THE JOURNAL OF Organic Chemistry

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY

BOOKS AND JOURNALS DIVISION

D. H. Michael Bowen, *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

Graphics and Production Department: Bacil Guiley, Head

Research and Development Department: Seldon W. Terrant, Head

Advertising Office: Centcom, Ltd., 50 W. State St., 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 ACS Easton address.

Page charges of $70.00 per page are assessed for papers published in this journal. Ability to pay 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

1976 subscription rates—including surface postage:

	Domestic	PUAS	Canada, Foreign
Member	$26.00	$33.25	$34.25
Nonmember	104.00	111.25	112.25
Supplementary material	15.00	19.00	20.00

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

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 ACS Columbus address. 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 at the ACS Columbus address.

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 Business Operations, Books and Journals Division, at the ACS Washington address or call (202) 872-4444.

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 must be ordered directly from Business Operations, Books and Journals Division, at the ACS Washington address. Orders over 20 pages

	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

are available only on microfiche, 4 × 6 in., 24X, 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.

Notice to Authors last printed in the issue of January 9, 1976

THE JOURNAL OF Organic Chemistry®

1A

NOTES

COMMUNICATIONS

■ 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 inquiries about the paper should be addressed.

AUTHOR INDEX

TIMELY TEARSHEETS

Here's an opportunity to choose any article you wish which has been published during the past 12 months in any one of the American Chemical Society journals.*

The price for this service is very modest—just $2.50 for the first copy and $1.25 for each additional copy.

Also, if you wish, you may select articles which have appeared in earlier non-current ACS journal issues, but these will be photocopies rather than tearsheets and an additional 50¢ is required per article.

All you have to do is fill in the order forms below, *include your payment,* mail now, and we'll do the rest.

1. Give complete details for each article. Sorry, we cannot provide a search service.

2. **PRINT** or **TYPE** all information, including label.

3. Make check or money order payable to the AMERICAN CHEMICAL SOCIETY, and mail to: ACS, Business Operations, Books and Journals Division, 1155 16th Street, N.W., Washington, D.C. 20036.

Name _____

Address _____

City _____

State/Zip _____

AMERICAN CHEMICAL SOCIETY JOURNALS
TIMELY TEARSHEETS   Order Form

The following article(s) came to my attention in a recent issue of one of the ACS journals. I would like to order the number of tearsheets of each article indicated in the box(es).

ACS Journal _____ ☐

Title _____

Author(s) _____

Issue Date _____ Page(s) _____

ACS Journal _____ ☐

Title _____

Author(s) _____

Issue Date _____ Page(s) _____

ACS Journal _____ ☐

Title _____

Author(s) _____

Issue Date _____ Page(s) _____

$2.50 for the first tearsheet.

$1.25 for each additional tearsheet ordered at the same time.

$ _____
Total Enclosed

These prices do not apply to articles from Chemical Reviews and Journal of Physical and Chemical Reference Data. For information regarding cost of these copies, contact the Books and Journals Division, ACS.

* Copyright restrictions prevent us from providing copies from other than ACS journals

Molecular Rearrangements with Ethoxycarbonyl Group Migrations. 2. Rearrangement of 1,2-Glycols, Halohydrins, and Azidohydrins[1,2]

Jacques Kagan,* Dalmacio A. Agdeppa, Jr., David A. Mayers, S. P. Singh, Mary J. Walters, and Richard D. Wintermute

Chemistry Department, University of Illinois, P.O. Box 4348, Chicago, Illinois 60680

Received September 29, 1975

The ethoxycarbonyl group has been shown to undergo a facile 1,2 migration during the pinacol rearrangement of glyceric esters in fluorosulfonic acid. Pyruvic esters and 2-hydroxy-3-butenoic esters were also formed, and the prolonged treatment of some pyruvic esters in fluorosulfonic acid led to their isomerization into β-keto esters. The product of ethoxycarbonyl group migration was also found in the treatment of an azidohydrin with nitrosonium tetrafluoroborate, and that of halohydrins with silver salts. The rearrangement of tert-butyl 2-hydroxy-3-chloro-3-phenylbutyrate (24) without fragmentation upon treatment with silver carbonate argued against a mechanism involving a carboxylium ion, and in favor of a process in which the alkoxycarbonyl moiety acts as an internal nucleophile.

The migration of a carboethoxyl group in preference to hydrogen, alkyl, or aryl groups in the well-known pinacol rearrangement has not been previously noted,[3] but we were encouraged to look for it by its discovery in the acid-catalyzed isomerization of epoxides.[1,4] Glyceric esters 1, obtained by mild hydrolysis of glycidic esters (I) or by hydroxylation of

h, R = H
m, R = Me
e, R = Et
f, R = Ph

cinnamic esters, were treated with sulfuric acid, alone or in acetic acid, trifluoroacetic acid, or boron trifluoride, with poor results. For example, treatment of 1m with sulfuric acid in acetic acid yielded the allylic alcohol 4m with only minor

amounts of 3-phenyl-2-butanone and of the desired rearrangement product 3m. Fluorosulfonic acid used as solvent was found to be a most convenient catalyst for the desired pinacol rearrangement, and the standard procedure in this work consisted in dissolving 1 in pure fluorosulfonic acid, both having been precooled to 0 °C, pouring the reaction mixture over ice after 3 min at this temperature, and extracting with carbon tetrachloride. The crude extract was free from starting material.

The experimental results, presented in Table I, were very reproducible. They were generally similar to those obtained in the reaction of the related glycidic esters with boron trifluoride,[1,4] and the same sequence of apparent migratory aptitudes was deduced. The allylic alcohols 3 were not detected, but independent treatment of 4m, 4e, and 4f under the reaction conditions confirmed their reactivity and their partial conversion into the lactones 5m and 5e and the indene 6, respectively.

The synthesis of indenes from phenyl substituted allylic cations has been previously described.[5] The intramolecular Friedel–Crafts reaction requires the allylic–benzylic cation to have the geometry shown in E-7. Whether or not the other

E-7   Z-7

isomer was formed was not established directly. The observed cyclization to 6 from each diastereoisomer of 1f in the presence of boron trifluoride agreed with a facile interconversion of both cations,[5] but the absence of the lactone 5f indicated a slow rate of cyclization from Z-7. Note that the indene 6 had not been observed in the boron trifluoride catalyzed rear-

Table I. Pinacol Rearrangement of Glyceric Esters with FSO$_3$H at 0 °C for 3 min (Yields from NMR Analyses)

Precursor	2	3	5	Others
		\% products		
1h	*a*	6.5	*a*	*a*
1m (threo + erythro)	*b*	84	16	
threo-**1m**	*b*	84	16	
erythro-**1m**	*b*	84	16	
1m-d_3 (threo + erythro)	*b*	90	10	
1e (threo + erythro)	9	75	9	
1f (threo + erythro)	60	13		**6** (12), **8** (6), **9** (9)

a Too complex for analysis. *b* Trace.

Table II. Isomerization of 2f Catalyzed by FSO$_3$H at 0 °C

Time, min	2f	3f	8
5	79	15	6
10	71	21	8
20	50	33	17
40	28	50	22
80	16	57	27
120	8	64	28
150	5	65	30
180	2	71	27
210	0	71	29

Table III. Isomerization of 2m Catalyzed by FSO$_3$H at 0 °C

Time, min	2m	3m	11
3	95	3	2
90	48	32	20
180	19	46	35
300	5	55	40
450	0	56	44

rangement of If, which yielded a single product, resulting from phenyl group migration, further indicating that **4f** was not formed under the conditions of that reaction.[1]

The dehydration of both isomers of **1m** into an almost single rearranged product **3m** (Table I) contrasted with the results of the boron trifluoride treatment of Im, from which the three rearranged products **2m**, **3m**, and **4m** were obtained.[1] However, the isomerization of **1m** into the allylic alcohol was the preferred process in weaker acids, such as trifluoroacetic or dilute fluorosulfonic acids, and the treatment of Im with pure fluorosulfonic acid under conditions identical with those used with **1m** gave a somewhat different product distribution, 52% of **3m**, 48% of **5m**, and a trace of **2m**.

The migration of the phenyl group from the 3 to the 2 position would also have given **3m** from **1m**, but this process was ruled out by the study of **1m**-*3-methyl-d$_3$*, which yielded **3m**-d_3 with no deuterium at the acetyl position, a result which agrees with the behavior of Im.[1]

The acid treatment of **1f** yielded two unexpected products, ethyl 2,2-diphenylacetoacetate (**8**) and acetophenone (**9**), along with **2f**, **3f**, and **6** (Table I). This reaction contrasted with that of If with boron trifluoride, which yielded only **2f**,[2] and where the allylic alcohol **4f** could not have been an intermediate, since its treatment with boron trifluoride yielded the indene **6** as the sole product. Shorter reaction times did not have a marked effect on the yield of **9**, but reduced the formation of **8**, and these studies also demonstrated the very fast rate of this pinacol rearrangement, which was complete in less than 15 s at −5 °C and where only 6% of starting material was left after 15 s at −50 °C.

The formation of acetophenone described above must have taken place in the reaction of the starting material, since the reaction products did not yield it when submitted to the treatment with fluorosulfonic acid. The idea that an air oxidation reaction had taken place, formally the reverse of a pinacol synthesis, was dismissed by checking that bubbling air through a solution of If did not lead to any detectable fragmentation. The most reasonable mechanism for the fragmentation of glyceric esters into carbonyl products involves a protonation at the ester carbonyl, followed by a retro-aldol cleavage reaction. This type of acid-catalyzed β fission had not

been previously reported with esters, although it was known for carboxylic acids[6] and ketones.[7] We also found that 2,3-diphenyl-3-hydroxybutyric acid yielded acetophenone and methyl phenylacetate upon attempted esterification with methanol catalyzed by sulfuric acid. However, a control experiment disclosed that fragmentation had taken place prior to exterification, since the ester formed by reaction with diazomethane did not undergo the fragmentation reaction when it was treated in the same acidic conditions.

We previously reported on the acid-catalyzed formation of benzophenone from ethyl 3,3-diphenylpyruvate, which we tentatively ascribed to a retro-pinacol rearrangement to a glyceric ester, followed by the above β fission.[8] Later work on the rearrangement of chlorohydrins, which also led to fission,[9] attracted our attention to the facile autoxidation of ethyl 3-phenylpyruvates, a reaction which best explains the formation of **9** in this case.

In the effort to establish whether acetophenone had been formed by reaction of the starting material or of the reaction products, **2f** was treated in the usual reaction conditions. To our surprise, it was converted into two other products, and acetophenone was not formed (Table II). These two products were purified by preparative TLC and identified as **3f** and **8**, the β-keto esters isomeric with **2f**, which were also observed in the direct reaction of **1f**.

We do not know the exact mechanism of the α-keto to β-keto ester rearrangement, for which there are at least two alternatives, differing by whether or not the ethoxycarbonyl group migrates,[8] and we still hope to see this problem elucidated in the near future, by studying the rearrangement of properly labeled precursors.

The generality of the fluorosulfonic acid catalyzed rearrangement of α-keto to β-keto esters has not been fully established, but we found that **2m** [the main product formed in

Table IV.　Solvolysis of 17

Solvent	Temp, °C	Time, h	Ag salt	Ih	2h	3h	4h	1h	17	Other
None	132	22	None		50		50			9 (Tr)
None[a]	132	63	None		100					
None	132	63	None		25		44			9 (31)
50% EtOH	r.t.									23 (100)
MeOH	r.t.	4	Nitrate							22 (100)
C_6H_6	r.t.	21	Carbonate	60	5	14	18		4	
Acetone	r.t.	21	Carbonate	70	10	14	5			
Me_2SO	r.t.	21	Carbonate		17		3		80	
HMPTA	r.t.	21	Carbonate	c	c	0	b	c	b	c
CCl_4	r.t.	41	Carbonate	68	2	19	11			
THF	r.t.	41	Carbonate	35	2	10	3		50	
CH_3CN	r.t.	41	Carbonate	80	2	16	2			
Hexanes	r.t.	65	Carbonate	50	2	28	20			
Ether	r.t.	65	Carbonate	25	5	9	20		40	
Me_2SO	r.t.	96	Carbonate	c	c	0	c	c	c	
DMF	r.t.	96	Carbonate	c	c	b	c	c	c	
88% HCOOH	r.t.	16	None					100		
AcOH	r.t.	16	None						100	
AcOH	118	16	None				50			AcO-4h (50)
Ether	-10	1.5	Triflate				100			
Ether	0	2	Tosylate						100	
C_6H_6	r.t.	20	Tosylate	c	c	0	29	0	c	
C_6H_6	r.t.	46	Mesylate		80				14	14 (6)

a In the absence of air. *b* Detected by NMR. *c* Mixture too complex for NMR analysis.

the acid treatment of ethyl 2-phenyl-3,3-dimethylglycerate (10)] did rearrange to yield the isomeric β-keto esters 3m and 11 (Table III).
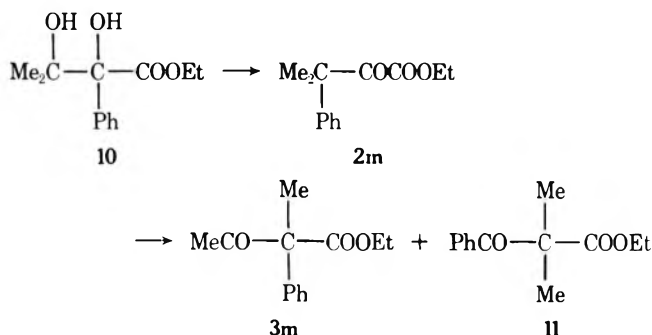
Finally, in the course of this work glyceric esters having different substitution patterns at the 3 position were also treated with fluorosulfonic acid, and the results are shown here:

12, R_1 = Ph; R_2 = H	88%	0	12%
13, R_1 = H; R_2 = Me	0	100%	0
14, R_1 = H; R_3 = Ph	95%	0	5%
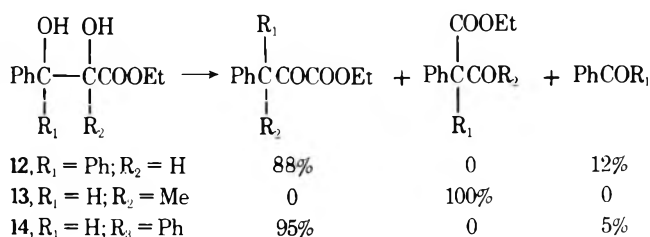
Ethoxycarbonyl Group Migration from an Azidohydrin Precursor. Following the report of easy generation of carbonium ions by the nitrosonium tetrafluoroborate decomposition of azides,[10] the procedure was utilized with ethyl 2-hydroxy-3-azido-3-phenylbutyrate (15), which was readily obtained by treating Ih with hydrazoic acid.
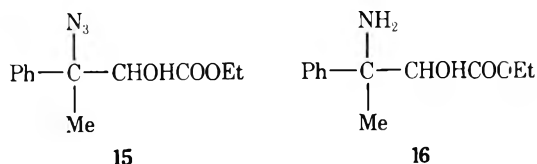
There was no reaction when 15 was treated with an excess of the salt at room temperature in acetonitrile, benzene, or dimethoxyethane for up to 60 h. The starting material disappeared completely upon refluxing for 6 h in benzene, and the product of ethoxycarbonyl migration was detected in 18% yield, along with a trace of 2h and 10% of the allylic alcohol 4h. Acid-catalyzed decarbonylation and condensation reactions were probably responsible for the low yield of identified products, a situation similar to that observed with Ih[1] and 1h.

The identification of 3h in this reaction mixture was sufficient proof that the ethoxycarbonyl group could migrate when the azohydrin was used in the generation of the initial cation, and no further work was devoted to this reaction.

The synthesis of the amino alcohol 16 proved to be much more difficult than anticipated.[11] The treatment of the epoxide Ih with ammonia or sodamide did not yield 16. Ring opening took place when Ih was treated with benzylamine, but the nitrogen was then doubly benzylic, and the hydrogenolysis cleaved the bond between the nitrogen and the adjacent tertiary carbon, rather than the desired one.

Acid-catalyzed reactions, such as the condensation with a nitrile to form the required carbon–nitrogen bond, instead resulted in the dehydration into 3h. The reduction of 15 with sodium borohydride gave a low yield of 16, which was purified with difficulty. Upon diazotization of this product with isoamyl nitrite, a very complex mixture was generated, where 3h was absent as judged by NMR. Further work in this area will have to await the development of a convenient synthesis for 16.

Ethoxycarbonyl Group Migrations from Halohydrins. Because of the ease with which the product of rearrangement with ethoxycarbonyl group migration could be detected by the NMR analysis of the aldehyde proton, much work was devoted to the chlorohydrin 17, derived from Ih by treatment with hydrogen chloride in ether, and which was a 1:1 mixture of diastereoisomers.

The solvolysis of 17 in 88% formic acid at room temperature for 16 h resulted in hydrolysis to the glyceric ester 1h. No reaction was observed under the same conditions in acetic acid, but following reflux in this latter solvent for 16 h, the allylic alcohol 4h and its acetate were formed in equal amounts.

Table V.　Dehydrochlorination of 20 and 21 in the Presence of Silver Carbonate

Compd	Solvent	Time, h	Temp, °C	COOC$_2$H$_5$ migr	Epoxide	Starting material	Others
20	C$_6$H$_6$	15.5	65	8	61	31	
	Ether	16	r.t.	a	a	a	
	DMF	15	r.t.	0	a	a	
	DMF	40	75	100			
	CH$_3$CN	15.5	r.t.			100	
	CH$_3$CN	24	82	100			
	Acetone	15	r.t.	a	a	a	
21	DMF	66	68				4m (100)
	C$_6$H$_6$	16	r.t.	0	a	0	4m,^{a} 5m^a

^{a} Identified by NMR, but spectrum too complex for analysis.

The reaction of **17** was then carried out in a variety of solvents. Nucleophilic displacement of the chloride, but no rearrangement, was the rule in hydroxylic solvents. In aprotic
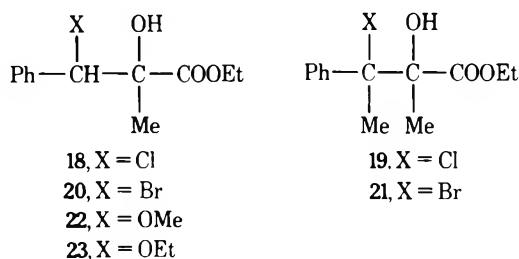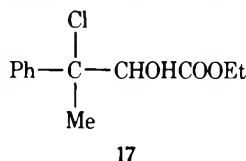
solvents, the dehydrochlorination took place in all possible manners, yielding the allylic alcohol and the epoxide as well as the products of molecular rearrangement, the α-keto ester **2h**, and the aldehyde **3h**. Qualitative variations in the product distribution were observed as a function of the solvent chosen, and they are recorded in Table IV. The nature of the silver salt used also had an effect on the product distribution, and no **3h** was detected with silver tosylate, mesylate, or triflate.

After this series of experiments was completed, silver carbonate was utilized with other halohydrins, in order to ensure that no strong Bronsted acidity would be developed during the course of the reaction, thereby ensuring that the migration of the ethoxycarbonyl group would not actually involve a protonated ester moiety. No reaction was observed at room temperature with the chlorohydrins **18** and **19,** but the corresponding bromohydrins **20** and **21** did undergo dehydrobromination in these conditions, yielding the epoxide and the product of ethoxycarbonyl group migration in each case, as well as the allylic alcohol in the case of **21** (Table V).[12]

These observations confirmed the preference for the migration of the ethoxycarbonyl group over the methyl which was previously encountered in the rearrangement of glyceric and glycidic esters under certain conditions.

Much more work remains to be done to correlate the effect of the temperature and the stereochemistry of starting materials with the product composition. However, the present results are in line with those described for the rearrangement of the corresponding glycidic esters. The allylic alcohol **4** was the major product at low temperature. In the absence of electrophilic assistance, the product of methyl migration **2h** was formed next, and the formation of the product of ethoxycarbonyl migration **3h**, which has the highest activation energy, required electrophilic assistance.

Conclusion

The simplest explanation for the pinacol and pinacol-like rearrangements described in this work starts with an ionization at the 3 position. We have no information yet on the lifetime of the 3-carbonium ion generated, compared to the rate of the subsequent migration of one group from the 2 to the 3 position, but it is anticipated to depend on the reaction conditions. The concertedness reported in other pinacol rearrangements,[13] and the recently disclosed concerted rearrangement of the epoxide Ih to **3h**,[14] suggest that a group migration from the 2 to the 3 position could well take place synchronously with the departure of the leaving group, resulting in inversion of configuration at the 3 position.

Formally, a distinction may be established between a process in which the carbonyl carbon remains with eight electrons throughout (path A) and that in which the bonding electrons are first attracted to the adjacent electron-deficient site (written here as a full cation for convenience), yielding an enol–carboxylium ion pair, which further undergoes the acylation reaction required by the structure of the final product (path B).
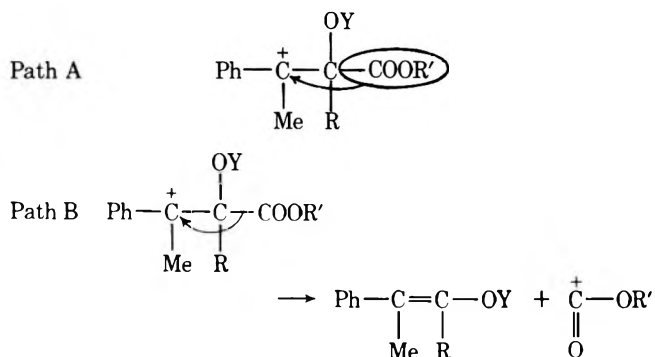
The fact that all the attempted syntheses of carboxylium ions have resulted in their decomposition with loss of carbon dioxide[15] gave a strong presumption against path B. Additional support for this view was derived from the study of *tert*-butyl 2-hydroxy-3-chloro-3-phenylbutyrate (**24**), which was treated with silver carbonate in benzene. If path B had been operative, decomposition to carbon dioxide and isobutene would have been expected. Instead, the rearrangement with ester group migration was observed, indicating that little or no positive charge was generated at the ester carbonyl, and that the carbon–carbon bonding electrons act as an internal nucleophile in the rearrangement.

Each diastereoisomer of **24** was treated under the same conditions. Although they yielded the same products, **25, 26,** and **27,** considerable stereoselectivity was displayed and one isomer gave predominantly the aldehyde resulting from ester group migration (ca. 50% of the products) with only 25% of epoxide, while the other gave only 33% of this aldehyde and

Ph—C—C—COOMe$_3$ → Ph—C—CHO

24 → 25

+ Ph—C—CH—COOMe$_3$ + Ph—C——CHCOOMe$_3$

26 + 27

Ph—CH—CHO

28
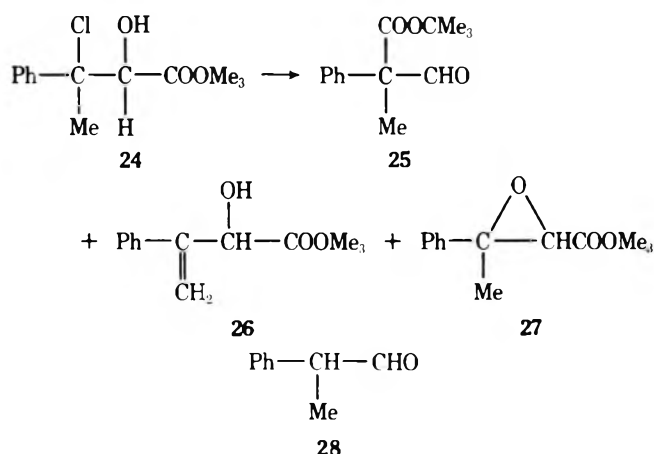
5€% of the diastereomeric epoxide (27). The formation of acetophenone in these dehydrochlorination reactions is interpreted as resulting from the autoxidation of *tert*-butyl 2-keto-3-phenylbutyrate,[9] giving a measure of the extent of hydrogen migration from the 2 to the 3 position. In contrast, the treatment of 27 with boron trifluoride in benzene resulted in complete cleavage to 2-phenylpropionaldehyde (28), coupled with the alkylation of the solvent, a decomposition reaction reminiscent of the thermal process.[16]

Although further work is obviously needed, the ability of the alkoxycarbonyl group to undergo 1,2 migrations in a variety of pinacol-like rearrangements is now firmly established. The ready availability of glycidic and glyceric esters, as well as chlorohydrins, suggests that the introduction of a carboxylic ester function adjacent to a carbonyl group via a pinacol-like rearrangement may occasionally compete with current methods based on nucleophilic reactions of enolate ions. From the practical viewpoint, a competition between two different substituents is usually the rule for the migration from the carbinol to the adjacent cationic position in these rearrangements. We previously demonstrated that a judicious choice of the reaction parameters often provided an effective control over the formation of the primary products.[1] Some selectivity over the subsequent isomerization of these products is also available, and may even lead to products not directly accessible from the starting material, such as 8 from 1f. Further work will be directed at gaining a more effective control over the selection of the group which migrates in these competitive rearrangement reactions.

Experimental Section

Rearrangement of Ethyl 3-Methyl-3-phenylglycerate (1h). Fluorosulfonic acid (1 ml) precooled to 0 °C was added dropwise with stirring to 472 mg of the diastereoisomer of 1h melting at 93–94 °C.[17] The reaction mixture was stirred for 3 min and poured onto an ice–water–carbon tetrachloride mixture. After separating the organic layer and extracting the aqueous phase twice with 50 ml of CCl$_4$, the combined organic layers were washed with two 50-ml portions of 5% NaHCO$_3$, dried, and concentrated. The NMR (CCl$_4$) was very complex, but showed the aldehyde signal of 3h at 9.90 ppm. Preparative TLC on silica gel, developed successively with EtOAc–petroleum ether (1:9) and EtOAc–CCl$_4$ (1:9), led to many overlapping bands. The only product isolated in pure form was ethyl 2-formyl-2-phenylpropionate (3h, 20 mg), identical with an authentic sample. The same results were observed when either the lower melting or a mixture of both diastereoisomers of 1h was treated as above.

Ethyl 2,3-Dimethyl-3-phenylglycerate (1m). The hydration of 2.0 g of Im with 30% by weight of perchloric acid in 50% aqueous THF for 16 h at room temperature led, after workup, to 1.5 g of 1m, as a viscous oil which was purified by chromatography over silica gel. A mixture of both diastereoisomers was obtained: NMR (CDCl$_3$) 7.0–7.6 (br, 5 H), 4.07 (q, J = 7 Hz, 2 H), 3.55 (br, 2 H), 1.65 (s, 3 H), 1.40 (s, 3 H), and 1.13 ppm (tr, J = 7 Hz, 3 H) for one isomer, and 7.0–7.6 (m, 5 H), 4.03 (q, J = 7 Hz, 2 H), 3.55 (br, 2 H), 1.60 (s, 3 H), 1.43 (s, 3 H), and 1.08 ppm (tr, J = 7 Hz, 3 H) for the other. The signal at 3.55 ppm disappeared when D$_2$O was added. The fraction collected before 1m

was 4m, obtained in 10% yield, and identified by comparison of the NMR with the known material. The same procedure was used to hydrate 400 mg of 1m-3-Me-d$_3$, yielding 400 mg (92%) of ethyl 2-methyl-3-trideuteriomethyl-3-phenylglycidate (1m-d$_3$), which was 72% deuterated from the NMR analysis.

Rearrangement of 1m. A 576-mg sample of 1m was treated with 1.15 ml of FSO$_3$H at 0 °C for 3 min, poured into an ice–water–CCl$_4$ mixture, and worked up as usual. The crude reaction products were fractionated by preparative TLC using EtOAc in petroleum ether (once with 6% and twice with 4% v/v). Three bands were visible under uv light. Ethyl 3,3-dimethyl-3-phenylpyruvate (2m), an oil (3.7 mg, 0.7%), was isolated from the fastest moving band. Its NMR (CCl$_4$) and mass spectra were superimposable onto those of the FSO$_3$H-catalyzed rearrangement of ethyl 3,3-dimethyl-2-phenylglycerate (10). Ethyl 2-methyl-2-phenylacetoacetate (3m, 418 mg, 78%), an oil, was obtained from the second band. Its NMR (CCl$_4$) and mass spectra were superimposable onto those of the major product of the BF$_3$-catalyzed rearrangement of ethyl 2,3-dimethyl-3-phenylglycidate (Im). The third band yielded 59.5 mg (14%) of 2-methyl-3-phenyl-4-hydroxy-2-butenoic acid lactone (5m): mp 120–122 °C (lit. mp 121–122 °C[18]); λ_{max} (cyclohexane) 211 and 260 nm; NMR (CDCl$_3$) 7.45 (s, 5 H), 5.04 (q, J = 2 Hz, 2 H), and 2.12 ppm (tr, J = 2 Hz, 3 H). The NMR analysis of the mixture before separation showed 84% of 3m and 16% of 5m, the signal at 1.18 ppm for 2m being barely noticeable.

The same treatment was supplied to 300 mg of 1m-d$_3$, which yielded 2 mg of 2m-d$_3$, 209 mg of 3m-d$_3$ in which the singlet at 1.67 ppm integrated for only 0.67 H, and 15 mg of 5m-d$_2$, having a full methyl at 2.12 ppm.

Rearrangement of *threo-* and *erythro*-1m. The above reaction was repeated using 133 mg of either *threo-* or *erythro*-1m in 0.26 ml of FSO$_3$H. After workup, 107 and 90 mg of an oil were obtained, respectively, each analyzing by NMR for 84% 3m, 16% 5m, and a trace of 2m.

Rearrangement of Ethyl 2,3-Dimethyl-3-phenylglycidate (1m). Treatment of 200 mg of Im with 0.43 ml of fluorosulfonic acid for 3 min at 0 °C and workup yielded 140 mg of an orange semisolid product which contained 52% 3m and 48% 5m plus a trace of 2m (NMR analysis).

Reaction of 1m in Dilute Fluorosulfonic Acid. Qualitative tests were performed using 200 mg of 1m in (a) 0.4 ml of acid and 0.05 ml of water, (b) 0.3 ml of acid and 0.05 ml of water, and (c) 0.3 ml of acid and 0.1 ml of water. The major products were 3m (along with some 4m and 5m), 4m (along with some 3m), and 4m, respectively. In the last two experiments some starting material remained.

Ethyl 2-Ethyl-3-methyl-3-phenylglycerate (1e). A solution of 482 mg (2.06 mmol) of E-Ie in 2 ml of tetrahydrofuran was added to 25 ml of perchloric acid in 50% aqueous tetrahydrofuran (30% by weight). The reaction mixture was heated in an oil bath at 45 °C for 1 h, diluted with 150 ml of water, and extracted with two 50-ml portions of ether. The combined ether extracts were washed with two 50-ml portions of 5% aqueous sodium bicarbonate, dried, and concentrated.

Purification of the product mixture by preparative TLC, using 7.5% ethyl acetate in petroleum ether, yielded 385 mg (74%) of 1e, a thick oil, as a 1:1 mixture of threo and erythro isomers: NMR (CCl$_4$) 7.0–7.6 (m, 10 H), 4.02 (q, J = 7 Hz, 2 H) and 4.13 (q, J = 7 Hz, 2 H), 3.33 (br s, exchanged with D$_2$O, 4 H), 1.5–2.1 (m, 4 H), 1.58 (s, 3 H) and 1.5 (s, 3 H), 1.18 (tr, J = 7 Hz, 3 H), and 0.5–0.85 ppm (m, 6 H).

Ethyl 2-ethyl-3-phenyl-2-hydroxy-3-butenoate (4e, 43 mg, 9%) was also obtained from the first band and was identified by NMR (CCl$_4$): 7.20 (s, 5 H), 5.45 (d, J = 1 Hz, 1 H), 5.14 (d, J = 1 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 3.28 (s, 1 H, exchanged with D$_2$O), 1.90 (q, J = 7 Hz, 2 H), 1.12 (tr, J = 7 Hz, 3 H), and 0.90 ppm (tr, J = 7 Hz, 3 H).

Rearrangement of Ethyl 2-Ethyl-3-methyl-3-phenylglycerate (1e). This compound (385 mg, 1.53 mmol) was treated with 0.73 ml of FSO$_3$H at 0 °C for 3 min and worked up as described above. NMR analysis of the mixture showed 75% 3e, 9% 2e, and 16% 5e. These components were separated by preparative TLC developing the plates four times with 5% ethyl acetate in petroleum ether. Three bands were seen under uv light. The bands were scraped off and extracted with 10% ethyl acetate in chloroform.

The lactone 5e was obtained in 14% yield (40 mg) from the slowest moving band as prisms, mp 79 °C when recrystallized from CCl$_4$–petroleum ether: NMR (CCl$_4$) 7.50 (s, 5 H), 5.02 (2 H, tr, J = 1 Hz), 2.22–2.75 (d, q, J = 1 and 7 Hz, 2 H), and 1.21 ppm (tr, J = 7 Hz, 3 H); mass spectrum m/e 188 (M$^+$), 187, 159, 143, 129, 128, 115 (base peak), 91, 77, and 29.

The second band yielded 203 mg (58%) of 3e identified by comparison of the NMR and mass spectra with those of the known compound.[1]

The fastest moving band yielded 29 mg of an oil which was purified further by preparative TLC (the plate was developed once in 3% ethyl acetate in petroleum ether, twice in 2% ethyl acetate in petroleum ether, once in 2% chloroform in carbon tetrachloride, and once in carbon tetrachloride) to give 11 mg of products which were not identified and 18 mg (5%) of **2e**, identified by NMR and mass spectral comparisons.

Ethyl 2,3-Diphenyl-3-methylglycerate (1f). Perchloric acid (120 ml, 30% by weight in 50% aqueous tetrahydrofuran) was added to a solution of 3.5 g (0.0124 mol) of ethyl 2,3-diphenyl-3-methylglycidate (**1f**) in 2.5 ml of tetrahydrofuran. The reaction mixture was stirred at 60–65 °C (oil bath) for 20 min, poured onto ice, diluted with 300 ml of water, and extracted with three 100-ml portions of ether. Washing and drying of the ether extracts and removal of the solvent yielded an oily residue. Crystallization from ether–petroleum ether yielded 1.73 g (48%) of a 1:1 mixture of *threo-* and *erythro-* **1f**, white needles: mp 101–105 °C; NMR (CCl$_4$) 7.0–7.9 (m, 20 H), 4.27 (q, J = 7 Hz, 2 H), 4.09 (q, J = 7 Hz, 2 H), 3.7 (s, exchanged with D$_2$O, 4 H), 1.67 (s, 3 H) and 1.42 (s, 3 H), 1.26 (tr, J = 7 Hz, 3 H) and 1.12 ppm (tr, J = 7 Hz, 3 H).

Anal. Calcd for C$_{18}$H$_{20}$O$_4$: C, 71.97; H, 6.72. Found: C, 71.91; H, 6.54.

Rearrangement of 1f. A. Treatment of 500 mg of **1f** with 0.8 ml of FSO$_3$H at 0 °C for 3 min and workup as above yielded a mixture containing (NMR analysis) 60% **2f**, 13% **3f**, 12% **6**, 6% **8**, and 9% **9**. This mixture, an oil, was treated by preparative TLC, developed four times in 1:3 benzene–carbon tetrachloride. Three almost overlapping bands seen under a uv light were scraped off and extracted with 10% EtOAc in CHCl$_3$. The first band yielded 49 mg of an oil which was a mixture of **2f** (5%) and **6** (6%), identified by GLC–mass and NMR spectra. Pure **2f** (215 mg) was obtained from the second band to yield a total of 51%. The third band yielded a mixture of **3f** (38 mg, 8%), **8** (19 mg, 4%), and **9** (10 mg, 5%), after further TLC with 0.5 and 0.3% EtOAc in petroleum ether. The identification of **6** was based on the NMR (CCl$_4$) at 4.21 (q, J = 7 Hz, 2 H), 3.77 (s, 2 H), 1.15 (tr, J = 7 Hz, 3 H), in addition to the aromatic protons between 7.00 and 7.50 ppm. The GLC–mass spectrum had signals at m/e 264 (M$^+$), 191 (base peak), and 189. The NMR (CCl$_4$) of **3f** was at 6.95–7.8 (m, 10 H), 4.05 (q, J = 7 Hz, 2 H), 1.78 (s, 3 H), and 0.98 ppm (tr, J = 7 Hz, 3 H), and its mass spectrum at m/e 282 (M$^+$), 239 (base peak), 194, 166, 77, and 43. The NMR (CCl$_4$) of **8** was at 7.00–7.80 (10 H), 4.18 (q, J = 7 Hz, 2 H), 2.05 (s, 3 H), and 1.17 ppm (tr, J = 7 Hz, 3 H), and its mass spectrum showed peaks at m/e 282 (M$^+$), 239 (base peak), 194, 166, 77, and 43.

The treatment of **1f** (50 mg) with concentrated FSO$_3$H (0.08 ml) at −50 °C for 15 s, followed by the usual workup, yielded an oil which contained 90% **2f**, 4% **9**, and 6% unreacted **1f** (NMR analysis). Various experiments were run at −5 °C with reaction times ranging from 4 to 45 s; 2% of starting material was left after 8 s, and none under 15 s. In this last case the product distribution was 91% **2f**, 4% **3f**, and 5% **9**.

Rearrangement of 1f with Dilute FSO$_3$H. A 75-mg sample of **1f** was treated for 3 min at 0 °C with 0.15 ml of acid and 0.05 ml of water. The reaction mixture was poured onto an ice–water–CCl$_4$ mixture and extracted with CCl$_4$. After drying and concentrating 65 mg of oil was obtained, containing 97% **2m** and 3% **9** (NMR analysis).

Ethyl 3,3-Dimethyl-2-phenylglycerate (10). A mixture of 2.5 g (22.36 mmol) of ethyl 3,3-dimethyl-2-phenylglycidate and 150 ml of 30% aqueous perchloric acid was allowed to stand at room temperature for 2 weeks, and extracted with two 150-ml portions of ether. The combined ether extracts were washed with 5% aqueous bicarbonate, dried, and concentrated. The oily residue was purified by column chromatography to yield 0.963 g of **10** (35%), a viscous oil which crystallized on standing: NMR (Me$_2$SO-d_6) 7.2–7.9 (m, 5 H), 5.50 (s, 1 H), 4.42 (s, 1 H), 4.24 (q, J = 7 Hz, 2 H), 1.22 (tr, J = 7 Hz, 3 H), 1.17 (s, 3 H), and 1.10 ppm (s, 3 H). The signals at 5.50 and 4.42 ppm disappeared upon addition of D$_2$O.

Rearrangement of 10. A 440-mg sample was treated with 0.88 ml of FSO$_3$H for 3 min at 0 °C and worked up as above to yield 353 mg (87%) of ethyl 3,3-dimethyl-3-phenylpyruvate (**2m**): NMR (CCl$_4$) 7.18 (s, 5 H), 4.0 (q, J = 7 Hz, 2 H), 1.58 (s, 6 H), and 1.07 ppm (tr, J = 7 Hz, 3 H); mass spectrum m/e 220 (M$^+$), 119 (base peak), 91, and 77. It gave a 2,4-DNP derivative in 63% yield after recrystallization: mp 153.5–154.5 °C; NMR (CDCl$_3$) 13.9 (br s, 1 H), 9.15 (d, J = 2 Hz, 1 H), 8.52 and 8.35 (d of d, J = 2, 9 Hz, 1 H), 8.16 (d, J = 9 Hz, 1 H), 7.28 (s, 5 H), 4.12 (q, J = 7 Hz, 2 H), 1.72 (s, 6 H), and 0.95 ppm (tr, J = 7 Hz).

Anal. Calcd for C$_{19}$H$_{20}$N$_4$O$_6$: C, 56.99; H, 5.04; N, 13.99. Found: C, 57.26; H, 5.01; N, 14.22.

Ethyl 2,3-Diphenylglycerate (12). A solution of 2.000 g of ethyl 3,3-diphenylglycidate in 75 ml of 30% perchloric acid in 60% aqueous tetrahydrofuran was heated with stirring in an oil bath at 65 °C for 25 min, diluted with 300 ml of water, and extracted with two 100-ml portions of ether. The combined ether extracts were washed with

50-ml portions of 5% aqueous bicarbonate and water, dried, and concentrated to yield an oil which crystallized on standing. Recrystallization from aqueous ethanol yielded 900 mg (38%) of **12** as white crystals: mp 131–132 °C; NMR (CDCl$_3$) 7.05–7.78 (m, 10 H), 5.08 (s, 1 H), 3.98 (q, J = 7 Hz, 2 H), 3.35–3.40 (br, 2 H, disappeared in D$_2$O), and 0.92 ppm (tr, J = 7 Hz, 3 H).

Rearrangement of 12. A 200-mg sample of **12** was treated with 0.34 ml of FSO$_3$H at 0 °C for 3 min. After the usual workup the crude product was purified by preparative TLC, developing the plates twice with 5% ethyl acetate in petroleum ether. Two bands were seen under uv light and yielded 14 mg (12%) of benzophenone and 100 mg (53%) of ethyl 3,3-diphenylpyruvate: NMR (CDCl$_3$) 7.27 (s, 10 H), 5.91 (s, 1 H), 4.11 (q, J = 7 Hz, 2 H), and 1.11 ppm (tr, J = 7 Hz, 3 H) (an additional small singlet at 10.32 and a triplet at 0.7 ppm revealed the presence of the enol tautomer); mass spectrum m/e 268 (M$^+$), 195, 167 (base peak), and 77. These spectra were superimposable onto those of the major product of the boron trifluoride rearrangement of ethyl 2,3-diphenylglycidate.[1]

Ethyl 2-Methyl-3-phenylglycerate (13). A solution of 4 g of ethyl (*E*)-2-methylcinnamate and 4.65 g of *m*-chloroperoxybenzoic acid in 100 ml of chloroform was refluxed for 25 h and washed with 10% aqueous sodium sulfite and with 5% aqueous bicarbonate. The organic layer was dried and concentrated to yield 4.1 g (95%) of ethyl (*E*)-2-methyl-3-phenylglycidate, an oil: NMR (CCl$_4$) 7.3 (s, 5 H), 4.3 (s, 1 H), 4.2 (q, J = 7 Hz, 2 H), 1.27 (tr, J = 7 Hz, 3 H), and 1.25 ppm (s, 3 H).

A mixture of 2 g of this product and 100 ml of 30% aqueous sulfuric acid was stirred for 24 h at room temperature, and extracted with two 100-ml portions of ether. The combined ether extracts were washed with 5% sodium bicarbonate, dried, and concentrated to yield a viscous oil. After purification by column chromatography, there was obtained 1.5 g (69%) of a mixture of *threo-* and *erythro-* **13**, an oil: NMR (Me$_2$SO-d_6) 7.1–7.62 (m, 5 H), 4.6–5.6 (broad, 2 H, disappeared upon the addition of deuterium oxide), 4.82 (s, 1 H), 4.78 (s, 1 H), 4.18 and 4.11 (each a q, J = 7 Hz, 2 H), 1.24 and 1.18 (each a tr, J = 7 Hz, 3 H), 1.18 and 1.05 ppm (each a s, 3 H).

Rearrangement of 13. A 500-mg sample of **13** was treated with fluorosulfonic acid at 0 °C for 10 min. After workup the product (435 mg) had the NMR spectrum (CCl$_4$) of ethyl 2-phenylacetoacetate as a mixture of the ketonic (76%) and enolic (24%) forms: NMR (CCl$_4$) 14.17 (br s, 1 H), 7.08–7.50 (m, 5 H), 4.13 (q, J = 7 Hz, 2 H), 1.80 (s, 3 H), and 1.13 ppm (tr, J = 7 Hz, 3 H) for the enol; 7.08–7.50 (m, 5 H), 4.61 (s, 1 H), 4.15 (q, J = 7 Hz, 2 H), 2.07 (s, 3 H), and 1.22 ppm (tr, J = 7 Hz, 3 H) for the keto tautomer. Preparative TLC yielded 280 mg of this product and 101 mg of material with broad NMR signals, which appeared to be polymeric in nature.

Ethyl 2,3-Diphenylglycerate (14). A solution of 2 g of ethyl (*E*)-2,3-diphenylglycidate in 75 ml of 30% by weight perchloric acid in 65% aqueous tetrahydrofuran was heated in an oil bath with stirring at 65–70 °C for 15 min. The reaction mixture was poured onto 50 g of ice, diluted with 200 ml of water, and extracted with three 50-ml portions of ether. Washing the combined ether extracts with 5% aqueous bicarbonate followed by drying and evaporation of the solvent yielded 1.4 g of a semisolid residue. Crystallization from carbon tetrachloride yielded 330 mg (15.5%) of **14** as white needles, mp 135–137 °C. After recrystallization from benzene, the mp was 139–139.5 °C; NMR (CDCl$_3$) 7.17–7.77 (m, 10 H), 5.5 (br s, 1 H), 4.44 (q, J = 7 Hz, 2 H), 4.12 and 3.0 (each a broad s which disappeared in the presence of D$_2$O, 2 H), and 1.37 ppm (tr, J = 7 Hz, 3 H). Only one of the two possible diastereoisomers was obtained, judging from the NMR spectrum. Anal. Calcd for C$_{17}$H$_{18}$O$_4$: C, 71.31; H, 6.34; Found: C, 71.35; H, 6.33.

Rearrangement of 14. A 192-mg sample of **14** was treated with FSO$_3$H (0.32 ml) at 0 °C for 3 min and worked up as described above. NMR showed the crude product to consist of 60% keto and 40% enol tautomers of ethyl 3,3-diphenylpyruvate. However, purification by preparative TLC on silica gel (5% ethyl acetate in petroleum ether) yielded 7.5 mg (6%) of benzophenone in addition to 153 mg (85%) of ethyl 3,3-diphenylpyruvate: NMR (CDCl$_3$) 7.27 (s, 10 H), 5.91 (s, 1 H), 4.11 (q, J = 7 Hz, 2 H), and 1.1 ppm (tr, J = 7 Hz, 3 H) for the keto tautomer; 8.5 (s, enol H), 7.27 (s, 10 H), 3.98 (q, J = 7 Hz, 2 H), and 0.72 ppm (tr, J = 7 Hz, 3 H) for the enol form. The keto:enol ratio was 90:10. This NMR was superimposable onto that of the major product of the boron trifluoride rearrangement of ethyl 2,3-diphenylglycidate. The mass spectrum had peaks at m/e 268 (M$^+$), 195, 167 (base peak), and 77.

Ethyl 2-Hydroxy-3-phenyl-3-azidobutyrate (15). A mixture of 35 g of sodium azide, 50 ml of water, and 100 ml of ether was treated with 30 ml of concentrated sulfuric acid, maintaining the temperature below 10 °C. The ether layer was dried over CaCl$_2$ and distilled. In

65 ml of this HN_3 solution, 6 g of Ih and 60 mg of *p*-toluenesulfonic acid were allowed to stand at room temperature for 3 days. After concentration under vacuum, 50 ml of ether was added, and the solution was washed with 25 ml of water, 25 ml of saturated aqueous $NaHCO_3$, and 25 ml of aqueous NaCl and dried.

The crude product, 15, was used in further reactions. A sample distilled bulb-to-bulb at 75 °C (0.07 Torr). This material was contaminated with a trace of 4h (seen by NMR). Ir showed the characteristic signal at 2150 cm^{-1}. NMR (CCl_4) 7.10–7.45 (m, 5 H), 4.26 and 4.20 (each a s, 1 H), 4.02 (q, J = 7 Hz, 2 H), 3.65 (1 H, disappeared in the presence of D_2O), 1.80 and 1.75 (each a s, 3 H), 1.08 and 0.90 ppm (each a tr, 3 H). The ratio of diastereomers was 1:3.9.

Reaction of 15 with Nitrosonium Tetrafluoroborate. A solution of 665 mg of 15 and 1.25 g of $NO^+BF_4^-$ in 20 ml of benzene was refluxed for 6 h, concentrated under vacuum, treated with water, and extracted with ether.[10] After drying and concentration, NMR analysis showed 18% 3h, 10% 4h, and a trace of 2h. No starting material remained.

No reaction was observed at room temperature for up to 60 h when 15 was treated with $NO^+BF_4^-$ in benzene, acetonitrile, or dimethoxyethane.

Ethyl 2-Hydroxy-3-chloro-3-phenylbutyrate (17). A 6.39-g sample of Ih cooled at −190 °C was treated with 75 ml of HCl-saturated ether, allowed to warm up to room temperature with stirring, and kept for 18 h. After concentration under vacuum, 50 ml of ether were added and the solution was washed with 25 ml of saturated aqueous NaCl, 25 ml of saturated $NaHCO_3$, and 25 ml of saturated NaCl, dried over $MgSO_4$, and concentrated to yield 6.50 g of 17, mp 53–59 °C, a mixture of diastereomers (1:1). Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 59.42; H, 6.22; Cl, 14.60. Found: C, 59.44; H, 6.22; Cl, 14.58.

NMR (CCl_4) 7.2–7.6 (m, 5 H), 4.50 and 4.34 (each a d, J = 8 Hz, 1 H), 4.12 and 3.96 (each a q, J = 7 Hz, 2 H), 3.15 and 2.99 (each a d, J = 8 Hz, 1 H), and 1.15 and 0.95 ppm (each a tr, J = 7 Hz, 3 H).

Reaction of Ethyl 2-Methyl-3-phenyl-2-hydroxy-3-butenoate (4m) with Fluorosulfonic Acid. An 82-mg sample of 4m was treated with 0.178 ml of FSO_3H at 0 °C for 3 min and poured onto a mixture of ice, water, and 20 ml of CCl_4, and the aqueous layer was extracted with 20 ml of ether. After washing each of the organic extracts with 20 ml of 5% aqueous sodium bicarbonate, they were combined, dried, and concentrated to yield 60 mg of a semisolid product which was analyzed by NMR to contain 70% 3m, 30% 5m, and a trace of 2m.

Reaction of Ethyl 3-Phenyl-2-hydroxy-3-butenoate (4e) with Fluorosulfonic Acid. At 0 °C for 3 min, 90 mg (0.384 mmol) of 4e was treated with 0.18 ml of FSO_3H. The mixture was poured onto a mixture of ice, water, and 20 ml of CCl_4. The aqueous phase was extracted again with 10 ml of chloroform and the organic layers were combined, washed with two 15-ml portions of 5% aqueous $NaHCO_3$, dried, and concentrated to yield 50 mg of a semisolid residue, which contained 45.5% 3e, 7.5% 2e, and 47% 5e (NMR).

Reaction of Ethyl 2,3-Diphenyl-2-hydroxy-3-butenoate (4f) with Boron Trifluoride. Boron trifluoride was bubbled through a solution of 40 mg of 4f in 2 ml of carbon tetrachloride for 10 min at 28 °C. After quenching the reaction with aqueous sodium chloride, the mixture was extracted with 10 ml of carbon tetrachloride and with 10 ml of chloroform. The combined organic phases were washed with 5% aqueous bicarbonate, dried, and concentrated. The NMR spectrum of the product (90% yield) was superimposable onto that of 2-phenyl-3-carbethoxyindene (6).

Reaction of Halohydrins with Silver Salts. A mixture of 200 mg of the halohydrin and ca. 1.5 equiv of silver salt in 20 ml of solvent was stirred in the dark. The spent silver salt was filtered over Celite and the filtrate was concentrated and analyzed by NMR (Tables IV and V).

Ethyl 2-Hydroxy-2-methyl-3-chloro-3-phenylpropionate (18). A solution of 500 mg of ethyl (*E*)-2-methyl-3-phenylglycidate in 20 ml of hydrogen chloride saturated ether was allowed to stand at room temperature for 1 h, washed thrice with water, dried, and concentrated to yield 565 mg of 18. The major isomer (ca. 90%) had NMR (CCl_4) at 7.10–7.60 (5 H), 5.00 (s, 1 H), 4.05 (q, J = 7 Hz, 2 H), 3.50 (br, 1 H), 1.51 (s, 3 H), and 1.16 ppm (tr, J = 7 Hz, 3 H). The minor isomer had its corresponding signals at 7.10–7.60, 5.20, 4.20, 3.50, 1.15, and 1.16 ppm, respectively.

Ethyl 2-Hydroxy-2-methyl-3-bromo-3-phenylpropionate (20). A solution of 200 mg of ethyl 2-methyl-3-phenylglycidate in 7 ml of hydrogen bromide saturated ether was allowed to stand at room temperature for 44 h. After dilution with 15 ml of ether, it was washed thrice with water, dried, and concentrated to yield 787 mg of an oil, a mixture of the two diastereoisomers of 20: NMR (CCl_4) 7.00–7.50 (m, 5 H), 5.05 (s, 1 H), 3.94 (q, J = 7 Hz, 2 H), 3.58 (br, 1 H), 1.53 (s,

1 H), and 1.07 (tr, J = 7 Hz, 3 H) for the major isomer (80%), and 7.00–7.50 (m, 5 H), 5.30 (s, 1 H), 4.07 (q, J = 7 Hz, 2 H), 3.58 (br, 1 H), 1.72 (s, 3 H), and 1.24 ppm (tr, J = 7 Hz, 3 H) for the minor isomer (20%).

Ethyl 2-Hydroxy-2-methyl-3-chloro-3-phenylbutyrate (19). A solution of 250 mg of Im in 10 ml of HCl-saturated ether was allowed to stand for 26 h at room temperature, washed several times with water, dried, and concentrated to give a mixture of 4m (16%) and 19 (84%) as a mixture of diasteisomers: NMR (CCl_4) 7.15–7.65 (m, 5 H), 4.02 and 4.12 (each a q, J = 7 Hz, 2 H), 3.56 (br, 1 H), 2.02 (s, 3 H), 1.38 (s, 3 H) and 1.16 ppm (q, J = 7 Hz, 3 H).

