), added dropwise over 10–15 min (exothermic reaction). The reaction mixture was heated to 50 °C for 1 h to complete the oxidation, then cooled to room temperature. The water layer was saturated with anhydrous potassium carbonate and the THF layer was separated and dried over anhydrous magnesium sulfate. The water layer was extracted with 15 mL of pentane. This was dried over magnesium sulfate and combined with the first extract. A small aliquot (~3 mL) was removed by disposable pipet and stored over 3 Å molecular sieves (Matheson Coleman and Bell). This aliquot was used for GC analysis. Then about 25–50 mL of pentane was added to the remaining organic fraction to precipitate *cis*-1,5-cyclooctanediol. The pentane was decanted off from the diol, which separated either as a viscous oil or a crystalline solid in the bottom of the flask. Purification by preparative gas chromatography (XE-60, 6 ft × 0.5 in.) of the organic material afforded essentially pure (>98%) unsaturated alcohol. ^{1}H NMR (Varian T-60) and IR (PE-137 and/or PE-700) were run to confirm the identity of the product. The GC correction factor was determined. The product distributions are summarized in Table I.

The hydroboration–oxidation of 4-vinylcyclohexene, 1,5-cyclooctadiene, 1,4-pentadiene, 1,3-cyclohexadiene, 5-methylene-2-norbornene, and bicyclo[2.2.1]hepta-2,5-diene were performed following the same general procedure described above, except that the products were not isolated. In these cases, authentic samples were available for comparison. These results are likewise presented in Table I.

Registry No.—9-BBN, 280-64-8; *cis*-2-methyl-1,5-heptadiene, 41044-64-8; *trans*-2-methyl-1,5-heptadiene, 41044-63-7; *cis*-1,4-hexadiene, 7318-67-4; *trans*-1,4-hexadiene, 7319-00-8; *cis*-1,5-heptadiene, 7736-34-7; *trans*-1,5-heptadiene, 7736-22-3.

References and Notes

(1) Graduate research assistant on Grant GM 10937-14 of the National Institutes of Health.
(2) H. C. Brown, E. F. Knights, and C. G. Scouten, *J. Am. Chem. Soc.*, **96**, 7765 (1974).
(3) H. C. Brown, R. Liotta, and L. Brener, *J. Am. Chem. Soc.*, **99**, 3427 (1977).
(4) H. C. Brown, R. Liotta, and C. G. Scouten, *J. Am. Chem. Soc.*, **98**, 5297 (1976).
(5) H. C. Brown, G. W. Kramer, A. B. Levy, and M. M. Midland, "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(6) H. C. Brown, G. Zweifel, and K. Nagase, *J. Am. Chem. Soc.*, **84**, 190 (1962).
(7) H. C. Brown and A. W. Moerikofer, *J. Am. Chem. Soc.*, **85**, 2063 (1963).
(8) H. C. Brown and J. H. Kawakami, *J. Am. Chem. Soc.*, **92**, 1990 (1970).

Ring-Closure Reactions. 8.[1] Synthesis and Ultraviolet Spectra of Macrocyclic Aromatic Ethers

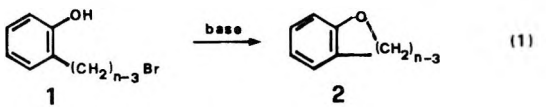
Luigi Mandolini* and Bernardo Masci

Centro C.N.R. dei Meccanismi di Reazione, c/o Istituto di Chimica Organica, Università di Roma, 00185 Roma, Italy

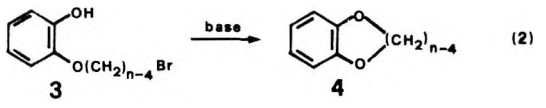
Received January 25, 1977

Macrocyclic mono- and diethers have been prepared in fairly good yields by means of a very convenient, straightforward procedure starting from the open-chained bifunctional precursors, namely, *o*-ω-bromoalkyl and *o*-ω-bromoalkoxyphenols. In some cases small amounts of the dimeric cycles were also isolated. The present work provides a further example of the effectiveness of the NaOH–Me_2SO base–solvent system in promoting ring formation via intramolecular Williamson synthesis. The UV spectral data of the present compounds, when combined with those of the already available lower homologues, exhibit significant ring-size dependent effects, which are discussed in some detail.

In connection with our studies on ring-closure reactions we have undertaken an extensive investigation of the cyclization reactions 1 and 2,[2,3] leading to the aromatic mono- and diethers 2 and 4, respectively, by intramolecular Williamson



1 2 (1)



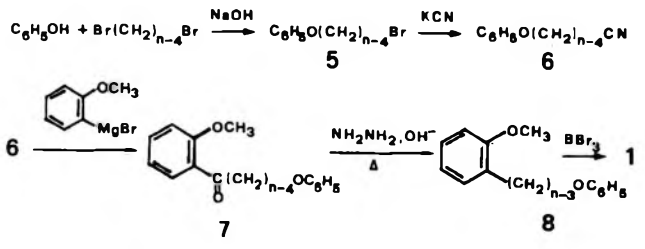
3 4 (2)

synthesis.[4] The scope of these studies includes physical and mechanistic aspects as well as the attainment of better insight for the improvement of synthetic procedures for ring compounds. The preparation of the eight-, nine-, and ten-membered monoethers 2 by means of an extremely convenient cyclization procedure has already been described.[5] We report now the extension of the above procedure to the synthesis of compounds **2**, n = 11, 14, and 16, and **4**, n = 11, 12, 13, 14, 16, and 24. The UV absorption spectra of the above compounds and of the lower homologues in both series were recorded and compared with those of suitable open-chained models. The observed ring-size dependent features provide an insight into the conformational restrictions imposed by the different ring structures to the degree of coplanarity of the chromophoric groups.

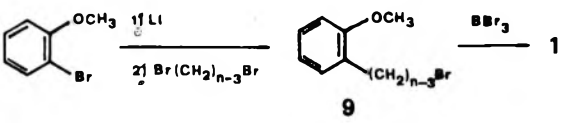
Syntheses of the Open-Chained Precursors. *o*-ω-Bromoalkoxyphenols **3** were prepared by mono-O-alkylation of catechol with the appropriate α,ω-dibromoalkane. Yields, physical constants, and analytical data of the synthesized compounds are listed in Table I.

For the preparation of the *o*-ω-bromoalkylphenols **1**, n = 11, 14, and 16, the five-step synthetic procedure (Scheme I) previously developed for the smaller members of the series was followed in the early part of this work. Poor yields of the desired compounds were obtained by this method (method A), probably due at least in part to the difficulties encountered

Scheme I



Scheme II



in the isolation and purification of the low-melting, high-boiling long-chain compounds. A more convenient procedure was developed subsequently (method B), involving a two-step reaction scheme (Scheme II) from the same commercially available starting materials, i.e., *o*-bromoanisole and the appropriate α,ω-dibromoalkane. The lithiation of *o*-bromoanisole with lithium metal proceeds smoothly in dry ether at room temperature. When 1 mol of the lithium derivative was treated with 1 mol of dibromo compounds the monoalkylated products were isolated in 31–35% yield, satisfactory for a reaction of a monofunctional reagent with an equimolar amount of a bifunctional one. The desired *o*-ω-bromoalkylphenols **1** were obtained by simple cleavage with BBr_3 of the methoxyl group of **9**. It is apparent from Table I, where the pertinent yield data are shown, that the latter procedure is definitely better than the former one.

It is worth noting that the interaction of aromatic lithium derivatives with alkylating agents appears to have been carried out previously but seldom with reagents other than methyl derivatives or ethylene oxide. In fact, we are aware of only one case in which a long-chain alkyl halide has been employed for the alkylation of an aryllithium compound.[6] Moreover, ortho alkylanisoles (and phenols) are not easily prepared. Most of the available synthetic procedures lead to mixtures of ortho and para derivatives. Lately a new method for the synthesis of ortho-alkylated phenols from phenols and dialkyl sulfides has been published.[7] However, this method, which appears to be far superior to previously reported ones, suffers from the general unavailability of the cyclic polymethylene sulfides which are required for the introduction of alkyl groups other than methyl.

It seems therefore that the reaction sequence of Scheme II has the potential of providing a convenient general synthetic route to ortho-alkylated anisoles (and phenols) from readily available starting materials.

Cyclization Reactions. In a previous paper of this series we have shown that compounds **1**, n = 8, 9, and 10, could be conveniently cyclized to the corresponding macrocycles **2** by treatment with a suspension of excess concentrated aqueous NaOH in Me_2SO solution at 55 °C.[5] This simple procedure, successfully applied in the present work, avoided the long reaction times and large volume of solvent usually required for the synthesis of macrocycles according to the Ziegler high-dilution technique. Typically, a few grams of a given bifunctional precursor were cyclized employing 150 mL of

Table I. Yields and Physical Constants for the Preparation of o-ω-Bromoalkylphenols 1, o-ω-Bromoalkoxyphenols 3, Cyclic Monoethers 2, and Cyclic Diethers 4[a]

Registry no.	Compd	n	Yield, %	Mp, °C, or n^{20}_D
62587-18-2	1[b]	11	3.3 (A), 21 (B)	1.5386
62587-19-3		14	7.2 (A), 23 (B)	27.5–30
62587-20-6		16	2.6 (A), 25 (B)	41–43.5
62587-21-7	3	11	26	29–31[c]
62587-22-8		12	34	1.5261
62587-23-9		13	29	23–24.5[d]
62587-24-0		14	26	1.5197
62587-25-1		16	22	25.5–26.5
62587-26-2		24	35[e]	51–52.5
62587-27-3	2	11	70	1.5416
62609-07-8		14	79	1.5328[f]
62587-28-4		16	79	1.5247[g]
7125-07-7	4	11	70	1.5384
7125-08-8		12	62	41–43[h]
7198-62-1		13	58	54–56[i]
7198-63-2		14	62	1.5356
62587-29-5		16	73	46.5–48
62587-30-8		24	69[e]	55–56

[a] Analytical data were within ±0.3% in all cases, with the sole exception of **3**, $n = 24$. For the latter compound: Anal. Calcd for $C_{26}H_{45}BrO_2$: C, 66.51; H, 9.66. Found: C, 67.25; H, 9.83. [b] Yields reported are overall yields. For the meaning of the symbols A and B see text. [c] From pentane at 5 °C, lit.[4] mp 32 °C. [d] From pentane at 5 °C, lit.[4] mp 19°. [e] Yields not comparable with others. See text. [f] Bp 120–125 °C (1.5 mm). [g] Bp 158 °C (1.8 mm). [h] Lit.[4] mp 46 °C. [i] Lit.[4] mp 58 °C.

solvent and reaction times of 1 h or so. Fair to good yields of cyclic compounds in both series were obtained (Table I). In some cases minor amounts of the dimeric cycles **10** were isolated. No trace was found of the isomeric open-chain alkenyl derivatives **11** which were found to accompany the eight- and nine-membered ring formation in both series[2,3,5] and which were attributed to a competing intramolecularly assisted elimination reaction of the E_2 type. Since on increasing molecular weight purification became more difficult, the cyclization of compound **3**, $n = 24$, was run in the presence of K_2CO_3 in aqueous ethanol, under conditions similar to those of the kinetic runs,[3] and to those previously adopted for the cyclization of compounds **3**, $n = 8$ and 9.[2] A small amount of the dimeric 48-membered tetraether **10**, Z = O, $n = 24$, was also isolated in this case. Apart from the diethers with ring size up to 14,[4] none of the ring compounds has been reported in the literature. Structure assignments were based mainly on elemental analyses (Table I) and ^1H NMR spectrometry. In the ^1H NMR spectra of the diethers **4** the protons are grouped in three areas at δ 6.7 (singlet, aromatic protons), 3.8–4.1 (broad triplet, CH_2 next to oxygen), and 1.2–2.0 (multiplet, "central" methylene protons). The latter signal is broad, but a prominent sharp peak stands out at ca. δ 1.4 in the 13- and higher membered rings. A similar situation appears in the ^1H NMR spectra of the monoethers **2**, for which the corresponding signal is a broad and featureless multiplet at δ 1.0–2.0 for ring size 11, while the 14- and 16-membered rings exhibit a signal at δ 1.3–2.0, with a prominent peak at δ 1.4. In all the monoethers the benzylic and ethereal methylenes appear as partially resolved triplets at ca. δ 2.5–2.8 and 3.8–4.1, respectively. In addition, the aromatic protons are shown as a complex multiplet at δ 6.4–7.2. In all cases the intensity ratios are as expected, and no extra peak is present.

10, Z = O, CH_2 **11**, Z = O, CH_2

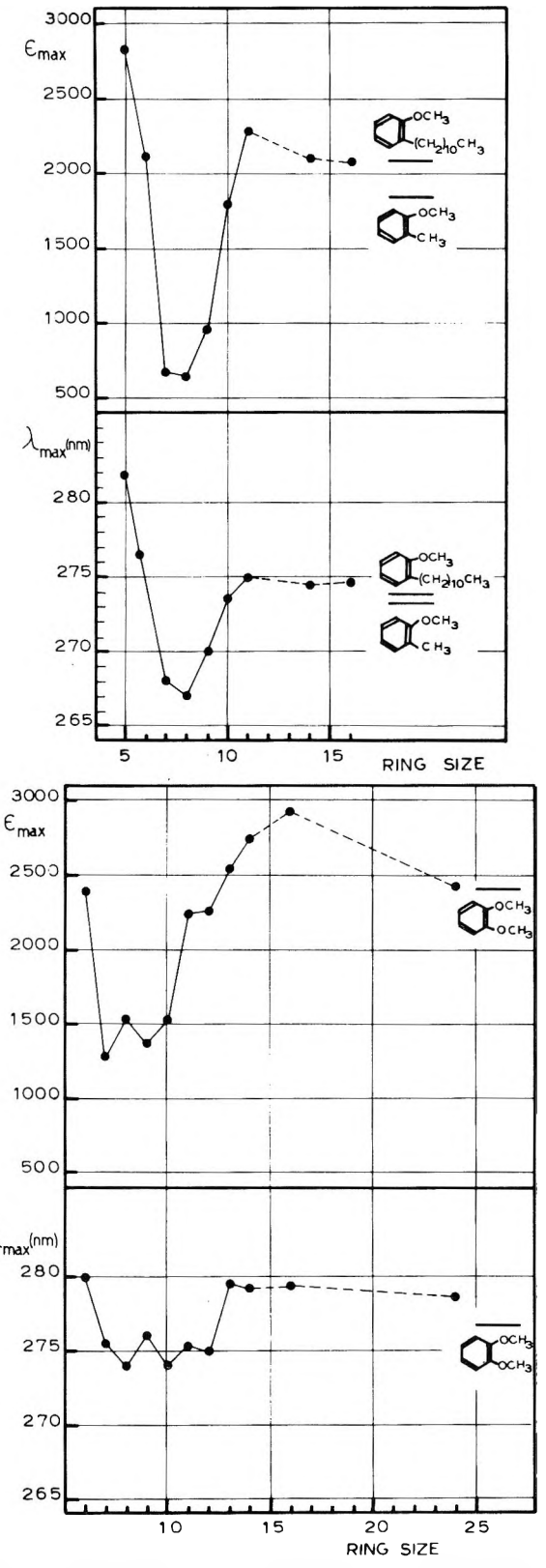


Figure 1. Ultraviolet spectral data for the monoethers **2** (top) and diethers **4** (bottom) in ethanol solution. The pertinent data of open-chained model compounds are also shown.

Structure assignment to the dimeric cycles was based mainly on molecular weight determinations by means of mass spectrometry, since their ^1H NMR spectra are expected to be quite similar to those of the corresponding monomeric cycles.

Table II. Ultraviolet Spectral Data for the Monoethers 2, Diethers 4, and Open-Chained Model Compounds in Ethanol Solution

Registry no.	Compd	n	λ_{max}, nm			ϵ_{max}, cm^{-1} M^{-1}			ϑ, deg
496-16-2	2	5	289*	281.8	274*		2829		0
493-08-3		6	284.4	276.5	270*	2079	2122		30
6169-78-4		7	274.0	268.0	261*	665	670		61
51060-43-6		8	273.5	267.0	261*	651	651		61
51795-92-7		9	275.0	270.0	262*	882	961		54
51795-93-8		10	279.6	273.6	267*	1669	1794		37
		11	281.4	274.9	267*	2198	2289		26
		14	280.5	274.4	267*	1972	2105		30
		16	280.8	274.7	267*	1922	2083		31
578-58-5	o-Methyl-anisole		279.2	273.2	267*	1711	1825		37
20056-62-6	o-Undecyl-anisole		279.8	273.8	267*	1938	2081		31
493-09-4	4	6	286.0	280.0	274*	2130	2392		
7216-18-4		7	283*	275.5	271*		1285		
7124-91-6		8	282*	274.0	268*		1539		
7124-99-4		9		276.1	272*		1364		
7198-60-9		10	280*	274.0			1527		
		11	280.6	275.3	267*	2024	2241		
		12	280.0	275.0		2249	2258		
		13	285*	279.5	276.9		2540	2020	
		14	285*	279.2	276*		2748		
		16	285*	279.4	276*		2929		
		24	284*	278.6	276.0		2415	2385	
91-16-7	Veratrole		282*	276.7			2400		

* Shoulder.

UV Spectra of the Ring Compounds. Inspection of space-filling molecular models indicates that the degree of coplanarity between the benzene ring and the O–C_{aliph} chromophore(s) in both mono- and diethers is affected to a significant extent by the size of the ring. A particularly severe hindrance to planarity is apparent in the neighborhood of ring size 8 and 9. Since maximum conjugative interaction between the chromophoric groups requires a planar arrangement, it is expected that increasing the degree of twist results in both an increasing hypochromic effect and hypsochromic shift relative to the spectrum of a planar model.[8] Compounds in which a chromophoric group attached to a benzene ring has been incorporated into cyclic structures, mostly in the ring size range 5–8, have been reported to exhibit ring-size dependent spectral features, in accordance with the above arguments.[9–11]

The UV spectral data of the cyclic compounds prepared in this work, together with those of the lower homologues in both series and of suitable open-chained reference compounds, are presented in Table II and plotted in Figure 1 as a function of ring size. None of the given compounds displays a simple absorption band; generally either a second closely spaced maximum and a shoulder or two shoulders are present besides the principal maximum. The trends in both λ_{max} and ϵ_{max} can be interpreted in terms of the varying degree of coplanarity of the O–C_{aliph} moiety with the aromatic ring for different ring sizes. Steric hindrance to coplanarity appears to be a maximum for ring size 7–9, while the conformations of the strainless or nearly strainless large rings are closely akin to those of the open-chained models. In the case of the monoethers the angle of twist ϑ has been calculated by means of the relationship $\epsilon^{\vartheta}/\epsilon^{0} = \cos^2 \vartheta$,[8] where ϵ^{0} refers to ϵ_{max} of coumaran (**2**, $n = 5$), in which the chromophoric groups are required to be coplanar because of steric reasons. However, it must be noted that the simple $\cos^2 \vartheta$ relationship is expected to hold mainly in cases where a hypochromic effect is not accompanied by a relevant hypsochromic shift.[12] Moreover, such a relationship cannot account for any effect due to possible geometrical distortions in the aromatic portion caused by the annelation with a strained ring. No doubt the latter effect plays some role, as shown by the fact that the five- to eight-membered cycloalkenobenzenes have been reported[13] to exhibit UV spectral data markedly dependent on ring size. In the latter compounds steric inhibition to conjugation, if any, is likely to give but a small contribution. The observed effect has been explained on the basis of strain on the π-electron sextet both in the ground and excited state.[13] It is thus concluded that the ϑ values reported in Table II are probably not meaningful as such, but should rather be regarded as providing a rough indication of steric hindrance to coplanarity in the various ring compounds.

Experimental Section

Most apparatuses were as previously described.[2] IR and ^1H NMR spectra were taken in CCl_4 solutions. UV spectra were measured in ethanol solution on a Beckman DB GT spectrometer, fitted with a W+W 1100 recorder. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, Elbach über Engelskirchen, West Germany. All melting points are uncorrected.

Materials. Catechol (Erba RPE) and Veratrole (Fluka) were commercial samples and used as such. o-Bromoanisole (Schuchardt) and o-methylanisole (Schuchardt) were redistilled before use. All the α,ω-dibromoalkanes up to C_{12} were from Fluka and used without further purification. All the cyclic mono-[3,5] and diethers[2] up to ring size ten and 1,20-dibromoeicosane[1] were available from previous investigations. 1,13-Dibromotridecane was obtained in 53% yield from 14-bromotetradecanoic acid[1] by the Cason and Welba's modification (procedure P)[14] of the Hunsdiecker reaction, bp 138–142 °C (0.05 mm), n^{25}_D 1.4881 (lit.[15] n^{27}_D 1.4880).

***o*-ω-Bromoalkoxyphenols (3, *n* = 11, 12, 13, 14, 16, and 24).** All the compounds except that with $n = 24$ were prepared according to a previously described procedure,[2] with the sole difference that increasing times were required on increasing chain length of the dibromo compound in order to achieve complete reaction, namely, 3.5, 7, 15, 24, and 40 h for $n = 11$, 12, 13, 14, and 16, respectively. With the aim of avoiding unconveniently long reaction times, the alkylation reaction with 1,20-dibromoeicosane ($n = 24$) was run under different reaction conditions, namely, in homogeneous solution of boiling ethanol, where the reaction was complete in 4 h. The compounds were purified by

chromatography on silica gel, with $CHCl_3$–light petroleum (1:1) as eluent. For analytical purposes the products were further purified by microdistillation under vacuum with the ball tube. The ^1H NMR spectra were in all cases consistent with the expected structures.

***o*-ω-Bromoalkylphenols (1, *n* = 11, 14, and 16). Method A.** The identity of all intermediates and final products was checked by ^1H NMR spectroscopy. The ^1H NMR spectra were analogous to those of the lower homologues,[5] with the obvious difference of an increased intensity of the signal due to the "central" methylene protons. ω-Phenoxy bromides **5** were obtained by reacting sodium phenoxide (1 mol) with the appropriate α,ω-dibromoalkane (1 mol) in refluxing ethanol (4 h). After standard workup, the pure compounds were obtained by chromatography on silica gel, using CCl_4–light petroleum (3:1) as eluent: *n* = 11, 28% yield, $n^{21}D$ 1.5229; *n* = 14, 34% yield, mp 31–31.5 °C; *n* = 16, 29% yield, mp 37–40 °C. The conversions **5** → **6**, **6** → **7**, **7** → **8**, and **8** → **1** were carried out as previously described.[5] For each compound the pertinent yields and physical constants, when available, are reported below in the given order. All nitriles **6** and ketones **7** showed the expected IR bands at 2250 and 1680 cm^{-1}, respectively. Compounds **6**: *n* = 11, 92%, oil (crude); *n* = 14, 96%, mp 25–27 °C (crude); *n* = 16, 87%, mp 33–35 °C (crude). Compounds **7**: *n* = 11, 88%, oil (crude); *n* = 14, 89%, oil (crude); *n* = 16, 68%, oil (crude). Compounds **8** were purified by chromatography on silica gel, with $CHCl_3$–light petroleum (1:1) as eluent: *n* = 11, 26%, $n^{24}D$ 1.5365; *n* = 14, 30%, mp 30–32 °C; *n* = 16, 33%, mp 41–43 °C. Compounds **1**, *n* = 11, 14, and 16, were repeatedly chromatographed on silica gel with $CHCl_3$–light petroleum (1:2) and/or $CHCl_3$ until pure by TLC. For analytical purposes the compounds were microdistilled with the ball tube under vacuum (0.05 mm or less).

Method B. All operations before aqueous workup were carried out under argon. 2-Lithioanisole was prepared from *o*-bromoanisole (1 mol) and freshly cut small pieces of lithium metal (2 mol) in dry ether. After the dissolution of lithium was complete, the solution was filtered through glass wool with the aid of an argon overpressure. To the clear filtrate the appropriate α,ω-dibromoalkane was added dropwise. The resulting solution was refluxed for 2 h. In order to ensure complete reaction the solvent was evaporated and the residue was heated for additional 2 h at 120 °C. After cooling, water was added and the aqueous mixture was neutralized with H_2SO_4 and extracted with $CHCl_3$. The latter was dried over Na_2SO_4 and evaporated. Compound **9**, *n* = 11, was isolated by fractional distillation of the residue in 35% yield, bp 120–130 °C (0.3 mm). Compound **9**, *n* = 14, was obtained likewise in 35% yield, bp 154–164 °C (0.1 mm). In the latter case a small amount (ca. 1%) of 2,2′-dimethoxybiphenyl separated on standing from the forerun as white crystals, mp 150–152 °C from EtOH, lit.[15] mp 155 °C, ^1H NMR as expected. Compound **9**, *n* = 16, was obtained in 31% yield by column chromatography on silica gel using benzene–light petroleum (1:1) as eluent. All three compounds were pure by TLC and gave ^1H NMR spectra consistent with the expected structure. Cleavage of the methoxy group afforded compounds **1**, *n* = 11, 14, and 16, in 72, 60, and 79% yield, respectively.

Cyclic ethers 2, *n* = 11, 14, and 16, and 4, *n* = 11, 12, 13, 14, 16, and 24, were synthesized by cyclization of the corresponding open-chained precursor as outlined in the general part. After aqueous workup and ether extraction the crude products were eluted on silica gel with $CHCl_3$–light petroleum (1:2), then further purified either by distillation or sublimation under vacuum. In some cases the dimeric cycles **10** separated as white, crystalline solids from solutions of the crude products in light petroleum (compounds **10**, Z = CH_2, *n* = 14 and 16) or light petroleum–$CHCl_3$ (2:1) (compound **10**, Z = O, *n* = 24). The solids were collected by filtration and thoroughly washed with light petroleum. Compound **10**, Z = CH_2, *n* = 14, 1.2% yield, mp 124.5–126 °C, M^+ *m/e* 492. Compound **10**, Z = CH_2, *n* = 16, 2% yield, mp 130.5–132 °C, M^+ *m/e* 548. Compound **10**, Z = O, *n* = 24, 4% yield, mp 143.5–145 °C, M^+ *m/e* 776.

***o*-Undecylanisole** was obtained as an unexpected product on attempted bishomologation of **9**, *n* = 14, via the interaction of the Grignard reagent derived therefrom with ethylene oxide. After standard workup, the title compound was obtained in 10% yield by chromatography on silica gel, using $CHCl_3$–light petroleum (1:2) as eluent: $n^{19}D$ 1.4922; ^1H NMR δ 7.2–6.5 (m, 4 H, nuclear protons), 3.8 (s, 3 H, OCH_3), 2.8–2.4 (distorted t, 2 H, benzylic CH_2), 1.9–0.7 (m, 21 H, central methylene and terminal methyl protons). The recovery was not quantitative, since several fractions containing the given compound in a less pure form were discarded.

Acknowledgment. The authors wish to thank Professor G. Illuminati for helpful discussions and critical reading of the manuscript.

Registry No.—**5** (*n* = 11), 51795-98-3; **5** (*n* = 14), 2033-87-6; **5** (*n* = 16), 62587-31-9; **6** (*n* = 11), 62587-32-0; **6** (*n* = 14), 62587-33-1; **6** (*n* = 16), 62587-34-2; **7** (*n* = 11), 62587-35-3; **7** (*n* = 14), 62587-36-4; **7** (*n* = 16), 62587-37-5; **8** (*n* = 11), 62587-38-6; **8** (*n* = 14), 62587-39-7; **8** (*n* = 16), 62587-40-0; **9** (*n* = 11), 62587-41-1; **9** (*n* = 14), 62587-42-2; **9** (*n* = 16), 62587-43-3; **10** (Z = CH_2; *n* = 14), 62587-44-4; **10** (Z = CH_2, *n* = 16), 62587-45-5; **10** (Z = O, *n* = 24), 62587-46-6; 1,8-dibromooctane, 4549-32-0; 1,11-dibromoundecane, 16696-65-4; 1,13-dibromotridecane, 31772-05-1; 1,7-dibromoheptane, 4549-31-9; 1,10-dibromodecane, 4101-68-2; 1,12-dibromododecane, 3344-70-5; *o*-bromoanisole, 578-57-4; phenol, 108-95-2; 1,20-dibromoeicosane, 14296-16-3.

References and Notes

(1) Part 7: C. Galli, G. Illuminati, L. Mandolini, and P. Tamborra, *J. Am. Chem. Soc.*, **99**, 2591 (1977).
(2) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **96**, 1422 (1974).
(3) G. Illuminati, L. Mandolini, and B. Masci, *J. Am. Chem. Soc.*, **97**, 4960 (1975).
(4) The synthesis of aromatic macrocyclic ethers via intramolecular alkylation of phenols has been extensively used; see K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, *Justus Liebigs Ann. Chem.*, **528**, 162 (1937).
(5) G. Illuminati, L. Mandolini, and B. Masci, *J. Org. Chem.*, **39**, 2598 (1974).
(6) H. Lettrè and A. Jahn, *Chem. Ber.*, **85**, 346 (1952).
(7) P. G. Gassman and D. R. Amick, *Tetrahedron Lett.*, 889 (1974).
(8) H. H. Jaffè and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy", Wiley, New York, N.Y., 1962, Chapter 15.
(9) W. R. Remington, *J. Am. Chem. Soc.*, **67**, 1838 (1945); G. Baddeley, J. Chadwick, and S. B. Rawlinson, *Nature (London)*, **164**, 833 (1949).
(10) G. D. Hedden and W. G. Brown, *J. Am. Chem. Soc.*, **75**, 3744 (1953).
(11) G. Baddeley, N. H. P. Smith, and M. A. Vickars, *J. Chem. Soc.*, 476 (1956); G. Baddeley and N. H. P. Smith, *ibid.*, 2516 (1961).
(12) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).
(13) V. H. Meier, J. Heiss, H. Suhr, and E. Müller, *Tetrahedron*, **24**, 2307 (1968).
(14) J. Cason and D. H. Welba, *J. Org. Chem.*, **37**, 669 (1972).
(15) "Handbook of Chemistry and Physics", 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969–1970.

Cage Aza Polycyclics. An Investigation of the Cyclization Oriented to Twisted—or Nontwisted—Tricyclic Aza Bridged Molecules. Synthesis and Structure Determination by 250-MHz Nuclear Magnetic Resonance Spectroscopy

R. Furstoss, R. Tadayoni,[‡] and B. Waegell*

Université d'Aix-Marseille III, Centre de Saint-Jérôme Laboratoire de Stéréochimie associé au CNRS (109), rue H. Poincaré, 13397 Marseille Cedex 4, France

Received July 21, 1976

Analysis of the 250-MHz NMR spectrum of *N*-methyl-2-azatwistane and of its azahomobrendane isomer, which have been synthesized independently, allows the assignment of twisted—or nontwisted—structure to this type of cage compounds.

The synthesis of cage polycyclics, and particularly of twisted derivatives, is of interest in the carbocyclic and heterocyclic series.[1-3] We recently have described the cyclization of *N*-chloro-*N*-methylaminobicyclo[2.2.2]oct-5-ene (**1**) (Scheme I), and assigned a "homobrendane" [28] structure to the tricyclic derivative **2** thus obtained.[4] However, a twistane structure has since been proposed by others[5] for the same product.

Similarly, we have studied the cyclization of *N*-chloroamine **5** under the conditions of the well-known Hofmann–Loeffler–Freytag reaction,[6] where a similar structural problem arises (Scheme II). The regioselectivity of the Hofmann–Loeffler–Freytag reaction has been explained on the basis of steric arguments (such as lining up of C–H---N atoms), and energetic considerations (minimum steric interactions in the transition state[7,8]). Accordingly, cyclization generally occurs in the δ position relative to nitrogen; however, some exceptions are known,[9] when the conformation of the molecule is more favorable to γ or ϵ cyclization.

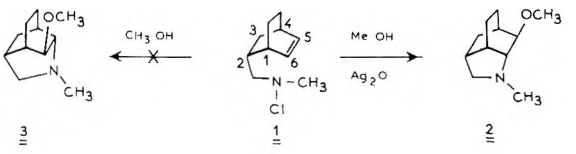
With both substrates **1** and **5** (Schemes I and II), it is clear from inspection of molecular models that the cyclization can occur "frontwise", to yield a homobrendane type structure (**2** or **6**), or "crosswise" to give a twistane derivative (**3** or **7**). A "frontwise" cyclization would lead to products where about all C–C and C–H bonds are in energetically disfavored conformations. This is particularly clear in the case of the *N*-chloro amine **5**, where a twisted or a nontwisted conformation can be considered for the bicyclo[2.2.2]octane skeleton.[10] In order to obtain the homobrendane structure **6**, a cyclization on the δ position, which implies a transition state such as **8b**, must occur. However, the strong eclipsing interactions apparently involved in this transition state should disfavor it relative to transition state **8a**, the latter leading to a twistane structure via a cyclization in ϵ position.

Undoubtedly, prediction of the cyclization direction will be problematical and risky. The situation is quite similar for the cyclization reaction of the ethylenic *N*-chloro amine **1**, where the nitrogen–carbon bond can be formed at both ends of the double bond.

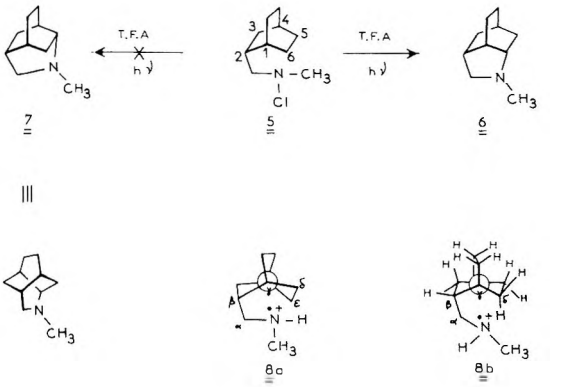
However, in each of these reactions, *only one* cyclized product is formed. Consequently their structures have to be exactly determined in order to have information on the reaction regioselectivity. This question is of interest as a similar problem occurs in the formation of lactones having this type of structure, where erroneous structural assignments have led to questionable theoretical conclusions.[11]

In order to determine the exact structure (homobrendane or twistane) of compound **2** (from **1**) and **6** (from **5**), we examined their 250-MHz NMR spectra. This led us to the conclusion that the spectra analysis was not sufficient to make unambiguous structure assignments. It appeared necessary to prepare model compounds using unequivocal synthetic pathways. Nontwisted **6** and twisted **7** were synthesized independently, respectively from **9** and **13** (Scheme III). Using decoupling experiments, the 250-MHz NMR spectra of the azatricyclic amines **6** and **7** were carefully analyzed in detail. This comparative study enabled us to assign a homobrendane structure to the intramolecular cyclization product **2** of the olefinic *N*-chloroamine **1**.[4]

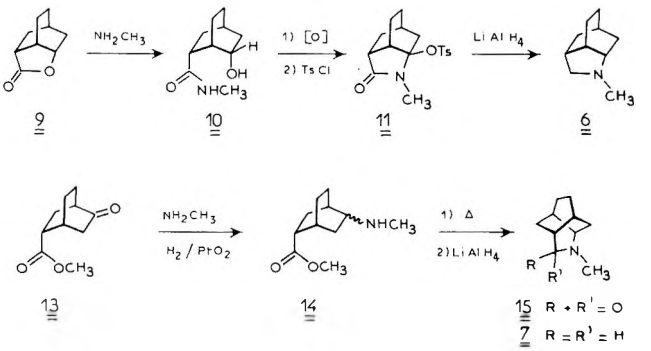
Scheme I



Scheme II

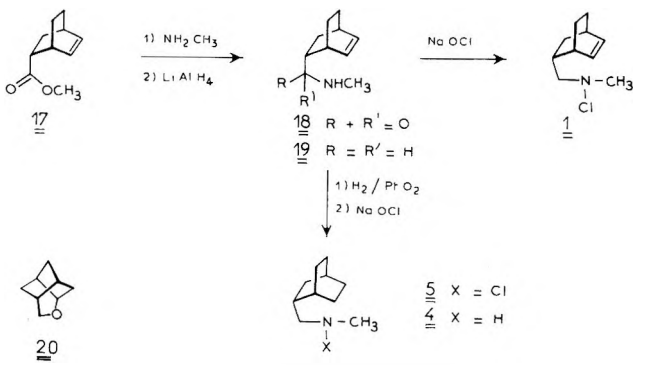


Scheme III



‡ This work is part of Rahim Tadayoni's Doctorat ès-Sciences, Marseille, Nov 1974, CNRS A0 10592.

Scheme IV



It is the purpose of this paper to describe (1) the synthesis of tricyclic amines **2, 6,** and **7;** (2) the 250-MHz NMR spectral analysis of these compounds and the use of these spectral data for structure assignment to the cyclization product of unsaturated *N*-chloroamine **1.**

Results and Discussion

A. Synthesis. Independent synthesis of tricyclic amines **6** and **7,** as well as preparation of *N*-chloroamines **1** and **5,** respectively, are shown in Schemes III and IV.[4,12] Details will be found in the Experimental Section. The 250-MHz NMR features of **6** and **7** (**7** obtained from **13**) and the signal assignments are described below.

Cyclization of *N*-Chloroamine 5 (Scheme II). Although two structures **6** or **7** may be predicted, a single compound is obtained when *N*-chloroamine **5** is submitted to the conditions of the Hofmann–Loeffler–Freytag reaction. Its structure is identical with the nontwisted model **6** obtained from **9** (Scheme III).

Cyclization of *N*-Chloroamine 1 (Scheme I). Similarly, a unique product which might have structure **2** or **3** is obtained in good yield (75%) when *N*-chloroamine **1** is treated for 3 h with silver oxide in boiling methanol. The same compound is formed (56%) besides five other products (18%) and starting amine (26%) when **1** is treated in boiling methanol for 36 h. The mechanisms of these reactions will be discussed elsewhere.[13]

The comparison of the NMR spectrum of **2** with those of **6** and **7** (see below) allows us to assign without any doubt a "nontwisted" homobrendane structure **2**[14] to the solvolysis product of *N*-chloroamine **1.**

B. 250-MHz NMR Spectroscopy. As there has been some disagreement in signal assignments, for instance on compound **2**,[5,14] or for octahydroindol[15,16] derivatives, the analyses we propose for the different spectra are essentially based on spin decoupling experiments, which allow unambiguous signal assignments to the various protons (see Tables I–III).

Compound 6 (Spectra 1a, 1b, 1c, Figure 1, Table I). The recording of the spectrum of this compound is of particular interest, as we have observed a variation of its aspect with the time. Spectrum 1a is obtained when the recording is carried out immediately after dissolution of the sample in deuteriochloroform. First-order analysis on this spectrum is very difficult, and the interpretation of decoupling experiments would have been problematic. When a drop of trifluoroacetic acid is added to the solution, spectrum 1c is obtained, and six protons can quite easily be identified (see Table I and discussion below). The general aspect of the spectrum is in between these two extreme situations, when the recording is carried out on a deuteriochloroform solution which has been left standing for a certain time. For example, spectrum 1b was obtained on a 3 weeks old solution. The explanation is as follows: in presence of trifluoroacetic acid, the amine is rapidly and totally protonated,[17] whereas in deuteriochloroform, the protonation—in fact deuteration—is only partial. In the latter case the phenomenon is due to DCl formed by slow decomposition of deuteriochloroform.[18] The NMR spectra clearly show that these protonations are clean reactions. Furthermore, it is always possible to recover unchanged tricyclic amine from the solutions (when trifluoroacetic acid is used an alkaline treatment is needed). Consequently, molecular

Table I. Analysis of Spectrum 1c

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
3.37	1H	dd	H_6	$J_{H_6,H_{5exo}} = 8$ Hz $J_{H_6,H_1} = 5$ Hz $J_{H_6,H_{5endo}} \leq 1$ Hz $J_{H_6,H_2} \leq 1$ Hz
3.15	1 H	dd	H_{8a}	$J_{H_{8a},H_{8b}} = 10$ Hz $J_{H_{8a},H_2} = 5$ Hz
3.06	1 H	d	H_{8b}	$J_{H_{8b},H_{8a}} = 10$ Hz $J_{H_{8b},H_2} \leq 1$ Hz
2.72	3 H	s	CH_3	
2.36	1 H	m	H_2	$J_{H_2,H_{3exo}} = 11$ Hz $J_{H_2,H_{8a}} = 5$ Hz $J_{H_2,H_{8b}} \leq 1$ Hz $J_{H_2,H_1} = 4.5$ Hz $J_{H_2,H_6} \leq 1$ Hz
2.13	1 H	m	H_1	$J_{H_1,H_6} = 5$ Hz $J_{H_1,H_2} \simeq 4.5$ Hz $J_{H_1,H_9} \simeq 4$ Hz
1.36–2.02	9 H	m		

Table II. Analysis of Spectrum 2

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
2.89	1 H	dd	H_{7b}	$J_{H_{7b},H_{7a}} = 9$ Hz $J_{H_{7b},H_2} = 3.5$ Hz
2.62	1 H	dd	H_5	$J_{H_5,H_{10exo}} = 5$ Hz $J_{H_5,H_4} = 5$ Hz
2.30	3 H	s	CH_3	
2.26	1 H	d	H_{7a}	$J_{H_{7a},H_{7b}} = 9$ Hz $J_{H_{7a},H_{3exo}} = 2$ Hz
2.06	1 H	m	H_4	$J_{H_4,H_5} = 5$ Hz
1.84	1 H	m	H_2	$J_{H_2,H_{7b}} = 3.5$ Hz
1.32–1.80	8 H	m		
1.17	1 H	dd	H_{10exo}	$J_{H_{10exo},H_1} = 0$ $J_{H_{10exo},H_{10endo}} = 12$ Hz $J_{H_{10exo},H_5} = 5$ Hz

Table III. Analysis of Spectrum 3

Chemical shift, δ	Integration	Multiplicity	Assignments	Coupling constants
3.35	3 H	s	OCH_3	
3.27	1 H	d	H_5	$J_{H_5,H_4} = 4.5$ Hz
2.64	1 H	dd	H_{8a}	$J_{H_{8a},H_{8b}} = 9$ Hz $J_{H_{8a},H_2} = 4.5$ Hz
2.56	1 H	d	H_6	$J_{H_6,H_1} = 5$ Hz
2.50	3 H	s	NCH_3	
2.44	1 H	d	H_{8b}	$J_{H_{8a},H_{8b}} = 9$ Hz
2.10	1 H	m	H_2	
1.91–1.60	5 H	m		
1.17	2 H	m	H_{3exo} H_{10a}	

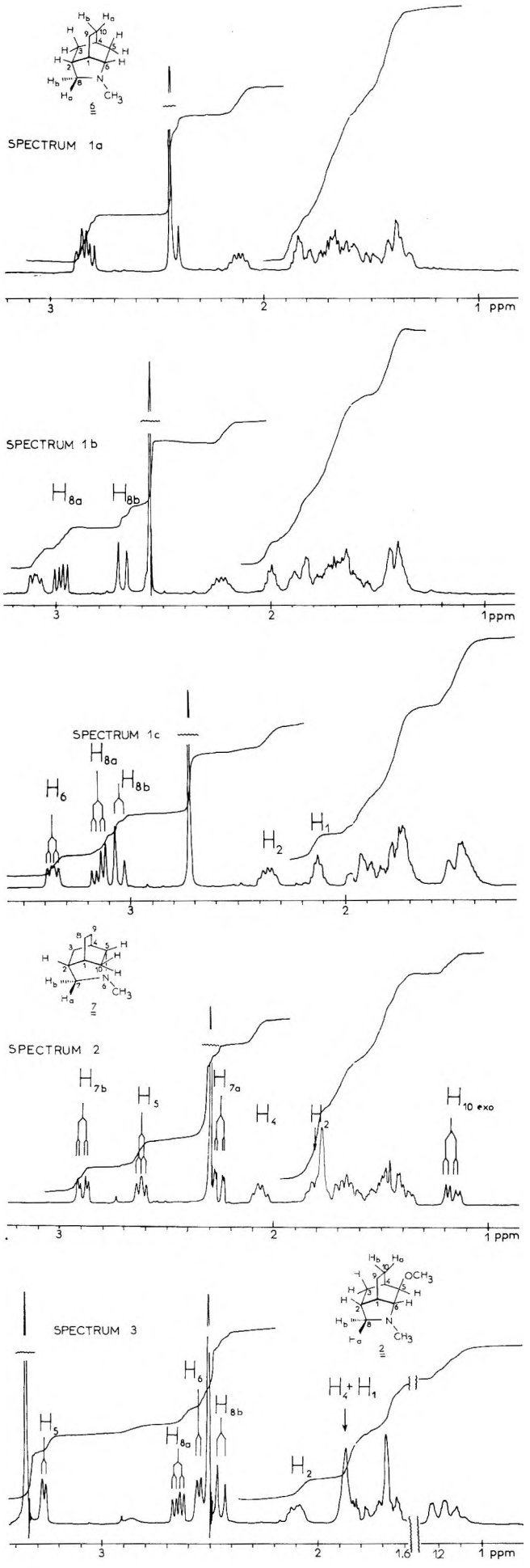


Figure 1.

modifications can be definitely excluded. We report, in Table I, the detailed analysis of easily reproducible spectrum 1c, resulting from complete protonation at the nitrogen atom.

As can be seen on spectrum 1b, the low-field signals centered at 2.98 and 2.69 ppm are the typical AB part of an ABX system, deshielded by nitrogen. These A and B signals are spread apart in spectrum 1a, but the low-field multiplet results from the overlap of two signals due to different protons (see below). The A and B signals start merging together in spectrum 1b, to get even closer in spectrum 1c. Similar signals have been reported in various azapolycyclic compounds such as octahydroindol derivatives[15] or decahydroquinolines.[19] Furthermore, polycyclic ethers, having structures similar to **6**, exhibit comparable spectra.[20] As spectrum 1b easily permits spin decoupling on each signal of the above mentioned ABX system, all the decoupling experiments necessary to allow signal assignments to the various protons have been conducted on the corresponding solution.

The ABX structure is confirmed by irradiation of the doublet of doublets centered at 2.98 ppm, which transforms the doublet at 2.69 ppm into a singlet, and sharpens the signal at 2.23 ppm. However, a small perturbation is also observed around 1.6 ppm, and is very likely due to partial irradiation of the signal at 3.1 ppm (assigned to H_6, see below) which is quite near the irradiated signal. The only protons which can correspond to signals having these fine structure and chemical shifts, in molecule **6**, are protons H_{8a} and H_{8b} (AB) and H_2 (X). Molecular models clearly show the 90° dihedral angle between C_8H_{8b} and C_2H_2, which results in a practically zero value for the corresponding coupling constant. Therefore, the signal at 2.69 ppm can be assigned to H_{8b}. According to these experiments, the signal at 3.10 ppm, which is strongly deshielded, can only be due to proton H_6, expected to exhibit a long-range coupling with H_2. Indeed, the irradiation of the signal centered at 3.10 ppm (H_6) does not perturb the signal at 2.69 ppm assigned to H_{8b}; but the signals at 2.23 (H_2) and 1.98 ppm are sharpened, whereas a modification is observed in the 1.6-ppm region. Consequently the signal at 1.98 ppm is assigned to proton H_1. Even so, the signals centered at 2.23 and 1.98 ppm are pretty close; one observes that irradiation of H_2 (at 2.23 ppm) modifies the fine structure of the signal at 1.98 ppm due to H_1. Accordingly, the proton which gives a signal around 1.6 ppm can only be due to exo H_5 (endo H_5 and H_6 form a dihedral angle of about 90°).

The irradiation of H_2 (2.23 ppm) also transforms the doublet of doublets at 2.98 ppm (H_{8a}) into a simple doublet and sharpens the signal centered at 3.10 ppm (H_6), showing the existence of a small long-range coupling. The spectrum analysis and the spin decoupling experiments are self-consistent and in perfect agreement with the structure of compound **6**.

Compound 7 (Spectrum 2, Figure 1, Table II). With the exception of the high-field doublet of doublets centered at 1.17 ppm, the general aspect of this spectrum is somewhat similar to the one of spectrum 1c; in particular, there are three low-field signals at 2.26, 2.62, and 2.89 ppm which are very likely to be due to the three protons next to the nitrogen atom (H_{7a}, H_{7b}, and H_5). However, their fine structure is quite different from the one observed in spectrum 1c but similar to the one reported for the twisted ether **20**[21] (Scheme IV). The two peaks at 1.84 and 2.06 ppm are more delicate to assign on the basis of the chemical shifts; by analogy with spectrum 1c, they could be due to H_2 and H_1 but, because of the twisted structure, proton H_4 (see model) (which is now pretty close to nitrogen) could also appear in this area. All these observations clearly show that decoupling experiments are absolutely necessary to make unequivocal signal assignments.

The first decoupling experiments are meant to identify the ABX system due to protons H_{7b}, H_{7a}, and H_2 (which appear

respectively at 2.89, 2.26, and 1.84 ppm). Irradiation of the signal centered at 2.89 ppm transforms the doublet of doublets at 2.26 ppm into a doublet (with a small coupling constant), and perturbs the signal centered at 1.84 ppm; this irradiation does not affect the signals at 2.62 and 2.06 ppm. Therefore, neither of these two latter signals corresponds to protons H_2. At this point, we would like to emphasize that, if the assignment of the signal at 2.06 ppm had been made by analogy with spectrum 1c, it should have been related with proton H_2. The above mentioned decoupling experiments show that this is definitely not correct. In fact, this signal corresponds to proton H_4 (see below).

According to the above mentioned decoupling experiments, proton H_2 is most likely to appear at 1.84 ppm. Irradiation of the signal at 1.84 ppm (H_2) leads to the collapse of the signal at 2.89 ppm into a simple doublet, but does practically not perturb the signal at 2.26 ppm. As the Dreiding models clearly show that the C_2H_2–C_7H_{7a} dihedral angle is very close to 90°, the signal at 2.26 ppm must be assigned to H_{7a}. The doublet of doublet at 2.89 ppm can therefore only be due to H_{7b}. A small long-range coupling (probably with exo H_3) is at the origin of the fine structure of the signal of H_{7a} at 2.26 ppm.

The remaining low-field signal at 2.62 ppm can now only be assigned to proton H_5. Indeed, when it is irradiated, the *only* modifications observed are as follows: the signal at 2.06 ppm collapses into a wide triplet, whereas the doublet of doublets at 1.17 ppm is transformed into a doublet. As the C_5H_5–$C_{10}H_{10\,endo}$ dihedral angle is practically equal to 90°, the doublet of doublets at 1.17 ppm can only be assigned to proton exo H_{10} coupled with endo H_{10} and H_5. Consequently the multiplet at 2.06 ppm must be due to H_4. This is confirmed by irradiation at 2.06 ppm (H_4) which leads to the collapse of the H_5 triplet (at 2.62 ppm) into a doublet. It was not possible to locate precisely the other vicinal protons (H_3 and H_9) which appear between 1.3 and 1.8 ppm.

It can be seen from the above discussion that, in order to effect unambiguous proton–signal correlations, it was absolutely necessary to carry out detailed analysis and spin decoupling experiments on samples of known structure. This clearly shows that it was not possible to determine the structure of an unknown compound (such as **2**) on the sole basis of its NMR spectrum, without any reference spectra. These are needed because similar signals in the spectrum of compounds **6** and **7** correspond to different protons. For instance, the chemical shift of the H_2 proton of each tricyclic amine are quite different (2.12 ppm in spectrum 1a and 1.84 ppm in spectrum 2; the signal which appears at 2.06 ppm in spectrum 2 is due to proton H_4).

Having these analyses in hand, it is now possible to compare the spectrum of compound **2** to those of **6** and **7**, and thus to deduce the structure of methoxy amine **2.**

Compound 2 (Spectrum 3, Figure 1, Table III). Spectrum 3 of compound **2** (Table III) is much more similar to spectrum 1b of tricyclic amine **6** than to spectrum 2 of 2-azatwistane **7.** In spectrum 3, the AB part of the ABX system, assigned to H_{8a} (at 2.64 ppm) and to H_{8b} (at 2.44 ppm), exhibits the same fine structure as in spectrum 1b, and is clearly different from the corresponding signals of H_{7a} and H_{7b} in spectrum 2 of compound **7.** As these features seem to be characteristic of the azahomobrendane structure, we therefore assigned—and confirmed by decoupling experiments (see below)—this type of skeleton to compound **2.** Furthermore, on the basis of chemical arguments, the methoxy group was expected to be exo.[13] Consequently proton H_6 should appear as a doublet (90° dihedral angle between C_5H_5 and C_6H_6) which must be the one at 2.56 ppm. The signal at 3.27 ppm can only be due to proton H_5 deshielded by the methoxy group.

Irradiation experiments completely agree with these signal assignments (presented in Table III). As in tricyclic amine **6,** irradiation of the signal at 2.44 ppm (H_{8b}) transforms the doublet of doublets at 2.64 ppm (H_{8a}) into a simple doublet. Irradiation at 2.10 ppm (H_2) transforms this same signal (H_{8a}) into another doublet. Finally, irradiation at 1.84 ppm (H_1 and H_4) leads to collapse of the doublets centered at 2.56 (H_6) and 3.27 ppm (H_5) into singlets, and also perturbs the signals centered at 2.10 ppm.

Mass Spectrometry. The mass spectrometry fragmentations observed for compounds **2, 6,** and **7** are not in disagreement with the proposed structures. In particular, the spectra of compounds **2** and **6** exhibit a fragment at *m/e* 82 (respectively 26 and 44%), which possibly corresponds to an ion of type **21.** This kind of ion has been observed for similar compounds.[22-24] Interestingly enough, this type of ion does not exist in the spectrum of **7.** Although not a proof of structure by itself, this is a supplementary clue for the determination of the twisted—or nontwisted—structure of this type of cage compound.

21

Experimental Section

Infrared spectral data were obtained from a Perkin-Elmer 257 spectrophotometer. Routine nuclear magnetic resonance spectra were obtained from a Varian XL 100 WG spectrometer, and 250-MHz spectra were obtained from a Cameca spectrometer. Mass spectra were obtained from a Varian MAT CH 5 and from a Varian MAT 111 spectrometer. All melting points and boiling points are uncorrected.

Lactone 9. This lactone has been prepared by the method described by Wagner and co-workers.[25]

Amido Alcohol 10. Lactone **9** (5 g, 33 mmol) is dissolved in a 30% methanol–methylamine solution and kept for 2 days at normal temperature in a stoppered flask. The solvent is distilled under reduced pressure, to give crude amido alcohol **10.** This is recrystallized in cyclohexane to yield 5.5 g of product (90%): mp 125–130 °C; M^+ *m/e* 183; IR ($CHCl_3$) 3460, 3300, 2940, and 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.1–2.65 (m, 11 H), 2.8 (d, 3 H), 3.8 (m, 1 H), 5.59 (d, 1 H), and 6.52 (m, 1 H).

A solution of this compound (4.5 g, 24 mmol) in 40 mL of CH_3COOH is treated with stirring by slow addition of a solution of 2.8 g of CrO_3 in 36 mL of CH_3OH/H_2O (90%). After 4 h at room temperature the solvents are distilled under vacuum and one adds 40 mL of water. The aqueous solution is continuously extracted with $CHCl_3$ for 24 h. The organic phases are washed successively with a 10% aqueous $NaHCO_3$ solution, then with brine, and dried over magnesium sulfate. Stripping the solvent gives 4 g of crude product, purified by chromatography on an alumina column (pentane–methylene chloride). One gets 2.6 g (14 mmol) of lactam **10** (58%): mp 60–65 °C; M^+ *m/e* 181; IR ($CHCl_3$) 1675 cm^{-1}; NMR δ 1.2–3 (m, 14 H) (with a singlet at 2.7), 5.2 (s, 1 H).

Tosylate 11. *p*-Toluenesulfonyl chloride (1 g) is added in small portions to a 500-mg solution of **10** in 3 mL of pyridine cooled in an ice bath. After 24 h at room temperature, pyridine is stripped under reduced pressure. Water (10 mL) is added and extracted with three portions of 10 mL of chloroform. The organic phase is washed with a 10% solution of sodium bicarbonate, then with brine, and dried over magnesium sulfate. Evaporation of the solvent gives 500 mg of tosylate **11** (30%): NMR (CCl_4) δ 7–8 (m, 4 H), 1.1–3.5 (m, 17 H) with two singlets at 2.28 and 2.4.

Amine 6. This tosylate is directly reduced by action of 200 mg of lithium aluminum hydride in 30 mL of dry tetrahydrofuran (15 h reflux). After normal workup one gets 80 mg of amine **6,** which proves to be identical in all points with the compound obtained by photocyclization of **5** (see below) (yield 50%): M^+ *m/e* 151; picrate mp 264–265 °C; NMR, see the 250-MHz NMR spectra previously described.

Keto Ester 13. This keto ester was prepared following the method described by Lee.[26]

Amine 14. A suspension of PtO_2 (200 mg) in 15 mL of methanol is placed under hydrogen for 0.5 h. Keto ester **13** (3.64 g) and 3.45 mL of a 30% methanol solution of methylamine are added. The solution

is kept under hydrogen with efficient stirring, until absorption of the stoichiometric quantity of hydrogen. The catalyst is then filtered and the solvent stripped under reduced pressure. One gets 3.4 g of amine **14** (87%): IR (CCl_4) 3340 cm^{-1}; NMR ($CDCl_3$) δ 3.34 (s, 3 H), 2.30 (m, 2 H), 2.19 (s, 3 H), 2.19–1.0 (m, 11 H).

Amide 15. Amino ester **14** (5.3 g) placed in a small distillation apparatus is heated by means of a metallic bath to 250–270 °C for 1.5 h. Methanol slowly distills. The residue is taken off with chloroform and passed through a 30-g column of silica gel (chloroform elution). The solvent is stripped to yield 2.89 g of practically pure lactam **15** (65%). This can be purified further by preparative GC on a 3% SE-30, 3-m column at 140 °C: IR ($CHCl_3$) 1680 cm^{-1}; NMR (CCl_4) δ 3.40 (m, 1 H), 2.75 (s, 3 H), 2.48 (m, 1 H), and 2.25–1.10 (m, 11 H). This spectrum proves to be identical with the one kindly supplied by Professor Tichy.[27]

***N*-Methyl 2-azatwistane.** Lactam **15** (2.89 g) is reduced by reaction with 1.3 g of lithium aluminum hydride in 50 mL of refluxing dry ether for 15 h. After normal workup and distillation (68 °C, 5 mm), one gets 2.15 g of *N*-methyl-2-azatwistane **7** (78%): picrate mp 245–258 °C dec; NMR (CCl_4) δ 2.9–0.9 (m, 14 H), 2.19 (s, 3 H); high-resolution mass spectrum M^+ 151.1358 (calcd for $C_{10}H_{17}N$, 151.1360).

***N*-Chloroamines.** The *N*-chloroamines have been obtained by following the usual procedure as follows. The amine is placed in about ten times its volume of methylene chloride, and this solution is vigorously stirred in the dark with an excess of 1–1.5 M commercial bleach for 1.5 h and then extracted with three portions of methylene chloride. The organic phases are washed with brine, then water, and dried over magnesium sulfate. The solvent is stripped under vacuum without heating, in the dark. The yield of *N*-chloroamine is practically quantitative and its purity, which can be checked by iodometry, is around 95–98%.

Solvolysis of 1 in the Presence of Silver Oxide. Chloroamine **1** (3 g) is dissolved in 100 mL of dry methanol. The flask is flushed with nitrogen and 3 g of silver oxide is added. The mixture is heated to boiling under vigorous stirring for 3 h.

After cooling, the solution is passed through a short Florisil column. The solvent of the filtrate is then stripped to yield 2.3 g of **2** (75–77%): bp 49–51 °C (0.7 mm); high-resolution mass spectrum M^+ found 181.146755 (calcd, 181.146156); picrate mp 175–176 °C; IR ($CHCl_3$) 1098 cm^{-1}; NMR, see description of the 250-MHz spectrum.

5-Carbomethoxybicyclo[2.2.2]octene (17). Freshly distilled methyl acrylate (10 g) is placed in a sealed tube together with 13.5 g of 1,3-cyclohexadiene and 100 mg of hydroquinone. The solution is heated at 90 °C for 36 h. The product is distilled under vacuum to give 16.3 g of adduct **17** (70%): bp 90–94 °C (10 mm); IR 3040, 2940, 1680, and 600 cm^{-1}; NMR (CCl_4) δ 5.9–6.4 (m, 2 H), 3.55 (s, 3 H), 2.34–3 (m, 3 H), 1–1.9 (m, 6 H).

Carboxamide 18. This ester (10 g) is dissolved in 100 mL of a 30% methylamine solution in methanol and placed in a stoppered flask. After 5 days, the solvent is stripped and the residue is recrystallized in cyclohexane to give 7.9 g of **18** (80%): mp 140 °C; IR ($CHCl_3$) 3460, 2940, and 1650 cm^{-1}; NMR ($CDCl_3$) δ 6.1–6.58 (m, 2 H), 5.65 (s, 1 H), 2.75 (d, 3 H), and 1–3 (m, 9 H).

Amine 19. This amine is obtained by usual reduction of **18** by means of lithium aluminum hydride in boiling tetrahydrofuran. After normal workup and distillation under vacuum (58–61 °C 2 mm) one gets amine **19** (70% yield): IR (CCl_4) 3640, 3350, 3040, 2940, 2860, and 695 cm^{-1}; NMR (CCl_4) δ 6.25 (m, 2 H), 2.70–0.67 (m, 15 H), with two singlets at 2.55 and 2.49.

Amine 8. This amine can be obtained by direct hydrogenation of **19** in ethanol over PtO_2 (yield 27%): IR (CCl_4) 2820, 2860, 2790, and 1460 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 1 H), 1–1.98 (m, 14 H) (singlet at 1.5), and 2.3–2.6 (m, 5 H) (singlet at 2.38).

Cyclization of 8 by Hofmann–Loeffler–Freytag Reaction. Amine **8** (700 mg) is transformed, following the standard procedure, into the chloroamine **5**. This chloroamine is added *dropwise* to 10 mL of trifluoroacetic acid contained in a quartz tube, which is cooled in an ice water bath. The solution is carefully flushed with nitrogen (0.5 h) and irradiated with a 150-W mercury high-pressure Hanovia lamp. After disappearance of the *N*-chloroamine (iodometric test) (2 h), the acid is distilled under reduced pressure and the residue, dissolved in 10 mL of methanol, treated with potassium carbonate until the solution is alkaline (pH 9–10).

The methanol is stripped off under reduced pressure and the residue taken up with a minimum of water. This aqueous phase is extracted with ether, and the ether layer is washed with brine and dried over magnesium sulfate. After filtration and stripping off the solvent, one gets 500 mg of amine **6** (70%). This amine can be purified by gas chromatography (PEG 4000, OH^-, 1.5 m, 150 °C): mp picrate 264–265 °C; IR (CCl_4) 2930, 2860, 1450, and 1340 cm^{-1}; NMR, see 250-MHz spectrum previously described; high-resolution mass spectrum M^+ found 151.1369 (calcd, 151.1360).

Registry No.—**1**, 55751-48-9; **2**, 55751-50-3; **2** picrate, 62520-73-4; **5**, 62460-66-6; **6**, 62460-67-7; **6** picrate, 62460-68-8; **7**, 59238-80-1; **8**, 62460-69-9; **9**, 6715-18-0; **10** alcohol, 62460-70-2; **10** lactam, 62460-71-3; **11**, 62460-72-4; **13**, 49826-55-3; **14**, 62504-20-5; **15**, 59238-79-8; **17**, 25578-17-0; **18**, 62460-73-5; **19**, 62460-74-6; methylacrylate, 96-33-3; 1,3-cyclohexadiene, 592-57-4.

References and Notes

(1) M. Nakasaki, K. Naemura, and Y. Kondo, *J. Org. Chem.*, **41**, 1229 (1976).
(2) H. G. Caprard and C. Ganter, *Helv. Chim. Acta*, **59**, 97 (1976).
(3) P. Deslongchamps, L. Ruest, and S. Dube, *Can. J. Chem.*, **53**, 3613 (1975).
(4) R. Tadayoni, J. Lacrampe, A. Heumann, R. Furstoss, and B. Waegell, *Tetrahedron Lett.*, 735 (1975).
(5) R. W. Lockhart, K. Hanaya, F. W. B. Einstein, and Y. L. Chow, *J. Chem. Soc., Chem. Commun.*, 344 (1975).
(6) M. E. Wolff, *Chem. Ber.*, **63**, 55 (1963).
(7) S. Wawzonek and T. P. Culbertson, *J. Am. Chem. Soc.*, **81**, 3367 (1959).
(8) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **82**, 1657 (1960).
(9) R. M. Dupeyre and A. Rassat, *Tetrahedron Lett.*, 2699 (1973).
(10) J. Fournier and B. Waegell, *Bull. Soc. Chim. Fr.*, 436 (1973).
(11) R. M. Moriarty and T. Adams, *J. Am. Chem. Soc.*, **95**, 4070 (1973).
(12) R. Furstoss and B. Waegell, *Tetrahedron Lett.*, 365 (1976).
(13) R. Furstoss, R. Tadayoni, and B. Waegell, *Nouv. J. Chim.*, **1**, 167 (1977).
(14) Y. L. Chow, private communication. We have been in correspondence with Professor Y. L. Chow, Simon Fraser University, Burnaby, British Columbia, Canada, on structure determinations of such compounds (letters from March 10, 1975 to June 3, 1975) and Professor Y. L. Chow has recently confirmed (EUCHEM Conference on Nitrogen and Oxygen Intermediates in Organic Synthesis, St-Raphael, France, Sept 1975, and letter of Oct 6, 1976 referring to the Ph.D. Thesis of R. W. Lockhart, Simon Fraser University) by x-ray crystallography the nontwisted structure we had originally correctly assigned.
(15) M. Mokotoff and R. F. Sprecher, *Tetrahedron*, **30**, 2623 (1974).
(16) M. Mokotoff, *J. Heterocycl. Chem.*, **10**, 1063 (1973).
(17) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, p 180.
(18) J. A. Riddick and W. B. Bunger, "Organic Solvents", Wiley-Interscience, 1970. New York, N.Y., 1970, p 771.
(19) H. Booth and A. H. Bostock, *J. Chem. Soc., Perkin Trans. 2*, 615 (1972).
(20) K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Welsh, *J. Am. Chem. Soc.*, **89**, 2401 (1967).
(21) P. J. Kropp and H. J. Krauss, *J. Am. Chem. Soc.*, **91**, 7466 (1969).
(22) C. R. Johnson and W. D. Kinsburry, *J. Org. Chem.*, **38**, 1803 (1973).
(23) R. Furstoss, A. Heumann, B. Waegell, and J. Gore, *Org. Mass. Spectrom.*, **6**, 1207 (1972).
(24) O. E. Edwards, G. Bernath, J. Dixon, J. M. Paton, and D. Vocelle, *Can. J. Chem.*, **51**, 2123 (1974).
(25) A. F. Wagner, P. E. Wittreich, B. H. Arison, and L. H. Sarett, *J. Org. Chem.*, **36**, 2609 (1971).
(26) R. A. Lee, *Tetrahedron Lett.*, 3333 (1973).
(27) M. Tichy, E. Duskova, and K. Blaha, *Tetrahedron Lett.*, 237 (1974).
(28) We prefer the term "homobrendane", which clearly shows the analogy with the brendane derivatives, rather than the term isotwistane, which is misleading.

Ene Reactions of Conjugated Dienes. Rate Enhancements in Cyclic 1,3-Dienes and Dependence of Ene Adduct:Diels–Alder Adduct Ratio on Enophile Structure

Barry M. Jacobson,* Adrianne C. Feldstein, and Joan I. Smallwood

Department of Chemistry, Barnard College, New York, New York 10027

Received March 3, 1977

The cis hexalin **1** gives varying proportions of ene and Diels–Alder adducts with a variety of dienophiles. The rate constants for the Diels–Alder reaction with maleic anhydride showed a marked drop in the sequence isoprene, 1,3-cyclohexadiene, **1**, but the ene reaction rate constant with diethyl azodicarboxylate showed a marked increase in the same series. For **1** the percentage of ene adduct increased with a more highly substituted enophile/dienophile. Azo dienophiles gave more ene adduct than the correspondingly substituted carbo dienophile. Although the first trend is loosely consistent with a differential steric effect for the two reactions, the results with some enophiles do not fit such an explanation well. It is concluded that acceleration of the ene process, not just hindrance of the Diels–Alder, is responsible for the formation of ene adducts in some cases. Stereoelectronic factors are proposed as being of primary significance, ahead of steric ones.

Although the Alder ene reaction[1] is quite common with simple alkenes,[2] it occurs relatively infrequently with conjugated dienes because most good enophiles are also effective Diels–Alder dienophiles. Ene reactions are seen with highly hindered dienes which cannot achieve the syn arrangement required for the Diels–Alder reaction[3] and with a few cyclic dienes and trienes, particularly when azodicarboxylate esters are the reaction partners or when the diene is a steroidal system that is simply too crowded to allow for a Diels–Alder reaction.[4] Gillis has suggested[3a,5] that the trans arrangement of the azo esters, combined with some hindrance from ethano or larger bridges, suffices to explain the appearance of the ene products observed with cyclic dienes, although the ene reaction appears to be subject to steric hindrance also,[6] probably because of the preferred orbital geometry[7] for the concerted hydrogen migration.[8]

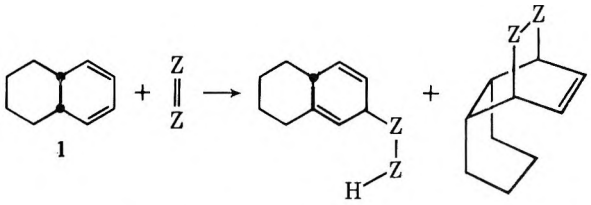
However, in discussions of these reactions[3-5] the implicit assumption seems to have been made that an ene reaction with a 1,3-diene makes its appearance solely because the Diels–Alder reaction has been blocked; i.e., the ene reaction is merely unmasked and in the absence of steric hindrance could not compete successfully. Indeed, rarely do both ene and Diels–Alder products appear simultaneously,[9] but no test directly addressing the matter of this supposed unmasking seems to have been made.

Conversely, since a single substrate diene which consistently affords both ene and Diels–Alder products has not been available, there seems also to have been no direct comparison between the enophilic and dienophilic behavior of the reacting partner. It has been noted that *trans*-diethyl azodicarboxylate (DEAD) has greater enophilic reactivity than its cis isomer[5] or than 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD),[5,10] while dienophilic character runs oppositely,[5,11] but otherwise no general characterizations with respect to enophile constitution have been made.

We report here some evidence that enhanced reactivity in the ene reaction rather than (or at least in addition to) decreased reactivity in the Diels–Alder reaction is responsible for the appearance of ene products with cyclic 1,3-dienes. Furthermore, the trend to lower ene reactivity with increasing substitution[6] (and thus presumably steric hindrance) in simple alkenes is reversed in some cases as well. Finally, one of the compounds used in this study does behave as a fair diene for the Diels–Alder reaction while being highly reactive in an ene fashion. This allowed for some exploration of the factors influencing enophilic vs. dienophilic behavior in a single system.

Results and Discussion

Compound **1**, *cis*-1,2,3,4,4a,8a-hexahydronaphthalene, was previously found to undergo appreciable ene reaction in competition with a Diels–Alder process using any of a number of dienophiles[12,13] (eq 1). Of itself, this was unremarkable,



1 (1)

since **1** may simply be regarded as a more hindered version of 1,3-cyclohexadiene. The latter reacts in similar fashion with azodicarboxylate esters.[3a,4b,c] We have measured the second-order rates for the reaction of **1** with maleic anhydride, yielding 98% Diels–Alder adduct, and with diethyl azodicarboxylate (DEAD), yielding an ene adduct exclusively. Table I gives the values of the rate constants as well as those for the same pair of reagents reacting with 1,3-cyclohexadiene and with isoprene. The 1,3-cyclohexadiene gives only a Diels–Alder product with maleic anhydride[14] and mostly ene product with DEAD.[3a,4b,c] Isoprene yields only Diels–Alder adducts with both reagents.[15,16] The rate constant for the reaction of isoprene with DEAD has not previously been published. The latter reaction was found to be cleanly second order, though at very high isoprene concentrations some curvature of the second-order plots could be seen.

While the rate constants for the reactions with maleic anhydride do show the expected decline, the rate constants for reaction with DEAD increase markedly. Thus, although **1** must surely be more crowded than 1,3-cyclohexadiene and indeed gives a much slower reaction with maleic anhydride, it reacts some 14 times faster with DEAD. The comparison with isoprene is perhaps somewhat uncertain, since the latter gives only Diels–Alder products, but the very absence of an ene component indicates again a large rate difference; the total rates for reaction of DEAD with both 1,3-cyclohexadiene and isoprene are similar so that any ene reaction with isoprene must have a much smaller rate constant. Thus, the decrease in the rate of the Diels–Alder reaction is not the sole cause for appearance of an ene product.

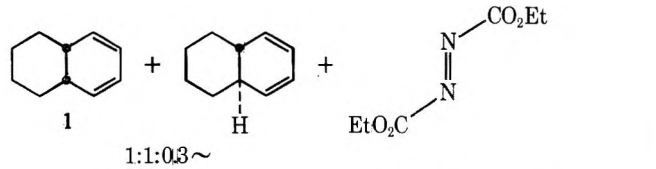
These results do not at all imply that steric hindrance actually accelerates the ene reaction. A simple competition was run between **1** and its trans isomer, **10**, for DEAD and for

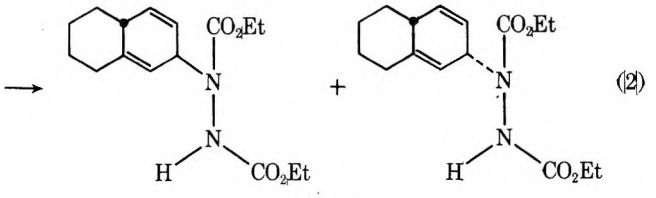
Table I. Rate Constants for Diels–Alder and Ene Reactions

Diene	Rate constant with maleic anhydride,[a] $\times 10^7$ L mol^{-1} s^{-1}	Source	Rate constant with DEAD[b] $\times 10^7$ L mol^{-1} s^{-1}	Source
Isoprene	1540	*c*	670[d]	This work
1,3-Cyclohexadiene	1320	*c*	760	*e*
1	8.7	This work	11 500	This work

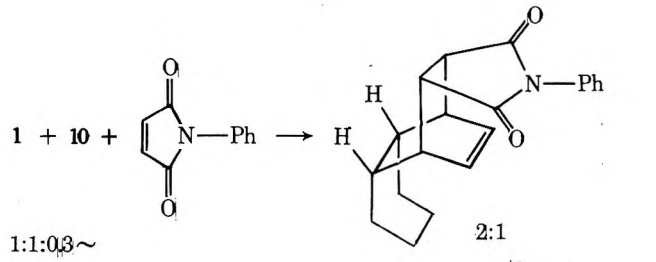
[a] In dioxane at 30 °C. [b] In cyclohexane at 25 °C. [c] Reference 17. [d] Diels–Alder product only, no ene product detected. [e] Reference 20.

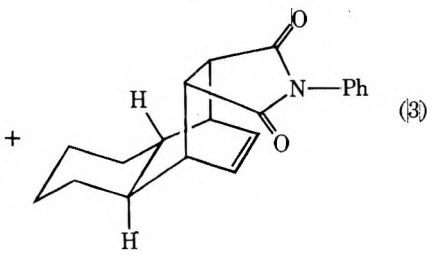
N-phenylmaleimide (eq 2 and 3). Compound **10**, like **1**, gives only ene product with DEAD and greater than 95% Diels–Alder product with *N*-phenylmaleimide, but **1** is at least ten times more reactive toward DEAD (at room temperature; it is four times more reactive at 150 °C) and two times more reactive toward the imide (at 150 °C). This result was at first somewhat surprising; **10** has a statistical advantage over **1** (in the ene reaction), since it has both its allylic hydrogens in the axial position and thus in the preferred parallel alignment to the diene's π orbitals. However, examination of models showed that if the dienophile or enophile extended out over the second ring, there would be more steric repulsion to both reagents upon approach to *either* face of **10**. *cis*-**1** has greater hindrance on the side lacking the allylic hydrogens, but far less on the other, reactive face (see Figure 1).





(2)





(3)

To explain all these results, it would appear that a stereoelectronic factor is at least as important as pure steric

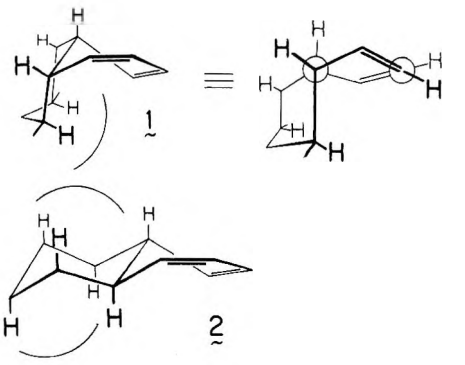


Figure 1.

hindrance. In all the cyclic dienes, both here and in earlier work, at least one abstractable hydrogen is held in rough alignment with the π system and rotation away from this favored alignment is either slow or impossible. No such limit to rotation applies, in general, to the acyclic alkenes and dienes.[18] Unfortunately, simple cyclic alkenes, the compounds that could be used most easily to test the generality of this stereoelectronic effect, react with azo esters through a free-radical mechanism[19] and rate constants do not seem to be available for other enophiles. It may be noteworthy, however, that 1,4-cyclohexadiene reacts a good deal more rapidly with DEAD than do the simple alkenes.[6,20]

It may also be noted that the abstracted hydrogens in **1** and **10** are tertiary, that removed in the cyclohexadienes is secondary, and the hydrogen that would have to be abstracted in isoprene is primary. In their work with simple alkenes, Thaler and Franzus claimed that the primary, secondary, or tertiary character of the hydrogen was irrelevant.[6] However, since all the compounds involved except 1,4-cyclohexadiene were acyclic, any such effect could have been compensated for by the steric differences previously mentioned, and dependence on bond strength or on other characteristics paralleling the primary, secondary, or tertiary nature of the hydrogens might be observable only with cyclic or other relatively rigid compounds. Of course, it may be the fact that it is a *diene* reacting which has introduced a dependence of the rate on the type of hydrogen abstracted. In this connection, it should be noted that the rate constants for **1**, **10**, and 1,3-cyclohexadiene are also all significantly greater than that for 1,4-cyclohexadiene. It remains to be seen if acyclic dienes will show any such dependence or rate accelerations. Synthesis of an appropriate set is underway.

Since **1** does give both Diels–Alder and ene adducts simultaneously, it served as a "standard" substrate for a number of dienophiles in a survey of the competition between the two processes. The dienophiles used are listed in Chart I. Reactions were run in *N*,*N*-dimethylacetamide, generally at 165 °C with the solutions being degassed and sealed in ampules.

Chart I. Dienophiles Used

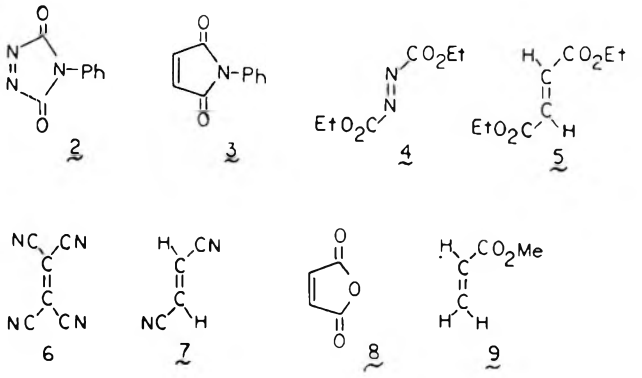
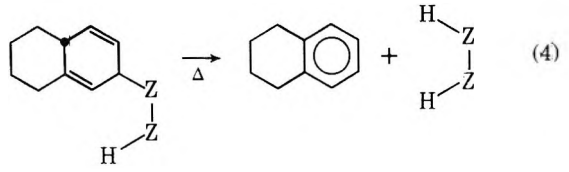


Table II. Ene and Diels–Alder Adducts from Reaction of 1

Registry no.	Dienophile	Diels–Alder: ene adduct ratio	Temp, °C	Material balance,[a] %
4233-33-4	**2**	90:10[b,c]	25	99
	2	75:24[b,c]	164	99
941-69-5	**3**	97.7:2.3[c]	165	89
4143-61-7	**4**	0:100[b,c]	60	97
	4	0:100[b,c]	165	96
623-91-6	**5**	80:20[d]	165	98
670-54-2	**6**	40:60[c]	60[e]	87
764-42-1	**7**	79:21[d]	165	101
108-31-6	**8**	97.7:2.3[d]	165	99
96-33-3	**9**	45:55[d]	165	75

[a] Sum of Diels–Alder and surviving ene adduct, tetralin from ene adduct that had decomposed, and recovered diene. Dienophile usually used in excess. [b] Determined by NMR. [c] Determined by NMR (Diels–Alder) and by VPC (yield of tetralin). [d] Determined by NMR (Diels–Alder and undecomposed portion of ene adduct) and VPC (tetralin from decomposed ene adduct). [e] Appreciable charring at higher temperatures with lower material balance.

Exceptions were the reaction with PTAD (**2**), which reacted too rapidly for an ampule to be prepared, and tetracyanoethylene (**6**), which gave charring above 60 °C. In all cases, both Diels–Alder and ene adducts were isolated and characterized in separate additional runs, though the latter were usually conducted at lower temperatures to ensure the preservation of the less stable ene adducts (vide infra). The ratios of ene to Diels–Alder adducts were obtained from absolute yields (measured against added internal standards). The yields of all Diels–Alder products and of stable ene products were determined by NMR. Without exception, the Diels–Alder adducts showed their alkene resonances between δ 6.1 and 6.5. The ene adducts contrastingly came between δ 5.1 and 6.0, and of course gave larger integrals relative to the upfield signals. Partial or complete decomposition of the ene adduct under the reaction conditions occurred with several enophiles (eq 4) but, as the decomposition in every case cleanly yielded



(4)

tetralin, determination of the latter by VPC allowed the original ene product yield to be measured. In fact, it was frequently convenient to pyrolyze the initial products, converting all the ene adduct to tetralin. The Diels–Alder adducts and starting diene were found to be thermally stable under the pyrolysis conditions (180–200 °C, sealed degassed ampules). Although the decomposition of the ene adducts was specifically shown to be quantitative in only a few cases,[21] when both the NMR and VPC methods could be applied the yields generally agreed to within 1–2%. Determination of recovered diene as well as adducts gave a high material balance in almost all cases as further assurance that the product ratios measured were meaningful.

The proportions of Diels–Alder vs. ene adduct are shown in Table II. Certain items stand out. Azo dienophiles give more ene reaction than the corresponding carbo dienophiles (compare results using **2** with those using *N*-phenylmaleimide (**3**) and then diethyl azodicarboxylate (**4**) with diethyl fumarate (**5**)). Trans substitution in the dienophile yields more ene adduct than cis, and tetrasubstitution apparently even more.[22] Although this trend may well be the result of steric crowding and hence preferential suppression of the Diels–Alder reaction, such an argument is subject to some criticism. First, the result with methyl acrylate (**9**) is clearly anomalous, even given the limited material balance in this case. Second, diethyl fumarate and fumaronitrile (**7**) give very similar product ratios, although one might expect the carbethoxyl group to show a greater steric effect.[23] Third, the absolute rates of all the reactions vary enormously, from essentially as fast as mixing (for PTAD (**2**) even at room temperature) to having a half-life of over 2 days (for **7** and **9**), and there is no relationship between these rates and the percentage of ene adduct. In view of this rate difference, any steric effect is being superimposed on a very much larger electronic one, with the latter affecting both ene and Diels–Alder reactions in *almost* identical fashion. Thus, many of the apparent steric effects may be no more than a coincidental pattern: the result of some very slight electronic difference between cis and trans dienophiles, for example. Perhaps a secondary orbital interaction[26] between a π-electron-containing substituent on the enophile and the other double bond of the diene or a slight difference in orbital energies of the cis and trans enophiles[27] is what tips the balance between Diels–Alder and ene pathways. In the hope that substitution of the dienophile with non-π-electron-containing substituents might throw some light on this, reaction of **1** was attempted with ethyl crotonate (for comparison to the fumarate). However, there was negligible reaction of any kind at 170 °C even after several days, and at 210 °C the decomposition of the diene to undetermined products became the predominant process. This matter remains to be explored.

Experimental Section

Capillary melting points (uncorrected) were taken on a Thomas-Hoover melting-point apparatus. NMR spectra were obtained using a Varian T-60 instrument. IR data were from a Perkin-Elmer 710A or Beckman IR-5. Analyses were done by Galbraith Laboratories, Knoxville, Tenn.

Materials and Purification Procedures. Dienes **1** and **10** were prepared as in earlier work[13] and purified by preparative VPC (20% Carbowax 20M on Chromosorb P) before use. Isoprene (Eastman white label) was distilled and stored under refrigeration. Cyclohexane (Fisher Spectrograde) was used as received. Maleic anhydride (Eastman white label) was resublimed before use. *p*-Dioxane (Fisher) was dried and partially purified by passage through grade I basic alumina, stirred overnight with $LiAlH_4$, and distilled from the $LiAlH_4$ under N_2. 4-Phenyl-1,2,4-triazoline-3,5-dione was prepared according to the literature,[28] and resublimed before use. Diethyl fumarate (Eastman white label) and methyl acrylate (Aldrich) were used as received. Tetracyanoethylene (Aldrich) was sublimed before use. Fumaronitrile and *N*-phenylmaleimide were prepared by literature procedures.[29] Decane was used as received (Aldrich) after VPC showed a single peak. *m*-Dinitrobenzene was prepared by nitration of nitrobenzene and recrystallized twice from 95% ethanol. *N,N*-Dimethylacetamide was prepared by treatment of acetic anhydride with 40% dimethylamine, distillation, removal of the acetic acid in the azeotrope by stirring with a saturated solution of $NaHCO_3$, extraction of the amide into benzene, and redistillation on a 3-ft column of glass helices. A cut boiling from 163–164 °C was used. Ethyl crotonate was prepared by Fischer esterification of crotonic acid (Eastman White Label).

Kinetics, 1 and Diethyl Azodicarboxylate. The rates were high enough to permit direct measurements of the DEAD concentration by UV without dilution of the sample. The diene was weighed into a 5-mL volumetric flask partially filled with cyclohexane from which the oxygen had been removed by entrainment with nitrogen. The DEAD was weighed in and the flask transferred to a bath at 25.0 °C, swirled 1 min, and filled to the mark. A UV cell was immediately filled with this solution and placed in the thermostated cavity of a Beckman DB-G spectrometer. Initial diene concentrations were varied by a factor of 10 and initial DEAD concentrations by a factor of 3. All runs were done in duplicate. Data were plotted by standard methods[30] and rate constants calculated by a least-squares fit. R values for all runs were >0.99. One set of runs in which no attempt was made to exclude atmospheric oxygen gave the same rate constant within 10%, values being scattered among the oxygen-free numbers.

Isoprene and DEAD. The same procedure as above was followed for runs at low DEAD concentration, but for a reasonable rate when

the isoprene concentration was reduced the initial DEAD concentration needed became too high for direct measurement in the reaction mixture. In these cases, the reaction was run in a 25-mL volumetric flask; aliquots were removed periodically, diluted, and checked by UV. Initial concentrations of the reactants were varied by factors of 6 (DEAD) and 13 (isoprene).

1 and Maleic Anhydride. Diene, maleic anhydride, and 1,3-dinitrobenzene (as in internal standard for integration) were weighed into a 1-mL volumetric flask, the flask placed in a bath at 30 °C, and purified dioxane added to the mark. The solution was transferred to a jointed NMR tube, degassed by freeze–pump–thaw sequences, and sealed. The tube was immersed in a bath held at 30 °C and monitored periodically by NMR. (At the concentrations and temperature used the half-lives were generally 24 h or more, so that sample preparation time and measurement times introduced a negligible error.) Initial concentrations of diene were varied from 0.5 to 1.0 M, those of maleic anhydride from 0.6 to 3.0 M; greater variation was precluded by the low rate of reaction and limited sensitivity of the NMR method.

Competition between 1 and 10 for DEAD or *N*-Phenylmaleimide. Decane was used as an internal VPC integration standard; FID relative responses for **1**:**10**:decane were 1.00:1.00:1.09. For a typical run, a solution equimolar in **1** and **10** in dimethylacetamide with a weighed amount of *n*-decane was prepared. One-third of an equivalent of DEAD or *N*-phenylmaleimide was added and the solution was sealed in vacuo after degassing by freeze–pump–thaw cycling. After reaction was complete (overnight at room temperature or 1 h at 150 °C for DEAD, overnight at 150 °C for the imide), the tube was opened and all volatiles were distilled trap-to-trap at 0.01 mm. Ratios of unreacted starting dienes vs. decane were determined by VPC on a 10 ft × ⅛ in. 10% Carbowax 20M column (Chromosorb W) using a Varian Model 1200 Chromatograph equipped with a Linear Instruments Model 252A electronic integrating recorder. At the relatively high ratios of dienophile to diene used, competition ratios are obviously only an approximation to rate-constant ratios, but at lower concentrations the amount of diene reacted becomes too small for precise measurements and the ene products with DEAD are thermally unstable; adducts from *both* dienes yield tetralin and *sym*-diethyl hydrazinedicarboxylate on heating or passage through the VPC, so that determination of competition ratios by product analysis is not possible.

Reactions of 1 with Dienophiles 3–9; General Procedure. A stock solution of **1** (0.681 g) and decane (0.445 g) in *N,N*-dimethylacetamide (total volume 10 mL) was prepared and 1-mL aliquots were pipetted into jointed test tubes. A 5–10% molar excess of dienophile was weighed into the tube which then was immediately immersed in a dry ice bath. Each tube was degassed by repeated freeze–pump–thaw sequences and sealed. The tubes were then immersed in a stirred oil bath held at 165 ± 3 °C for varying lengths of time (5 min for DEAD and TCNE; overnight for maleic anhydride, diethyl fumarate, and *N*-phenylmaleimide; and 3–4 days for fumaronitrile and methyl acrylate). Reactions with DEAD were also heated for longer times on occasion at 180–200 °C when complete decomposition of the ene adduct was desired. The tubes were then cooled and opened, their contents were washed into a small flask with more dimethylacetamide, and the solutions distilled trap-to-trap (30 °C at 10^{-2} mm). The distillates were examined by VPC (10 ft × ⅛ in. Carbowax 20M on 60/80 acid-washed Chromosorb W, temperature programmed 6 °C/min from 50 to 180 °C). VPC traces were recorded on a Linear Instruments Model 252A recorder equipped with an electronic integrator. All samples were injected in triplicate. The FID response factors for the diene **1** and tetralin relative to decane were measured earlier (0.91 for the diene, 0.90 for tetralin). The residue from the distillation was completely dissolved in a minimum volume of $CDCl_3$ after addition of a weighed amount of *m*-dinitrobenzene (used as an NMR integration standard, since its signals fell below all of those from the reaction products) and examined by NMR. Reactions with TCNE and DEAD as dienophiles were also carried out at 60 °C, with the former to prevent charring and the latter to preserve the ene adduct.

Reaction of 1 with PTAD (2). An aliquot of the diene–decane solution was heated to 165 °C and a solution of PTAD in dimethylacetamide was added dropwise until the red color remained more than a second. The solution was then treated as with the other dienophiles. Two samples were transferred to jointed test tubes, degassed, sealed, and heated at 180–200 °C for several hours to decompose the ene adduct.

Isolation and Characterization of Products.[31] Ene Adduct of TCNE and 1. Freshly sublimed TCNE (0.65 g) and a slight excess of **1** (0.70 g) were placed in a jointed test tube in 3 mL of tetrahydrofuran (distilled from $LiAlH_4$). The tube was cooled in dry ice, evacuated to 10 mm pressure by a water aspirator, and sealed. The tube was placed in a freezer at −10 °C until the purple color of the solution had faded to yellow. The tube was opened and its contents were poured into ice-cold 10% NaOH. The mixture was shaken well and the aqueous layer then extracted twice with portions of ether. The pH of the aqueous layer was then adjusted to approximately 3 with cold 2 M HCl and the precipitated ene adduct immediately collected, rinsed with ice-water, and dried under a vacuum desiccator in a refrigerator. This procedure removes the bulk of the Diels–Alder adduct, but complete purification is not possible. The ene adduct is moderately stable in solid form but solutions decompose rapidly, especially if the solvent is polar or heated. The adduct does not survive chromatography of any sort. Low-temperature crystallization from ether is possible but also fails to purify it completely. Acetone or ethanol solutions decompose in a few hours to give tetralin and tetracyanoethane, both of which were isolated and compared to authentic samples: Adduct NMR (acetone-d_6) δ 1–2.0 (m, 6 H), δ 2.2–2.5 (m, 2 H), δ 2.8 (m, 1 H), δ 3.8 (m, 1 H), δ 5.5–6.1 (m, 4 H).

Diels–Alder Adduct of *N*-Phenylmaleimide and 1. *N*-Phenylmaleimide (120 mg) and diene **1** (70 mg) were dissolved in 1 mL of *o*-dichlorobenzene in a jointed test tube, the tube was cooled, the air pumped out, and the tube sealed. The sample was heated overnight at 130 °C. On opening, most of the *o*-dichlorobenzene was evaporated under a stream of N_2 and the residue chromatographed on 20 g of silica gel (10:1 petroleum ether/ether eluent). The product (75 mg) was recrystallized from 95% ethanol to give white crystals: mp 204–205.5 °C; NMR ($CDCl_3$) δ 1–2.0 (m, 10 H), δ 3.05 (m, 4 H), δ 6.23 (d of d, J = 3, 4 Hz, 2 H). There was no evidence that more than one isomer was present, though a second isomer cannot be ruled out.[12] Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.50; H, 6.98; N, 4.52.

Products from Methyl Acrylate and 1. Diene **1** (0.5 g, 3.7 mmol) and methyl acrylate (0.5 g, 5.8 mmol) were degassed and sealed in a jointed test tube and heated at 165 °C for 4 days. The tube was cooled and opened and the colorless liquid distilled (molecular still) at 0.01 mm to free the adducts from polymeric material. The distillate was then injected 50 μL at a time through a 6 ft × ¼ in. 20% Carbowax column at 190 °C. Three slightly overlapping peaks were collected but only the last (a Diels–Alder product) could be obtained completely pure. The first peak appeared to be a Diels–Alder product: NMR (CCl_4) δ 0.8–2.7 (m, 15 H), δ 3.60 (s, 3 H), δ 6.1 (m, 2 H). The second peak was the ene adduct: NMR (CCl_4) δ 1.0 (d, J = 7 Hz, 3 H), δ 1.0–2.8 (m, 10 H), δ 3.2 (m, 1 H), δ 3.65 (s, 3 H), δ 5.2–5.6 (m, 3 H). The third peak had: NMR (CCl_4) δ 1.0–2.0 (m, 12 H), δ 2.2–2.8 (m, 3 H), δ 3.60 (s, 3 H), δ 6.05 (m, 2 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.47; H, 9.12. The isolated first two peaks did not give satisfactory analyses; however, a sample of the distilled but not VPC'd material did, so that it appears partial decomposition on the column of either the first Diels–Alder product, or, more likely, the ene product, was occurring.

Products from Fumaronitrile and 1. Diene **1** (0.5 g, 3.7 mmol) and fumaronitrile (0.5 g, 6.4 mmol) were degassed and sealed in a tube which was then heated to 165 °C for 4 days. After cooling and opening, the tube's dark-brown contents were chromatographed on Florisil (5:1 hexane/ethyl acetate eluant) to yield brown oily crystals. The crude product was sublimed at 0.02 mm to yield 0.2 g of light-yellow sticky crystals. These were dissolved in 1 mL of hot ethanol and 3 mL of 1 M KOH in ethanol was added and the solution refluxed for 2 days. The ethanol was evaporated and the residue dissolved in water. Acidification yielded a white solid. The NMR of the solid was virtually identical to that yielded by hydrolysis of a mixture of the crude adducts of diethyl fumarate and diene **1** (also a 80:20 mixture of Diels–Alder and ene adducts).

Product from DEAD and 1. **1** (0.3 g, 2.2 mmol) and DEAD (0.32 g, 1.8 mmol) were mixed in a few milliliters of solvent (benzene, cyclohexane, or dimethylacetamide) from which oxygen had been removed by entrainment with nitrogen. The solution was allowed to sit under nitrogen until the yellow color of the dienophile faded to colorless (overnight). The solvent was evaporated without heating. The residue was recrystallized by dissolving in a 1:1 mixture of ether and petroleum ether at room temperature and then cooling to −30 or −40 °C. Alternatively, the product may be chromatographed on Florisil using an elutant of 3:1 petroleum ether/ether. If the latter method is used, it is important that an excess of diene be present in the original reaction because any unreacted DEAD will decompose on the column and contaminate the product. The white crystalline ene product melts at 103.5–105 °C: IR (CCl_4) 3400, 3030, 2980, 2940, 2860, 1760, and 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (two overlapping t, J = 8 Hz, 6 H), δ 1.2–2.5 (m, 9 H), δ 4.15 (two overlapping q, J = 8 Hz, 4 H), δ 5.2–6.0 (m, 4 H), δ 6.25 (br s, 1 H). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.50; H, 7.86; N, 9.06. Upon heating to 170

°C for a few hours in a sealed degassed tube, a quantitative yield of tetralin and *sym*-diethyl hydrazinedicarboxylate was isolated.

Product from Maleic Anhydride and 1. (Product isolated as the diacid) 120 mg of maleic anhydride and 70 mg of **1** were dissolved in 1 mL of purified dioxane in a jointed test tube. The tube was degassed and sealed and heated in an oil bath at 100 °C overnight. The tube was cooled and opened, and its contents were poured into 5 mL of 95% ethanol containing excess KOH. The solution was refluxed for 0.5 h, cooled, poured into 25 mL of H_2O, extracted with ether, and then acidified with concentrated HCl. An oil separated which crystallized on trituration with petroleum ether. Recrystallization from 95% ethanol yielded white crystals: mp 175–177 °C; NMR ($CDCl_3$) δ 1.0–2.1 (m, 10 H), δ 2.8 (m, 2 H), δ 3.1 (m, 2 H), δ 6.25 (d of d, J = 4 Hz, J = 3 Hz, 2 H), δ 10.2 (br, 2 H). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.60; H, 6.57.

Acknowledgment. We thank the Research Corporation for a Cottrell College Science Grant in partial support of this work.

Registry No.—**1**, 13304-05-7; **1–3** Diels–Alder adduct, 62707-86-2; **1–3** ene adduct, 62707-87-3; **1–4** ene adduct, 62707-88-4; **1–6** ene adduct, 62707-89-5; **1–6** Diels–Alder adduct, 41181-97-9; **1–7** Diels–Alder adduct, 62707-90-8; **1–7** ene adduct, 62707-91-9; **1–8** ene adduct, 62707-92-0; **1–8** Diels–Alder adduct, 62707-93-1; **1–9** Diels–Alder adduct, 62707-94-2; **1–9** ene adduct, 62707-95-3; **10**, 7360-96-5.

References and Notes

(1) K. Alder, F. Pascher, and A. Schmitz, *Chem. Ber.*, **76**, 27 (1943).
(2) H. M. R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969).
(3) (a) B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962); **28**, 3177 (1963); (c) E. K. von Gustorf, *Tetrahedron Lett.*, 4693 (1968).
(4) Nonsteroidal systems: (a) J. M. Cinnamon and K. Weiss, *J. Org. Chem.*, **26**, 2644 (1961); (b) B. Franzus and J. H. Surridge, *ibid.*, **27**, 1951 (1962); (c) S. G. Cohen and R. Zand, *J. Am. Chem. Soc.*, **84**, 586 (1962); (d) A. Shah and M. V. George, *Indian J. Chem.*, **9**, 411 (1971). Steroidal systems: (e) K. Schubert and K.-H. Böhme, *Chem. Ber.*, **93**, 1878 (1960); (f) A. Van der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron*, **20**, 2521 (1964); (g) A. Van der Gen, J. Lakeman, U. K. Pandit, and H. O. Huisman, *ibid.*, **21**, 3641 (1965); (h) A. Van der Gen, W. A. Zunnebeld, U. K. Pandit, and H. O. Huisman, *ibid.*, **21**, 3651 (1965); (i) J. Lakeman, W. N. Speckamp, and H. O. Huisman, *ibid.*, **24**, 5151 (1968); (j) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *ibid.*, **24**, 5215 (1968); (k) A. L. Andrews, R. C. Fort, and P. W. LeQuesne, *J. Org. Chem.*, **36**, 83 (1971).
(5) B. T. Gillis, "1,4-Cycloaddition Reactions", J. Hamer, Ed., Academic Press, New York, N.Y., 1967, pp 147–148.
(6) W. A. Thaler and B. Franzus, *J. Org. Chem.*, **29**, 2226 (1964).
(7) (a) R. K. Hill and M. Rabinovitz, *J. Am. Chem. Soc.*, **86**, 965 (1964); (b) J. Lambert and J. J. Napoli, *ibid.*, **95**, 294 (1973); (c) R. K. Hill, J. W. Morgan, R. V. Shetty, and M. E. Snyerholm, *ibid.*, **96**, 4201 (1974); (d) V. Garsky, D. F. Koster, and R. T. Arnold, *ibid.*, **96**, 4207 (1974).
(8) (a) R. T. Arnold and J. F. Dowdall, *J. Am. Chem. Soc.*, **70**, 2590 (1948); (b) R. T. Arnold and J. S. Showell, *ibid.*, **79**, 419 (1957); (c) R. T. Arnold and P. Veeravagu, *ibid.*, **82**, 5411 (1960); S. Dai and W. R. Dolbier, *ibid.*, **94**, 3953 (1972).
(9) For exceptions, see ref 4e and 4h.
(10) B. T. Gillis and J. D. Hagarty, *J. Org. Chem.*, **32**, 330 (1967).
(11) R. Askani, *Chem. Ber.*, **98**, 2551 (1965).
(12) Depending on the configuration of the dienophile, formation of more than one Diels–Alder adduct is conceivable. The conditions governing the actual (and infrequent) appearance of such multiple adducts were dealt with in an earlier paper.[13] In the few cases of multiple Diels–Alder adducts arising here, their sum will be treated as if it was a single compound, but a notation of the multiplicity and characterization of each when they can be separated will be made in the Experimental Section.
(13) B. M. Jacobson, *J. Am. Chem. Soc.*, **95**, 2579 (1973).
(14) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 98 (1928).
(15) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **470**, 62 (1929).
(16) (a) P. Barancer and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957). (b) Isoprene was chosen for convenience and because its rate constant for reaction with maleic anhydride is close to that of 1,3-cyclohexadiene's[17].
(17) J. Sauer, D. Lang, and A. Mielert, *Angew. Chem., Int. Ed. Engl.*, **1**, 268 (1962).
(18) (a) A referee has pointed out that all conformations of an acyclic diene such as isoprene should have one of the methyl's hydrogens parallel or nearly so to the π system at all times. The point is well taken, but the methyl group should certainly be undergoing far greater libration as well as rotation than **1**, or 1,3-cyclohexadiene, since the barrier to rotation (V_3) is so much smaller than the barrier for ring flipping. Whether or how such motions would affect the ene or other reactions is an intriguing question but very much unexplored territory. It should also be noted that Nickon and coworkers found the same preference for abstraction of an axial endocyclic hydrogen over that of a methyl hydrogen in some photooxygenations,[18b] but the latter may not be a true ene reaction. (b) A. Nickon, J. B. DiGiorgio, and P. J. L. Daniels, *J. Org. Chem.*, **38**, 533 (1973).
(19) R. Huisgen and H. Pohl, *Chem. Ber.*, 93, 527 (1960).
(20) B. Franzus, *J. Org. Chem.*, **28**, 2954 (1963).
(21) In most cases the isolation of ene adduct of known purity was difficult because of either very low yields or limited adduct stability. The varied mechanisms of the decomposition of the ene adducts will be the subject of a later paper.
(22) It is conceivable, but only in one case (with DEAD where no Diels–Alder adduct was observed), that the Diels–Alder/ene ratio was determined by thermodynamic rather than kinetic control; the Diels–Alder reaction could have been reversible under the reaction conditions, while the ene reaction was not. But with all the other dienophiles, prolonged heating produced no increase in the amount of ene or ene plus ene-derived product nor decrease in Diels–Alder product, even when the ene product broke down to give tetralin. Kinetic control is thus substantiated.
(23) For example, compare the stability of axial vs. equatorial cyano and carbethoxyl groups in cyclohexane. The ΔG value for the former has been measured as 0.15–0.25 kcal/mol,[24] while that for the latter is 1.0–1.2 kcal/mol.[25]
(24) (a) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, 27, 4601 (1962); (b) B. Rickborn and F. R. Jensen, *ibid.*, **27**, 4606 (1962).
(25) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, 83, 2351 (1961).
(26) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, N.Y., 1971, p 145–147.
(27) K. N. Houk and L. L. Munchousen, *J. Am. Chem. Soc.*, **98**, 937 (1976).
(28) R. C. Cookson, S. S. Gupta, I. D. R. Stevens, and C. T. Watts, *Org. Synth.*, **51**, 121 (1971).
(29) For fumaronitrile: D. T. Mowry and J. M. Butler, "Organic Syntheses", Collect., Vol. IV, N. Rabjohn, Ed., Wiley, New York, N.Y., 1963, p 468. For *N*-phenylmaleimide: M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, *Org. Synth.*, **41**, 93 (1961).
(30) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd ed., Wiley, New York, N.Y., 1961, pp 15–17.
(31) Certain products have been characterized previously:[13] all products with PTAD, all products with diethyl fumarate, and the Diels–Alder product with TCNE.

Two-Bond Carbon–Proton Couplings in 1,2,3,4,5,7,7-Heptachloronorbornene

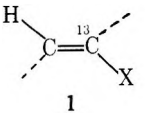
Anne H. Cain and John D. Roberts*

Contribution No. 5522 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125

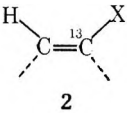
Received March 1, 1977

The coupling constants of the carbon–proton and proton–proton bonds were determined for *endo*-1,2,3,4,5,7,7-heptachloronorbornene. Signs were determined for most of the couplings. Comparisons of the norbornene couplings were made with those found in chloroethene and chlorocyclopropane.

Research with a variety of compounds[2] has shown large differences between the two-bond carbon–hydrogen couplings of the type **1** and **2**, and, in fact, with halogenated ethenes,[3] such couplings showed unexpected positive and negative



1



2

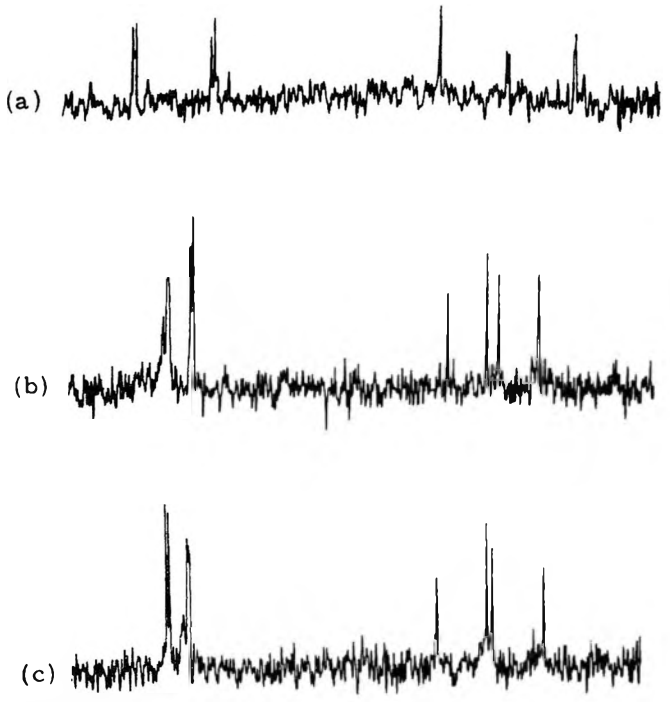
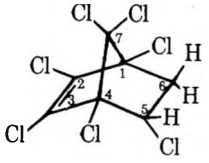


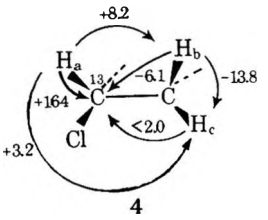
Figure 1. (a) Coupled spectrum of high-field carbons of **4.** (b) and (c) Selectively decoupled spectra of high-field carbons: (b) decoupler set at high-field ^{13}C satellite, and (c) decoupler set at low-field ^{13}C satellite.

couplings. In hope of determining whether positive and negative couplings such as **1** and **2** might be observed more generally than for alkenes we have investigated the couplings in *endo*-1,2,3,4,5,7,7-heptachloronorbornene (**3**).



endo-1,2,3,4,5,7,7-heptachloronorbornene (**3**)

The proton-coupled ^{13}C spectrum of **3** is shown in Figure 1a. From this spectrum and the proton spectrum, the proton–proton and carbon–proton couplings were assigned as in **4.** The proton–proton couplings were assigned by analogy with

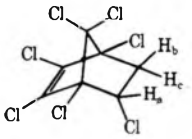
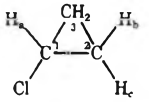
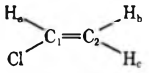


4

related compounds. With the usual assumption that vicinal couplings are positive,[4] $J_{H_aH_b}$ was given a positive sign. Independent determinations by Cox and Smith[5] and by Williamson[6] strongly suggest a negative sign for $J_{H_bH_c}$. Selective decoupling of the ^{13}C satellites of H_a, the low-field proton, gave the spectra shown in Figures 1b and 1c. These spectra show that the sign of $^2J_{CH_b}$ is opposite to that of $J_{H_aH_b}$, and $^2J_{CH_b}$ is therefore taken to be negative.

The two-bond carbon–hydrogen couplings in **3** are compared with analogous two-bond couplings in Table I. The coupling of $^2J_{CH_b}$ of **3** is similar in magnitude to the trans carbon–hydrogen coupling in monosubstituted ethenes, but is of opposite sign. The cis coupling is much smaller in **3** than in substituted ethenes.

Table I. Two-Bond Carbon–Hydrogen Couplings

Compd and coupling examined		Coupling,[a] Hz	Ref
	$^2J_{CH_b}$ (trans)	−6.1	This paper
	$^2J_{CH_c}$ (cis)	<2.0	
	$^2J_{C_1H_b}$ (trans)	−1.15	2
	$^2J_{C_1H_c}$ (cis)	−5.05	
	$^2J_{CH_b}$ (trans)	+7.1	3
	$^2J_{CH_c}$ (cis)	−8.3	

[a] Positive and negative signs have been included where they are known.

Comparison of the couplings in chloroethenes, heptachloronorbornene (**3**), and chlorocyclopropane is interesting, although some care must be taken when discussing couplings in cyclopropane rings because one could question whether the observed couplings are actually the result of two-bond or three-bond interactions; in general three-bond proton–carbon couplings are larger than corresponding two-bond couplings. Ignoring this problem, the coupling $^2J_{CH_b}$ is negative in both **3** and chlorocyclopropane, as is the case for $^2J_{CH}$ in alkanes and cycloalkanes. There seems to be a general progression of $^2J_{CH_b}$ in these compounds from large positive values in chloroethenes to large negative values in **3**, with $^2J_{CH_b}$ for chlorocyclopropane being intermediate. There is a corresponding change in $^2J_{CH_c}$ which becomes more positive through the series, and was too small to measure for **3.** Why these changes occur is by no means clear. The difference in sign for $^2J_{CH_b}$ and $^2J_{CH_c}$ has been rationalized by Jameson and Damasco[7] but it is not obvious how the argument should be extended to **3** and chlorocyclopropane. It will be interesting to determine whether similar trends in $^2J_{CH}$ will be observed with other series of substances.

Experimental Section

All of the NMR spectra were taken of 0.53 M solutions in $CDCl_3$ referenced to Me_4Si. Proton spectra were obtained with a Varian A-60A NMR spectrometer or on a Varian HR-220 NMR spectrometer. Carbon-13 spectra were taken on a Bruker WH-180 NMR spectrometer using the deuterium in the solvent as a field-frequency lock. The theoretical spectra were calculated using the computer program LEQUOR.

Acknowledgment. We would like to thank Dr. Victor Mark for providing the sample of *endo*-1,2,3,4,5,7,7-heptachloronorbornene used in this work.

Registry No.—**3**, 2440-02-0.

References and Notes

(1) Supported in part by the National Science Foundation and by the Public Health Service, Research Grant 11072 from the Division of General Medical Science.
(2) D. Ewing, *Annu. Rep. NMR Spectrosc.*, **6A**, 389 (1975).
(3) (a) F. J. Weigert and J. D. Roberts, *J. Phys. Chem.*, **73**, 449 (1969); (b) K. M. Crecely, R. W. Crecely, and J. H. Goldstein, *ibid.*, **74**, 2680 (1970); (c) R. M. Lynden-Bell, *Mol. Phys.*, **6**, 537 (1963).
(4) This assumption is supported by a collection of vicinal proton–proton couplings, which are all positive, in F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, Appendix E, Sections B and D.
(5) R. Cox and S. Smith, *J. Phys. Chem.*, **71**, 1809 (1967).
(6) K. L. Williamson, *J. Am. Chem. Soc.*, **85**, 516 (1963).
(7) C. J. Jameson and M. C. Damasco, *Mol. Phys.*, **18**, 491 (1970).

Mechanism of Diphenyl Disulfide Catalysis of the Thermal Thia-allylic Rearrangement

H. Kwart* and N. A. Johnson

Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received February 7, 1977

The effects of added concentrations of PhSSPh in solutions of deuterated allyl phenyl sulfide follow the rate law $k_0 = k_c[cat]^{1.0}$. Neither allyl cyclohexyl sulfide nor propyl phenyl sulfide shows a significant tendency to undergo thia-allylic rearrangement in the presence of an equivalent amount of PhSSPh. These and other pertinent considerations appear to disqualify all radical chain mechanisms or dissociation–recombination processes of catalysis. The evidence is arrayed in support of a mechanism involving initial formation of a trigonal-bipyramid complex of catalyst and substrate, followed by a rate-determining pseudorotation step which occurs over a lower barrier than in the uncatalyzed complex.

Since their discovery[1] in 1970, thermal thia-allylic rearrangements have found applications in synthesis.[2] Recent efforts to elucidate the mechanism of the thermal rearrangement, which is not experienced by first-row elements, have brought to light the necessity for an octet-expansion step,[3] presumably involving a trigonal-bipyramid intermediate undergoing the required act of permutational isomerism (pseudorotation) in the rate-determining step.[4]

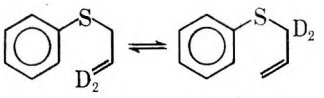
Catalysis of the thia-allylic rearrangement has been the subject of considerable interest.[2,5] Warren and co-workers[6] have advocated a variety of catalytic mechanisms ranging from radical chain processes[6,7] to allyl cation-intermediated, dissociation–recombination processes.[8] Such speculations claim, in effect, that the catalyzed thia-allylic rearrangement represents a complete departure from the established sulfur octet-expansion mechanism of the uncatalyzed thermal reaction.[3,4] However, the lack of substantiation by careful kinetic studies and experimental controls raises some doubt as to the validity of such conclusions. Moreover, the converse conclusion, namely, that the essential features of the uncatalyzed mechanism are retained in the course of powerful catalysis by both singlet and triplet oxygen species, has been verified through kinetic studies discussed in a recent communication from these laboratories.[5] These results are closely consistent with the assumption of a trigonal-bipyramid intermediate complex in which the central sulfur atom enjoys a state of higher hypervalency stemming from initial coordination with the catalytic species. The catalytic effect is a derivative of the fact that the ease of permutational isomerism increases with increasing hypervalency of the central atom; for example, a >15 kcal lowering of the barrier to permutational isomerism in $C_6H_5SF_3$ is produced by traces of HF.[9]

All the catalysts of thermal thia-allylic rearrangement we have investigated thus far appear to follow the same rate law (eq 2), expressing clean first-order dependency on the initial concentration of the catalyst. That is to say, none of the catalysts studied previously is consumed or permanently altered in the course of exerting its influence, and all participate with the first-power concentration dependency expressed by this rate law.

Against this background we have undertaken to characterize the catalytic effect displayed by additions of diaryl disulfides on the rates and product compositions derived from thermal thia-allylic isomerizations.

Results

Addition of diphenyl disulfide to a thermally isomerizable solution of deuterated allyl phenyl sulfide (1 ⇌ 1a) increases the rate of reaction in accordance with the previously noted[5] relationship (eq 2), where $[S_e]$ is the equilibrium concentration of the thia-allylic substrate and $[S_0]$ is its initial concentration; k_0, k_1, and k_2 are the respective observed, unimolecular, and bimolecular rate constants; k_c is the catalytic coefficient of the catalyst at constant concentration designated by [cat].



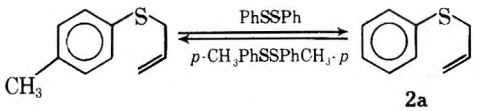
(1)

1 1a

$$k_0 = -\ln([S] - [S_e])/2t = (k_1 + k_2[S_0]) + k_c[cat]^{1.0} \quad (2)$$

A series of observed rate constants determined at different concentrations of diphenyl disulfide is listed in Table I. The plot of k_0 vs. [PhSSPh] was found to be perfectly linear over the entire range of catalyst concentrations studied (0 → 1.0 M). The catalytic coefficient ($k_c = 7.25 \pm 0.05 \times 10^{-5}\ M^{-1}\ s^{-1}$) was calculated from the slope of this plot (Figure 1) in the course of a regression analysis.[10]

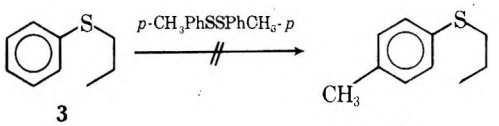
When allyl *p*-tolyl sulfide (2) was rearranged in the presence of diphenyl disulfide, the crossed product (eq 3) could be identified in the product composition. Similarly the reverse reaction took place when the allyl phenyl sulfide was rearranged in the presence of some *p*-tolyl disulfide. Under exactly



(3)

2 2a

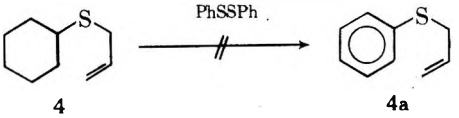
the same conditions the (nonallylic) propyl phenyl sulfide (3) did not undergo the exchange with *p*-CH_3PhSSPhCH_3-*p* to give 3a.