Ethyl 2-Hydroxy-2-methyl-3-bromo-3-phenylbutyrate (21). A solution of 250 mg of Im (mixture of *E* and *Z*) in 10 ml of HBr-saturated ether was refluxed for 2 h, washed with water, dried, and concentrated to yield a mixture of 21% 4m and 79% 21 (a mixture of diastereoisomers). Similar results were obtained at room temperature for 1 h. The NMR of 21 (CCl_4) had signals at 7.1–7.8 (m, 5 H), 4.09 and 3.95 (each a q, J = 7 Hz, 2 H), 3.78 (br, 1 H), 2.29 and 2.30 (each a s, 3 H), 1.53 and 1.48 (each a s, 3 H), and 1.35 and 1.10 ppm (each a tr, J = 7 Hz, 3 H).

Acid Treatment of *tert*-Butyl 3-Methyl-3-phenylglycidate (27). A 200-mg sample of 27[16] (mixture of diastereoisomers) in 20 ml of benzene was treated with BF_3 for 30 s at room temperature. The solution was washed with aqueous $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$. The NMR (CCl_4) showed a mixture of 28 at 9.70 (d, J = 1.5 Hz, 1 H), 6.9–7.3 (5 H), 3.45 (q, d, J = 7 and 1.5 Hz, 1 H), and 1.35 ppm (d, J = 7 Hz, 3 H), and *tert*-butylbenzene at 6.9–7.3 (4 H) and 1.26 ppm (s, 12 H). This was proved by GLC against authentic samples. Using an internal standard of *p*-nitrotoluene, the two components were shown to have been formed in ca. 25% yield each. The remainder probably had polymerized, as in the reaction of the ethyl ester analogue Ih.[1]

***tert*-Butyl 3-Chloro-3-phenyl-2-hydroxybutyrate (24).** A 300-mg sample of 27 was treated at room temperature for 30 min with 10 ml of anhydrous ether saturated with HCl. After concentration under vacuum, addition of CCl_4, and concentration again, 345 mg of residue was obtained, which was a mixture of *threo*- and *erythro*-24. Pure samples of both diastereoisomers were obtained after fractional crystallization in several solvents. The isomer of mp 79–80 °C had NMR (CCl_4) at 7.67–7.10 (m, 5 H), 4.30 (d, J = 7 Hz, 1 H), 3.03 (d, J = 7 Hz, 1 H, exchanged in D_2O), 2.00 (s, 3 H), and 1.30 ppm (s, 9 H), and the isomer of mp 36–38 °C had NMR (CCl_4) at 7.33–7.17 (m, 5 H), 4.30 (d, J = 7 Hz, 1 H), 3.25 (d, J = 7 Hz, 1 H, exchanged in D_2O), 1.97 (s, 3 H), and 1.15 ppm (s, 9 H).

Reaction of 24 with Silver Carbonate. A mixture of 130 mg of 24, 207 mg of silver carbonate, and 10 ml of benzene was refluxed for 23 h, cooled, and filtered through Celite. The filtrate was concentrated under vacuum and the residue analyzed by NMR in CCl_4. From the isomer of mp 79–80 °C, the mixture contained ca. 8% of 26, 11% of 9, 51% of 25, 25% of *E*-27 and 5% of *Z*-27. From the isomer of mp 36–38 °C the mixture contained 4% of 26, 7% of 9, 33% of 25, 56% of *E*-27, and a trace of *Z*-27. The NMR spectra of the individual compounds in CCl_4 follow. **26:** 7.15–7.50 (m, 5 H), 5.40 (m, 1 H), 5.35 (m, 1 H), 4.80 (br, 1 H), 3.10 (br, OH), and 1.22 ppm (s, 9 H). **25:** 9.78 (s, 1 H), 7.15–7.55 (s, 5 H), 1.57 (s, 3 H), and 1.45 ppm (s, 9 H). *E*-27:[19] 7.20–7.55 (m, 5 H), 3.18 (s, 1 H), 1.72 (s, 3 H), and 1.50 ppm (s, 9 H). *Z*-27:[19] 7.20–7.50 (m, 5 H), 3.38 (s, 1 H), 1.68 (s, 3 H), and 1.05 ppm (s, 9 H). The phenylhydrazone of 25 had mp 151 °C; mass spectrum *m/e* 324, 267, 223 (base peak), 130, 92, and 77; NMR (Me_2CO-d_6) 7.65 (s, 1 H), 7.10–7.43 (m, 9 H), 2.75 (s, 1 H, exchanged with D_2O), 1.73 (s, 3 H), and 1.43 ppm (s, 9 H).

21309-20-6; *erythro*- 28, 93-53-8; *E*-Ie, 19464-94-9; If, 59069-98-6; Ih,
77-83-8; *E*-Im, 59069-99-7; *Z*-Im, 59070-00-7; Im-*d₃*, 59070-01-8; ethyl
3,3-dimethyl-2-phenylglycidate, 59070-02-9; ethyl 3,3-diphenylgly-
cidate 5449-40-1; ethyl 3,3-diphenylpyruvate 6362-64-7; ethyl (*E*)-
2-methylcinnamate, 7042-33-3; ethyl (*E*)-2 methyl-3-phenylglycidate,
7141-24-4; ethyl 2-phenylacetoacetate, 5413-05-8; ethyl 2-phenyl-
acetoacetate enol, 59070-03-0; ethyl (*E*)-2,3-diphenylglycidate,
7042-27-5; ethyl 3,3-diphenylpyruvate enol, 59070-04-1.

References and Notes

(1) Part 1: J. Kagan, D. A. Agdeppa, Jr., S. P. Singh, D. A. Mayers, C. Boyajian, and C. Poorker, *J. Am. Chem. Soc.*, in press.
(2) Preliminary communication: J. Kagan and D. A. Agdeppa, Jr., *Helv. Chim. Acta,* **55**, 2252 (1972).
(3) C. J. Collins, *Q. Rev., Chem. Soc.,* **14**, 357 (1960).
(4) S. P. Singh and J. Kagan, *J. Am. Chem. Soc.,* **91**, 6198 (1969).
(5) C. U. Pittman, Jr., and W. G. Miller, *J. Am. Chem. Soc.,* **95**, 2947 (1973).
(6) D. Ivanoff, N. Marecoff, and B. Amidjine, *Bull. Soc. Chim. Fr.,* 1214 (1963).
(7) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, New York, N.Y., 1972, p 636.
(8) J. Kagan and D. A. Agdeppa, Jr., *Helv. Chim. Acta,* **55**, 2255 (1972).

(9) D. A. Mayers and J. Kagan, *J. Org. Chem.,* **39**, 3147 (1974).
(10) M. P. Doyle and W. Wierenga, *J. Am. Chem. Soc.,* **94**, 3896, 3901 (1972).
(11) A similar observation was made by S. P. McManus, C. A. Larson, and R. A. Hearn, *Synth. Commun.,* **3**, 177 (1973).
(12) The rearrangement of halohydrins in the presence of silver carbonate was recently described by M. Fetizon, M. Golfier, M. T. Montaufier, and J. Rens, *Tetrahedron,* **31**, 987 (1975), and M. Fetizon, J. M. Louis, and M. Golfier, *Tetrahedron Lett.,* 1931 (1973). The formation of allylic alcohols was not described by these authors.
(13) For one example, see G. Berti, B. Macchia, F. Macchia, and L. Monti, *J. Chem. Soc. C,* 3371 (1971).
(14) R. C. Bach, J. Domagala, and J. Wemple, *J. Am. Chem. Soc.,* in press. We are grateful to Professor Wemple for informing us of this work prior to its publication.
(15) P. Beak, R. J. Trancik, and D. A. Simpson, *J. Am. Chem. Soc.,* **91**, 5073 (1969); D. N. Kevill, W. A. Reis, and J. B. Kevill, *Tetrahedron Lett.,* 957 (1972); W. E. Dupy, H. R. Hudson, and D. A. Karom, *ibid.,* 3193 (1972); D. N. Kevill, "The Chemistry of Acyl Halides", S. Patai, Ed., Wiley-Interscience, New York, N.Y., 1972, p 381.
(16) E. P. Blanchard, Jr., and G. H. Buchi, *J. Am. Chem. Soc.,* **85**, 955 (1963).
(17) H. H. House and J. W. Blaker, *J. Am. Chem. Soc.,* **80**, 6389 (1958).
(18) P. S. Steyn, W. J. Conradie, C. F. Garbers, and M. J. de Vries, *J. Chem. Soc.,* 3075 (1965).
(19) V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.,* **31**, 2509 (1966).

Valence Photoisomerization of 1-Ethoxycarbonyl-1*H*-azepine and Its Thermal Reversion. Quantitative Aspects Including Energy Surface Relationships

Guilford Jones, II,* and Laura J. Turbini

Department of Chemistry, Boston University, Boston, Massachusetts 02215

Photolysis of 1-ethoxycarbonyl-1*H*-azepine (**3**) at 325–385 nm gives quantitatively the valence isomer, 2-ethoxy-carbonyl-2-azabicyclo[3.2.0]hepta-3,6-diene (**4**). The quantum yield in benzene is 0.013, virtually unchanged in other solvents including *n*-propyl bromide and with the addition of triplet quenchers. Sensitization with fluo-renone, benzophenone, or valerophenone does not lead to valence isomerization. Azepine **3** acts as a quencher of the photoelimination of valerophenone ($k_q = 7.0 \times 10^9$ M^{-1} s^{-1}) and the phosphorescence of biacetyl ($k_q = 5.3 \times 10^8$ M^{-1} s^{-1}). Laser photolysis at 457.9 nm affects isomerization **3** → **4** with a quantum efficiency of 0.013. On the basis of absorption, sensitization, and quenching data for **3**, energies of low-lying excited states are estimated ($E_{S_1} = 60 \pm 1$ kcal/mol and $E_{T_1} = 55 \pm 1$ kcal/mol). Pyrolysis of **4** gives **3** in a clean, exothermic, first-order reaction at 113–143 °C in diglyme-*d₁₄* ($E_a = 28.7$ kcal/mol, $A = 10^{12.3}$ s^{-1}) or in hexadecane ($k = 4.60 \times 10^{-4}$ s^{-1}, 127.5 °C). A mechanism for **3** → **4** and related photochemical isomerizations is suggested, with emphasis on the proximity of ground and excited state potential surfaces at diradical or biradicaloid geometries. For cyclic triene systems, charge separation in diradical species appears to be important in facilitating photochemical ring closure and thermal back reaction.

The photochemistry of 1,3,5-cycloheptatriene (**1a**), its heterocyclic analogues, 1*H*-azepine (**1b**) and oxepin (**1c**), and their derivatives has received considerable attention.[1] A re-action of general importance is valence photoisomerization to bicyclic dienes **2**; in many cases the process is thermally reversible. We became interested in the photoisomerization of 1-ethoxycarbonyl-1*H*-azepine (**3**), since the reported[1d] behavior of this system showed promise for the storage and conversion of radiant energy (in principle, a portion of solar

energy). In particular, photolysis of **3**, which absorbs light in the visible, gives **4** cleanly and photochromatically (with bleaching). Photoisomer **4** is kinetically stable but reverts to **3** in a thermal reaction which is uncatalyzed and apparently exothermic.[1d] We wish to provide quantitative details con-cerning this isomerization of a sort not generally available for the cyclic trienes. The data allow characterization of inter-converting states and suggestions for pathways for photo-chemical and thermal reaction.
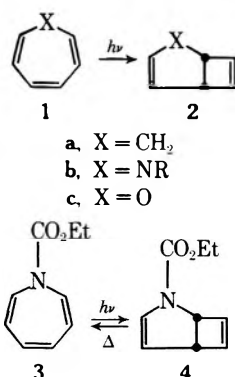
Results

The ultraviolet spectrum of **3**[2] displays a weak transition at 330 nm. This absorption, which is blue shifted in polar solvent and probably n,π* in character,[3] tails into the visible with onset at about 480 nm and gives **3** its orange color. Lu-minescence was not observed for **3**, either in benzene at room temperature or in EPA glass at 77 K. Irradiation of **3** at 325–385 nm gave **4** without the appearance of side products (>97% yield by GLC and NMR). Quantum yields for isom-erization as a function of solvent and the presence of additives are shown in Table I. Notably, the photolysis was not appre-ciably altered by (1) moderate concentrations of potential

1   2

a, X = CH₂
b, X = NR
c, X = O

3   4

Table I. Quantum Yields for Photoisomerization 3 → 4

[3]	Solvent	Additives (M)	ϕ^a
0.08	Cyclohexane		0.010
0.09	Diglyme[b]		0.013
0.10	Benzene		0.013
0.03	n-Propyl bromide		0.013
0.08	Benzene	COT[c] (0.11)	0.014
0.10	Benzene	Diene[d] (0.02–0.08)	0.012
0.10	Benzene	Fluorenone[e] (0.9)	<0.003[g]
0.09	Benzene	Benzophenone[f] (1.0)	<0.003[g]
0.007	Benzene	Valerophenone[f] (0.4)	<0.003[g]
0.03	Benzene	DMAC[h] (0.08)	0.010[i]

[a] Rayonet reaction (355 ± 30 nm), 30 ± 1 °C, valerophenone actinometer (ref 4), estimated error, ±15%. [b] Bis(2-methoxyethyl) ether. [c] Cyclooctatetraene. [d] 2,4-Dimethyl-2,5-hexadiene. [e] Sensitizer absorbed >88% of light. [f] Sensitizer absorbed >75% of light. [g] Upper limit corrected for azepine absorption. [h] Dimethyl acetylenedicarboxylate. [i] Some light absorption by DMAC.

Table II. Kinetics of Thermally Induced Isomerization 4 → 3

Solvent	Temp, °C	k, 10^4 s^{-1}	
Diglyme-d_{14}	112.5	1.45 ± 0.06	
	122.5	3.44 ± 0.15	
	127.5	5.34 ± 0.05	E_a = 28.7 kcal/mol
	133.0	8.21 ± 0.58	A = $10^{12.3}$ s^{-1}
	142.5	19.30 ± 0.11	
Hexadecane	127.5	4.60 ± 0.44	

quenchers of excited triplets, 2,5-dimethyl-2,4-hexadiene and cyclooctatetraene, (2) a heavy atom[5] reagent, n-propyl bromide, as solvent, or (3) the addition of dimethyl acetylenedicarboxylate (DMAC), a good dipolarophile.[6]

In experiments where photosensitizers, benzophenone (E_T = 69 kcal/mol), fluorenone (E_T = 53 kcal/mol), and valerophenone, absorbed most of the light, photoisomerization of 3 was negligible. That the excited triplet of 3 could in fact be produced was inferred from experiments in which the photoelimination of valerophenone to acetophenone[7] was quenched. Measurement of ϕ_0/ϕ at concentrations of 3 between 4.5 and 8.2 × 10^{-3} M gave $k_q\tau$ = 56 ± 8 M^{-1}, from which the quenching constant, k_q = 7.0 × 10^9 M^{-1} s^{-1}, could be calculated assuming τ (valerophenone) = 8.0 × 10^{-9} M^{-1} s.[8] For comparison, the estimated rate constant for diffusion controlled quenching, according to the modified Debye equation,[9] in benzene at 30 °C is 1.8 × 10^{10} M^{-1} s^{-1}, and the "upper limit" quenching constant for dienes in benzene (25 °C) has been determined in several studies to be 5 × 10^9 M^{-1} s^{-1}.[9] Quenching of the phosphorescence of biacetyl with 1.0–4.0 × 10^{-5} M azepine was observed at room temperature. From the plot of ϕ_0/ϕ vs. [3], $k_q\tau$ = 2.3 ± 0.5 × 10^5 M^{-1} was obtained, from which k_q = 5.2 × 10^8 M^{-1} s^{-1} could be calculated assuming τ (biacetyl) = 4.6 × 10^{-4} s.[10]

Sealed ampule pyrolysis of 4 proceeded nearly quantitatively in solvents at temperatures above 100 °C. Appearance of 3 (NMR analysis) was smoothly first order over 2 half-lives. Kinetics data are shown in Table II along with activation parameters for pyrolysis in diglyme-d_{14}. The results are in good agreement with the approximate rate data for pyrolysis of neat 4 reported by Paquette and Barrett[1d] from which k (4 → 3, 126.5 °C) = 6.6 × 10^{-4} s^{-1} may be calculated.

The photoisomerization 3 → 4 could be carried out in direct sunlight and with use of an argon ion laser. The quantum yield for isomerization at 457.9 nm in benzene was 0.013. The valence isomers could be "cycled". A sealed Pyrex tube containing 3 and 4 in diglyme-d_{14} was alternately irradiated (sunlight or near uv) and pyrolyzed (generally 130 °C). The isomerizations were followed to high conversion by NMR (benzene internal standard). Although the photochemical step was extraordinarily clean, the back reaction built up a small amount of by-product (dimer[11] or polymer), such that after ten passes material balance was about 50%.

Discussion

The failure of dienes, 2,4-dimethyl-2,5-hexadiene (E_T < 58 kcal/mol[12]), a well-known efficient quencher of reasonably

long-lived excited triplets,[9] and COT, for which a very low triplet energy has been calculated,[13] to alter the photolysis of 3 implicates a reactive singlet state for valence isomerization. The sensitization data, in which common energy transfer agents representing a range of triplet excitation energies (E_T = 53–73 kcal/mol[14]) are ineffective, confirm that a singlet state (probably of n,π* character) is responsible for formation of 4. The quenching of valerophenone photoelimination at a rate near the diffusion limit further establishes that a triplet state of 3 is accessible but unreactive. It is not certain that this quenching of valerophenone photoelimination by 3 is of the classical energy transfer sort in view of the effective charge transfer mechanism suggested for quenching by tertiary amines.[15] However, 3 quenches valerophenone triplet at a rate more than twice that of the amines (k_q = 3 × 10^9 M^{-1} s^{-1}), yet because of the substitution pattern, 3 should be a less effective electron (charge) donor. Accepting the energy transfer mechanism for photoelimination quenching provides one reference point for the triplet energy of 3 (E_T < 72 kcal/mol).

The phosphorescence of biacetyl is quenched by 3 at a rate short of diffusion control. This quenching might also have energy or charge[10] transfer components, but it is clear that energy transfer from biacetyl to a triplet level of 3 *well below* that of biacetyl (E_T = 55–56 kcal/mol[16]) is not important.[17] The n,π* absorption for 3 (λ_{max} 330 nm, tailing past 450 nm) and the success of laser photolysis at 458 nm (61 kcal/einstein), a wavelength which must be very close to the 0–0 transition, narrow the acceptable range for the energy of S_1. Values of E_{S_1} = 60 ± 1 and E_{T_1} = 55 ± 1 kcal/mol would be consistent with the data and allow for a reasonable n,π* singlet–triplet separation.

Interestingly, the existence of a very low-lying triplet (e.g., E_T < 50 kcal/mol), analogous to "aromatic" species (π,π* triplets) predicted for cyclic polyenes having formally 4N cyclic electronic arrays which enjoy resonance stabilization,[13] or analogous to triplet 1a (E_T = 47 kcal/mol[1c]) appears unlikely for 3. On the other hand it is probable that the π,π* triplet level lies slightly below 60 kcal/mol if 3 be dienelike.[12] The excited state model then for the heterocyclic triene is one of closely spaced singlet n,π* and triplet n,π* and π,π* states in the region of 55–60 kcal/mol.[18]

Data for 3 complete an excited state structure–reactivity pattern (Table III) for several cyclic polyene systems which have been the object of comparison in numerous studies.[20] Excited singlets in the series are uniformly reactive whereas triplets do not bring about valence isomerization.[24] The latter is noteworthy in view of the established reactivity under sensitization conditions of diverse seven- and eight-membered conjugated cyclic dienes and trienes such as 1,3-cycloocta-diene,[25] cyclohepta-3,5-dien-1-one,[26] a derivative of 2-aza-1,3-cycloheptadiene,[27] and including cycloocta-2,4,6-trien-1-one[28] (where the reactive state is most likely a triplet for direct irradiation). A mechanism considered for valence isomerization in each case involves cis–trans isomerization via the excited triplet to a strained ring system (with formally one trans double bond), which ring closes to bicyclic product in a symmetry unrestricted thermal reaction. Such a course for

Table III. Photolysis and Pyrolysis Characteristics for Selected Reversible Valence Isomerizations [a]

Cyclic polyene $\xrightarrow{h\nu}$ Bicyclic $\xleftarrow{\Delta}$ diene		Direct irradiation	Sensitized irradiation	Ref	E_a, kcal/mol[d]	Ref
1a	2a	X	O	1a,c	39.5	21
1c	2c	X	O	1h		
3	4	X	O	This work	28.7	This work
COT[b]	BOT[c]	X	O	22	18.7	23

[a] X = isomerization of polyene observed; O = isomerization of polyene unobserved. [b] 1,3,5,7-Cyclooctatetraene. [c] Bicyclo[4.2.0]-octa-2,4,7-triene. [d] Activation parameters for thermal back reaction. Log A values for 2a, 4, and BOT are 14, 12.3, and 12.0, respectively.

trienes 1 is shown below in which 5 is one of several possible geometric photoisomers of 1. In two of the previous studies,[25,28] the intermediate analogous to 5 has been either isolated or trapped. The failure of triplets of 1 to give bicyclic product almost certainly reflects the relatively more severe restrictions due to bond angle strain in 5 compared to the other twisted cyclopolyenes (molecular models show this impressively). Triplet COT may indeed reach a configuration analogous to 5, but the overall result is formation of semibullvalene.[22c]
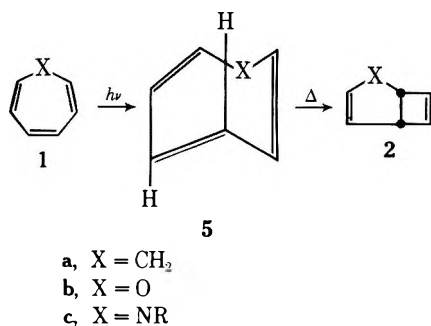
Excited singlets of 1 may give intermediates 5 prior to valence isomerization. Indeed there is direct evidence that 1,3,5-cyclooctatriene (6),[29] 1,2,4,7-tetraphenylcyclooctatetraene (7),[30] and 1,3-cyclooctadiene (8)[31] give geometric isomers on direct irradiation. The isomers of 6 and 8 may lead to valence isomeric bicyclic polyenes, while the isomer of 7 may be responsible for formation of diphenylacetylene and p-terphenyl (via a bicyclic triene).[30b] However, Nebe and Fonken have shown that 8 gives 9 under conditions where geometric isomer 10 is stable. In addition, thermal reversion to 7 from its geometric photoisomer is "quantitative",[30a] meaning that valence photoisomerization of 7 by way of the geometric isomer is extremely inefficient if not absent.

The point here is that in the singlet manifold for the cyclic dienes and trienes, there exists a path for ring closure to a bicyclic valence isomer which does not require formation of a *geometric* isomer. For the cyclic polyene triplets, valence isomerization proceeds through prior cis–trans isomerization and thermal ring closure, but only where the geometric isomer is accessible (not the case for trienes 1 on geometric grounds) and reactive enough to give bicyclic product under photolysis
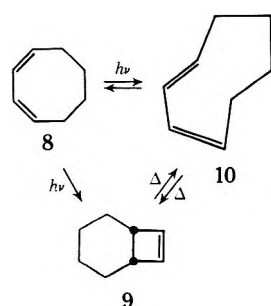
conditions (marginally the case for 8[31]).[32] After examination of the thermal surface for 4 → 3, we will return to the mechanism of singlet valence isomerization of 3.

Circumstantial arguments may be brought against two mechanisms for the thermal isomerization 4 → 3. The first mechanism involves formation of 5 via conrotatory ring opening of 4, following the suggestion of Baldwin and Kaplan[33] in their study of ring openings of bicyclic dienes. Such a mechanism is apparent in the thermal degenerate rearrangement which accompanies valence isomerization of deuterium labeled bicyclo[4.2.0]octa-2,7-diene[34] and in the pyrolytic ring opening of 9.[35] The evidence for cis–trans isomers appears again for the more flexible ring systems, in fact those cases where the strained geometric isomers are available photochemically from the all-cis cyclic polyenes.[25,29,31] The relatively low barriers observed for ring opening of the seven-membered bicyclic dienes (see activation parameters, Table III, especially 4 → 3) do not support a general mechanism involving a cis,trans,cis intermediate. That 5 would be prohibitively strained is revealed in the sizable (24.1 kcal/mol) strain energy estimated for marginally accessible 10.[36]

Thermal disrotatory ring opening of 4 may give 3 directly in a concerted process. It is apparent from the magnitude of the activation energy for valence isomerization (Table III) that BOT enjoys significant six-electron transition state stabilization (11) (for disrotatory opening, a 6e Huckel[37] aromatic[38] system) and suffers little from four-electron destabilization such as in 12 (a 4e Huckel, antiaromatic transition state).[39] Ring opening of 4 could likewise benefit from delocalization as in 13, to the extent that the lone pair on nitrogen could
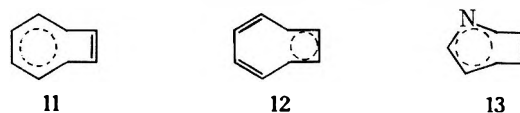
contribute to a pyrrolelike aromatic sextet.[40] However, the heteroatom substituent effect appears to be more general and manifest in accelerations of thermal disrotatory ring openings of fused cyclobutenes in which a stabilizing six-electron transition state cyclic array is not available. For example, 14 is thermally stable, while 15 ring opens readily.[41] Likewise
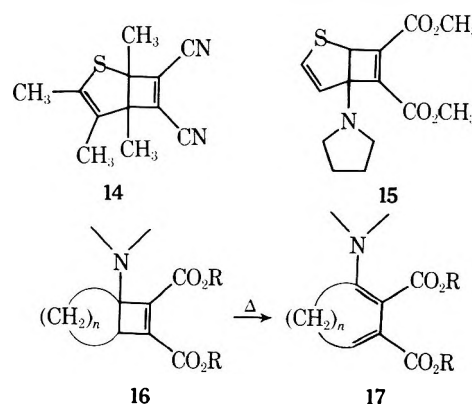
cycloadducts **16** of dimethyl acetylenedicarboxylate and cyclic enamines are generally unstable even near room temperature with respect to ring opening to **17**.[42]

We prefer a mechanism for the thermal isomerization **4 →
3** involving a nonsynchronous ring opening in which all-cis **3** emerges following motions which are overall disrotatory but where π bond development in **3** lags bond breaking in **4** early along the reaction coordinate. In the extreme, diradical **18** (geometry unspecified) would be important. Orbital overlap for such a species (from **4, 15,** or **16**) as in **19** would be involved. Structures **18** and **19** could correspond to transition states or to intermediates[36] (secondary minima on the ground state potential surface, vide infra), the important point being that the central cyclobutene bond is essentially broken.

Diradical **18** may well have more complicated electronics than that associated with canonical form **18a**. The latter would be substituent stabilized relative to the analogous species for **2a** by an amount associated with the degree to which the carboxamido group (RCONR'–) stabilizes a radical center. This value is unknown but may be approximated by the effect of the acyloxy (RCO₂–) substituent on C–H bond dissociation energies (ΔBDE < 1 kcal/mol).[43] The reduction in activation energy for **4** vs. **2a** (11 kcal/mol) is inconsistent with this kind of transition state stabilization. An alternative view recognizes the extent to which the odd electron centers in **18** interact with adjacent polarizing fragments (e.g., **19**). Respecting the electron releasing ability of nitrogen, contributing structures of the type **18b** gain importance; i.e., the singlet diradical wave

19
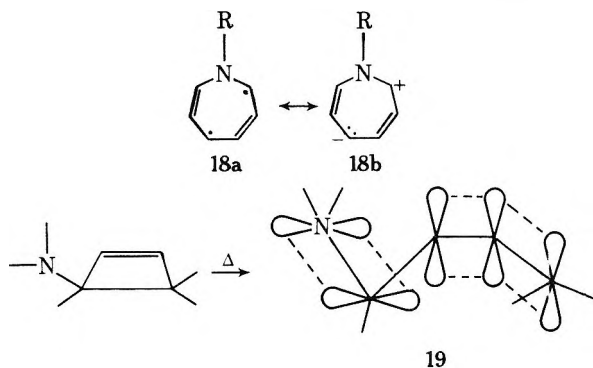
function has some ionic character.[44] In the extreme, **18** would be a discrete zwitterion as suggested by Criegee and co-workers[45] for ring opening of highly polarized cyclobutenes.

Our analysis respects the basic similarity between isomerizations **2 → 1** and the disrotatory cyclobutene → 1,3-butadiene ring opening, a reaction restricted by orbital topology in the ground state.[37,38] The important relationships between ground and excited state potential surfaces for systems which involve formal surface crossings have been known for some time.[46] We wish to emphasize the linked dependence between photochemical and thermal reactivities for these systems and the effect of substituents thereon. A proposed energy surface scheme for the **3,4** couple is shown in Figure 1. (The heat of reaction **4 → 3** has been measured by differential scanning calorimetry.[47])

The scheme submits to the following considerations. (1) Isomerization **3 → 4** is a G-type photochemical reaction[48] in which adiabatic formation of the excited state of product is energetically prohibited[49] and dissociation into fragments is not important. (2) The similarity with cyclobutene ring opening requires that the ground state isomerization **4 → 3** be "forbidden" involving at some point along the reaction coordinate a formal HOMO–LUMO orbital crossing.[50] (3) The orbital crossing or avoided crossing[51] provides an orbitally degenerate (diradical) ground state in proximity with a minimum in the excited singlet manifold, radiationless transition between which is facilitated.[52] (4) The minimum in the triplet
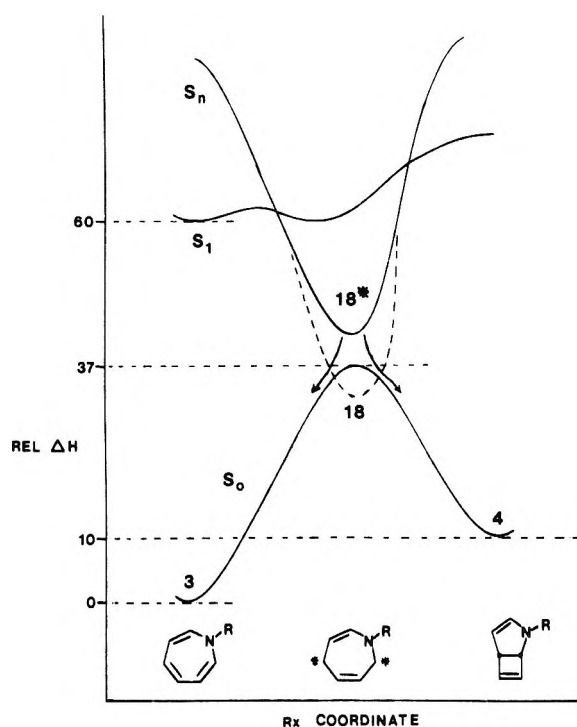
Figure 1. Potential energy surfaces for photochemical and thermal interconversions of **3** and **4**, $\Delta H^{\ddagger}$ (**4 → 3**, 128 °C) = 27 kcal/mol.

surface (not shown) will occur at a loose geometry (flexible somewhat flattened ring) resembling more the boatlike ground state of **3**, whereas the minimum or funnel in the excited singlet surface will assume a tight geometry (more folded or "pinched", less flexible ring) resembling the ground state of **4** to a degree related to the extent of charge separation (zwitterionic character[44]) (vide infra) at the diradical geometry.[52] (5) Decay from S_1 proceeds with little or no activation (no accompanying fluorescence) by way of mixing with the upper, "double excited" singlet (S_n), the state of intended crossing with the ground configuration.[53]

The substituent effect on reactivity in the cyclic diene and triene series, which we wish to relate to the energy surface scheme, is modest for **3,4** (i.e., moderately efficient formation of an energy-rich product coupled with a fairly rapid thermal back reaction). The effect is more pronounced in the facile photochemical–thermal interconversions of **20**[1b]**–22** and their

20 **21** **22** **23**
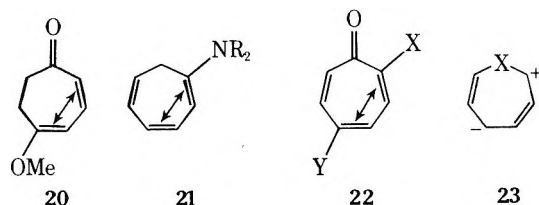
valence isomers (modes of ring closure as shown). For example, the relative quantum efficiency for isomerization of **21** is 50 000 times that of the parent cycloheptatriene.[54] Likewise, efficient photoisomerization of **22** (directed as shown) is coupled with an extremely rapid thermal back reaction of the valence isomer (at or below room temperature) in cases where X = electron-donating and Y = electron-withdrawing substituents.[55] Other similar directive substituent effects have been noted for tropones[56] and cycloheptatrienes.[57]

Although the importance of a substituent stabilized polar state (e.g., **23**) in these valence photoisomerizations has been recognized,[1b,57] the linked dependence of the thermal reversion has not been noted and the driving force has been incompletely understood. (For example, Herndon[58] has pointed

out that electron distribution in the *lowest vertical* excited state[59] does not uniformly correlate with modes of ring closure for substituted tropones.) We suggest that it is substituent control of the relative positioning of the ground and *upper* excited state surfaces which is responsible for the variance in photothermal reactivity in these isomerizations. "Push-pull" substitution serves to greatly stabilize the upper doubly excited configuration (S_x) at the diradical[44] or biradicaloid[60] geometry. Correspondingly, the ground surface is stabilized through configuration interaction[61] (mixing with the upper surface) which is quite large at the transition state (at the point of lowest total bond order, the diradical geometry). This admixing of ground and doubly excited configurations assures efficient radiationless decay to a point on the ground surface which is near product geometry.[62] For isomerization systems involving avoided crossings, substituent control of dipolar character and the positioning of minima for excited surfaces should be quite general.[63]

The extent of polarization in the transition state (ground surface) diradical 18 is uncertain. However, development of *substantial* charge in this species (predominance of canonical form 18b) is unlikely since a solvent effect on the rate of the thermal back reaction is absent. In addition, it appears improbable that the doubly excited or zwitterionic state (18*) has become the ground state of the system at the diradical geometry.[64,65] With a good dipolarophile (DMAC) in photochemical experiments with 3, trapping of such an intermediate would be possible but is unobserved.[66] Whereas the substituent polarizing influence on the rate of ring opening of 4 is predictably[39a] intermediate, the influence on 15 and 16 is quite large,[67] implicating a high degree of charge separation (configuration interaction) for the ground surface. In cases where a more polarizing substitution pattern is present, formation and partitioning of a ground state diradical–zwitterion could be important (note dashed line in Figure 1).

Experimental Section

General. 1-Ethoxycarbonyl-1*H*-azepine (3)[2] was photolyzed in acetonitrile on a preparative scale (Hanovia immersion apparatus) to give 4, following generally the procedure of Paquette and Barrett.[1d]

Benzene, cyclohexane, and *n*-propyl bromide were purified for use in photolysis by washing with (1) sulfuric acid, (2) aqueous NaHCO$_3$, and (3) distilled water followed by distillation from P$_2$O$_5$ or sodium. Valerophenone (Aldrich) was distilled under reduced pressure. Biacetyl was purified by spinning band distillation (bp 87–88 °C). Diglyme was distilled over sodium. Cyclooctatetraene, 2,4-dimethyl-2,5-hexadiene, fluorenone, and dimethyl acetylenedicarboxylate were commercial reagent grade materials used as received.

Varian 920 (thermal conductivity detector) and 1400 (flame ionization detector) instruments were used for analytical GLC. Columns employed were (A) 5 ft × 0.25 in., 3% SE-30 on 100/120 Varaport 30 and (B) 8 ft × 0.125 in., 3% FFAP on Chromosorb W.

Quantum Yields. Solution samples in 15-mm stoppered cylindrical Pyrex tubes were irradiated in a Rayonet chamber reactor (Model RPR 204) equipped with RUL 3500A lamps and a merry-go-round accessory (Model MGR 100) (Southern New England Ultraviolet Co.). Samples were purged with nitrogen prior to irradiation. Solutions of 3 in the appropriate solvents (with additives) were irradiated in parallel with valerophenone (0.4 M in benzene) which served as actinometer and for which a quantum yield of production of acetophenone of 0.33[4] was assumed. Concentrations for all parallel irradiation samples were employed which ensured complete absorption (measured absorbance >1 at 0.1 path maximum) over the range of lamp emission (325–385 nm). Samples were analyzed by GLC for the appearance of 4 (column A, 100 °C, vs. 3) and acetophenone (column B, 150 °C, vs. dodecane internal standard). Quantum yields are averages of at least two runs at low conversions of valerophenone (~15%) and 3 (5–10%). Statistical analysis of area ratios for 4 (area from cut out and weigh procedure) and acetophenone (area from disk integration) in replicate runs indicated a precision of ±15%.

Quenching of Valerophenone Photoelimination. The appearance of acetophenone from valerophenone was monitored as previously indicated for samples of valerophenone in benzene with increasing concentrations of 3 (4.5–8.2 × 10^{-3} M). Relative amounts of

acetophenone formed, obtained with good precision (±5%), were used for ϕ_0/ϕ. Values were corrected for competitive absorption by 3 by computing relative absorbances at several wavelengths in the region of lamp emission. This correction became significant at higher concentrations of 3, and at lower concentrations, values of ϕ_0/ϕ were within experimental error of 1.0; therefore, quenching behavior was assessed only over a limited range.

Luminescence Experiments and Biacetyl Phosphorescence Quenching. Using an Hitachi Model MFP fluorescence spectrophotometer, emission from 3 was undetectable for samples at room temperature (0.02 M in benzene) and at 77 K (EPA glass, 0.001 M). The phosphorescence emission of biacetyl in benzene (λ_{max} 522 nm) at room temperature was monitored as a function of [3]. Samples were degassed through several freeze-thaw cycles on a vacuum line. Relative intensities at the emission maximum gave ϕ_0/ϕ. The fluorescence of biacetyl was not quenched with the addition of 3.

Pyrolysis Experiments. Samples of 4 in diglyme-d_{14} or hexadecane (with benzene internal standard) were degassed in cleaned medium wall Pyrex NMR tubes (Wilmad Co.). Sealed ampules were pyrolyzed in an insulated oil bath, thermostated using a Therm-o-watch (Instruments for Research and Industry) and a calibrated ASTM thermometer. Temperature fluctuation was <0.5 °C. Ampules were quenched and analyzed by NMR. Formation of 3 was followed by the appearance of a multiplet at δ 5.58 (vinyl C–H), and disappearance of 4 was monitored with reference to signals at δ 4.9 and 5.2 (multiplets, C$_1$ and C$_4$[1d]). In experiments where benzene signal integration was used as an internal standard, a material balance for isomerization of >95% was obtained. Rate constants were calculated from the integrated first-order rate equation and errors are average deviations for at least four points at each temperature.

Laser Photolysis of 3. Samples of 3, 0.1 M in benzene, were irradiated with an argon ion laser (Spectra-Physics, Model 164). The emission at 457.9 nm (rated at 250 mW) was focused on the optically flat circular window of a standard 5-cm Pyrex cell containing sample. Beam intensity was checked by irradiation of a 10-cm cell containing potassium ferrioxalate[68] actinometer solution. The quantum yield for appearance of Fe(II) was assumed to be 0.95. Concentrations of sample and actinometer solutions were employed which ensured complete absorption of incident light. With a beam intensity of 1.05 ± 0.05 mE/h, a measurable conversion of 3 → 4 was observed (GLC analysis) in 4 h. The calculated quantum yield for isomerization was 0.013 ± 0.004.

References and Notes

(1) For leading references see (a) L. B. Jones and V. K. Jones, *Fortschr. Chem. Forsch.*, **13**, 307 (1969); (b) O. L. Chapman, *Adv. Photochem.*, **1**, 323 (1963); (c) R. Srinivasan, *ibid.*, **4**, 113 (1966); (d) L. A. Paquette and J. H. Barrett, *J. Am. Chem. Soc.*, **88**, 1718 (1966); (e) L. A. Paquette in "Nonbenzenoid Aromatics", Vol. 1, J. P. Snyder, Ed., Academic Press, New York, N.Y., 1969, p 249; (f) J. S. Swenton, K. A. Burdett, D. M. Madigan, and P. D. Rosso, *J. Org. Chem.*, **40**, 1280 (1975); (g) G. Kan, M. T. Thomas, and V. Snieckus, *Chem. Commun.*, 1022 (1971); (h) J. M. Holouka and P. D. Gardner, *J. Am. Chem. Soc.*, **89**, 6390 (1967).
(2) R. J. Cotter and W. F. Beach, *J. Org. Chem.*, **29**, 751 (1964).
(3) L. A. Paquette, D. E. Kuhla, J. H. Barrett, and R. J. Haluska, *J. Org. Chem.*, **34**, 2866 (1969).
(4) P. J. Wagner, P. A. Kelso, and R. G. Zepp, *J. Am. Chem. Soc.*, **94**, 7480 (1972).
(5) For recent references on heavy atom solvent effects on the course of photochemical reactions, see (a) D. O. Cowan and J. C. Koziar, *J. Am. Chem. Soc.*, **97**, 249 (1975); (b) R. H. Fleming, F. H. Quinn, and G. S. Hammond, *ibid.*, **96**, 7738 (1974); (c) W. I. Ferree, Jr., B. F. Plummer, and W. W. Schloman, Jr., *ibid.*, **16**, 7741 (1974).
(6) R. Huisgen, W. Scheer, and H. Huber, *J. Am. Chem. Soc.*, **89**, 1753 (1967).
(7) P. J. Wagner, *J. Am. Chem. Soc.*, **89**, 5898 (1967).
(8) P. J. Wagner and A. E. Kemppainen, *J. Am. Chem. Soc.*, **89**, 5898 (1967).
(9) For a discussion, see P. J. Wagner and I. Kochevar, *J. Am. Chem. Soc.*, **90**, 2232 (1968), and references cited therein.
(10) N. J. Turro and R. Engel, *J. Am. Chem. Soc.*, **91**, 7113 (1969).
(11) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Am. Chem. Soc.*, **91**, 3616 (1969).
(12) R. E. Kellogg and W. T. Simpson, *J. Am. Chem. Soc.*, **87**, 4230 (1965).
(13) N. C. Baird, *J. Am. Chem. Soc.*, **94**, 4941 (1972); the actual S_0–T_1 gap will be larger than that calculated for planar COT (27 kcal/mol) when the equilibrium conformation of the ground state is considered.
(14) The triplet energy for valerophenone lies probably within the range found for a number of phenones (E_T = 73 ± 2 kcal/mol): (a) P. J. Wagner, M. May,

and A. Harig, *Chem. Phys. Lett.*, **13**, 545 (1972); (b) J. N. Pitts, Jr., D. R. Burley, J. C. Mani, and A. D. Broadbent, *J. Am. Chem. Soc.*, **90**, 5902 (1968); (c) D. R. Kearns and W. A. Case, *ibid.*, **88**, 5087 (1966).

(15) P. J. Wagner, A. E. Demppainen, and T. Jellinek, *J. Am. Chem. Soc.*, **94**, 7512 (1972).

(16) (a) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Am. Chem. Soc.*, **86**, 4537 (1964); (b) H. L. J. Backstrom and K. Sandros, *Acta Chem. Scand.*, **12**, 823 (1958).

(17) Since the charge transfer quenching by amines involved *both* biacetyl singlet and biacetyl triplet,[10] and since the fluorescence of biacetyl was unaltered by **3**, it is tempting to attribute the phosphorescence quenching by **3** to endothermic energy transfer alone.

(18) To check for an intrinsically rapid and efficient intersystem crossing between states of different configuration,[19] a triplet counting experiment was performed. Azepine **3** sensitized the dimerization of 1,3-cyclohexadiene (E_T = 51–52 kcal/mol[12]) with no more than $\frac{1}{10}$ the efficiency of benzophenone. Either intersystem crossing for **3** is not important, or energy transfer from triplet **3** to cyclohexadiene is insufficiently exothermic, or triplet **3** is too short lived to be quenched by diene. If the first of these options holds, especially rapid singlet deactivation must also preclude intersystem crossing induced by collision with heavy-atom solvents.

(19) (a) M. A. El-Sayed, *Acc. Chem. Res.*, **4**, 23 (1971); (b) S. K. Lower and M. A. El-Sayed, *Chem. Rev.*, **66**, 199 (1966).

(20) See, for example, ref 1e.

(21) M. R. Willcott and E. Goerland, *Tetrahedron Lett.*, 6341 (1966).

(22) (a) G. J. Fonken, *Chem. Ind. (London)*, 1625 (1963); (b) E. Migirdicyan and S. Leach, *Bull. Soc. Chim. Belg.*, **71**, 845 (1962); (c) Zimmerman and Iwamura did not find BOT on direct irradiation under somewhat different conditions and showed that COT gives semibullvalene upon sensitization; H. E. Zimmerman and H. Iwamura, *J. Am. Chem. Soc.*, **92**, 2015 (1970).

(23) E. Vogel, H. Kiefer, and W. R. Roth, *Angew. Chem., Int. Ed. Engl.*, **3**, 442 (1964).

(24) Photochemical pathways other than four-electron valence isomerization are well known, notably sigmatropic rearrangement for cycloheptatrienes,[1a] formation of phenol from oxepin,[1h] and semibullvalene from COT.[22c]

(25) R. S. H. Liu, *J. Am. Chem. Soc.*, **89**, 112 (1967).

(26) D. I. Schuster and D. J. Blythin, *J. Org. Chem.*, **35**, 3190 (1970).

(27) T. H. Koch and D. A. Brown, *J. Org. Chem.*, **36**, 1934 (1971).

(28) L. L. Barber, O. L. Chapman, and J. D. Lassila, *J. Amer. Chem. Soc.*, **91**, 531 (1969).

(29) T. D. Goldfarb and L. Lindquist, *J. Am. Chem. Soc.*, **89**, 4588 (1967).

(30) (a) E. H. White, E. W. Friend, R. L. Stern, and H. Maskill, *J. Am. Chem. Soc.*, **91**, 523 (1969); (b) E. H. White and R. L. Stern, *Tetrahedron Lett.*, 193 (1964).

(31) W. J. Nebe and G. J. Fonken, *J. Am. Chem. Soc.*, **91**, 1249 (1969).

(32) (a) For a thorough discussion of photodecomposition pathway dependence on multiplicity for mono- and bicyclic unsaturated ketones, see D. I. Schuster and C. W. Kim, *J. Am. Chem. Soc.*, **96**, 7437 (1974). (b) For other triplet isomerizations in rigid *bicyclic* systems clearly not involving geometric isomers, see R. C. Hahn and R. P. Johnson, *J. Am. Chem. Soc.*, **97**, 212 (1975), and D. W. Jefford and F. Delay, *ibid.*, **97**, 2272 (1975).

(33) J. E. Baldwin and M. S. Kaplan, *J. Am. Chem. Soc.*, **94**, 668 (1972).

(34) J. E. Baldwin and M. S. Kaplan, *J. Am. Chem. Soc.*, **93**, 3969 (1971).

(35) J. J. Bloomfield and J. S. McConaghy, *Tetrahedron Lett.*, 3723 (1969).

(36) H. E. O'Neal and S. W. Benson, *Int. J. Chem. Kinet.*, **2**, 423 (1970).

(37) H. E. Zimmerman, *Acc. Chem. Res.*, **4**, 272 (1971).

(38) M. J. S. Dewar, *Angew. Chem., Int. Ed. Engl.*, **10**, 761 (1971).

(39) BOT undergoes substantially accelerated ring opening compared to bicyclo[4.2.0]octa-2,4-diene ($\Delta H^\ddagger$ = 25 kcal/mol) in which potential 4e destabilization is absent; see, R. Huisgen, G. Boche, A. Dahmen, and W. Hechti, *Tetrahedron Lett.*, 5215 (1968).

(40) (a) Cyclic delocalization of the nitrogen lone pair in [13]annulenes as a function of the substituent on nitrogen has been assessed; the –NCO$_2$Me group shows diminished electron availability; see A. G. Anastassiou, R. L. Elliott, and E. Reichmanis, *J. Am. Chem. Soc.*, **96**, 7823 (1974). (b) For comparison, cyclic delocalization in pyrrole appears to be about two-thirds as important as in benzene in terms of calculated resonance energies; see B. A. Hess and L. J. Schaad, *Tetrahedron*, **28**, 3647 (1972).

(41) D. N. Reinhoudt, H. C. Volger, C. G. Kouwenhoven, H. Wynberg, and R. Helder, *Tetrahedron Lett.*, 5269 (1972).

(42) K. C. Brannock, R. D. Bupitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1464 (1963).

(43) R. K. Solly and S. W. Benson, *Int. J. Chem. Kinet.*, **3**, 509 (1971).

(44) L. Salem and C. Rowland, *Angew. Chem., Int. Ed. Engl.*, **11**, 92 (1972).

(45) R. Criegee, D. Seebach, R. E. Winter, R. Borretzen, and H.-A. Brune, *Chem. Ber.*, **98**, 2339 (1965).

(46) (a) H. E. Zimmerman, *J. Am. Chem. Soc.*, **88**, 1566 (1966); (b) W. Th. A. M. van der Lugt and L. J. Oosterhoff, *ibid.*, **91**, 6042 (1969).

(47) In work which is to be reported separately, the enthalpy of reaction **4** → **3** was found to be 10.4 kcal/mol. This value was determined on a Perkin-Elmer DSC-2 instrument (isothermal mode, 140 °C) with samples of **4** in diphenyl ether. We are grateful to Mr. R. L. Fyans for making this measurement.

(48) R. C. Dougherty, *J. Am. Chem. Soc.*, **93**, 7187 (1971).

(49) (a) W. G. Dauben, R. L. Cargill, R. M. Coates, and J. Saltiel, *J. Am. Chem. Soc.*, **87**, 3996 (1965); (b) G. S. Hammond, *Adv. Photochem.*, **7**, 373 (1969).

(50) (a) M. J. S. Dewar, S. Kirschner, and H. W. Kollmar, *J. Am. Chem. Soc.*, **96**, 5240 (1974); (b) M. J. S. Dewar and S. Kirschner, *ibid.*, **96**, 5244 (1974).

(51) (a) W. G. Dauben, L. Salem, and N. J. Turro, *Acc. Chem. Res.*, **8**, 41 (1975); (b) L. Salem, C. Leforesteier, G. Segal, and R. Wetmore, *J. Am. Chem. Soc.*, **97**, 479 (1975).

(52) J. Michl, *Fortschr. Chem. Forsch.*, **46**, 1 (1974).

(53) The doubly excited configuration probably does not correspond to S_2 in this case since an n,π^* state is low lying. The critical point is that there be some upper singlet state (S_n) which formally correlates with the ground state of **4**.

(54) A. P. ter Borg and H. Kloosterziel, *Chem. Commun.*, 1210 (1967).

(55) T. Kobayashi, T. Hirai, J. Tsunetsuga, H. Hayashi, and T. Nozoe, *Tetrahedron*, **31**, 1483 (1975).

(56) (a) D. J. Pasto in "Organic Photochemistry", Vol. 1, O. L. Chapman, Ed., Marcel Dekker, New York, N.Y., 1967, p 155; (b) K. Koch, *Adv. Alicyclic Chem.*, **1**, 258 (1966).

(57) A. R. Brember, A. A. Borman, R. L. Leyland, and H. B. Sheridan, *Tetrahedron Lett.*, 2511 (1970).

(58) W. C. Herndon, *Chem. Rev.*, **72**, 157 (1972).

(59) J. P. Malrieu, *Photochem. Photobiol.*, **5**, 301 (1966).

(60) J. Michl, *Mol. Photochem.*, **4**, 257 (1972).

(61) N. D. Epiotis, *Angew. Chem., Int. Ed. Engl.*, **13**, 751 (1974).

(62) It would be helpful to be able to correlate the ability of a pair of substituents to stabilize a dipole with quantum efficiency for (or rate of) valence isomerization (and by inference with the "tightness" of the diradical geometry). However, the fate of S_1 in these systems is complicated by having a number of excited diradical–zwitterionic minima into which to funnel. There are, for example, excited state minima (i.e., a family of valence isomeric diradicals) which relate to thermal surfaces which (in principle) connect the open trienes with geometric isomers. (The norcaradiene-like surface would not have diradical character but could offer another mode of decay.) In short, the initially formed excited state may partition among several decay modes, which essentially employ the same radiationless decay "mechanism" but which do not all lead to valence isomeric product.

(63) (a) V. Bonacic-Koutecky, P. Bruckmann, P. Hiberty, J. Koutecky, C. Leforesteier, and L. Salem, *Angew. Chem., Int. Ed. Engl.*, **14**, 575 (1975); (b) J. Michl in "Physical Chemistry", Vol. VIII, Academic Press, New York, N.Y., 1975, Chapter 3.

(64) L. Salem and W.-D. Stohrer, *J. Chem. Soc., Chem. Commun.*, 140 (1975).

(65) Resonance contributors **18a** and **18b** are to varying extents important for both of the low-lying diradical states. The more "covalent" state (the transition state on the ground surface) is richer in **18a** whereas **18b** is more important for the excited, "ionic" state (the minimum in the S_x surface).[44,60]

(66) For a classic example of trapping by DMAC of a thermally or photochemically generated diradical-zwitterion (an azomethine ylide) which has a crude similarity to **18**, see ref 6.

(67) For a semiquantitative comparison of rates of cyclobutene ring opening see ref. 40, 41, and 45.

(68) C. G. Hatchard and C. A. Parker, *Proc. R. Soc. London, Ser. A*, **235**, 518 (1965).

Migration Aptitudes in the Photolysis of Some Tertiary Alkyl Azides[1]

Frederick C. Montgomery[2] and William H. Saunders, Jr.*

Department of Chemistry, University of Rochester, Rochester, New York 14627

Received December 23, 1975

The ethyl/methyl migration aptitudes were determined for photolysis of a series of 2-substituted 2-butyl azides, where the 2 substituent was an aryl group (1a–f), $Ph(CH_2)_n$ (2–4), or a n-propyl group (5). Comparison of n-propyl/methyl and n-propyl/ethyl migration aptitudes were also made (7–8). When an aryl group was directly attached to the carbon bearing the azido group, the ethyl/methyl and n-propyl/methyl migration aptitudes ran 1.4–1.6, and the ethyl/n-propyl migration aptitudes 1.2–1.3. Otherwise, observed migration aptitudes were within experimental error of the statistical values. The results are not in line with ground-state conformational preferences, nor do they show any obvious correlations with expected intrinsic migration aptitudes. The ultraviolet spectrum of 1a differs significantly from that of an equimolar mixture of toluene and *tert*-amyl azide, suggesting that the aryl group interacts with, and perhaps stabilizes, the excited azide. Anomalous migration aptitudes with bromine-substituted azides appear to result from photolysis of the carbon–bromine bond.

Early work on migration aptitudes in the photolysis of organic azides (eq 1) revealed little or no dependence on the

$$R_2-\overset{\overset{\displaystyle R_1}{|}}{\underset{\underset{\displaystyle R_3}{|}}{C}}-N_3 \xrightarrow{h\nu} \overset{\displaystyle R_2}{\underset{\displaystyle R_3}{>}}C=N-R_1$$

$$+ \quad \overset{\displaystyle R_1}{\underset{\displaystyle R_3}{>}}C=N-R_2 \quad + \quad \overset{\displaystyle R_1}{\underset{\displaystyle R_2}{>}}C=N-R_3 \quad + \quad N_2 \quad (1)$$
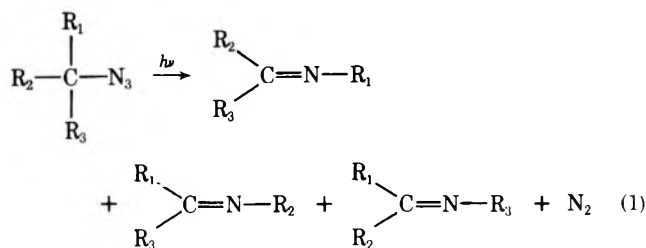
nature of the migrating group. Triarylmethyl azides showed at most a slight preference for the substituted group, regardless of its electronic character, and there appeared to be no significant difference between methyl and phenyl.[3,4] On the basis of these results, reaction via a discrete nitrene was proposed, and supported by trapping experiments in which small amounts of amine corresponding to the nitrene resulted from photolysis in the presence of butyl mercaptan or tributyltin hydride.[4] The possibility that the amine arose from reduction of excited azide could not be ruled out, however.

Migration is not statistical in all cases. Hydrogen migrates up to five times faster than alkyl,[5,6] and cases in which the smaller of two alkyl and/or aryl groups migrate better have been reported.[7,8] These examples of apparent conformational preferences suggest that migration occurs in an excited azide rather than in a nitrene.

The present work on a series of aryl-substituted tertiary alkyl azides was undertaken to determine the effect of the proximity of a phenyl group to the azide function on quantum yields and products of photolysis. The ultraviolet spectra of 1a and 3 are compared with the spectrum of an equimolar mixture of *tert*-amyl azide and toluene in Figure 1. The spectrum of 3 is rather similar to that of the mixture, but the spectrum of 1a is markedly different from either. This ap-

parent interaction of the two chromophores is analogous to that reported earlier for phenylacetate esters.[9,10]
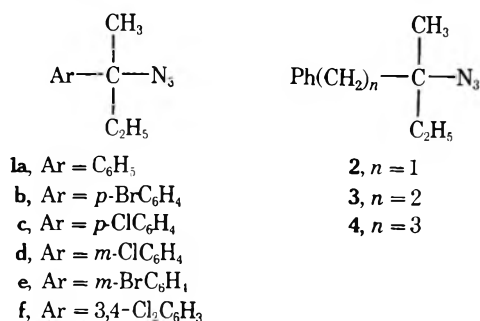
In the absence of interactions between the chromophores, one would expect absorption of light by the benzene ring and energy transfer from the benzene ring to the azide prior to loss of nitrogen and rearrangement, since substituted benzenes absorb at least ten times more strongly than alkyl azides in the 253.7-nm region. The quantum yields for nitrogen evolution (Table I) do not, however, show any consistent trend from 1a to 4. Some caution is needed in interpreting these figures, for it was not always possible to remove olefin and alcohol impurities completely from the azide samples. The minimum purity was 94%, so neither is major error expected from this source.

The azides used for quantum yields and migration aptitudes were prepared by standard procedures (see Experimental Section). Photolyses were carried out on carefully degassed solutions, except as otherwise noted, to low (<8%) conversions to minimize secondary reactions. The products were hydrolyzed to mixtures of the corresponding ketones, which were analyzed as such by GLC or reduced to the corresponding alcohols and then analyzed. Control experiments showed that hydrolysis and reduction were complete, and that there was no interference from unreacted azide or its decomposition products. Known mixtures of azides and ketones were run through the complete workup procedure to calibrate the analyses. The migration aptitudes reported in Tables II and III were reproducible to 10% or better.

Examination of Table II reveals an interesting dichotomy. The results for 1a–f show a clear preference for ethyl over methyl migration (usually 1.4–1.6), while the results for 2–4

$$\underset{\text{1a, } Ar = C_6H_5}{\underset{\text{b, } Ar = p\text{-}BrC_6H_4}{\underset{\text{c, } Ar = p\text{-}ClC_6H_4}{\underset{\text{d, } Ar = m\text{-}ClC_6H_4}{\underset{\text{e, } Ar = m\text{-}BrC_6H_4}{\underset{\text{f, } Ar = 3,4\text{-}Cl_2C_6H_3}{}}}}}}{Ar-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}}-N_3}$$

$$\underset{\substack{\text{2, } n=1 \\ \text{3, } n=2 \\ \text{4, } n=3}}{Ph(CH_2)_n-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle C_2H_5}{|}}{C}}-N_3}$$

Table I. Quantum Yields of Nitrogen Evolution for the Photolysis of 2-Substituted 2-Butyl Azides[a]

Compd	Φ_{N_2} for photolysis time[c]		
	6 min	18 min	60 min
1a	0.32 ± 0.01	0.30 ± 0.01	0.19 ± 0.01
2	0.16[b]	0.27 ± 0.10	0.14[b]
3	0.57[b]	0.53 ± 0.02	0.42[b]
4	0.45 ± 0.02	0.37 ± 0.01	0.22 ± 0.01

[a] Run in a Rayonet RPR-208 reactor with RUL 2537 (253.7 nm) lamps in hexane solution. A uranyl oxalate actinometer was used, and Φ corrected for light not absorbed by the azide. [b] Single run only. [c] Percent of theoretical yield of nitrogen was below 10% in most cases, but 10–15% in a few.

Table II. Ethyl/Methyl Migration Aptitudes in the Photolysis of 2-Substituted 2-Butyl Azides[a]

Entry no.	Compd	λ, nm	Solvent	Et/Me
1	1a	253.7	Hexane	1.41 ± 0.04
2	1b	253.7	Hexane	1.43 ± 0.07
3	1b	253.7	Hexane	1.99 ± 0.05[b]
4	1c	253.7	Hexane	1.38 ± 0.01
5	1d	253.7	Hexane	1.36 ± 0.02
6	1e	253.7	Hexane	1.31 ± 0.05
7	1e	253.7	Hexane	1.97 ± 0.08[b]
8	1f	253.7	Hexane	1.27 ± 0.01
9	1a	300	Hexane	1.56 ± 0.03
10	1b	300	Hexane	1.31 ± 0.04
11	1e	300	Hexane	1.38 ± 0.01
12	1f	300	Hexane	1.37 ± 0.02
13	2	253.7	Hexane	1.10 ± 0.20
14	3	253.7	Hexane	1.01 ± 0.04
15	4	253.7	Hexane	1.03 ± 0.03
16	2	300	Hexane	1.07 ± 0.01
17	3	300	Hexane	1.08 ± 0.05
18	4	300	Hexane	1.03 ± 0.03
19	1a	300˙	Chloroform	1.46 ± 0.04[b]
20	1a	300	Benzene	1.60 ± 0.03[b]
21	1a	300	Mesitylene	1.50 ± 0.03[b]
22	3	300	Chloroform	1.06 ± 0.02[b]
23	3	300	Benzene	1.16 ± 0.03[b]
24	3	300	Mesitylene	1.07 ± 0.01[b]
25	1b	253.7	Hexane	1.53 ± 0.03[c]
26	1e	253.7	Hexane	1.59 ± 0.03[c]

[a] Run in a Rayonet RPR-208 reactor with RUL 2537 (253.7 nm) or RUL 3000 (300 nm) lamp with Pyrex filter. Reactions were carried to less than 8% and in 0.05–0.08 M degassed solution unless otherwise noted. Each number is the average of three or more runs. [b] Not degassed. [c] In presence of 0.7 M 2,3-dimethyl-2-butene.

are essentially within experimental error of showing no ethyl:methyl preference. No significant effect of wavelength, solvent, or para substituent is discernible. The only entries out of line are 3 and 7, for undegassed photolyses of 1b and 1e, and these will be commented on later.

Table III gives further information on these trends. It is evidently not just the bulk of the aryl group which is responsible for the Et/Me preference in 1a–f, for the cyclohexyl group in 6 produces no such preference. Similarly, no differences in the tendencies of methyl, ethyl and n-propyl to migrate in 5 are distinguishable. There is, however, an n-Pr/Me preference of 1.4–1.5 in 7, and, surprisingly, an Et/n-Pr preference of 1.2–1.3 in 8. The results as a whole exclude any

5   **6**

7   **8**
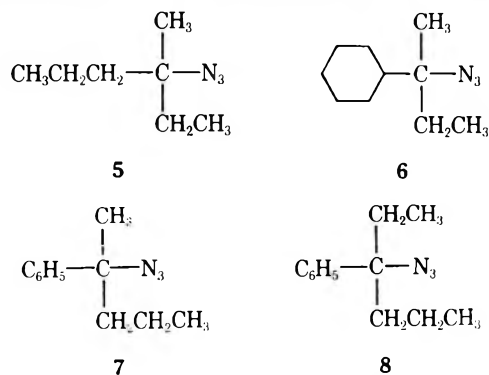
conformational effect depending simply on the bulk of the groups attached to the α carbon.

The absence of any regular dependence on steric requirements in turn casts doubt on the assertion that migration tendencies are determined mainly or entirely by ground-state conformational effects.[5,8] The order Me < Et > n-Pr suggests that at least two effects are operating. Ground-state conformational preferences may well be decisive with the very hindered 2-biphenylyl compounds studied by Abramovitch and

Kyba,[7,8] but it seems that some role must be ascribed to intrinsic migration aptitudes in other cases. If the rates of migration and of rotation about the carbon–nitrogen bond of the
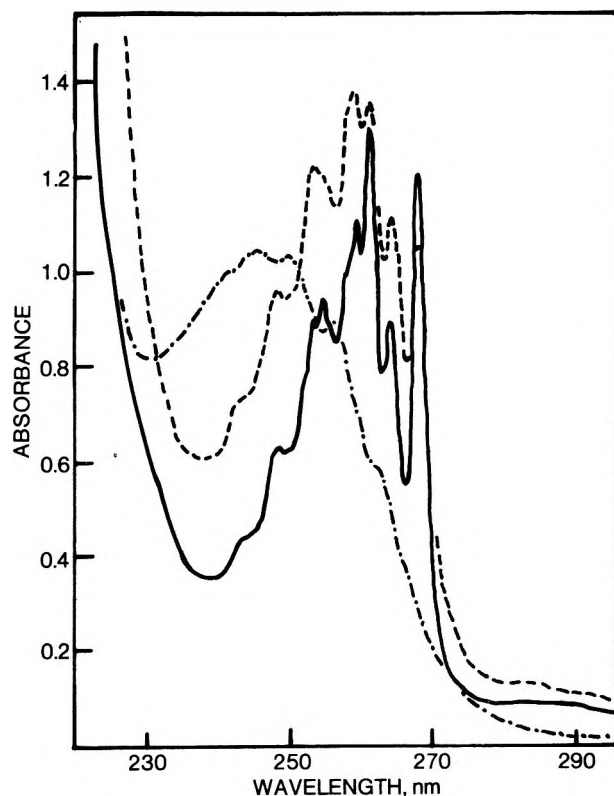
Figure 1. Ultraviolet spectra in hexane solution of 2-phenyl-2-butyl azide (1a), 0.00145 M, - - - -; 3-methyl-1-phenyl-3-pentyl azide (3), 0.0029 M, - - - -; and an equimolar mixture of *tert*-amyl azide and toluene, 0.0029 M, —.

Table III. Miscellaneous Migration Aptitudes in the Photolysis of 2-Substituted 2-Butyl Azides[a]

Entry no.	Compd	λ, nm	Migrating groups, R':R	R'/R
1	5	300	Et:Me	0.99 ± 0.02
2	5	300	n-Pr:Me	1.05 ± 0.03
3	5	300	Et:n-Pr	0.94 ± 0.04
4	6	300	Et:Me	1.00 ± 0.03
5	1a	300	Et:Me	1.56 ± 0.06
6	1a	253.7	Et:Me	1.48 ± 0.03
7	1a	253.7	Ph:Me	1.04 ± 0.06
8	7	300	n-Pr:Me	1.41 ± 0.05
9	7	253.7	n-Pr:Me	1.52 ± 0.07
10	7	253.7	Ph:Me	0.93 ± 0.03
11	8	300	Et:n-Pr	1.31 ± 0.02
12	8	253.7	Et:n-Pr	1.21 ± 0.04

[a] Conditions same as in footnote *a* of Table II, except that nondegassed solutions were used.

excited azide are comparable, then intrinsic migration aptitudes may affect the results unless there are fairly large energy differences between the possible conformations.

There may also be some specific effect of aryl substitution on the α-carbon atom. With one marginal exception (2-phenylethyl:methyl of 0.89:1.00[8]), the only cases of nonstatistical migration in tertiary alkyl azides involve reactants possessing α-aryl groups. The α-aryl group might interact with the orbitals on the nitrogen attached to carbon so as to stabilize and increase the discrimination of the electrophilic nitrogen resulting from a π,π^* excitation,[11] or so as to favor one conformation of the excited azide over another. The fact that the uv spectrum of 1a differs markedly from that of 3 and that of an equimolar mixture of *tert*-amyl azide and toluene (Figure 1) provides evidence for interaction of the α-aryl and azide functions in the singlet excited state. The interaction cannot be very strong or specific, however, for substituents in the aryl group have little or no effect on ethyl:methyl migration aptitudes (Table II), and phenyl:methyl migration aptitudes are near unity (Table III). A more detailed analysis of the complex pattern of small migrational preferences (and the frequent lack thereof) in the photolysis of tertiary alkyl azides does not seem worthwhile at the present time.

We now return to the results with 1b and 1e in nondegassed solution (entries 3 and 7, Table II). These bromo compounds were originally studied to see if a heavy-atom substituent would affect the results by promoting intersystem crossing.[12] The unusual migration aptitudes were, however, found only in undegassed solution. The values in degassed solution (entries 2 and 6, Table II) were not out of line with the values from other compounds in the 1a-f series. Similarly, "normal" migration aptitudes are observed in the presence of 2,3-dimethyl-2-butene (entries 25–26, Table II) and several other olefins, but the quantum yields for nitrogen evolution from 1b and 1e remain 0.20 ± 0.02 in either the presence or absence of *cis*-4-methyl-2-pentene.

This last fact indicates that bromine substitution does not interfere with loss of nitrogen. Table IV shows that 1b and 1e cause cis–trans isomerization when photolyzed in the presence of *cis*-4-methyl-2-pentene, as does 4-bromotoluene. That the bromine is responsible for the isomerization is shown by the fact that isomerization is ca. 10[4] less efficient with azides lacking a bromo substituent. Finally, some unsubstituted azide (1a) is isolated after partial photolysis of 1b and 1e.

The most likely explanation of these results is that photolysis of 1b and 1e generates bromine atoms, which can then cause cis–trans isomerization of added olefin via reversible

Table IV. Quantum Yields for Isomerization of *cis*-4-Methyl-2-pentene[a]

Sensitizer	$\Phi_{c \to t}$[c]
3	8×10^{-4}
1a	8×10^{-4}
1c	8×10^{-4}
1f	8×10^{-4}
1e	1.2×10^0
1b	1.2×10^0
4-Bromotoluene	4×10^0

[a] Conditions the same as in footnote *a* of Table I, except that degassed heptane solutions were used. [b] Not corrected for back reaction.

addition.[13] In the absence of olefin, the bromine atoms can cause selective destruction of product imines. That the migration aptitudes are out of line only in undegassed solution is puzzling, but may indicate that oxygen is trapping an otherwise reversibly formed addition product from the imine and a bromine atom. The quantum yields in Table IV suggest that as much as 30% of the azide may be losing bromine atoms, but quantitative estimates are uncertain. Determination of the proportion of debrominated azide in the products is precluded by partial thermal decomposition in the GLC injector of both substituted and unsubstituted azide, and some of the bromine atoms could be generated from product imine rather than starting azide, which would cloud the significance of any analysis for debrominated products.

Experimental Section[14]

2-Cyclohexyl-2-butanol. Cyclohexylmagnesium bromide and 2-butanone gave 2-cyclohexyl-2-butanol in 68% yield, bp 57–57.5 °C (0.45 mm), n^{25}D 1.4702. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.91. Found: C, 76.83; H, 12.96.

2-Phenyl-2-butanol was obtained from phenylmagnesium bromide and 2-butanone in 75% yield, bp 47.5 °C (0.08 mm), n^{20}D 1.5199 [lit.[15] bp 97 °C (15 mm), n^{23}D 1.5195].

2-Aryl-2-butanols, except for 2-phenyl-2-butanol, were prepared from ethylmagnesium bromide and the appropriate acetophenone.

2-(3-Bromophenyl)-2-butanol was obtained in 77% yield, bp 73 °C (0.1 mm), n^{24}D 1.5537. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br, 34.88. Found: C, 52.43; H, 5.80; Br, 34.92.

2-(4-Bromophenyl)-2-butanol was obtained in 72% yield, bp 76–78 °C (0.04 mm), n^{25}D 1.5530. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br 34.88. Found: C, 52.32; H, 5.66; Br, 35.08.

2-(3-Chlorophenyl)-2-butanol was obtained in 66% yield, bp 135–138 °C (28 mm), $n^{36.5}$D 1.5300. Anal. Calcd for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10; Cl, 19.20. Found: C, 65.05; H, 6.92; Cl, 19.28.

2-(3,4-Dichlorophenyl)-2-butanol was obtained in 73% yield, bp 102–103 °C (4.2 mm), n^{20}D 1.5525. Anal. Calcd for $C_{10}H_{12}Cl_2O$: C, 54.81; H, 5.52; Cl, 32.36. Found: C, 54.84; H, 5.46; Cl, 32.25.

3-Methyl-3-hexanol was obtained in 94% yield from ethylmagnesium bromide and 2-pentanone, bp 139.5–141 °C (757 mm) (lit.[16] bp 143 °C).

3-Methyl-6-phenyl-3-hexanol was obtained in 78% yield from 3-phenylpropylmagnesium bromide and 2-butanone, bp 80–82 °C (0.35 mm), n^{20}D 1.5053 [lit.[17] bp 154–163 °C (23 mm), n^{25}D 1.5050].

3-Methyl-1-phenyl-3-pentanol was obtained in 73% yield from 2-phenylethylmagnesium bromide and 2-butanone, bp 70–72 °C (0.1 mm), n^{27}D 1.5083 [lit.[18] bp 132–133 °C (12 mm), n^{20}D 1.5114].

3-Phenyl-3-hexanol was obtained from ethylmagnesium bromide and butyrophenone, bp 105–110 °C (3 mm) [lit.[19] bp 134 °C (27 mm)].

2-Phenyl-2-pentanol was obtained from phenylmagnesium bromide and 2-pentanone, bp 115–118 °C (13 mm) [lit.[20] bp 100–102 °C (5 mm)].

Preparation of Azides. The azides were prepared from the corresponding tertiary alcohols by a procedure similar to that used by Saunders and Caress[21-23] for 2-phenyl-2-propyl azide. The azides were all obtained as oils which could not be crystallized and which decomposed on attempted distillation at 0.5 mm. Chromatography on alumina effected decolorization, but failed to remove all olefin and/or unreacted alcohol. Shaking a solution of the azide in hexane with

alumina was as effective as chromatography, leaving less than 5–6% of impurities as judged by ir and NMR spectra, GLC analysis, and the amount of nitrogen evolved on thermolysis. The azides were stable in the dark at 0 °C for at least several months. Two typical preparations are described below.

3-Phenyl-3-hexyl Azide. To a solution of 0.2 mol of hydrazoic acid in chloroform[24] and 0.1 mol of 3-phenyl-3-hexanol was added dropwise with stirring over 1 h 0.1 mol of concentrated sulfuric acid. The mixture was stirred for another 1 h and neutralized with 20% sodium hydroxide, and the chloroform layer separated. The chloroform solution was washed twice with 10% sodium bicarbonate and five times with water, and dried over anhydrous magnesium sulfate. Removal of the chloroform in vacuo left a pale yellow liquid which was decolorized by shaking a hexane solution with alumina. Removal of the hexane left a colorless liquid with no ir absorption at 3600 cm⁻¹ (hydroxyl) and a strong band near 2100 cm⁻¹ (azide).

2-(4-Chlorophenyl)-2-butyl and 2-(4-methoxyphenyl)-2-butyl azides were prepared in 50–60% yields from mixtures of the corresponding alcohols and their olefinic dehydration products by reaction with hydrazoic and trichloroacetic acids.[25]

1-Cyclohexylethanol was prepared in 62% yield from cyclohexylmagnesium bromide and acetaldehyde, bp 58–61 °C (3 mm) [lit.[26] 85–87 °C (17 mm)].

Cyclohexyl methyl ketone was obtained in 92% yield from 1-cyclohexylethanol by chromic acid oxidation according to the procedure of Van Woerden.[27] The product had bp 62–63 °C (7 mm), n^{32}D 1.4478, 2,4-dinitrophenylhydrazone mp 140–141 °C [lit.[28] bp 60–61 °C (8 mm), n^{27}D 1.4500, 2,4-dinitrophenylhydrazone[29] mp 149–151 °C].

1-Cyclohexylpropanol was prepared in 70% yield from cyclohexylmagnesium bromide and propionaldehyde, bp 91–92 °C (15 mm), n^{40}D 1.4585 [lit.[30] bp 96 °C (18 mm), n^{20}D 1.4688].

Cyclohexyl ethyl ketone was obtained in 91% yield by chromic acid oxidation of 1-cyclohexylpropanol.[31] The product had bp 62 °C (4 mm), 2,4-dinitrophenylhydrazone mp 150.5–152 °C [lit.[32] bp 73–77 °C (8 mm), 2,4-dinitrophenylhydrazone mp 150–151 °C].

6-Phenyl-3-hexanol was prepared in 87% yield from 3-phenyl-propylmagnesium bromide and propionaldehyde, bp 81–82 °C (0.25 mm) [lit.[33] bp 145–146 °C (14 mm)].

6-Phenyl-3-hexanone was obtained in 93% yield by chromic acid oxidation[31] of 6-phenyl-3-hexanol. The product had bp 67 °C (0.25 mm), n^{25}D 1.5314, semicarbazone mp 150–151 °C [lit.[33] bp 132–134 °C (14 mm), n^{19}D 1.515, semicarbazone mp 153–154 °C].

1-Phenyl-3-pentanol was prepared in 63% yield from 2-phenylethylmagnesium bromide and propionaldehyde, bp 91–95 °C (1.2 mm) (lit.[34] bp 130 °C (15 mm)].

1-Phenyl-3-pentanone was obtained in 56% yield by chromic acid oxidation[31] of 1-phenyl-3-pentanol. The product had bp 62 °C (0.3 mm), n^{29}D 1.5045 [lit.[35] bp 130–132 °C (19 mm)].

5-Phenyl-2-pentanone. To 200 ml of dry ethanol in a flask fitted with a reflux condenser and a dropping funnel was added 7.6 g (0.33 g-atom) of sodium. After the sodium had dissolved, 43 g (0.33 mol) of ethyl acetoacetate was added dropwise over 1 h. The mixture was refluxed for 1 h and 65 g (0.35 mol) of 2-phenylethyl bromide added slowly. The mixture was then refluxed for 21 h, cooled, filtered, and distilled to yield 71% of the alkylation product. Fifty grams (0.21 mol) of this product was heated at 90 °C for 5 h with 330 ml of 5% sodium hydroxide. The mixture was treated with 150 ml of 50% (by weight) sulfuric acid, stirred for 5 h at 90 °C, cooled to room temperature, and stirred for another 48 h. The acid solution was extracted with ether, and the extracts dried over sodium sulfate and distilled to give 87% of 5-phenyl-2-pentanone, bp 132–134 °C (17 mm), n^{25}D 1.5068 [lit. bp 134 °C (17 mm),[36] n^{25}D 1.5070[37]].

1-(3-Chlorophenyl)propanol was obtained in 85% yield from ethylmagnesium bromide and 3-chlorobenzaldehyde, bp 75–76 °C (0.4 mm), n^{25}D 1.5357. Anal. Calcd for $C_9H_{11}ClO$: C, 63.35; H, 6.50; Cl, 20.77. Found: C, 63.39; H, 6.45; Cl, 20.85.

3'-Chloropropiophenone resulted in 93% yield from the chromic acid oxidation[31] of 1-(3-chlorophenyl)propanol, mp 46–47 °C (lit.[38,39] mp 45–46 °C).

1-(3-Bromophenyl)propanol was obtained in 77% yield from ethylmagnesium bromide and 3-bromobenzaldehyde, bp 115 °C (2.7 mm) [lit.[40] bp 125–130 °C (11 mm)].

3'-Bromopropiophenone resulted in 90% yield from the chromic acid oxidation[31] of 1-(3-bromophenyl)propanol, mp 40–41 °C (lit.[38,39] 37.5–40 °C).

1-(3,4-Dichlorophenyl)propanol was obtained in 82% yield from ethylmagnesium bromide and 3,4-dichlorobenzaldehyde, bp 78–79 °C (0.04 mm), n^{22}D 1.5550. Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.92; Cl, 34.57. Found: C, 52.65; H, 4.92; Cl, 34.70.

3',4'-Dichloropropiophenone resulted in 64% yield from the chromic acid oxidation[31] of 1-(3,4-dichlorophenyl)propanol, mp 42–43 °C, oxime mp 116–117 °C (lit.[41] mp 44 °C, oxime mp 121–122 °C).

Acetophenone Ethylimine. A solution of 0.50 mol of benzonitrile was added dropwise with stirring to 0.49 mol (163 ml) of 3 M methylmagnesium bromide in ether. The mixture was refluxed for 18 h and cooled, and 200 ml of 9 M ethylamine in anhydrous methanol added over 2 h. After 2 h at reflux, the mixture was treated successively with 17.5 ml of water and 21 ml of 20% sodium carbonate, and then cooled. The suspension was extracted with ether, and the extracts dried over sodium sulfate and then fractionated to yield 35% of product, bp 52–55 °C (0.5 mm), n^{24}D 1.5367 [lit.[43] bp 44 °C (0.13 mm), n^{20}D 1.5362]. Analysis by GLC indicated ca. 3% contamination with acetophenone.

Acetophenone phenylimine was obtained in 96% yield by the procedure of Saunders and Caress,[21] mp 38.5–40 °C (lit.[44] 41 °C).

Benzophenone phenylimine was obtained by adding 0.39 mol of distilled aniline to 0.10 mol of dichlorodiphenylmethane over a 1-h period. The resulting mixture was filtered and the product recrystallized from ethanol, mp 112–113 °C (lit.[45] 114 °C).

Benzophenone ethylimine was prepared in the same manner as benzophenone phenylimine from dichlorodiphenylmethane and ethylamine. The product had bp 137–138 °C (3.5 mm) [lit.[46] 144 °C (7 mm)]. Analysis by GLC showed ca. 1% benzophenone.

2-Butanone Phenylimine. 2-Butanone diethyl ketal was obtained from 0.50 mol of 2-butanone, 0.50 mol of ethyl orthoformate, and 0.09 mol of ammonium chloride in 60 ml of absolute ethanol. The mixture was allowed to stand for 7 days and then distilled to yield 62% of ketal, bp 44–45 °C (25 mm) [lit.[47] 41 °C (16 mm)]. A mixture of 0.1 mol of the ketal and 0.1 mol of aniline was heated until ethanol no longer distilled. Vacuum distillation of the residue gave 92% of 2-butanone phenylimine, bp 53 °C (2.0 mm) [lit.[48] 106–108 °C (25 mm)].

Propiophenone Phenylimine. Propiophenone diethyl ketal was prepared in the same manner as 2-butanone diethyl ketal, bp 66 °C (0.8 mm) [lit.[49] 93–96 °C (6 mm)]. The ketal was then heated with distilled aniline until ethanol no longer distilled to yield a solid which was recrystallized from ethanol, mp 51–53 °C (lit.[50] 50 °C).

Propiophenone Methylimine. The same procedure as for acetophenone ethylimine[42] was used, preparation of the Grignard complex from ethylmagnesium bromide and benzonitrile, followed by treatment with ethanolic methylamine. Distillation afforded the imine, bp 94 °C (16 mm), $n^{28.5}$D 1.5270 [lit.[42] bp 102 °C (20 mm), n^{20}D 1.5299]. The imine was very sensitive to atmospheric moisture. Freshly prepared material contained ca. 20% of propiophenone as shown by ir and GLC, and further hydrolysis occurred when it was kept for more than a few days at 0 °C.

Photolysis Procedure. Solvents were Mallinckrodt Spectrograde. Solutions 0.05–0.08 M in azide were used, and the percent conversion kept below 8% to minimize secondary reactions. Degassing was conducted using six freeze–pump–thaw cycles on a vacuum line which could be evacuated to less than 10⁻⁵ Torr. A Rayonet reactor, Model RPR-208, was used with a merry-go-round apparatus. Photolyses were conducted at 253.7 nm in quartz tubes with unfiltered light from RUL 2537 lamps, and photolyses at 300 nm with light from RUL 3000 lamps and Kimax tubes and/or Pyrex filters. Uranyl oxalate actinometry was used, assuming quantum yields of oxalate decomposition of 0.60 at 253.7 nm and 0.57 at 300 nm.[51,52] Correction for light absorbed by the actinometer but not the azides (>300 nm) was made by dividing the observed quantum yield by 0.74 (obtained by irradiating the actinometer with light from RUL 2537 lamps through a Pyrex filter). Azide concentrations for quantum yield determinations were chosen such that >99.9% of the incident 253.7-nm light was absorbed by the solution. Nitrogen yields were determined by carrying out the photolyses in degassed tubes equipped with break seals. The tubes were then slowly frozen in liquid nitrogen from the bottom up. The break seal was opened to the evacuated system and the nitrogen pumped into a gas buret with a Toepler pump. The stopcock to the photolysis tube was closed and the contents thawed with warm water. The freezing and pumping process was repeated three times. The nitrogen yield was calculated from the pressure, temperature, and volume of the sample assuming the ideal gas law.

Determination of Photolysis Products. The photolyzed sample, including solvent, was added to 5 ml of 10% sulfuric acid and the mixture stirred magnetically and heated to 80–90 °C under a reflux condenser for 1 h. The mixture was cooled and neutralized with saturated sodium bicarbonate. The organic layer was separated and the aqueous layer extracted with two 2-ml portions of chloroform. In most instances the combined organic layer and extracts were reduced by stirring with excess sodium borohydride in 95% methanol for 1 h, so as to avoid overlap in the GLC analysis of the thermal decomposition

peaks of the azide and the ketone peaks of the hydrolysis products. Excess borohydride was removed by filtration and the resulting solution analyzed.

Analyses were done on a Hewlett-Packard F and M Model 700 gas chromatograph equipped with a flame ionization detector and a Model 240 temperature programmer. The ethyl/methyl migration aptitudes were the 1-aryl-1-propanol/1-arylethanol ratios determined on a 6 ft × 0.125 in. column of 20% FFAP (Applied Science) on Anakrom ABS 100/110 (Analabs) at oven temperatures of 135–190 °C, injector temperatures of 210–280 °C, and nitrogen flow rates of 24–91 ml/min. Retention times ranged from 8 to 37 min. Cyclohexanol or cyclopentanol were used as internal standards to permit comparison with the aryl migration product, 2-butanol, which was analyzed on a 10 ft × 0.125 in. column of Emulphor-O (Applied Science) on Chromosorb P (Varian) employing programmed runs (10 °C/min) from 85 to 152 °C. The products from 3-azido-3-methylhexane were analyzed on a 10.5 ft × 0.125 in. column of Chromosorb 101 (no liquid phase) at 150 °C and 61 ml/min.

Control Experiments. Authentic samples of the ketone and alcohol products were coinjected with the product mixtures. Detector response was calibrated with known mixtures of azide and ketones run through the entire hydrolysis and reduction procedure. No acid-catalyzed decomposition products resulted when the azides alone were put through the hydrolysis and reduction procedures. Azides used for photolysis runs were shown to be free of ketone by GLC. Acetophenone ethylimine and propiophenone methylimine were >99.9% hydrolyzed in 1 h. Reduction of known ketones by the standard procedure gave >99.9% reduction.

References and Notes

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.
(2) NDEA Fellow.
(3) W. H. Saunders, Jr., and E. A. Caress, *J. Am. Chem. Soc.*, **86**, 861 (1964).
(4) F. D. Lewis and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, 90, 7031 (1968).
(5) R. M. Moriarty and M. Rahman, *Tetrahedron*, 21, 2877 (1965).
(6) R. M. Moriarty and R. C. Reardon, *Tetrahedron*, **26**, 1379 (1970).
(7) R. A. Abramovitch and E. P. Kyba, *Chem. Commun.*, 265 (1969).
(8) R. A. Abramovitch and E. P. Kyba, *J. Am. Chem. Soc.*, **93**, 1537 (1971).
(9) R. Brainard and H. Morrison, *J. Am. Chem. Soc.*, **93**, 2685 (1971).
(10) M. L. Yarchak, J. C. Dalton, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **95**, 5228 (1973).
(11) W. D. Closson and H. B. Gray, *J. Am. Chem. Soc.*, **85**, 290 (1963).
(12) S. P. McGlynn, T. Azumi, and M. Kinoshita, "Molecular Spectroscopy of the Triplet State", Prentice-Hall, Englewood Cliffs, N.J., 1969, Chapter 7.
(13) C. Walling, "Free Radicals in Solution", Wiley, New York, N.Y., 1957, p 302.
(14) Melting points are corrected; boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.
(15) K. Serijan and P. Wise, *J. Am. Chem. Soc.*, 74, 365 (1952).
(16) P. Girningo and M. Hauser, *J. Am. Chem. Soc.*, 60, 2581 (1938).
(17) H. Adkins and J. Davis, *J. Am. Chem. Soc.*, **71**, 2955 (1949).
(18) H. Pires and J. Arrigo, *J. Am. Chem. Soc.*, **79**, 4958 (1957).
(19) H. Gilman and R. Meals, *J. Org. Chem.*, 8, 126 (1943).
(20) M. Protiva, O. Exner, M. Borovicka, and J. Pliml, *Chem. Listy*, **46**, 37 (1952).
(21) W. H. Saunders, Jr., and E. A. Caress, *J. Am. Chem. Soc.*, **86**, 861 (1964).
(22) A. L. Logothetis, *J. Am. Chem. Soc.*, **87**, 749 (1965).
(23) C. L. Arcus and R. J. Mesley, *J. Chem. Soc.*, 178 (1953).
(24) H. Wolff, *Org. React.*, 3, 327 (1946).
(25) C. H. Gudmundsen and W. E. McEwen, *J. Am. Chem. Soc.*, **79**, 329 (1957).
(26) W. K. Johnson, *J. Org. Chem.*, 24, 864 (1959).
(27) S. Van Woerden, *Recl. Trav. Chim. Pays-Bas*, 45, 124 (1926).
(28) S. L. Friess and N. Farnham, *J. Am. Chem. Soc.*, 72, 5518 (1950).
(29) J. Meinwald and S. L. Emerman, *J. Am. Chem. Soc.*, 78, 5087 (1956).
(30) D. Nightingale and H. D. Radford, *J. Org. Chem.*, 14, 1089 (1949).
(31) A. Vogel, "Practical Organic Chemistry", Wiley, New York, N.Y., 1956, p 336.
(32) P. T. Izzo and S. R. Safir, *J. Org. Chem.*, 24, 701 (1959).
(33) M. Tiffenean and Y. Deux, *C. R. Acad. Sci.*, 214, 892 (1942).
(34) R. O. Robbin, Jr., D. Davidson, and M. T. Bogert, *J. Am. Chem. Soc.*, **57**, 151 (1935).
(35) L. M. Roch, *Ann. Chim. (Paris)*, 6, 105 (1961).
(36) C. M. Clark and J. D. A. Johnson, *J. Chem. Soc.*, 126 (1962).
(37) R. T. Arnold and P. Veeravagu, *J. Am. Chem. Soc.*, 82, 5411 (1960).
(38) B. L. Zenitz and W. H. Hartung, *J. Org. Chem.*, 11, 444 (1946).
(39) J. R. Keneford and J. C. E. Simpson, *J. Chem. Soc.*, 354 (1948).
(40) J. Frejka and H. Zamis, *Cas. Cesk. Lek.*, 63, 157 (1950); *Chem. Abstr.*, 47, 2131e (1953).
(41) V. V. Devasthale, P. B. Sattur, and K. S. Nargund, *J. Karnatak Univ.*, 1, 39 (1956); *Chem. Abstr.*, 52, 8086c (1958).
(42) G. Charles and M. Mazet, *C. R. Acad. Sci.*, 87, 491 (1962).
(43) F. Asinger, H. W. Becker, W. Schafer, and A. Saus, *Monatsh. Chem.*, 97, 301 (1966).
(44) G. Reddelien, *Ber.*, 43, 2476 (1910).
(45) C. K. Ingold and S. D. Weaver, *J. Chem. Soc.*, 125, 1456 (1924).
(46) B. K. Campbell and K. N. Campbell, *J. Org. Chem.*, 9, 178 (1944).
(47) H. E. Carswell and H. Adkins, *J. Am. Chem. Soc.*, 50, 235 (1928).
(48) P. Ramart-Lucas and M. J. Hoch, *Bull. Soc. Chim. Fr.*, 3, 918 (1936).
(49) E. L. Beals and F. A. Gilfillam, *J. Am. Pharm. Assoc.*, 25, 226 (1926).
(50) G. Reddelien, *Ber.*, 47, 1364 (1914).
(51) G. S. Forbes and W. G. Leighton, *J. Am. Chem. Soc.*, 52, 3139 (1930).
(52) J. G. Calvert and J. W. Pitts Jr., "Photochemistry", Wiley, New York, N.Y., 1966, p 787.

Photochemistry of Diazonium Salts. 4. Synthesis of Ring-Fluorinated Tyramines and Dopamines[1]

Kenneth L. Kirk

*Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health,·
Bethesda, Maryland 20014*

3-Fluorotyramine, 3,5-difluorotyramine, and 6-fluorodopamine were synthesized from ring-hydroxylated N-trifluoroacetylphenethylamine precursors by sequences involving ring nitration, catalytic reduction, diazotization of the resulting arylamine, photochemical decomposition of the diazonium fluoroborate in fluoroboric acid, and, finally, removal of the N-trifluoroacetyl protecting group. Photochemical decomposition of N-trifluoroacetyl-3-fluoro-4-hydroxyphenethylamine-5-diazonium fluoroborate in fluoroboric acid produced, in addition to the 3,5-difluorotyramine derivative, N-trifluoroacetyl-3,4-dihydroxy-5-fluorophenethylamine, the result of competitive solvolysis of the presumed arylcarbonium ion intermediate. Removal of the protecting group from the product afforded 5-fluorodopamine. 2-Fluorodopamine was synthesized by elaboration of 2-fluoro-3,4-dimethoxybenzaldehyde, this aldehyde being obtained by an analogous photochemical ring fluorination. As a result of the electronic effect of fluorine, phenol acidity is markedly enhanced in the fluorinated analogues, to the extent that considerable concentrations of phenolate anion will be present at physiological pH.

Ring-hydroxylated phenethylamines (tyramine, dopamine) play a central role in cellular function, particularly in the sympathetic nervous system;[2] accordingly, the biosynthesis, mechanism and sites of action, and transformations of these compounds have received much attention.[3] Several fluorinated derivatives of phenethylamine have been synthesized and tested pharmacologically; in these compounds, however, the fluorine substituent(s) appear on the side chain or on a nonhydroxylated benzene ring.[4-6]

Several considerations prompted our interest in the preparation of phenethylamines with the ring both hydroxylated and fluorinated. The ubiquity of the phenolic function in biogenic amines suggests a unique role for this group in specificity and physiological action. The fluorine atom, through induction and hydrogen bonding, should effect strong perturbation in such properties of the phenolic groups as pK and oxidation potential. The several possible ring positions for the fluorine atom would also provide a series in which each isomer possesses a unique electron density distribution. The value of studying such a series is indicated by the large differences in biological behavior already observed for 2- and 4-fluorohistidine.[7]

The fluorination procedure involves the photochemical decomposition of an aryldiazonium ion in aqueous fluoroboric acid, the diazonium ion being generated in situ from the corresponding arylamine and nitrous acid. Photodecomposition generates, presumably, a carbonium ion which reacts competitively with fluoride ion and with water. Except for one case (see below), the products of the water reaction were not isolated in the present work. The fluorine atom is considered to occupy the same ring position as its precursor functions, the absence of any rearrangements being supported by NMR spectral data, as discussed below.

Illustrative of the general procedure is the conversion of tyramine to 3-fluorotyramine (**1d**). N-Trifluoroacetyltyramine[8] was nitrated[9] to **1a**, the latter compound was hydro-

genated, and the resulting amine (**1b**) was diazotized in 50% aqueous fluoroboric acid. Irradiation of the solution of diazonium ion afforded N-trifluoroacetyl-3-fluorotyramine (**1c**) in 36% yield (based on **1a**). The trifluoroacetyl protecting group was removed by acid hydrolysis, and **1d** was isolated as its hydrochloride.

N-Trifluoroacetyl-3-fluorotyramine (**1c**), in turn, was nitrated in the available ortho position to give **2a**, and the sequence of steps repeated, as above, to produce N-trifluoroacetyl-3,5-difluorotyramine (**2c**) in 40% yield, which was converted to 3,5-difluorotyramine hydrochloride (**2d** HCl) by acid hydrolysis. The hydroxylated compound **3a** was isolated as a by-product of the irradiation procedure, and was converted into the hydrochloride of 5-fluorodopamine (**3b**) by methanolysis of **3a**. Attempts to produce o,o'-difluorophenols by utilization of the corresponding dinitrophenols were thwarted because of the instability of the intermediate diaminophenol.

In this study, no attempt was made to compare directly the photochemical procedure with thermal methods for decomposition of diazonium fluoroborates.[10,11] While higher yields have been reported for the pyrolysis of certain structurally related diazonium fluoroborates,[6b] the photochemical method was chosen for its reliability (yields of aryl fluoride are consistently 20–40%) and convenience—reaction times of 0.5–1.5 h are sufficient, the diazonium ion is generated and decomposed in situ, and the desired products are isolated with relative ease.

Of the three isomeric ring-fluorinated dopamines, the 6-fluoro isomer (**4d**) is the most readily accessible, because mononitration of N-trifluoroacetyl-3,4-dimethoxyphenethylamine[8] occurs exclusively in the 6 position to give **4a**. This
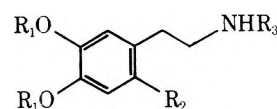
	R_1	R_2	R_3
4a	CH_3	NO_2	$COCF_3$
b	CH_3	NH_2	$COCF_3$
c	CH_3	F	$COCF_3$
d	H	F	H
e	H	F	$COCF_3$

	R_1	R_2	R_3		R_1	R_2	R_3		R_1	R_2	R_3
1a	H	NO_2	$COCF_3$	**2a**	NO_2	F	$COCF_3$	**3a**	OH	F	$COCF_3$
b	H	NH_2	$COCF_3$	**b**	NH_2	F	$COCF_3$	**b**	OH	F	H
c	H	F	$COCF_3$	**c**	F	F	$COCF_3$				
d	H	F	H	**d**	F	F	H				

result, clearly shown by the absence of any detectable coupling of the two aromatic protons in the NMR spectrum of **4a**, is in agreement with an earlier report of the mononitration of

<div align="center">Table I.   Aromatic Proton and Fluorine NMR Parameters</div>

Compd	^{1}H, ppm[a]	^{19}F, ppm[b]	J, Hz
1d HCl	6.97–7.30 (m), H-2, H-5, H-6	29.7 (m), F-3	
2d HCl	6.88 (m), H-2, H-6	33.5 (m), F-3, F-5	$J_{HF}^{ortho} = +11.3, J_{HF}^{para} = -2.1,^c J_{HH}^{meta} = 2.6$ $J_{FF}^{meta} = 12.6$
3b HCl	6.55 (q), H-6;^{d} 6.51 (q), H-2	31.0 (m), F-5	$J_{HH}^{meta} = 2.2, J_{HF}^{ortho} = +10.8,^c J_{HF}^{para} = -1.6$
4d HBr	6.78 (d), H-2;^{d} 6.66 (d), H-5	37.0 (dd), F-6	$J_{HF}^{meta} = 7.6, J_{HF}^{ortho} = 11.0$
9 HCl	6.61 (q), H-6; 6.57 (q), H-5	26.3 (m), F-2	$J_{HH}^{ortho} = 8.6, J_{HF}^{meta} = +8.2,^c J_{HF}^{para} = -1.8$

^{a} Proton spectra were measured at 60 MHz in CD$_3$OD. Chemical shifts are relative to (CH$_3$)$_4$Si. ^{b} Fluorine spectra were measured at 100 MHz in D$_2$O. Chemical shifts are recorded in parts per million downfield from hexafluorobenzene. ^{c} The two HF coupling constants are of opposite sign. The assignment of the negative value to the para coupling constant is arbitrary. ^{d} The numbering of the ring is such that the fluorine is assigned the 5 position in 3b HCl and the 6 position in 4d HBr.

3,4-dimethoxyphenethylamine.[12] Reduction of 4a, followed by diazotization and photolysis as before, produced 4c in 20% yield (based on 4b). Deacylation and demethylation[6b] of 4c with hydrobromic acid afforded 6-fluorodopamine (4d) as its hydrobromide.

The compounds to this point were prepared by ring functionalization of preexisting phenethylamines. No such direct route was obvious for the synthesis of the remaining isomer, 2-fluorodopamine (9).[13] 2-Nitro-3,4-dimethoxybenzaldehyde[14] was chosen as a starting point for the synthesis of 9. Protection of the aldehyde as the dimethyl acetal, hydro-

genation, diazotization in situ, and photochemical decomposition afforded 2-fluoro-3,4-dimethoxybenzaldehyde (5) in 20% yield, based on the nitrobenzaldehyde acetal. The fluoroaldehyde was condensed with nitromethane to give the nitrostyrene 6, which was reduced to 7 with sodium borohydride.[15] Catalytic hydrogenation reduced 7 smoothly to the ethylamine 8, from which the hydrobromide of 2-fluoro-dopamine (9) was produced by demethylation with hydrobromic acid. Because 9 was difficult to purify as its hydrobromide, it was converted to its trifluoroacetyl derivative 10, purified by sublimation. Acid-catalyzed methanolysis of 10 regenerated 9 as its hydrochloride.
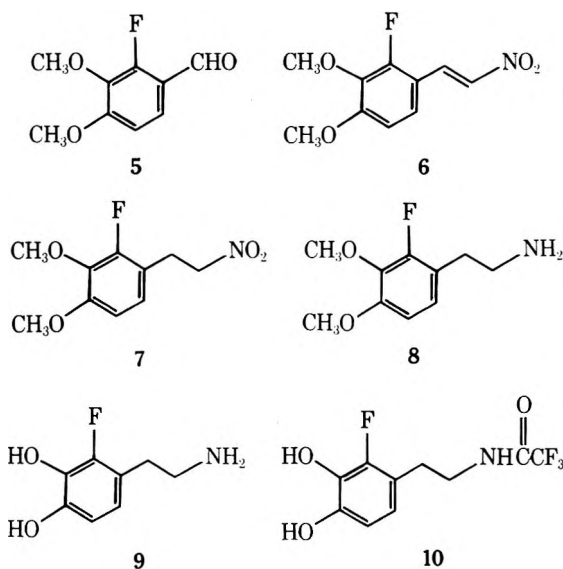
Structural assignments for the ring-fluorinated products are based, in part, on the structures of known precursors. Although replacement of the amino group by the fluorine atom had occurred without rearrangement in all our previous cases, ^{1}H and ^{19}F NMR analyses of the fluorinated products were used as additional support for structural assignments (Table I). Both the ^{1}H and ^{19}F spectra of 1d HCl are quite complex, and no attempt is made to interpret them at this time.[16] While these spectra do not place the fluorine uniquely adjacent to the hydroxyl group (2-fluorotyramine would probably exhibit

similar coupling), the conversion of 1a to the 3 series (the structures of which are unambiguously assigned below) appears to rule out this alternate structure. The ^{1}H spectrum of 2d HCl displays a symmetrical multiplet of some ten lines, consistent with an AA'XX' system and from which the parameters given in Table I were derived.[17] Again, while the coupling pattern does not in itself accommodate only structure 2d HCl, the symmetry implied by the spectrum, together with the known structure of precursor 1a, render alternatives untenable. The ^{19}F spectrum of 2d HCl is in complete agreement with the interpretation given the ^{1}H spectrum, but owing to difficulty in identifying low-intensity lines, it was not further analyzed. The ^{1}H spectrum of 3b HCl appears as an unsymmetrical multiplet comprised of two overlapping quartets, from which coupling constants consistent with meta proton–proton and ortho and para proton–fluorine spin interactions were extracted,[17] and thus establishes the position of the fluorine atom in this series. A similar analysis of the ^{1}H spectrum of 9 HCl, also an ABX system, revealed ortho proton–proton coupling and meta and para proton–fluorine coupling, confirming the assignment of the fluorine substituent to the 2 position. The para proton–fluorine coupling constants of 3b HCl and 9 HCl (as well as of 2d HCl) and the companion proton–fluorine interactions are of opposite signs, with the para coupling constant arbitrarily being assigned the negative value. The appearance of the ^{19}F spectra of 3b HCl and 9 HCl reflects these sign differences, in that the two most intense peaks are separated by the sum of the two proton–fluorine coupling constants. Thus, the fluorine signal of 3b HCl is an unresolved singlet, while that of 9 HCl appears as a symmetrical doublet separated by 9 Hz. No attempt was made to identify and analyze additional lines in the ^{19}F spectra of these compounds because of their low intensity and tendency to coalesce. Finally, the presence of ortho and meta hydrogen–fluorine coupling in both the ^{1}H and ^{19}F spectra of 4d HBr, readily extracted by first-order analysis, requires that the fluorine substituent be in the 6 position.

pK_a values were obtained spectrophotometrically for the fluorophenols: 3-fluorotyramine (1d), 8.35; 3,5-difluorotyramine (2d), 7.03; N-trifluoroacetyl-2-fluorodopamine (10), 7.52; N-trifluoroacetyl-5-fluorodopamine (3a), 7.42. Reliable values for 6-fluorodopamine (4d or 4e) could not be obtained, possibly owing to air oxidation of the catechol system. Literature values for related compounds are: phenol, 9.98;[18] tyramine, 9.50;[19] catechol, 9.45,[20] dopamine, 8.90;[19] o-fluorophenol, 8.81;[18] and m-fluorophenol, 9.28.[18] As a result of the acid-strengthening effect of fluorine substitution, the phenolic groups of these fluorinated phenethylamines will be significantly ionized at physiological pH, a factor which may be significant in the interaction of these compounds with biomembranes and receptor sites.[21] It is also clear that in the isomeric 2- and 5-fluorodopamines, different phenolic groups, relative to the aminoethyl side chain, will be ionized under physiological conditions.

The likelihood of side-chain hydrogen bonds to fluorine in **4d** and **9** may have physiological significance and conformational studies are in progress. At present, it is impossible to predict the biological properties of these fluoro analogues; a variety of studies are in progress, however, and results will be reported separately.

Experimental Section

Microanalyses, NMR spectra, and mass spectra were provided by the Microanalytical Services and Instrumentation Section of this Laboratory, under the direction of Dr. David F. Johnson. Homogeneities of all compounds were confirmed by TLC; identities of all compounds were checked by mass spectrometry. Physical data are given in Table II.

Fluorination Procedure. The arylamine (10–20 mmol) was dissolved in 150 ml of 50% fluoroboric acid; the solution was cooled to 0 °C and was treated dropwise with a 10% molar excess of aqueous sodium nitrite ($\sim$2 M). After 1 h at 0 °C, the solution of diazonium fluoroborate was diluted to 200 ml with ice-cold 50% fluoroboric acid and was irradiated in the apparatus previously described[22] (equipped with a Pyrex filter), until absence of color formation with an alkaline solution of β-naphthol indicated complete decomposition of the diazonium ion. The cold solution was neutralized with concentrated sodium hydroxide and was extracted with ether until TLC showed complete absence of product in the aqueous phase. After drying and removal of solvent, the product was purified by column chromatography or sublimation.