(4)

3 3a

When phenyl is replaced by alkyl, as in allyl cyclohexyl sulfide (4), it has been previously shown that thia-allylic rearrangement does not occur to any significant extent under conditions which rapidly bring about the isomerization 1 ⇄ 1a. Attempts to exchange 4 with PhSSPh have resulted in less than 1% of 4a after a prolonged period of heating under con-



(5)

4 4a

ditions which effect nearly complete exchange according to

Table I. Effect of PhSSPh on the Rate of Rearrangement (1 ⇌ 1a) at 0.954 M Substrate in Dichlorobenzene at 160.0 °C[a]

$k_{obsd} \times 10^4$ s^{-1}	[PhSSPh], M	$k_{obsd} \times 10^4$ s^{-1}	[PhSSPh], M
0.162	0	0.530	0.491
0.192	0.071	0.675	0.701
0.248	0.100	0.860	0.972
0.380	0.312		

[a] $k_c = 7.25 \pm 0.05 \times 10^{-5}$ M^{-1} s^{-1} (calculated).

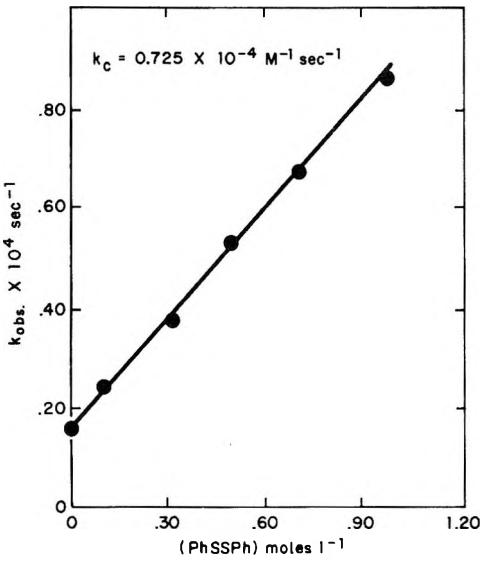


Figure 1. Plot of k_{obsd} vs. (PhSSPh) for the rearrangement of 1 to 1a in dichlorobenzene at 160.0 °C.

eq 3 in a fraction of the heating time at the same temperature.

Discussion

The Role of the Phenyl Group in Allyl Phenyl Sulfide Catalyzed Thermal Isomerization. The indispensability of the electronegative phenyl substituent on sulfur in bringing about the thia-allylic rearrangement has been correlated[4] with the requirements for octet expansion among third-row elements. In accordance with the preference rule,[11] the apical positions would be preferentially occupied by the more electronegative substituents in the stabilized trigonal-bipyramid intermediate implicated in the isomerization process. From many sources[12] it is now apparent that the barrier to pseudorotation parallels the apicophilicities of the TBP ligands; such electronegativity effects may control the ease of pseudorotation, though they may not entirely prevent its occurrence.

The fact that allyl cyclohexyl sulfide does not undergo rearrangement, or only very reluctantly, both in the uncatalyzed and disulfide catalyzed cases, would suggest that the catalyzed reaction is not strikingly different in its mechanistic requirements; i.e., pseudorotation (permutational isomerism)[13] is the rate-determining step in both cases. It therefore seems reasonable to assume that octet expansion is also involved in the disulfide-catalyzed process; this deduction is supported by analogy to the oxygen-catalyzed mechanism,[5] wherein an initially formed donor complex between catalyst and substrate is structured as a trigonal-bipyramid centered on a hypervalent sulfur atom. In the case of disulfide catalysis, this structure is capable of undergoing rearrangement, here accompanied by exchange, at a faster rate than was characteristic of the trigonal-bipyramid centered on a sulfur with less polar ligands.

Mechanistic Possibilities. (A) The Radical Dissociation–Recombination Process. Considerable evidence[14] has been advanced suggesting that thermal homolysis of the S–S bond in diaryl disulfides proceeds at relatively low temperatures (30–150 °C), although some reservations have also been expressed.[15,16] For example, Leandri and Tundo[17] found clear evidence of unsymmetrical disulfides dissociating homolytically to give symmetrical diaryl at 170 °C. This can be accepted as the basis for assuming that, at the temperatures which bring about thermal isomerization and exchange of allyl phenyl sulfides in the presence of diphenyl disulfide, a certain extent of arylthiyl radical concentration does exist in the catalytically isomerizing solution; but do these thiyl radicals intermediate the course of the disulfide-catalyzed thia-allylic rearrangement?

This possibility has been considered in the work of Krusic and Kochi[18] who observed that when dimethyl disulfide is photolyzed in the presence of allyl methyl sulfide (**6**) in the cavity of an ESR spectrometer the symmetrical radical **6a** is generated. The photochemical mechanism postulated is expressed by eq 6.

$$CH_3SSCH_3 \rightleftharpoons 2CH_3S\cdot$$

$$CH_3S\cdot + \underset{\mathbf{6}}{CH_2{=}CHCH_2SCH_3} \rightleftharpoons \underset{\mathbf{6a}}{CH_3SCH_2\dot{C}HCH_2SCH_3} \quad (6)$$

It is thus made conceivable that the disulfide-catalyzed thia-allylic rearrangement could involve attack of an arylthiyl radical in a Michael-type adduct with 1. This step could be the vehicle for (both) enhancement of the isomerization rate as well as the exchange reaction yielding crossed product, as expressed in eq 7.

$$ArS\cdot + CD_2{=}CHCH_2SPh \rightleftharpoons \underset{\mathbf{7}}{(ArSCD_2\dot{C}HCH_2SPh)} \rightleftharpoons ArSCD_2CH{=}CH_2 + PhS\cdot \quad (7)$$

This mechanistic scheme, however, can be discounted for several reasons stemming from the kinetic results presented above. One reason is that the Krusic–Kochi path[18] has been shown to be equally accessible to allyl alkyl and allyl aryl sulfides, since the effect of the sulfur substituent on the stability of the intermediate radical **6a** is damped by separation from the carbon radical center. Consequently, this mechanism does not explain the indispensability of an electronegative aryl substituent on sulfur which has been found here to be characteristic of both the catalyzed and uncatalyzed thia-allylic cases.

The second and most telling argument against the radical dissociation–recombination pathway of catalysis is its failure to account for the catalytic kinetics as seen from the following kinetic analysis of this mechanism in the case of 1 ⇄ 1a in the presence of PhSSPh.

$$PhSSPh \overset{K_{eq}}{\rightleftharpoons} 2PhS\cdot$$

$$PhS\cdot + \underset{\mathbf{A}}{CD_2{=}CHCH_2SPh} \overset{k_c}{\underset{k_{-c}}{\rightleftharpoons}} \mathbf{7}$$

$$\mathbf{7} \overset{k_c}{\underset{k_{-c}}{\rightleftharpoons}} \underset{\mathbf{B}}{PhSCD_2CH{=}CH_2} + PhS\cdot$$

$$-d[A]/dt = k_c[PhS\cdot][A] - k_{-c}[PhS\cdot][B]$$

where $k_c = k_{-c}$, and $[B] = [A_0] - [A]$

$$-d[A]/dt = k_c[PhS\cdot](2[A] - [A_0])$$

and at equilibrium

$$0 = k_c[\text{PhS}\cdot](2[A_e] - [A_0])$$

where $[A_e]$ = equilibrium [A], and $[A_0]$ = initial [A]. Thus, by substraction:

$$-d[A]/dt = 2k_c[\text{PhS}\cdot]([A] - [A_e])$$

and by integration

$$\ln([A] - [A_e])/2t = k_0 = k_c[\text{PhS}\cdot] + \text{constant}$$

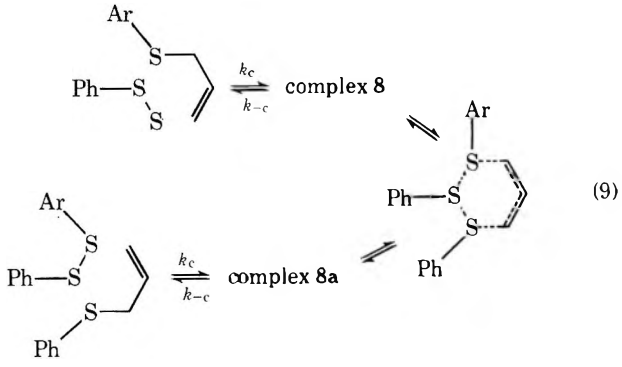
but, since

$$[\text{PhS}\cdot] = K_{eq}^{1/2}[\text{PhSSPh}]^{1/2} = [\text{cat}]^{1/2}$$

$$k_0 = k_c[\text{cat}]^{1/2} + \text{constant} \quad (8)$$

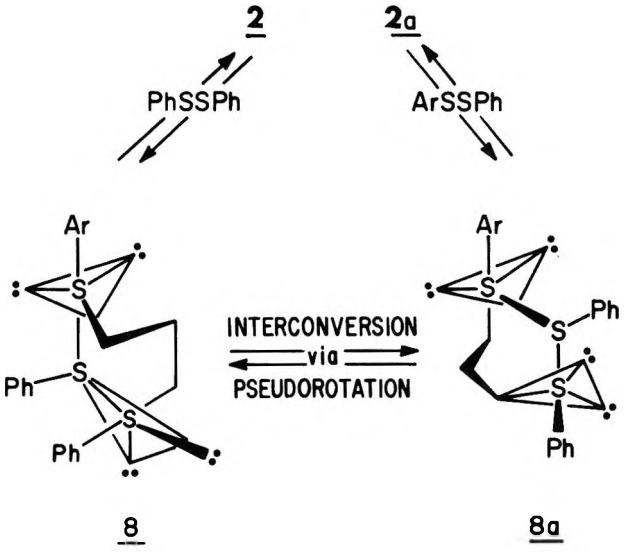
This mechanism which, according to the derived eq 8, predicts that the catalytic coefficient k_c is dependent on the half-power of the catalyst concentration is completely at variance with the experimental data (Table I, Figure 1) which corroborate unequivocally a first-power dependency. In fact, it should be evident that any catalytic mechanism involving preliminary dissociation of diphenyl disulfide into phenylthiyl radicals cannot fit the observed kinetic dependencies. When taken in conjunction with the observation that propyl phenyl sulfide (3) does not undergo aryl exchange with *p*-tolyl disulfide, all mechanisms based on radical displacement on sulfur are also eliminated from consideration.

(B) The Process of Rearrangement in the TBP Structure of the Substrate–Catalyst Complex. The rapidly reversible formation of a donor complex between disulfide and the allyl aryl sulfide, pictured in eq 9, is fully supported by the



(9)

experimentally determined kinetic dependencies (eq 2). However, this is only a specious representation of the bonding changes which must occur and their thermodynamic consequences. Assuming that such a complex would have a TBP structure (although a square pyramid formulation (sp) or a distorted TBP are not excluded),[19-21] there must be at least two such complexes, one formed by apical attack of the disulfide on the reactant yielding complex 8 and the other formed analogously with the product yielding the complex **8a**. Since apical and basal bonds are of unequal energies, it is obvious that 8 and **8a** cannot be interconverted without the intervention of an energy-expending step. That is to say, since a complex arises by forming the appropriate apical bonds between the catalyst and substrate reaction centers, it can revert to these (equilibrium) components only by breaking the same kinds of apical bonds. The energy expenditure involved in the apical–basal bond transformations (8 ⇌ **8a**) corresponds to the familiar pathway of permutational isomerism; i.e., the rate-determining step in the disulfide-catalyzed reaction must occur as a polytopal rearrangement process.[13] An increase in rearrangement rate stemming from such catalysis is the consequence of lowering the so-called pseudorotation barrier of sulfur by creating a TBP complex between substrate and catalyst possessing ligands of higher apicophilicity.[12a-d]



Finally, it must be clear that, although the action of diaryl disulfides in accelerating the thia-allylic rearrangement has here been identified as catalysis, these reagents are not truly catalysts; that is to say, a true catalyst would be a reagent that participates in the rate-determining step of the rearrangement and arrives at the product stage without experiencing an alteration of its structure. The title subject is therefore not to be regarded as a catalyzed thia-allylic rearrangement but rather as an analogous bimolecular reaction mechanism.

Experimental Section

General. NMR measurements were recorded on a Varian Associates A-60 spectrometer equipped with an electronic digital voltmeter. Spectral data are recorded in δ (ppm) with reference to Me_4Si in carbon tetrachloride solution. Mass spectral data were obtained using a Model C.E.C. 21-110B double-focusing, high-resolution, mass spectrometer. The GLC analyses were performed on an F & M Model 700 flame-ionization gas chromatograph. An injection-port temperature of 250 °C, detector temperature of 270 °C, and a flow rate of 40 mL/min were maintained throughout.

Kinetic Procedures. Sulfide and disulfide solutions of specified molarity were syringed into 5-mm o.d. Pyrex or NMR tubes. The contents were then thoroughly degassed on a high-vacuum line by freeze–pump–thaw cycling and the tubes sealed at 0.01–0.05 mm pressure. All tubes were thoroughly cleaned with chromic acid cleaning solution, rinsed with H_2O, dilute NH_4OH, and distilled H_2O, and annealed in an oven before use. The solvent, *o*-dichlorobenzene, was distilled twice before use. The disulfides (Aldrich) were purified by recrystallization from ethanol–water.

Kinetic runs were carried out at 160 °C in an oil bath equipped with a power-proportionating temperature controller. Temperatures were controlled to within ±0.05 °C. Rates and standard deviations were calculated on a Wang 700 programmable calculator equipped with a print-out system. Standard deviations were calculated on the basis of a 95% confidence interval and rate constants were reproducible to within ±2%.

Preparation of Allyl-*3,3-d*$_2$ Chloride. Allyl-*3,3-d*$_2$ alcohol[22] (5 g, 0.0835 mol) and pyridine (7.1 g, 0.090 mol) were combined in a 25-mL flask equipped with a short distilling column and dropping funnel. The flask was cooled to −60 °C with dry ice–acetone and $SOCl_2$ (10.7 g, 0.090 mol) was added dropwise. After addition was complete, ca. 15 min, the contents of the flask were warmed to 45 °C with a small oil bath. The distillate, allyl-*3,3-d*$_2$ chloride (~4 g), was collected: bp 40 °C (760 mm) [lit.[23] undeuterated allyl chloride, 40 °C (760 mm)]; NMR δ 3.83 (2 H, d, J = 6 Hz), 5.49–6.18 (1 H, m), <5% 4.84–5.32 (2 H, m).

Preparation of Sulfides. The following modified procedure[24] was used to prepare all of the sulfide compounds. The corresponding thiophenol, or cyclohexyl mercaptan (0.10 mol), was added to sodium hydroxide (4 g, 0.10 mol) dissolved in 250 mL of H_2O and the mixture shaken vigorously in a separatory funnel until all of the mercaptan was dissolved. The aqueous solution was washed with methylene chloride to remove any unreacted mercaptan and disulfides which may have formed. The corresponding alkyl chloride (0.05 mol) was added and the solution again shaken vigorously. The aqueous solution

was extracted three times with 25-mL portions of methlene chloride and the combined extracts were washed twice with 5% NaOH, H_2O, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Distillation through a short column under high vacuum yielded 80–85% of the corresponding sulfide. Molecular weights of all sulfides, as determined by mass spectroscopy, agreed with calculated values. The deuterated sulfides contained a minimum of 96% deuterium as determined by both proton NMR and mass spectroscopy.

Rearrangement of Allyl-*3,3-d*$_2$ Phenyl Sulfide in the Presence of Diphenyl Disulfide (1 ⇌ 1a). The deuterated allyl phenyl sulfide (0.954 *m*) and diphenyl disulfide (0.071–0.972 *m*) were dissolved in o-dichlorobenzene, syringed into an NMR tube, degassed, and sealed under vacuum. The tubes were heated to 160 °C in an oil bath for various time intervals, quenched in cold water, and analyzed by NMR. The disappearance of the S–CH_2 absorption (δ 3.30) and the appearance of the C=CH_2 absorption (δ 4.90) were monitored, and integration of the corresponding peak areas enabled calculation of the concentration of 1 at any time *t*. Triplicate runs were made for each concentration of diphenyl disulfide.

Analysis of Crossed Product Compositions. In general, a solution of the sulfide and disulfide dissolved in equimolar concentrations in o-dichlorobenzene (1.0 M) was syringed into Pyrex tubes. These were completely degassed and sealed under high vacuum before immersion in a 160 °C thermostated bath for given lengths of time. The product composition was analyzed on a polar ⅛ in. × 12 ft DEGA column and also on a ⅛ in. × 10 ft SE-30 column (10% liquid phase on 80/100 mesh Chromosorb WAW at 160 °C). The products of reaction were identified mainly by analytical comparison with authentic samples after isolation, as well as by retention times on the gas chromatograph.

Reaction tried	Disulfide reagent	Hours at 160 °C
2 ⇌ 2a	Diphenyl	6
4 ⇌ 4a	Diphenyl	16
3 ⇌ 3a	Di-*p*-tolyl	6

Registry No.—1, 61614-40-2; 1a, 62698-33-3; PhSSPh, 882-33-7.

References and Notes

(1) H. Kwart and N. A. Johnson, *J. Am. Chem. Soc.*, **92**, 6064 (1970).
(2) P. Brownbridge and S. Warren, *J. Chem. Soc., Chem. Commun.*, 820 (1975).
(3) H. Kwart and J. L. Stanulonis, *J. Am. Chem. Soc.*, **98**, 4009 (1976).
(4) H. Kwart and N. A. Johnson, *J. Am. Chem. Soc.*, **99**, 3441 (1977).
(5) H. Kwart, N. A. Johnson, T. Eggerichs, and T. J. George, *J. Org. Chem.*, **42**, 172 (1977).
(6) P. Brownbridge and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 2125 (1976).
(7) (a) E. S. Huyser and R. M. Kellog, *J. Org. Chem.*, **30**, 2867 (1965); (b) S. J. Cristol and R. Kellman, *ibid*, **36**, 1866 (1971); (c) S. N. Lewis, J. J. Miller, and S. Winstein, *ibid.*, **37**, 1478 (1972); (d) Y. Maki and M. Sako, *Tetrahedron Lett.*, 851 (1976).
(8) J. I. G. Cadogan and S. Kulik, *J. Chem. Soc. C*, 2621 (1971).
(9) W. A. Sheppard and D. W. Ovenall, *Org. Magn. Reson.*, **4**, 695 (1972).
(10) H. D. Young, "Statistical Treatment of Experimental Data", McGraw-Hill, New York, N.Y., 1961, pp 98–101.
(11) (a) E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963); (b) E. L. Muetterties and R. A. Schunn, *Q. Rev., Chem. Soc.*, **20**, 345 (1966).
(12) (a) J. W. Gilje, R. W. Brown, and A. H. Cowley, *J. Chem. Soc., Chem. Commun.*, **15** (1974); (b) W. Mahler and E. L. Muetterties, *Inorg. Chem.*, **4**, 1520 (1965); (c) C. G. Moreland, G. O. Doak, L. B. Littlefield, N. S. Walker, J. W. Gilje, R. W. Braun, and A. H. Cowley, *J. Am. Chem. Soc.*, **98**, 2161 (1976); (d) C. G. Moreland, G. O. Doak, and L. B. Littlefield, *ibid.*, **95**, 255 (1973).
(13) The term pseudorotation is used here interchangeably with the terms permutational isomerism and polytopal rearrangement; for further discussion see I. Ugi, D. Marquarding, H. Klusacek, G. Gokel, and P. Gillespie, *Angew. Chem., Int. Ed. Engl.*, **9**, 703 (1970); F. Ramirez et al. *Acc. Chem. Res.*, **4**, 288 (1971). For a discussion of the justification for ignoring others among the many possible modes of permutational isomerism in pentacoordinated molecules, see D. Britton and J. D. Dunitz, *J. Am. Chem. Soc.*, **97**, 3836 (1975).
(14) L. Bateman, C. G. Moore, and M. Porter, *J. Chem. Soc.*, 2866 (1958).
(15) M. S. Kharasch, W. Nudenberg, and T. H. Meltzer, *J. Org. Chem.*, **18**, 1233 (1953).
(16) H. Z. Lecher and K. Simon, *Ber.*, **54**, 632 (1921).
(17) G. Leandri and A. Tundo, *Ann. Chim. (Rome)*, **44**, 63 (1954).
(18) P. J. Krusic and J. K. Kochi, *J. Am. Chem. Soc.*, **93**, 846 (1971); see also ref 7.
(19) R. R. Homes, *J. Am. Chem. Soc.*, **96**, 4143 (1974).
(20) But see also, R. Sarma, F. Ramirez, and J. F. Maracek, *J. Org. Chem.*, **41**, 473 (1976).
(21) See J. C. Martin and T. M. Balthazor, *J. Am. Chem. Soc.*, **99**, 152 (1977), for a full discussion of the fact that the real geometries in sulfurane species may be considerably distorted from idealized TBP or SP constructions.
(22) K. D. McMichael, *J. Am. Chem. Soc.*, **89**, 2943 (1967).
(23) J. Timmermans and Hennault-Roland, *J. Chim. Phys., Phys.-Chim. Biol.*, **29**, 529 (1932).
(24) H. Kwart and E. R. Evans, *J. Org. Chem.*, **31**, 413 (1966).

Reactions of Aromatic Radical Anions.[1] 13. Contributing Factors for the Partitioning Reaction of Sodium Naphthalene with Phenylacetonitrile

Shelton Bank* and Stephen P. Thomas[2]

Department of Chemistry, State University of New York at Albany, Albany, New York 12222

Received February 8, 1977

The products, stoichiometry, and lack of reversibility of the partitioning reaction of sodium naphthalene and phenylacetonitrile have been studied. While the reaction has both reduction and hydrogen transfer pathways the latter dominate. The kinetic and product deuterium effect confirm this and indicate that the nitrile is the sole source of hydrogen. Structure variation of the nitrile indicates that only when the nitrile is not enolizable is reduction complete or even the predominant reaction. Solvent changes bring about a moderate change in reduction leading to a dampened ion-pairing effect. A proposal involving the intermediacy of the phenylacetonitrile radical anion is discussed. Additionally from competition experiments an extended scale of relative reactivities of many diverse reactions has been constructed.

Aromatic radical anions have an intrinsic duality of nature, and perhaps not surprisingly exhibit complex chemical behavior.[3] One widely exploited reaction is the ability to transfer electrons to another substrate, thus functioning as reducing agents. Examples of this mode of reaction include the reaction with metal halides,[4a] alkyl[1a,b,3c,4b] and aryl halides,[4c] alkyl and aryl tosylates,[4d] oxygen,[4e] sulfur dioxide,[4f] hydrogen,[4g] and nitrogen.[4h] Radical anions can also react as nucleophiles, abstracting a proton from a suitable acid or adding in a nucleophilic manner to a reactive center. Examples of these reactions include the reactions with water,[5a] alcohols,[5b] ethylene oxide,[5c] and trimethylsilyl chloride.[5d] In addition to these two primary reactions, radical anions exhibit some radical reactions such as radical–radical coupling. This reaction has been observed as a secondary process in the reactions of naphthalene radical anion with alkyl halides where the initially formed alkyl radical couples with a radical anion to yield an alkyl dihydronaphthyl anion.[6] Additionally hydrogen atoms are thought to couple with the naphthalene radical anion to give the dihydronaphthyl anion.[7]

Table I. Reaction of Sodium Naphthalene with Phenylacetonitrile in THF at 25 °C

Compd	Product yield, % Mode of addition	
	Direct	Inverse
3a[a]	91.2	82.1
4[b]	48.1	52.9
5[b]	36.5	40.2
6[a]	4.2	2.6
7[a]	4.0	2.3
8[b]	1.8	1.8
9[b]	0.4	0.4
10[b]	8.1	0.0
11[a]	0	7.8

[a] Yields of products are based on initial concentration of phenylacetonitrile. [b] Yields of products are based on initial sodium naphthalene concentration.

In select cases both primary reactions are seen. Aromatic radical anions can react with a molecule containing electron-withdrawing functionalities with α hydrogens by competitive reduction and abstraction processes. Such a competition is reported for the reaction of aromatic radical anions with *N*-*p*-tolyl-*p*-toluenesulfonamide.[8] Similarly, the reaction of aromatic radical anions with α-(diethylamino)phenylacetonitrile results in competitive abstraction of the α hydrogen forming the anion,[9] and electron transfer resulting in decyanation and eventual formation of diethylbenzylamine.[9]

The factors affecting reaction path or partitioning have been in some cases identified, but in the main are largely undefined. Understanding and control of the bifunctional reactivity of radical anions, while useful in itself for synthetic purposes, bears on related questions concerning other bifunctional reagents, notably anions. Accordingly this study was undertaken with the purpose of identifying and defining those factors which contribute significantly to the determination of the relative importance of electron transfer and nucleophilic reaction pathways in the reaction of an aromatic radical anion with a substrate capable of reacting via both pathways.

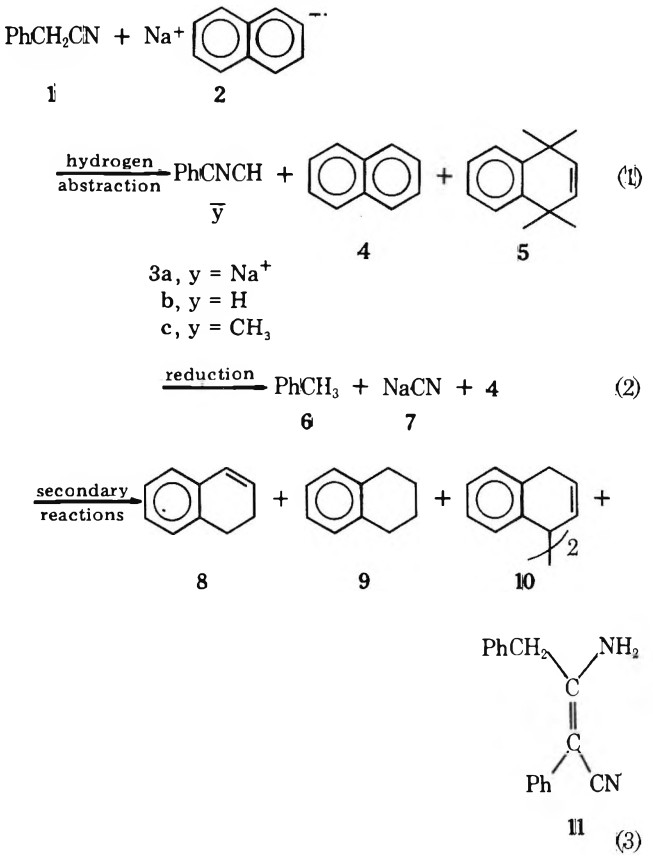
The compound selected for study is phenylacetonitrile. The hydrogens are known to be acidic with reported pK_a values of 20.8[10a] and 21.9.[10b] Additionally reductive decyanation should lead to resonance stabilized benzyl species. Moreover much is known about the corresponding halide and comparisons are facilitated. The subsequent sections of this paper describe experiments designed to probe the stoichiometry, material balance, reversibility, kinetic and product deuterium effect, competition with benzyl chloride, effect of reaction variables upon competition of hydrogen abstraction and reduction, and finally the effect of structural variations upon the nitrile.

Products

Stoichiometry and Material Balance. The reaction of phenylacetonitrile with sodium naphthalene in tetrahydrofuran (THF) yields (Scheme I and Table I) products derived from hydrogen abstraction and reduction as well as products of secondary reactions. Quenching the reaction mixture in H_2O led to **3b** and quenching in methyl iodide led to **3c**.

Product identification of compounds **4**, **5**, **6**, **8**, and **9** was accomplished via gas chromatography retention times with authentic compounds. Additionally samples were trapped and analyzed by mass spectrometry. The phenylacetonitrile dimer (**11**) was shown to be identical with the authentic material prepared by an unambiguous synthesis[11] and shown spectroscopically to be β-amino-α,γ-diphenylcrotonitrile. The

Scheme I



structure of the naphthalene dimer (**10**) was not rigorously proved. Its identification rests upon the fact that it has the same gas chromatographic retention time as the known dimer produced when sodium naphthalene reacts with water.[12]

By quantitative gas chromatographic analysis of the reaction products employing an internal standard, 95 ± 7% of the initial naphthalene could be accounted for as recovered naphthalene, dihydronaphthalene, tetralin, and naphthalene dimer. Moreover 89 ± 6% of the initial phenylacetonitrile was accounted for as recovered phenylacetonitrile, toluene, and nitrile dimer. Material balances are thus acceptable and indicate that the major reactions are indeed being monitored. The mole ratio of the reactants required for complete reaction was determined with the use of internal standards in both the nitrile (**1**) and radical anion (**2**) solutions and titration to decolorization. The experimentally determined stoichiometry was found to be 1.0–1.1 which is close to the value of 1.0 required by Scheme I.

The absence of three possible products (phenethylamine, bibenzyl, and benzylated dihydronaphthalenes) was confirmed by adding small amounts of these materials to the reaction mixture and assaying their presence. Thus the analytical procedures would have detected 0.5% of these products had they been formed. These compounds are unreactive to the reaction conditions.

Reversibility. The potential reversibility of intermediate steps in product formation was demonstrated to be unimportant. For the product toluene, a likely intermediate is the phenylacetonitrile radical anion formed by electron transfer from sodium naphthalene (eq 4). That this electron transfer is not reversible was established by monitoring the yield of toluene as a function of added neutral naphthalene.

$$\text{Naph}^{-\cdot} + \text{PhCH}_2\text{CN} \rightarrow \text{Naph} + \text{PhCH}_2^{-}\cdot\text{CN} \quad (4)$$

Application of mass action to eq 4 predicts a decrease in electron transfer with increasing naphthalene. Addition of 100 mol % excess naphthalene to a solution 0.38 M in sodium

Table II. Isotopic Composition of Products of the Reaction of Sodium Naphthalene with Phenylacetonitrile-d_2

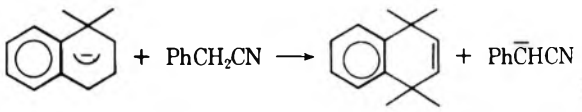
Compd	% d_0	% d_1	% d_2	% d_3
$PhCD_2CN$[a]	7.7	25.0	27.3	
$PhCH_3$	0.1	0.1	25.0	74.7
Dihydro	6.2	35.0	57.8	1.8

[a] Initial isotopic composition. The composition of the nitrile recovered after quenching the reaction mixture with saturated aqueous ammonium chloride was 97.5% d_0 and 2.5% d_1. Control experiments showed that phenylacetonitrile-d_2 underwent similar exchange under the workup conditions. There is substantial analogy for this observation.

naphthalene brought about an increase in the yield of toluene from 9 to 15%. A further doubling of the concentration of naphthalene led to a toluene yield of 17%. Whatever the reasons for the modest increase in yield of toluene may be, clearly toluene is not formed by a reversible electron transfer from naphthalene radical anion.

The reversibility of initial proton or hydrogen abstraction was probed by isolating naphthalene after reaction of sodium naphthalene with phenylacetonitrile-d_2. The recovered naphthalene was analyzed by high-resolution mass spectrometry and contained less than 0.5% deuterium. These results preclude reversibility of the initial proton or hydrogen transfer.

Finally, the reversibility shown in eq 5 of the dihydronaphthalene formation was investigated. Dihydronaphthalene exposed to a THF-d_8 solution of the phenylacetonitrile-d_1 anion (prepared by the reaction of sodium hydride with phenylacetonitrile-d_2) in an evacuated and sealed NMR tube exhibited no deuterium incorporation over a period of 5 h. Thus the phenylacetonitrile anion is insufficiently basic to remove a proton from dihydronaphthalene and hence the protonation of the dihydronaphthyl anion by phenylacetonitrile is irreversible.



(5)

Deuterium Isotope Effect. The deuterium isotope effect upon the competition between reduction and hydrogen abstraction and upon the products was examined. The reaction of sodium naphthalene with phenylacetonitrile-d_2 led to 11.1% toluene under conditions where the proton analogue gave 8.1%. Thus a small increase in the relative amount of reduction is observed. The kinetic isotope effect for the hydrogen abstraction is therefore small and can be estimated to be ~1.6 ± 0.3. This value is quite similar to the value of 1.4 ± 0.4 obtained for the reaction of sodium naphthalene with water.[13] (See Experimental Section, Table VIII, for calculations.)

The products of reaction of sodium naphthalene with phenylacetonitrile-d_2 were isolated and analyzed by mass spectrometry to determine the isotopic compositions. The results are presented in Table II. Examination of the table reveals several interesting observations. Recovered toluene is predominantly d_3 and recovered dihydronaphthalene is predominantly d_2. For this to be true, protonation of the intermediate benzyl-d_2 and dihydronaphthyl-d_1 anions must occur through reaction of the respective anions with phenylacetonitrile-d_2. If solvent molecules were providing protons the expected products would have been toluene-d_2 and/or dihydronaphthalene-d_1.

Competition Studies. Competition studies with a substrate which reacts exclusively via reduction with sodium naphthalene were performed. The reaction of benzyl chloride with sodium naphthalene in THF yields 83% bibenzyl, 12% toluene, and 5% benzylated dihydronaphthalene. Additionally there is ample evidence that this reaction proceeds via initial electron transfer.[14] When an equimolar mixture of benzyl chloride and phenylacetonitrile was reacted with a deficiency of sodium naphthalene the major product was bibenzyl and >90% of reaction involved benzyl chloride. Two facts emerge from these experiments. First, reaction of sodium naphthalene with benzyl chloride is considerably faster than reaction with phenylacetonitrile. Second, bibenzyl production is not affected by the presence of the acidic protons on phenylacetonitrile as it is when *tert*-butyl alcohol is present.[15]

Table III. Comparison of Reduction Determinations

Reaction	Temp, °C	Mode of addn	% redn Organic[a]	% redn Inorganic[b]
IV-15-3	25	Dir	10.1 ± 1.2	8.7
IV-15-4	25	Inv	7.0 ± 1.0	7.6
IV-15-5	0	Dir	9.7 ± 0.7	8.5
IV-31-10	0	Inv	8.1 ± 0.6	7.0
IV-31-22	−23	Dir	4.5 ± 0.4	5.0
IV-31-23	−23	Inv	6.6 ± 0.6	6.5

[a] Determined by the equation $2[PhCH_3]_{obsd}/[naph^{-}\cdot]_{initial}$, where $PhCH_3$ was analyzed by quantitative gas chromatography with internal standards and the factor of 2 is in analogy with the reduction of organic halides where 2 mol of radical anion is required to produce 1 mol of hydrocarbon. [b] Determined by the equation 2[NaCN]/([NaCN] + [NaOH]) where the concentrations of NaCN and NaOH were determined by titration (see Experimental Section) and the factor of 2 is in analogy with reductions of organic halides.

Table IV. Effect of Temperature and Mode of Addition on the Partitioning between Reduction and Hydrogen Abstraction

Mode of addn[a]	% redn 25 °C	0 °C	−23 °C
Direct	8.9 ± 0.7	8.1 ± 0.5	2.9 ± 0.4
Inverse	5.5 ± 0.4	7.2 ± 0.8	8.6 ± 0.7

[a] Direct addition refers to addition of the nitrile to the radical anion and inverse addition refers to the addition of the radical anion to the nitrile solution.

Effect of Reaction Variables. Quantitative determination of the relative amounts of reduction and hydrogen abstraction in the reaction of sodium naphthalene with phenylacetonitrile utilized analyses of the products of reaction. Since toluene was shown to be the sole reduced organic product from phenylacetonitrile, the yield of toluene is simply related to the fraction of radical anion molecules that react via reduction. Moreover, since sodium cyanide is the sole inorganic product of reduction there should be a correspondence between the amount of reduction calculated by analysis of the inorganic products. Accordingly, Table III records the analyses calculated by the independent methods and reveals good agreement. In sum the competition between reduction and hydrogen abstraction can be conveniently and quantitatively assayed by monitoring the yields of toluene.

Initially attention was focused on the effect of temperature and mode of addition on the partitioning. These data are recorded in Table IV. The effects of temperature changes and mode of addition upon the competition are modest to nil. Accordingly the molecularity and activation energies of the processes giving rise to the two sets of products are similar. The possibility that they are in fact identical is precluded by the following solvent variation studies.

Table V. Effect of Solvent Variation on the Competition between Reduction and Proton Abstraction

Solvent system[a]	Ion pairing state[b]	% redn
THF–DEE	Tight[d]	6.4 ± 0.5
THF–THF	Tight[e]	8.8 ± 0.9
THF–DME	Mixture[e]	32.5 ± 2.0
THF–tetraglyme[c]	Glymated[f]	48.2 ± 3.2
THF–tetraglyme	Glymated[f]	19.6 ± 1.9
DME–DEE	Tight[d]	22.1 ± 1.2
DME–THF	Mixture[e]	36.0 ± 2.4
DME–DME	Loose[e]	44.5 ± 3.8
DME–tetraglyme[c]	Glymated[f]	47.8 ± 3.1
DME–tetraglyme	Glymated[f]	33.8 ± 2.7

[a] Radical anion (ca. 0.75 M) was prepared in the solvent listed first and diluted with an equal volume of the second solvent, unless otherwise noted. [b] States of iron pairing as listed were determined by others for dilute solutions, and are listed here as indicative of the strength of solvent–cation interactions. [c] Solutions were ca. 0.38 M in tetraglyme and 0.38 M in radical anion. [d] This solvent system provides tighter ion pairs than in pure THF or DME alone: N. Hirota, R. Carraway, and W. Schook, *J. Am. Chem. Soc.*, **90**, 3611 (1968). [e] P. Chang, R. U. Slates, and M. Szwarc, *J. Phys. Chem.*, **70**, 3180 (1966). [f] K. Hofelman, J. Jogur-Grodzinski, and M. Szwarc, *J. Am. Chem. Soc.*, **91**, 4645 (1969).

Table V records the effect of solvent variation on the competition reaction. Thus reduction can be varied from a minor process (~6%) to a major process (~50%) by solvent variation; however, we were unable to find conditions that would completely eliminate reduction or provide 100% reduction with this nitrile.

Structural Effects. The generality of the competition for other nitriles with acid hydrogens and the effect of nitrile structure were investigated by reacting a variety of nitrile compounds with sodium naphthalene in THF solution under comparable conditions. For those compounds recorded in Table VI, the sole reduced product was the hydrocarbon. There were no dimers, alkylated dihydronaphthalenes, or amines, and dihydronaphthalene accounted for the major portion of the hydrogen abstraction reaction. The reactions of *p*-chlorophenylacetonitrile and isobutyronitrile with sodium naphthalene led to complexities in the reaction mixtures which preclude analyses of the amounts of reduction occurring in these reactions. In the reaction with *p*-chlorophenylacetonitrile, the principal reaction was reduction of the carbon–chlorine bond. The major low-boiling product was phenylacetonitrile and a small amount of toluene. Additionally no *p*-chlorotoluene was formed and significant quantities of *p*-chlorophenylacetonitrile were recovered. Evidently hydrogen transfer still occurs, and since the reduction of the carbon–chlorine bond in chlorobenzene by sodium naphthalene in THF has a rate constant of 6.0×10^2 $[M]^{-1}$ s^{-1},[1a,16] an estimate of 10^2 $[M]^{-1}$ s^{-1} can be made for this reaction. The reaction of sodium naphthalene with isobutyronitrile is unusual as well. Addition of 1 equiv of the nitrile to the radical anion results in an intense red reaction mixture. Aqueous workup yields nearly equal quantities of 1,2- and 1,4-dihydronaphthalene and significant quantities of a naphthalene dimer. The yield of these products does not correspond to the theoretical yield for complete hydrogen transfer. Clearly there is hydrogen transfer, but important differences in products and yields from those observed with the other nitriles prevent meaningful comparison.

Discussion

While the effect of many of the reaction parameters can be rationalized by a competitive scheme with independent and precedented mechanisms, taken as a whole there is more evidence for a common genesis of the products. Critical among these factors are the absence of some expected products and the similarity of product yield with marked changes in reaction condition and structure.

Table VI. Effect of Nitrile Structure on the Competition between Reduction and Hydrogen Transfer

Registry no.	Nitrile	% redn[a]
140-29-4	$PhCH_2CN$	9
1823-91-2	$PhCH(CH_3)CN$	23
1195-98-8	$PhC(CH_3)_2CN$	100
86-29-3	Ph_2CHCN	48
2947-61-7	*p*-$MePhCH_2CN$	7
140-53-4	*p*-$ClPhCH_2CN$	*b*
78-82-0	$(CH_3)_2CHCN$	*b*

[a] Determined from the amount of reduced hydrocarbon toluene, ethylbenzene, cumene, etc., and a treatment similar to that in Table III. [b] Could not be determined; see text.

The products of the hydrogen transfer reaction of sodium naphthalene with phenylacetonitrile are unexceptional and bear strong similarity to the products of proton transfer with water[5a] and alcohols.[5b] This includes the small amounts of secondary products, 1,2-dihydronaphthalene, tetralin, and the naphthalene dimer. The fact that this dimer is found only when the radical anion is in excess is consistent with the proposed mechanism for dimer formation with small quantities of water. On the other hand, in spite of the product similarities, there are strong indications that the mechanism in this instance involves hydrogen atom transfer rather than proton transfer. Further discussion follows. The production of the phenylacetonitrile dimer when nitrile is in excess (inverse addition) is not unexpected considering the ability of α-cyano anions to add nucleophilically to the nitrile carbon of a second nitrile (Thorpe reaction).[11]

The reduction products merit some note. The absence of amine products contrasts with the reduction using sodium in ethanol.[17] The mechanism of both amine formation and reductive elimination of cyanide are thought to proceed via a nitrile radical anion.

$$RCN + \text{electron} \longrightarrow RCN^{-\cdot} \quad (6)$$

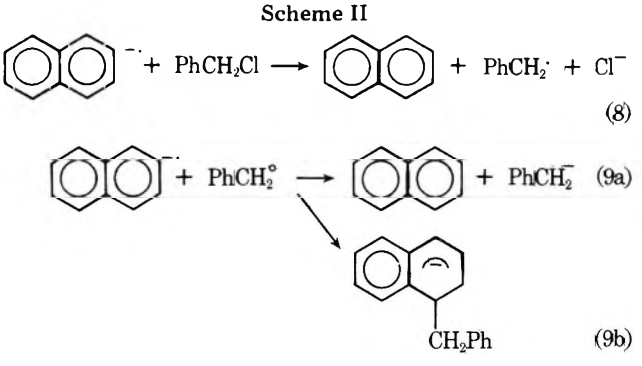
$$RCN^{-\cdot} \longrightarrow RCH_2NH_2 \quad (7a)$$

$$\hookrightarrow RH + NaCN \quad (7b)$$

However, proton transfer steps are required for reaction 7a and it is likely that in the absence of strong proton donors bond cleavage predominates.

The absence of benzylated dihydronaphthalenes and bibenzyl is more surprising, since the reaction of sodium naphthalene and benzyl chloride, known to be electron transfer, gives rise to significant quantities of bibenzyl and small amounts of benzyldihydronaphthalene. The mechanism for this reaction is considered to be that shown in Scheme II.

Scheme II



$$PhCH_2^- + PhCH_2Cl \longrightarrow PhCH_2CH_2Ph \quad (10)$$

$$PhCH_2^- + \text{proton source} \longrightarrow PhCH_3 \quad (11)$$

The absence of bibenzyl from the nitrile reaction could arise from the fact that the corresponding reaction with cyanides is much slower.

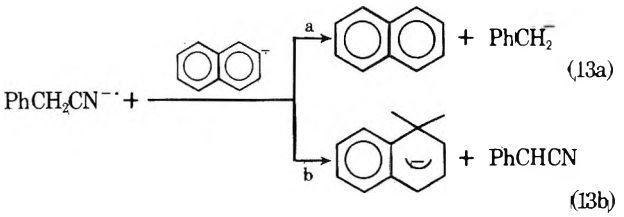
$$PhCH_2^- + PhCH_2CN \rightarrow PhCH_2CH_2Ph \quad (12)$$

However, since the product-determining step (eq 9) is leaving group independent, formation of benzylated dihydronaphthalene should be observed, unless the nitrile radical anion could react with sodium naphthalene to go directly to anion, thus bypassing the radical stage.

$$PhCH_2^-{\cdot}CN + Naph^{-}\cdot \rightarrow PhCH_2^- + \bar{C}N + Naph \quad (13a)$$

There is analogy from electrochemistry both for the existence of the radical anion of a nitrile and for subsequent reductive cleavage at higher potentials.[18] Therefore reduction of the nitrile radical anion would lead to the observed reduction products (eq 13a). Moreover, hydrogen abstraction from this species would lead to the remaining observed products (eq 13b, Scheme III), the nitrile radical anion thus being a common intermediate for both processes. While hydrogen atom abstraction is unusual, it has important analogy. The reaction is related to a known, rapid disproportionation reaction of neutral radicals. Radical–radical anion and radical anion–radical anion coupling reactions are similarly known to be fast reactions.[3c,19] Accordingly, it is reasonable that the radical anion–radical anion disproportionation by hydrogen atom transfer to give two resonance stabilized anions would be similarly rapid. Moreover, the electrochemical reduction of 4-nitrobenzyl cyanide gives rise to hydrogen gas and the α-cyano anion.[18b] Importantly Scheme III accommodates the following seemingly disparate findings.

$$Naph^{-}\cdot + PhCH_2CN \longrightarrow Naph + PhCH_2CN^{-}\cdot \quad (4)$$



As seen in Table I, the yield of $PhC\bar{H}CN$ is far greater than that of $PhCH_3$. To have proton transfer products dominate over reduction products is surprising since activation energies for electron transfer are normally lower than those for proton transfer.[20] Additionally, the initial electron transfer appears to be irreversible, and therefore exothermic, as evidenced by the effect of added neutral naphthalene. Accordingly it is more likely that there is a rapid electron transfer in line with the favorable thermodynamics followed by competing steps. The similar temperature dependencies and molecularities of the processes agree with this scheme. Moreover, the dampened effect of ion pairing is understood better accordingly. The importance of solvation and ion pairing in radical anion chemistry is well documented.[21] Of particular importance to the current study, contrasting reactivities have been observed for electron transfer[22] and proton transfer with sodium naphthalene.[23] Interestingly, in each case the range of the effect is approximately two orders of magnitude. It is clear from Table V that the trend of product distribution with solvent variation is in the direction anticipated by kinetic studies of ion-pairing effect. Thus solvent systems that favor loosening of ion pairs give rise to more reduction. Nevertheless the magnitude of the effect is significantly dampened. The opposing order of reactivities from kinetic studies lead to an expected rate difference of 10^4 between electron transfer and proton transfer at the extremes of ion-pairing states used in this study. The observed difference of ~8 is sufficiently low to raise serious concerns. In contrast the common intermediate in Scheme III more easily accommodates these results.

Additionally, the effect of nitrile structure (Table VI) upon the competition between reduction and hydrogen transfer is not easily compatible with independent mechanisms. For example, replacement of the α hydrogen by a methyl group as in α-phenylethylnitrile leads to an essentially statistical increase in reduction product. This is surprising since methyl substitution should stabilize the radical and destabilize the anion. Even more dramatically perhaps, replacement of a hydrogen by a phenyl group brings about an increase in reduced product by a factor of ~2.7 (statistically corrected) in spite of the large differences in the stability of any decyanated fragments. Also, reaction with isobutyronitrile leads to substantial quantities of dihydronaphthalene. Clearly the preference for hydrogen removal is dominant, and only when the nitrile is not enolizable is there complete or even predominant reduction. Finally, the effect of aromatic radical anion structure is supportive of the proposed scheme. The reaction of nitriles with sodium naphthalene bears only some similarity with the reaction of lithium anthracene and nitriles.[24] While hydrogen abstraction dominates for both reactions when there are α hydrogens, the reduction products differ considerably. For sodium naphthalene the exclusive electron transfer product is the reduced hydrocarbon, whereas for sodium anthracene, the alkylated product predominates. This difference is readily explained by the one-electron reduction with sodium anthracene leading to radical, and the proposed two-electron reduction with sodium naphthalene leading to anion.

In another context, considerable information can be extracted from the competition reaction with benzyl chloride and phenylacetonitrile for sodium naphthalene. One goal of this competition reaction was to compare the reduction reactivity of phenylacetonitrile with a documented electron transfer reaction. In this regard reduction of the nitrile is orders of magnitude slower than of the halide.

Several other competitive steps are revealing. Lee has found that addition of t-BuOH to benzyl chloride followed by reaction with sodium naphthalene leads to complete formation of toluene at the expense of bibenzyl.[16] Thus one can write the following steps and consider the relative rates.

$$Naph^{-}\cdot + PhCH_2Cl \rightarrow PhCH_2\cdot + Naph + Cl^- \quad (8)$$

$$Naph^{-}\cdot + PhCH_2\cdot \rightarrow PhCH_2^- + Naph \quad (9a)$$

$$PhCH_2^- + PhCH_2Cl \rightarrow PhCH_2CH_2Ph + Cl^- \quad (10)$$

$$PhCH_2^- + t\text{-BuOH} \rightarrow PhCH_3 + t\text{-BuO}^- \quad (14)$$

$$Naph^{-}\cdot + t\text{-BuOH} \rightarrow Naph\ H\cdot + t\text{-BuO}^- \quad (15)$$

To account for the effect of t-BuOH the rate of 14 must be greater than that of 10. Moreover to account for the products the rates of 8, 10, and 15 must be comparable.

The fact that phenylacetonitrile has no effect upon the production of bibenzyl when benzyl chloride reacts with sodium naphthalene adds additional steps that can be sequenced.

$$2Naph^{-}\cdot + PhCH_2CN \rightarrow Naph\ H^- + Ph\bar{C}HCN + Naph \quad (16)$$

$$2Naph^{-}\cdot + PhCH_2CN \rightarrow 2Naph + PhCH_2^- + CN^- \quad (17)$$

$$PhCH_2^- + PhCH_2CN \rightarrow PhCH_3 + Ph\bar{C}HCN \quad (18)$$

Interestingly, reaction 18 must be much slower than reaction 14 and slower than 11, 13, and 15 in spite of the similar pK_a

Table VII. Relative Rates Estimated from Competition Experiments

	Fastest					Slowest
Reaction no.[a]	9a >	14	> 8 ≃ 10 ≃ 15 >	16	>[b]	18 > 17
Log estimated rate constant	8[c]	5[d]	4–3[e]	2[f]		1[g]

[a] For reactions see text. [b] This order is based on some dihydronaphthalene formation in the competition experiment. [c] Estimated from data of Garst et al.; see reference. [d] Estimated by complete interruption of reaction 10 when *t*-BuOH is present. [e] Estimated from the rates of reaction of halides with sodium naphthalene (ref 1a,b) and the relative rates of reaction of sodium naphthalene with halide and *t*-BuOH (ref 16). [f] Estimated from known rate of reaction of chlorobenzene with sodium naphthalene and products from reaction of *p*-chlorophenylacetonitriles with sodium naphthalene. [g] From competition experiments in this work.

values of *t*-BuOH and $PhCH_2CN$. The effect could be kinetic. In this regard there is considerable analogy in the disparity between rates of protonation and equilibria which have been adequately accounted for by the principle of least motion.[25]

The remaining reactions may be sequenced to obtain the data shown in Table VII. These relative rates provide a potentially useful scale of reactivities. Of particular note in this table is the conclusion that the nucleophilic displacement reaction of benzyl anion with benzyl chloride competes with the electron transfer reaction of sodium naphthalene with benzyl chloride.

Summary and Conclusions

In reactions of sodium naphthalene with nitriles containing α hydrogens the predominant reaction is hydrogen transfer. Reduction and decyanation can be increased to a moderate degree by changes in solvent. This dampened ion-pairing effect upon competitive products differs from the effect observed in known independently competing paths.[26] The phenylacetonitrile radical anion, a likely common intermediate, can account for the several observations. Additionally from competition experiments a scale of relative reactivity has been constructed, covering some 8 power of 10 and including such diverse reactions as electron transfer, anion trapping, proton transfer, hydrogen atom transfer, cleavage, and nucleophilic displacement reactions.

Experimental Section

General. Reactants were commercial products often redistilled, and purity was checked via GLC analysis. Phenylacetonitrile-d_2 was prepared by three exchanges between the nitrile in CCl_4 and NaOD in D_2O (Stohler Isotope Chemicals), and was distilled from calcium hydride (Alfa Inorganics) prior to use. α,α-Dimethylphenylacetonitrile was prepared by successive alkylations of phenylacetonitrile in THF solution by the addition of butyllithium followed by methyl iodide, and was purified by GC trapping prior to use. Chromatoquality solvents were distilled from sodium benzophenone ketyl prior to use.

Gas chromatographic analyses were performed on a Hewlett-Packard Model 5750 chromatograph employing flame ionization detectors. Mass spectra were recorded on a AEI MS-902 high-resolution mass spectrometer, NMR spectra were recorded on a Varian Associates Model A-60A NMR spectrometer, and infrared spectra were recorded on a Beckman Model IR-10 spectrometer. Titrations were performed with a Fisher Model 36 Titrimeter.

Typical Procedures. Preparation and Standardization of Radical Anion. Solutions of sodium naphthalene (0.5 M) were prepared by stirring freshly cut sodium metal (4.8 g, 0.20 mol) with 16.0 g (0.13 mol) of naphthalene and 3.7 g (0.03 mol) of *tert*-butylbenzene internal standard in 250 mL of freshly distilled THF in a modified organometallic storage buret for 10 h under a dry nitrogen atmosphere. Aliquots (2 mL) of the sodium naphthalene solution were run from the buret into oven-dried, nitrogen-filled, septum-capped 4-dram vials and quenched with saturated aqueous ammonium chloride (1 mL) by syringe injection. Hexane (1 mL) was added by syringe and the organic phases analyzed by gas chromatography on a 4 ft, 10% Carbowax 20M column operating on a temperature program between 90 and 160 °C for *tert*-butylbenzene, dihydronaphthalene, and naphthalene. The completeness of radical anion formation and the mole ratio of radical anion to internal standard were then determined.

Reactions of Sodium Naphthalene. Direct addition reactions of sodium naphthalene with the various substrates examined were performed by introducing a 3-mL sample of the radical anion solution from the buret into an oven-dried, nitrogen-filled, septum-capped 5-dram vial fitted with a glass-coated magnetic stirring bar, allowing the solution to equilibrate for ~10 min in a bath at the appropriate temperature, and adding dropwise from a syringe with stirring a solution of the appropriate reactant (~3 mL) until the initially dark green sodium naphthalene solution decolorized (~3 min). Saturated aqueous ammonium chloride (1 mL) and hexane (1 mL) were added and the organic phase was analyzed by gas chromatography on a 4 ft, 10% Carbowax 20M column operating between 90 and 160 °C for low-boiling products and on a 4 ft, 10% silicon rubber SE-30 or UCW-98 column operating between 90 and 270 °C for any high-boiling products.

Inverse addition reactions were performed by syringing the nitrile solution (3 mL) into the vial and adding the radical anion solution dropwise with stirring until the theoretical amount had been added and the green color of the radical anion persisted for a few seconds. Saturated aqueous ammonium chloride (1 mL) and hexane (1 mL) were added and the organic phase was analyzed by gas chromatography.

Solutions of sodium naphthalene in solvent pairs were prepared by adding concentrated (0.75 M) THF or DME solutions (3 mL) of the radical anion to the reaction vials and diluting with an equal volume of the appropriate cosolvent. Aliquots (1 mL) were removed by hypodermic syringe and injected into septum-capped vials containing saturated aqueous ammonium chloride (1 mL) and hexane (1 mL), and the organic phases were analyzed by gas chromatography. Reactions with phenylacetonitrile in solvent pairs were accomplished by adding the nitrile solution in the same solvent pair (prepared in an analogous manner) dropwise from a syringe to the stirred radical anion solution.

Reactions of sodium naphthalene with phenylacetonitrile in the presence of added neutral naphthalene or added sodium tetraphenylboron were performed in a manner analogous to the reactions in solvent pairs, except that weighed quantities of the addenda were placed in the reaction vials prior to the addition of the radical anion solution.

Methyl Iodide Quench. To 5 mL of a 0.5 M THF solution of sodium naphthalene in a dry, nitrogen-filled, septum-capped 5-dram vial fitted with a glass-coated magnetic stirring bar was added 5 mL of a 0.5 M THF solution of phenylacetonitrile over a period of 5 min. The resulting solution was taken up in a dry 10-mL syringe and added dropwise to a solution of 9.1 g (0.06 mol) of methyl iodide in 50 mL of dry THF in a 100-mL, two-necked, round-bottomed flask fitted with a glass-coated magnetic stirring bar and septum stoppers. After quenching with saturated aqueous ammonium chloride, the reaction mixture was analyzed by gas chromatography. Regenerated nitrile was found to be composed of 78% α-methylphenylacetonitrile, 19% α,α-dimethylphenylacetonitrile, and 3% phenylacetonitrile. A control experiment indicated that no methylation occurred when phenylacetonitrile and methyl iodide were exposed to aqueous sodium hydroxide. Thus methylation of the reaction mixture must have occurred prior to the workup conditions.

Material balance and stoichiometry were determined for direct and inverse addition reactions between (0.5 M THF solutions of) sodium naphthalene and phenylacetonitrile, carried out and quenched in the usual manner, except that prior to reaction a second internal standard was added to the nitrile solution. The resulting organic solutions were analyzed by gas chromatography as were the initial nitrile solution and the organic solution resulting from water quenching of the radical anion solution. Multiple GLC traces were recorded and Xeroxed two to three times each, and the relevant peaks were cut out and weighed. Area ratios were then corrected to mole ratios by dividing by the appropriate molar response factors.

Titrations. A reaction between (3 mL each of 0.5 M THF solutions of) sodium naphthalene and phenylacetonitrile was performed in the usual manner, but was quenched by the addition of 1 mL of water. Hexane (1 mL) was added, and the aqueous and organic phases separated. The organic phase was extracted with two 1-mL portions of

Table VIII. Relative Intensities in the Mass Spectra of Isotopically Labeled Reaction Products

Substance	Rel intensity[c]				
$PhCD_2CN$[a]	117	118	119		
	11.04	35.90	96.77		
$PhCH_2CN$[b]	100.00	2.60	0.00		
Naphthalene		128	129		
		100.00	0.00		
Dihydro	130	131	132	133	134
	16.12	63.48	103.03	39.75	3.59
Toluene	92	93	94	95	
	0.18	0.16	32.66	97.53	

[a] Initial composition. [b] Nitrile recovered after reaction. [c] Corrected for ^{13}C and ^{15}N contributions. Calculated isotope effect of 1.6 ± 0.3; K_H/K_D = (yield dihydro H/toluene H)/(yield dihydro D/yield toluene D).

water, and the aqueous phases were combined, diluted to 40 mL with distilled and degassed water, and titrated with 0.10 M hydrochloric acid employing a Fisher Titrimeter to continuously monitor the pH of the solution. A titration curve was constructed and compared with standard titration curves obtained from known prepared mixtures of sodium cyanide and sodium hydroxide.

Isotopic Studies. A reaction between (0.5 M THF solutions of) sodium naphthalene and phenylacetonitrile-d_2 was performed and worked up in the usual manner. The organic products of the reaction were collected by preparative gas chromatography and analyzed by mass spectrometry at low ionizing voltages for isotopic composition. Relative intensities of the relevant molecular ion peaks (corrected for ^{13}C and ^{15}N contributions) are recorded in Table VIII from which the isotopic compositions in Table II were determined.

Competition Reaction with Phenylacetonitrile and Benzyl Chloride. To a solution of 7.1 g (0.06 mol) of phenylacetonitrile and 7.6 g (0.06 mol) of benzyl chloride in 50 mL of dry THF contained in a 100-mL round-bottomed flask fitted with a glass-coated magnetic stirring bar and a septum stopper was added 25 mL of a 0.5 M THF solution of sodium naphthalene (0.01 mol) over a period of 9 min. The reaction mixture was quenched with saturated aqueous ammonium chloride (3 mL), and the organic phase was analyzed by gas chromatography. The major reaction product was found to be bibenzyl with less than 10% of the theoretical amount of dihydronaphthalene being produced, indicating that in excess of 90% of the sodium naphthalene reacted with benzyl chloride.

NMR Exchange. In a dry, nitrogen-filled, septum-capped, 5-mL, pear-shaped flask fitted with a glass-coated magnetic stirring bar were placed 0.07 g (3.07 mmol) of sodium hydride, ca. 0.2 g (ca. 1.7 mmol) of phenylacetonitrile-d_2, and 1.0 g of THF-d_8. The mixture was allowed to stir for 4 h after which the supernatant liquid was transferred by cannula tubing with nitrogen pressure to a dry, nitrogen-filled NMR tube containing 0.10 g (0.81 mmol) of naphthalene and 0.15 g (1.15 mmol) of dihydronaphthalene. The NMR tube was evacuated at liquid nitrogen temperature and sealed. Spectra were obtained over a period of 4 h which were invariant with time and showed no loss of dihydronaphthalene protons or loss of phenylacetonitrile deuterons. After 4 h a precipitate accumulated in the NMR tube and spectra could no longer be taken. On aqueous workup, the reaction mixture was found to have produced significant quantities of the material identified as the nitrile dimer.

Nitrile Dimer Formation. To a dry, nitrogen-filled, septum-capped, 5-dram vial fitted with a glass-coated magnetic stirring bar were added 0.44 g (3.77 mmol) of phenylacetonitrile, 2 mL of THF, and 1.2 mL (1.8 mmol) of butyllithium in hexane (1.5 M). The resulting solution was stirred for 20 h and quenched with aqueous ammonium chloride. Benzene (1 mL) was added, and the organic phase was analyzed by gas chromatography. In addition to unreacted phenylacetonitrile, one major reaction product was observed. The aqueous and organic phases were separated, and the organic phase was dried over anhydrous magnesium sulfate. The dried organic phase was placed on a high vacuum line and benzene and unreacted phenylacetonitrile were removed at the pump leaving a dark red-brown oil. This material exhibited a molecular ion in the mass spectrometer at m/e 234 indicating a dimer of phenylacetonitrile. The NMR spectrum of this material consisted of a singlet at δ 3.82, 2 protons (benzylic protons), a broad singlet at δ 4.75, 2 protons (amine protons), and a resonance at δ 7.29, 10 protons (aromatic protons); the infrared spectrum (solution in CCl_4) exhibited major absorbances at 3500, 3400, 3360, 3240, 3220, 3075, 3040, 2960, and 2200 cm^{-1} indicating the presence of both amino and cyano functionalities. The infrared spectrum is in agreement with that reported[11] for β-amino-α,γ-diphenylcrotononitrile (KBr pellet), the known product of base-catalyzed dimerization of phenylacetonitrile, and the mass spectral and NMR data further confirm the assignment of this structure to the product of this reaction.

Acknowledgments. We thank the National Science Foundation (Grant GP19227) for partial support of the research. S.P.T. acknowledges with gratitude financial support as a National Defense Education Act Title IV Fellow.

Registry No.—Phenylacetonitrile-d_2, 935-66-0; sodium naphthalene, 3481-12-7; benzyl chloride, 100-44-7; β-amino-α,γ-diphenylcrotononitrile, 18029-64-6.

References and Notes

(1) (a) Part 12: S. Bank and D. A. Juckett, *J. Am. Chem. Soc.*, **98**, 7742 (1976). (b) Part 11: S. Bank and D. A. Juckett, *ibid.*, **97**, 567 (1975). (c) Part 10: S. Bank and M. Platz, *Tetrahedron Lett.*, 2097 (1973).
(2) (a) Part 9: S. Bank and S. P. Thomas, *Tetrahedron Lett.*, 305 (1973). (b) Abstracted in part from the Ph.D. Dissertation of S. J. Thomas, SUNY at Albany, 1972. (c) S. Bank and S. P. Thomas, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, No. ORGN-57.
(3) (a) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 1 (1928); (b) J. Vidal and Y. Chavin, *Rev. Inst. Fr. Pet.*, **19**, 1219 (1964); (c) J. F. Garst, *Acc. Chem. Res.*, **4**, 400 (1971).
(4) (a) N. D. Scott and J. F. Walker, U.S. Patent 2 177 412 (Oct 24, 1940); *Chem. Abstr.*, **34**, 974 (1940); (b) J. F. Garst in "Free Radicals", Vol. 1. J. Kochi, Ed., Wiley, New York, N.Y., 1973, Chapter 9, and references cited therein; (c) T. C. Cheng, L. Headley, and A. F. Halasa, *J. Am. Chem. Soc.*, **93**, 1502 (1971); G. D. Sargent, *Tetrahedron Lett.*, 3279 (1971); (d) W. D. Closson, P. Wriede, and S. Bank, *J. Am. Chem. Soc.*, **88**, 1581 (1966); (e) A. LeBerre and P. Goasguen, *Bull. Soc. Chim. Fr.*, 1838 (1963); (f) S. Bank and D. A. Noyd, *Tetrahedron Lett.*, 1413 (1969); (g) S. Bank and T. A. Lois, *J. Am. Chem. Soc.*, **90**, 4505 (1968); M. Ichikawa, M. Soma, T. Onishi, and K. Tamuru, *ibid.*, **91**, 6505 (1969); E. E. van Tamelen and R. B. Fechter, *ibid.*, **90**, 6854 (1968); (h) E. E. van Tamelen et al., *ibid.*, **89**, 5707 (1967); **90**, 1677, 4492 (1968); **91**, 1551 (1969); D. R. Gray and C. H. Brubaker, *Chem. Commun.*, 1239 (1969).
(5) (a) S. I. Weissman, J. Townsend, D. E. Paul, and G. E. Pake, *J. Chem. Phys.*, **21**, 2227 (1953); D. Lipkin, D. E. Paul, J. Townsend, and S. I. Weissman, *Science*, **117**, 534 (1953); D. E. Paul, D. Lipkin, and S. I. Weissman, *J. Am. Chem. Soc.*, **78**, 116 (1956); (b) S. Arai, E. L. Tremba, J. R. Brandon, and L. M. Dorfman, *Can. J. Chem.*, **45**, 1119 (1967); (c) C. S. Rondestvedt, Jr. and I. Nicholson, *J. Org. Chem.*, **20**, 346 (1955); (d) D. R. Weyenberg and L. H. Topcarcer, *ibid.*, **30**, 943 (1965).
(6) (a) J. F. Garst, J. T. Barbas, and F. E. Barton, II, *J. Am. Chem. Soc.*, **90**, 7159 (1968); (b) G. D. Sargent and G. A. Lux, *ibid.*, **90**, 7160 (1968).
(7) S. Bank, T. A. Lois, and M. C. Prislopski, *J. Am. Chem. Soc.*, **91**, 5407 (1969).
(8) W. D. Closson, S. Ji, and S. Schulenberg, *J. Am. Chem. Soc.*, **92**, 650 (1970).
(9) C. Fabre and Z. Welvart, *Bull. Soc. Chim. Fr.*, 2620 (1965).
(10) (a) K. Faharava, J. N. Stefanovsky, and J. Pojarhoff, *Tetrahedron Lett.*, 1663 (1971); (b) F. Bordwell, *J. Org. Chem.*, **41**, 1885 (1976).
(11) R. A. Shaw, *J. Chem. Soc.*, 2779 (1956).
(12) N. D. Scott and J. F. Walker, U.S. Patent 2 194 450 (March 19, 1940).
(13) S. Bank and B. Bockrath, *J. Am. Chem. Soc.*, **93**, 430 (1971).
(14) H. E. Zieger, I. Angres, and D. Mathisen, *J. Am. Chem. Soc.*, **98**, 2580 (1976).
(15) Y. Lee, Ph.D. Thesis, SUNY at Albany, Sept 1974.
(16) D. A. Juckett, Ph.D. Dissertation, SUNY at Albany, Sept 1974.
(17) (a) T. Cuvigny, M. Larcheveque, and H. Normant, *Bull. Soc. Chim. Fr.*, 1174 (1973); (b) D. G. Arapokos, *J. Am. Chem. Soc.*, **89**, 6794 (1967).
(18) (a) C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems", Marcel Dekker, New York, N.Y., 1970, Chapters 7 and 10; (b) D. E. Bartak and M. D. Hawley, *J. Am. Chem. Soc.*, **94**, 640 (1972).
(19) M. Szwarc, "Carbanions, Living Polymers, and Electron Transfer Processes", Interscience, New York, N.Y., 1968. The bimolecular rate constant for dimerization of 1,1-diphenylethylene radical anion in THF is 1.2×10^6 M^{-1} s^{-1} (p 369).
(20) Typical values of $\Delta G^{\ddagger}$ for proton transfer are of the order of 10–20 kcal/mol (ref 13) whereas electron transfer reactions have values in the range of 3–10 kcal/mol [L. M. Dorfman, *Acc. Chem. Res.*, **3**, 224 (1970)].
(21) M. Szwarc, Ed., "Ions and Ion Pairs in Organic Reactions," Wiley-Interscience, New York, N.Y., 1973.
(22) (a) R. L. Ward and S. I. Weissman, *J. Am. Chem. Soc.*, **79**, 2086 (1957); (b) M. T. Jones and S. I. Weissman, *ibid.*, **84**, 4269 (1962); (c) N. Hirota and S. I. Weissman, *ibid.*, **86**, 2537 (1964).
(23) S. Bank and B. Bockrath, *J. Am. Chem. Soc.*, **94**, 6076 (1972), and references cited therein.
(24) J. P. Mazaleyrat, *Can. J. Chem.*, **53**, 3158 (1975).
(25) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966).
(26) R. D. Guthrie, G. W. Pendygraf, and A. T. Young, *J. Am. Chem. Soc.*, **98**, 5877 (1976), and references cited therein.

Micellar Effects upon Dephosphorylation and Deacylation by Oximate Ions[1]

Clifford A. Bunton* and Yasuji Ihara[2]

Department of Chemistry, University of California, Santa Barbara, California, 93106

Received January 18, 1977

Micelles of cetyltrimethylammonium bromide (CTABr) are very effective catalysts of the reactions of *p*-nitrophenyl diphenyl phosphate and *p*-nitrophenyl 3-phenylpropionate with *p*-nitrobenz-, 2-, 3-, and 4-pyridine- and 2-quinolinecarbaldoximate ion. The rate enhancements depend upon hydrophobicity of the nucleophile and for reactions of the phosphate range from 140-fold for 3-pyridinecarbaldoxime to 3700-fold for 2-quinolinecarbaldoxime, based on concentration of oximate ion. The rate constants measured using oxime in excess over substrate are approximately twice those measured under "burst" conditions using substrate in large excess over oxime. Although metal cations increase the nucleophilicity of the oximes, they do not assist reaction in the presence of CTABr.

Oximes are reactivators of phosphorylated acetylcholine esterase and related enzymes,[3] and their reactions with organic phosphates model this reactivation. It has also been found that the introduction of hydrophobic groups into the oxime can increase in vivo activity. They are also efficient deacylating agents, and the hydrolyses of their acyl and phosphoryl derivatives have been studied extensively.[4,5]

Our interest was in the effect of micelles upon these reactions,[6] because reactions at such submicroscopic interfaces should be better than reactions in homogeneous solution as models for the biological reactions. Reactions of benzaldoximes with *p*-nitrophenyl carboxylates are catalyzed by cationic micelles of cetyltrimethylammonium bromide (CTABr). There are many examples of deacylations by functional micelles or comicelles.[7-9,11] We have examined reactions of pyridine-, quinoline-, and *p*-nitrobenzaldoxime (I) with *p*-nitrophenyl diphenyl phosphate (II) because the pyridine aldoximes have been used as reactivators of choline esterase deactivated by various toxic phosphates.[3] We also examined the reactions with *p*-nitrophenyl 3-phenylpropionate (III) for purposes of comparison:

$$\underset{\text{I}}{RCH{=}NOH} + \underset{\text{II}}{(PhO)_2POOC_6H_4NO_2} \longrightarrow RCH{=}NOPO(OPh)_2 + \bar{O}C_6H_4NO_2$$

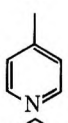
$$RCH{=}NOH + \underset{\text{III}}{PhCH_2CH_2COOC_6H_4NO_2} \longrightarrow RCH{=}NOCO{\cdot}CH_2CH_2Ph + \bar{O}C_6H_4NO_2$$

Ia, R− = O_2N−C$_6$H$_4$−

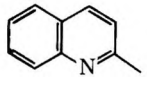
b, R− =

c, R− =

d, R− =



e, R− =



Experimental Section

Materials. The substrates, surfactants, and the pyridinecarbaldoximes were prepared or purified by standard methods.[12,13] *p*-Nitrobenzaldoxime (Ia), prepared from aldelyde and hydroxylamine and recrystallized (aqueous EtOH), had mp 130–131 °C (lit.[5a] 130 °C). 2-Quinolinecarbaldoxime, similarly prepared,[14,15] had mp 185–186 °C (lit.[15] 184, 185–186, 188–190 °C). All the aldoximes have the syn configuration.[5,14-16] *N*-Decylglycine hydrochloride and N^{α}-decanoylhistidine were prepared by standard methods.[11e,17]

Dissociation Constants. The pK_as of the aldoximes were determined spectrophotometrically in water and CTABr (Table I), using the following wavelengths: Ia, 350 nm; Ib, d, 290 nm; Ic, 275 nm; Ie, 325 nm. Our pK_a values in water agreed reasonably well with other data. As expected, incorporation in the cationic micelle reduced pK_a, but the decrease was largest for the hydrophobic 2-quinolinecarbaldoxime (Ie), and for the pyridine aldoximes it was largest for the 2 isomer (Ib). These differences reflect the way in which the oxime fits into the micelle, and similar differences are found for micellar effects upon the strengths of carboxylic acids.[19] These pK_a values are apparent because they depend upon the pH at the micellar surface and the extent of oxime incorporations.

Kinetics. The formation of *p*-nitrophenoxide ion was followed spectrophotometrically at 410 (pH 8.0 and 10.0) and 350 nm (pH 6.0) and in most experiments the oxime concentration was much larger than that of the substrate ($0.75–1.5 \times 10^{-5}$ M). The buffers follow: pH 6.0, 0.02 M acetate; pH 8.0, 0.015 M borate; pH 10.0, 0.01 M borate. The pH of the reaction mixture was adjusted to these values. All reactions were at 25.0 °C.

Products

Hydrolysis of *O*-acylpyridine oxime gives oxime, with no dehydration to nitrile,[5b] and similar observations have been made on phosphorylated oximes.[4] We found no evidence of nitrile formation in the reaction of 10^{-4} M *p*-nitrobenz- or 2-quinolinealdoxime phosphate with 10^{-4} M *p*-nitrophenyl diphenyl phosphate in 5×10^{-3} M CTABr at pH 10. The products were examined by TLC (Eastman silica gel 13181 in 20% MeOH–$CHCl_3$).

Results and Discussion

Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Oxime. Reaction in Absence of Surfactant. The second-order rate constants, k_2, are given in Table II, based on the concentration of oximate ion. The values at pH 10.0 are more reliable than those at pH 8.0 where only a small amount of the oxime is ionized to oximate and allowance has to be made for an appreciable contribution from reaction with water. All these oximate ions have very similar reactivities toward *p*-nitrophenyl diphenyl phosphate.

Reactions in CTABr. The reactions of the oximate ions with *p*-nitrophenyl diphenyl phosphate are very strongly catalyzed by cationic micelles (Figures 1 and 2). These rate constants are calculated using the concentrations of oximate ions and allowance is made for the reaction in the absence of oxime. The maximum rate enhancements (calculated in terms of concentrations of oximate ions) at pH 10.0 are in Table III, together with the concentration of CTABr for maximum rate enhancement.

The larger rate enhancements of the reactions of the *p*-nitrobenzaldoximate and 2-quinolinecarbaldoximate ion accord with the larger micellar effect upon the acid dissociations of the corresponding oximes as compared with those upon the

Table I. pK_a of the Oximes[a]

10^3[CTABr], M	Ia[b]	Ib[c]	Ic[d]	Id[e]	Ie[f]
	9.95 (9.91)	10.05	10.23	9.88	(9.79)
0.10	9.90 (9.90)	10.02		9.86	(9.74)
1.00	9.73 (9.59)	10.00	10.21	9.85	(8.88)
3.00	9.53 (9.34)				
5.00	9.47 (9.30)	9.88	10.18	9.82	(8.69)

[a] At 25.0 °C with 10^{-3} M oxime unless specified; values in parentheses are for 10^{-4} M oxime. Literature values: Ia, 10.36 in 12% EtOH;[5a] Ib, 10.4,[16a] 10.14,[18] Ic, 10.2,[18a] 10.36; [16b] Id, 10.2,[16a] 9.99.[16a] [b] Registry no., 1129-37-9. [c] Registry no., 873-69-8. [d] Registry no., 1193-92-6. [e] Registry no., 696-54-8. [f] Registry no., 1131-68-6.

Table II. Reactions with *p*-Nitrophenyl Diphenyl Phosphate in Water[a]

Oxime	k_2, M^{-1} s^{-1}
Ia	1.38 (1.00)
Ib	1.60 (1.26)
Ic	1.58 (1.31)
Id	1.16 (1.22)
Ie	1.87

[a] At 25.0 °C, with 10^{-4}–10^{-3}M oximate and pH 10.0. (The values in parentheses are at pH 8.0.)

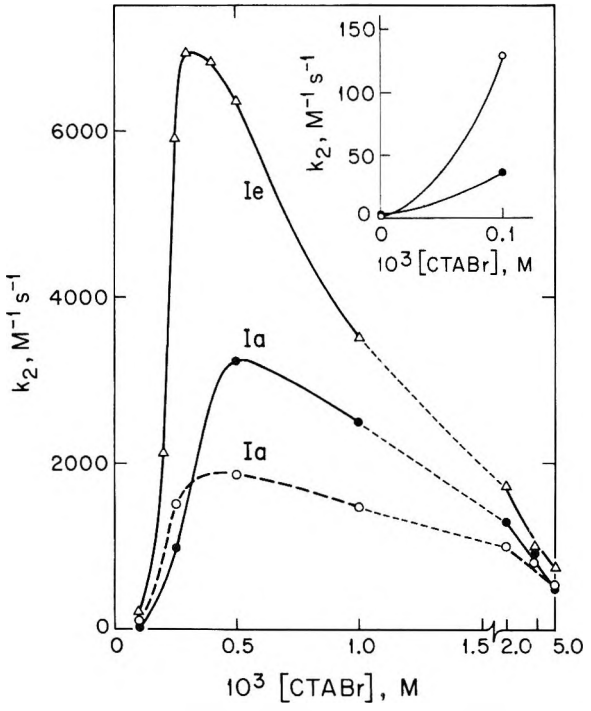


Figure 1. Reactions of *p*-nitrophenyl diphenyl phosphate with *p*-nitrobenz- and 2-quinolinealdoximate ions (Ia and Ie, respectively). Solid points at pH 10, open points at pH 8.0.

pyridine oximes (Table I), and the larger effect found with the 2-quinolinecarbaldoximate ion relative to the pyridine derivatives is typical of the beneficial effects of hydrophobicity upon micellar catalysis of nucleophilic attack.[7-9].

We include data for reaction at pH 8.0 in Figures 1 and 2 for purposes of comparison, and to illustrate the micellar catalysis at a pH close to that of physiological conditions. Comparison of micellar catalysis at the different pH is artificial, because we do not know the pH at the micellar surface,[20a] and the second-order rate constants at pH 8.0, based on our apparent pK_a values (Table I), are smaller than those at pH 10.0.

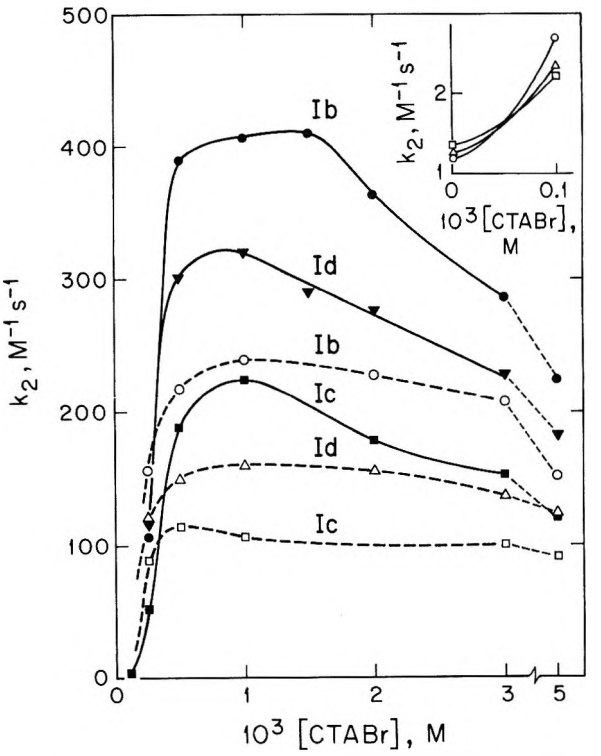


Figure 2. Reactions of *p*-nitrophenyl diphenyl phosphate with pyridinecarbaldoximate ions: 2-Ib; 3-Ic; 4-Id. Solid points at pH 10, open points at pH 8.0.

Table III. Micellar Catalysis of Reaction of *p*-Nitrophenyl Diphenyl Phosphate with Oximate Ions[a]

Nucleophile	k_2, M^{-1} s^{-1}	k_{rel}[b]	10^3[CTABr] max, M
p-Nitrobenzaldoximate	3230	2340	0.5
2-Pyridinecarbaldoximate	410	254	1.5
3-Pyridinecarbaldoximate	225	142	1.0
4-Pyridinecarbaldoximate	319	275	1.0
2-Quinolinecarbaldoximate	6940	3700	0.3

[a] At 25.0 °C, pH 10. [b] Calculated using rate constants at pH 10 in water and CTABr.

Table IV. Second-Order Rate Constants for Reaction of *p*-Nitrophenyl 3-Phenylpropionate[a]

	$10^{-2}k_2$, M^{-1} s^{-1}		
Nucleophile	H_2O	CTABr	k_{rel}
p-Nitrobenzaldoximate[b]	0.63	1380 (0.5)	2210
2-Pyridinecarbaldoximate[c]	0.78	239 (1.0)	307
3-Pyridinecarbaldoximate[c]	0.74	112 (1.0)	152
4-Pyridinecarbaldoximate[c]	0.55	155 (1.0)	283
2-Quinolinecarbaldoximate[d]	1.17	2230 (0.3)	1910

[a] At 25.0 °C; pH 8.0. The values in parentheses are the concentrations of CTABr (mM) for maximum catalysis. [b] 10^{-4} M. [c] 10^{-3} M. [d] 5×10^{-5} M.

Reaction of *p*-Nitrophenyl 3-Phenylpropionate with Oxime. Because of the fast deacylation at pH 10, we followed these reactions only at pH 8.0. The second-order rate constants for reactions with oximate ions are in Table IV, and the dependence on CTABr is shown in Figure 3 (allowance is made for reaction in the absence of oxime).

The rate constants for reaction of both the carboxylate and

Table V. Burst Kinetics[a]

Substrate	$10^5[S_0]$, M	Oxime $10^5[N_0]$, M	b, s^{-1}	$10^5\pi$, M	k_{II}, $M^{-1}\ s^{-1}$	10^3k_3, s^{-1}
III	12.0	Ie 2.5	0.31	2.67	2670	~0
III	12.0	Ie 5.0	0.32	4.97	2670	~2
II	10.0	Ie 2.5	0.0036	2.30	35	~0.2
II	10.0	Ie 5.0	0.0039	4.09	35	~0.4
II[b]	10.0	Ie 2.5	0.052	2.30	499	2.1
II[b]	10.0	Ie 5.0	0.043	4.62	417	1.6
II[b]	10.0	Ia 2.5	0.022	2.37	213	0.6
II[b]	10.0	Ia 5.0	0.019	4.15	178	1.6

[a] At 25.0 °C, 5×10^{-3} M CTABr and pH 8.0 unless specified. [b] pH 10.0.

Table VI. Secondary Release of *p*-Nitrophenoxide Ion[a]

Substrate	10^5 [substrate], M	Oxime	10^5 [oxime], M	10^3k_ψ, s^{-1}
III	1.5			1.6
III	12.0			2.2
III	12.0	Ie	2.5	3.4
III	12.0	Ie	5.0	3.7
II	1.5			0.066
II	10.0			0.057
II	10.0	Ia	2.5	0.078
II	10.0	Ia	5.0	0.077
II	10.0	Ie	2.5	0.062
II	10.0	Ie	5.0	0.063

[a] At 2.5 °C, pH 8.0 and 5×10^{-3} M CTABr.

phosphate ester increase sharply with increasing CTABr at low surfactant concentration when micelles begin to form (Figures 1–3, inserts); they rise to maxima and then decrease steadily. This behavior is common for bimolecular micellar catalyzed reactions and can be rationalized in terms of the partitioning of the two reagents between aqueous and micellar phases.[7-10,20]

In water there is little difference between the reactivities of the various oximate ions, and for reaction in CTABr the pattern is similar to that found with *p*-nitrophenyl diphenyl phosphate (Table III) except that the rate enhancements by CTABr are very similar for *p*-nitrobenzaldoximate and 2-quinolinecarbaldoximate ion.

"Burst" Experiments. In most of our experiments the aldoxime was in large excess over the substrate, but we also examined reaction in CTABr using excess substrate, so that there was a rapid evolution of *p*-nitrophenoxide ion followed by a slow reaction as the phosphorylated or acylated oxime was hydrolyzed to regenerate the nucleophile.

$$\mathrm{RCH{=}N\overline{O}} + \quad + (\mathrm{PhO})_2\mathrm{PO.OAr} \xrightarrow{k_{II}} \mathrm{RCH{=}NOH}$$

$$\mathrm{O\overline{A}r} + \mathrm{RCH{=}NOPO(OPh)_2} \xrightarrow[\mathrm{H_2O}]{k_3} \mathrm{RCH{=}N\overline{O}}$$

A corresponding scheme can be written for deacylation, and k_{II} is calculated in terms of the total concentration of oxime.

The kinetic treatment is that of Bender and has been used by others.[22,23] If the initial concentrations of nucleophile and substrate are $[N_0]$ and $[S_0]$, respectively, π is the absorbance under steady-state conditions, extrapolated to time zero, t_0, and ΔA is the difference between the observed and extrapolated absorbances at time t, we obtain

$$\Delta A = \pi e^{-bt} \quad (1)$$

$$k_{II} = b\pi^{1/2}/[S_0][N_0]^{1/2} \quad (2)$$

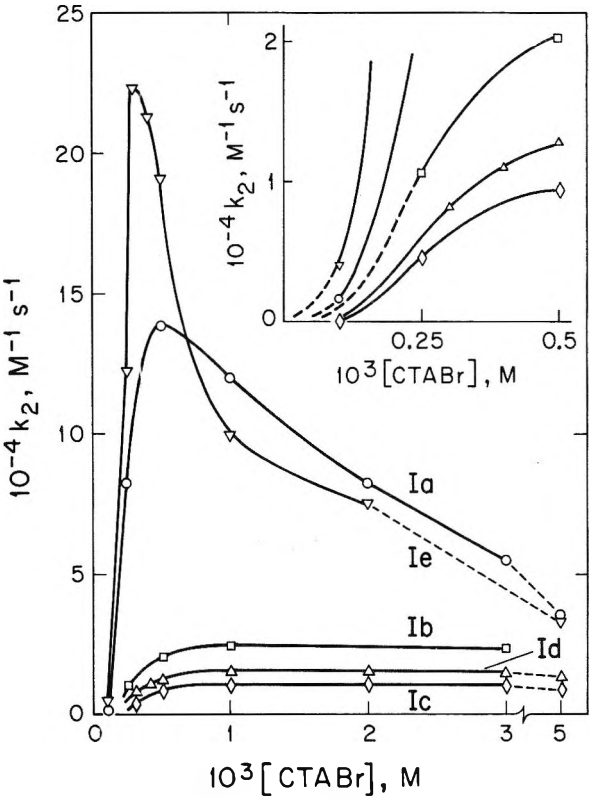


Figure 3. Reactions of *p*-nitrophenyl 3-phenylpropionate with oximate ions at pH 8.0.

Table VII. Second-Order Rate Constants Obtained under Different Conditions[a]

Substrate	Nucleophile	k_2, $M^{-1}\ s^{-1}$ "Burst"	k_2, $M^{-1}\ s^{-1}$ First order
II	Ia	320	510
II	Ie	480	760
III	Ie	16 000	34 600

[a] At 25.0 °C in 5×10^{-3} M CTABr; the reactions of the phosphate (II) were at pH 10.0 and those of the carboxylic ester (III) were at pH 8.0.

$$k_3 = b - k_{II}[S_0] \quad (3)$$

The values of b are obtained from the logarithmic form of eq 1 and give the parameters in Table V.

This treatment does not in our system give good values of k_3, which is calculated as the small difference between two larger numbers, so we also followed the secondary release of *p*-nitrophenoxide ion after establishment of steady-state conditions using substrate in excess over the oxime. Under these conditions some reactions are slow, and we then calcu-

Table VIII. Effect of Zinc (II) upon Deacylation[a]

		Nucleophile					
10^3[CTABr], M		Ib	Zn:Ib[c] 1:1	Zn:Ib[d] 1:2	Ie[b]	Zn:Ie[b,e] 1:1	Ia
	0.00095	0.0044	0.29		0.0046	0.0075	0.0034
0.25							0.90
0.50							38.4
1.00	0.034	5.59	3.11	3.83	37.6	36.9	58.3
2.00		5.67	3.19	3.47	31.9	28.8	53.3
3.00		6.01	3.29	3.53	21.7	20.5	43.3
5.00		4.60	2.75	3.40			34.0

[a] Values of 10^3k_ψ, s^{-1} at 25.0 °C, pH 6.0, 1.5×10^{-5} M substrate and added Zn(NO). The oxime concentration was 10^{-3} M unless specified. [b] 10^{-4} M. [c] Registry no., 35038-18-7. [d] Registry no., 15661-88-8. [e] Registry no., 62708-13-8.

Table IX. Effects of *N*-Decylglycine on Deacylation[a]

	Nucleophile	
10^4[$C_{10}H_{21}NHCH_2CO_2H$], M	Ib	Zn Ib
	5.59 (0.29)	3.11
2.5	5.23 (0.30)	4.63
5.0	6.23 (0.34)	5.50
7.0		5.80

[a] Values of 10^3k_ψ, s^{-1}, 10^{-3} CTABr, pH 6.0 and 1:1 zinc complex. The values in parentheses are in water.

Table X. Effect of Zinc(II) upon Dephosphorylation[a]

	10^4k_ψ, s^{-1}	
Nucleophile	H_2O	10^{-3} M CTABr
	0.020	1.48
10^{-3} M Ib		2.19
5×10^{-3} M Ib	0.028	
10^{-3} M Zn Ib		1.20
5×10^{-3} M Zn Ib	0.041	
10^{-4} M Ie		5.27
10^{-3} M Ia		6.39

[a] At 25.0 °C, pH 6.0.

lated the first-order rate constants by Guggenheim's method. These first-order rate constants (Table VI) are not much larger than those for the spontaneous hydrolysis in the absence of oxime, showing that the first formed oxime esters are hydrolyzed slowly, so that turnover of the oxime does not occur rapidly after the initial "burst" reaction.

One problem in following the initial burst of *p*-nitrophenoxide ion is that this has to be done, of necessity, using substrate in excess over the nucleophilic oxime,[24] whereas more usually the nucleophile is in large excess and reaction follows first-order kinetics. In Table VII, we compare the second-order rate constants, obtained from the "burst" kinetics and those with oximes in excess, calculated in terms of the total concentration of oximate ion. Consistently we obtain larger values of k_2 when we use oxime in excess, but the differences are not large, suggesting that at least for these reactions large changes in the reagent concentrations cause no major problems. The second-order rate constants in Table VII are lower than those given in Tables III and IV because the "burst" experiments were not carried out at the optimum surfactant concentration, but at a higher concentration where the reagents should be wholly in the micelles in order to minimize changes in micellar structure caused by high concentrations of the esters.

Effects of Structure of the Nucleophiles. Micellar catalysis of a bimolecular reaction requires that both reagents be incorporated into the micelles and the rate of the micellar catalyzed reaction depends upon the reactant concentrations and the second-order rate constant in the micelle. In water there are only small differences in the nucleophilicities of the oximate ions (Tables II and IV) suggesting that differences in k_{rel} (Tables III and IV) depend largely upon differences in micellar incorporation of the various oximate ions. This rationalization readily fits the results for the pyridine- and quinolinecarbaldoximes. It also suggests that the *p*-nitro group does not inhibit incorporation of *p*-nitrobenzaldoximate ion into the micelle, even though the hydrophilic groups (oximate- and nitro-) are at opposite ends of the ion so that if one is to be at the micellar surface the other would be expected to be in the micellar core. The micellar effects upon the apparent pK_a (Table I) are largest for *p*-nitrobenz- and 2-quinolinealdoxime as expected if these oximes are more effectively incorporated into the micelle than the pyridine aldoximes, so that both the rate and dissociation constants depend in similar ways upon the orientation of the oxime in the micelle.

It is customary to calculate micellar rate enhancements from the data at the rate maxima, but this approach is not particularly satisfactory because the rate–surfactant concentration profiles depend upon the distribution of both reagents between water and the micelles[10,20] so that we do not attach more than qualitative significance to the values of k_{rel} (Tables III and IV). However, these uncertainties appear to be most serious when one reagent is hydrophobic and the other hydrophilic, whereas in our system both nucleophile and substrate are relatively hydrophobic.

Reactions in the Presence of Zinc Ions. The zinc complex of 2-pyridinecarbaldoxime and other pyridine derivatives is a good nucleophile toward carboxylic esters,[18] and the role of zinc in activating carboxypeptidase has been reviewed.[25] However, metal chelates of 2-pyridinecarbaldoxime are not effective reactivators of phosphorylated acetylcholine esterase.[26] We have examined the effects of some zinc–aldoxime complexes in deacylation and dephosphorylation in the presence and absence of CTABr at pH 6.0. (The pK_a of these complexes is ca. 6.5.[18])

In agreement with existing evidence, these zinc complexes are effective reagents for the deacylation of *p*-nitrophenyl 3-phenylpropionate (III), but the rate enhancements by added CTABr were less than with the oxime alone (Table VIII), possibly because the cationic complex was not taken up readily by the micelle. The results with *p*-nitrobenzaldoxime (Ia) with no added zinc show that the pattern of the micellar catalysis is similar to those found at higher pH.

We also examined the effect of *N*-decylglycine on the deacylations (Table IX), because it seemed possible that additional chelation with the hydrophobic *N*-decylglycine might make it easier for the zinc complex to be taken up by the cationic micelle. The rate enhancements were small, and only slightly larger than those in the absence of zinc or CTABr, so

Table XI. Reaction of *p*-Nitrophenyl 3-Phenylpropionate in Comicelles of N^{α}-Decanoylhistidine

10^4[IV],[b] M	10^4[CTABr],[c] M	10^4[$Zn(NO_3)_2$],[d] M	10^3k_{ψ}, s^{-1}
1.0			0.14
1.0		1.0	0.15
1.0	1.0		1.71
1.0	1.0	1.0	2.70
5.0			0.27
5.0	50.0		11.2
5.0	50.0	5.0	9.48

[a] At 25.0 °C and pH 8.00. [b] Registry no., 55258-10-1. [c] Registry no., 57-09-0. [d] Registry no., 7779-88-6.

Table XII. Reactions in Comicelles of CTABr and N^{α}-Decanoylhistidine[a]

Substrate	Metal ion	10^3k_{ψ}, s^{-1}
II		0.58
II	0.5 mM $Zn(NO_3)_2$	0.64
II	0.5 mM $MgCl_2$	0.61
III		33.6[b]
III	0.1 mM $Zn(NO_3)_2$	46.0[b,c]
III	0.1 mM $MgCl_2$	39.3[b]
III	0.1 mM $Ca(NO_3)_2$	36.0[b]
III	0.1 mM Cd $(NO_3)_2$	31.9[b,c]
III	0.1 mM $CuSO_4$	54.3[b,c]
III	0.2 mM KCl	36.3[b]
III		33.1
III	0.5 mM $Zn(NO_3)_2$	36.6
III	0.5 mM $MgCl_2$	34.0

[a] At 25.0 °C and pH 8.0 with 5×10^{-3} M CTABr and decanoylhistidine unless specified. [b] 5×10^{-4} M CTABr and decanoylhistidine. [c] Precipitation occurred during reaction.

that any effects of *N*-decylglycine are relatively unimportant.

At pH 6.0 the reactions of *p*-nitrophenyl diphenyl phosphate are only slightly assisted by added aldoximes or their zinc complexes (Table X), which is reminiscent of the results with phosphorylated acetylcholineesterase.[26]

Reactions in the Presence of N^{α}-Decanoylhistidine (IV). Functional micelles or comicelles containing an imidazole moiety are effective deacylating and dephosphorylating agents. We carried out a few preliminary experiments (Tables XI and XII). When the surfactant concentrations were reduced so that precipitation did not occur we found only slight rate enhancement with added zinc nitrate, but in agreement with earlier evidence the catalytic effectiveness of hydrophobic histidine derivatives is strikingly increased by comicellization with CTABr.[11] We did not examine the kinetic effects of other metal ions systematically, but they appear to be small (Table XII).

Registry No.—II, 10359-36-1; III, 17895-71-5; *p*-nitrophenoxide ion, 14609-74-6; zinc, 7440-66-6; *N*-decylglycine, 20933-56-6.

References and Notes

(1) Support of this work by the National Science Foundation and the National institute of Arthritis, Metabolism and Digestive Diseases is gratefully acknowledged.
(2) Laboratory of Dyeing and Surface Chemistry, Yamaguchi Women's University, Yamaguchi, Japan.
(3) I. B. Wilson, *Biochim. Biophys. Acta*, **27**, 196 (1958); W. Cohen and B. R. Erlanger, *J. Am. Chem. Soc.*, **82**, 3928 (1960); A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958); R. Zech, H. Engelhard, and W.-D. Erdmann, *Biochim. Biophys. Acta*, **128**, 363 (1966); N. Bodor, E. Shex, and T. Higuchi, *Science*, **190**, 155 (1975).
(4) A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956); R. F. Hudson and L. Keay, *ibid.*, 1859 (1960); B. E. Hackley, G. M. Steinberg, and J. C. Lamb, *Arch. Biochem. Biophys.*, **80**, 211 (1959); J. H. Blanch and J. Anderson, *J. Chem. Soc.*, 169 (1968).
(5) (a) A. Raoult and M. Vilkas, *Bull. Soc. Chim. Fr.*, 3315 (1968); (b) J. H. Blanch and O. T. Onsager, *J. Chem. Soc.*, 3729, 3734 (1965); J. H. Blanch, *ibid.*, 167 (1968).
(6) For discussions of micellar catalysis see ref 7–9.
(7) E. H. Cordes and R. B. Dunlap, *Acc. Chem. Res.*, **2**, 329 (1969); E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973).
(8) E. J. Fendler and J. H. Fendler, *Adv. Phys. Org. Chem.*, **8**, 271 (1970).
(9) C. A. Bunton, *Prog. Solid State Chem.*, **8**, 239 (1973).
(10) A. K. Yatsimirski, K. Martinek, and I. V. Berezin, *Tetrahedron*, **27**, 2855 (1971).
(11) (a) C. Gitler and A. Ochoa-Solano, *J. Am. Chem. Soc.*, **90**, 5004 (1968); (b) P. Heitmann, R. Husung-Bublitz, and H. J. Zunft, *Tetrahedron*, **30**, 4137 (1974); J. M. Brown and C. A. Bunton, *J. Chem. Soc., Chem. Commun.*, 969 (1974); R. A. Moss, R. C. Nahas, S. Ramaswami, and W. J. Sanders, *Tetrahedron Lett.*, 3379 (1975).
(12) C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34**, 773 (1969).
(13) I. Vogel, "Elementary Practical Organic Chemistry", Part 2, Longmans, Green and Co., New York, N.Y., 1957.
(14) H. Kaplan, *J. Am. Chem. Soc.*, **63**, 2654 (1941).
(15) D. L. Hammick, *J. Chem. Soc.*, 1303 (1926); K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **18**, 1 (1964); C. E. Kwartler and H. G. Lindwall, *J. Am. Chem. Soc.*, **59**, 524 (1937).
(16) (a) S. Ginsburg and I. B. Wilson, *J. Am. Chem. Soc.*, **79**, 481 (1957); (b) S. F. Mason, *J. Chem. Soc.*, 22 (1960).
(17) S. Sakakibana, N. Kunata, and S. Komori, *J. Chem. Soc. Jpn., Ind. Chem. Sect.*, **60**, 1294 (1957).
(18) (a) R. Breslow and D. Chipman, *J. Am. Chem. Soc.*, **87**, 4195 (1965); R. Breslow, D. E. McClune, R. S. Brown, and J. Eisenbach, *ibid.*, **97**, 194 (1975); (b) P. Wooley, *J. Chem. Soc., Chem. Commun.*, 579 (1975).
(19) C. A. Bunton and M. J. Minch, *J. Phys. Chem.*, **78**, 1490 (1974).
(20) (a) C. A. Bunton and B. Wolfe, *J. Am. Chem. Soc.*, **95**, 3742 (1973); (b) L. S. Romsted, Symposium on Micellization, Solubilization and Microemulsions, Albany, N.Y., Aug 1976.
(21) M. L. Bender and T. H. Marshall, *J. Am. Chem. Soc.*, **90**, 201 (1968).
(22) T. Kunitake and Y. Okahata, *Bioorg. Chem.*, **4**, 136 (1975).
(23) See ref 24 for other examples of burst kinetics using substrate in excess over micellized nucleophile.
(24) W. Tagaki, M. Chigira, T. Amada, and Y. Yano, *J. Chem. Soc., Chem. Commun.*, 219 (1972); K. Martinek, A. V. Levashov, and I. V. Berezin, *Tetrahedron Lett.*, 1275 (1975).
(25) E. T. Kaiser and B. L. Kaiser, *Acc. Chem. Res.*, **5**, 219 (1972); W. N. Lipscomb, *Tetrahedron*, **30**, 1725 (1974).
(26) S. Bouton and A. Beckett, *J. Pharm. Sci.*, **53**, 55 (1964).

Palladium(II)-Induced Alkylation of Styrenes. Kinetics, Stereochemistry, and Mechanism

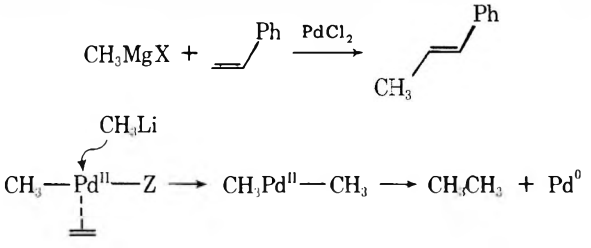
Shun-Ichi Murahashi,* Masaaki Yamamura, and Nobuaki Mita

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka, Japan 560

Received March 22, 1977

Reaction of styrene with methyllithium in the presence of Pd(II) complexes gave an anti-Markownikoff product, β-methylstyrene, whose yield increases in the order Cl (3%) < OAc (75%) < acac (90%). A competitive method has been used to measure the relative reactivities of this reaction toward a series of styrenes. The data correlate well ($\gamma = 0.98$) with the Hammett σ constants yielding a ρ value of $+2.68 \pm 0.189$, indicating that in the transition state there is considerable negative charge at the benzylic carbon atom, resulting from nucleophilic attack of methyl moiety. *cis*- and *trans*-β-deuteriostyrenes can be converted into *trans*-β-methylstyrene and *cis*-β-deuterio-*trans*-β-methylstyrene, respectively, with inversion of configuration. The kinetic and stereochemical results demonstrate that methylation of styrene proceeds via a cis addition of methylpalladium species followed by a cis elimination of hydridopalladium species. In contrast to this, reaction of styrene with a softer carbanion, diethyl sodiomalonate, afforded a Markownikoff product, α-methyl benzylidenemalonate. Nucleophilic attack of the carbanion toward the α position of palladium-coordinated styrene directly on the side remote from palladium seems to occur.

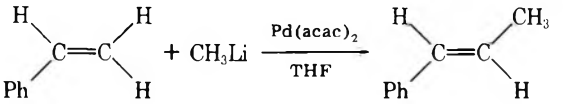
Palladium alkyls, which are prepared in situ by the exchange reaction of the corresponding metal alkyl compounds with palladium salts, has been reported to react with olefins to give alkyl olefins.[1] Direct alkylation of olefins by Grignard reagents in the presence of palladium chloride was attempted, but its yield was extremely poor (less than 5%).[2] This low yield can be rationalized by assuming that the reaction of methylpalladium species with styrene proceeds slower than that with excess methylmagnesium bromide, giving ethane and palladium metal. If this is the case, retardation of the latter reaction[3] and promotion of the former[4] can accomplish a palladium-induced direct alkylation of olefins with Grignard reagents or alkyllithium compounds. Increasing the electron density on palladium would satisfy these conditions. Indeed, we have found that the reaction of styrenes with methyllithium affords methylstyrenes in high yields upon using a palladium complex bearing more basic ligands. Thus, styrene can be converted into β-methylstyrene in 90% yield on treatment with methyllithium in the presence of palladium acetylacetonate.



Studies on the palladium(II)-induced reaction of nucleophiles such as hydroxide,[5] acetate,[6] chloride,[7] amide,[8] methoxide,[9] and methoxycarbonyl[10] with olefins have been extensively investigated, and hence considerable understanding has been obtained. On the other hand, concerning the reaction of carbanionoids with a simple olefin, studies have focused on arylpalladium species,[11-13] although the reaction of carbanionoid with preformed olefin complexes which have a second olefinic group has been reported.[14] We report here the results of kinetics and stereochemical studies of palladium(II)-induced methylation of styrene giving β-methylstyrene and discuss the mechanism in relation to the reaction of styrene with a softer carbanion such as diethylmalonate anion, giving a Markownikoff-type product.

Results and Discussion

Reaction of Styrenes with Methyllithium in the Presence of Pd(II) Salts. Reaction of styrene and methyllithium



(90%)

in the presence of a palladium(II) complex in THF at room temperature gave β-methylstyrene. Among various palladium(II) complexes palladium acetylacetonate gave the best yield of β-methylstyrene. The yields are dependent on the basicity of anionic ligands of the palladium complexes and increase in the order Cl (3%) < OAc (75%) < acac (90%).[15] The excess methyllithium was required to neutralize the HX (or HPdX). Addition of phosphines or phosphites as an additional ligand retarded the reaction completely, and the starting materials were recovered. This is consistent with the fact that triphenylphosphine, for example, has a higher dissociation energy from palladium than olefins by 10 kcal/mol.[16]

The results of the reaction of substituted styrenes summarized in Table I show the tendency that styrenes bearing a strong electron-withdrawing substituent are converted into β-methylstyrene in a higher yield. For quantitative treatment of the substituted effect, rate-constant ratios were determined by a competitive method in which two olefins were allowed to compete for a limited amount of methylating reagent. For a system in which a methylating reagent adds irreversibly in a single stage to competing olefins A and B to form intermediates X and Y, respectively, which are quantitatively converted into products by β-elimination of hydridopalladium species, the reaction can be represented as

$$A + [CH_3M] \xrightarrow{k_a} X \quad (1)$$

$$B + [CH_3M] \xrightarrow{k_b} Y \quad (2)$$

The rate constant ratio (k_{rel}) is given by

$$k_{rel} = \frac{k_b}{k_a} = \frac{\log [B^0]/[B]}{\log [A^0]/[A]} \quad (3)$$

where $[A^0]$ and $[A]$ represent respectively the initial and final concentrations of olefin A, and similarly for B. In experiments, when the extent of reaction is low, eq 3 reduces to

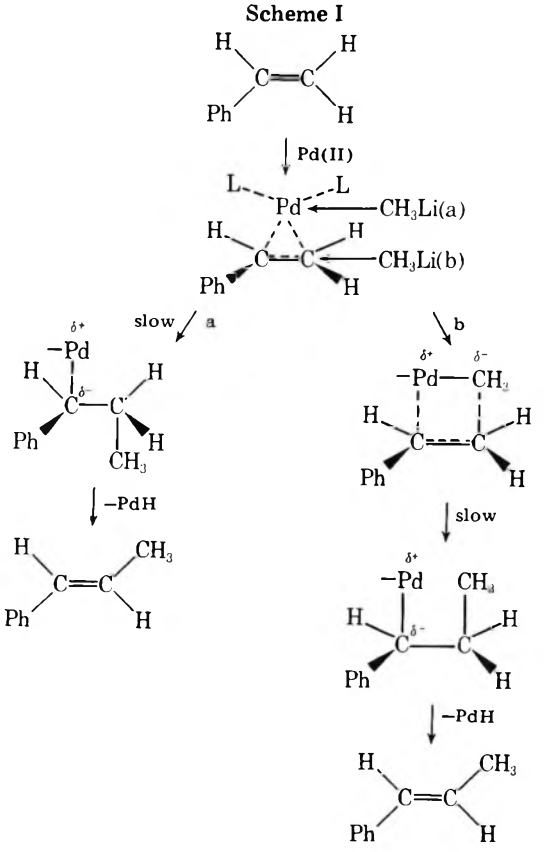
$$k_{rel} = \frac{[Y]}{[X]}\frac{[A]}{[B]} \quad (4)$$

The validity of this equation depends on maintaining an essentially constant ratio of the olefins under the reaction conditions. This point was confirmed by removal of aliquots from

the reaction mixture of styrene vs. *p*-chlorostyrene at 10, 30, 60, 120, and 180 min and observing that the relative ratio of styrenes and products did not change with time. In Figure 1 the values of log k_x/k_a for substituted styrenes are plotted against the Hammett σ constants (see Table I). A good linear relationship (correlation coefficient γ = 0.98) is obtained leading to a value for ρ of 2.68 ± 0.189. Poorer correlation was obtained when σ^+ constants were used, indicating the absence of a strong resonance contribution to stabilization.[17] The ^{13}C NMR spectroscopic studies of a series of para-substituted styrene–palladium complexes indicated that electron donor groups increase the coordination ability of the styrene.[18,19] Further, calorimetric investigation showed that the relative displacement energies for palladium generally increase when electron-donating substituents are present on the olefin.[16] Therefore, the substituent effect observed indicates that coordination of olefin to palladium is not the rate-determining step. However, the value of K for a preequilibrium step involving π complex will also depend on electronic factors.[19] This means that the value ρ is a combination of ρ for this equilibrium and a ρ for alkylpalladation. Therefore, the ρ value we observed is an underestimate of the true ρ value for alkylpalladation. The correlation obtained in the present work implies that in the transition state there is considerable negative charge at the benzylic carbon atom, presumably resulting from nucleophilic attack of methyl moiety toward an asymmetric partial delocalization of the π electrons of the double bond.

One can consider two paths, whether bonding of the attacking reagent occurs initially at the metal with subsequent insertion of methylpalladium species to an olefin (a) or directly at the carbon of an olefin (b) (Scheme I). These require that

Scheme I



methylpalladium species[20] or methyllithium initially approaches styrenes displaced toward not the α carbon but the β carbon atom. Apparently palladium is effectively the smallest part of the organopalladium species. The relatively long palladium–carbon bond and the square planar geometry about the palladium combine to produce a relatively small

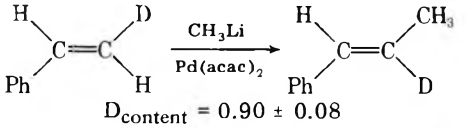
Table I. Relative Rate Constants for the Reaction of Substituted Styrenes with Methyllithium in the Presence of Palladium Acetylacetonate

Registry no.	Substituent	Yield,[a] %	σ	k_x/k_a[b]
2039-85-2	*m*-Cl	80	+0.373	13.4
1073-67-2	*p*-Cl	99	+0.227	7.69
100-42-5	H	90	0.00	1.00
622-97-9	*p*-CH_3	60	−0.70	0.718
637-69-4	*p*-OCH_3	15	−0.268	0.240

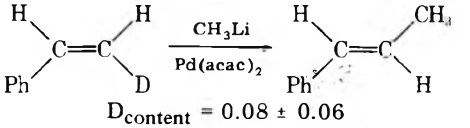
[a] Yields based on palladium were determined by GLC; see Experimental Section. [b] Relative rates of substituted styrene (k_x) to that of styrene (k_a); see Experimental Section.

effective size for the palladium group compared with the usual trigonal or tetragonal carbon groups.[21] Further, it is striking that the value obtained, 2.7, is virtually identical with the value of ρ (4.0) obtained in the study of relative exchange rates of substituted α-tritiotoluenes toward lithium cyclohexylamide in cyclohexylamine.[22] Although the sign and magnitude of ρ in some organometallic systems are a function of many factors and vary in an unpredictable manner,[23] the conclusion to be drawn from the present Hammett study, therefore, is that the nucleophilic attack of methyl moiety is the rate-determining step and its direction is influenced by both electronic and steric factors.

From the kinetic study one cannot distinguish these two paths (a and b), and hence we undertook an examination of the stereochemistry of the reaction of methyllithium with *cis*- and *trans*-β-deuteriostyrenes.[24] Considerable investigation about the stereochemistry of nucleophilic attack of carbanionoids toward olefins have been carried out; however, most of these have involved olefins that are part of a chelating ligand containing a second olefinic group,[14] and it has become apparent that the stereochemistry of nucleophilic attack on chelating olefins is not necessarily the same as that observed for unidentate olefins.[25] The reaction of *trans*-β-deuteriostyrene with methyllithium under these conditions gave *cis*-β-deuterio-*trans*-β-methylstyrene along with a small amount of *trans*-β-methylstyrene. The NMR analysis indicated that the component of the deuteriated compound is 90 ± 8%. Similarly, the reaction of *cis*-β-deuteriostyrene gave *trans*-β-methylstyrene whose deuterium content was 8%. These results clearly indicate that the β-cis hydrogen or deuterium are substituted by methyl group giving *trans*-β-methylstyrene, and hence the reaction proceeds with inversion of configuration. The major products in both of the above reactions are ones expected from a cis-addition–cis-elimination mechanism. Since elimination of "hydridopalladium species" has



$D_{content}$ = 0.90 ± 0.08

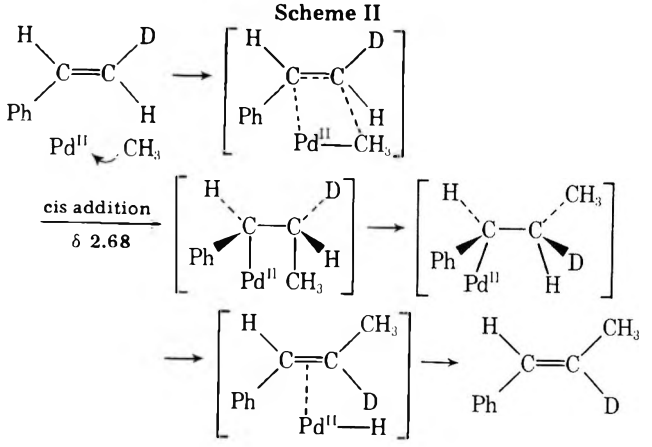


$D_{content}$ = 0.08 ± 0.06

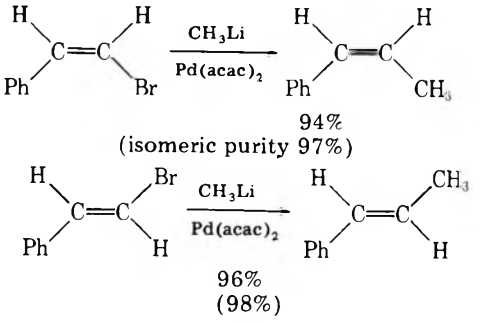
been accepted to be cis, the trans-addition mechanism should give a product with retention of configuration. Therefore, a cis addition of methylpalladium species to olefin followed by a covalent (four-centered) cis elimination of hydridopalladium species depicted in Scheme II seems to best explain the results.[21]

Reaction of β-Bromostyrene with Methyllithium in the Presence of Pd(II) Salts. Should the reaction of β-bromostryene with methyllithium proceeds with the above addi-

Scheme II



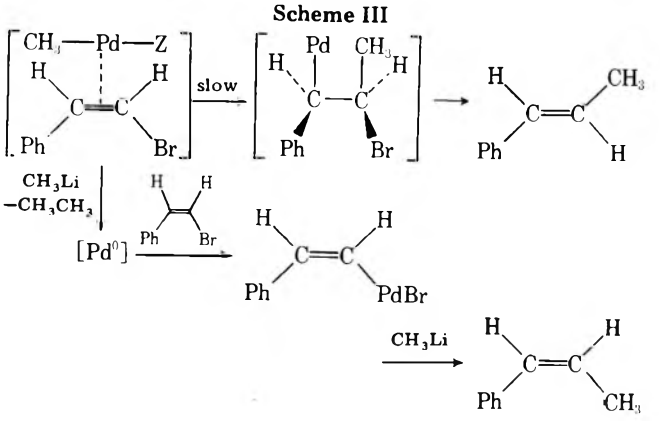
tion–elimination mechanism, the bromo group can be substituted by methyl group with inversion of configuration, since elimination of bromopalladium species occurs more readily than that of hydridopalladium species.[26] The results are, however, opposite to the expected one, and the bromo group was substituted by methyl group with retention of configuration. Thus, reaction of *cis*-β-bromostyrene with methyllithium in the presence of $Pd(acac)_2$ gave *cis*-β-methylstyrene in 94% yield along with *trans*-β-methylstyrene (3%). Similarly, reaction of *trans*-β-bromostyrene afforded *trans*-β-methylstyrene in 96% yield in addition to 2% of *cis*-β-methylstyrene.