N-Trifluoroacetyl-3-nitrotyramine (1a). To a stirred solution of 8 g (0.034 mol) of N-trifluoroacetyltyramine[8] in 40 ml of acetic acid, cooled to 5 °C, was added dropwise 1.8 ml of fuming nitric acid.[9] Following addition, the solution was stirred in an ice bath for 1 h, then poured over ice. The yellow precipitate was filtered and recrystallized from aqueous ethanol to give 8.9 g (94%) of **1a.**

N-Trifluoroacetyl-3-fluorotyramine (1c). A solution of **1a** (2.78 g, 10 mmol) in 100 ml of ethanol was hydrogenated at atmospheric pressure over 10% Pd/C. Removal of catalyst and solvent produced N-trifluoroacetyl-3-aminotyramine (**1b**). Without further purification, **1b** was diazotized and irradiated (1 h) to give, after chromatography on silica gel (1% methanol–chloroform), 0.904 g (36%) of **1c,** which was further purified by crystallization from aqueous ethanol.

3-Fluorotyramine Hydrochloride (1d HCl). A solution of 122 mg (0.5 mmol) of **1c** in 5 ml of 3 N hydrochloric acid and 1 ml of ethanol was heated on a steam bath for 20 h. After thorough evaporation of solvent, the residue was dissolved in methanol. Addition of ether effected precipitation of 57 mg of 3-fluorotyramine hydrochloride (**1d HCl**) (60%), recrystallized from methanol–ether.

N-Trifluoroacetyl-3-fluoro-5-nitrotyramine (2a). Nitration as above of a solution of 1.47 g (5.85 mmol) of **1c** in 30 ml of acetic acid with 0.30 ml of fuming nitric acid afforded 1.55 g (89%) of **2a,** recrystallized from aqueous ethanol.

3,5-Difluorotyramine Hydrochloride (2d HCl). Hydrogenation at atmospheric pressure of 1.50 g (5.06 mmol) of **2a** in ethanol produced N-trifluoroacetyl-3-fluoro-5-aminotyramine (**2b**). Without further purification, **2b** was subjected to diazotization and irradiation as described. The crude product was chromatographed over silica gel, elution with 1% methanol in chloroform giving 529 mg (40%) of N-trifluoroacetyl-3,5-difluorotyramine (**1c**), which was recrystallized from aqueous ethanol. This material was hydrolyzed by heating (steam bath) its solution in 6 N hydrochloric acid for 10 h to give **2d** HCl in 67% yield, recrystallized from methanol–ether.

3,4-Dihydroxy-5-fluorophenethylamine Hydrochloride (5-Fluorodopamine Hydrochloride) (3b HCl). Further elution of the crude product obtained in the photolysis of the diazonium fluoroborate derived from **2b,** with 3% methanol in chloroform, gave 461 mg (34%) of N-trifluoroacetyl-3,4-dihydroxy-5-fluorophenethylamine (**3a**), purified by sublimation. Compound **3a** was dissolved in 10 ml of methanol saturated with dry hydrogen chloride, and the solution was stored for 4 days, after which time TLC showed complete deacylation. (This procedure was found to give a cleaner product than hydrolysis in aqueous acid.) Removal of solvent and recrystallization from methanol–ether afforded **3b** HCl in 72% yield.

N-Trifluoroacetyl-2-nitro-4,5-dimethoxyphenethylamine (4a). Nitration of a solution of 22.5 g (0.081 mol) of N-trifluoroacetyl-3,4-dimethoxyphenethylamine[8] in 100 ml of acetic acid, with 4.0 ml of fuming nitric acid, was carried out as above, to give 19.6 g (74%) of **4a.**

N-Trifluoroacetyl-2-fluoro-4,5-dimethoxyphenethylamine (4c). A solution of **4a** (3.22 g, 10 mmol) in 250 ml of ethanol was hy-

Table II. Yields and Physical Data

Compd	Yield, %	Mp, °C	Formula[b]
1a	94	130–131	$C_{10}H_9F_3N_2O_4$
1c	36	107–108	$C_{10}H_9F_4NO_2$
1d HCl	60	268–270 dec	$C_8H_{11}ClFNO$
2a	89	133–134	$C_{10}H_8F_4N_2O_4$
2c	40	113–114	$C_{10}H_8F_5NO_2$
2d HCl	67	260–273 dec	$C_8H_{10}ClF_2NO$
3a	34	132–133	$C_{10}H_9F_4NO_3$
3b HCl	72	205–215 dec	$C_8H_{11}ClFNO_2$
4a	74	143–144	$C_{12}H_{13}F_3N_2O_5$
4c	22	130–131	$C_{12}H_{13}F_4NO_3$
4d HBr	95	207–209	$C_8H_{11}BrFNO_2$
4e		100–101	$C_{10}H_9F_4NO_3$
5	20	52.5–53.5	$C_9H_9FO_3$
6	75	62–63	$C_{10}H_{10}FNO_4$
7	93	42–43	$C_{10}H_{12}FNO_4$
8 HBr	63	174–177	$C_{10}H_{15}BrFNO_2$
9 HBr[a]	78	158–160	$C_8H_{11}BrFNO_2$
9 HCl	78	158–160	$C_8H_{11}ClFNO_2$
10	76	127–127	$C_{10}H_9F_4NO_3$

[a] Could not be recrystallized. See text. [b] Satisfactory analytical data ($\pm$0.35% for C, H, N) were reported for all compounds except 9 HBr (no data), 5 (no N), 1c, 2d HCl, 9 HCl (C 0.6% low), and 7 (C 0.6% high). Ed.

drogenated over 500 mg of 10% Pd/C to give the arylamine **4b.** This amine, without purification, was diazotized and irradiated for 1 h to give, after chromatography over silica gel (1% methanol in chloroform), 650 mg of **4c** (22%).

2-Fluoro-4,5-dimethoxyphenethylamine Hydrobromide (6-Fluorodopamine Hydrobromide) (4d HBr). A solution of 300 mg (1.02 mmol) of **4c** in 10 ml of 48% hydrobromic acid was heated in an oil bath at 140 °C for 4 h.[6b] A stream of hydrogen was bubbled through the solution during the reaction. The solvent was removed under vacuum and traces of hydrogen bromide were removed by addition and evaporation of water, this process being repeated three times. After drying the residue over potassium hydroxide, white crystals were obtained. Recrystallization from methanol–ether gave 260 mg of **4d** HBr (95%).

A small sample of **4d** HBr was treated with excess trifluoroacetic anhydride. After 2 h of storage at room temperature, removal of excess anhydride, addition of methanol, and evaporation, sublimation of the residue produced N-trifluoroacetyl-2-fluoro-4,5-dihydroxyphenethylamine (**4e**).

2-Fluoro-3,4-dimethoxybenzaldehyde (5). Hydrogen chloride was bubbled briefly into a solution of 4.22 g (20 mmol) of 2-nitro-3,4-dimethoxybenzaldehyde[14] in 250 ml of methanol. After 1 day, TLC indicated the absence of aldehyde. The solution was neutralized with methanolic potassium hydroxide and evaporated. Water was added and the resulting solution was extracted three times with ether. After drying and removal of solvent, the product, 2-nitro-3,4-dimethoxybenzaldehyde dimethyl acetal, was dissolved in 250 ml of ethanol containing 0.2 ml of triethylamine and the solution was hydrogenated over platinum at 40 psi for 6 h. Removal of catalyst and solvent afforded 2-amino-3,4-dimethoxybenzaldehyde dimethyl acetal, 3.53 g (78%). This amine, 2.27 g (10 mmol), was diazotized and irradiated for 1 h to yield, after chromatography over silica gel (chloroform–carbon tetrachloride, 1:1), 359 mg (20%) of the fluoro aldehyde **5,** purified further by sublimation.

1-(2-Fluoro-3,4-dimethoxyphenyl)-2-nitroethylene (6). A solution of 560 mg (3.04 mmol) of **5** and 500 mg of ammonium acetate in 30 ml of nitromethane was heated on a steam bath for 5 h. Water was added and the solution was extracted three times with ether. After drying, solvent was removed to give 525 mg (75%) of **6,** crystallized from aqueous ethanol.

1-(2-Fluoro-3,4-dimethoxyphenyl)-2-nitroethane (7). Sodium borohydride, 105 mg (2.8 mmol), was dissolved in 3.5 ml of ethanol. The solution was cooled in an ice bath and stirred under nitrogen while a solution of 285 mg (1.25 mmol) of the nitrostyrene **6** in 10 ml of ethanol was added over 2 h.[15] After storage overnight in a refrigerator, the solution was made slightly acidic with 3 N hydrochloric acid, water was added, and the solution was extracted three times with ether. After drying and removal of solvent, the residue was sublimed to give 267 mg of **7** (93%).

Table III. Ultraviolet Spectral Data [a]

Compd-(solvent) [b]	λ_{max}, nm	ϵ	Compd-(solvent) [b]	λ_{max}, nm	ϵ
1d (A)	271	1476	3a (C)	277	2407
1d (B)	288	2558	4e (A)	281	3162
2d (A)	262	552	4e (C)	290	5260
2d (B)	277	2016	10 (A)	270	866
3a (A)	270	991	10 (C)	276	2227

[a] Spectra were measured on a Cary Model 15 recording spectrophotometer. [b] Solvents: A, 0.05 N HCl; B, 0.05 N NaOH; C, 0.05 M phosphate buffer, pH 9.40.

2-Fluoro-3,4-dimethoxyphenethylamine Hydrobromide (8 HBr). A solution of 267 mg (1.16 mmol) of the nitroethane 7 in 50 ml of ethanol was hydrogenated overnight over 300 mg of PtO₂ at 40 psi. Removal of catalyst, addition of 1.3 ml of 1 N hydrobromic acid, and removal of solvent gave, after recrystallization from methanol–ether, 205 mg of 8 HBr (63%).

2-Fluoro-3,4-dihydroxyphenethylamine Hydrobromide (2-Fluorodopamine Hydrobromide) (9 HBr). Compound 8, 100 mg (0.5 mmol), was demethylated as described above for the preparation of 4d, with a 6-h reaction time. Removal of solvent and drying of the residue over potassium hydroxide gave 76 mg (85%) of 9 HBr as off-white crystals. Repeated attempts to recrystallize this material were unsuccessful.

***N*-Trifluoroacetyl-2-fluoro-3,4-dihydroxyphenethylamine (10).** Using the procedure described above for the preparation of 4e, 9 HBr, 60 mg (0.21 mmol), was converted to the trifluoroacetyl derivative 10 in 76% yield (after sublimation).

2-Fluoro-3,4-dihydroxyphenethylamine Hydrochloride (9 HCl). A solution of 44 mg (0.16 mmol) of 10 in 10 ml of methanol was saturated with dry hydrogen chloride and stored. After 6 days, TLC demonstrated complete deacylation. Removal of solvent and excess hydrogen chloride produced 9 HCl, 26 mg (78%), recrystallized from methanol–ether.

pK_a Determinations. The uv spectra of the fluorinated phenols and catechols display the expected increase in intensity and bathochromic shift when their solutions are made alkaline (Table III). Aliquots (100 μl) of a stock solution of the material being investigated were diluted to 3.00 ml with 0.05 M phosphate buffers and the degree of ionization determined as a function of pH by measurement of the optical density at that wavelength corresponding to the largest spectral difference between the neutral species and monoanion. Determinations were made at no less than five pH values, with agreement of at least ±0.05 pH unit.

Registry No.—1a, 59043-60-6; 1c, 59043-61-7; 1d, 404-84-2; 1d HCl, 458-33-3; 2a, 59043-62-8; 2c, 59043-63-9; 2d, 59043-64-0; 2d HCl, 59043-65-1; 3a, 59043-66-2; 3b HCl, 59043-67-3; 4a, 59043-68-4; 4c, 59043-69-5; 4d HCl, 59043-70-8; 4e, 59043-71-9; 5, 37686-68-3; 6, 59043-72-0; 7, 59043-73-1; 8 HBr, 59043-74-2; 9 HBr, 59043-75-3; 9 HCl, 59043-76-4; 10, 59043-77-5; *N*-trifluoroacetyltryamine, 13230-73-4; nitric acid, 7697-37-2; HCl, 7647-01-0; *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine, 13230-71-2; HBr, 10035-10-6; 2-nitro-3,4-dimethoxybenzaldehyde, 55149-84-3.

References and Notes

(1) For part 3 see K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **38**, 3647 (1973).
(2) L. L. Iverson, Ed., *Br. Med. J.*, **29**, 91 (1973).
(3) For example, A. Rotman, J. Lundstrom, E. McNeal, J. Daly, and C. R. Creveling, *J. Med. Chem.*, **18**, 138 (1975), and references cited therein.
(4) (a) R. W. Fuller, H. D. Snoddy, B. B. Mollow, and K. M. Hauser, *Psychopharmacologia*, **28**, 205 (1973); R. W. Fuller and B. B. Mollow, Abstracts, 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, No. FLUO-5; (b) H. Bercher, H. Blayer, and A. Grisk, *Acta Biol. Med. Ger.*, **33**, 335 (1974); H. Bercher and A. Grisk, *ibid.*, **34**, 667 (1975).
(5) A preliminary report has appeared on the preparation of [¹⁸F]-6-fluorodopamine: A. P. Wolf, Proceedings of the 21st Annual Meeting of the Society of Nuclear Medicine, *J. Nucl. Med.*, **15**, 513 (1974). A series of polyfluorophenylalkylamines, including a 4-methoxy-2,3,5,6-tetrafluoro analogue of (+)-amphetamine, has been reported: W. L. White and R. Filler. *J. Chem. Soc.*, 2062 (1971).
(6) (a) Aromatic amino acids having both fluoro and hydroxy functionality in the ring are well known: F. Weygand and W. Oettmeier, *Russ. Chem. Rev. (Engl. Transl.)*, **39**, 290 (1970). (b) 3,4-Dihydroxy-5-fluoro-DL-phenylalanine (5-fluoro-Dopa) and [¹⁸F] -5-fluoro-Dopa have been reported: G. Firnau, C. Nahmias, and S. Garnett, *J. Med. Chem.*, **16**, 419 (1973).
(7) K. L. Kirk and L. A. Cohen. ACS Symposium Series: "Biochemistry of the Carbon–Fluorine Bond", in press.
(8) D. D. Clarke, S. Wilk, and S. E. Gillow, *J. Gas Chromatogr.*, **4**, 310 (1966).
(9) K. C. Roberts and J. A. Rhys, *J. Chem. Soc.*, 39 (1937).
(10) M. Hudlicky, "Organic Fluorine Chemistry", Plenum Press, New York, N.Y., 1970, p 42.
(11) Initial efforts to decompose diazonium fluoroborates in this series thermally gave disappointing results, either because of difficulties in isolation of the diazonium fluoroborate (from 1b) or inability to effect clean pyrolytic decomposition (fluoroborate derived from 4b). A direct comparison of the thermal and photochemical decomposition procedures would require a study of structural parameters affecting each procedure, a study beyond the scope of the present work.
(12) J. Harley-Mason, *J. Chem. Soc.*, 200 (1953).
(13) Preliminary experiments designed to direct nitration of *N*-trifluoroacetyl-3,4-dimethoxyphenethylamine to the 2 position, by prior blocking of the 6 position by halogenation, were unrewarding. Apparently steric and electronic effects combine to prevent ring nitration of the 6-bromo or 6-chloro derivative.
(14) A. Butenandt and H. G. Schlossberger, *Chem. Ber.*, **85**, 565 (1952).
(15) J. Gal, L. D. Gruenke, and N. Castagnoli, Jr., *J. Med. Chem.*, **18**, 683 (1975).
(16) Computer-assisted analyses of the NMR spectra of this and other fluorinated phenols and catechols are in progress.
(17) E. D. Becker, "High Resolution NMR", Academic Press, New York, N.Y., 1969, pp 152–170.
(18) V. M. Vlasov and G. G. Yakobson, *Russ. Chem. Rev. (Engl. Transl.)*, **43**, 781 (1974).
(19) R. B. Martin, *J. Phys. Chem.*, **75**, 2657 (1971).
(20) C. F. Timerlake, *J. Chem. Soc.*, 4987 (1957).
(21) The physiological properties of β,β-difluorophenethylamines may be due, in part, to the reduced basicity of the side chain amino groups (ref 4a).
(22) K. L. Kirk, W. Nagai, and L. A. Cohen, *J. Am. Chem. Soc.*, **95**, 8389 (1973).

Fluorinated Cyclopropenyl Methyl Ethers. New Stable Cyclopropenium Cations

Bruce E. Smart

Contribution No. 2354 from the Central Research and Development Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

The first fluorinated cyclopropenyl ethers, 1-methoxytrifluorocyclopropene, 1-methoxy-2-chlorodifluorocyclopropene, and 1,2-dimethoxydifluorocyclopropene, have been synthesized. These ethers are exceedingly reactive and much less stable than homologous polyfluorocycloalkenyl ethers, but they react with antimony pentafluoride to give unusually stable cyclopropenium hexafluoroantimonate salts.

The reaction of nucleophiles, especially alkoxides, with perfluoroalkenes and perfluorocycloalkenes (having four, five, and six carbons) has received considerable mechanistic and synthetic attention.[1,2] However, similar studies on polyfluorocyclopropenes generally have been limited and often unsuccessful. West and co-workers[3] described the synthesis of various fluorinated cyclopropenes where polyhalocyclopropenes were treated with fluoride ion. Sargeant and Krespan[4] reported that perfluorocyclopropene reacted, often uncontrollably, with amines to give extensive degradation products. Polyfluorocyclopropenes are reported here to react with methoxide ion to give the first examples of polyfluorocyclopropenyl ethers.

Preparation and Properties of Cyclopropenyl Ethers. 1-Methoxytrifluorocyclopropene (**1a**), bp 67–68 °C, and 1,2-dimethoxydifluorocyclopropene (**1b**), bp 74 °C (80 mm),

1a, R = F
b, R = OCH₃
c, R = Cl

2
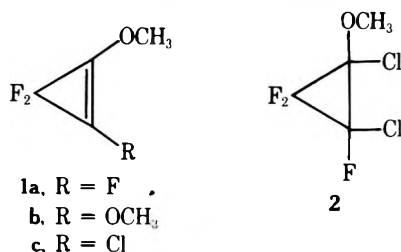
were prepared by cautiously adding perfluorocyclopropene to a slurry of 1 or 2 equiv of sodium methoxide in dry diglyme at −78 °C. The products were flash distilled from the reaction mixture at room temperature and purified by fractional distillation. 1-Methoxy-2-chlorodifluorocyclopropene (**1c**), bp 61–62 °C (150 mm), was similarly prepared from 1,2-dichlorodifluorocyclopropene.

It is essential in these syntheses that the cyclopropene be added to the alkoxide suspension while keeping the reaction temperature below −60 °C. In some cases the reaction mixture has ignited when sodium methoxide powder was added to perfluorocyclopropene in diglyme at low temperature. Methanol solvent must be avoided in these reactions (vide infra).

Caution: The cyclopropenes **1a–c** *are exceedingly reactive molecules and should be handled with great care. They must be prepared under anhydrous conditions as directed, purified immediately, and stored at −78 °C in an inert atmosphere.*

The cyclopropenyl ether structures were readily confirmed by ir (Table I), NMR (Table II), and mass spectral data. The cyclopropenes **1a** and **1b** could not be combustion analyzed owing to their instability. 1-Methoxytrifluorocyclopropene (**1a**) is unusually volatile and flashes into a black mushroom cloud when placed near an open flame. Cyclopropane **2** was prepared in 47% yield when **1a** was treated with molecular chlorine.

Cyclopropenes (**1a–c**) are hydrolytically very unstable. For example, **1b** splatters when added to water, and a sealed vial containing **1a** and water or methanol exploded after standing at room temperature. Under controlled conditions, **1a** reacts with methanol to give methyl *cis*-2,3-dimethoxyacrylate, $CH_3OCH=C(OCH_3)CO_2CH_3$.

The cyclopropenyl ether reactivity is in marked contrast with the behavior of homologous 1-alkoxyperfluorocycloalkenes. For example, the 1-methoxy- or 1,2-dimethoxyperfluorocyclobutenes do not appreciably react with water at room temperature; in fact, these derivatives are routinely prepared in methanol solvent followed by aqueous workup.[5–7] The well-known hydrolysis of 1,2-diethoxytetrafluorocyclobutene to squaric acid requires prolonged heating at 100 °C in 50% sulfuric acid.[8]

Fluorocyclopropenium Cations. The cyclopropenes **1a–c** readily react with SbF₅ in SO₂ at −78 °C to give the cyclopropenium hexafluoroantimonates **3a–c**. At room tempera-

3a, R = F
b, R = OCH₃
c, R = Cl
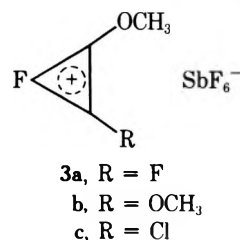
ture, **1a–c** react explosively with SbF₅. This contrasts with the 1-methoxypolyfluorocyclobutenes which smoothly react with neat SbF₅ at room temperature.[9]

The hexafluoroantimonates **3a–c** can be isolated as colorless, crystalline solids which are indefinitely stable at room temperature if moisture is rigorously excluded. Furthermore, the isolated salts can be heated to ca. 90 °C for several minutes (liquefied), and the solid cation salts are recovered unchanged on cooling. Salts **3a–c** are therefore more thermally stable than the previously reported fluorinated cyclopropenium hexafluoroantimonates which decompose at 80 °C or less.[3,4]

The ¹⁹F and ¹H NMR spectral data for **3a–c** and related cations are shown in Table III. In all cases, a singlet in the ¹⁹F NMR spectra is observed. The ¹H and ¹⁹F NMR spectra are unchanged in the −78 to 80 °C temperature range. The allyl and vinyl fluorines of the precursor cyclopropenes are deshielded by 35 ± 1 and 61–82 ppm, respectively, on ionization to **4a–c**. However, in **3a** the fluorines are deshielded by only 8.4 ppm from the allyl fluorines and 69.9 ppm from the vinyl fluorines in **1a**. In **3c**, the deshielding is 18.2 ppm from the allyl fluorines, and in **3b** the fluorine atom is shielded 9.4 ppm from the allyl fluorines in **1b**.

These results suggest that there is important conjugative interaction of the oxygen lone pair electrons which diminishes the electron density at the carbon atom bound to fluorine, i.e.,

Table I. Cyclopropene Carbon–Carbon Double Bond Vibrational Stretching Frequencies

Cyclopropene	νC=C, cm^{-1}	Cyclopropene	νC=C, cm^{-1}
(triangle)	1641 [a,d]	F,F triangle F$_2$	1945 [a,f]
Cl,Cl triangle Cl$_2$	1810 [a,e]	CH$_3$O,F triangle F$_2$ (1a)	1907 [b]
Cl,Cl triangle F$_2$	c,e	CH$_3$O,CH$_3$O triangle F$_2$ (1b)	1895 [b,g]
F,Cl triangle F$_2$	1860 [a,e]	CH$_3$O,Cl triangle F$_2$ (1c)	1832 [b]

[a] Gas phase. [b] Neat liquid phase. [c] Inactive C=C ir, 1760 cm^{-1} (Raman). [d] Reference 14. [e] Reference 3. [f] Reference 4. [g] Exceedingly weak.

Table II. NMR Data for Fluorocyclopropenes[a]

Cyclopropene	Chemical shift (multiplicity)			J_{FF}, Hz
	C$_1$	C$_2$	C$_3$	
F,F triangle F$_2^h$	-145.1 (d)		-96.7 (t)	43.5
F,Cl triangle F$_2^c$		-127.8 (t)	-98.5 (d)	41.4
Cl,Cl triangle F$_2^c$			-99.8	
CH$_3$O,F triangle F$_2$	3.68	-154.6 (t)	-93.1 (d)	48.2
CH$_3$O,CH$_3$O triangle F$_2$		3.84	-93.5	
CH$_3$O,Cl triangle F$_2$	3.97		-99.1	

[a] All chemical shifts in parts per million relative to tetramethylsilane (^{1}H) or trichlorofluoromethane (^{19}F); multiplicities are singlets unless noted; d = doublet, t = triplet. [b] Reference 4. [c] Reference 3.

resonance hybrid **5** is an important contribution. The 0.46–0.81-ppm downfield shift of the methyl protons in **3** further indicates delocalization of electrons from oxygen into the ring.

$$3 \leftrightarrow \quad \text{R---} \triangle \text{---F} =\overset{+}{O}CH_3$$

5
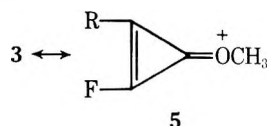
In **3b**, positive charge can be equally delocalized onto both methoxy groups, and the fluorine in **3b** has more vinyl character compared with the fluorines in **3a** and **3c**.

It should be pointed out that hybrid **5** can exist in two isomeric forms (R $\neq$ F), **5a** and **5b**. The magnitude of the me-

5a ⇌ **5b**
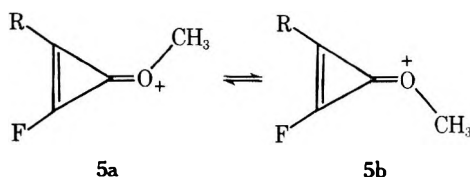
thoxy group rotational barriers will depend upon the contribution of hybrid **5** to the cation. If hybrid **5** is unimportant, the rotational activation barrier will be approximately that in dimethyl ether, 2.7 kcal/mol.[10] Assuming no ring charge delocalization, the **5a** ⇌ **5b** barrier can be estimated to be greater than 17 kcal/mol.[11] The inability to observe temperature-dependent ^{1}H NMR or ^{19}F NMR spectra is strong evidence that cations **3b,c** have relatively low methoxy group rotational barriers[12] and they retain a substantial degree of their delocalized, two π electron aromatic character.

The unusual reactivity of **1a–c** is due to the lability of their allyl fluorines. Solvolysis of these derivatives most likely

Table III. NMR Data for Cyclopropenium Cations

Cation[a]	Chemical shift, ppm[b]	
	^{19}F	^{1}H
C$_3$F$_3^+$ (4a)	-63.1	
C$_3$Cl$_2$F$^+$ (4b)	-63.4	
C$_3$ClF$_2^+$ (4c)	-63.6	
C$_4$H$_3$F$_2$O$^+$ (3a)	-84.7	4.49
C$_5$H$_6$FO$_2^+$ (3b)	-102.9	4.30
C$_4$H$_3$ClFO$^+$ (3c)	-80.9	4.63

[a] Cation derived from corresponding cyclopropene in Table II; see references therein. [b] External reference.

proceeds through stabilized cyclopropenium cations or cyclopropenones. Dehmlow[13] has reported products analogous to the methanolysis product of **1a** or **1b** in the ethanolysis of 1,2-diethoxycyclopropenone or trialkoxycyclopropenium cations.

Experimental Section

The ^{1}H and ^{19}F NMR spectra were obtained on Varian Associates Model A56/60 or XL-100 spectrometers equipped with variable temperature accessories. The proton chemical shifts are referred to tetramethylsilane, and the fluorine chemical shifts are referred to trichlorofluoromethane. All melting and boiling points are uncorrected.

Tetrafluorocyclopropene was prepared following the procedure of Sargeant and Krespan.[4] The literature procedure[3] for the synthesis of 1,2-dichlorodifluorocyclopropene was slightly modified in order to improve the overall yield.

1,2-Dichlorodifluorocyclopropene. A mixture of 24.9 g (0.14 mol) of tetrachlorocyclopropene and 30.3 g (0.17 mol) of antimony trifluoride was placed in a single-neck flask attached to a 12-in. spinning-band column. All operations were performed in a nitrogen atmosphere. The mixture was heated to 90 °C in an oil bath and after ca. 5 min the reaction mixture vigorously boiled, although no distillate was collected. The reaction mixture was heated to 120 °C where the product began to distill, and finally to 140 °C. A total of 14.0 g (69%) of pure product was collected, bp 59 °C [lit.[3] bp 60 °C (733 mm)].

1-Methoxytrifluorocyclopropene (1a). A slurry of 27 g (0.5 mol) of sodium methoxide in 300 ml of diglyme was chilled in a dry ice/acetone bath and 56 g (0.5 mol) of tetrafluorocyclopropene was slowly introduced. The temperature was kept below -60 °C during the addition. After complete addition the reaction mixture was slowly warmed to room temperature, then stirred for 2 h. The product was flash distilled from the reaction mixture at 15–20 mm into a -78 °C trap. The trap content was fractionated to give 38.8 g (63%) of 1a: bp 67–68 °C; ir (neat) 1907 cm^{-1} (C=C); NMR (CCl$_4$) ^{1}H δ 3.68 (s), ^{19}F ϕ -93.1 (d, 2, J = 48.2 Hz), -154.6 (t, 1, J = 48.2 Hz); mass spectrum m/e 124.0111 (P) (calcd, 124.0136).

1,2-Dimethoxydifluorocyclopropene (1b). Precondensed tetrafluorocyclopropene (22.4 g, 0.2 mol) was slowly added to a slurry of 21.6 g (0.4 mol) of sodium methoxide in 200 ml of diglyme chilled in a dry ice/acetone bath. Upon slowly warming to room temperature, the reaction mixture evolved heat and was immediately chilled in an ice bath. After stirring for ca. 30 min at 0 °C and an additional 30 min at room temperature, the product was flash distilled at 20 mm into a -78 °C trap. The trap content was redistilled, and 13.1 g (48%) of crude 1b was collected: bp 53–55 °C (60 mm); ir (neat) 1895 cm^{-1} (w, C=C); NMR (CCl$_4$) ^{1}H δ 3.84 (s), ^{19}F ϕ -93.5 (s); redistilled, bp 74 °C (80 mm); mass spectrum (CI) 136 (P).

1-Methoxy-2-chlorodifluorocyclopropene (1c). A slurry of 16.2 g (0.3 mol) of sodium methoxide in 150 ml of diglyme was treated dropwise with 43.5 g (0.3 mol) of 1,2-dichlorodifluorocyclopropene at such a rate to keep the reaction temperature below -60 °C. After the addition was completed, the mixture was slowly warmed to room temperature and stirred for 1 h. The product was flash distilled from the reaction mixture into a -78 °C trap at ca. 10 mm and was redistilled to afford 33.1 g (79%) of 1c: bp 61–62 °C (150 mm); ir (neat) 1832 cm^{-1} (C=C); NMR (CCl$_4$) ^{1}H δ 3.97 (s), ^{19}F ϕ -99.1 (s).

Anal. Calcd for C$_4$H$_3$ClF$_2$O: C, 34.19; H, 2.15; F, 27.04. Found: C, 34.26; H, 2.43; F, 27.20.

Samples of **1a–c** are best stored as solids at -70 °C under argon. Materials which have been contaminated turn yellow or red and may spontaneously decompose. It is particularly difficult to store **1b**, and it is recommended that this material be used immediately when prepared.

1-Methoxy-1,2-dichloro-2,3,3-trifluorocyclopropane (2). A solution of 24.8 g (0.2 mol) of **1a** in 100 ml of methylene dichloride was protected from the light and treated slowly with 14.2 g (0.2 mol) of precondensed chlorine while keeping the reaction temperature below 0 °C. After stirring in the dark at room temperature overnight, the reaction mixture was distilled at atmospheric pressure to remove the solvent, and the residual oil was fractionated in vacuo to give 18.2 g (47%) of **2**: bp 60–63 °C (190 mm); NMR (CCl₄) ^{1}H δ 3.66 (s), ^{19}F ϕ −142.0, −147.2 (AB m of m, 2, $J_{AB} \simeq$ 166 Hz: A, d, $J \simeq$ 2.8 Hz; B, d, $J \simeq$ 2.2 Hz), −152.0 (d of d, 1, J = 2.8, 2.2 Hz).

Anal. Calcd for C₄H₃Cl₂F₃O: C, 24.64; H, 1.55; F, 29.23. Found: C, 24.68; H, 1.53; F, 29.07.

Methanolysis of 1a. A mixture of 2 ml of methanol in 10 ml of carbon tetrachloride was treated dropwise at room temperature with 1.24 g (10 mmol) of **1a**. After stirring overnight, the reaction mixture was concentrated, and the product was taken up in methylene dichloride, filtered, and concentrated to give 1.37 g (94%) of methyl *cis*-2,3-dimethoxyacrylate: bp 61–62 °C (1.2 mm); ir (neat) 1711 (C=O), 1645 cm^{-1} (C=C); NMR (CCl₄) δ 3.58 (s, 3), 3.66 (s, 3), 3.82 (s, 3), 6.90 (s, 1).

Ion Preparations. Under anhydrous conditions a solution of freshly distilled antimony pentafluoride in sulfur dioxide (ca. 2 M) was treated dropwise with 1 equiv of the respective cyclopropene (1) while keeping the reaction temperature below −65 °C. After the cyclopropene was added, the solutions were slowly warmed to room temperature while the sulfur dioxide was removed in a slow stream of nitrogen. The hexafluoroantimonate salts (3) were deposited as colorless, crystalline solids and were bottled under argon. The solutions for NMR study can be prepared by directly withdrawing samples from the reaction mixture or by redissolving the stock salts in sulfur dioxide.

Registry No.—**1a**, 59034-32-1; **1b**, 59034-33-2; **1c**, 59034-34-3; **2**, 59034-35-4; **3a**, 59015-63-3; **3b**, 59015-65-5; **3c**, 59015-67-7; cyclopropene, 2781-85-3; tetrafluorocyclopropene, 19721-29-0; 1,2-di-chlorodifluorocyclopropene, 6262-45-9; methyl *cis*-2,3-dimethoxyacrylate, 59034-36-5.

References and Notes

(1) R. D. Chambers and R. H. Mobbs, *Adv. Fluorine Chem.*, **4**, 50 (1965).
(2) J. D. Park, R. J. McMurtry, and J. H. Adams, *Fluorine Chem. Rev.*, **2**, 55 (1968).
(3) D. C. F. Law, S. W. Tobey, and R. West, *J. Org. Chem.*, **38**, 768 (1973).
(4) P. B. Sargeant and C. G. Krespan, *J. Am. Chem. Soc.*, **91**, 415 (1969).
(5) J. T. Barr et al., *J. Am. Chem. Soc.*, **72**, 4480 (1950).
(6) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Am. Chem. Soc.*, **73**, 2342 (1951).
(7) J. D. Park, S. M. Sharrah, and J. R. Lacher, *J. Am. Chem. Soc.*, **71**, 2337 (1949).
(8) J. D. Park, S. Cohen, and J. R. Lacher, *J. Am. Chem. Soc.*, **84**, 2919 (1962).
(9) B. E. Smart and G. S. Reddy *J. Am. Chem. Soc.*, submitted for publication.
(10) J. G. Astin in "Determination of Organic Structures by Physical Methods", Vol. I, E. A. Brande and F. C. Nachod, Ed., Academic Press, New York, N.Y., 1955, p 525.
(11) Barriers to rotation about the carbonyl-carbon oxygen bond in methylated or protonated ketones and aldehydes are not experimentally known; calculated barriers for the protonated carbonyl species range from a minimum of 17 kcal/mol [D. M. Brouwer, *Recl. Trav. Chim. Pays-Bas*, **86**, 879 (1967)] to 25–30 kcal/mol [P. Roos, *J. Chem. Phys.*, **49**, 4902 (1968)].
(12) This assumes that the chemical shift difference of the protons or fluorines between **5a** and **5b** is sufficiently large that line shape effects will be observed in the temperature range studied. (The exchange rate at coalescence for a two-site exchange process is approximately proportional to the differences of the individual site resonance frequencies.) This is the case in the homologous series of cyclobutenyl cations **6** which have observed activation barriers to methoxy rotation of ca. 15–17 kcal/mol (ref 9).

(R = F, Cl, OCH₃)

6
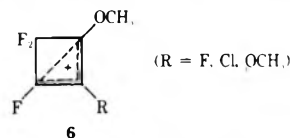
(13) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 209 (1974).
(14) K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **83**, 1266 (1961).

Stabilization of Cyclopropenium Ion and Cyclopropenone by Guaiazulene[1]

Israel Agranat* and Eliezer Aharon-Shalom

Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem, Israel

C₃Cl₃⁺AlCl₄⁻ (from tetrachlorocyclopropene and aluminum chloride) reacts with 2 molar equiv of guaiazulene (8) in dichloromethane solution to give, after aqueous workup, di-3-guaiazulenylcyclopropenone (7). An analogous reaction of C₃Cl₃⁺AlCl₄⁻ with 3 molar equiv of 8 followed by treatment of perchloric acid (70%) afforded tri-3-guaiazulenylcyclopropenium perchlorate (6). The dipole moment of 7, 5.13 D, is analyzed in terms of the dipole moment orientations of the azulenyl groups relative to the cyclopropenone moiety. The ^{1}H NMR spectra of 6 and 7 are analyzed in comparison with the corresponding spectra of 8 and various of its 3-acyl derivatives. The interactions of the guaiazulenyl groups with the cyclopropenone (in 7) and the cyclopropenium ion (in 6) are discussed. The high pK_{R^+} of 6, >10, indicates the remarkable effect of the three guaiazulenyl groups in delocalizing the positive charge of the three-membered ring.

Azulene (1)[2,3] and cyclopropenium ion (2)[3–7] are considered two independent milestones in the chemistry of nonbenzenoid aromatics. The interest in azulene, the "aromatic" nonalternant polycyclic prototype, had somewhat declined during the past decade. The origin of this decline may be traced to the dominant role played by the Hückel $4n + 2$ rule and its experimental "verifications" for $n \neq 1$.[8] Recent cyclopropenium ion (2) and cyclopropenone (3)[9,10] studies have focused on the stabilization of the "aromatic" but highly strained 2π3C ring system by appropriate electron-donating substituents, particularly heteroatoms.[11–14] In a search for alternative substituents which are capable of delocalizing the positive charge of the three-membered ring, we have considered the azulenyl group. The rationale underlying this approach is based on the extra "aromatic" stabilization of 1-azulenylcarbenium ion (4), a variation of the tropylium ion theme.[9,15] 1-Azulenylcyclopropenium ion (5) may formally be considered as a triapentafulvalene system condensed to tropylium ion (5a). We report straightforward syntheses and various properties of cyclopropenium ion and cyclopropenone *totally* substituted by guaiazulenyl groups: tri-3-guaiazulenylcyclopropenium perchlorate (6) and di-3-guaiazulenylcyclopropenone (7). Few examples of azulenyl- (and pseudoazulenyl-) *diphenyl*cyclopropenium salts have previously been described.[16–18] Azulene derivatives of cyclopropenone are unknown.[10]

The synthetic route of choice was the electrophilic substitution of aromatic substrates by trichlorocyclopropenium-salts via a Friedel–Crafts pathway (method of West and Tobey),[10,19–22] applied in dichloromethane. In principle, this

1 **2** **3** **3a** **4**

5 **5a**

6, $R_1 = CH_3$; $R_2 = CH(CH_3)_2$

6a, $R_1 = CH_3$; $R_2 = CH(CH_3)_2$

7

7a

8

9, $R = CH_3$
10, $R = C_6H_5$
11, $R = H$

12

13
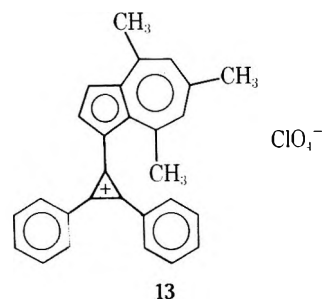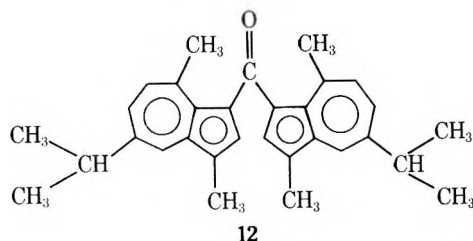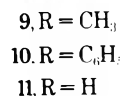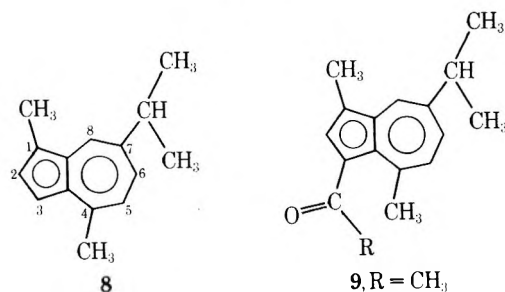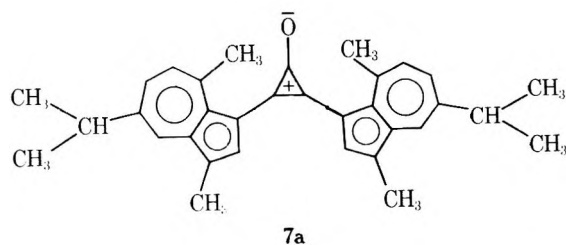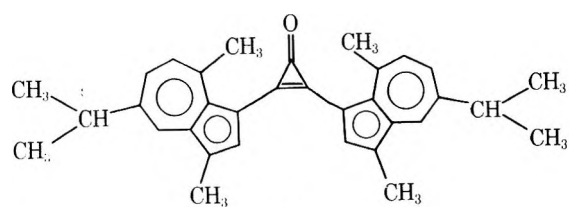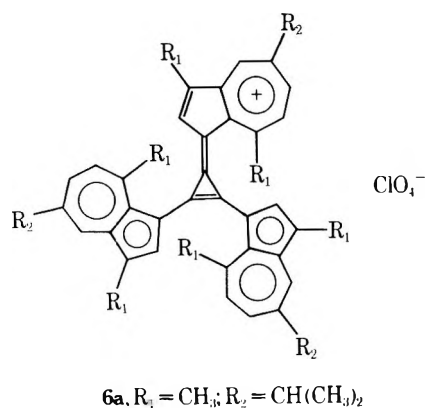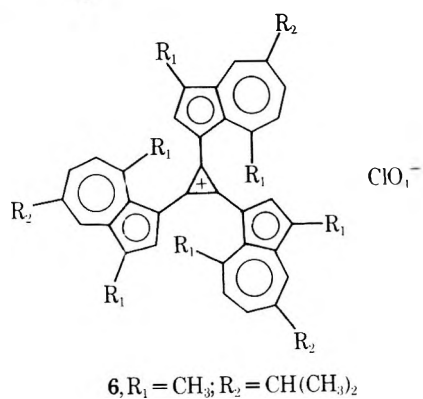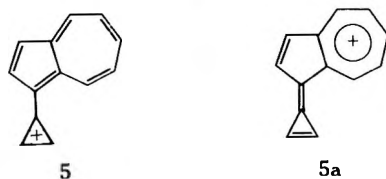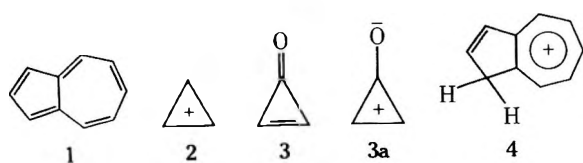
method may result in mono-, di-, and trisubstitution products, providing (after working up the reaction mixture) aryltri-chlorocyclopropene, diarylcyclopropenone, and triarylcy-clopropenium cation. Guaiazulene (**8**) was preferred over az-ulene (**1**) as the aromatic substrate on the following grounds: (1) in azulene, double consecutive electrophilic substitution may occur (at positions 1 and 3), while in guaiazulene only single electrophilic substitution is expected (as position 1 is blocked);[2b,23] (2) the NMR spectra of the derivatives of **8** are expected to be simpler than those of **1**; (3) **8** is more readily available than azulene. Treatment of $C_3Cl_3{}^+AlCl_4{}^-$ (prepared from tetrachlorocyclopropene and aluminum chloride) with 2 molar equiv of guaiazulene in dichloromethane at −90 to −80 °C gave a dark red complex which was decomposed with aqueous acetone (20%) at −60 °C. Purification by dry column chromatography on silica gel afforded **7**. Analogous reaction with 3 molar equiv of guaiazulene at −70 °C gave a dark red complex which was decomposed with aqueous acetone fol-lowed by treatment with perchloric acid (70%) leading to **6**. Purification was effected by column chromatography on mi-crocrystalline cellulose. Elemental analyses and spectral properties were all consistent with the formulation of **6** and **7**.

The mass spectrum of **7** revealed an initial elimination of CO from the molecular ion to give the parent di-3-guaiazu-lenylacetylene radical cation: M·+ (*m/e* 446, 2%) → [M − CO]·+ (*m/e* 418, 100%). This most facile fragmentation was

substantiated by appropriate metastable transitions. The following prominent signals indicated fragmentations of the alkyl substituents from the parent ion: [M − CO − CH₃]·+ (*m/e* 403, 32%), [M − CO − *i*-Pr]·+ (*m/e* 375, 24%), [M − CO − CH₃ − *i*-Pr]+ (*m/e* 360, 18%), [M − CO − CH₃ − *i*-Pr − *i*-Pr]·+ (*m/e* 317, 24%).

The infrared spectrum of **7** contained the two molecular bands at 1552 and 1837 cm⁻¹ which are diagnostic for the cyclopropenone nucleus.[10,24–26] Although specific assignments have been controversial,[27] it seems to be established that the two fundamental frequencies are out-of-phase and in-phase mixtures of the C=O and the C=C stretches, with some contribution from the symmetric C–C stretch. If the assign-ment of the band in the 1600-cm⁻¹ region to a molecular vi-bration that predominantly involves the stretching of the carbonyl band is valid,[28] then the occurrence of this band at such a low wavenumber (1552 cm⁻¹) may indicate a consid-erable contribution of an "aromatic" dipolar form (e.g., **7a**)

Table I. ^{1}H NMR Spectra of 6, 7, 8, and Related Guaiazulene Derivatives

Compd	Solvent	H-2	H-5	H-6	H-8	CH_3-1	CH_3-4	$(CH_3)_2CH$-7	$(CH_3)_2CH$-7
								δ, ppm^a	
8	CDCl$_3$	7.59 s	6.92 d (11)	7.32 dd (11, 2)	8.17 d (2)	2.63 s	2.76 s	3.02 h (7)	1.32 d (7)
8[30]	CDCl$_3$	7.59 d (4)	6.94 d (11)	7.37 dd (11, 2)	8.17 d (2)	2.63 s	2.78 s	3.04 h (7)	1.32 d (7)
8	CD$_3$CN	7.56 d (4)	6.97 d (11)	7.39 dd (11, 2)	8.20 d (2)	2.61 s	2.75 s	3.04 h (7)	1.31 d (7)
6	CDCl$_3$	8.04 s	7.56 d (10)	7.84 dd (10, 1)	8.41 d (1)	2.65 s	2.92 s	3.25 h (7)	1.44 d (7)
7	CDCl$_3$	8.31 s	7.29 d (11)	7.50 dd (11, 2)	8.24 d (2)	2.67 s	3.39 s	3.10 h (7)	1.36 d (7)
9[31]	CCl$_4$	7.78 s	7.14 d	7.39 dd	8.10 d	2.54 s	2.79 s	3.03 m	1.34 d
10[32]	CDCl$_3$	7.55 s	7.12 d (11)	7.3–8.0 m^b	8.20 d (1.8)	2.55 s	2.71 s	3.09 m	1.37 d (6)
11[33]	c	8.22 s	7.36 d	7.55 dd	8.27 d	2.57 s	3.08 s	c	1.38 d (6.5–7.0)
12[33]	c	7.53 s	7.05 d	7.32 dd	8.10 d	2.52 s	2.86 s	c	1.33 d (6.5–7.0)

^{a} Chemical shifts are followed by multiplicity and coupling constants (J) in hertz: s, singlet; d, doublet; dd, doublet of doublets; h, heptet; m, multiplet. ^{b} Including phenyl ^{c} Not given.

Table II. Electronic Absorption Spectra of 6, 7, and 13

Compd	Solvent				λ, nm (ϵ)					
6	CH$_3$CN	240s (32 300)	290 (25 900)		335 (20 300)		483 (26 200)			
7	CH$_3$CN	242 (39 000)	289 (26 000)		335 (30 000)	455 (47 000)	478 (53 000)	520s (1500)		
7	EtOH	244 (40 000)	290 (27 000)	326 (24 000)	336 (28 000)	456s (46 000)	479 (53 000)		590s (3100)	650 (1600)
7	Dioxane		291 (25 000)		336 (27 000)	459 (42 000)	482 (46 000)	556s (2600)	600s (25 500)	660s (1500)
7	C$_6$H$_6$		293 (28 000)		338 (30 000)	460 (45 000)	484 (50 000)	560s (2700)	600s (2700)	650s (1500)
7	C$_6$H$_{12}$	242 (36 000)	290 (25 000)	325s (24 000)	336 (30 000)	456 (41 500)	480 (46 000)	564 (2300)	610s (2300)	660s (1500)
13[16]	CH$_3$CN	249 (36 300)	272 (31 600)		341 (26 900)	416 (33 900)				

to the ground state of **7**. (On the other hand, the 1552-cm^{-1} vibration may still be mainly a C=C stretch.[27]) The infrared spectrum of **6** shows strong absorptions at 1468 and 1448 cm^{-1} which are indicative of cyclopropenium ion.[11,25,29] The cyclopropenium structure of **6** was verified by the characteristic Raman line at 1815 cm^{-1} due to the totally symmetric stretching vibration (A_1') of the "aromatic" C_3^+ ring.[11,25,29] In comparison, the corresponding absorptions of trimethyl-, triphenyl-, tris(dimethylamino)-, and trichlorocyclopropenium ion appear at 1880, 1845, 1985, and 1791 cm^{-1}, respectively.[11,29] It should be noted that no infrared band appears at the 1820-cm^{-1} region either in solution or in the solid. Such a band was reported in the spectrum of 1-azulenyldiphenylcyclopropenium perchlorate and was ascribed to the corresponding triapentafulvalenic structure of this salt.[17]

The NMR data of **6** and **7** are given in Table I along with the relevant data of guaiazulene (**8**),[30] 3-acetylguaiazulene (**9**),[31] 3-benzoylguaiazulene (**10**),[32] 3-formylguaiazulene (**11**),[33] and 3,3'-diguaiazulene ketone (**12**).[33] A number of conclusions may be drawn. (1) In each of the guaiazulenyl derivatives under study, the seven-membered ring protons (H-5, H-6, H-8) give rise to an ABX system. (2) The guaiazulenyl substituents in **6** and **7** are magnetically equivalent. (3) The seven-membered ring protons of **6** are significantly shifted to lower field relative to the parent guaiazulene (**8**): δ(6) − δ(8) = 0.64 (H-5), 0.52 (H-6), and 0.24 ppm (H-8). This effect probably reflects partial delocalization of the positive charge from the three-membered ring into the seven-membered ring indicating a

contribution of the tropylium structure (**6a**) to the ground state of **6**. An analogous trend but much smaller in extent is seen in **7**: δ(7) − δ(8) = 0.37 (H-5), 0.17 (H-6), and 0.07 ppm (H-8). It is noteworthy that even with respect to the corresponding absorption of 3,3-diguaiazulenyl ketone (**12**) the seven-membered ring protons of **7** are shifted to lower field indicating, in this particular case, greater fractional charge separation than in the ordinary ketones: (4) The five-membered ring methyl protons in CH_3-1 in **6** as well as in **7** are hardly shifted relative to **8**. (5) The five-membered ring proton (H-2) in **6** and **7** is substantially shifted to lower field relative to **8**; $\Delta\delta$ (H-2) = 0.45 for **6** and 0.72 ppm for **7**. The considerable shift in **7** is mainly due to the carbonyl anisotropy, while the effect of the partial positive charge in the three-membered ring is only marginal. On the other hand, the shift in **6** is mainly due to the anisotropy of the C_3^+ system. (6) The CH_3-4 protons in **7** are affected in the same way as H-2, $\Delta\delta$ (CH_3-4) = 0.63 ppm. In **6** the corresponding shift is only 0.16 ppm and corresponds to the change of the electron density at the seven-membered ring.

The electronic absorption spectra of **6** and **7** are summarized in Table II. The disappearance of the low-intensity but significant absorption at the 600-nm region of the azulene moiety in **6** indicates change in the character of the substituent moiety to resemble tropylium cation. Noteworthy also is the substantial red shift of the high intensity longest wavelength absorption band from 416 nm in 4,6,8-trimethylazulenyldiphenylcyclopropenium perchlorate (**13**)[16] to 484 nm in **6**.
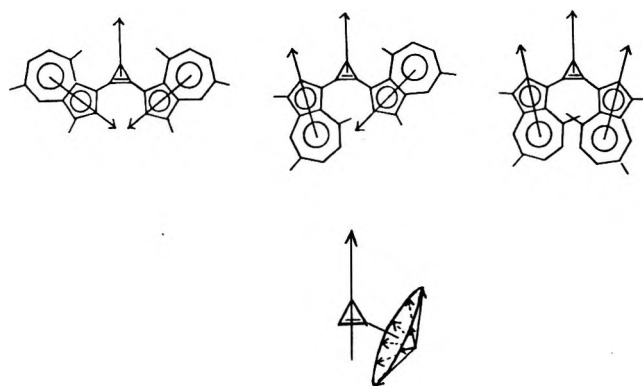
Figure 1. Dipole moment orientations of the azulenyl groups relative to the cyclopropenone moiety in **7**.

The electric dipole moment of **7** (in benzene) is 5.13 D and closely resembles that of diphenylcyclopropenone (5.08 D).[10] The relatively high dipole moment of cyclopropenones was originally attributed to high contribution of the cyclopropenium oxide structure (**3a**) to the ground state of **3**. However, Tobey had effectively shown that this is not a necessary rationale.[34] The fractional charge separation is comparable with that in ordinary ketones but the effective conjugation in the three-membered ring causes shifting of the center of the positive charge into the three-membered ring and increasing the charge separation distance. Ammon's recent x-ray crystallographic investigation of diphenylcyclopropenone, in conjunction with CNDO/2 calculations, led to the conclusion that the three-membered ring of the ketone has some cyclopropenium ion character.[35-37] The overall moment of **7** is a combination of two contributions: the cyclopropenone moiety and the azulenyl groups (ca. 1.1 D oriented from the seven-membered ring to the five-membered ring). Figure 1 shows various dipole moment orientations of the azulenyl groups relative to the cyclopropenone moiety. Models show steric hindrance of the type 2-2', 2-4', and for much greater extent of the type 4-4'. Relief of this strain can be achieved in two ways: (a) by correlation of the groups free rotation maintaining phase difference between the two substituents, and (b) by widening the angle between the substituents. Both effects tend to decrease the overall contribution of the azulenyl moiety to the electrical moment dipole. The wider angle between the two substituents forces H-2 and CH₃-4 into the diamagnetic anisotropic field of the carbonyl. A rapid equilibrium between such conformations as the central one in Figure 1 may also be favored on the basis of the ¹H NMR deshielding effect noted for H-2 and CH₃-4. The similarity in the dipole moment of **7** and diphenylcyclopropenone could be rationalized in terms of this conformer, in view of the partial cancellation of the azulenyl contributions. In **6** the introduction of the third substituent does not permit wider angle between the substituents. The steric strain may be relieved only by mechanism a. This imposes twisting of the substituents in a propeller-like arrangement with respect to the cyclopropenium ion ring. The twist angles are probably larger than in the case of the triphenylcyclopropenium ion. (This can explain the lack of absorption at 1820 cm⁻¹ found in the infrared of 1-azulenyldiphenylcyclopropenium perchlorate.)

The "aromatic" stabilization of **6** may be inferred from its high pK_{R^+}, >10, determined by the equilibrium between the cyclopropenium ion and the cyclopropenol as measured by potentiometric titration method, in 50% aqueous acetonitrile. The corresponding values of triphenyl-, tris(*p*-anisyl)-, and tris(diphenylamine)cyclopropenium ion are 3.1, 6.75, and >10, respectively.[11,29,38] The result indicates the remarkable effect

of the three guaiazulenyl groups in delocalizing the positive charge of the three-membered ring of **6**.

Finally, the interaction of the guaiazulenyl groups with the cyclopropenium ion **6** closely resembles the recently observed "aromatic" stabilization in the highly delocalized triferrocenylcyclopropenium ion.[39] The interaction with the cyclopropenone imposes higher charge separation than in known cyclopropenones. A more general picture will emerge from the study of the unsubstituted 1-azulenyl substituents, tri-1-azulenylcyclopropenium ion, and di-1-azulenylcyclopropenone.

Experimental Section

Melting points were taken on a Unimelt Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer in Nujol and in KBr disks. Ultraviolet spectra were recorded on a Unicam Model SP800A spectrophotometer. The ¹H NMR spectra were taken on a Varian HA-100 spectrometer at 100 MHz. ¹H chemical shifts are reported in parts per million downfield from Me₄Si (internal standard). Mass spectra were measured on a Varian MAT-311 double focusing instrument operating at 70 eV, employing the direct insertion technique. Metastable transitions were detected by the defocusing method (alteration of accelerating voltage mode). Analytical TLC separations were carried out at 24 °C on precoated plastic sheets (layer thickness 0.2 mm), Polygam Sil N-HR/UV₂₅₄ and Polygam Cel 400/UV₂₅₄ (Machery-Nagel and Co.). Materials were detected with uv light. Column chromatography separations were performed on silica gel 60 (Kieselgel 60 Merck) and on microcrystalline cellulose (Merck). For dry column chromatography, silica was deactivated with ethyl acetate. Dipole moment was determined in benzene solution at 30 °C. The dielectric constants of the solutions were measured in a heterodyne beat apparatus (500 kHz), the specific volumes, with a Sprengel-Oswald type pycnometer. The molar refraction was calculated according to LeFevre and Steel.[40] The polarization $P_{2\infty}$ and the dipole moment were calculated according to Halverstadt and Kumler.[41] The pK_{R^+} values of the cyclopropenium ions were determined by the potentiometric titration method in 50% aqueous acetonitrile.[6,54] The pH measurements were made in a Radiometer Type TTT IC pH meter equipped with glass-calomel electrodes. The pH meter was standardized with an appropriate buffer before each measurement.[38] Raman spectra were obtained on a rotating KBr pellet. Instrumentation consists of a Spex 1401 monochromator, a Spex 1419A sample illuminator, and a Spectra Physics Model 164 Kr⁺ laser supplying about 50 mW power at the sample. Tetrachlorocyclopropene was obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis. Guaiazulene (puriss), mp 30–31.5 °C, was obtained from Fluka AG (Buchs, Switzerland). Petroleum ether (bp 40–60 °C) and dry dichloromethane were used.

Di-3-guaiazulenylcyclopropenone (7). A solution of tetrachlorocyclopropene (1.78 g, 10 mmol) in dry dichloromethane (5 ml) was added dropwise, under inert anhydrous atmosphere, to a magnetically stirred suspension of anhydrous aluminum chloride (1.47 g, 11 mmol) in dry dichloromethane (100 ml). The mixture was gradually heated to 20 °C, and left at this temperature for 15 min, to give trichlorocyclopropenium tetrachloroaluminate. More dichloromethane (50 ml) was added and the resulting suspension was cooled to −85 °C and treated dropwise, during 105 min, below −80 °C, with a solution of guaiazulene (8, 3.72 g, 19 mmol) in dry dichloromethane (100 ml). The dark complex was stirred at −90° for an additional 75 min and treated below −60 °C with aqueous acetone (20%, 50 ml). After gradual heating to room temperature, the organic layer was washed with water to neutrality, dried over magnesium sulfate, and evaporated to dryness under vacuum. The resulting crude oily product was purified by dry column chromatography over deactivated silica, using a mixture (1:1) of ethyl acetate and petroleum ether as developers. Three main spots were obtained. The middle, green-colored spot (R_f 0.16) was extracted with methanol, the solvent was evaporated under vacuum, and the remaining product dissolved in dichloromethane, dried over magnesium sulfate, and the solvent evaporated to dryness to give crude **7** as a dark green solid (14% yield). Further purification was effected by column chromatography on silica, using 5% of ethyl acetate in dichloromethane as developer. The remaining solid, after evaporation of the solvent from the main dark green fraction, was triturated with petroleum ether to give pure **7**, mp 176–177 °C (0.27 g, 6%), R_f [silica, petroleum ether–ethyl acetate (5:1)] 0.24. Anal. Calcd for $C_{33}H_{34}O$: C, 88.74; H, 7.07. Found: C, 88.55; H, 7.49. Ir ν_{max} (KBr) 2960 (m), 2920 (m), 2860 (m), 1850 (s), 1837 (s), 1820 (s), 1552 (s), 1433 (vs),

1393 (s), 1368 (s), 1242 (s), and 1010 cm^{-1} (s); μ (C_6H_6, 30 °C) 5.13 ± 0.03 D ($\alpha' = 33.93$, $\beta' = -1.40$, $P_{2\infty} = 628.1$ cm, MR_{calcd} 97.9 cm^{-1}).

Tri-(3-guaiazulenyl)cyclopropenium Perchlorate (6). A magnetically stirred suspension of trichlorocyclopropenium tetrachloroaluminate prepared as described above from tetrachlorocyclopropene (1.78 g, 10 mmol) and anhydrous aluminum chloride (1.47 g, 11 mmol) in dry dichloromethane (85 ml) was cooled to −70 °C and treated dropwise, below −70 °C, under anhydrous inert atmosphere, during 50 min, with a solution of guaiazulene (8, 5.58 g, 28.2 mmol) in dry dichloromethane (50 ml). The resulting red complex, which darkened during the addition, was kept at −70 °C for 40 min, heated gradually to room temperature, and kept at room temperature overnight. The complex was decomposed below −60 °C by the addition of aqueous acetone (20%, 50 ml). The mixture was heated to room temperature, water and dichloromethane were added, and the organic fraction was washed with water and dried over magnesium sulfate. The solution was concentrated under vacuum to a volume of 100 ml and treated with perchloric acid (70%, 15 ml), and stirred magnetically for 150 min. The layers were separated, the organic layer was washed with water and dried over magnesium sulfate, and the solvent evaporated under vacuum. Treatment of the remaining oil with petroleum ether gave crude 6 as a dark solid (4.48 g, 69%). Purification was effected by column chromatography on microcrystalline cellulose, using 15% dichloromethane in petroleum ether. The resulting oily product was dissolved in dichloromethane and precipitated with petroleum ether (four times) to give 6 as a dark solid, mp 171–173 °C dec (23% yield), R_f [microcrystalline cellulose, petroleum ether–dichloromethane (1:1)] 0.66. Anal. Calcd for $C_{48}H_{51}ClO_4$: C, 79.25; H, 7.07. Found: C, 79.52; H, 7.15%. Ir ν_{max} (KBr) 2955 (m), 2920 (m), 2860 (m), 1760 (w), 1705 (w), 1524 (m), 1468 (vs), 1448 (vs), 1392 (vs), 1368 (vs), 1335 (s), 1270 (vs), 1215 (s), 1120 (m), 1090 (s), 1010 (s), 891 (m), 649 (m), 618 (m), and 592 cm^{-1} (m).

References and Notes

(1) Fulvenes and Thermochromic Ethylene. Part 88. For part 87, see I. Agranat, I. B. Berlman, and Y. Richter in "Environmental Effects on Molecular Structure and Properties", The Jerusalem Symposia on Quantum Chemistry and Biochemistry VIII, B. Pullman, Ed., D. Riedel Publishing Co., Dordrecht, Holland, 1976, p 573.
(2) (a) E. Heilbronner in "Non-Benzenoid Aromatic Compounds", D. Ginsburg, Ed., Interscience, New York, N.Y., 1959, p 171; (b) W. Keller-Schierlein and E. Heilbronner, *ibid.*, p 277.
(3) D. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds", Elsevier, Amsterdam, 1966.
(4) A. W. Krebs, *Angew. Chem., Int. Ed. Engl.*, **4**, 10 (1965).
(5) I. A. D'yaknov and R. R. Kostikov, *Russ. Chem. Rev.*, **36**, 557 (1967).
(6) R. Breslow, *Pure Appl. Chem.*, **28**, 111 (1971).
(7) D. Wendisch in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 4, Part 3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1973, p 729.
(8) (a) P. J. Garratt, "Aromaticity", McGraw-Hill (U.K.), Maidenhead, Berkshire, 1971; (b) P. J. Garratt and M. V. Sargent, *Adv. Org. Chem.*, **6**, 1 (1969).
(9) K. T. Potts and J. S. Baum, *Chem. Rev.*, **74**, 189 (1974).
(10) T. Eicher and J. L. Weber, *Top. Curr. Chem.*, **57**, 1 (1975).
(11) Z. Yoshida, *Top. Curr. Chem.*, **40**, 47 (1973).
(12) E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **13**, 209 (1974).
(13) Z. Yoshida, S. Araki, and H. Ogoshi, *Tetrahedron Lett.*, 19 (1975).
(14) Z. Yoshida, H. Konishi, and H. Ogoshi, *J. Chem. Soc., Chem. Commun.*, 359 (1975).
(15) K. Hafner, *Pure Appl. Chem.*, **28**, 153 (1971).
(16) B. Föhlisch and P. Bürgle, *Justus Liebigs Ann. Chem.*, **708**, 164 (1967).
(17) T. Eicher and A. Hansen, *Tetrahedron Lett.*, 4321 (1967).
(18) D. Lloyd and N. W. Preston, *Chem. Ind. (London)*, 1055 (1969).
(19) S. W. Tobey and R. West, *J. Am. Chem. Soc.*, **86**, 4215 (1964).
(20) R. West, D. C. Zecher, and S. W. Tobey, *J. Am. Chem. Soc.*, **92**, 168 (1970).
(21) R. West, *Acc. Chem. Res.*, **3**, 130 (1970).
(22) J. S. Chickos, E. Patton, and R. West, *J. Org. Chem.*, **39**, 1647 (1974).
(23) M. Sucky, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **21**, 477 (1956).
(24) A. Krebs, B. Schrader, and F. Höfler, *Tetrahedron Lett.*, 5935 (1968).
(25) B. Schrader, *Angew. Chem., Int. Ed. Engl.*, **12**, 884 (1973).
(26) F. Höfler, B. Schrader, and A. Krebs, *Z. Naturforsch. A*, **24**, 1617 (1969).
(27) F. R. Brown, D. H. Finseth, F. A. Miller, and K. A. Rhee, *J. Am. Chem. Soc.*, **97**, 1011 (1975).
(28) D. Bostwick, H. F. Henneike, and H. P. Hopkins, Jr., *J. Am. Chem. Soc.*, **97**, 1505 (1975).
(29) Z. Yoshida, H. Ogoshi, and S. Hirota, *Tetrahedron Lett.*, 869 (1973).
(30) R. Hagen, E. Heilbronner, and P. A. Straub, *Helv. Chim. Acta*, **51**, 45 (1968).
(31) S. Kurokawa, *Bull. Chem. Soc. Jpn.*, **43**, 509 (1970).
(32) S. Kurokawa, M. Hashimoto, and S. Hayashi, *Bull. Chem. Soc. Jpn.*, **45**, 3559 (1972).
(33) A. J. Fry, B. D. Bowen, and P. A. Leermakers, *J. Org. Chem.*, **32**, 1970 (1967).
(34) S. W. Tobey in "Aromaticity, PseudoAromaticity, AntiAromaticity", The Jerusalem Symposia on Quantum Chemistry and Biochemistry III, E. D. Bergmann and B. Pullman, Ed., The Israel Academy of Sciences and Humanities, Jerusalem, 1971, p 351.
(35) H. L. Ammon, *J. Am. Chem. Soc.*, **95**, 7093 (1973).
(36) H. Tsukada, H. Shimanouchi, and Y. Sasada, *Chem. Lett.*, 639 (1974).
(37) Obviously, cyclopropenone is not completely "delocalized"; it is a hybrid of 3 and dipolar structures which differ in energy. Cf. R. C. Benson, W. H. Flygare, M. Oda, and R. Breslow, *J. Am. Chem. Soc.*, **95**, 2772 (1973).
(38) R. C. Kerber and C.-M. Hsu, *J. Am. Chem. Soc.*, **95**, 3239 (1973).
(39) I. Agranat and E. Aharon-Shalom, *J. Am. Chem. Soc.*, **97**, 3829 (1975).
(40) R. J. W. LeFe'vre and K. D. Steel, *Chem. Ind. (London)*, 670 (1961).
(41) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

Organometallic Chemistry. 10.[1] Carbon-13 Nuclear Magnetic Resonance Study of *cis-π*-Pentadienyliron Tricarbonyl Cations and Protonated Norbornadieneiron Tricarbonyl

George A. Olah,* Simon H. Yu,[2] and Gao Liang[2]

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Acyclic and cyclic cisoid π-pentadienyliron tricarbonyl cations were studied by ^{13}C NMR spectroscopy in strong acids. The origin of the unusual stability of these ions and their fluxional behavior are discussed. The nature of bonding and the structure of the protonated norbornadieneiron tricarbonyl were also studied and are discussed.

The preparation of the tropyliummolybdenum tricarbonyl cation via hydride abstraction from tropylidenemolybdenum tricarbonyl by Dauben and Honnen[3] and that of cyclohexadienyliron tricarbonyl cation by Fischer and Fischer[4] have drawn considerable interest from both organic and inorganic chemists, and particularly theoretical chemists, in recent years. A large variety of organometallic cations has since been prepared and their chemistry reviewed.[5] All these cationic species exhibit remarkable stability due to the complexation of the unsaturated organic moiety with the metal atom (i.e., transition metals).

Acyclic *trans*-pentadienyliron tricarbonyl cations 1 have

1   2   3, $n = 1$; 4, $n = 2$
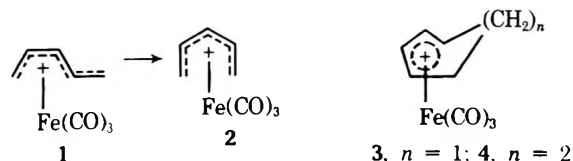
been demonstrated to rearrange to the related cis isomer 2[6] indicating the greater thermodynamic stability of 2. Although ample work has been carried out in the obtaining of the ^{1}H NMR spectra of these ions, limited ^{13}C NMR data have been reported.[7] In the continuation of our interest in metal stabilized cations, we wish to report a study of the relative charge distribution pattern in a series of cyclic and acyclic cisoid π-pentadienyliron tricarbonyl cations via ^{13}C NMR spectroscopy.

Furthermore, protonated diene–iron complexes are of substantial current interest. Depending on the acidity of the media differing species are obtained.[8] In contrast to iron tricarbonyl derivatives of conjugated dienes, norbornadieneiron tricarbonyl (5) was reported to undergo protonation on iron.[9] Based on a ^{1}H NMR study, structure 6 was proposed for protonated norbornadieneiron tricarbonyl. An unusual stereospecific coupling ($J = 13$ Hz) of the hydrido hydrogen with H_2 and H_6 was observed. Recently, the protonated species of 5 was suggested to be formulated in terms of rapidly equilibrating homoallylic σ,π species 7.[10]

5

6

$(CO)_3FeH$ $HFe(CO)_3$

7
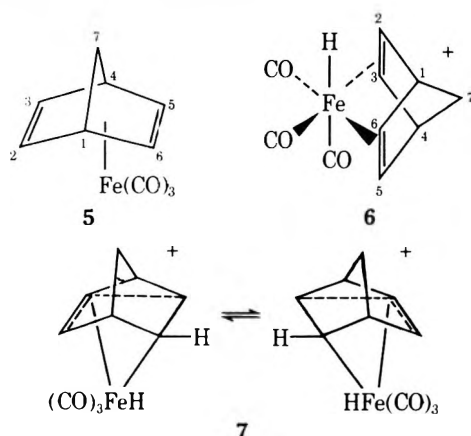
In order to provide better understanding of the bonding nature and the structure of the protonated norbornadieneiron tricarbonyl, we also report the high-resolution ^{13}C NMR spectra of the parent and the protonated species.

Results and Discussion

cis-π-Pentadienyliron Tricarbonyl Cations.

The parent and methyl substituted *cis*-π-pentadienyliron tricarbonyl cations were prepared from their corresponding alcohols 9 in

2, R = H
8, R = CH_3

9
R = H or CH_3

10
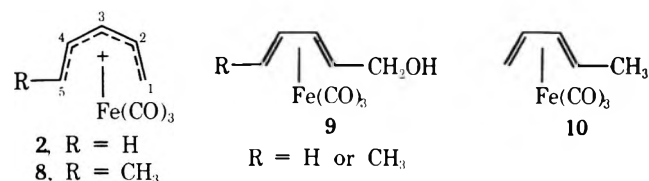
fluorosulfuric acid–sulfur dioxide solution at dry ice–acetone bath temperature (ca. −78 °C). The ^{1}H NMR spectra of these ions are in good agreement with those previously reported.[6] The Fourier transform carbon-13 proton-noise nondecoupled NMR spectra of 2 and 8 were then obtained. Assignments of carbon resonances, multiplicities, and coupling constants are summarized in Table I. The symmetrical nature of the parent *cis*-π-pentadienyliron tricarbonyl cation is clearly seen from the observation of three carbon resonances in the dienyl region and two in the carbonyl region. Both ^{1}H and ^{13}C NMR spectra thus rule out a transoid conformation 1.

Upon methyl substitution at one of the terminal positions (C_5), a deshielding of approximately 25 ppm of this carbon absorption is observed, while carbon resonances of the other positions did not much vary. There are, however, three carbonyl absorptions found in 8 indicating the unsymmetrical

nature of this ion. The deshielding at C_5 in 8 reflects the methyl substituent effect at this carbon.

Cyclohexadienyl- and Cycloheptadienyliron Tricarbonyl Cations. The cyclohexadienyliron tricarbonyl cation 3[4,11] was prepared from their corresponding dienyliron tricarbonyl precursors 11 via hydride abstraction by trityl tetrafluoroborate in CH_2Cl_2 solution at room temperature. Cycloheptadienyliron tricarbonyl cation 4 was obtained by the protonation of free double bond in cycloheptadieneiron tricarbonyl 12 with HBF_4.[12] Both ^{1}H and ^{13}C NMR parameters

11   12
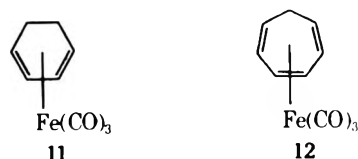
are summarized in Table I along with their assignments.

Going from 2 to 3 does not produce much effect on the C_1, C_2, and C_3 carbon shifts. The insertion, however, of an ethylidene group (two methylene groups) causes about 30 ppm deshielding effect on the terminal pentadienyl carbons (C_1 and C_5) and 10 ppm on the central carbon (C_3), while only minimal changes on the C_2 and C_4 carbons. The negligible methyl substituent effect observed in 3 is consistent with previous studies that the six-membered ring is nonplanar and highly distorted with the methylene carbon C_6 moving out of the C_1–C_5 plane and away from the iron tricarbonyl moiety.[13]

Another interesting aspect was revealed when a cyclopropanyl group was introduced into the *cis*-π-pentadienyliron tricarbonyl cation 2 at the terminal carbons. Carbon resonances of the cycloheptadienyl moiety going from *cis*-π-cycloheptadienyl- (4) to bicyclo[5.1.0]octadienyliron tricarbonyl (13)[13] does not seem to draw much positive charge from the *cis*-π-cycloheptadienyl moiety.

Fe(CO)₃   Fe(CO)₃   Fe
                                           (CO)₃
3   4   13
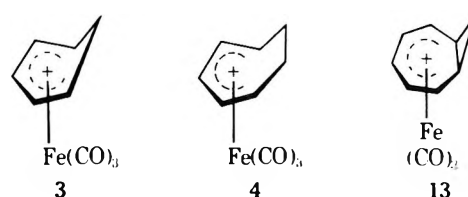
The nature of bonding in dieneiron tricarbonyls was originally discussed by Pettit et al.[13] by modifying the Dewar–Chatt–Duncanson description.[14] The bonding has been pictured as derived from the σ forward donation from filled π orbitals to vacant metal orbitals and π back-donation from filled metal orbital to π-antibonding orbitals.[15] The origin of the unusual stability of the pentadienyl tricarbonyl cations has been attributed to the formation of a nonbonding orbital upon ionization.[13,16] The decrease of the energy level of the lowest unoccupied orbital favors back-donation. In the case of the *cis*-π-pentadienyliron tricarbonyl cations back-donation is of particular importance. It not only strengthens the metal–ligand bonding but also transmits the electron density into the pentadienyl tricarbonyl cations studied; the C_2 carbon is generally more deshielded than both C_1 and C_3, whereas the reverse is seen in the uncomplexed pentadienyl cations. The present ^{13}C NMR shielding pattern is thus in agreement with a bonding picture in which the dienyl carbons (C_1 and C_3) which are not at the nodal in the nonbonding orbital become less deshielded because of greater back-donation effect from the metal atom.

Protonation of Norbornadieneiron Tricarbonyl. The ^{13}C NMR spectrum of 5 in $CDCl_3$ at −20 °C consists of a triplet at δ_C 59.77 ($J_{CH} = 133.0$ Hz) for the methylene carbon, doublets at 44.00 (151.6 Hz) and 38.74 (180.7 Hz) for the bridgehead, tertiary, and olefinic carbons, respectively, and

Table I. ^{13}C NMR Data of Pentadienyliron, Cycloalkyldienyliron, and Norbornadieneiron Tricarbonyl Cations [a]

Ion	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	CO
2	65.43	104.62	98.58						206.02
	(d-d, 165.4, 164.4)[c]	(d-m, 170.8)	(d-t, 180.3)						197.29
8[b]	62.19	103.53	94.84	104.07	91.31				207.46
	(d-d, 166.6, 165.6)[c]	(d, 171.1)	(d, 178.5)	d, 170.4	(d, 166.0)				198.50
									198.06
3	63.74	101.35	89.0			23.07			208.12
	(d, 175.4)	(d, 175.3)	(d, 183.5)			(t, 139.9)			198.36
4	92.58	102.60	99.43			31.09			107.89
	(d, 161.8)	(d, 171.4)	(d, 179.3)			(t, 131.6)			198.24
13	97.90	104.00	99.20			35.80		47.0	210.0
	(d, 174.3)	(d, 164.2)	(d, 178.7)			(d. 171.6)		(d-d)	196.3
5	44.00	38.74					59.77		218.27
	(d, 180.7)	(d, 151.6)					(t, 133.0)		
6	42.83	39.78	55.84	44.15			59.18		205.61
	(d, 155.7)	(d-d, 177.1)	(d, 181.4)	(d, 157.6)			(t, 137.2)		197.32

[a] All carbon shifts are referred to external Me_4Si (capillary). Multiplicity and coupling constants (Hz) are given in parentheses: d = doublet, t = triplet, d-d = doublet of doublets, d-m = doublet of multiplets, d-t = doublet of triplets, t-d = triplet of doublets, q-d = quartet of doublets. [b] Shift for methyl carbon δ_{13C} 20.37 (q-d, 129.4, 4.0). [c] Each doublet is further split into a doublet with $J_{C-H} \simeq 8$ Hz.

a singlet at δ_C 218.27 for the carbonyl carbons (Table I). The substantial shielding (Δ 105 ppm) of the olefinic carbons upon complexation (compared with the parent norbornadiene) indicates the importance of the back-donation in diene–iron bonding.[17] The shielding of C_7 (Δ 15 ppm) is also consistent with the reduced participation of π bonding being responsible for the effect,[18] because of the drastic decrease of the π-electron density on the exo side of the norbornadiene ligand upon coordination.[19,20]

Consistent with the C_s symmetry structure with the mirror plane containing C_1, C_7, and C_4, the ^{13}C NMR spectrum of protonated 5 in SO_2 solution at -50 °C consists of a triplet at δ_C 59.18 (J_{C-H} = 133.0 Hz) for the methylene carbon, two doublets at δ_C 42.83 (155.7) and 44.15 (157.6) for the bridgehead tertiary carbons, a doublet at δ_C 55.85 (181.4) for olefinic C_3 and C_5 carbons, a doublet of doublets at δ_C 39.78 (177.1 and 37.8) for C_2 and C_6 carbons, and two singlets at δ_C 205.6² and 197.32 ppm for the axial and equatorial carbonyl carbons, respectively. The unusual long-range ^1H–Fe–^{13}C coupling (38 Hz) of the hydrido proton with C_2 and C_6 olefinic carbons, and the large difference in the shielding (Δ 16 ppm) between the two olefinic carbon resonances, are rather striking and are difficult to rationalize based on the proposed structure 6. To account for the experimental data the hydrido proton may be in simultaneous interaction with the iron and the olefinic C_2 and C_6 carbon atoms instead of being solely bound to iron. Since C_3 and C_5 do not seem to interact with the hydrido hydrogen, no coupling is observed. The slight upfield shifts of C_2 and C_6 compared with C_3 and C_5 probably occur because of the further decrease in the π character and (or) the forward donation in metal bonding by the formation of a four-center bond. It is of interest to note that shielding of C_7 is nearly unaffected upon protonation indicating the net change of π electron density on the exo side of the ligand diene is negligible.

The proposed structure 7, a rapidly equilibrating σ,π species, provides a reasonable explanation for the long-range $J_{^1H-Fe-^{13}C}$ coupling and the upfield shifts of C_2 and C_6 by the direct bonding with iron.[21,22] However, the observed J_{C-H} coupling (157.6 Hz) on C_4 is not different from that on C_1 (155.7 Hz) and is too small to indicate the homoallylic participation by comparison with J_{C-H} in the quadricyclene (170.5 Hz)[20d] and 3-nortricyclyl cations ($\sim$185 Hz).[23] By the same argument, the possible structures 14 and 15 are also excluded.

14

15
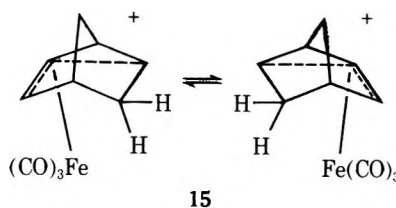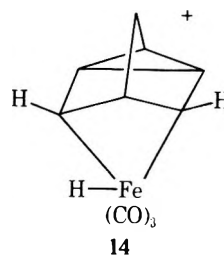
Carbonyl Region. The fluxional behavior of dieneiron tricarbonyls has been demonstrated recently by ^{13}C NMR study.[24] Consistent with a tetragonal pyramidal structure,[25] the limiting spectra of these compounds with conjugated dienes show the two expected resonances for the basal and apical carbonyls in the ratio 2:1 at -90 °C or below. On the other hand, the fluxionality increases drastically in 5, and no broadening of the carbonyl resonance is observed down to -110 °C.[24a,26] It is of interest to note that the fluxionality decreases substantially upon the formation of cations via protonation, and in some cases two resonances are observed even up to -30 °C for carbonyl carbons. The observed upfield shifts of the carbonyl absorptions is compatible with the corresponding increase in their ir stretching frequency.[27] Both are attributed to the decrease of the electron density of the iron.

Experimental Section

$Fe(CO)_5$, $Fe_2(CO)_9$, divinylcarbinol, 2,4-hexadien-1-ol, 1,4-cyclohexadiene, cycloheptatriene, cyclooctatetraene, and norbornadiene are commercially available. 2,4-Pentadien-1-ol was prepared by the rearrangement of divinylcarbinol with the presence of 1% sulfuric acid solution at room temperature for 24 h under nitrogen.[28] 2,4-Pentadien-1-ol- and 2,4-hexadien-1-oliron tricarbonyls were prepared by the reaction of freshly distilled corresponding alcohols with excess $Fe_2(CO)_9$ in anhydrous diethyl ether with reflux under nitrogen for 12 h.[6e] Norbornadieneiron tricarbonyl was prepared from the reaction of norbornadiene with iron pentacarbonyl in benzene with uv irradiation at 80 °C for 48 h. After workup, the fraction 98–103 °C (1.0 mmHg) was collected. Norbornadieneiron tricarbonyl was protonated

in SO_2 at -80 °C with excess fluorosulfuric acid.

cis-Pentadienyl- and *cis*-1-methylpentadienyliron tricarbonyl cations were generated by the slow addition of excess cooled HSO_3F–SO_2 at -78 °C.

Cyclohexadienyliron Tricarbonyl Cation. 1,3-Cyclohexadieneiron tricarbonyl was prepared by the reaction of 1,4-cyclohexadiene with $Fe(CO)_5$ in benzene at 80 °C with uv irradiation under nitrogen for 48 h.[10c] Cyclohexadieneiron tricarbonyl cation was prepared by the hydride abstraction of distilled 1,3-cyclohexadieneiron tricarbonyl with triphenylmethyl tetrafluoroborate in methylene chloride.

Cycloheptadienyliron Tricarbonyl Cation. Cycloheptatrieneiron carbonyl was prepared by the reaction of cycloheptatriene with $Fe(CO)_5$ in methylcyclohexane with reflux under nitrogen for 48 h.[11d] Cycloheptadienyliron tricarbonyl cation is formed upon protonation of the free double bond in distilled cycloheptatrieneiron tricarbonyl with 40% aqueous HBF_4 in acetic anhydride at 0 °C.

Bicyclo[5.1.0]octadienyliron Tricarbonyl Cation. Cyclooctatetraeneiron tricarbonyl was prepared by the reaction of cyclooctatetraene with $Fe_2(CO)_9$ in anhydrous diethyl ether with reflux under nitrogen for 4 h. Bicyclo[5.1.0]octadienyliron tricarbonyl cation was obtained upon protonation of one of the free double bonds in chromatographically purified cyclooctatetraeneiron tricarbonyl with excess HSO_3F in SO_2 at -50 °C.

Instrumentation. The carbon-13 spectra were obtained on a Varian XL-100 spectrometer equipped with Fourier transform accessory, a spin decoupler, and a variable-temperature probe. A Varian 620L computer was used to accumulate data. Fluorobenzene was used as external lock and all chemical shifts are referred to external Me_4Si (5% ^{13}C enriched) capillary.

Registry No.—2, 45977-75-1; 3, 49654-90-2; 4, 46238-85-1; 5, 12307-07-2; 6, 59034-05-8; 8, 46134-85-4; 13, 41853-19-4; carbon-13, 14762-74-4.

References and Notes

(1) Part 9: G. A. Olah and S. H. Yu, *J. Org. Chem.*, **41**, 1694 (1976).

(2) Postdoctoral Fellow.

(3) H. J. Dauben and L. R. Honnen, *J. Am. Chem. Soc.*, **80**, 5570 (1958).

(4) (a) E. O. Fischer and R. D. Fischer, *Angew. Chem.*, **72**, 919 (1960); (b) R. D. Fischer, *Chem. Ber.*, **93**, 165 (1960).

(5) (a) R. Pettit and L. W. Haynes in "Carbonium Ions", Vol. V, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N.Y., in press; (b) M. Cais, E. D. Bergmann, and B. Pallman, "Aromaticity, Pseudoaromaticity, Anti-Aromaticity", Academic Press, New York, N.Y., 1971; (c) E. W. Abel and S. P. Tyfield, *Adv. Organomet. Chem.*, **8**, 117 (1970); (d) M. A. Haas, *Organomet. Chem. Rev., Sect. A*, **4**, 307 (1969); (e) M. Cais, *Organomet. Chem. Rev.*, **1**, 436 (1966).

(6) (a) E. Mahler and R. Pettit, *J. Am. Chem. Soc.*, **85**, 3955 (1963); (b) D. E. Mahler, D. H. Gibson, and R. Pettit, *ibid.*, **85**, 3959 (1963); (c) C. P. Lillya and R. A. Sahatjian, *J. Organomet. Chem.*, **32**, 371 (1971); **25**, C67 (1970); (d) T. S. Sorensen and C. R. Jablonski, *ibid.*, **25**, C62 (1970); *Can. J. Chem.*, **52**, 2085 (1974); (e) N. A. Clinton and C. P. Lillya, *Chem. Commun.*, 579 (1968); *J. Am. Chem. Soc.*, **92**, 3065, 3058 (1970).

(7) A. I. Rezvukhin, V. N. Piottukh-Peletskii, R. N. Berezine, and V. G. Shubin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 705 (1973).

(8) (a) F. J. Impastato and K. G. Ihrman, *J. Am. Chem. Soc.*, **83**, 3726 (1961); (b) G. F. Emerson and R. Pettit, *ibid.*, **84**, 4591 (1962); (c) G. F. Emerson, J. E. Mahler, and R. Pettit, *Chem. Ind. (London)*, 836 (1964); (d) T. H. Whitesides and R. W. Arhart, *J. Am. Chem. Soc.*, **93**, 5296 (1971); (e) T. H. Whitesides, R. W. Arhart, and R. W. Slaven, *ibid*, **95**, 5792 (1973); (f) T. H. Whitesides and R. W. Arhart, *Inorg. Chem.*, **14**, 209 (1975); (g) D. A. T. Young, J. R. Holmes, and H. D. Haesz, *J. Am. Chem. Soc.*, **91**, 6968 (1969); (h) D. H. Gibson and R. L. Vonnahme, *ibid.*, **94**, 5090 (1972); *J. Chem. Soc., Chem. Commun.*, 1021 (1972).

(9) D. R. Falkowski, D. F. Hunt, C. P. Lillya, and M. D. Rausch, *J. Am. Chem. Soc.*, **89**, 6387 (1967).

(10) M. Brookhart and D. L. Harris, *Inorg. Chem.*, **13**, 1540 (1974).

(11) (a) A. J. Birch, K. B. Chamberlain, M. A. Haas, and D. J. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1882 (1973); (b) A. J. Birch and D. H. Williamson, *ibid.*, 1892 (1973); (c) A. J. Birch, P. E. Cross, J. Lewis, D. A. White, and S. B. Wild, *J. Chem. Soc. A*, 332 (1968); (d) D. Jones, L. Pratt, and G. Wilkinson, *ibid.*, 4458 (1962).

(12) (a) H. J. Dauben and D. J. Bertelli, *J. Am. Chem. Soc.*, **83**, 497 (1961); (b) R. Burton, L. Pratt, and G. Wilkinson, *J. Chem. Soc.*, 594 (1961); (c) A. Davison, W. McFarlane, L. Pratt, and G. Wilkinson, *ibid.*, 4821 (1962); (d) B. F. G. Johnson, J. Lewis, P. McArdle, and G. L. P. Randal, *J. Chem. Soc., Dalton Trans.*, 457 (1972).

(13) (a) R. Pettit, G. F. Emerson, and J. E. Mahler, *J. Chem. Educ.*, **40**, 175 (1963); (b) R. Hoffmann and P. Hofmann, *J. Am. Chem. Soc.*, **98**, 598 (1976).

(14) (a) M. J. S. Dewar, *Bull. Soc. Chim. Fr.*, **18**, C79 (1951); (b) J. Chatt and L. A. Duncanson, *J. Chem. Soc.*, 2937 (1953).

(15) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 3d ed, Interscience, New York, N.Y., 1972, Chapter 23.

(16) C. A. Coulson and A. Stretiwieser, Jr., "Dictionary of π-Electron Calculations", W. H. Freeman, San Francisco, Calif., 1965.

(17) (a) J. Evans and J. R. Norton, *Inorg. Chem.*, **13**, 3042 (1974); (b) L. F. Farnell, E. W. Randall, and E. Rosenberg, *Chem. Commun.*, 1078 (1971); (c) P. C. Aluterbur and R. B. King, *J. Am. Chem. Soc.*, **87**, 3266 (1965); (d) H. L. Retcofsky, E. N. Frankel, and H. S. Gutowsky, *ibid.*, **88**, 2710 (1966); (e) H. E. Mann, *Adv. Organomet. Chem.*, **12**, 135 (1974).

(18) D. F. Hunt, C. P. Lillya and M. D. Rausch, *J. Am. Chem. Soc.*, **90**, 2561 (1968).

(19) The chemical shift of C_7 is shielded from δ 7.4 to 48.8 to 38.7 as the π-electron density decreases from norbornadiene to norbornene to norbornane.[20] The upfield shift of C_7 is also reported in $C_7H_8Pt(CH_3)_2$,[21] $C_7H_8Mo(CO)_4$,[22] and $C_7H_8W(CO)_4$.[22]

(20) (a) E. Lippma, T. Pehk, J. Passivirta, N. Belikova, and A. Plate. *Org. Magn. Reson.*, **2**, 581 (1972); (b) J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970); (c) K. Tori, Y. Hata, R. Maneyuki, Y. Takano, T. Tsuji, and H. Tanida, *Can. J. Chem.*, **42**, 921 (1964); (d) K. Tori, R. Muneyulci, and H. Tanida, *ibid.*, **41**, 3142 (1963).

(21) H. C. Clark, L. E. Manzer, and J. E. H. Ward, *Can. J. Chem.*, **52**, 1165 (1972).

(22) (a) E. E. Mann, *J. Chem. Soc., Dalton Trans.*, 2012 (1973); *Chem. Commun.*, 976 (1971); (b) B. E. Mann, *Adv. Organomet. Chem.*, **12**, 135 (1974).

(23) (a) G. A. Olah and G. Liang, *J. Am. Chem. Soc.*, **95**, 3792 (1973); (b) G. A. Olah and G. Liang, *ibid.*, **97**, 1920 (1975).

(24) (a) L. Kruczynski, L. K. K. LiShingman, and J. Takats, *J. Am. Chem. Soc.*, **96**, 4006 (1974); (b) S. T. Wilson, N. J. Coville, J. R. Shapely, and J. A. Osborn, *ibid.*, **96**, 4038 (1974); (c) G. Rigatti, G. Boccalon, A. Ceccon, and G. Giacometti, *J. Chem. Soc., Chem. Commun.*, 1165 (1972).

(25) F. A. Cotton, V. W. Day, B. A. Frenz, K. I. Hardcastle, and J. M. Troup, *J. Am. Chem. Soc.*, **95**, 4522 (1973), and references cited therein.

(26) O. A. Gansow, A. R. Burke, and W. D. Vernon, *J. Am. Chem. Soc.*, **94**, 2550 (1972).

(27) (a) G. M. Bodner and L. J. Todd, *Inorg. Chem.*, **13**, 1385 (1974); (b) O. A. Gansow, B. T. Kimera, G. R. Dibson, and R. A. Brown, *J. Am. Chem. Soc.*, **93**, 5992 (1971); (c) O. A. Gansow, D. A. Schexnayder, and B. Y. Kimura, *ibid.*, **94**, 3406 (1972).

(28) I. M. Heilbron, E. R. H. Jones, J. T. McCombie, and B. C. L. Weedon, *J. Chem. Soc.*, 84 (1945).

Transmission of Substituent Effects in Spiro[3.4]octane-2-carboxylic Acid Derivatives[1]

Curtis L. McLendon, Harry C. Dorn, Phillip N. Crabtree, Arturo G. Bellettini, and Edward J. Grubbs*

Department of Chemistry, San Diego State University, San Diego, California 92182

The synthesis, separation, and characterization of *cis-* and *trans*-spiro[3.4]-6-octanone-2-carboxylic acids (**6a** and **6b**, respectively) is described. The pK_a's for these keto acids, for spiro[3.4]octane-2-carboxylic acid (**5**), spiro[3.4]-6-octene-2-carboxylic acid (**4**), and a cis–trans mixture of 6-methylenespiro[3.4]octane-2-carboxylic acid (**9**) have been determined. The experimentally determined ΔpK_a's are compared with values calculated using spherical and ellipsoidal cavities in the Tanford-modified Kirkwood–Westheimer expression. The base-catalyzed deuterium exchange of the spiro keto acids at C_5 and C_7 is also briefly discussed.

In an earlier publication[2] we suggested several geometric characteristics which should prove useful in attempts to evaluate the relative applicabilities of the Kirkwood–Westheimer electrostatic field model and the inductive model for polar substituent effects. In that report[2] the synthesis of a model spirooctane system was described. Subsequently we applied similar structural requirements to demonstrate the dependence of acidities and reactivities of carboxylic acids and esters on the angular orientation of remote dipoles.[3,4] The inductive model cannot accommodate such an angular dependence. The results were understandable in terms of the K and W field model, but were not quantitatively in accord. Numerous studies during the past 10 years have supported electrostatic field models in various modifications as more effective than inductive models.[5-8]

The initial objective of the present study was the preparation of the spiro[3.4]-6-octanone-2-carboxylic acids (**6a** and **6b**) (Scheme I). This system with a fairly rigid molecular framework facilitates reasonably accurate estimates of R and cos θ employed in the K and W expression. These keto acids also possess a molecular cavity which approximates the shape of an ellipsoid of revolution more closely than other systems which had been studied at the time that this work was initiated.[9] Thus it was of interest to test whether the success of the K and W model in predicting ΔpK_a's for more "ellipsoid-shaped" systems was sensitive to choice of ellipsoidal or spherical cavity models. Studies of relative reactivities at the 5 position of geometrically isomeric spiro[3.4]octane-2-carboxylic acids were also envisioned. For example, comparisons between **6a** and **6b** or between **7a** and **7b** of rate-constant ratios k_5/k_7 for base-catalyzed deuterium exchange (at α methylene carbons) should provide information regarding charge–charge and charge–dipole effects on rate processes. These latter studies are yet in preliminary stages.

Results

Syntheses and Characterizations. The preparations of the various spiro[3.4]octane derivatives employed in this study are outlined in Scheme I.

Catalytic hydrogenation of the olefinic acid **4**[10] provided the parent saturated acid previously reported by Buchta.[11] Oxymercuration–demercuration of **3** followed by dichromate oxidation and decarboxylation afforded a mixture of the isomeric keto acids **6a** and **6b**. The intermediates **3a** and **3b** were used directly without complete characterization because of purification difficulties. The keto acids **6a** and **6b** were separated chromatographically. The cis isomer **6a** melts at 81–83.5 °C; the trans isomer **6b** melts at 85.5–87.5 °C. Geometric assignments were made on the basis of the dipole moments of the corresponding methyl esters.[12] The dipole moment of **7a** is 3.40 D, that for the trans isomer **7b** is 2.82. The order of

Scheme I
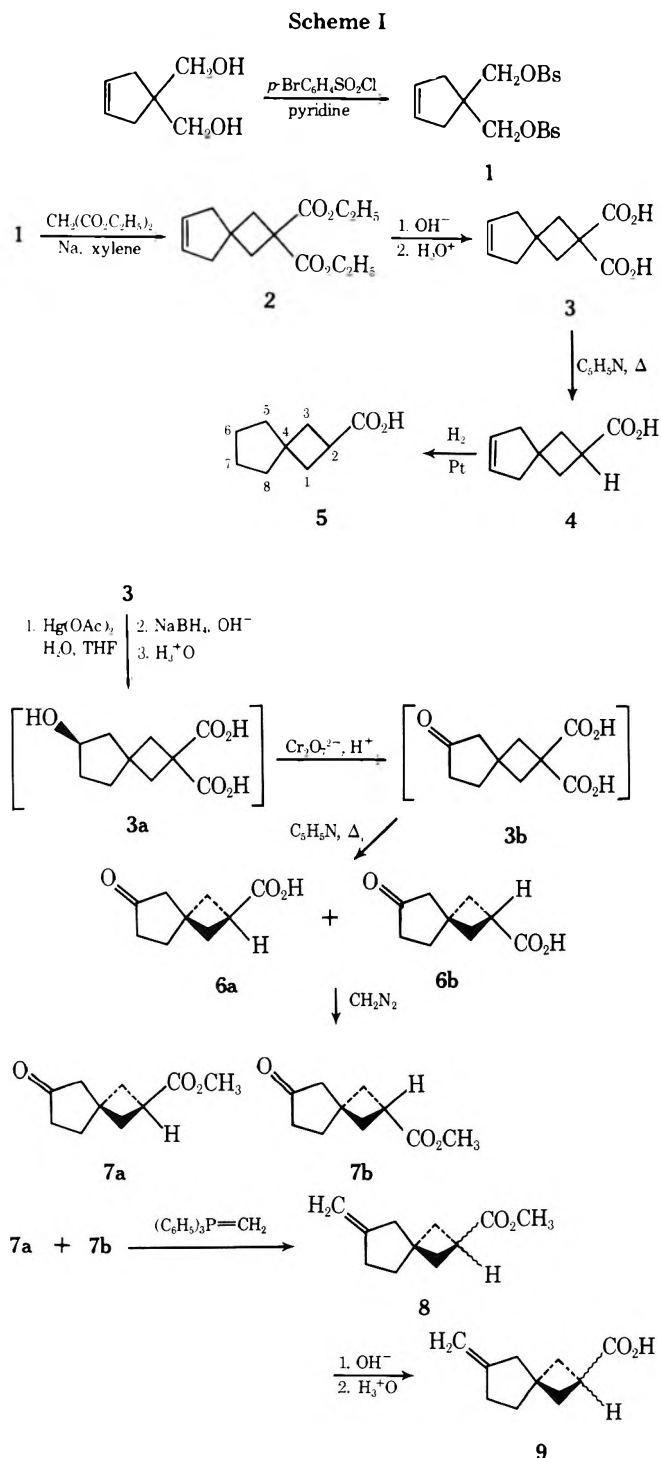
Table I. Thermodynamic pK_a's for Spiro[3.4]octane-2-carboxylic Acid and Related Acids in Water at 25 °C

Compd	$pK_a{}^a$	Std dev^b
4	4.754	(0.008)
5	4.856	(0.003)
6a	4.585	(0.004)
6b	4.567	(0.003)
9	4.747	(0.005)
C$_6$H$_5$CO$_2$H	4.192^c	(0.004)

^{a} Each pK_a is considered accurate within ±0.025. ^{b} The standard deviation for the 18 points of a two-run set is shown in parentheses. See the Experimental Section for further discussion. ^{c} Average of four separate determinations performed at various times during the period of the other measurements.

elutions (trans before cis) for **6a** and **6b** (liquid chromatography) and for **7a** and **7b** (GLC) usually expected is also in accord with the geometric assignments. That the carbonyl is located at the 6 position and not the 5 position was demonstrated by the exchange of four protons (followed by NMR) when the keto acid is dissolved in D$_2$O containing NaOD at room temperature. The dominant mass spectral fragmentation paths for both the keto acids and the keto esters appear to involve elimination of acrylic acid or methyl acrylate from the molecular ion as evidenced by a prominent peak at m/e 96.

In order to assess the extent to which rehybridization (sp^3 → sp^2) at C$_6$ is responsible for the increased acidity of **6a** and **6b** over **5** (Table I), a mixture of the keto esters was converted to the 6-methylene esters by the Wittig reagent. Hydrolysis to the mixture of 6-methylene acids **9** provided the requisite model compounds.

Acid Dissociation Constants. The thermodynamic pK_a's were determined in water at 25 °C as outlined in the Experimental Section. They are listed in Table I. Although the pK_a's for **6a** and **6b** are nearly identical, the possibility of epimerization at C$_2$ during the pK_a determinations was excluded. This was done by reisolating the acids (following simulated pK_a measurements) with unchanged geometry which was demonstrated by conversions to methyl esters and examination of the separate esters on GLC.

Discussion

The introduction of a carbonyl group at C$_6$ increases the acidity of **6a** and **6b** over **5** by about 0.28 pK_a units. However, not all of this modest acid enhancement can be attributed to an electrostatic effect of the carbon–oxygen dipole. As seen in Table I, a carbon–carbon double bond at C$_6$ results in a pK_a lowering of 0.10 when compared with the saturated parent acid **5**. This increase in acidity is the same whether the carbon–carbon double bond is endocyclic or exocyclic. It is unlikely that these double bonds at such a remote position (ϵ to the CO$_2$H carbon) exert their influence via successive polarizations of intervening σ bonds. Dewar, for example, has concluded that the σ-inductive effect may be unimportant at positions separated from a substituent by more than one or two bonds.[14] Nonetheless, it would be reassuring to find that straight-chain olefinic acids bearing the carbon–carbon double bond at remote positions possessed the same pK_a as the saturated analogue. However, data bearing on this question are surprisingly few and sometimes conflicting, and a precise indication of the probable error is rarely found. Furthermore, acidity data for a series of unsaturated acids obtained by one group must usually be compared with the acidity of saturated analogues determined by different workers.[15] An alternate source of the acidity enhancement of **4** and **9** over **5** (and a portion of the increase in acidity of **6a** and **6b** over **5**) could be

a conformational transmission effect similar to that discovered by Barton and co-workers.[16] These effects presumably arise from conformational distortions which are relayed to the reaction site where rehybridization is usually occurring. The transmission is believed to be effected by small flexings of valency angles and changes of atomic coordinates. As applied to **6a** or **6b**, this would suggest that the introduction of the carbonyl group at C$_6$ would result in a slight increase in the C$_5$C$_4$C$_8$ bond angle compared with **5**. The effect of this would
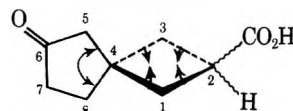
be a small contraction of $\angle C_1C_4C_3$ and $\angle C_1C_2C_3$. Such a deformation of the four-membered ring would increase the s character in external bonds at C$_2$ and thus enhance the acidity.[17] In support of this hypothesis is the observation that the C$_2$C$_3$C$_4$ bond angle in cyclopentanone[18] (105.1°) is slightly expanded [with $\angle C_1C_2C_3$ contracted (102.2°)] compared with the average CCC bond angle (103.3°) for puckered cyclopentane.[19] A similar conformational transmission could be expected with an exomethylene group at C$_6$ of the spirane system (compounds **9**) or internal unsaturation at C$_6$ (compound **4**).[20] Although these interatomic angle deformations are small, they may reflect only a portion of interorbital angle changes. It would also seem reasonable that in systems wherein substantial rehybridization is absent at the reacting site, rigid molecular frameworks would provide the best opportunity to observe conformational transmission effects. For in these cases the alterations of valency angles at a remote site would be directly linked to the reaction site by concomitant changes in hybridization of methylene groups incapable of rotational accommodation.[22]

The data in Table I and the discussion above suggest that as little as 0.18 pK unit of the acid-strengthening effect of the carbonyl group at C$_6$ may be attributable to a charge–dipole interaction. Thus it is against approximately this value that the applicability of the various modifications of the K and W model is measured. The experimental and calculated[23] values for log K_X/K_H are listed in Table II along with molecular parameters and effective dielectric constants.

These calculations show that the ellipsoidal cavity model provides the better agreement with experiment. It should be recalled that the portion of the experimental ΔpK's attributable to interactions directly addressed by the K and W expressions may be close to 0.18. It is interesting that the nearly identical ΔpK values calculated for the two geometric isomers may be the consequence of a more favorable $\cos\theta$ value for **6b** almost perfectly compensated by a shorter distance, R, and a lower effective dielectric constant for **6a**. For those advocates of the inductive model (who remain unconvinced of the dependency of reactivity on the angular orientation of substituent dipoles) these data may buttress their skepticism.