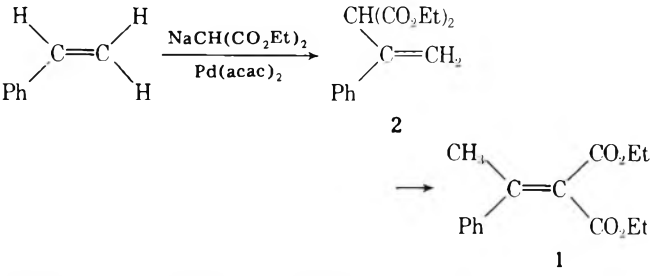
These results can be rationalized by assuming that the addition of the methylpalladium species toward β-bromostyrene is simply retarded by steric effects,[27] and hence nucleophilic attack of methyllithium toward the methylpalladium species occurs, producing zerovalent palladium species,[3] which then catalyzes methylation of the vinyl halides with methyllithium by the oxidative addition–reductive elimination mechanism.[28] Therefore, it should be noted that the stereochemistry of the methylation of styrenes depends upon the valency of palladium.

Reaction of Styrene with Diethyl Sodiomalonate in the Presence of Palladium(II) Acetylacetonate. Reaction of styrene with diethyl sodiomalonate in the presence of $Pd(acac)_2$ was investigated. Although reactions of such soft carbanions with olefin complexes have been reported, they are limited to olefin complexes that are part of a chelating ligand containing a second olefinic group.[14]

Scheme III



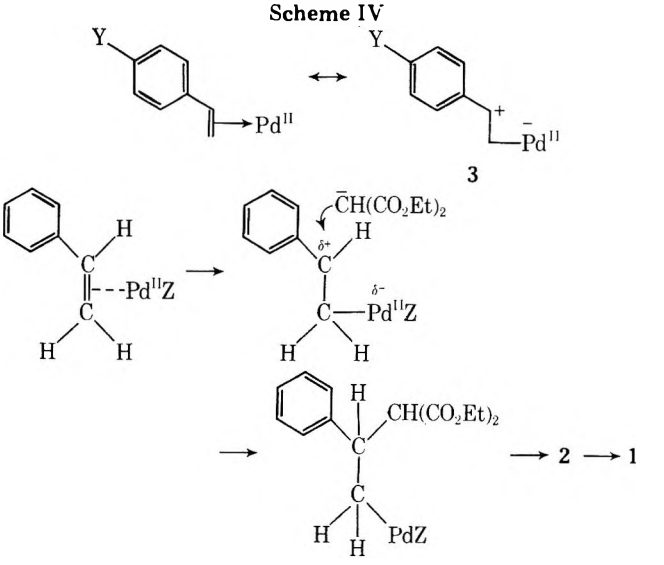
A mixture of styrene and $Pd(acac)_2$ was allowed to react with ⅔ molar equiv of diethyl sodiomalonate in THF at reflux for 5 h. Quenching with an 1 N acetic acid solution followed by usual workup gave an 18% yield of diethyl α-methylbenzylidenemalonate (**1**), probably derived from the initial product **2** by base-induced 1,3-hydride shift, along with diethyl *trans*-styrylmalonate (4%). In the absence of the palladium complex, the starting materials were recovered. In contrast to the β-carbon attack of methyl moiety in the reaction of methyllithium, diethylmalonate anion attacks at the α position of styrene, indicating that direct attack of diethylmalonate anion toward the α carbon of styrene coordinating to palladium occurs slowly, probably because nucleophilic attack toward palladium(II) of olefin–palladium complexes is retarded. Powell showed that from ^{13}C NMR studies of a series of para-substituted styrene–palladium(II) complexes there is a significant ionic contribution to the styrene–palladium bond in palladium–styrene complexes,[18,19] and electron donor Y groups would increase the contribution of canonical form **3** to the overall styrene–Pd bonding, i.e., the equilibrium position of Pd to the styrene C=C bond lies closer to the β carbon for electron donor Y groups. Moreover, x-ray study of $[(PhCH{=}CH_2)PdCl_2]_2$ showed the terminal olefinic carbon C_β to be closer to the coordination plane than C_α.[29] This consideration was again confirmed by the fact that when *p*-methoxystyrene was reacted under the same reaction condition, diethyl *p*-methoxybenzylidenemalonate was obtained in 23% yield without losing regioselectivity. A stronger electron-donating group increases the contribution of canonical form **3**, leading to the attack of diethylmalonate anion toward the α carbon of *p*-methoxystyrene. Therefore, diethylmalonate anion can attack the α position of styrenes directly on the side remote from palladium[6,8,9] as shown in Scheme IV.[30]



2

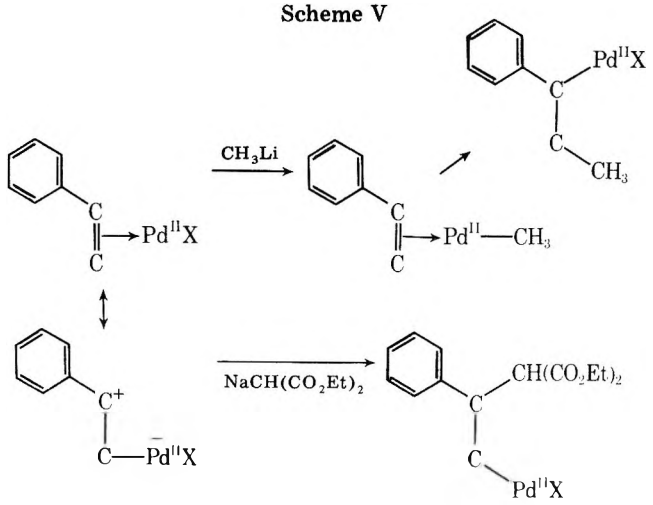
1

Scheme IV



In conclusion, addition of nucleophiles and palladium(II) across double bonds can have either cis or trans stereochemistry on the nature of nucleophiles; diethylmalonate anion

Scheme V



attacks the α position of coordinated styrene directly, while methyl carbanion initially coordinates to palladium, giving methylpalladium species which subsequently attacks the β position in a cis fashion. The most important factor is probably the ability of the nucleophile to coordinate to palladium(II) prior to addition across the double bond. It should be noted that alkylation of π-allylpalladium complexes occurs readily with soft carbanions such as anions of diethylmalonate[31] and methyl 2-phenylsulfinylacetate,[32] and enamines,[33] while alkylation does not with harder anions such as methyllithium. Further, in the former reaction nucleophilic attack occurs directly at carbon on the face of the π-allyl unit opposite to that of the palladium.[34]

Experimental Section

General Comments. All reactions were carried out under nitrogen atmosphere. Infrared spectra were recorded using a Hitachi 215 grating spectrometer. The proton magnetic resonance spectra were recorded in solution either with JNM-MH-60 or HNM-4H-100 spectrometers (internal Me_4Si).

Materials. Palladium complexes [$Pd(acac)_2$,[35] $Pd(OAc)_2$,[36] $PdCl_2(PhCN)_2$,[37] and $PdCl_2(PPh_3)_2$[38]] were prepared by literature procedures. Methyllithium was prepared from methyl iodide and lithium in ether and titrated by Watson and Eastham's method.[39] Substituted styrenes were made from the reactions of the corresponding aldehydes with methylmagnesium bromide followed by dehydration with iodide.

Reaction of Styrenes with Methyllithium in the Presence of a Palladium(II) Salt. To a solution of styrene (0.312 g, 3.0 mmol) and palladium(II) salt (1.0 mmol) in dry THF (15 mL) was added a solution of methyllithium in ether (1.6 mL, 2.0 mmol) at 0 °C under nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was treated with water (1.0 mL) and filtered off. Extraction with ether, drying ($MgSO_4$), and concentration gave products to which internal standard (naphthalene) was added. GLC analyses (Carbowax 20M, 130 °C) gave the results summarized in Table I. When an additional ligand (2.0 mmol) such as PPh_3, $P(n\text{-}Bu)_3$, and $P(OPh)_3$ was added under the reaction condition, none of β-methylstyrenes was obtained, and the starting materials were recovered.

Characterization of the Products. In the first set of experiments product samples were isolated by preparative GLC; in the second set, yield determination was accomplished by GLC. The products were as follows. *trans*-β-Methylstyrene: 90% yield; IR (liquid film) 687, 734, 960 cm^{-1}; NMR (CCl_4) δ 1.83 (d, 3 H, J = 5.0 Hz), 5.37 (d-q, H, J = 16.0 and 5.0 Hz), 6.33 (d, H, J = 16 Hz), 7.03–7.40 (m, 5 H). *trans*-β-Methyl-*p*-chlorostyrene: 99% yield; IR 680, 780, 960 cm^{-1}; NMR δ 1.82 (d, 3 H, J = 5.0 Hz), 5.87 (d-q, H, J = 15.8, 5.0 Hz), 6.27 (d, H, J = 15.8 Hz), 7.02 (s, 2 H), 7.23 (s, 2 H). *trans*-β-Methyl-*m*-chlorostyrene: 80% yield; IR 680, 760, 960 cm^{-1}; NMR δ 1.88 (d, 3 H, J = 5.0 Hz), 6.10–6.35 (m, 2 H), 7.12–7.35 (m, 4 H). *trans*-β-Methyl-*p*-methylstyrene: 60% yield; IR 690, 770, 960 cm^{-1}; NMR δ 1.85 (d, 3 H, J = 5.2 Hz), 2.30 (s, 3 H), 6.02 (d-q, H, J = 14.8, 5.2 Hz), 6.35 (d, H, J = 14.8 Hz), 6.97–7.27 (m, 5 H). *trans*-β-Methyl-*p*-methoxystyrene: 15% yield; IR 780, 960, 1040, 1250 cm^{-1}; NMR δ 1.83 (d, 3 H, J = 5.5 Hz), 3.72 (s, 3 H), 6.03 (d-q, H, J = 15.2, 5.5 Hz), 6.30 (d, H, J = 15.2 Hz), 6.70 (d, 2 H, J = 7.0 Hz), 7.15 (d, 2 H, J = 7.0 Hz).

General Comments Concerning the Competitive Experiments. The competing olefins were selected so that an adequate separation of the olefins, internal standard, and adduct peaks would be obtained on the final chromatogram. A solution of the competing olefins (6.0 mmol of each) and $Pd(acac)_2$ (1.0 mmol) in dry THF (15 mL) was stirred under nitrogen atmosphere at 25 °C for 10 min. A solution of methyllithium (2.0 mmol) in ether (1.6 mL) was added. After quenching with water (1.0 mL) the mixture was carefully extracted with ether. To the ethereal solution a measured amount of biphenyl was added as an internal standard, and the mixture was analyzed by GLC (Carbowax 20M). The methylated styrenes, which it was necessary to prepare separately, were amenable to direct analysis by GLC. Aliquots from the reaction mixture of styrene vs. *p*-chlorostyrene were removed at 10, 30, 60, 120, and 180 min. The relative ratio of styrenes and products was observed not to change with time. The relative rate constants thus obtained were analyzed, the data being fit to the best straight line for σ and σ^+ constants using a least-squares program. The following value of ρ were obtained: using σ constant 2.69 ± 0.189 (γ = 0.98); using σ^+ constants 1.51 ± 0.237 (γ = 0.92).

Stereochemistry of the Reactions of β-Deuteriostyrenes. *cis*- and *trans*-β-deuteriostyrenes were prepared from the corresponding β-bromostyrenes by Yoshino's method.[40] Pure samples were collected by preparative GLC and the deuterium contents were checked by NMR spectrum. *trans*-β-Deuteriostyrene: NMR (CCl_4) δ 5.67 (d, H, J = 17.5 Hz), 6 63 (d-t, H, J = 17.5 and 1.2 Hz), 7.07–7.47 (m, 5 H). *cis*-β-Deuteriostyrene: NMR δ 5.17 (d, H, J = 10.7 Hz), 6.63 (d-t, H, J = 10.7 and 2.6 Hz), 7.07–7.47 (m, 5 H). *trans*-β-Deuteriostyrene was reacted by the same method as described above in the reaction of styrenes with methyllithium in the presence of $Pd(acac)_2$. The β-methylstyrene fraction was collected by preparative GLC (Carbowax 20M, 130 °C) and subjected to measurement of NMR spectra. Careful analysis of the spectra showed that *trans*-β-deuterio-β-methylstyrene was obtained exclusively and its deuterium content was 0.90 ± 0.08: NMR δ 1.81 (t, 3 H, J = 0.2 Hz), 6.20 (t, J_{HD} = 4.0 Hz), 7.10 (m, 5 H). Similarly, the reaction of *cis*-β-deuteriostyrene gave *trans*-β-methylstyrene, whose deuterium content was 0.08 ± 0.06. Therefore, the stereochemistry of the reaction is inversion of configuration.

Reaction of β-Bromostyrene with Methyllithium in the Presence of $Pd(acac)_2$. A solution of $Pd(acac)_2$ (0.304 g, 1.0 mmol) and *cis*-β-bromostyrene[41] (0.552 g, 3.0 mmol) in dry THF (15 mL) was treated with a solution of methyllithium (6.0 mmol) in ether (2.4 mL) similarly as described above. The GLC analysis (Carbowax 20M, internal standard method using biphenyl) showed that *cis*-β-methylstyrene[42] were obtained (0.110 g, 94%) along with *trans*-β-methylstyrene (0.04 g, 4%). *cis*-β-Methylstyrene: IR 690, 1644 cm^{-1}; NMR (CCl_4) δ 1.87 (d-d, 3 H), 4.77 (m, H), 6.05 (d-q, H, J = 11 and 2 Hz), 7.68 (m, 5 H). Similar reaction of *trans*-β-bromostyrene[43] gave *trans*- and *cis*-β-methylstyrene in 96 and 2% yields, respectively.

Reaction of Styrene with Diethyl Sodiomalonate in the Presence of $Pd(acac)_2$. To 0.305 g (1.0 mmol) of $Pd(acac)_2$ in 50 mL of freshly distilled dry THF was added 0.312 g (3.0 mmol) of styrene and the solution was stirred for 20 min. To this solution was added a THF solution of diethyl sodiomalonate, which was prepared upon treatment of diethyl malonate (0.320 g, 2.0 mmol) with sodium hydride (50% in Bayol, 0.096 g) in THF (5 mL). The mixture was stirred at reflux for 12 h, cooled, quenched with aqueous acetic acid solution (2 N), filtered off, and extracted with ether. The ether solution was washed with a solution of sodium hydrogen carbonate, dried over $MgSO_4$, and concentrated with a rotary evaporator. The bulb-to-bulb distillation (bath temperature 187–190 °C, 2 mmHg) gave oily products, which subsequently chromatographed on a 20 × 20 cm Merck silica gel F 254 preparative layer plate in benzene. A band (R_f 0.58) was eluted to afford diethyl α-methylbenzylidenemalonate (1): *m/e* 262; IR (liquid film) 1625, 1720 cm^{-1}; NMR (CCl_4) δ 0.88 (t, 3 H, J = 6.5 Hz), 1.31 (t, 3 H, J = 6.5 Hz), 2.42 (s, 3 H), 3.86 (q, 2 H), 4.23 (q, 2 H), 7.26 (s, 5 H). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.93; H, 7.07. A band (R_f 0.61) gave diethyl *trans*-styrylmalonate: *m/e* 262; IR (liquid film) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, 6 H, J = 8 Hz), 4.12 (d, H, J = 4 Hz), 4.18 (q, 4 H, J = 8 Hz), 6.31 (d-d, J = 16 and 4 Hz), 6.54 (d, J = 16 Hz), 7.16–7.40 (m, 5 H). The authentic sample was prepared by the reaction of ethoxymethylenemalonic ester with benzylmagnesium bromide in ether at reflux followed by separation with silica gel chromatography. Nabar et al.[44] reported that this reaction gave diethyl phenethylidenemalonate; however, the structure should be assigned to be the isomerized product, diethyl *trans*-styrylmalonate, from the NMR spectrum. Treatment of a solution of diethyl *trans*-styrylmalonate in THF with sodium hydride followed by quenching with water gave the recovered ester. The accurate yields of the reaction products were determined by GLC analyses (SE-30, 10%, 1m, column temperature 100–230 °C)

using an internal standard of biphenyl. An unknown minor product was detected in GLC analysis.

When a mixture of $Pd(OAc)_2$ (5 mmol), styrene (50 mmol), and diethyl sodiomalonate (10 mmol) in THF was reacted under similar reaction conditions, 1 (21%), diethyl phenethylmalonate (4%), α-phenylnaphthalene (1.6%), and α-phenyltetralin[45] (1%) were obtained.

Reaction of *p*-Methoxystyrene with Diethyl Sodiomalonate in the Presence of $Pd(acac)_2$. The reaction of *p*-methoxystyrene (0.402 g, 3.0 mmol), $Pd(acac)_2$ (0.305 g, 1.0 mmol), and diethyl sodiomalonate (2.0 mmol) in THF was carried out and worked up under the same condition employed on the reaction of styrene. The oily product obtained from the bulb-to-bulb distillation (bath temperature 199–201 °C, 2 mmHg) was subjected to TLC. A band (R_f 0.560) was eluted with benzene to afford diethyl α-methyl(*p*-methoxybenzylidene)malonate: *m/e* 292; IR (liquid film) 1715 cm^{-1}; NMR (CCl_4) δ 0.96 (t, 3 H, J = 6.6 Hz), 1.30 (t, 3 H, J = 6.6 Hz), 2.40 (s, 3 H), 3.80 (s, 3 H), 3.93 (q, 2 H, J = 6.6 Hz), 4.24 (q, 2 H, J = 6.6 Hz), 6.92 (d, 2 H, J = 9 Hz), 7.28 (d, 2 H, J = 9 Hz). A band (R_f 0.625) gave a minor unknown product: mp 97.5–98.5 °C (recrystallized from petroleum ether); *m/e* 230; IR (Nujol mull) 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.61 (s, 3 H), 3.81 (s, 3 H), 6.72 (s, H), 6.95 (d, 2 H, J = 9 Hz), 7.61 (d, 2 H, J = 9 Hz).

Acknowledgments. This research was supported financially by a grant from the Ministry of Education, Japan (in part 110305). Thanks are given to Osamu Kuramoto and Takashi Hori for their assistance in the experimental work. We wish also to thank Emeritus Professor I. Moritani for his interest and encouragement.

Registry No.—1, 5294-56-4; *trans*-β-methylstyrene, 873-66-5; *trans*-β-methyl-*p*-chlorostyrene, 1879-53-4; *trans*-β-methyl-*m*-chlorostyrene, 23204-80-0; *trans*-β-methyl-*p*-methylstyrene, 2077-30-7; *trans*-β-methyl-*p*-methoxystyrene, 4180-23-8; *trans*-β-deuteriostyrene, 6911-81-5; *cis*-β-deuteriostyrene, 21370-59-2; *trans*-β-deuterio-β-methylstyrene, 21370-50-3; *cis*-β-bromostyrene, 588-73-8; *cis*-β-methylstyrene, 766-90-5; diethyl sodiomalonate, 996-82-7.

References and Notes

(1) (a) R. Heck, *J. Am. Chem. Soc.*, **90**, 5518 (1968); (b) R. F. Heck, *J. Organomet. Chem.*, **37**, 389 (1972); (c) M. E. Vol'pin, L. G. Volkova, I. Ya. Lefitin, N. N. Boronina, and A. M. Yurkevich, *Chem. Commun.*, 849 (1971).
(2) H. Okada and H. Hashimoto, *Kogyo Kagaku Zasshi*, **70**, 2152 (1967).
(3) M. Tamura and J. K. Kochi, *Bull. Chem. Soc. Jpn.*, **44**, 3063 (1971).
(4) H. C. Clark and R. J. Puddephantt, *Inorg. Chem.*, **9**, 2670 (1970).
(5) P. M. Henry, *J. Org. Chem.*, **38**, 2415 (1973); I. I. Moiseev, O. G. Levanda, and M. N. Vargaftik, *J. Am. Chem. Soc.*, **96**, 1003 (1974).
(6) P. M. Henry, *J. Am. Chem. Soc.*, **94**, 7305 (1972).
(7) P. M. Henry, *J. Org. Chem.*, **38**, 1140 (1973).
(8) B. Åkermark and J.-E. Backvall, *Tetrahedron Lett.*, 819 (1975).
(9) D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1806 (1976).
(10) D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, **98**, 1810 (1976).
(11) Phenylpalladium species are directly prepared by the electrophilic substitution of benzenes with palladium(II) salts in acetic acid. See I. Moritani and Y. Fujiwara, *Synthesis*, 525 (1973); Y. Fujiwara, R. Asano, I. Moritani, and S. Teranishi, *J. Org. Chem.*, **41**, 1681 (1976).
(12) Phenylpalladium species are prepared by oxidative addition of aryl halides to palladium(0) complexes. See H. A. Diek and R. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974); K. Mori, T. Mizoroki, and A. Ozaki, *Bull. Chem. Soc. Jpn.*, **46**, 1505 (1973); M. Juria and M. Duteil, *Bull. Soc. Chim. Fr.*, 2790 (1973).
(13) Phenylpalladium species derived from phenylmercurials, see ref 1; H. Horino, M. Arai, and N. Inoue, *Tetrahedron Lett.*, 647 (1974).
(14) (a) H. Takahashi and J. Tsuji, *J. Am. Chem. Soc.*, **90**, 2387 (1968); (b) J. K. Stille and D. B. Fox, *ibid.*, **92**, 1274 (1970); (c) B. F. G. Johnson, J. Lewis, and M. S. Subramanian, *J. Chem. Soc. A*, 1993 (1968); (d) A. Segnitz, P. M. Bailey, and P. M. Maitlis, *J. Chem. Soc., Chem. Commun.*, 698 (1973); (e) A. Kasahara, T. Izumi, K. Endo, T. Takeda, and M. Ookita, *Bull. Chem. Soc. Jpn.*, **47**, 1967 (1974).
(15) Alternatively, the factor in determining product yield may be the ability to alkylate the palladium(II) species.
(16) W. Partenheimer and B. Durham, *J. Am. Chem. Soc.*, 96, 3800 (1974).
(17) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **79**, 1913 (1957); **80**, 4979 (1958).
(18) D. G. Cooper, G. K. Hamer, J. Powell, and W. F. Reynolds, *J. Chem. Soc., Chem. Commun.*, 449 (1973).
(19) E. Ban, R. P. Hughes, and J. Powell, *J. Organomet. Chem.*, **69**, 455 (1974).
(20) G. Calvin and G. E. Coates, *J. Chem. Soc.*, 2008 (1960).
(21) R. Heck, *J. Am. Chem. Soc.*, **93**, 6896 (1971); **91**, 6707 (1969).
(22) A. Streitwieser, Jr., and H. R. Koch, *J. Am. Chem. Soc.*, **86**, 404 (1964).
(23) J. K. Stille and M. T. Regen, *J. Am. Chem. Soc.*, **96**, 1508 (1974), and references cited therein.
(24) The similar deuterium labeling results [see P. M. Henry and G. A. Ward, *J. Am. Chem. Soc.*, **94**, 673 (1972)].
(25) (a) B. C. Shaw, *Chem. Commun.*, 464 (1968); (b) F. R. Hartley, *Nature (London)*, **223**, 615 (1969).
(26) R. Heck, *J. Am. Chem. Soc.*, **90**, 5531, 5535 (1968).
(27) β-Methylstyrene was recovered on treatment with methyllithium in the presence of $Pd(acac)_2$ because of steric effect.[1b]
(28) M. Yamamura, I. Moritani, and S.-I. Murahashi, *J. Organomet. Chem.*, **91**, C39 (1975).
(29) J. R. Holden and N. C. Baenziger, *J. Am. Chem. Soc.*, **77**, 4987 (1955).
(30) The refree suggested one reason: that diethylmalonate anion can better exist uncomplexed to metal than CH_3^- in solution and is thus better able to attack trans.
(31) B. M. Trost and T. B. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976), and references cited therein.
(32) B. M. Trost, W. P. Conway, P. E. Strege, and T. J. Dietsche, *J. Am. Chem. Soc.*, **96**, 7165 (1974).
(33) (a) H. Onoue, I. Moritani, and S.-I. Murahashi, *Tetrahedron Lett.*, 121 (1973); (b) J. Tsuji, *Bull. Chem. Soc. Jpn.*, **46**, 1896 (1973).
(34) B. M. Trost and L. Weber, *J. Am. Chem. Soc.*, **97**, 1611 (1975).
(35) A. A. Grinberg and L. K. Simonova, *Zh. Prikl. Khim.*, **26**, 880 (1953).
(36) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, 3632 (1965).
(37) J. R. Doyle, P. E. Slide, and H. B. Jonassen, *Inorg. Synth.*, **6**, 218 (1960).
(38) J. Chatt and F. G. Mann, *J. Chem. Soc.*, 1622 (1939).
(39) S. C. Watson and J. F. Eastham, *J. Organomet. Chem.*, **9**, 165 (1967).
(40) Y. Yoshino, Y. Manabe, and Y. Kikuchi, *J. Am. Chem. Soc.*, **86**, 4670 (1964).
(41) G. Labbe, M. J. Miller, and H. Hassner, *Chem. Ind. (London)*, 1321 (1970).
(42) M. Schlosser, G. Muller, and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, 5, 667 (1966).
(43) G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Basche, and H. O. House, *J. Am. Chem. Soc.*, **91**, 4871 (1969).
(44) D. P. Nabar and S. V. Sunthankar, *Bull. Chem. Soc. Jpn.*, **42**, 2991 (1969).
(45) R. Weiss, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y., 1955, p 729.
(46) **Note Added in Proof.** A minor product (mp 97.5–98.0 °C) from the reaction of *p*-methoxystyrene with diethyl sodiomalonate was assigned to 1-[2-methyl-5-(*p*-methoxyphenyl)-3-furanyl]ethanone (4%), which can be formed by nucleophilic attack of acetylacetone ligand of $Pd(acac)_2$ toward *p*-methoxystyrene. Similarly, a small amount of 1-(2-methyl-5-phenyl-3-franyl)ethanone, mp 57.5 °C, was detected among the products from the reaction of styrene with diethyl sodiomalonate in the presence of $Pd(acac)_2$.

Mercuric Salt Catalyzed Nitration of Toluene

Leon M. Stock* and Terry L. Wright

Department of Chemistry, University of Chicago, Chicago, Illinois 60637

Received March 16, 1977

The mercuric acetate catalyzed nitration of toluene in acetic acid at 80 °C produces 36% 2-, 12% 3-, and 52% 4-nitrotoluene. Other soluble mercury compounds produce similar results. Under these conditions, toluene is 6.1-fold more reactive than benzene. The reaction of 4-deuteriotoluene proceeds with a primary kinetic isotope effect of 3.1. 4-Tolylmercuric acetate reacts with nitric acid under these conditions to yield 4-nitrotoluene rapidly and quantitatively. The addition of urea to the reaction mixture inhibits the catalyzed nitration reaction and the reaction of 4-tolylmercuric acetate with nitric acid. The mercuration of toluene is not inhibited by urea. 4-Tolylmercuric acetate reacts with nitrosation agents to yield 4-nitrosotoluene and with nitration reagents to yield 3-nitro-4-methylphenylmercuric acetate. These results indicate that the reaction occurs in three steps: mercuration, nitrosodemercuration (rather than nitrodemercuration), and oxidation of nitrosotoluene to nitrotoluene. The relative rate and product distribution are determined in the initial mercuration reaction.

The catalytic properties of mercury in the nitration reaction became apparent in 1908, when Wolffenstein and Boeters patented a procedure, later termed oxynitration, by which benzene was transformed into di- and trinitrophenols in the presence of mercuric nitrate in nitric acid.[1] In the decades that followed, the reaction was actively investigated and several mechanistic interpretations emerged.[2] Simultaneous reports by Westheimer, Segel, and Schramm,[3] and Titov and Laptev[4] in 1947 established the mechanism. They showed that the initial intermediate, phenylmercuric nitrate, was converted to nitrosobenzene in dilute nitric acid.[3,4] They also showed that nitrosobenzene could be converted to the observed products of the oxynitration reaction. Early workers reported that the yield of nitrobenzene approached 50% when the oxynitration reaction was carried out in concentrated nitric acid.[5] Tsutsumi and Iwata and Osawa and his co-workers studied the effects of other metal oxides and metal nitrates on nitration with nitric acid.[6-8] However, only mercuric oxide and mercuric nitrate accelerated the reaction importantly and altered the isomer distribution.[6,7,9] Komoto and his associates examined the mercuric acetate catalyzed nitration of toluene using concentrated nitric acid in acetic acid at 80 °C.[10] Under these conditions, the catalyzed reaction produced the isomeric nitrotoluenes in good yield.

Several investigators have proposed that electrophilic aromatic mercuration is the first step in this reaction.[7,10] The nature of the subsequent steps in the process remains unclear. Both nitrodemercuration and nitrosodemercuration followed

$$C_6H_5HgOAc + NO_2^+ \rightarrow C_6H_5NO_2 + HgOAc^+$$

$$C_6H_5HgOAc + NO^+ \rightarrow C_6H_5NO + HgOAc^+$$

$$C_6H_5NO + HNO_3 \rightarrow C_6H_5NO_2 + HNO_2$$

by oxidation have been suggested.[7,10] In addition, the available experimental evidence is in conflict with the proposal that mercuration is the key step in the reaction. To illustrate, the mercuration of toluene typically yields about 13% 3-tolylmercuric acetate.[11] Komoto and his associates[10] do not comment on the formation of the 3 isomer, Tsutsumi and Iwata[6] report only 3% of this isomer, and Osawa and his associates[7] report that the reaction yields 10% 3-nitrotoluene. Such uncertainty and the singular success of mercury compounds in the catalysis of the nitration reaction prompted us to undertake an investigation of the reaction mechanism prior to the study of other methods for the control of isomer distributions in nitration reactions.

Results and Discussion

Komoto and his associates report excellent material balances for the mercuric acetate catalyzed reaction of equimolar quantities of toluene with 90% nitric acid in acetic acid at 80 °C.[10] They also note that the reaction rate depends on the concentration of mercuric acetate.[10] We confirmed these observations in preliminary experiments. The use of anhydrous nitric acid rather than 90% nitric acid provides equivalent results. The catalyzed nitration reaction also occurs when nitrogen dioxide is used rather than nitric acid. However, the reaction is unsuccessful when sodium nitrate or sodium nitrite are used in place of nitric acid. Accordingly, we adopted the conditions used by Komoto and his associates for the investigation of the influence of mercury compounds on the reaction. The results are summarized in Table I.

The reaction proceeds readily in the presence of 1.6 mol % catalyst as shown by the major increase in the yield of nitrotoluenes in the initial experiments with mercuric acetate. The isomer distribution changes importantly with increased amounts of 3- and 4-nitrotoluene produced in the catalytic reaction. Other mercury compounds which are soluble in the reaction medium, mercuric oxide, mercuric nitrate, and 4-tolylmercuric acetate, also catalyze the reaction. Mercurous nitrate and mercury, which are oxidized to mercuric nitrate under the conditions of these experiments, are also effective catalysts. Mercuric sulfate, which is only partially soluble in the reaction medium, gives an intermediate result. Mercuric chloride, although soluble, does not catalyze the reaction. Indeed, the addition of sodium chloride, 3.2 mol %, inhibits the catalytic reaction with mercuric acetate whereas the addition of other salts, sodium nitrite, sodium nitrate, and sodium acetate, has no discernible influence on the yield and isomer distribution. The failure of the reaction with mercuric chloride and the inhibition of the catalytic reaction by sodium chloride are compatible with the viewpoint that mercuration is the key step in the process because it has long been known that mercuric chloride is ineffective as a mercuration reagent.[12]

At low catalyst concentration, the nitration reaction and the mercuric acetate catalyzed nitration reaction are competitive processes. This feature of the reaction is shown by the results presented in Table II.

These results indicate that the conventional nitration reaction and the catalyzed nitration reaction are both significant at short reaction times when the nitric acid to mercuric acetate ratio is large. The results presented in Table I indicate that, after 2 h, the uncatalyzed nitration reaction is responsible for only 7% of the observed nitration products. When the observed product distribution is adjusted for this result, the isomer distribution in the mercuric acetate catalyzed reaction is established as 33% 2-, 13% 3-, and 54% 4-nitrotoluene.

Mercuration. The intramolecular selectivity, the intermolecular selectivity, and the primary kinetic isotope effect

Table I. Catalytic Properties of Mercury Compounds for the Nitration of Toluene at 80 °C [a]

Registry no.	Catalyst	Isomer distribution 2	3	4	Conversion, %
	None	58	3	39	7
1600-27-7	$Hg(OAc)_2$	36	12	52	64
21908-53-2	HgO	36	13	51	62
10045-94-0	$Hg(NO_3)_2$	36	13	51	63
10415-75-5	$HgNO_3$	36	12	52	67
7439-97-6	Hg [b]	36	12	52	46
2440-35-9	$4\text{-}H_3CC_6H_4HgOAc$	36	12	52	63
7783-35-9	$HgSO_4$ [c]	48	6	46	*d*
7487-94-7	$HgCl_2$	62	*d*	38	7

[a] The mole ratio is 1.0:1.0:0.016:5.0 for toluene–90% nitric acid–mercury compound–acetic acid. The reactions were carried out for 2 h. [b] Reaction becomes homogeneous after the addition of nitric acid. [c] Reaction is heterogeneous. [d] Quantity too small for accurate measurement.

Table II. Isomer Distribution for the Nitration of Toluene [a]

Conversion, %	Isomer distribution 2	3	4
1	45	*b*	55
3	48	4	48
6	53	*b*	47
11	47	4	49
21	38	11	51
60	36	12	52

[a] See Table I for reaction conditions. [b] Quantity insufficient for accurate measurement.

Table III. Isomer Distribution for the Mercuration of Toluene

Reaction conditions	Isomer distribution 2	3	4
$Hg(OAc)_2$, HOAc, 70 °C [a]	32	15	53
$Hg(OAc)_2$, HOAc, 90 °C [a]	32	16	52
$Hg(OAc)_2$, $HClO_4$, HOAc, 75 °C [b]	18	13	69
$Hg(OAc)_2$, 90% HNO_3, HOAc, 80 °C [c,d]			
30 s	26	14	61
3 min	30	15	55
6 min	29	16	55
15 min	31	15	55

[a] Reference 13. [b] Reference 14. [c] This study. [d] Urea present.

Table IV. Toluene to Benzene Relative Rates for Mercuration and Nitration

Reaction	Rel rate, k_T/k_B
Nitration, 90% HNO_3, HOAc, 80 °C [a]	20.5 ± 3.0
Nitration, NO_2, $Hg(OAc)_2$, HOAc, 80 °C [a]	4.8 ± 0.4
Nitration, 90% HNO_3, $Hg(OAc)_2$, HOAc, 80 °C [a]	
5% conversion	22.6 ± 3.0
20% conversion	9.9 ± 2.1
60% conversion	6.1 ± 1.5
Mercuration, $Hg(OAc)_2$, HOAc, 70 °C [b]	4.3
Mercuration, $Hg(OAc)_2$, HOAc, 90 °C [b]	3.6
Mercuration, $Hg(OAc)_2$, $HClO_4$, HOAc, 75 °C [c]	5.9
Mercuration, $Hg(OAc)_2$, 90% HNO_3, HOAc, 80 °C [a]	5.6 ± 0.4

[a] This study. [b] Reference 13. [c] Reference 14.

Table V. Primary Kinetic Isotope Effects in Nitration and Mercuration

Reaction, substrate, reagents	k_H/k_D
Nitration, C_6H_6 [a]	1.00
Mercuration, C_6H_6, $Hg(OAc)_2$, HOAc [b]	3.2 (25 °C), 2.6 (50 °C), 1.9 (90 °C)
Mercuration, C_6H_6, $Hg(OAc)_2$, $HClO_4$, HOAc [b]	6.0 (25 °C)
Nitration, $4\text{-}CH_3C_6H_4D$ 90% HNO_3, $Hg(OAc)_2$, HOAc [c]	3.1 (80 °C)

[a] Reference 16a. [b] Reference 16. [c] This study.

in the mercuration of toluene are distinctive.[11,13,14] Accordingly, we compared the results for the catalyzed nitration of toluene with the results for the mercuration of toluene to establish the role of mercuration in the process.

The intramolecular selectivities of the two reactions were assessed by measurement of the isomer distribution for the nitric acid catalyzed mercuration of toluene in acetic acid at 80 °C for comparison with the isomer distribution in the nitration reaction. As discussed subsequently, the nitration reaction is efficiently inhibited by the addition of urea. The results are presented in Table III.

The isomer distribution in the mercuration of toluene in the presence of nitric acid is initially rich in the 4 isomer. This distribution is similar to the isomer distribution observed at short reaction time in the perchloric acid catalyzed mercuration reaction.[13] The product distribution observed after 3 min reaction time, 30% 2-, 15% 3-, and 55% 4-tolylmercuric acetate, closely resembles the product distribution found in the catalyzed nitration reaction, 33% 2-, 13% 3-, and 54% 4-nitrotoluene. These results indicate that the intramolecular selectivities in the two processes are virtually identical.

The intermolecular selectivities for the nitration and mercuration reactions were assessed by competition experiments with toluene and benzene. The results are summarized in Table IV.

The relative rate, $k_T/k_B = 20.5$, for the uncatalyzed nitration of toluene at 80 °C is comparable with other observations for the noncatalytic nitration of toluene.[11] The relative rate, $k_T/k_B = 6.1$, for the catalyzed nitration of toluene observed after 2 h reaction time (60% conversion) is virtually identical with the value, 5.6, for the nitric acid catalyzed mercuration of toluene and benzene under identical conditions. The relative rate, $k_T/k_B = 4.8$, for the catalyzed nitration of toluene with nitrogen dioxide is also near the value, 4.3, for the uncatalyzed mercuration in acetic acid at 70 °C. These results indicate that the intermolecular selectivities of the nitration and mercuration reactions are very similar.

Mercuration reactions generally exhibit a primary kinetic isotope effect.[16] In contrast, nitration proceeds without an isotope effect.[16a] This feature of the catalyzed nitration reaction was investigated by the study of the mercuric acetate catalyzed nitration of 4-deuteriotoluene. The reaction pro-

Table VI. The Influence of Urea on the Reactions of Toluene and Tolylmercuric Acetate with Nitric Acid [a]

Compd	Conditions	Isomer distribution 2	3	4	Conversion, %
Toluene	90% HNO_3, $Hg(OAc)_2$, HOAc, 80 °C	36	12	52	64
Toluene	Same with urea	61	*b*	39	8
4-Tolylmercuric acetate	90% HNO_3, HOAc, 80 °C			100	100
4-Tolylmercuric acetate	Same with urea	59	*b*	41	11

[a] See Table I for conditions. [b] Quantity too small for accurate measurement.

duces 55% 2-, 19% 3-, and 26% 4-nitrotoluene compared to 36% 2-, 12% 3-, and 52% 4-nitrotoluene in the reaction of unlabeled toluene. The isotope effect calculated from these results and the isotope effects for several related reactions are presented in Table V.

The observed k_H/k_D value, 3.1, for the mercuric acetate catalyzed nitration of toluene is quite comparable with prior observations of primary kinetic isotope effects in the mercuration reaction. Thus, the catalyzed nitration reaction shows all the distinctive features of the mercuration reaction with modest intra- and intermolecular selectivities and a kinetic isotope effect. These results establish that mercuration is the rate-determining and product-determining step in the catalyzed nitration reaction.

Nitrosodemercuration. The conclusion that mercuration is the key step requires that the isomeric tolylmercuric acetates formed in this step be rapidly converted to nitrotoluenes under the reaction conditions. To test this point, we studied the reactions of 4-tolylmercuric acetate. This compound is rapidly and quantitatively converted to 4-nitrotoluene by 90% nitric acid in acetic acid at 80 °C. Neither 2- nor 3-nitrotoluene is obtained in detectable (1%) amount. This nitrodemercuration reaction can be accomplished either by nitrodemercuration or by nitrosodemercuration followed by oxidation.

It is well known that nitrosation reactions are inhibited by urea and related compounds.[17] We, therefore, examined the catalytic nitration of toluene and the reactions of 4-tolylmercuric acetate in the presence and absence of urea. The results are summarized in Table VI.

The isomer distribution and conversion observed for the reaction in the presence of urea are indicative of the uncatalyzed nitration reaction. Both the catalyzed nitration reaction and the conversion of 4-tolylmercuric acetate to 4-nitrotoluene are inhibited by urea. These observations are compatible with interpretations which involve nitrosodemercuration and are incompatible with interpretations which center on nitrodemercuration. The nitro compounds obtained in the presence of urea are clearly formed from toluene produced in a protodemercuration reaction.

Further experimental evidence for nitrosodemercuration was obtained by study of the reactions of 4-tolylmercuric acetate with nitrosation and nitration reagents. The treatment of 4-tolylmercuric acetate with nitrosonium tetrafluoroborate in sulfolane at 25 °C provides 4-nitrosotoluene in 96% yield. Similar treatment of this acetate with nitronium tetrafluoroborate provides a more complex product distribution. The dominant product is 3-nitro-4-methylphenylmercuric acetate. Lesser amounts of 4-nitroso- and 4-nitrotoluene are produced in these reactions. For example, the reaction of purified nitronium tetrafluoroborate with 4-tolylmercuric acetate in sulfolane in a dry atmosphere yields 9% 4-nitrosotoluene, 29% 4-nitrotoluene, and 36% 3-nitro-4-methylphenylmercuric acetate. These products are also obtained in replicate experiments. However, they are formed in quite different relative amounts as described in the Experimental Section. These erratic results apparently originate from nitrosation reagents present in the starting material[18] and from the reactions of nitrogen oxides which are produced in the course of reaction. The freezing point of sulfolane prohibits the study of this reaction at low temperature.

Challenger and Rothstein report that phenylmercuric nitrate reacts with nitric acid at −20 °C to provide nitrophenylmercuric nitrates in 86% yield.[19] Accordingly, we adopted these conditions for the further study of the reaction of the arylmercuric acetates with nitration reagents. The reaction of phenylmercuric acetate with cold nitric acid which is free of nitrosation agents gives only nitrophenylmercuric acetates. Similarly, the heterogeneous reaction of 4-tolylmercuric acetate with this reagent yields only 3-nitro-4-methylphenylmercuric acetate. Under the conditions of these experiments the formation of cleavage products is completely suppressed.

These observations indicate that the arylmercury compounds react differently with nitrosation reagents than with nitration reagents. Nitrosation reagents, represented by the nitrosonium ion, clearly provide the nitrosodemercuration product.

$$4\text{-}CH_3C_6H_4HgOAc + NO^+ \rightarrow 4\text{-}CH_3C_6H_4NO + HgOAc^+$$

Nitrosodeprotonation apparently does not occur. On the other hand, nitration reagents, represented by nitronium ion, selectively yield the nitrodeprotonation product rather than the nitrodemercuration product.

$$4\text{-}CH_3C_6H_4HgOAc + NO_2^+ \rightarrow 3\text{-}NO_2\text{-}4\text{-}CH_3C_6H_3HgOAc + H^+$$

The experimental results offer strong support for the view that nitrosodemercuration rather than nitrodemercuration is the second reaction in the mercuric acetate catalyzed nitration reaction.

It is very surprising that the arylmercuric acetates react so differently with nitrosation reagents than with nitration reagents. However, many organometalloid compounds including arylthallium,[20] arylsilicon,[21] aryllead,[19] and aryltin[19] compounds selectively undergo nitrodeprotonation rather than nitrodemetalation. In contrast, many other electrophilic reagents including bromine, chlorine, proton acids, mercury salts, and nitrosation reagents very selectively cleave the carbon–metal bond. Eaborn and his students noted this anomaly.[21] They suggest that steric effects increase the energy requirements for nitrodetrimethylsilylation. Olah and Kuhn also suggest that steric effects have a major impact on the nitrodealkylation reactions of isopropylbenzene and *tert*-butylbenzene derivatives.[22] Indeed, the nitrodeisopropylation of 4-isopropyltoluene is at least 15-fold more rapid than the nitrode-*tert*-butylation of 4-*tert*-butyltoluene.[23] Clearly, steric interactions play an important role in these replacement reactions. The large steric effect may originate in the requirement that the central atom of the linear nitration reagent must interact with the aromatic carbon atom in the rate-determining step.[24]

Oxidation. Ogata and Tezuka studied the oxidation of nitrosobenzene to nitrobenzene by nitric acid in aqueous dioxane.[25] This complex reaction depends on the acidity of the reaction medium and on the concentration of nitric acid. The

reaction is autocatalytic apparently because there is a progressive increase in the concentration of nitrous acid. Ogata and Tezuka propose that both nitrogen dioxide and protonated nitrogen dioxide are effective reagents for the oxidation reaction. We did not investigate this aspect of the catalyzed nitration reaction in detail. However, 2-nitrosotoluene is rapidly oxidized to 2-nitrotoluene under the conditions of the mercuric acetate catalyzed nitration reaction.

Conclusion

The relative rate measurements, the isomer distributions, the kinetic isotope effect, and the related findings establish that mercuration is the first step in the mercuric salt catalyzed nitration of toluene. The inhibition of the reaction by urea and the observations of facile reactions of nitrosation reagents with 4-tolylmercuric acetate indicate that nitrosodemercuration is the second step in the sequence. The information available in the literature and the work with 2-nitrosotoluene support the view that the nitroso compounds are oxidized to nitro compounds in the third step of the reaction. The product distributions are determined in the initial, rate-determining mercuration reaction.

Experimental Section

Materials. The starting materials and other reagents used in this work were analyzed reagents or were purified by well-known methods prior to use. The molecules used as reference compounds in analytical procedures were purified by fractionation or crystallization and shown to be free of isomeric contamination by suitable analytical methods.

4-Deuteriotoluene. This compound was prepared by the reaction of 4-tolylmagnesium bromide with deuterium oxide by the procedure of Turkevich et al.[26] The product was fractionated twice. Analysis by mass spectroscopy indicated that the compound was minimally 90% 4-deuteriotoluene.

4-Tolylmercuric Acetate. This compound was prepared by the perchloric acid catalyzed mercuration of toluene as described by Brown and McGary.[13] The initial product was recrystallized three times from ethanol to yield 4-tolylmercuric acetate (mp 150–151 °C, lit.[27] 153 °C) which was shown by nuclear magnetic resonance to contain less than 1% of the 2 isomer and no trace of the 3 isomer.

2-Nitro-4-bromotoluene. 4-Bromotoluene (4.4 g, 0.026 mol) was added to a mixture of nitric acid (70%, d = 1.42, 7.0 g) and sulfuric acid (9.0 g). The mixture was warmed on a steam bath for 30 min and then poured into cold water (25 mL). The product was collected by filtration and recrystallized from ethanol to give yellow crystals of 2-nitro-4-bromotoluene (mp 43–45 °C, lit.[28] 43 °C).

Nitration Reactions. All the reactions were carried out in flasks equipped with a reflux condenser, addition funnel, and Thermowatch temperature controller. In a typical experiment, toluene (10.0 g, 0.109 mol), mercuric acetate (0.50 g, 0.0016 mol), and acetic acid (30.0 g, 0.50 mol) was stirred and heated to 80 °C. Nitric acid (Fischer Certified Reagent, 90%, d = 1.5, 5.5 mL, 0.109 mol) was then added dropwise. The solution was heated at 80 °C for 2 h. The mixture was poured into water and then transferred to a separatory funnel containing ether and 1,2-dichlorobenzene (7.0 g). The organic materials were extracted into ether which was washed with water and dried (sodium sulfate) prior to concentration in vacuo.

The product distribution was established by gas chromatography on 5% QF-1 on Chromosorb G using a 2.5 m × 0.63 cm column. The relationship between peak area and composition was established by the analysis of known mixtures of 1,2-dichlorobenzene and the nitro compounds. These analytical experiments showed thatd acetic acid (30.0 g, 0.50 mol) was stirred and heated to 80 °C. Nitric acid (Fischer Certified Reagent, 90%, d = 1.5, 5.5 mL, 0.109 mol) was then added dropwise. The solution was heated at 80 °C for 2 h. The mixture was poured i the isomer distributions could be established within ±1%.

Nitration of 4-Deuteriotoluene. 4-Deuteriotoluene (2.00 g, 0.021 mol), mercuric acetate (0.10 g, 0.0003 mol), and acetic acid (6 mL) were heated to 80 °C. Nitric acid (90%, d = 1.5, 1.1 mL, 0.021 mol) was added dropwise. The reaction was allowed to proceed for 2 h. The reaction products were isolated and analyzed as described. The isomer distribution was 55% 2-, 19% 3-, and 26% 4-nitrotoluene. The isotope effect was calculated from the ratios, $(para)_H/(ortho)_H \times (ortho)_D/(para)_D$ and $(para)_H/(meta)_H \times (meta)_D/(para)_D$, obtained in three experiments to be 3.1 ± 0.2. A small correction (3%) for the presence of unlabeled toluene in the starting material was applied.

Nitration and Nitrosation of 4-Tolylmercuric Acetate. Nitronium and nitrosonium tetrafluoroborate were purified as described by Olah and Kuhn.[29] The compounds were manipulated in a nitrogen atmosphere in a drybox. A solution of the nitronium or nitrosonium salt (0.0015 mol) in sulfolane (10 mL) was added dropwise to a stirred solution of 4-tolylmercuric acetate (0.0015 mol) in sulfolane (10 mL). These reaction solutions became green during the initial stages of the reaction. The nitrosation reactions remained green. However, the nitration reactions turned brown. The mixture was poured into water. Ether and 1,2-dichlorobenzene were added and the layers were separated. The ether layer was examined by vapor phase chromatography. The aqueous layer was treated with sodium bromide to precipitate the organomercury compounds. These products, if any, were collected and dried in vacuo. The dry powder was suspended in chloroform and treated with bromine until the solution remained red. This mixture was allowed to stand overnight, then washed with aqueous sodium bisulfite and water prior to drying with sodium sulfate. The aryl bromides produced in these reactions were determined by gas chromatography.

No arylmercuric bromides were formed in the nitrosation reaction. Analysis of the ether layer indicated 96% 4-nitrosotoluene.

The results obtained in the reactions with nitronium tetrafluoroborate were erratic. The yields of 4-nitrosotoluene ranged from 4 to 24%, the yields of 4-nitrotoluene ranged from 6 to 29%, and the yields of 2-nitro-4-bromotoluene ranged from 11 to 41%. We believe that nitrosation reagents are present in the starting materials and that these reagents are responsible for the production of both 4-nitroso- and 4-nitrotoluene.

Nitration of Arylmercuric Acetates. Nitric acid (90%) was freed of nitrogen oxides by treatment with urea and nitrogen.[30] In separate experiments, phenylmercuric acetate (0.7 g, 0.002 mol) and 4-tolylmercuric acetate (0.5 g, 0.0015 mol) were slowly added over 1 h to nitric acid (4.5 mL) at −25 °C. The reactions were stirred for 1 or 2 days at −25 °C. The reactions with phenylmercuric acetate were homogeneous; the reactions with 4-tolylmercuric acetate were not homogeneous throughout the course of reaction.

The reaction mixtures were poured onto ice. The organomercury compounds were converted to bromo compounds by the procedure of Challenger and Rothstein.[19] The product distributions were assessed by vapor phase chromatography. 4-Tolylmercuric acetate provided only 3-nitro-4-methylbromobenzene. Phenylmercuric acetate gave 23% 2-, 51% 3-, and 19% 4-nitrobromobenzene. This product distribution is comparable with prior results.[19]

Competition Experiments. In a typical experiment, benzene (15.6 g, 0.20 mol), toluene (9.2 g, 0.10 mol), and mercuric acetate (1.5 g, 0.0047 mol) were dissolved in acetic acid (60 mL). The solution was heated to 80 °C and a solution of nitric acid (90%, d = 1.5, 0.30 mol) and acetic acid (30 mL) was added dropwise with vigorous stirring. Aliquots of the reaction mixture were taken at regular intervals and analyzed as described previously. The relative rates were assessed by measurement of the product ratios using the Ingold–Shaw expression.

Nitric Acid Catalyzed Mercuration. A solution of mercuric acetate (12.8 g, 0.040 mol), urea (2.0 g, 0.033 mol), acetic acid (120 g, 2.0 mol), and nitric acid (22 mL, 0.47 mol) was heated to 80 °C. A solution of toluene (40.0 g, 0.44 mol) in acetic acid (40 g, 0.67 mol) was added rapidly with stirring. Aliquots (20 mL) were taken from the reaction mixture at various intervals and quenched with an equal volume of water. The mixture was treated with sodium bromide (0.08 mol) to precipitate the tolylmercuric bromides. The precipitate was collected and dried in vacuo. This product mixture was converted to a mixture of bromotoluenes as described previously. The mixture was analyzed by NMR spectroscopy at 270 MHz using the intensity of the methyl resonances. This analytical approach was tested with known mixtures of the isomeric bromotoluenes.

Acknowledgment is made to the U.S. Army Research Office, Grant ARO DAAG-29-76-6-025, for the support of this work.

Registry No.—Toluene, 108-88-3; 4-deuteriotoluene, 4409-83-0.

References and Notes

(1) R. Wolffenstein and O. Boeters, German Patent 194 883; *Chem. Abstr.*, **2**, 1861 (1908).
(2) A concise review of the reaction is presented by A. V. Topchiev, "Nitration of Hydrocarbons and Other Organic Compounds", Pergamon Press, Elmsford, N.Y., 1959, p 43.
(3) F. H. Westheimer, E. Segel, and R. Schramm, *J. Am. Chem. Soc.*, **69**, 773

(1947).
(4) (a) A. I. Titov and A. N. Baryshnikova, *J. Gen. Chem. USSR*, **17**, 829 (1947); (b) A. I. Titov and N. G. Laptev, *ibid.*, **19**, 267 (1949).
(5) T. L. Davis, D. E. Worrall, N. L. Drake, R. W. Helmkamp, and A. M. Young, *J. Am. Chem. Soc.*, **43**, 594 (1921).
(6) S. Tsutsumi and E. Iwata, *J. Chem. Soc. Jpn., Pure Chem. Sect.*, **72**, 141 (1951); *Chem. Abstr.*, **46**, 6604a (1952).
(7) T. Osawa, T. Yoshida, and K. Namba, *Kogyo Kayaku Kyokaishi*, **27**, 162 (1966).
(8) The oxides of Ag, Cu, Pb, Pt, and W and the nitrates of Ag, Al, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, K, Mg, Mn, Na, Ni, Pb, Sn, Sr, U, and Zn were examined.[6,7]
(9) R. O. C. Norman, W. J. E. Parr, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 369 (1974). These workers have achieved limited success using palladium salts and nitrogen dioxide in chloroacetic acid.
(10) H. Komoto, F. Hayano, T. Takami, and S. Yamato, *J. Polym. Sci., Part A-1*, **9**, 2983 (1971).
(11) A summary of the relative rates and isomer distributions for mercuration under several different conditions is found in L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).
(12) F. C. Whitemore, "Organic Compounds of Mercury", Chemical Catalog Co., New York, N.Y., 1921, p 34.
(13) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2300 (1955).
(14) H. C. Brown and C. W. McGary, *J. Am. Chem. Soc.*, **77**, 2306 (1955).
(15) Perchloric acid catalyzes the isomerization of the arylmercuric acetates in acetic acid: ref 14.
(16) (a) H. Zollinger, *Adv. Phys. Org. Chem.*, **2**, 168 (1964); (b) W. Kitching, *Organomet. Chem. Rev., Sect. A*, **3**, 35 (1968).
(17) D. L. H. Williams, *J. Chem. Soc., Perkin Trans. 2*, 655 (1975).
(18) (a) D. Cook, S. J. Kuhn, and G. A. Olah, *J. Chem. Phys.*, **33**, 1669 (1960). (b) R. W. Sprague, A. B. Garrett, and H. H. Sisler, *J. Am. Chem. Soc.*, **82**, 1059 (1960).
(19) F. Challenger and E. Rothstein, *J. Chem. Soc.*, 1258 (1934).
(20) (a) E. C. Taylor, R. H. Danforth, and A. McKillop, *J. Org. Chem.*, **38**, 2088 (1973); (b) B. Davies and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 65 (1975); (c) E. C. Taylor, H. W. Altland, and A. McKillop, *J. Org. Chem.*, **40**, 3441 (1975).
(21) C. Eaborn, Z. S. Salih, and D. R. M. Walton, *J. Chem. Soc., Perkin Trans. 2*, 172 (1972).
(22) G. A. Olah and S. J. Kuhn, *J. Am. Chem. Soc.*, **86**, 1067 (1964).
(23) The nitrode-*tert*-butylation of 4-*tert*-butyltoluene in acetic anhydride gives no more than 1.0% 4-nitrotoluene: M. Bishop, unpublished results.
(24) The steric requirements of nitration reagents are always greater than the steric requirements of comparable nitrosation reagents, e.g., the nitronium ion compared to the nitrosonium ion or acetyl nitrate compared to acetyl nitrite.
(25) Y. Ogata and H. Tezuka, *J. Am. Chem. Soc.*, **89**, 5428 (1967).
(26) J. Turkevich, H. A. McKenzie, L. Friedman, and R. Spurr, *J. Am. Chem. Soc.*, **71**, 4045 (1949).
(27) E. Drener and R. Otto, *Justus Liebigs Ann. Chem.*, **154**, 174 (1870).
(28) E. Wroblevsky, *Justus Liebigs Ann. Chem.*, **168**, 176 (1873).
(29) G. A. Olah and S. J. Kuhn, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 480.
(30) J. P. Freeman and I. G. Shepard, *Org. Synth.*, **43**, 84 (1963).

Stereoselective Total Synthesis of Diterpene Resin Acids

S. C. Welch,* C. P. Hagan, J. H. Kim, and P. S. Chu

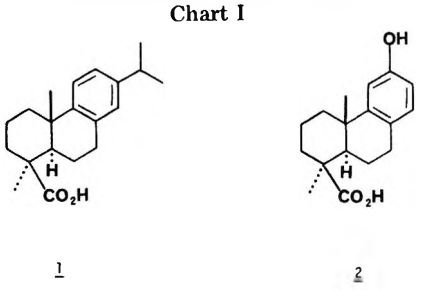
Department of Chemistry, University of Houston, Houston, Texas 77004

Received January 26, 1977

Stereoselective total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2) are described. The synthetic approach to both natural products utilizes a highly stereoselective reductive elimination–alkylation reaction for establishing the axial stereochemistry of the carbomethoxyl functional group at position 1 in esters **12A** and **12B**. Thus treatment of vinyl esters **11A** or **11B** with lithium metal in liquid ammonia/DME followed by methyl iodide effects comcomitant reduction, deoxygenation, and stereoselective alkylation in a single step, therefore providing a general synthetic procedure for the construction of podocarpane type natural products.

The diterpene class of naturally occurring substances forms an enormous group of plant and fungal products derived, biogenetically, from four isoprene units via geranylgeranyl pyrophosphate.[1] Notable features of the diterpene natural products are the fascinating variation encountered in their structures and the wide range of their biological activities. Two diterpene molecules, which have common structure features in rings A and B, are resin acids callitrisic acid (1) and podocarpic acid (2). Callitrisic acid (1) was isolated from the Australian white cypress pine *Callitris columelaris* in 1967.[2] Several syntheses of callitrisic acid (1) have been reported.[3] Interestingly enough Haworth and Baker's synthesis,[3a] the first total synthesis of a diterpenoid natural product, occurred 28 years before callitrisic acid (1) was isolated. Podocarpic acid (2) was first isolated in 1873 from *Podocarpus cupressium*.[4] The structure and stereochemistry of podocarpic acid (2), however, were not characterized until 1940.[5] A number of syntheses of podocarpic acid (2) and deoxypodocarpic acid have been published.[6] The latter acid has been successfully converted to podocarpic acid (2); therefore, synthesis of it also constitutes a total synthesis of podocarpic acid (2). Both callitrisic acid (1) and podocarpic acid (2) have common structural features in rings A and B; namely, they both have a trans A,B ring fusion, an axially oriented carboxylic acid functional group at position 1, an axial methyl group at position 4a, and an equatorial methyl group at position 1. During the course of our investigations aimed at a total synthesis of the antifungal antibiotic LL-Z1271α we developed a new and highly stereoselective method for the construction of ring A of podocarpane type natural products. This new method has general applicability in the synthesis of podocarpane type naturally occurring substances as exemplified by our previously reported syntheses.[3g,6g,7] We wish to report, herein, the full details of our total syntheses of diterpene resin acids (±)-callitrisic acid (1) and (±)-podocarpic acid (2).

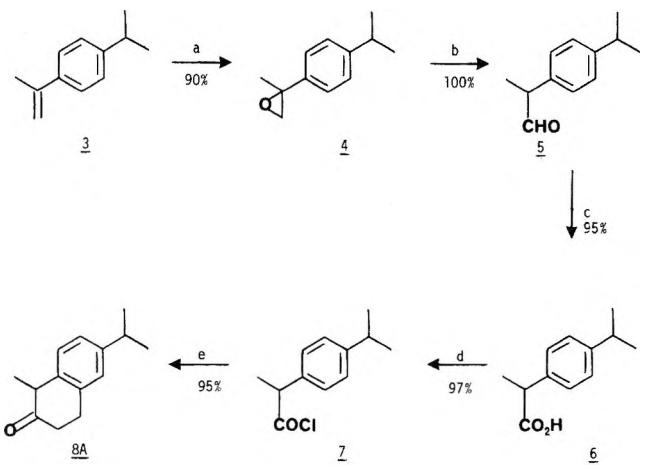
Chart I



1 2

Synthesis of (±)-Callitrisic Acid (1). The starting material chosen for our synthesis of (±)-callitrisic acid (1) is 6-isopropyl-1-methyl-2-tetralone (**8A**, Scheme I), which was previously prepared by Stork and Schulenberg[8] from cumene as well as 2-acetonaphthone by lengthy multistep sequences. We have developed a short and efficient alternate route to tetralone **8A** beginning with 4-isopropenylisopropylbenzene (3).[9] Epoxidation of alkene **3** with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of disodium hydrogen phosphate

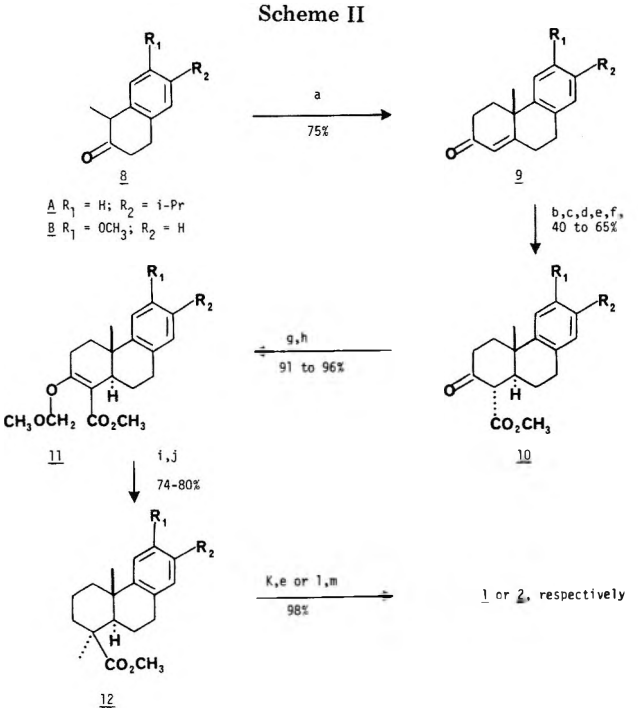
Scheme I



3 4 5 8A 7 6

a) m-CPBA, Et_2O, Na_2HPO_4; b) BF_3-OEt_2, Et_2O; c) CrO_3, H_2SO_4, H_2O, acetone; d) $SOCl_2$, C_6H_6; e) anhydrous $AlCl_3$, CH_2Cl_2, -20±2°, $CH_2=CH_2$.

Scheme II



8 (A R_1 = H; R_2 = i-Pr; B R_1 = OCH_3; R_2 = H) 9 10 11 12

1 or 2, respectively

a) MVK, EtOH, NaOEt; b) Li, NH_3, Et_2O; c) $-NH_3$; d) CO_2; e) H_3O^+, 0°; f) CH_2N_2, Et_2O; g) NaH, HMPA; h) CH_3OCH_2Cl; i) Li, NH_3, DME; j) CH_3I; k) KO-t-Bu, DMSO; l) n-PrSLi, HMPA m) HI, HOAc.

in ether gives oxirane **4** in 90% yield.[10] Treatment of epoxide **4** with 1.2 equiv of boron trifluoride etherate in ether for 40 min at 0–25 °C followed by an aqueous workup affords aldehyde **5** in quantitative yield.[11] Oxidation of aldehyde **5** with Jones reagent at 0–25 °C for 30 min produces crystalline carboxylic acid **6** (mp 68–69 °C) in 95% yield.[12] Treatment of carboxylic acid **6** with 1.5 equiv of thionyl chloride at room temperature for 24 h followed by removal of excess thionyl chloride via codistillation with benzene gives acid chloride **7** in 97% yield.[13] Finally, tetralone **8A** was prepared from acid chloride **7** utilizing Sims and co-workers' modification of the Friedel–Crafts reaction.[14] Acid chloride **7** was added dropwise to a stirred suspension of 1.03 equiv of anhydrous aluminum chloride in dry dichloromethane at −20 ± 2 °C. As soon as a homogeneous, light green solution of acid chloride–aluminum chloride complex formed (about 5 min after the addition) then a gentle stream of ethylene was allowed to bubble into the stirred reaction mixture over a period of 20 min. The resulting green-brown solution was stirred for an additional 10 min at −20 ± 2 °C, and then allowed to stir for 3 h at room temperature. After aqueous workup at 0 °C, tetralone **8A** was obtained in 95% yield (83% overall yield from alkene **3**). This reaction can be monitored by GLC, but it can also be conveniently monitored, simply and reproducibly, by the color change of the reaction mixture.

Robinson annelation of tetralone **8A** with 1.3 equiv of methyl vinyl ketone in the presence of a catalytic amount of sodium ethoxide in absolute ethanol affords tricyclic enone **9A** (Scheme II, R_1 = H; R_2 = *i*-Pr) in 75% yield.[15] Simultaneous reduction of enone **9A** to a trans A,B ring fusion and introduction of the carbomethoxyl group at position 1 were accomplished using Stork and co-workers' reductive carbomethoxylation procedure.[16] Sequential treatment of enone **9A** with 3 equiv of lithium metal in anhydrous liquid ammonia–ether, quickly removing the ammonia, adding excess anhydrous dry ice (freshly sublimed twice), quenching with water, extracting with ether to remove neutral side products, acidifying with 10% hydrochloric acid solution at 0 °C, and esterification with ethereal diazomethane produces crystalline β-keto ester **10A** in 64% yield. Keto ester **10A** was found to exist exclusively in the keto form. Compounds with 2-keto-1-carbomethoxyl functional groups in *trans*-decalin rings are reported to exist in the keto form as opposed to the enol form.[17] Wenkert and Jackson rationalize this observation by a combination of two facts: first, $\Delta^{1,2}$-alkenes in trans-fused decalin rings are energetically unfavorable configurations; second, there is a strong steric repulsion between the carbomethoxyl group at position 1 and the equatorial hydrogen at position 10 (the peri effect).[17,18]

Alkylation of β-keto ester **10A** using 1.2 equiv of sodium hydride in hexamethylphosphoric triamide (HMPA) followed by addition of 1.2 equiv of chloromethyl methyl ether gives vinyl ether ester **11A** in 96% yield.[19,20] Finally, reductive elimination–alkylation of vinyl ether ester **11A** using 7 equiv of lithium metal in anhydrous liquid ammonia/1,2-dimethoxyethane (DME), followed by quenching with excess methyl iodide, affords (±)-methyl callitrisate (**12A**) in 74% yield as the only isomer observed (NMR, GLC) or isolated (LC). Methyl ester **12A** was cleaved to (±)-callitrisic acid (**1**) in 98% yield using potassium *tert*-butoxide in anhydrous dimethyl sulfoxide (Me_2SO) at 100 °C for 6 h followed by acidification.[2] Both synthetic callitrisic acid and methyl callitrisate were identical with authentic samples[21] with respect to IR, NMR, TLC, GLC, and LC.

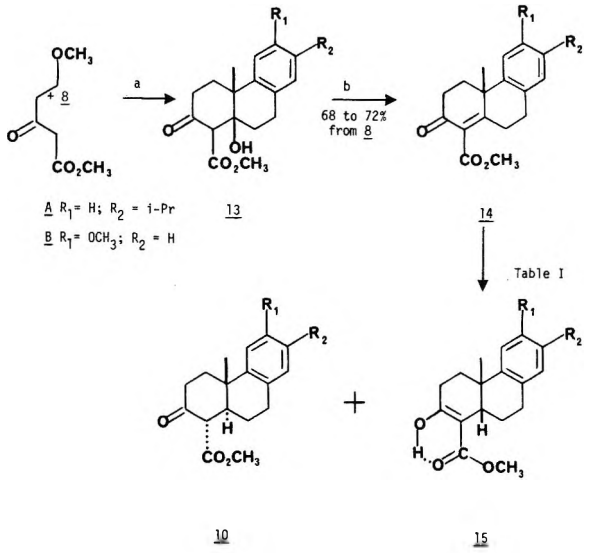
Synthesis of (±)-Podocarpic Acid (2). The starting material chosen for our synthesis of podocarpic acid (**2**) is tricyclic enone **9B** (Scheme II, R_1 = OCH_3; R_2 = H) previously prepared by Kuehne from 2,7-dimethoxynaphthalene via 7-methoxy-1-methyl-2-tetralone (**8B**).[22,23] Reductive carbomethoxylation[16] of enone **9B** affords crystalline β-keto ester **10B** in 40% yield. Alkylation of β-keto ester **10B** using sodium hydride in HMPA followed by chloromethyl methyl ether gives vinyl ether ester **11B** in 91% yield.[19,20] Reductive elimination–alkylation of vinyl ether ester **11B** using 6.1 equiv of lithium metal in DME followed by the addition of excess methyl iodide produces (±)-methyl *O*-methylpodocarpate (**12B**) in 80% yield as the only isomer observed (NMR, GLC) or isolated (LC). Synthetic ether ester **12B** was identical with an authentic sample[24] prepared from (+)-podocarpic acid (**2**) with respect to IR, NMR, TLC, and GLC. Ester **12B** can be selectively and quantitatively cleaved to *O*-methylpodocarpic acid using lithium *n*-propylmercaptide in HMPA.[25] The latter ether has been converted to (±)-podocarpic acid (**2**) with hy-

driodic acid in refluxing glacial acetic acid; therefore, our synthesis of (±)-methyl *O*-methylpodocarpate (**12B**) constitutes a total synthesis of (±)-podocarpic acid (**2**).

This new reductive elimination–alkylation reaction which is utilized in converting vinyl ether esters **11A,B** to equatorially methylated esters **12A,B**, respectively, are highly stereoselective. This high degree of stereoselectivity results from two reinforcing principles of stereoelectronic control: first, it is well known that exocyclic enolate anions (such as the ester enolate anion generated by reduction of vinyl ether esters **11A,B**, with lithium in liquid ammonia/DME) in cyclohexane rings have a decided preference for alkylation in which the alkylating agent approaches from the less hindered equational direction;[26a] second, the exocyclic enolate anions, generated in the reaction (**11A,B** → **12A,B**, respectively), are also seriously hindered on the β side (axial direction) by a 1,3-axial methyl interaction of the methyl group at position 4a.[26b] This sequence of events from vinyl ether ester **11A,B**, to esters **12A,B**, respectively, represents a new type of reductive elimination–alkylation reaction. This reaction sequence is unique because it effects reduction, deoxygenation, and concomitant stereoselective methylation is a single step, thus providing an efficient and general pathway for the construction of podocarpane type natural products.

An Alternate Synthetic Route to β-Keto Esters 10A,B. An alternate synthetic route to β-keto esters **11A,B** (Scheme III) was investigated in the hope of circumventing the often-

Scheme III



a) p-TsOH, C_6H_6; b) CF_3SO_3H, C_7H_8

times troublesome reductive carbomethoxylation reaction (**9A,B** → **10A,B**, respectively). Although this alternate route produces keto esters **10A,B**, in good overall yield (44–52%), the stereoeselectivity in the reduction step (**14A,B** → **10A,B** + **15A,B**, respectively) is considerably less efficient (Table I). Acid-catalyzed Robinson annelation of 1.6 equiv of methyl 5-methoxy-3-oxopentanoate with 6-isopropyl-1-methyl-2-tetralone (**8A**) in refluxing benzene for 60 h in the presence of a catalytic amount of *p*-toluenesulfonic acid[28] gives a mixture of tricyclic alcohol **13A** (15%) and keto ester **14A** (38%). When the same annelation is performed in refluxing toluene for 48 h a mixture of keto ester **14A** (39%) and enone **9A** (25%) was obtained. Utilizing trifluoromethanesulfonic acid in refluxing toluene for 70 h to effect the annelation reaction also affords a mixture of keto ester **14A** (20%) and enone **9A** (24%). Optimum conditions for the conversion of tetralone **9A** to tricyclic enone ester **14A** were determined to be as follows. A solution of 1.6 equiv of methyl 5-methoxy-3-oxopentanoate, 6-isopropyl-1-methyl-2-tetralone (**9A**), and a catalytic amount of *p*-toluenesulfonic acid in toluene was allowed to stir at reflux for 8 h using a Dean-Stark water separator to afford a mixture of ketol **13A** and enone **14A** in a 3:2 ratio, respectively. This crude mixture was then heated at reflux for 1 h in toluene in the presence of a catalytic amount of trifluoromethanesulfonic acid using a Dean-Stark water separator to give enone **14A** in 68% overall yield from tetralone **8A**. The best method found for the acid-catalyzed Robinson annelation of methyl 5-methoxy-2-oxopentanoate with 7-methoxy-1-methyl-2-tetralone was to heat this mixture in refluxing benzene in the presence of *p*-toluenesulfonic acid for 72 h using a Dean-Stark water separator followed by treatment with a catalytic amount of trifluoromethanesulfonic acid in refluxing toluene for 1 h again using a Dean-Stark water separator to give tricyclic enone ester **14B** in 72% overall yield from tetralone **8B**.

Table I

Compd	Reagents and conditions	Product ratio 10:15	Yield, %
14A	5% Pd–$BaSO_4$/EtOH/50 min/1 atm/RT	63.2:36.8	95[a]
		68.6:31.4	94[b]
	5% Pd/C/EtOH/1 h/1 atm/RT	52:48	90[a]
	5% Pd–$SrCO_3$/MeOH/17 h/1 atm/RT	46:54	85[a]
	PtO_2/HOAc/18 h/1 atm/RT	Trace Trace	*c*
	Li/NH_3/*t*-BuOH/THF	68.5:31.5	90[a]
	Zn/HOAc/Et_2O/6 h/RT	69:31	60[a]
	$NaBH_4$/pyridine/50 min/RT	58:42	90[a]
	$LiAlH(Ot\text{-}Bu)_3$/Et_2O/20 h/RT	Trace Trace	*d*
	$NaAlH_2(CH_3OCH_2CH_2O)_2$/CuBr/THF	No reaction	
14B	5% Pd–$BaSO_4$/EtOH/3 h/1 atm/RT	69.5:30.5	95[a]
		73.5:26.5	98[b]

[a] Estimated by GLC. [b] Isolated yield. [c] Complex mixture. [d] Allylic alcohol in 85% yield.

A number of methods for reduction of enones **14A,B** to β-keto esters **10A,B**, respectively, were explored (Table I). The best conditions for catalytic hydrogenation of enones **14A,B** were with 5% palladium on barium sulfate in absolute ethanol, which affords a mixture of trans β-keto esters **10A,B** and cis β-keto esters **15A,B** in 73.5–68.6 and 26.5–31.4% yield, respectively.[17,30] Compounds **15A,B** were each homogeneous on TLC; however, each showed two peaks in a ratio of 81–80:19–20, respectively, on GLC analysis. Spectral analysis (IR, NMR) showed that each compound **15A,B** exists as a mixture of enol–keto tautomers in a ratio of 70–75:30–25, respectively.

The use of dissolving metal reagents for the reduction of α,β-unsaturated ketones to saturated ketones with the more stable configuration at the β-carbon atom has been widely utilized in stereoselective syntheses.[31] Interestingly enough, when enone **14A** is reduced with 2.2 equiv of lithium metal in liquid ammonia/tetrahydrofuran (THF)/*tert*-butyl alcohol (1.25 equiv) both trans β-keto ester **10A** and cis β-keto ester **15A** were produced in 90% yield as a 68.5:31.5 ratio, respectively. Reduction of enone **14A** with zinc powder in glacial acetic acid—ether[32] for 6 h at room temperature also gives a mixture of trans β-keto ester **10A** and cis β-keto ester **15A** in 60% yield as a 69:31 ratio, respectively.

Enone esters **14A,B** should be good electrophiles in a Michael reaction and therefore compounds **14A,B** may readily undergo 1,4-reduction with appropriate hydride reducing agents. Reduction of enone esters **14A,B** in this fashion is

expected to be a facile process because these reactions should produce very stable enolate anions of either β-keto esters **10A,B** or **15A,B**. Adank and co-workers reported the use of sodium borohydride in pyridine to effect 1,4-reduction of some enones.[33] Reduction of enone **14A** with 1.23 equiv of sodium borohydride in dry pyridine at room temperature for 50 min produces a mixture of trans β-keto ester **10A** and cis β-keto ester **15A** in 90% yield as a 58:42 ratio, respectively. Dilling and Plepys recently reported that the reduction of certain α,β-unsaturated ketones could be effected by lithium tri-*tert*-butoxyaluminum hydride in ether to give primarily saturated ketones.[34] However, when enone **14A** was treated with 2.56 equiv of lithium tri-*tert*-butoxyaluminum hydride in ether for 20 h at room temperature only reduction to the corresponding allylic alcohol was observed. This was confirmed spectroscopically (IR 3400 cm^{-1}, OH; 1725 cm^{-1}, conjugated ester) and by oxidation of this alcohol back to enone **14A** with Jones reagent.[12] Recently, Semmelhack and Stauffer reported that complex hydridometallic species generated from sodium bis(2-methoxyethoxy)aluminum hydride and copper(I) bromide in THF at 0 °C selectively reduces some α,β-unsaturated esters and ketones.[35] But, when enone ester **14A** was allowed to react with this complex, generated in situ, only unchanged starting material was recovered quantitatively.

Conclusion

Both (±)-callitrisic acid (**1**) and (±)-podocarpic acid (**2**) have been successfully synthesized in a limited number of specific and highly stereoselective steps. The best method for the preparation of trans β-keto esters **10A,B** is via Stork and co-workers' reductive carbomethoxylation procedure, although reduction of enone esters **14A,B** provides a good, but less stereoselective, alternative pathway. Reductive elimination–alkylation of vinyl ether esters **11A,B** has been shown to be a very efficient and stereoselective method with general applicability for the construction of ring A of podocarpane type natural products.

Experimental Section

General Procedure. Melting points were determined on a Fisher-Johns, a Thomas-Hoover, or a Büchi melting point apparatus. All melting points and boiling points are uncorrected. Evaporative distillation refers to bulb to bulb short-path distillation in which the bulb was heated in an Aldrich Kugelrohr apparatus.[36] The temperatures cited for these distillations refer to the maximum temperature attained by the air chamber during the distillation. Microanalyses were preformed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Analytical gas phase chromatography (GLC) was performed on a Varian Aerograph Model 1400, equipped with a flame ionization detector with helium as the carrier gas, using the following types of columns and flow rates: (a) 5-ft, stainless steel, 0.125-in. column, packed with 3% SE-30 on Varaport-30, 100/120 mesh (Varian); (b) 6-ft, stainless steel, 0.125-in. column, packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian); (c) 6-ft, stainless steel, 0.125-in. column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian); flow rates of 15 mL/min at ambient temperature for all columns. Silica gel PF 254 + 336 (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70–230 mesh, available from Brinkmann Instruments) were used for thin layer and column chromatography, respectively. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 700, or a Perkin-Elmer grating infrared spectrophotometer, Model 237B. Samples were taken as 10% solutions in spectroquality carbon tetrachloride or chloroform using balanced 0.1-mm sodium chloride cells or were taken as thin films between sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were measured on a Varian Associates Model T-60 spectrometer in the solvent indicated. Mass spectra (MS) were obtained on a Hitachi Perkin-Elmer Model RMU-6H single-focusing mass spectrometer.

Finally, for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120 °C for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[37] All liquid transfers were made with nitrogen-filled syringes. The term "petroleum ether" refers to Baker "Analyzed Reagent", bp 30–60 °C. The general workup procedure was to extract the aqueous layer with ether (three times); the combined ethereal extracts were washed with water (three times) and saturated sodium chloride solution (once), and then dried (Na_2SO_4), filtered (through Na_2SO_4 or $MgSO_4$), and concentrated in vacuo.

2-Methyl-2-(4-isopropyl)phenyloxirane (4).[10] *m*-Chloroperbenzoic acid (*m*-CPBA, 40.2 g of 81.3% assay,[38] 189.4 mmol, Aldrich), disodium hydrogen phosphate (Na_2HPO_4, 30.7 g, 216.2 mmol), and anhydrous ether (300 mL, freshly distilled from lithium aluminum hydride) were placed in a 1-L three-necked round-bottomed flask, equipped with a mechanical stirrer, a thermometer, and a pressure-equalizing addition funnel. The stirred suspension was cooled in an ice bath and 4-isopropenylisopropylbenzene[9] (16.03 g, 100.0 mmol) dissolved in dry ether (100 mL) was added under nitrogen as a slow stream over a period of 30 min. The rate of addition was adjusted so that the temperature of the reaction did not rise above 5 °C. After stirring for 1 h the ice bath was removed and the mixture was further allowed to stir at room temperature with monitoring by GLC (column a). After stirring for 4 h at room temperature, the reaction was complete and the resulting white suspension was transferred to a separatory funnel using ether and enough water to dissolve all the solid material. The organic layer was separated and the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with cold 5% sodium hydroxide solution (3 × 100 mL), then worked up in the usual way. Evaporative distillation (50 °C at 0.2 mm) gave 15.88 g (90.1%) of pure oxirane **4**: IR (film), 3060 (C–H, epoxy), 3030 (C–H, aromatic), 2980, 2960, and 2890 (C–H. aliphatic), 1895, 1795, and 1720 (1,4-disubstituted aromatic overtone), 1604, 1510, 1450, and 1418 (aromatic skeletal), 1455 (–CH_3, bending), 1380 and 1365 (isopropyl), 910, 865, 790, and 750 (epoxy ring), and 835 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.25 (d, 6, *J* = 7 Hz, –CH**Me**$_2$), 1.56 (s, 3, –CH_3), 2.38–3.12 (two overlapped m, 3, epoxy methylene and –C**H**Me$_2$), and 6.96–7.29 ppm (m, 4, aromatic).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.71; H, 9.26.

2-(4-Isopropyl)phenylpropanal (5).[11] Boron trifluoride etherate (3.0 mL, 24.4 mmol, distilled from calcium hydride) was added at 0 °C (ice bath) to a stirred solution of oxirane **4** (3.55 g, 20.1 mmol) dissolved in anhydrous ether (50 mL, freshly distilled from lithium aluminum hydride) under nitrogen. After stirring for 10 min, the ice bath was removed and the reaction mixture was allowed to stir for 30 min at room temperature. The reaction mixture was then diluted with ether (100 mL), washed with saturated sodium bicarbonate solution (4 × 40 mL), then worked up in the usual way to give 3.55 g (100%) of aldehyde **5** as a colorless liquid. The crude product was used immediately for the next reaction without further purification. The analytical sample was prepared by evaporative distillation (35 °C at 0.02 mm) of a small sample: IR (CCl_4) 2960 and 2875 (C–H, aliphatic), 2800 and 2700 (–CHO and overtone), 1725 (CO), 1506, 1455, and 1420 (aromatic skeletal), 1380 and 1365 (isopropyl), 1280, 1055, 1015, and 825 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.25 (d, 6, *J* = 7 Hz, –CH**Me**$_2$), 1.40 (d, 3, *J* = 8 Hz, COCHC**H**$_3$), 2.88 (m, 1, *J* = 7 Hz, –C**H**Me$_2$), 3.52 (quartet of doublets, 1, CH_3CHCHO), 6.90–7.30 (m, 4, aromatic), and 9.60 ppm (d, 1, *J* = 2 Hz, –HCCHO).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.63; H, 9.01.

2-(4-Isopropyl)phenylpropanoic Acid (6).[12] To a vigorously stirred solution of aldehyde **5** (30.0 g, 170.0 mmol) in reagent grade acetone (800 mL) at 5 °C (ice bath) was added Jones reagent (70 mL of 2.67 M solution, 187 mmol) at such a rate that the reaction temperature was maintained at 5 °C (over a period of 1 h). After stirring for 10 min, the ice bath was removed and the resulting orange mixture was further stirred for 30 min at room temperature. The excess oxidizing reagent was then quenched by dropwise addition of 2-propanol until the orange color disappeared in the upper layer of the two-phase mixture. The reaction mixture was diluted with ether (600 mL) and water (400 mL), then the organic layer was separated, and the aqueous layer was extracted with ether (4 × 150 mL). The combined organic extracts were washed with water (once), then extracted with saturated sodium bicarbonate solution (5 × 300 mL). The total basic extracts were acidified at 0 °C (ice bath) with stirring, with 10% hydrochloric acid solution. This acidified solution was then worked up in the usual way to afford 31.1 g (95.1%) of crystalline carboxylic acid **6**. The analytical sample was prepared by recrystallization (three times) from methanol and water, followed by sublimation (40 °C at 0.02 mm): mp 68–69 °C; IR (CCl_4) 3300–2500 (–CO_2H, dimeric), 1710 (CO), 1510, 1460, and 1410 (aromatic skeletal), 1420 (–OH bending), 1290 (C–O), 1230 (–CO_2–), and 925 cm^{-1} (–OH bending, dimeric); NMR (CCl_4) δ 1.26 (d, 6, *J* = 7 Hz, –CH**Me**$_2$), 1.48 (d, 3, *J* = 8 Hz, –CH_3), 2.86 (m, 1, *J* = 7 Hz, –C**H**Me$_2$), 3.63 (q, 1, *J* = 8 Hz, –C**H**CO_2H), 6.95–7.32 (m, 4, aromatic), and 12.01 ppm (s, 1, –CO_2H).

Anal. Calcd for $C_{12}H_{16}C_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.28.

2-(4-Isopropyl)phenylpropanoic Acid Chloride (7).[13] Carboxylic acid **6** (14.65 g, 76.3 mmol, dried over phosphorus pentoxide for 24 h at room temperature under reduced pressure), thionyl chloride (8.2 mL, 115.0 mmol), and a few boiling stones (silicon carbide) were introduced in a flask attached with an efficient condenser carrying a calcium chloride drying tube. The mixture was allowed to react for 24 h at room temperature followed by 30 min at 50 °C (bath temperature). The resulting yellowish-green liquid was then transferred to a round-bottomed flask with anhydrous benzene (10 mL, freshly distilled from calcium hydride) and the excess thionyl chloride was removed azeotropically with benzene on a Büchi rotoevaporator. After about an equal volume of dry benzene (20 mL) was added to the concentrate, the azeotropic distillation was repeated. Evaporative distillation (45 °C at 0.02 mm) of the crude product afforded 15.63 g (97.3%) of pure acid chloride **7** as a colorless liquid: IR (CCl_4) 3030 (C–H, aromatic), 2960 and 2870 (C–H, aliphatic), 1785 and 1840 (CO), 1510, 1450, and 1420 (aromatic skeletal), 1375 and 1365 (isopropyl), 920 (C–CO–Cl), and 710 cm^{-1} (C–Cl); NMR (CCl_4) δ 1.28 (d, 6, J = 7 Hz, $-CHMe_2$), 1.56 (d, 3, J = 7 Hz, $COCHCH_3$), 2.88 (m, 1, J = 7 Hz, $-CHMe_2$), 4.02 (q, 1, J = 8 Hz, $-COCHCH_3$), and 7.23 ppm (s, 4, aromatic).

Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.18. Found: C, 68.38; H, 7.22.

1-Methyl-6-isopropyl-2-tetralone (8A).[14] Anhydrous aluminum chloride (6.80 g, 51.0 mmol, J. T. Baker) and dry dichloromethane (500 mL, freshly distilled from phosphorus pentoxide) were placed under nitrogen in a 1-L three-necked flask equipped with a magnetic stirrer, a condenser, a gas inlet tube, and a pressure-equalizing dropping funnel. Acid chloride **7** (10.40 g, 49.4 mmol) dissolved in anhydrous dichloromethane (120 mL) was added to the stirred suspension at −20 ± 2 °C (external, temperature dry ice/acetone) slowly over a period of 15 min. As soon as a homogeneous light green solution of acid chloride–aluminum chloride complex started to form (5 min after the addition of **7** started), a gentle stream of ethylene was bubbled into the vigorously stirred mixture at −20 ± 2 °C (external temperature) over a period of 20 min. After stirring for 10 min the cooling bath was removed. The resulting brown solution was allowed to stir for 3 h at room temperature, then cooled in an ice bath and the red-brown reaction was carefully quenched with ice–water (150 mL). The resulting mixture was then stirred until all of the solid material was dissolved to give a colorless two-phase system (30 min). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with 5% hydrochloric acid solution (once), water (once), and saturated sodium bicarbonate solution (twice), then worked up in the usual way to give a slightly yellow oil of crude ketone **8A.** Evaporative distillation (55 °C at 0.02 mm) of the crude product 9.44 g (94.5%) of pure ketone **8A** as a colorless liquid. 2,4-Dinitrophenylhydrazone derivative, recrystallized (three times) from ethanol and water, mp 143–144 °C (lit.[8] 142.5–144 °C). Semicarbazone, recrystallized (three times) from methanol: mp 166–167 °C (lit.[8] 166–166.5 °C); IR (CCl_4) 3030 (C–H, aromatic), 2960 and 2870 (C–H, aliphatic), 1890 and 1762 (1,2,4-substituted aromatic overtone), 1715 (CO), 1495, 1452, and 1425 (aromatic skeletal), 1385 and 1360 (isopropyl), 1165, 1050, and 1015 (1,2,4-substituted aromatic ring, bending), and 985, 880, and 820 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.28 (d, 6, J = 7 Hz, $CHMe_2$), 1.42 (d, 3, J = 7 Hz, $-COCHCH_3$), 2.3–3.1 (m, 5, ring methylenes, $-CHMe_2$), 3.39 (q, 1, J = 7 Hz, benzylic methine), and 7.06 ppm (unresolved s, 3, aromatic); GLC analysis on column a (column temperature 150 °C, retention time 11.4 min) and column b (column temperature 180 °C, retention time 14.0 min) shows the product to be greater than 99.9% of a single substance.

2,3,4,4a,9,10-Hexahydro-7-isopropyl-4a-methyl-2-oxophenanthrene (9A)[15] To a stirred solution of ketone **8A** (0.744 g, 3.67 mmol) in absolute ethanol (2 mL) at −30 °C (bath temperature, dry ice/acetone) under nitrogen atmosphere was added sodium ethoxide (6.8 mg, 0.1 mmol). After stirring for 10 min at −30 °C, the pale yellow solution was cooled to −65 °C (bath temperature, dry ice/acetone) and methyl vinyl ketone (0.40 mL, 4.93 mmol, freshly distilled, bp 81 °C) was added dropwise to it. After the temperature of the cooling bath was allowed slowly to rise to 0 °C (30 min), the reaction mixture was stirred for 1.5 h at 0 °C (ice bath), then for 24 h at room temperature, followed by 3 h at reflux. After the red-brown reaction mixture was cooled to room temperature, it was poured into a separatory funnel containing water (29 mL), ether (20 mL), and 5% hydrochloric acid solution (5 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (1 × 20 mL), then worked up in the usual way to give 1.102 g (118%) of a red oil. Chromatography on silica gel (100 g, 70–230 mesh, E. Merck) in a 1.5-cm diameter column using a 20:80 mixture of ether and petroleum ether to elute 50-mL sized fractions gave 0.70 g (75.0%) of pure enone **9A** in fractions 24–31. The analytical sample was prepared by evaporative distillation (72 °C at 0.02 mm) of a small sample of chromatographed product: IR (CCl_4) 3050 (=CH), 3030 (C–H, aromatic), 2960, 2930, and 2870 (C–H, aliphatic), 1675 (CO), 1625 (C=C), 1495, 1450, and 1410 (aromatic skeletal), and 950, 880, and 820 cm^{-1} (C–H bending aromatic); NMR (CCl_4) δ 1.22 (d, 6, J = 7 Hz, $-CHMe_2$), 1.55 (s, 3, $-CH_3$), 1.82–3.03 (m, 9, methylenes), 5.75 (s, 1, –C=CH), and 6.80–7.22 ppm (m, 3, aromatic); GLC analysis on column a (column temperature 200 °C, retention time 15.6 min) and column b (column temperature 240 °C, retention time 12.8 min) indicates the product to be greater than 99.5% of a single product. Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.90; H, 8.61.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-2-oxo-1α-phenanthrenecarboxylate (10A).[16] Anhydrous liquid ammonia (100 mL, distilled through two potassium hydroxide towers) was collected in a 250-mL, three-necked, round-bottomed flask equipped with a magnetic stirrer and a dry ice condenser carrying a soda-lime drying tube. Lithium wire (5 cm, 29.0 mg-atom) was cut, washed in hexane to remove mineral oil, quickly dried with Kimwipe, and then added to the vigorously stirred ammonia in four small pieces. After the resulting dark blue mixture was stirred at reflux (−33 °C) for 10 min, a solution of enone **9A** (2.460 g, 9.67 mmol) dissolved in anhydrous ether (40 + 10 + 10 mL, freshly distilled from lithium aluminum hydride) was added rapidly (5 min) to it (after the addition, the reaction mixture remained blue). As soon as the addition was complete, dry ice and acetone in the condenser were replaced with ice–water and the remaining ammonia was evaporated in a warm water bath as quickly as possible (15 min). After the soda-lime drying tube was replaced by two Drierite towers, 40 mL of dry ether was added and the resulting suspension was heated (hot water bath) at reflux for 15 min to drive off any residual ammonia. The reaction contents were then cooled to −78 °C (dry ice/acetone) and excess anhydrous, powdered dry ice (ca. 2.5 g, doubly sublimed and condensed with liquid nitrogen) was added to the white slurry. The cooling bath was then removed and the resulting slurry was allowed to stir for 30 min at room temperature, followed by quenching at −78 °C with a large excess of powdered dry ice (50 g) and cold water (50 mL). After the cooling bath was removed and the slightly yellow reaction mixture thawed, it was transferred, with a small amount of cold water, to a precooled separatory funnel. The ether layer was then separated and set aside; it was subsequently washed with saturated sodium chloride solution, then dried (Na_2SO_4) and concentrated in vacuo to give 0.758 g (30.6%) of a red oil, which was found largely to be the trans reduction product of enone **9A.** Very cold ether (200 mL) was then added to the aqueous layer and the resulting two-phase system was carefully acidified (pH ~2) at 0 °C with stirring by dropwise addition of cold 10% hydrochloric acid solution. The aqueous layer turned cloudy and then became clear as the freed carboxylic acid dissolved in the ether layer. After the layers were separated, the aqueous layer was extracted with very cold ether (4 × 50 mL). The very cold ethereal extracts were combined and washed with cold saturated sodium chloride solution (2 × 200 mL), then allowed to filter (glass wool) into a stirred excess ethereal diazomethane solution at 0 °C (ice bath). After the mixture was stirred for 30 min at room temperature, the excess diazomethane was titrated with glacial acetic acid until only faintly yellow diazomethane color remained. The resulting solution was then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 1.982 g (65.2%) of a slightly yellow, crystalline keto ester **10A.** Trituration of the crude product in ether gave 1.940 g (63.7%) of pure keto ester **10A:** mp 106.5–107 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2955 and 2870 (C–H, aliphatic), 1740 (CO, ester), 1710 (CO), 1495, 1455, and 1428 (aromatic skeletal), 1380 and 1355 (isopropyl), 1270 and 1150 (C–O–C), and 820 cm^{-1} (C–H bending, aromatic); NMR ($CDCl_3$) δ 1.22 (d, 6, J = 7 Hz, $CHMe_2$), 1.35 (s, 3, $-CH_3$), 1.5–3.1 (m, 10, methylenes and methine), 3.40 (d, 1, J = 12 Hz, $-COCHCO-$), 3.80 (s, 3, $COOCH_3$), and 6.90–7.33 ppm (m, 3, aromatic); GLC analysis on column a (column temperatures 222 °C, retention time 9.84 min) and column b (column temperature 225 °C, retention time 9.13 min) shows β-keto ester **10A** to be a single product.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.27; H, 8.30.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-6-methoxy-4aβ-methyl-2-oxo-1α-phenanthrenecarboxylate (10B).[16] To a stirred solution of lithium (0.047 g, 6.77 mg-atoms) in anhydrous liquid ammonia (50 mL) was added rapidly enone **9B** (0.482 g, 1.99 mmol, dried over phosphorus pentoxide under reduced pressure) dissolved in anhydrous ether (10 + 2 + 2 mL, freshly distilled from lithium alu-

minum hydride). Then the ammonia was quickly evaporated with a hot water bath (5 min). The soda-lime drying tube of the dry ice condenser was replaced by a Drierite tower and 10 mL of dry ether was then added to the reaction mixture, followed by refluxing for 15 min to drive off any residual ammonia. The reaction was then cooled to −78 °C (dry ice/acetone) and excess anhydrous dry ice powder (ca. 2 g, sublimed through two Drierite towers, condensed by liquid nitrogen, resublimed, and recondensed) was added. After the cooling bath was removed, the reaction mixture was stirred for 30 min at room temperature followed by 30 min in a water bath at room temperature. Then, the reaction was cooled to −78 °C and excess powdered dry ice (10 g) was added followed by 10 mL of water. When the solid reaction mixture melted, it was transferred, with cold water (three times) and ether (three times), to a separatory funnel containing ice–water. The ether layer was separated and set aside; subsequent evaporation of the solvent gave 0.210 g (43%) of a yellow solid, the major component of which was identified to be the trans reduction product of enone **9B**. After 25 mL of ether was added, the aqueous layer was acidified with hydrochloric acid solution (1:1 mixture of concentrated HCl and ice). The layers were separated and the aqueous layer was extracted with cold ether (2 × 50 mL). The combined cold ethereal extracts were washed with cold saturated soidum chloride solution (2 × 25 mL) and then allowed to filter (glass wool plug) into excess ethereal diazomethane solution at 0 °C (ice bath). After the mixture was stirred for 30 min at 0 °C and 30 min at room temperature, the excess diazomethane was titrated with glacial acetic acid. The resulting solution was then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.332 g (55.2%) of crude keto ester **10B**. Chromatography of the crude product on silica gel (75 g, 75–325 mesh, E. Merck) using a 50:50 mixture of ether and petroleum ether to elute 35-mL fractions, gave 0.238 g (39.6%) of pure keto ester **10B** in fractions 8–12. The analytical sample was prepared by recrystallization (three times) from ether and chloroform: colorless, cubic crystals, mp 146–147 °C; IR ($CHCl_3$) 2945 and 2835 (C–H), 1740 (CO, ester), 1710 (CO), 1605, 1500, and 1430 (aromatic skeletal), 1290 and 1145 (C–O–C), and 1045 cm^{-1} (Ph–O–C); NMR ($CDCl_3$) δ 1.35 (s, 3, $-CH_3$), 1.4–3.0 (m, 9, methylenes and methine), 3.40 (d, 1, J = 12 Hz, –COCHCO–), 3.78 (s, 6, $PhOCH_3$ and $-COOCH_3$), and 6.6–7.2 ppm (m, 3, aromatic).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.35. Found: C, 71.38; H, 7.26.

Methyl 3,4,4a,9,10,10aα-Hexahydro-7-isopropyl-2-(methoxymethoxy)-4aβ-methyl-1-phenanthrenecarboxylate (11A).[19,20] Sodium hydride (0.0994 g of 50% dispersion in mineral oil, 4.14 mmol, Ventrol) was worked up with anhydrous ether (2 × 3 mL, freshly distilled from lithium aluminum hydride) under dry nitrogen. The residual ether was thoroughly evaporated with warming (infrared heat lamp) and nitrogen purging. Keto ester **10A** (1.0832 g, 3.44 mmol) dissolved in anhydrous hexamethylphosphoric triamide (HMPA, 25 + 10 + 5 mL, freshly distilled from calcium hydride and collected over moleculear sieves 13X) was slowly added to the sodium hydride. After stirring for 3 h at room temperature, the pink-brown mixture was cooled to 0 °C (ice bath) and chloromethyl methyl ether (9.32 mL, 4.2 mmol) was added. The cooling bath was then removed and the reaction mixture was allowed to stir for 2 h at room temperature. The resulting white slurry was poured into ice–water (200 mL) and saturated sodium bicarbonate solution (100 mL), and worked up in the usual way to give 1.4062 g (113.7%) of a light green oil. The crude oil was chromatographed on silica gel (100 g, 70–230 mesh, E. Merck) in a 1.5-cm diameter column using 20:80 mixture of ether and petroleum to elute 25-mL fractions. Fractions 19–26 gave 1.194 g (96.4%) of pure vinyl ether ester **11A** as a colorless liquid. The analytical sample was prepared by evaporative distillation (102 °C at 0.02 mm) of small sample: IR (CCl_4) 2960 and 2900 (C–H, aliphatic), 1725 (CO, ester), 1670 (C=C), 1498, 1460, and 1428 (aromatic, skeletal), 1375 and 1365 (isopropyl), 1290 and 1150 (CO–C), 1250 (=C–O–C), 1190, 1165, 1070, and 1038 (–C–O–C–O–C–), and 985, 880, and 820 cm^{-1} (C–H bending aromatic); NMR (CCl_4) δ 1.10 (s, 3, $-CH_3$), 1.26 (d, 6, J = 7 Hz, $-CHMe_2$), 1.4–2.6 (m, 9, methylenes and methine), 2.86 (q, 1, J = 7 Hz, $-CHMe_2$), 3.45 (s, 3, $-OCH_2CH_3$), 3.75 (s, 3, $-COOCH_3$), 4.85 (AB, 2, J = 7 and 4 Hz, $-OCH_2O-$), and 6.85–7.10 ppm (m, 3, aromatic).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.69; H, 8.50.

Methyl 3,4,4a,9,10,10aα-Hexahydro-6-methoxy-2-(methoxymethoxy)-4aβ-methyl-1-phenanthrenecarboxylate (11B).[19,20] Sodium hydride (0.573 g of 57% dispersion in oil, 13.6 mmol, Ventron) was washed with anhydrous ether (3 × 5 mL, freshly distilled from lithium aluminum hydride) under dry nitrogen atomosphere. After the ether was removed as above, anhydrous hexamethylphosphoric triamide (HMPA, 10 mL, freshly distilled from calcium hydride and stored over molecular sieves 13X) was added, followed by keto ester **10B** (3.024 g, 10.0 mmol) dissolved in dry HMPA (20 + 5 + 5 mL). After stirring for 3 h at room temperature, the resulting brown reaction mixture was quenched with chloromethyl methyl ether (2.0 mL, 26.3 mmol) and the mixture was allowed to stir for an additional 2 h at room temperature. The resulting yellow mixture was then poured into a separatory funnel containing ice–water (100 mL), saturated sodium bicarbonate solution (50 mL), and ether (50 mL). After the layers were separated, the aqueous layer was extracted with ether (5 × 40 mL). The combined ethereal extracts were washed with water (5 × 100 mL) and saturated sodium bicarbonate solution (2 × 100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 3.60 g (104%) of yellow oil. The crude product was recrystallized from ether and hexane to give 3.140 g (90.6%) of pure crystalline **11B**, mp 87–88 °C. An analytical sample was prepared by recrystallization from ether: mp 88–89 °C; IR (CCl_4) 2960 and 2870 (C–H, alipahtic), 2850 ($PhOCH_3$), 1720 (CO, ester), 1670 (C=C), 1604, 1500, 1450, and 1425 (aromatic skeletal), 1360, 1290 (C–O–C), 1250 (=C–O–C), 1195, 1170, 1070, and 1040 (–C–O–C–O–C–), and 985 cm^{-1} (C–H bending, aromatic); NMR (CCl_4) δ 1.09 (s, 3, $-CH_3$), 1.4–3.0 (m, 9, methylenes and methine), 3.40 (s, 3, $-OCH_2OCH_3$), 3.66 (s, 3, $-COOCH_3$), 3.70 (s, 3, $PhOCH_3$), 4.80 (AB, 2, J = 6 Hz, $-OCH_2O-$), and 6.6–7.2 ppm (m, 3, aromatic).

Anal. Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.30; H, 7.53.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylate (Methyl Callitrisate) (12A). Lithium wire (3.4 cm, 19.6 mg-atoms) was cut, then added to anhydrous liquid ammonia (100 mL, distilled through two potassium hydroxide towers, then from sodium metal). After the dark blue mixture was refluxed (−33 °C) for 20 min with stirring, was added to it vinyl ether ester **11A** (1.005 g, 2.80 mmol) dissolved in anhydrous 1,2-dimethoxyethane (DME, 30 + 15 + 15 mL, freshly distilled from lithium aluminum hydride and collected over activated molecular sieves 3A), followed by stirring at reflux (−33 °C) for 10 min. The blue reaction mixture was then rapidly quenched with excess methyl iodide (2 mL, 32.2 mmol) and the resulting white slurry was allowed to stir at reflux (−33 °C) for 1 h. The reaction flask was warmed (hot water bath) with stirring for 1 h, allowing ammonia to evaporate. After the mixture was cooled to room temperature, it was poured into ice–water (100 mL) and acidified to pH ~2 with 10% hydrochloric acid solution. After the layers were separated, the aqueous layer was extracted with ether (5 × 50 mL). The combined ethereal extracts were washed with saturated sodium sulfite solution (3 × 100 mL), then worked up in the usual way to give 0.926 g (105%) of a light yellow oil. The crude product was chromatographed on silica gel (100 g, 70–230 mesh, E. Merck) in a column of 1.5 cm diameter using a 5:95 mixture of ether and petroleum to elute 25-mL size fractions. Fractions 24–31 gave 0.655 g (74.4%) of pure crystalline (±)-methyl callitrisite (**12A**), mp 94–95 °C. Recrystallization (three times) of a small sample from ether gave analytically pure ester **12A** as elongated prisms: mp 94–94.5 °C (lit. 91–92,[3a] 98–99 °C[3b]); IR (CCl_4) 3030 (C–H, aromatic), 2960, 2875, and 2850 (CH, aliphatic), 1728 (CO, ester), 1610, 1495, 1455, and 1415 (aromatic skeletal), 1378 and 1360 (isopropyl), 1265 and 1150 (C–O–C), 985, 880, and 820 (C–H bending, aromatic), and 1180, 1230, and 1130 cm^{-1}; NMR (CCl_4) δ 0.95 (s, 3, $C_{4a}CH_3$), 1.20 (d, 6, J = 7 Hz, $-CHMe_2$), 1.24 (s, 3, C_1CH_3), 1.42–2.95 (m, 11, methylenes and methines), 3.58 (s, 3, $-OCH_3$), 6.75 (s, 1, C_8 H, aromatic), and 6.98 (AB, 2, C_5H and C_6 H, aromatic).

Synthetic (±)-methyl callitrisate was found to have identical physicochemical properties with the authentic sample;[21] IR and NMR spectra of both samples were superimposable; both samples had identical R_f values on TLC and retention time on GLC both in separate and coinjected samples using columns a and b. GLC data on separate and coinjected samples of (±)-methyl callitrisate are listed below.

Column	Column temp, °C	Retention time, min
a	220	10.31
b	240	13.00

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.30; H, 9.61.

Methyl 1,2,3,4,4a,9,10,10aα-Octahydro-6-methoxy-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylate (Methyl *O*-Methyl Podocarpate) (12B). To a stirred solution of lithium (0.122 g, 17.6 mg-atoms) in anhydrous liquid ammonia (100 mL) was added vinyl ether ester **11B** (1.005 g, 2.90 mmol) dissolved in anhydrous 1,2-dimethoxyethane (DME, 20 + 5 + 5 mL, distilled from lithium aluminum hydride and stored over molecular sieves 3A). After the blue reaction mixture was stirred at reflux (−33 °C) for 10 minutes, it was rapidly quenched with methyl iodide (1.0 mL, 16.1 mmol). The resulting slightly yellow slurry was allowed to stir at reflux (−33 °C) for 1 h, then the ammonia

was removed by distillation in a hot water bath for over a period of 1 h. The reaction mixture was then poured into ice–water (50 mL) and acidified (pH ~2) with 10% hydrochloric acid solution, and the aqueous mixture was extracted with ether (5 × 50 mL). The combined ethereal extracts were washed with 10% sodium sulfite solution (50 mL), water (4 × 50 mL), and saturated sodium chloride solution (50 ml), then worked up in the usual way to give 0.863 g (98.4%) of crude product. Recrystallization of crude product from chloroform and hexane afforded 0.699 g (79.7%) of pure crystalline (±)-methyl *O*-methyl podocarpate (**12B**), mp 129–134 °C. The analytical sample (mp 136–137 °C, lit. 128–129,[6b] 128–130 °C[6c]) was prepared by column chromatography on silica gel followed by recrystallization (twice) from chloroform and hexane: IR ($CHCl_3$) 3030 (C–H, aromatic), 2985 and 2860 (C–H, aliphatic), 1720 (CO, ester), 1610, 1578, 1500, and 1455 (aromatic skeletal), 1465 and 1380 (CH_2, bending), 1250 and 1050 (C–O–C), and 980, 880, 810 cm^{-1} (C–H, bending, aromatic); NMR ($CDCl_3$) δ 1.05 (s, 3, $C_{4a}CH_3$), 1.28 (s, 3, C_1 CH_3), 1.35–2.90 (m, 11, methylenes and methine), 3.66 (s, 3, $-COOCH_3$), 3.76 (s, 3, $PhOCH_3$), and 6.7–7.3 ppm (m, 3, aromatic).

Synthetic (±)-methyl *O*-methyl podocarpate was identical with an authentic sample[24] prepared for (+)-podocarpic acid with respect to IR, NMR, TLC, and GLC. GLC data both on separate and coinjected samples using columns a, b, and c are listed below.

Column	Column temp, °C	Retention time, min
a	220	13.1
b	250	13.8
c	240	24.9

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.33; H, 8.59.

1,2,3,4,4a,9,10,10aα-Octahydro-7-isopropyl-4aβ-methyl-1α-methyl-1β-phenanthrenecarboxylic Acid (Callitrisic Acid or 4-*epi*-Dehydroabietic Acid) (1).[2] A mixture of methyl callitrisate (**12A**, 0.080 g, 0.25 mmol) and potassium *tert*-butoxide (0.100 g, 0.89 mmol) in anhydrous dimethyl sulfoxide (Me_2SO, 6 mL, freshly distilled from calcium hydride and stored over activated molecular sieves 4A) was stirred at 100 °C (bath temperature) for 6 h. After the reaction mixture was cooled to room temperature, it was poured into ice–water (20 mL). The aqueous mixture was then extracted with ethyl acetate (2 × 10 mL) to remove neutral impurities, followed by acidification at 0 °C, with stirring, with 10% hydrochloric acid solution. The freed carboxylic acid was extracted with ethyl acetate (5 × 10 mL). The combined ethyl acetate extracts were worked up in the usual way to give 0.078 g (101.4%) of light yellow crystals. The crude product was chromatographed on silica gel (16 g, 70230 mesh, E. Merck) in a 1-cm diameter column using a 20:80 mixture of ether and petroleum ether to elute 5-mL fractions. Fractions 15–20 yielded 0.0745 g (97.5%) of pure (±)-callitrisic acid (1). Recrystallization from ethyl acetate gave (±)-callitrisic acid (1) as colorless prisms: mp 200–201 °C (lit. 202–203,[3a] 202 °C[3b]); IR ($CHCl_3$, saturated solution) 3300–2500 (OH, dimeric carboxylic acid), 2960 and 2875 (C–H, aliphatic), 1725 (shoulder) and 1695 (CO, acid), 1609, 1495, 1470, and 1410 (aromatic skeletal), 1455 ($-CH_2$, bending), 1378 and 1365 (isopropyl), 1265 (C–O), and 987, 885, and 825 cm^{-1} (C–H, bending, aromatic); NMR ($CDCl_3$, saturated solution) δ 1.09 (s, 3, C_{4a} CH_3), 1.22 (d, 6, J = 7 Hz, $-CHMe_2$), 1.35 (s, 3, C_1 CH_3), 1.4–3.0 (m, 12, methylenes and methine), 6.90 (s, 1, C_8 H, aromatic), 7.10 ppm (AB, 2, C_5 H and C_6 H, aromatic), and 11.0 ppm (bs, 1, $-CO_2H$).

Methyl 2,3,4,4a,9,10-Hexahydro-7-isopropyl-4aβ-methyl-2-oxo-1-phenanthrenecarboxylate (14A)[28] Isopropyl ketone **8A** (3.480 g, 17.2 mmol), methyl 5-methoxy-3-oxopentanoate[27] (4.135 g, 25.8 mmol), toluene (80 mL), and *p*-toluenesulfonic acid (0.150 g) were placed, under nitrogen, in a 100-mL two-necked flask fitted with a Dean-Stark water separator. After refluxing for 8 h, the resulting red-brown mixture was diluted with ether (100 mL), then poured into water (100 mL) and saturated sodium bicarbonate solution (100 mL). After the layers were separated, the aqueous layer was extracted with ether (three times). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (once), then worked up in the usual way to give 6.507 g of a red oil. The IR and NMR spectra of this crude product showed that it was a mixture of enone ester **14A** and keto ester alcohol **13A** in about 3:2 ratio. This crude product dissolved in toluene (80 mL) was refluxed with a catalytic amount of trifluoromethanesulfonic acid (2 drops) for 1 h under nitrogen atomosphere. The water formed during the reaction was removed by a Dean-Stark water separator. The resulting dark red reaction mixture, after a similar workup as described above, gave 5.440 g of crude enone ester **14A.** The crude product was chromatographed on silica gel (544 g, 70–230 mesh, E. Merck) in a 3-cm diameter column using a mixture of 25:75 ether and petroleum to elute 250-mL fractions. Fractions 35–45 gave 3.6709 g (68.3%) of pure crystalline enone ester **14A.** The analytical sample was prepared by recrystallization (four times) from ether: mp 139.5–140 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2985, 2950, and 2840 (C–H, aliphatic), 1725 (CO, ester), 1665 (CO), 1623 (C=C), 1495, 1450, and 1430 (aromatic skeletal), and 1245 and 1030 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.26 (d, 6, J = 7 Hz, $-CHMe_2$), 1.63 (s, 3, $-CH_3$), 2.0–3.1 (m, 9, methylenes and methine), 3.86 (s, 3, $-OCH_3$), and 6.8–7.3 ppm (m, 3, aromatic); MS *m/e* 312 (P^+), 297, 280, 265, 252, 238, and 223.

Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.80; H, 7.74. Found: C, 76.82; H, 7.73.

Methyl 2,3,4,4a,9,10-Hexahydro-6-methoxy-4aβ-methyl-2-oxo-1-phenanthrenecarboxylate (14B).[28] A mixture of ketone **8B** (2.44 g, 12.8 mmol), methyl 5-methoxy-2-oxopentanoate[27] (2.097 g, 13.09 mmol), and *p*-toluenesulfonic acid (0.10 g) in anhydrous benzene (50 mL, freshly distilled from calcium hydride) was refluxed, with a Dean-Stark water separator, for 72 h under nitrogen. The resulting greenish-brown mixture was diluted with ether (100 mL), then poured into saturated sodium bicarbonate solution (200 mL). After the layers were separated, the aqueous layer was extracted with ether (3 × 100 mL). The combined organic extracts were then washed with saturated sodium bicarbonate solution (once), then worked up in the usual way to give a greenish-yellow oil. This crude product dissolved in toluene (40 mL) was allowed to reflux for 1 h in the presence of a catalytic amount of trifluoromethanesulfonic acid (2 drops). The water formed from the reaction was removed by a water separator. The resulting dark red reaction mixture, after a similar workup as described above, afforded 3.925 g of crude enone ester **14B** as a red oil. The crude product was chromatographed on silica gel (600 g, 70–230 mesh, E. Merck) in a 4-cm diameter column. The column was eluted with 8 L of 25:75, 6 L of 30:70, 5 L of 35:65, and 5 L of 40:60 ether and petroleum ether solutions, respectively, taking 250-mL fractions. Fractions 59–75 yielded 2.786 g (72.3%) of pure enone ester **14B** as yellow crystals. A small sample was recrystallized from ether (four times) to give analytically pure **14B:** mp 98.0 °C; IR ($CHCl_3$) 3030 (C–H, aromatic), 2990 and 2935 (C–H, aliphatic), 1728 (CO, ester), 1665 (CO), 1620 (C=C), 1610, 1575, 1500, 1450, and 1430 (aromatic skeletal), and 1290, 1245, and 1040 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.62 (s, 3, $-CH_3$), 1.95–3.05 (m, 9, methylenes and methine), 3.80 (s, 3, $PhOCH_3$), 3.86 (s, 3, $-COOCH_3$), and 7.33–6.66 (m, 3, aromatic); MS *m/e* 300 (P^+), 268, 253, 240, 225, 198, 197, 83, 74, and 31.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.97; H, 6.63.