The study of base-catalyzed deuterium exchange α to the cyclopentanone carbonyl in **6a** and **6b** has not yet been completed. However, several preliminary observations provide structural insight. The high-field portion of the ^{1}H NMR spectrum of the trans acid **6b** (in H$_2$O) is shown in Figure 1. Spectra of the sodium salt of **6b** in water and in NaOD–D$_2$O determined at room temperature at 18, 78, and 208 min are also shown in Figure 1. The three two-proton singlets at 2.13, 2.27, and 2.39 ppm in **6b** show that the methylenes at C$_7$ and C$_8$ are not coupled. The remaining multiplet partially obscured by these singlets is produced by the cyclobutane methylenes coupled to the C$_2$ proton whose multiplet is centered at 3.1 ppm. When **6b** is converted to its sodium salt (titrimetrically using aqueous NaOH) and then dissolved in water, a methylene singlet attributed to C$_5$ H$_2$ becomes a

Table II. Experimental and Calculated[23] Values of ΔpK for 6a and 6b and K–W Parameters

Compd	R, Å; $\cos \theta$	Sphere		Ellipsoid		Exptl ΔpK
		D_E	ΔpK	D_E	ΔpK	
6a	6.94; 0.688	4.92	0.442	9.64	0.226	0.271
6b	7.68; 0.939	5.32	0.479	11.65	0.219	0.289

multiplet presumably via long-range coupling with the cyclobutane methylenes. This leaves two singlets at 2.17 (C_8 H_2) and 2.39 ppm (C_7 H_2). It is seen that the two-proton singlet at 2.39 ppm is completely removed by exchange after 18 min. Most of the second set of exchangeable methylene protons have also been replaced by deuterium at this point. However, further exchange is clearly observable during the following 3-h period. During this time, the complex multiplet between 1.7 and 2.1 ppm slowly diminishes (approximately 90% of the second methylene set exchanged) and evolves into an approximate doublet ($J = 8$ Hz). Excluding the C_8 H_2 singlet, the remainder of the spectrum then closely approximates the $A_2A_2'X$ system observed for cyclopropylamine in benzene which has been analyzed by Hutton and Schaefer.[28] These spectra confirm the structure of 6b and are in accord with expectation that the C_7 methylene protons should exchange more rapidly than the C_5 methylene protons. Both steric and electrostatic effects contribute to this order. Similar preliminary observations have been made with 6a. A quantitative study comparing the exchange behavior of the two isomers and directed toward a separation of the steric and electrostatic effects is in progress.

Experimental Section[29]

1,1-Dimethylol-3-cyclopentene Di-p-bromobenzenesulfonate (1). The dibrosylate was prepared as previously described for the ditosylate.[2] Reaction of 89.2 g (0.696 mol) of 1,1-dimethylol-3-cyclopentene[2] in 1 l. of dry pyridine with 400 g (1.565 mol) of o-bromobenzenesulfonyl chloride afforded the crude dibrosylate. This was recrystallized from a 50/50 by volume mixture of benzene/petroleum ether (bp 60–90 °C) affording 288 g (73%) of the dibrosylate, mp 143–146 °C.

The dibrosylate (1) from a similar preparation was recrystallized a second time from methanol, affording an analytical sample, mp 146–147 °C.

Anal. Calcd for $C_{19}H_{18}O_6Br_2S_2$: C, 40.32; H, 3.18; Br, 28.75; S, 11.31. Found: C, 40.53; H, 3.34; Br, 28.70; S, 11.27.

The ¹H NMR spectrum of 1 in CDCl₃ shows a narrow multiplet at δ 7.72 (8, aromatic) and three singlets at δ 5.54 (2, vinyl), 3.95 (4, –CH₂OBₛ), and 2.18 (4, allyl).

Diethyl spiro[3.4]-6-octene-2,2-dicarboxylate (2) was prepared in 75% yield (based on unrecovered dibrosylate) by the cycloalkylation of diethylmalonate by the dibrosylate 1 as previously reported[2] using the corresponding ditosylate.

Spiro[3.4]-6-octene-2,2-dicarboxylic acid (3), mp 165–169 °C, was prepared in 86% yield by the hydrolysis of the diester 2 as previously described.[2]

Spiro[3.4]octane-2-carboxylic acid[30] (5) was prepared by the platinum-catalyzed hydrogenation of 4[2] in ethanol at atmospheric pressure. The sample was analytically pure and the NMR spectrum (CCl₄) showed no residual olefinic hydrogen. The saturated acid obtained in this way in 91% yield was a waxy solid, mp 31–32 °C (lit.[30] mp 39 °C).

cis- and trans-Spiro[3.4]-6-octanone-2-carboxylic Acid (6a and 6b). To a suspension of 35.8 g (0.112 mol) of mercuric acetate in 95 ml of water plus 95 ml of tetrahydrofuran was added 19.9 g (0.101 mol) of the olefinic diacid 3 dissolved in 380 ml of water. The mixture was stirred for 55 h. Then 111 ml of 3.0 N sodium hydroxide was added, followed by a solution of 2.13 g of sodium borohydride and 1.12 g of sodium hydroxide in 190 ml of water. The resulting black precipitate was filtered. The filtrate was acidified with 6 N hydrochloric acid to a pH of approximately 6. This aqueous phase was then subjected to continuous ether extraction for 24 h. The ether extract was dried and concentrated affording 14.3 g (65%) of 6-hydroxy-

spiro[3.4]octane-2,2-dicarboxylic acid (3a) which was used in the next step without further purification.

To a stirred solution of 7.56 g (0.0353 mol) of the hydroxy diacid 3a in 140 ml of ether was added a solution prepared from 5.95 g (0.0585 mol) of sodium dichromate dihydrate and 7 ml of 96% sulfuric acid diluted with water to 175 ml. During the addition, which required 10 min, the temperature was maintained at 25 °C. After 55 h, the ether layer was separated and the aqueous layer extracted with six 150-ml portions of ether. The combined ether extract was dried and concentrated to give 6.5 g (86%) of the crude spiro[3.4]-6-octanone-2,2-dicarboxylic acid (3b). Similar oxidations of hydroxy diacid 3a yielded an additional 24 g of the keto diacid. The infrared spectrum of 3b (KBr disk) shows three bands in the carbonyl region at 1680, 1710, and 1740 cm⁻¹ and a broad absorption centered at 3200 cm⁻¹ (acid O–H). These products were subjected to decarboxylation without further purification.

A solution of 5.8 g (0.028 mol) of the above keto diacid 3b in 37 ml of pyridine was boiled under reflux for 6 h. The resulting mixture was cooled, acidified with 84 ml of 6 N hydrochloric acid, and subjected to continuous extraction with ether for 24 h. The ether extract was dried and concentrated to give 4.0 g of a yellow oil. A second decarboxylation of 10.9 g of 3b afforded 7.2 g of yellow oil.

The isomeric keto acids 6a and 6b were separated chromatographically using a 7 × 75 cm column packed with a silicic acid–Celite mixture. The mixture was prepared from 500 g of 100 mesh silicic acid (Mallinckrodt), 100 g of Celite, 51 ml of water, and 270 ml of methanol. Using columns of this size and crude keto acid mixtures (2–3 g) the separations were effected. An initial chromatograph was followed by second chromatographs on intermediate fractions of the partially purified isomers. The trans isomer was eluted with a 45/30/1 (v/v/v) mixture of hexane, ether, and acetic acid, respectively. The cis isomer was eluted with a 45/45/1 (v/v/v) mixture of hexane, ether, and acetic acid, respectively. From a total of 8.02 g of the original unresolved crude mixture of keto acids was obtained 1.97 g of the trans keto acid 6b as an oily semisolid. GLC (5 ft × 0.12 in. FFAP) analysis of the methyl ester (prepared from diazomethane) revealed its isomeric purity to be approximately 88%. Two recrystallizations from ether afforded 0.905 g of 6b, mp 85.5–87.5 °C, containing less than 2% of the cis isomer. From the same 8.02 g of unresolved sample was similarly obtained 1.95 g of the cis keto acid 6a as an oily semisolid. Its isomeric
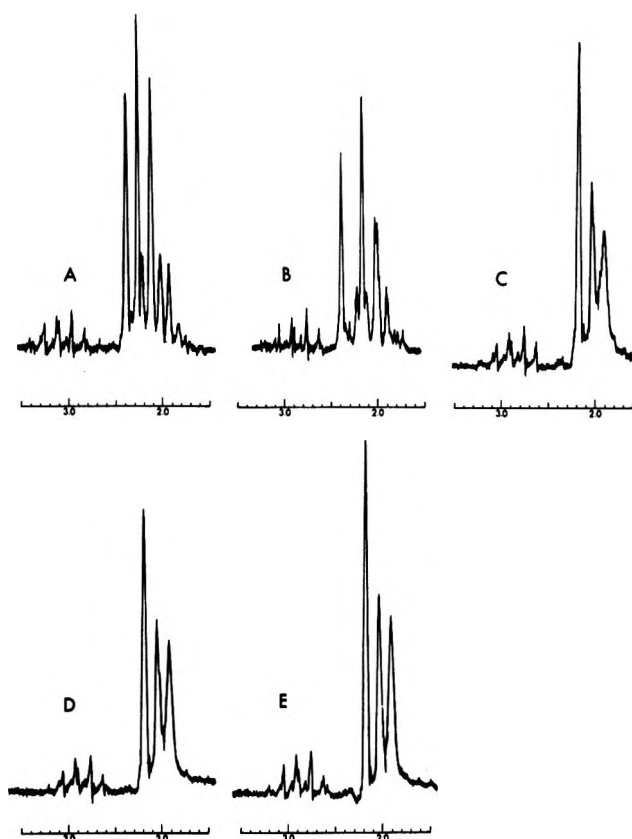

Figure 1. ¹H NMR spectra of (A) 6b in H_2O, (B) sodium salt of 6b in H_2O, (C) sodium salt (40 mg) in 0.6 N NaOD–D_2O after 19 min, (D) after 78 min, and (E) after 208 min at 35 °C.

purity was also approximately 88%. Two recrystallizations of this material from ether gave 0.814 g of **6a**, mp 81–83.5 °C, containing less than 2% of the trans isomer. The mixture melting point of pure **6a** added to **6b** was 45–57 °C.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found for **6b**: C, 64.29; H, 7.08. Found for **6a**: C, 64.50; H, 7.23.

The infrared spectra (saturated in CCl_4) of **6a** and **6b** show bands at 1704 (CO_2H carbonyl) and 1744 cm^{-1} (ketone C=O) and a broad absorption envelope in the region 2500–3400 cm^{-1} attributable to a combination of O–H and C–H stretching vibrations. Subtle differences mainly in intensities were observable in the fingerprint region.

The ^1H NMR spectrum of the trans keto acid **6b** (CDCl$_3$) shows the following: δ 10.37 (s, 1, CO_2H), 2.8–3.4 (m, 1, $J \sim 8$ Hz, C_2 H), and 1.7–2.5 (m, 10, ring CH_2). The ^1H NMR spectrum of the cis isomer **6a** under the same conditions (CDCl$_3$) shows the following: δ 9.60 (s, 1, CO_2H), 2.8–3.5 (m, 1, $J \sim 8$ Hz, C_2 H), and 1.7–2.6 (m, 10, ring CH_2). The mass spectra for **6a** and **6b** are very similar. In addition to other lower molecular weight fragments, the trans isomer **6b** shows at 15 eV the following peaks: m/e (rel intensity) 168 M$^+$ (100), 150 M$^+$ – H_2O (36), 140 M$^+$ – CO (12), 123 M$^+$ – CO_2H (10), 96 M$^+$ – CH_2=CHCO$_2$H (64). The corresponding intensities for these same peaks in the mass spectrum of the cis isomer **6a** at approximately the same ionization voltage are 100, 18, 8, 4, and 28, respectively.

Methyl *trans*-Spiro[3.4]-6-octanone-2-carboxylate (7b). A 0.432-g (2.57 mmol) sample of pure trans keto acid **6b** in 10 ml of methanol was converted to the methyl ester using ethereal diazomethane. After removing the ether, the residual oil was distilled under reduced pressure using a micro-Hickman still. The ester distilled at 0.025 mmHg at a pot temperature of 55–70 °C. The ester (a colorless oil) [0.385 g (82%)] contained less than 2% of the cis isomer as determined by GLC using a 5 ft × 0.25 in. DEGS on Chromosorb W column.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.69. Found: C, 66.02; H, 7.47.

The spectral features are as follows: ir (CCl$_4$) 1740 cm^{-1} (ester and ketone C=O); NMR (CDCl$_3$) δ 3.70 (s, 3, CO_2CH_3), 2.80–3.45 (m, 1, C_2 H), 1.8–2.7 (m, 10, ring methylene protons); MS (15 eV) m/e (rel intensity) 182 M$^+$ (38), 123 M$^+$ – CO_2CH_3 (17), 96 M$^+$ – CH_2=CHCO$_2$CH$_3$ (100).

Methyl *cis*-Spiro[3.4]-6-octanone-2-carboxylate (7a). Using the same procedure as employed for the trans isomer, 0.421 g (2.50 mmol) of the cis keto acid **6a** was esterified. Distillation [pot temperature 55–70 °C (0.025 mm)] of the product yielded 0.378 g (83%) of **7a** as a colorless oil. GLC analysis (as above) showed it to contain less than 2% of the trans isomer.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.69. Found: C, 65.86; H, 7.75.

The spectral features are very similar to those of the trans isomer and are as follows: ir (CCl$_4$) 1740 cm^{-1} (ester and ketone C=O); NMR (CDCl$_3$) δ 3.68 (s, 3, CO_2CH_3), 2.87–3.50 (m, 1, C_2 H), 1.8–2.7 (m, 10, ring methylene protons); MS (15 eV) m/e (rel intensity) 182 M$^+$ (35), 123 M$^+$ – CO_2CH_3 (10), 96 M$^+$ – CH_2=CHCO$_2$CH$_3$ (100).

Methyl *cis*- and *trans*-6-Methylenespiro[3.4]octane-2-carboxylates (8). Freshly distilled dimethyl sulfoxide (5.00 ml) was treated with sodium hydride (0.281 g of ca. 57% NaH in mineral oil) which had been washed repeatedly with pentane under nitrogen. The total base content was determined by titration. Methyltriphenylphosphonium bromide (1.09 g, 2.79 mmol) was dissolved in 4 ml of warm Me$_2$SO and added to 2 ml (2.66 mequiv) of the Me$_2$SO–carbanion solution. This reaction mixture was stirred at room temperature for 20 min. To this Wittig reagent was added 0.461 g (2.52 mmol) of a ca. 50/50 mixture of the keto esters **7a** and **7b**. An additional 1 ml of Me$_2$SO was added. The light-orange solution was stirred at room temperature for 2 h and poured into 25 ml of water. This was acidified with 0.1 N HCl and continuously extracted with pentane for 24 h. The extract was dried and concentrated to a yellow oil (0.480 g). The mixture of esters was isolated from this reaction mixture by preparative GLC using a 5 ft × 0.25 in. DEGS on Chromosorb W column at 160 °C. In addition to 0.065 g of unreacted starting esters was collected 0.231 g (59% based on unrecovered starting keto esters) of the two methylene esters as a ca. 50/50 mixture. These isomers were not appreciably separable with a variety of columns. Partial resolution was achieved with the DEGS and FFAP columns, but it was not sufficient for preparative scale separation.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.30; H, 8.81.

The spectral features of the mixed esters **8** are as follows: ir (neat) 3070 (olefinic C–H), 1730 (ester C=O), 1660 (>C=CH$_2$), and 875 cm^{-1} (gem-disubstituted alkene C–H bend); NMR (CDCl$_3$) δ 4.77 (narrow m, 2, >C=CH$_2$), 3.61 (s, 3, CO_2CH_3), 2.50–3.16 (m, 1, C_2 H), and 1.50–2.50 (m, 10, ring methylene protons); MS (12 eV) m/e (rel intensity) 180 M$^+$ (33), 121 M$^+$ – CO_2CH_3 (35), 94 M$^+$ – CH_2=

CHCO$_2$CH$_3$ (100).

cis- and *trans*-6-Methylenespiro[3.4]octane-2-carboxylic Acids (9). A 0.151-g (0.840 mmol) sample of the methylene esters **8** was hydrolyzed in 0.423 ml of 1.99 N aqueous NaOH at 80 °C for 3 h. The cooled basic reaction mixture was then continuously extracted with ether for 12 h. The aqueous phase was acidified and continuously extracted with ether for 12 h. This extract was dried and concentrated affording 0.133 g (95%) of the methylene acids **9** as an oil. GLC analyses of this acid mixture (and a small portion reconverted to the methyl esters with diazomethane) showed it to contain only a mixture of the geometric isomers.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.62; H, 8.60.

The spectral features of the mixed methylene spiro acids **9** are as follows: ir (neat) 3070 (olefinic C–H), 2500–3600 (broad envelope, C–H and acid O–H), 1700 (CO_2H carbonyl), 1660 (>C=CH$_2$), and 875 cm^{-1} (gem-disubstituted alkene C–H bend); NMR (CCl$_4$) δ 11.6 (s, 1, CO_2H), 4.80 (narrow m, 2, >C=CH$_2$), 2.6–3.3 (m, 1, C_2 H), and 1.50–2.50 (m, 10, ring methylene protons); MS (15 eV) m/e (rel intensity) 166 M$^+$ (63), 121 M$^+$ – CO_2H (77), 94 M$^+$ – CH_2=CHCO$_2$H (100).

Measurements of pK_a's. These measurements were performed in water at 25 °C. The values were determined potentiometrically with the aid of a Beckman Research pH meter. The electrodes (glass, Beckman Model 39000 or 41263, and calomel, Beckman Model 39071 or 39402) were standardized using an aqueous potassium hydrogen phthalate buffer (0.0500 M) and an aqueous phosphate buffer (0.02500 M KH$_2$PO$_4$ and 0.02500 M Na$_2$PO$_4$). Titrations were carried out using approximately 0.01 N NaOH. Distilled or deionized water was redistilled and stored under nitrogen prior to preparation of stock solutions. Titrations were conducted under nitrogen in a water-jacketed cell maintained at 25.0 °C.

A modified version of the method described by Albert and Serjeant[31] was used to calculate the pK_a values from the experimental data. The method involves a preliminary determination of the concentration of the titrating base. Next a value for the pK_a was calculated for each of the nine points in the midrange of the titration by use of the equation pK_a = pH + log [HA]/[A$^-$]. The activities of the species were calculated using appropriate activity coefficients. A correction (0.025 pH units) was made for the liquid junction potential error.[32] The pK_a values reported are the average values for 18 points of a two-run set and are considered to be accurate to 0.025 pK units (the approximate uncertainty in the liquid potential correction). The pK_a of benzoic acid was determined at various times during the course of this study. The largest difference between average values for sets of two runs was 0.013 and the average deviation was 0.004, which can be taken as a measure of the precision.

Test for Possible Equilibration of 6a and 6b during pK_a Measurements. Because of the near identity in pK_a values for spiro keto acids **6a** and **6b**, the possibility of epimerization at C_2 was investigated. Samples of **6a** and **6b** were separately subjected to conditions of the pK_a determinations. The basic solutions were acidified, extracted with ether, and dried. The recovered acids were then converted to their methyl esters by diazomethane and examined by GLC (5 ft × 0.25 in. FFAP on Chromosorb W at 180 °C). No detectable (<2%) epimerization had occurred.

Registry No.—1, 59015-16-6; **3**, 14377-07-2; **3a**, 59015-17-7; **3b**, 59015-18-8; **4**, 14377-08-3; **5**, 18386-63-5; **6a**, 59015-19-9; **6b**, 59015-20-2; **7a**, 59015-21-3; **7b**, 59015-22-4; *cis*-8, 59015-23-5; *trans*-8, 59015-24-6; *cis*-9, 59015-25-7; *trans*-9, 59015-26-8.

References and Notes

(1) Abstracted in part from the Ph.D. Thesis of Curtis Lee McLendon, University of California, San Diego, and San Diego State University, 1974.
(2) E. J. Grubbs, D. J. Lee, and A. G. Bellettini, *J. Org. Chem.*, **31**, 4069 (1966).
(3) E. J. Grubbs and R. Fitzgerald, *Tetrahedron Lett.*, 4901 (1968).
(4) E. J. Grubbs, R. Fitzgerald, R. E. Phillips, and R. Petty, *Tetrahedron*, 935 (1971).
(5) (a) T. W. Cole, Jr., C. J. Mayers, and L. M. Stock, *J. Am. Chem. Soc.*, **96**, 4555 (1974); (b) L. M. Stock, *J. Chem. Educ.*, **49**, 400 (1972), and references cited therein.
(6) C. L. Liotta, W. F. Fisher, G. H. Greene, Jr., and B. L. Joyner, *J. Am. Chem. Soc.*, **94**, 4891 (1972).
(7) C. F. Wilcox and C. Leung, *J. Am. Chem. Soc.*, **90**, 336 (1968).
(8) M. J. S. Dewar, R. Golden, and J. M. Harris, *J. Am. Chem. Soc.*, **93**, 4187 (1971).
(9) Subsequent to our report[2] on the synthesis of our parent system Liotta and co-workers[6] described the syntheses and pK_a measurements of 6-substituted spiro[3.3]heptane-2-carboxylic acids which also approximate an ellipsoid of revolution.
(10) R. D. Miller and M. Schneider [*Tetrahedron Lett.*, 1557 (1975)] have recently employed this olefinic acid as a starting point for their synthesis of spiro[3.4]octa-1,5,7-triene.

(11) E. Buchta and K. Geibel, *Justus Liebigs. Ann. Chem.*, **648**, 36 (1961).
(12) Dielectric constants of solutions were measured using a Dipolmeter Type DM 01 (Wissenschaftlich-Technische Werkstätten GmbH, Weilheim,-Germany). The Guggenheim method[13] was employed for obtaining dipole moments.
(13) E. A. Guggenheim, *Trans. Faraday Soc.*, **74**, 2193 (1952).
(14) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3548 (1962).
(15) (a) See G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961, for a compendium of acid-dissociation constants and a discussion of measurement methods. (b) A reviewer has suggested that an estimate of the magnitude of an inductive effect of our carbonyl at C-6 might be made on the basis of data from appropriate 6-keto acids or from analogous chloro acids. Such data do not appear to be available, and were they available their ΔpK magnitudes would not suffice to establish the better model accounting for the transmission of the substituent's effect. The question regarding the source of the unexpected acid-strengthening effect of the carbon–carbon double bond at the 6 position may be resolved by pK_a comparisons of 4, 5, and trans-spiro[3.4]-5-octene-2-carboxylic acid (see note 22).
(16) See D. H. R. Barton, F. McCapra, P. J. May, and F. Thudium, *J. Chem. Soc.*, 1297 (1960), for evidence that a remote carbon–carbon double bond can influence rates of base-catalyzed condensations of benzaldehyde with steroidal ketones.
(17) The relationship between electronegativity and s character has been documented by H. A. Bent, *Chem. Rev.*, **61**, 275 (1961), and by J. Hinze and H. H. Jaffé, *J. Am. Chem. Soc.*, **84**, 540 (1962), among others. A wealth of data are available which demonstrate the effects of bond-angle deformation on acidities (presumably through s-character alterations). See, for example, K. B. Wiberg and B. R. Lowry, *ibid.*, **85**, 3188 (1963); F. W. Baker, R. C. Parish, and L. M. Stock, *ibid.*, **89**, 5677 (1967); A. Streitwieser, Jr., R. A. Caldwell, and W. R. Young, *ibid.*, **91**, 529 (1969); A. G. Cook and G. W. Mason, *J. Org. Chem.*, **37**, 3342 (1972); A. Streitwieser, Jr., P. H. Owens, R. A. Wolf, and J. E. Williams, Jr., *J. Am. Chem. Soc.*, **96**, 5448 (1974), and references cited therein.
(18) H. J. Geise and F. C. Mijlhoff, *Recl. Trav. Chim. Pays-Bas*, **90**, 577 (1971).
(19) C. S. Foote [*Tetrahedron Lett.*, 579 (1963)] cites a value of 103.3° for the pseudorotating cyclopentane which is an average value obtained from J. B. Hendrickson, *J. Am. Chem. Soc.*, **83**, 4537 (1961).
(20) The $C_3C_4C_5$ bond angle of cyclopentene is reported to be 104.0°; that for $C_2C_3C_4$ is 103.0°.[2]
(21) M. I. Davis and T. W. Muecke, *J. Phys. Chem.*, **74**, 1104 (1970).
(22) A planned test for conformational transmission in these spirane systems is the determination of the pK_a's of 5-methylenespiro[3.4]octane-2-carboxylic acid or spiro[3.4]-5-octene-2-carboxylic acid. In these derivatives the bond-angle deformations conformationally transmitted to C_2 should decrease the s character of its external orbitals. ^{13}C–H coupling constants

at C_2 may also reveal these effects.
(23) Because of uncertainties in the conformations of the five-membered ring and to greatly simplify calculations estimating R and cos θ, the cyclopentane ring was assumed to be planar. Consequently a 108° bond angle was employed for the five-membered ring. Calculations were performed with the cyclobutane ring either planar or bent with a dihedral angle of 152.6°[24] (moving the carboxyl group into a more equatorial position). The difference in ΔpK_a's (≤ 0.01) obtained using these two geometries were insignificant and thus only the "planar model" results are given. Other bond angles and lengths used[24-26] were 1.55 Å for the C–C bonds of the five-membered ring, 90° and 1.55 Å for the C–C–C bond angles and C–C bond lengths, respectively, for the cyclobutane, 109° for the H–C_2–CO_2H bond angle, and 1.50 Å for the C–CO_2H bond. The ketone C═O bond was assigned a length of 1.24 Å and the position of the carboxyl proton located at 1.45 Å beyond the carboxyl carbon on the extension of the C–C bond. The C═O dipole was assigned a group moment of 3.0 D from Smyth's data[27] for cyclopentanone.
The effective dielectric constants (D_E) and ΔpK's were calculated from the Kirkwood–Westheimer equations using alternately a sphere and an ellipsoid to approximate the molecular cavity. Tanford's modification was employed locating the point dipoles and charges 1.5 and 1.0 Å, respectively, below the surface of the cavity. A value of 78.5 was used for the external (solvent) dielectric constant and a value of 2.0 for the internal dielectric constant.
(24) L. A. Hulshof, A. Vos, and H. Wynberg, *J. Org. Chem.*, **37**, 1767 (1972).
(25) W. J. Adams, H. J. Geise, and L. S. Bartell, *J. Am. Chem. Soc.*, **92**, 5013 (1970).
(26) "Tables of Interatomic Distances and Configuration in Molecules and Ions", The Chemical Society, Burlington House, London, 1958, and Supplement 1956–1959.
(27) C. P. Smyth, "Dielectric Behavior and Structure". McGraw-Hill, New York, N.Y., 1955.
(28) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **41**, 2774 (1963).
(29) Melting points were determined on a Fisher-Johns or a Hoover apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer Model 621 recording spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Model A-60 spectrometer. Gas–liquid chromatographic analyses and preparative-scale separations were conducted with a Varian Model 90-P or Model A-700 chromatograph. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-6E spectrometer. Calculations were performed with the aid of IBM Model 1130 and Model 360/45 computers. Analyses were performed by M-H-W Laboratories.
(30) E. Buchta and K. Geibel, *Justus Liebigs Ann. Chem.*, **648**, 36 (1961).
(31) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases", Wiley, New York, N.Y., 1962, Chapters 2 and 3.
(32) The method of A. L. Bacarella, E. Grunwald, H. P. Marshall, and E. L. Purlee [*J. Org. Chem.*, **20**, 747 (1955)] was employed.

Carbon Acids. 10. Resonance Saturation of Substituent Effects in the Fluorene Series

F. G. Bordwell* and Gregory J. McCollum

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Equilibrium acidities for 14 2-substituted fluorenes were found to vary over a range of 6.1 pK units in dimethyl sulfoxide solution. A rather poor Hammett plot was obtained with σ_m ($\rho = 7.5 \pm 0.53$, $r = 0.969$). Groups capable of strong electron acceptor resonance interactions (CN, PhCO) or strong electron donor resonance interactions (MeO, F) deviated most from the line, indicating that the 2 position in the fluorene ring has considerable "para character", as well as "meta character". The effect of substituting a second CN, Et_2NSO_2, or Br atom into an equivalent position on the fluorene nucleus (the 7 position) was substantially less than additive (by 0.5–0.8 pK units). This is attributed to a resonance saturation effect. Similar resonance saturation effects were observed for $PhSO_2$, Ph, and p-MeC_6H_4S groups in 2,9-disubstituted fluorenes, but no saturation of the effects of MeO or PhS was observed in 2,7-disubstituted fluorenes. The conclusion is drawn that, in the absence of steric effects, saturation effects result from changes in electron distribution in the anion caused by resonance delocalization, and that polar saturation effects are of little or no importance.

Three distinct mechanisms for "saturation" of the electronic effects of substituents, namely, polar, resonance, and steric, were visualized in 1941 by Branch and Calvin in their classical book on theoretical organic chemistry.[1] In discussing acidities of acids without resonance, including aliphatic carboxylic acids, they remark that "there should be a tendency for polar effects of groups to increase less rapidly than the calculated values when the sum of the inductive constants of the component parts becomes very great (a saturation effect)". In addition, they suggested that two π-electron-donor groups

in para positions on a benzene ring should destabilize the system by what they termed "cross-conjugation", and that the effects of the two π donors should be nonadditive.[1] (Additional evidence for a "saturation" effect of this kind was provided later.[2]) Finally, Branch and Calvin recognized that ortho groups could interfere with quinoidal resonance giving rise to steric inhibition of resonance, which causes a damping or "saturation" of substituent effects.

Experiments in the ensuing years have provided abundant examples of attenuation ("saturation") of electronic effects

caused by steric inhibition of resonance, but clear-cut examples of attenuation of electronic effects by polar or resonance saturation are not common. Branch and Calvin were not able to obtain evidence for a polar saturation effect, but predicted that one should become apparent for measurements of substituent constants for weaker acids than those with which they were concerned. Taft's polar substituent constants (σ^*), derived from aliphatic carboxylic esters or acids, also failed to reveal saturation effects in aliphatic systems, i.e., "σ^* constants were generally found to be approximately additive".[3] The theoretical basis for the polar saturation effect apparently lies in the Lewis "electron-shift" hypothesis, which assumes that substitution of an electron-withdrawing group (EWG) for a hydrogen atom in an aliphatic system causes a decrease in electron density at the acidic site by successive electron displacements in the σ bond framework.[4] Analyses of substituent effects on acidities of carboxylic acids in rigid aliphatic systems during the past decade indicate, however, that transmission of electronic effects through bonds is of minor importance. The data are accommodated much more satisfactorily by assuming that the effects are primarily electrostatic in nature, and are transmitted through a dielectric cavity which includes the framework of the molecule and the solvent.[5] As has been pointed out by Ingold, the electrostatic effects of substituents should not be subject to saturation if the substituents are spaced so as to act independently.[6] According to this view, saturation of polar effects should play little or no role in most aliphatic systems, and the failure of Branch and Calvin, and of Taft, to observe such effects is understandable. We conclude that not only is there no experimental evidence for a polar saturation effect, but that there is no longer any theoretical reason to expect that an appreciable effect of this kind will be observed in aliphatic systems.

In sharp contrast to the lack of evidence for saturation of polar effects, there are theoretical reasons to expect saturation of resonance effects, and there is experimental evidence to support this view. When introduction of a substituent causes delocalization of charge from a reaction site we can expect that, because the charge density at the reaction site has been decreased thereby, the effect of introduction of a second substituent will be less than the first. Hine called attention to a resonance saturation effect of this kind on the stability of triaryl cations, $Ar_2Ar'C^+$.[7] He cited data to show that the destabilizing effect of a p-NO_2 group in Ar' is greatly decreased by the presence of p-Me_2N groups in Ar. The p-Me_2N groups in the two Ar rings delocalize the charge away from the central carbon atom thus diminishing the destabilizing effect of p-NO_2 in the third ring.[7] A similar effect was observed for triaryl anions, Ar_3C^-.[8] Here the stabilization energy of (p-$NO_2C_6H_4)_3C^-$ was found to be only about 1.2 times that of (p-$NO_2C_6H_4)(C_6H_5)_2C^-$, pointing to a marked saturation of the π-acceptor ability of the p-NO_2 group.[8] In Ar_3C^+ and Ar_3C^- ions a large part of the attenuation of multiple substituent effects must be due to steric inhibition of resonance, as the authors recognized.[7,8] Similar effects have also been obtained, however, for Ar_2CH^+ ions, where steric effects are less severe. Nonadditivity of multiple substituent effects on rates of solvolysis of benzhydryl halides, $ArAr'CHX$, have been reported by several investigators.[9] Similar effects have been observed for rates of bromination of diphenylethenes, $ArAr'C{=}CH_2$,[10] and Dubois has pointed out that, while part of the attenuation must be due to steric inhibition of resonance, there is nevertheless good reason to believe that part is also due to a resonance saturation effect.[10]

Hammett σ_m constants are believed to contain an appreciable resonance component,[11] and would therefore be expected to be subject to resonance saturation. However, careful examination of the acidities in protic solvents of benzoic acids

containing substituents in 3,4, 3,5, or 3,4,5 positions has failed to reveal any evidence of nonadditivity (saturation).[12] We have observed large resonance saturation effects on equilibrium acidities in dimethyl sulfoxide (Me_2SO) solution for carbon acids of the type GCH_2EWG with various groups, G (e.g., Ph or PhS) when EWG is changed so as to increase progressively the delocalization of the negative charge in the $GCHEWG^-$ anion, as in the series where EWG is changed from CN to CH_3CO to NO_2.[13] These results led us to expect resonance saturation in aromatic systems. In view of the previous failures to observe such effects,[12] it was clear that a system more sensitive to substituent effects was needed. The fluorene system appeared to be ideal for our purpose since a good correlation with σ_m for five 2-substituted fluorenes had been reported ($r = 0.997$) for equilibrium acidities in Me_2SO-H_2O, and the system had been found to be highly sensitive to substituent effects ($\rho = 7.5$).[14] The fluorene system also has the advantage over the benzoic acid system that its "meta" positions (2 and 7) are in different rings, thus ensuring independent action of dipoles. The fluorene system is comparable in general type to the diarylmethane (anion or cation) system,[9,10] but has the advantage that steric inhibition of resonance can be eliminated, as in 2,7-disubstituted fluorenes (1), or minimized, as in 2,9-disubstituted fluorenes (2). Examination of the equilibrium acidities of 1 and 2 has revealed
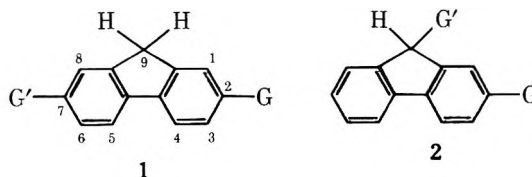
the presence of sizable resonance saturation effects for π-acceptor substituents, but not for π-donor substituents.

Experimental Section

Sources of Fluorenes. Samples of 2-bromo- and 2-nitrofluorenes were purchased from the Aldrich Chemical Co., Milwaukee, Wis. 2-Bromofluorene was purified by recrystallization from 95% ethanol. 2-Nitrofluorene was purified by repeated recrystallization from glacial acetic acid followed by recrystallization from cyclohexane. 2,7-Dimethoxyfluorene was prepared from a sample of 2,7-dihydroxyfluorenone, kindly provided by the Ash-Stevens Chemical Co. The syntheses of the 2-, 2,7-, and 2,9-substituted fluorenes will be reported in a separate publication.

pK Measurements. pK values for fluorene and 14 2-substituted fluorenes were measured in pure Me_2SO by the general titration method previously described.[15] All of the fluorenes discussed herein produced anions which absorbed strongly at wavelengths in the visible spectrum. Consequently, either of two methods of measurements were available. In method A the fluorene derivative was used as the indicator and measured against a standard acid.[16] In method B the fluorene derivative was used as the acid and measured against an indicator whose anion absorbed at a longer wavelength in the visible spectrum. The two methods gave results agreeing to within ±0.1 pK unit.

All of the substituted fluorenes behaved well as indicators[16] with the exception of the 2-Br, 2-Cl, 2,7-di-Br, and 2-benzoyl derivatives. Addition of a standard acid to a solution of the halofluorenyl anions (method A) resulted in immediate equilibration, followed by a very slow rise in the visible absorbance of the solution. (The cause of the rise in absorbance was not investigated.) Measurement of the halofluorenes by method B (4-chloro-2-nitroaniline as the indicator) eliminated this problem and gave the same pK values as did method A to within experimental error (±0.1 pK unit).

In the titration of potassium dimsyl (KCH_2SOCH_3) with 2-benzoylfluorene the first increment of 2-benzoylfluorene added produced slightly less of the 2-benzoylfluorenyl anion than did the second, the second produced less than did the third, etc. This became apparent when the amount of 2-benzoylfluorene added was plotted against the absorbance of the 2-benzoylfluorenyl anion formed. The simplest explanation of this behavior is that some of the potassium dimsyl added across the carbonyl group rather than effecting deprotonation. The problem was alleviated by converting $K^+CH_3SOCH_2^-$ to $K^+PhCHSO_2CH_3$ (presumably a less nucleophilic and more hindered

**Table I. Equilibrium Acidities of 2-Substituted
Fluorenes in Dimethyl Sulfoxide**

Registry no.	Substituent	pK^a	$\sigma_m{}^b$
13261-62-6	2-$(CH_3)_2N$	24.2	−0.15
1430-97-3	2-CH_3	23.1	−0.07
2523-46-8	2-CH_3O	22.7$_5$	0.12
86-73-7	H	22.6	(0.00)
343-43-1	2-F	21.0	0.34
59014-80-1	2-CH_3S	21.6$_5$	0.15
59014-81-2	2-PhS	20.5	0.27^c
2523-44-6	2-Cl	20.2$_5$ (±0.15)	0.37
1133-80-8	2-Br	20.0 (±0.15)	0.39
59014-82-3	2-CH_3SO	19.7$_5$	+0.52
15860-31-8	2-PhCO	19.5$_5$ (±0.15)	0.36
59014-83-4	2-Et_2NSO_2	18.8	0.46^d
59014-84-5	2-CH_3SO_2	18.5	+0.60
2523-48-0	2-CN	18.2	0.56
59014-85-6	2-$PhSO_2$	18.1	0.62^e

^{a} pK's are ±0.1 unit unless otherwise noted. ^{b} From pK's of benzoic acids unless otherwise noted (see ref 4b, p 66). ^{c} Based on pK's of acetophenone in Me_2SO (F. J. Cornforth, Ph.D. Dissertation, Northwestern University, August 1976). ^{d} σ_m for H_2NSO_2. ^{e} O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 65 (1966).

base) prior to titration. The titrations were then carried out with several standard acids using 2-benzoylfluorene as an indicator; the range of pK's observed was slightly larger than usual, however (±0.15 unit).

We were unable to obtain a point for 2-nitrofluorene because, in pure Me_2SO, treatment with a variety of bases generated a green-colored species absorbing strongly in the visible, but lacking the three-band pattern characteristic of 2-substituted fluorenyl anions. Dilution with water gave a red anion, apparently that observed previously.[14]

Results and Discussion

Hammett Plot Using σ_m. A plot of pK's (Table I) for the 15 fluorenes vs. Hammett σ_m constants gave a least-squares line of slope (ρ) equal to 7.5 ± 0.53, r = 0.969 (Figure 1). This ρ agrees with that obtained by Bowden and Cockerill for five 2-substituted fluorenes (MeO, Cl, Br, CN, and NO_2) in Me_2SO–H_2O (45–90% Me_2SO), but their correlation coefficient was much better (0.997).[14] The correspondence of ρ's is, however, fortuitous. Note that if we select a comparable group of substituents from Figure 1 (MeO, Cl, Br, and CN) the correlation coefficient would also be high (r = 0.999), but ρ = 10.3. Comparison shows that the pK's determined by the H_- method are compressed, relative to those in Me_2SO (e.g., the range for 2-MeO to 2-CN fluorene is 3.40 pK units by the H_- method,[14] as compared to 4.55 pK units in pure Me_2SO). For the more acidic fluorenes the H_- method probably gives high values, because pK's for fluorenes in water are higher than in Me_2SO.[15] As the water content of the Me_2SO–H_2O mixture is decreased to permit H_- measurements for the less acidic fluorenes, a reversal occurs, and the values become low relative to those in pure Me_2SO.[17] The overall result is a smaller ρ.

The standard deviation of the points from the line in Figure 1 is 0.467 pK units. This is far beyond the deviation expected from the experimental errors in the measurements (estimated at <0.1 pK unit) or the deviation in Hammett σ_m constants (estimated at 0.1–0.2 pK unit). A number of factors that might lead to the unexpectedly large deviations can be imagined: (1) the σ_m constants determined in water (or 50% aqueous ethanol) may not be applicable to Me_2SO since we are changing from a strongly H-bonding (donor) medium to a very weakly H-bonding (donor) medium; (2) the 2-substituted fluorenes may constitute an unusually severe test for the Hammett relationship since the data are spread over a range of 6.1 pK units, as compared to only 0.83 pK units for the corresponding
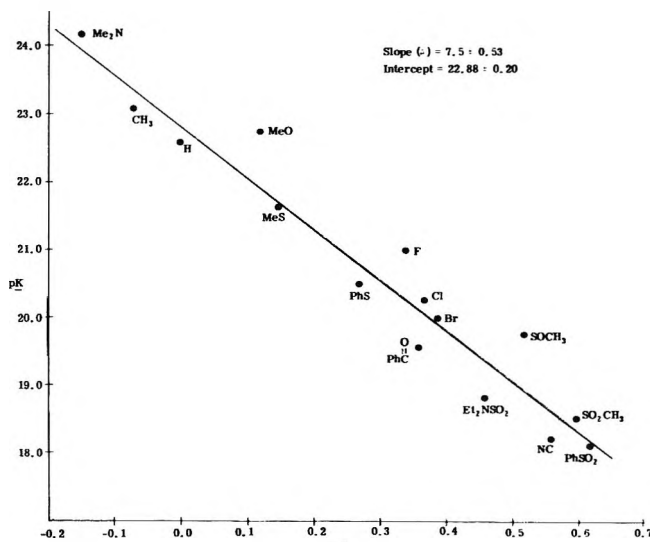
Figure 1. Hammett plot of equilibrium acidities of 15 2-substituted fluorenes in dimethyl sulfoxide solution.

meta-substituted benzoic acids; (3) the geometric relationships between the negative charge and the 2 substituent in 2-substituted fluorenyl anions may differ so markedly from that in meta-substituted benzoate ions as to give rise to the observed deviations. Surprisingly enough, factors 1 and 2 appear to be relatively unimportant, since an excellent Hammett relationship has been observed with meta-substituted acetophenones,[18] the carbon acid analogues of benzoic acids, and a reasonably good relationship has been observed with meta-substituted arylacetonitriles,[19] which have pK's of a comparable magnitude to the fluorenes and where ρ is also large (5.5).[19]

Comparison of the structure of a meta-substituted benzoate ion (3) with that of a 2-substituted fluorenyl ion (4) shows that in 3 the negative charge is located on the oxygen atoms, which are one or more atoms farther removed from substituent G than are the carbon atoms bearing the charge in 4. The distribution of the negative charge in the fluorenyl anion, as judged by molecular orbital calculations,[20] is shown in formula 5. We see from 5 that about 65% of the charge is located in the
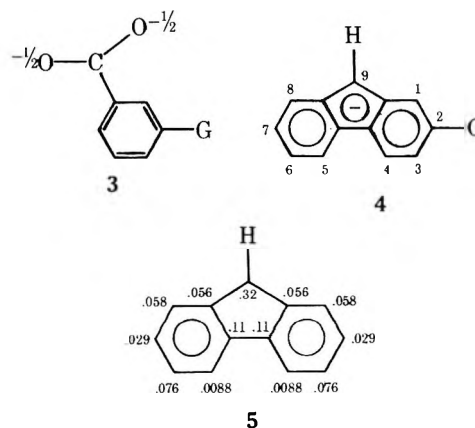
cyclopentadienyl ring and about 35% is distributed over the two phenyl rings. About 49% of the charge in the five-membered ring is located at the 9 position (a "meta" benzylic position), about 17% appears at the 4b position (a "para" benzylic position), and about 17% appears at the 4a position (a "para" ring position). Although only about 3% of the charge is expected to be located in the 2 position of the fluorenyl anion itself (5), this percentage will no doubt be increased (or decreased) when the hydrogen atom in this position is replaced by a substituent, G. If G is capable of playing an electron-pair

Table II.   Comparison of Substituent Effects for 2- and 2,7-Substituted Fluorenes

Registry no.	Substituent(s)	pK	$\Delta pK_1{}^a$	$\Delta pK_2{}^b$
	2-CH$_3$O	22.7$_5$	−0.15	
42523-30-8	2,7-(CH$_3$O)$_2$	22.9$_5$		−0.20
	2-PhS	20.5	2.1	
59014-86-7	2,7-(PhS)$_2$	18.5		2.0
	2-Br	20.0	2.6	
16433-88-8	2,7-(Br)$_2$	17.9		2.1
	2-Et$_2$NSO$_2$	18.8	3.8	
59014-87-8	2,7-(Et$_2$NSO$_2$)$_2$	15.6		3.2
	2-CN	18.2	4.4	
39150-36-2	2,7-(CN)$_2$	14.6		3.6

[a] Relative to fluorene (pK = 22.6). [b] Relative to the corresponding 2-substituted fluorene.

acceptor role, delocalization of charge to G is possible through resonance contributor **6**, whereas if G is capable of playing an electron-pair donor role the relative distribution of charge in the two phenyl rings can be altered through resonance contributors such as **7**. The extent of contribution of **6** and **7** is in some doubt, however, since they are quinoidal forms and the resonance of both benzene rings must be destroyed therein; in addition, for **7**, there is extensive charge separation.

6   **7**
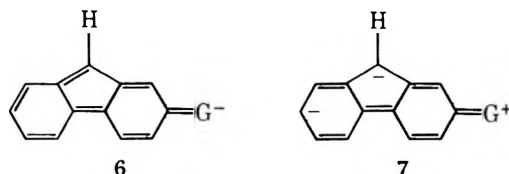
Focusing attention first on resonance electron-acceptor groups, we see by examination of Figure 1 that the points for PhCO, Et$_2$NSO$_2$, and CN deviate from the line by somewhat more than the standard deviation of 0.467 pK units, whereas the points for CH$_3$SO$_2$ and PhSO$_2$ are close to the line, and the point for CH$_3$SO deviates markedly and in the opposite direction. These results suggest enhanced electron-accepting ability for at least the PhCO and CN groups.[21]

The points for the resonance electron-donor substituents, F and MeO, deviate from the line by somewhat more than 0.467 pK units in a direction opposite to that observed for the resonance-acceptor groups. (It is surprising that the Me$_2$N group does not follow suit.) There is some indication, therefore, of electron donation for these groups beyond that observed in meta-substituted benzoic acids.[22]

We conclude from this analysis that the much larger ρ observed for 2-substituted fluorenes in Me$_2$SO, as compared to meta-substituted benzoic acids in water (7.5 vs. 1.0), is due primarily to the much closer proximity of the center of charge to the substituent G in **4** than in **3**; in addition, there is a solvent effect on ρ, which is probably related principally to the change in the effective dielectric constant of the medium.[23] The behavior of groups capable of electron acceptor and electron donor resonance suggests that the poor correlation with σ_m (Figure 1) is due to the presence of appreciable "para character" in the effects of substituents located in the 2 position of the fluorene nucleus.[25]

Nonadditivity of Substituent Effects (Resonance Saturation). The additivity (or lack thereof) of substituent effects for CH$_3$O, PhS, Br, Et$_2$NSO$_2$, and CN groups when substituted in the 2,7- vs. the 2 position(s) on the fluorene nucleus is brought out in Table II.

Examination of Table II shows that substitution of CN for H in the 2 position of fluorene results in an increase in acidity of 4.4 pK units (ΔpK_1), which can be attributed in part to stabilization of the 2-cyanofluorenyl anion by delocalization

of the negative charge into the cyano group, as in resonance contributors **8b** and **8c**. This results in a decrease in negative

8a   **8b**

9   **8c**
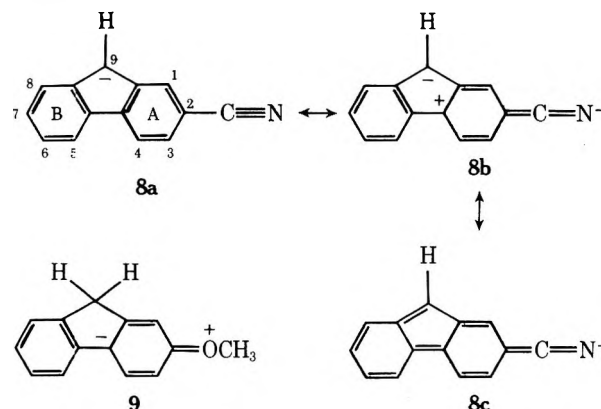
charge in ring A, and to a lesser extent in the cyclopentadienyl ring and in ring B, relative to that found in the fluorenyl anion itself. Substitution of a second cyano substituent into an equivalent position of ring B (the 7 position) therefore causes an appreciably smaller acidifying effect ($\Delta pK_2 = 3.6$). The difference of 0.8 pK units represents the size of the resonance saturation effect. Comparable results were obtained for the Et$_2$NSO$_2$ group ($\Delta pK_1 - \Delta pK_2 = 0.6$) and even Br showed a resonance saturation effect of 0.5 pK units (Table II). The effect for the PhS substituent (0.1 pK unit) is only slightly greater than experimental error, but the presence of a resonance saturation effect for an arylthio substituent is supported by evidence obtained from 2,9-disubstituted fluorenes (see below).

The points for the 2-MeO and 2-F substituents fall appreciably above the line in Figure 1, suggesting that their acid-strengthening polar effects are being balanced by an acid-weakening π-donor resonance effect, presumably operating mainly to stabilize the undissociated acid (e.g., contributor **9**). One might have expected the resonance effect of a second methoxyl group at the 7 position in 2,7-dimethoxyfluorene to be impeded by the buildup of charge in the cyclopentadienyl ring (as in **9**). There is no evidence, however, that such an effect occurs, since ΔpK_2 is the same as ΔpK_1, within experimental error (Table II).

Since the charge density at the 9 position is much greater than at the 2 position in the fluorenyl anion (**5**), one would expect a 9 substituent to show much the larger effect, and this is observed. For example, a 9-CN substituent increases the equilibrium acidity by 14.5 pK units,[15] whereas the effect of a 2-CN substituent is only 4.4 pK units (Table I). 9-Phenyl and 9-p-tolylthio substituents are also strongly acid strengthening (ΔpK's of 5.0 and 6.9, respectively). Scheme I shows that these effects are attenuated to 4.6 and 6.5 pK units, respectively, if a 2-PhSO$_2$ group is already present in the fluorene nucleus (a 0.4 pK unit resonance saturation of the acidifying effects of Ph or of p-CH$_3$C$_6$H$_4$S caused by the 2-PhSO$_2$ group). Similarly, Scheme I shows that the acid-strengthening effect of the 2-PhSO$_2$ group is larger relative to fluorene ($\Delta pK = 4.5$) than relative to 9-phenylfluorene ($\Delta pK = 4.1$) or 9-p-tolylthiofluorene ($\Delta pK = 3.8$). The 9-Ph and 9-p-MeC$_6$H$_4$S groups thus attenuate the effect of the 2-PhSO$_2$ group by 0.4 and 0.7 pK units, respectively.

Conclusions

We conclude that the failure of saturation of substituent effects to materialize in (saturated) aliphatic systems[1,3] is understandable because these effects are polar (electrostatic) in nature, and saturation of such effects is small or nonexistent. The additivity of Hammett σ_m constants is also understandable, since these effects are also primarily polar in nature, and the benzoic acid system is relatively insensitive to

Scheme I
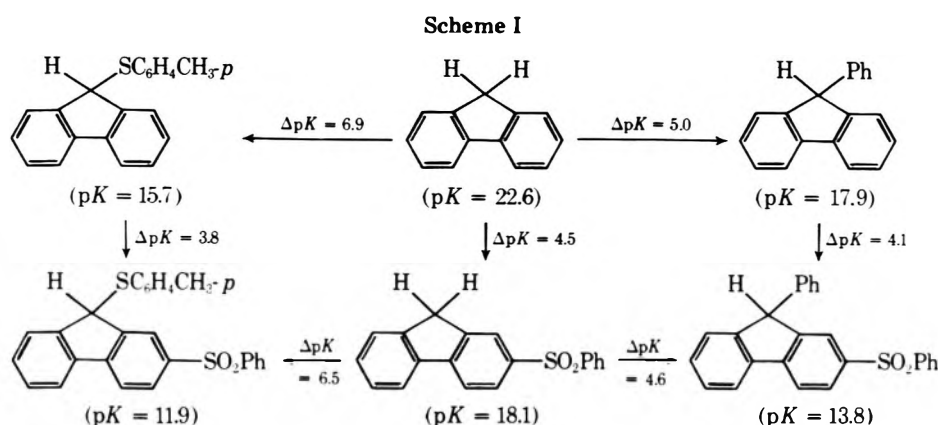
substituent effects. On the other hand, we believe that the resonance saturation effect is a general phenomenon in chemistry. In fact, it often constitutes the principal basis for the physical organic chemists' "rule of thumb" that substituent effects on an equilibrium or rate involving an unstable species (anion, cation, radical, carbene, etc.) become smaller as the stability of this species increases. Unfortunately, in many instances attenuation of substituent effects due to resonance saturation is accompanied by attenuation of substituent effects by steric inhibition of resonance, and it is difficult to judge the relative magnitudes of the two effects.[10] The present results show, however, that the resonance saturation effect can be large even when the substituents are widely separated in an aromatic system. Subsequent papers will show that much larger resonance saturation effects are present when the substituents are attached directly to the acidic site, as in GCH_2EWG,[13] rather than being separated from the acidic site by a benzene ring.

References and Notes

(1) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry", Prentice-Hall, Englewood Cliffs, N.J., 1941, pp 205–206, 251–252, 260–261.

(2) H. Van Bekkum, P. E. VerKade, and B. M. Wepster, Recl. Trav. Chim. Pays-Bas, **78**, 815 (1959).

(3) R. W. Taft, "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, pp 575–576, 623–625.

(4) (a) G. N. Lewis, "Valence and Structure of Atoms and Molecules", The Chemical Catalog Co., New York, N.Y., 1923, p 139. (b) J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975, Chapter 2.

(5) See L. M. Stock, J. Chem. Educ., **49**, 400 (1972), and references cited therein.

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2d ed, Cornell University Press, Ithaca, N.Y., 1969, p 1193.

(7) J. Hine, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1962, pp 101–102.

(8) L. D. McKeever and R. W. Taft, J. Am. Chem. Soc., **88**, 4544 (1966).

(9) (a) J. R. Fox and G. Kohnstam, Proc. Chem. Soc., London, 115 (1964); (b) S. Nishida, J. Org. Chem., **32**, 2697 (1967); (c) E. Berliner and M. Q. Malter, ibid., **33**, 2595 (1968).

(10) A. F. Hegarty, J. S. Lomas, W. V. Wright, E. D. Bergmann, and J. E. Dubois, J. Org. Chem., **37**, 2222 (1972).

(11) R. W. Taft and I. C. Lewis, J. Am. Chem. Soc., **81**, 5343 (1959), have estimated that $R^m/R^p \simeq 0.33$. A recent analysis by Hansch points to a relatively higher resonance component for meta substituents (ca. 30% for σ_m vs. ca. 50% for σ_p). [See C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lein, J. Med. Chem., **16**, 1207 (1973).]

(12) (a) H. Jaffé, Chem. Rev., **53**, 243–244 (1953); (b) O. Exner, Adv. Linear Free Energy Relat., 41 (1972); (c) C. D. Johnson, "The Hammett Equation", Cambridge University Press, New York, N.Y., 1973, pp 26, 67, 103, 107, 164–166; (d) K. Kalfus, J. Kroupa, M. Vecera, and O. Exner, Collect. Czech. Chem. Commun., **40**, 3009 (1975).

(13) Unpublished results; the papers where G is Ph and PhS have been submitted for publication.

(14) K. Bowden, A. F. Cockerill, and J. R. Gilbert, J. Chem. Soc. B, 179 (1970).

(15) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, Z. Margolin, R. McCallum, G. J. McCollum, and N. R. Vanier, J. Am. Chem. Soc., **97**, 7006 (1975).

(16) The five requirements of an indicator are given in ref 15. A standard acid is any compound whose pK is well established and whose anion is transparent at the wavelength used for measurement.

(17) The acidities in pure Me₂SO are on an absolute scale,[15] whereas those in Me₂SO–H₂O are relative to 9-phenylfluorene, pK = 18.49, as an arbitrary standard. The absolute pK of 9-phenylfluorene in Me₂SO is 17.9.[15] Using this as a standard, comparison shows that the pK of 2-cyanofluorene is 0.2 unit "too high" in Me₂SO–H₂O, whereas the pK's of fluorene and 2-methoxyfluorene are 1.1 and 1.0 units "too low".

(18) F. J. Cornforth, unpublished results.

(19) J. E. Bares, unpublished results.

(20) A. Streitwieser and J. I. Brauman, "Supplemental Tables of Molecular Orbital Calculations", Pergamon Press, Elmsford, N.Y., 1965, p 247.

(21) The result for SO₂NEt₂ is in some doubt since no σ_m for this group appears to be available, and it was necessary to use σ_m for SO₂NH₂ in the plot. Judging from the CH₃SO₂ and PhSO₂ points, the (tetrahedral) sulfonyl groups appear to behave differently from the PhCO and CN groups in which the functions are planar. We will not comment on the surprising behavior of the CH₃SO function until this result can be checked with other sulfinyl groups and in other carbon acid systems.

(22) The m-CH₃O point deviates somewhat from the line for the meta-substituted acetophenones but the m-Me₂N and m-F points do not.[18] For the arylacetonitriles the m-CH₃O point deviates, but m-F does not.[19]

(23) The ρ for benzoic acids in Me₂SO is about 2.4.[24]

(24) (a) C. D. Ritchie and R. E. Uschold, J. Am. Chem. Soc., **90**, 2821 (1968); (b) I. M. Kolthoff and M. K. Chantooni, ibid., **93**, 3843 (1971).

(25) Professor R. W. Taft has applied a dual parameter treatment[26] to our data and found support for the idea of small exaltations in resonance effects for the π-acceptor substituents (private communication).

(26) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, Prog. Phys. Org. Chem., **10**, 1 (1973).

Enthalpy–Entropy Relationships in the Reduction of Hindered and Unhindered Cyclohexanones by Sodium Borohydride[1]

Donald C. Wigfield* and David J. Phelps

Department of Chemistry, Carleton University, Ottawa, Canada

The second-order rate constants and stereochemical product ratios for the reduction of 19 cyclohexanones by sodium borohydride in 2-propanol at temperatures between 0 and 35 °C are reported. Overall activation parameters and specific activation parameters for axial and equatorial attack of borohydride have been obtained. The major component of the free-energy barrier is entropy, but the reaction is enthalpy controlled. Specific isokinetic plots for axial and equatorial attack have been constructed; in both plots there appears to be a substantial and clear-cut difference in isokinetic behavior between the reduction of hindered and unhindered cyclohexanones.

For over 20 years sodium borohydride has been extensively used as the reagent for reduction of ketones to alcohols[2] and for most of this period the remarkable stereoselectivity exhibited in the reduction of cyclohexanones has been known.[3] There seems to be, in general, an intrinsic preference for axial attack of borohydride resulting in the formation of the equatorial alcohol, and unhindered cyclohexanones are reduced with stereoselectivities up to 95%. However, this ster-

eoselectivity is markedly attenuated with increasing steric hindrance around the carbonyl group, and is eventually inverted, highly hindered cyclohexanones being reduced to yield predominantly axial alcohols. Despite a variety of explanations having been advanced to account for this remarkable and highly useful behavior,[3-6] the real origin of the phenomenon remains experimentally unestablished.[7] Clearly the key to such an understanding lies in a detailed knowledge of the nature of the transition states involved in these reductions; however, there is, at the present time, only scanty knowledge in this regard.

It is surprising, considering the extent to which the reaction has been put and the fact that four kinetic methods have been established,[8-10] that so little information is available on the activation parameters for reduction of substituted cyclohexanones.[11] These parameters are important in a variety of ways. Firstly, they are interesting in their own right. Secondly, they permit an analysis of whether enthalpy or entropy represents the major barrier for reaction, and, in the reduction of a series of ketones, permit the question to be answered as to whether *changes* in enthalpy or entropy are responsible for differing reactivity and stereoselectivity. Thirdly, since isokinetic plots have been regarded as indicators of whether a series of reactions proceed by the same or differing mechanisms or transition state,[14] they provide an approach to the vital question of whether the transition states for the reductions of hindered and unhindered ketones occur at the same point on the reaction coordinate, a question that distinguishes the steric approach control–product development control hypothesis[3] from other rationalizations of the origin of the stereoselectivity.[4-6] Isokinetic plots of *specific* activation parameters (i.e., referring specifically to axial or equatorial attack as opposed to overall reduction) would, in a similar fashion, be relevant to the question of whether the transition states for axial and equatorial attack (two independent processes) on the *same ketone* occur at the same point on the reaction coordinate. This question, although it has, as far as we are aware, never been specifically formulated, is clearly also critical in the development of sufficient knowledge on the transition states to establish the origin of the stereoselectivity. This paper reports activation parameter data on 19 ketones in connection with these questions.

Results

Ketones Studied. The ketones used in this study are shown (1–19).

5-*n*-Butyl-3,3-dimethylcyclohexanone (**17**) was synthesized from 3-isobutoxy-5,5-dimethylcyclohex-2-en-1-one[15] by 1,4 addition using tetrakis[iodo(tri-*n*-butylphosphine)copper(I)][16] and *n*-butyllithium in the usual[17] manner. Cholestan-2-one (**19**) was synthesized from cholestan-3β-ol by the known oxygen transposition route.[18] Our preparation of 5α-lanost-8-en-3-one has previously been described.[19] All
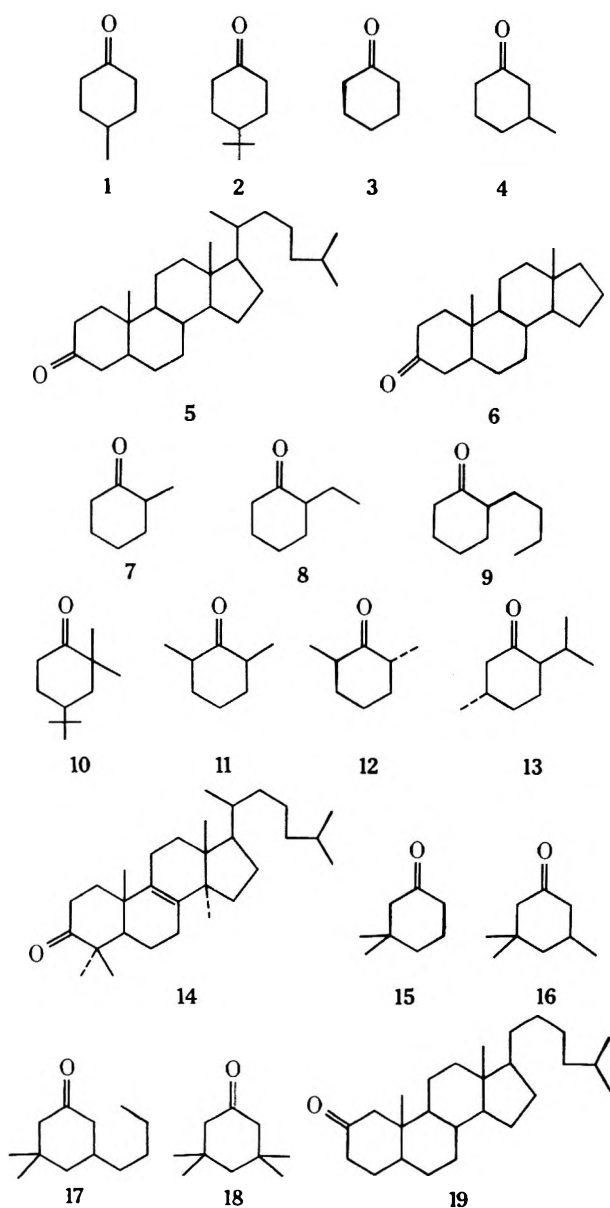
Table I. Second-Order Rate Constants for the Reduction of Cyclic Ketones by Sodium Borohydride in 2-Propanol[a]

			$k \times 10^4$, M^{-1} s^{-1}			
Ketone	0 °C	15 °C	20 °C	25 °C	30 °C	35 °C
1	342 ± 12	609 ± 6	756 ± 7	890 ± 6	1049 ± 44	
2	326 ± 5	629 ± 14	738 ± 22	856 ± 14		
4	187 ± 1	426 ± 21	493 ± 5	605 ± 12		
5	136 ± 1	269 ± 12		456 ± 4	566 ± 16	
6	131 ± 3	246 ± 0.5	338 ± 10	425 ± 6	518 ± 17	
14	2.40 ± 0.02	5.34 ± 0.14	6.35 ± 0.45	8.59 ± 0.38	10.1 ± 0.3	12.4 ± 0.3
15	5.84 ± 0.18	14.4 ± 0.05		24.9 ± 1.2		39.6 ± 1.4
16	4.76 ± 0.30	11.6 ± 0.3		21.8 ± 0.4		39.0 ± 1.5
17	3.38			17.6 ± 0.2	21.2 ± 0.6	28.0 ± 0.2
18	0.31	1.06 ± 0.04		1.92 ± 0.21		3.76 ± 0.08
19	1.26 ± 0.02	3.58 ± 0.02	4.68 ± 0.36	5.98 ± 0.37	7.37 ± 0.02	9.84 ± 0.86

[a] Rate constants for reduction of ketones 3 and 7–13 are reported in ref 13.

Table II. Overall Activation Parameters for the Sodium Borohydride Reduction of Ketones

Ketone	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}_{298}$, kcal/mol	Corr coeff
1	5.6 ± 0.1	−44.7 ± 0.3	18.9	0.999
2	5.7 ± 0.2	−44.4 ± 0.8	18.9	0.997
3	6.4 ± 0.1	−42.1 ± 0.1	18.9	0.999
4	7.0 ± 0.4	−40.4 ± 1.2	19.0	0.995
5	7.3 ± 0.4	−40.1 ± 0.8	19.2	0.998
6	7.1 ± 0.2	−41.0 ± 0.8	19.3	0.997
7	7.9 ± 0.3	−40.6 ± 1.1	20.0	0.996
8	6.9 ± 0.1	−45.2 ± 0.5	20.4	0.999
9	7.7 ± 0.3	−42.7 ± 1.1	20.4	0.996
10	7.5 ± 0.4	−43.8 ± 1.5	20.6	0.993
11	8.6 ± 0.1	−41.1 ± 0.3	20.8	0.999
12	7.8 ± 0.2	−43.6 ± 0.5	20.8	0.999
13	9.2 ± 0.3	−40.6 ± 0.9	21.3	0.998
14	7.2 ± 0.2	−48.4 ± 0.6	21.6	0.998
15	8.5 ± 0.2	−42.0 ± 0.8	21.0	0.999
16	9.4 ± 0.1	−39.3 ± 0.5	21.1	0.999
17	9.6 ± 0.2	−39.1 ± 0.8	21.2	0.999
18	11.1 ± 0.3	−38.3 ± 1.1	22.5	0.998
19	9.1 ± 0.3	−42.7 ± 1.0	21.8	0.997

other ketones, except 2,2-dimethyl-4-*tert*-butylcyclohexanone (10) and androstan-3-one (6),[20] were either commercially available or were available by oxidation of the corresponding commercially available alcohol.

These ketones gave a representative selection of unhindered, hindered (in particular by axial substituents at C-3), and 2-alkylcyclohexanones to tackle the questions posed above.

Rate Determination and Activation Parameters. Rates of reduction were measured by the spectrophotometric method we have previously described.[10] The overall second-order rate constants obtained are summarized in Table I. The activation parameters that follow from these data are summarized in Table II. In order to partition the overall rate constants into the specific rate constants for axial and equatorial attack, the stereochemical product ratios as a function of temperature were determined. In general, these ratios varied only slightly with temperature. Therefore, they were measured over a wider temperature range than was possible for the kinetic measurements, and the ratios at the individual temperatures of the rate determinations were obtained by graphical interpolation. These stereochemical product ratios are summarized in Table III. Using these ratios, a series of specific rate constants for axial and equatorial attack at various temperatures is obtained, from which the specific activation parameters, summarized in Tables IV and V, follow. The isokinetic plots of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ for axial and equatorial

attack that may thus be constructed are shown in Figures 1 and 2, respectively.

Discussion

Dissection of Rate Constants. Rickborn and Wuesthoff[9] have pointed out the difficulties associated with simply proportioning the observed overall rate constant into its components using the observed stereochemical product ratio, namely, that the rate constant refers only to the first step of a four-stage reaction whereas the stereochemical product ratio represents the average ratio of the four steps. Clearly if these four steps have markedly different stereoselectivities, the rate constant dissection is invalid and meaningless. Rickborn and Wuesthoff have presented evidence suggesting that the stereoselectivities are in fact, different, and use an extrapolation technique to predict what the product ratio would be at 0% reaction, the value representing the best possible approximation to the stereoselectivity of the first step (i.e., delivery of the first hydride from $^-$BH$_4$) of the reaction. In our previous work on conformationally mobile 2-alkylcyclohexanones,[13] we have defended the position of rate constant subdivision using overall product ratios on a number of grounds, the principal one being that errors of the magnitude indicated by Rickborn and Wuesthoff are not large enough to increase significantly the inherent error of activation parameters so derived (see footnote 7 of ref 13). Despite the adequacy of this defence (for the purpose of activation parameter determination), we nevertheless have made stereochemical investigations of the same type as Rickborn and Wuesthoff and it was our intention to use "0% reaction" product ratios in the present work, since these clearly would, in principle, represent an improvement over our previous practice. That we have not done so is due to our inability to reproduce the type of data reported by Rickborn and Wuesthoff. Despite extensive experimentation on reductions of 2-methylcyclohexanone[21] (the ketone with apparently the widest spread of stereoselectivities[9]) we have been unable to obtain more than about 4% spread of stereoselectivity as a function of the extent of reaction, as compared to the 10.8% spread reported in ref 9. Ironically, however, our prevalent value of 27% *cis*-2-methylcyclohexanol is rather close to the "0% reaction" value reported by Rickborn and Wuesthoff[9] of 28.6%. We have not been able to obtain any values higher than 33%, in contrast to the values of nearly 40% reported for product ratios at "100% reaction".[9] While we do not understand these discrepancies between results in the different laboratories, it should perhaps be noted that an individual product ratio determination is in any case subject to an error of 1–2%, and therefore the order of magnitude of these discrepancies is approximately three times the experimental error.

Table III. Stereochemical Product Ratios and Specific Rate Constants as a Function of Temperature[a]

Ketone	Temp, °C	eq:ax[b]	$k_{ax} \times 10^4$, M^{-1} s^{-1} [c]	$k_{eq} \times 10^4$, M^{-1} s^{-1} [c]
1	0	89:11	304	38
	15	87:13	530	79
	20	87:13	658	98
	25	86:14	765	125
	30	86:14	902	147
2	0	87:13	284	42
	15	87:13	547	82
	20	86:14	635	103
	25	86:14	736	120
3	0	88:12	230	31
	20	86:14	533	87
	25	86:14	658	107
	30	86:14	795	129
4	0	88:12	165	22
	15	87:13	371	55
	20	87:13	429	64
	25	86:14	520	85
5	0	96:4	131	5
	15	95:5	256	13
	25	94:6	429	27
	30	94:6	532	34
6	0	93:7	122	9
	15	92:8	226	20
	20	92:8	311	27
	25	91:9	387	38
	30	91:9	471	47
7	0	73:27	28.5	10.5
	15	71:29	55.7	22.7
	25	70:30	104	45
	30	70:30	130	55
	35	69:31	155	69
8	0	68:32	14.7	6.9
	15	66:34	31.2	16.0
	25	65:35	46.3	24.9
	30	65:35	54.9	29.5
	35	65:35	70.2	37.8
9	0	66:34	11.2	5.7
	15	65:35	26.3	14.1
	20	65:35	29.5	15.9
	25	65:35	43.5	23.4
	35	64:36	62.7	35.3
10	0	94:6	13.6	0.7
	25	92:8	51.2	4.5
	30	91:9	61.1	6.0
	35	90:10	66.6	7.4
11	0	62:38	4.58	2.80
	21	62:38	14.5	9.1
	35	62:38	32.1	19.7
13	0	67:33	2.12	1.04
	15	68:32	5.81	2.74
	25	69:31	9.8	4.4
	30	70:30	13.4	5.7
15[d]	0	43:57	2.51	3.33
	15	46:54	6.6	7.8
	25	48:52	12.0	12.9
	35	50:50	19.8	19.8
16	0	43:57	2.05	2.71
	15	46:54	5.34	6.26
	25	48:52	10.5	11.3
	35	50:50	19.5	19.5
17	0	39:61	1.32	2.06
	25	45:55	7.9	9.7
	30	45:55	9.5	11.7
	35	46:54	12.9	15.1
19	0	43:57	0.54	0.72
	15	45:55	1.61	1.97
	20	45:55	2.11	2.57
	25	46:54	2.75	3.23
	30	46:54	3.39	3.98
	35	47:53	4.62	5.22

Table III (*footnotes*)

[a] In view of the small changes in product ratio, ratios were measured over a wider temperature range, and the reported values obtained by graphical interpolation. These values are reproducible to ±1%. [b] For conformation with the other substituent in an equatorial configuration. [c] k_{ax} refers to the process of axial attack of hydride, yielding the equatorial alcohol. [d] "Product ratio" from analogy with ketones 16 and 17 (ratio essentially independent of equatorial groups at C-3).

Table IV. Specific Activation Parameters for Axial Attack[a]

Ketone	$\Delta H_{ax}^{\ddagger}$, kcal/mol	$\Delta S_{ax}^{\ddagger}$, eu	$\Delta G_{ax}^{\ddagger}$ (298 K), kcal/mol	Corr coeff
1	5.4 ± 0.1	−45.5 ± 0.3	19.0	0.999
2	5.6 ± 0.3	−44.9 ± 0.9	19.0	0.996
3	6.2 ± 0.1	−43.0 ± 0.2	19.0	0.999
4	6.8 ± 0.4	−41.5 ± 1.3	19.2	0.994
5	7.2 ± 0.2	−40.6 ± 0.7	19.3	0.998
6	7.0 ± 0.3	−41.6 ± 0.9	19.4	0.997
7	7.8 ± 0.3	−41.4 ± 1.0	20.1	0.997
8	6.8 ± 0.1	−46.3 ± 0.5	20.6	0.999
9	7.8 ± 0.3	−43.4 ± 1.1	20.7	0.996
10	7.3 ± 0.4	−44.7 ± 1.4	20.6	0.994
11	8.6 ± 0.1	−42.1 ± 0.3	21.1	0.999
13	9.5 ± 0.3	−40.5 ± 0.9	21.6	0.999
15	9.4 ± 0.1	−40.3 ± 0.2	21.4	0.999
16	10.3 ± 0.3	−37.7 ± 0.9	21.5	0.999
17	10.5 ± 0.2	−37.8 ± 0.7	21.8	0.999
19	9.6 ± 0.3	−42.5 ± 1.0	22.3	0.997

[a] See footnotes to Table III.

Table V. Specific Activation Parameters for Equatorial Attack[a]

Ketone	$\Delta H_{eq}^{\ddagger}$, kcal/mol	$\Delta S_{eq}^{\ddagger}$, eu	$\Delta G_{eq}^{\ddagger}$ (298 K), kcal/mol	Corr coeff
1	6.9 ± 0.1	−44.0 ± 0.2	20.0	0.999
2	6.3 ± 0.2	−46.3 ± 0.6	20.1	0.999
3	7.4 ± 0.1	−42.8 ± 0.5	20.2	0.999
4	8.0 ± 0.4	−41.0 ± 1.3	20.2	0.995
5	10.1 ± 0.2	−36.4 ± 0.6	20.9	0.999
6	8.6 ± 0.2	−40.8 ± 0.8	20.8	0.998
7	8.7 ± 0.3	−40.2 ± 0.9	20.7	0.998
8	7.5 ± 0.2	−45.2 ± 0.6	21.0	0.999
9	8.2 ± 0.3	−43.2 ± 1.1	21.1	0.996
10	10.0 ± 0.4	−40.3 ± 1.3	22.0	0.997
11	8.6 ± 0.1	−43.0 ± 0.2	21.4	0.999
13	8.7 ± 0.3	−44.6 ± 0.9	22.0	0.998
15	8.1 ± 0.1	−44.7 ± 0.2	21.4	0.999
16	8.9 ± 0.2	−42.1 ± 0.8	21.4	0.999
17	9.1 ± 0.1	−41.9 ± 0.4	21.6	0.999
19	8.9 ± 0.3	−44.8 ± 0.9	22.2	0.998

[a] See footnotes to Table III.

Owing to these difficulties, it was clear that we were not in a position to use "0% reaction" product ratios, and therefore a return to our previous practice of using actual product ratios was dictated. It is worth noting, however, that if our smaller product ratio spreads observed are accurate, the error these spreads will carry through to the activation parameters will be even less significant than was previously thought (footnote 7 of ref 13).

Values of Activation Parameters. Inspection of the values in Table II show that the major barrier to reaction in the borohydride reduction of ketones is entropy, this providing 50–70% of the free-energy barrier. In contrast to this, vertical
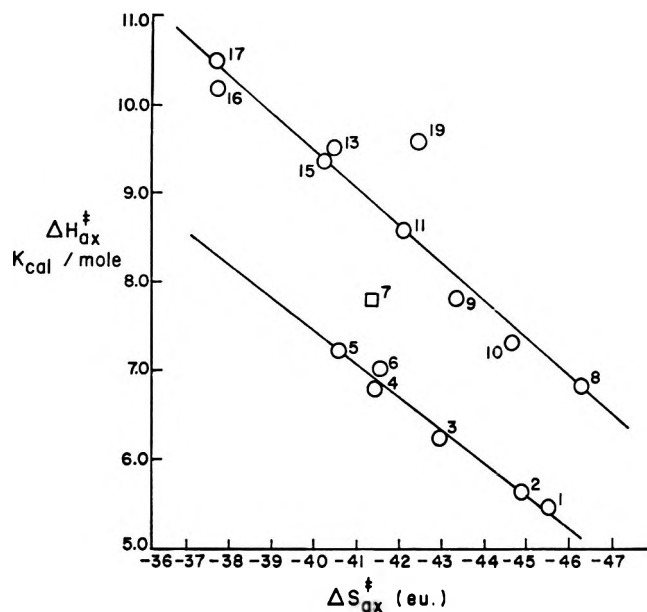
Figure 1. Enthalpy–entropy plot for axial attack of borohydride on cyclohexanones.

Figure 2. Enthalpy–entropy plot for equatorial attack of borohydride on cyclohexanones.

comparisons in Tables II, IV, and V show that decreasing rate with increasing steric hindrance is due to increase in the enthalpy of activation, the entropy of activation becoming more favorable in the usual compensating manner. Similarly, comparison of corresponding entries between Tables IV and V reveals that the predominance of one stereochemical epimer over the others is due to a more favorable enthalpy of activation, the entropies of activation not being very different. Thus, this reaction is an interesting one with *entropy being the major component of the free-energy barrier, yet, being enthalpy controlled* in terms of both rate and stereoselectivity. Thus, in any rationalization of stereoselectivity, the major differential factors to be considered should be those likely to affect the enthalpy, rather than entropy of the transition states—a somewhat relieving consideration.

Treatment of Data. Isokinetic Plots. An isokinetic relationship is defined as

$$\Delta H^{\ddagger} = \Delta H_0^{\ddagger} + \beta \Delta S^{\ddagger}$$

Thus, a linear plot of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ for a series of related reactions will yield $\Delta H_0^{\ddagger}$ as the intercept and β as the slope. $\Delta H_0^{\ddagger}$ is the value of $\Delta H^{\ddagger}$ when $\Delta S^{\ddagger} = 0$, and is also equal to $\Delta G^{\ddagger}$ at the isokinetic temperature; it is not considered to have any physical significance. The slope of the isokinetic plot, β, has the units of temperature and is termed the isokinetic temperature. Since Leffler's epic paper on these enthalpy–entropy relationships in 1955,[14] isokinetic plots have been the subject of considerable criticism. In 1964 Petersen[22] pointed out that, because of the insensitivity of the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ plot, a reasonably linear plot did not establish the existence of an isokinetic temperature; he questioned whether indeed there were data on any reaction which met or approximated the conditions for proof of such existence. More recently, Exner,[23] in a detailed analysis of isokinetic plots, has suggested an alternative method of demonstrating the existence of an isokinetic temperature and determining its value.

In view of these discussions it is clear that the present data provide no evidence as to the existence of an isokinetic temperature. The idea of interest is the reasonable (but unproved) notion that an isokinetic relationship applies only to a series of reactions of the same mechanism and similar transition state.[14] In this connection it was of considerable interest to examine the activation parameter data derived both from dissected and undissected rate constants. The plot of the ac-

tivation parameters from the original overall rate constants was initially somewhat disappointing, giving a rather poor degree of correlation. The situation became immediately clear, however, on constructing the isokinetic plot from the specific activation parameters for axial and equatorial attack. *These plots (Figures 1 and 2) clearly show that in neither case is a single line obtained, but that, with one or two exceptions, the data produce two distinct lines, both with good degrees of correlation. It is highly significant that in both cases the lower line consists of, and only of, the unhindered ketones in the series, whereas the upper line contains the hindered and 2-alkyl ketones.* The distinction is absolute: no unhindered ketones appear on the upper line and no hindered ketones on the lower.
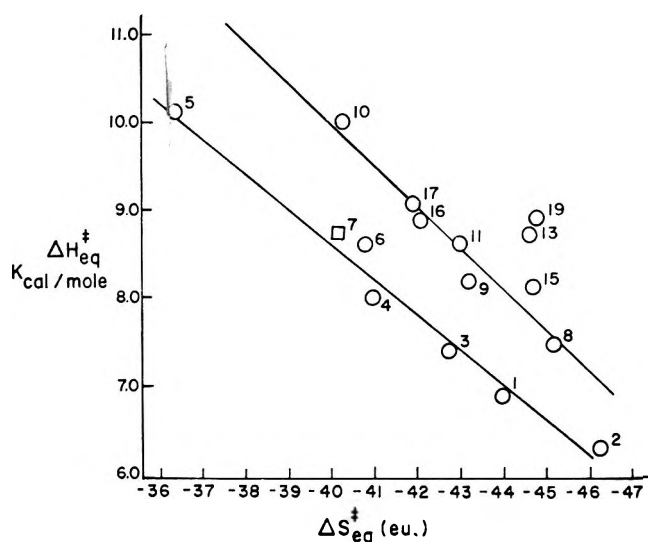
These plots deserve some comment. Firstly, in view of the above-mentioned criticisms, it must be emphasized that the data do not establish the existence of an isokinetic temperature for any of the linear relationships. Such a demonstration would not, in fact, be possible directly, since the apparent isokinetic temperatures lie above the boiling point of the solvent, 2-propanol. It is convenient to characterize the lines by their slopes, but these slopes (β) should simply be regarded as the slopes of the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ plot in the vicinity of 300 K.

Secondly, it should be noted that the values of β—(a) axial attack on unhindered ketones, 376 ± 20 K; (b) equatorial attack on unhindered ketones, 397 ± 24 K; (c) axial attack on hindered ketones, 440 ± 17 K; and (d) equatorial attack on hindered ketones, 466 ± 43 K—meet the stated requirement for theoretical significance of being approximately 100 K removed from the temperature of experimental measurements.[14]

Thirdly, the fact that the linear correlations appear only when the dissected activation parameters are used is, in fact, unremarkable. There is actually no reason for the *overall* activation parameters to exhibit linear behavior since in each case they represent a variable mixture of two independent reaction pathways. The fact, however, that the linear correlations emerge from the dissected rate constants provides additional support for the dissection procedure discussed above.

Fourthly, it is clear from Figures 1 and 2 that not all the ketones fit on any of the isokinetic plots. Most immediately obvious is 2-methylcyclohexanone (7), and this is interesting because we have recently shown that formation of *cis*-2-methylcyclohexanol occurs almost equally from *both* chair conformations.[1a,13] In fact, the apparent behavior of 2-

methylcyclohexanone as an unhindered ketone as far as equatorial attack is concerned (Figure 2) is very deceptive; that particular point actually being between that for *equatorial* attack on a *hindered* ketone (Figure 2) and *axial* attack on an *unhindered* ketone (Figure 1), and thus fortuitously landing near the line for equatorial attack on an unhindered ketone. It is noteworthy that 2-methylcyclohexanone is the only 2-alkylcyclohexanone with this behavior, all others behaving simply as hindered ketones both for axial and equatorial attack.

The other deviations all involve high degrees of steric hindrance, some coupled with attack on the steroid nucleus. Actually all the steroidal data lie somewhat above and to the right of the appropriate correlation line and this appears consistent with these ketone structures being more rigid and thus offering effectively more hindrance than the corresponding cyclohexane structure, this cyclohexane–steroid difference becoming more marked with the more crowded structures. These deviant points may, in fact, represent part of a third correlation line but there are insufficient data to establish this point. 3,3,5,5-Tetramethylcyclohexanone (18) is also well away from other points on the overall $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ plot but the specific activation parameters cannot be obtained owing to its unknown stereochemical product ratio. Interestingly, equatorial attack on menthone (13) with an adjacent isopropyl group is apparently severe enough for the point to be deviant, although axial attack is normal.

From his extensive examination and analysis of enthalpy–entropy relationships in organic reactions, Leffler[14] has concluded that "a critical degree of steric hindrance once surpassed initiates a new isokinetic series corresponding to a qualitatively different transition state or ground state". This type of behavior is unquestionably observed in this present study, and while reaction mechanism conclusions may be drawn from such studies only with extreme caution, the *failure* of the relationship does appear to be an unchallenged indicator of a change of reaction mechanism or of transition state. In this connection, the abrupt separation between reduction of unhindered and of 2-alkyl and hindered ketones, and this identical correspondence with the distinctions in stereochemical outcome, cannot be overlooked. While reiterating the above disclaimer, *if* the data may be interpreted in terms of transition state structure, and *if* the slope β of the $\Delta H^{\ddagger}$–$\Delta S^{\ddagger}$ plot is a useful characterization of the plot, then it must be concluded (a) that there are significant differences between reduction of hindered and unhindered ketones; (b) that there are not significant differences between axial and equatorial attack on the same ketone; and (c) that 2-alkylcyclohexanones are to be considered as hindered ketones. In connection with current theories on the origin of stereoselectivity in these reactions, it is noteworthy that the only explanation involving differential transition states between hindered and unhindered ketones is that of Dauben, Fonken, and Noyce, involving the concepts of steric approach control (hindered ketones) and product development control (unhindered ketones[3]).

Conclusions

1. Determinations of activation parameters from the second-order rate constants of reductions of simple and steroidal cyclohexanones by sodium borohydride in 2-propanol show that enthalpies of activation vary from 5.4 to 11.1 kcal mol^{-1}, and entropies of activation from −36.4 to −48.4 eu.

2. Changes both in rate of reduction and in stereochemical product ratio in going from ketone to ketone are due to changes in the enthalpies of activation. Thus the reaction, on both these criteria, is enthalpy controlled, despite the major barrier to reduction being entropy.

3. The isokinetic relationship fails to correlate all the data

obtained on reduction of the 19 cyclohexanones, thus indicating some reaction mechanism or transition state change in the series of ketones.

4. At least four correlation lines have been identified; one pair of lines correlate axial and equatorial attack, respectively, on unhindered ketones; another pair of lines correlate these two modes of attack on more hindered, including 2-alkylcyclohexanones, ketones. There appears to be a large difference between attack (axial or equatorial) on hindered and attack on unhindered ketones but little difference between axial and equatorial attack on the same ketone.

Experimental Section

5-*n*-Butyl-3,3-dimethylcyclohexanone (17). To freshly recrystallized tetrakis[iodo(tri-*n*-butylphosphine)copper(I)] (12.77 g, 32.5 mmol) prepared by the method of Kauffman and Teter[16] in anhydrous ether (150 ml) under a dry nitrogen atmosphere and in an ice–acetone bath was added *n*-butyllithium in *n*-hexane (27 ml, 2.4 M, 64.8 mmol). After 10 min of stirring, 5,5-dimethylcyclohex-2-en-1-one (2.04 g, 16.1 mmol) was added dropwise over 25 min. The reaction mixture was stirred for 2 h at 0 °C and then allowed to warm to room temperature and stand overnight. The reaction mixture was poured into saturated aqueous NH$_4$Cl (200 ml), stirred for 30 min, and filtered by suction to remove the gelatinous precipitate. After ether extraction (3 × 50 ml), drying of the ether extracts (brine, Na$_2$SO$_4$), and rotary evaporation of the ether, a residue (10.8 g) was obtained. Purification of the title compound was achieved by a rapid chromatography column [silica gel, petroleum ether (bp 30–60 °C), benzene] and distillation of the carbonyl-containing fractions; formation of the tosylhydrazone and regeneration of the ketone by the method of Nagata and co-workers;[24] and finally rechromatography on silica gel (100 g), the desired material (λ_{max} 285 nm, ϵ 25.0; ν_{max} 1750 cm^{-1}. Anal. Calcd for C$_{12}$H$_{22}$O: C, 79.06; H, 12.16. Found: C, 79.04; H, 12.24) being eluted by 75% benzene in petroleum ether.

Cholestan-2-one (19), mp 128–129 °C (lit.[18] mp 126–127 °C), was prepared from cholestan-3β-ol by the known ketone transposition route.[18] Other ketones were either commercially available, were available simply by oxidation[25] of the corresponding alcohols, or have been previously described.[13]

Kinetic Method and Stereochemical Product Ratio Determination. The method of performing reductions, the determination of the stereochemical product ratios, the methods of identification of the epimeric alcohols, and the spectrophotometric method (disappearance of the n–π* band of the ketone at about 287 nm) of following the kinetics have all been published in detail.[7b,10,13] Kinetic runs were all done at least in duplicate or until satisfactory reproducibility was obtained, and error limits quoted are the mean deviations from the mean.[10] The ranges of concentrations used were 0.25–6.0 × 10^{-2} M for ketone and 0.3–4.4 × 10^{-2} M for BH$_4$$^-$. Kinetics and activation parameters for the reduction of ketones 12 and 18 are reported although data on these ketones for Figures 1 and 2 cannot be obtained as the symmetry of these ketones precludes product ratio determination. The use of product ratios for cyclohexanone itself has previously been described.[13]

Registry No.—1, 589-92-4; 2, 98-53-3; 3, 108-94-1; 4, 591-24-2; 5, 15600-08-5; 6, 1224-95-9; 7, 583-60-8; 8, 4423-94-3; 9, 1126-18-7; 10, 774-97-0; 11, 766-42-7; 12, 766-43-8; 13, 89-80-5; 14, 1255-26-1; 15, 2979-19-3; 16, 873-94-9; 17, 59005-34-4; 18, 14376-79-5; 19, 16020-93-2; 5,5-dimethylcyclohex-2-en-1-one, 4694-17-1.

References and Notes

(1) For previous papers in this series, see (a) D. C. Wigfield, S. Feiner, and D. J. Phelps, *J. Org. Chem.*, **40**, 2533 (1975); (b) D. C. Wigfield, D. J. Phelps, R. F. Pottie, and R. Sander, *J. Am. Chem. Soc.*, **97**, 897 (1975), and references cited therein.

(2) H. I. Schlesinger, H. C. Brown, H. R. Hoekstra, and L. R. Rapp, *J. Am. Chem. Soc.*, **75**, 199 (1953).

(3) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(4) J.-C. Richer, *J. Org. Chem.*, **30**, 324 (1965).

(5) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199, 2205 (1968).
(6) J. Klein, *Tetrahedron Lett.*, 4307 (1973); *Tetrahedron*, **30**, 3349 (1974).
(7) For recent discussions of the problem see (a) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970); (b) D. C. Wigfield and D. J. Phelps, *Can. J. Chem.*, 50, 388 (1972), and references cited therein.
(8) (a) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953); (b) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).
(9) B. Rickborn and M. T. Wuesthoff, *J. Am. Chem. Soc.*, **92**, 6894 (1970).
(10) D. C. Wigfield and D. J. Phelps, *J. Chem. Soc., Perkin Trans. 2*, 680 (1972).
(11) H. C. Brown and his co-workers have reported the activation parameters for reduction of a number of acyclic, cyclic, and bicyclic ketones,[8b,12] including several substituted cyclohexanones. These overall parameters have not been subdivided into the specific parameters for axial and equatorial attack. We have already published some activation parameter data specifically relating to the problems associated with conformationally mobile 2-alkylcyclohexanones.[13] H. C. Brown has also noted the rate constant dissection problem.[12]
(12) H. C. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).
(13) D. C. Wigfield and D. J. Phelps, *J. Am. Chem. Soc.*, **96**, 543 (1974).

(14) J. E. Leffler, *J. Org. Chem.*, **20**, 1202 (1955).
(15) A. W. Allan, R. P. A. Sneedon, and J. M. Wilson, *J. Chem. Soc.*, 2186 (1959).
(16) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7**, 9 (1963).
(17) J. Hooz and R. B. Layton, *Can. J. Chem.*, **48**, 1626 (1970).
(18) T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. Pharm. Bull.*, **11**, 465 (1963).
(19) D. C. Wigfield, S. Feiner, and D. J. Phelps, *Steroids*, **20**, 435 (1972).
(20) We are very grateful to Drs. J. W. ApSimon and J.-C. Richer for samples of ketones **6** and **10**, respectively.
(21) We thank Mr. Steve Feiner and Mr. Peter Marshall for performing great numbers of these rather tedious experiments.
(22) R. C. Petersen, *J. Org. Chem.*, **29**, 3133 (1964).
(23) O. Exner, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, pp 8–10, and references cited therein; O. Exner, *Nature (London)*, **201**, 488 (1964).
(24) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961).
(25) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 142.

Perhydroindan Derivatives. 17. Application of the Reduction–Methylation Sequence to 7-Methoxyhexahydrofluorene Derivatives[1]

Herbert O. House,* Roger C. Strickland, and Edward J. Zaiko

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

Received February 6, 1976

The reductive methylation of each epimeric diacid **1a** and **2a** was studied by successive reaction with Li in THF–liquid NH3 followed by CH3I. In each case, the diacid product (18 from **1a** and **22** from **2a**) was formed by introduction of the C-8 methyl group into the intermediate **6** from the side of the molecule opposite to the carboxylate group at C-9. Thus, the stereochemistry of the C-9 carboxyl group may be used to control the stereochemistry of methylation at C-8. Each of the syn-diacid products **18** or **22** formed an anhydride **21** or **25** with infrared absorption typical for an unstrained cyclic anhydride.

In earlier publications[2] we have described the synthesis of the epimeric acid derivatives **1** and **2** (Scheme I) which we wished to use as models to explore the preparation of the acid lactone **3**, a model for certain of the gibberellins. To accomplish this objective we wished to introduce a methyl group at C-8 by the scheme of Lowenthal[3] in which the aromatic acid

Scheme I

1a. $R_1 = OH$; $R_2 = H$
b. $R_1 = OCH_3$; $R_2 = CH_3$
c. $R_1 = NHCH_3$; $R_2 = H$

2a. $R_1 = OH$; $R_2 = H$
b. $R_1 = OCH_3$; $R_2 = CH_3$
c. $R_1 = NHCH_3$; $R_2 = H$

3

4a, $R = H$
b, $R = CH_3$

5a, $R = H$
b, $R = CH_3$

6

1a or **2a** would be reduced with lithium in ammonia to form an enolate anion **6** which could be methylated. For this reaction to be useful, it is apparent that the new methyl group must be introduced at C-8 from above the plane of the polycyclic system of the enolate anion **6** to produce one of the epimeric products **4** or **5**. In this paper we report our study of the stereochemistry of the reduction–methylation sequence with the epimeric acids **1a** and **2a**.

The less stable[2] diacid **2a** was obtained from the alcohol **7** as indicated in Scheme II. In this procedure, a modification of an earlier sequence,[2a] n-BuLi rather than n-BuLi and t-BuONa was used in the initial regiospecific metalation of the alcohol **7**,[4] selective esterification of the isomeric diacids **10** and **11** was used to facilitate separation of the diester **12** from the acid ester **13a**, and n-BuLi in hexane rather than MeLi in Et2O–THF was used to metalate the unsaturated ester **9**. The intermediate diester **12** in this sequence could also be used to obtain more stable diacid **1a** by hydrogenation (to form diester **2b**) followed by saponification with accompanying epimerization.

An alternative route to the more stable diacid **1a** is summarized in Scheme III. In this sequence, also a modification of an earlier procedure,[2b] the amide **15**, obtained from hydroxy acid **8**,[2b] was converted to an easily separable mixture of amide acids **1c** and **2c**. Although the diacid **1a** could be converted to the corresponding cyclic anhydride **17**, examination of molecular models suggested that significant distortion of the five-membered B ring was required in this transformation. Evidence for this conformational change is provided by a change in the NMR coupling constant between protons at C-9 and C-1a from $J = 4$ Hz in the acid **1a** to $J \sim 11$ Hz in the anhydride **17**. Presumably because of the distortion required to
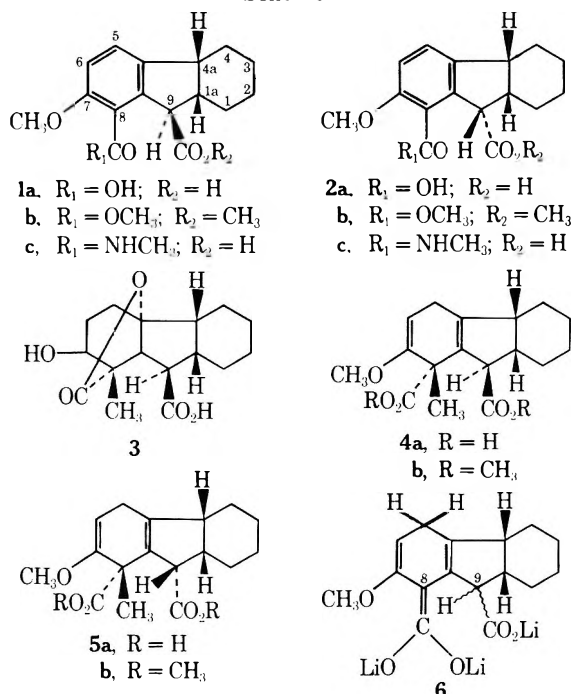
Scheme II
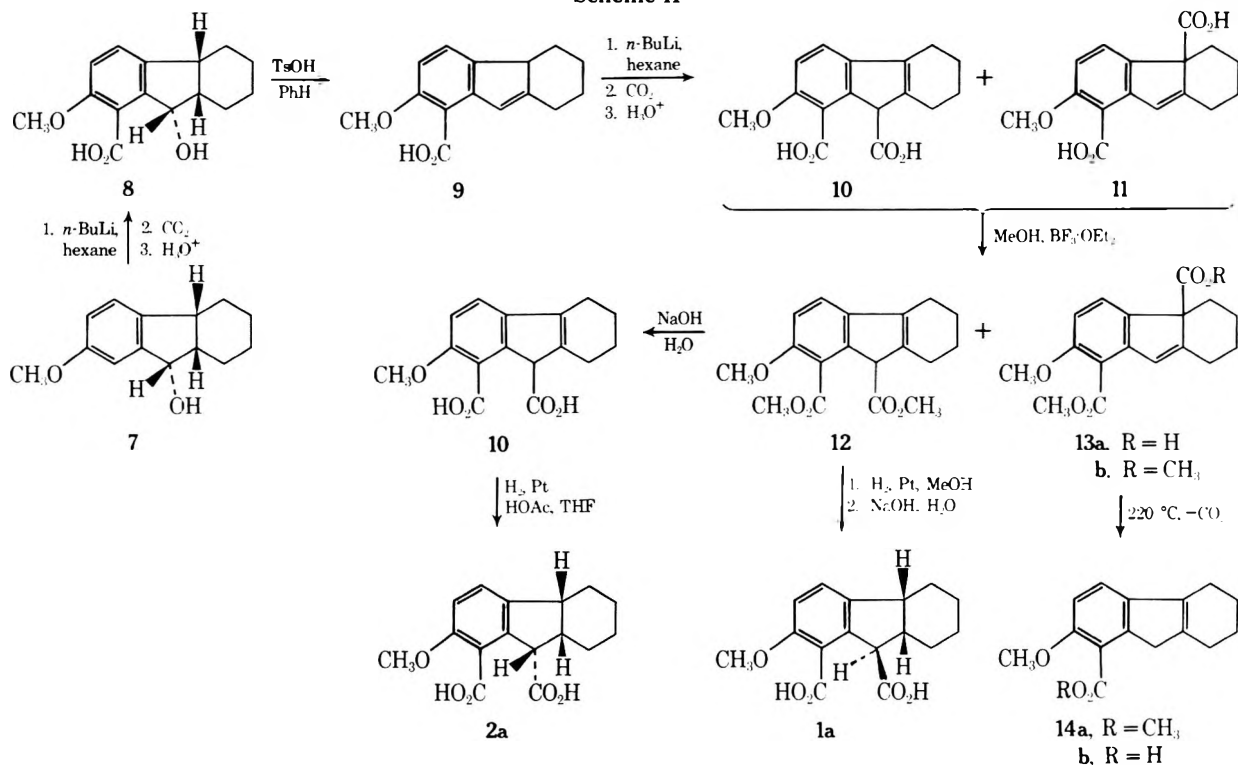
Scheme III
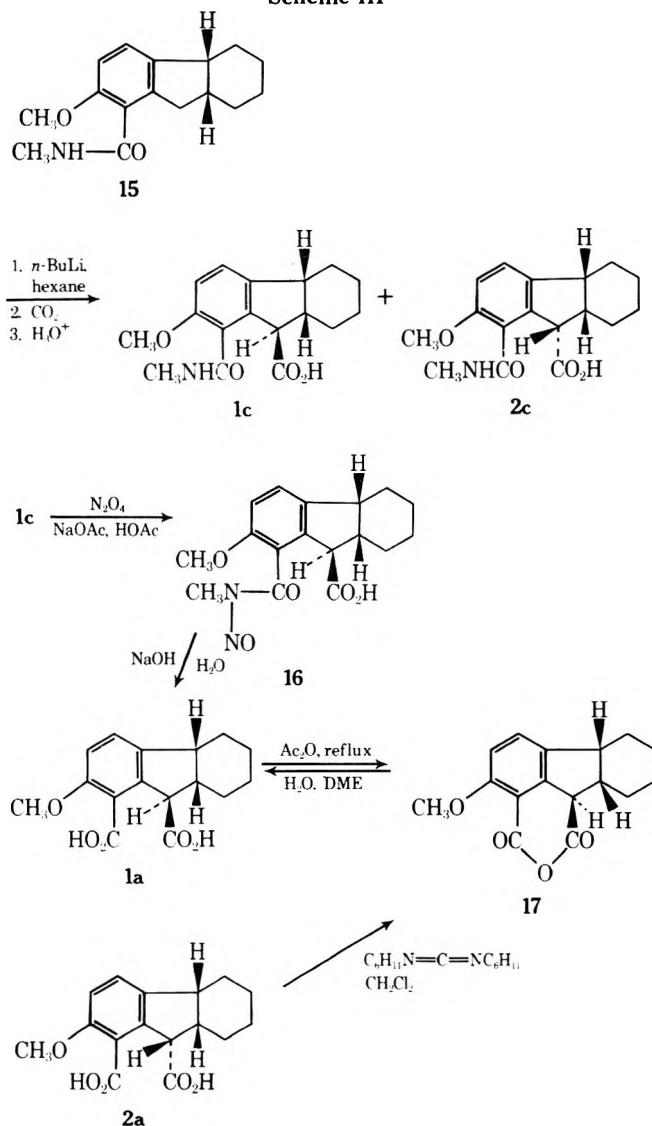
form a cyclic anhydride, reaction of the more rigid diacid 10 with Ac_2O failed to form a cyclic anhydride; the crude reaction product appeared to contain (NMR analysis) one or more mixed anhydrides from HOAc and the diacid 10. Interestingly, an attempt to convert the less stable diacid 2a to the corresponding cyclic anhydride by reaction with dicyclohexylcarbodiimide in CH_2Cl_2 solution resulted in accompanying epimerization at C-9 to form the same anhydride 17 obtained from the more stable diacid 1a.

Reductive methylation of the diacid 1a (Scheme IV) produced a single methylated methoxy diacid 18 accompanied by a crude by-product apparently formed by cleavage of the methoxyl group. The thermally unstable enol ether diacid 18 was characterized as its diester 19 which could be hydrolyzed with dilute acid to the keto diester 20. Reaction of the diacid 18 with dicyclohexylcarbodiimide under mild conditions produced the cyclic anhydride 21 that could be hydrolyzed to the starting diacid 18.

Similarly, the reductive methylation of the diacid 2a produced a single methylated methoxy diacid 22 that was characterized as its diester 23 and keto diester 24. The diacid 22 could also be easily converted to its cyclic anhydride 25 by treatment with dicyclohexylcarbodiimide.

Since each of the epimeric diacids 1a and 2a give a different product in the reductive methylation sequence, it was apparent that epimerization of these diacids 1a and 2a at C-9 before reduction was not occurring. Treatment of the diester 23 with NaOMe in MeOH produced a mixture containing 23 and a new product, believed to be diester 29; however, the mixture from this epimerization lacked NMR absorption characteristic of diester 19. Furthermore, the NMR coupling constants between protons at C-9 and C-1a in the aromatic acids ($J = 4$ Hz for 1a and $J = 7$ Hz for 2a) were unchanged in the reduced products ($J = 4$ Hz in 19 and $J = 7$ Hz in 22). Consequently, it was clear that the two diacid products 18 and 22 have the same configuration at C-9 as the starting diacids 1a and 2a.