Catalytic Hydrogenation of Isopropyl Enone Ester (14A).[29,30] Catalytic hydrogenation was performed on a Sloping-Manifold hydrogenator,[29] at room temperature and essentially under atmospheric pressure of hydrogen. Enone ester **14A** (0.0814 g, 0.26 mmol) was added to a magnetically stirred suspension of 5% palladium on barium sulfate (0.0273 g, MCB) in 4 mL of absolute ethanol. After 30 min, the theoretical amount of hydrogen had been consumed and with an additional 20 min, there was no more change in hydrogen uptake. The reaction mixture was then filtered through Celite on a sintered glass filter and the solvent was removed in vacuo to give 0.0957 g of a light yellow oil. The crude product on TLC (microscope glass coated with silica gel, eluted by a mixture of 40:60 ether and petroleum ether) showed two spots of R_f values 0.44 and 0.91. On the other hand, GLC analysis of the crude product on column a (column temperature 210 °C) showed essentially three peaks of retention times 6.6, 8.1, and 12.0 min in a ratio of 30.0:63.2:6.8, respectively.

The crude product was chromatographed on silica gel (11 g, 70–230 mesh, E. Merck) in a 1-cm diameter column. The column was eluted with a mixture of 20:80 ether and petroleum ether taking 5-mL sized fraction per every 15 min. Fractions 4–9 gave 0.02412 g (31.4% of total

yield) of A/B cis-fused keto ester **15A** as a colorless liquid and fractions 15–21 gave 0.05272 g (68.6%) of crystalline A/B trans-fused keto ester **10A** (mp 105–107 °C) in 94% total yield.

Keto ester **10A** prepared by catalytic hydrogenation was found to have identical properties on TLC and GLC, and superimposable NMR and IR spectra with the one prepared via the reductive carbomethoxylation procedure.

On the other hand, in GLC analysis using column a (column temperature 210 °C), cis-fused keto ester **15A**, homogeneous on TLC, showed two peaks of retention times 6.0 and 12.6 min in a ratio of 81:10, respectively. Evaporative distillation (140 °C at 0.5 mm) provided analytically pure keto ester **15A**: IR ($CHCl_3$) 3030 (C–H, aromatic), 3000, 2960, and 2875 (C–H, aliphatic), 1745, 1715 (small shoulder, CO, ester and ketone), 1650 (CO, conjugated ester), 1618 (C=C), 1496, 1455, 1445, and 1420 (aromatic skeletal), 1380 and 1360 (isopropyl), 1285 and 1240 (C–O–C), 1190 (=C–O), 1055, 1010, and 825 cm^{-1} (C–H bending, aromatic); NMR ($CDCl_3$) δ 1.25 (distorted d, 9, $-CHMe_2$ and $-CH_3$), 1.5–3.1 (m, 10, methylenes and methine), 3.80–3.84 (fused s, 3, $-OCH_3$), 6.85–7.45 (m, 3, aromatic), and 12.40 ppm (s, 0.7, =COH).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.33. Found: C, 76.45; H, 8.35.

Catalytic Hydrogenation of Methoxy Enone Ester 14B.[29,30] A solution of enone ester **14B** (9.3778 g, 1.26 mmol) in dry ethanol (10 mL) was hydrogenated in the presence of 5% palladium on barium sulfate (0.1265 g, MCB). After stirring for 2 h, 1 equiv of hydrogen was consumed and the reaction mixture was further stirred for 1 h without additional hydrogen uptake. After filtration followed by concentration of the filtrate in vacuo, 0.3785 g of a viscous liquid was obtained, which was crystallized on standing. The crude product on TLC (microscope glass coated with silica gel, eluted with 30:70 ether and petroleum ether solution) showed two spots of R_f values 0.18 and 0.63, respectively. GLC analysis of the crude product on column a showed (column temperature 220 °C) three peaks of retention times 5.02, 6.0, and 8.63 min in a ratio of 17.8:69.5:12.7, respectively.

The crude product was chromatographed on silica gel (38 g, 70–230 mesh, E. Merck) using a 1.5-cm diameter column eluting with a solution of 30:70 ether and petroleum ether, taking 15-mL size fractions. Fractions 4–7 gave 0.0989 g (26.5% of total yield) of crystalline cis-fused keto ester **15B** (mp 120–120.5 °C) and fractions 16–20 afforded 0.2750 g (73.5%) of crystalline trans-fused keto ester **10B** (mp 144–145.5 °C) in 98% total yield.

The trans-fused keto ester **10B** produced by catalytic hydrogenation was found to have superimposable IR and NMR spectra with those of the one synthesized via the reductive carbomethoxylation procedure. TLC and GLC analysis of the two samples revealed that they were identical. On the other hand, A/B cis-fused keto ester **15B**, homogeneous on TLC, in GLC analysis using column a (column temperature 220 °C) produced two peaks of retention times 5.02 and 8.63 min in a ratio of 80:20, respectively. An analytical sample of keto ester **15B** was prepared by recrystallization (three times) from ether: mp 120–120.5 °C; IR (CCl_4) 3030 (C–H, aromatic), 3000, 2950, and 2925 (C–H, aliphatic), 2850 ($PhOCH_3$), 1745–1725 (CO, ester and ketone), 1654 (CO, ester, enolic), 1610 (C=C), 1500, 1445, and 1425 (aromatic skeletal), 1280 (=C–O), and 1230 and 1045 cm^{-1} (C–O–C); NMR ($CDCl_3$) δ 1.32 (s, 3, $-CH_3$), 1.5–2.9 (m. 9, methylenes and methine), 3.73 (s, 3 $PhOCH_3$), 3.79 (s, 3, $-COOCH_3$) 6.45–6.98 (m, 3, aromatic), and 12.26 ppm (s, 0.75, =COH).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.57; H, 7.32.

Dissolving Metal Reductions of Isopropyl Enone Ester 14A.[31,32] To a stirred solution of lithium (4 mg, 0.58 mg/atom) in anhydrous liquid ammonia (10 mL) was added enone ester **14A** (0.040 g, 0.128 mmol) dissolved in a mixture of anhydrous tetrahydrofuran (THF) and dry *tert*-butyl alcohol (3.0 mL, 0.16 mmol); the solution was made by mixing 19.8 mL of THF (freshly distilled from lithium aluminum hydride) to 0.2 mL of *tert*-butyl alcohol (freshly distilled from calcium hydride). After addition of enone **14A**, the blue color persisted for 2 min, then the reaction was quenched with solid ammonium chloride. After the ammonia was evaporated, the reaction mixture was extracted with ether (5 × 100 mL). The combined ethereal extracts were washed with saturated sodium chloride solution (3 × 100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to yield 0.0405 g of a light yellow oil. GLC analysis of the crude product on column a (column temperature 210 °C, retention times 6.94, 8.40, and 12.0 min) indicated that trans-fused keto ester **10A** and cis-fused keto ester **15A** were produced in a ratio of 68.5:31.5 in 90% total yield.

Metal Hydride Reduction of Isopropyl Enone Ester 14A.[33,34] A mixture of enone ester **14A** (0.020 g, 0.064 mmol) and sodium borohydride (3 mg, 0.079 mmol) in anhydrous pyridine (1.5 mL, freshly distilled from calcium hydride) was stirred for 50 min at room temperature. Then, the mixture was poured into water (100 mL) and 10% hydrochloric acid solution (10 mL), followed by extraction with ether (5 × 50 mL). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (100 mL), then dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to afford 0.0228 g of an oil. The crude product of GLC analysis using column a (column temperature 210 °C, retention times 7.12, 8.63, and 12.81 min) showed that trans-fused keto ester **10A** and cis-fused keto ester **15A** were produced in 58:42 ratio in 90% total yield.

Acknowledgment. We graciously thank the National Institute of General Medical Sciences (PHS Research Grant 1R01 GM 1875), the Robert A. Welch Foundation (Grant E-518), and The University of Houston Faculty Research Incentive Fund for support of this research program. J. H. Kim extends his thanks to the Lynne Murray Sr. Scholarship Foundation for their generous support.

Registry No.—**1**, 21699-54-7; **4**, 58812-64-9; **5**, 58812-65-0; **6**, 58812-67-2; **7**, 58840-14-5; **8A**, 58812-66-1; **8B**, 58209-23-7; **9A**, 58846-74-5; **9B**, 41437-73-4; **10A**, 58812-68-3; **10B**, 41437-69-8; **11A**, 58812-69-4; **11B**, 41437-70-1; **12A**, 21699-55-8; **12B**, 41437-72-3; **13A**, 62462-00-4; **14A**, 62462-01-5; **14B**, 62462-02-6; **15A**, 62462-03-7; **15B**, 62462-04-8; 4-isopropenylisopropylbenzene, 2388-14-9; methyl vinyl ketone, 107-25-5; chloromethyl methyl ether, 107-30-2; methyl 5-methoxy-3-oxopentanoate, 62462-05-9.

References and Notes

(1) (a) J. A. Barltrop and N. A. J. Rogers, *Q. Rev., Chem Soc.*, **16**, 117 (1962); (b) J. R. Hanson in "Chemistry of Terpenes and Terpenoids", A. A. Newman, Ed., Academic Press, New York, N.Y., 1972, pp 186–191; (c) T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. 2, Academic Press, New York, N.Y., pp 185–274; (d) K. Nakanishi in "Natural Products Chemistry", Vol. 1, K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, Ed., Academic Press, New York, N.Y., 1974, pp 185–312.
(2) (a) R. M. Carmen and H. C. Deeth, *Aust. J. Chem.*, **20**, 2789 (1967); (b) L. J. Gough, *Tetrahedron Lett.*, 295 (1968).
(3) (a) R. D. Haworth and R. L. Baker, *J. Chem. Soc.*, 1299 (1939); (b) M. Sharma, U. R. Ghatau, and P. C. Dutta, *Tetrahedron*, **19**, 985 (1963); (c) R. M. Carmen, H. C. Deeth, R. A. Marty, K. Mori, and M. Matsui, *Tetrahedron Lett.*, 3359 (1968); (d) K. Mori and M. Matsui, *Tetrahedron*, **24**, 6573 (1968); (e) J. W. Huffman, *J. Org. Chem.*, **35**, 3154 (1970); (f) S. W. Pelletier and D. L. Herald, Jr., *Chem. Commun.*, 10 (1971); (g) S. C. Welch and J. H. Kim, *Synth. Commun.*, **6**, 27 (1976).
(4) A. C. Oudemans, *Ber.*, **6**, 1122 (1873).
(5) (a) I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 1006 (1938); (b) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **62**, 1287 (1940); **64**, 928 (1942).
(6) (a) B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **22**, 165 (1945); (b) R. D. Haworth and B. P. Moore, *J. Chem. Soc.*, 633 (1946); (c) W. E. Parham, E. L. Wheeler, and R. M. Dodson, *J. Am. Chem. Soc.*, **77**, 1166 (1955); (d) F. E. King, T. J. King, and J. G. Topliss, *Chem. Ind. (London)*, 113 (1956); (e) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **80**, 211, 217 (1958); (f) E. Wenkert and A. Tahara, *ibid.*, **82**, 3229 (1960); (g) U. R. Ghatak, D. K. Datta, and S. C. Ray, *ibid.*, **82**, 1728 (1960); (h) S. N. Mahapatra and R. M. Dodson, *Chem. Ind. (London)*, 253 (1963); (i) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964); (j) W. L. Meyer and K. K. Maheshwari, *Tetrahedron Lett.*, 2175 (1964); (k) K. Mori and M. Matsui, *ibid.*, 175 (1966); (l) F. Giarrusso and R. E. Ireland, *J. Org. Chem.*, **33**, 3560 (1968); (m) T. A. Spencer, R. J. Friary, W. W. Schmiegel, J. F. Simeone, and D. S. Watt, *ibid.*, **33**, 719 (1968); (n) S. W. Pelletier, R. L. Chappell, and S. Prabhakar, *J. Am. Chem. Soc.*, **90**, 2889 (1968); (o) V. Mancini, F. Frigvelli, and A. Taticchi, *Gazz. Chim. Ital.*, **99**, 953 (1969); (p) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35**, 161 (1970); (q) S. C. Welch and C. P. Hagan, *Synth. Commun.*, **3**, 29 (1973); (r) B. M. Trost and M. Precel, *J. Am. Chem. Soc.*, **95**, 7862 (1973); (s) T. Sone, S. Terashima, and S. K. Yamada, *Chem. Pharm. Bull.*, **24**, 1288 (1976).
(7) S. C. Welch and C. P. Hagan, *Synth. Commun.*, **2**, 221 (1972); S. C. Welch, C. P. Hagan, D. H. White, W. P. Fleming, and J. W. Trotter, *J. Am. Chem. Soc.*, **99**, 549 (1977).
(8) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **84**, 284 (1962).
(9) Available from Aldrich Chemical Co., Milwaukee, Wis. (Catalog No. I-1,965-9).
(10) H. Hibbert and P. Burt, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1964, p 494.
(11) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957); E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).
(13) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, N.Y., 1967, p 1159.
(14) J. J. Sims, L. H. Selman, and M. Cadogan, *Org. Synth.* **51**, 109 (1972); J. J. Sims, M. Cadogan, and L. H. Selman, *Tetrahedron Lett.*, 951 (1971).
(15) J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **29**, 2501 (1964).
(16) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965); T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J.

Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, **33**, 712 (1968).
(17) (a) E. Wenkert and B. G. Jackson, *J. Am. Chem. Soc.*, **81**, 5601 (1959); (b) T. A. Spencer, T. D. Weaver, M. A. Schwartz, W. J. Greco, Jr., and J. L. Smith, *Chem. Ind. (London)*, 577 (1964).
(18) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).
(19) R. M. Coates and J. E. Shaw, *J. Org. Chem.*, **35**, 2597 (1970).
(20) This reaction must be conducted in a well-ventilated hood; the chemist should wear rubber gloves during the workup because both hexamethylphosphoric triamide and chloromethyl methyl ether are carcinogens.
(21) We are grateful to Professor R. M. Carman for providing an authentic sample of (±)-methyl callitrisate.
(22) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1493 (1961).
(23) We are grateful to Professor S. R. Wilson, Indiana University, for providing generous samples of 7-methoxy-2-tetralone and tricyclic enone **9B**.
(24) L. H. Briggs, R. C. Cambie, and J. L. Hoare, *Tetrahedron*, **7**, 262 (1959). *O*-Methyl methyl podocarpate was prepared from (+)-podocarpic acid (Aldrich 11,979-2) by esterification with ethereal diazomethane followed by alkylation using methyl iodide and anhydrous potassium carbonate in refluxing acetone for 18 h.
(25) P. A. Bartlett and W. S. Johnson, *Tetrahedron Lett.*, 4459 (1970).
(26) (a) For examples of alkylation of unhindered exocyclic enolate anions see H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968); R. E. Ireland and L. N. Mander, *ibid.*, **32**, 689 (1967); **34**, 142 (1969); (b) For an example of alkylation of a hindered exocyclic enolate anion see F. E. Ziegler and J. A. Kloek, *Tetrahedron Lett.*, 315 (1974).
(27) Prepared by Mr. P. S. Chu in our laboratory from methyl hydrogen malonate, isopropylmagnesium chloride, and 3-methoxypropanoyl chloride in 70% yield according to the procedure of R. E. Ireland and J. A. Marshall, *J. Am. Chem. Soc.*, **81**, 2907 (1959).
(28) C. H. Heathcock and J. E. Ellis, *Chem. Commun.*, 1474 (1971); J. E. Ellis, J. S. Dutcher, and C. H. Heathcock, *Synth. Commun.*, **4**, 71 (1974); I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *J. Gen. Chem. USSR (Engl. Transl.)*, **23**, 1793 (1953).
(29) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, N.Y., 1965, pp 11–14.
(30) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); Z. G. Hajos and D. R. Parrish, *ibid.*, **38**, 3239 (1973).
(31) D. Caine, *Org. React.*, **23**, 1–258 (1976); G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964).
(32) L. F. Fieser and J. E. Herz, *J. Am. Chem. Soc.*, **75**, 121 (1953); S. K. Pradham, G. Subrahmanyam, and H. J. Ringlod, *J. Org. Chem.*, **32**, 3004 (1967).
(33) K. Adank, H. A. Pfenninger, W. G. Stoll, and M. Viscontini, *Helv. Chim. Acta*, **46**, 1030 (1963); S. B. Kadin, *J. Org. Chem.*, **31**, 620 (1966).
(34) W. L. Dilling and R. A. Plepys, *J. Org. Chem.*, **35**, 2971 (1970).
(35) M. F. Semmelhack and R. D. Stauffer, *J. Org. Chem.*, **40**, 3619 (1975).
(36) Aldrich Chemical Co., Milwaukee, Wis., Catalog No. Z10,046-3.
(37) W. S. Johnson and W. P. Schneider, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132.
(38) R. L. Augustine, "Oxidation", Vol. 1, Marcel Dekker, New York, N.Y., 1969, p 222.

Rearrangements of Penicillin Sulfoxides. 1

Abraham Nudelman[1] and Ronald J. McCaully

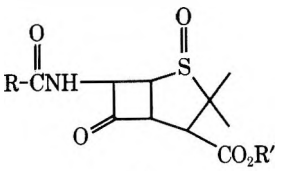
Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087

Received February 3, 1977

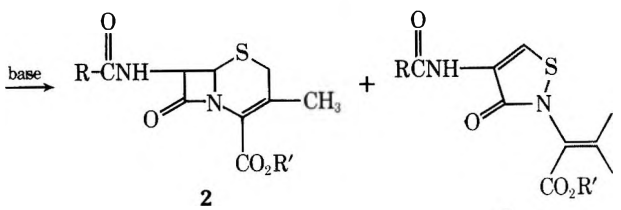
Penicillin sulfoxides are converted to 3-halo-3-methylcepham-4-carboxylic acid esters or the corresponding cephem derivatives by heating the penicillin sulfoxide precursor in the polyhaloalkane solvent in the presence of an equimolar amount of a neutral or basic catalyst, respectively. Basic catalysts such as pyridine or 4-picoline afford cephem derivatives, whereas the quaternary ammonium salts bring about the formation of 3-halocepham derivatives.

Several recent articles have reported the conversion of penicillins into cephalosporins by treatment of penicillin sulfoxides with reagents such as anhydrides,[2] acids,[3] diazo compounds–amine hydrochlorides,[4] 2-mercaptobenzothiazole followed by halogenation and dimethylformamide treatment,[5] thionyl chloride–triethylamine,[6] and trimethylchlorosilane–α-picoline.[7]

The present paper describes a novel, convenient process for the conversion of penicillin sulfoxides to a variety of cephalosporin derivatives. Most of the reported reactions, whereby the expansion of penicillin sulfoxides to ceph systems have been carried out, have involved acidic reagents. It was speculated that the reaction should also proceed under basic conditions. For this purpose, sulfoxide **1** was treated with a number of basic reagents in a variety of solvents. The desired deacetoxycephem **2** was indeed obtained in certain instances; however, in most cases the major or only product was the known[2,8] isothiazole **3** (Table I).



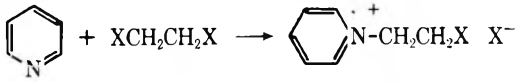
1



2 **3**

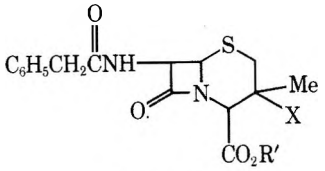
R = $C_6H_5CH_2$-, R′ = *p*-$NO_2C_6H_4CH_2$-

The best yields of cephem **2** were obtained in the presence of pyridine in 1,2-dichloroethane. The reaction was then repeated with various molar ratios of pyridine:sulfoxide **1**, ranging from trace amounts to very large molar excesses of base. The best results were obtained when 2 mol of pyridine/mol of sulfoxide **1** was used. In the presence of a large excess of pyridine, the quaternary salt **4a** precipitated out of solution



4a, X = Cl
b, X = Br

in crystalline form and it was found that this salt was a better catalyst for the rearrangement than pyridine itself. In 1,2-dichloroethane in the presence of 1 to 2 mol of salt **4a**/mol of sulfoxide **1**, the only detectable product obtained was a novel cephalosporin, which was subsequently shown to be cepham **5a**.[10]



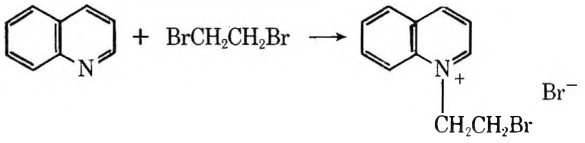
5a, X = Cl
b, X = Br

Table I. Rearrangement of Penicillin 1 to Cepham 2 and Isothiazole 3

Catalyst	Solvent	Product
Imidazole	1,2-Dichloroethane	Only **3**
N-Methylimidazole	1,2-Dichloroethane	Only **3**
4-Picoline	1,2-Dichloroethane	1:1 mixture of 2:3
Pyridine	Acetonitrile	Only **3**
Pyridine	Dioxane	Only **3**
Pyridine	Trichloroethylene	**3** quantitative yield
Pyridine	1,2-Dichloroethane	Mostly **2**
Pyridine	Chloroform	No reaction
Pyridine	*n*-Butyl chloride	No reaction
	1,2-Dichloroethane	No reaction

The catalytic effect of salt **4a** was further substantiated by the formation of cepham **5a** when the reaction was carried out in solvents where pyridine failed to produce ceph products. (Table II).

Other quaternary ammonium salts such as tetramethylammonium chloride or *N*-ethylpyridinium bromide failed to effect the penicillin–cephalosporin rearrangement. The reaction proceeded with *N*-(2-bromoethyl)pyridinium bromide[9] (**4b**) as well as with the corresponding chloro analogue to give the corresponding 3-bromocepham **5b** (X–Br). Similar results were obtained with the quinolinium salt **6**. The halogen

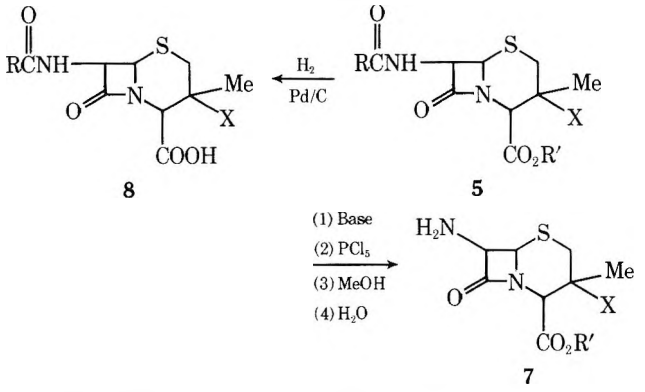


6

component of the salt used and the solvent had to be the same, otherwise halogen exchange took place, and chloro cepham **5a** was obtained when salt **4b** was used in 1,2-dichloroethane.

The attempted displacement of the 3-halo group in cepham **5** by silver acetate resulted in the formation of cephem **2**. The most efficient reagent found for the dehydrohalogenation reaction was 1,5-diazabicylo[4.3.0]non-5-ene (DBN) where an almost quantitative yield of cephem **2** was obtained.

Hydrogenolysis of **5** afforded the corresponding free acids **8**. Removal of the amido side chain was accomplished by a variation of the imino ether cleavage reaction.[12]



8 **5**

7

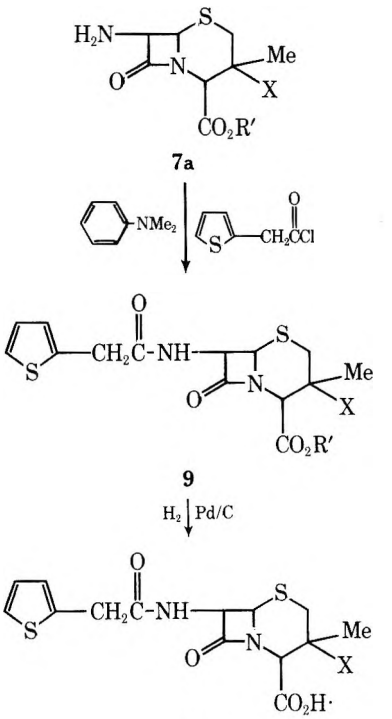
The preferred base for this cleavage reaction was *N*,*N*-dimethylaniline. Other bases, such as pyridine, caused a large degree of dehydrohalogenation.

The amine **7** was successfully reacylated, and the *p*-nitrobenzyl protecting group was easily removed by hydrogenation. No evidence of dehydrohalogenation was observed during the catalytic hydrogenolysis.

The NMR spectra of **8** and **10** indicated that the 3-halo group and the 4-H appear cis to each other.[10]

Table II. Rearrangement of Penicillin 1 to Cepham 5a in the Presence of Salt 4

Solvent	Product
1,2-Dichloroethane	Only **5**
Trichloroethylene	3:2 ratio of **3**:**5**
Acetonitrile	Only **5** (low yield)
Nitromethane	Only **5**
Dimethylacetamide	Only **5** (low yield)
Dioxane (95 °C)	No reaction
Dioxane (reflux)	Only **5** (low yield)



7a **9** **10**

R′ = *p*-$CH_2C_6H_4NO_2$

X = Cl

Discussion

The mechanism of the penicillin sulfoxide–cephalosporin rearrangement has been shown[2] to involve sulfenic acid intermediates, which, in turn, have been trapped by a variety of reagents.[11]

The unique characteristics of the haloethylpyridinium (and quinolinium) halide catalyst in effecting the rearrangement has led to the mechanism suggested in Scheme I.

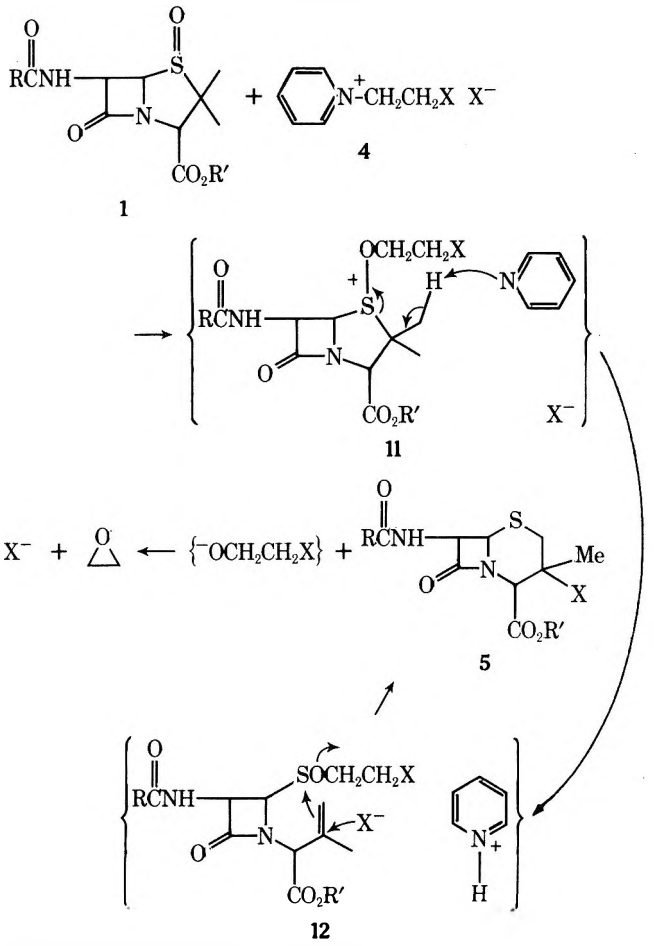
All attempts to isolate or identify 2-chloroethanol by vapor-phase chromatography proved futile. Under the reaction conditions, a further breakdown of **13** into ethylene oxide **14** and halide ion may occur, and the oxide **14** probably evaporated or decomposed. By the proposed mechanism, no free base is present for any length of time, and dehydrohalogenation of **5** does not occur. In the presence of free bases, the reaction may proceed by two alternative paths, A and B, leading to the formation of cephem **2** or isomer **3** (Scheme II).

Experimental Section

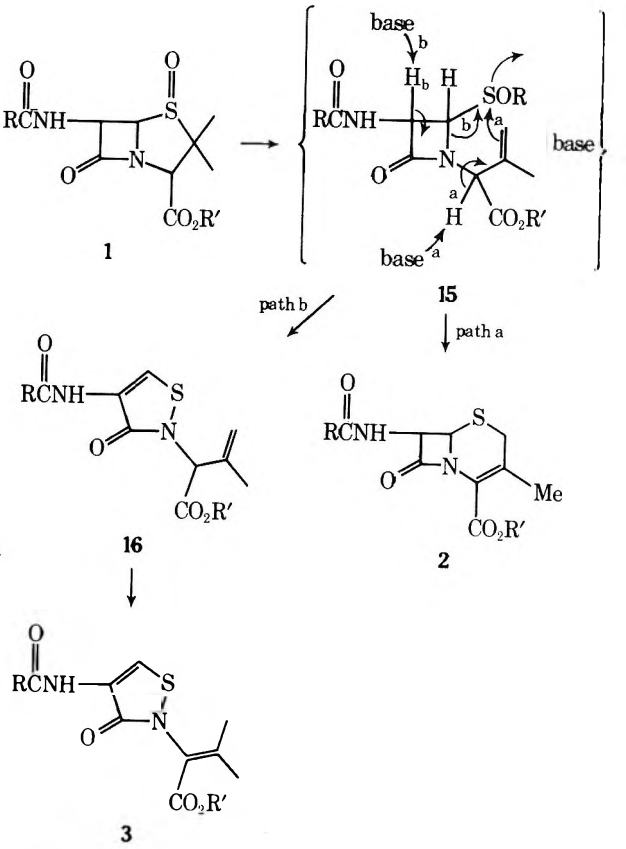
The course of the rearrangement reaction was followed by thin-layer chromatography on silica gel plates. A 10:7 1,2-dichloroethane:ether eluent solution gave excellent separation of penicillin, cephalosporins, and isothiazole components of the reactions. In some cases, the products of the reaction were not isolated and only a qualitative estimate of product composition is reported (Tables I and II) as detected by the thin-layer chromatography.

1-(2-Chloroethyl)pyridinium Chloride (4a). A solution of pyr-

Scheme I



Scheme II



idine (100 g, 1.25 mol) in 800 mL of 1,2-dichloroethane was refluxed for 72 h. The white crystalline material which formed was filtered, washed repeatedly with fresh 1,2-dichloroethane, and dried: collected 200 g (89% yield); NMR (D_2O) ppm (δ), 4.3 (t, 3), 5.6 (t, 3), 8.1–9.3 (m, 5).

1-(2-Bromoethyl)quinolinium Bromide (6). A solution of quinoline (20 mL) in 200 mL of 1,2-dibromoethane was heated under nitrogen at 70 °C for 18 h. The crystalline solid was filtered, washed with dichloromethane, and recrystallized from methanol–ether: collected 32 g (65% yield); mp 205–207 °C; NMR (D_2O) 4.22 (t, 2), 5.63 (t, 2), 7.8–8.6 (m, 5), 9.1–9.6 (m, 3).

3-Chloro-3-methyl-8-oxo-7-(2-phenylacetamido)-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid *p*-Nitrobenzyl Ester (5a). To a solution of 6-(2-phenylacetamido)penicillanic acid *p*-nitrobenzyl ester 1-oxide (1) (5 g, 10.3 mmol) in 2.4 L of dry 1,2-dichloroethane was added 1-(2-chloroethyl)pyridinium chloride (3.8 g, 21.3 mmol). The mixture was heated to reflux for 21 h; it was then concentrated to 500 mL, washed with water, treated with charcoal, dried, and flash evaporated. The residual oil was dissolved in dichloromethane and the solution obtained was added to pentane. A light yellow solid was obtained (4.3 g, 83% yield), which was further recrystallized from dichloromethane–pentane: mp 134–136 °C; NMR ($DCCl_3$) ppm (δ), 1.63 (s, 3, 3-methyl), 3.12 (ABq, δ 0.925 ppm, J = 15 Hz, 2-CH_2), 3.68 (s, 2, CH_2CO) 4.80 (s, 1, 4-H), 5.16 (d, 1, 6 H), 5.30 (s, 2, OCH_2), 5.68 (q, 1, 7 H), 6.6 (d, 1, NH) 7.30 (s, 5, C_6H_5), 7.95 (ABq, δ 0.75 ppm, J = 9 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd for $C_{23}H_{22}ClN_3O_6S$ (mol wt 503.96): C, 54.81, H. 4.40; N, 8.34; Cl, 7.04; S, 6.36. Found: C, 54.42; H, 4.59; N, 7.95; Cl, 7.08; S, 6.49.

3-Bromo-3-methyl-8-oxo-7-(2-phenylacetamido)-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid *p*-Nitrobenzyl Ester (5b). Method I. To a solution of 6-(2-phenylacetamido)penicillanic acid *p*-nitrobenzyl ester 1-oxide (1 g, 2.06 mmol) in 100 mL of dry 1,2-dibromoethane was added 1-(2-bromoethyl)pyridinium bromide (1.13 g, 4.2 mmol). The mixture was heated at 90 °C for 10 h. The solvent was flash evaporated, and the residue was chromatographed on 25 g of silica gel which was eluted with ether. The residue obtained after evaporation of the eluent was crystallized from dichloromethane–pentane to give 300 mg (26.4% yield) of the title compound: mp 136–137.5 °C; NMR (Me_2SO-d_6) ppm (δ), 1.81 (s, 3, 3-CH_3), 3.1 (ABq, δ 0.775 ppm, J = 15 Hz, 2-CH_2), 3.62 (s, 2 CH_2CO), 4.86 (s, 1, 4-H), 5.23 (d, 1, 6 H), 5.70 (s, 2, OCH_2), 5.60 (q, 1, 7 H), 6.57 (d, 1 NH), 7.32 (s, 5, C_6H_5), 7.90 (ABq, δ 0.725 ppm, J = 9 Hz, *p*-$NO_2C_6H_4$). Anal. Calcd for $C_{23}H_{22}BrN_3O_6S$ (mol wt 548.45): C, 50.37; H, 4.04; N, 7.66; Br, 14.57. Found: C, 51.20; H, 4.15; N, 7.76; Br, 14.67.

The NMR spectrum indicated a small amount of dehydrohalogenated product which accounts for the high C analysis.

Method II. To a solution of 6-(2-phenylacetamido)penicillanic acid *p*-nitrobenzyl ester 1-oxide (2.42 g, 5 mmol) in 150 mL of 1,2-dibromethane was added 1-(2-bromoethyl)quinolinium bromide (1.6 g, 5 mmol). The mixture was heated for 16 h at 85 °C. The solvent was washed with water, mixed with charcoal, dried over magnesium sulfate, and flash evaporated to an oil which was chromatographed on 40 g of silica gel eluted with ether. The desired product crystallized in the eluent: collected 1.32 g (48% yield); melting point and NMR identical with those described in method I. Anal. Found: C, 50.80; H, 4.02; N, 7.69.

3-Chloro-3-methyl-8-oxo-7-(2-phenylacetamido)-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (8a). 3-Chloro-3-methyl-8-oxo-7-(2-phenylacetamido-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic acid *p*-nitrobenzyl ester (1.06 g, 2.1 mmol) was hydrogenated in 60 mL of ethyl acetate over 1 g of 10% palladium on charcoal. The catalyst was filtered and washed with ethyl acetate. The filtrate was extracted with ice-cold saturated sodium bicarbonate (100 mL). The aqueous phase was covered with fresh ethyl acetate (100 mL) and was acidified with concentrated hydrochloric acid to pH 1.5. The organic phase was separated, dried, and flash concentrated to a total of 10 mL. The residual solution was added to pentane to give 475 mg (61% yield) of the desired acid, which did not melt, but slowly decomposed above 90 °C: NMR (Me_2SO-d_6) ppm (δ), 1.75 (s, 3, CH_3), 3.32 (ABq, δ 0.975 ppm, J = 14.2 Hz, 2-CH_2), 3.63 (s, 2, $CH_2C{=}O$) 4.55 (s, 1, 4-H), 5.22 (s, 1, 6 H), 5.51 (q, 1, 7 H), 7.34 (s, 5, C_6H_5), 9.1 (d, 1, NH).

Anal. Calcd for $C_{16}H_{17}ClN_2O_4S$ (mol wt 368.81): C, 52.10; H. 4.65; N, 7.60; Cl, 9.60; S, 8.70. Found: C, 52.00; H, 4.60; N, 7.48; Cl, 9.29; S, 8.29.

3-Bromo-3-methyl-8-oxo-7-(2-phenylacetamido)-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (8b). The title compound was prepared in 65% yield from the *p*-nitrobenzyl ester by the same procedure as that described for **8a**: NMR ($DCCl_3$) ppm (δ), 1.83 (s, 3, CH_3), 3.18 (ABq, δ 0.875 ppm, J = 15 Hz, 2-CH_2), 3.70 (s, 2, $CH_2C{=}O$) 4.81 (s, 1, 4 H), 5.28 (s, 1, 6 H), 5.60 (q, 1, 6 H), 6.85 (exchangeable protons) 7.40 (s, 5, C_6H_5).

3-Methyl-8-oxo-7-(phenylacetamido)-5-thia-1-azabicyclo-

[4.2.0]oct-2-ene-2-carboxylic Acid *p*-Nitrobenzyl Ester, 2. To a solution of 6-(2-phenylacetamido)penicillanic acid *p*-nitrobenzyl ester 1-oxide (1.2 g, 2.47 mmol) in 100 mL of 1,2-dichloroethane was added pyridine (200 mg, 2.47 mmol). The solution was heated to reflux for 29 h, it was then washed with dilute hydrochloric acid and water, treated with charcoal, dried, and flash evaporated. The residual oil was chromatographed on 25 g of silica gel using 2:1 diethyl ether, dichloromethane as eluents. Evaporation of the combined eluents gave 0.51 g (45% yield) of the title compound, **2**, melting point and NMR identical to the literature values,[2b] and 0.26 g (22% yield) of the known isomer α-isopropylidene-3-oxo-4-(2-phenylacetamido)-4-isothiazoline-2-acetic acid *p*-nitrobenzyl ester (**3**).

When this reaction was carried out under the same conditions as method I, but replacing the pyridine by other amines such as picolines, lutidine, quinoline, etc., larger amounts of the isothiazoline isomer and small amounts of the title compound were isolated.

Dehydrohalogenation of 5a. To a solution of **5a** (1 g, 2 mmol) in 25 mL of acetone was added 1,5-diazabicyclo[4.3.0]non-5-ene (247 mg, 2 mmol); the purple solution was stirred for 15 min, and was added to water. A solid precipitated which was filtered, dissolved in dichloromethane, dried over magnesium sulfate, treated with charcoal, and evaporated to a solid, 800 mg (86.5% yield), whose NMR spectrum was identical with that of compound 2 obtained by method I.

7-Amino-3-chloro-3-methyl-8-oxo-5-thia-1-azabicyclo-[4.2.0]octane-2-carboxylic Acid *p*-Nitrobenzyl Ester (7a). To an ice-cold solution of 3-chloro-3-methyl-8-oxo-7-(2-phenylacetamido)-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic acid *p*-nitrobenzyl ester (5.04 g, 10 mmol) in 100 mL of dichloromethane were added in rapid succession phosphorus pentachloride (3.1 g, 15 mmol) and *N,N*-dimethylaniline (1.8 g, 15 mmol). The mixture was stirred at 0 °C for 15 min and at 25 °C for 3 h, then 30 mL of absolute methyl alcohol was added and the solution was further stirred for 1 h. The solvent was flash evaporated. To the residue were added 25 mL of ethyl acetate and 30 mL of water, and the mixture was stirred thoroughly. The crystalline solid thus obtained was filtered and air-dried to give 2.75 g (65.2% yield) of product, which decomposed above 160 °C: NMR (Me_2SO-d_6) ppm (δ), 1.74 (s, 3, 3-CH_3), 3.38 (ABq, δ 0.45 ppm, J = 14.5 Hz, 2-CH_2), 4.92 (s, 1, 4 H), 5.0 (d, 1, 6 H), 5.34 (d, 1, 7 H), 5.51 (s, 2, CO_2CH_2), 8.05 (ABq, δ 0.525 ppm, J = 7.5 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd for $C_{15}H_{16}N_3ClO_5S$·HCL·0.5H_2O: C, 41.77; H, 4.21; N, 9.74. Found: C, 41.54; H, 4.11; N, 9.80.

3-Chloro-3-methyl-8-oxo-7-[2-(2-thienylacetamido)]-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid *p*-Nitrobenzyl Ester (9a). To a mixture of 7-amino-3-chloro-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic acid *p*-nitrobenzyl ester hydrochloride (1.05 g, 2.5 mmol), and 2-thienylacetyl chloride (0.4 g, 2.5 mmol) in 50 mL of dichloromethane, *N,N*-dimethylaniline (0.61 g 5 mmol) was added. The mixture was stirred at 0 °C for 1 h and was then washed with ice-cold 1 N hydrochloric acid and ice-cold water. The organic phase was dried, decolorized with charcoal, concentrated to 10 mL, and added to vigorously stirred pentane. The product, 1.04 g (86% yield), was obtained as a white powder which decomposed at ~70 °C. NMR (Me_2SO-d_6 ppm (δ) 1.69 (s, 3, 3-CH_3), 3.28 (Abq, δ, 0.575 ppm, J = 16 Hz, 2-CH_2), 3.85 (s, 2, CH_2CO), 4.86 (s, 1, 4 H), 5.25 (d, 1, 6 H), 5.42 (s, 2, CO_2CH_2), 5.53 (d, 1, 7 H) and 7.0 (m, 2), and 7.4 (m, 1, 2-thienyl) and 8.04 (ABq, δ 0.575 ppm, J = 8 Hz, *p*-$NO_2C_6H_4$).

Anal. Calcd for $C_{21}H_{20}N_3ClO_6S_2$: C, 49.46; H, 3.95; N, 8.24. Found: C, 49.43; H, 3.92; N, 8.01.

3-Chloro-3-methyl-8-oxo-7-[2-(2-thienylacetamido)]-5-thia-1-azabicyclo[4.2.0]octane-2-carboxylic Acid (10a). The title compound was prepared from the ester **9a** by the same procedure as that described in the preparation of **8a**. The product obtained in 70% yield decomposed above 80 °C: NMR ($DCCl_3$) ppm (δ), 1.73 (s, 3, 3-CH_3), 3.20 (ABq, 1.0 ppm, J = 14.5 Hz, 2-CH_2), 3.88 (s, 2, CH_2CO) 4.70 (s, 1, 4-H), 5.26 (d, 1, 6-H), 5.60 (d, 1, 7 H), 7.0 (m, 2) and 7.3 (m, 1, 2-thienyl).

Anal. Calcd for $C_{14}H_{15}N_2ClO_4S_2$: C, 44.85; H, 4.03; N, 7.47. Found: C, 44.59; H, 4.19; N, 7.14.

Registry No.—**1**, 29124-80-9; **2**, 34104-27-3; **3**, 58681-34-8; **4a**, 7041-27-2; **5a**, 58865-64-8; **5b**, 58844-04-5; **6**, 58844-03-4; **7a** HCl, 62532-97-2; **8a**, 58844-05-6; **8b**, 58844-06-7; **9a**, 58844-07-8; **10a**, 58844-08-9; pyridine, 110-86-1; 1,2-dichloroethane, 75-09-2; quinoline, 91-22-5; 1,2-dibromoethane, 106-93-4; *N,N*-dimethylaniline, 121-69-7; 2-thienylacetyl chloride, 39098-97-0.

References and Notes

(1) Address correspondence to this author at the Weizmann Institute of Science, Rehovot, Israel, Department of Organic Chemistry.
(2) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969); (b) D. H. R. Barton, F. Comer, D. G. T. Creig, P. G. Sammes, C. M. Cooper, G. Hewitt, and W. G. E. Underwood, *J. Chem. Soc., C*, 3540 (1971).
(3) W. J. Gottstein, P. F. Misco, and L. C. Cheney, *J. Org. Chem.*, **37**, 2765 (1972).
(4) M. Numata, Y. Imashiro, I. Minamida, and M. Yamaoka, *Tetrahedron Lett.*, 5097 (1972).
(5) T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi, and T. Oku, *Tetrahedron Lett.*, 3001 (1973).
(6) S. Kukolja, S. R. Lammert, M. R. Gleissner, and A. I. Ellis, *J. Am. Chem. Soc.*, **97**, 3192 (1975).
(7) J. J. de Koning, H. J. Kooreman, H. S. Tan, and J. Verweij, *J. Org. Chem.*, **40**, 1346 (1975).
(8) M. Fukumura, N. Hamma, and T. Nakagome, *Tetrahedron Lett.*, 4123 (1975).
(9) J. D. Barnhurst, *J. Org. Chem.*, **26**, 4520 (1961).
(10) S. Kukolja, N. D. Jones, M. O. Cheney, T. A. Elzey, M. R. Gleissner, J. W. Paschal, and D. E. Dorman, *J. Org. Chem.*, **40**, 2388 (1975).
(11) See Penicillin and Cephalosporin Sulfoxides Section: (a) A. Nudelman, *Int. J. Sulfur Chem., Part B*, **7**, 241 (1975); (b) *Phosphorous Sulfur*, **2**, 51 (1976).
(12) B. Fechtig, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, **57**, 1108 (1969).

Synthesis of Holomycin and Derivatives[1]

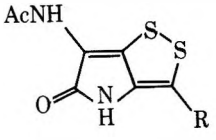
John E. Ellis, John H. Fried, Ian T. Harrison,* Erich Rapp, and Carl H. Ross

Institute of Organic Chemistry, Syntex Research, Stanford Industrial Park, Palo Alto, California 94304

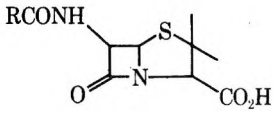
Received April 5, 1977

Holomycin, 6-acetamido-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (**1a**), and the 3-carboxylated derivative (**1b**) have been prepared by a ten-stage synthesis designed around two key reactions. Cyclization of 5-methoxalylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (**6**) by base gave 7-hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (**7**) containing the required pyrrolinone ring. A contraction of the dithioketal 7-*p*-methoxybenzylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (**9**) afforded the cyclic enol disulfide 6-*p*-methoxybenzylamino-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (**10a**). Further elaboration led to holomycin (**1a**) and the carboxy derivative **1b**.

The structure of the antibiotic holomycin (**1a**)[2] bears a formal resemblance to that of the penicillins **2**. Both substances are bicyclic lactams incorporating a sulfur heteroatom and have an acylamine side chain. We have devised a synthesis



1a, R = H, holomycin
b, R = CO_2H



2, penicillins

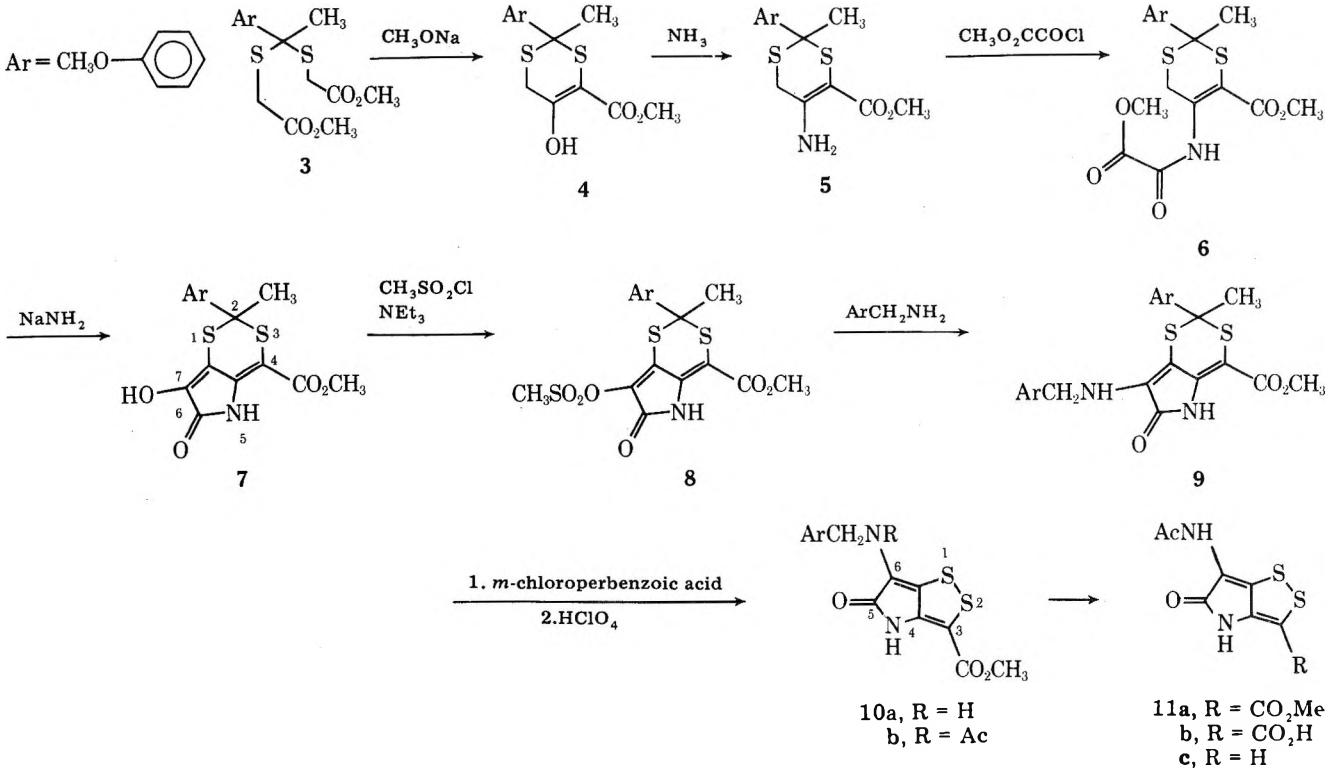
of the carboxyl substituted derivative **1b** of holomycin, a substance in which this analogy is advanced one step further, and have prepared holomycin itself by decarboxylation.

Our synthetic scheme was designed around two key reactions, formation of the pyrrolinone ring by cyclization of the methoxalylamine **6** to **7** and contraction of the dithioketal **9** to disulfide **10a** following the general method developed by Kishi and co-workers.[3] Previous syntheses[4a-c] of holomycin have relied upon the oxidation of dithiols to create the disulfide ring and have not been adaptable to the preparation of nuclear substituted holomycins.

The dithioketal **3** was prepared from *p*-methoxyacetophenone and methythioglycolate and cyclized in a Dieckmann reaction to the keto ester **4**. Replacement of the enolic hydroxyl group by the amino function proceeded readily on treatment with ammonia, forming the enamine **5** which was acylated by methoxalyl chloride. The resulting methoxamide **6** was cyclized by sodium amide yielding the pyrrolinone **7**.

Difficulties were encountered in the elaboration of the enolic hydroxyl group of **7**. Direct replacement by the amino group did not occur on treatment with ammonia. The methanesulfonate **8** could, however, be induced to react with higher amines. For example, reaction with *p*-methoxybenzylamine gave the amine **9** in 12% yield, together with the products of attack of the amine at the sulfur atom of the methanesulfonyl group, *N*-methanesulfonyl-*p*-methoxybenzylamine and the enol **7**.

Treatment of the dithioketal **9** with *m*-chloroperbenzoic acid followed by perchloric acid gave the required disulfide **10a**. The remaining nontrivial step in the synthesis consisted of the cleavage of the *N*-*p*-methoxybenzyl group. This was accomplished by treatment of the acetylated amine **10b** with anhydrous hydrofluoric acid and anisole[5] affording 3-carbomethoxyholomycin (**11a**). Hydrolysis with base gave the desired 3-carboxyholomycin (**11b**). Holomycin **11c** was obtained in a single step from the methyl ester **11a** by cleavage and concomitant decarboxylation with lithium iodide in pyridine,



a reaction presumably requiring isomerization of the double bond α,β to the carboxyl group to the β,γ position. Thermal decarboxylation of carboxyholomycin at the melting point (202 °C) also gave holomycin.

The 3-carboxyholomycin **11b** inhibited *Staphylococcus aureus* at 50 μg/mL. The minimum inhibitory concentration of holomycin has been quoted as 100 μg/mL.[2] The acid **11b** was, however, considerably less active than holomycin against other organisms.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are corrected. NMR spectra were recorded with Varian A-60, HA-100, and Brucker WH-90 spectrometers using Me_4Si as an internal standard. Mass spectra were obtained with a Varian MAT CH-7 spectrometer.

1,1-Bis(methoxycarbonylmethylthio)ethyl-*p*-methoxybenzene (3). A mixture of *p*-methoxyacetophenone (23 g, 153 mmol), methyl thioglycolate (32.5 g, 307 mmol), and *p*-toluenesulfonic acid (1.2 g, 7 mmol) in benzene (400 mL) was heated under reflux with separation of water formed by a Dean-Stark trap. After 40 h separation of water was complete and the cooled deep red solution was washed with saturated $NaHCO_3$ solution and with water. Evaporation of the solvent and chromatography of the residue (alumina, 50% hexane in Et_2O) gave the thioketal **3** as an oil (22.5 g, 43%): NMR ($CDCl_3$, 60 MHz) δ 1.98 (s, 3, CH_3), 3.33 (s, 4, CH_2), 3.61 (s, 6, CO_2CH_3), 3.71 (s, 3, OCH_3), 6.85 (d, 2, J = 9 Hz, ArH), 7.76 (d, 2, J = 9 Hz, ArH). A sample was distilled at 150 °C (0.1 mm) for elemental analysis.

Anal. Calcd for $C_{15}H_{20}O_5S_2$: C, 52.31; H, 5.85; S, 18.62. Found: C, 51.90; H, 5.68; S, 18.68.

5-Hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (4). A solution of the thioketal **3** (16.34 g, 47.5 mmol) in ether (50 mL) was added to a solution of sodium methoxide (from 1.1 g, 47.5 mmol, of sodium) in methanol (25 mL) at 0 °C under a nitrogen atmosphere. Stirring was continued for 7 h at 0 °C and for a further 40 h at about 25 °C. The mixture was acidified with dilute HCl and the products were extracted into ether. The ether was washed with saturated $NaHCO_3$ and then was extracted by NaOH solution (4%, 100 mL). The aqueous layer was acidified with dilute HCl and extracted with ether. After washing with water and saturated NaCl solution, the ether was dried over $MgSO_4$ and the solvent removed giving the keto ester **4** as an oil (10.85 g, 73%): NMR ($CDCl_3$, 60 MHz) δ 2.01 (s, 3, CH_3), 3.45 (s, 2, SCH_2), 3.78 (s, 6, OCH_3, CO_2CH_3), 6.84 (d, 2, J = 9 Hz, ArH), 7.64 (d, 2, J = 9 Hz, ArH). The *p*-nitrobenzoyl derivative, mp 191–192 °C from tetrahydrofuran, was prepared for characterization.

Anal. Calcd for $C_{21}H_{19}NO_7S_2$: C, 54.65; H, 4.15; N, 3.04; S, 13.90. Found: C, 54.55; H, 4.04; N, 3.06; S, 13.82.

5-Amino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (5). Ammonia was passed into a solution of the keto ester **4** (10.8 g, 34.6 mmol) in benzene (120 mL) and the solution heated to 80 °C. The cooled mixture was evaporated to dryness in vacuo giving a mixture of **4** and **5** in a ratio of ca. 3:1 (TLC, silica gel, 50% EtOAc–hexane). Repetition of the process five times increased the ratio of product to about 90%. Evaporation and crystallization of the residue from acetone gave the enamine **5** (7.1 g, 66%): mp 132–133 °C; NMR (Me_2SO-d_6, 100 MHz) δ 1.85 (s, 3, CH_3), 3.44, 3.70, 3.83 (2 doublets, incompletely resolved, SCH_2) 3.56 (s, 3, CO_2CH_3), 3.74 (s, 3, OCH_3), 6.85 (d, 2, J = 9 Hz, ArH), 7.56 (d, 2, J = 9 Hz, ArH), 8.2 (br s, 2, NH_2).

Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 54.00; H, 5.50; N, 4.50; S, 20.59. Found: C, 53.90; H, 5.50; N, 4.49; S, 20.54.

5-Methoxalylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-1,3-dithiin (6). Methoxalyl chloride (15 g, 122 mmol) was added to a stirred suspension of the enamine **5** (5.63 g, 18.1 mmol) in ether (300 mL). After 30 min a small amount of insoluble material was removed by filtration and the solution allowed to stand for 24 h during which time yellow crystals were deposited. Filtration gave **6** (3.7 g), and cooling of the mother liquors gave a further crop (0.9 g, total yield 64%): mp 116–117 °C; NMR ($CDCl_3$, 60 MHz) δ 2.00 (s, 3, CH_3), 3.77 (s, 3, CO_2CH_3), 3.81 (s, 3, OCH_3), 3.92 (s, 3, CO_2CH_3), 4.07 (part of incompletely resolved doublet, SCH), 4.54 (d, 1, J = 15 Hz, SCH), 6.83 (d, 2, J = 8.5 Hz, ArH), 7.58 (d, 2, J = 8.5 Hz, ArH), 12.5 (s, 1, NH).

Anal. Calcd for $C_{17}H_{19}NO_6S_2$: C, 51.38; H, 4.82; N, 3.52; S, 16.13. Found: C, 51.14; H, 4.96; N, 3.27; S, 16.04.

7-Hydroxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (7). A solution of the ester **6** (5.0 g, 12.6 mmol) in THF (50 mL) was added to a stirred suspension of $NaNH_2$ (1.0 g, 25.6 mmol) in THF (50 mL) under nitrogen. The mixture was heated under reflux for 4 h and then cooled and most of the solvent removed in vacuo. After acidification with dilute HCl the products were extracted into $CHCl_3$ which was then washed with water. Concentration of the solution and filtration yielded yellow crystals of **7** (3.21 g, 70%): mp 257–259 °C dec; NMR ($CDCl_3$, 60 MHz) δ 1.99 (s, 3, CH_3), 3.78 (s, 3, CO_2CH_3), 3.83 (s, 3, OCH_3), 6.83 (d, 2, J = 8.5 Hz, ArH), 7.58 (d, 2, J = 8.5 Hz, ArH), 8.58 (br, 1, OH), 12.2 (br, 1, NH).

Anal. Calcd for $C_{16}H_{15}NO_5S_2$: C, 52.59; H, 4.14; N, 3.83; S, 17.55. Found: C, 52.62; H, 4.09; N, 3.79; S, 17.35.

7-Methanesulfonyloxy-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]pyrrole (8). A stirred suspension of the enol **7** (2.0 g, 5.5 mmol) in dichloromethane (50 mL) was treated with triethylamine (1.56 mL, 11.3 mmol) followed by methanesulfonyl chloride (0.54 mL, 7.0 mmol). The mixture was then diluted with chloroform and washed with water, with dilute HCl, and finally with brine. After drying (Na_2SO_4), the solution was concentrated in vacuo to about 15 mL affording yellow crystals of **8** (1.65 g, 68%), mp 235 °C.

Anal. Calcd for $C_{17}H_{17}NO_7S_3$: C, 46.04; H, 3.86; N, 3.16; S, 21.69. Found: C, 45.94; H, 3.88; N, 3.12; S, 21.64.

Reaction of the Enol 7 with Ammonia. Dry NH_3 was passed into a solution of the enol **7** (1.01 g, 2.76 mmol) in benzene (15 mL) for 2 h. Analysis by TLC indicated that a large number of compounds were produced. No pure products could be isolated. A similar result was obtained using NH_4OAc in ethanol under reflux.

7-*p*-Methoxybenzylamino-4-methoxycarbonyl-2-*p*-methoxyphenyl-2-methyl-6-oxo-5,6-dihydro-1,3-dithiino[5,4-*b*]-pyrrole (9). A solution of the mesylate **8** (2.0 g, 4.5 mmol) and *p*-methoxybenzylamine (5.25 g, 38.3 mmol) in tetrahydrofuran was heated under reflux for 15 h. The cooled solution was evaporated to dryness and triturated with ethyl acetate. Filtration gave a residue of the enol **7** (1.01 g, 2.76 mmol). The filtrate was concentrated and triturated with carbon tetrachloride giving white crystals of *N*-methanesulfonyl-*p*-methoxybenzylamine (560 mg, 2.60 mmol): mp 95–96 °C; NMR ($CDCl_3$, 60 MHz) δ 2.80 (s, 3, SO_2CH_3), 3.79 (s, 3, OCH_3), 4.24 (d, 2, J = 5.5 Hz, NCH_2), 4.92 (br s, 1, NH), 6.88 (d, 2, J = 8.5 Hz, ArH), 7.29 (d, 2, J = 8.5 Hz, ArH). The filtrate was purified by TLC (silica gel, hexane–EtOAc, 1:1) and the product crystallized from acetone–hexane affording the amine **9** as red crystals (0.26 g, 12%): mp 157–159 °C; NMR ($CDCl_3$, 60 MHz) δ 1.99 (s, 3, CH_3), 3.80 (s, 9, OCH_3 and CO_2CH_3), 4.55 (d, 2, CH_2N), 5.22 (br t, 1, NH), 6.87 (d, 4, J = 8.5 Hz, ArH), 7.22 (d, 2, J = 8.5 Hz, ArH), 7.65 (d, 2, J = 8.5 Hz, ArH), 9.43 (s, 1, NH).

Anal. Calcd for $C_{24}H_{24}N_2O_5S_2$: C, 59.50; H, 4.99; N, 5.78; S, 13.21. Found: C, 59.45; H, 5.17; N, 5.80; S, 12.91.

6-*p*-Methoxybenzylamino-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (10a). A solution of the dithiin **9** (98 mg, 0.20 mmol) and *m*-chloroperbenzoic acid (50 mg, 0.29 mmol) in CH_2Cl_2 was kept at room temperature for 30 min. The solution was washed successively with solutions of Na_2SO_3, $NaHCO_3$, and NaCl. The solvent was removed in vacuo and CH_2Cl_2 (15 mL) and 70% $HClO_4$ (40 mg) in tetrahydrofuran (2 mL) added. After standing for 48 h the solution was washed by $NaHCO_3$ solution and the solvent removed in vacuo. Purification by TLC (silica gel, EtOAc–hexane, 1:1) and crystallization from acetone gave the dithiole **10a** (52 mg, 74%) as brown crystals: mp 169–170 °C; NMR ($CDCl_3$, 60 MHz) δ 3.80 (s, 3, CO_2CH_3), 3.86 (s, 3, OCH_3), 4.47 (br, 2, NCH_2Ar), 4.5–4.8 (br, 1, NH), 6.92 (d, 2, J = 8.5 Hz, ArH), 7.30 (d, 2, J = 8.5 Hz, ArH), 8.7 (br, 1, NH); MS m/e 350 (M^+).

Anal. Calcd for $C_{15}H_{14}N_2O_4S_2$: C, 51.42; H, 4.03; N, 7.99. Found: C, 51.16; H, 4.15; N, 7.90.

6-Acetamido-3-methoxycarbonyl-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (11a). The amine **10a** (48 mg, 0.14 mmol) was heated under reflux in dry benzene (4 mL) and acetic anhydride (2 mL) for 8 h. Evaporation in vacuo gave the amide **10b** which was not purified. A mixture of **10b** (50 mg, 0.13 mmol) and anisole (80 mg, 0.74 mmol) was stirred with anhydrous HF (10 mL) for 20 h. Evaporation gave a dark red residue which was purified by TLC (silica gel, $CHCl_3$–MeOH, 14:1) and recrystallized from tetrahydrofuran affording 3-carbomethoxyholomycin **11a** (30 mg, 86% from **10a**) as a red powder: mp 259–262 °C dec; NMR (Me_2SO-d_6, 90 MHz) δ 2.16 (s, 3, CH_3CO), 3.94 (s, 3, CO_2CH_3), 10.16 (br s exchanged by D_2O, 1, NH), 11.05 (br s exchanged by D_2O, 1, NH); UV max (MeOH) 223 (sh), 257, 336, 448 nm (log ε 3.96, 3.75, 3.54, 3.79); MS (70 eV) m/e (rel intensity) 272 (M^+, 38), 230 (100), 198 (26), 170 (24), 142 (14).

Anal. Calcd for $C_9H_8N_2O_4S_2$: C, 39.70; H, 2.96; N, 10.29. Found: C, 39.39; H, 2.80; N, 10.35.

6-Acetamido-3-carboxy-5-oxo-4,5-dihydro-1,2-dithiolo-[4,3-*b*]pyrrole (11b). A solution of KOH (25 mg, 0.45 mmol) in methanol (0.5 mL) was added to the ester **11a** (8.7 mg, 0.032 mmol) in tetrahydrofuran (5 mL). After 7 h at room temperature crystals of the sodium salt of **11b** were separated by filtration and washed by tetrahydrofuran. A solution of this salt in water (0.3 mL) was acidified with excess 2 N HCl and the precipitated **11b** filtered and washed with water. Drying in vacuo and crystallization from tetrahydrofuran gave the acid **11b** as solvated orange crystals (4.1 mg, 50%): mp 201–202 °C (TLC of material recovered from the melting point determination showed the presence of holomycin formed by thermal decarboxylation); MS (70 eV) *m/e* (rel intensity) 214 ($M^+ - CO_2$, 40), 172 ($M^+ - CO_2 - CH_2CO$, 81), 44 (CO_2, 100).

Anal. Calcd for $C_8H_6N_2O_4S_2 \cdot {}^2/_3(C_4H_8O)$: C, 41.82; H, 3.73; N, 9.15. Found: C, 41.54; H, 3.87; N, 8.96.

6-Acetamido-5-oxo-4,5-dihydro-1,2-dithiolo[4,3-*b*]pyrrole (Holomycin, 11c). A mixture of the ester **11a** (10 mg, 0.037 mmol) and anhydrous LiI (70 mg, 0.52 mmol) in pyridine (2 mL) was heated on a steam bath for 35 h. Dilute HCl was added and the products extracted into ethyl acetate which was then washed with dilute HCl and brine. After drying ($MgSO_4$) the solvent was removed in vacuo and the residue purified by TLC (silica gel, ethyl acetate–hexane–acetic acid, 1:1:0.04) yielding holomycin (**11c**) as an orange powder (3.5 mg, 44%), mp 265–270 °C dec. A sample sublimed at 200 °C (0.4 mm) had mp 271–274 °C dec, not depressed by admixture with an authentic sample of mp 270–273 °C[6] (lit.[2,4b] 264–271 °C dec); UV max (CH_3OH) 230 (sh), 246 (sh), 299, 386 nm (log ϵ 3.48, 3.37, 3.11, 3.54); IR (KBr) 1660, 1635, 1595, 1545 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 214 (M^+, 19), 172 (50), 43 (100). The physical data are consistent with the literature values.[2,4b]

Acknowledgments. We would like to thank A. Braemer and S. Hitt for the microbiological data and L. Tökés, M. Maddox, J. Nelson, and L. Kurz for the spectral data. We also thank E. J. Corey and G. Stork for very helpful suggestions. The authentic specimen of holomycin used for comparison with synthetic material was kindly supplied by G. H. Büchi.

Registry No.—**3**, 62698-38-8; **4**, 62698-39-9; **4** *p*-nitrobenzoyl derivative, 62698-37-7; **5**, 62698-40-2; **6**, 62698-41-3; **7**, 62698-42-4; **8**, 62698-43-5; **9**, 62698-44-6; **10a**, 62698-45-7; **10b**, 62698-46-8; **11a**, 62698-47-9; **11b** Na salt, 62698-48-0; **11b**, 62698-49-1; **11c**, 488-04-0; *p*-methoxyacetophenone, 100-06-1; methyl thioglycolate, 2365-48-2; methoxalyl chloride, 5781-53-3; methanesulfonyl chloride, 124-63-0; *p*-methoxybenzylamine, 2393-23-9; *N*-methanesulfonyl-*p*-methoxybenzylamine, 42060-31-1.

References and Notes

(1) Publication No. 480 from the Syntex Institute of Organic Chemistry.
(2) L. Ettlinger, E. Gauemann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, and H. Zähner, *Helv. Chim. Acta*, **42**, 563 (1959).
(3) Y. Kishi, T. Fukuyama, and S. Nakatsuka, *J. Am. Chem. Soc.*, **95**, 6490 (1973).
(4) (a) U. Schmidt and F. Geiger, *Justus Liebigs Ann. Chem.*, **664**, 168 (1963); (b) G. Büchi and G. Lukas, *J. Am. Chem. Soc.*, **86**, 5654 (1964); (c) K. Hagio and N. Yoneda, *Bull. Chem. Soc. Jpn.*, **47**, 1484 (1974).
(5) P. G. Pietta and G. R. Marshall, *Chem. Commun.*, 650 (1970).
(6) Kindly supplied by G. H. Büchi.

Nucleophilic Substitution Reactions on *N*-Nitropyrazoles[1]

Clarisse L. Habraken* and Eduard K. Poels

Gorlaeus Laboratory, The University, Leiden, The Netherlands

Received February 22, 1977

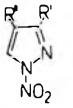
1,4-Dinitropyrazoles **1c–d** undergo "cine" substitution with secondary amines to give 3(5)-di-R-amino-4-nitropyrazoles. 1-Nitro-4-bromo- and 1,3-dinitropyrazoles **1a** and **1b** with cyclic secondary amines undergo displacement on the nitrogen of the *N*-nitro group to give the *N*-nitro amines.

The examples reported in the literature of aromatic nucleophilic substitution in azole rings[2] all follow, according to Miller,[3] an addition–elimination mechanism. In the case of halogeno pyrazoles the presence of strong electron-withdrawing groups appears to be required for the reaction to proceed as was recently confirmed by Alcalde et al.[4] Nevertheless, aromatic nucleophilic substitution in pyrazoles[2,5–7] has not been studied extensively and nothing systematic is known about the susceptibility or the point of attack in the ring and of its dependence on the activating effect of substituents in other positions in the ring.

To our knowledge, in all but one of the reported examples for pyrazoles, the activating group was at C-4 and the halogen displaced by nucleophiles was in either the 3(5) position for N-unsubstituted pyrazoles or C-5 for *N*-arylpyrazoles. The one exception reported by Coburn[8] is the reaction of 4-bromo-3,5-dinitro-1-methylpyrazole with amines to give the 4-amino derivatives, the nucleophilic substitution taking place in the 4 position and the two activating groups situated in positions 3 and 5.

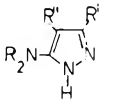
In continuation of our investigations of *N*-nitroazoles[1,9] we were interested in the reactivity toward nucleophiles of *N*-nitro-substituted pyrazoles. Therefore we investigated the reaction of some 3- and 4-substituted *N*-nitropyrazoles with secondary amines as nucleophiles.

Expecting nucleophilic substitution at the 4 position we refluxed 4-bromo-1-nitropyrazole (**1a**) with piperidine in



1a, R′ = H; R″ = Br
b, R′ = NO_2; R″ = H
c, R′ = H; R″ = NO_2
d, R′ = CH_3; R″ = NO_2

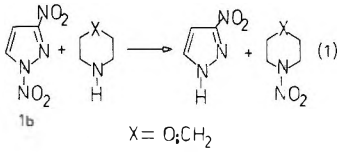
ethanol solution and in excess piperidine, respectively. However, the reaction products were a trace of 4-bromo-3(5)-piperidylpyrazole (**2a**), 4-bromopyrazole, and *N*-nitro-



2a, R′ = H; R″ = Br; R_2N = piperidyl
b, R′ = H; R″ = NO_2; R_2N = piperidyl
c, R′ = H; R″ = NO_2; R_2N = morpholyl
d, R′ = H; R″ = NO_2; R_2N = $(C_2H_5)_2N$
e, R′ = CH_3; R″ = NO_2; R_2N = piperidyl
f, R′ = CH_3; R″ = NO_2; R_2N = morpholyl

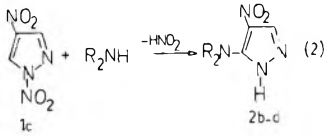
piperidine, the latter compound most likely originating from a nucleophilic displacement by piperidine on the nitrogen of the *N*-nitro group of **1a**. Assuming then that dinitropyrazoles might be even better molecules to undergo such a displacement reaction by considering that 3- or 4-nitropyrazole anions would be even better leaving groups than 4-bromopyrazole anion, we treated 1,3-dinitropyrazole (**1b**) and 1,4-dinitropyrazole (**1c**) with morpholine and with piperidine. The re-

action of 1b at reflux temperature either in ethanol or in acetonitrile solution indeed afforded respectively *N*-nitromorpholine and *N*-nitropiperidine besides 3(5)-nitropyrazole (see reaction 1). The only other product observed in both instances



was a nitroso amine, i.e., nitrosomorpholine and nitrosopiperidine, respectively.

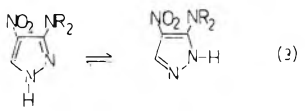
On the other hand, the isomeric 1,4-dinitropyrazole (**1c**) when subjected to reaction with piperidine in ethanol solution at room temperature afforded chiefly 4-nitro-3(5)-piperidylpyrazole (**2b**) and no formation of *N*-nitropiperidine was observed (reaction 2). In the same way, from the reactions with



morpholine and with diethylamine 3(5)-morpholyl-4-nitropyrazole (**2c**) and 3(5)-diethylamino-4-nitropyrazole (**2d**) were obtained. Again, no nitro amines were formed, whereas just as in the reactions of **1b** *N*-nitroso amines were formed as minor products. In the reactions of **1c** these nitroso amines presumably are formed in a secondary reaction, a nitrosation of the amine by the nitrous acid produced along with the aromatic nucleophilic substitution in the ring (reaction 2). However, the question remains how to explain the occurrence of *N*-nitroso amines as by-products in the reactions of **1b** with secondary amines, i.e., how to explain the presence of a nitrosating agent when no products of a nucleophilic aromatic substitution are observed.

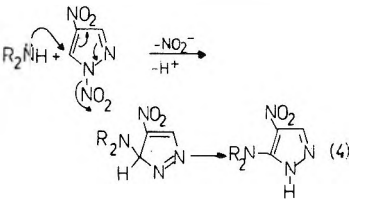
The results described above clearly indicate two modes of nucleophilic substitution on *N*-nitropyrazoles: an aromatic nucleophilic substitution in the pyrazole ring (reaction 2) and a nucleophilic displacement on the nitrogen of the *N*-nitro group as depicted in reaction 1.

From the products of the aromatic substitution in **1c** no conclusion can be drawn about the point of attack in the ring. Attack on either the 3 or the 5 position affords 3(5)-substituted 4-nitropyrazoles **2b–d** because these actually consist of equilibrium mixtures of two tautomers.[2]



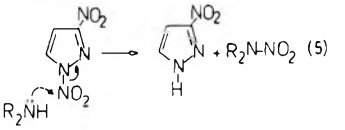
To determine whether the nucleophile attacks the 3 or the 5 position in the ring in **1c** we synthesized 1,4-dinitro-3-methylpyrazole (**1d**) and subjected it to the reaction with piperidine and with morpholine. The products isolated were 3(5)-methyl-4-nitro-5(3)-piperidylpyrazole (**2e**) and 3(5)-methyl-5(3)-morpholyl-4-nitropyrazole (**2f**) establishing unambiguously that **1d** and consequently also **1c** undergoes the aromatic nucleophilic substitution reaction in the 5 position of the ring and not in the 3 position.

These examples of aromatic nucleophilic substitution in the pyrazole ring show that we are dealing here with a "cine" substitution reaction[10] of the 1,2-addition–elimination type as described by Miller.[3] In general the occurrence of a "cine" substitution, i.e., the entering group comes in ortho to the leaving group, is evidence for a 1,2-elimination–addition mechanism. In such a 1,2-elimination–addition sequence the elimination step gives the aryne intermediate and the following addition step commonly gives a mixture of two products, one of which is a "cine" substitution product. However, no aromatic nucleophilic substitution proceeding via a hetaryne intermediate has ever been established unambiguously for a five-membered heterocycle.[11] Therefore, we assume that we are dealing here with the less common "cine" substitution reaction of the 1,2-addition–elimination mechanism, the actual molecule initially formed being a 3*H*-pyrazole:



The ultimate product obtained is then formed in a subsequent fast hydrogen rearrangement reaction.

The other nucleophilic substitution reaction consists of a displacement on the *N*-nitro group by a nucleophile of a pyrazole anion (see reaction 1). Such nucleophilic substitution reactions on the nitrogen of a nitro group are well documented. For example, the use of nitrate esters for the preparation of *N*-nitro amines is considered to be a nucleophilic displacement on the nitro group of the ester.[12] Another example is the alkaline hydrolysis of tetranitromethane where the trinitromethane anion is the leaving group.[13]



In *N*-nitropyrazoles presumably a delicate balance operates between the capacities of a 3 or a 4 substituent for activating the 5 position in the ring for nucleophilic attack and for making the pyrazole anion a better leaving group. Apparently a nitro group in the 4 position activates primarily for nucleophilic attack in the ring whereas for a 3-nitro group no such activation is found and nucleophilic displacement takes place on the *N*-nitro group. The fact that the reactions of **1c**, contrary to those of **1a** and **1b**, occur at room temperature almost instantaneously supports this assumption.

Finally, 3(5)-(*N*,*N*-dialkylamino)pyrazoles cannot be synthesized by alkylation of the 3(5)-amino group because that would also result in alkylation of the pyrazole nitrogen giving a mixture of 1,3 and 1,5 isomers. In fact no 3(5)-(*N*,*N*-dialkylamino)pyrazoles are described in the literature.[7] Consequently, this "cine" substitution reaction of 1,4-dinitropyrazoles, in addition to its mechanistic merits, provides a convenient way for the synthesis of 3(5)-[*N*,*N*-dialkylamino]pyrazoles.

Experimental Section

General. NMR spectra (δ expressed in parts per million) were recorded on a JEOL 60-MHz Minimar or on a JEOL PS-100 instrument; IR spectra (KBr) were recorded on a Beckman IR-10 instrument; mass spectra were recorded on a AE MS-902 spectrometer. Elemental analyses were performed by Mr. W. J. Buis, TNO Laboratory of Organic Chemistry, Utrecht, The Netherlands. For the separation of products the short-column chromatography technique of Hunt and Rigby[14] was used on silica gel H according to Stahl (Merck). Spraying with Rhodamine B solution (0.05% in ethanol) was used for detection of nitropyrazoles on TLC.

N-Nitropyrazoles **1a–c** were prepared as has been previously described;[9] these compounds must be stored under exclusion of moisture to prevent slow hydrolysis to nitric acid and the original N-unsubstituted pyrazole.

N-Nitropiperidine and *N*-nitromorpholine were identified by comparison with an independently synthesized specimen.[12] The identification of *N*-nitrosopiperidine and *N*-nitrosomorpholine was based on comparison of NMR and mass spectral data reported in the

literature.[15,16] The structure assignments of compounds **2a–f** were primarily based on NMR and IR spectra. In particular the NMR spectra recorded in acetone-d_6 of **2b–d** showed two signals for the 3(5) proton. This, according to Elguero and Jacquir et al.,[17] is typical for NMR spectra of 3(5)-substituted 4-nitropyrazoles taken in acetone-d_6 only and not in other solvents.

Reactions of 1a–b. TLC analysis showed that after refluxing for 10 min of 1 g of **1a** in 4 mL of piperidine all **1a** had reacted, whereas after refluxing for 5 days in ethanol (15 mL) solution of 0.6 g of **1a** and 0.3 g of piperidine some unreacted **1a** was still present. Column chromatography (heptane–acetone, 7:1) of the first reaction mixture afforded 0.2 g of *N*-nitropiperidine (30% based on **1a**), 0.42 g of 4-bromopyrazole (53%), and 0.14 g of a mixture of **2a** and 4-bromopyrazole according to the NMR spectrum. By sublimation enough of **2a** was isolated to obtain a mass spectrum, mol wt 231.01890 and 229.02045 (calcd for $C_8H_{12}BrN_3$, 231.01954 and 229.02151).

1b was reacted with piperidine and morpholine in a number of ways and the reactions were followed by TLC (chloroform–ethyl acetate, 9:1). The reaction with piperidine in acetonitrile was very slow at room temperature (5 days); after refluxing, however, for 0.75 h all **1b** had reacted. Also **1b** reacted very slowly with morpholine in ethanol solution at room temperature; on the other hand, the reaction in refluxing ethanol was completed in 16 h. No difference was observed on addition of urea, K_2CO_3, or $MgCO_3$ to the reaction mixture in an attempt to suppress the formation of nitroso amines. Column chromatography (chloroform–ethyl acetate, 9:1) afforded pure samples of *N*-nitro- and *N*-nitrosopiperidine, *N*-nitro- and *N*-nitrosomorpholine, and 3(5)-nitropyrazole. No other products were obtained. In one case the reaction of **1b** with morpholine in refluxing ethanol afforded after column chromatography 84% of *N*-nitromorpholine, 14% of *N*-nitrosomorpholine, and 84% of 3(5)-nitropyrazole.

General Procedure for the Synthesis of 2b–f. To a solution of 3 mmol of the *N*-nitropyrazole in 10–15 mL of ethanol, under stirring and while maintaining the temperature under 30 °C, a solution of 1.1–2.0 equiv of the secondary amine in 5 mL of ethanol was added slowly. Completion of the reaction was determined by TLC (chloroform–ethyl acetate, 9:1). Workup, i.e., separation from the nitroso amine, was done either by column chromatography or in the following way. The solvent was evaporated under vacuum, and the residue taken up in 5% sodium hydroxide solution, which solution in turn was evaporated. This residue was then dissolved in a small amount of water, the resulting solution was acidified, and the precipitate was collected on a Buchner funnel and recrystallized from the appropriate solvent. No attempts were made to optimize the yields, which varied from 85 to 20%.

4-Nitro-3(5)-piperidylpyrazole (2b): pale yellow, mp 129 °C (from benzene); IR 3130, 2950, and 2860 (NH and CH), 1600 and 1315 cm^{-1} (NO_2); NMR (100 MHz, Me_2SO-d_6) δ 1.64 (m, 6, β and γ piperidyl H), 3.26 (m, 4, α piperidyl H), and 8.32 [s, 1, 5(3)-H]; (100 MHz, acetone-d_6) δ 1.76 (m, 6, β and γ piperidyl H), 3.36 (m, 4, α piperidyl H) and two signals for the 5(3)-H at 8.32 and 8.52 in the ratio 1:15 consistent for a 3(5)-substituted 4-nitropyrazole.[17] Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.17; N, 28.56. Found: C, 48.70; H, 6.42; N, 28.56.

3(5)-*N*-Morpholyl-4-nitropyrazole (2c): pale yellow, mp 162 °C (from ethyl acetate); IR 3220, 3160 (CH and NH), 1600 and 1310 cm^{-1} (NO_2); NMR (100 MHz, acetone-d_6) δ 3.32 (m, 4) and 3.82 (m, 4) and two signals for the 5(3)-H in the ratio of 14:3 at 8.44 and 8.52 (see **2b**; ref 17). Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.42; H, 5.09; N, 28.27. Found: C, 42.77; H, 5.21; N, 28.08.

3(5)-Diethylamino-4-nitropyrazole (2d): pale yellow, mp 82–83 °C (sublimation); IR 3120 (NH), 1490 and 1320 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.76 (t, 6, CH_3), 3.43 (q, 4, CH_2), and 8.26 [s, 1, 5(3)-H]. Anal. Calcd for $C_7H_{12}N_4O_2$: C, 45.64; H, 6.57; N, 30.42. Found: C, 45.54; H, 6.36; N, 30.24.

3(5)-Methyl-4-nitro-5(3)-*N*-piperidylpyrazole (2e): yellow crystals, mp 124 °C (petroleum ether, bp 80–100 °C); IR 3230 (NH), 1600 (C=C), 1500 and 1322 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 1.70 (m, 6, CH_2), 2.56 (s, 3, CH_3), and 3.24 (m, 4, CH_2). Anal. Calcd for $C_9H_{14}N_4O_2$: C, 51.42; H, 6.71; N, 26.65; O, 15.22. Found: C, 51.02; H, 6.63; N, 26.21; O, 15.43. High-resolution mass spectrum: calcd for $C_9H_{14}N_4O_2$, 210.1117; found, 210.1120.

3(5)-Methyl-5(3)-morpholyl-4-nitropyrazole (2f): yellow crystals, mp 165 °C (ethyl acetate); IR 3230 (NH), 1600 (C=C), 1530 and 1360, 1380 cm^{-1} (NO_2); NMR ($CDCl_3$) δ 2.71 (s, 3, CH_3), 3.46 (m, 4, CH_2) and 3.96 (m, 4, CH_2). Anal. Calcd for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40; O, 22.62. Found: C, 45.24; H, 5.83; N, 26.20; O, 22.73.

3-Methyl-1,4-dinitropyrazole (1d) was synthesized according to the previously described procedure[9,18] by nitration of 0.87 g of 3(5)-methyl-4-nitropyrazole in 3 mL of acetic acid by successive treatment with 0.7 mL of nitric acid (d = 1.52) and 2 mL of acetic anhydride while maintaining the temperature below 25 °C. For workup the reaction mixture was poured onto 50 mL of ice and the formed precipitate was filtered off affording 0.74 g of **1d**. Crystallization from hexane gave colorless crystals: mp 47 °C (lit. 48 °C[18]); IR 1640 and 1270 (N–NO_2), 1565 and 1370 cm^{-1} (C–NO_2); NMR ($CDCl_3$) δ 2.73 (s, 3, CH_3) and 9.13 (s, 1, H). Neutralization of the filtrate with sodium carbonate, extraction with ether, drying the ether extracts over magnesium sulfate, and evaporation of the ether afforded 0.38 g of a yellow oil. The NMR spectrum of this oil (100 MHz, $CDCl_3$) showed this oil to be a mixture of **1d** (79%) and its isomer 5-methyl-1,4-dinitropyrazole (21%), with signals for the latter compound at 3.12 (s, 3, CH_3) and 8.12 (s, 1, H) confirming that indeed in **1d** the methyl group occupies the 3 position.

Acknowledgments. We thank Steven M. Bonser for the preparation of *N*-nitropiperidine and *N*-nitromorpholine and Robert Jan Visser for performing the synthesis of **2d.** We also express our thanks to Dr. J. van Thuyl, J. van Houte, and W. C. M. M. Luyten for the mass spectral analyses and to J. Stikkelorum, A. van der Linden, and C. Erkelens for IR and NMR spectral data.

Registry No.—**1a,** 7185-93-5; **1b,** 38858-81-0; **1c,** 35852-77-8; **1d,** 62563-09-1; **2a,** 62563-10-4; **2b,** 62563-11-5; **2c,** 62563-12-6; **2d,** 62563-13-7; **2e,** 53960-82-0; **2f,** 53960-83-1; piperidine, 110-89-4; morpholine, 110-91-8; 5-methyl-1,4-dinitropyrazole, 62563-14-8.

References and Notes

(1) Pyrazoles. 15. For previous papers see: 14, J. W. A. M. Janssen, C. L. Habraken, and R. Louw, *J. Org. Chem.*, **41,** 1758 (1976); 13, J. W. A. M. Janssen, C. G. Kruse, H. J. Koeners, and C. L. Habraken, *J. Heterocycl. Chem.*, **10,** 1055 (1973).
(2) K. Schofield, M. R. Grimmett, and B. R. T. Keene, "The Azoles", Cambridge University Press, New York, N.Y., 1976.
(3) J. Miller, "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968.
(4) E. Alcalde, J. M. Garcia-Maquina, and J. De Mendoza, *An. Quim.*, **70,** 959 (1974).
(5) A. N. Kost and I. I. Grandberg, *Adv. Heterocycl. Chem.*, **6,** 347 (1966).
(6) T. L. Jacobs, "Heterocyclic Compounds", Vol. V, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, p 45.
(7) R. Fusco, "The Chemistry of Heterocyclic Compounds", Vol. 22, A. Weissberger, Ed., Interscience, New York, N.Y., 1967, p 3.
(8) M. D. Coburn, *J. Heterocycl. Chem.*, **8,** 153 (1971).
(9) (a) J. W. A. M. Janssen, H. J. Koeners, C. G. Kruse, and C. L. Habraken, *J. Org. Chem.*, **38,** 1777 (1973); (b) J. W. A. M. Janssen and C. L. Habraken, *ibid.*, **36,** 3081 (1971).
(10) J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12,** 1 (1958).
(11) See, however, M. G. Reinecke and J. G. Newsom, *J. Am. Chem. Soc.*, **98,** 3021 (1976), and references cited therein.
(12) W. D. Emmons and J. P. Freeman, *J. Am. Chem. Soc.*, **77,** 4387, 4391 (1955); "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 839.
(13) D. J. Glover, *J. Phys. Chem.*, **74,** 21 (1970).
(14) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(15) R. K. Harris and R. A. Spragg, *J. Mol. Spectrosc.*, **23,** 158 (1967); Y. L. Chow and C. J. Colon, *Can. J. Chem.*, **46,** 2827 (1968).
(16) G. Schroll, R. G. Cooks, Per Klemmensen, and Sven-Olov Laweson, *Ark. Kemi*, **28,** 413 (1968).
(17) M. L. Roumestant, P. Viallefout, J. Elguero, and R. Jacquier, *Tetrahedron Lett.*, 495 (1969).
(18) R. Hüttel and F. Büchele, *Chem. Ber.*, **88,** 1586 (1955).

Derivatives of 4-Chloro-3,5-dinitrobenzotrifluoride. 3. Synthesis of 1,6-Dinitro-3,8-bis(trifluoromethyl)thianthrene and Related Compounds[1]

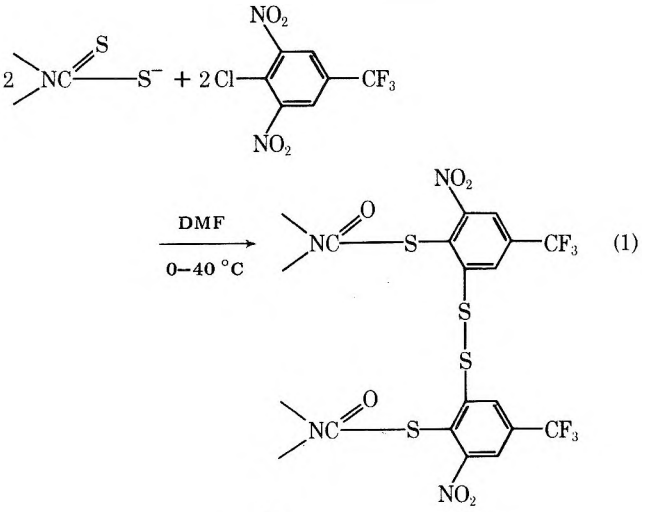
J. J. D'Amico,* C. C. Tung, W. E. Dahl, and D. J. Dahm

Monsanto Agricultural Products Company, Research Department, St. Louis, Missouri 63166

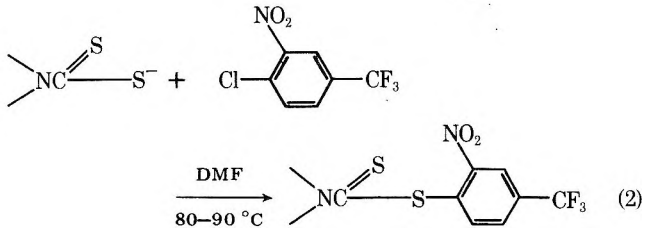
Received March 21, 1977

The reaction of potassium ethyl or isopropyl dithiocarbonate with 4-chloro-3,5-dinitrobenzotrifluoride afforded 1,6-dinitro-3,8-bis(trifluoromethyl)thianthrene (1). Depending on reaction conditions, temperature, and solvent, the reaction of 4-chloro-3-nitrobenzotrifluoride with potassium ethyl or isopropyl dithiocarbonate furnished either bis(2-nitro-4-trifluoromethyl) sulfide (2) and dialkyl dithiocarbonate (4 or 5) or 2-nitro-4-trifluoromethylphenyl alkyl sulfide (6 or 7) or bis(2-nitro-4-trifluoromethyl) disulfide (3). Possible mechanisms and supporting NMR and mass spectral data are discussed. The assigned structure for 1 was verified by x-ray crystal structure analysis.

In a previous communication[2] we reported that the reaction of sodium or triethylamine salts of disubstituted dithiocarbamic acids with 4-chloro-3,5-dinitrobenzotrifluoride or 4-chloro-3-nitrobenzotrifluoride afforded the products as illustrated by reactions 1 and 2, respectively.

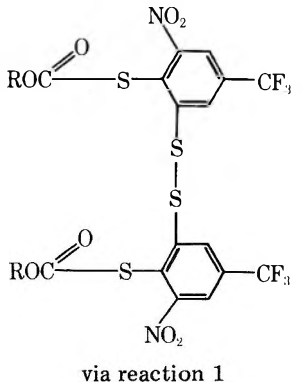


(1)

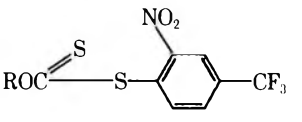


(2)

It was anticipated that replacing the sodium or triethylamine salts of disubstituted dithiocarbamic acids in the above reactions 1 and 2 with potassium alkyl dithiocarbonates would have furnished the following analogous products:



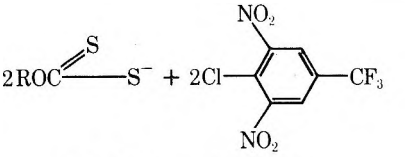
via reaction 1



via reaction 2

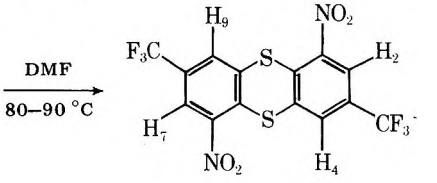
However, this was not the case, for the reaction of potassium ethyl or isopropyl dithiocarbonate with 4-chloro-3,5-dinitrobenzotrifluoride in DMF at 80–90 °C afforded 1,6-dinitro-3,8-bis(trifluoromethyl)thianthrene (1) in fair yields. However, based on elemental analysis, molecular weight, NMR, and mass spectral data structure A had to be considered.

Since the above spectral data could not distinguish between structure 1 and A, x-ray crystallographic study was under-



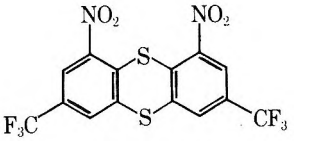
(3)

R = C_2H_5 or $CH(CH_3)_2$



1

or



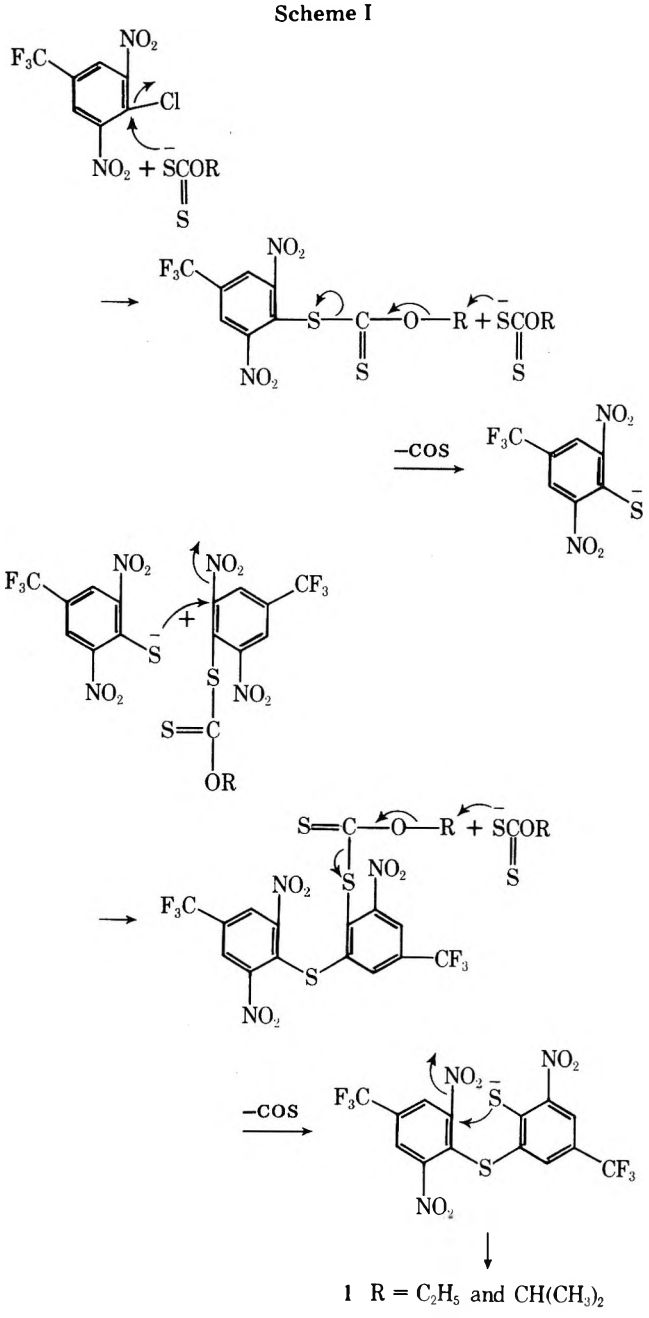
structure A

taken. As noted in Figure 1, this study furnished definitive proof that the compound isolated in reaction 3 possessed structure 1. The molecule 1 has two planar halves which form an angle of 137°. Each sulfur atom is in the plane of one benzene ring, to which it is slightly more closely bonded, and 0.13 (1) Å out of the planes of the rings to which they are attached by 32 (1)°. The S1 to O3 distance of 2.727 (9) Å is the same as the S2 to O1 distance of 2.722 (9) Å.

The proposed mechanism for reaction 3 is depicted in Scheme I. The possible mass spectral fragmentation route for 1 is shown in Scheme II (microfilm edition; see paragraph concerning supplementary material).[3]

Depending on reaction conditions, temperature, and solvent, the reaction of 4-chloro-3-nitrobenzotrifluoride with potassium ethyl or isopropyl dithiocarbonate afforded different products. Szmant and Lapinski[4] reported that the reaction of the above halogen compound with potassium ethyl dithiocarbonate in refluxing ethanol for 2 days furnished

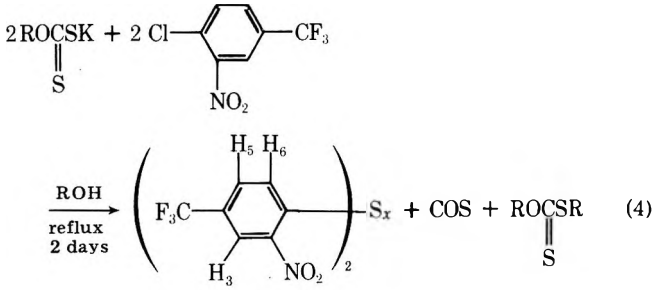
Scheme I



1 R = C_2H_5 and $CH(CH_3)_2$

bis(2-nitro-4-trifluoromethylphenyl) sulfide (**2**). Upon reinvestigation of this reaction, we obtained a crude product in 64% yield containing 93% of **2** and 7% of bis(2-nitro-4-trifluoromethylphenyl) disulfide (**3**). Moreover, a 44% yield of diethyl dithiocarbonate (**4**) was also isolated from this reaction mixture.

Repeating the above reaction except using potassium isopropyl dithiocarbonate and isopropyl alcohol furnished a crude product in 33% yield containing 45 and 55% of **2** and **3**,



(4)

2, $x = 1$ **4**, R = C_2H_5
3, $x = 2$ **5**, R = $CH(CH_3)_2$

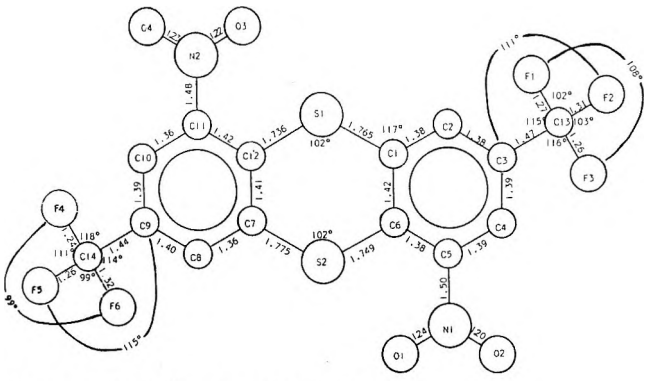
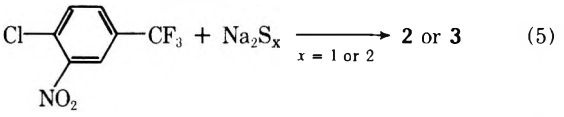
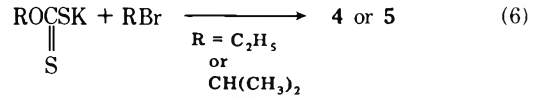


Figure 1. Bond distance and angles for **1**.

respectively. In addition a 41% yield of diisopropyl dithiocarbonate (**5**) was obtained. The lower yield of crude **2** and the higher percentage of **3** contained in the crude product when potassium isopropyl dithiocarbonate was employed in reaction 4 could be explained on the basis of the steric hindrance effect of the bulky isopropyl group. The structures of **2**, **3**, **4**, and **5**



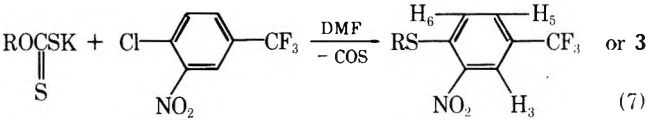
(5)



(6)

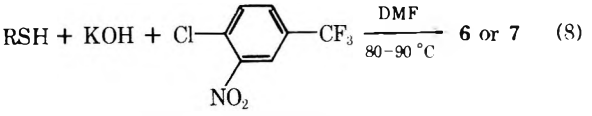
were elucidated by the conventional reactions 5 and 6. The proposed mechanism for reaction 4 is illustrated in Scheme III.

Employing the same reactants as specified in reaction 4 except replacing ethyl or isopropyl alcohol with DMF furnished a novel method for the synthesis of 2-nitro-4-trifluoromethylphenyl ethyl sulfide (**6**), the isopropyl sulfide (**7**), or **3** in yields as noted below. Proof of structure for **6** and **7** was



(7)

R	Temp, °C	Time, days	% yield 6	7	3
C_2H_5	75–80	2	96		
$CH(CH_3)_2$	75–80	2		47	
C_2H_5	25–30	5	64		
$CH(CH_3)_2$	25–30	5			50

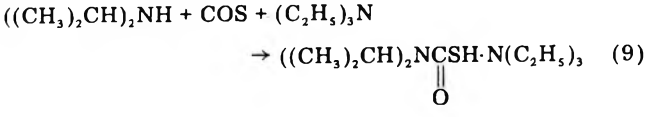


(8)

R = C_2H_5 or $CH(CH_3)_2$

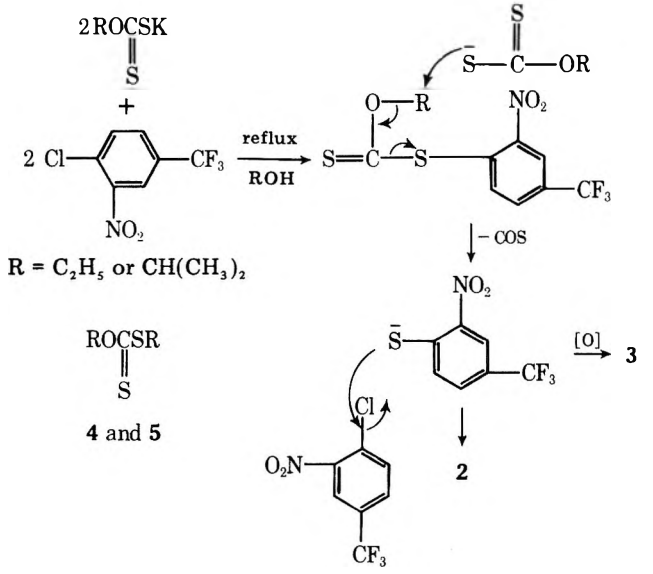
established by the conventional reaction 8. The proposed mechanism for reaction 7 is depicted in Scheme IV.

Evidence for the liberation of carbonyl sulfide in reactions 3, 4, and 7 was obtained by the formation of the triethylamine salt of diisopropylthiolcarbamic acid when the gas was allowed to bubble through a solution containing diisopropylamine and triethylamine at 0–10 °C. The identification of

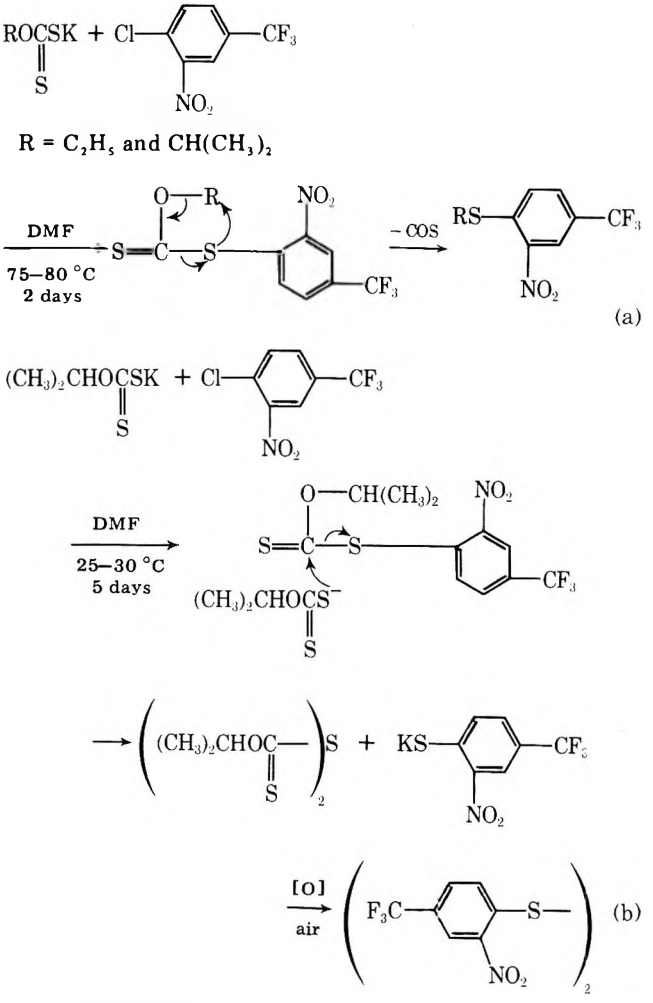


(9)

Scheme III



Scheme IV



the liberated carbonyl sulfide lends support for the proposed mechanisms depicted in Schemes I, III, and IV. Moreover, the isolation and identification of **4** and **5** in reaction 4 afforded additional evidence for the proposed mechanism cited in Scheme III.

Experimental Section

NMR spectra were obtained with a Varian A-60 NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. The mass spectra for **1**, **3**, **6**, and **7** were determined with a Varian MAT CH-7 mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250 °C. Vapor phase chromatographic analyses of **2** and **3** were performed with an F and M 720 gas chromatograph. A 0.125 in. × 1 ft stainless steel column packed with 10% OV-17 on Chromosorb W-HP 80–100 mesh was operated isothermally at 203 °C with a He pressure of 40 psi. The peak areas were determined by disk integration. A disk integration factor of 1.216 was determined for baseline corrections. **2** and **3** were run to determine the elution times. Three authentic mixtures were made up containing known amounts of **2** and **3** for determination of area correction factors, 1.0269 for **2** and 0.9743 for **3**. Tetrahydrofuran was the diluent for all samples. X ray for **1** was determined by using a Syntex $P2_1$ and XTL using a 2θ–θ scan with graphite monochromatized Cu K$\bar{\alpha}$ radiation.

1,6-Dinitro-3,8-bis(trifluoromethyl)thianthrene (1). To a stirred solution containing 0.22 mol of potassium ethyl or isopropyl dithiocarbonate dihydrate in 200 mL of dimethylformamide, 54 g (0.2 mol) of 4-chloro-3,5-dinitrobenzotrifluoride was added in one portion. An exothermic reaction set in causing a temperature rise from 25 to 50 °C over a 1-min period. The stirred reaction mixture was heated at 80–90 °C for 28 h and at 25–30 °C for 18 h. During the heating period carbonyl sulfide was liberated. After cooling to 0 °C, 800 g of ice water and 200 mL of ethyl ether were added and stirring continued at 5–25 °C for 2 h. The oily solid was collected by filtration, washed successively with water until the washings were neutral to litmus, then with 200 mL of ethyl ether, and air dried at 25–30 °C. The crude product, mp 245–248 °C, was obtained in 34% yield. After two recrystallizations from ethyl acetate it melted at 275–276 °C: NMR (THF) δ 7.90 (m, 2, H_4 and H_9), 8.07 (m, 2, H_2 and H_7); mass spectrum *m/e* (rel intensity) 442 (100), 396 (13.1), 364 (37.1), 350 (16.6), 338 (26.2), 331 (18.1), 318 (23.6), 306 (18.3), 281 (19.9), 269 (30.0), and 69 (16.1).

Anal. Calcd for $C_{14}H_4F_6N_2O_4S_2$: C, 38.02; H, 0.91; F, 25.77; N, 6.33; S, 14.50; mol wt, 442.3. Found: C, 37.98; H, 0.93; F, 25.90; N, 6.40; S, 14.41; mol wt, 450 ($CHCl_3$).

The ethyl ether of the filtrate was removed in vacuo. The filtrate was extracted with three 450-mL portions of chloroform. The combined chloroform extracts were washed with water until neutral to litmus and dried over sodium sulfate and the chloroform was removed in vacuo on a rotary evaporator at a maximum temperature of 70 °C at 1–2 mm. The residue (43 g) was dissolved in 200 mL of 60/40 mixture of cyclohexane/chloroform. One-half of this solution was chromatographed over 540 g of silica gel. Elution with 60/40 mixture of cyclohexane/chloroform gave four unidentifiable fractions.

Bis(2-nitro-4-trifluoromethylphenyl) Sulfide (2), Diethyl Dithiocarbonate (4), and Diisopropyl Dithiocarbonate (5). 2 and 4. A procedure reported by Szmant and Lapinski[4] was employed. To a stirred solution containing 158 g (0.7 mol) of 4-chloro-3-nitrobenzotrifluoride in 350 mL of ethanol, 120 g (0.75 mol) of purified potassium ethyl dithiocarbonate was added and heated to 80 °C over a 1-h period. At reflux a very exothermic reaction set in causing a rapid liberation of carbonyl sulfide. After the initial vigorous reaction had subsided, the stirred reaction mixture was heated at reflux for 2 days. After cooling to 0 °C, thethe precipitate was collected by filtration, slurried with 1 L of water in order to remove the potassium chloride, filtered, and air dried at 50 °C. The crude product **2**, mp 123–130 °C, was obtained in 64% yield. The crude **2** was analyzed by VPC and found to contain 93% of **2** and 7% of bis(2-nitro-4-trifluoromethylphenyl) disulfide (**3**). After three recrystallizations from heptane–ethyl acetate (3:1), **2** melted at 146–147 °C; NMR (Me_2SO-d_6) δ 7.70 (d, 2, H_6), 8.00 (d, 2, H_5), 8.65 (s, 2, H_3). A mixture melting point with authentic samples[2,5] was not depressed and their NMR spectra were identical.

Anal. Calcd for $C_{14}H_6F_6N_2O_4S$: C, 40.79; H, 1.47; N, 6.79; S, 7.78. Found: C, 40.72; H, 1.48; N, 6.75; S, 7.91.

The ethanol in the filtrate was removed in vacuo at maximum temperature of 60 °C at 10–12 mm. The residue was filtered to remove a small amount of solids and distilled in vacuo. Diethyl dithiocarbonate (**4**), bp 42 °C (0.25 mm) (n^{25}_D 1.5337), was obtained in 44% yield: NMR ($CDCl_3$) δ 1.32 (t, 6, SCH_2CH_3), 1.42 (t, 6, OCH_2CH_3), 3.15 (q, 2, SCH_2), 4.70 (q, 2, OCH_2).

Anal. Calcd for $C_5H_{10}O_2S_2$: C, 39.97; H, 6.71; S, 42.68. Found: C, 39.95; H, 6.71; S, 42.58.

2 and 5. The same procedure described above was employed except that 0.75 mol of potassium isopropyl dithiocarbonate dihydrate and 500 mL of isopropyl alcohol were used. Crude **2**, mp 121–143 °C, was obtained in 33% yield. The crude **2** was analyzed by VPC and found to contain 45% of **2** and 55% of the disulfide (**3**). After three recrystallizations from heptane–ethyl acetate, the crude product contained

43% of **2** and 57% of **3** and no further purification was attempted. Diisopropyl dithiocarbonate **5**, bp 57–58 °C (0.4 mm) (n^{25}D 1.5140), was obtained in 41% yield: NMR ($CDCl_3$) δ 1.40 [2 d, 12, $(CH_3)_2$-CHOC(=S)SCH$(CH_3)_2$], 3.85 (h, 1, SCH), 5.88 (h, 1, OCH).

Anal. Calcd for $C_7H_{14}OS_2$: C, 47.15; H, 7.91; S, 35.96. Found: C, 47.27; H, 7.94; S, 35.86.

4 and 5 (Conventional Method).—A stirred slurry containing 0.42 mol of potassium ethyl or isopropyl dithiocarbonate and 0.4 mol of ethyl or isopropyl bromide in 200 mL of acetone was heated at reflux for 2 days. The potassium bromide was removed by filtration and the acetone removed in vacuo at maximum temperature of 60 °C at 10–12 mm. The residue was distilled in vacuo. **4** and **5** having the identical boiling point, n^{25}D, and NMR spectra as above were obtained in 87 and 91% yield, respectively.

Anal. For **4**. Calcd for $C_5H_{10}OS_2$: C, 39.17; H, 6.71; S, 42.68. Found: C, 40.17; H, 6.76; S, 42.67. For **5**. Calcd for $C_7H_{14}OS_2$: C, 47.15; H, 7.91; S, 35.36. Found: C, 47.22; H, 7.93; S, 35.93.

2-Nitro-4-trifluoromethylphenyl Ethyl Sulfide (6) and 2-Nitro-4-trifluoromethylphenyl Isopropyl Sulfide (7). Method I. To a stirred solution containing 0.75 mol of purified potassium ethyl or isopropyl dithiocarbonate in 300 mL of DMF, 158 g (0.7 mol) of 4-chloro-3-nitrobenzotrifluoride in 200 mL of DMF was added dropwise in 1 h while not allowing the temperature to exceed 60 °C. After the exothermic reaction had subsided, the stirred reaction mixture was heated at 80–85 °C for 2 days. During the first several hours of the heating period carbonyl sulfide was liberated. After cooling to 0 °C, 1000 g of ice water was added and stirring continued at 0–10 °C for 1 h. The oily precipitate was collected by filtration, washed with cold water until neutral to litmus, and air dried at 25–30 °C. **6**, mp 66–68 °C, and **7**, mp 73–75 °C, were obtained in 96 and 47% yield, respectively. After recrystallization from heptane, **6** and **7** melted at 71–72 and 79–80 °C, respectively. **6**: NMR ($CDCl_3$) δ 1.45 (t, 3, CH_3CH_2S), 3.10 (q, 2, CH_3CH_2S), 7.65 (m, 2, H_5 and H_6), 8.55 (s, 1, H_3); mass spectrum *m/e* (rel intensity) 251 (6.5), 219 (2.3), 206 (13.5), 174 (4.5), 159 (6.8), 146 (3.3), 140 (3.3), 126 (3.2), 95 (2.1), 69 (4.7), 45 (4.2), and 18 (100).

Anal. Calcd for $C_9H_8F_3NO_2S$: C, 43.03; H, 3.21; N, 5.58; S, 12.76. Found: C, 43.01; H, 3.22; N, 5.65; S, 12.86.

7: NMR ($CDCl_3$) δ 1.45 (d, 6, $C(CH_3)_2$), 3.65 (h, 1, CH), 7.65 (m, 2, H_5 and H_6), 8.42 (s, 1, H_3); mass spectrum *m/e* (rel intensity 265 (3.8), 233 (19.6), 206 (19.8), 159 (23.6), 157 (8.1), 95 (8.5), 69 (8.1), 43 (100), 41 (45.7), 39 (15.1), and 27 (25.8).

Anal. Calcd for $C_{10}H_{10}F_3NO_2S$: C, 45.28; H, 3.80; F, 21.49; N, 5.28; S, 12.09. Found: C, 45.54; H, 3.73; F, 21.60; N, 5.40; S, 12.07.

Method II. Conventional. To a stirred slurry containing 0.2 mol of ethyl or isopropyl mercaptan, 13.2 g (0.2 mol) of 85% potassium hydroxide, and 200 mL of DMF, 45.2 g (0.2 mol) of 4-chloro-3-nitrobenzotrifluoride was added in one portion. An exothermic reaction set in causing a temperature rise from 23 to 70 °C. The stirred reaction mixture was heated at 80–90 °C for 18 h. The products **6** and **7** were isolated as described in method I. **6**, mp 67–68 °C, and **7**, mp 64–66 °C, were obtained in 94 and 85% yield, respectively. After recrystallization from heptane, **6** and **7** melted at 71–72 and 79–80 °C, respectively. The mixture melting point of **6** and **7** derived from methods I and II was not depressed and their NMR spectra were identical.

Anal. (**6**) Calcd for $C_9H_8F_3NO_2S$: C, 43.03; H, 3.21; F, 22.69; N, 5.58; S, 12.76. Found: C, 43.01; H, 3.24; F, 22.80; N, 5-61; S, 12.88.

Anal. (**7**) Calcd for $C_{10}H_{10}F_3NO_2S$: C, 45.28; H, 3.80; F, 21.49; N, 5.28; S, 12.09. Found: C, 45.16; H, 3.81; F, 21.25; N, 5.18; S, 12.21.

Reaction of Potassium Ethyl or Isopropyl Dithiocarbonate with 4-Chloro-3-nitrobenzotrifluoride in DMF at 25–30 °C. 6 and Bis(2-nitro-4-trifluoromethylphenyl) Disulfide (3). To a stirred slurry at −20 °C containing 0.22 mol of potassium ethyl or isopropyl dithiocarbonate in 200 mL of DMF, 45.1 g (0.20 mol) of 4-chloro-3-nitrobenzotrifluoride was added in one portion. The stirred reaction mixture was maintained at 25–30 °C for 5 days. After cooling to 0 °C, 800 g of ice water was added and stirring continued at 0–10 °C for 1 h. The oily precipitate was collected by filtration, washed with water until neutral to litmus, then with 300 mL of heptane, and air dried at 25–30 °C. **6**, mp 71–72 °C, and **3**, mp 140–146 °C, were obtained in 64 and 50% yield, respectively. After recrystallization, **6** from heptane and **3** from heptane–ethyl acetate (5:2), **6** and **3** melted at 72 and 163–164 °C, respectively. The mixture melting point of **6** derived from methods I and II was not depressed and their NMR spectra were identical.

Anal. (**6**) Calcd for $C_9H_8F_3NO_2S$: C, 43.03; H, 3.21; F, 22.69; N, 5.58; S, 12.76. Found: C, 43.21; H, 3.11; F, 22.83; N, 5.56; S, 12.83.

3: NMR (Me_2SO-d_6) δ 8.05 (s, 4, H_5 and H_6), 8.75 (s, 2, H_3); mass spectrum *m/e* (rel intensity) 444 (1.1), 425 (1.8), 222 (11.1), 206 (7.8), 176 (7.3), 174 (33.5), 166 (100), 164 (74.3), 158 (8.3), 157 (10.6), 146 (19.8), 126 (17.3), 113 (15.9), and 95 (87.5).

Anal. Calcd for $C_{14}H_6F_6N_2O_4S_2$: C, 37.84; H, 1.36; F, 25.66; N, 6.30; S, 14.43. Found: C, 37.83; H, 1.40; F, 25.75; N, 6.32; S, 14.38.

3. Conventional Method. The procedure using 4-chloro-3-nitrobenzotrifluoride and sodium disulfide in ethanol was employed.[6] Crude **3**, mp 151–153 °C, was obtained in 94% yield. After recrystallization from heptane–ethyl acetate (5:2), **3** melted at 163–164 °C. The mixture melting point with the product derived above was not depressed and their NMR spectra were identical.

Anal. Calcd for $C_{14}H_6F_6N_2O_4S_2$: C, 37.84; H, 1.36; F, 25.66; N, 6.30; S, 14.43. Found: C, 37.71; H, 1.32; F, 25.86; N, 6.26; S, 14.50.

X-Ray Crystallography for 1.[7]—Crystal Data. From single crystal diffractometry using Cu $K\bar{\alpha}$ radiation with λ = 1.5418 Å, a = 4.898 (2) Å, b = 6.640 (3) Å, c = 49.54 (3) Å, β = 92.6 (7)°, v = 1609 (1) Å^3; Z = 4; space group $P2_1/c$, D_x = 1.83 g/cm^3, D_m = 1.75 g/cm^3.

Structure Determination. The data collection and structure solution were carried out using a Syntex $P2_1$ diffractometer and XTL structure calculation package. Only the intensities of 1353 unique reflections judged to be significantly above background were used in refinement. The data were corrected for Lp but not for absorption. The structure was solved straightforwardly using direct methods. Twenty-four atoms were found on an E map calculated from 147 E's using the phase set having the highest figure of merit as determined by MULTAN.[8] The remaining four nonhydrogen atoms were found on a Fourier map. The F atoms had elongated and overlapping peaks characteristic of high thermal motion. The model refined isotropically to R = 0.15 and anisotropically to R = 0.099 with the F atoms having large temperature factors. A difference Fourier was calculated and showed a peak having electron density of 1.4 e/Å.[3] Four of the peaks were at positions calculated for the H atoms. All calculated H atoms were input with associated parameters held constant and refinement proceeded to R = 0.092. The interatomic distances and angles are depicted in Figure 1.

A conventional Fourier was calculated and the above mentioned large residual peak on the difference Fourier showed up again. This was attributed to our model of three ellipsoidal atoms being a poor approximation for the electron distribution in a nearly freely rotating CF_3 group. Since the objective of the work, to determine the molecular structure, had been accomplished, no adjustment to the model was made.

Acknowledgment. The assistance of R. W. Fuhrhop and F. L. May is kindly appreciated.

Registry No.—**1**, 62796-18-3; **2**, 365-55-9; **3**, 860-39-9; **4**, 623-79-0; **5**, 19615-06-6; **6**, 22057-35-8; **7**, 62796-19-4; 4-chloro-3,5-dinitrobenzotrifluoride, 393-75-9; potassium ethyl dithiocarbonate, 140-89-6; potassium isopropyl dithiocarbonate, 140-92-1; ethyl mercaptan, 75-08-1; isopropyl mercaptan, 75-33-2; potassium hydroxide, 1310-58-3; 4-chloro-3-nitrobenzotrifluoride, 121-17-5.

Supplementary Material Available. Mass fragmentation route for **1** (Scheme II) and atomic coordinate tables (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented at the 173rd National Meeting of the American Chemical Society, Organic Division, New Orleans, La., March 1977.
(2) J. J. D'Amico, C. C. Tung, W. E. Dahl, and D. J. Dahm, *J. Org. Chem.*, **41**, 3564 (1976).
(3) See paragraph at end of paper regarding supplementary material.
(4) H. H. Szmant and R. L. Lapinski, *J. Am. Chem. Soc.*, **75**, 6338 (1953).
(5) A. Roe, J. A. Montgomery, W. A. Yarnall, and V. A. Hoyle, Jr., *J. Org. Chem.*, **21**, 28 (1956).
(6) L. C. Cheney and Y. G. Perron, U.S. Patent 3 284 498 (Nov 8, 1966).
(7) Final parameters and a list of observed and calculated structure factors are available from Dr. D. J. Dahm.
(8) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

1,2-Bis(2-hydroxyethyl)hydrazine and Derivatives[1]

Arnold T. Nielsen* and G. William Lawrence[2]

Organic Chemistry Branch, Chemistry Division, Research Department, Code 3856, Naval Weapons Center, China Lake, California 93555

Received March 15, 1977

Glycolaldehyde was condensed with 2-hydroxyethylhydrazine to yield hydrazone **2** which has been hydrogenated (Pd/C catalyst) to produce the title compound (**3**). The tetraacetyl and *N,N'*-diacetyl derivatives of **3** (**7** and **8**, respectively) and the oxidation product, bis(2-hydroxyethyl)diazene (**6**), are described. The nuclear magnetic resonance spectra of the new compounds, including rotamers of **8**, are discussed.

Hydrazine reacts with various alkylating agents to yield principally the unsymmetrical 1,1-disubstituted product. Michael addends such as acrylonitrile, as well as alkyl halides, behave in this fashion.[3,4] Ethylene oxide, for example, forms 1,1-bis(2-hydroxyethyl)hydrazine (**1**).[5] Symmetrical derivatives of this type—1,2-dialkylhydrazines having reactive functional groups attached to alkyl—are available by various other routes, e.g., hydrazoacetic acid[6] and hydrazoisobutyronitrile.[7]

$$N_2H_4 \xrightarrow{2\ \triangledown O} H_2NN(CH_2CH_2OH)_2$$

1

In the present work, as part of a study of new polyhydrazine compounds,[8,9] 1,2-bis(2-hydroxyethyl)hydrazine (**3**) and some of its derivatives have been synthesized. Glycolaldehyde, generated in situ, was condensed with 2-hydroxyethylhydrazine forming hydrazone **2** which was hydrogenated with palladium/charcoal catalyst to yield **3**.

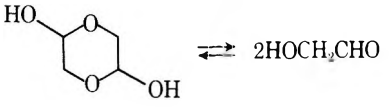
$$HOCH_2CHO + H_2NNHCH_2CH_2OH \rightarrow HOCH_2CH{=}NNHCH_2CH_2OH$$

2

$$\xrightarrow{H_2,Pd/C} HOCH_2CH_2NHNHCH_2CH_2OH$$

3

Two procedures leading to **3** were developed. In one, commercially available crystalline glycolaldehyde dimer (principally **4**)[10] was employed in ethanol, in which solvent it exists



4

primarily as the monomer and its hemiacetal.[10,11] Reaction of **4** with 2-hydroxyethylhydrazine in absolute ethanol containing Drierite led to hydrazone **2** which was isolated as an oil. Hydrogenation of **2** with 10% palladium/charcoal catalyst (50 psi, 25 °C) gave pure diol **3** in 50% overall yield from glycolaldehyde. Identical results were achieved without isolation of **2**.

In a second route leading to **3**, glycolaldehyde diethyl acetal (**5**) was the glycolaldehyde precursor.[12] The acetal was conveniently prepared from chloroacetaldehyde diethyl acetal by reaction with excess aqueous potassium hydroxide at 125 °C by an improved procedure (60–70% yield).

$$ClCH_2CH(OC_2H_5)_2 \xrightarrow[125\ °C]{aq\ KOH} HOCH_2CH(OC_2H_5)_2$$

5

$$\xrightarrow{H^+} HOCH_2CHO$$

Hydrolysis of **5** in 1 N aqueous hydrochloric acid at 25–30 °C, followed by adjustment of the pH to 6–6.5 and addition of 2-hydroxyethylhydrazine, led to formation of hydrazone **2** in aqueous medium. Without isolation, **2** was hydrogenated to diol **3** (50% yield from acetal **5**). 1,2-Bis(2-hydroxyethyl) hydrazine (**3**) is a stable, white, crystalline solid, mp 58–60 °C, in contrast to the unsymmetrical diol **1** which is described as an oil.[5]

A few glycolaldehyde hydrazones have been described previously, including those derived from phenylhydrazine[13] and 1,1-dimethylhydrazine.[14] The latter derivative has been reduced to 1,1-dimethyl-2-(2-hydroxyethyl)hydrazine by sodium cyanoborohydride (23% overall yield from glycolaldehyde).[14]

Bis(2-hydroxyethyl)diazene (**6**) was prepared readily by mercuric oxide oxidation of **3** in ether or ether–methanol solvent.

$$3 \xrightarrow{HgO} HOCH_2CH_2N{=}NCH_2CH_2OH \rightleftarrows 2$$

6

It was isolated in high yield as a low-melting crystalline solid (mp 19–20 °C). In protic solvents such as methanol or water it tautomerizes slowly to hydrazone **2** (assay by NMR spectroscopy). The diazene was characterized by its bisphenylurethane derivative.

Acetylation of hydrazine **3** with excess acetic anhydride produced the tetraacetyl derivative **7**. Fractional saponification of **7** was achieved by slow addition of aqueous sodium hydroxide (10%) while maintaining the pH below 12 throughout the reaction period. Acetyl derivatives **7** and **8** were obtained in high purity and high yield (isolated as oils, purified by column chromatography).

$$3 \xrightarrow{Ac_2O} CH_3CO_2CH_2CH_2N(COCH_3)CH_2CH_2O_2CCH_3$$

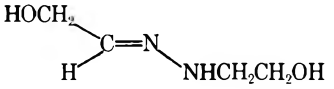
7

$$\xrightarrow[pH\ 10\text{–}12]{aq\ NaOH} HOCH_2CH_2N(COCH_3)CH_2CH_2OH$$

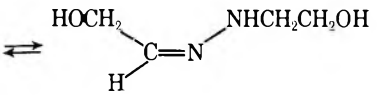
8

Structures of **3** and its derivatives are supported by molecular formulas and spectra. The nuclear magnetic resonance spectrum of crude **2** (in D_2O) reveals two vinyl proton signals and two methylol methylene signals in a ratio of ca. 10:1, suggesting a mixture of *Z* and *E* forms with (*E*)-**2** predominating. Tautomerization of **6** to **2** in D_2O also yields the same equilibrium mixture.

In agreement with the studies of Potekhin and Vikulina[15] no evidence was found for formation of the hexahydro-1,3,4-oxadiazine tautomer **9** derived from **2** in chloroform or D_2O solvents. It has been established that only 4-substituted

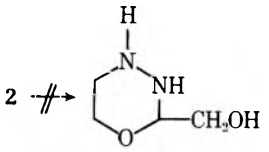


(*E*)-**2**; 91% in D_2O



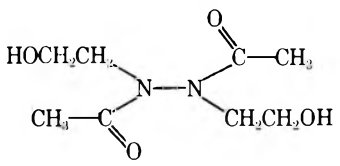
(*Z*)-**2**; 9% in D_2O

derivatives of **9** exist in tautomeric equilibrium with the parent hydrazone.[15]



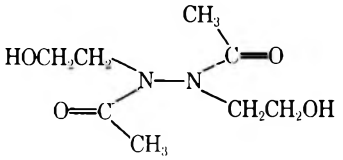
9

The NMR spectrum of the *N,N'*-diacetyl derivative **8** reveals a four-line methyl signal corresponding to the three possible rotamers (cis,cis, trans,trans, and cis,trans, respectively).[16,17] The proportions of the three forms were determined from the integrated peak intensities (measurements in $CDCl_3$ and D_2O). The results are similar to those reported previously for 1,2-diacetyl-1,2-dimethylhydrazine (**10**, measurements in pentachloroethane and D_2O).[17] In both compounds the predominant form in aprotic solvents is trans,trans (78% for **10**) and the minor one is cis,cis (4% for **10**). In D_2O the ratios of the three forms for the two compounds (**8**, **10**) are very similar (34% trans,trans and 12% cis,cis for **10**). In the tetraacetyl derivative **7** the four-line signal found in **8** is obscured by the intense acetoxy methyl singlet.



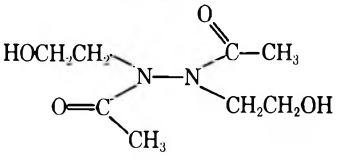
cis, cis-**8**

in D_2O 19%
in $CDCl_3$ 20%



trans, trans-**8**

in D_2O 32%
in $CDCl_3$ 48%



cis, trans-**8**

in D_2O 49%
in $CDCl_3$ 32%

Experimental Section

Infrared spectra were determined on a Perkin-Elmer Model 137, ^1H NMR spectra on a Varian EM 360 or XL-100. Chemical shifts determined at ca. 30 °C are referenced to tetramethylsilane internal standard [sodium 3-(trimethylsilyl)-1-propanesulfonate in deuterium oxide]. Melting points were determined on a Kofler hot stage and are corrected unless otherwise noted. Elemental analyses and molecular weights (by vapor osmometry) were determined by Galbraith Laboratories, Knoxville, Tenn. Organic solutions were dried over $MgSO_4$ unless otherwise stated.

2,2-Diethoxyethanol (5). A mixture of 61.0 g (0.40 mol) of chloroacetaldehyde diethyl acetal (Aldrich Chemical Co.), KOH (45.0 g of 85% assay, 0.60 mol), and water (1 L) was heated at 125 ± 2 °C in a 1.5-L stainless steel bomb (Aminco) with gentle rocking for 120 h. The clear, yellow liquid product was extracted once with 150 mL of ether; after drying and concentration the extract yielded 7.7 g of an oily mixture of reactant chloroacetal (75%) and product **5** (25%) by NMR assay. The aqueous part was treated cautiously with 900 g of anhydrous K_2CO_3 with stirring and ice-bath cooling (temperature below 35 °C) until a clear solution resulted. The solution was extracted three times with ether (150-mL portions). The dried extracts on concentration gave an oil which was distilled through a short column to yield at 17 mm: (1) 1.0 g of a forerun, bp 40–70 °C; (2) 33 g (62%) of pure acetal **5**, bp 70–72 °C; and (3) 0.5 g of residue; fraction 2 NMR ($CDCl_3$) δ 4.58 (t, 1, CH), 3.4–3.9 (m, 6, CH_2), 2.32 (s, 1, OH), 1.26 (t, 6, CH_3) [lit. bp 74–74.5 °C (14 mm)].[12] Repeat runs gave yields of **5** of 60–70%.

The above procedure was repeated except for reaction times of 45 and 78 h to provide yields of **5** of 22 and 53%, respectively (recovered unreacted chloroacetaldehyde diethyl acetal was isolated in yields of 63 and 27%, respectively). Substitution of bromoacetaldehyde diethyl acetal for chloroacetaldehyde acetal in the above procedure gave yields of **5** of ca. 70%.

3,4-Diaza-2-hexene-1,6-diol (2). A solution of 2-hydroxyethylhydrazine (Aldrich, 1.52 g, 0.020 mol) and glycolaldehyde dimer (Aldrich, 1.20 g, 0.020 mol of glycolaldehyde) in 2 mL of water and 50 mL of absolute ethanol was concentrated at 30 mm to remove volatiles (water bath temperature below 48 °C) during 1.5 h. A second 50-mL portion of absolute ethanol was added to the residue and Drierite (10 g) added. After standing at 25 °C overnight the mixture was filtered and concentrated, followed by final pumping at 0.1 mm, 25 °C, to constant weight to yield 2.30 g (97%) of **2** as a colorless oil: IR (film) 1620 cm^{-1} (C=N); NMR (D_2O) δ 7.32, 6.78 (t, J = 5 Hz, 1 proton total, =CH, ratio of signals 10:1, respectively), 4.84 (s, 3, NH and OH), 4.28, 4.18 (d, J = 5 Hz, 2 protons total, $=CHCH_2OH$, ratio of signals 1:10, respectively), 3.72 (t, 2, $HOCH_2CH_2NH$), 3.19 (t, 2, $HOCH_2CH_2NH$).

Diol **2** was hydrogenated to 1,2-bis(2-hydroxyethyl)hydrazine (**3**) by the procedure described below (method A; 90% yield of crude product).

1,2-Bis(2-hydroxyethyl)hydrazine (3). Method A. Glycolaldehyde dimer (6.0 g, 0.10 mol of glycolaldehyde) was added to a solution of 2-hydroxyethylhydrazine (7.6 g, 0.10 mol) in 50 mL of absolute ethanol. After stirring for 10 min the glycolaldehyde dimer had dissolved and the temperature risen from 25 to 31 °C. After the solution had stood at 25–30 °C for 3 h, 6.0 g of 10% Pd/C catalyst was added and the mixture shaken with hydrogen in a Parr apparatus (ca. 50 psi, 25 °C) until hydrogen uptake ceased (2 h, 1.0 molar equiv of hydrogen absorbed). The mixture was filtered through Celite and washed several times with absolute ethanol. Concentration of the filtrate under reduced pressure at 25 °C gave 10.8 g (90%) of crude **3** as waxy crystals, mp 40–48 °C. The product was purified by crystallization from 2-propanol as small, rectangular prisms, mp 55–56 °C (56% recovery, 50% yield); recrystallization gave mp 58–60 °C (70% recovery).

Method B. To 33.5 g (0.25 mol) of 2,3-diethoxyethanol (**5**) was added 1 N hydrochloric acid (125 mL). After an initial temperature rise to 30 °C, the solution was allowed to stand at ambient temperature for 2 h; it was then concentrated under reduced pressure at 25 °C to remove ethanol during 1.5 h. Aqueous NaOH (35 mL of a 10% solution) was added to the solution slowly (with ice-bath cooling keeping the temperature below 25 °C) to adjust the pH to ca. 6–6.5. 2-Hydroxyethylhydrazine (18.9 g, 0.25 mol) was then added with ice-bath cooling keeping the temperature below 25 °C. After the solution had stood at 25 °C for 3 h, 10.0 g of 10% Pd/C catalyst was added and the mixture hydrogenated in a Parr apparatus (40–50 psi, 25 °C) until hydrogen uptake ceased (6 h). The mixture was filtered through Celite and the catalyst washed thoroughly with water. The filtrate was concentrated to remove volatiles under reduced pressure. The oily residue was dissolved in absolute ethanol (200 mL) and the solution again concentrated to remove solvents; the process was repeated and the residue finally pumped at 0.1 mm until reaching constant weight (25.7 g, 88% of crude **3** as oily crystals). Recrystallization from 2-propanol (25 mL) gave 13.2 g (48%) of **3** as chunky crystals, mp 43–51 °C; a second recrystallization gave 8.85 g of pure **3**, mp 58–60 °C (capillary). An analytical sample was prepared by

dissolving in absolute methanol and adding Drierite. After filtration and removal of solvents from the filtrate an anhydrous product of unchanged melting point was obtained. The material is quite hygroscopic: NMR (D_2O) δ 4.88 (s, 4, NH, OH), 3.70 (t, J = 5 Hz, CH_2O), 2.90 (t, J = 5 Hz, 4, CH_2N).

Anal. Calcd for $C_4H_{12}N_2O_2$: C, 39.98; H, 10.07; N, 23.32; mol wt, 120.15. Found: C, 39.85; H, 10.14; N, 23.11; mol wt, 125 (H_2O).

Bis(2-hydroxyethyl)diazene (6). A mixture of pure 1,2-bis(2-hydroxyethyl)hydrazine (3, 1.20 g, 0.010 mol), mercuric oxide (2.50 g, 0.011 mol), and 50 mL of ether was stirred magnetically at 25 °C for 3 h. Methanol (10 mL) was added and stirring continued for an additional 1 h. The mixture was filtered and the precipitate washed with ether–methanol (5:1). Drierite (4 g) was added to the filtrate and the mixture stirred for 30 min. After filtration and removal of solvents by pumping at 25 °C (0.1 mm) there remained 1.13 g (96%) of **6** as a hydroscopic oil, mp 16–18 °C. In a parallel run, omitting the addition of methanol (3 h stirring), there was obtained a 66% yield of **6**: mp 19–20 °C; NMR ($CDCl_3$) δ 4.08 (s, 8, CH_2), 3.28 (s, broad, 2, OH); NMR (D_2O) δ 4.72 (s, 2, OH), 4.05 (s, 8, CH_2), =CH peaks absent. On standing for several hours the =CH peaks of 2 isomers appeared in the same 10:1 ratio. Elemental analysis indicated the presence of oxygenated impurity, possibly water, in the unrecrystallized crude product. Anal. Calcd for $C_4H_{10}N_2O_2 \cdot 0.25H_2O$: C, 39.18; H, 8.63; N, 22.84. Found: C, 39.25; H, 8.90; N, 22.46.

A solution of 0.236 g (2.0 mmol) of diol **6** and phenyl isocyanate (0.476 g, 4.0 mmol) in 3.0 mL of chloroform was stored at 25 °C for 16 h. Chilling at −15 °C deposited 0.22 g (30%) of the crystalline bisphenylurethane derivative, mp 137–140 °C; the melting point was unchanged on recrystallization from chloroform; NMR ($CDCl_3$) δ 6.8–7.5 (m, 12, C_6H_5 and NH), 4.66, 4.10 (A_2B_2 m, $J_{AB} \simeq$ 5 Hz, 8, CH_2CH_2).

Anal. Calcd for $C_{18}H_{20}N_4O_4$: C, 60.66; H, 5.66; N, 15.72; mol wt, 356.37. Found: C, 60.56; H, 5.77; N, 15.49; mcl wt, 350 (C_6H_6).

1,2-Bis(2-acetoxyethyl)-1,2-diacetylhydrazine (7). 1,2-Bis(2-hydroxyethyl)hydrazine (**3**, 5.0 g, 0.0416 mol) was dissolved in 50 mL of acetic anhydride; a slightly exothermic reaction resulted. After remaining at ambient temperature for 2.5 h the solution was heated on the steam bath for 2.5 h, then concentrated under reduced pressure on the steam bath to remove volatiles including acetic acid (final pressure 0.1 mm). The process was repeated after addition of a second portion of 50 mL of acetic anhydride to yield ultimately 11.8 g of an oil (98% yield of high-purity **7** as indicated by infrared and NMR spectra). An analytical sample was obtained by column chromatography on alumina (elution with methylene chloride containing 1% methanol gave pure **7** in the first eluate fractions); some hydrolysis occurred on the column during the chromatography. The eluate was shaken with Drierite and filtered and solvents were removed at 0.1 mm to yield pure **7** as a colorless oil: IR (film) 1725 (C=O, ester), 1670 cm^{-1} (C=O, amide); NMR ($CDCl_3$) δ 4.32, 3.84 (A_2B_2 m, $J \simeq$ 5 Hz, 8, CH_2CH_2), 2.22, 2.10 (major), 1.97 (m, 12, CH_3).

Anal. Calcd for $C_{12}H_{20}N_2O_6$: C, 49.99; H, 6.99; N, 9.72, mol wt, 288.3. Found: C, 49.83; H, 7.05; N, 9.74; mol wt, 288 (C_6H_6).

1,2-Bis(2-hydroxyethyl)-1,2-diacetylhydrazine (8). To 1,2-bis(2-acetoxymethyl)-1,2-diacetylhydrazine (**7**, 25.0 g, 0.0865 mol) was added dropwise, with stirring during 1.5 h, 53 mL of 10% aqueous NaOH solution, keeping the temperature at 20 °C by ice-bath cooling. The pH of the reaction mixture was monitored continuously keeping its value between 10 and 12 during the addition. The mixture was treated immediately with sufficient K_2CO_3 to obtain a saturated solution and then extracted with five 50-mL portions of methylene chloride–methanol (15% methanol). The combined extracts were dried over K_2CO_3 and filtered through Celite; concentration of the filtrate gave 17.3 g (98%) of crude diol **8**. Chromatography on an alumina column [elution with methylene chloride–methanol (3% methanol)] gave, after drying with Drierite, 12.5 g (70%) of high-purity **8** as a viscous oil: IR (film) 3400 (OH), 1670 cm^{-1} (C=O, amide), ester C=O absent; NMR ($CDCl_3$) δ 4.47 (s, 2, OH), 3.3–4.0 (m, 8, CH_2), 2.28 (trans,trans), 2.26, 2.02 (cis,trans), 2.08 (cis,cis) (four lines, 12, CH_3); NMR (D_2O) δ 4.80 (s, 2, OH), 3.6–4.0 (A_2B_2 m, 8, CH_2), 2.30 (trans,trans), 2.27, 2.05 (cis,trans), 2.12 (cis,cis) (four lines, 12 CH_3); discussion of peak intensities in text.

Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72; mol wt, 204.2. Found: C, 46.85; H, 7.80; N, 13.63; mol wt, 200 (H_2O).

Acknowledgment. The authors are indebted to D. W. Moore for assistance in securing some of the experimental data and for helpful discussions.

Registry No.—*E*-**2**, 62562-61-2; *Z*-**2**, 62562-62-3; **3**, 2488-95-1; **5**, 621-63-6; **6**, 62562-63-4; **6** bisphenylurethane derivative, 62562-64-5; **7**, 62562-65-6; **8**, 62562-66-7; chloroacetaldehyde diethyl acetal, 621-62-5; 2-hydroxyethylhydrazine, 109-84-2; glycolaldehyde, 141-46-8; phenyl isocyanate, 103-71-9.

References and Notes

(1) Presented, in part, at the 31st Northwest Regional Meeting of the American Chemical Society, Reno, Nev., June 15, 1976.
(2) National Research Council Postdoctoral Research Associate, 1973–1974.
(3) S. Patai, Ed., "The Chemistry of the Hydrazo, Azo and Azoxy Groups", Parts 1 and 2, Wiley, New York, N.Y., 1975.
(4) R. Ohme and A. Zubek, *Z. Chem.*, **8**, 41 (1968).
(5) (a) L. Knorr and H. W. Brownsdon, *Chem. Ber.*, **35**, 4474 (1902); (b) R. Preussmann, *Arzneim.-Forsch.*, **12**, 260 (1962); (c) I. V. Podgornaya and I. Ya. Postovskii, *Zh. Obshch. Khim.*, **33**, 744 (1963).
(6) B. Gisin and M. Brenner, *Helv. Chim. Acta*, **53**, 1030 (1970).
(7) J. Thiele and K. Heuser, *Justus Liebigs Ann. Chem.*, **290**, 1 (1896).
(8) A. T. Nielsen, *J. Heterocycl. Chem.*, **12**, 1233 (1975).
(9) A. T. Nielsen, *J. Heterocycl. Chem.*, **13**, 101 (1976).
(10) H. Michelsen and P. Klaboe, *J. Mol. Struct.*, **4**, 293 (1969).
(11) G. C. S. Collins and W. O. George, *J. Chem. Soc. B*, 1352 (1971).
(12) E. Gryszkiewicz-Trochimowski, O. Gryszkiewicz-Trochimowski, and R. S. Levy, *Bull. Soc. Chim. Fr.*, 605 (1958).
(13) H. Simon, G. Heubach, and H. Wacker, *Chem. Ber.*, **100**, 3106 (1967).
(14) D. F. Morrow, P. C. Johnson, H. Torabi, D. Williams, D. L. Wedding, J. W. Craig, and R. F. Majewski, *J. Med. Chem.*, **16**, 736 (1973).
(15) (a) A. A. Potekhin and M. N. Vikulina, *Khim. Geterotsikl. Soedin.*, 1167 (1971); (b) A. A. Potekhin and B. D. Zaitsev, *ibid.*, 301 (1971); (c) A. A. Potekhin, *Zh. Org. Khim.*, **7**, 16 (1971).
(16) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).
(17) F. Conti and C. Franconi, *Ric. Sci.*, **36**, 1205 (1966); *Chem. Abstr.*, **66**, 120640t (1967).

The Chemistry of Azocines. Intermediates for the Synthesis of Pyrrolizidines[1]

Patrick S. Mariano,*[2] Morey E. Osborn, Debra Dunaway-Mariano, Brian C. Gunn, and Roger C. Pettersen

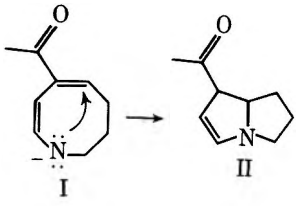
Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received February 28, 1977

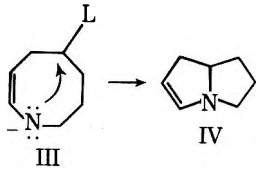
Investigations concerned with the preparation of 1,8-dihydro- and 1,6,7,8-tetrahydroazocines and the utilization of transannular reactions of $\Delta^{4,5}$-epoxyhexahydroazocines for the generation of highly functionalized pyrrolizidines are described. Methods to synthesize 3,4-dicarbomethoxy-1,8-dihydro- and 1,6,7,8-tetrahydroazocines, **19** and **21**, starting with 1,2-dihydropyridines, **22** and **16**, having the *N*-β-styryl and *N*-bromomethyldioxolylethyl substituents as nitrogen protecting groups, are discussed and compared to unsuccessful attempts using a variety of common nitrogen blocking groups. In addition, procedures to convert azocines to functionalized pyrrolizidines using transannular cyclization reactions have been explored. A high yielding sequence starting with the $\Delta^{4,5}$-epoxyhexahydroazocine **33** and proceeding through the intermediate bicyclic amino ether **34** has been developed. The synthetic and mechanistic details of the chemistry regarding the preparation and reactions of azocines are discussed.

A moderate amount of attention has been given recently to the development of general methods to prepare highly functionalized pyrrolizidines which comprise the basic skeletal unit in members of the Senecio alkaloid class[3] and the BC ring system of the potent antitumor and antibacterial agent, mitomycin C.[4] Investigations in this area have led to several novel approaches to the synthesis of these compounds. Synthetic designs followed to date include cycloadditions of γ-substituted crotonic acid esters to 1-pyrroline 1-oxides,[5] intramolecular cyclizations of perhydroazocinones,[6] additions of acetylenes to Munchnone intermediates,[7] photo-Fries rearrangements of lactones,[8] and intramolecular nucleophilic additions to cyclopropane-1,1-dicarboxylic acid derivatives[9] as well as a variety of more classical methodologies.[10]

As part of recent studies targeted at the synthesis of the mitomycins, we have investigated several, potentially novel approaches for the preparation of highly functionalized pyrrolizidines. The strategy of one of these approaches is to employ transannular Michael addition (I → II) and displacement (III → IV) reactions of appropriately substituted azocinyl



I II

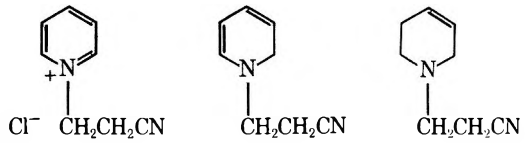


III IV

anions in key ring-building steps. One of the attractive features of sequences based upon these synthetic designs is the demonstrated availability of substituted 1,8-dihydroazocines from cycloaddition reactions of acetylenic esters to 1,2-dihydropyridines[11,12] which in turn are easily prepared by sodium borohydride reduction of corresponding pyridinium salts.[13] Therefore, the plan of the present studies was to investigate methods for generation of appropriately substituted azocines which contain nitrogen protecting groups and for effecting transannular cyclization to pyrrolizidines.

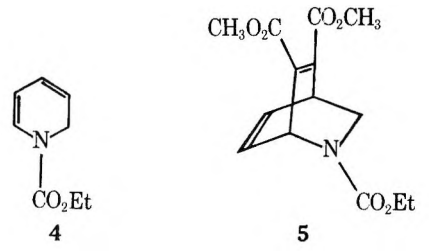
Preparation of N-Protected Azocines. The 1,2-dihydropyridine–acetylene cycloaddition route has been used previously to prepare a variety of 1,8-dihydro- and 1,6,7,8-tetrahydroazocines having alkyl and aryl substitution on nitrogen.[11,12] As a result of our desire to investigate transannular cyclization reactions of azocinyl anions, initial efforts were directed at the development of methods to obtain hydroazocines which lack substitution on nitrogen. Our design was to use nitrogen protecting groups which could be introduced at the pyridinium salt stage and removed at later points in the synthetic sequences after the azocine ring systems are constructed. A variety of typical nitrogen blocking groups, including the carbomethoxy, β-cyanoethyl, and diphenylmethyl, were explored without success. It is instructive to discuss these unsuccessful attempts since the results obtained aid in an evaluation of the types of restrictions that need to be placed on satisfactory blocking groups required for this specific application.

The β-cyanoethyl protecting group appeared applicable for the purpose outlined owing to both its projected ease of removal under base-catalyzed β-elimination conditions and the availability of the starting β-cyanoethylpyridinium salt **1**.[14] Attempts to prepare the intermediate 1-(2-cyanoethyl)-1,2-dihydropyridine (**2**) by borohydride reduction of **1** were futile, however, as a result of the need to conduct these reactions at elevated pH (aqueous sodium carbonate or sodium hydroxide).[13] Thus, from reactions of **1** in aqueous sodium borohydride solutions at varying pH only the cyanoethyltetrahydropyridine **3** (pH 7) or acrylonitrile and pyridine (pH > 7) could be isolated. It appears that at elevated pH reduction is not significantly competitive with β-elimination.



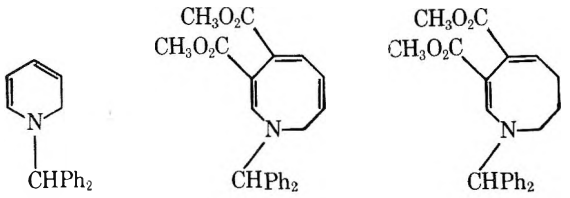
1 2 3

An alternate approach investigated takes advantage of the convenient blocking group properties of alkoxycarbonyl substituents which allows them to be easily removed using a variety of acidic and basic conditions. 1-Carboethoxy-1,2-dihydropyridine (**4**), prepared in a 73% yield by a procedure similar to that described earlier by Fowler,[15] smoothly adds dimethyl acetylenedicarboxylate (neat, room temperature, 71%) via a Diels–Alder [4 + 2] reaction pathway rather than by the typical [2 + 2] mode followed when alkyl- or aryl-substituted 1,2-dihydropyridines are employed. It is evident from the efficiency of the Diels–Alder process, leading to the isoquinuclidiene **5**, that the carbonyl grouping on nitrogen causes significant deactivation of the enamine function required for [2 + 2] cycloaddition to the acetylenic diester.[16]



4 5

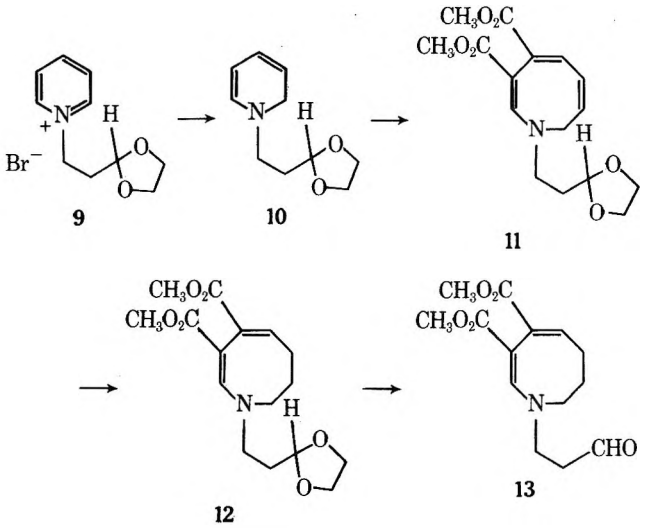
Our attention next turned to the employment of arylmethyl blocking groups since problems associated with the preparation of the corresponding N-substituted 1,2-dihydropyridines and reactions with dimethyl acetylenedicarboxylate should be minimal. Indeed, 1-diphenylmethyl-1,2-dihydropyridine (**6**), prepared from the reported pyridinium salt[17] using borohydride reduction (10% Na_2CO_3, room temperature, ca. 60%), reacts cleanly with the acetylene (C_6H_6, room temperature, 62%) to produce the benzhydryl substituted dihydroazocine **7** in high yield. However, one further limitation on the type



6 7 8

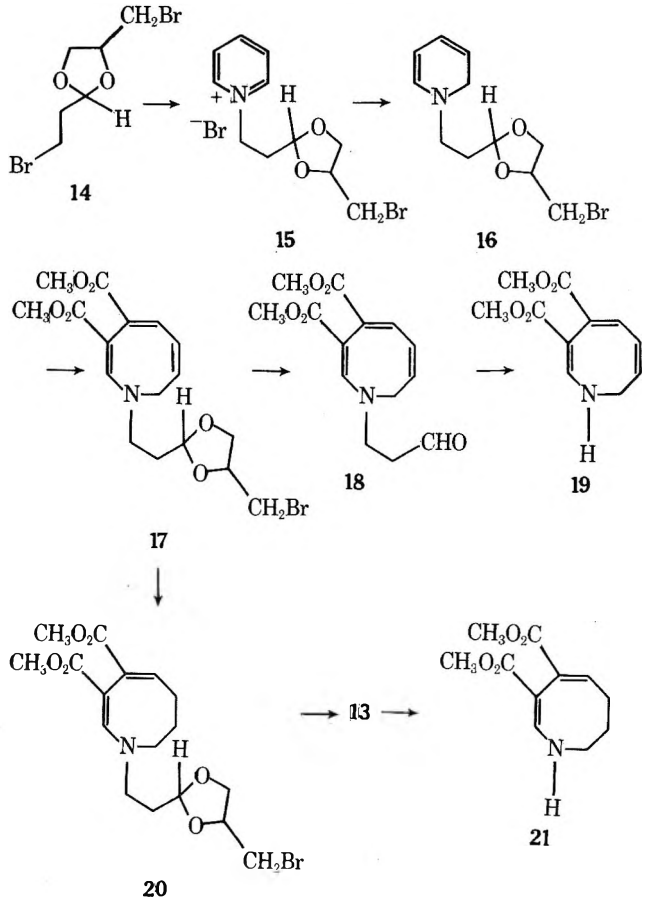
of blocking group required for the preparation of nitrogen unsubstituted azocines is pointed out by the behavior of **7** under reaction conditions normally employed for removal of the diphenylmethyl group. Exhaustive catalytic hydrogenation of **7** at 50 psi using a Pd/C catalyst led only to quantitative formation of the 1,6,7,8-tetrahydroazocine **8** retaining the diphenylmethyl substituent. Additionally, mild acid treatment of **7** or **8** led to rapid decomposition generating a host of unidentifiable products.

As documented by these findings, several of the more typical procedures for nitrogen protection appear incompatible with the general methods used to prepare azocines and the acid sensitivity of these heterocyclic compounds. It is clear that unique types of nitrogen blocking are required in applications of the routes proposed for preparation of pyrrolizidines. As a result, an alternate method to generate dihydroazocines which utilizes base-catalyzed eliminative deblocking of intermediate β-azocinylpropionaldehydes was explored. The strategy used to gain entry into this series of azocine precursors took into account the requirement for utilization of masked carbonyl functions which would survive conditions needed to produce appropriate 1,2-dihydropyridines and which could be removed using methods compatible with the extreme acid lability of dihydro- and tetrahydroazocines. Initial difficulties were encountered with the dioxolane masked propionaldehyde blocking group. Although the dihydroazocine ethylene acetal **11** can be easily prepared in an overall yield of 47% from the known 2-(2-bromoethyl)-1,3-dioxolane,[18] via the pyridinium salt **9** and dihydropyridine **10**, unmasking of the aldehyde function under a variety of acid-catalyzed conditions failed to produce detectable quantities of the desired azocinyl aldehyde **18**. Similarly, the tetrahydroazocine acetal **12**, derived by reduction of **11**, can be converted in only poor yield (17%) to the corresponding aldehyde **13** using aqueous hydrochloric acid in tetrahydrofuran at room temperature. Significant improvement was noted when masked propionaldehyde groups which require nonacidic conditions for liberation of the aldehyde function were used. Accordingly, the bromoethylbromomethyldioxolane **14** was generated from 1-bromopropane-2,3-diol[19] and



9 10 11 12 13

acrolein in the presence of hydrogen bromide and converted to the corresponding pyridinium salt **15**. Reduction of **15** under the normal conditions led to the dihydropyridine **16** which added dimethyl acetylenedicarboxylate to furnish the dihydroazocinylbromomethyldioxolane **17** in an overall yield of 45% from the bromopropanediol. Aldehyde deprotection was carried out of this stage, using the reported activated zinc fragmentation conditions (MeOH, reflux) developed by Corey,[20] to yield quantitatively the desired aldehyde **18**.

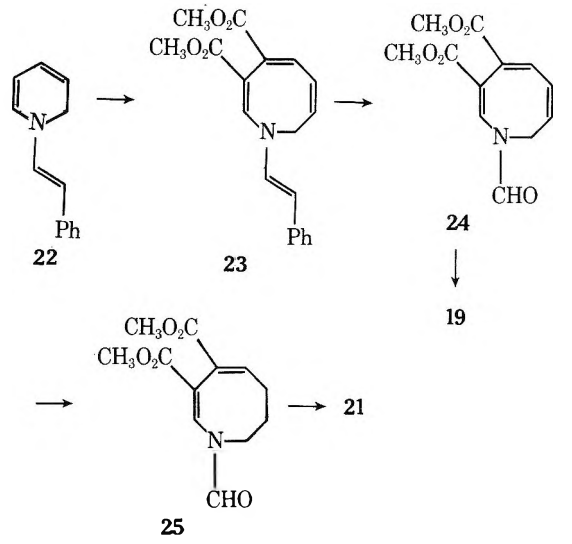


14 15 16 17 18 19 20 21

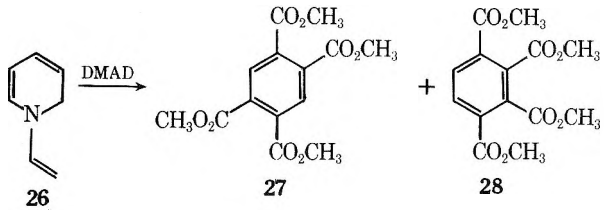
Similarly, the tetrahydroazocinyl aldehyde **13** can be derived from **17** by catalytic hydrogenation (10% Pd/C, MeOH, quantitative) to form **20** followed by zinc deblocking (94%). The final steps in routes to azocines which employ the masked propionaldehyde protecting group employ conditions which affect β-elimination. The most efficient procedure found for this purpose is exemplified by the reactions of **13** and **18** with potassium *tert*-butoxide in dilute *tert*-butyl alcohol solutions

at room temperature. Under these conditions the dihydro- and tetrahydroazocines, **19** and **21**, can be obtained in respective yields of 33 and 43%.

With the goal of providing an alternate and more efficient route to the nitrogen-unsubstituted azocines, the less obvious *N*-β-styryl protecting group was investigated. Several of the attractive features of this group are indicated by observations[12] which show that 1-*trans*-β-styryl-1,2-dihydropyridine (**22**)[21] is an easily prepared, stable solid, its reaction with dimethyl acetylenedicarboxylate proceeds in high yield to furnish the 1-β-styryl-1,8-dihydroazocine **23**, and electrophilic addition reactions of **23** are selective for the exocyclic π bond. Advantage can be taken of this latter property in developing procedures for removal of the β-styryl moiety. Accordingly, we have found that controlled ozonolysis of **23** in methanol followed by reductive decomposition of the intermediate ozonide using dimethyl sulfide leads to cleavage of the styryl π bond and liberation of the 1-formyldihydroazocine **24** (60%). Final deprotection is accomplished in a 72% yield by room temperature treatment of benzene solutions of **24** with sodium methoxide. The tetrahydroazocine **21** can be derived in an analogous fashion by catalytic hydrogenation of **24** (Pd/C, MeOH, 50 psi, quantitative) to yield the formamide **25** followed by deformylation (90%) using sodium methoxide.

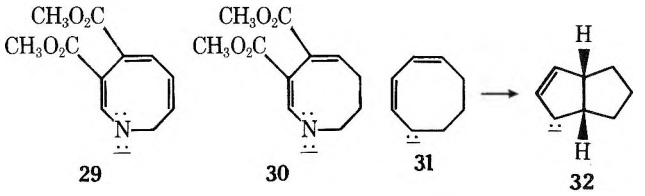


As a consequence of this tailored, stepwise deblocking method it is possible to obtain both the dihydro- and tetrahydroazocines in reasonably high yield. We have attempted, without success, to circumvent the only major limitation held by this last method which derives from the moderately lengthy procedure required to prepare the starting 1-β-styrylpyridinium salt.[21] It was our thought that simple *N*-vinyl groups might serve equally as well in these sequences. However, dramatic differences between the reactivity of 1-vinyl-1,2-dihydropyridine (**26**), prepared by borohydride reduction of the pyridinium bromide salt,[22] and **22** have been observed. Reaction of **26** with dimethyl acetylenedicarboxylate appears to take place exclusively at the exocyclic enamine function and leads to a complex mixture of products containing the tetramethyl esters of 1,2,4,5- and 1,2,3,4-benzenetetracarboxylic acid, **27** and **28**. Thus it appears that the



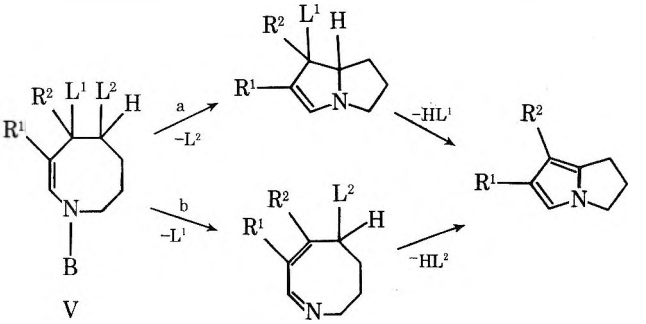
phenyl substituent in **22** is required for selective deactivation of the exocyclic vinyl moiety toward reaction with the acetylenic diester.

Transannular Cyclization. With these initial efforts as background attention was next directed at the development of methods for internal cyclization of the azocines to generate the pyrrolizidine ring systems. The azocinyl anions, **29** and **30**, appeared attractive for this purpose since both possess nucleophilic nitrogen centers correctly located for Michael addition to C-5 of the α,β-unsaturated ester moiety. From an alternate view, both anions contain the heteropentadienyl anion chromophore analogous to those in hydrocarbon systems which undergo $[_{\pi}4_s + _{\pi}2_s]$ electrocyclizations to produce cyclopentenyl anions.[23] Of particular relevance is the observation that the 1,3-cyclooctadien-5-yl anion (**31**) is efficiently transformed to the bicyclic allyl ion **32**.[23a] Despite this prec-



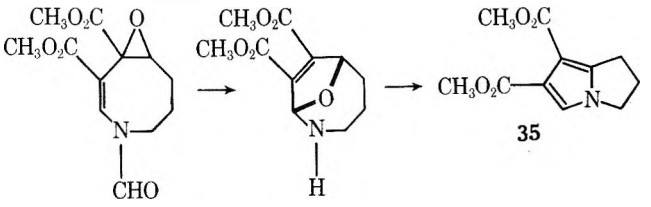
edent, both **29** and **30**, generated using sodium hydride in dimethoxyethane or dimsyl sodium in dimethyl sulfoxide, fail to produce detectable quantities of the corresponding pyrrolizidines. Specifically, the tetrahydroazocinyl anion **30** [^{1}H NMR (Me_2SO-d_6) δ 7.84 (s, H-2), 5.24 (t, H-5); ^{13}C NMR, see Table I] is remarkably stable at room temperature for extended periods, and is transformed back to its amine progenitor upon quenching with water or methanol. The remarkable stability of **30** in contrast to the behavior of **31** appears temporarily rationalized on the basis of an equilibrium between cyclic and bicyclic forms which heavily favors the open anion in the base and solvent systems explored. The thermodynamic stability of the azocinyl anion **30** due to extended conjugation and the low C–N bond dissociation energy may be such as to disfavor the less conjugated cyclized anion. Thus, in the base and solvent systems chosen, reaction would go undetected. Alternatively, steric constraints placed on the tetrahydroazocinyl anion by the medium-sized ring may prevent proper orientation of nitrogen for approach to the α,β-unsaturated ester moiety.[24] However, in light of the observations with **31**, this seems to be a less likely rationale.

In contrast to this, a successful procedure for conversion of hydroazocines to pyrrolizidines resulted from studies of an $\Delta^{4,5}$-epoxyazocine. Consideration was given to the possibility that hydroazocines, having leaving groups at C-4 and C-5 (V), might be useful starting materials for cyclization reactions since generation of the amide anion could be followed by transannular substitution at C-5 followed by elimination of the group at C-4 (pathway a) or by internal elimination followed by cyclization (pathway b). In order to test this hypothesis, the epoxyazocine **33** was prepared by high-temperature oxidation of the formamide **25** with *m*-chloroperbenzoic acid ($ClCH_2CH_2Cl$, Na_2PO_4, reflux, 75%). As can be seen, the



oxirane functionality of **33** can serve as the leaving group at both the C-4 and C-5 azocine positions. Interestingly, deformylation of **33** using sodium methoxide (C_6H_6, 0 °C, 95%) generates in high yield a product which has been characterized as the bicyclic amino ether **34** on the basis of its spectroscopic properties and by single-crystal x-ray diffraction of its tosylamide derivative **36** (*p*-TsCl, pyridine, reflux, 65%).

Crystals of **36** (0.46 × 0.33 × 0.16 mm) suitable for analysis



were grown from ethanol. Diffraction data indicated that the system was monoclinic with unit cell dimensions a = 10.069 (4), b = 11.214 (4), c = 16.668 (7) Å, and β = 97.12 (2)°. The space group is $P2_1/c$ with Z = 4, ρ(calcd) = 1.33 g cm^{-3}, mol wt 374.3 ($C_{20}H_{21}NO_5S$), and V = 1867.5 (1.3) Å^3. Intensity data were collected with a manual General Electric diffractometer using Mo Kα radiation (λ = 0.71069 Å) and balanced zirconium/yttrium filters. The stationary counter–stationary crystal method was employed with 10-s counts recorded for each filter. A total of 2368 independent reflections was measured with 1461 classified as statistically above background. The structure was solved by means of the MULTAN system[26] and then refined by full-matrix least-squares calculations. Reasonable positions for 14 of the 21 hydrogen atoms were located in a subsequent difference Fourier map. These together with the calculated positions for the remaining seven hydrogen atoms were used in the final structure factor calculations, but the hydrogen parameters were not allowed to refine. All of the nonhydrogen atoms were refined with anisotropic temperature factors. The final agreement index is 0.059 where $R = \Sigma||F_o| - |F_c||/\Sigma F_o$ and the weighted agreement index is 0.084 where $R_w = [\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2]^{1/2}$. Figure 1 shows an ORTEP[27] plot of the molecular structure with 30% probability ellipsoids for the nonhydrogen atoms.[28]

Although seemingly unusual, the bicyclic amino ether **34** is one of the more likely products expected if the internal elimination pathway is followed in reactions of the anion produced by deformylation of **33**. Accordingly, assisted heterolytic cleavage of the C_4–O epoxide bond would furnish the intermediate **37** having the alkoxy anionic and imine centers correctly disposed for transannular addition to form the bicyclic structure. In this way, the conversion of **33** to **34** can be thought of as the first step in a sequence which is modeled after pathway b for transformation of azocines of general structure V to pyrrolizidines. This feature is demonstrated by the observation that the bicyclic amino ether **34** can be efficiently converted to the pyrrolizidine diester **35** under acid-catalyzed dehydrative conditions using pyridinium hydrochloride (pyridine, reflux, 70%). The structural assignment to **35** rests on firm spectroscopic grounds [^{1}H NMR δ 7.18 (s, 1 H, H-2), 3.98 and 3.07 (t, CH_2), and 2.56 (q, CH_2)].

Although the origin of pyrrolizidine **35** under these reaction conditions can be explained using several mechanisms, it appears quite reasonable that the intermediate iminium ion **38** resulting from acid-catalyzed opening of **34** would undergo a facile hydride shift to furnish the β-keto ester **39**. This substance now possesses the correct functionality and structure for precedented cyclodehydration[6] to the dicarbomethoxy substituted pyrrolizidine.

It is clear from these initial observations that synthetic designs for the preparation of highly functionalized pyrrolizidines which utilize transannular cyclization of hydroazocines hold promise.

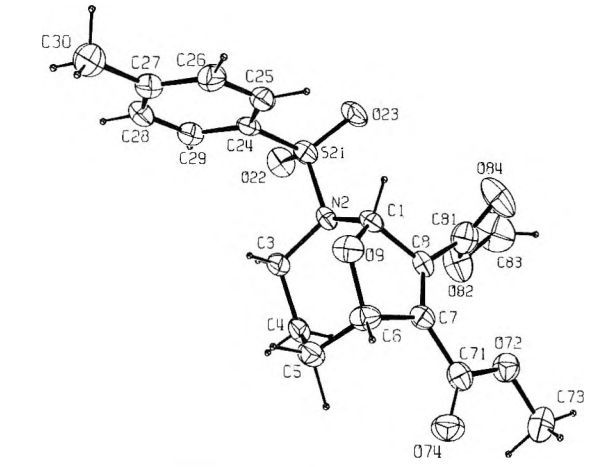
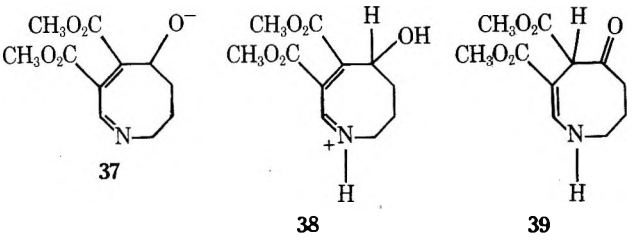


Figure 1. ORTEP perspective drawing of **36** with thermal ellipsoids scaled to 30% probability for nonhydrogen atoms.



Experimental Section

General. ^{1}H NMR spectra were taken on a Varian EM-360, T-60, or HA-100 spectrometer using tetramethylsilane as an internal standard. ^{13}C NMR spectra were obtained from a JEOL PS-100 NMR with dedicated probe using a Nic pulsed FT data collection system at an operating frequency of 25.0345 MHz with Me_4Si as an internal standard. Mass spectra were taken on a Du Pont CEC21-110B high-resolution mass spectrometer. UV data were obtained from a Beckman spectrophotometer, Model ACTA III. Infrared spectra were recorded on a Perkin-Elmer 237B, Beckman IR8, or Beckman IR12 spectrophotometer.

Melting points were taken on a Griffin Mel-Temp 110-V capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Preparative chromatographic work was done with either Baker "TLC" silica gel 7GF, Baker "TLC" aluminum oxide 9F, Grace silica gel, Davison grade 923, or MCB Type F-20 activated alumina. Hydrogenations were carried out on a Parr low-pressure hydrogenation apparatus. Ozonolyses were performed using a Welsbach T-408 laboratory ozonator. Unless otherwise mentioned Na_2SO_4 was used as drying agent in workup of reaction mixtures.

1-(2-Cyanoethyl)-1,2,5,6-tetrahydropyridine (3). To a solution of 0.225 g (5.95 mmol) of $NaBH_4$ in 20 mL of 10% aqueous Na_2CO_3 at 0 °C was added a solution of 1.00 g (5.90 mmol) of 1(2-cyanoethyl)pyridinium chloride[14] in 2 mL of water. After stirring at room temperature under N_2 for 15 min, the solution was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo giving an air-unstable, colorless liquid, 0.571 g (71%), characterized as the substituted tetrahydropyridine: IR (CCl_4) 3010, 2235, 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.70 (m, 2 H), 3.02 (m, 2 H), 2.64 (m, 6 H), 218 (m, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 136 (12, M$^+$), 96 (100), 83 (7), 54 (44); high-resolution mass spectrum *m/e* 136.099640 ($C_8H_{12}N_2$ requires 136.100040).

1-Carboethoxy-1,2-dihydropyridine (4). A procedure similar to that reported by Fowler[15] for preparation of 1-carbomethoxy-1,2-dihydropyridine was used. A solution of 3.46 mL (44 mmol) of ethyl chloroformate in 6 mL of ether was added to a mixture containing 1.78 g (47 mmol) of sodium borohydride in 3.58 mL (44 mmol) of dry pyridine and 17 mL of ethanol at −78 °C under N_2. After stirring at −78 °C for an additional 1.5 h the mixture was poured into 200

mL of ice water and the resulting solution extracted with ether. The ethereal extracts were washed with water, dried, and concentrated in vacuo, giving a pale yellow oil consisting of pure (>95%) 1-carboethoxy-1,2-dihydropyridine (5.05 g, 73%). Spectra characteristics of this compound follow: IR ($CHCl_3$) 1700, 1645, and 1588 cm^{-1}; UV max ($CHCl_3$) 304 nm; ^1H NMR ($CDCl_3$) δ 6.76 (d, 1 H, J = 8 Hz, H-6), 5.54 (m, 1 H, H-4), 5.16 (t, 1 H, J = 8 Hz, H-5), 5.84 (m, 1 H, H3), 4.38 (q, 2 H, J = 1 Hz, NCH_2), 4.24 (q, 2 H, OCH_2), 1.30 (t, 3 H, CH_3).

2-Carboethoxy-5,6-dicarbomethoxy-2-azabicyclo[2.2.2]-octa-5,7-diene (5). To 0.294 g (1.92 mmol) of freshly prepared 1-carboethoxy-1,2-dihydropyridine at 0 °C under Ar was added 0.734 mL (5.98 mmol) of dimethyl acetylenedicarboxylate. The solution was warmed to room temperature, stirred for 7 days, and chromatographed on a Florisil column. Elution with ether–hexane (0–25%) gave 0.402 g (71%) of the tricarboalkoxyisoquinuclidiene as a yellow oil. Attempts at further purification of this material by distillation at reduced pressure and at temperatures as low as 50 °C cause fragmentation to dimethyl phthalate. Spectral properties of this compound follow: IR (CCl_4) 3030, 1724, and 1699 cm^{-1}; UV max (CH_3CN) 207 nm (log ϵ 3.89); ^1H NMR ($CDCl_3$) δ 8.72 (m, 2 H, vinyl), 5.90 (m, 1 H, bridghead NCH), 4.14 (m, 1 H, bridgehead CH), 4.14 (q, 2 H, J = 7 Hz, OCH_2), 3.14 (m, 2 H, NCH_2), 1.25 (t, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 165.7 (s, co), 163.8 (s, CO), 155.5 (s, CO), 144.7 (s, vinyl C), 140.8 (s, vinyl C), 135.8 (d, vinyl CH), 133.9 (d, vinyl CH), 61.4 (t, NCH_2), 52.3 (q, OCH_3's), 50.6 (d, NCH), 44.3 (t, OCH_2), 40.1 (d, bridgehead CH), 14.7 (q, CH_3); mass spectrum (70 eV) m/e (rel intensity) 295 (7), 263 (1), 236 (3), 194 (4), 163 (100); high-resolution mass spectrum m/e 295.106229 ($C_{14}H_{17}NO_6$ requires 295.106555).

1-Benzhydryl-1,2-dihydropyridine (6). A solution containing 5.00 g (17 mmol) of 1-benzhydrylpyridinium chloride[17] and 0.151 g (4.0 mmol) of $NaBH_4$ in 30 mL of 10% aqueous Na_2CO_3 was stirred at room temperature under Ar. After 15 min a yellow solid had separated from the reaction mixture. This substance was rapidly filtered, washed with water, and dried under an Ar stream. This procedure gave 2.50 g (60%) of the desired dihydropyridine as an exceptionally unstable solid: ^1H NMR ($CDCl_3$) δ 7.28 (s, 10 H, aromatic), 6.05 (d, 1 H, H-6), 5.14 (s, 1 H, Ph_2CH), 5.10 (m, 1 H, H-4), 4.68 (td, 1 H, H-5), 4.36 (m, 1 H, H-3), 3.81 (dd, 2 H, NCH_2). NMR indicated that this material was contaminated with ca. 20% of the tetrahydropyridine and ca. 5% with the 1,4-dihydro isomer.

1-Benzhydryl-3,4-dicarbomethoxy-1,8-dihydroazocine (7). A mixture of 2.00 g (8.00 mmol) of 1-benzhydryl-1,2-dihydropyridine and 4.50 g (32.0 mmol) of dimethyl acetylenedicarboxylate in 30 mL of C_6H_6 was stirred at room temperature for 10 h under Ar. Concentration of the reaction mixture in vacuo gave a red oil which was subjected to column chromatography on silica gel. Elution with hexane followed by 40% Et_2O–hexane gave the pure azocine, 1.90 g (62%), as orange flakes (from EtOH): mp 73–77 °C; IR (CCl_4) 2910, 3010, 1715, 1675, 1690, 1235, 1450, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.66 (t, 2 H, J = 4.0 Hz, $-CH_2-$), 5.61 (dt, 1 H, J = 4.0 and 10.0 Hz), 6.35 (dd, 1 H, J = 3.0 and 10.0 Hz), 6.70 (d, 1 H, J = 3.0 Hz), 7.61 (s, 1 H, H-2), 3.50 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 5.67 (s, 1 H, methine), 7–7.4 (m, 10 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 389 (2.5, M^+), 358 (2), 349 (s), 300 (1), 167 (100), 152 (5), 77 (1), 59 (1), 165 (7.5); UV max (EtOH) 288 nm (log ϵ 4.02); ^{13}C NMR ($CDCl_3$) 149.2 (d), 95.7 (s, C-3), 131.3 (s, C-4), 128.1 (d, C-5), 126.9 (d, C-6), 127.9 (d, C-7), 56.1 (t, $-CH_2-$), 169.0 (s, CO), 169.4 (s, CO), 51.1 (q, OCH_3), 52.0 (q, OCH_3), 74.1 (d, methine), 128–135 (aromatic); high-resolution mass spectrum m/e 389.161825 ($C_{24}H_{23}NO_4$ requires 389.162685).

1-Benzhydryl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (8). Catalytic hydrogen of 1.00 g (2.60 mmol) of 1-benzhydryl-3,4-dicarbomethoxy-1,8-dihydroazocine in 300 mL of MeOH containing 0.5 g of 10% Pd/C was conducted in a Parr apparatus at room temperature and 55 psi for extended time periods. The calculated H_2 uptake was 1 equiv. The crude reaction mixture was filtered and concentrated in vacuo giving 1.02 g (100%) of the benzhydryltetrahydroazocine: IR (CCl_4) 3010, 2930, 1700, 1580, 1440, 1250, 1105 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (s, 1 H, H-1), 6.32 (dd, 1 H, J = 8.0 and 1.0 Hz), 2.2–3.8 (m, 6 H, methylenes), 3.52 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 5.56 (s, 1 H, methine), 7.0–7.4 (m, 10 H, aromatic); mass spectrum (70 eV) m/e (rel intensity) 391 (16, M^+), 360 (s), 224 (4), 192 (6), 167 (100), 152 (10); UV max (EtOH) 310 nm (log ϵ 3.83), 281 (4.03); ^{13}C NMR ($CDCl_3$) 149.5 (d), 92.8 (s, C-3), 133.8 (s, C-4), 134.9 (d, C-5), 25.1 (t, C-6), 17.7 (t, C-7), 45.6 (t, C-8), 169.5 (s, CO's), 51.1 (q, OCH_3), 51.8 (q, OCH_3), 73.6 (d, methine), 128.7–138.7 (aromatic); high-resolution mass spectrum m/e 391.179313 ($C_{24}H_{25}NO_4$ requires 391.178335).

1-(2-Dioxol-2-ylethyl)pyridinium Bromide (9). A mixture of 3.86 g (47.9 mmol) of pyridine and 8.67 g (47.9 mmol) of 2-(3-bromopropyl)-1,3-dioxolane[18] in 10 mL of C_6H_6 was refluxed under Ar for 3 days. Concentration of this mixture in vacuo gave a pale yellow oil, 12.49 g (ca. 100%), which crystallized at 0 °C. A reasonably pure sample, mp 74–82 °C, was prepared by Et_2O trituration followed by rigorous drying over P_2O_5. ^1H NMR ($CDCl_3$) δ 9.36 (d, 2 H), 8.26 (t, 2 H), 8.74 (t, 1 H), 5.04 (t, 1 H), 4.90 (t, 2 H), 3.82 (m, 4 H), 2.40 (sextet, 2 H); UV max (H_2O) 260 nm (log ϵ 3.66), 234 (2.95). Attempts to obtain samples pure enough for elemental analysis failed owing to the extreme hydroscopic nature of this compound.

1-(2-Dioxol-2-ylethyl)-1,2-dihydropyridine (10). To 0.502 g (1.932 mmol) of 1-(2-dioxol-2-ylethyl)pyridinium bromide in 4 mL of 2 N aqueous NaOH at 0 °C under N_2 was added 73.1 mg (1.932 mmol) of $NaBH_4$. $CHCl_3$ (6 mL) was quickly added to this solution and after 30 min the $CHCl_3$ layer was separated, dried, and concentrated in vacuo giving 0.256 g (73%) of a labile oil characterized as the dihydropyridine which was used immediately in ensuing reactions: UV max ($CHCl_3$) 339 nm; ^1H NMR ($CDCl_3$) δ 6.01 (d, 1 H, J = 7 Hz), 58.2 (m, 1 H), 5.08 (m, 1 H), 4.94 (t, 1 H), 4.66 (t, 1 H), 3.91 (m, 6 H), 3.02 (t, 2 H), and 1.88 (m, 2 H).

1-(2-Dioxol-2-ylethyl)-3,4-dicarbomethoxy-1,8-dihydroazocine (11). A solution prepared by adding 15.78 mL (0.129 mol) of dimethyl acetylenedicarboxylate to 15.63 g (85.6 mmol) of freshly prepared 1-(2-dioxol-2-ylethyl)-1,2-dihydropyridine in 50 mL of C_6H_6 at 0 °C under Ar was stirred at room temperature for 4 h. The mixture obtained by solvent removal in vacuo was subjected to column chromatography on silica gel. Elution with Et_2O–hexane mixtures ranging from 10 to 100% Et_2O gave a red oil, 17.69 g (64%), characterized as pure dihydroazocine: IR (CCl_4) 2995, 1729, 1705, 1617, and 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H, H-2), 6.68 (t, 1 H, H-5), 6.54 (d, 1 H), 6.34 (dt, 1 H), 4.89 (t, 1 H), 3.92 (m, 6 H), 3.74 (s, 3 H), 3.60 (s, 3 H), 3.27 (m, 2 H), 1.92 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 323 (52, M^+), 292 (17), 264 (8), 237 (81), 202 (100); UV max (MeOH) 286 nm (log ϵ 4.08), 229 (4.07); ^{13}C NMR ($CDCl_3$) 169.3 (s, CO), 168.7 (s, CO), 149.9 (d), 131.3 (d), 133.4 (d), 135.0 (d), 132.5 (s), 101.7 (d), 94.9 (s), 64.9 (t), 53.5 (t), 51.9 (q, OCH_3), 50.9 (q, OCH_3), 46.6 (t), 32.9 (t); high-resolution mass spectrum m/e 323.136042 ($C_{16}H_{21}NO_6$ requires 323.136855).

1-(2-Dioxol-2-ylethyl)-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (12). Catalytic hydrogenation of 15.50 g (48 mmol) of 1-(2-dioxol-2-ylethyl)-2,3-dicarbomethoxy-1,8-dihydroazocine in 150 mL of MeOH containing 20 mg of 5% Pd/C at 53 psi was conducted in a Parr apparatus until 1 equiv of H_2 was consumed. Preparative TLC on silica gel (Et_2O) of the crude mixture obtained after filtration and concentration in vacuo gave 15.68 g (quantitative) of pure tetrahydroazocine: IR ($CHCl_3$) 1713, 1680, 1658, 1605, and 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.55 (s, 1 H, H-2), 6.31 (t, J = 9 Hz, H-5), 4.92 (t, 1 H, J = 4 Hz, OCHO), 3.93 (m, 6 H, OCH_2 and H-8), 3.74 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 3.29 (dt, 2 H, NCH_2), 2.87 (m, 2 H, H-6), 2.48 (m, 2 H, H-7), 1.97 (m, 2 H, CH_2); mass spectrum (70 eV) m/e (rel intensity) 325 (68, M^+), 294 (62), 266 (23), 239 (45), 204 (70), 73 (100); UV max (MeOH) 281 nm (log ϵ 3.89), 211 (3.92); ^{13}C NMR ($CDCl_3$) 169.4 (s, CO), 169.3 (s, CO), 150.5 (d), 134.5 (d), 133.7 (s), 101.8 (d), 92.2 (s), 64.9 (t), 52.9 (t), 51.8 (q, OCH_3), 51.0 (q, OCH_3), 44.9 (t), 32.8 (t), 25.1 (t), 17.6 (t); high-resolution mass spectrum m/e 325.151190 ($C_{16}H_{23}NO_6$ requires 325.152505).

2-(2-Bromoethyl)-4-bromomethyl-1,3-dioxolane (14). To a solution of 96.50 g (0.68 mol) of 1-bromopropane-2,3-diol[19] in 125 mL of $CHCl_3$ containing 63.00 g (0.77 mol) of dissolved HBr at 0 °C was added 37 mL (0.57 mol) of acrolein. The resulting mixture was stirred at room temperature for 3 h and concentrated in vacuo. A pentane solution of the remaining viscous oil was washed with H_2O and 5% $NaHCO_3$, dried, and concentrated in vacuo giving 166.0 g (quantitative) of pure dioxclane. Analytically pure samples of this material were obtained by vacuum distillation: bp 70–71 °C (0.05 mm); ^1H NMR ($CDCl_3$) δ 5.08 (m, 1 H), 4.26 (m, 1 H), 3.50 (m, 6 H), 2.18 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 275, 273, 271 (2, 4, 2, M^+), 165 (100), 167 (95), 57 (29), 137 (9). Anal. Calcd for $C_6H_{10}O_2Br_2$: C, 26.31; H, 3.68; Br, 58.33. Found: C, 26.16; H, 3.62; Br, 58.02.

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]pyridinium Bromide (15). A solution containing 1.10 g (4.01 mmol) of the bromomethyldioxolane of 3-bromopropionaldehyde and 0.33 mL (4.1 mmol) of pyridine in 5 mL of C_6H_6 was refluxed under Ar for 3 days. Concentration of this mixture gave 1.58 g of an extremely viscous oil characterized as the desired pyridinium bromide: ^1H NMR (Me_2SO-d_6) δ 9.23 (d, 2 H), 8.65 (t, 1 H), 8.17 (t, 2 H), 5.18 (dt, 1 H), 4.83 (dt, 2 H), 4.24 (m, 1 H), 3.54 (m, 4 H), 2.42 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 193, 195 (0.6, $C_6H_{10}O_2Br$), 167 (4), 165 (4), 129 (1), 125 (3), 99 (5), 79 (100); UV max (H_2O) 260 nm (log ϵ 3.69) and 204 (3.91).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-1,2-dihydropyridine (16). To a solution of 25.1 g (70.8 mmol) of 1-[2-(4-bromometh-

yl)dioxol-2-ylethyl]pyridinium bromide in 80 mL of 2 N NaOH was added 2.68 g (70.9 mmol) of $NaBH_4$ in 20 mL of 2 N NaOH under N_2 at 0 °C. Stirring of this reaction mixture for 30 min was followed by $CHCl_3$ extraction. The $CHCl_3$ extracts were dried and concentrated in vacuo to give 15.5 g (80%) of a labile yellow oil characterized as the desired dihydropyridine. This material was used immediately after its formation: UV ($CHCl_3$) max 339 nm; ^1H NMR ($CDCl_3$) δ 6.00 (d, 1 H, J = 7.0 Hz), 5.84 (m, 1 H), 5.08 (m, 1 H), 4.66 (t, 1 H), 4.32 (m, 3 H), 3.92 (m, 2 H), 3.38 (m, 2 H), 3.00 (dt, 2 H), 1.92 (m, 2 H).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine (17). A solution of 10.32 mL (84 mmol) of dimethyl acetylenedicarboxylate and 15.50 g (56.0 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-1,2-dihydropyridine in 50 mL of C_6H_6 was stirred at room temperature under Ar for 1 h. The crude mixture obtained by removal of the solvent in vacuo was subjected to column chromatography on silica gel. Elution with Et_2O–hexane ranging from 10 to 100% Et_2O gave 13.05 g (56%) of a maroon oil characterized as the pure dihydroazocine: IR (CCl_4) 2985, 1717, 1695, 1605, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 1 H), 6.68 (t, 1 H), 6.54 (d, 1 H), 6.32 (dt, 1 H), 5.06 (dt, 1 H), 4.10 (m, 4 H), 3.75 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.36 (m, 4 H), 1.93 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 417 (M^+), 415 (12), 384 (6), 358 (5), 356 (5), 237 (69), 202 (100); UV max (MeOH) 287 nm (log ϵ 4.14), 229 (4.07); ^{13}C NMR ($CDCl_3$) δ 168.7 (s, CO), 149.8 (d), 135.1 (d), 133.5 (d), 132.5 (s), 131.2 (d), 102.8 (d), 102.2 (d), 95.0 (s), 77.5 (d), 75.3 (d), 74.8 (d), 69.8 (t), 68.8 (t), 53.3 (t), 52.0 (q), 51.0 (q), 46.6 (t), 32.8 (t); high-resolution mass spectrum m/e 417.059689 ($C_{17}H_{22}NO_6Br$ requires 417.06110).

1-[2-(4-Bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (20). Catalytic hydrogenation of 0.21 g (0.52 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine in 150 mL of CH_3OH containing 20 mg of 10% Pd/C was conducted in a Parr apparatus at 53 psi until 1 equiv of hydrogen was consumed. The material obtained after concentration in vacuo of the crude reaction mixture was purified by TLC on silica gel (Et_2O) giving 0.21 g (96%) of the pure tetrahydroazocine as a light yellow oil: IR ($CHCl_3$) 3000, 1713, 1687, 1605, and 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (s, 1 H), 6.33 (t, 1 H, J = 8.0 Hz), 5.05 (dt, 1 H), 4.10 (m, 6 H), 3.73 (s, 3 H), 3.61 (s, 3 H), 2.85 (2 H), 2.46 (m, 2 H), 1.97 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 419, 417 (45, M^+), 388, 386 (28), 360 (31), 338 (60), 192 (100); UV max (MeOH) 281 nm (log ϵ 4.09), 211 (4.02); ^{13}C NMR ($CDCl_3$) 169.5 (s, CO), 150.5 (d), 134.6 (d), 133.7 (s), 102.9 (d), 120.4 (d), 92.4 (s), 77.1 (d), 75.3 (t), 69.8 (t), 68.9 (t), 52.7 (t), 51.8 (q, OCH_3), 51.1 (q, OCH_3), 44.9 (t), 32.5 (t), 25.1 (t), 17.6 (t); high-resolution mass spectrum m/e 417.076491 ($C_{17}H_{24}NO_6Br$ requires 417.078720).

3-(3,4-Dicarbomethoxy-1,8-dihydroazocin-1-yl)propionaldehyde (18). A solution of 6.67 g (16.0 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,8-dihydroazocine in 365 mL of MeOH containing 16.0 g (0.245 g-atom) of activated Zn was refluxed under Ar for 15 h. The resulting mixture was filtered and added to a sufficient quantity of $CHCl_3$ to cause precipitation of ZnBr. The filtrate obtained by filtration of this $CHCl_3$ solution was washed with H_2O, dried, and concentrated in vacuo giving 4.46 g (100%) of a yellow oil characterized as the desired propionaldehyde derivative: IR (CCl_4) 3000, 2810, 2690, 1724, 1703, 1685, 1610, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.82 (s, 1 H), 7.58 (s, 1 H), 6.70 (t, 1 H), 6.53 (d, 1 H), 6.32 (dt, 1 H), 3.75 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.50 (m, 4 H), 2.80 (t, 2 H); mass spectrum (70 eV) m/e (rel intensity) 279 (86, M^+), 248 (31), 220 (100), 202 (33); UV max (MeOH) 286 nm (log ϵ 4.01), 229 (3.99); ^{13}C NMR ($CDCl_3$) 199.6 (d, aldehydic), 169.2 (s, CO), 149.5 (d), 135.2 (d), 133.9 (d), 132.3 (s), 131.0 (d), 94.7 (s), 54.6 (t), 52.1 (q, OCH_3), 51.3 (q, OCH_3), 47.0 (t), 43.4 (t); high-resolution mass spectrum m/e 279.109852 ($C_{14}H_{17}NO_5$ requires 279.110645).

3-(3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocin-1-yl)propionaldehyde (13). A method similar to that described above was employed using 2.38 g (5.68 mmol) of 1-[2-(4-bromomethyl)dioxol-2-ylethyl]-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine and 5.66 g (0.16 g-atom) of activated Zn in 70 mL of CH_3OH. This procedure gave 1.50 g (94%) of the pure propionaldehyde derivative as a yellow oil: IR ($CHCl_3$) 2970, 2825, 2680, 1712, 1680, 1600, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.80 (s, 1 H), 7.53 (s, 1 H), 6.32 (t, 1 H), 3.90 (m, 2 H), 3.73 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.44 (m, 2 H), 2.86 (m, 4 H), 2.46 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 281 (31, M^+), 250 (21), 222 (55), 117 (100); UV max (MeOH) 281 nm (log ϵ 4.09), 211 (4.01); ^{13}C NMR ($CDCl_3$) 199.8 (d, aldehydic), 169.3 (s, CO), 150.2 (d), 134.8 (d), 133.7 (s), 92.8 (s), 51.8 (q, OCH_3), 51.0 (q, OCH_3), 50.8 (t), 45.0 (t), 43.1 (t), 25.1 (t), 17.4 (t); high-resolution mass spectrum m/e 281.125139 ($C_{14}H_{19}NO_5$ requires 281.126295).

3,4-Dicarbomethoxy-1,8-dihydroazocine (19). Acrolein Elimination Method. A solution containing 4.32 g (3.87 mmol) of potassium *tert*-butoxide in 175 mL of *tert*-butyl alcohol was mixed with a solution containing 0.360 g (1.29 mmol) of 3-(3,4-dicarbomethoxy-1,8-dihydroazocin-1-yl)propionaldehyde in 25 mL of *tert*-butyl alcohol was stirred at room temperature for 1 h under Ar. The mixture was then neutralized with concentrated HCl and poured into an ice–H_2O mixture. The aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and concentrated in vacuo giving an oil which was purified by TLC on silica gel (Et_2O) giving 0.096 g (33%) of the pure dihydroazocine. The physical and spectroscopic properties were identical with those given below.

3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocine (21). Acrolein Elimination Method. A procedure similar to the one given above was used employing 0.386 g (3.45 mmol) of potassium *tert*-butoxide and 0.323 g (1.15 mmol) of 3-(3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocin-1-yl)propionaldehyde in 200 mL of *tert*-butyl alcohol. Reaction time was 2 h at room temperature under Ar. The procedure gave after TLC purification 0.110 g (43%) of pure tetrahydroazocine having identical spectroscopic and physical properties with those given below.

1-Formyl-3,4-dicarbomethoxy-1,8-dihydroazocine (24). Ozone in an oxygen stream was bubbled through a vigorously stirred solution of 3.5 g (11 mmol) of 1-*trans*-β-styryl-3,4-dicarbomethoxy-1,8-dihydroazocine[12] in dry MeOH at −50 °C. After 1 equiv of O_3 had passed through the sample, 25 mL of DMS in 25 mL of MeOH was added. The reaction mixture was warmed to room temperature and concentrated in vacuo. The odor of benzaldehyde was prevalent. This material was subjected to column chromatography on silica gel. Elution with 70% Et_2O–hexane gave 1.60 g (60%) of the desired 1-formyl-3,4-dicarbomethoxy-1,8-dihydroazocine: IR ($CHCl_3$) 3100, 2850, 1720, 1640, 1250, 1060, and 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (s, 1 H, formyl), 7.9 (s, 1 H, H-2), 7.2 (d, 1 H, J = 3.2 Hz, H-5), 6.6 (dd, 1 H, J = 3.2 and 10 Hz, H-6), 6.3 (dt, 1 H, J = 7.5 and 10 Hz, H-7), 4.50 (d, 2 H, J = 7.5 Hz, $-CH_2-$), 3.75 (s, 3 H, OCH_3), 3.59 (s, 3 H, OCH_3); mass spectrum (70 eV) m/e (rel intensity) 251 (50, M^+), 220 (18), 192 (81), 163 (31), 132 (81), 104 (100), 77 (56); UV max (MeOH) 337 nm (log ϵ 4.02), 262 (3.84); ^{13}C NMR ($CDCl_3$) 163.5 (d, formyl), 140.4 (d, C-2), 108.1 (s, C-3), 130.5 (s, C-4), 136.6 (d, C-5), 134.6 (d, C-6), 128.3 (d, C-7), 37.8 (t, C-8), 167.4 (s, CO), 52.9 (q, OCH_3), 167.2 (s, CO), 52.1 (q, OCH_3).

Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.44; H, 5.51; N, 5.14.

1-Formyl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine (25). Hydrogenation of 1-formyl-2,3-dicarbomethoxy-1,8-dihydroazocine (1.00 g, 4.0 mmol) was conducted on a methanolic solution (124 mL) containing 0.5 g of Pd/C at 55 psi in a Parr apparatus. After uptake of 1 equiv of H_2, the catalyst was separated by filtration. Concentration of the filtrate in vacuo gave 0.99 g (quantitative) of the desired tetrahydroazocine: IR (CCl_4) 3010, 2990, 1730, 1690, 1610, 1440, 1270, and 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.50 (s, 1 H, formyl), 7.82 (s, 1 H, H-2), 3.76 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 6.79 (t, J = 8.2 Hz), 1.5–3.5 (m, 4 H), ~4.0 (m, 2 H); mass spectrum (70 eV) m/e (rel intensity) 253 (40, M^+), 238 (48), 224 (60), 222 (24), 194 (16), 192 (100), 180 (16), 165 (16), 134 (40), 105 (24); UV max (MeOH) 280 nm (log ϵ 3.95); ^{13}C NMR ($CDCl_3$) 38.1 (t, C-8), 19.6 (t, C-7), 25.1 (t, C-6), 139.8 (d, C-5), 128.6 (s, C-4), 106.0 (s, C-3), 140.9 (d, C-2), 164.2 (d, formyl), 167.2 (s, CO), 167.7 (s, CO), 52.1 (q, OCH_3's); high-resolution mass spectrum m/e 253.095483 ($C_{12}H_{15}NO_5$ requires 253.094995).

3,4-Dicarbomethoxy-1,8-dihydroazocine (19). Deformylation Route. To a solution of sodium methoxide in MeOH [from 0.125 g (5.4 mg-atoms) of Na in 3 mL of MeOH] was added 0.425 g (1.7 mmol) of 1-formyl-3,4-dicarbomethoxy-1,8-dihydroazocine in 7 mL of C_6H_6 at room temperature under N_2. The mixture was then refluxed for 45 min. Extraction with $CHCl_3$ followed by concentration of the organic layer in vacuo gave a solid which was crystallized from CCl_4 to give 0.273 g (72%) of pure dihydroazocine: mp 146–149 °C; IR (CCl_4) 3420, 3030, 2995, 1735, 1610, 1445, and 1255 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.65 (d, 1 H, J = 7.5 Hz), 7.65 (d, 1 H, J = 7.5 Hz), 3.75 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3), 6.76 (d, 1 H, J = 3.0 Hz), 6.58 (dd, 1 H, J = 10.0 and 3.0 Hz, H-6), 6.26 (dt, 1 H, H-7); mass spectrum (70 eV) m/e (rel intensity) 223 (30, M^+), 192 (15), 164 (75), 132 (30), 104 (100), 77 (25), 59 (10), 51 (25); UV max (MeOH) 226 nm (log ϵ 3.97), 276 (3.94); ^{13}C NMR ($CDCl_3$) 40.9 (t), 132.5 (d), 134.5 (d, C-6), 134.3 (d, C-5), 128.6 (s, C-4), 95.6 (s, C-3), 147.2 (d, C-2), 169.2 (s, CO), 169.5 (s, CO), 52.0 (q, OCH_3), 51.0 (q, OCH_3); high-resolution mass spectrum m/e 223.084791 ($C_{11}H_{13}NO_4$ requires 223.084435).

3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocine (21). Deformylation Route. A procedure similar to the one used for preparation of the dihydroazocine from the *N*-formyl precursor was used employing 6.0 g (23.7 mmol) of 1-formyl-3,4-dicarbomethoxy-

Table I. ^{13}C NMR Resonances for the Tetrahydroazocine 21 and Tetrahydroazocinyl Anion 30

Carbon[a]	Chemical shift, ppm rel to Me_4Si[b] Tetrahydroazocine 21	Tetrahydroazocinyl anion 30[c]
C-2	147.9	161.8
C-3	90.8	81.8
C-4	133.8	139.8
C-5	134.7	124.2
C-6	24.8	24.4
C-7	19.9	19.8
C-8		45.4
C=O	168.4	172.0
	168.4	168.9
C–O	50.3	48.4
	51.3	50.5

[a] Assignments were based upon multiplicities obtained from coupled spectra. [b] Spectra were recorded on Me_2SO-d_6 solutions. [c] The anion is generated from dimsyl-d_6 sodium in Me_2SO-d_6.

1,6,7,8-tetrahydroazocine, sodium methoxide [from 1.59 g (69 mg-atoms) of sodium in 50 mL of MeOH], and 55 mL of C_6H_6. Workup in a similar manner after 35 min at reflux gave 5.01 g (94%) of the pure tetrahydroazocine: mp 144–145 °C (from CCl_4); IR (CCl_4) 3420, 2990, 3020, 1720, 1600, 1450, 1265, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.69 (d, 1 H, J = 7.0 Hz, NH), 7.60 (d, 1 H, J = 7.0 Hz, H-2), 3.68 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 6.36 (dd, 1 H, J = 5.0 and 9.0 Hz), 2.3–3.4 (m, 4 H, CH_2's), ~3.8 (2 H); mass spectrum (70 eV) m/e (rel intensity) 225 (29, M^+), 194 (19), 166 (100), 138 (23), 134 (21), 106 (19), 77 (10), 59 (8); UV max (MeOH) 272 nm (log ϵ 4.31), 300 (3.88), 209 (4.12); ^{13}C NMR ($CDCl_3$) 39.3 (t), 19.6 (t), 24.9 (t), 135.5 (d), 133.6 (s), 92.1 (s), 147.8 (d), 169.3 (s), 169.1 (s), 50.7 (q), 51.4 (q).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.36; H, 6.64; N, 6.04.

1-Vinyl-2,3-dihydropyridine (26). A mixture of 0.133 g (3.52 mmol) of $NaBH_4$ in 6 mL of cold 20% Na_2CO_3 was added to a solution of 1.308 g (7.03 mmol) of 1-vinylpyridinium bromide[22] in 4 mL of H_2O at −4 °C under N_2. $CHCl_3$ (11 mL) was quickly added and after 20 min the $CHCl_3$ layer was separated. The $CHCl_3$ solution was dried and concentrated in vacuo giving 0.338 g (45%) of a light-colored, labile oil characterized as the 1-vinyl-1,2-dihydropyridine: UV max ($CHCl_3$) 344 nm; ^1H NMR ($CDCl_3$) δ 6.47 (AB q, 1 H), 6.09 (d, 1 H), 5.80 (m, 1 H), 5.34 (m, 1 H), 4.56 (m, 1 H), 4.19 (m, 1 H), 3.90 (d, 1 H, J = 13 Hz), 3.75 (d, 1 H, J =16 Hz).

Generation and NMR Spectra of 3,4-Dicarbomethoxy-1,6,7,8-tetrahydroazocinyl Anion (30). Method A. To a suspension of 216 mg (8.90 mmol) of NaH (washed repeatedly with DME to remove dispersion oil) in 30 mL of DME under Ar at room temperature was added 0.30 g (0.34 mmol) of 3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine in 20 mL of DME. A bright red color appeared immediately. After a short period of time, ca. 3 h, the mixture was poured into ice–water and immediately extracted with $CHCl_3$. Concentration of the $CHCl_3$ layer after drying gave quantitative recovery of the starting tetrahydroazocine. It should be mentioned that prolonged standing of the aqueous solution obtained by quenching the tetrahydroazocinyl anion leads to complete destruction of the azocine skeleton.

Method B. A solution containing dimsyl-d_5 sodium in Me_2SO-d_6 [prepared from CaH_2 purified and dried Me_2SO-d_6 and 0.094 g (2.00 mmol) of NaH] and 0.30 g (0.34 mmol) of 3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine was prepared under N_2 at room temperature. Again the characteristic red color of the azocinyl anion was present. ^1H NMR and ^{13}C NMR spectra were recorded for this anion solution: ^1H NMR δ 7.84 (s, 1 H, H-2), 1.21 (m, 2 H, H-7), 3.26 (s, 3 H, OCH_3), 3.52 (s, 3 H, OCH_3), 5.22 (t, 1 H, H-5); ^{13}C NMR (see Table I).

1-Formyl-3,4-dicarbomethoxy-4,5-epoxy-1,4,5,6,7,8-hexahydroazocine (33). To a solution of 0.300 g (1.20 mmol) of 1-formyl-3,4-dicarbomethoxy-1,6,7,8-tetrahydroazocine in 30 mL of 1,2-dichloroethane containing finely powdered dry Na_2HPO_4 (0.382 g, 2.40 mmol) at reflux was added 0.479 g (2.40 mmol) of m-chloroperbenzoic acid in 20 mL of 1,2-dichloroethane over a 45-min period. The pH of the reaction medium was constantly monitored and Na_2HPO_4 was added to ensure neutrality. The reaction mixture was refluxed until KI/starch tests indicated the absence of unreacted MCPBA. The reaction mixture was then washed with 10% Na_2SO_3, added to water, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated $NaHCO_3$, dried, and concentrated in vacuo, giving an oil which was purified by TLC on silica gel (Et_2O). The procedure gave pure epoxyazocine, 0.230 g (73%), as a clear oil: IR ($CHCl_3$) 2990, 1740, 1635, 1445, 1260, 1143, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (s, 1 H, H-2), 3.40 (dd, 1 H), 1.80–2.48 (m, 4 H), 4.40 (dd, 2 H), 8.56 (s, 1 H), 3.80 (s, 6 H, OCH_3's); mass spectrum (70 eV) m/e (rel intensity) 269 (14, M^+), 240 (100), 238 (13), 210 (11), 209 (13), 182 (39), 153 (33), 150 (36), 122 (22), 94 (22), 77 (12), 59 (39); UV max (acetonitrile) 261 nm (log ϵ 4.24); ^{13}C NMR ($CDCl_3$) 142.4 (d), 104.1 (s), 56.7 (s), 62.3 (d), 25.0 (t), 24.6 (t), 39.5 (t), 163.7 (d), 170.2 (s), 167.2 (s), 53.1 (q), 52.4 (q).

Anal. Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.28; H, 5.53; N, 5.09.

7,8-Dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene (34). To a solution of 0.100 g (0.360 mmol) of 1-formyl-3,4-dicarbomethoxy-4,5-epoxy-1,4,5,6,7,8-hexahydroazocine in 10 mL of C_6H_6 at 0 °C under N_2 was added rapidly a mixture of $NaOCH_3$ in CH_3OH (from 0.72 g-atom of Na in 10 mL of CH_3OH). The reaction mixture was stirred at 0 °C for 10 min and poured into water. The $CHCl_3$ layer obtained by extraction was dried and concentrated in vacuo to give the bicyclic amino ether, 0.84 g (94%), which was purified further by TLC on silica gel (Et_2O): IR (CCl_4) 2980, 1740, 3400, 1450, 1270, 1670, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (s, 1 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 2.50 (s, 1 H), 5.14 (dd, 1 H, J = 1.5 and 6.0 Hz), 1.88–2.20 (m, 4 H), 2.94 (dd, 2 H); mass spectrum (70 eV) m/e (rel intensity) 241 (8, M^+), 223 (8), 210 (15), 200 (17.5), 192 (15), 184 (50), 182 (95), 153 (100), 122 (35), 98 (13), 58 (80); UV max (EtOH) 210 nm (log ϵ 3.85), 270 (3.44); ^{13}C NMR ($CDCl_3$) 142.7 (s, olefinic), 134.5 (s, olefinic), 94.6 (d, bridgehead), 82.4 (d, bridgehead), 31.3 (t, $-CH_2-$), 28.6 (t, $-CH_2-$), 42.8 (t, $-CH_2-$), 163.2 (s, CO), 163.0 (s, CO), 52.4 (q, OCH_3's); high-resolution mass spectrum m/e 241.094216 ($C_{11}H_{15}NO_5$ requires 241.094995).

7,8-Dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene 2-*p*-Toluenesulfonamide (36). A solution containing 0.189 g (0.780 mmol) of 7,8-dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene and 0.165 g (0.860 mmol) of p-toluenesulfonyl chloride in 10 mL of pyridine was refluxed under N_2 for 1 h. The cooled reaction mixture was poured into H_2O and the resulting solution extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and concentrated in vacuo giving material which was purified by TLC on silica gel (Et_2O). This procedure afforded 0.199 g (65%) of the crystalline tosylamide derivative: mp 136–137 °C (from EtOH); IR ($CHCl_3$) 3050, 2980, 1730, 1750, 1475, 1450, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.72 (s, 1 H, H-1), 3.83 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 5.13 (t, 1 H, J = 4.0 Hz, H-6), 2.4 (s, 3 H), 1.70–3.40 (m, 6 H, methylenes), 7.75 (d, 2 H, J = 8.0 Hz, aromatic), 7.31 (d, 2 H, J = 8.0 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity) 395 (2, M^+), 364 (9.5), 326 (76.4), 305 (3), 240 (43.7), 208 (47), 179 (100), 153 (32); UV max (EtOH) 230 nm (log ϵ 4.22); ^{13}C NMR ($CDCl_3$) 92.4 (d), 143.6 (s, C-8), 140.6 (s, C-7), 84.3 (d, C-6), 32.6 (t, C-5), 23.2 (t, C-4), 45.3 (t, C-3), 52.5 (s, CO's), 127.4–136.5 (aromatics), 21.6 (q, methyl); high-resolution mass spectrum m/e 395.102393 ($C_{18}H_{21}NO_7S$ requires 395.103837).

3,4-Dicarbomethoxy-1-azabicyclo[3.3.0]octa-2,4-diene (35). A saturated solution of pyridinium hydrochloride in pyridine (40 mL) containing 0.490 g (2.00 mmol) of 7,8-dicarbomethoxy-9-oxa-2-azabicyclo[4.2.1]non-7-ene was refluxed under N_2 for 30 min. The crude reaction mixture was poured into ice–water and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated NaCl, dried, and concentrated in vacuo giving an oil which was purified by Tlc on silica gel (Et_2O) giving 0.310 g (70%) of the desired pyrrolizidine as a clear, light yellow glass: IR (CCl_4) 2990, 1730, 1445, 1540, 1270, 1105, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (s, 1 H, H-2), 2.56 (quintet, 2 H, methylene), 3.07 (t, 2 H, J = 8.0 Hz, methylene), 3.98 (t, 2 H, J = 8.0 Hz, methylene), 3.81 (s, 6 H, OCH_3's); mass spectrum (70 eV) m/e (rel intensity) 223 (42, M^+), 192 (100), 162 (18), 133 (21), 105 (24), 77 (18); UV max (EtOH) 260 nm (log ϵ 3.77); ^{13}C NMR ($CDCl_3$) 164.3 (s, C=O), 146.1 (s, C-3 and C-4), 121.5 (d, C-2), 119.3 (s, C-5), 51.3 (q, OCH_3), 47.2 (t, C-8), 26.8 (t, C-6), 25.4 (t, C-7); high-resolution mass spectrum m/e 223.083697 ($C_{11}H_{13}NO_4$ requires 223.084435).

Acknowledgments. Financial support for this research from the National Cancer Institute (CA-16695) and the Robert A. Welch Foundation is acknowledged. The JEOL PFT-100 spectrometer used in this research was purchased with grant support from the National Science Foundation. We would like to thank Ms. H. Mireles, Mr. M. Peters, and Dr. E. Krochmal for technical assistance.

Registry No.—**1**, 15201-08-8; **3**, 62562-86-1; **4**, 57956-33-9; **5**, 62587-48-8; **6**, 62562-87-2; **7**, 62562-88-3; **8**, 62562-89-4; **9**, 62587-49-9; **10**, 62562-90-7; **11**, 62562-91-8; **12**, 62562-92-9; **13**, 62562-93-0; **14**,

62562-94-1; **15**, 62562-95-2; **16**, 62562-96-3; **17**, 62562-97-4; **18**, 62562-98-5; **19**, 62562-99-6; **20**, 62587-50-2; **21**, 62563-00-2; **24**, 62563-01-3; **25**, 62563-02-4; **26**, 62563-03-5; **30**, 62587-52-4; **33**, 62563-04-6; **34**, 62563-05-7; **35**, 62563-05-8; **36**, 62587-51-3; ethyl chloroformate, 541-41-3; pyridine, 110-86-1; dimethyl acetylenedicarboxylate, 762-42-5; 1-benzhydrylpyridinium chloride, 26156-88-7; 2-(3-bromopropyl)-1,3-dioxolane, 62563-07-9; 1-bromopropane-2,3-diol, 4704-77-2; acrolein, 107-02-8; 1-*trans*-β-styryl-3,4-dicarbomethoxy-1,8-dihydroazocine, 62563-08-0; 1-vinylpyridinium bromide, 45590-50-9; *p*-toluenesulfonyl chloride, 98-59-9.

References and Notes

(1) A preliminary discussion of this work has been presented at the 32nd Southwest Regional Meeting of the American Chemical Society, Dec 1976, No. ORGN-32.
(2) Camille and Henry Dreyfus Foundation Teacher-Scholar Grant recipient, 1975–1980.
(3) N. J. Leonard, "The Alkaloids", Vol. 6, R. H. Manske, Ed., Academic Press, New York, N.Y., 1960, Chapter 3.
(4) W. Szybalski and V. N. Iyer, "Antibiotics", Vol. 1, D. Gottlieb and P. D. Shaw, Ed., Springer-Verlag, West Berlin, 1967, p 230.
(5) J. J. Tufariello and J. P. Tette, *J. Org. Chem.*, **40**, 3866 (1975).
(6) J. W. Lown and T. Itoh, *Can. J. Chem.*, **53**, 960 (1975); N. J. Leonard and T. Sata, *J. Org. Chem.*, **34**, 1066 (1969).
(7) M. T. Pizzorno and S. M. Abonico, *J. Org. Chem.*, **39**, 731 (1974); F. M. Hershenson, *Ibid.*, **40**, 1260 (1975); R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Shafer, *Chem. Ber.*, **103**, 2611 (1970).
(8) D. R. Crump, R. W. Franck, R. Gruska, A. A. Ozorio, M. Pagnotta, G. J. Siuta, and J. G. White, *J. Org. Chem.*, **42**, 105 (1977).
(9) S. Danishefsky and J. Dynak, *J. Org. Chem.*, **39**, 1978 (1974).
(10) N. K. Kochetkov and A. M. Likhosherstov, *Adv. Heterocycl. Chem.*, **5**, 315 (1965).
(11) R. M. Acheson and G. Paglietti, *J. Chem. Soc., Perkin Trans. 1*, **45** (1976).
(12) P. S. Mariano, M. E. Osborn, and E. Krochmal, *Tetrahedron Lett.*, 2741 (1975).
(13) R. E. Lyle and P. S. Anderson, *Tetrahedron Lett.*, 553 (1962); R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Ibid.*, 153 (1964).
(14) S. A. Heininger, *J. Org. Chem.*, **22**, 704 (1957).
(15) F. W. Fowler, *J. Org. Chem.*, **37**, 1321 (1972).
(16) (a) Diels–Alder additions to 1,2-dihydropyridines, bearing electron-withdrawing groups on nitrogen,[15,16b] and the diene moiety,[16c] using active dienophiles have been reported; (b) E. Knaus, F. Pasutto, and C. S. Giam, *J. Heterocycl. Chem.*, **11**, 843 (1974); (c) K. Schenker and J. Druey, *Helv. Chim. Acta.*, **45**, 1344 (1962), **52**, 1971 (1969); G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. Ziegler, *J. Am. Chem. Soc.*, **87**, 2073 (1965).
(17) Y. Okamoto and Y. Shumakawa, *J. Org. Chem.*, **35**, 3752 (1970).
(18) G. Buchi and H. Wuest, *J. Org. Chem.*, **34**, 1122 (1969).
(19) S. Winstein and L. Goodman, *J. Am. Chem. Soc.*, **76**, 4368 (1954).
(20) E. J. Corey and R. A. Ruden, *J. Org. Chem.*, **38**, 834 (1973).
(21) L. C. King and W. B. Brownell, *J. Am. Chem. Soc.*, **72**, 2507 (1950); S. S. Berg, B. J. Broughton, M. Davis, and R. F. Phillipson, South African Patent 6800, 346 (1968); *Chem. Abstr.*, **72**, 55273h (1970).
(22) C. C. Price and I. N. Duling, *J. Am. Chem. Soc.*, **84**, 578 (1962).
(23) (a) C. W. Shoppee and G. N. Henderson, *J. Chem. Soc., Chem. Commun.*, **561** (1974); (b) L. H. Slaugh, *J. Org. Chem.*, **32**, 108 (1967); R. B. Bates and D. A. McCombs, *Tetrahedron Lett.*, 977 (1969).
(24) When considered as an internal Michael addition, the conversion of anion **30** to a cyclized pyrrolizidinyl anion would be an example of what Baldwin[25] has classified as a disfavored 5-endo-trig ring closure.
(25) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734, 736, 738 (1976).
(26) (a) G. Germain, P. Main, and M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971); (b) J. P. Declerq, G. Germain, P. Main, and M. Woofson, *Ibid.*, **29**, 231 (1973); M. J. H. Koch, *Acta Crystallogr., Sect. B*, **30**, 67 (1974).
(27) C. K. Johnson, ORTEP, Oak Ridge National Laboratory, Report ORNL 3794 (1965).
(28) Complete details of the crystallographic study will be published separately: R. Pettersen, P. S. Mariano, D. Dunaway-Mariano, and M. Osborn, manuscript in preparation.

Bis(methylsulfonoxymethyl) Ether

D. M. Burness,* C. J. Wright, and W. C. Perkins

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received December 23, 1976

Reaction of acetyl mesylate (3) with trioxane and certain other polyoxymethylene derivatives gives the previously unknown title compound in yields as high as 70%. This extremely active compound undergoes the expected dialkylation reactions with mercaptides and with pyridine, but in a few other reactions cleavage occurs leading to derivatives of formaldehyde. Reaction of 3 with paraformaldehyde gives good yields of methylene dimesylate which is the main product from trioxane when a substantial amount of free methanesulfonic acid is present.

Restrictions on the use of bis(chloromethyl) ether (BCME) because of its high level of carcinogenicity to man[1] have produced a need for a suitable substitute for this useful intermediate. Obviously, the bromo- or iodomethyl ethers would serve this purpose, but because of their close relationship to BCME they also are suspect. Utilization of a sulfonate ester, such as bis(methylsulfonoxymethyl) ether (**1**), appeared

$$RSO_3CH_2OCH_2OSO_2R$$

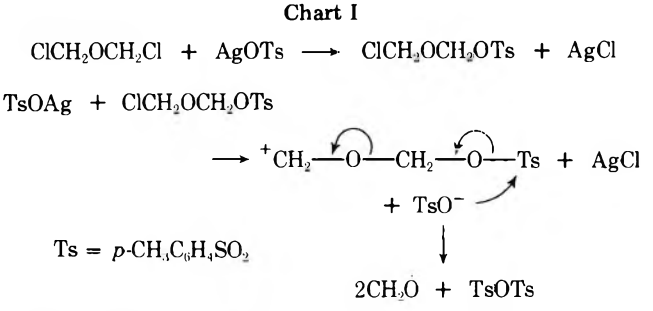
$$1, R = CH_3$$

$$2, R = p\text{-}CH_3C_6H_4$$

to offer the advantages of easier containment, due to a very low vapor pressure, and quite different physiological activity because of its high chemical reactivity as exemplified by a monofunctional analogue, methoxymethyl methanesulfonate.[2] [This compound was found to be 10^4 times more reactive with pure benzene (no catalyst) than is the corresponding chloromethyl ether (in acetic acid).] In fact, recent tests of **1** for mutagenic activity by microbial assay, with and without mammalian metabolic activation (Ames test[3]), gave negative results,[4] in contrast to BCME. (A positive test is suggestive that a chemical may be carcinogenic; on the other hand, a negative result cannot be taken as conclusive evidence to the contrary.[5])

A search of the literature produced no reference to a sulfonate analogue of BCME.[6] An early attempt to prepare for study bis(tosyloxymethyl) ether (**2**) by the direct reaction of silver tosylate with BCME led only to the isolation of *p*-toluenesulfonic anhydride in fair yield. A possible reaction path is shown in Chart I. This result might explain the absence in

Chart I

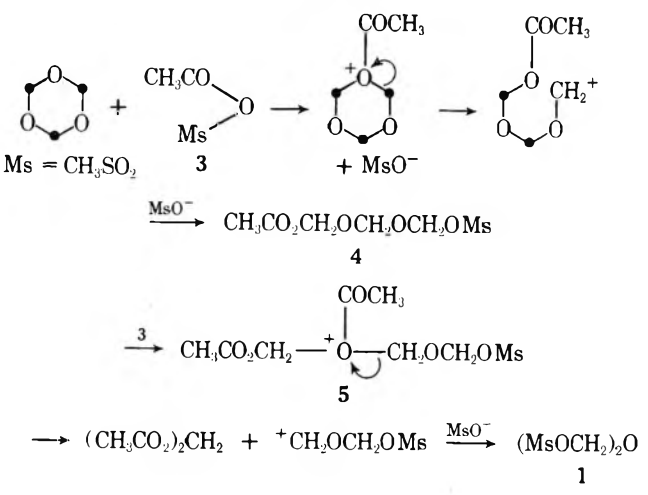


the literature of any reference to either **1** or **2**. Other examples of failures of double displacements on BCME have been noted elsewhere.[7]

Synthesis of Bis(methylsulfonoxymethyl) Ether (1). In 1968 Karger and Mazur[8a] first reported a new, facile synthesis of mixed carboxylic–sulfonic anhydrides which are powerful electrophilic reagents capable of selective ether cleavage without added Lewis acid catalysts.[8b] The cleavage of several cyclic ethers to give good yields of mixed acetate–sulfonate diesters was described. The only formal investigated was dimethoxymethane, which underwent reaction with acetyl methanesulfonate to form methoxymethyl methanesulfonate.[2] It has now been found that this reaction, when applied to certain polyoxymethylene compounds, gives bis(alkylsulfonoxymethyl) ethers such as the dimesylate 1.

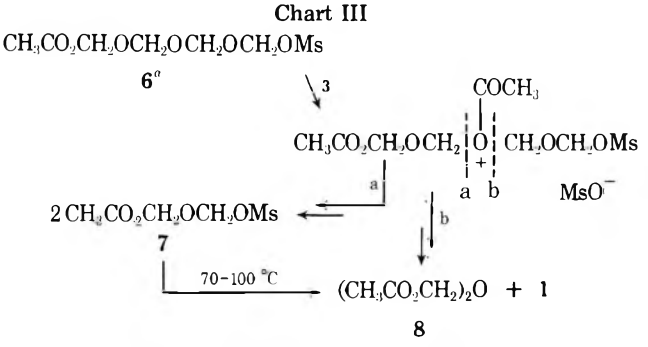
The most convenient source of 1, in 60–70% yield, has proved to be from the neat reaction[9] of acetyl methanesulfonate (3) with trioxane at 90 °C (Chart II). Addition of ca. 3.5%

Chart II



methanesulfonic acid reduced the reaction time from 20–24 h to 4 h. With a larger amount of acid (ca. 7.5%), although 1 was formed initially (ca. 30% detected by NMR after 3 h), it gradually declined, paraformaldehyde was evolved, and the major reaction product was methylene dimesylate.[10] Reaction times are also reduced by elevated temperatures; for example, at 110 °C, without added acid, reaction was complete in 5 h but the yield suffered (52%) due to thermal instability of the product. Isolation of 1 by distillation (at 10–20 μ) is possible, but crystallization from tetrahydrofuran is more convenient and equally productive of pure product. Tetroxane was reacted with 3 under similar conditions to give 1 in 70% yield. In this case, the volatile by-product contained a high percentage of bis(acetoxymethyl) ether (8), as indicated by the reaction path in Chart III.

Chart III



[a] From tetroxane, analogous to 4 in Chart II.

The reaction of trioxymethylene diacetate with an equimolar amount of acetyl mesylate was explored with the primary aim of preparing the mixed ester 7, one of the suggested by-products in the preparation of 1 from tetroxane. Based on NMR analysis of the crude product mixture, at 25 °C about 60% of the trioxymethylene diacetate reacted to form 7. Distillation at 65–115 °C, however, caused an unexpected disproportionation resulting in the total disappearance of 7 in favor of the dimesylate 1, which was isolated in 29% yield, and diacetate 8.

Equimolar amounts of 3 and bis(acetoxymethyl) ether (8) heated at 70–80 °C for 3.5 h under vacuum (0.5 mm) produced an approximately 2:1:1 (molar basis by NMR analysis) mixture of ester 7, dimesylate 1, and unreacted 8 with acetic anhydride as the volatile by-product. Distillation of a portion of the reaction mixture gave a 57% yield of 1 and only traces of 7 in the forerun. In a similar reaction, a 2:1 molar ratio of 3 and 8, heated at 65 °C for 32 h under vacuum, afforded a 2:1 molar ratio of 1 and 7 with only a trace of 8 remaining. Crystallization of the reaction mixture from dry tetrahydrofuran gave a 33% yield of pure dimesylate 1.

Reaction of 3 with paraformaldehyde, rather unexpectedly, produced 75% of methylene dimesylate and only about 7% 1. This dimesylate, which has been of considerable pharmacological interest,[11] had been prepared previously from methylene iodide and silver mesylate.[10] No other synthesis appears to have been reported.

Possible Reaction Pathways for the Acetyl Mesylate Reactions. Charts II and III show possible reaction pathways for the reaction of acetyl mesylate (3) with trioxane and tetroxane, respectively. Both proceed via attack of acetylium ion on a ring oxygen atom. The mixed esters 4 and 6 are again attacked by acetylium ion, preferentially on the least electron-deficient oxygen atom, with subsequent cleavage to form the more stable carbonium ion. In the trioxane case (Chart II) the dimesylate 1 and methylene diacetate are the expected and observed products. Catalysis of the reaction by a small amount of methanesulfonic acid could be due to protonation of the carbonyl group as was observed in the Karger and Mazur studies.[8b] The higher concentrations of acid undoubtedly protonate the trioxane, resulting in ring cleavage and formation of formaldehyde and the symmetrical final products methylene dimesylate and methylene diacetate, also observed in the reaction of 3 with paraformaldehyde.

As shown in Chart III the oxonium ion resulting from acetylium ion attack on 6 can cleave with nearly equal apparent ease at bond a or b. Cleavage at b leads directly to 1 and 8, while cleavage of bond a produces the mixed ester 7, which, being thermally unstable, disproportionates to give the same product mixture. The reaction of 3 and trioxymethylene diacetate also leads to the intermediate formation of 7 by an analogous pathway. The disproportionation is likely promoted by methanesulfonic acid, known to be ever present in unpurified 3. This is reminiscent of acid-catalyzed mixed-anhydride disproportionations observed by Karger and Mazur.[12] In reactions of 3 and bis(acetoxymethyl) ether (8) the unexpected formation of 7 and 1 (presumably from initially formed 7), with acetic anhydride as the only volatile product, must be due to a preferential attack of acetylium ion on the carbonyl oxygen of 8 rather than the ether oxygen, owing to inhibition by the inductive influence of the two acetoxy groups.

The fact that different products are obtained with paraformaldehyde than are usual with trioxane and tetroxane may not be surprising in view of the poor solubility of the polymer in 3 and the probable formation of a significant amount of methanesulfonic acid from the acetylation, by 3, of the hydroxyl end groups of paraformaldehyde. As has already been mentioned, increasing amounts of methanesulfonic acid in the reaction of 3 with trioxane favor the formation of methylene dimesylate at the expense of 1.

These reactions provide further examples of the unusually high order of selectivity of ether cleavage by the mixed anhydrides observed by Karger and Mazur.[8b]

Physical Properties, Stability, and Reactions.

Bis(methylsulfonoxymethyl) ether is a low-melting solid (mp 57–59 °C) which can be distilled at low pressures (5–15 μ). Like methoxymethyl mesylate it is so reactive that even aromatic hydrocarbons undergo reaction and cannot be used as solvents. However, it reacts only slowly with THF at 25 °C from which solvent it is readily recrystallized. It can also be purified by precipitation with ethyl ether in which it is insoluble. Reaction mixtures and *distilled* dimesylate are stable for weeks at room temperature if kept in tightly capped containers. However, **1** which has been crystallized from THF degrades with a half-life of a few days at room temperature (presumably owing to reaction with traces of THF) but it can be stored for months at −35 °C.

The reactions of **1** with mercaptans are somewhat complicated owing to the severe limitation on the choice of solvent imposed by the ease of solvolysis of **1** in some hydroxylic solvents, the usual choice for such reactions. The solvents which *were* found suitable required either sodium or sodium hydride as base in order to form the mercaptide without introducing or forming water or methanol in the reaction mixture. Dioxane or THF can be used to dissolve **1**, and EtOH (at −20 °C) or 2-PrOH (at 0–30 °C) serves as an appropriate reaction medium with mercaptides. In MeOH, even at −20 °C, considerable solvolysis occurs. There is no apparent problem, even with 2-mercaptoethanol, at 25–30 °C in 2-PrOH, and yields are 80–90%.

Pyridine reacts readily with **1** to give the expected 2-oxapropane-1,3-bis(pyridinium mesylate). Secondary amines, such as pyrrolidine, on the other hand, cause ether cleavage of **1** leading to aminals of formaldehyde, a reaction typical of methoxymethyl mesylate.[2] Similar reactions occur with primary alcohols and aromatic hydrocarbons under ambient conditions; for example, **1** in butanol produced the formal derivative, and in toluene a mixture of isomeric ditolylmethanes was formed. However, reaction of **1** with sodium *n*-butoxide afforded the bis(butoxymethyl) ether as the major product.

Analogues of 1. Bis(ethylsulfonoxymethyl) ether, a liquid, was prepared from acetyl ethanesulfonate and trioxane in 36% yield. As expected, it is essentially as reactive as **1**, giving the same reaction with toluene, for example. Since it was isolated by distillation, it was quite stable to ambient conditions in tightly capped bottles.

Efforts to obtain bis(tosyloxymethyl) ether (**2**) by reaction of acetyl tosylate with trioxane under a variety of conditions failed, although the NMR spectra of reaction mixtures held at 25 °C showed strong evidence of its formation. Instability of the compound very likely prevented its isolation. Attempts to prepare a methyl homologue of **1** by reaction of **3** with paraldehyde led only to exothermic polymerizations, initiating at temperatures as low as 10 °C.

Experimental Section

^{1}H NMR spectra were determined on a Varian T-60 spectrometer in $CDCl_3$. Small variations in δ values were observed for a given group depending on other components where mixtures were involved, slight temperature changes, etc.

IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer.

Bis(methylsulfonoxymethyl) Ether (1). A. From *s*-Trioxane. Acetyl methanesulfonate[12] (285.2 g, 2.06 mol, undistilled) was transferred by syringe to a dry-N_2-filled flask fitted with thermometer, stirrer, N_2 inlet, and vacuum take-off. The anhydride was cooled to −5 °C, and 92.9 g (1.03 mol) of trioxane was added over a 10-min period with good stirring at <0 °C. When solution was complete (ca. 20 min) it was heated slowly to 90 °C, with a 0.5-mm vacuum applied when the temperature reached 35 °C. Heating, with stirring under vacuum, was continued for 24 h,[13] during which time 118.5 g (90%) of methylene diacetate, containing a small amount of bis(acetoxymethyl) ether, was collected in a cold trap. The brown reaction mixture was brought to ambient conditions under dry N_2, dissolved in 120 mL of dry THF, treated with carbon, and filtered. The filtrate was seeded and cooled to −35 °C. The crystalline product was collected under N_2 in a glove box, washed with cold THF, then ether, and dried, yield 168.4 g (70%), mp 52–58 °C. It was stored in a well-sealed container at −35 °C. Alternatively, isolation by distillation using a short-path pot still [pot temperature 105–122 °C (7–10 μ)] gave a 60% yield of pure compound, mp 57–59 °C.

Anal. Calcd for $C_4H_{10}O_7S_2$: C, 20.5; H, 4.3; S, 27.4. Found: C, 20.3; H, 4.9; S, 27.6. NMR δ 3.13 (s, 6 H), 5.52 (s, 4 H).

B. With Methanesulfonic Acid Catalysis. In a reaction using the procedure of A above 5 mol % (3.5% by weight based on the mixed anhydride) of methanesulfonic acid was added to the freshly prepared acetyl methanesulfonate just before the trioxane. After 3.5 h of heating the reaction at 90 °C at 0.5 mm pressure, an NMR of the reaction mixture was essentially identical with the NMR of the reaction without methanesulfonic acid (A) after 24 h.

C. From *s*-Tetroxane. Substitution of an equivalent amount of tetroxane[14] for the trioxane in A gave a similar yield of **1**. The byproduct in this case consisted of nearly equal amounts of bis(acetoxymethyl) ether (**8**) and methylene diacetate.

D. From Trioxymethylene Diacetate. To 9.15 g (0.066 mol) of acetyl mesylate at 0 °C was added 12.7 g (0.066 mol) of trioxymethylene diacetate.[15] After stirring for 18 h at 25 °C NMR indicated the presence of approximately 4 mol % **1** (16% by weight of theory), and 31 mol % (62% by weight of theory) of the expected mixed ester **7** (methylene peaks at δ 5.40 and 5.47). Distillation, using a short-path pot still, produced 4.5 g (29% yield) of **1**, mp 57–59 °C, and lower boiling fractions consisting almost entirely of methylene diacetate and **8** (methylene peak δ 5.33).

E. From Bis(acetoxymethyl) Ether (8). 1. 1:1 Reaction. Acetyl methanesulfonate (27.03 g, 0.196 mol) was placed in the apparatus described above (A) and cooled to 0 °C. Neat **8** (31.73 g, 0.196 mol) was added dropwise, and the solution was allowed to warm to 25 °C and stirred for 30 min. The reaction was slowly heated to 75 °C under reduced pressure, held there for 3.5 h, and cooled to 25 °C, and the vacuum was broken under dry N_2. The NMR spectrum of the *crude* product (34.9 g) contained eight singlets assigned to **1** (3.13, 5.51), **7** (2.13, 3.10, 5.40, 5.47), and **8** (2.09, 5.35). The trap contents gave a singlet at 2.23 ppm in the NMR spectrum and the IR spectrum contained anhydride bands at 1750 and 1825 cm^{-1}. Based on the integral of the four singlets in the δ 5 region of the NMR the approximate composition of the crude product mixture was 33% (by weight) **1**, 51% **7**, and 16% **8**.

A 25-g portion of the crude product was distilled in an oil-jacketed pot still to give 8.7 g (53% of theoretical yield) (105–121 °C, 8–3 μ) of the dimesylate **1**. Only traces of the mixed ester **7** were seen in the NMR spectrum of the forerun.

2. 2:1 Reaction. Using the procedure described above, 53.54 g (0.388 mol) of acetyl methanesulfonate was reacted with 31.42 g (0.194 mol) of **8**. To ensure a nearly complete reaction the heating period of 65 °C under vacuum was extended to 32 h. Based on the NMR, the crude product mixture contained 70% (by weight) **1**, 27% **7**, and 3% **8**. The reaction mixture was worked up as in A to give 14.8 g (33%) of **1** (mp 56–59 °C).

F. Attempt with Paraformaldehyde. To 69 g (0.50 mol) of acetyl mesylate, in the system already described, was added 22.5 g (0.75 mol of CH_2O) of paraformaldehyde. The mixture was slowly warmed to 40 °C and after 16 h evacuated to 0.5 mmHg (vigorous bubbling). The temperature was raised to 75 °C during 4 h and finally heated at 80 °C for 4 h. Distillation of the reaction mixture in a short-path pot still produced a 25.0-g main fraction [pot temperature 76–82 °C (11–18 μ)] consisting almost entirely of methylene dimesylate. Analysis by NMR of the total distillate showed that it consisted of ca. 75% of the latter, 7% of **1**, and some methanesulfonic acid and anhydride. Recrystallization from THF–ether produced 17.6 g of methylene dimesylate: mp 74–74.5 °C (lit.[10] 75–76 °C); NMR δ 3.20 (s, 6 H), 5.78 (s, 2 H).

Bis(ethylsulfonoxymethyl) Ether. Acetyl ethanesulfonate[16] (76.1 g, 0.50 mol) was placed in the apparatus described for the preparation of **1** above (A) and cooled to −5 °C, and 22.5 g (0.25 mol) of trioxane was added over a 20-min period. After the solution was heated at 60 °C with stirring under dry N_2 for 1 h, a 0.5-mm vacuum was applied and the reaction continued at 80 °C for 18 h. The dark brown reaction mixture was brought to ambient conditions under dry N_2. Distillation in a short-path pot still [pot temperature 110–113 °C (3–8 μ)] afforded 23.8 g (36%) of colorless liquid product: NMR δ 1.43 (t, 6 H), 3.22 (q, 4 H), 5.50 (s, 4 H).

Anal. Calcd for $C_6H_{14}O_7S_2$: C, 27.5; H, 5.4; S, 24.4. Found: C, 27.5; H, 5.7; S, 24.0.

Attempted Preparation of Bis(*p*-tolylsulfonoxymethyl) Ether

(2). **A. From Bis(chloromethyl) Ether.**[17] A 2:1 mixture of silver tosylate and BCME dissolved in dry acetonitrile was held at 25 °C for 18 h, protected from light, and filtered. Evaporation of the solvent at 30 °C and recrystallization of the crystalline residue from dry acetone gave a 36% yield of *p*-toluenesulfonic anhydride: mp 124–129 °C (lit.[18] 125 °C); NMR δ 2.51 (s, 6 H), 7.86 (m, 8 H).

B. From Acetyl Tosylate. Several attempts to isolate the ditosylate from the reaction of acetyl tosylate and trioxane were unsuccessful, apparently owing to instability of the product. A strong singlet at δ 5.33 in the NMR spectra of reaction mixtures held at 25 °C, and before attempted isolation, was indicative of product formation.[19] The only solid isolated from such mixtures was some unreacted acetyl tosylate.

Reaction of 1 with Mercaptans. A. 7-Oxa-5,9-dithiatridecane. To a suspension of sodium butylmercaptide, prepared from 1.53 g of butanethiol and 0.6 g of NaH (1.2 g of 50% oil suspension) in 40 mL of dry THF, was added under a nitrogen atmosphere at 0 °C a solution of 2.0 g of **1** in 10 mL of THF. After 2.5 h at 25 °C 2 mL of MeOH was added, and after filtration and evaporation the residue was extracted with ethyl acetate. Evaporation produced 1.9 g (85%) of product, the NMR of which matched that of an authentic sample: δ 0.88 (t, 6 H), 1.5 (m, 8 H), 2.53 (t, 4 H), 4.7 (s, 4 H).

B. 5-Oxa-3,7-dithia-1,9-nonanediol. To a suspension of sodium isopropoxide, under nitrogen, prepared from 9.2 g (0.40 mol) of sodium and 500 mL of dry 2-PrOH,[20] was added 31 g (0.40 mol) of 2-mercaptoethanol, followed by the dropwise addition of a solution of 46.5 g of **1** in 200 mL of dry THF at 25–30 °C. After 1 h the mixture was neutralized with concentrated HCl in 2-PrOH, charcoal added, and the sodium mesylate removed by filtration. Evaporation yielded 32.2 g (81%) of pale yellow oil, the NMR of which matched that of an authentic sample prepared from BCME: δ 2.77 (t, 4 H), 3.72 (t, 4 H), 4.75 (s, 4 H).

Reaction of 1 with Toluene. Addition of 11.7 g of **1** to 100 mL of dry toluene at 25 °C produced a dark brown mixture which after 18 h was poured into water. The organic layer upon evaporation yielded 14.7 g (76%) of a light oil identified by NMR and mass spectroscopy as a mixture of ditolylmethanes: NMR δ 2.24 (3 s, 6 H), 3.89 (2 s, 2 H), 7.12 (m, 8 H). The mass spectrum was run on a Perkin-Elmer RMS-4 instrument at 70 eV with all-glass reservoir inlet at 175 °C, ion source 200 °C, acceleration voltage 1500: *m/e* (rel intensity) 197 (14), 196 (82), 182 (15), 181 (100), 180 (8), 179 (10), 178 (11), 166 (20), 165 (24), 105 (15), 104 (40), 77 (10).

Reaction of 1 with Amines. A. Pyridine. A solution of 8.8 g (0.038 mol) of **1** in 20 mL of dry MeCN was added dropwise to a solution of 6 g (0.075 mol) of pyridine in 40 mL of MeCN at 25 °C. After 1 h the mixture was cooled to −40 °C and filtered. Recrystallization from MeOH produced 11.1 g (79%) of 2-oxapropane-1,3-bis(pyridinium mesylate), mp 187–189 °C.

Anal. Calcd for $C_{14}H_{20}N_2O_7S_2$: C, 42.8; H, 5.1; N, 7.1. Found: C, 42.5; H, 5.0; N, 7.1.

B. Pyrrolidine. To a solution of 8.09 g (0.114 mol) of pyrrolidine in 75 mL of dry ether was added 6.66 g (0.028 mol) of **1**. The suspension gradually became pasty. After 2 h the ether solution was decanted and evaporated to a pale oil (2.9 g, 66%) which proved to be the aminal, dipyrrolidinomethane: NMR δ 1.78 (t, 8 H), 2.63 (t, 8 H), 3.28 (s, 2 H).

Reaction of 1 with 1-Butanol. A 5.7-g (0.024 mol) sample of **1** was dissolved in 10 mL of dry MeCN and added dropwise to 50 mL of dry 1-butanol at 25 °C. The reaction mixture was stirred for 1 h, 5 g of anhydrous sodium bicarbonate added, and the mixture filtered. The crude product solution, analyzed by gas chromatography–mass spectroscopy, contained the formal, dibutoxymethane. The instrument used was an AEI MS-30 equipped with a 0.125 in. × 7 ft glass column with a 10% Carbowax 20M packing. A membrane separator at 150 °C was used, ion source temperature 200 °C, spectrum run at 70 eV. The gas chromatography column was held at 50 °C. For the major peak of the chromatogram: *m/e* (rel intensity) 159 (2), 117 (2), 103 (3), 101 (2), 87 (52), 57 (100).

Reaction of 1 with Sodium *n*-Butoxide. Sodium (1.12 g, 0.049 mol) was reacted with 50 mL of dry 1-butanol and a solution of 5.7 g (0.0244 mol) of **1** in 10 mL of dry MeCN added dropwise, with stirring at 25 °C. After 0.5 h the precipitated sodium mesylate was removed by filtration and the crude product solution analyzed by gas chromatography–mass spectroscopy. The two major peaks, area ratio ~2:1, were examined by mass spectroscopy. The larger peak was identified as bis(butoxymethyl) ether and the smaller peak was tentatively identified as bis(butoxymethoxy)methane because of the *m/e* 147 peak ($BuOCH_2OCH_2OCH_2^-$) in the mass spectrum. The AEI MS-30 was used as above with the Carbowax 20M column held at 50 °C for 2 min, then heated at 10 °C/min to 150 °C. Bis(butoxymethyl) ether: *m/e* (rel intensity) 189 (1), 159 (8), 117 (49), 116 (22), 103 (16), 101 (6), 87 (47), 86 (39), 57 (100), 56 (78). Bis(butoxymethoxy)methane: *m/e* (rel intensity) 189 (1), 159 (4), 147 (1), 117 (8), 116 (3), 103 (6), 101 (3), 87 (98), 57 (100), 56 (25).

Acknowledgment. We are grateful to Mr. M. Fichtner for help with the synthetic work, Mr. D. Cox for distillations, and Mr. D. Maier and Mr. R. Gohlke for mass spectral determinations.

Registry No.—**1**, 62609-70-5; **3**, 5539-53-7; **7**, 62609-71-6; **8**, 4082-91-1; trioxane, 110-88-3; tetroxane, 291-15-6; trioxymethylene diacetate, 62609-72-7; paraformaldehyde, 30525-89-4; methylene dimesylate, 156-72-9; bis(ethylsulfonoxymethyl) ether, 62609-73-8; acetyl ethanesulfonate, 6744-63-4; 7-oxa-5,9-dithiatridecane, 62609-74-9; sodium butylmercaptide, 4779-86-6; 5-oxa-3,7-dithia-1,9-nonanediol, 36727-72-7; 2-mercaptoethanol, 60-24-2; toluene, 108-88-3; ditolylmethane, 1335-47-3; pyridine, 110-86-1; 2-oxapropane-1,3-bis(pyridinium mesylate), 62609-75-0; pyrrolidine, 123-75-1; dipyrrolidinomethane, 7309-47-9; 1-butanol, 71-36-3; dibutoxymethane, 2568-90-3; bis(butoxymethyl) ether, 5614-25-5; bis(butoxymethoxy)methane, 62609-76-1.

References and Notes

(1) *Fed. Regist.*, **39**, Section 1910.93h (Jan 29, 1974).
(2) M. H. Karger and Y. Mazur, *J. Am. Chem. Soc.*, **91**, 5663 (1969).
(3) B. N. Ames, J. McCann, and E. Yamasaki, *Mutat. Res.*, **31**, 347 (1975).
(4) Private communication from Litton Bionetics, Inc.
(5) J. McCann and B. N. Ames, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 5135 (1975).
(6) A reaction of trioxane with methanesulfonic anhydride was found to give a gross mixture of products with evidence of the presence of **1**, but it was not isolated (J. P. Cleveland, private communication).
(7) P. Y. Johnson and J. Zitsman, *J. Org. Chem.*, **38**, 2346 (1973).
(8) (a) M. H. Karger and Y. Mazur, *J. Am. Chem. Soc.*, **90**, 3878 (1968); (b) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 532 (1971).
(9) Polar solvents promote disproportionation of the mixed anhydrides to the symmetrical counterparts.[12]
(10) W. D. Emmons and A. F. Ferris, *J. Am. Chem. Soc.*, **75**, 2257 (1953).
(11) *Chemical Abstracts* lists several papers (1965–1971) dealing with studies of insect sterilization, mutagenic, antitumor, and related effects of this potent compound.
(12) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).
(13) When 2.5% by weight of methanesulfonic acid was present the reaction time was reduced to 4 h. Heating for 5 h at 110 °C gave a 52% yield of slightly less pure product.
(14) *s*-Tetroxane was obtained from Tokyo Kasei, Japan.
(15) J. Tomiska and E. Spousta, *Angew. Chem.*, **74**, 248 (1962).
(16) Prepared from ethanesulfonic acid and acetyl chloride according to ref 12 and used without purification.
(17) Use now restricted.[1]
(18) H. Meyer, *Justus Liebigs Ann. Chem.*, **433**, 335 (1923).
(19) The δ 5.33 value for the methylene protons vs. δ 5.52 for those in **1** is consistent with the relative values for the methyl protons in methyl tosylate (3.70 ppm) and methyl mesylate (3.88 ppm).
(20) EtOH has also been used successfully but a reaction temperature of −20 °C must be used to avoid solvolysis.

Intramolecular Cyclization of 2-Biarylsulfonyl Azides

Rudolph A. Abramovitch,* Therinadar Chellathurai, Ian T. McMaster, Takao Takaya, Christopher I. Azogu, and Danny P. Vanderpool

Departments of Chemistry, University of Alabama, University, Alabama 35486, and University of Saskatchewan, Saskatoon, Saskatchewan, Canada

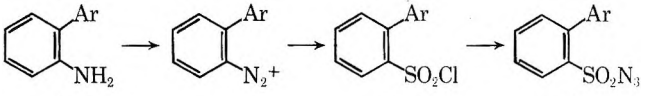
Received January 17, 1977

Thermolysis of biphenyl- and 4′-bromobiphenyl-2-sulfonyl azides in various solvents gave the expected sultams (**6**) together with solvent insertion or hydrogen abstraction products, depending on the solvent and reaction conditions. In no case could an *N*-sulfonylazepine be isolated. No rearrangement via a spiro intermediate occurred in the cyclization of 4′-bromobiphenyl-2-sulfonylnitrene, but the bromophenyl nucleus was less reactive than the corresponding phenyl, leading to appreciably more competition by solvent for the nitrene. No cyclization occurred onto sulfur in the thermolysis of 2-*o*-nitrenosulfonylphenylthiophene, thieno[3,2-*c*]-6*H*-benzo[*e*][1,2]thiazine 5,5-dioxide (**25**) being obtained together with solvent insertion product. Photolysis of biphenyl-2-sulfonyl azide and of biphenyl-2-sulfonyliminotriphenylphosphonium ylide did not lead to any sultam, but irradiation of the azide in the presence of di-*tert*-butyl sulfide did produce a small amount of sultam together with 2-biphenyl *tert*-butyl sulfone and 2-biphenyl disulfide.

When this work was initiated[1] it was established that while arylnitrenes could undergo intramolecular aromatic substitution to give five- and six-membered heterocycles readily,[2,3] no examples of their undergoing intermolecular aromatic substitution were known.[3] On the other hand, sulfonylnitrenes do undergo intermolecular aromatic substitution readily.[3,4] It has since been established that if strongly electron-withdrawing substituents are present in the aromatic nucleus making the nitrene more electrophilic then the latter will undergo intermolecular aromatic substitution reactions.[5-8] It seemed likely, therefore, that suitably ortho-substituted arylsulfonylnitrenes would undergo intramolecular cyclization to give cyclic sulfonamides. In this paper, the intramolecular cyclizations of 2-biarylsulfonyl azides are described.

Results and Discussion

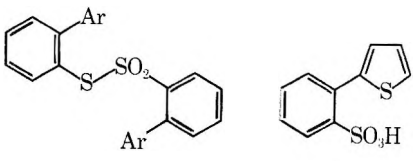
The azides (**3**) were obtained from the corresponding sulfonyl chlorides (**2**) which, in turn, could be prepared from the appropriate diazonium salt via a modified Meerwein synthesis.[9,10] In these latter reactions with both 2-amino- (**1a**) and 2-amino-4′-bromobiphenyl (**1c**), thiosulfonates **4a** (14%) and **4c** (20%) were formed as by-products. This is consistent with the formation of aryl radicals which are trapped by SO_2 to give $ArSO_2$·. These react with ArS·, formed by disproportionation, to give **4**. In the reaction with **1d** the corresponding sulfonic



1 2 3

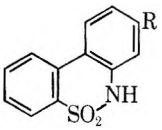
a, Ar = Ph
b, Ar = 2,4,6-$Me_3C_6H_2$
c, Ar = *p*-BrC_6H_4
d, Ar = 2-thienyl

acid (**5**) was isolated besides the sulfonyl chloride and also probably arises by disproportionation of $ArSO_2$· to $ArSO_3$· and subsequent reactions.[11,12]

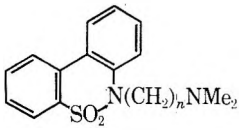


4 5

Thermolysis of biphenyl-2-sulfonyl azide (**3a**) in dodecane at 175 °C gave the desired sultam **6a** (73%)[13] which was N-alkylated via the thallium salt to give *N*-2-dimethylaminoethyl- (**7**) and *N*-3-dimethylaminopropyl-6*H*-dibenzo[*c*,*e*]-[1,2]thiazine 5,5-dioxide (**8**). When the thermolysis was carried out at 150 °C, the yield of sultam **6a** was much lower (38%) and



6a, R = H
b, R = Br



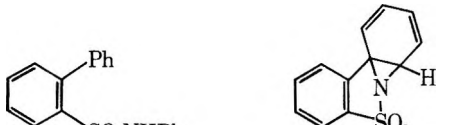
7, *n* = 2
8, *n* = 3

a mixture of (*N*-dodecyl)biphenyl-2-sulfonamides was obtained (15%), resulting from the insertion of the sulfonylnitrene into the solvent.

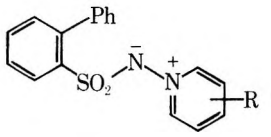
When methanesulfonyl azide is heated in benzene or substituted benzenes an *N*-mesylbenzaziridine is formed which, under kinetic control conditions, ring-expands to an *N*-mesylazepine. Though an azepine cannot be detected as such at 120 °C, it can be trapped by tetracyanoethylene present in the reaction mixture to give the [4 + 2] π adduct. At lower temperatures, the azepine is thermally stable and can be isolated (albeit in very low yield because of low conversion of azide to nitrene at these temperatures).[6] When the thermolysis of **3a** in dodecane was carried out in the presence of TCNE no Diels–Alder adduct could be characterized, though two solids, mp >300 °C, were isolated but could not be purified or identified. On the other hand, no sultam **6a** was formed either. The only products identified were the above mixture of (*N*-dodecyl)biphenyl-2-sulfonamides (12%) and the hydrogen-abstraction product, biphenyl-2-sulfonamide (10%). It would appear that either the sulfonylnitrene is diverted from attacking the adjacent aromatic nucleus by TCNE, which appears somewhat unlikely, or else an *N*-sulfonylazepine is formed and trapped and this then gives rise to the high-melting unidentified products. The TCNE may also catalyze singlet → triplet conversion of the nitrene (though the reason for this is unclear), which would explain the formation of hydrogen-abstraction product.

The best yields of sultam **6a** (80.6%) were obtained when **3a** was heated in cyclohexane at 120 °C. Interestingly, no C–H insertion product, (*N*-cyclohexyl)biphenyl-2-sulfonamide, could be detected in this reaction. An attempt to isolate a possible fused *N*-sulfonylazepine by carrying out the thermolysis at 81 °C for 35 days gave only a small yield of sultam together with some tar. Thermolysis in benzene at 120 °C gave a mixture of sultam (36.8%) and intermolecular substitution product, biphenyl-2-sulfonanilide (**9**) (21.8%). This suggests

that the transition state leading to intermediate **10** is sufficiently strained that competition from intermolecular attack



9 **10**

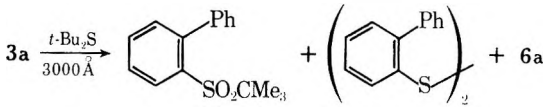


11, R = H, 2-Me, 2,6-Me_2, 2,4,6-Me_3

on benzene becomes appreciable (vide infra). After 35 days at 80 °C in benzene, the azide gave low yields of the sultam **6a** and of **9**, but no azepines could be detected. This contrasts with the behavior of methanesulfonyl azide[6] and ferrocene-1,1′-disulfonyl azide.[14]

As expected,[15] decomposition of **3a** in cyclohexane occurred at room temperature in the presence of diiron nonacarbonyl and did not lead to any products of intramolecular cyclization, the main product being biphenyl-2-sulfonamide. Copper-catalyzed decomposition in cyclohexane or methanol was much slower but led to the same result. Methanesulfonyl azide was similarly decomposed at 80 °C in benzene in the presence of copper to give methanesulfonamide but no product of addition to benzene, confirming[16] that the reactive species is probably a copper nitrenoid. On the other hand, thermolysis of **3a** in pyridine and some methylpyridines gave the corresponding ylides **11** (18–52%) together with **6a**.

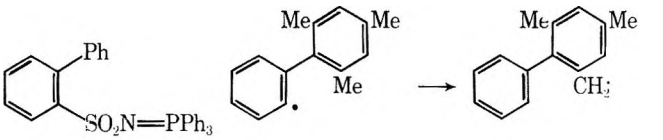
Photolysis of aliphatic and aromatic (except ferrocenyl[17]) sulfonyl azides in nonprotic, nonpolar solvents such as benzene or cyclohexane produces insoluble, high-melting materials that have not been characterized.[6,18,19] Only very small amounts of *N*-mesylazepine were formed in the photolysis of methanesulfonyl azide in benzene.[6] Photolysis (2537 Å) of **3a** in cyclohexane gave a high-melting product which could not be purified, but no azepine or sultam. On the other hand, irradiation of *p*-toluenesulfonyl azide in the presence of 4-butylthiacyclohexane gave a low yield (2–3%) of epimeric sulfimines,[20] while photolysis in the presence of dimethyl sulfide gave the sulfimine in poor yield.[18] Since sulfides seem to assist photolytic generation of singlet[20] sulfonylnitrenes the azide **3a** was photolyzed (3000 Å) in deoxygenated cyclohexane containing di-*tert*-butyl sulfide to give 2-biphenyl *tert*-butyl sulfone (**12**, 4%), 2-biphenyl disulfide (**13**, 20%), and sultam **6a** (3%), together with a tan-colored polymer. Thus, some singlet nitrene seems to be produced under those conditions though a major pathway probably involves formation of $ArSO_2$· radicals.



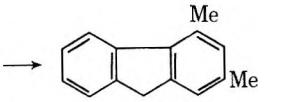
12 **13**

Heating biphenyl-2-sulfonamide in dodecane at 150 °C gave unchanged amide as did its attempted oxidation with lead tetraacetate in acetic acid. In neither case was any sultam detected. It has been reported[21] that some *N*-alkylphosphinimines give nitrenes on photolysis. Irradiation of biphenyl-2-sulfonyliminotriphenylphosphonium ylide (**14**) led mainly to recovered starting material.

Thermolysis of 2′,4′,6′-trimethylbiphenyl-2-sulfonyl azide (**3b**) in cyclohexane gave only one product that could be characterized, namely, 2,4-dimethylfluorene (**15**, 35%). This



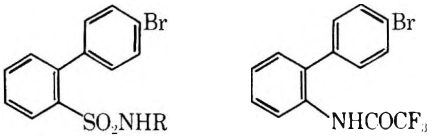
14



15

can conceivably arise from the $ArSO_2$· radical, loss of SO_2 to the aryl radical,[1] intramolecular hydrogen abstraction from the adjacent 2′-methyl group, and intramolecular homolytic substitution by the benzyl radical so formed. Other routes are also possible.

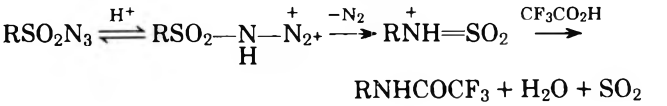
When 4′-bromobiphenyl-2-sulfonyl azide (**3c**) was thermolyzed in cyclohexane, two products were isolated: the sultam **6b** (5%) and the solvent insertion product, 4′-bromo-(*N*-cyclohexyl)biphenyl-2-sulfonamide (**16**, 27%). This is in marked contrast to the behavior of **3a** in the same solvent, when a high yield of **6a** was formed and no solvent insertion product was isolated. This suggests that the bromophenyl group is deactivated compared with phenyl toward intramolecular attack by sulfonylnitrene, allowing solvent to compete effectively with the aromatic nucleus for the nitrene's favors. This can readily be understood when it is remembered that $\frac{Cl}{H}K$ = 0.44 for attack by $MeSO_2\ddot{N}$ on chlorobenzene relative to benzene,[6] though one would perhaps have expected the product ratios to be reversed since a benzene "double bond" has been shown to be approximately eight times more reactive toward a sulfonylnitrene than a C–H bond in cyclohexane.[22] Indeed, when the thermolysis was carried out in benzene at 120 °C, **6b** (27%) and 4′-bromobiphenyl-2-sulfonanilide (**17**, 47%) were obtained. Decomposition of **3c** in chlorobenzene at 130 °C gave the sultam **6b** (24%) and 4′-bromo-(*N*-*o*- (**18**, 10%) and -*p*-chlorophenyl)biphenyl-2-sulfonamide (**19**, 13%), the lower overall yields of **18** and **19** relative to **6b** being expected from the lower reactivity of chlorobenzene than benzene. Interestingly, when **3c** in benzene was heated with trifluoroacetic acid, the sultam **6b** (25%), the anilide **17**, and 4′-bromo-2-trifluoroacetamidobiphenyl (**20**, 4%) were obtained.



16, R = C_6H_{11}
17, R = C_6H_5
18, R = C_6H_4-*o*-Cl
19, R = C_6H_4-*p*-Cl

20

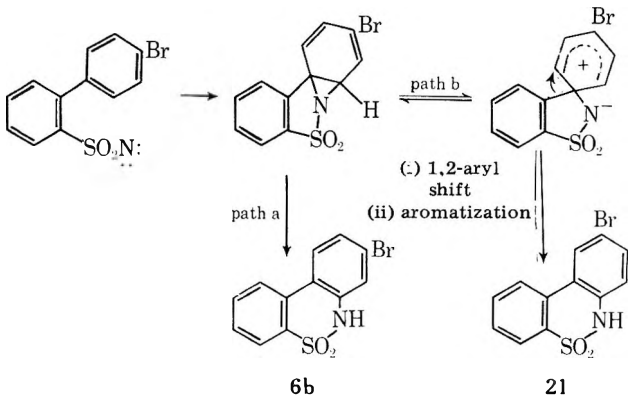
The latter undoubtedly arises by an acid-catalyzed Curtius-type rearrangement of the sulfonyl azide to give the sulfonylamine which is solvolyzed by the trifluoroacetic acid.



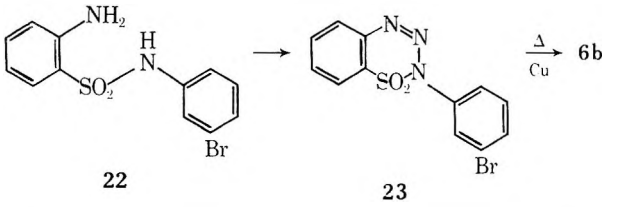
$$RNHCOCF_3 + H_2O + SO_2$$

An interesting point to be determined was the location of the bromine atom in the sultam. It was known[23] that intramolecular cyclization of some arylnitrenes leads to rearranged products via proposed spiro intermediates, and it was conceivable that the isomeric 9-bromosultam (**21**) could be

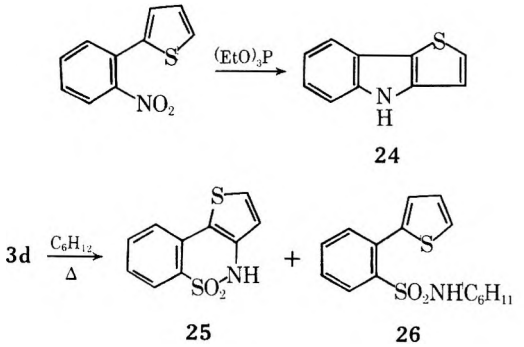
Scheme I



formed from the cyclization of **3c** (Scheme I). In the event, an authentic sample of **6b** was synthesized from 2-amino-*N*-(*m*-bromophenyl)benzenesulfonamide (**22**) via the thiatriazine (**23**) which, on heating with copper, gave the desired **6b**, identical with the product obtained from the sulfonylnitrene. Path a in Scheme I thus appears to be followed without any rearrangement according to path b.



Thermolysis of diphenyl sulfide 2-sulfonyl azide gave 3-phenylbenzo-1,3,2-dithiazole 1,1-dioxide resulting from cyclization at divalent sulfur.[1] On the other hand, cyclization of 2-azidophenylthiophene gave only 4*H*-thieno[3,2-*b*]indole (**24**), no cyclization at sulfur being observed,[24] an observation we have now confirmed. Similarly, thermolysis of **3d** in cyclohexane gave thieno[3,2-c]-6*H*-benzo[*e*]-1,2-thiazine 5,5-dioxide (**25**) in good yield, together with *N*-cyclohexyl-*o*-(2-thienyl)benzenesulfonamide (**26**), but no product of cyclization at the thiophene sulfur atom. Again, contrary to the behavior of 2-*o*-nitrophenylpyridine, which on deoxygenation with ferrous oxalate[25] or triethyl phosphite[26] gives mainly attack of the arylnitrene at the pyridine nitrogen atom rather than at a ring carbon, deoxygenation of 2-*o*-nitrophenylthiophene gave only **24**.



Experimental Section

Melting points are uncorrected.

Biphenyl-2-sulfonyl Azide. Biphenyl-2-sulfonyl chloride[10] (2.65 g) in ice-cold acetone (25 mL) was treated with a cold solution of sodium azide (1 g) in water (5 mL) portionwise. The solution was stirred for 1 h and diluted with water (50 mL), and the sulfonyl azide which separated as an oil solidified on stirring (2.53 g, 93%): mp 60–61 °C (from methanol); IR (KBr) 2120 (s) (N_3), 1360, 1160 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.58; H, 3.50; N, 16.20. Found: C, 55.49; H, 3.28; N, 15.91.

Thermolysis of Biphenyl-2-sulfonyl Azide. A. In Dodecane. (a) The azide (0.4 g, 0.002 mol) was suspended in *n*-dodecane (18 mL, 0.2 mol), and the system was degassed and then covered with oxygen-free dry nitrogen. The mixture was heated slowly and stirred until the bath temperature reached 175 °C when nitrogen evolution had ceased. The cooled dark solution deposited 6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide (0.26 g, 72.9%), mp 198–200.5 °C, which was purified by chromatography on a column of alumina and recrystallized from benzene: mp 197–199 °C (lit.[13] mp 196 °C); IR (KBr) 3200 (m) (NH), 1300 (s), 1150 cm^{-1} (s) (SO_2).

Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.34; H, 3.92; N, 6.06. Found: C, 62.61; H, 4.22, N, 5.88.

(b) When the thermolysis of the azide (2.59 g) in *n*-dodecane (25 mL) was repeated at 150 °C for 21 h and the reaction mixture was chromatographed on alumina, elution with ether–light petroleum (1:1 v/v) gave a yellow gum (0.58 g) which appears to be a mixture of isomeric (***N*-dodecyl)biphenyl-2-sulfonamides** (15%): IR (film) 3370–3290 (NH), 3060, 3030, 2950, 2920, 2850, 1320, 1175 cm^{-1} (SO_2); NMR (CCl_4) δ 8.04 (m, 1 H, aromatic), 7.53–7.15 (m, 8 H, aromatic), 4.70 (br, NH, exchangeable with D_2O), 3.08 (br s, CH), 1.40–0.60 (m, 24 H).

Anal. Calcd for $C_{24}H_{35}NO_2S$: C, 71.88; H, 8.80. Found: C, 71.95; H, 8.62.

Elution with ether–methanol (4:1 v/v) gave a light brown solid (1.95 g) which, on recrystallization from benzene, gave the above sultam (0.88 g, 38%), mp 200–202 °C.

(c) The thermolysis of the azide (1.29 g) in *n*-dodecane (25 mL) at 150 °C for 20.5 h was repeated in the presence of tetracyanoethylene (0.67 g) and the products were chromatographed on a column of neutral alumina (160 g). Elution with ether–light petroleum (1:1 v/v) gave the mixture of (*N*-dodecyl)biphenyl-2-sulfonamides (0.237 g, 12%). Elution with ether–methanol (2:3 v/v) gave a dark gum (0.317 g) which, on repeated recrystallization from ethanol, gave a light brown solid (0.022 g), mp >300 °C, which could not be characterized. Elution with methanol gave a dark solid (0.36 g) which, after recrystallization from ether–ethanol, gave a buff solid (0.27 g): mp >300 °C; IR (KBr) 3450 (NH), 3070, 1600, 1330, 1310, 1215, 1160, 1145, 1118, 1085, 705 cm^{-1}; no band due to C≡N was observed and the product could not be characterized further.

If the crude reaction mixture was chromatographed on a column of basic alumina, elution with methanol gave biphenyl-2-sulfonamide (10%), identical with an authentic sample (see below).

B. In the Absence of Solvent. The azide (0.29 g) was heated under nitrogen in a sealed tube at 120 °C for 48 h, and the product then chromatographed on neutral alumina (20 g) to give the sultam (0.17 g, 61%), mp 198–200 °C.

C. In Cyclohexane at 120 °C. The azide (1 g) in cyclohexane (20 mL) was heated under nitrogen in a sealed tube at 120 °C for 72 h. Chromatography of the products on a column of silica gel (70 g) gave recovered azide (0.15 g, 15%), the sultam (0.65 g, 80.8%), and an unidentified dark brown solid (0.038 g), mp >300 °C (insoluble in most common solvents). No (*N*-cyclohexyl)biphenyl-2-sulfonamide was detected (for authentic sample, see below).

D. In Cyclohexane at 81 °C. The azide (1 g) in cyclohexane (100 mL) was heated at 81 °C for 35 days under dry nitrogen. A brownish-black intractable solid deposited on the sides of the reaction vessel. Workup as above gave starting azide (0.78 g, 78%) and the sultam (0.06 g, 30.5%), but no azepine derivative.

E. In Benzene at 120 °C. The azide (0.8 g) in benzene (12 mL) was heated in a glass-lined bomb at 120 °C for 72 h. A black, intractable solid was formed on the sides of the vessel. The solution was evaporated and the residue chromatographed on a column of silica gel (60 g). Elution with benzene gave starting azide (0.11 g, 13.75%). Elution with benzene–ether (1:1 v/v) gave **biphenyl-2-sulfonanilide** (0.18 g, 21.8%): mp 135–136 °C (dilute EtOH); IR (KBr) 3375 (s) (NH), 1340, 1178 (SO_2), 770 (s), 760 (s), 742 (m), 708 cm^{-1} (m), identical with that of the authentic sample prepared below; *m/e* 309 ($M^{+\cdot}$).

Anal. Calcd for $C_{18}H_{15}NO_2S$: C, 69.87; H, 4.89. Found: c, 69.68; H, 5.07.

Further elution with benzene–ether (1:1 v/v) gave the sultam (0.24 g, 36.8%), mp 198–200 °C.

F. In Benzene at 80 °C. This was carried out for 35 days as for the reaction in cyclohexane to give biphenyl-2-sulfonanilide (2.2%), the sultam (23.5%), and starting azide (81%).

G. In Cyclohexane with Diiron Nonacarbonyl at 25 °C. The azide (1 g) in cyclohexane (80 mL) was stirred at room temperature for 2 days with $Fe_2(CO)_9$ (0.73 g) under N_2. The mixture was filtered, the solid was washed with acetone, and the combined filtrates were evaporated and chromatographed on a column of silica gel (40 g) to give biphenyl-2-sulfonamide (81.5%), mp 118–119 °C, identical with

an authentic sample. The residue, mp >300 °C, did not show any SO_2 or CO absorptions in the infrared.

H. In Cyclohexane with Gatterman Copper at 81 °C. The azide (1 g) in cyclohexane (80 mL) was heated under N_2 with freshly prepared Gatterman copper for 10 days. Workup gave unchanged azide (0.42 g, 42%) and biphenyl-2-sulfonamide (0.41 g, 78.6%).

When methanesulfonyl azide was heated in benzene at 80 °C for 84 h in the presence of copper powder 62% was recovered unchanged and methanesulfonamide (67%, based on azide consumed) was isolated.

I. In Pyridines. The azide (3 g) in dry pyridine (80 mL) was boiled under reflux under N_2 for 48 h. The solvent was evaporated and the residue chromatographed on a column of silica gel (60 g). Elution with light petroleum (bp 30–60 °C) gave starting azide (0.6 g, 26.4%). Elution with methanol gave ***N*-(biphenyl-2-sulfonylimino)pyridinium ylide** (1.5 g, 52.2%): mp 213–214 °C (from MeOH); IR (KBr) 1295 (s), 1162 (s) (SO_2), 765 (s), 697 cm^{-1} (s); *m/e* 310 ($M^{+}\cdot$).

Anal. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.78; H, 4.55. Found: C, 65.93; H, 4.60.

The same thermolysis was repeated but in 2-picoline at 115–120 °C for 48 h to give starting azide (10%), sultam (54.8%), and ***N*-(biphenyl-2-sulfonylimino)-2-picolinium ylide** (32.5%): mp 164–165 °C (from benzene–light petroleum); IR (KBr) 1285, (s), 1145 (s), (SO_2), 760 (m), 695 cm^{-1} (m); *m/e* 324 ($M^{+}\cdot$).

Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97. Found: C, 66.66; H, 5.06.

The thermolysis in 2,6-lutidine gave starting azide (6.7%), sultam (44%), and ***N*-(biphenyl-2-sulfonylimino)-2,6-dimethylpyridinium ylide** (22%): mp 179–180 °C (from benzene–light petroleum); *m/e* 338 ($M^{+}\cdot$).

Anal. Calcd for $C_{19}H_{18}N_2O_2S$: C, 67.43; H, 5.36. Found: C, 67.50; H, 5.42.

The thermolysis in 2,4,6-collidine gave starting azide (10%), sultam (54%), and ***N*-(biphenyl-2-sulfonylimino)-2,4,6-trimethylpyridinium ylide** (17.7%), mp 184–186 °C (from benzene–light petroleum), identical with the authentic sample prepared as described below.

J. In Methanol with Copper. A solution of the azide (1 g) in methanol (50 mL) was stirred with copper (freshly precipitated) and boiled under reflux for 16 h. The solution gradually turned blue. Workup and chromatography on silica gel gave starting azide (0.01 g, 1%), biphenyl-2-sulfonamide (0.8 g, 89.8%), mp 118–119 °C, and a blue, crystalline solid (0.02 g), mp >300 °C [from benzene–light petroleum (bp 30–60 °C)]; IR (KBr) 3050 (w), 2925 (w), 1575 (w), 1450 (m), 1270 (s), (SO_2), 1120 (s), 985 (m), 850 (w), 755 (s), 700 cm^{-1} (m).

Anal. Found: C, 56.90; H, 4.13.

No structure can be assigned to this product at the present time.

Photolysis of Biphenyl-2-sulfonyl Azide. A. In Cyclohexane. The azide (1 g) in cyclohexane (200 mL) was irradiated in a quartz vessel at 26 °C for 19 h using 2537-Å light. The solution turned orange and an orange-brown pasty mass formed on the sides of the vessel. The reaction mixture was chromatographed on a column of basic alumina to give starting azide (0.15 g, 15%) and a product (0.65 g), mp 266–268 °C (from benzene–acetone), which could not be obtained sufficiently pure for analysis. When the irradiation was carried out for only 4 h, starting azide was recovered (92%).

B. In Cyclohexane and Di-*tert*-butyl Sulfide. The azide (0.286 g) in cyclohexane (50 mL) containing di-*tert*-butyl sulfide (0.21 mL) was deoxygenated and then photolyzed under dry N_2 for 2 h at 32 °C in a Rayonet reactor using 3000-Å lamps. A tan precipitate formed which showed no resolved bands in its infrared spectrum. The whole suspension was evaporated to dryness and subjected to preparative TLC on silica gel [cyclohexane–benzene (9:1 v/v) as developer] to give **2-biphenyl *tert*-butyl sulfone** as a colorless oil (8 mg, 4%): R_f 0.72; IR (KBr) 1360 (m), 1170 cm^{-1} (SO_2); NMR (CCl_4) δ 7.80 (m, 1, H ortho to SO_2), 7.2 (m, 8, ArH), 1.15 (s, 9, *t*-Bu); mass spectrum (70 eV) *m/e* (rel intensity) 274 (20, $M^{+}\cdot$), 218 (60, $M^{+}\cdot - C_4H_8$), 185 (100, $M^{+}\cdot - C_4H_9S$ or $M^{+}\cdot - C_4H_9O_2$).

Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.07; H, 6.57. Found: C, 69.80; H, 6.41.

2-Biphenyl disulfide (44 mg, 20%); R_f 0.5; mp 113.5–114 °C (EtOH) (lit.[27] mp 114 °C), undepressed on admixture with an authentic sample; mass spectrum (70 eV) *m/e* (rel intensity) 370 (76, $M^{+}\cdot$), 185 (93, $M^{+}\cdot - 185$), 184 (100, $M^{+}\cdot - 186$).

Recovered azide (140 mg, 49%), R_f 0.02.

Dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide (4 mg, 3%), R_f 0.05, identical with samples of the sultam obtained above.

The photolysis was repeated using equivalent amounts of azide and di-*tert*-butyl sulfide but in acetonitrile solution. Only a trace of sultam was isolated, together with 2-biphenyl disulfide (4%) and 2-biphenyl *tert*-butyl sulfone (10%). Photolysis of the azide in neat di-*tert*-butyl sulfide similarly yielded a trace of sultam, disulfide (17%), and sulfone (15%).

Biphenyl-2-sulfonamide. Biphenyl-2-sulfonyl chloride (5.05 g) in concentrated ammonium hydroxide solution (200 mL) was stirred at room temperature for 24 h. The solution was filtered, the filtrate acidified, and the amide (4.36 g, 94%), mp 121–122 °C (from aqueous EtOH), filtered: IR (KBr) 3340, 3280 (NH_2), 1330, 1170 cm^{-1} (SO_2).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.72. Found: C, 62.20; H, 4.91.

Biphenyl-2-sulfonanilide. It was prepared in 71.4% yield from biphenyl-2-sulfonyl chloride and aniline in hot benzene, mp 135–136 °C (dilute EtOH), identical with the sample obtained above.

***N*-Cyclohexylbiphenyl-2-sulfonamide** (60%) was prepared from biphenyl-2-sulfonyl chloride and cyclohexylamine in boiling benzene and had mp 96–97 °C (dilute EtOH).

Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.57; H, 6.71. Found: C, 68.23; H, 6.69.

***N*-(Biphenyl-2-sulfonylimino)-2,4,6-trimethylpyridinium Ylide.** 2,4,6-Trimethylpyrylium perchlorate (2.23 g) and biphenyl-2-sulfonyl hydrazide (2.48 g) [from biphenyl-2-sulfonyl chloride and 50% hydrazine hydrate in benzene at <20 °C (96%); mp 121 °C dec (MeOH); IR (KBr) 3480 (s), 3230 (s), 1340 (s), 1150 cm^{-1} (s); *m/e* 248 ($M^{+}\cdot$). Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87. Found: C, 58.40; H, 4.96] were boiled under reflux in absolute ethanol (150 mL) for 10 h and filtered hot to give recovered pyrylium salt (0.28 g, 13%). The filtrate was concentrated to about 30 mL and treated with 30% KOH solution (2 mL) at 0–5 °C. $KClO_4$ (1.04 g, 75%) separated and was filtered. The solution was evaporated to dryness onto basic alumina (10 g) and the residue chromatographed on a column of basic alumina (2.5 × 40 cm). Elution with ether and then with $CHCl_3$ gave the ylide (1.25 g, 36%): mp 184–185 °C (from benzene–cyclohexane), identical with the sample prepared above; mass spectrum *m/e* (rel intensity) 354 ($M^{+}\cdot + 2$, 6), 353 ($M^{+}\cdot + 1$, 25), 352 ($M^{+}\cdot$, 6.7), 288 (22), 135 (100), 121 (42), 107 (64), 106 (42), 79 (22); NMR ($CDCl_3$) δ 7.94 (m, 1, ortho to SO_2), 7.62 (m, 2), 7.35 (m, 6), 7.13 (s, 2, pyridine β protons), 2.49 (s, 6, 2,6-Me_2), 2.35 (s, 3, 4-Me).

Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 68.15; H, 5.72. Found: C, 68.32; H, 5.80.

Thermolysis of Biphenyl-2-sulfonamide. The amide (0.466 g) in *n*-dodecane (10 mL) was heated and stirred at 150 °C for 14 h. The products were chromatographed on a column of neutral alumina (150 g). Elution with ether–light petroleum (1:1 v/v) gave a yellow liquid (68 mg) not characterized further. Elution with ether–methanol (19:1 v/v) gave unchanged amide (0.358 g), mp 119–120 °C.

Reaction of Biphenyl-2-sulfonamide with $Pb(OCOCH_3)_4$. The amide (0.405 g) in acetic acid (25 mL) was heated at 80 °C with stirring with lead tetraacetate (1.520 g) for 4 h. Starting amide (0.352 g, 87%) was recovered. TLC indicated the absence of sultam **6a**. A similar result was obtained when the reaction was carried out at 120 °C. Amide (67%) was recovered together with some black solid, mp >300 °C.

No sultam was obtained when the amide (2.5 mmol) in trifluoroacetic acid (25 g) was heated at 20 °C for 5 h with lead tetra(trifluoroacetate) (5.0 mmol). Amide (70%) was recovered, together with two other very minor products (detected by TLC), but no sultam.

When the oxidation was attempted with $Pb(OCOCH_3)_4$ in boiling benzene, amide (61%) was again recovered.

Biphenyl-2-sulfonyliminotriphenylphosphonium Ylide. Biphenyl-2-sulfonyl azide (3 g) and triphenylphosphine (3 g) were heated in benzene for 1 h and the solvent was evaporated to give the ylide (5 g, 87%), mp 226–228 °C (from benzene).

Anal. Calcd for $C_{30}H_{24}NO_2PS$: C, 73.00; H, 4.90. Found: C, 72.84; H, 5.01.

Attempted Photolysis of Phosphonium Ylide. The ylide (0.5 g) in acetonitrile (400 mL) was photolyzed at 35–40 °C using 3000-Å lamps for 24 h. Starting material was recovered.

When the photolysis was carried out for 24 h at 26 °C in a quartz vessel using 2537-Å lamps the solution turned pale yellow. Chromatography on a column of silica gel gave starting ylide (0.42 g, 84%), together with a light brown solid, mp >300 °C, which could not be purified further.

2′,4′,6′-Trimethylbiphenyl-2-sulfonyl Azide. 2-Amino-2′,4′,6′-trimethylbiphenyl[2c] (1 g) in acetic acid (8 mL) containing concentrated HCl (3 mL) was treated with sodium nitrite (0.5 g) in water (2 mL) at 0 °C, and the diazonium salt solution was added to a mixture of a 30% solution of SO_2 in acetic acid (11 mL), benzene (10 mL), and $CuCl_2 \cdot 2H_2O$ (0.5 g). The mixture was stirred for 1 h at 0 °C, 1 h at

room temperature, and 0.5 h at 40 °C, diluted with water (200 mL), and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated and the residue recrystallized from benzene to give the sulfonyl chloride (0.6 g, 56%), mp 100–103 °C dec.

Without further purification this was treated as above with sodium azide in aqueous acetone to give the sulfonyl azide (70%), mp 69–70 °C (EtOH), *m/e* 269 ($M^{+\cdot}$).

Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02. Found: C, 59.83; H, 5.07.

Thermolysis of 2′,4′,6′-Trimethylbiphenyl-2-sulfonyl Azide. The azide (0.52 g) in cyclohexane (30 mL) was heated under nitrogen at 135 °C for 2 days. The reaction mixture was concentrated and resolved by preparative TLC on silica gel [benzene–light petroleum (1:1 v/v) as developer] to give two main bands and four minor ones. The fastest moving band was extracted to give 2,4-dimethylfluorene (0.09 g, 35%): mp 64–65 °C (EtOH) (lit.[28] mp 67–67.5 °C); NMR (CCl_4) δ 7.40 (m, 4, ArH), 6.86 (s, 2, ArH), 3.70 (s, 2, CH_2), 2.60 (s, 3, CH_3), 2.31 (s, 3, CH_3); *m/e* 194 ($M^{+\cdot}$). The second band was due to recovered azide (0.133 g, 26%). Other products were not identified.

4′-Bromobiphenyl-2-sulfonyl Chloride. 2-Amino-4′-bromobiphenyl[29] (7.4 g) was diazotized at 0 °C in acetic acid (40 mL) and concentrated HCl (7 mL) with sodium nitrite (3.1 g) in water (5 mL). The diazonium salt solution was poured into a saturated solution of SO_2 in acetic acid (80 mL) and benzene (80 mL) containing $CuCl_2 \cdot 2H_2O$ (1.0 g). After stirring for 6 h the solution was poured into ice water (600 mL) and extracted with $CHCl_3$ (100 mL), and the extract was washed with water (2 × 25 ml), dried ($MgSO_4$), and evaporated to give an oil (8 g). On trituration with ethanol **bis-4′-bromobiphenyl 2-disulfide *S,S*-oxide** (1.6 g, 20%) precipitated: mp 175–176 °C; IR (KBr) 1455 (m), 1320 (s), 1145 cm^{-1} (s).

Anal. Calcd for $C_{24}H_{16}Br_2O_2S_2$: C, 51.44; H, 2.88. Found: C, 51.50; H, 2.88.

The ethanolic filtrate gave **4′-bromobiphenyl-2-sulfonyl chloride** (4 g, 46%): mp 93–94 °C (EtOH); IR (KBr) 1375 (s), 1180 cm^{-1} (s) (SO_2); NMR (CCl_4) δ 8.25 (m, 1, H ortho to SO_2), 7.5 (m, 7, an AB pattern is visible within the multiplet, J = 9 Hz).

Anal. Calcd for $C_{12}H_8BrClO_2S$: C, 43.46; H, 4.43. Found: C, 43.52; H, 2.41.

4′-Bromobiphenyl-2-sulfonyl Azide. The sulfonyl chloride (2 g) in acetone (50 mL) was treated with NaN_3 (2.2 g) in water (10 mL) at 0 °C. The solution was stirred for 6 h at room temperature and poured into ice water (200 mL) to precipitate the azide (1.5 g, 60%): mp 82–83 °C (EtOH); IR (KBr) 2110 (s), 1365 (s), 1160 cm^{-1} (s); mass spectrum (70 eV) *m/e* (rel intensity) 344 [10, $(M + 2)^{+\cdot}$], 342 (10, $M^{+\cdot}$), 264 (99), 262 (100), 234 (80), 232 (80).

Anal. Calcd for $C_{12}H_8BrN_3O_2S$: C, 42.62; H, 2.38. Found: C, 42.53; H, 2.48.

4′-Bromobiphenyl-2-sulfonamide. Ammonia was bubbled through a solution of 4′-bromobiphenyl-2-sulfonyl chloride (0.1 g) in benzene (15 mL) for 2 h at room temperature. The precipitated NH_4Cl was filtered and the filtrate concentrated to give the sulfonamide (0.033 g, 35%): mp 194–195 °C (EtOH); IR (KBr) 3350 (s), 3250 (s), 1320 (s), 1170 cm^{-1} (s); NMR (acetone-d_6) δ 8.2 (m, 1, ortho to SO_2), 7.5 (m, 7, ArH), 6.1 (br s, 2, exchangeable with D_2O, NH_2); mass spectrum (70 eV) *m/e* (rel intensity) 313 (13, $M^{+\cdot}$ + 2), 311 (13, $M^{+\cdot}$).

Anal. Calcd for $C_{12}H_{10}BrNO_2S$: C, 46.16; H, 3.23. Found: C, 46.30; H, 3.30.

4′-Bromobiphenyl-2-sulfonanilide. Prepared from the sulfonyl chloride and aniline it was obtained in 41% yield: mp 151–152 °C (EtOH); IR (KBr) 3220 (s), 1330 (s), 1150 cm^{-1} (s); NMR [$CDCl_3$/$(CD_3)_2CO$] δ 8.2 (m, 1, ortho to SO_2), 8.1 (br s, exchanges with D_2O, NH), 7.3 (m, 7, ArH); *m/e* 390 (12, $M^{+\cdot}$ + 2), 338 (12, $M^{+\cdot}$).

Anal. Calcd for $C_{18}H_{14}BrNO_2S$: C, 55.68; H, 3.63. Found: C, 55.85; H, 3.68.

4′-Bromo-*N*-cyclohexylbiphenyl-2-sulfonamide. Prepared from cyclohexylamine and the sulfonyl chloride in benzene at 90 °C, the amide (55%) had mp 106–107 °C (EtOH); IR (KBr) 3240 (s), 1320 (s), 1150 cm^{-1} (s); NMR ($CDCl_3$) δ 8.2 (m, 1, ortho to SO_2), 7.5 (m, 7, ArH), 3.8 (d, 1, exchangeable, NH), 2.9 (br, 1, C–H of cyclohexyl), 1.3 (br m, 10, cyclohexyl).

Anal. Calcd for $C_{18}H_{20}BrNO_2S$: C, 54.83; H, 5.11. Found: C, 54.94; H, 5.21.

4′-Bromo-*N*-(*o*-chlorophenyl)biphenyl-2-sulfonamide (50%), mp 105–106 °C (EtOH). Anal. Calcd for $C_{18}H_{13}BrClNO_2S$: C, 51.14; H, 3.10. Found: C, 51.18; H, 3.12.

4′-Bromo-*N*-(*p*-chlorophenyl)biphenyl-2-sulfonamide (50%), mp 135–137 °C (EtOH).

Anal. Calcd for $C_{18}H_{13}BrClNO_2S$: C, 51.15; H, 3.10. Found: C, 51.14; H, 3.34.

4′-Bromo-2-trifluoroacetamidobiphenyl (50%), mp 97 °C (hexane), was prepared from 2-amino-4′-bromobiphenyl in $CHCl_3$ and trifluoroacetic anhydride: IR (KBr) 3200 (br s), 1700 (s), 1520 (s), 1470 (s), 1150 cm^{-1} (s); NMR ($CDCl_3$) δ 7.5 (m).

Anal. Calcd for $C_{14}H_9BrF_3NO$: C, 48.86; H, 2.64. Found: C, 49.09; H, 2.70.

Thermolysis of 4′-Bromobiphenyl-2-sulfonyl Azide. A. In Cyclohexane. The azide (0.5 g) in cyclohexane (30 mL) was heated under dry N_2 at 120–130 °C for 2 days. The cyclohexane was evaporated and the residue was resolved by preparative TLC on silica gel (1.5 mm thick, benzene as developer) to give recovered azide (53 mg, 10%), R_f 0.8, mp 83–84 °C, and 4′-bromo-*N*-cyclohexylbiphenyl-2-sulfonamide (144 mg, 27%), R_f 0.5, mp 106–107 °C, identical with authentic material. Also obtained was **8-bromodibenzo[c,e][1,2]-thiazine 5,5-dioxide** (22 mg, 5%): R_f 0.1; mp 224–226 °C (EtOH); identical with an authentic sample prepared as described below; IR (KBr) 3150 (br s), 1290 (s), 1150 cm^{-1} (s); NMR (acetone-d_6) δ 7.9 (m); *m/e* 311 (32, $M^{+\cdot}$ + 2), 309 (31, $M^{+\cdot}$).

Anal. Calcd for $C_{12}H_8BrNO_2S$: C, 46.47; H, 2.60. Found: C, 46.37; H, 2.66.

B. In Benzene. The azide (0.5 g) in benzene (50 mL) was heated as described above and the products were resolved by preparative TLC to give recovered azide (182 mg, 36%); 4′-bromobiphenyl-2-sulfonanilide (170 mg, 47%), mp 149–150 °C, identical with an authentic sample; and the 8-bromosultam (77 mg, 27%), mp 224 °C, identical with an authentic sample.

C. In Chlorobenzene. The azide (2.76 g) in chlorobenzene (140 mL) was heated at 130 °C for 3 days, and the products were resolved by preparative TLC to give 4′-bromo-*N*-(o-chlorophenyl)biphenyl-2-sulfonamide (366 mg, 10%), mp 106–108 °C; 4′-bromo-*N*-(*p*-chlorophenyl)biphenyl-2-sulfonamide (423 mg, 13%), mp 136–137 °C; and the 8-bromosultam (353 mg, 24%), mp 225–229 °C, all identical with authentic samples.

D. In Benzene Containing Trifluoroacetic Acid. The azide (2.0 g) in benzene (100 mL) and CF_3CO_2H (5.3 mL) was heated at 130 °C for 2 days. The solution was washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was resolved by preparative TLC to give starting azide (323 mg, 16%); 4′-bromo-2-trifluoroacetamidobiphenyl (37 mg, 4%), mp 98 °C; 4′-bromobiphenyl-2-sulfonanilide (316 mg, 34%), mp 151–152 °C; and 8-bromosultam (147 mg, 25%), mp 226–227 °C, all identical with authentic samples.

***N*-(*m*-Bromophenyl)-2-nitrobenzenesulfonamide.** *o*-Nitrobenzenesulfonyl chloride (20 g) and *m*-bromoaniline (30.9 g) in benzene (30 mL) were stirred at room temperature for 6 h. The solution was washed with cold 5% HCl (2 × 15 mL), dried ($MgSO_4$), and concentrated to give the sulfonamide (23 g, 70%): mp 128–129 °C; IR (KBr) 3300 (s), 1530 (s), 1355 (s), 1330 (s), 1170 cm^{-1} (s); NMR (acetone-d_6) δ 9.25 (br s, 1, exchangeable, NH), 7.6 (m, ArH).

Anal. Calcd for $C_{12}H_9BrN_2O_4S$: C, 40.35; H, 2.54. Found: C, 40.40; H, 2.60.

2-Amino-*N*-(*m*-bromophenyl)benzenesulfonamide. The nitro compound (10 g), zinc powder (5.7 g), and calcium chloride (2.5 g) in 78% ethanol (50 mL) were boiled under reflux for 3 h and then poured onto ice. The amine (6.5 g, 71%) had mp 114–115 °C (from CCl_4); IR (KBr) 3400 (m), 3320 (m), 3140 (m), 1320 (s), 1150 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{11}BrN_2O_2S$: C, 44.05; H, 3.39; N, 8.56. Found: C, 43.74; H, 3.40; N, 8.60.

8-Bromodibenzo[c,e][1,2]thiazine 5,5-Dioxide. *N*-(*m*-Bromophenyl)-2-aminobenzenesulfonamide (3.28 g), sodium hydroxide (0.5 g), and sodium nitrite (0.7 g) were dissolved in water (25 mL) and added to cold concentrated HCl (5 mL) and water (25 mL). After 15 min the solution was filtered and diluted to 150 mL and sodium acetate (6 g) was added. 2-(*m*-Bromophenyl)benzo[*e*]-1,2,3,4-thiatriazine 1,1-dioxide separated as a tan powder (1.6 g, 47%) which was immediately dissolved in EtOH (30 mL) and decomposed with Gatterman copper at room temperature. After a rapid gas evolution (15 min) the solution was heated to 80 °C for 30 min. The copper was filtered and the filtrate was evaporated to dryness to give a red oil. This was chromatographed on silica gel. Elution with $CHCl_3$ gave the 8-bromosultam (0.77 g, 25%), mp 224–226 °C (EtOH), identical with the sample prepared above.

2-*o*-Chlorosulfonylphenylthiophene. 2-*o*-Aminophenylthiophene[7] (1.3 g) in 20% HCl (10 mL) was diazotized at 0 °C with sodium nitrite (1 g) in water (10 mL) and the solution was stirred into acetic acid (20 mL) saturated with SO_2 mixed with benzene (20 mL) and $CuCl_2 \cdot 2H_2O$ (0.25 g) at 5–10 °C. After 1 h at that temperature the stirred mixture was warmed at 40 °C for 40 min and then poured into water (200 mL). The mixture was extracted with ether, and the extract was dried ($MgSO_4$) and evaporated. The residual brown oil (1 g) was heated with light petroleum (bp 30–60 °C) (20 mL) for 5 min, the

cooled light petroleum was decanted, and benzene (3 mL) was added to give the solid sulfonyl chloride (0.78 g, 40.7%), mp 82–83 °C (light petroleum), *m/e* 258 ($M^{+\cdot}$, ^{35}Cl).

Anal. Calcd for $C_{10}H_7ClO_2S_2$: C, 46.43; H, 2.73. Found: C, 46.15; H, 2.88.

Some sulfonic acid, mp 87–88 °C, *m/e* 240 ($M^{+\cdot}$), was also isolated in some cases by chromatography of the reaction mixture on a column of silica gel.

2-*o*-Azidosulfonylphenylthiophene. The sulfonyl chloride (0.65 g) in acetone (30 mL) at 0–5 °C was treated with sodium azide (0.75 g) in water (5 mL). The solution was stirred at 0–5 °C for 1 h, diluted with water (75 mL), and extracted with ether. The dried ($MgSO_4$) extract was evaporated to give the azide (0.54 g, 80.8%) as an oil. Chromatography through a column of silica gel (20 g) and elution with benzene gave an oil with solidified: mp 70–71 °C (dilute MeOH); IR (film) 2330 (w), 2130 (s), (N_3), 1360 (s), 1350 (s), 1165 cm^{-1} (br s).

Anal. Calcd for $C_{10}H_7N_3O_2S_2$: C, 45.29; H, 2.66. Found: C, 45.45; H, 2.82.

Thermolysis of 2-*o*-Azidosulfonylphenylthiophene. A. In Cyclohexane. The azide (0.5 g) in freshly distilled cyclohexane (20 mL) was heated under dry N_2 in a glass bomb at 120 °C for 72 h. The solvent was evaporated and the residue was chromatographed on a column of silica gel (40 g). Elution with light petroleum (bp 30–60 °C)-benzene (1:1 v/v) gave starting azide (0.15 g, 30%). Elution with benzene gave ***N*-cyclohexyl-*o*-(2-thienyl)benzenesulfonamide** (0.15 g, 35.4% based on azide consumed): mp 97–98 °C (dilute EtOH); IR (KBr) 3340 (s), 1310 (s), 1160 cm^{-1} (s); *m/e* 321 ($M^{+\cdot}$); identical with an authentic sample prepared (72%) from the sulfonyl chloride and cyclohexylamine.

Anal. Calcd for $C_{16}H_{19}NO_2S_2$: C, 59.78; H, 5.96. Found: C, 59.85; H, 6.10.

Elution with benzene–ether (1:1 v/v) gave **thieno[3,2-*c*]-6*H*-benzo[*e*][1,2]thiazine 5,5-dioxide** (0.19 g, 60.7% based on azide consumed): mp 204–205 °C (dilute EtOH); IR (KBr) 3200 (m), 1315 (s), 1180 cm^{-1} (s).

Anal. Calcd for $C_{10}H_7NO_2S_2$: C, 50.61; H, 2.97. Found: C, 50.75; H, 3.12.

B. With Cu in Benzene. The azide (0.5 g) in benzene (80 mL) containing copper powder (0.2 g) was heated at 80 °C for 84 h. The filtered solution was evaporated and the residue chromatographed on a column of silica gel (40 g) to give recovered azide (0.4 g, 80%) and **o-(2-thienyl)benzenesulfonamide** (0.06 g, 66.6%): mp 144–146 °C (dilute EtOH); IR (KBr) 3370 (s), 3270 (s), 1320 (s), 1160 cm^{-1} (s); *m/e* 239 ($M^{+\cdot}$); identical with an authentic sample prepared in 76% yield from the sulfonyl chloride and ammonia.

Anal. Calcd for $C_{10}H_9NO_2S_2$: C, 50.19; H, 3.79. Found: C, 50.44; H, 3.97.

***N*-2-Dimethylaminoethyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-Dioxide.** 6*H*-Dibenzo[c,*e*][1,2]thiazine 5,5-dioxide (0.46 g) in ethanol (20 mL) was treated with thallous ethoxide (0.5 g) to give a precipitate of the thallium salt (0.84 g, 97%). A well-stirred suspension of β-dimethylaminoethyl chloride hydrochloride (0.37 g) in toluene (10 mL) was treated with 50% aqueous KOH (5 mL), the mixture was stirred for 15 min, the aqueous layer was extracted with toluene (2 × 5 mL), and the combined toluene solutions were dried (Na_2CO_3). They were added to a boiling suspension of the thallium salt (0.87 g) in toluene (25 mL) and the mixture boiled under reflux for 22 h. It was then filtered and the solvent evaporated to give the product (0.24 g, 39%), mp 102–103 ° (from light petroleum).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.50; H, 6.00. Found: C, 63.60; H, 6.16.

***N*-3-Dimethylaminopropyl-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide** (48%), mp 94–95 °C, was prepared similarly.

Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37. Found: C, 64.63; H, 6.44.

Deoxygenation of 2-*o*-Nitrophenylthiophene with Triethyl Phosphite. The nitro compound (1 g) and triethyl phosphite (3.5 g) were boiled under reflux under N_2 for 9 h. The excess phosphite was distilled in vacuo and the residue was chromatographed on a column of silica gel (50 g). Elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave 4*H*-thieno[3,2-*b*]indole (0.4 g, 47.4%), mp 174–175 °C (dilute EtOH), identical with the product obtained from the thermolysis of 2-*o*-azidophenylthiophene in decalin.[7]

Acknowledgment. The research was initially supported by a grant from the Warner-Lambert Research Institute and then by NIH Grant NBO-8716 and NSF Grant MPS-75-09309 for which we are grateful.

Registry No.—**1b,** 25627-20-7; **1c,** 62532-98-3; **1d,** 62532-99-4; **2a,** 2688-90-6; **2b,** 62533-00-0; **2c,** 62533-01-1; **2d,** 62533-02-2; **3a,** 40182-14-7; **3b,** 62533-03-3; **3c,** 62533-04-4; **3d,** 62533-05-5; **6a,** 1864-33-1; **6b,** 62533-06-6; **7,** 14858-84-5; **8,** 14858-85-6; **9,** 40182-08-9; **11** (R = H), 40949-59-5; **11** (R = 2-Me), 62562-59-8; **11** (R = 2,6-Me_2), 62533-07-7; **11** (R = 2,4,6-Me_3), 40949-60-8; **12,** 62533-08-8; **13,** 19813-97-9; **14,** 62533-09-9; **15,** 2928-44-1; **16,** 62533-10-2; **17,** 62533-11-3; **18,** 62533-12-4; **19,** 62533-13-5; **20,** 62533-14-6; **22,** 62533-15-7; **23,** 62533-16-8; **25,** 62533-17-9; **26,** 62533-18-0; sodium azide, 12136-89-9; *n*-dodecane, 112-40-3; (*n*-dodecyl)biphenyl-2-sulfonamide, 62533-19-1; benzene, 71-43-2; pyridine, 110-86-1; 2-picoline, 109-06-8; 2,6-lutidine, 108-48-5; biphenyl-2-sulfonamide, 40182-06-7; di-*tert*-butyl sulfide, 107-47-1; aniline, 62-53-3; *n*-cyclohexylbiphenyl-2-sulfonamide, 62533-20-4; cyclohexylamine, 108-91-8; 2,4,6-trimethylpyridinium perchlorate, 61244-34-6; biphenyl-2-sulfonyl hydrazide, 62533-21-5; triphenylphosphine, 603-35-0; cyclohexane, 110-82-7; bis-4′-bromobiphenyl 2-disulfide *S,S*-oxide, 62533-22-6; 4′-bromobiphenyl-2-sulfonamide, 62533-23-7; 2-amino-4′-bromobiphenyl, 62532-98-3; chlorobenzene, 108-90-7; *n*-(*m*-bromophenyl)-2-nitrobenzenesulfonamide, 62533-24-8; *o*-nitrobenzenesulfonyl chloride, 1694-92-4; *m*-bromoaniline, 591-19-5; o-(2-thienyl)benzenesulfonic acid, 62533-25-9; *o*-(2-thienyl)benzenesulfonamide, 62533-26-0; β-dimethylaminoethyl chloride hydrochloride, 4584-46-7.

References and Notes

(1) For preliminary communication, see R. A. Abramovitch, C. I. Azogu, and I. T. McMaster, *J. Am. Chem. Soc.*, **91**, 1219 (1969).
(2) (a) P. A. S. Smith and J. H. Hall, *J. Am. Chem. Soc.*, **84**, 480 (1962); (b) P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *ibid.*, **75**, 6335 (1953); (c) G. Smolinsky, *ibid.*, **82**, 4717 (1960); **83**, 2489 (1961).
(3) R. A. Abramovitch and B. A. Davis, *Chem. Rev.*, **64**, 149 (1964).
(4) R. A. Abramovitch and R. G. Sutherland, *Fortschr. Chem. Forsch.*, **16**, 1 (1970).
(5) They are described as "substitution" reactions for convenience. It has been shown[6,7] that in many cases they are really addition–ring opening–hydrogen migration reactions.
(6) R. A. Abramovitch and V. Uma, *Chem. Commun.*, 797 (1968); R. A. Abramovitch, G. N. Knaus, and V. Uma, *J. Org. Chem.*, **39**, 1101 (1974); R. A. Abramovitch, T. D. Bailey, T. Takaya, and V. Uma, *ibid.*, **39**, 340 (1974).
(7) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Am. Chem. Soc.*, **94**, 1374 (1972).
(8) R. A. Abramovitch and E. F. V. Scriven, *Chem. Commun.*, 787 (1970); R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Org. Chem.*, **37**, 2705 (1972).
(9) H. Meerwein, G. Dittmar, R. Goellner, K. Haffner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957).
(10) A. J. Neale, T. J. Rawlings, and E. B. McCall, *Tetrahedron*, **21**, 1299 (1965).
(11) M. Kobayashi, K. Tanaka, and H. Minato, *Bull. Chem. Soc. Jpn.*, **45**, 2906 (1972), and references cited therein.
(12) R. Hisada, M. Kobayashi, and H. Minato, *Bull. Chem. Soc. Jpn.*, **45**, 2902 (1972).
(13) F. Ullman and G. Grosse, *Ber.*, **43**, 2694 (1910).
(14) R. A. Abramovitch and W. D. Holcomb, *J. Org. Chem.*, **41**, 991 (1976).
(15) R. A. Abramovitch, G. N. Knaus, and R. W. Stowe, *J. Org. Chem.*, **39**, 2513 (1974).
(16) H. Kwart and A. A. Kahn, *J. Am. Chem. Soc.*, **89**, 1950 (1967).
(17) R. A. Abramovitch, C. I. Azogu, and R. G. Sutherland, *Chem. Commun.*, 1439 (1969); *Tetrahedron Lett.*, 1637 (1971).
(18) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963).
(19) W. Lwowski and E. Scheiffele, *J. Am. Chem. Soc.*, **87**, 4359 (1965).
(20) J. M. McKenna, J. McKenna, and A. R. Walley, *J. Chem. Soc., Chem. Commun.*, 140 (1974).
(21) H. Zimmer and M. Jayawant, *Tetrahedron Lett.*, 5061 (1966).
(22) D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.*, **91**, 2273 (1969).
(23) J. I. G. Cadogan, *Acc. Chem. Res.*, **4**, 240 (1971).
(24) P. A. S. Smith and J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 2626 (1951).
(25) R. A. Abramovitch, *Chem. Ind. (London)*, 422 (1957); R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.*, **39**, 2516 (1961); R. A. Abramovitch and J. Kalinowski, *J. Heterocycl. Chem.*, **11**, 857 (1974).
(26) P. J. Bunyan and J. I. g. Cadogan, *J. Chem. Soc.*, 42 (1963); J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *ibid.*, 4831 (1965).
(27) A. Schonberg, L. U. Vazgha, and W. Paul, *Justus Liebigs Ann. Chem.*, **483** 107 (1930).
(28) J.-J. Godfroid, *Bull. Soc. Chim. Fr.*, 2929 (1964).
(29) R. A. Benkeser, W. Shroeder, and O. H. Thomas, *J. Am. Chem. Soc.*, **80**, 2283 (1958).

Intramolecular Insertion of Arylsulfonylnitrenes into Aliphatic Side Chains[1]

Rudolph A. Abramovitch,* Therinadar Chellathurai, William D. Holcomb, Ian T. McMaster, and Danny P. Vanderpool

Department of Chemistry, University of Alabama, University, Alabama 35486

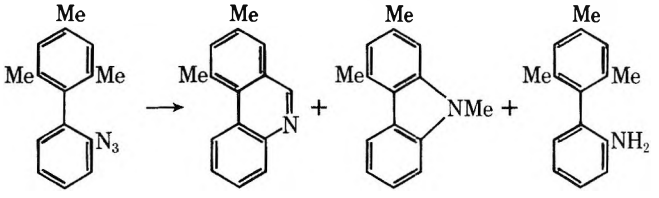
Received January 17, 1977

The thermolysis of *o*-methylbenzenesulfonyl azides in solution leads to the low-yield intramolecular insertion of the sulfonylnitrene into the ortho C–H group. Intermolecular insertion into, and hydrogen abstraction from, the solvent compete efficiently with cyclization. Curtius-type rearrangements of the sulfonyl azides have been observed and, in one case, the intermediate sulfonylimine (**15**) has been trapped as the sulfanilide (**14**). Sulfonyl azides are, therefore, no longer to be considered "rigid" azides. Intramolecular C–H insertion occurs also with an ortho cyclohexyl group to give a mixture of axial and equatorial isomers, but not into an ortho methoxyl, thiomethoxyl, or dimethylamino group. In the latter case, the sulfonylnitrene is trapped by the nucleophilic amine to give a zwitterion (**46**) which rearranges thermally to the *N,N'*-dimethyl compound **47**. Hydrogen abstraction and intermolecular insertion products, as well as products resulting from a free-radical decomposition of the sulfonyl azide, are also observed.

In the preceding paper[2] intramolecular aromatic substitution of arylsulfonylnitrenes was reported in the cases of the thermolysis and photolysis of 2-biarylsulfonyl azide. The present paper deals with some intramolecular insertions of arylsulfonylnitrenes into aliphatic side chains and the observation of Curtius-type rearrangements of sulfonyl azides in nonprotic solvents.

Results and Discussion

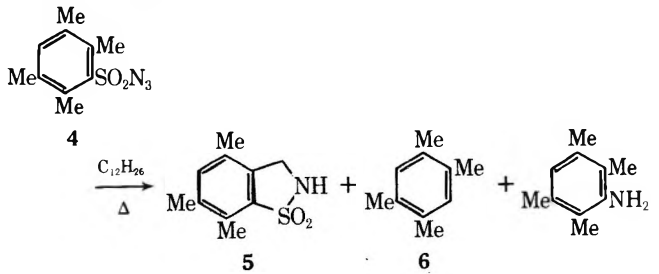
We first examined intramolecular insertions into a methyl group ortho to the sulfonyl azide. Intramolecular arylnitrene insertion into a suitably located methyl group has been reported previously. Thus, 2-azido-2′,4′,6′-trimethylbiphenyl gives the phenanthridine **1** (48%), as well as the carbazole **2**



1 **2** **3**

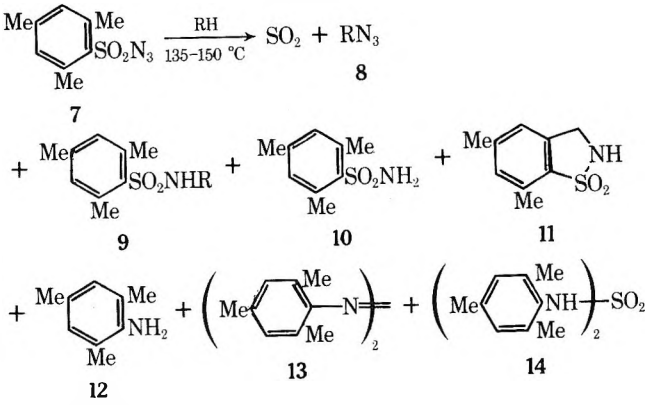
(5%) and the hydrogen-abstraction product **3** (29%) on thermolysis.[3] Similar cyclizations to give phenanthridines and indolines have also been reported.[4] On the other hand, thermolysis of 2-azido-*m*-xylene led only to polymer formation, which can readily be understood in terms of the geometrical constraints imposed by a C–H insertion process, so that hydrogen abstraction leading to an *o*-quinone imine methide can occur and thence lead to polymer. Such geometrical constraints should not apply to toluene-*o*-sulfonylnitrenes so that C–H insertion was expected to occur, at least to a moderate extent, and thus open up a new route to 2,3-dihydro-1,2-benzoisothiazole 1,1-dioxides.

Durene-3-sulfonyl azide (**4**) was readily prepared from the sulfonyl chloride (76% overall from durene). Thermolysis of **4** in *n*-dodecane gave the desired C–H insertion product **5**



4 **5** **6**

Scheme I



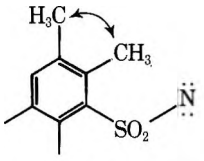
(10–15%), together with some durene (**6**) (12–36%) and some 3-aminodurene (11%). The hydrocarbon probably arises by a competing radical process: $ArSO_2N_3 \rightarrow N_3\cdot + ArSO_2\cdot \rightarrow SO_2 + Ar\cdot \rightarrow ArH$.[1,2] The amine undoubtedly results from a Curtius-type rearrangement (see below).

The thermolysis of mesitylene-2-sulfonyl azide (**7**) was studied in much greater detail (Scheme I). When **7** was heated in *n*-dodecane at 150 °C at atmospheric pressure seven products were isolated: SO_2 (18–22%), a mixture of dodecyl azides (**8**, R = $C_{12}H_{25}$) (2–4%), *N*-dodecylmesitylene-2-sulfonamides (**9**, R = $C_{12}H_{25}$) (19–23%), mesitylene-3-sulfonamide (**10**) (1–3%), 2,3-dihydro-5,7-dimethyl-1,2-benzoisothiazole 1,1-dioxide (**11**) (2–3%), mesitylamine (**12**) (18–21%), and 2,2′,4,4′,6,6′-hexamethylazobenzene (**13**) (trace). When the reaction was repeated in degassed *n*-dodecane in a sealed tube at 150 °C, one additional product was obtained, namely, 2,2′,4,4′,6,6′-hexamethylsulfanilide (**14**) (33%). These results, as well as the thermolyses of **7** in cyclohexane and benzene at 135 °C, are summarized in Table I.

These results make clear a number of points, the main one being that the geometry for intramolecular insertion into an ortho methyl group is still not that favorable as to compete very effectively with intermolecular processes. In all cases, though the desired cyclization product was obtained, the main products were those of intermolecular insertion or hydrogen abstraction, or of rearrangement. In this connection, it is interesting to note that the yield of intramolecular insertion product form durene-3-sulfonyl azide, though low, is appreciably (and reproducibly) higher than that from mesitylene-2-sulfonyl azide under otherwise identical conditions. This would suggest that some buttressing effect (A) by the 3-methyl group brings the ortho methyl closer to the nitrene nitrogen,

Table I. Thermolysis of Mesitylene-2-sulfonyl Azide in Various Solvents

Solvent RH	Temp, °C	Yield, % 8	9	10	11	12	13	14
n-Dodecane (1 atm)	150	2–4	19–23	1–3	2–3	18–21	Tr	0
n-Dodecane (pressure)	150	Tr	21	Tr	4	2.2	Tr	33
n-Dodecane (pressure)	135	Tr	22	1	3	Tr	2.2	32
Cyclohexane (pressure)	150	0	27	0	7.7	3.1	Tr	43
Cyclohexane (pressure)	135	0	27	1	5	3	0	43
Benzene (pressure)	135	0	2	10	1	12	0	10



A

facilitating insertion somewhat relative to the mesitylene derivative. Formation of **8** supports the mechanism for loss of SO_2 proposed by Breslow and his co-workers.[5]

$$R'\cdot + RSO_2N_3 \rightarrow R'N_3 + RSO_2\cdot$$

$$RSO_2\cdot \rightarrow R\cdot + SO_2$$

$$R'H + R\cdot \rightarrow R'\cdot + RH$$

The source of the original alkyl radical could be hydrogen abstraction by the triplet sulfonyl nitrene formed from the originally generated singlet by intersystem crossing, or triplet arylnitrene formed as discussed below. Such a mechanism accounts also for the formation of *some* of the SO_2 (vide infra), of the sulfonamide **10**, and of durene (**6**).

Formation of aniline (**12**), azobenzene (**13**), and sulfanilide (**14**) are all best accounted for by a Curtius-type rearrangement of the sulfonylnitrene to the unstable sulfonylaniline (**15**). This can either lose SO_2 (the balance of the SO_2 isolated) to give the arylnitrene which can hydrogen abstract or dimerize[6] to give **12** and **13**, respectively. When the reaction is carried out in a sealed tube to prevent loss of SO_2, decomposition of **15** is apparently either sufficiently retarded or is reversible so that **15** can trap the aniline formed giving the sulfanilide (**14**). An attempt was made to synthesize authentic **14** but treatment of **12** with sulfuryl chloride in pyridine at −5 to 0 °C[7] gave none of the desired sulfanilide, the only product isolated being the azobenzene (**13**). Others[8] also reported low

$$ArSO_2\ddot{N} \xrightarrow{a} ArN{=}SO_2 \longrightarrow\longrightarrow 12 + 13$$

15

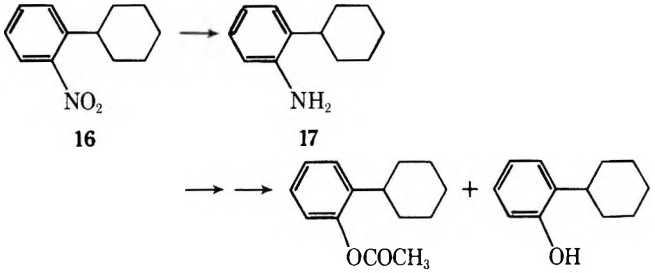
↓ 12

14

yields of azobenzene in this type of reaction (in ether solvent) but did get good yields of the corresponding sulfanilide. The structure of our sulfanilide is supported by microanalysis, its infrared spectrum [ν_{NH} 3255 cm^{-1}, ν_{SO_2} (1295, 1140 cm^{-1})], its mass spectrum [$M^+\cdot$ 332, *m/e* 134 (100) ($Me_3C_6H_2NH^+$)], and its NMR spectrum [4 H singlet at δ 6.92 (ArH), 2 H singlet (exchangeable) at δ 5.91 (NH), 12 H singlet at δ 2.33 (ortho CH_3), 6 H singlet at δ 2.27 (para CH_3)].

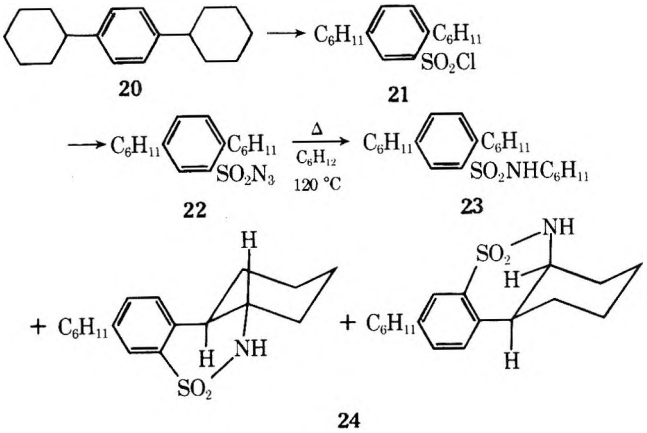
Until part of the present work was originally published[1] sulfonyl azides were generally thought to be "rigid" (Curtius' "starre" azides[9]), i.e., they did not undergo Curtius-type rearrangements. Photolysis of benzenesulfonyl azide in methanol did give *N*-methoxysulfamate,[10] and decomposition of the triethylammonium salt of *N*-*p*-nitrobenzenesulfonoxybenzenesulfonamide in methanol, ethanol, and aniline gave products derived from a Lossen-type rearrangement to sulfurylaniline.[10] It was felt[10] that these rearrangements involved a protonated species and not a free sulfonylnitrene. The vapor-phase pyrolysis of benzenesulfonyl azide at 625 °C gave a 17.5% yield of azobenzene,[11] and trace amounts of the latter could be obtained by boiling the azide in cyclohexanone.[12] The work reported here shows that sulfonyl nitrenes will indeed also undergo the Curtius rearrangement readily in nonprotic solvents provided that competing reactions are rendered less likely.

It was next attempted to determine whether, if a choice were available, C–H insertion by a sulfonylnitrene would occur at the more reactive α proton of an ortho isopropyl side chain or at the more accessible β proton. To this end we attempted to prepare 2-cyclohexylbenzenesulfonyl azide. Nitration of cyclohexylbenzene gave a mixture of *o*- and *p*-nitrocyclohexylbenzenes which were resolved by preparative gas–liquid chromatography. The *o*-nitro derivative (**16**) was reduced to the primary amine (**17**) which, on diazotization and treatment with SO_2 in acetic acid and benzene containing $CuCl_2$,[13] did not give the desired sulfonyl chloride. Instead, a mixture of *o*-acetoxyphenylcyclohexane (**18**) and the corresponding phenol (**19**) was obtained. When the solid diazonium tetrafluoroborate of **17** was decomposed similarly (but in the absence of water) **18** (47%) was the only product isolated. Attempted chlorosulfonation of *p*-nitrocyclohexylbenzene with $ClSO_3H$ in $CHCl_3$ at 60 °C or in cyclohexane at 80 °C gave only starting material; at 110 °C tarry products were obtained.



16 17 18 19

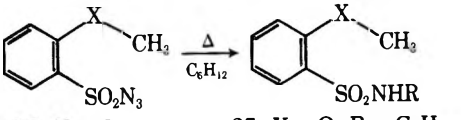
Chlorosulfonation of *p*-dicyclohexylbenzene (**20**) with $ClSO_3H$ in $CHCl_3$ at 0–55 °C failed. At 80 °C in $(CH_2Cl)_2$ the product formed analyzes correctly for a 4-cyclohexylbiphenyldisulfonyl chloride. Successful chlorosulfonation could be



20 21 22 23 24

effected, however, in cyclohexane at 80 °C, whereby an 80% yield of **21** was obtained. This was converted readily to the azide **22**, thermolysis of which in cyclohexane gave the *intermolecular* insertion product **23** (48%), and a mixture (cis and trans) of the intramolecular insertion products (**24**) (9%) which could not be resolved. Insertion does appear to have occurred at the β-C–H position since **24** exhibits a signal for two benzylic protons in the NMR.

2-Methoxy- (**25**) and 2-methylthiobenzenesulfonyl azide (**26**) were synthesized and thermolyzed. The methoxy derivative **25** (from o-anisidine) was decomposed in cyclohexane at 130 °C to give *N*-cyclohexyl-2-methoxybenzenesulfonamide (**27**) (42%) together with much tar. Its decomposition in Freon E 3 at 130 °C gave only tarry products. Similar thermolysis of the methylthio derivative **26** (prepared from o-chloronitrobenzene with sodium thiomethoxide followed by reduction to the amine, diazotization, modified Meerwein reaction, and treatment of the sulfonyl chloride with sodium azide) in cyclohexane at 130 °C gave *N*-cyclohexyl-2-methylthiobenzenesulfonamide (**28**) (20%) and 2-methylthiobenzenesulfonamide (**29**) (21%). Interestingly, no attack by the nitrene or the azide occurred at the ortho sulfur atom (cf. ref 1). Neither was any intramolecular C–H insertion product observed in either of these cases.



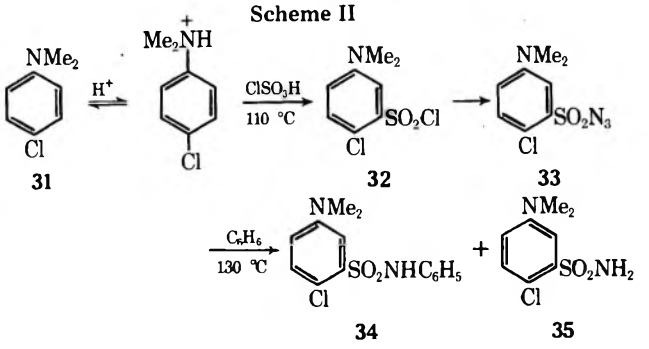
25, X = O
26, X = S
30, X = NMe

27, X = O; R = C_6H_{11}
28, X = S; R = C_6H_{11}
29, X = S; R = H

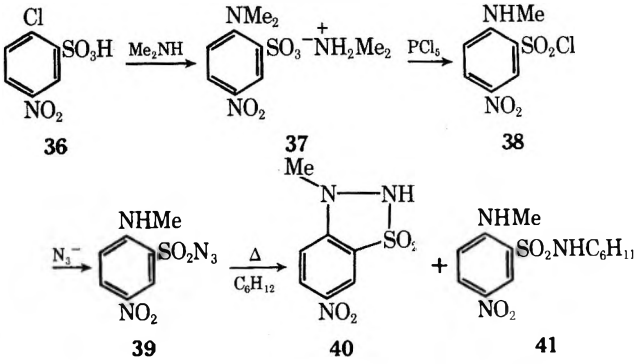
We next turned our attention to the synthesis and decomposition of *N,N*-dimethylaniline-2-sulfonyl azides (**30**). A number of attempts to chlorosulfonate *N,N*-dimethyl-*p*-nitroaniline and *p*-chloro-*N,N*-dimethylaniline (**31**) failed. Chlorosulfonation of **31** with chlorosulfonic acid for 18 h at 110 °C gave 4-chloro-*N,N*-dimethylaniline-3-sulfonyl chloride (**32**) (20%). Presumably, the amino group is protonated under these conditions and electrophilic substitution occurs meta to the ammonium ion. The sulfonyl chloride was converted to the azide (**33**) which was thermolyzed in benzene at 130 °C to give products of insertion into the solvent (**34**) (14%) and hydrogen abstraction (**35**) (15%) (Scheme II). The fact that none of the characteristic products obtained from the thermolysis of *o*-dimethylaminobenzenesulfonyl azides (see below) are formed in this reaction confirms the orientation assigned to **32**.

Treatment of 2-chloro-5-nitrobenzenesulfonic acid (**36**) with dimethylamine gave the dimethylammonium salt of 2-dimethylamino-5-nitrobenzenesulfonic acid (**37**), which, with PCl_5, gave 2-methylamino-5-nitrobenzenesulfonyl chloride (**38**), mono-N-demethylation accompanying chlorination. The secondary amine so formed could not be N-acetylated or N-mesylated with Ac_2O and $MeSO_2Cl$, respectively. It was converted to the sulfonyl azide (**39**), which, on thermolysis in

Scheme II

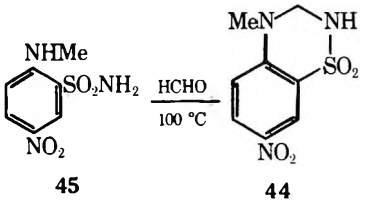


Scheme III



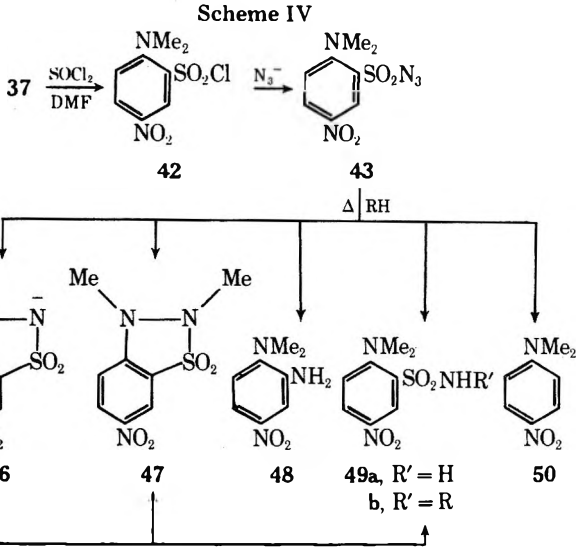
cyclohexane at 135 °C, gave **40** (30%) and **41** (10%) (Scheme III).

Heating **37** with thionyl chloride and dimethylformamide gave the desired sulfonyl chloride (**42**) which was converted to the azide (**43**). Thermolysis of **43** in cyclohexane or benzene at 120 °C gave an array of products shown in Scheme IV. Again, as with **25** and **26**, no product of intramolecular C–H insertion (**44**) was observed. An authentic sample of **44** was



prepared from 2-methylamino-5-nitrobenzenesulfonamide (**45**) and formaldehyde. After this work was completed, Martin, Meth-Cohn, and Suschitzky[14] reported the thermolysis of a number of 2-dialkylamino-5-nitrosulfonyl azides with results somewhat similar to the above. They prepared their sulfonyl azides from 2-chloro-5-nitrobenzenesulfonyl azide and the secondary amine. Of great interest was the fact that their 2-*N*-pyrrolidyl derivative did undergo intramolecular C–H insertion (13%) but that, as also reported here, the *N,N*-dimethyl derivative **43** did not. These authors did not obtain a product corresponding to **47** above. Indeed, the only product they reported isolating from the thermolysis of **43** itself was **46**. Both **47** and **49a** arise from **46** as shown by the thermolysis of the latter in cyclohexane at 130 °C. The electrophilic nitrene is trapped by the nucleophilic amino group to give the ylide **46**, a process for which there is precedent.[15] The amine **48** probably arises as discussed above via a Curtius-type rearrangement, while formation of **50** most likely involves a free-radical process. The 1,2-alkyl shift **46** → **47** is

Scheme IV



not unexpected. One unusual feature is the absence of solvent insertion product **49b** (R′ = C_6H_5) when benzene is used as the solvent but its formation (**49b**, R′ = C_6H_{11}) in cyclohexane since it has been estimated[16] that a singlet sulfonylnitrene adds to a benzene double bond about eight times as fast as it inserts into a cyclohexane C–H bond.

Experimental Section

Melting points are uncorrected.

Durene-3-sulfonyl Azide (4). Sodium azide (1.30 g) in water (10 mL) was poured into a stirred solution of durene-3-sulfonyl chloride[17] (4.65 g) in acetone (50 mL) at room temperature and the mixture was stirred for a further 10 h. It was then concentrated in vacuo down to one-third of its volume and poured into water (20 mL) and the precipitated solid was filtered, washed with water, and dried to give the azide (4.83 g, 100%): mp 68.5 °C (EtOH); IR (KBr) 2330, 2120, 1350, 1155 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.21; H, 5.44. Found: C, 50.58; H, 5.76.

Thermolysis of Durene-3-sulfonyl Azide in *n*-Dodecane. A suspension of **4** (1.195 g) in *n*-dodecane (25 mL) was heated with stirring at 150 °C for 21 h. The mixture was cooled to room temperature and chromatographed on a column of neutral alumina (140 g). Elution with light petroleum gave *n*-dodecane. Further elution with light petroleum gave durene **6** (0.083 g, 12%), mp 78–79 °C (sublimation, then recrystallization from aqueous EtOH), identical with an authentic sample. Elution with ether gave a light brown solid (0.072 g) which crystallized from EtOH as a buff solid (0.053 g), mp 157–198 °C. Vacuum sublimation gave a colorless solid (0.042 g): mp 190–202 °C; mass spectrum M^+· *m/e* 360; IR (KBr) 3310, 3260, 1290, 1170, 1160 cm^{-1}. This was not characterized further. Elution with ether gave 3-aminodurene (11%), identical with an authentic sample. Elution with ether–methanol (95:5 v/v) gave **2,3-dihydro-4,6,7-trimethyl-1,2-benzoisothiazole 1,1-dioxide (5,** 0.153 g, 15%): mp 229.5–230 °C (vacuum sublimation and recrystallization from EtOH); mass spectrum M^+· *m/e* 211; IR (KBr) 3270, 1305, 1285, 1160 cm^{-1}; NMR (acetone-d_6) δ 8.04 (s, 1, NH), 7.52 (s, 1, ArH), 4.54 (s, 2, CH_2), 2.68 (s, 3, CH_3), 2.55 (s, 3, CH_3), 2.49 (s, 3, CH_3).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.87; H, 6.16. Found: C, 56.91; H, 6.38.

Mesitylene-2-sulfonyl Azide (7). This was prepared from mesitylene-2-sulfonyl chloride as for **4** above. The azide (79%) had bp 79–80 °C (22 μ); IR (film) 2120 (N_3), 1360, 1165 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.06 (s, 2, ArH), 2.68 (s, 6, 2 CH_3), 2.35 (s, 3, CH_3); mass spectrum *m/e* (rel intensity) 225 (M^+·, 3.5), 197 (3), 183 (20), 119 (100), 91 (28).

Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.95. Found: C, 47.98; H, 4.77.

Thermolysis of Mesitylene-2-sulfonyl Azide. A. In *n*-Dodecane at 1 Atm. The azide **7** (4.402 g) in *n*-dodecane (37.8 g) was placed in a thermolysis vessel connected to sulfur dioxide traps filled with 5% aqueous NaOH solution (25 mL each), the system was purged with dry, O_2-free nitrogen, and the thermolysis vessel was immersed in an oil bath at 150 °C and kept at that temperature for 20 h, at which time no more nitrogen was evolved. The volume of N_2 collected over water at 25 °C corrected to STP was 408 mL (93%). The system was cooled and purged with dry, O_2-free N_2 for 30 min to remove any further SO_2. The SO_2 traps were each transferred to 250-mL flasks, rinsed with water (2 × 25 ml), and hydrogen peroxide (30%, 1 mL) was added to each flask (and to a blank). After stirring the solutions for 5 min at room temperature they were acidified with 3 N HCl and heated almost to boiling and $BaCl_2$ solution (2.61 g/100 mL) was added with stirring until no more precipitate formed. Gravimetric workup of the $BaSO_4$ as usual gave a yield of 22.5% of SO_2.

The reaction mixture was chromatographed on a column of neutral alumina (2.5 × 45 cm). Elution with light petroleum (bp 30–60 °C) gave first *n*-dodecane, followed by a mixture of dodecyl azides (**8**, 0.098 g, 1.5%): bp 50 °C (20 μ); IR (film) 2960, 2940, 2860, 2100, 1260, 665 cm^{-1}; mass spectrum *m/e* (rel intensity) 183 (M^+· − 28, 0.9), 182 (1.3), 168 (4), 154 (14), 140 (14), 126 (16), 112 (21), 98 (28), 85 (14), 84 (35), 71 (42), 70 (40), 69 (13), 58 (10), 57 (100), 56 (37), 55 (29).

Elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave 2,2′,4,4′,6,6′-hexamethylazobenzene (**13,** 0.006 g), identical (IR and mass spectrum) with an authentic sample.[18] Elution with benzene–trichloroethylene (95:5 v/v) gave 2,4,6-trimethylaniline (**12,** 0.469 g), identical [IR, NMR, mass spectrum, and GLC retention time on an OV-17 (10%) on Gas Chrom Q column] with an authentic sample (Aldrich). Elution with benzene–ether (85:15 v/v) gave a viscous oil of ***N*-dodecylmesitylene-2-sulfonamides** (1.414 g, 19.5%): bp 150–152 °C (9 μ); IR (film) 3300, 2970, 2930, 2865, 1325, 1165 cm^{-1}; NMR ($CDCl_3$) δ 6.98 (s, 2, ArH), 4.58–4.44 (d, 1, $J_{H,NH}$ = 8 Hz, exchanges with D_2O, NH), 3.35–2.95 (br s, 1, RR′CHNH), 2.67 (s, 6, 2 CH_3), 2.30 (s, 3, CH_3), 1.6–0.9 (br m, 24); mass spectrum *m/e* (rel intensity) 367 (M^+·, 0.3), 352 (0.9), 338 (0.8), 324 (9), 310 (9), 296 (9), 282 (9), 268 (12), 254 (15), 183 (27), 135 (64), 134 (41), 120 (64), 105 (13), 91 (22), 77 (14).

Anal. Calcd for $C_{21}H_{37}NO_2S$: C, 68.62; H, 10.15. Found: C, 68.68; H, 10.12.

Elution with ether gave mesitylene-2-sulfonamide (0.113 g, 30%), identical with an authentic sample.[19] Elution with ether–methanol (98:2 v/v) gave a tan solid which was sublimed (110 °C at 10 μm) and recrystallized from light petroleum (bp 60–110 °C)–ethyl acetate to give colorless needles of **2,3-dihydro-5,7-dimethyl-1,2-benzoisothiazole 1,1-dioxide** (0.118 g, 3.1%): mp 114.5–115.5 °C; IR (KBr) 3220, 1280, 1170 cm^{-1}; NMR ($CDCl_3$) δ 7.1 (s, 1, ArH), 7.01 (s, 1, ArH), 5.3–4.9 (br s, 1, exchanges with D_2O, NH), 4.46 (d, 2, $J_{C_3H,NH}$ = 5.6 Hz, becomes singlet on D_2O exchange, C_3 H, NH), 2.60 (s, 3, CH_3), 2.41 (s, 3, CH); mass spectrum *m/e* (rel intensity) 197 (M^+·, 4.5), 196 (2), 58 (23), 43 (100).

Anal. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62. Found: C, 54.96; H, 5.88.

B. In *n*-Dodecane under Pressure. Mesitylene-2-sulfonyl azide (1.997 g) was dissolved in *n*-dodecane (40 mL), and the solution was degassed and flushed with dry, O_2-free nitrogen and thermolyzed in a glass-lined steel bomb at 135 °C with stirring under a N_2 atmosphere for 16 h. The thermolysis solution was pale yellow and contained much black solid and a few white crystals in suspension. The odor of SO_2 was detected when the bomb was opened. The whole suspension was chromatographed on a column of neutral alumina (2.3 × 25 cm). Elution as above gave dodecyl azides (0.045 g, 2%), 2,2′,4,4′,6,6′-hexamethylazobenzene (trace), 2,4,6-trimethylaniline (0.026 g, 2.2%), *N*-dodecylmesitylene-2-sulfonamides (0.722 g, 22%), and a series of fractions which were not resolved but recombined and rechromatographed on a column of neutral alumina (2.3 × 25 cm). Elution with benzene–ethyl acetate (85:15 v/v) gave a tan solid which was recrystallized from light petroleum (bp 60–110 °C) to give **2,2′,4,4′,6,6′-hexamethylsulfanilide (14,** 0.484 g, 32%): mp 164–166 °C; IR (KBr) 3255, 1295, 1140 cm^{-1}; NMR discussed in text; mass spectrum *m/e* (rel intensity) 332 (M^+·, 6), 136 (12), 135 (55), 134 (100), 120 (27).

Anal. Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28. Found: C, 65.49; H, 7.43.

Elution with ethyl acetate gave mesitylene-2-sulfonamide (0.017 g, 1%), identical with an authentic sample. Elution with ethyl acetate–ethanol (98:2 v/v) gave 2,3-dihydro-5,7-dimethyl-1,2-benzoisothiazole 1,1-dioxide (0.046 g, 2.6%).

C. In Cyclohexane under Pressure. The reaction was carried out as under B above except that cyclohexane (40 mL) was used as the solvent. The results are summarized in Table I. ***N*-Cyclohexylmesitylene-2-sulfonamide** (**9,** R = C_6H_{11}) (27%) eluted with benzene–ethyl acetate (85:15 v/v) and had mp 95–96 °C [from light petroleum (bp 60–110 °C)]; IR (KBr) 3260, 1310, 1145 cm^{-1}; NMR ($CDCl_3$) δ 7.00 (s, 2, ArH), 4.8–4.0 (br s, 1, exchanges with D_2O, NH), 3.3–2.9 (br s, 1, CHN<), 2.69 (s, 6, 2 CH_3), 2.32 (s, 3, CH_3), 2.0–0.9 (br m, 10); mass spectrum *m/e* (rel intensity) 281 (M^+·, 12), 238 (13), 183 (21), 120 (26), 119 (100), 118 (34), 105 (24), 98 (31), 91 (30), 77 (23), 57 (39), 56 (26), 55 (41).

Anal. Calcd for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.23. Found: C, 63.92; H, 8.19.

An authentic sample was prepared in 77% yield from mesitylene-2-sulfonyl chloride and cyclohexylamine.

Attempted Preparation of 2,2′,4,4′,6,6′-Hexamethylsulfanilide. Sulfuryl chloride (2.33 g) was slowly added dropwise to a stirred solution of 2,4,6-trimethylaniline (4.82 g) in dry pyridine (20 mL) cooled in an ice–salt bath. After stirring for 30 min the temperature of the solution was allowed to reach that of the room, and the solution was poured into 3 N HCl (100 mL) and extracted with $CHCl_3$ (3 × 50 mL). The extracts were dried ($CaCl_2$), evaporated, and chromatographed on neutral alumina (2.3 × 25 cm). Elution with light petroleum–benzene (85:15 v/v) gave the azobenzene **13** (0.338 g, 8%), mp 73–74 °C, identical with an authentic sample.[18] No **14** could be detected.

Attempted Preparation of 2-Cyclohexylbenzenesulfonyl Chloride. 2-Cyclohexylnitrobenzene (**16**) was prepared from cyclohexylbenzene and fuming nitric acid by the method of Neunhoeffer.[21] It was purified from traces of para isomer remaining after distillation on a spinning band column by preparative gas–liquid chromatography. It was reduced[13b] to 2-cyclohexylaniline (85%), bp 89–90 °C (0.15 mm). The amine (1.3 g) in 20% aqueous HCl (10 mL) at 0 °C was diazotized with sodium nitrite (1 g) in water (5 mL). The solution was added to a cold solution of acetic acid (20 mL) and cupric chloride

(0.25 g). The solution was stirred for 1 h at 0–5 °C and for 3 h at 40 °C, and then poured into water (100 mL). It was extracted with ether, and the ether was dried (Na_2SO_4) and distilled. The residue was chromatographed on a column of silica gel (30 g). Elution with light petroleum–benzene (1:1 v/v) gave *o*-acetoxyphenylcyclohexane (**18**, 0.54 g, 33%), identical with an authentic sample prepared[22] by acetylation of the phenol. Elution with benzene gave *o*-cyclohexylphenol (**19**, 0.2 g, 15%), mp 56–57 °C (from light petroleum), identical with an authentic sample.[23]

The dry diazonium tetrafluoroborate (1.9 g) was prepared (95%) from the amine **17**. It was added at 0 °C to the above solution of SO_2, stirred for 1 h at 0 °C, and then heated at 50 °C for 1 h. Workup as above gave **18** (0.76 g, 47%) as the only identifiable product.

Chlorosulfonation of *p*-Dicyclohexylbenzene. A. In Ethylene Chloride. *p*-Dicyclohexylbenzene (1 g) in ethylene chloride (25 mL) was cooled in an ice bath and treated dropwise with chlorosulfonic acid (6 mL). The mixture was heated at 80 °C for 1 h, poured over ice, and extracted with ether. The dried (Na_2SO_4) ether extract was evaporated and chromatographed on a silica gel column (30 g). Elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave 4-cyclohexylbiphenyldisulfonyl chloride (0.35 g): mp 145–146 °C [light petroleum (bp 60–110 °C)]; NMR ($CDCl_3$) δ 8.2 (s, 1), 7.9 (d, 1), 7.8–7.5 (m, 5 H), 2.1–1.0 (m, 11 H); M^+· *m/e* 432 (2 ^{35}Cl).

Anal. Calcd for $C_{18}H_{18}Cl_2O_4S_2$: C, 49.93; H, 4.17. Found: C, 50.22; H, 4.36.

B. In Cyclohexane. *p*-Dicyclohexylbenzene (1 g) in cyclohexane (20 mL) at 0 °C was treated dropwise with chlorosulfonic acid (6 mL) and the mixture was then heated at 80 °C for 3 h. Workup as above followed by chromatography on silica gel (30 g) and elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave **1,4-dicyclohexylbenzene-2-sulfonyl chloride** (**21**, 1.13 g, 80%), mp 99–100 °C, M^+· (^{35}Cl) *m/e* 340.

Anal. Calcd for $C_{18}H_{25}ClO_2S$: C, 63.41; H, 7.39. Found: C, 63.25; H, 7.56.

1,4-Dicyclohexylbenzene-2-sulfonyl Azide (22). The sulfonyl chloride (1 g) in acetone (25 mL) at 0 °C was treated with sodium azide (1 g) in water (5 mL) and the mixture stirred for 1 h at 0 °C. It was then diluted with ice water (75 mL) and extracted with ether. The dried (Na_2SO_4) ether extract was evaporated to give the azide (0.87 g, 85%), mp 62–63 °C (MeOH), M^+· *m/e* 347.

Anal. Calcd for $C_{18}H_{25}N_3O_2S$: C, 62.20; H, 7.25. Found: C, 62.22; H, 7.28.

Thermolysis of 1,4-Dicyclohexylbenzene-2-sulfonyl Azide. The azide (1 g) in freshly distilled cyclohexane (20 mL) was heated in a glass-lined steel bomb under dry, O_2-free nitrogen for 72 h at 120 °C. The solvent was evaporated and the residue chromatographed on a column of silica gel (40 g). Elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave unchanged azide (0.1 g, 10%). Elution with benzene gave ***N*,1,4-tricyclohexylbenzene-2-sulfonamide** (**23**, 0.5 g, 48%): mp 145–146 °C (aqueous MeOH); M^+· *m/e* 403; identical with an authentic sample prepared (50% yield) from the sulfonyl chloride (**21**) and cyclohexylamine in boiling benzene for 12 h.

Anal. Calcd for $C_{24}H_{37}NO_2S$: C, 71.42; H, 9.24. Found: C, 71.58; H, 9.39.

Elution with benzene–ether (1:1 v/v) gave a mixture of sultams (**24**) (0.077 g, 9%), mp 65–85 °C (dilute EtOH or MeOH), which could not be resolved: IR (KBr) 3300 (s) (NH), 1325, 1160, 1150 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.6–7.2 (m, 3, ArH), 5.2 (d, 0.75, exchanges with D_2O, NH), 5.06 (s, 0.25, exchanges with D_2O, NH), 3.4 (br m, 0.25, equatorial (?) CHN<), 2.6 (br m, 0.75, axial (?) CHN<, overlapping with 2 H due to benzylic protons), 2.2–1.0 (br m, 18); mass spectrum *m/e* (rel intensity) 321 (M^+· + 2, 6), 320 (M^+· + 1, 8), 319 (M^+·, 32), 278 (20), 277 (100), 256 (35), 255 (M^+· − SO_2, 20), 197 (31), 142 (22), 130 (25), 78 (35), 57 (25), 56 (39), 55 (50), 43 (48), 41 (64).

Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.90. Found: C, 67.48; H, 8.07.

2-Methoxybenzenesulfonyl Azide (25). 2-Methoxybenzenesulfonyl chloride[24] (2.5 g) in acetone (60 mL) at 0 °C was treated with a solution of sodium azide (2.5 g) in water (15 mL) and stirred for 1 h at 0 °C. It was then poured into water (100 mL) and extracted with ether. The dried (Na_2SO_4) extract was evaporated to give the azide (2.2 g, 85%): mp 75–76 °C (MeOH); IR (KBr) 2140 (N_3), 1360, 1160 cm^{-1} (SO_2); M^+· *m/e* 213 (8).

Anal. Calcd for $C_7H_7N_3O_3S$: C, 39.43; H, 3.31. Found: C, 39.53; H, 3.42.

Thermolysis of 2-Methoxybenzenesulfonyl Azide. The azide (1 g) in cyclohexane (20 mL) under dry, O_2-free N_2 was heated in a glass-lined steel bomb at 120 °C for 72 h. The solvent was evaporated and the black residual mass was chromatographed on a column of silica gel (40 g). Elution with benzene–ether (1:1 v/v) gave ***N*-cyclohexyl-2-methoxybenzenesulfonamide** (**27**, 0.53 g, 42%): mp 103–104 °C (dilute MeOH); IR (KBr) 3280 (NH), 1320, 1160 cm^{-1} (SO_2); NMR ($CDCl_3$) δ 7.9 (dd, 1), 7.5 (m, 1), 7.04 (m, 2), 5.1 (d, 1, exchanges with D_2O, NH), 3.96 (s, 3, OCH_3), 3.1 (br m, 1, CH<), 1.73–1.2 (m, 10); mass spectrum *m/e* (rel intensity) 271 (1), 270 (3), 269 (M^+·, 17), 226 (76), 177 (100), 92 (22), 79 (24), 77 (97).

Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.96; H, 7.11. Found: C, 58.39; H, 7.24.

An authentic sample of **27** was prepared (84% yield) from the sulfonyl chloride and cyclohexylamine in boiling benzene and was identical with the above product.

2-Thiomethoxybenzenesulfonyl Chloride. 2-Nitrothioanisole[25] (5.5 g) in ethanol (10 mL) was treated with iron powder (14 g) and then 10% HCl (8 drops) and the mixture was boiled under reflux for 20 h. It was cooled, ether (75 mL) was added, and the mixture was filtered through a plug of cotton. The filtrate was extracted with ether, and the combined ether extracts were dried (Na_2SO_4) and evaporated to give 2-aminothioanisole (3.3 g, 73%). This was used without further purification. It was dissolved in glacial acetic acid (15 mL) and concentrated HCl (6 mL), and the solution was cooled to 0 °C and diazotized with sodium nitrite (2.7 g) in water (15 mL). The solution was added at 0 °C to acetic acid (60 mL) and cupric chloride (0.66 g). After 0.5 h at 0 °C the mixture was stirred at 45 °C for 2 h and then poured into ice–water (200 mL). It was extracted with ether and the dried (Na_2SO_4) extracts were evaporated. The semisolid residue was chromatographed on a silica gel column (30 g). Elution with light petroleum (bp 30–60 °C)–benzene (1:1 v/v) gave the sulfonyl chloride (2.2 g, 42%): mp 67–68 °C (light petroleum); IR (KBr) 1370, 1175 cm^{-1}; M^+· (^{37}Cl) *m/e* 224, (^{35}Cl) 222.

Anal. Calcd for $C_7H_7ClO_2S_2$: C, 37.75; H, 3.17. Found: C, 37.70; H, 3.11.

2-Thiomethoxybenzenesulfonyl Azide (26). This was prepared in the usual way from the sulfonyl chloride to give the azide (81%): mp 47–48 °C (dilute MeOH); IR (KBr) 2140, 1355, 1165 cm^{-1}; M^+· *m/e* 229.

Anal. Calcd for $C_7H_7N_3O_2S_2$: C, 36.67; H, 3.08. Found: C, 36.80; H, 3.14.

Thermolysis of 2-Thiomethoxybenzenesulfonyl Azide. The azide (0.6 g) in cyclohexane (20 mL) was thermolyzed as usual at 130 °C for 72 h. Chromatography of the reaction products on silica gel and elution with benzene gave ***N*-cyclohexyl-2-thiomethoxybenzenesulfonamide** (**28**, 0.14 g, 19.7%), mp 83–84 °C (MeOH), identical with an authentic sample prepared (74% yield) from the sulfonyl chloride and cyclohexylamine in boiling benzene.

Anal. Calcd for $C_{13}H_{19}NO_2S_2$: C, 54.74; H, 6.67. Found: C, 54.40; H, 6.91.

Elution with ether gave **2-thiomethoxybenzenesulfonamide** (**29**, 0.11 g, 20.7%), mp 182–183 °C (MeOH), identical with an authentic sample prepared from the sulfonyl chloride and ammonium hydroxide (79% yield).

Anal. Calcd for $C_7H_9NO_2S_2$: C, 41.38; H, 4.43. Found: C, 40.97; H, 4.20.

2-Chloro-5-dimethylaminobenzenesulfonyl Chloride (32). *p*-Chloro-*N*,*N*-dimethylaniline (1 g) was heated with chlorosulfonic acid (6 mL) dropwise at 0 °C over a period of 20 min. The mixture was then heated at 110 °C for 18 h, cooled to room temperature, poured over crushed ice, and extracted with ether. The dried (Na_2SO_4) extract was evaporated to give a green oil which was chromatographed on a column of silica gel (30 g). Elution with benzene gave the sulfonyl chloride (0.33 g, 20.2%) as yellow needles, mp 105–106 °C (light petroleum).

Anal. Calcd for $C_8H_9Cl_2NO_2S$: C, 37.81; H, 3.57. Found: C, 38.00; H, 3.67.

2-Chloro-5-dimethylaminobenzenesulfonyl Azide (33). This was prepared as usual from **32** in 60% yield and had mp 54–55 °C [from light petroleum–$CHCl_3$ (9:1 v/v)].

Anal. Calcd for $C_8H_9ClN_4O_2S$: C, 36.85; H, 3.48. Found: C, 37.07; H, 3.64.

Thermolysis of 2-Chloro-5-dimethylaminobenzenesulfonyl Azide in Benzene. The azide (1 g) in benzene (20 mL) was decomposed as usual at 130 °C for 48 h. The products were chromatographed on silica gel (40 g). Elution with benzene–light petroleum (1:1 v/v) gave recovered azide (0.1 g, 10%). Elution with benzene gave **2-chloro-5-dimethylaminobenzenesulfonanilide** (**34**, 0.15 g, 14%), mp 215–216 °C (dilute MeOH), identical with an authentic sample prepared in 96% yield from **32** and aniline.

Anal. Calcd for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.87. Found: C, 53.74; H, 5.24.

Elution with benzene–ether (1:1 v/v) gave **2-chloro-5-dimethylaminobenzenesulfonamide** (0.12 g, 15%), mp 160–161 °C (ben-

zene–light petroleum), identical with an authentic sample prepared in 67% yield from the sulfonyl chloride and ammonium hydroxide.

Anal. Calcd for $C_8H_{11}ClN_2O_2S$: C, 40.94; H, 4.72. Found: C, 41.29; H, 4.64.

2-Methylamino-5-nitrobenzenesulfonyl Chloride (38). Dimethylammonium 2-dimethylamino-5-nitrobenzenesulfonate[26] (7.0 g) was heated with phosphorus pentachloride (7.0 g) at 150 °C for 3 h. Water (30 mL) was added, the mixture was extracted with chloroform (3 × 50 mL), and the chloroform was washed with water (2 × 20 mL), 1% aqueous NaOH (10 mL), and then again with water (20 mL). It was dried ($MgSO_4$) and concentrated to afford a dark residue which was chromatographed on a column of silica gel (50 g). Elution with chloroform (200 ml) gave **2-methylamino-5-nitrobenzenesulfonyl chloride** as yellow prisms (3.1 g, 50%): mp 146–147 °C (from chloroform); IR (KBr) 3400 (s) (NH), 1360 (s), 1330 (s), 1310 (s) (SO_2), 1160 cm^{-1} (SO_2); NMR (acetone-d_6) δ 8.57 (d, 1, J = 3 Hz, H_6), 8.35 (dd, 1, J = 3 and 9 Hz, H_4), 7.25 (d, 2, J = 9 Hz, one proton exchanges with D_2O, H_3 and NH), 3.21 (d, 3, J = 6 Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 252 (42), 250 (100), 234 (1), 222 (1), 220 (2), 215 (25), 197 (50), 167 (33), 151 (75), 155.3*.

Anal. Calcd for $C_7H_7ClN_2O_4S$: C, 33.54; H, 2.82. Found: C, 33.60; H, 2.84.

2-Methylamino-5-nitrobenzenesulfonyl Azide (39). The sulfonyl chloride (1.3 g) in acetone (30 mL) at 0 °C was treated with sodium azide (1.2 g) in water (6 mL). After stirring the mixture for 1 h it was poured into water (100 mL) and extracted with chloroform to give the azide (**39**, 1 g, 75%), mp 138–139 °C (MeOH).

Anal. Calcd for $C_7H_7N_5O_4S$: C, 32.68; H, 2.74. Found: C, 32.81; H, 2.81.

Thermolysis of 2-Methylamino-5-nitrobenzenesulfonyl Azide in Cyclohexane. The azide (1 g) in cyclohexane (20 mL) was decomposed as usual at 135 °C for 30 h. Chromatography of the products on a column of silica gel (40 g) and elution with light petroleum–benzene (1:1 v/v) gave recovered azide (0.2 g) and ***N*-cyclohexyl-2-methylamino-5-nitrobenzenesulfonamide** (41), mp 161–162 °C (dilute MeOH), identical with an authentic sample prepared from the sulfonyl chloride **38** and cyclohexylamine in boiling benzene.

Anal. Calcd for $C_{13}H_{19}N_3O_4S$: C, 49.82; H, 6.11. Found: C, 49.87; H, 6.21.

Elution with benzene–ether (1:1 v/v) gave **3-methyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (40,** 0.22 g, 30.8%): mp 233–234 °C (dilute MeOH); NMR ($CDCl_3$) δ 7.95 (s, 1), 7.62 (d, 1), 7.10 (d, 1), 7.0 (br s, 1, exchangeable, NH), 3.32 (s, 3, NCH_3); M^+· m/e 229.

Anal. Calcd for $C_7H_7N_3O_4S$: C, 36.68; H, 3.08. Found: C, 36.91; H, 3.20.

2-Dimethylamino-5-nitrobenzenesulfonyl Chloride (42). Dimethylammonium 2-dimethylamino-5-nitrobenzenesulfonate (10 g) was heated with thionyl chloride (10 mL) and dimethylformamide (0.5 mL) until the mixture became homogeneous, then for 1 h more. Excess thionyl chloride was removed in vacuo and water was added to the residue. An oil separated which crystallized. Recrystallization from benzene–hexane gave yellow crystals of **2-dimethylamino-5-nitrobenzenesulfonyl chloride** (7 g, 74%): mp 111–113 °C dec (benzene–light petroleum); IR (KBr) 1360 (s), 1325 (vs), 1265, 1155 cm^{-1} (s); NMR ($CDCl_3$) δ 8.98 (d, 1, J = 2.5 Hz, H_6), 8.33 (dd, 1, J = 2.5 and 10 Hz, H_4), 7.12 (d, 1, J = 10 Hz, H_3), 3.30 (s, 6, dimethylamino); mass spectrum m/e (rel intensity) 266 (7), 264 (19), 166 (90), 165 (30), 136 (45), 135 (27), 120 (31), 119 (100).

Anal. Calcd for $C_8H_9ClN_2O_4S$: C, 36.72; H, 3.43. Found: C, 36.83; H, 3.58.

2-Dimethylamino-5-nitrobenzenesulfonyl Azide (43). To an acetone (25 mL) solution of 2-dimethylamino-5-nitrobenzenesulfonyl chloride (0.5 g) at 0 °C was was added an aqueous solution (50 mL) of sodium azide (1.1 g). The mixture was stirred for 12 h at ambient temperature, then poured over ice water (100 mL). The organic portion was extracted with chloroform (30 mL), dried ($MgSO_4$), and concentrated to afford 2-dimethylamino-5-nitrobenzenesulfonyl azide as a yellow solid (0.4 g, 78%): mp 87–88.5 °C dec (lit.[14] 87 °C); IR (KBr) 2120 (s), 1355 (s), 1320 (s), 1160 cm^{-1} (s); NMR ($CDCl_3$) δ 8.88 (d, 1, J = 2.5 Hz, H_6), 8.40 (dd, 1, J = 2.5 and 7 Hz, H_4), 7.35 (d, 1, J = 7 Hz, H_3), 3.11 (s, 6, dimethylamino); mass spectrum m/e (rel intensity) 271 (M^+· 22), 229 (22), 228 (27), 214 (14), 167 (13), 151 (15), 150 (13), 149 (11), 136 (18), 135 (11), 133 (14), 132 (65), 119 (100), 118 (39), 105 (51), 104 (30).

Anal. Calcd for $C_8H_9N_5O_4S$: C, 35.42; H, 3.34. Found: C, 35.53; H, 3.29.

2-Dimethylamino-5-nitrobenzenesulfonamide (49a). Ammonia was bubbled through a benzene solution (30 mL) of 2-dimethylamino-5-nitrobenzenesulfonyl chloride (0.5 g) at room temperature. After 1 h ammonium chloride was filtered. The filtrate was concentrated to give a yellow solid. Recrystallization from benzene afforded **2-dimethylamino-5-nitrobenzenesulfonamide** (0.27 g, 55%): mp 164–166 °C: IR (KBr) 3340 (s), 3250 (s), 1340 (vs), 1155 cm^{-1} (s); NMR (CD_3CN) δ 8.90 (d, 1, J = Hz, H_6), 8.55 (dd, 1, J = 3 and 9 Hz, H_4), 7.75 (d, 1, J = 9 Hz, H_3), 6.2 (br s, 1, exchanges with D_2O, NH), 3.05 (s, 6, dimethylamino); M^+·, m/e 245.

Anal. Calcd for $C_8H_{11}N_3O_4S$: C, 39.18; H, 4.52. Found: C, 39.29; H, 4.54.

***N*-Cyclohexyl-2-dimethylamino-5-nitrobenzenesulfonamide (49b).** 2-Dimethylamino-5-nitrobenzenesulfonyl chloride (0.5 g) and cyclohexylamine (0.5 g) in benzene (25 mL) were stirred at room temperature for 1 h. The cyclohexylamine hydrochloride (0.24 g, 90%) was filtered. The filtrate was concentrated to give a yellow solid, recrystallization of which from benzene–hexane gave ***N*-cyclohexyl-2-dimethylamino-5-nitrobenzenesulfonamide** (0.44 g, 70%): mp 141–142 °C; IR (KBr) 3240 (s), 1130 (vs), 1150 cm^{-1} (s); M^+·, m/e 327.

Anal. Calcd for $C_{14}H_{21}N_3O_4S$: C, 51.36; H, 6.47. Found: C, 51.19; H, 6.55.

2-Dimethylamino-5-nitrobenzenesulfonanilide (49b). 2-Dimethylamino-5-nitrobenzenesulfonyl chloride (0.1 g) and aniline (0.5 mL) in benzene (10 mL) were kept at room temperature for 4 h. Aniline hydrochloride was filtered and the filtrate concentrated to give **2-dimethylamino-5-nitrobenzenesulfonanilide** (0.1 g, 82%): mp 129–130 °C (EtOH); IR (KBr) 3260 (s), 1340 (s), 1157 cm^{-1} (s); NMR ($CDCl_3$) δ 8.87 (d, 1, J = 3 Hz, H_6), 8.37 (dd, 1, J = 3 and 9 Hz, H_4), 7.92 (br s, 1, exchanges with D_2O, NH), 7.40 (d, 1, J = 9 Hz, H_3), 7.15 (s, 5, phenyl), 3.05 (s, 3, methyl); M^+·, m/e 321.

Anal. Calcd for $C_{14}H_{15}N_3O_4S$: C, 52.33; H, 4.70. Found: C, 52.29; H, 4.79.

2-Methylamino-5-nitrobenzenesulfonamide (45). Ammonia was bubbled through a 1,2-dimethoxyethane (20 mL) solution of 2-methylamino-5-nitrobenzenesulfonyl chloride (**38**) for 30 min at room temperature. Filtration of the ammonium chloride and concentration of the filtrate gave **2-methylamino-5-nitrobenzenesulfonamide** (0.39 g, 64%): mp 260–262 °C (Me_2SO); IR (KBr) 3360 (s), 3240 (s), 1325 (vs), 1155 cm^{-1} (s); NMR ($CDCl_3$) δ 8.72 (d, 1, J = 3 Hz, H_6), 8.30 (dd, 1, J = 3 and 9 Hz, H_4), 7.42 (d, 1, J = 9 Hz, H_3), 5.64 (br s, 1, NH), 2.92 (s, 3, methyl); M^+· m/e 231.

Anal. Calcd for $C_7H_9N_3O_4S$: C, 36.35; H, 3.92. Found: C, 36.41; H, 3.94.

3,4-Dihydro-4-methyl-7-nitro-(2*H*)-benzo[e]-1,2,4-thiadiazine 1,1-Dioxide (44). 2-Methylamino-5-nitrobenzenesulfonamide (1.2 g) in aqueous 37% formaldehyde solution (9 mL) was heated in a sealed tube at 100 °C for 2 days. On cooling, a yellow oil separated. Crystallization from acetonitrile afforded **3,4-dihydro-4-methyl-7-nitro-(2*H*)-benzo[e]-1,2,4-thiadiazine 1,1-dioxide** (0.8 g, 67%): mp 226–228 °C; IR (KBr) 3300 (m), 1300 (vs), 1165 cm^{-1} (s); NMR (CD_3CN) δ 3.1 (s, 3, CH_3), 4.8 (d, 2, J = 8 Hz, CH_2), 6.2 (br s, 1, NH), 6.8 (d, 1, J = 12 Hz, H_5), 8.2 (dd, 1, J = 12 Hz and 3 H_6), 8.4 (d, 1, J = 3 Hz, H_8); M^+· m/e 243.

Anal. Calcd for $C_8H_9N_3O_4S$: C, 39.50; H, 3.73. Found: C, 39.52; H, 3.77.

Decomposition of 2-Dimethylamino-5-nitrobenzenesulfonyl Azide. a. In Cyclohexane. 2-Dimethylamino-5-nitrobenzenesulfonyl azide (1.0 g) in cyclohexane (60 mL) was heated at 120 °C for 2 days. The cyclohexane was decanted from orange 3,3-dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (**46,** 0.65 g, 72%): mp 183–186 °C dec (acetonitrile) (lit.[14] 188 °C); IR (KBr) 1350 (s), 1280 (s), 1160 (s), 1120 cm^{-1} (s); NMR (CD_3CN/D_2O) δ 8.8 (m, 3, aromatic), 4.09 (s, 6, methyl); mass spectrum m/e (rel intensity) 243 (M^+·, 85), 241 (19), 227 (10), 215 (34), 214 (56), 213 (19), 211 (41), 207 (29), 178 (14), 167 (33), 151 (45). 150 (34), 121 (20), 120 (49), 105 (100).

Anal. Calcd for $C_8H_9N_3O_4S$: C, 39.50; H, 3.73. Found: C, 39.58; H, 3.83.

Evaporation of the cyclohexane solution afforded an orange oil (0.17 g) which was resolved by TLC (silica gel, 1.5 mm thick, benzene development) into the following.

(a) 2-Dimethylamino-5-nitroaniline (**48,** 5.2 mg, 1%): R_f 0.7; mp 59–60 °C (from water) (lit.[27] 63 °C); identical with an authentic sample.

(b) **2,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (47,** 33 mg, 4%): R_f 0.5; mp 135 °C (from ethanol); IR (KBr) 1500 (s), 1320 (s), 1160 cm^{-1} (s); NMR ($CDCl_3$) δ 8.45 (d, 1, J = 2 Hz, H_6), 8.39 (dd, 1, J = 2 and 9 Hz, H_4), 7.05 (d, 1, J = 9 Hz, H_3), 3.33 (s, 3, methyl), 2.96 (s, 3, methyl); mass spectrum m/e (rel intensity) 243 (M^+·, 25), 179 (54). 178 (32), 151 (14), 150 (26), 149 (11), 133 (38), 132 (81), 120 (21), 106 (13), 105 (78), 92 (100).

Anal. Calcd for $C_8H_9N_3O_4S$: C, 39.51; H, 3.73. Found: C, 39.35; H, 3.82.

(c) *N*-Cyclohexyl-2-dimethylamino-5-nitrobenzenesulfonamide (**49b**, 16 mg, 2%): R_f 0.4; mp 140–142 °C (from ethanol); mmp 140–142 °C; identical with an authentic sample.

(d) An orange oil (38 mg, 4% by weight of azide): R_f 0.3; IR (KBr) 3120 (s, br), 1500 (s), 1340 (vs), 1310 (s), 1170 cm^{-1} (s); NMR (acetone-d_6) δ 8.78 (br s, 1, exchanges with D_2O, NH), 8.48 (d, 1, J = 2 Hz, H_6), 8.38 (dd, 1, J = 2 and 9 Hz, H_4), 7.36 (d, 1, J = 9 Hz, H_3), 3.42 (s, 3, methyl); this was different from **40** and has not been identified yet.

(e) 2-Dimethylamino-5-nitrobenzenesulfonamide (**49a**) (43 mg, 4%): R_f 0.2; mp 164–164.5 °C (from ethanol); identical with the sample prepared above.

B. In Benzene. 2-Dimethylamino-5-nitrobenzenesulfonyl azide (2 g) in benzene (130 mL) was heated at 120 °C for 2 days. 3,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (1.47 g, 81%), mp 183–186 °C, identical with that obtained above, separated. The filtrate was concentrated to afford an oil (0.344 g) which was resolved into its components by TLC (silica gel, 1.5 mm thick, benzene development) to give the following fractions. (a) 2-dimethylamino-5-nitrobenzenesulfonyl azide (44 mg, 2%), mp 88–89 °C, IR (KBr) 2110 cm^{-1}. (b) 2-Dimethylamino-5-nitroaniline (**48**, 42 mg, 3%), mp 60 °C. (c) 2,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (**47**, 16 mg, 1%), mp 129–132 °C. (d) The same unidentified orange oil (62 mg, 3%) as that obtained above. (e) 2-Dimethylamino-5-nitrobenzenesulfonamide (**49a**, 65 mg, 3%), mp 173–175 °C.

C. In Chlorobenzene. 2-Dimethylamino-5-nitrobenzenesulfonyl azide (1.5 g) was heated in chlorobenzene at 150 °C for 50 h. The solution had turned from yellow to red-brown. Concentration afforded a dark oil which was resolved into its components by TLC (silica gel, benzene–2-propanol, 9:1 v/v, developer). There were thus isolated the following. (a) 2,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (118 mg, 9%), mp 135 °C. (b) 4-Nitrodimethylaniline (137 mg, 15%), mp 162–163 °C (lit.[28] 163 °C), identical with an authentic sample.

Thermolysis of 3,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiazoline 1,1-Dioxide (46). 3,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (197 mg) was heated in cyclohexane (30 mL) for 2 days at 130 °C. Undecomposed thiadiazoline (0.13 g) was filtered off, and the cyclohexane solution was concentrated to an orange residue which was resolved into its components by TLC (silica gel, 1.5 mm thick, benzene then ethanol developer). The following components were separated. (a) 2,3-Dimethyl-6-nitrobenzo[*d*]-1,2,3-thiadiazoline 1,1-dioxide (11 mg, 19%), mp 135 °C. (b) An unidentified oil (17 mg): IR (KBr) 3120 (s, br), 1500 (s), 1360 (s), 1170 cm^{-1} (s). (c) 2-Dimethylamino-5-nitrobenzenesulfonamide (**49a**, 3 mg, 4%), identical with an authentic sample.

Acknowledgments. We wish to thank the National Institutes of Health (NBO-8716) and the National Science Foundation (MPS 75-09309) for grants in support of this work (1970–1975) and the University of Alabama for the award of a Research Fellowship (to D.P.V.) (1970–1971).

Registry No.—**4**, 62533-27-1; **5**, 22172-75-4; **6**, 95-93-2; **7**, 24906-63-6; **8** (R = $C_{12}H_{25}$), 25167-18-4; **9** (R = $C_{12}H_{25}$), 24906-65-8; **9** (R = C_6H_{11}), 62533-28-2; **11**, 24906-66-9; **14**, 62533-29-3; **21**, 62533-30-6; **22**, 62533-31-7; **23**, 62533-32-8; *cis*-**24**, 62533-33-9; *trans*-**24**, 62533-34-0; **25**, 62533-35-1; **26**, 62533-36-2; **27**, 62533-37-3; **28**, 62533-38-4; **29**, 62533-39-5; **32**, 62533-40-8; **33**, 62533-41-9; **34**, 62533-42-0; **35**, 62533-43-1; **37**, 62571-49-7; **38**, 62533-44-2; **39**, 62533-45-3; **40**, 62533-46-4; **41**, 62533-47-5; **42**, 62533-48-6; **43**, 35032-59-8; **44**, 62533-49-7; **45**, 62533-50-0; **46**, 35032-44-1; **47**; 62533-51-1; **48**, 5367-52-2; **49a**, 16611-57-7; **49b** (R = C_6H_{11}), 62533-52-2; **49b** (R = Ph), 62533-53-3; sodium azide, 12136-89-9; durene-3-sulfonyl chloride, 60706-63-0; dodecane, 112-40-3; cyclohexane, 110-82-7; *p*-dicyclohexylbenzene, 1087-02-1; 4-cyclohexylbiphenyldisulfonyl chloride, 62533-84-0; 2-methoxybenzenesulfonyl chloride, 10130-87-7; 2-thiomethoxybenzenesulfonyl chloride, 60036-45-5; 2-nitrothioanisole, 3058-47-7; 2-aminothioanisole, 2987-53-3; *p*-chloro-*N*,*N*-dimethylaniline, 698-69-1; cyclohexylamine, 108-91-8; aniline, 62-53-3.

References and Notes

(1) For preliminary communications on part of this work, see R. A. Abramovitch, C. I. Azogu, and I. T. McMaster, *J. Am. Chem. Soc.*, **91**, 1219 (1969); R. A. Abramovitch and W. D. Holcomb, *Chem. Commun.*, 1298 (1969).
(2) R. A. Abramovitch, T. Chellathurai, I. T. McMaster, T. Takaya, C. I. Azogu, and D. P. Vanderpool, preceding paper in this issue.
(3) G. Smolinsky, *J. Am. Chem. Soc.*, **82**, 4717 (1960).
(4) G. Smolinsky, *J. Am. Chem. Soc.*, **83**, 2487 (1961); *J. Org. Chem.*, **26**, 4108 (1961).
(5) D. S. Breslow, M. F. Sloan, N. R. Newburg, and W. B. Renfrow, *J. Am. Chem. Soc.*, **91**, 2273 (1969).
(6) P. A. S. Smith, in "Nitrenes", W. Lwowski, Ed., Interscience, New York, N.Y., 1970, Chapter 4, p 99; R. A. Abramovitch in "Organic Reactive Intermediates", S. P. McManus, Ed., Academic Press, New York, N.Y., 1973, Chapter 3, p 127.
(7) E. W. Parnell, *J. Chem. Soc.*, 4366 (1960).
(8) A. Wohl and F. Koch, *Ber.*, **43**, 3295 (1910).
(9) T. Curtius, *Angew. Chem.*, **27**, 213 (1914); A. Bertho, *J. Prakt. Chem.*, **120**, 89 (1929); T. Curtius, *ibid.*, **125**, 303 (1930).
(10) W. Lwowski and E. Scheiffele, *J. Am. Chem. Soc.*, **87**, 4359 (1965).
(11) W. T. Reichle, *Inorg. Chem.*, **3**, 402 (1964).
(12) G. P. Balabanov, Yr. I. Dergunov, and V. A. Gal'perin, *J. Org. Chem. USSR (Engl. Transl.)*, **2**, 1797 (1966).
(13) (a) H. Meerwein, G. Dittmar, R. Göllner, K. Haffner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1957). (b) A. J. Neale, T. J. Rawlings, and E. B. McCall, *Tetrahedron*, **21**, 1299 (1965).
(14) J. Martin, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 2451 (1974); *Chem. Commun.*, 1319 (1971).
(15) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).
(16) M. F. Sloan, T. J. Prosser, N. R. Newburg, and D. S. Breslow, *Tetrahedron Lett.*, 2945 (1964).
(17) H. R. Snyder and R. E. Heckert, *J. Am. Chem. Soc.*, **74**, 2006 (1952).
(18) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).
(19) E. H. Huntress and J. S. Autenrieth, *J. Am. Chem. Soc.*, **63**, 3446 (1941).
(20) R. A. Abramovitch and J. S. Williams, *Chem. Ind. (London)*, 1786 (1965).
(21) O. Neunhoeffer, *J. Prakt. Chem.*, **133**, 95 (1932).
(22) G. T. Bottger, A. P. Yerington, and S. I. Gertler, *U.S. Bur. Entomol. Plant Quarantine*, E-859 (1953); *Chem. Abstr.*, **47**, 7724c (1953).
(23) S. Skraup and W. Beifuss, *Ber.*, **60**, 1070 (1927); J. F. Bartlett and C. E. Garland, *J. Am. Chem. Soc.*, **55**, 2064 (1933).
(24) H. J. Weigmann and G. Malewski, *Spectrochim. Acta*, **22**, 1045 (1966).
(25) M. Claasz, *Ber.*, **45**, 1022 (1912).
(26) L. W. Jones and E. B. Hartshorn, *J. Am. Chem. Soc.*, **46**, 1852 (1924).
(27) A. I. Vogel, "A Textbook of Practical Organic Chemistry", 3rd. ed, Longmans, Green and Co., New York, N.Y., 1958, p 573.
(28) E. Heim, *Ber.*, **21**, 2308 (1888).

Reaction of Some Benzo[b]thiophene 1,1-Dioxides with Hydroperoxide Ion

Solomon Marmor

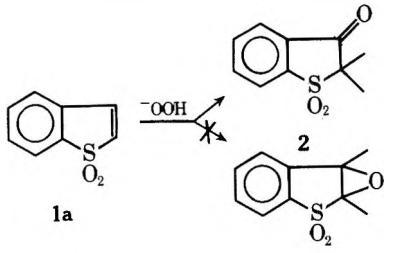
Department of Chemistry, California State College—Dominguez Hills, Dominguez Hills, California 90747

Received December 30, 1976

Unlike open-chain α,β-unsaturated sulfones, benzo[b]thiophene 1,1-dioxide (**1a**) and 3-R-benzo[b]thiophene 1,1-dioxides (**1b**, R = Me; **1c**, R = Et; **1d**, R = Ph) react anomalously with hydroperoxide ion. Rather than the epoxide, 3-oxo-2*H*-benzo[b]thiophene 1,1-dioxide (**2**) is obtained from **1a**, and **1b–d** react to form the corresponding 3-hydroxy-2*H* derivatives **5**. Hydration of **1b–d** is presumed to involve decomposition of the hydroperoxide intermediate and is not merely hydroxide ion catalyzed addition of water, since the rate of reaction with aqueous sodium hydroxide is far slower than with alkaline hydrogen peroxide. Compound **1c** was also isomerized to 3-ethylidene-2*H*-benzo[b]thiophene 1,1-dioxide (**6**) with alkaline hydrogen peroxide, but was converted to **5** (R = Et) only with sodium hydroxide. Possible mechanisms are considered.

The conversion of phenyl styryl sulfone and related compounds to the corresponding epoxides via the reaction with alkaline hydrogen peroxide[1] appears to parallel the behavior of α,β-unsaturated carbonyl compounds.[2] The reaction was shown to be stereoselective, resulting in the formation of the trans epoxide, and presumably follows the accepted mechanism for the epoxidation of enones.[3] However, application of the reaction to the cyclic unsaturated sulfone, benzo[b]thiophene 1,1-dioxide (**1a**), has been found to lead to an apparently anomalous result.

Treatment of **1a** with hydrogen peroxide and aqueous sodium hydroxide in pyridine[4] results in the formation of 3-oxo-2,3-dihydrobenzo[b]thiophene 1,1-dioxide (**2**), rather than the expected epoxide **3**. The identity of the ketone was verified by comparison of the infrared and NMR spectra with those of an authentic sample prepared by an alternate route.[5]



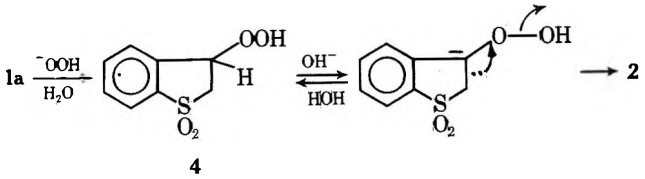
1a **2** **3**

The possibility of a rapid rearrangement of initially formed **3** to **2** is considered unlikely, since such rearrangements normally are effected by acid catalysis or occur at elevated temperatures,[6a–c] or via prolonged heating with a strong base such as lithium diethylamide.[6d] One possible route to the ketone, which requires removal of the proton from C-3, is shown in Scheme I.

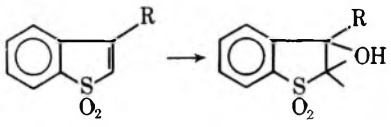
Subjection of some 3-substituted benzo[b]thiophene 1,1-dioxides to the reaction also led to some unexpected results, as shown below (yield data in Table I). It was also observed that 2,3-dimethylbenzo[b]thiophene 1,1-dioxide did not react at all with OOH^-.

The formation of **6** from **1c** would appear to be a simple base-catalyzed isomerization. However, treatment of **1c** with NaOH with or without pyridine gave no **6**; this reaction is being further examined. It is noteworthy that dehydration of **5** (R = Et) by treatment with benzoyl chloride led to **6**, rather

Scheme I



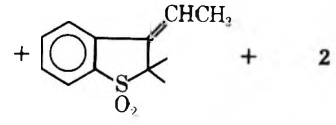
4



1 **5**

a, R = H
b, R = Me
c, R = Et
d, R = Ph

(from **1b–d**)



6

(from **1c**) (from **1a**)

than **1c**, pointing to the higher degree of stability of the exocyclic double-bond structure. The 3-methylene isomer was not obtained either in the reaction of **1b** with hydroperoxide ion or of **5** (R = Me) with benzoyl chloride. However, **5** (R = Ph) was dehydrated with PhCOCl to **1d**, as expected.

The formation of the 3-hydroxy products **5** appears on the surface to be a simple case of base-catalyzed hydration. However, the unusual character of the reaction is evident when comparisons are made of the attempts to prepare the alcohols via direct hydration of the parent compounds, using aqueous sodium hydroxide, with the reactions involving the alkaline hydrogen peroxide reagent. Using a modification of the method reported[7] for the preparation of 3-hydroxy-2,3-dihydrobenzo[b]thiophene 1,1-dioxide, **5** (R = Me) was obtained in 85% yield, and **5** (R = Et) in 47% yield (71% unreacted starting material recovered), only after mixtures of the parent compounds and aqueous sodium hydroxide in pyridine were refluxed for extended periods (7–30 h). On the other hand, with hydroperoxide ion the exothermic reaction was found to be essentially complete after 4 h at temperatures no higher than 35 °C. To account for the difference, an analogy may be drawn to the recently reported rapid hydrolysis of amides with hydroperoxide ion.[8] The postulated intermediate adduct was believed to decompose to ammonia and peroxycarboxylate ion, the latter in turn decomposing to carboxylate. It may, therefore, be presumed that the anion resulting from the initial attack of hydroperoxide ion on **1b–d** decomposes to the anion of **5**. Further studies involving other substituted benzo[b]thiophene 1,1-dioxides, as well as other five- and six-membered heterocyclic unsaturated sulfone systems are in progress.

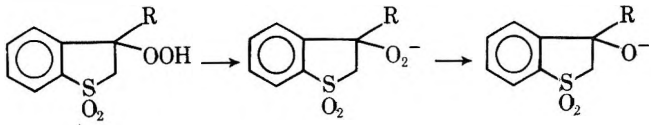


Table I. Reactions of 1 with OOH^- in Pyridine

Registry no.		R	Products (% yield)
825-44-3	**1a**	H	**2** (47%)
6406-91-3	**1b**	Me	**5**, R = Me (65%)[a]
16958-00-2	**1c**	Et	**6** (62%); **5**, R = Et (20%); **2** (1%)
27183-55-7	**1d**	Ph	**5**, R = Ph (47%)[a]

[a] Based on amount of starting material converted to product.

Experimental Section

Infrared spectra were obtained on a Beckman Acculab 2 or 4250 spectrophotometer; NMR spectra were recorded on a Varian Associates T-60 instrument. All melting points are uncorrected. Elemental analyses were done by Galbraith Laboratories, Knoxville, Tenn.

Materials. Benzo[*b*]thiophene 1,1-dioxide was prepared from benzo[*b*]thiophene (Aldrich Chemical Co.) by oxidation[9] with hydrogen peroxide in acetic acid. 3-Methylbenzo[*b*]thiophene was prepared by cyclization of 1-phenylthio-2-propanone (Parish Chemical Co.) with P_2O_5.[10] 3-Ethylbenzo[*b*]thiophene was obtained via the reaction of 1-bromo-2-butanone[11] with sodium thiophenoxide, followed by cyclization,[10] or by acetylation of benzo[*b*]thiophene, followed by Clemmensen reduction.[12] 2,3-Dimethylbenzo[*b*]thiophene was formed by cyclization[10] of 3-phenylthio-2-butanone (from 3-bromo-2-butanone[11] + PhSNa). The alkylbenzothiophenes were then converted to the 1,1-dioxides by oxidation with hydrogen peroxide in acetic acid. 3-Phenylbenzo[*b*]thiophene 1,1-dioxide was prepared through the sequence of reactions described by Bordwell et al.[13] from 1,1-diphenylethene.[14]

General Procedure for Reaction of Benzo[*b*]thiophene 1,1-Dioxides with Hydroperoxide Ion. To a solution of 1 mmol of **1** in pyridine (2–6 mL/mmol; sufficient to produce a homogeneous solution when the aqueous reagents are included) was added an excess of 30% hydrogen peroxide (2.5–3.0 mmol/mmol of **1**). A 10% excess of 1 or 2 M NaOH was then added[15] over a period of 10 min, while maintaining the temperature at 30–35 °C. Stirring was continued at 30–35 °C until titration of aliquots with 0.1 N Ce(IV)[16] indicated no further consumption of H_2O_2. The reaction mixture was poured into ice–water (10–15 mL/mmol of **1**) and processed as noted below.

Benzo[*b*]thiophene 1,1-Dioxide (1a). Following the oxidation of 1.0 g (6.0 mmol) of **1a**, which was carried out at 0–5 °C for 1 h, the resulting bright-yellow solution was acidified with concentrated HCl, which caused the separation of a small amount of solid (not removed by filtration). The mixture was extracted three times with 20-mL portions of methylene chloride, and the combined extracts were dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure, leaving 0.74 g of residue, mp 127–132 °C. After recrystallization from methanol, 0.51 g (47%) of **2**, mp 131–132 °C (lit. mp 133 °C,[5,17a] 136–137 °C[17b]), was obtained. Comparison of the infrared and NMR spectra with those of an authentic sample[5] verified the identity of **2**.

3-Methylbenzo[*b*]thiophene 1,1-Dioxide (1b). The diluted reaction mixture (from 3.0 g, 17 mmol of **1b**) was reduced to a volume of about 40 mL by rotary evaporation and the residue was extracted three times with 20-mL portions of methylene chloride. Evaporation of the dried ($MgSO_4$) combined extracts left 2.4 g of solid residue, mp 80–97 °C.

Five recrystallizations of the solid product from chloroform–hexane (1:1) raised the mp to 97.5–99.5 °C, but TLC on silica gel with chloroform revealed the presence of small amounts of two other substances which could not be removed by recrystallization. A portion of the solid product (1.81 g) was chromatographed on a silica gel column with chloroform, and 1.63 g of colorless solid (**5**, R = Me), mp 105–106 °C (recrystallized from chloroform–hexane, 1:1), was obtained. (The first fractions of eluate contained unreacted **1b** and a miniscule amount of another unidentified substance.)

NMR (in $CDCl_3$) δ 1.73 (s, 3, $-CH_3$), 3.53 (s, 2, CH_2), 3.67 (s, 1, OH), 7.63 (m, 4, Ar–H); infrared 3460 (s), 2930, 2990 (1600 cm^{-1} band in precursor absent in product). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.17. Found: C, 54.42; H, 5.20; S, 16.17.

3-Ethylbenzo[*b*]thiophene 1,1-Dioxide (1c). The reaction was carried out with 4.0 g (21 mmol) of **1c**. After dilution, the initially homogeneous mixture was chilled, causing the separation of a white solid within a few minutes. The solid was filtered, washed, and air-dried; 1.4 g, mp 134–135.5 °C, was obtained. Evaporation of the filtrate to 50 mL resulted in the separation of an additional 1.1 g of solid, mp 133–134.5 °C. The combined solids were recrystallized twice from methanol, yielding pure **6**, mp 133.5–134.5 °C: NMR (in $CDCl_3$) δ 1.83 (d of t, 3, CH_3), 4.05 (s, 2, CH_2), 6.45 (m, 1, =CH), 7.59 (m, 4, Ar–H). Anal. Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19; S, 16.51. Found: C, 62.32; H, 5.40; S, 16.39.

The aqueous filtrate was acidified with concentrated HCl and the resulting solution was extracted with methylene chloride (3 × 20 mL). Evaporation of the organic solvent left a syrupy residue (1.1 g), which was chromatographed on silica gel with chloroform to yield three components: 0.04 g of **2**,[18] 0.91 g of a very viscous syrup (**5**, R = Et), and 0.01 g of a yellow solid which was not further identified. All attempts to crystallize the hydroxy compound failed. However, the NMR and infrared spectra were in conformity with the proposed structure: NMR (in $CDCl_3$) δ 0.82 (t, 3, CH_2CH_3), 2.22 (q, 2, CH_2CH_3), 3.5 (s, 2, CH_2), 4.48 (br s, 1, OH), 7.56 (m, 4, Ar-H); infrared 3468 (s).

An attempt to prepare the benzoate via the reaction with benzoyl chloride[7] resulted in the formation of **6**, mp 133–134 °C, as verified by mixture melting point and comparison of the infrared and NMR spectra with those obtained for **6** earlier (see above).

2,3-Dimethylbenzo[*b*]thiophene 1,1-Dioxide. The reaction with hydrogen peroxide and aqueous NaOH was carried out as described above, and at temperatures ranging from 0 to 50 °C. In every case, the starting material was recovered almost quantitatively.

3-Phenylbenzo[*b*]thiophene 1,1-Dioxide (1d). After a 7-h reaction period, during which 1.6 g (6.6 mmol) of **1d** was oxidized, the mixture was diluted with water. After chilling in an ice bath, a solid precipitated and 0.52 g of unreacted **1d**, mp 158–160.5 °C, was collected. The volume of the filtrate was reduced by evaporation under reduced pressure to about 40 mL. The residue, a clear aqueous solution plus some insoluble tacky material, was extracted with three 15-mL portions of methylene chloride. After washing once with 20 mL of 3 M HCl and drying over $MgSO_4$, the solvent was removed, leaving 0.55 g of a colorless semisolid residue. All attempts to crystallize the product were futile. No chromatographic evidence that the product was a mixture was obtained. The NMR and infrared spectra indicate the product is **5** (R = Ph): NMR (in $CDCl_3$) δ 3.81 (s, 2, CH_2), 4.0 (br s, 1, OH), 7.46 (m, 4, Ar–H), 7.63 (m, 5, Ar–H); infrared 3461 (s) (1600 cm^{-1} band present in spectrum of parent compound absent in product).

Reaction of 0.10 g of the hydroxy compound with benzoyl chloride resulted in the formation of 0.075 g of **1d**, mp 159–160 °C, whose infrared spectrum was identical with that of an authentic sample.

Base-Catalyzed Hydration of 3-Alkylbenzo[*b*]thiophene 1,1-Dioxides. A solution of 1 mmol of **1b** or **1c** in pyridine (2.5–4 mL/mmol; sufficient to produce a homogeneous solution after addition of aqueous reagent) was combined with 0.5 M NaOH (4–6 mL/mmol). The solution was stirred and heated to reflux (**1b**, 7 h, followed by 18 h at 25 °C; **1c**, 30 h). The mixture was then evaporated under reduced pressure to remove all solvent. Water (3 mL/mmol) was added to the residue and insoluble solid (unreacted starting material) was removed by filtration. The basic filtrate was acidified with concentrated HCl and extracted three times with methylene chloride. Removal of the solvent under reduced pressure left a syrupy residue. Specific results for the individual compounds are given below.

3-Hydroxy-3-methyl-2,3-dihydrobenzo[*b*]thiophene 1,1-Dioxide (**5**, R = Me). From 0.634 g (3.52 mmol) of **1b** there was obtained 0.052 g of unreacted starting material and 0.60 g of syrup, which solidified on vigorous stirring. Recrystallization from chloroform–hexane (1:1) afforded 0.50 g of product, mp 99.5–101 °C; a second recrystallization raised the melting point to 100–101 °C. Chromatography of 110 mg of the product on a silica gel column (chloroform) resulted in the separation of 10 mg of unreacted **1b** (identity from infrared spectrum), and the remaining material which was eluted was essentially pure **5** (R = Me). Recrystallization from chloroform–hexane (1:1) gave white crystals, mp 107–107.5 °C. The infrared and NMR spectra were identical with those obtained for the product isolated from the reaction of **1b** with OOH^-.

3-Hydroxy-3-ethyl-2,3-dihydrobenzo[*b*]thiophene 1,1-Dioxide (**5**, R = Et). A total of 1.42 g of unreacted starting material was recovered from the reaction of 2.0 g (10 mmol) of **1c**. The viscous syrup residue (0.30 g) left after the removal of the methylene chloride could not be induced to crystallize. The infrared and NMR spectra of this material were identical to those of the product **5** (R = Et), obtained in the reaction of **1c** with OOH^-. Treatment of the product with benzoyl chloride (reflux for 1 h) also resulted in the formation of **6**, as verified by infrared and NMR spectra comparisons.

Acknowledgments. I am indebted to Dr. James Lyle for helpful discussions. Technical assistance provided by Laura Wright and Clayton Harris is gratefully noted.

Registry No.—**5** (R = Me), 62521-48-6; **5** (R = Et), 62521-49-7; **5** (R = Ph), 62521-50-0; **6**, 62521-51-1; hydroperoxide ion, 14691-59-9; 2,3-dimethylbenzo[*b*]thiophene 1,1-dioxide, 16958-01-3.

References and Notes

(1) B. Zwanenburg and J. ter Weil, *Tetrahedron Lett.*, 935 (1970).
(2) (a) E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921); (b) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y. 1965, pp 116–118.
(3) (a) C. Bunton and G. Minkoff, *J. Chem. Soc.*, 665 (1949); (b) H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 2428 (1958); (c) H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *ibid.* **81**, 108 (1959).
(4) Dioxane may be used, but yields are generally lower. In methanol, 3-methoxy-2,3-dihydrobenzo[*b*]thiophene 1,1-dioxide is also formed and complicates the separation procedure. Acetone (see ref 1) is satisfactory if the temperature is maintained at 40–50 °C.
(5) A. W. Weston and C. M. Suter, *J. Am. Chem. Soc.*, **61**, 389 (1939).
(6) (a) T. Durst and K.-C. Tin, *Tetrahedron Lett.*, 2369 (1972); (b) D. F. Tavares, R. E. Estep, and M. Blezard, *ibid.* 2373 (1970); (c) H. O. House, ref 2b, pp 122–123; (d) J. K. Crandall and L.-H. Chang, *J. Org. Chem.*, **32**, 435 (1967).
(7) F. G. Bordwell and W. H. McKellin, *J. Am. Chem. Soc.*, **72**, 1985 (1950): **1a** was stirred with 1 N NaOH for 6 days, resulting in the formation of a liquid (no reported boiling point) product.
(8) H. L. Vaughn and M. D. Robbins, *J. Org. Chem.*, **40**, 1187 (1975).
(9) F. G. Bordwell, B. B. Lampert, and W. H. McKellin, *J. Am. Chem. Soc.*, **71**, 1702 (1949).
(10) E. G. G. Werner, *Recl. Trav. Chim., Pays-Bas* **68**, 509 (1949).
(11) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).
(12) Ng. Ph. Buu-Hoi and P. Cagniant, *Ber.*, **B76**, 1269 (1943).
(13) F. G. Bordwell and C. E. Osborne, *J. Am. Chem. Soc.*, **81**, 1995 (1959).
(14) C. F. H. Allen and S. Converse, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1932, p 226.
(15) Reversing the order of addition of hydrogen peroxide and sodium hydroxide did not affect the outcome of the reaction.
(16) F. P. Greenspan and D. G. MacKellar, *Anal. Chem.*, **20**, 1061 (1948).
(17) (a) H. Kloosterziel and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **71**, 361 (1952); (b) F. G. Bordwell and C. J. Albisetti, *J. Am. Chem. Soc.*, **70**, 1558 (1948); (c) F. Arndt, A. Kirsch, and P. Nachtwey, *Ber.*, **B59**, 1074 (1926).
(18) In another run, in which the temperature was maintained at 20–25 °C, compound **2** comprised 15% of the product mixture.

Notes

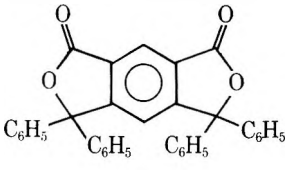
3,3,5,5- and 3,3,7,7-Tetraphenylpyromellitide and Their Tetrathio Analogues

Newton C. Fawcett, Patrick E. Cassidy,*[1] and Ju Chui Lin

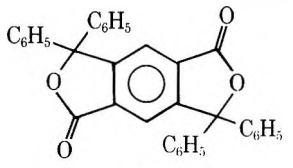
Southwest Texas State University, San Marcos, Texas 78666

Received January 11, 1977

A synthesis of 3,3,7,7-tetraphenylpyromellitide (**2**) from pyromellityl chloride via a Friedel–Crafts reaction has been reported;[2] however, on the basis of the present work it appears that the reported compound was actually the 3,3,5,5-tetraphenylpyromellitide (**1**). Apparently the trans isomer was lost

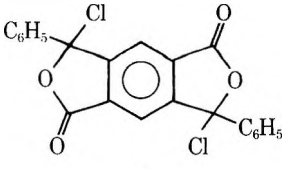


1

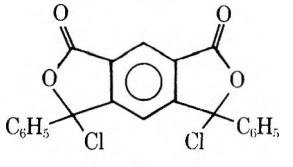


2

in the purification procedure owing to its greater reactivity. The pseudo acid chloride (**3**) of 2,5-dibenzoylterephthalic acid has also been isolated and identified[3,4] as has the pseudo-4,6-dibenzoylisophthaloyl chloride (**4**).[4] These materials were used to produce polyamides or polyanthrazolines and were not reacted further to the tetraphenylpyromellitides.



3

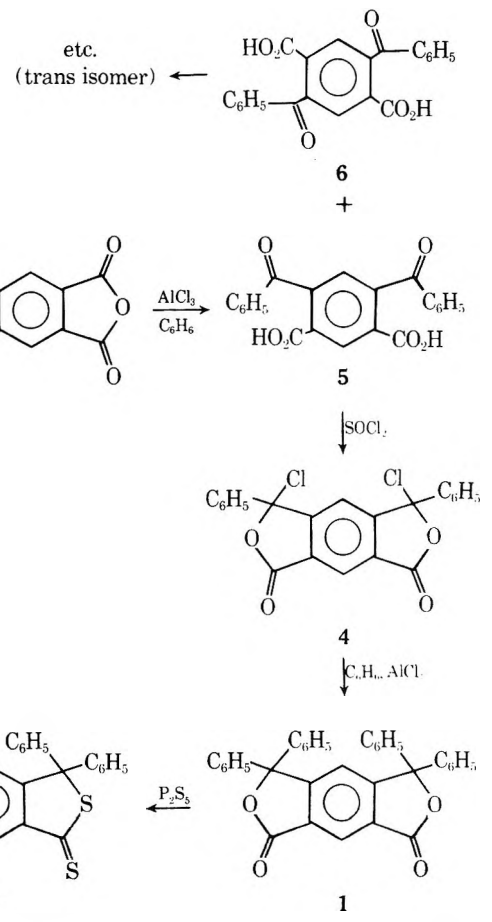


4

It is the purpose of this paper to report the novel, high-yield, unequivocal syntheses of the cis and trans isomers, **1** and **2**, of tetraphenylpyromellitide. Further the tetrathio analogue of each was prepared.

The cis oxo- and thiotetraphenylpyromellitides have been used as monomers for a new type of heterocyclic polymer, polyimidines.[7,8]

The salient features of this reaction scheme are twofold. First, the isomeric dibenzoylphthalic acids, **5** and **6**, can be



separated as their potassium salts. The potassium salt of the terephthalic acid isomer crystallizes from aqueous KOH whereas the sodium salts of both isomers are soluble in NaOH solutions. Previous investigators also have used KOH solutions but apparently neutralized them soon after dissolution without waiting for a crystalline precipitate to form. In earlier work[4,5] the isomer separation was performed with more difficulty and lower yields by crystallizing the acids from acetic acid or aqueous ethanol or methanol.

The second important finding is the fact that the pseudo

acid chloride (4) will undergo a Friedel–Crafts reaction to result in the cyclic phenylated pyromellitides (1). This could be predicted on the basis of work reported by Bhatt et al.[6]

All reactions occur readily to result in overall yields of the pyromellitides of 23% for the cis and 27% for the trans isomers from the dianhydride. For all compounds the cis form is more soluble but the trans isomers are more reactive.

NMR spectra serve to distinguish between the cis and trans structures, 1 and 2. The central aromatic hydrogens in the trans structure are in identical environments and therefore give rise to just one singlet at δ 8.08, whereas two singlets are observed for the nonidentical, central hydrogens in the cis structure: one at δ 7.58, the other at δ 8.29.

Experimental Section

Dibenzoyliso-(and tere-) phthalic Acids (5 and 6). The Friedel–Crafts addition of benzene to pyromellitic dianhydride was carried out as described previously[4,5] with the exception of the procedure used for purification of the products. The 71.2 g of crude mixture of dibenzoylphthalic acids from reaction of 73 g (0.333 mol) of pyromellitic dianhydride was dissolved in 2500 mL of boiling 6 M aqueous KOH, filtered hot, and cooled overnight in a refrigerator to precipitate the potassium salt of 2,5-dibenzoylterephthalic acid. The precipitate was collected by suction filtration and dissolved in water, and the solution was filtered again. The filtrate was acidified with dilute HCl to precipitate the diacid which was recrystallized from glacial acetic acid, mp 324 °C (lit.[5] 319–320 °C), yield 39.2 g (31.5% based on pyromellitic dianhydride).

The aqueous basic solution from which the above salt precipitated was then acidified with 600 mL of dilute HCl. To this, 500 mL of water was added and the solution was cooled in ice to precipitate 36.2 g of crude 4,6-dibenzoylisophthalic acid. The acid was dissolved in a minimum amount of 6 M aqueous NaOH and dilute HCl was added to lower the pH to less than 1. The precipitate was isolated by filtration, washed briefly with cold water, and dried to yield 31.2 g (25% based on pyromellitic dianhydride), mp 278–280 °C (lit.[5] 277–278 °C).

3,3,5,5-Tetraphenylpyromellitide (1). A solution of 24.0 g (0.07 mol) of 4,6-dibenzoylisophthalic acid and 120 mL of thionyl chloride was heated to reflux for 3 h to give a clear yellow solution. A vacuum line was attached to the flask, and the excess thionyl chloride was removed with the aid of an aspirator until the pseudo acid chloride was left as an off-white paste in the bottom of the flask. Radiant heat from an infrared lamp was useful in this last step. The last vestiges of thionyl chloride need not be removed. To the paste of pseudo acid chloride was added 1 L of dry benzene followed by slow addition with stirring of 70.09 g (0.52 mol) of aluminum chloride. The resulting heterogeneous mixture was refluxed for 16 h, and then the benzene layer was concentrated to about 500 mL by distillation. After cooling, the aluminum chloride complex was destroyed by addition of 500 g of ice and 200 mL of 6 M HCl. The benzene layer was separated from the resulting mixture, filtered, and dried over Na_2SO_4. After filtering again, the benzene solution was concentrated to 200 mL and 800 mL of absolute alcohol was added. Upon cooling 3,3,5,5-tetraphenylpyromellitide precipitated. The precipitate was collected, dried, and dissolved in a minimum amount of boiling benzene. To this was added an equal amount of absolute alcohol and the solution was cooled to yield white platelets: mp 280–282 °C (lit.[2] 275–276 °C); yield 14.9 g (47.0%); NMR ($CDCl_3$) δ 7.16 (20 H), 7.58 (1 H), and 8.29 (1 H). Anal. Calcd for $C_{34}H_{22}O_4$: C, 80.57; H, 4.45. Found: C, 80.02; H, 4.44.

3,3,7,7-Tetraphenylpyromellitide (2). The process described above was repeated except that 2,5-dibenzoylterephthalic acid was used. The reaction mixture workup was changed as described below.

The final reaction mixture (after $AlCl_3$ addition) was steam distilled to remove the benzene and the solid residue was isolated by filtration and dried. The filtrate was extracted twice with 100-mL portions of benzene and twice with 100-mL portions of chloroform. The extracts were evaporated on a steam bath and the residue was added to that solid removed directly from the steam distillation residue. The combined solids were subjected to Soxhlet extraction by benzene for 3 days. The benzene solution was reduced in volume to 200–300 mL and an equal amount of absolute alcohol was added to precipitate the tetraphenylpyromellitide. The solid was recrystallized from benzene or benzene–ethanol to yield 15.4 g (48.6%): mp 354–356 °C; NMR ($CDCl_3$) δ 7.31 (20 H, s), 8.08 (2 H, s).

Anal. Calcd for $C_{34}H_{22}O_4$: C, 80.57; H, 4.45. Found: C, 80.50; H, 4.64.

3,3,5,5-Tetraphenyltetrathiopyromellitide (7). A solution of 3.0 g (0.006 mol) of 3,3,5,5-tetraphenylpyromellitide and 0.80 g (0.012 mol) of phosphorus pentasulfide in 50 mL of xylene was heated at reflux for 36 h. The resulting clear red solution was filtered hot and steam distilled until a red residue precipitated in the still pot. After the residue was cooled to room temperature it was collected by vacuum filtration and dissolved in a minimum amount of hot chloroform, filtered, and cooled. The yellow precipitate, probably the dithio derivative, was removed by filtration and the filtrate was concentrated to one-half of its original volume. An equal amount of alcohol was then added and the solution was cooled to 0 °C to facilitate precipitation of the tetrathio compound. The fine, red precipitate that forms was collected by vacuum filtration and dried in a vacuum desiccator overnight to yield 3.1 g (90%) of 3,3,5,5-tetraphenyltetrathiopyromellitide, mp 338–340 °C.

Anal. Calcd for $C_{34}H_{22}S_4$: C, 73.11; H, 3.94; S, 22.94. Found: C, 73.13; H, 3.88; S, 22.89.

3,3,7,7-Tetraphenyltetrathiopyromellitide. The reaction as described above was carried out on the trans isomer except that the reaction was complete in less than 12 h. The crude product was obtained in 90% yield and was extracted with boiling $CHCl_3$. The solution was concentrated and cooled to yield beautiful, deep-maroon crystals, mp 357 ± 2 °C. (Slow heating results in polymerization and no melting point. The value reported was obtained by inserting capillaries into a preheated block.)

Anal. Calcd for $C_{34}H_{22}S_4$: C, 73.11; H, 3.94; S, 22.94. Found: C, 72.95; H, 4.05; S, 22.68.

Acknowledgment. The authors wish to express their appreciation to the Robert A. Welch Foundation, Houston, Texas, and Southwest Texas State University for their support of this work. Further, the able assistance of Mr. Dennis Davis and Mr. Walter Zoch during this project was of great value.

Registry No.—**1**, 59914-21-5; **2**, 3886-00-8; **4**, 52496-56-7; **5**, 52497-38-8; **6**, 52497-37-7; **7**, 60095-15-0; phosphorus pentasulfide, 1314-80-3; 3,3,7,7-tetraphenyltetrathiopyromellitide, 62586-46-3.

References and Notes

(1) To whom correspondence should be addressed.
(2) V. G. Drechsler and S. Heidenreich, *J. Prakt. Chem.*, **27**, 52 (1965).
(3) M. Ueda, M. Ohkura, and Y. Imai, *J. Polym. Sci., Polym. Chem. Ed.*, **12**, 719 (1974).
(4) Y. Imai, E. F. Johnson, T. Katto, M. Kurihara, and J. K. Stille, *J. Polym. Sci., Polym. Chem. Ed.*, **13**, 2233 (1975).
(5) W. H. Mills and M. Mills, *J. Chem. Soc.*, **101**, 2194 (1912).
(6) M. V. Bhatt, K. M. Kamath, and M. Ravindranathan, *J. Chem. Soc. C*, 1772 (1971).
(7) P. E. Cassidy and A. R. Syrinek, *J. Polym. Sci., Polym. Chem. Ed.*, **14**, 1485 (1976).
(8) P. E. Cassidy and F. W. C. Lee, *J. Polym. Sci., Polym. Chem. Ed.*, **14**, 1519 (1976).

Diels–Alder Synthesis of Hindered Aromatic Amines

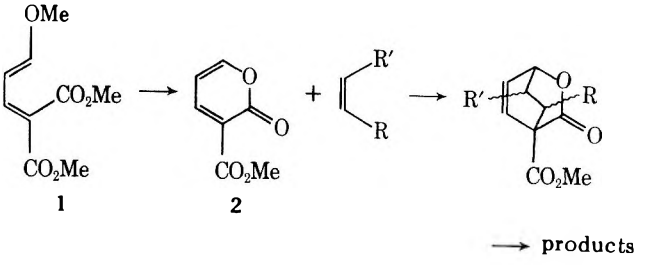
T. A. Bryson* and D. M. Donelson

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

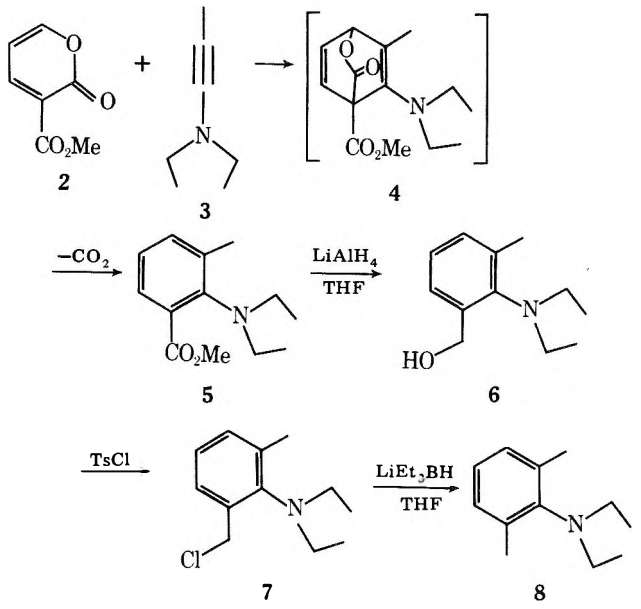
Received February 25, 1977

Recent interest in this laboratory in highly functionalized butadienes for use as synthons for natural product synthesis has led us to a simple preparation of symmetrical and unsymmetrical, highly hindered aromatic amines. Studies with butadiene 1[1] have shown that it will undergo a variety of ad-

Scheme I



Scheme II



dition reactions,[2] but it has proved to be a poor Diels–Alder reagent. However, diene **2**, derived from 1,[3] readily undergoes cycloaddition (Diels–Alder) reactions as demonstrated previously by Corey[4] and others as illustrated in Scheme I.

When ynamine **3** is added to a benzene solution of **2**, an exothermic reaction occurs affording adduct **5** (Scheme II). The initial assumption as to the favored orientation of the diene (**2**) and dienophile (**3**), based on the polarization of these reagents, proved to be correct. The reaction proceeds in a unidirectional cycloaddition process, presumably through an adduct such as **4**, that spontaneously loses CO_2 resulting in formation of **5**. Amino ester **5** exhibits the physical and spectral properties expected for an aromatic amine with hindered rotation about the nitrogen–aromatic ring carbon bond.

Reduction of ester **5** affords a second unsymmetrical hindered amine **6** which is further transformed to chloride **7** on treatment with *p*-toluenesulfonyl chloride. Although it is not unusual to form chlorides from the reaction of an alcohol with tosyl chloride, it is suspected that the severe crowding present in the tosylate **6** probably accelerates the formation of chloride **7**. Symmetrical diethylamino-*o*-xylene **8** is readily available from lithium triethylborohydride ($LiEt_3BH$/THF) reduction of **7**. As in the case for amines **5** and **6**, the steric crowding about the *N,N*-diethylamino group in **7** and **8** seems to preclude any effective overlap of the nitrogen lone pair with the aromatic ring. Clearly alterations in the ynamine to be added to butadiene **2** would conveniently provide other hindered amines in this series that are of some theoretical interest.

Experimental Section

Methyl 2-(*N,N*-Diethylamino)-3-methylbenzoate (5). 1-Diethylamino-1-propyne (**3**, 1.08 g, 9.73 mmol) was added to α-pyrone **2**[6] (1.49 g, 9.73 mmol) in dry benzene (35 mL at room temperature). After addition the reaction mixture was stirred and heated under reflux overnight, cooled, poured into CH_2Cl_2 (50 mL), washed with H_2O (50 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure and distillation (Kugelrohr oven, 80–90 °C, 0.5 mmHg) afforded 1.70 g (79%) of substituted **5**: ^1H NMR δ_{CDCl_3} (Me_4Si) 7.43–6.90 (m, 3 H, PhH), 3.88 (s, 3 H, $-OCH_3$), 3.07 (q, J = 7 Hz, 4 H, $-CH_2-$), 2.31 (s, 3 H, $PhCH_3$), 1.02 (t, J = 7 Hz, 6 H, $-CH_3$); ^{13}C NMR (relative to Me_4Si, $CDCl_3$) 169.89 (carbonyl), 148.58, 138.70, 132.11 (fully substituted aromatic carbons), 133.63, 127.23, 123.93 (aromatic methynes), 51.96 ($-OCH_3$), 47.53 (R_2NCH_2-), 19.26 ($PhCH_3$), 14.68 ppm ($-CH_3$'s); IR (film) 1735, 1650, 1590 cm^{-1}; λ_{max} (EtOH) 235 nm; *m/e* 221. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65. Found: C, 70.63; H, 8.59.

***N,N*-Diethyl-2-hydroxymethyl-6-methylaniline (6).** Aminomethyl benzoate **5** (0.5 g, 2.26 mmol) in THF (10 mL) was added to lithium aluminum hydride (0.08 g, 2.26 mmol) in THF (20 mL) at 0 °C. The suspension was stirred at room temperature (1 h) and excess hydride was quenched with 10% NaOH. The reaction mixture was filtered and the aluminum salts were washed with cold THF (25 mL) and H_2O (25 mL). The filtrate was dissolved in CH_2Cl_2 (75 mL), washed with H_2O (50 mL) and saturated NaCl (75 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure and the reaction mixture was distilled (Kugelrohr oven, 90–100 °C, 0.5 mmHg) affording 0.30 g (71%) of amino alcohol **6**: ^1H NMR δ_{CDCl_3} (Me_4Si) 7.01 (s, 3 H, PhH), 5.06 (s, broad, 1 H, –OH), 4.75 (s, 2 H, $-CH_2-$), 3.10 (q, J = 7 Hz, 4 H, $-CH_2-$), 2.29 (s, 3 H, $-CH_3$), 1.04 (t, J = 7 Hz, 6 H, $-CH_3$); IR (film) 3380 cm^{-1}; *m/e* 193.

***N,N*-Diethyl-2-chloromethyl-6-methylaniline (7).** Tosyl chloride (1.48 g, 7.77 mmol) in CH_2Cl_2 (15 mL) was added at room temperature to amino alcohol **6** (1.50 g, 7.77 mmol) and triethylamine (0.78 g, 7.77 mmol) in CH_2Cl_2 (75 mL). After stirring for 12 h, the reaction mixture was diluted with CH_2Cl_2 (75 mL), washed with H_2O (100 mL) and saturated aqueous NaCl (100 mL), and dried ($MgSO_4$). The solvent was removed at reduced pressure and distilled (Kugelrohr oven, 60–70 °C, 0.5 mmHg) yielding 1.20 g (73%) of amino chloride **7**: ^1H NMR δ_{CDCl_3} (Me_4Si) 7.38–6.97 (m, 3 H, PhH), 4.77 (s, 2 H, $-CH_2Cl$), 3.08 (q, J = 8 Hz, 4 H, $-CH_2-$), 2.25 (s, 3 H, $PhCH_3$), 1.01 (t, J = 8 Hz, 6 H, $-CH_3$); IR (film) 1590 cm^{-1}; *m/e* 211.

***N,N*-Diethyl-2,6-dimethylaniline[5] (8).** Lithium triethylborohydride (2.38 mmol, 1 M in THF) was added to amino chloride (0.25 g, 1.18 mmol) in THF (20 mL) at 0 °C. The reaction mixture was allowed to equilibrate to room temperature and stirred for 2 h. Excess hydride was destroyed by the addition of H_2O, and the organoborane intermediates were oxidized by stirring at room temperature overnight with 10% NaOH (10 mL) and H_2O_2 (30%, 10 mL). The reaction mixture was poured into $CHCl_3$ (25 mL) and extracted with $CHCl_3$ (3 × 25 mL). The organic extracts were washed with H_2O (50 mL) and saturated NaCl (50 mL) and dried ($MgSO_4$). The solvent was removed at room temperature and distillation (Kugelrohr oven, 50–75 °C, 0.5 mmHg) afforded 0.17 g (81%) of the desired substituted aniline **8**: ^1H NMR δ_{CDCl_3} (Me_4Si) 6.95 (s, 3 H, PhH), 3.07 (q, J = 8 Hz, 4 H, $-CH_2-$), 2.27 (s, 6 H, $PhCH_3$), 0.99 (t, J = 8 Hz, 6 H, $-CH_3$); ^{13}C NMR (relative to Me_4Si, $CDCl_3$) 138.30, 128.8, 128.62, 124.84 (aromatic carbons), 47.37 (R_2NCH_2), 19.54 ($PhCH_3$), 14.77 ppm ($-CH_3$); IR (film) 1590 cm^{-1}; *m/e* 177.

Acknowledgment. We gratefully acknowledge the support of this work by the Public Health Service, Grant CA 17490.

Registry No.—**2**, 25991-27-9; **3**, 4231-35-0; **5**, 41895-85-6; **6**, 62601-02-9; **7**, 62601-03-0; **8**, 3995-38-8.

References and Notes

(1) T. A. Bryson, J. C. Wisowaty, R. B. Dunlap, R. R. Fisher, and P. D. Ellis, *J. Org. Chem.*, **39**, 3436 (1974).
(2) T. A. Bryson, D. M. Donelson, R. B. Dunlap, R. R. Fisher, and P. D. Ellis, *J. Org. Chem.*, **41**, 2066 (1976).
(3) T. B. Windholz, L. H. Peterson, and G. J. Kent, *J. Org. Chem.*, **28**, 1443 (1963).
(4) E. J. Corey and D. S. Watt, *J. Am. Chem. Soc.*, **95**, 2303 (1973).
(5) C. H. Yoder, B. A. Kaduck, and R. E. Hess, *Tetrahedron. Lett.*, 3711–3714 (1970).
(6) Reference 3 describes the preparation of ethyl α-pyrone-3-carboxylate which was followed for the preparation of the methyl ester **2**.

Intramolecular Decomposition of Isopropylidene Diazomalonate (Diazo Meldrum's Acid)[1c]

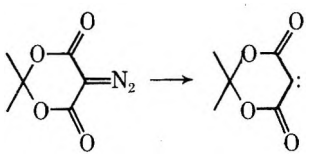
Seetha L. Kammula,[1a,b] Howard L. Tracer,[1b] Philip B. Shevlin,*[1a] and Maitland Jones, Jr.*[1b]

Departments of Chemistry, Auburn University, Auburn, Alabama 36830, and Princeton University, Princeton, New Jersey 08540

Received March 15, 1977

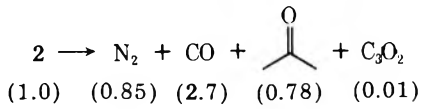
In a discussion of the nonstereospecific addition to olefins of the carbene **1** derived from Meldrum's acid via the diazo compound **2**, it was noted that direct irradiation of **2** led, in addition to 1–2% of addition products, to "very little product of any kind".[2] We report here on the fate of **1** generated by pyrolysis and photolysis of **2**.

Pyrolysis of **2** at 320 °C was carried out under vacuum in



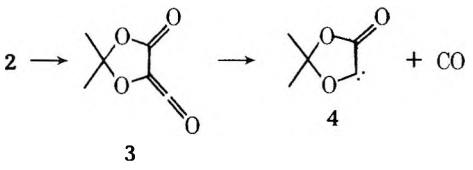
2 1

sealedPyrex bombs for 15 min. The products were separated and analyzed using standard vacuum line techniques and conventional spectroscopic characterization. All products were carefully compared with known materials. Pyrolysis of 0.29 mmol of **2** gave nitrogen (0.25 mmol), carbon monoxide (0.80 mmol), acetone (0.23 mmol), a small amount of carbon suboxide (0.003 mmol), and traces of propylene.



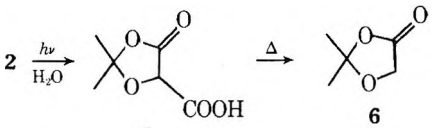
(1.0) (0.85) (2.7) (0.78) (0.01)

It is extraordinarily tempting to begin a mechanistic analysis of this reaction with the postulate that the first step in the decomposition of **2** is the Wolff rearrangement (in either the carbene **1** or **2** itself) to give ketene **3**. Such a process is precedented in the gas-phase chemistry of carboalkoxycarbenes,[3] and ketene **3** is a likely source of carbon monoxide and the new carbene **4**. This cleavage of a ketene to a carbene of type **4** is also known.[3]

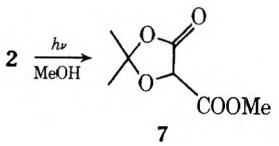


3

Ketene **3** can be trapped. Photolysis of **2** in benzene/water leads to the unstable β-keto acid **5** which, on heating or gas chromatography, decarboxylates to the known dioxolanone **6**.[4] Although the decomposition of **5** could be followed by NMR spectroscopy, its instability prevented a quantitative analysis of its formation. However, irradiation of **2** in benzene/methanol resulted in the formation of the known[5] ester **7** in 69% yield.

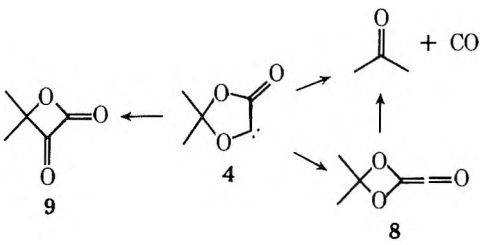


5 6



7

Thus the presence of ketene **3** is demonstrated, and its conversion to **4** seems very likely under the reaction conditions. Carbene **4** can either undergo direct cleavage to two more molecules of carbon monoxide and one of acetone, or undergo another Wolff rearrangement to **8**, which could then yield carbon monoxide and acetone. Rearrangement to **9** seems less likely on the grounds that this path is not favored in the related decomposition of dicarbomethoxycarbene.[3]



9 4 8

The small amounts of propylene and carbon suboxide are more difficult to explain, although propylene could be formed by deoxygenation of acetone by any of the carbenes present in the reaction. Carbon suboxide is a possible product of direct fragmentation of **1**, although this appears to be an unprecedented reaction.

Experimental Section

Synthesis of 2,2-Dimethyl-4,6-diketo-5-diazo-1,3-dioxane (Meldrum's Diazo). The procedure followed was similar to that reported by Eistert and Geiss.[6] Trimethylamine (8.4 g) was added dropwise to a solution of 11.6 g of Meldrum's acid[7] in 40 mL of ethanol. The solution was stirred in a dry ice/acetone bath until the temperature reached −15 °C. Tosyl azide (16 g) was slowly added, keeping the temperature below −10 °C. After 30 min of stirring, a yellow-orange solid precipitated. The solution was concentrated for 15 min on the rotary evaporator with no heat. It was cooled for 1 h in the dry ice/acetone bath at −20 °C and filtered. The yellow crystals were recrystallized twice from absolute alcohol at 0 °C to yield 7.4 g (50%), mp 93–95 °C.

Pyrolysis of Meldrum's Diazo. Meldrum's diazo (50 mg, 0.294 mmol) was pyrolyzed in a sealed Pyrex bomb (125 mL) at 320 °C in a molten salt ($NaNO_3/NaNO_2$) bath. The bombs were opened on a vacuum line and the products distilled into a trap at −196 °C. The products noncondensable at −196 °C (N_2 and CO) were injected into a 16-ft 13X molecular sieve column. Condensable products were distilled from a trap at −78 to −196 °C in order to separate the products further. Each of the fractions were analyzed by IR and gas chromatography on 6- and 20-ft dimethylsulfolane columns. All the products were identified by comparison of their physical characteristics (GC and IR) with those of authentic samples. The quantity of acetone was measured by calibration of the IR band at 1750 cm^{-1} and the carbon suboxide yields were measured following its IR band at 2260 cm^{-1}.

Photolysis of Meldrum's Diazo in Wet Benzene. Meldrum's diazo (170 mg, 0.001 mol) was dissolved in 12 mL of benzene and 0.1 mL of water. The emulsion was photolyzed for 18 h with a 450-W medium-pressure Hanovia mercury arc. The solution was filtered and the benzene evaporated to yield white crystals of β-keto acid **5**.

Pyrolysis of 5. Pyrolysis in acetone-d_6 in a sealed Pyrex tube at 110 °C yields dioxolanone **6** quantitatively.

Photolysis of Meldrum's Diazo in Benzene and Methanol. Meldrum's diazo (170 mg) was dissolved in 12 mL of benzene and 0.1 mL of methanol. The solution was photolyzed as above for 18 h and the products were analyzed directly on a 10-ft, 10% Carbowax 20M column at 140 °C. The yield of ester **7** was estimated at 69% by use of dimethyl malonate as internal standard.

Registry No.—**2**, 7270-63-5; **5**, 62609-78-3; **6**, 4158-86-5; **7**, 62609-79-4; Meldrum's acid, 2033-24-1; tosyl azide, 938-10-3; nitrogen, 7727-37-9; carbon monoxide, 630-08-0; acetone, 67-64-1; carbon suboxide, 504-64-3.

References and Notes

(1) (a) Auburn University. (b) Princeton University. (c) We thank the Research Corporation[1a] and the National Science Foundation[1b] for support. One of us (S.L.K.) thanks Auburn University for support through an Auburn University Fellowship and Princeton University for support through the Office of the Dean of Student Affairs. Portions of this work are taken from the Ph.D. Thesis of S.L.K., Auburn University, 1974.
(2) M. Jones, Jr., W. Ando, M. E. Hendrick, A. Kulczycki, Jr., P. M. Howley, K. F. Hummel, and D. S. Malament, *J. Am. Chem. Soc.*, **94**, 7469 (1972).
(3) D. C. Richardson, M. E. Hendrick, and M. Jones, Jr., *J. Am. Chem. Soc.*, **93**, 3790 (1971).
(4) M. Farines and J. Soulier, *Bull. Soc. Chim. Fr.*, 332 (1970).
(5) This compound has been characterized by T. M. Ford in his A.B. Thesis, Princeton University, 1974. It appears as the major product from the irradiation of methyl diazomalonate in acetone.
(6) B. Eistert and F. Geiss, *Chem. Ber.*, **94**, 929 (1961).
(7) D. Davidson and S. A. Bernhard, *J. Am. Chem. Soc.*, **70**, 3426 (1948).

Heats of Hydrolysis of Phenyl α-Disulfone and Phenyl Benzenesulfinyl Sulfone[1a]

John L. Kice,*[1b] Henry C. Margolis, Wiltshire S. Johnson, and Claus A. Wulff

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

Received February 8, 1977

Phenyl benzenesulfinyl sulfone ($PhS(O)SO_2Ph$, **1**) is very unstable thermally[2a] ($t_{1/2} \simeq 30$ min at 50 °C) compared to phenyl α-disulfone[2b] ($PhSO_2SO_2Ph$, **2**) ($t_{1/2} \simeq 13$ h at 145 °C). The sulfinyl sulfone also undergoes either spontaneous[3a] or alkaline[3b] hydrolysis about 10 000 times faster than the α-disulfone.[4] Combined with its much greater thermal instability, one might tend to get the impression from this that the sulfinyl sulfone was much less thermodynamically stable relative to its hydrolysis products than is the α-disulfone.

We have now carried out measurements of the heats of hydrolysis of both **1** and **2** which show that this is not the case, and that sulfinyl sulfones (sulfinic anhydrides) are apparently significantly more stable relative to their hydrolysis products than is true of the most acid anhydrides.

Results and Discussion

The heats of reaction, ΔH_{rxn}, for the alkaline hydrolyses of both phenyl α-disulfone (eq 1) and phenyl benzenesulfinyl sulfone (eq 2)

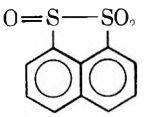
$$\underset{\mathbf{2}}{PhSO_2SO_2Ph} + 2OH^- \rightarrow PhSO_3^- + PhSO_2^- + H_2O \quad (1)$$

$$\Delta H°_1 = -57.3 \pm 0.2 \text{ kcal/mol}$$

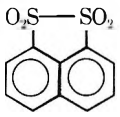
$$\underset{\mathbf{1}}{PhS(O)SO_2Ph} + 2OH^- \rightarrow 2PhSO_2^- + H_2O \quad (2)$$

$$\Delta H°_2 = -34.1 \pm 2.0 \text{ kcal/mol}$$

were measured by determining the amount of heat liberated when a weighed sample of the sulfur compound was added to 60% dioxane containing excess 0.1 M sodium hydroxide. To obtain $\Delta H°$ for each reaction one must also obtain the heat of solution, ΔH_{soln}, for each of the sulfur compounds in 60% dioxane, since $\Delta H° = \Delta H_{rxn} - \Delta H_{soln}$. While the heat of solution of the α-disulfone ($\Delta H^2_{soln} = 5.90 \pm 0.06$ kcal/mol) was easily determined, the rapid spontaneous hydrolysis of **1** in aqueous dioxane[3a] makes it impossible to measure ΔH_{soln} for **1** directly. However, since we could show that ΔH_{soln} for the cyclic sulfinyl sulfone **3** (which is stable to hydrolysis in acidic



3



4

aqueous dioxane[5a]) was virtually the same as ΔH_{soln} for the analogous cyclic α-disulfone **4**,[5b] we believe that it is reasonable[5c] to assume that ΔH_{soln} for **1** in 60% dioxane is essentially the same as ΔH_{soln} for **2**, and we have accordingly used an estimated value of $\Delta H_{soln}^1 = 6 \pm 2$ kcal/mol in calculating $\Delta H°$ for reaction **2** from ΔH_{rxn} for the alkaline hydrolysis of **1**. The values for $\Delta H°$ for the alkaline hydrolyses of **1** (eq 2) and **2** (eq 1) are shown under the respective equations. One sees that the alkaline hydrolysis of the α-disulfone is more exothermic than that of the sulfinyl sulfone by somewhat over 20 kcal/mol.

We have also measured the heats of reaction associated with neutralization of $PhSO_2H$ (eq 3) and $PhSO_3H$ (eq 4)

$$PhSO_2H + OH^- \rightarrow PhSO_2^- + H_2O \quad (3)$$

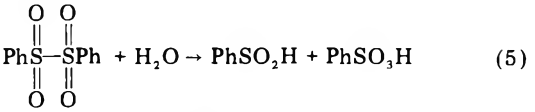
$$\Delta H°_3 = -16.3 \pm 0.1 \text{ kcal/mol}$$

$$PhSO_3H + OH^- \rightarrow PhSO_3^- + H_2O \quad (4)$$

$$\Delta H°_4 = -24.8 \pm 2.4 \text{ kcal/mol}$$

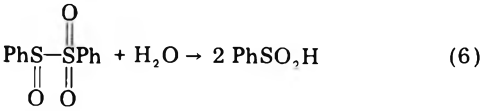
by hydroxide ion in 60% dioxane. While ΔH_{soln} for $PhSO_2H$ (4.02 ± 0.04 kcal/mol) in 60% dioxane could be determined accurately by measuring the heat of solution of the compound in 60% dioxane containing 0.3 M $HClO_4$, a medium of sufficient acidity that dissociation of $PhSO_2H$ is negligible, the same was not true for $PhSO_3H$, for even in the presence of added perchloric acid the dissociation of $PhSO_3H$ ($PhSO_3H \rightarrow PhSO_3^- + H^+$) was still virtually complete. For this reason we had to estimate ΔH_{soln} for $PhSO_3H$ in 60% dioxane. We have used a value of 4.0 ± 2.0 kcal/mol, trusting that in all likelihood ΔH_{soln} for the sulfonic acid should be similar to that for the sulfinic acid in this medium.[6] The values of $\Delta H°$ for reactions 3 and 4 computed from the measured ΔH_{rxn} for each process and the measured ($PhSO_2H$) and estimated ($PhSO_3H$) ΔH_{soln}s are shown under the respective reactions.

From the $\Delta H°$s for reactions 3 and 4 and those for reactions 1 and 2 one can calculate $\Delta H°$ for the hydrolysis of both the α-disulfone (eq 5) and the sulfinyl sulfone (eq 6).



$$PhS(O)_2SPh + H_2O \rightarrow PhSO_2H + PhSO_3H \quad (5)$$

$$\Delta H°_5 = \Delta H°_1 - \Delta H°_3 - \Delta H°_4 = -16.2 \pm 2.5 \text{ kcal/mol}$$



$$PhS(O)_2SPh + H_2O \rightarrow 2\,PhSO_2H \quad (6)$$

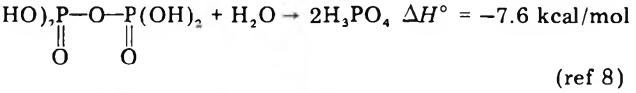
$$\Delta H°_6 = \Delta H°_2 - 2\Delta H°_3 = -1.5 \pm 2.1 \text{ kcal/mol}$$

The $\Delta H°$s for eq 5 and 6 show that the hydrolysis of the α-disulfone (eq 5) is much more exothermic than the hydrolysis of the sulfinyl sulfone (eq 6). The estimated difference is 15 ± 5 kcal/mol. Clearly the high kinetic reactivity of the sulfinyl sulfone compared to the α-disulfone in hydrolysis reactions has *nothing* to do with any greater thermodynamic instability of **1** relative to its hydrolysis products.

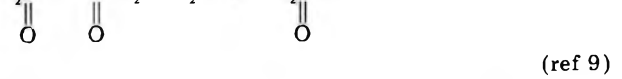
Both the sulfinyl sulfone and the α-disulfone can be considered "anhydrides", the sulfinyl sulfone being the anhydride of benzenesulfinic acid, and the α-disulfone being a mixed anhydride of benzenesulfonic and benzenesulfinic acids. Heats of hydrolysis of a number of other anhydrides are known, albeit in water rather than 60% dioxane as solvent. Values are shown below.

$$Ac_2O + H_2O \rightarrow 2AcOH \quad \Delta H° = -14.0 \text{ kcal/mol (ref 7)}$$

$$AcOPO_3H^- + H_2O \rightarrow AcOH + H_2PO_4^- \quad \Delta H° = -8.6 \text{ kcal/mol (ref 8)}$$



$$(HO)_2P(O)OP(O)(OH)_2 + H_2O \rightarrow 2H_3PO_4 \quad \Delta H° = -7.6 \text{ kcal/mol (ref 8)}$$



$$Ph_2P(O)OP(O)Ph_2 + H_2O \rightarrow 2Ph_2P(O)OH \quad \Delta H° = -17.6 \text{ kcal/mol (ref 9)}$$

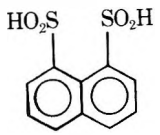
While the difference in solvent (water vs. 60% dioxane) makes it risky to draw any detailed quantitative conclusions from comparison of these values with those in eq 5 and 6, the results would seem to at least suggest that the heat of hydrolysis of the sulfinyl sulfone is probably smaller than those for most anhydrides and that, for an anhydride, particularly considering its thermal instability, a sulfinyl sulfone is from a thermodynamic point of view surprisingly stable relative to its hydrolysis products.

Table I. Calorimetric Data for Individual Runs

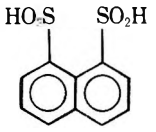
Registry no.	Reaction	Heats of Reaction: mmol of substrate	q'_{main}, cal	ΔH, kcal/mol
10409-06-0 (2)	2 + OH^-	0.25135	−12.9087	−51.36
14280-30-9 (OH^-)		0.24972	−12.7970	−51.25
		0.25135	−12.9863	−51.66
				av −51.42 ± 0.15
784-81-6	1 + OH^-	0.24890	−6.9037	−27.74
		0.24962	−7.0481	−28.24
		0.24711	−6.9859	−28.27
				av −28.08 ± 0.23
618-41-7	$PhSO_2H + OH^-$	0.25103	−3.0933	−12.32
		0.25723	−3.1761	−12.35
		0.25505	−3.1144	−12.21
				av −12.29 ± 0.06
98-11-3	$PhSO_3H + OH^-$	0.25310	−5.3594	−21.17
		0.25817	−5.2321	−20.27
		0.26756	−5.6060	−20.95
				av −20.79 ± 0.35

Registry No.	Compd	Heats of Solution: mmol of compd	q'_{main}, cal	ΔH, kcal/mol
	2	0.25057	1.4851	5.93
		0.25057	1.4582	5.82
		0.24837	1.4815	5.97
				av 5.90 ± 0.06
	$PhSO_2H$	0.26537	1.0682	4.03
		0.30383	1.2033	3.96
		0.31418	1.2812	4.08
				av 4.02 ± 0.04
57821-65-5	3	0.22608	0.9421	4.07
		0.22566	1.0136	4.49
		0.22322	1.0394	4.66
				av 4.44 ± 0.21
62609-77-2	4	0.19799	0.7506	3.79
		0.19732	0.8090	4.10
		0.19976	0.8283	4.15
				av 4.01 ± 0.15

If that is true, then in general K_{eq}, the equilibrium constant for formation of a sulfinyl sulfone from the corresponding sulfinic acid, is likely to be considerably more favorable than the equilibrium constants for formation of most other types of anhydrides. One manifestation of this which has already been reported[5a] is the fact that in the equilibrium between naphthalene-1,8-disulfinic acid (5) and 3 in aqueous dioxane at equilibrium [3]/[5] ≃ 3, while there is no evidence for any detectable amount of the analogous α-disulfone 4 in equilibrium with naphthalene-1-sulfonic-8-sulfinic acid (6) under the same conditions.



5



6

Experimental Section

Preparation and Purification of Materials. Phenyl α-disulfone and dioxane were purified as previously described.[4a] Benzenesulfinic acid was prepared from commercial sodium benzenesulfinate (Aldrich Chemical Co.) by dissolving the salt in the minimum amount of distilled water and then slowly adding 50% sulfuric acid with stirring in the cold until the solution was strongly acid (pH <1). The sulfinic acid which precipitated was filtered off, washed carefully with a small amount of ice-cold water, and then redissolved in ether. The ether solution was dried over sodium sulfate to remove water and the ether then removed under reduced pressure. The residue was recrystallized from chloroform–hexane to give benzenesulfinic acid, mp 82–83 °C (lit.[10] 85 °C), which was shown by titration to be greater than 99% pure. Phenyl benzenesulfinyl sulfone[2a] was synthesized from benzenesulfinic acid using the general procedure developed by Lerch and Moffat.[11] To 1.42 g of benzenesulfinic acid in 25 mL of dry methylene chloride was added 1.03 g of dicyclohexylcarbodiimide. After stirring for 10 min the precipitated dicyclohexylurea was filtered off and the filtrate evaporated to dryness under reduced pressure. The pure sulfinyl sulfone was obtained by recrystallization of the residue from chloroform–hexane. The benzenesulfonic acid used was anhydrous, electronic grade (Eastman Kodak Co.). Titration with sodium hydroxide showed it to be at least 99% pure. All handling of this deliquescent material was carried out in a dry nitrogen atmosphere. Compounds 3 and 4 were samples prepared in other work.[5]

Procedure for Calorimetric Measurements. All the thermochemical data were obtained using a commercial LKB 8700-1 calorimetry system.[12] All experiments were carried out in a single 100-mL calorimeter vessel of standard design. To reduce experimental deviations the mechanical ampule breaking device was employed. The ampules used were the commercial LKB 8727-1 with a 1-mL capacity.

Ampules were weighed accurately and filled carefully with approximately 0.25 mmol of the proper compound. Great care was taken in all weighings to obtain the precise weight of the substance in the ampule to ±0.01 mg. For those substances which tended to be hygroscopic, weighings were carried out in a dry nitrogen atmosphere. The unsealed ampules were placed in a specially designed cold-water jacket that made it possible to seal the opening of the ampule with hot, molten glass (cold seal) without affecting the substance contained in the ampule.

Heats of reaction were determined by measuring the heat evolved upon breaking a filled ampule in the calorimeter vessel containing 100 mL of a 60% dioxane solution which was 0.1 N in sodium hydroxide. At least three different determinations were made for each substance.

The heat of solution for phenyl α-disulfone was determined by measuring the heat absorbed upon breaking an ampule containing 2 in the calorimeter vessel containing 100 mL of 60% dioxane. For

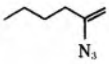
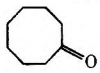
benzenesulfinic acid the heat of solution was determined in 60% dioxane containing 0.34 M perchloric acid, in order to suppress any tendency for $PhSO_2H$ to dissociate. Dissociation of benzenesulfonic acid could not be suppressed by this same procedure, and so the heat of solution of $PhSO_3H$ itself in 60% dioxane could not be measured experimentally. Because of its rapid spontaneous hydrolysis, the heat of solution of sulfinyl sulfone 1 also could not be determined experimentally. Since cyclic sulfinyl sulfone 3 does not undergo appreciable hydrolysis in acidic 60% dioxane its heat of solution could be determined satisfactorily. Since it was found to be essentially the same (4.4 ± 0.21 kcal/mol) as that of cyclic α-disulfone 4 (4.01 ± 0.15 kcal/mol), we assumed that, to an excellent approximation, ΔH_{soln} for 1 would be the same as the measured ΔH_{soln} for α-disulfone 2.

The procedure by which either heats of solution or heats of reaction were obtained was as follows. With calorimeter, solvent, and filled ampule in place, the change in resistance, R, with time was measured (foredrift). The reaction was then activated by breaking the ampule (main experiment). A fast change in resistance was observed, followed by a slower change which was again monitored (afterdrift). The thermistor for the calorimetry system is of such a type that a decrease in temperature (endothermic process) within the calorimeter vessel results in an increase in resistance across the thermocouple. After the reaction was over (stable afterdrift), an exact amount of electrical energy (heat) was pumped into the calorimeter and the change in resistance with time was recorded (calibration run). Using a linear regression program and the data from the calibration run, q_{calib} was calculated (Hewlett-Packard 9100-A calculator, Program No. 70803). This value was then correlated with ΔR for the main experiment to give q_{main}. Minor corrections were then made for sample bouyancy and vaporization of solvent to give q'_{main}. Dividing q'_{main} by the number of moles of substance used in the main experiment gives ΔH. The same procedure was followed whether obtaining ΔH_{soln} or ΔH_{rxn}. The data for the individual runs are given in Table I. A more detailed description of the data handling procedures used is given elsewhere.[13]

References and Notes

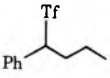
(1) (a) This research was supported by the National Science Foundation, Grant GP 35927X. (b) Address correspondence to this author at the Department of Chemistry, Texas Tech University, Lubbock, Texas 79409.
(2) (a) J. L. Kice and N. E. Pawlowski, *J. Am. Chem. Soc.*, **86**, 4898 (1964); (b) J. L. Kice and N. A. Favstritsky, *J. Org. Chem.*, **35**, 114 (1970).
(3) (a) J. L. Kice and G. Guaraldi, *J. Am. Chem. Soc.*, **89**, 4113 (1967); (b) J. L. Kice and L. F. Mullan, *ibid.*, **98**, 4259 (1976).
(4) (a) J. L. Kice and G. J. Kasperek, *J. Am. Chem. Soc.*, **91**, 5510 (1969); (b) J. L. Kice, *J. Org. Chem.*, **37**, 1865 (1972); J. L. Kice and E. Legan, *J. Am. Chem. Soc.*, **95**, 3912 (1973).
(5) (a) J. L. Kice and H. Margolis, *J. Org. Chem.*, **40**, 3623 (1975). (b) H. Margolis, Ph.D. Thesis, University of Vermont, 1976. (c) A referee has suggested that ΔH_{soln} for **1** might be significantly different than that for **2**, because **2** has a much higher melting point than **1** and could therefore have a significantly higher crystal lattice energy. However, since **4** also has a much higher melting point than **3** and yet shows virtually the same ΔH_{soln} as **3**, we personally doubt that ΔH_{soln} for **1** differs much from that of **2**.
(6) This assumption could be subject to a few kilocalories error, but, even if it is, it is certainly not going to be large enough to change significantly the basic and important conclusion, namely, that the heat of hydrolysis of the α-disulfone is substantially more exothermic than that of the sulfinyl sulfone.
(7) (a) I. Wadso, *Acta Chem. Scand.*, **16**, 471 (1962); (b) J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *J. Am. Chem. Soc.*, **64**, 1747 (1942).
(8) P. George et al., *Biochim. Biophys. Acta*, **223**, 1 (1970).
(9) G. M. Kosolapoff and H. G. Kirksey, *Dokl. Akad. Nauk. SSSR*, **176**, 1339 (1967).
(10) J. L. Kice, D. C. Hampton, and A. Fitzgerald, *J. Org. Chem.*, **30**, 882 (1965).
(11) U. Lerch and J. G. Moffat, *J. Org. Chem.*, **36**, 3861 (1971).
(12) S. Sunner and I. Wadso, *Sci. Tools*, **13**, 1 (1966).
(13) W. S. Johnson, Ph.D. Thesis, University of Vermont, 1976.

Table I. Synthesis of Ketones from Vinyl Azides

Vinyl azide	Registry no.	Ketone	Registry no.	Yield, %
	61795-22-0		451-40-1	85[a]
	16717-64-9		98-86-2	93
	34910-43-5		591-78-6	86
	40934-24-5		502-49-8	91
	16719-57-6		83-33-0	87

[a] Yield from iodoazide.

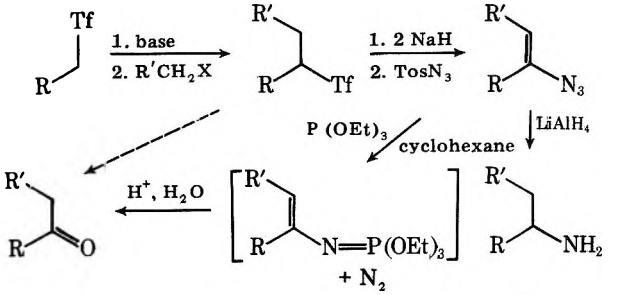
Table II. Synthesis of Ketones from Triflones

Triflone	Registry no.	Ketone	Registry no.	Yield, %
	52208-98-7			76
	62654-00-6		495-40-9	83
	62654-01-7		123-19-3	86

thesis, especially in the formation of carbon–carbon bonds.[1-3] One prerequisite for any such group is that after the construction step it must be easily removed or converted into other desired functionality. Previously, it was known that triflones ($C-SO_2CF_3$) could be reduced to the parent alkanes or thiols, or thermally eliminated to give olefins.[2] In addition, it was recently shown that triflones could react with toluenesulfonyl azide in the presence of 2 equiv of base (NaH/glyme) to give vinyl azides in good yield (Scheme I).[3] Reduction of these compounds with lithium aluminum hydride gave the corresponding saturated amines.

Initial attempts to hydrolyze vinyl azides to the corresponding ketones with acid were only partially successful.[3] In addition to ketones, amides were also produced via Schmidt rearrangement of the protonated vinyl azide.[3d] We reasoned that to avoid this we must first extrude the nitrogen that acts as the initiating leaving group for the rearrangement. Accordingly, we investigated the Staudinger reaction of azides with phosphines.[5,6] Although many kinds of azides have been studied, there appear to be few prior examples of the reaction with simple, unconjugated vinyl azides to form iminophosphoranes.[7]

Scheme I



Conversion of Triflones to Ketones

James B. Hendrickson,* Kenneth W. Bair, and Philip M. Keehn

Department of Chemistry, Brandeis University, Waltham, Massachusetts 02154

Received February 16, 1977

The trifluoromethanesulfonyl group (trifyl, CF_3SO_2-) has found extensive utility as an activating group in organic syn-

The conversion of triflones to ketones was then envisioned as a "one-pot" process (Scheme I) with no intermediate purification of vinyl azide or iminophosphorane. Since the triflone–vinyl azide conversion was well established,[3] we first examined the reaction of vinyl azides, which can also be synthesized from olefins (via iodoazides) by treatment with iodine azide followed by base.[8,9] We found that treatment of vinyl azides with 1 equiv of triethyl phosphite in cyclohexane, followed directly by mild acid hydrolysis, yielded the corresponding ketones in good yield (Table I).

We then examined the direct conversion of triflones to ketones. The results obtained from these reactions, shown in Table II, reveal a very satisfactory "one-pot" operation. This conversion is particularly useful for several reasons. First, the synthesis of vinyl azides from triflones is complementary to the iodine azide method and can be used in cases when the latter method gives mixtures of ketones. With triflones the carbonyl functionality is always produced at the position originally occupied by the CF_3SO_2– group. Second, since triflones are easily obtained from readily available primary alkyl halides, and may be alkylated in high yield,[2,3] they represent useful synthons for the preparation of a wide variety of ketones.

Experimental Section

General. Triflones,[1-3] $TosN_3$,[10] and vinyl azides[8,9] were prepared by known methods. All compounds exhibited physical properties and give IR and NMR spectra consistent with those of known compounds.

Synthesis of Ketones from Vinyl Azides. General Procedure. The vinyl azide (10 mmol) was dissolved in 40 mL of dry cyclohexane. To this was added a solution of $P(OEt)_3$ (1.58 g, 9.50 mmol) in 10 mL of dry cyclohexane (addition time 10 min). The flask warmed during the addition and N_2 gas was evolved. The reaction mixture was then stirred for 18–24 h and then warmed briefly to reflux. After cooling the mixture was poured into a separatory funnel and shaken intermittently for 5 min with an equal volume of 10% HCl. The two phases were then extracted with pentane (3 × 50 mL). The organic extracts were combined, washed with H_2O (2 × 50 mL) and saturated NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated to give the crude ketone. The product was further purified by crystallization or distillation for comparison with authentic sample.

Synthesis of Ketones from Triflones. General Procedure. To a round-bottom flask was added 57% NaH–oil dispersion (926 mg, 22 mmol). The oil was removed by washing the dispersion with dry hexane (2 × 10 mL). Dry glyme [distilled from Na/benzophenone ketyl (50 mL)] was then added to the flask. To the flask was then added dropwise a solution of the triflone (10 mmol) in 10 mL of dry glyme. After 1 h the flask was cooled to 0 °C and a solution of $TosN_3$ (1.97 g, 10 mmol) in 10 mL of dry glyme was added dropwise over 10 min. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was diluted with an equal volume of Et_2O and washed with H_2O (3 × 100 mL) and saturated NaCl (1 × 100 mL). The aqueous washings were combined and extracted with Et_2O (1 × 100 mL). The Et_2O washings were combined, dried ($MgSO_4$), and concentrated to give the crude vinyl azide, which was suspended in 40 mL of dry cyclohexane and the treatment continued as in the procedure above.

References and Notes

(1) J. B. Hendrickson, D. Sternbach, and K. Bair, *Acc. Chem. Res.*, submitted for publication, and references cited therein.
(2) J. B. Hendrickson, A. Giga, and J. Wareing, *J. Am. Chem. Soc.*, **96**, 2275 (1974).
(3) J. B. Hendrickson and P. Skipper, *Tetrahedron*, **32**, 1627 (1976).
(4) A. Hassner, E. Ferdinand, and R. Isbister, *J. Am. Chem. Soc.*, **92**, 1672 (1970).
(5) G. L'Abbé, *Ind. Chim. Belge*, **34**, 519 (1969).
(6) G. L'Abbé, *Angew. Chem., Int. Ed. Engl.* **14**, 775 (1975).
(7) E. Ciganek, *J. Org. Chem.*, **35**, 3631 (1970). See also G. R. Harvey and K. W. Ratts, *ibid.*, **31**, 3907 (1966); G. L'Abbé and A. Hassner, *ibid.*, **36**, 258 (1971).
(8) F. Fowler, A. Hassner, and L. Levy, *J. Am. Chem. Soc.*, **89**, 2077 (1967).
(9) A. Hassner and F. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).
(10) W. von E. Doering and C. DePuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953).

Stereospecific Cyclopentane Synthesis via Intramolecular Nitrone Cycloaddition

Fredric J. Vinick,* Ingrid E. Fengler, and Heinz W. Gschwend

Research Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Summit, New Jersey 07901

Ronald K. Rodebaugh

Analytical Research Department, CIBA-GEIGY Corporation, Ardsley, New York 10502

Received March 8, 1977

In 1964 LeBel and co-workers[1] reported an intramolecular nitrone cycloaddition[2] in which 2,6-dimethyl-5-heptenal (melonal) was condensed with *N*-methylhydroxylamine to give a fused cyclopentane derivative. The noteworthy feature of this reaction is the fact that a cyclopentane with three contiguous asymmetric centers is stereospecifically constructed in a single step from an acyclic precursor. We wish to report further examples of this synthetic method in which functionalized cyclopentanes, again with three contiguous asymmetric centers, are prepared in good yield.

The requisite olefinic aldehyde precursors, 2-methyl-2-phenyl-5-hexenal (**3a**) and 2-(methylthio)-2-phenyl-5-hexenal (**3b**), were synthesized according to Scheme I.

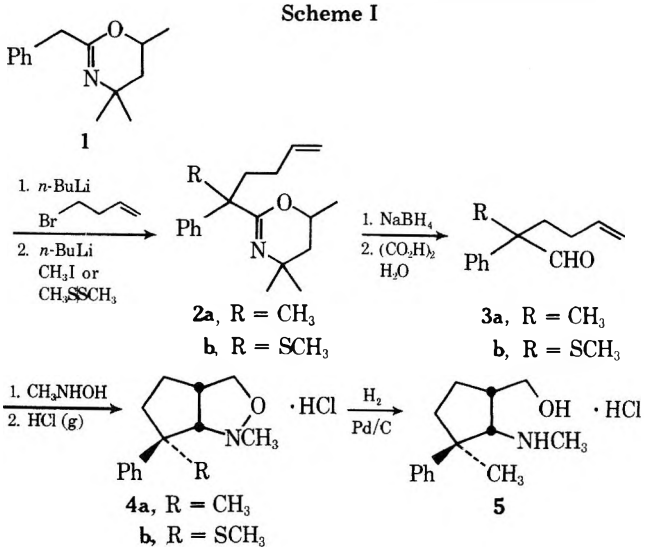
2-Benzyl-4,4,6-trimethyl-5,6-dihydro-1,3(4*H*)-oxazine (**1**) was sequentially alkylated[3] with 4-bromo-1-butene and then either methyl iodide or dimethyl disulfide. Products **2a,b** were reduced with sodium borohydride and hydrolyzed with aqueous oxalic acid to afford the oily aldehydes **3a,b.** The intramolecular nitrone cycloadditions were carried out by heating **3a,b** at reflux in absolute ethanol containing *N*-methylhydroxylamine hydrochloride and pyridine. Aqueous workup yielded the cycloadducts **4a,b** as oils which were converted to crystalline hydrochloride salts. The 60-MHz ^1H NMR spectrum of the crude free base **4a** indicated the presence of only one isomer.

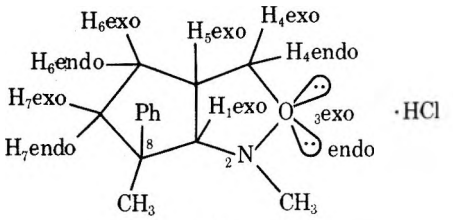
Based on literature precedents,[1] it was anticipated that the ring juncture of **4a** would be cis rather than the more highly strained trans. This hypothesis was verified upon consideration of the 100-MHz ^1H NMR spectrum of **4a**·HCl (see Table I, supplementary material).

First, a long-range W coupling of 1 Hz is observed between H_1exo (δ 4.26) and H_7exo (δ 2.40). A reasonable W (i.e., approximately coplanar arms) exists between these two protons in the cis but not in the trans geometry. Secondly, the signals for the C_7 protons reveal two widely different net coupling patterns with the C_6 protons, an observation more consistent with the flexible cis structure than with the rigid trans.[4]

The assignment of the relative stereochemistry at C_8 was

Scheme I





4a

accomplished by means of paramagnetic shift reagent studies (see Table II, supplementary material). When **4a**·HCl is treated with $Eu(fod)_3$ the exo protons at C_1, C_4, C_5, and C_7 show little or no downfield shift. More significantly, the methyl group at C_8 shows a marked downfield shift while the aromatic region is virtually unchanged. Assuming that the endo lone pair on oxygen is the probable site of complexation of the shift reagent,[5] it thus appears that the C_8 methyl group is endo. As in the case of melonal, the thermodynamically more stable product is formed in which the less bulky group occupies the more sterically congested endo position.

Hydrochloride **4a** was smoothly hydrogenolyzed to **5**, an attractive precursor for a number of further synthetic transformations involving either the alcohol or amine functions.

Experimental Section

Melting points were obtained in a Thomas-Hoover melting point apparatus (uncorrected). Infrared spectra were determined on a Perkin-Elmer Model 521 spectrometer. Proton magnetic resonance spectra were recorded on either a Varian A-60 or a Varian XL-100 spectrometer using Me_4Si as the internal standard. Mass spectra were obtained on an AEI MS 902 mass spectrometer by direct insertion. The following abbreviations are used: (b) broad, (ex) exchangeable with D_2O, (s) singlet, (d) doublet. (t) triplet, (q) quartet, and (m) multiplet.

2-Methyl-2-phenyl-5-hexenal (3a). To a solution of 30.8 g (0.14 mol) of 1 in 270 mL of dry THF at −78 °C under N_2 was added 110 mL (0.165 mol) of 1.5 M *n*-BuLi/hexane. The solution was stirred for 1 h at −78 °C, 20.3 g (0.15 mol) of 4-bromo-1-butene in 30 mL of THF was added, and the mixture was warmed to room temperature. The solution was again cooled to −78 °C, 105 mL (0.16 mol) of 1.5 M *n*-BuLi/hexane was added, the mixture was stirred for 1 h at −78 °C, and 15 mL (0.24 mol) of MeI was added. The solution was warmed to room temperature, stirred overnight, quenched with water, and extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, and evaporated to give 40 g (~100%) of crude oily **2a** as a diastereomeric mixture.

The above product was dissolved in 140 mL of THF/140 mL of 95% ethanol at −35 to −45 °C. A solution of 5.4 g (0.14 mol) of $NaBH_4$ in 8 mL of water was added dropwise; 9 N HCl was added as needed to maintain pH 6–8. The solution was stirred for 1 h at −35 °C and kept at pH 7. The mixture was poured into 200 mL of water, made basic with 1 N NaOH, and extracted with ether. The ether extracts were washed with brine, dried over Na_2SO_4, and evaporated to give 40 g (~99%) of crude oily product.

The tetrahydrooxazine was heated at reflux for 2 h in 220 mL of water containing 70.6 g of oxalic acid. The solution was extracted with ether, washed with water and saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to give 17.8 g (68% overall) of **3a** as an oil: bp 72–75 °C (0.20 mm); IR (film) 1721, 1634, 991, 910, 756, 697 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.95 (m, 4 H), 4.95 (m, 2 H), 5.71 (m, 1 H), 7.27 (s, 5 H), 9.49 (s, 1 H); MS *m/e* 188 (M^+) 159, 144, 105, 91.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.31; H, 8.31.

2-(Methylthio)-2-phenyl-5-hexenal (3b). The procedure described for the preparation of **2a** was carried out on a 0.14-mol scale using 14.1 g (0.15 mol) of dimethyl disulfide in place of MeI to give 44 g (~100%) of crude **2b.** A 0.07-mol sample of **2b** was reduced with $NaBH_4$ and hydrolyzed to give 5.0 g (32% overall) of oily **3b:** bp 86–88 °C (0.28 mm); IR (film) 1703, 1637, 990, 910, 693 cm^{-1}; NMR ($CDCl_3$) δ 1.78 (s, 3 H), 1.91 (m, 4 H), 4.40 (m, 2 H), 5.64 (m, 1 H), 3.33 (s, 5 H), 9.19 (s, 1 H); MS *m/e* 220 (M^+), 205, 191, 143, 103, 91, 77, 41.

The 2,4-dinitrophenylhydrazone was recrystallized from 95% ethanol, mp 108–109 °C.

Anal. Calcd for $C_{19}H_{20}N_4O_4S$: C, 56.98; H, 5.03; N, 13.99. Found: C, 56.97; H, 5,19; N, 14.21.

***cis-trans*-2,8-Dimethyl-8-phenyl-3-oxa-2-azabicyclo-[3.3.0]octane Hydrochloride (4a).** A solution of 17.6 g (0.093 mol) of **3a,** 23.3 g (0.28 mol) of *N*-methylhydroxylamine hydrochloride, 24 mL (0.30 mol) of pyridine, and 300 mL of absolute ethanol was heated at reflux under N_2 for 24 h. The mixture was acidified with 1 N HCl, washed with ether, and made basic with 1 N NaOH. After extraction with CH_2Cl_2, drying over Na_2SO_4, and evaporation of solvent, the cycloadduct was obtained as an orange oil. The crude product was dissolved in ether/acetone at 0 °C and treated with excess HCl gas. Crystalline **4a** was collected by filtration, washed with ether, and dried to give 13.4 g (57%): mp 176–177 °C; IR (Nujol) 2400, 1106, 766, 700 cm^{-1}; NMR ($CDCl_3$) (see Tables I and II and accompanying spectrum); MS *m/e* 217 (M^+), 200, 105.

Anal. Calcd for $C_{14}H_{20}ClNO$: C, 66.26; H, 7.94; N, 5.52. Found: C, 65.89; H, 7.89; N, 5.34.

***cis-trans*-2-Methyl-8-(methylthio)-8-phenyl-3-oxa-2-azabicyclo[3.3.0]octane Hydrochloride (4b).** The procedure described for the preparation of **4a** was followed using 2.5 g (0.011 mol) of **3b** and 3.1 g (0.037 mol) of *N*-methylhydroxylamine hydrochloride. The yield of **4b**·HCl was 1.95 g (62%): mp 177–178 °C; IR (Nujol) 2320, 1139, 981, 722, 698 cm^{-1}; NMR (Me_2SO-d_6) δ 1.60 (s, 3 H, and m, 2 H), 2.44 (m, 2 H), 3.19 (s, 3 H), 3.30 (m, 1 H), 3.88 (m, 1 H), 4.59 (q, 2 H), 7.45 (m, 5 H), 10.8 (b ex, 1 H); MS *m/e* 249 (M^+), 220, 172.

Anal. Calcd for $C_{14}H_{20}ClNOS$: C, 58.82; H, 7.05; N, 4.90. Found: C, 58.97; H, 7.15; N, 4.69.

***N*-Methyl-*cis-trans*-2-hydroxymethyl-5-methyl-5-phenylcyclopentylamine Hydrochloride (5).** A mixture of 13.8 g (0.054 mol) of **4a**·HCl and 2 g of 10% Pd/C in 330 mL of 95% ethanol was hydrogenated at 25 °C and 40 psi until uptake ceased. The mixture was filtered through Celite, concentrated, and crystallized from ether/acetone to give 12.1 g (88%) of **5:** mp 178–180 °C; IR (Nujol) 3346, 2708, 1588, 1068, 1041, 761, 692 cm^{-1}; NMR (Me_2SO-d_6) δ 1.53 (s, 3 H), 1.89 (m, 4 H), 2.46 (s, 3 H, and m, 1 H), 3.77 (m, 1 H), 3.72 (d, 2 H), 7.42 (m, 5 H); MS *m/e* 219 (M^+), 100, 70.

Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.73; H 8.67; N, 5.48. Found: C, 65.43; H, 8.57; N, 5.27.

Acknowledgment. We wish to acknowledge the support and encouragement of Dr. Neville Finch and the assistance of Ms. Ruth Behnke (NMR), Mr. Michael Hotolski and Ms. Natalie Cahoon (IR), and Mrs. Barbara Warren (MS).

Registry No.—**1,** 26939-22-0; **2a** epimer 1, 62744-02-9; **2a** epimer 2, 62744-03-0; **2b** epimer 1, 62744-04-1; **2b** epimer 2, 62744-05-2; **3a,** 62744-06-3; **3b,** 62744-07-4; **3b** DNP, 62744-08-5; **4a,** 62744-09-6; **4b,** 62744-10-9; **5,** 62744-11-0; 4-bromo-1-butene, 5162-44-7; *N*-methylhydroxylamine HCl, 4229-44-1.

Supplementary Material Available. The NMR spectrum of **4a**·HCl and LIS data (Tables I and II; 2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) N. A. LeBel, M. E. Post, and J. J. Whang, *J. Am. Chem. Soc.*, **86,** 3759 (1964); (b) N. A. LeBel and J. J. Whang, *ibid.*, **81,** 6334 (1959); (c) N. A. LeBel, *Trans. N.Y. Acad. Sci.*, **27,** 858 (1965).

(2) Two recent reviews which deal with the subject of intramolecular 1,3-dipolar cycloadditions of nitrones are (a) D. S. Black, R. F. Crozier, and V. C. Davis, *Synthesis,* **7,** 205 (1975); (b) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15,** 123 (1976).

(3) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. Portnoy, *J. Org. Chem.*, **38,** 36 (1973); (b) I. R. Politzer and A. I. Meyers, *Org. Synth.*, **51,** 24 (1971).

(4) Examination of molecular models shows the trans compound to be very rigid with the C_6 and C_7 protons held in an approximately cis eclipse relationship. This geometry requires that the coupling patterns for C_6 and C_7 be nearly the same, in contrast to the actual spectral data.

(5) The endo lone pair is the more sterically accessible owing to an unfavorable exo_2, exo_3 interaction.

Organotellurium Chemistry. 2. Dibenzyl Ditelluride: Some Transformations Involving Loss of Tellurium

H. Kenneth Spencer and Michael P. Cava*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received February 25, 1977

Dibenzyl diselenide (**4**) has been known for over a century,[1] and its chemistry has been extensively investigated.[2-4] In

contrast, the corresponding dibenzyl ditelluride (1) was first synthesized only in 1968,[5] and no chemistry of this compound has as yet been reported. Recently, we described a convenient synthesis of 1.[6] We now report some further properties of this compound, including several chemical reactions which result in tellurium extrusion.

Results and Discussion

NMR Properties. The ^1H NMR spectrum of dibenzyl ditelluride (1) in $CDCl_3$ shows an aromatic singlet (10 H) at δ 7.22 and a benzylic singlet (4 H) at δ 4.25. The aromatic signal of the corresponding diselenide 4 appears at almost the same position (δ 7.29), but the benzylic signal now appears upfield at δ 3.89. Substitution of tellurium for selenium in this system thus produces an appreciable deshielding effect on the adjacent methylene protons.

The ^{13}C NMR of ditelluride 1 in $CDCl_3$ shows aromatic carbon signals at δ 141.5, 128.2, 127.9 and 126.0, as well as a benzylic carbon signal at δ 6.58. Dibenzyl diselenide (4) shows corresponding signals at δ 138.3, 128.3, 127.7, 126.3, and 32.6. The benzylic carbon signal of dibenzyl disulfide has been reported as δ 43.1.[7] In the benzylic signals of the dibenzyl dichalcongenides, there is therefore an upfield shift observed on going from S to Se to Te as neighboring atoms. The unusually large shift (δ 32.6 to 6.58) observed on going from Se to Te emphasizes the metallic nature of the Te atom.

Photochemical Lability of Dibenzyl Ditelluride (1). The most striking property of ditelluride 1 is its extraordinary photochemical lability. Exposure of solutions of 1 to ordinary laboratory ceiling lights leads to the rapid appearance of black elemental tellurium; the ditelluride could be crystallized and chromatographed only while working under red photographic safety lights.

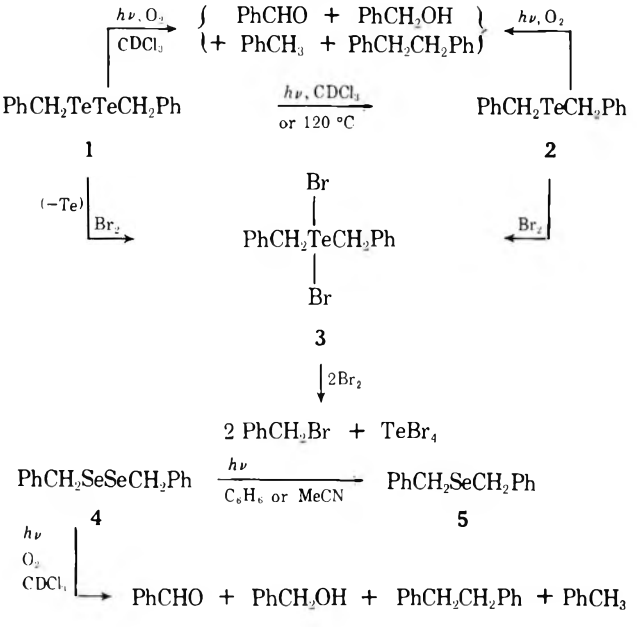
Irradiation of ditelluride 1 in $CDCl_3$ (Hanovia lamp) under nitrogen led to a rapid deposition of Te and a shift of the benzylic ^1H NMR signal to δ 4.0, due to the formation of dibenzyl telluride (2); the latter decomposed further only very slowly under the reaction conditions employed. When ditelluride 1 was irradiated under oxygen, however, the monotelluride signal at δ 4.0 soon appeared but then vanished after 5 h, the major reaction products being benzaldehyde, toluene, and benzyl alcohol, as well as some 1,2-diphenylethane. Irradiation of authentic dibenzyl telluride (2) under oxygen in the same manner afforded the same products; in a control experiment, monotelluride 2 was unchanged after irradiation (4 h) under nitrogen. Proof that the oxidation of monotelluride 2 was a photochemical process was obtained by allowing a $CDCl_3$ solution of 2 to stand in the dark under oxygen for 24 h, after which time no transformation products were detected.

The corresponding photolysis of dibenzyl diselenide (4) to dibenzyl selenide (5) under nitrogen has been reported using both benzene[3] and acetonitrile[4] as solvents. In benzene solution in the presence of oxygen diselenide 4 has been reported to give benzaldehyde (up to 63%) but not benzyl alcohol.[3] For comparison purposes, we have now irradiated diselenide 4 under oxygen in $CDCl_3$ for 30 h; the products of our reaction were unchanged diselenide 4, benzaldehyde, benzyl alcohol, toluene, and 1,2-diphenylethane. The greater variety of products observed in our photooxidation undoubtedly resulted from our use of a closed NMR tube, resulting in an incomplete oxidation of the intermediate benzyl radicals.

Thermal Decomposition of Dibenzyl Ditelluride (1). Although ditelluride 1 can be crystallized without appreciable decomposition from hot hexane (80 °C) under red lights, it is largely decomposed thermally in 10 min at 120 °C (red lights) under nitrogen, the only discernible products being tellurium and monotelluride 2. Under the same conditions, diselenide 4 was recovered completely unchanged. Thermal decomposition of 4 has been reported to occur at temperatures above 150 °C.[8]

Reaction of Dibenzyl Ditelluride (1) with Bromine. The reaction of either ditelluride 1 or monotelluride 2 with excess bromine in CCl_4 afforded only $TeBr_4$ and benzyl bromide, as determined by NMR and GC. The result seemed to confirm the earlier expressed opinion that benzylic tellurides were converted by bromine to benzylic bromides in a manner which precluded the isolation of intermediates.[9] A more careful experiment showed, however, that reaction of ditelluride 1 with a little under 1 equiv of bromine gave a dark precipitate (presumably Te) along with a new compound having a benzylic NMR signal at δ 4.60. Preparative isolation of this crystalline material revealed it to be the previously unknown dibenzyltellurium dibromide (3). An independent synthesis of dibromide 3 was achieved by the careful addition of 1 equiv of bromine to dibenzyl telluride (2). As expected, dibromide 3 reacts further with bromine to give benzyl bromide and $TeBr_4$.

The mechanism of the conversion of ditelluride 1 to dibromide 3 is not clear at present. It is interesting to note, however, that the migration of a benzyl group from one tellurium to the other in this reaction is in contrast to the reaction of bromine with diaryl ditellurides, a process which leads to a simple brominolysis of the Te–Te bond.[10]



Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass, infrared (KBr), and ultraviolet (cyclohexane) spectra were determined using Perkin-Elmer 270B, 137, and 202 spectrometers, respectively. All tellurium-containing mass peaks are reported for ^{130}Te. NMR spectra were recorded in $CDCl_3$ solutions (Me_4Si standard) and are reported in δ units; a Varian A-60A instrument and a JEOL PS-100 instrument were used for ^1H and ^{13}C spectra, respectively. GC analyses were determined with an Aerograph Autoprep A-700, using 4- and 6-ft Teflon-coated 3% SE-30 on Chromosorb W-HP 80/100 columns; authentic compounds were used as product standards. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Dibenzyl Telluride (2). A. Rongalite Method. Sodium formaldehyde sulfoxylate (Rongalite, 18.0 g) was added under nitrogen at 80 °C to a suspension of tellurium (2.56 g) in a solution of sodium hydroxide (12 g) in water (125 mL). After stirring for 1 h, a solution of benzyl chloride (1.26 g) in a small amount of EtOH was added dropwise at room temperature to the almost colorless telluride solution. After stirring for a further 1 h, extraction with Et_2O, followed by removal of the dried solvent and crystallization from petroleum ether (red light illumination), gave dibenzyl telluride (2) as yellow needles (1.09 g, 70%): mp 49–57 °C (lit.[11] mp 53–53.5 °C); NMR δ 4.00

(s, 4 H), 7.22 (br s, 10 H); λ_{max} 209 nm (log ϵ 4.38), 233 (4.46), 390 (1.70); mass spectrum *m/e* (rel intensity) M^+ 312 (44), 91 (100).

B. Borohydride Method. A mixture of tetramethylammonium borohydride (1.78 g), tellurium powder (1.27 g), and water (100 mL) was heated on the steam bath under nitrogen until the initially produced purple color was discharged. After cooling to room temperature, a solution of benzyl chloride (2.53 g) in EtOH (20 mL) was added slowly with stirring, air being rigorously excluded. After stirring for a further 2 h, the reaction mixture was worked up as in the above experiment to give crystalline **2** (2.56 g, 82%), mp 49–57 °C.

Photochemical Decomposition of 1. A solution of dibenzyl ditelluride (**1**, 50 mg) in $CDCl_3$ (0.5 mL) in an NMR tube was irradiated in the presence of nitrogen, using a Hanovia lamp, until no more tellurium deposited. The only detectable reaction product (by both NMR and GC) was monotelluride **2**, which was unchanged after a further 4 h of irradiation (nitrogen), as confirmed in a control reaction using crystalline **2**.

Repetition of the above irradiation of **1** in the presence of oxygen showed (by NMR) that monotelluride **2** was initially formed, but then slowly disappeared with the formation of the following products (by NMR and GC): benzaldehyde (42%), benzyl alcohol (21%), toluene[12] (21%), and 1,2-diphenylethane (7%). The relative amounts of these products were somewhat variable, and seemed dependent upon oxygen concentration.

Thermolysis of 1. Ditelluride **1** was heated at 120 °C without solvent for 10 min under nitrogen and under red lights. The dark melt was dissolved in $CDCl_3$, filtered from tellurium, and analyzed by NMR, which indicated **2** as the only product formed.

Photochemical Oxidation of 2. In a typical photooxidation in $CDCl_3$ under conditions used for **1**, the following were detected (NMR and GC) after 24 h: benzaldehyde (42%), benzyl alcohol (24%), unchanged **2** (8%), toluene[12] (4%), and 1,2-diphenylethane (5%). In another experiment using a low concentration of **2** and excess pure oxygen, only benzaldehyde (66%) and benzyl alcohol (33%) were detected. The photooxidation of **2** was done in CCl_4. The products detected were benzaldehyde (56%), benzyl alcohol (12%), dibenzyl (2%), toluene (2%), and benzyl chloride (8%).

Photochemical Oxidation of 4. A photooxidation of diselenide **4** in $CDCl_3$, using insufficient oxygen, showed the following products (NMR and GC) after 30 h: unchanged **4** (20%), benzaldehyde (25%), benzyl alcohol (14%), toluene[12] (25%), and 1,2-diphenylethane (5%).

Dibenzyltellurium Dibromide (3). From 1. A solution of **1** (0.500 g) in CCl_4 was treated in the dark with a solution of bromine in CCl_4. The reaction was monitored by NMR, and GC showed that benzyl bromide was not present. After 10 min, the black precipitate was removed by filtration and the solution concentrated to give **3** (0.340 g, 63%) as white prisms: mp 136–137 °C; NMR δ 4.60 (s, 4 h), 7.40 (m, 10 H); mass spectrum *m/e* (rel intensity) 389 (M − Br, 62), 91 (100). Anal. Calcd for $C_{14}H_{14}Br_2Te$: C, 35.80; H, 3.00; Br, 34.02; Te, 27.17. Found: C, 35.66; H, 2.93; Br, 34.26; Te, 27.27.

Treatment of **3** in CCl_4 with bromine gave only benzyl bromide, as shown by NMR and by GC.

From 2. A solution of bromine (0.160 g) in CCl_4 was added carefully to a solution of **2** (0.344 g) in CCl_4. After 10 min, concentration followed by crystallization (CCl_4–Et_2O) gave **3** (0.375 g, 72%), identical (IR, melting point) with material obtained from **1**.

Acknowledgment. This work was supported by the National Science Foundation through a grant (MPS 74-03279).

Registry No.—**1**, 20727-11-1; **2**, 62654-03-9; **3**, 62654-04-0; **4**, 1482-82-2; tellurium, 13494-80-9; benzyl chloride, 100-44-7; benzaldehyde, 100-52-7; benzyl alcohol, 100-51-6; toluene, 108-88-3; 1,2-diphenylethane, 103-29-7.

References and Notes

(1) C. L. Jackson, *Justus Liebigs Ann. Chem.*, **179**, 1 (1875).
(2) D. L. Klayman and W. H. H. Günther, Ed., "Organic Selenium Compounds—Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973.
(3) W. Stanley, M. R. Van De Mark, and P. L. Kumler, *J. Chem. Soc., Chem. Commun.*, 700 (1974).
(4) J. Y. C. Chu, D. G. Marsh, and W. H. H. Günther, *J. Am. Chem. Soc.*, **97**, 4905 (1975).
(5) Y. N. Shlyk, G. M. Bogolyubov, and A. A. Petrov, *Zh. Obshch. Khim.*, 119 (1968).
(6) H. K. Spencer, M. V. Lakshmikantham, and M. P. Cava, *J. Am. Chem. Soc.*, 99, 1470 (1977).
(7) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972.
(8) M. A. Lardon, *Ann. N.Y. Acad. Sci.*, **192**, 132 (1972).
(9) G. Vicentini, *Chem. Ber.*, **91**, 801 (1958).
(10) K. J. Irgolic, "The Organic Chemistry of Tellurium", Gordon and Branch, New York, N.Y., 1974.
(11) L. Tschugaeff and W. Chlopin, *Ber.*, **47**, 1269 (1914).
(12) The toluene obtained is assumed to be toluene-d_1.

Nitroacetoxylation of Isoprene

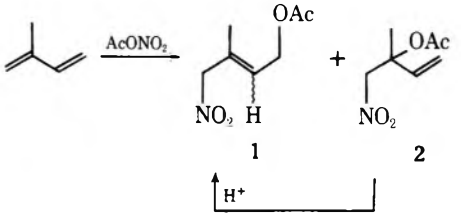
Pius A. Wehrli* and Beatrice Schaer

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received March 25, 1977

The C_5 carbon skeleton of isoprene is of fundamental importance in organic chemistry, since this basic unit is encountered in many natural products. It is therefore not surprising that numerous attempts have been made to utilize isoprene preparatively as a C_5 building block in the synthesis of naturally occurring substances such as terpenoids in general and vitamin A and carotenoids in particular.[1] In order to effectively use isoprene for these purposes, it has to be appropriately functionalized.[2] The only reaction in this regard which appears to have gained industrial importance[3] is the low-temperature addition of anhydrous hydrogen chloride. Yields of over 90% of isolated product have been reported,[4] indicating very little polymerization of starting material.

The present contribution describes a novel and preparatively efficient *bis* functionalization of isoprene: *nitroacetoxylation.* Treatment of isoprene with acetyl nitrate at room temperature leads, in a fast and highly exothermic reaction, to a virtually quantitative weight yield of an approximately 7:3 mixture of nitro acetates **1** and **2**. It appears that within



the temperature range of about −20 to 30 °C the ratio of **1** to **2** is not changed substantially, although the highest content of the 1,4-addition product is observed at 25–30 °C. Complete conversion of tertiary acetate **2** into the 1,4-addition product is achieved by treating **2** in acetic acid with a catalytic amount of sulfuric acid. Moreover, subjecting the initial reaction product to rearrangement conditions results in the isolation of **1** as a 85:15 trans/cis mixture in over 80% yield.

A close formal analogy is evident between the low-temperature hydrogen chloride addition and the nitroacetoxylation reaction. Both processes appear to proceed virtually exclusively via a heterolytic pathway.[5] This is borne out by (a) the equally high regiospecificity for both the proton and nitro group introductions at C_1 of the isoprene skeleton, (b) the negligible degree of polymerization of starting material observed, and (c) the mixtures of 1,4- and 1,2-addition products obtained.[6] The predominant *E* configuration for nitro acetate **1** may be primarily the result of the spatial requirements of the *O*-acetyl and nitromethyl groups.

The novel structures thus produced appear potentially useful as C_5 synthons, especially in the area of polyolefin terpenoids. Pertinent studies are currently being carried out in this laboratory.

Experimental Section

Infrared (IR) spectra were determined as films. The superscripts s, m, and w designate strong, medium, and weak absorption bands. NMR spectra were recorded in deuteriochloroform solutions on a Varian T-60 spectrometer with tetramethylsilane as internal standard. A Hewlett-Packard Model 5720 gas chromatograph equipped with 6-ft UC-W 98 10% columns was used for GC analysis. The temperature program was set from 100 to 200 °C at 10 °C/min. *Caution: Thermal instability of acetyl nitrate has been reported.*[5b] *It is also recommended that nitro acetates* **1** *or* **2** *not be heated above 100 °C either neat or in solution.*

3-Methyl-4-nitro-2-buten-1-yl Acetate (1) and 3-Methyl-4-nitro-1-buten-3-yl Acetate (2). Nitric acid (90%, 100 g, 1.43 mol) was dropped into stirred and ice bath cooled acetic anhydride (735 g, 7.2 mol) at such a rate that the internal temperature was maintained at 20–25 °C.[7] This was followed by the dropwise addition of isoprene (68 g, 1 mol), which required 1 h and continuous cooling with an ice bath in order to maintain the internal temperature at a constant 25 °C. The reaction mixture was stirred for an additional 1 h at room temperature and worked up by quenching in ice and water and extracting with methylene chloride. Solvent and excess acetic anhydride were removed in vacuo (aspirator, then high vacuum) at ≤40 °C water bath temperature[8] to give 194.2 g of dark yellow oily residue. GC analysis indicated that besides a small amount of acetic anhydride, the crude mixture consisted essentially only of **1** and **2** in the ratio of 7:3. The *Z* isomer of **1** was estimated to be 5% of the total weight. The pure compounds *E*-**1**, *Z*-**1**, and **2** were isolated from a similar experiment via silica gel column chromatography using benzene–ethyl acetate mixtures for elution.

Nitro Ester *E*-1:[9] IR 1740^s, 1635^m, 1560^s cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85 (broadened s, 3 H, CH_3), 2.05 (s, 3 H, OAc), 4.65 (d, J = 7 Hz, 2 H, OCH_2), 4.85 (s, 2 H, $-CH_2NO_2$), 5.78 (t, J = 7 Hz, 1 H, vinyl); λ_{max} (EtOH) 280 nm (ϵ 370); λ_{max} (0.1 N KOH) 221 nm (ϵ 8840), 284 (7255); MS *m/e* M^+ not observed, 127 (8%, $M^+ - NO_2$), 85 (9%, $M^+ - NO_2 - CH_3CO$), 43 (100%, CH_3CO).

Nitro Ester *Z*-1:[9] ^{1}H NMR ($CDCl_3$) δ 1.94 (broadened s, 3 H, CH_3), 2.05 (s, 3 H, OAc), 4.66 (d, J = 7 Hz, 2 H, OCH_2), 5.08 (s, 2 H, $-CH_2NO_2$), 5.83 (t, J = 7 Hz, 1 H, vinyl).

Nitro Ester 2: IR 1720^s, 1630^w, 1535^s cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 3 H, CH_3), 2.05 (s, 3 H, OAc), 4.85 (s, 2 H, CH_2NO_2), 5.25–6.0 (m, 3 H, vinyl group); λ_{max} (EtOH) 280 nm (ϵ 250); λ_{max} (0.1 N KOH) 231 nm (ϵ 10 320), 285 (6720); MS *m/e* M^+ not observed, 127 (23%, $M^+ - NO_2$), 85 (95%, $M^+ - NO_2 - CH_3CO$), 67 (100%, $M^+ - NO_2 -$ AcOH).

Allylic Rearrangement 2 → 1. Nitro ester **2** (100 mg) was dissolved in 1 mL of a solution of 230 mg of concentrated sulfuric acid in 33.7 mL of acetic acid. After 16 h at 75 °C the reaction was quenched with ice. There was obtained 91 mg of a 7:3 *E*/*Z* mixture of **1** as determined by GC.

Allylic Rearrangement of a Crude Mixture of 1 and 2. The crude product (194.2 g) obtained in the experiment described above was dissolved in 450 mL of acetic acid to which had been added 7.3 g of concentrated sulfuric acid. Stirring at 75 °C overnight, quenching with ice, and extractive workup yielded 162.8 g (94%) of brown oil. For the purpose of yield determination, an aliquot (1.401 g) was evaporatively distilled[10] in a Kugelrohr apparatus [oven temperature 120–140 °C (0.5–0.8 mm)]. The light yellow distillate [1.158 g, 82% (based on isoprene)] was shown by GC analysis to be an 85:15 mixture of *E*-**1** and *Z*-**1**.

Acknowledgments. We thank the staff of our Physical Chemistry Department for the determination of the spectral data.

Registry No.—*E*-**1**, 62842-04-0; *Z*-**1**, 62842-05-1; **2**, 61447-07-2; isoprene, 78-79-5; acetyl nitrate, 591-09-3.

References and Notes

(1) O. Isler, Ed., "Carotenoids", Birkhaeuser Verlag, Basel, 1971.
(2) E. C. Leonard, Ed., "High Polymers", Vol. XXIV, Part 2, Wiley-Interscience, New York, N.Y., 1971.
(3) W. C. Meuly, *An. Acad. Bras. Cienc.*, 375 (1972); *Chem. Abstr.* **83**, 97574q (1975).
(4) W. J. Jones and H. W. T. Chorley, *J. Chem. Soc.*, 832 (1946).
(5) (a) Mechanistic studies of the HCl addition to isoprene are reported by M. D. Jordan, Jr., and F. L. Pilar, *Theor. Chim. Acta*, **10**, 325 (1968). (b) Acetyl nitrate additions to simple olefins have been studied in detail by F. G. Bordwell and F. W. Garbisch, Jr., *J. Am. Chem. Soc.*, **82**, 3588 (1960); *J. Org. Chem.*, **27**, 3049 (1962).
(6) A. J. Ultée, *J. Chem. Soc.*, 530 (1948).
(7) *Caution! Acetylnitrate is reported*[5b] *to be a thermally labile compound.*
(8) In view of the general thermal instability of aliphatic nitro compounds, we recommend that the lowest practical temperature be used.
(9) Assignments for the *E* and *Z* structures are based on the chemical shifts of the methyl group in relation to the allylic oxygen function: D. J. Faulkner, *Synthesis*, 175 (1971).
(10) It is recommended that larger amounts not be distilled since decomposition "fume-offs" have occurred in isolated instances. A safety shield is advisable.

Carbon-13 Spectral Parameters of Some Polycyclic Hydrocarbons

Ernest W. Della,* Philip T. Hine, and Harish K. Patney

School of Physical Sciences, Flinders University, Bedford Park, S. A., 5042, Australia

Received January 25, 1977

In connection with work on polycyclic hydrocarbons substituted at the bridgehead position, in particular those derived from the molecules **1**–**5** below, we felt it desirable to report the ^{13}C NMR spectra of the parent hydrocarbons. While chemical shifts of the carbon atoms in bicyclo[2.2.2]octane (**1**) and norbornane (**2**) have been well documented,[1,2] and the ^{13}C–H one-bond coupling constants have been reported for **2**[3] and tricyclo[4.1.0.0^{2,7}]heptane (**5**),[4] there is a surprising lack of information on the remainder. In addition to chemical shift data, we were particularly interested in the one-bond bridgehead carbon–proton couplings. There has been considerable activity in recent years in the measurement of $^1J(^{13}C–H)$, and in attempts to correlate this parameter with the s character of the carbon bonding orbital, according to the empirical relationship described by Muller and Pritchard.[5]

$$\%\,s = \frac{J(^{13}C–H)}{5}$$

Although this suggested correlation has been criticized, there is good evidence that the empirical relationship holds for hydrocarbons, but is rather less tenuous when applied to molecules containing heteroatoms. ^{13}C–H coupling constants have been suggested to correlate similarly with other phenomena that are sensitive to hybridization, and hence the electronegativity of the carbon orbital, such as the pK_as of the corresponding amines and carboxylic acids,[6] as well as the acidity of the proton.[7]

The substrates **1**, **2**, and **4** were obtained as previously reported,[8] and **5** was obtained by known procedures.[9] Bicyclo[2.1.1]hexane (**3**) was synthesized from bicyclo[2.1.1]hexan-2-one by sodium cyanoborohydride reduction of the derived *p*-toluenesulfonylhydrazone.

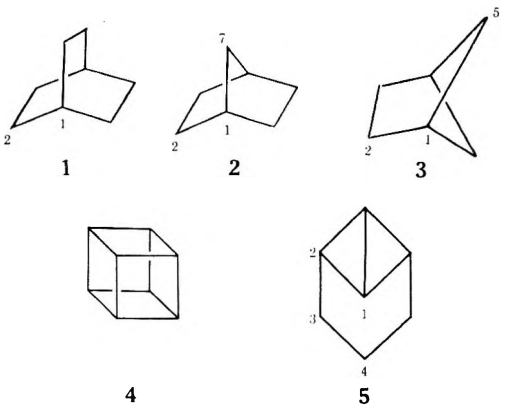


Table I contains the carbon-13 chemical shifts, of which the values for **1** and **2** are in excellent agreement with those recorded. For shifts previously unknown, viz., in **3**, **4**, and **5**, assignments were made with the aid of off-resonance de-

Table I. ^{13}C Chemical Shifts of the Polycyclic Hydrocarbons 1–5

Registry no.	Compd	C_1	C_2	Others
280-33-1	1	24.0[a]	26.0[a]	
279-23-2	2	36.6[b]	30.0[b]	C_7 38.6[b]
285-86-9	3	39.5	26.3[c]	C_5 39.0[c]
277-10-1	4	47.3	47.3	
287-13-8	5	5.6	40.0	C_3 20.8 C_4 21.3

[a]For literature values see ref 1. [b]For literature values see ref 2. [c]Shifts may be interchanged.

Table II. One-Bond ^{13}C–H Coupling Constants in the Polycyclic Hydrocarbons 1–5

Compd	$^1J(^{13}C_1$–H)	% s character	$^1J(^{13}C$–H) others	% s character
1	134.3	26.9	C_2 125.7	25.1
2	140.1[a,b]	28.0	C_2 130.3[b]	26.1
			C_7 131.3[b]	26.3
3	150.5	30.1	C_2 132.5[d]	26.5
			C_5 135.1[d]	27.0
4	153.8	30.8		
5	200.3[c]	40.0	C_2 154.2[c]	30.8
			C_3 126.2[c]	25.4
			C_4 126.2[c]	25.4

[a]For literature values see ref 3a. [b]For literature values see ref 3b. [c]For literature values see ref 4. [d]Coupling constants may be interchanged.

coupled spectra, and by relative intensities in the proton-decoupled spectra. Coupling constants of directly bonded ^{13}C–H are displayed in Table II. As expected there is a pronounced increase in the magnitude of the bridgehead carbon–proton coupling with increased strain at the bridgehead. Thus, the value of $^1J(^{13}C_1$–H) in the relatively strain-free molecule, **1**, is essentially identical with that in adamantane (133.5 Hz).[3a] On the other hand, the highly strained hydrocarbons such as cubane (**4**) and tricyclo[4.1.0.0^{2,7}]heptane (**5**) show markedly higher values. The calculated fractional s characters of the C–H bonds are also included in Table II. Clearly, in both **4** and **5**, the bridgehead skeletal angles are substantially smaller than those in **1**, resulting in an increase in the p character of the endocyclic hybrid orbitals of the bridgehead carbon atom with a corresponding increase in the s component of the exocyclic hybrid orbital.

Experimental Section

^{13}C NMR spectra were measured on a Bruker Scientific Inc. WH-270 Fourier transform NMR spectrometer operating at 67.89 MHz, or, in a few instances, on a WH-90 spectrometer operating at 22.625 MHz. Samples were ca. 3 M in deuteriochloroform with Me_4Si added as an internal reference. Chemical shifts are estimated to be accurate to ±0.1 ppm, and coupling constants to ±0.6 Hz. Bicyclo[2.2.2]octane, norbornane, and cubane were obtained from the corresponding bridgehead-substituted bromides by reaction with tributyltin hydride under ultraviolet irradiation as described.[8] Tricyclo[4.1.0.0^{2,7}]heptane was synthesized by the improved procedure reported by Gassman and Richmond.[9]

Bicyclo[2.1.1]hexane. Bicyclo[2.1.1]hexan-2-one[10] (1.0 g, 10.4 mmol) and *p*-toluenesulfonylhydrazine (2.4 g, 13.0 mmol) in ethanol (70 mL) were boiled under reflux for 20 h. The solution was cooled and the crystalline deposit was recrystallized from ethanol to give bicyclo[2.1.1]hexan-2-one *p*-toluenesulfonylhydrazone (1.9 g, 70%) as needles, mp 184–185 °C.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.35; H, 6.34; N, 10.57; S, 11.9.

The hydrazone (1.8 g, 6.8 mmol) was dissolved in 1:1 DMF/sulfolane (32 mL), heated to 110 °C, and then treated with three portions each containing sodium cyanoborohydride (1.7 g, 27.4 mmol) and *p*-toluenesulfonic acid (0.3 g) added every 3 h as outlined by Hutchins and co-workers.[11] The product which distilled and was collected in a cold trap (−40 °C) was shown (VPC) to be practically pure and was identified as bicyclo[2.1.1]hexane by comparison of its physical and spectral properties (MS, IR, NMR) with those of the authentic material

Acknowledgment. This work was supported in part by a grant made available by the Australian Research Grants Committee.

Registry No.—Bicyclo[2.1.1]hexan-2-one, 5164-64-7; *p*-toluenesulfonylhydrazine, 1576-35-8; bicyclo[2.1.1]hexan-2-one *p*-toluenesulfonylhydrazone, 62708-51-4.

References and Notes

(1) P. J. Garratt and R. Rlguera, *J. Org. Chem.*, **41**, 465 (1976), and ref 3 therein.
(2) G. S. Poindexter and P. J. Kropp, *J. Org. Chem.*, **41**, 1215 (1976), and ref 3–6 therein.
(3) (a) E. Lippmaa, T. Pehk, J. Paasivirta, N. Belikova, and A. Platé, *Org. Magn. Reson.*, **2**, 581 (1970); (b) G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, **91**, 3954 (1969).
(4) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **85**, 2022 (1963).
(5) N. Muller and D. E. Pritchard, *J. Chem. Phys.*, **31**, 768, 1471 (1959).
(6) See, for example, K. B. Wiberg and B. R. Lowry, *J. Am. Chem. Soc.*, **85**, 3188 (1963); T. W. Cole, C. J. Mayers, and L. M. Stock, *ibid.*, **96**, 4555 (1974).
(7) Z. B. Maksić and M. Eckert-Maksić, *Tetrahedron*, **25**, 5113 (1969).
(8) E. W. Della and H. K. Patney, *Synthesis*, 251 (1976).
(9) P. G. Gassman and G. D. Richmond, *J. Am. Chem. Soc.*, **92**, 2090 (1970).
(10) J. Meinwald and R. A. Chapman, *J. Am. Chem. Soc.*, **90**, 3218 (1968).
(11) R. O. Hutchins, C. A. Milenski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).

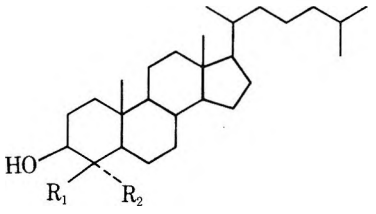
Synthesis of 4-Spiro[cyclopropanecholestan-3β-ol]

Michael R. Czarny, James A. Nelson, and Thomas A. Spencer*

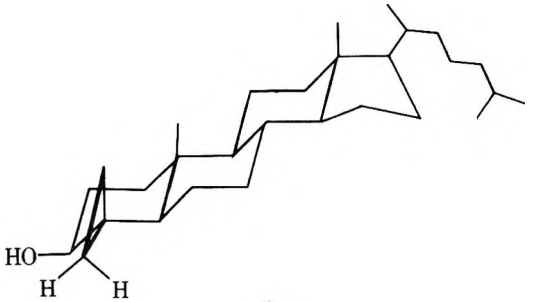
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received February 3, 1977

Previous studies of the interaction of rat liver enzyme preparations with cholestane derivatives having various substituents at C4 have indicated that there is a high degree of substrate specificity in the biological demethylations at that position during the conversion of lanosterol to cholesterol.[1–3] Specifically, steroids **1–5** are converted to cholestan-3β-ol by



1, R_1, R_2 = CH_3
2, R_1 = H; R_2 = CH_3
3, R_1 = CH_3; R_2 = CH_2OH
4, R_1 = CH_3; R_2 = CHO
5, R_1 = CH_3; R_2 = COOH
6, R_1 = CH_2OH; R_2 = CH_3
7, R_1 = CH_3; R_2 = CH_2CH_3
8, R_1 = CH_2CH_3; R_2 = CH_3

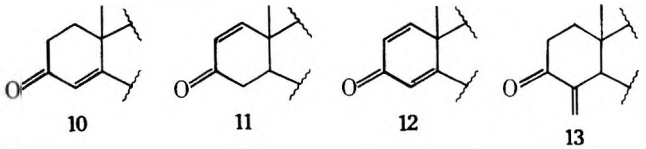


9

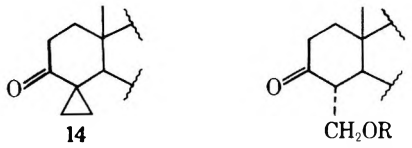
the same enzymes which convert lanosterol to cholesterol, whereas steroids **6–8** are unaffected by that enzyme system.[1-3] In order to probe further the geometric requirements of substrates for enzymic C4 oxidative demethylation, it was decided to study the spirocyclopropyl alcohol **9**. If **9** were unchanged by an active rat liver homogenate, it might suggest that the key initial biochemical hydroxylation of the 4α methyl group[1-4] occurs at a carbon–hydrogen bond with a geometry different from those depicted in **9**. This note describes the synthesis of **9**; the results of incubation of **9** will be reported subsequently.

Direct cyclopropanation by bisalkylation at C4 using a 1,2-dihaloethane seemed the simplest route to **9**, and such a reaction has been successfully performed on 17α-methyltestosterone.[5] However, attempts to effect cyclopropanation of cholest-4-en-3-one (**10**) using a variety of bases followed by 1,2-dibromoethane or 1,2-diiodoethane failed. Similar alkylations were also attempted on cholest-1-en-3-one[6] (**11**), which can form an enolate anion only at C4. Aside from recovered **11**, the only identified product obtained was a small amount of dienone 12[7] from a reaction using 1,2-diiodoethane. Formation of **12** presumably occurred via iodination at C4 followed by elimination of hydrogen iodide. It is not clear why this precedented[5] method of cyclopropanation was unsuccessful in our hands.

Attention was then turned to the synthesis of **9** via 4-methylenecholestan-3-one (**13**). If **13** could be prepared, its reaction with a methylene transfer reagent, such as dimethylsulfoxonium methylide, would presumably produce spirocyclopropyl ketone **14**.[8] Hydride reduction would then be expected to afford **9** without difficulty. Synthesis of **13** was first attempted by application to **10** of the method of Stork and d'Angelo,[9] involving reaction of the trimethylsilyl enol ether of a kinetically generated C4 enolate anion with methyllithium followed by treatment with formaldehyde. If successful, this procedure would lead to **15**, which presumably would be easily convertible to **13**. Unfortunately, efforts to prepare trimethylsilyl enol ether **16** failed. The major product (48%) from treatment of **10** with lithium and ammonia, followed by trimethylsilyl chloride,[9] was the monotrimethylsilyl ether of **17**, a pinacol which is well known as the unwanted product of dissolving metal reduction of **10**.[10,11] Isolation of only the monoether is probably a consequence of steric hindrance to introduction of a second trimethylsilyl group.



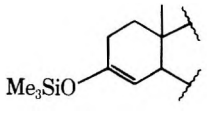
10 **11** **12** **13**



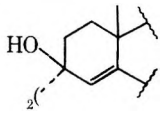
14

CH_2OR

15, R = H
24, R = Ms



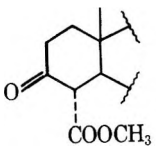
16



17

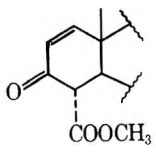
Hajos and co-workers have studied the synthesis of α-methylene ketones,[12] and essentially one of their methods was used in a successful preparation of **13**, starting with the familiar β-keto ester **18**.[1,10,13] Preparation of **18** by reductive carbomethoxylation of **10** is much less effective than preparation of other β-keto esters by this procedure, owing to formation of **17**,[10] so a more efficient route to **18** was sought. Carboxylation of enone **11** with methylmagnesium carbonate,[14,15] followed by treatment with diazomethane, afforded **19** in 82% yield, and hydrogenation of **19** to **18** was essentially quantitative. The overall yield of **18** from cholesterol by this route in six steps is ca. 45%, whereas the overall yield of **18** from cholesterol via **10** is only ca. 15%.

For the synthesis of **13**, **18** was converted in the usual manner in 77% yield to ketal **20**, which was then reduced with $LiAlH_4$ to afford 93% of **21**. Conversion of **21** to **13** was first accomplished by the reaction of acetate **22** with *p*-toluenesulfonic acid in benzene. However, treatment of mesylate **23** with dilute methanolic hydrochloric acid in methylene chloride, followed by heating of the resulting mixture (containing principally **13** and **24**) with 1,5-diazabycyclo[5.4.0]undec-5-ene (DBU) in toluene,[16] proved to be a more reliable synthesis of **13**, affording 59% overall yield from **21**. Enone **13** [ν 1690 cm^{-1}, λ_{max}(cyclohexane) 225 nm (ϵ 4000), and δ 5.0 and 5.8 ppm] tended to decompose on standing to an unidentified compound, mp 228–235 °C dec, so it was used soon after preparation.



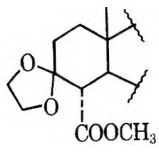
$COOCH_3$

18



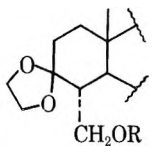
$COOCH_3$

19



$COOCH_3$

20



CH_2OR

21, R = H
22, R = Ac
23, R = Ms

Dimethylsulfoxonium methylide[8] gave a complex mixture of products upon reaction with **13**. Effective cyclopropanation was achieved when **13** was treated with diazomethane in the presence of palladium acetate,[17] which afforded 70% of **14**, mp 100–101 °C, ν 1710 cm^{-1}. Reduction of **14** with either $LiAlH_4$ or $NaBH_4$ readily produced the desired 4-spiro[cyclopropanecholestan-3β-ol] (**9**), mp 173–174 °C. The 3β configuration was assigned to the hydroxyl group of **9** on the basis of the NMR signal of the 3αH[10] and the known stereochemistry of hydride reduction of other 4,4-disubstituted cholestan-3-ones.[10]

Experimental Section

Melting points were determined in open capillaries in a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 137 or 337 spectrometer. Unless otherwise specified, IR spectra were taken as KBr pellets. Ultraviolet (UV) spectra were recorded on a Unicam SP 800B spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer R-24 instrument, equipped with a spin-decoupler unit, using $CDCl_3$ as solvent unless otherwise noted. Tetramethylsilane was used as an internal standard. Mass spectra were determined by Dr. Catherine Costello at the MIT Mass Spectra Facility sponsored by the USPHS Division of Research Resources through Grant RR 00317. Preparative thin layer chromatography (TLC) was performed on 20 × 20 cm plates coated with 1.45-mm thick layers of silica gel $PF_{(254+366)}$ (Brinkmann Instruments Inc., Westbury, N.Y.) which had been mixed with 0.002% Rhodamine 6G dye (Eastman Kodak Co., Rochester, N.Y.). UV light was used to visualize TLC plates. Qualitative plates (0.25-mm thick layers of silica gel $PF_{(254+366)}$) were sprayed with a 5% methanol–water (70:30) solution of phosphomolybdic acid (Eastman Kodak) and heated briefly at 110 °C. Brine refers to saturated aqueous sodium chloride solution. Bicarbonate refers to saturated aqueous $NaHCO_3$ solution. The term "ether workup" refers to the following procedure: the material was dissolved in ~50 mL of ether which was washed twice with 25-mL portions of water. The combined aqueous layers were reextracted with 25 mL of ether. The combined ethereal layers were washed with 25 mL of water, dried ($MgSO_4$), and concentrated in vacuo.

Attempted Preparation of 4-Spiro[cyclopropanecholest-1-

en-3-one] by Bisalkylation of 11 with 1,2-Diiodoethane. Cholest-1-en-3-one (**11**) was prepared from 2α-bromocholestan-3-one essentially by the procedure of Green and Long[6] in 75% yield after recrystallization from ethanol as white needles: mp 96–97 °C (lit.[6] mp 98 °C); IR 1680 cm^{-1}; NMR δ 0.70 (s, 3, H_3C_{18}–), 0.81 (s, 3, H_3C_{19}–), 5.85 (d, 1, J = 8 Hz, HC_2=), and 7.1 ppm (d, 1, J = 8 Hz, HC_1=). 2α-Bromocholestan-3-one was prepared essentially by the procedure of Nace and Iacona,[18] except that the crude product was dissolved in benzene, washed twice with bicarbonate and twice with water, dried ($MgSO_4$), and evaporated to give a solid which was recrystallized from hexane to afford 80% of 2α-bromocholestan-3-one (free of cholestan-3-one by TLC) as fine needles, mp 171–173 °C (lit.[18] mp 174–174.5 °C).

Various combinations of bases (NaH, KH, NaO-t-Bu, KO-t-Bu, LICA) and solvents (Me_2SO, THF, DME, PhH, t-BuOH) were used with **11**, followed by either 1,2-dibromo- or 1,2-diiodoethane. In a representative experiment, an oven-dried flask was charged with 40 mL of dry DME, 1 drop of t-BuOH, and 0.150 g (0.40 mmol) of **11** under an N_2 atmosphere. This solution was brought to reflux and 0.050 g (1.0 mmol) of 50% NaH suspension in mineral oil was added. This mixture was allowed to reflux for 2 h, at which time 2 mL of DME containing 0.170 g (0.6 mmol) of 1,2-diiodoethane was added, and refluxing was continued for an additional 4 h. Ether workup gave 0.200 g of yellow oil. Preparative TLC (3:1 hexane–ether) gave 0.016 g of unidentified solid, 0.110 g (82%) of **11**, and 0.008 g (6%) of a more polar component, assigned structure **12**: mp 97–100 °C (lit.[7] mp 108–110 °C); IR 1690 cm^{-1}; NMR δ 0.71 (s, 3, H_3C_{18}–), 0.82 (s, 3, H_3C_{19}–), 6.2 (bs, HC_4= and HC_2=), 6.34 (d, $J \cong 2$ Hz, HC_2=), and 7.1 ppm (d, 1, J = 11 Hz, HC_1=), a pattern in the vinyl proton region of the spectrum characteristic of steroidal 1,4-dien-3-ones.[19]

Attempted Preparation of Trimethylsilyl Enol Ether 16. According to the procedure of Stork and d'Angelo,[9] 5.00 g (0.013 mol) of **10** afforded 5.502 g of orange oil. Chromatography on silica gel afforded 2.61 g (48%) of the monotrimethylsilyl ether of **17** as a yellow oil which cyrstallized on standing. Further elution gave 1.24 g of cholestan-3-one. The 2.61 g of the Me_3Si derivative of **17** was recrystallized, with difficulty, from pentane to give 1.76 g of white solid: mp 124–128 °C; further recrystallization from ether–methanol raised the mp to 128–134 °C; IR 3580 cm^{-1}; NMR (benzene-d_6) δ 0.20 [s, 9, $(CH_3)_3Si$–], 0.70 (s, 3, H_3C_{18}–), 3.78 (s, 1, HO–, exchangeable with D_2O), 5.48 (s, 1, HC_4=), and 5.58 ppm (s, 1, HC_4=).

Anal. Calcd for $C_{57}H_{98}O_2Si$: C, 81.17; H, 11.71. Found: C, 81.06; H, 11.74.

When 163 mg (0.193 mmol) of this substance dissolved in 50 mL of 1:1 ether–methanol was treated with 1 mL of 1 N NaOH solution for 1.5 h at room temperature, followed by an ether workup, there was obtained 160 mg of white solid, which was recrystallized from hexane to afford 137 mg (92%) of **17**, mp 208–211 °C dec, which was identical (TLC, IR, NMR, and mixture melting point) with an authentic sample of **17**.[10]

4α-Carbomethoxycholest-1-en-3-one (19). To a solution of 1.000 g (2.60 mmol) of **11** in 20 mL of DMF was added 30 mL (60 mmol) of freshly prepared methylmagnesium carbonate[14] in DMF, and the mixture was heated at 120 °C for 36 h under a slow stream of carbon dioxide. The resulting yellow solution was cooled to 5 °C, mixed with 100 mL of 10% sulfuric acid, and poured into 200 mL of ether. The aqueous layer was extracted with an additional 100 mL of ether. The combined organic layers were washed with water (2 × 100 mL), and then added dropwise to a freshly prepared ethereal diazomethane[20] solution. After 1 h, ether workup afforded 1.117 g of yellow solid. Preparative TLC (3:1 hexane–Et_2O, twice) afforded 0.147 g of **11** and 0.940 g (82%) of **19** as a white solid. Recrystallization from ether afforded 0.860 g (75%) of pure **19** as white flakes: mp 124–125 °C; IR 1735 and 1680 cm^{-1}; NMR δ 0.69 (s, 3, H_3C_{18}–), 3.38 (1, d, J = 12 Hz, HC_4), 3.79 (s, 3, H_3COOC–), 6.02 (1, d, J = 10 Hz, HC_2=), and 7.25 ppm (1, d, J = 10 Hz, HC_1=); M$^+$ m/e 442.3449 (calcd for $C_{29}H_{46}O_3$, 442.3447).

Preparation of 4α-Carbomethoxycholestan-3-one (18) by Hydrogenation of 19. A solution of 1.672 g (3.78 mmol) of **19** in 200 mL of cyclohexane and 50 mL of THF was hydrogenated over 250 mg of 10% palladium on carbon for 45 min. Removal of the catalyst by filtration and concentration in vacuo afforded 1.669 g (99%) of solid **18**. Recrystallization from ether afforded 1.525 g (91%) of **18** as white prisms: mp 171–172 °C (lit.[13] mp 171–172 °C); IR 1740 and 1710 cm^{-1}; NMR δ 0.67 (s, 3, H_3C_{18}–), 1.03 (s, 3, H_3C_{19}–), 3.23 (d, J = 12 Hz, 1, HC_4–), and 3.73 ppm (s, 3, H_3COOC–).

4α-Carbomethoxycholestan-3-one Ethylene Ketal (20). A solution of 300 mg (0.69 mmol) of **18** in 40 mL of benzene containing 0.02 mL (3.23 mmol) of ethylene glycol and one small crystal of p-toluenesulfonic acid was refluxed for 12 h with azeotropic removal of water. The solution was cooled, washed with 50 mL of bicarbonate and 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give 325 mg of yellow solid. Preparative TLC (1:1 hexane–Et_2O) afforded 310 mg (94%) of **20** as a white solid which was recrystallized from ether to give 252 mg (77%) of pure **20**: mp 195–196 °C; IR 1720 cm^{-1}; NMR δ 0.78 (s, 3, H_3C_{18}–), 2.80 (d, 1, J = 12 Hz, HC_4–), 3.70 (s, 3, H_3COOC–), and 3.95 ppm (bs, 4, $-OCH_2CH_2O$–); M$^+$ m/e 488.3866 (calcd for $C_{31}H_{52}O_4$, 488.3880).

4α-Hydroxymethylcholestan-3-one Ethylene Ketal (21). To a solution of 125 mg (0.26 mmol) of **20** in 20 mL of ether was added 100 mg of $LiAlH_4$. This mixture was allowed to stir for 10 h. An ether workup using bicarbonate for all aqueous washings afforded 120 mg of white solid. Preparative TLC (ether) gave 110 mg (93%) of **21**, which was recrystallized from ether to afford 101 mg (86%) of **21** as white prisms: mp 182–184 °C; IR 3600 cm^{-1}; NMR δ 0.68 (s, 3, H_3C_{18}–), 0.85 (s, 3, H_3C_{19}–), and 3.95–3.80 (6, bs and m, $-OCH_2CH_2O$– and 4α-CH_2O–); M$^+$ m/e 460.3966 (calcd for $C_{30}H_{52}O_3$, 460.3916).

Acetate (22) of 4α-Hydroxymethylcholestan-3-one Ethylene Ketal. A solution of 100 mg (0.216 mmol) of **21** and 100 mg (0.98 mmol) of freshly distilled acetic anhydride in 3 mL of pyridine was stirred at room temperature for 5 h. An ether workup afforded 112 mg of solid which was purified by preparative TLC (3:2 ether–hexane) to afford 104 mg (95%) of **22**. Recrystallization from hexane–ether afforded 91 mg (84%) of pure **22** as white plates: mp 177–179 °C; IR 1740 cm^{-1}; NMR δ 0.67 (s, 3, H_3C_{18}–), 2.00 (s, 3, H_3COO–), 3.94 (bs, 4, $-OCH_2CH_2O$–), and 4.13 ppm (d, 2, 4α-CH_2O–); M$^+$ m/e 502.4022 (calcd for $C_{32}H_{54}O_4$, 502.4022).

Mesylate (23) of 4α-Hydroxymethylcholestan-3-one Ethylene Ketal. According to the procedure of Crossland and Servis,[21] a mixture of 100 mL of methylene chloride, 1.746 g (3.79 mmol) of **21**, and 0.500 g (4.95 mmol) of triethylamine was cooled to 0 °C. Freshly distilled methanesulfonyl chloride (0.500 g, 4.35 mmol) was added and the solution was allowed to warm to room temperature and stirred for an additional 1 h. An ether workup using bicarbonate for the aqueous washings afforded 2.005 g (98%) of a white solid, which was homogeneous by TLC. Attempted recrystallization of this material from isopropyl alcohol–chloroform gave a gel, which after collection by filtration and drying in vacuo afforded 1.716 g (84%) of white, chalky solid **23**: mp 143–146 °C dec; IR 1340 and 1160 cm^{-1}; NMR δ 0.64 (s, 3, H_3C_{18}–), 2.98 (s, 3, H_3CSO_3–), 3.98 (bs, 4, $-OCH_2CH_2O$–), and 4.31 ppm (m, 2, 4α-CH_2O–); M$^+$ m/e 443.3780 (calcd for $C_{30}H_{50}O_2$ = **23** − CH_3SO_3H, 443.3810).

4-Methylenecholestan-3-one (13). To a solution of 0.360 g (0.67 mmol) of **23** in 50 mL of methylene chloride was added 20 mL of a mixture of 25 mL of MeOH and 5 mL of concentrated HCl and then 5 mL of methanol to restore homogeneity. This mixture was stirred for 16 h at room temperature and then concentrated in vacuo. The residue was mixed with 50 mL of ether and 25 mL of water and the aqueous layer was made basic by slow addition of solid sodium bicarbonate. Ether workup afforded 0.295 g of oil, which was dissolved in 20 mL of toluene containing 1 mL of DBU[22] and refluxed for 24 h. An ether workup gave 0.223 g of solid which was purified by preparative TLC (3:1 hexane–ether) to afford 0.210 g (78%) of **13** and 0.002 g of 4-methylcholest-4-en-3-one (TLC mobility in several solvent systems identical with that of an authentic sample[23]). Recrystallization of the **13** from 9:1 95% ethanol–methanol gave 0.186 g (70%) of pure **13** as white prisms: mp 99–100 °C; IR 1690 cm^{-1}; NMR δ 0.65 (s, 3, H_3C_{18}–), 5.00 (bs, 1 HC=), and 5.80 ppm (bs, 1, HC=); UV λ_{max} (cyclohexane) 225 nm (ε 4000); M$^+$ m/e 398.3568 (calcd for $C_{28}H_{46}O$, 398.3549).

When the crude product before treatment with DBU from a comparable experiment was purified by preparative TLC (3:1 hexane–ether) there was obtained 55% of **13**, 3% of 4-methylcholest-4-en-3-one, and 41% of **24**: mp 110–115 °C; IR 1710 cm^{-1}; NMR δ 0.65 (s, 3, H_3C_{18}–), 0.80 (s, 3, H_3C_{19}–), 3.30 (s, 3, H_3CSO_3–), and 3.65 ppm (bt, 2, 4α-CH_2O–).

4-Spiro[cyclopropanecholestan-3-one] (14). According to the procedure of Mende et al.,[17] an excess (8 mmol) of freshly prepared ethereal diazomethane[20] was added dropwise to a mixture of 240 mg (0.61 mmol) of **13**, 25 mg (1.5 mmol) of $Pd(OAc)_2$,[24] and 50 mL of ether cooled to 0 °C. The resulting mixture was stirred for 1 h at room temperature. The black solid was removed by filtration and the yellow solution was concentrated in vacuo to afford 281 mg of yellow oil. Preparative TLC (5:1 hexane–ether) afforded 192 mg (78%) of **14**, which had the same R_f as **13**. Recyrstallization from methanol gave 174 mg (70%) of pure **14** as white plates: mp 100–101 °C; IR 1710 cm^{-1}; NMR δ 0.68 (s, 3, H_3C_{18}–) and 0.81 ppm (s, 3, H_3C_{19}–); M$^+$ m/e 412.3738 (calcd for $C_{29}H_{48}O$, 412.3705).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.53; H, 11.59.

4-Spiro[cyclopropanecholestan-3β-ol] (9). A solution of 51 mg (0.12 mmol) of **14** and 25 mg (0.68 mmol) of $NaBH_4$ in 25 mL of methanol was stirred at room temperature for 1 h. Concentration in vacuo and an ether workup afforded 50 mg of white solid. Preparative TLC (2:1 hexane–ether) gave 48 mg (94%) of **9** and recrystallization from methanol gave 39 mg (76%) of pure **9** as silky needles: mp 173–174 °C; IR 3400 cm^{-1}; NMR δ 0.68 (s, 3, H_3C_{18}–), 0.84 (s, 3, H_3C_{19}–), and 3.5–3.9 ppm (bm, $3\alpha H^{25}$); M^+ *m/e* 414.3955 (calcd for $C_{29}H_{50}O$, 414.3861).

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.08; H, 12.10.

Acknowledgment. This research was generously supported by USPHS Research Grant AM 12855. The use of **9** as an enzymic substrate was suggested originally by Dr. D. J. Hupe.

Registry No.—**9**, 62742-97-6; **10**, 601-57-0; **11**, 601-55-8; **12**, 566-91-6; **13**, 62742-98-7; **14**, 62742-99-8; **17** Me_3Si ether, 62743-00-4; **18**, 38367-88-3; **19**, 62743-01-5; **20**, 62743-02-6; **21**, 62743-03-7; **22**, 62743-04-8; **23**, 62743-05-9; **24**, 62743-06-0; ethylene glycol, 107-21-1.

References and Notes

(1) K. B. Sharpless, T. E. Snyder, T. A. Spencer, K. K. Maheshwari, G. Guhn, and R. B. Clayton, *J. Am. Chem. Soc.*, **90**, 6874 (1968).
(2) K. B. Sharpless, T. E. Snyder, T. A. Spencer, K. K. Maheshwari, J. A. Nelson, and R. B. Clayton, *J. Am. Chem. Soc.*, **91**, 3394 (1969).
(3) J. A. Nelson, S. Kahn, T. A. Spencer, K. B. Sharpless, and R. B. Clayton, *Bioorg. Chem.*, **4**, 363 (1975).
(4) R. Rahman, K. B. Sharpless, T. A. Spencer, and R. B. Clayton, *J. Biol. Chem.*, **245**, 2667 (1970).
(5) G. A. Youngdale, U.S. Patent 3 793 308; *Chem. Abstr.*, **80**, 108756s (1974); cf. M. S. Newman, V. DeVries, and R. Darlak, *J. Org. Chem.*, **31**, 2171 (1966).
(6) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).
(7) K. Florey and A. R. Restivo, *J. Org. Chem.*, **22**, 406 (1957); cf. J. W. Huffman, *ibid.*, **41**, 3847 (1976).
(8) H.-G. Lehmann, H. Müller, and R. Weichert, *Chem. Ber.*, **98**, 1470 (1965), have prepared steroidal spirocyclopropyl ketones by this method.
(9) G. Stork and J. d'Angelo, *J. Am. Chem. Soc.*, **96**, 7114 (1974).
(10) M. R. Czarny, K. K. Maheshwari, J. A. Nelson, and T. A. Spencer, *J. Org. Chem.*, **40**, 2079 (1975).
(11) D. Caine, *Org. React.*, **23**, 1 (1976), especially pp 18–20 and 192. The stereochemistry shown in **17** was assigned by P. Bladon, J. W. Cornforth, and R. H. Jaeger, *J. Chem. Soc.*, 863 (1958).
(12) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3244 (1973); R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, and P. A. Wehrli, *ibid.*, **40**, 675 (1975).
(13) N. A. Nelson and R. N. Schut, *J. Am. Chem. Soc.*, **80**, 6630 (1958).
(14) H. L. Finkbeiner and G. W. Wagner, *J. Org. Chem.*, **28**, 215 (1963).
(15) Hajos et al., ref 12, have utilized the β-keto acids resulting from such carboxylations in an efficient synthesis of α-methylene ketones involving treatment with piperidine hydrochloride and formaldehyde. This method was not tried in the present work because of the possibility of decarboxylation during reduction of the double bond in the β-keto acid formed from **11**.
(16) Cf. P. A. Grieco, M. Nishizawa, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **98**, 1612 (1976).
(17) U. Mende, B. Radüchel, W. Skuballa, and H. Vorbruggen, *Tetrahedron Lett.*, 629 (1975).
(18) H. R. Nace and R. N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964).
(19) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field", Holden-Day, San Francisco, Calif., 1964, p 124.
(20) Prepared from EXR-101 according to J. A. Moore and D. E. Reed, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 351.
(21) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).
(22) Aldrich Chemical Co., Inc., Milwaukee, Wis.
(23) Prepared by the method of N. W. Atwater, *J. Am. Chem. Soc.*, **82**, 2847 (1960).
(24) Ventron Corp., Danvers, Mass.
(25) The broad multiplet is characteristic of an axial 3αH, as opposed to an equatorial 3βH, which shows a much narrower NMR signal: cf. ref 10; ref 19, p 77; and L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Oxford, 1969, p 228.

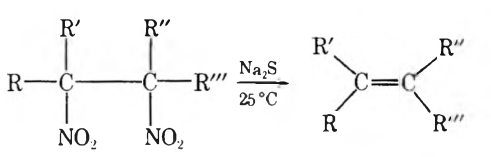
Communications

The Synthesis of Functionalized Tetrasubstituted Olefins. Calcium Amalgam—a Novel Reducing Agent

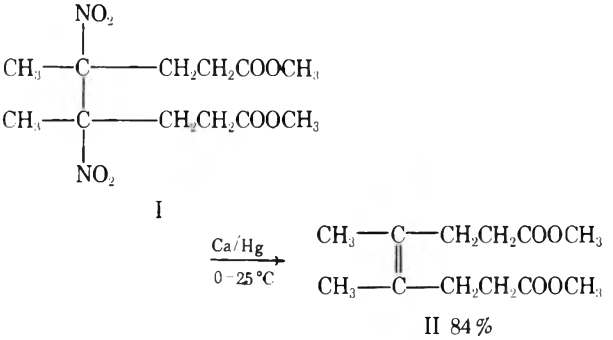
Summary: A general synthesis of symmetrical and unsymmetrical functionalized tetrasubstituted olefins is described.

Sir: In 1971 a synthesis of tetrasubstituted olefins was described which is noteworthy for its simplicity and which gives pure symmetrical and unsymmetrical olefins in high yields.[1] Since then several other very useful procedures for the synthesis of tetrasubstituted olefins have been reported.[2-7] However, except for two methyl ethers, none of the olefins prepared by these procedures contains a functional group. We now describe a simple method for the synthesis of symmetrical and unsymmetrical tetrasubstituted olefins bearing cyano, keto, ester, and ether groups. A further point of interest is the use of a novel reducing agent—calcium amalgam.

In our earlier olefin synthesis[1] vicinal dinitro compounds were treated with sodium sulfide (or sodium thiophenoxide), eq 1. Attempts to extend the reaction of eq 1 to the synthesis of functionalized olefins soon revealed that neither sodium sulfide, nor sodium thiophenoxide, was likely to prove satisfactory.[8] In contrast, amalgamated calcium, which is readily available and inexpensive,[9] is effective in bringing about elimination of vicinal nitro groups without attacking other functions. Equation 2 is illustrative.



(1)

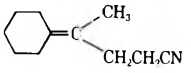
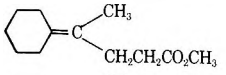
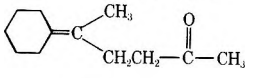
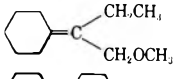
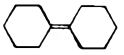


(2)

Table I lists the olefins obtained from vicinal dinitro compounds by the action of calcium amalgam. It should be noted that yields refer to pure, isolated, products which, when the possibility exists, contain both the cis and trans forms. Also, the yields of unsymmetrical olefins are lower than for the symmetrical compounds because the unsymmetrical dinitro compounds employed were not fully purified.

The general procedure is illustrated by the preparation of nitro ester (I) and its conversion to the olefin (II). Lithium methoxide (1.52 g, 40 mmol) in 40 mL of DMF is allowed to

Table I. Olefins Synthesized from Vicinal Dinitro Compounds

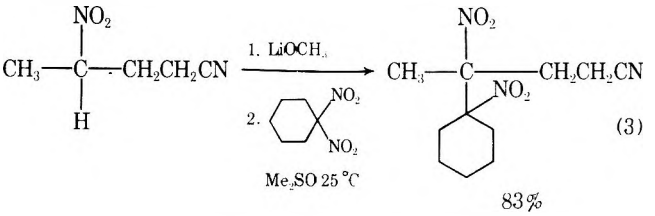
Olefin	% yield
$CH_3-C(=CH_2)-CH_2CH_2CN$ $CH_3-C(=CH_2)-CH_2CH_2CN$	87
$CH_3-C(=CH_2)-CH_2CH_2CO_2CH_3$ $CH_3-C(=CH_2)-CH_2CH_2CO_2CH_3$	84
$CH_3-C(=CH_2)-CH_2CH_2-C(=O)-CH_3$ $CH_3-C(=CH_2)-CH_2CH_2-C(=O)-CH_3$	77
$CH_3CH_2-C(=CH_2)-CH_2OCH_3$ $CH_3CH_2-C(=CH_2)-CH_2OCH_3$	78
	71
	66
	68
	65
	86

react for 15 min at room temperature with 6.44 g (40 mmol) of methyl 4-nitropentanoate.[10] The resulting solution is cooled to 0 °C, 5.08 g (20 mmol) of I_2 in 30 mL of cold DMF is added in the course of ca. 15 min, and the system is then brought to room temperature and held there for 2 h; stirring and a nitrogen atmosphere are maintained throughout. The reaction product is poured into 600 mL of water and repeatedly extracted with benzene–ether (1:1). The extracts are washed with water and dried, and the solvents removed under reduced pressure. The resulting pale yellow, viscous, residue (6.44 g) crystallizes on standing overnight; mp 51–77 °C. Recrystallization from methanol at −5 °C gives 5.38 g (84% yield) of colorless crystals, mp 71–84 °C. This is analytically pure I;[11] its NMR spectrum, ($CDCl_3$) δ 1.60 and 1.65 (2s, 6 H), 2.0–2.90 (m, 8 H), 3.70 (s, 6 H), is consonant with the view that it consists of roughly equal proportions of the *dl* and meso forms.

A mixture consisting of 0.64 g (16 mmol) of calcium shot[9] and 10 mL of hexamethylphosphoramide (HMPA) is stirred vigorously under argon and then a solution of mercuric chloride (1.35 g, 5 mmol) in 2 mL of DMF and 10 mL of HMPA is added rapidly. The temperature rises to ca. 40–50 °C, but soon drops back and the initially formed grey mixture, after 30 min, becomes black. The reaction flask is cooled in ice for 15 min and then the dinitro compound I (3.20 g, 10 mmol) is added without opening the system. After 1.5 h the ice bath is removed and the reaction is allowed to proceed at room temperature; TLC monitoring reveals that it is complete in 45 h. (With keto compounds the reduction is conducted entirely at 0 °C.)

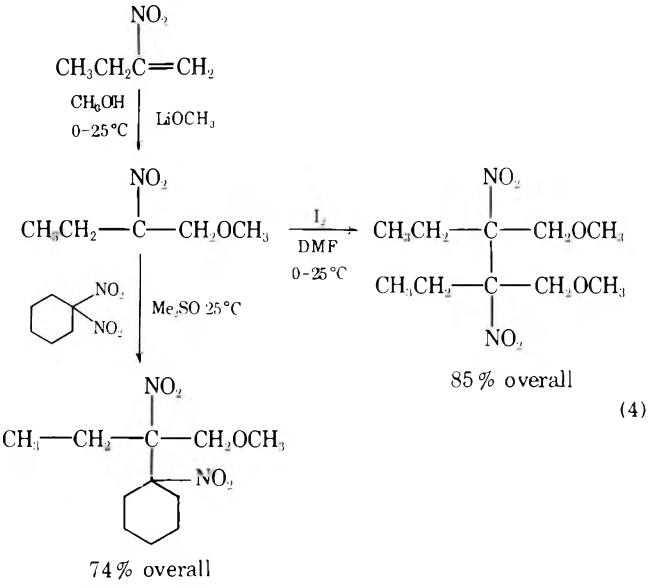
The reaction mixture is poured into ice–water and extracted with ether–benzene (1:1). The extracts are washed with ice–water and dried, and the solvents are removed under reduced pressure. The residue (1.94 g) on short-path distillation [bath 70 °C (0.15 mm)] gave 1.92 g (84% yield) of analytically pure II[11] as a mixture of a colorless oil and white crystals which melt from 48 to 54 °C. That this consists of the cis and trans isomers of dimethyl 4,5-dimethyl-4-octenedioate is clear from the elemental analysis and the NMR and IR spectra.

The requisite unsymmetrical vicinal dinitro compounds are readily obtained by treating a nitroparaffin salt with an α,α-dinitro compound,[1] e.g., as in eq 3.



(3)

The precursors of the ether functionalized olefins were prepared from 2-nitro-1-butene (eq 4).[12]



(4)

This synthesis of functionalized olefins involves the reductive elimination of nitro groups. Its success appears to derive from the fact that of all the common functional groups the nitro group is most readily induced to accept one electron;[13,14] this, coupled with the use of a mild reducing agent, provides the observed selectivity.

Acknowledgment. We thank the Hoffmann-La Roche Co. and the National Science Foundation for generous support. We are also indebted to Drs. Melvin M. Kestner and Harold W. Pinnick for assistance in the preliminary stages of this investigation.

References and Notes

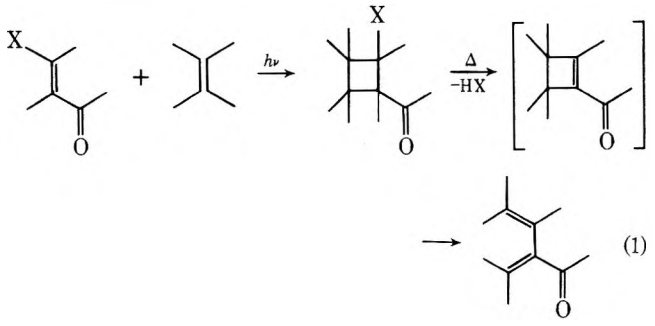
(1) N. Kornblum, S. D. Boyd, H. W. Pinnick, and R. G. Smith, *J. Am. Chem. Soc.*, **93**, 4316 (1971).
(2) M. Julia and J. M. Paris, *Tetrahedron Lett.*, 4833 (1973).
(3) A. P. Krapcho and E. G. E. Jahngen, *J. Org. Chem.*, **39**, 1650 (1974).
(4) G. H. Posner, G. L. Loomis, and H. S. Sawaya, *Tetrahedron Lett.*, 1373 (1975).
(5) S. Hara, H. Taguchi, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, 1545 (1975).
(6) J. E. McMurray and L. R. Krepski, *J. Org. Chem.*, **41**, 3929 (1976), and references cited therein.
(7) W. Dumont and A. Krief, *Angew. Chem., Int. Ed. Engl.*, **15**, 161 (1976).
(8) We shall discuss this matter in the full paper.
(9) Calcium shot, 99+%, 6-mesh is obtainable from Research Organic/Inorganic Chemical Corp., 507 Main Street, Bellville, N.J. 07109.
(10) From the Michael condensation of methyl acrylate with nitroethane.
(11) Satisfactory elementary analyses, as well as NMR and IR spectra, were obtained for all new compounds.
(12) A. T. Blomquist and T. H. Shelley, *J. Am. Chem. Soc.*, **70**, 147 (1948).
(13) P. H. Rieger and G. K. Fraenkel, *J. Chem. Phys.*, **39**, 609 (1963); R. C. Kerber, G. W. Urry and N. Kornblum, *J. Am. Chem. Soc.*, **87**, 4525 (1965), footnote 25.
(14) For a review of electron transfer processes see N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).

Nathan Kornblum,* Leung Cheng
Purdue University, Department of Chemistry
West Lafayette, Indiana 47907
Received May 7, 1977

A New Route to Linear, Polycyclic, Substituted Aromatics: Diels–Alder Reactions of Bicyclic Dimethoxycyclobutenes

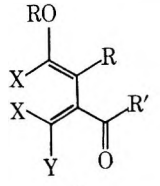
Summary: Photochemical cycloaddition of alkoxyolefins to enol acetates of β-diketones and β-chloroenones proceeds readily to afford the cyclobutane or derived cyclobutene. These substances, on thermolysis in the presence of a dienophile, readily eliminate the elements of mineral acid or acetic acid and/or undergo conrotatory opening to the butadiene followed by Diels–Alder reaction. This process provides a facile entry into certain polycyclic aromatic systems and highly substituted benzene derivatives.

Sir: The use of photochemical cycloadditions to produce substituted cyclobutanes is well documented.[1,2] We became interested in the utility of this process as a *general route* to substances which might serve as *stable, thermal precursors* of alkoxy-substituted butadienes by in situ conrotatory opening of a cyclobutene (eq 1).[3] This route would provide



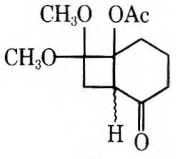
(1)

access to a variety of alkoxy dienes to which no routes presently exist and whose preparation would be extremely difficult by conventional methods. Of particular interest were the alkoxybutadienes (1), of which one precursor, 2, had previously



1

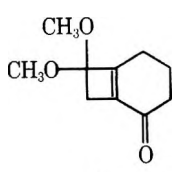
R = alkyl
X = H, OR
R′ = alkyl, OR
Y = H, OR



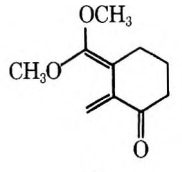
2

been prepared by Cantrell.[4] We initiated our investigation by preparing 2 and its elimination product 3.[4] We found that irradiation of ketene dimethylacetal and 3-acetoxy-2-cyclohexen-1-one in ether[5] produced a mixture of trans adduct 2 and cyclobutene 3. The latter substance apparently arises from extremely facile elimination of acetic acid from *cis*-2.[6] Cyclobutene 3 is reasonably stable and can be handled easily. *trans*-2 resists elimination of acetic acid up to 180 °C and is recovered unchanged. However, equilibration of the crude mixture of 2 and 3 with alumina produces 3 in up to 60% overall yield from the initial photoreactants.[7,8]

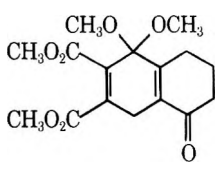
Reaction of 3 at temperatures from 150 to 170 °C in the presence of a dienophile readily generates the corresponding diene 4, which is efficiently trapped in situ. For example, with dimethylacetylene dicarboxylate, 3 affords 5 (mp 118.5–119.5 °C) and 6 in ~90% yield.[9] Ketal 5 readily eliminates methanol on treatment with sodium methoxide or by silica gel chromatography, producing 6. Cyclobutene 3 also reacts readily with maleic anhydride and methyl propiolate, affording adducts 7 (~90%) and 8a only (64%) after oxidation and elimination.[9] This high reactivity and high regiospecificity is especially noteworthy and suggests that considerable regiochemical control can be exercised in the cycloaddition reactions of dienes like 4.



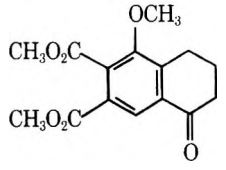
3



4



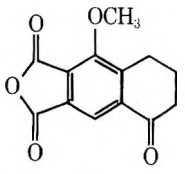
5



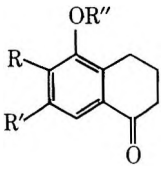
6

Treatment of 3 with 1,4-naphthoquinone followed by basic oxidation (O_2/$NaOCH_3$) affords tetracyclic ketone 9 (75%), thus providing a facile entry into these anthraquinone systems.[9] This route should have great utility toward a highly convergent synthesis of the tetracyclic ring systems present in the clinically useful antitumor agents daunomycin and adriamycin.

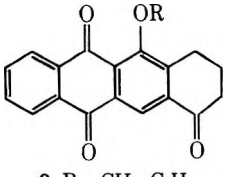
We have extended this process to the photochemical cycloadditions of *cis*-1,2-dimethoxy- and diethoxyethylene to 3-acetoxy- and 3-chloro-2-cyclohexen-1-ones. Irradiation of enone (1 mol) and olefin (3 mol) in dry acetone through Pyrex (8–24 h) affords, after chromatography, the cyclobutane adducts 10–11 in extremely high yields (80–93%).[10] This reaction proceeds much more efficiently in acetone than in other solvents investigated (ether, benzene). The halogen-containing adducts 11 proved to be quite sensitive, decomposing rapidly at room temperature. Both adducts 10 and 11 were obtained



7



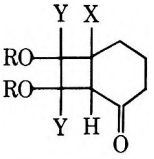
8a, R = CO_2CH_3; R′ = H; R″ = CH_3, C_2H_5
b, R = H; R′ = CO_2CH_3; R″ = CH_3, C_2H_5



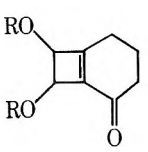
9, R = CH_3, C_2H_5

as mixtures of stereoisomers, and were utilized as such. The cycloaddition reactions of 1,2-dimethoxyethylene are unusually facile and clean, and proceed at stoichiometries much closer to the ideal (1:1) than comparable cycloadditions of simple olefins such as cyclohexene.[11] Furthermore, even the cycloaddition to 3-chlorocyclohex-2-en-1-one occurs cleanly, although chloroenones generally exhibit poor reactivity with ordinary olefins.[12] The cycloaddition process can be extended further to tetramethoxyethylene, affording 12 in low yield.[13] Attempts to prepare and isolate the cyclobutene 13 resulting from base treatment of 11 produced mixtures containing 13, but were contaminated by substantial amounts of β,γ isomer 14 when amine bases were utilized (DBN, 0 °C). When nucleophilic bases were utilized with 10 and 11 ($NaOCH_3$/

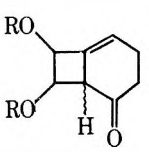
CH_3OH/room temperature), elimination–addition occurred, affording **15** cleanly.



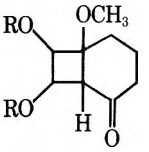
10a, X = OAc; R = CH_3; Y = H
b, X = OAc; R = CH_2CH_3; Y = H
11, X = Cl; R = CH_3, CH_2CH_3; Y = H
12, X = OAc; R = CH_3; Y = OCH_3



13, R = CH_3, CH_2CH_3

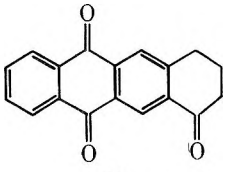


14, R = CH_3, CH_2CH_3

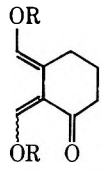


15, R = CH_3, CH_2CH_3

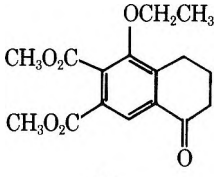
The reaction of a mixture containing **13** with 1,4-naphthoquinone at 137 °C (6 h) afforded the tetracyclic ketone **16** (mp 242–243 °C) in low yield, demonstrating the viability of the electrocyclic opening to generate **17** in situ. Since isolation and handling of **13** were precluded by its instability, we investigated direct generation of **17** from **10**. Exposure of dimethylacetylene dicarboxylate (1 mol) to **10b** (1 mol) in o-dichlorobenzene at 180 °C afforded ketone **18** in 50–60%



16



17, R = CH_3, CH_2CH_3

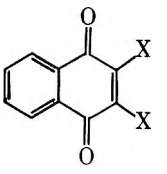


18

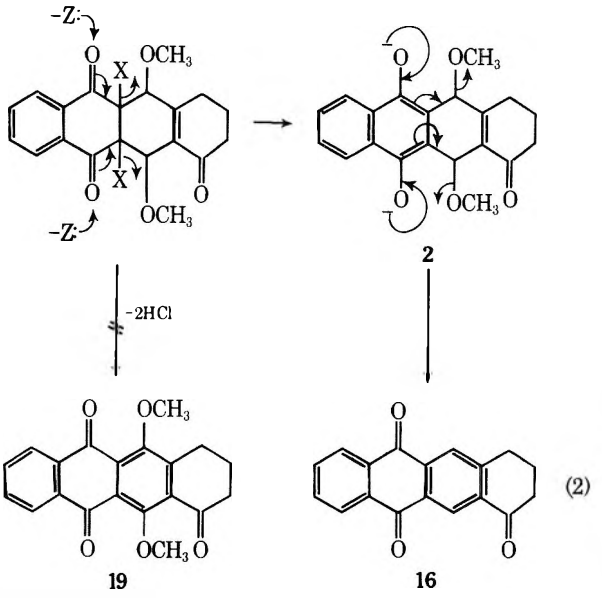
yield [bp 170 °C (0.3 mm) (Kugelrohr); NMR δ 1.43 (t, 3 H), 2.20 (m, 2 H), 2.80 (t, 2 H), 3.10 (t, 2 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 8.58 (s, 1 H)]. Reaction of **10a**, under similar conditions, with maleic anhydride afforded **6** identical with that from **3** in good yield. Reaction of **10a** with methyl propiolate (195 °C, sealed tube/3 h) afforded a mixture of regioisomers (3:2 o/m) **8a** and **8b** (66%). This result suggests that the 2-acyl group exerts little influence on the regiochemical outcome in the case where the normally dominant effects of the alkoxyl groups cancel. This is in accord with the frontier orbital theory predictions.[14]

The diene precursor **10** is, however, useful in the construction of polycyclic systems. Treatment of **10** (1 mol) in o-dichlorobenzene (180 °C; ~3 h) with 1,4-naphthoquinone (1 mol) provides **16** in ~60% yield. This yield could conceivably be improved by increasing the amount of quinone-trapping agent. Furthermore, we had interest in the production of bismethoxylated derivatives such as **19**. Such systems are present as indicated previously in the adriamycin/daunomycin class of antitumor agents. To accomplish this, the α positions of the dienophile were substituted with leaving groups (**20–21**). The reactivity of the dichloro derivative **20** was considerably diminished, and the only isolable crystalline product on reaction with **10a** was ketone **16** (~20%). An *unprecedented oxidation–reduction* had occurred, resulting in the apparent loss of 2 mol of MeOCl. A rationale for this result is given in eq 2.

To induce the elimination of HCl from the initial Diels–Alder adduct, an inorganic base (1 mol of Li_2CO_3)[16] was introduced. This modification permitted the elimination of *one but not both* moles of HCl (the second Cl being lost as



20, X = Cl
21, X = CN

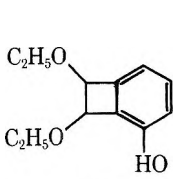


Z: = hydroquinone derived from dienophile

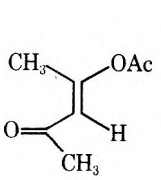
(2)

MeOCl), providing **9** in ~40–50% yield.[17] Other experimental modifications have thus far been unsuccessful in promoting the elimination of a second mole of HCl to produce **19**. The substitution of CN for Cl in the dienophile, e.g., **21**, in an effort to enhance its reactivity, surprisingly led to oxidation of the diene precursor **10b** to **22** and the quantitative production of the hydroquinone derived from **21**.[18] This occurs in spite of the apparently low reactivity of **21** in previous dehydrogenation studies.[19]

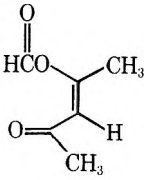
Preliminary attempts to extend this process to acyclic enol acetates such as **23** have been unsuccessful.[20] In these cases, energy depleting cis–trans isomerization may be preventing cycloaddition. Conceivably, proper choice of the protecting group, such as formate **24**, may restrict rotation, and allow the



22



23



24

desired process to occur. We are presently investigating this as well as substituent effects on the photoreaction with substituted enol acetates and β-chloroenones, and applications of this chemistry to the total synthesis of polycyclic anthraquinone natural products.

Acknowledgment. We wish to thank the National Institutes of Health (National Cancer Institute) for the award of a research grant (CA-15061) in support of this research and for a Career Development Award to one of us (R.K.B.) (CA-00273).

Supplementary Material Available: Experimental Section of this paper (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964), and references cited therein; (b) J. J. Partridge, N. K. Chadha, and M. R. Uskokovic, *ibid.*, **95**, 532 (1973); G. Buchi, J. A. Carlson, J. E. Powell, Jr., and L. F. Tietze, *ibid.*, **95**, 540 (1973); (c) R. S. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4645 (1966); (d) J. F. Bagli and T. Bogri, *ibid.*, 349 (1970).

(2) (a) P. DeMayo, *Acc. Chem. Res.*, **4**, 41 (1971); (b) P. G. Sammes, *Q. Rev., Chem. Soc.*, **24**, 37 (1970); (c) P. E. Eaton, *Acc. Chem. Res.*, **1**, 50 (1968), cf. also ref 20.

(3) (a) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395 (1965); (b) W. Oppolzer, *ibid.*, **93**, 3833, 3834 (1971); W. Oppolzer and K. Keller, *ibid.*, **93**, 3836 (1971); (c) B. J. Arnold and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, 1034 (1972); (d) M. E. Jung, *ibid.*, 956 (1974). (e) R. K. Hill and R. G. Carlson, *J. Org. Chem.*, **30**, 2414 (1965).

(4) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).

(5) The reactants were irradiated in anhydrous ether at room temperature with a medium-pressure lamp (Hanovia 450 W) through a corex sleeve. Typical irradiation times were 8–24 h. The enol acetate was purified by distillation to remove traces of acid, and all apparatus was washed with methanolic KOH, rinsed with methanol (anhydrous), and dried thoroughly.

(6) Cantrell (cf. ref 4) reports only the formation of *trans*-**2** in ~45% yield. This substance was isolated from the crude product mixture by preparative VPC. This procedure undoubtedly led to loss of any cis adduct **2** via loss of acetic acid to 3, opening to **4**, and decomposition. At no time did we isolate or characterize the cis adduct, although we cannot exclude its presence in the crude mixture and transformation to 3 during workup.

(7) Alumina is known to catalyze the epimerization of trans-fused bicyclo[4.2.0]octan-2-one systems to the thermodynamically more stable cis system (cf ref 1a). In this case elimination of acetic acid occurred simultaneously.

(8) All new substances described have satisfactory spectral data [NMR, UV, and mass spectra (low resolution)] and analytical data or high resolution data. All yields refer to isolated and purified materials.

(9) Spectral data. **5**: NMR δ 2–2.7 (m, 6 H), 3.18 (s, 6H), 3.28 [s (br), 2 H], 3.83 (s, 6 H). **7**: NMR δ 2.30 (m, 2 H), 2.90 (t, 2 H), 3.30 (t, 2 H), 3.98 (s, 3 H), 8.18 (s, 1 H). **8a**: NMR δ 2.16 (dt, 2 H), 2.65 (t, 2 H), 3.03 (t, 2 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 7.70 (dd, J_{ortho} = 8.0 Hz, 2 H). **9**: NMR δ 2.23 (dt, 2 H), 2.78 (t, 2 H), 3.18 (t, 2 H), 4.0 (s, 3 H), 7.71 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2 H), 8.22 (dd, J_{ortho} = 6.0, J_{meta} = 3.0 Hz, 2 H). **16**: NMR δ 2.26 (pentuplet, 2 H), 2.83 (t, 2 H), 3.23 (t, 2 H), 8.30 (s, 1 H), 9.03 (s, 1 H). **7** was characterized by conversion to diester **6**.

(10) The production of these photoadducts is particularly facile. An unusually low stoichiometric ratio of olefin to enone can be maintained, and high yields are still obtained. No evidence of significant amounts of oxetane formation by reaction with the solvent is seen; however, the yields are reduced markedly if corex-filtered UV is utilized as in the production of adducts **2**. Spectral data for **10b** [bp 113–120 °C (0.3 mm)]:NMR δ 1.25 (m, 6 H), 2.00, 2.05 (s, 3 H), 3.60 (m, 4 H). **11b** NMR: δ 1.20 (m, 6 H), 2.70 (d, 1 H), 4.0 (d, 1 H).

(11) H. Hikino and P. DeMayo, *J. Am. Chem. Soc.*, **86**, 3582 (1964).

(12) S. Arthur, Ph. D. Dissertation, University of California, Berkeley, Calif., 1976; cf. also ref 4 and T. Cantrell, *Tetrahedron*, **27**, 1227 (1970).

(13) The structure of the photoproduct (*hν*/corex/ether) is supported by IR, NMR, and mass spectra (low resolution). Apparently, elimination is not unidirectional (both methanol and acetic acid are lost), and under the usual reaction conditions no Diels–Alder adducts are obtained.

(14) (a) I. Fleming, F. L. Gianni, and T. Mah, *Tetrahedron Lett.*, 881 (1976); (b) K. Houk, *J. Am. Chem. Soc.*, 95, 4092 (1973).

(15) For example, daunomycin, adriamycin, the rhodomycins; cf. I.A. Scott and T. Devon, "Handbook of Naturally Occurring Compounds", Vol. 1, Academic Press, New York, N.Y., 1975.

(16) If excess base is utilized, the yields are lowered. A variety of amine bases were investigated and all proved unsatisfactory due to incompatibility with the haloquinone at elevated temperatures.

(17) This result may be due to the stereochemical orientation of the leaving groups and hydrogens in the intermediate Diels–Alder adduct. If the structure of the photoadducts have the alkoxyl groups cis, the diene must be cis,trans and the resulting adduct has only 1 mol of HCl trans deposed and readily eliminated. This result could also arise by sequential loss of Cl_2 and methanol.

(18) The structure of **22** is inferred from the quantitative production of the hydroquinone. Presently, we are attempting to trap the *o*-quinodimethane derived from **22**, which undoubtedly results from thermal opening of **22** under the reaction conditions.

(19) G. A. Reynolds and J. A. VanAllen, *J. Org. Chem.*, **29**, 3591 (1964).

(20) S. W. Baldwin, R. E. Gawley, R. J. Doll, and K. H. Leung, *J. Org. Chem.*, **40**, 1865 (1975).

(21) Fellow of the Alfred P. Sloan Foundation (1976–1978).

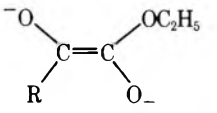
Robert K. Boeckman, Jr.,*[21] Mary H. Delton
Tatsuo Nagasaka, Tokuhiro Watanabe
Department of Chemistry, Wayne State University
Detroit, Michigan 48202

Received January 12, 1977

Alkoxy Enediolates

Summary: Multiple deprotonations of α-hydroxy esters by lithium diisopropylamide lead directly to alkoxy enediolates, which are useful as synthetic intermediates in electrophilic substitution reactions with primary and secondary alkyl halides and sulfonates to form disubstituted α-hydroxy esters, and with carbonyl compounds and ethylene oxide to form substituted glyceric acids and a substituted α-hydroxy-δ-butyrolactone, respectively.

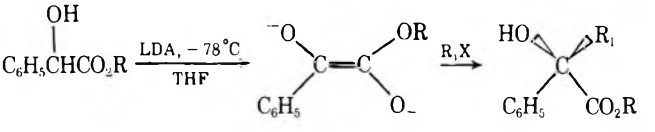
Sir: In this communication we describe procedures for the preparation, characterization, and use of dianions derived from α-hydroxy esters by reaction with lithium diisopropylamide (LDA) in THF. The alkoxy enediolates (**1**)[2] prepared in this fashion can be used in reactions with a variety of alkylation reagents to form more complex α-hydroxy esters. Preliminary results indicate that carbonyl compounds and epoxides also react as electrophiles with the alkoxy enediolates. Oxidative decarboxylation of the product α-hydroxy acids derived from these esters by hydrolysis leads to carbonyl compounds and makes intermediates like **1** acyl anion



1a, R = Ph
b, R = CH_3

equivalents.[3-6] While geminal enediolates from carboxylic acids[7] and vicinal enediolates from α-hydroxy ketones[8] have previously been prepared by deprotonation with LDA, alkoxy enediolates have not been prepared before. Enediolates are also postulated to be intermediates in the acyloin condensation.[9]

Alkoxy enediolates are synthetically useful in alkylation reactions such as eq 1, leading to disubstituted α-hydroxy



(1)

esters. These reactions are characterized by high isolated yields of products and can be utilized in a variety of systems as is shown by representative data in Table I. We find that primary alkyl iodides, bromides, tosylates, and mesylates work about equally well as alkylating agents in these reactions, but a less reactive primary alkyl chloride is unsatisfactory. Extension of these reactions to secondary systems shows that even cyclohexyl iodide, which is prone to elimination reactions, reacts with enediolate **1a** to give a 66% yield of ethyl cyclohexylhydroxyphenylacetate. Preliminary work indicates that these reactions are tolerant of some functional groups in the alkylating agent. For example, we have successfully used both allyl bromide and ethyl bromoacetate as reagents in reactions with **1a**. Halides known to be unreactive in S_N2 reactions (*e.g.*, tertiary and aryl halides) do not react with alkoxy enediolates.

Although most of our initial work has concerned reactions of enediolate **1a**, we have also examined enediolates in which the phenyl group of **1a** has been replaced by either a methyl or a hydrogen. While enediolates derived from ethyl lactate (**1b**) can be successfully alkylated with primary alkyl bromides and iodides, similar reactions with ethyl glycolate (**1**, R = H) fail. In both of these cases, elimination of HX from the alkyl halide to form alkene or possibly decomposition of the alkoxy enediolate is a limitation of these reactions. Addition of

Table I. Alkylation of Alkoxy Enediolates

α-Hydroxy acid ester precursor	Method used for preparation of enediolate[a]	Alkylation reagent	Product	Isolated yield, %[b]
Ethyl mandelate	A	n-C_4H_9Br	$C_6H_5C(OH)(n\text{-}C_4H_9)CO_2C_2H_5$	79 (92)[c]
	B	CH_3I	$C_6H_5C(OH)(CH_3)CO_2C_2H_5$	79 (96)[c]
	B	$C_6H_5CH_2Br$	$C_6H_5C(OH)(C_6H_5CH_2)CO_2C_2H_5$	85
	A	$(CH_3)_2CHI$	$C_6H_5C(OH)(CH(CH_3)_2)CO_2C_2H_5$	57[d] (75)[c]
	B	c-$C_6H_{11}I$	$C_6H_5C(OH)(c\text{-}C_6H_{11})CO_2C_2H_5$	66
	B	$BrCH_2CO_2C_2H_5$	$C_6H_5C(OH)(CH_2CO_2C_2H_5)CO_2C_2H_5$	69
	B	$CH_2{=}CHCH_2Br$	$C_6H_5C(OH)(CH_2CH{=}CH_2)CO_2C_2H_5$	82 (85)[c]
Ethyl lactate	B	n-$C_{10}H_{21}I$	$CH_3C(OH)(n\text{-}C_{10}H_{21})CO_2C_2H_5$	(69)[c]
	B	n-$C_{10}H_{21}Br$		(60)[c]
	B	n-C_4H_9I	$CH_3C(OH)(n\text{-}C_4H_9)CO_2C_2H_5$	(53)[c]
	B	$(CH_3)_2CHI$	*e*	0[e]
Ethyl glycolate	A or B	n-$C_{10}H_{21}I$	*e*	0[e,f]

[a] Details of these methods are provided in the text. [b] These yields are based on the starting ester and are spectroscopically pure products obtained by either chromatography or distillation. [c] Yield determined by gas chromatography. [d] This distilled product also contained 16% ethyl mandelate. [e] No alkylated products were found by gas chromatography. [f] In these cases, the starting halide mainly eliminated to form 1-decene.

HMPA as a cosolvent failed to circumvent this problem. The secondary halide, 2-iodopropane, does not alkylate enediolate **1b**.

We have employed two different experimental procedures in the alkylation reactions. In the first (method A), the halide is added to the α-hydroxy ester and LDA at −78 °C, and the reaction mixture is allowed to warm to room temperature. In the second procedure (method B), the enediolate is first generated by addition of the α-hydroxy ester to LDA in THF at −78 °C followed by warming at 0 °C for 0.5 h. Recooling to −78 °C and addition of an alkylation agent followed by warming to room temperature results in high isolated yields of alkylated mandelic acid esters, even when highly reactive alkylating reagents such as methyl iodide, benzyl bromide, allyl bromide, and ethyl bromoacetate are used. The latter procedure is preferable for synthetic purposes.

In a representative reaction, a solution of 788 mg (4.38 mmol) of ethyl mandelate in 4 mL of THF was added to 14 mL of a THF solution of 9.9 mmol of LDA (prepared from n-butyllithium and diisopropylamine in THF) at −78 °C.[10] After warming this solution to 0 °C and stirring for 90 min, the orange solution of the alkoxy enediolate was cooled to −78 °C. Addition of excess benzyl bromide (10 mmol) in 4 mL of THF at −78 °C gave a yellow solution which was stirred for 30 min at −78 °C and finally for several hours at room temperature. The reaction mixture was then quenched with 10% aqueous HCl and diluted with ether. The ethereal phase was washed successively with 10% aqueous HCl and saturated aqueous sodium chloride, and dried ($MgSO_4$). Distillation of the solvent in vacuo gave a residue which was purified by silica gel chromatography (1:1 hexane/benzene (v/v) elution) to give 1.0 g (3.7 mmol, 85%) of ethyl 2-hydroxy-2,3-diphenylpropionate, which was pure by both GC and NMR. Earlier chromatographic fractions contained unreacted benzyl bromide and stilbenes (from the reaction of benzyl bromide with excess base).

The presence of alkoxy enediolate **1a** has been confirmed by deuteration experiments in which the alkoxy enediolate prepared by method B from ethyl mandelate was quenched with deuterium oxide. NMR analysis of the products of this reaction showed only ethyl mandelate, which was >87% d_1. We have also briefly studied the stability of the enediolates by simply protonating the reaction mixtures after varying amounts of time and measuring the amount of starting α-hydroxy ester recovered. These studies show that the enediolate **1a** decomposes in THF at room temperature with a half-life of about 10 h. Other alkoxy enediolates like **1b** are qualitatively less stable, but can be kept for periods of up to 1 h at room temperature without significant decomposition. The products of these decomposition reactions are not known.

The procedures described above provide a useful alternative to existing routes to α-hydroxy-disubstituted carboxylic acid esters. Although the basicity of alkoxy enediolates is a problem in some cases, the use of readily available starting materials in these carbon–carbon bond forming reactions is advantageous. In other reactions such as cyanohydrin formation and hydrolysis, oxidation of ester enolates,[11] and Grignard additions to α-keto esters,[12] more synthetic steps are usually necessary and the final synthetic yields are consequently lower.

We have made a cursory study of reactions of alkoxy enediolates with other electrophiles. Propionaldehyde and ethylene oxide react with **1a** to give ethyl 2-phenyl-2,3-dihydroxypentanoate[13] (65% of a mixture of diastereomers) and α-phenyl-α-hydroxy-δ-butyrolactone[13] (60%), respectively. Similarly, enediolate **1b** and cyclohexanone give ethyl 2-hydroxy-2-(1-hydroxycyclohexyl)propanoate[13] (54%). In these reactions we used experimental method B described above. The fair to good yields obtained in these preliminary studies using enolizable carbonyl compounds and an epoxide suggest that alkoxy enediolates may have many synthetic applications, and further studies are in progress.

Acknowledgment is made to the Robert A. Welch Foundation and to Texas A&M Organized Research funds for the support of this work. We would also like to acknowledge the experimental assistance of Mr. Robert Burke in the early stages of this work.

References and Notes

(1) Welch Undergraduate Scholar.
(2) While our drawings of **1a** and **1b** show only the *E* configuration for these alkoxy enediolates, we have not excluded the possibility that significant amounts of the *Z* isomer are also present. However, consideration of the effect of the vicinal negatively charged centers on each other in the alkoxy enediolates suggests that the *E* configuration should be favored for both kinetic and thermodynamic reasons.
(3) O. W. Lever, *Tetrahedron*, **32**, 1943 (1976).
(4) For example, oxidation of α-benzylmandelic acid with potassium dichromate in acetic acid was reported to give phenyl benzyl ketone in "excellent" yield: O. Widman, *Ber.*, **49**, 477 (1916).
(5) P. A. Grieco and C.-L. J. Wang, *J. Chem. Soc., Chem. Commun.*, 714 (1975), have described acyl anion equivalents derived from phenylthioacetic acid dianions. Acyl anion equivalents from α-amino acid esters have also been described recently; cf. G. Stork, A. Y. W. Leong, and A. M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976). Oxidation of carbanions derived from nitriles and acids has also been used as a method for introduction of an acyl anion equivalent; cf. S. J. Selikson and D. S. Watt, *ibid.*, **40**, 267 (1975); H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 4611 (1976).

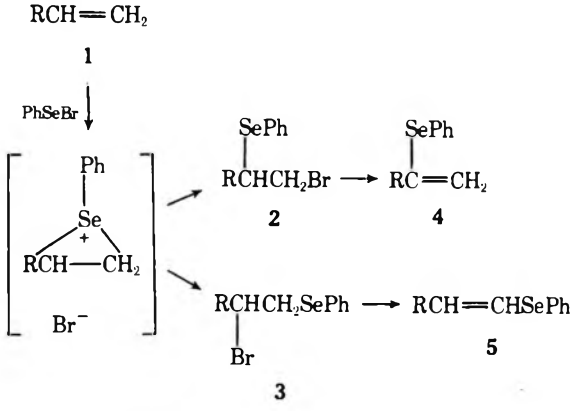
(6) Multi-charged anionic derivatives of amino esters have also been reported by A. P. Krapcho and E. A. Dundulis, *Tetrahedron Lett.*, 2205 (1976).
(7) P. L. Creger, *J. Am. Chem. Soc.*, **92**, 1396 (1970); A. J. Birch, *J. Chem. Soc.*, 1551 (1950); P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, *J. Org. Chem.*, **37**, 451 (1972).
(8) Thermodynamic formation of vicinal enediolates from α-hydroxy ketones has been described; cf. S. R. Wilson, M. E. Walters, and B. Orbaugh, *J. Org. Chem.*, **41**, 378 (1976).
(9) J. J. Bloomfield, D. C. Omsley, and J. M. Neike, *Org. React.*, **23**, 259 (1976).
(10) These procedures employ unexceptional organometallic experimental techniques similar to those described by H. C. Brown in "Organic Syntheses via Boranes", Wiley-Interscience, New York, N.Y., 1975.
(11) H. H. Wasserman and B. H. Lipshutz, *Tetrahedron Lett.*, 1731 (1975); E. Vedejs, *J. Am. Chem. Soc.*, **98**, 5944 (1974).
(12) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances", Prentice-Hall, New York, N.Y., 1954.
(13) The yields of these compounds were determined by gas chromatography. The compounds were characterized by NMR and mass spectra and elemental analyses.

Louis J. Ciochetto,[1] David E. Bergbreiter* Martin Newcomb*
Department of Chemistry, Texas A&M University College Station, Texas 77843
Received April 11, 1977

Regioselective Synthesis of Vinyl Phenylselenides[1]

Summary: Reaction of monosubstituted alkenes with phenylselenenyl bromide under either kinetically or thermodynamically controlled conditions followed by dehydrohalogenation of the resulting adducts provides a method for the regioselective synthesis of either 2-phenylselenoalkenes or 1-phenylselenoalkenes, respectively.

Sir: The utility and versatility of organoselenium compounds has become apparent.[2] Recently we undertook the preparation of both 2-phenylselenoalkenes **4** and 1-phenylselenoalkenes **5**, since these compounds are potentially useful for a number of synthetic transformations.[3] An obvious approach to the synthesis of **4** and **5** involves dehydrohalogenation of the appropriate β-bromoalkyl phenylselenides **2** and **3**, respectively. We therefore initiated a study to determine the feasibility of converting alkenes **1** to the desired vinyl phenylselenides **4** or **5** regioselectively via addition of PhSeBr and subsequent dehydrohalogenation.



The addition of PhSeBr to **1** probably involves the formation of a seleniranium ion, which may then be attacked by bromide ion, either at the less hindered but less electropositive primary carbon to give the anti-Markownikoff adduct **2**, or at the more electropositive but more hindered secondary carbon to give the Markownikoff adduct **3**.[4] Preliminary regioselectivity studies indicated that 1-hexene and PhSeBr react under kinetically controlled conditions (CCl_4, −20 °C) to give predominantly the anti-Markownikoff adduct **2b** [^{1}H NMR (CCl_4): δ 3.8–3.2 (m, 3 H)], which isomerizes[5] slowly in CCl_4 (48 h, 25 °C) or very rapidly in CH_3CN (<5 min, 25 °C) to give predominantly the Markownikoff adduct **3b** [^{1}H NMR (CCl_4): $-CH_2SePh$, δ 3.30 (dd, J = 12, 10 Hz) and 3.65 (dd, J = 12, 7 Hz), total 2 H; $-CHBr$, δ 4.3–3.8 (m, 1 H)]; however, due to the proximity and complexity of the ^{1}H NMR signals[6] and the thermal lability of the β-bromoalkyl phenylselenides, the exact determination of regioselectivity was deferred until both the addition and dehydrohalogenation were affected.

Table I. Percentage of 4/5 Formed Under Kinetic and Thermodynamic Conditions[a]

Entry	Alkene	Kinetic conditions[b] 4/5	Thermodynamic conditions[c] 4/5
a	Propene	85:15	9:91
b	1-Hexene	90:10	8:92
c	1-Octene	90:10	9:91
d	1-Hexadecene	90:10	7:93
e	4-Methyl-1-pentene	90:10	8:92
f	3-Phenyl-1-propene	98:2	2:98
g	3-Methyl-1-butene	98:2	3:97
h	3,3-Dimethyl-1-butene	100:0	0:100
i	3,3-Dimethyl-1-heptene	100:0	0:100

[a] Percentages determined by VPC (see ref 8). [b] PhSeBr (THF, −78 °C); *t*-BuOK (THF, −78 to 25 °C). [c] PhSeBr (CH_3CN, 25 °C); *t*-BuOK (THF, 25 °C).

For the kinetically controlled conditions the reaction of **1** with PhSeBr and subsequent dehydrohalogenation with *t*-BuOK was carried out in THF at −78 °C without isolation[7] of the intermediate β-bromoalkyl phenylselenide to give **4** regioselectively in high overall yield (Table I).[8] The regioselectivity of this process increases with increasing steric bulk at C-3 in **1**.

A typical procedure for the kinetically controlled conditions follows: a solution of 1-hexene (2.0 mmol) in dry THF (5 mL) was added dropwise (2 min) to a cooled (−78 °C) stirring solution of PhSeBr (2.0 mmol) in dry THF (20 mL). Stirring was continued until the dark brown color dissappeared (1 min) and *t*-BuOK (4.0 mmol) was added immediately.[9] The mixture was stirred at −78 °C for 5 min, allowed to warm to 25 °C, and stirred for 30 min. The THF was removed in vacuo, and the residue was extracted with ether, washed with brine, dried ($MgSO_4$), and purified by evaporative distillation (85 °C, 0.01 mm) to give a colorless liquid (430 mg, 90%): [^{1}H NMR (CCl_4) δ 2.4–2.1 (m, 2 H), 5.06 (s, 1 H), 5.45 (t, J = 0.5 Hz, 1 H)]. VPC analysis showed a 90:10 ratio of **4b/5b**.[8]

For the thermodynamically controlled conditions the reaction of **1** with PhSeBr was carried out in CH_3CN at 25 °C, the CH_3CN was removed in vacuo, and the resulting β-bromoalkyl phenylselenide was dehydrohalogenated with *t*-BuOK in THF at 25 °C to give **5** regioselectively in high overall yield (Table I). The ^{1}H NMR of **5h** [(CCl_4) δ 0.90 (s, 9H), 6.03 (d, J = 15 Hz, 1 H), 6.40 (d, J = 15 Hz, 1 H)] and **5i** [(CCl_4) δ 6.00 (d, J = 15 Hz, 1 H), 6.38 (d, J = 15 Hz, 1 H)] indicates that only the *E* isomer is formed; however, compounds **5a–g** are mixtures of *E* and *Z* isomers.

A typical procedure for the thermodynamically controlled conditions follows: a solution of 1-hexene (2.0 mmol) in CH_2Cl_2 (2 mL) was added to a solution of PhSeBr (2.0 mmol) in dry CH_3CN (10 mL) at 25 °C. The dark brown color disappeared immediately, and stirring was continued for 30 min. The solvents were removed in vacuo (25 °C), the residue was dissolved in THF (10 mL), and *t*-BuOK (4.0 mmol) was added. The mixture was stirred at 25 °C for 30 min, the THF removed in vacuo, the residue extracted with ether, washed with brine, dried ($MgSO_4$), and purified by evaporative distillation (85 °C, 0.01 mm) to give a colorless liquid (439 mg,

92%) [^{1}H NMR (CCl_4) δ 2.3–2.0 (m, 2 H), 7.6–5.5 (m, 2 H)]. VPC analysis showed an 8:92 ratio of **4b/5b**.[8]

Thus, it is now possible to convert monosubstituted alkenes to either 2-phenylselenoalkenes **4** or 1-phenylselenoalkenes **5** regioselectively. We are currently developing a variety of synthetic transformations for these substances and will report on them in due course.

References and Notes

(1) Organoselenium Chemistry. 1. This research was supported in part by a grant from the Petroleum Research Fund, administered by the American Chemical Society.

(2) (a) D. L. Klayman and W. H. H. Gunther, Ed., "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973; (b) K. B. Sharpless, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975), and references cited therein; (c) H. J. Reich and S. K. Shah, *J. Am. Chem. Soc.*, **99**, 263 (1977), and references cited therein.

(3) We have successfully utilized vinyl phenylselenides as synthons for the construction of new carbon to carbon bonds. This work will be reported soon.

(4) (a) Stable seleniranium ions have recently been prepared by the reaction of $ArSePF_6$ with alkenes: G. H. Schmid and D. G. Garrett, *Tetrahedron Lett.*, 3991 (1975). (b) PhSeCl reacts with propene in CH_2Cl_2 to give a 1:1 mixture of i and ii (R = CH_3, X = Cl), and in HOAc to give ii (R = CH_3, X = Cl) exclusively: E. G. Kataev, T. G. Mannafov, E. A. Berdnikov, and O. A. Komarovskaya, *Zh. Org. Khim.*, **9**, 1983 (1973); D. G. Garrett and G. H. Schmid, *J. Org. Chem.*, **42**, 1776 (1977). (c) PhSeOAc reacts with 1-dodecene to give a 1:1 mixture of i and ii (R = n-$C_{10}H_{21}$, X = OAc): K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **39**, 429 (1974). (d) $PhSeOCOCF_3$ gives mixtures of adducts with 1-methylcyclohexene and 1-hexene: H. J. Reich, *J. Org. Chem.*, 39, 428 (1974); S. Raucher, unpublished results. (e) For studies of the regioselectivity of PhSCl see W. H. Mueller and P. E. Butler, *J. Am. Chem. Soc.*, 90, 2075 (1968); D. G. Garrett and G. H. Schmid, *J. Org. Chem.*, **42**, 1776 (1977).

$$\underset{\text{i}}{RCH(SePh)CH_2X} \qquad \underset{\text{ii}}{RCH(X)CH_2SePh}$$

(5) This isomerization presumably involves the reversible formation of the seleniranium ion and the rate is dependent on the leaving group, X. For example, we have observed that for R = n-C_4H_9, i isomerizes to ii in <5 min when X = Br, but requires 24 h when X = Cl (CH_3CN, 25 °C). Also, for R = n-C_4H_9 a 1:1 mixture of i and ii isomerizes to ii in 48 h when X = $OCOCF_3$, but undergoes no apparent change even after 7 days when X = OAc (CH_3CN, 25 °C).

(6) Considerably simpler ^{1}H NMR spectra were obtained for the adducts of 3,3-dimethyl-1-butene and PhSeBr. Kinetic conditions gave exclusively **2h** [NMR (CCl_4): $(CH_3)_3C$– δ 1.15 (s, 9 H); >CHSePh δ 3.30 (dd, J = 6, 12 Hz, 1 H); $-CH_2Br$ δ 3.9–3.6 (m, 2 H)]. Thermodynamic conditions gave exclusively **3h** [NMR (CCl_4): $(CH_3)_3C$– δ 1.05 (s, 3 H); $-CH_2SePh$ δ 3.6–3.1 (m, 2 H); >CHBr δ 4.0 (dd, J = 4, 10 Hz, 1 H)].

(7) This procedure gave better regioselectivity than one which involved the reaction of **1** with PhSeBr in CCl_4 (−20 °C) or $PhCH_3$ (−78 °C), isolation of the β-bromoalkyl phenylselenide, and subsequent dehydrohaiogenation (t-BuOK, THF, 25 °C).

(8) (a) All compounds were fully characterized by spectroscopic methods. (b) Isolated overall yields from **1** of the vinyl phenylselenide mixtures indicated in Table I were >85% in all instances. (c) VPC analysis was carried out on a Varian 920 using a 5 ft × ¼ in. 1.5% OV 101 on 100/120 Chromosorb G column at 60 mL He/min. In all cases, the retention time of **4** was less than that of **5**. Ratios were determined by triangulation of peaks. (d) A sample of **5b** was prepared by the reaction of $Ph_3P{=}CHSePh$ with pentanal: N. Petragnani, R. Rodrigues, and J. V. Comasseto, *J. Organomet. Chem.*, **114**, 281 (1976); a sample of **4a** was prepared by an alternate procedure which will be detailed shortly: S. Raucher and G. Koolpe, unpublished results.

(9) The rate of disappearance of the dark brown color (THF, −78 °C) is <1 min for **1a–e**, and ~5 min for **1f–i**.

Stanley Raucher

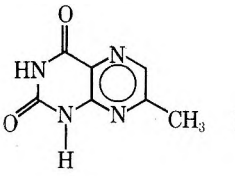
Department of Chemistry, University of Washington
Seattle, Washington 98195

Received June 20, 1977

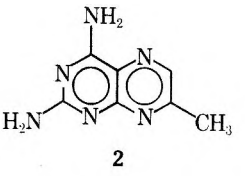
Novel α-Ionization of 7-Methylpteridines. Direct Synthesis of 7-Alkylidenepteridines[1]

Summary: 7-Methylpteridines containing amino or hydroxy groups in the 2,4-positions are converted by aqueous base to carbanions which readily condense with aromatic aldehydes to afford 7-alkylidenepteridines.

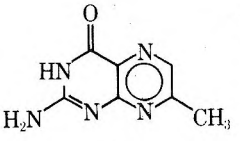
Sir: The carbanion chemistry of parent pteridine systems such as **1–3** which contain an aromatic pyrazine ring appears not to have been explored. In fact, such base-catalyzed chemistry of any pteridines seems limited to the conversion of the N-substituted 3,5,7-trimethylxanthopterin (**4**) to methyl ester **5** using dimethyl oxalate in the presence of potassium methoxide,[2] and to the reaction of N^8-lithio salts of various 2,4-diamino-7,8-dihydropteridines with alkyl halides to afford N^8-alkyl derivatives **6**.[3]



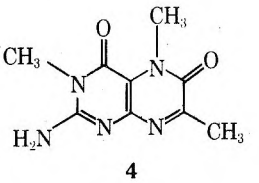
1



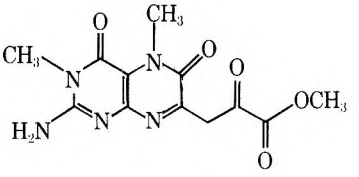
2



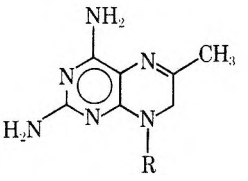
3



4

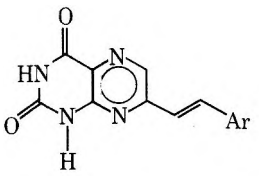


5

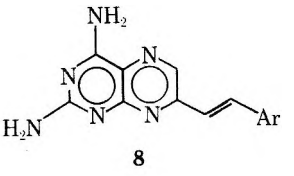


6

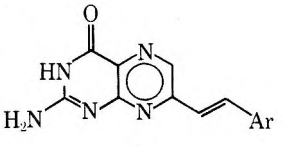
We have found that the methyl groups of 7-methyllumazine (**1**), 2,4-diamino-7-methylpteridine (**2**), and 7-methylpterin (**3**) are conveniently ionized by aqueous/ethanolic sodium hydroxide to afford carbanions α to the aromatic pyrazine rings. Such carbanions readily condense with aromatic aldehydes via the Claisen–Schmidt reaction[4] to give alkylidene derivatives **7**, **8**, and **9**, respectively. Thus, 7-alkylidenelumazines **7**[5] have been derived from **1** and benzaldehyde (53%), p-anisaldehyde (27%), 3,4-dimethoxybenzaldehyde (50%), and furfural (39%). Similarly, 7-alkylidene-2,4-diaminopteridines **8**[5] have been obtained from **2** and benzaldehyde (80%), piperonal (73%), and furfural (59%). 7-Methylpterin (**3**) also reacts with such aldehydes; however, the alkylidene derivatives **9** have resisted complete purification thus far since it has not been possible to remove all of the unreacted **3** from the products. As a result, the NMR spectra of these latter products derived from benzaldehyde, p-anisaldehyde, and piperonal, though consistent with **9**, contain small absorptions due to **3**.



7



8



9

In a typical experiment, a suspension of 10 mmol of 7-methyllumazine (**1**) and 36 mmol of sodium hydroxide in 20 mL of water is gently warmed until the heterocycle dissolves. The solution is then treated with 15 mmol of benzaldehyde in 10 mL of 95% ethanol and brought to reflux for 2–3 h. Upon

cooling, the precipitated salt of the alkylidene is collected, washed with ethanol and ether, then dried. After acidification with concentrated, boiling hydrochloric acid, the product is collected by filtration and purified by washing with 95% ethanol, then ether. The condensations with **2** are even faster, being essentially complete in 1 h, even though suspensions are present during the entire reaction period. Moreover, pteridines **8** themselves rather than sodium salts are obtained. These products are purified by recrystallization from dimethylformamide.

Though the yields of the alkylidene derivatives have not been maximized, these one-step preparations of **7** and **8** clearly present a viable alternative to earlier 7-alkylidenepteridine syntheses which involved cyclization of appropriate alkylidenepyrazines.[6] Efforts are currently being directed toward the study of various solvent and base combinations in the anticipation of finding ones more compatible with the extremely insoluble pteridines and with electrophiles other than aromatic aldehydes. The application of this methodology to the interesting 6-methylpteridines is also being investigated.

Supplementary Material Available: Full NMR and UV data for compounds 7–8 (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Support of this research by the National Institute of General Medical Sciences, National Institutes of Health, on Grant R01GM21500 is gratefully acknowledged.
(2) W. Pfleiderer, *Chem. Ber.*, **95**, 2195 (1962).
(3) M. Chaykovsky, *J. Org. Chem.*, **40**, 145 (1975).
(4) H. O. House, "Modern Synthetic Reactions", 2nd ed, W.A. Benjamin, Menlo Park, Calif., 1972, pp 632–653.
(5) The structures of these homogeneous compounds (by TLC) were supported by elemental analyses and by IR, UV, and NMR spectroscopy.
(6) E. C. Taylor and T. Kobayashi, *J. Org. Chem.*, **41**, 1299 (1976).

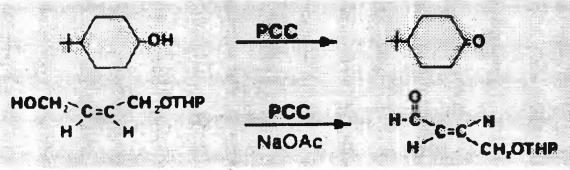
Edwin M. Kaiser,* Stephen L. Hartzell
Department of Chemistry
University of Missouri—Columbia
Columbia, Missouri 65201

Received May 17, 1977

Oxidizing Agents

Something old, something new

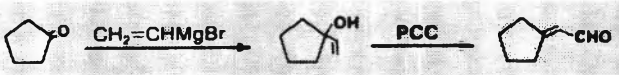
Corey and Suggs[1] have shown that **pyridinium chlorochromate (PCC)**, a stable crystalline reagent, readily oxidizes a variety of alcohols to the corresponding aldehydes and ketones in high yield under mild conditions. Yields of aldehydes and ketones obtained with 1.5 molar equivalents of **PCC** are equal or superior to those obtained with Collins reagent[2] (using a five- or six-fold excess).



The oxidation is performed by suspending **PCC** (1.5 mmol) in methylene chloride (*ca.* 2 ml) and adding the alcohol (1 mmol in 0.5 to 1.5 ml of CH_2Cl_2). After 1-2 hours the oxidation is complete as evidenced by a precipitate of the black reduced reagent. Dilution with five volumes of anhydrous ether, filtration of solid and evaporation of solvent give the product. Substrates containing acid-labile groups may be oxidized by buffering the reaction mixture with powdered sodium acetate.

Recently, it was observed that alkylative carbonyl transposition can be effected by the **PCC** oxidation of tertiary allylic alcohols obtained by the 1,2-addition of organometallic reagents to α,β-

unsaturated ketones.[3] Tertiary allylic alcohols generated from saturated ketones and vinylmagnesium bromide are transformed to α,β-unsaturated aldehydes.



PCC behaves as a dienophile and oxidant in the novel and useful ring enlargement of 2-furylcarbinols to pyran derivatives.[4]

R = CH_3, C_6H_{13}, CH_2=$CHCH_2$

References:

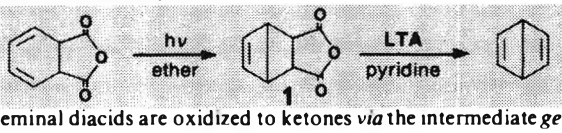
1) E.J. Corey and J.W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
2) J.C. Collins, W.W. Hess, and F.J. Franck, *ibid.*, 3363 (1968).
3) W.G. Dauben and D.M. Michno, *J. Org. Chem.*, **42**, 682 (1977).
4) G. Piancatelli, A. Scettri, and M. D'Auria, *Tetrahedron Lett.*, 2199 (1977).

19,014-4 Pyridinium chlorochromate (PCC)..... 100g $7.00
500g $24.00

Lead tetraacetate (LTA) is one of the most versatile oxidizing reagents known in organic chemistry because it reacts with a wide range of functional groups. The uses of **LTA** have been extensively reviewed.[1-4] A few highlights are presented below.

Oxidation of Carboxylic Acids

Vicinal dicarboxylic acids are oxidized to alkenes with **LTA** and pyridine in benzene as solvent at 50-60° or in dimethyl sulfoxide or dioxane at room temperature.[1] Dewar benzene has been prepared by oxidation of the anhydride **1**.[5]



Geminal diacids are oxidized to ketones *via* the intermediate *gem*-diacetates.[1]

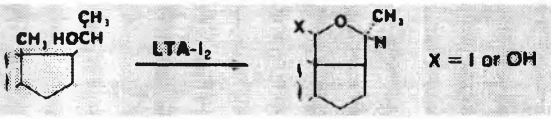
Oxidative decarboxylation of monocarboxylic acids affords mixtures of alkenes and acetates.[1] However, in the presence of cupric acetate, alkenes alone are obtained in good to excellent yield from primary and secondary acids.[2] The addition of lithium chloride or iodine results in halodecarboxylation.[1] Thus, *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acids give mixtures of the 4-chloro isomers consistent with a free-radical mechanism.

Oxidation of Amides

The oxidation of primary amides with **LTA** parallels the Hofmann reaction and offers an alternative route to isocyanates.[3]

Substitution of Methyl Groups

Oxidation of a steroid alcohol having a hydroxyl group strategically located for attack of an angular methyl group occurs with **LTA** in benzene or better with an **LTA**-iodine combination.[1]



Aliphatic alcohols react to give substituted furan or pyran derivatives.[4]

LTA has also been used to effect many other oxidations such as hydroquinones to quinones, thiols to disulfides or methyl sulfinates, and 1-aminobenzotriazole to benzyne.[1]

References:

1) Fieser and Fieser, *Reagents for Organic Synthesis*, **1**, 537; **2**, 234; **3**, 168; **4**, 278; **5**, 365.
2) R.A. Sheldon and J.K. Kochi, *Organic Reactions*, **19**, 279 (1972).
3) J.B. Aylwark, *Quart. Rev.*, **25**, 407 (1971).
4) M.L. Mihailovic and Z. Cekovic, *Synthesis*, 209 (1970).
5) E.E. van Tamelen and S.P. Pappas, *J. Am. Chem. Soc.*, **85**, 3297 (1963).

18,519-1 Lead tetraacetate (LTA)..... 100g $8.00
500g $24.00