It was apparent from examination of molecular models that while each of the syn diacids 18 and 22 could form a relatively strain-free cyclic anhydride (21 and 25), the formation of a

Scheme IV
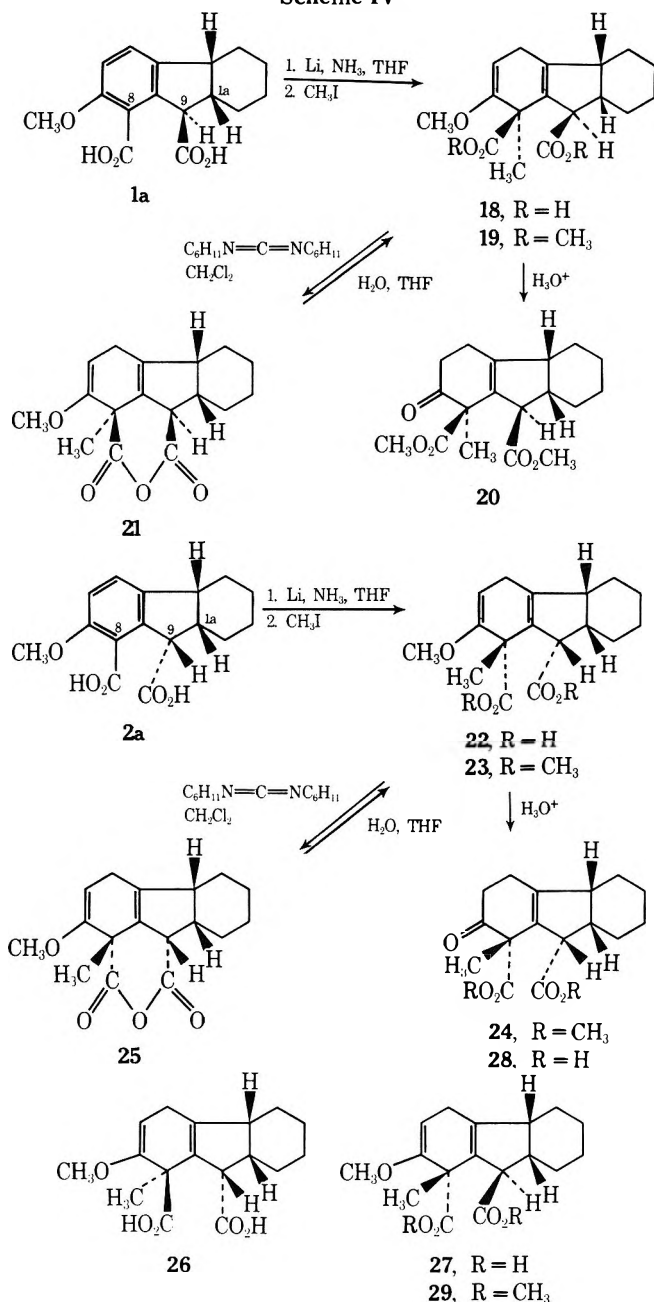
Scheme V
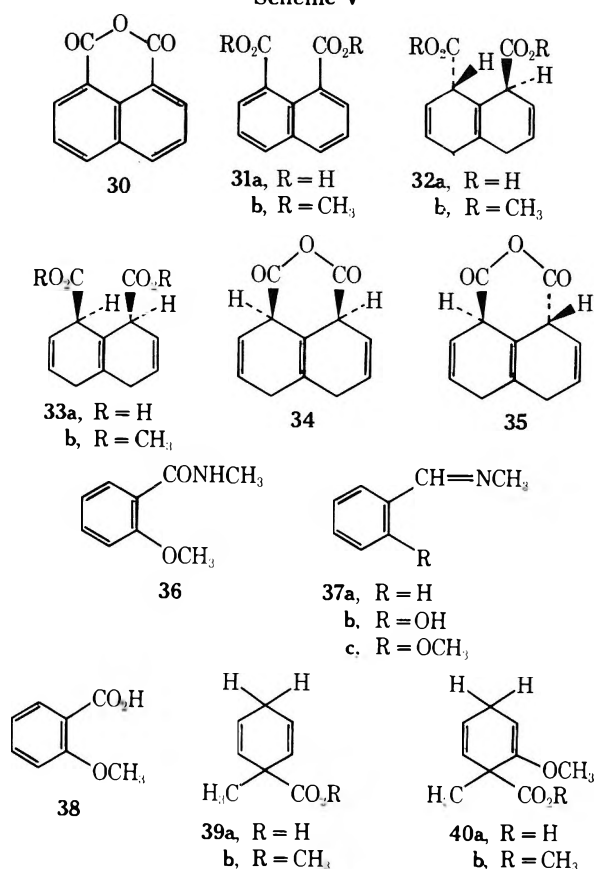
yield the anti diacid **32a** (favored in a kinetically controlled reduction) and the syn diacid **33a** (favored after equilibration of the diacids **32a** and **33a**). Reaction of either diacid with dicyclohexylcarbodiimide in CH_2Cl_2 formed the same anhydride **34** that could be hydrolyzed and esterified to yield the syn diester **33b**. The absorbance ratio, $A_{1762}/A_{1804} = 1.69$, observed in the infrared spectrum of this anhydride **34** was normal for an unstrained six-membered anhydride as would be expected for the syn anhydride **34** in its more stable conformation **41**. By contrast, in the reasonable conformation **42**

cyclic anhydride from either anti diacid **26** or **27** would be accompanied by introduction of substantial strain into the molecules. The fact that each diacid **18** or **22** could be converted to its anhydride **21** or **25** without epimerization while the same reaction conditions converted the diacid **2a** to anhydride **17** with epimerization strongly suggested that the carboxyl groups are syn in both diacids **18** and **22**.

Previous studies of the infrared spectra of cyclic anhydrides derived from dicarboxylic acids[5] have shown that for unstrained six-membered cyclic anhydrides, the ratio of absorbances for the lower frequency (asymmetrical stretching) and higher frequency (symmetrical stretching) carbonyl bonds is 2–3. For acyclic anhydrides this absorbance ratio was approximately 1 and an absorbance ratio of 7–11 was observed for five-membered cyclic anhydrides. The absorbance ratios, A_{1760}/A_{1800}, observed for $CHCl_3$ solutions of the anhydrides **17, 21**, and **25** prepared in this study all had values in the range 1.4–1.6 indicating these materials to have the geometry of normal, unstrained six-membered anhydrides.

To obtain further evidence concerning the possibility of forming anhydrides from anti diacids such as **26** and **27**, the diacid **31a** (Scheme V) was reduced with Li in liquid NH_3 to

for the anti anhydride **35**, the dipoles of the two carbonyl groups are approximately opposed and the shorter wavelength symmetrical stretching vibration should have significantly diminished intensity analogous to the situation observed with five-membered cyclic anhydrides. Thus, we conclude that the anti diacid, **32a**, is isomerized during reaction with dicyclohexylcarbodiimide to form the more stable syn anhydride **34**. Since comparable behavior would be expected for the geometrically similar anti diacids **26** and **27**, the foregoing stereochemical assignments are substantiated.

Since several attempts to apply the reduction–methylation sequence to the amide acids **1c** and **2c** produced complex mixtures of products, we examined this reaction briefly with the model methoxy amide **36**. After reduction of the amide **36** with Li in THF–NH₃ and addition of CH_3I, the resulting crude product was a mixture of imines **37** containing primarily the imine **37a** of benzaldehyde. We also examined briefly the reduction–methylation sequence with the model methoxy acid **38**. In addition to the expected product **40a** (characterized as

the ester **40b**), the product mixture (after esterification) also contained the product **39b** that no longer contained an aryl-OCH_3 function. Interestingly, this side reaction, presumably resulting from initial protonation of anion radical **43** to form intermediate **44**, was significantly more serious when the acid **38** was reduced with Li in NH_3 rather than Na in NH_3.

Experimental Section[6]

Preparation of the Unsaturated Acid 9. To a cold (0 °C) suspension of 44.4 g (0.204 mol) of the alcohol 7 in 250 ml of hexane was added, dropwise and with stirring during 30 min, 320 ml of a hexane solution containing 0.525 mol of n-BuLi. The resulting orange solution was stirred at 25 °C for 28 h. Then the resulting suspension was cooled to −78 °C and CO_2 was passed through the solution with vigorous stirring for 45 min. The reaction mixture was treated with CH_2Cl_2 and aqueous Na_2CO_3 and the precipitate, the Na salt of the acid **8**, was collected by filtration. This Na salt was stirred with aqueous HCl and then the mixture was extracted with CH_2Cl_2. After the CH_2Cl_2 extract had been dried, concentration left 43.9 g (82%) of the hydroxy acid **8** as a white solid, mp 133–135 °C (lit. mp 136–137,[2a] 134–135 °C[2b]), identified with previously described samples by comparison of ir spectra. A solution of 20.0 g (76 mmol) of this acid **8** and 1.9 g (10 mmol) of TsOH in 450 ml of benzene was refluxed with continuous separation of H_2O for 1 h and then washed with H_2O, dried, and concentrated to leave 17.5 g of the crude acid **9** as a yellow solid, mp 145–154 °C. Fractional recrystallization (CH_2Cl_2–hexane) separated 12.7 g of early fractions of white prisms, mp 151–157 °C (lit.[2a] mp 161.5–162.5 °C), containing (ir analysis) mainly the acid **9**. Later fractions (4.1 g, mp 125–145 °C) contained (NMR analysis) the acid **9** accompanied by increasing amounts of isomeric acid **14b**. The total yield of the mixture of isomeric acids **9** and **14b** (suitable for further reaction with n-BuLi) was 16.8 g (90%).

Preparation of the Diacid 2a. To a cold (0 °C) suspension of 16.5 g (67.6 mmol) of the unsaturated acid **9** (containing some of the isomeric acid **14b**) in 180 ml of Et_2O and 180 ml of THF was added, dropwise and with stirring, 100 ml of a hexane solution containing 156 mmol of n-BuLi. The resulting red solution was stirred at 25 °C for 1 h and then siphoned onto crushed dry ice. The reaction mixture was partitioned between Et_2O and aqueous Na_2CO_3 and the aqueous phase was acidified. The precipitate of crude diacids **10** and **11** was collected, combined with the CH_2Cl_2 extract of the aqueous filtrate, and concentrated to leave 13.9 g of a light brown solid containing (NMR analysis, CH_3O peaks at δ 3.75 and 3.80) an approximately equal mixture of the diacids **10** and **11**. A solution of this mixture of diacids and 5.0 ml of $BF_3·Et_2O$ in 400 ml of MeOH[7] was refluxed for 23 h and then concentrated and partitioned between aqueous Na_2CO_3 and CH_2Cl_2. The organic layer was dried and concentrated to leave 9.7 g of orange liquid containing [liquid chromatography, C-18 Corasil column with a H_2O–CH_3CN (3:2 v/v) eluent] the diester **12** (ca. 70%, retention time 2.0 min), the diester **13b** (ca. 30%, 1.5 min), and two minor unidentified impurities (4.1 and 8.2 min). Fractional crystallization from Et_2O separated 4.53 g of the crude diester **12**, mp 86–86.5 °C, that was recrystallized from MeOH to give 3.98 g of diester **12** as white needles, mp 88–89 °C (lit.[2a] 91–91.5 °C). The remaining materials from the mother liquors were chromatographed on silica gel (eluent PhH–Et_2O, 99:1 v/v) and subsequently crystallized to separate an additional 1.08 g (total yield 5.06 g or 26%) of the diester **12**, mp 88–89.5 °C. A mixture of 3.98 g (12.6 mmol) of the diester **12**, 1.90 g (47.4 mmol) of NaOH, and 75 ml of H_2O was refluxed for 45 min and the resulting orange solution was acidified. The crude product, collected on a filter, was recrystallized from aqueous MeOH to separate 3.117 g (86%) of the diacid **10** as a pale yellow solid, mp 197 °C dec (lit.[2a] mp 200 °C dec), that was identified with a previously described sample by comparison of ir spectra.

A solution of 3.102 g (10.8 mmol) of the diacid **10** in 50 ml of THF

and 50 ml of HOAc was hydrogenated at 1 atm and 27 °C over 573 mg of 5% Pt on C catalyst until the hydrogen uptake (9.74 mmol or 0.90 equiv) ceased. The mixture was filtered and concentrated to leave 3.053 g of crude product, mp 185–203 °C dec, that was recrystallized from an acetone–hexane mixture. The yield of the diacid **2a** was 2.647 g (85%) of white needles, mp 198–206 °C dec (lit.[2a] mp 201–203 °C dec), identified with a previously described[2a] sample by comparison of NMR spectra.

In another experiment, 1.52 g of a mixture of approximately equal amounts of diacids **10** and **11** in 45 ml of MeOH containing 0.8 ml of $BF_3·Et_2O$[7] was refluxed for 14 h and then concentrated and partitioned between aqueous $NaHCO_3$ and Et_2O. The Et_2O solution was dried and concentrated to leave 645 mg of orange liquid that contained (NMR analysis) mainly the diester **12** (ca. 80% of product). Chromatography on silica gel (Et_2O–PhH eluent) separated 489 mg of the diester **12** as white needles, mp 88–90 °C. Recrystallization from MeOH afforded the pure diester **12** as white needles, mp 88.5–90.5 °C (lit.[2a] 91–91.5 °C). The aqueous phase from the reaction was acidified and extracted with CH_2Cl_2 and the organic extract was dried and concentrated to leave 751 mg of the crude acid ester **13a** as a pale yellow solid, mp 191–197 °C dec. Recrystallization from an acetone–hexane mixture afforded a sample of the acid ester **13a** as white prisms: mp 202.5–205.5 °C dec; ir (KBr pellet) 2940 (broad, carboxyl OH), 1725 (ester C=O), and 1685 cm^{-1} (carboxyl C=O); NMR (pyridine-d_5) δ 7.78 (1 H, d, J = 8.5 Hz, aryl CH), 6.97 (1 H, partially resolved multiplet, vinyl CH), 6.77 (1 H, d, J = 8.5 Hz, aryl CH), 3.93 and 3.73 (singlets, CO_2CH_3 and OCH_3), and 0.8–3.4 (multiplet, aliphatic CH). A 910-mg sample of the acid ester **13a** was heated to 220 ° under a N_2 atmosphere for 15 min at which time gas evolution ceased. Chromatography of the crude product on silica gel with a PhH–Et_2O eluent separated 642 mg (78%) of the unsaturated ester **14a**, mp 98–100 °C. Recrystallization from hexane afforded the ester **14a** as pale yellow plates: mp 100–101.5 °C; ir (CCl_4) 1730 (ester C=O) and 1640 cm^{-1} (weak, C=C); uv maxima (95% EtOH) 268 nm (ε 14 800), 275 (inflection, 12 000), and 329 (1890); NMR (CCl_4) δ 7.03 (1 H, d, J = 8 Hz, aryl CH), 6.70 (1 H, d, J = 8 Hz, aryl CH), 3.85, 3.80 (two 3 H singlets, OCH_3 and CO_2CH_3), 3.30 (2 H, broad, benzylic CH_2), 2.1–2.6 (4 H, m, allylic CH_2), and 1.5–2.0 (4 H, m, aliphatic CH_2); mass spectrum m/e (rel intensity) 258 (M$^+$, 56), 227 (35), 226 (46), 225 (31), 211 (25), 199 (36), 198 (93), 185 (35), 183 (32), 165 (50), 155 (60), 153 (66), 152 (72), 141 (83), 140 (73), 139 (80), 128 (100), 127 (78), 115 (84), and 63 (40).

Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.21; H, 7.04.

Preparation of the Diacid 1a. A. From the Diester 12. A solution of 1.84 g (5.82 mmol) of the diester **12** in 43 ml of MeOH was hydrogenated over 360 mg of 5% Pt on C catalyst at 27 °C and 1 atm of H_2 to yield 1.93 g of the crude saturated diester **2b** as pale yellow oil identified with a previously described[2a] sample by comparison of ir and NMR spectra. A 1.76-g (5.5 mmol) sample of the crude diester **2b** was epimerized and saponified by treatment with 1.55 g (38.8 mmol) of NaOH in 55 ml of boiling H_2O for 2 h. The crude acidic product was recrystallized from a PhH–hexane mixture to separate 1.41 g (88%) of the diacid **1a** as white needles, mp 187–189.5 °C dec (lit.[2a] mp 189.5–190.5 °C dec), which was identified with an authentic sample by comparison of ir spectra.

B. From the Amide 15. Following a previous procedure,[2b] a cold (0 °C) suspension of 2.692 g (10.4 mmol) of the amide **15** in 30 ml of THF was treated with 20 ml of a hexane solution containing 31.2 mmol of n-BuLi and the resulting mixture was stirred at 0 °C for 1 h and at reflux for 30 min. After the resulting orange suspension had been diluted with 30 ml of THF, it was poured onto crushed dry ice. The crude acidic product, isolated in the usual way, amounted to 1.659 g of an Et_2O-soluble fraction and 1.020 g of a less soluble fraction containing (TLC, silica gel with a $CHCl_3$–EtOAc–HCO_2H eluent, 10:10:3 v/v/v) the amide acids **1c** (R_f 0.51) and **2c** (R_f 0.41). Repeated extraction with Et_2O left 497 mg of the less soluble amide acid **2c**, mp 212–214 °C dec, that was triturated with acetone to leave 434 mg (14%) of the pure (TLC) amide acid **2c**, mp 212 °C dec (lit.[2b] mp 213–215 °C). This material was identified with a previously described sample by comparison of ir spectra. The combined Et_2O-soluble portions of the crude acidic product were concentrated to leave 2.179 g (70%) of the crude acid amide **1c** (TLC analysis). Recrystallization from EtOH afforded 1.70 g (55%) of the pure acid amide **1c** as white needles, mp 150–152 °C (lit.[2b] 152–153 °C), identified with a previously described sample by comparison of ir spectra. In the present studies, the mixture of amide acids **1c** and **2c** obtained from this metalation–carbonation procedure has consistently contained a greater amount of the amide acid **1c** whereas the stereoisomer **2c** was the predominant product in earlier work.[2b] The reason for this difference is not apparent.

A cold (ca. 15 °C) solution of 515 mg (1.70 mmol) of the amide acid **1c** and 220 mg (2.68 mmol) of NaOAc in 15 ml of HOAc was treated with 0.5 ml (ca. 7 mmol) of N_2O_4 and the resulting green solution was stirred for 15 min during which time a yellow solid separated. After the mixture had been partitioned between H_2O and CH_2Cl_2, the CH_2Cl_2 layer was dried and concentrated to leave 617 mg of the crude nitroso compound **16** as an orange liquid containing (TLC, silica gel with a $CHCl_3$–EtOAc–HCO_2H eluent, 10:10:3 v/v/v) one major component (R_f 0.68) and lacking the starting amide **1c** (R_f 0.43). The crude product was added to 25 ml of cold (0 °C) aqueous 10% NaOH and then stirred at 0 °C for 15 min and at reflux for 15 min. Gas evolution was apparent as the solution was warmed above 0 °C. The resulting dark brown solution was acidified (HCl) and extracted with CH_2Cl_2. After the CH_2Cl_2 solution had been dried and concentrated, trituration with ether left 364 mg of the crude diacid **1a** as a brown solid, mp 184–185 °C. After an acetone solution of the product had been decolorized with carbon, crystallization from acetone–hexane mixtures separated 222 mg (45%) of the diacid **1a** as a tan solid, mp 188–190 °C (lit.[2a] 189.5–190.5 °C), that was identified with a previously described sample by comparison of NMR spectra.

A mixture of 478 mg (1.65 mmol) of the diacid **1a** and 6.0 ml of Ac_2O was refluxed for 1 h and then concentrated under reduced pressure. The residue was triturated with pentane to leave 393 mg of the crude anhydride **17** as a yellow solid, mp 142–155 °C. Recrystallization from acetone–hexane separated 205 mg (46%) of the anhydride **17** as white plates: mp 159–161 °C; ir ($CHCl_3$) 1802 and 1760 cm^{-1} (anhydride C=O, absorbance ratio $A_{1760}/A_{1802} = 1.50$); NMR ($CDCl_3$) δ 7.47 (1 H, d, $J = 8$ Hz, aryl CH), 6.90 (1 H, d, $J = 8$ Hz, aryl CH), 3.8–4.3 [4 H, m, benzylic CH doublet ($J \sim 11$ Hz) at 4.13 partially resolved from a CH_3O singlet at 3.97], and 0.9–3.3 (10 H, m, aliphatic CH); uv max (Et_2O) 321 nm (ϵ 4900) with intense end absorption; mass spectrum m/e (rel intensity) 272 (M$^+$, 34), 229 (20), 228 (100), 185 (75), 171 (24), 129 (25), 128 (29), and 115 (29).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.50; H, 5.92.

After a solution of 36 mg of this anhydride **17** and 1.3 ml of H_2O in 2.0 ml of DME had been heated on a steam bath for 30 min, concentration left 36 mg of the solid acid **1a**, identified with an authentic sample by comparison of ir spectra.

In an attempt to form the anhydride from the less stable diacid **2a**, 109 mg (0.376 mmol) of the diacid **2a** was added to a solution of 97 mg (0.47 mmol) of dicyclohexylcarbodiimide in 5 ml of CH_2Cl_2. After the resulting suspension had been stirred at 25 °C for 2.5 h, it was filtered and the filtrate was concentrated to leave a yellow semisolid. The crude product was washed with pentane, dissolved in PhH and filtered (to remove dicyclohexylurea), and again concentrated to leave 62 mg (60%) of the anhydride **17** as colorless prisms, mp 156–158 °C. Recrystallization (PhH–pentane) raised the melting point of the anhydride **17** to 159–161 °C. This product was identified with the previously described sample by a mixture melting point determination and by comparison of ir and NMR spectra.

Reductive Methylation of the Diacid 1a. To a refluxing (−33 °C) solution of 758 mg (108 mg-atoms) of Li in 100 ml of liquid NH_3 was added, dropwise and with stirring during 20 min, a solution of 659 mg (2.27 mmol) of the diacid **1a** in 20 ml of THF.[8] After the addition was complete, the resulting blue reaction mixture was stirred for 5 min and then 8.0 ml (18.4 g, 128 mmol) of CH_3I was added. As the CH_3I was added the blue reaction mixture changed progressively to a white suspension, a colorless solution, and finally a green solution. After the addition was complete, the reaction mixture was stirred for 30 min and then 5 ml of CH_3OH was added followed by 5 ml of H_2O and the NH_3 was allowed to evaporate. The remaining mixture was concentrated under reduced pressure, diluted with 50 ml of cold water, acidified to pH 4 with aqueous 1 M HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried and concentrated to leave 733 mg of crude yellow semisolid. Trituration of this residue with Et_2O left 351 mg (50.5%) of the crude diacid **18** as a white solid, mp 175–176 °C dec. The Et_2O-soluble material from this separation contained (NMR analysis) little, if any, of either methylated diacid **18** or **22**. Recrystallization from MeOH separated the diacid **18** as white prisms: mp 180–181.5 °C dec; ir (KBr pellet) 2920 (broad, associated OH), 1710 (broad, carboxyl C=O), and 1660 cm^{-1} (C=C); uv (95% EtOH), end absorption with ϵ 3900 at 210 nm; NMR (pyridine) δ 4.90 (1 H, t, $J = 3.5$ Hz, vinyl CH), 3.3–3.8 (4 H, m, $CHCO_2R$ and CH_3O singlet at 3.56), and 1.0–3.3 (15 H, m, aliphatic CH including a CH_3 singlet at 1.90); mass spectrum m/e (rel intensity) 262 (33), 247 (20), 218 (100), 203 (87), and 91 (97). Reaction of 622 mg (2.04 mmol) of the crude diacid **18** with excess ethereal CH_2N_2 yielded 678 mg (99%) of the crude diester **19**. Recrystallization from Et_2O–hexane afforded 580 mg (85%) of the pure diester **19** as white prisms: mp 145.5–147 °C; ir (CCl_4) 1740 (ester C=O), 1690 (enol ether C=C), and 1655 cm^{-1} (C=C); uv (95%

EtOH) end absorption with ϵ 3900 at 210 nm; NMR ($CDCl_3$) δ 4.82 (1 H, t, $J = 3.5$ Hz, vinyl CH), 3.63, 3.60, 3.56 (three 3 H, s, OCH_3 and CO_2CH_3), 3.1–3.3 (1 H, m, $CHCO_2R$), 2.2–3.0 (4 H, m, allylic and aliphatic CH), and 1.0–2.0 (11 H, m, aliphatic CH including a CH_3 singlet at 1.47); mass spectrum m/e (rel intensity) 334 (M$^+$, 0.5), 275 (11), 274 (11), 216 (47), 215 (100), 173 (70), 159 (68), 141 (62), 129 (65), 128 (68), 115 (68), 91 (56), and 59 (43). Measurement of the NMR spectrum ($CDCl_3$) of the diester **19** with irradiation at δ 2.8 to decouple the allylic CH and CH_2 protons from the C-9 proton left the signal for this C-9 proton as a doublet ($J = 4$ Hz) at δ 3.18 corresponding to the coupling constant between protons at C-9 and C-1a.

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.99; H, 7.71.

Preparation of the Keto Diester 20. Following the general procedure of Lowenthal and co-workers,[3a] 89 mg (0.27 mmol) of the enol ether **19** was dissolved in a warm mixture of 0.5 ml of MeOH, 0.3 ml of THF, and 0.08 ml of H_2O and the solution was treated with 0.2 ml of aqueous 12 M HCl. The resulting solution was allowed to stand for 3 h and then concentrated under reduced pressure and partitioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic phase was dried and concentrated to leave 94 mg of pale yellow liquid that was chromatographed on acid-washed silica gel with a PhH–Et_2O (9:1 v/v) eluent. The chromatographic fractions (76 mg, 89%) containing (TLC) the keto diester **20** crystallized as a white solid, mp 63.5–65.5 °C. Recrystallization from Et_2O–pentane separated the pure keto diester **20** as white prisms: mp 66–67 °C; ir (CCl_4) 1740 (ester C=O) and 1720 cm^{-1} (C=O); uv (95% EtOH) end absorption with ϵ 3800 at 210 nm and a maximum at 310 nm (ϵ 69); NMR ($CDCl_3$) δ 3.65 (6 H, s, CO_2CH_3), 2.2–3.7 (7 H, m, CH_2CO, allylic CH and CH_2, bridgehead CH, and $CHCO_2R$), and 1.0–2.0 (11 H, m, aliphatic CH including a CH_3 singlet at 1.44); mass spectrum m/e (rel intensity) 320 (M$^+$, 9), 305 (12), 273 (18), 261 (100), 260 (95), 201 (82), 159 (33), 91 (18), and 43 (42).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.31; H, 7.60.

In an alternative procedure, a solution of 235 mg (0.703 mmol) of the enol ether **19** and 0.2 ml of H_2O in 10 ml of trifluoroacetic acid was allowed to stand for 16 h and then concentrated under reduced pressure. After following the previously described isolation procedure, the crude product (251 mg of yellow solid) was recrystallized from Et_2O–pentane to separate 107 mg (48%) of the keto diester **20** as white prisms, mp 63.5–64.5 °C. An attempt to effect this hydrolysis with a mixture of 10 ml of DME and 5 ml of aqueous 50% HOAc at 25 °C for 40 h resulted in recovery of the starting enol ether **19**. Attempts to form a lactone by reaction of the enol ether **19** with trifluoroacetic acid at 25 °C for 16 h or with a refluxing mixture of 1 ml of THF and 0.1 ml of aqueous 50% H_2SO_4 converted the enol ether **19** to the keto diester **20**. Although ir absorption at 1780 cm^{-1} was observed in the THF–H_2SO_4 reaction, the lactone band apparently arose from degradation of the THF. Attempts to form a lactone from the keto diester **20** by reaction with TsOH in refluxing PhH or by reaction with refluxing trifluoroacetic acid resulted in recovery of the starting material (ir and TLC analyses) with no ir evidence for the formation of a γ-lactone.

Preparation of the Anhydride 21. A solution of 204 mg (0.668 mmol) of the diacid **18** and 162 mg (0.787 mmol) of dicyclohexylcarbodiimide in 7.0 ml of CH_2Cl_2 was stirred at 25 °C for 2 h during which time a white precipitate of dicyclohexylurea separated. The mixture was filtered and the filtrate was concentrated and triturated with pentane to leave 218 mg of a pale yellow solid. A solution of this material in PhH was centrifuged to remove additional insoluble dicyclohexylurea and then diluted with pentane and cooled to crystallize 143 mg (74.5%) of the anhydride **21** as white needles, mp 145–147 °c dec. The semisolid residue (15 mg) recovered from the mother liquors contained (ir analysis) the same anhydride **21**. Recrystallization from EtOAc gave the anhydride **21** as white needles: mp 148–150 °C dec (dependent on rate of heating); ir ($CHCl_3$) 1808 and 1765 cm^{-1} (anhydride C=O, absorbance ratio $A_{1765}/A_{1808} = 1.43$); NMR ($CDCl_3$) δ 4.88 (1 H, t, $J = 3.5$ Hz, vinyl CH), 3.4–3.8 (4 H, m, $CHCO_2R$ and a CH_3O singlet at 3.66), 2.3–3.0 (4 H, m, CH and allylic CH_2), and 0.8–2.3 (11 H, m, aliphatic CH including a CH_3 singlet at 1.58); mass spectrum m/e (rel intensity) 288 (M$^+$, 1), 260 (38), 217 (31), 216 (100), 215 (31), 201 (48), 185 (38), 174 (50), and 173 (68).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.83, H, 7.02.

A solution of 62 mg (0.22 mmol) of the anhydride **21** in 2.0 ml of THF and 1 ml of H_2O was stirred at 25 °C for 8.5 h during which time a white solid separated. After the mixture had been concentrated and extracted with CH_2Cl_2, the CH_2Cl_2 extract was dried and concentrated to leave 66 mg (100%) of the diacid **1a**, mp 178 °C dec, that was identified with an authentic sample by comparison of ir and NMR spectra.

Reductive Methylation of the Diacid 2a. The same procedure

used with the diacid 1a was followed with a solution of 862 mg (2.98 mmol) of the diacid 2a in 20 ml of THF being added during 20 min[8] to a solution of 949 mg (135 mg-atoms) of Li in 100 ml of liquid NH_3. After reaction with 10.0 ml (22.8 g, 161 mmol) of CH_3I and the previously described isolation procedure, the crude acidic product was obtained as 884 mg of yellow semisolid. Trituration with Et_2O left 360 mg of the diacid 22 as a white solid, mp 180–190 °C dec. The Et_2O-soluble material from this separation contained (NMR analyses) little, if any, of either of the methylated diacids 18 or 22. The crude diacid was recrystallized from EtOH to separate the diacid 22 as white prisms: mp 199–201 °C dec; ir (KBr pellet) 2920 (broad, associated OH), 1700 (broad, carboxyl C=O), 1660 and 1655 cm^{-1} (shoulder) (C=C); uv (95% EtOH) end absorption with ε 4200 at 210 nm; NMR (pyridine) δ 4.86 (1 H, t, J = 3.5 Hz, vinyl CH), 3.93 (1 H, doublet, J = 7 Hz, of multiplets, $CHCO_2R$), 3.55 (3 H, s, OCH_3), 1.82 (3 H, s, CH_3), and 1.1–3.1 (12 H, m, aliphatic CH); mass spectrum m/e (rel intensity) 262 (100), 247 (33), 219 (45), 217 (31), 91 (34), and 44 (55). Because of the thermal instability of the diacid 22, it was converted to the diester 23 for further characterization. Reaction of 270 mg (0.88 mmol) of the diacid 22 with excess ethereal CH_2N_2 yielded 284 mg (97%) of the crude diester 23. Recrystallization from ether–hexane afforded 225 mg (77%) of the pure diester 23 as white prisms: mp 126–128 °C; ir (CCl_4) 1738 (ester C=O), 1690 (enol ether C=C), and 1658 cm^{-1} (C=C); uv (95% EtOH) end absorption with ε 4000 at 210 nm; NMR ($CDCl_3$), δ 4.83 (1 H, t, J = 3.5 Hz, vinyl CH), 3.66, 3.63, 3.56, (three 3 H, s, OCH_3 and CO_2CH_3), 3.4–3.7 (1 H, m, $CHCO_2R$), 2.3–3.0 (4 H, m, allylic and aliphatic CH), and 1.1–1.9 (11 H, m, aliphatic CH including a CH_3 singlet at 1.39); mass spectrum m/e (rel intensity) 334 (M+, 1), 275 (15), 274 (15), 216 (31), 215 (100), and 59 (30).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.19; H, 7.79.

A mixture of 52 mg (0.17 mmol) of the diacid 22, 0.5 ml of HOAc, 0.5 ml of H_2O, 0.3 ml of aqueous 1 M HCl, and 2 ml of DME was stirred at 25 °C for 5.5 h and then concentrated under reduced pressure. The crude keto acid 28, 48 mg of tan semisolid, had the following spectral properties: ir (liquid film) 2500–3500 (broad, associated OH), 1725 (C=O), and 1705 cm^{-1} (carboxyl C=O); uv (95% EtOH), end absorption.

To a solution of NaOMe, prepared from 55 mg (2.4 mg-atoms) of Na and 4 ml of MeOH, was added a solution of 50 mg (0.15 mmol) of the enol ether 23 in 1.5 ml of MeOH. The resulting solution was allowed to stand for 3 days and then concentrated under reduced pressure and extracted with Et_2O. The Et_2O extract was concentrated and the residual semisolid (61 mg) was chromatographed on acid-washed silica gel with a PhH–Et_2O (93:7 v/v) eluent. The crude epimeric diester 29 (TLC analysis) was eluted as 24 mg of a pale yellow oil: ir (CCl_4) 1740 (ester C=O), 1694 (enol C=C), and 1660 cm^{-1} (C=C); uv (95% EtOH) end absorption with ε 4000 at 210 nm; NMR ($CDCl_3$) δ 4.84 (1 H, t, J = 3 Hz, vinyl CH), three 3 H singlets at 3.69, 3.66, 3.57 (CO_2CH_3 and OCH_3), 2.1–3.2 (5 H, m, $CHCO_2R$, allylic CH and CH_2, and bridgehead CH), and 1.0–2.0 (11 H, m, aliphatic CH including a CH_3 singlet at 1.32). The NMR spectrum of the crude reaction product before chromatography indicated the presence of the starting diester 23 and the epimer 29 but lacked absorption at δ 1.47 corresponding to the CH_3 singlet of the isomeric diester 19.

Preparation of the Keto Diester 24. The previously described hydrolysis and isolation procedures were followed with 79 mg (0.24 mmol) of the enol ether 23, 0.45 ml of MeOH, 0.25 ml of THF, 0.06 ml of H_2O, and 0.2 ml of aqueous 12 M HCl. Chromatography of the crude product (80 mg of yellow liquid) on silica gel separated 56 mg (73%) of the keto diester 24 as a pale yellow liquid: ir (CCl_4) 1740 (ester C=O) and 1720 cm^{-1} (C=O); uv (95% EtOH) end absorption with ε 3900 at 210 nm and a maximum at 295 nm (ε 92); NMR ($CDCl_3$) δ 3.70 (3 H, s, CO_2CH_3), 3.65 (3 H, s, CO_2CH_3), 3.3–3.7 (1 H, m, $CHCO_2R$), 2.2–3.3 (6 H, m, allylic CH and CH_2, $COCH_2$, and bridgehead CH), and 1.1–1.9 (11 H, m, aliphatic CH including a CH_3 singlet at 1.35); mass spectrum m/e (rel intensity) 320 (M+, 6), 288 (30), 261 (51), 260 (100), 202 (18), 201 (99), 173 (20), 159 (22), 91 (16), and 43 (46).

Anal. Calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 67.34; H, 7.55.

Hydrolysis of 190 mg (0.568 mmol) of the enol ether 23 with 3 ml of trifluoroacetic acid containing 0.2 ml of H_2O followed by chromatography of the crude product (192 mg) afforded 156 mg (86%) of the keto diester 24 as a pale yellow liquid.

Preparation of the Anhydride 25. A mixture of 159 mg (0.52 mmol) of the diacid 22, 129 mg (0.627 mmol) of dicyclohexylcarbodiimide, and 7.0 ml of CH_2Cl_2 was stirred at 25 °C for 2.5 h. After the resulting suspension had been filtered, the filtrate was concentrated, dissolved in PhH, filtered, and diluted with pentane. The anhydride 25 separated as 96 mg (64%) of white needles, mp 127–130 °C. Re-

crystallization from PhH–pentane gave the pure anhydride 25: mp 128–130 °C; ir ($CHCl_3$) 1805 and 1764 cm^{-1} (anhydride C=O, absorbance ratio A_{1764}/A_{1805} = 1.55); NMR ($CDCl_3$) δ 4.90 (1 H, t, J = 3.5 Hz, vinyl CH), 3.6–4.1 (4 H, m, $CHCO_2R$ and a CH_3O singlet at 3.67), 2.7–3.1 (4 H, m, CH and allylic CH_2), and 0.8–1.9 (11 H, m, aliphatic CH including a CH_3 singlet at 1.50); mass spectrum m/e (rel intensity) 288 (M+, 2), 260 (70), 242 (45), 217 (51), 216 (100), 215 (38), 201 (41), 199 (39), 185 (42), 174 (48), and 173 (80).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.53; H, 7.06.

A solution of 33 mg (0.12 mmol) of the anhydride 25 and 0.2 ml of H_2O in 1.0 ml of THF was stirred at 25 °C for 6 h and then concentrated under reduced pressure. The residual diacid 22 (35 mg or 100% of white solid, mp 190 °C dec) was identified with the previously described sample by comparison of ir and NMR spectra.

Other Reduction and Reduction–Methylation Reactions. A. Amide 36. The N-methyl amide 36 of o-methoxybenzoic acid was prepared from the corresponding acid chloride in 77% yield as a colorless liquid: bp 128–129 °C (0.9 mm); n^{25}D 1.5638 [lit. bp 175 °C (14 mm),[9a] 127–129 °C (1 mm)[9b]]; ir (liquid film) 3410 (NH) and 1645 cm^{-1} (amide C=O); NMR ($CDCl_3$) δ 8.17 (1 H, d of d, J = 7.5 and 2.5 Hz, aryl CH), 7.82 (1 H, broad, NH), 6.8–7.6 (3 H, m, aryl CH), 3.85 (3 H, s, OCH_3), and 2.95 (3 H, d, J = 5 Hz, NCH_3).

To a solution of 3.00 g (18.2 mmol) of the amide 36 in 45 ml of THF and 200 ml of liquid NH_3 was added 565 mg (81.5 mg-atoms) of Li. The resulting dark blue solution was stirred under reflux for 2 h and then 5.0 ml of CH_3I was added. The resulting yellow suspension was stirred under reflux for 30 min and then diluted successively with 25 ml of MeOH and with 25 ml of H_2O. After the NH_3 had evaporated, the remaining mixture was concentrated and partitioned between H_2O and CH_2Cl_2. The organic solution was dried and concentrated under reduced pressure to leave 2.195 g of yellow-brown liquid with NMR and ir absorption indicating the major products to be a mixture of the N-methylimines 37. A 1.00-g portion of the crude product was distilled to separate 213 mg of bright yellow liquid, bp 37–65 °C (0.7–1.0 mm), n^{25}D 1.5434–1.5534, containing (NMR and ir analysis) primarily the imine 37a:[10] ir (CCl_4) 1655 (s) and 1640 cm^{-1} (w) (C=N of both isomers); uv (95% EtOH) end absorption with ε 15 300 at 210 nm and a maximum at 245 nm (ε 14 400); NMR ($CDCl_3$) δ 8.1–8.3 (1 H, m, CH=N), 6.6–7.7 (5 H, m, aryl CH), and 3.48 (3 H, d, J = 1.5 Hz, NCH_3) with a weak doublet (J = 1.5 Hz) at δ 3.42 corresponding to a second imine isomer; mass spectrum m/e (rel intensity) 119 (M+, 87), 118 (100), 91 (29), 78 (25), 77 (36), 51 (21), and 42 (60). Reaction of a sample of this crude imine 37a with 2,4-dinitrophenylhydrazine and HCl in EtOH gave a sample of benzaldehyde 2,4-dinitrophenylhydrazone as orange needles from EtOH, mp 238–239 °C. This material was identified with an authentic sample (mp 238–239 °C) by a mixture melting point. The later fraction from the distillation, 553 mg of yellow liquid, bp 65–69 °C (0.7 mm), contained (ir and NMR analysis) mainly the second component believed to be the imine 37b accompanied by a minor amount of the imine 37c. Reaction with 2,4-dinitrophenylhydrazine yielded a crude 2,4-dinitrophenylhydrazone as orange-red needles, mp 251–254 °C. This material appears to be a mixture of the 2,4-dinitrophenylhydrazones of salicylaldehyde and o-methoxybenzaldehyde. When the reduction was repeated with the amide anion, formed from reaction of the amide 36 with n-BuLi before reaction with Li in liquid NH_3, the major reduction product (ir and NMR analysis) was again a mixture of the imines 37.

B. Acid 38. After a solution of 1.036 g (6.82 mmol) of the acid 38 in 10 ml of THF had been added to 50 ml of liquid NH_3, the resulting white suspension was treated, portionwise and with stirring, with 167 mg (24.1 mg-atoms) of Li. The reaction mixture changed successively from a white suspension to a colorless solution, then to a yellow solution, and finally to a blue solution. This cold (−33 °C) blue solution was treated with 4.56 g (32.1 mmol) of MeI and the resulting pale yellow solution was stirred at −33 °C for 90 min and then treated with 2 ml of H_2O. After the NH_3 had evaporated, the residue was partitioned between cold (0 °C) dilute aqueous HCl and CH_2Cl_2 and the organic phase was washed with aqueous NaCl, dried, and concentrated. The residual yellow oil (a mixture of acids 39a and 40a) was esterified with excess ethereal CH_2N_2 and this resulting solution was washed with aqueous $NaHCO_3$, dried, and concentrated. An aliquot of the residual neutral product (1.078 g of pale orange liquid) was mixed with a known weight of internal standard (naphthalene) and analyzed by GLC (LAC-728 on Chromosorb P). The product contained ester 39b (retention time 8.0 min, 47% yield), naphthalene (19.0 min), and ester 40b (25.2 min, 27% yield). The same general procedure was repeated with 1.059 g (7.02 mmol) of acid 38, 10 ml of THF, 50 ml of liquid NH_3, 528 mg (23.0 mg-atoms) of Na, and 4.56 g (32.1 mmol) of MeI. After following the same isolation and analysis procedures,

the yields of esters **39b** and **40b** were 31 and 41%, respectively. Thus, the demethoxylation side reaction leading to by-product **39** is less serious when the reduction is effected with Na rather than Li.

To identify the reaction products, the reduction was repeated with 10.0 g (69.7 mmol) of acid **38**, 300 ml of liquid NH_3, 75 ml of THF, 1.584 g (226 mg-atoms) of Li, and 34.2 g (240 mmol) of MeI. After esterification with CH_2N_2, the crude neutral product (11.62 g) was fractionally distilled through a 15-cm Vigreux column. From the early fractions [3.49 g, bp 85–86 °C (18 mm)] containing (GLC) mainly the ester **39b**, a pure sample of the ester **39b** was collected as a colorless liquid: $n^{25}D$ 1.4732; ir (CCl_4) 1734 cm^{-1} (ester C=O); uv (95% EtOH) end absorption with ϵ 1400 at 210 nm; NMR (CCl_4) δ 5.5–6.0 (4 H, m, vinyl CH), 3.60 (3 H, s, OCH_3), 2.4–2.8 (2 H, m, allylic CH_2), 1.26 (3 H, s, CH_3); mass spectrum *m/e* (rel intensity) 152 (M$^+$, 4), 93 (100), 92 (27), 91 (38), 77 (41), and 39 (14).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.00; H, 7.95.

After separation of an intermediate distillation fraction [1.35 g, bp 86–121 °C (18 min), a mixture of **39b** and **40b**], the final distillation fraction [4.09 g, bp 121–143 °C (18 min)] contained (GLC) mainly the ester **40b** accompanied (ir and NMR analysis) by some of the acid **39a**. This fraction was reextracted with aqueous $NaHCO_3$ and redistilled to separate 1.945 (15%) of the ester **40b** as a colorless liquid, bp 113–116 °C (16 min).[11] A collected (GLC) sample of the ester **40b** was obtained as a colorless liquid: $n^{25}D$ 1.4829; ir (CCl_4) 1740 (ester C=O), 1690 (enol ether C=C), and 1650 cm^{-1} (C=C); NMR (CCl_4) δ 5.2–5.9 (2 H, m, vinyl CH), 4.64 (1 H, t, J = 3 Hz, enol ether vinyl CH), 3.59 (3 H, s, OCH_3), 3.52 (3 H, s, OCH_3), 2.6–2.9 (2 H, m, allylic CH_2), and 1.33 (3 H, s, CH_3); uv max (95% EtOH) 272 nm (ϵ 53) with intense end absorption (ϵ 2360 at 210 nm); mass spectrum *m/e* (rel intensity) 182 (M$^+$, 8), 123 (100), 108 (25), and 91 (18).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.65; H, 7.64.

C. **Diacid 31.** To a cold (−33 °C) suspension of 10.0 g (47.7 mmol) of the diacid **31a** in 600 ml of liquid NH_3 containing 10 ml of H_2O was added, portionwise and with stirring during 60 min, 2.701 g (386 mg-atoms) of Li. An additional 10 ml of H_2O was added and this mixture was stirred overnight while the NH_3 was allowed to evaporate. A solution of the residue in H_2O was filtered, cooled in ice, and acidified with aqueous 12 M HCl. The resulting cold suspension (total volume 200 ml) was filtered to separate 9.6 g of the crude acids **32a** and **33a** as a tan solid. To analyze this mixture of acids **32a** and **33a**, an aliquot was esterified with excess ethereal CH_2N_2; the crude neutral product, a mixture of esters **32b** and **33b**, exhibited NMR peaks (CCl_4) at δ 3.67 (CH_3O of ester **32b**) and 3.57 (CH_3O of ester **33b**).

A commercial sample of the anhydride **30** was recrystallized from concentrated aqueous HNO_3 to separate the pure anhydride **30** as white needles: mp 273–274 °C (lit.[12] mp 274 °C); ir ($CHCl_3$) 1775 and 1737 cm^{-1} (anhydride C=O, absorbance ratio A_{1737}/A_{1775} = 0.86). Following a previously described procedure,[13] the anhydride **30** was dissolved in methanolic KOH and this solution was treated simultaneously with MeOH solutions of $(MeO)_2SO_2$ and of KOH. The neutral product was crystallized from MeOH to separate the diester **31b** as white needles: mp 100–101 °C (lit.[13] mp 102 °C) ir (CCl_4), 1728 cm^{-1} (ester C=O); uv max (95% EtOH) 299 nm (ϵ 3500); NMR (CCl_4), δ 7.2–8.0 (6 H, m, aryl CH) and 3.81 (6 H, s, OCH_3).

Alternatively, mixtures of the esters could be analyzed by GLC (Silicone, fluid, No. 710, on Chromosorb P) with the following retention times being observed for the esters: **32b**, 13.8 min; **33b**, 15.0 min; and **31b**, 31.8 min.

The crude product from the reduction contained (NMR analysis of the diesters) ca. 90% of acid **32a** and ca. 10% of acid **33a**. A 1.289-g aliquot of this mixture was fractionally recrystallized from MeOH to separate 451 mg of the pure (NMR analysis of diester) acid **32a** as white prisms: mp 218–223 °C dec (dependent on rate of heating); ir (KBr pellet) 1720, 1695 (carboxyl C=O), 1665, and 1630 cm^{-1} (C=C); uv (95% EtOH) end absorption with ϵ 1330 at 210 nm; NMR (pyridine-d_5) δ 13.0 (2 H, s, OH), 5.7–6.4 (4 H, m, vinyl CH), 4.4–4.9 (2 H, m, $CHCO_2R$), and 2.5–2.8 (4 H, m, allylic CH_2).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.53; H, 5.53.

To a cold (−33 °C) solution of $NaNH_2$, from 430 mg (18.7 mg-atoms) of Na and 180 ml of liquid NH_3, was added 1.54 g (7.00 mmol) of a mixture of diacids (ca. 80% of **32a** and 20% of **33a**). After the resulting gray-green suspension had been stirred at −33 °C for 1.5 h, a solution of 100 mg (5.6 mmol) of H_2O in THF was added, dropwise and with stirring during 1.5 h. Then 5 ml of H_2O was added, the NH_3 was allowed to evaporate, and a solution of the residue in 50 ml of cold (0 °C) H_2O was filtered and acidified with cold aqueous 12 M HCl. The crystalline acid that separated was collected as 1.252 g of tan solid containing (NMR analysis of diesters) ca. 67% of diacid **33a** and ca. 33% of diacid **32a**. Fractional recrystallization of an 836-mg aliquot

of this mixture from MeOH separated 230 mg of the pure (NMR analysis of the diester) diacid **33a** as white prisms: mp 211–215 °C dec (dependent on rate of heating); ir (KBr pellet) 1710 and 1685 cm^{-1} (carboxyl C=O); uv (95% EtOH) end absorption with ϵ 1320 at 210 nm; NMR (pyridine-d_5) δ 11.9 (2 H, broad, OH), 5.8–6.5 (4 H, m, vinyl CH), 3.9–4.3 (2 H, m, $CHCO_2R$), and 2.5–2.9 (4 H, m, allylic CH_2).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.46; H, 5.49.

A mixture of approximately equal amounts of the diacids **32a** and **33a** was esterified with excess ethereal CH_2N_2 and this crude neutral product was chromatographed on silica gel with an Et_2O–PhH eluent (1:49 v/v). The initial chromatographic fractions were recrystallized from Et_2O–hexane mixtures to separate the pure diester **32b** as white needles: mp 71–72.5 °C; ir (CCl_4) 1740 (ester C=O) and 1665 cm^{-1} (weak, C=C); uv (95% EtOH) end absorption with ϵ 1090 at 210 nm; NMR (CCl_4) δ 5.5–6.1 (4 H, m, vinyl CH), 3.5–3.9 (8 H, m, $CHCO_2R$ with a CH_3O singlet at 3.67), and 2.5–2.8 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 248 (M$^+$, 4), 216 (28), 188 (26), 156 (10), 129 (100), and 128 (25).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.49; H, 6.56.

The later chromatographic fractions were recrystallized from Et_2O–hexane to separate the pure diester **33b** as white prisms: mp 124–126 °C; ir (CCl_4) 1740 (ester C=O) and 1665 cm^{-1} (C=C); uv (95% EtOH) end absorption with ϵ 1050 at 210 nm; NMR (CCl_4) δ 5.5–6.1 (4 H, m, vinyl CH), 3.4–3.8 (8 H, m, $CHCO_2R$ with a CH_3O singlet at 3.57), and 2.5–3.0 (4 H, m, allylic CH_2); mass spectrum *m/e* (rel intensity) 248 (M$^+$, 5), 216 (7), 189 (16), 188 (14), 129 (100), and 128 (21).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.58.

After a suspension of 162 mg (0.74 mmol) of the anti diacid **32a** in 5 ml of CH_2Cl_2 containing 163 mg (0.79 mmol) of dicyclohexylcarbodiimide had been stirred at 25 °C for 75 min, the mixture was filtered to remove dicyclohexylurea. The yellow filtrate was concentrated under reduced pressure and triturated with pentane to leave 163 mg of the crude syn anhydride **34** as a yellow solid, ir ($CHCl_3$) 1804 and 1762 cm^{-1} (anhydride C=O). This crude product was stirred at 25 °C with 2 ml of DME and 1 ml of aqueous 3 M HCl for 10 h and the concentrated under reduced pressure and washed with H_2O. The residual red-brown solid (134 mg) was combined with additional material obtained from extraction of the aqueous washings with CH_2Cl_2 and the total crude product (154 mg) was esterified with excess ethereal CH_2N_2. After this mixture had been filtered and concentrated, the residue amounted to 121 mg of yellow solid with ir and NMR absorption corresponding to the syn diester **33b**. Analysis (GLC, Silicone, fluid, No. 710, on Chromosorb P) indicated the presence of the syn diester **33b** (retention time 13.3 min) accompanied by four minor, unidentified impurities (7.8, 12.1, 15.6, and 24.2 min). After an aliquot of the crude esterified product had been mixed with a known amount of internal standard (n-$C_{24}H_{50}$, retention time 29.5 min), the calculated (GLC) yield of the syn diester **33b** was 31%.[14] A collected (GLC) sample of the peak corresponding in retention time to the syn diester **33b** was identified with an authentic sample by comparison of ir spectra. In another comparable experiment, the crude syn anhydride **34** was partially purified by adding pentane to a $CHCl_3$ solution of the crude anhydride and by sublimation under reduced pressure at 85 °C. This partially purified solid anhydride **34** exhibited NMR Peaks ($CDCl_3$) at δ 6.0–6.3 (ca. 4 H, m, vinyl CH), 3.7–4.2 (ca. 2 H, m, allylic CHCO), and 2.5–2.9 (ca. 4 H, m, allylic CH_2) with ir absorption ($CHCl_3$) at 1804 and 1762 cm^{-1} (anhydride C=O, absorbance ratio, A_{1762}/A_{1804} = 1.69). As a control experiment to demonstrate that the anti acid **32a** was not epimerized by the hydrolysis conditions, a suspension of 105 mg (0.48 mmol) of the anti acid **32a** in 2 ml of DME and 1 ml of aqueous 3 M HCl was stirred for 10 h at 25 °C and then subjected to the previously described isolation and esterification procedures. The final neutral product obtained was 101 mg (85%) of the anti diester **32b**, mp 71–71.5 °C, that was identified with an authentic sample by GLC analysis and comparison of ir spectra.

A suspension of 119 mg (0.54 mmol) of the syn diacid **33a** in 5 ml of CH_2Cl_2 containing 125 mg (0.61 mmol) of dicyclohexylcarbodiimide was stirred at 25 °C for 75 min and then subjected to the previously described isolation procedure. The crude syn anhydride **34** (121 mg of yellow solid with ir absorption corresponding to the previously described sample) was hydrolyzed at 25 °C for 10 h with 2 ml of DME and 1 ml of aqueous 3 M HCl and subjected to the previously described isolation and esterification procedure. The crude neutral product (95 mg of yellow solid) contained (GLC) the syn diester **33b** accompanied by the same minor impurities noted in the preparation from the anti-acid. After an aliquot of this neutral product had been mixed with a known amount of internal standard (n-$C_{24}H_{50}$), the calculated (GLC) yield of the syn diester **33b** was 25%.[14]

References and Notes

(1) This research has been supported by Public Health Service Grant RO1-GM-20197 from the National Instiute of General Medical Science. The execution of this research was also assisted by Institution Research Grants from the National Science Foundation for the purchase of a mass spectrometer and a Fourier transform NMR spectrometer.

(2) (a) H. O. House, T. M. Bare, and W. E. Hanners, *J. Org. Chem.*, 34, 2209 (1969); (b) H. O. House, W. E. Hanners, and E. J. Racah, *ibid.*, 37, 985 (1972).

(3) (a) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Lowenthal, *J. Org. Chem.*, 34, 126 (1969); (b) M. D. Bachi, J. W. Epstein, and H. J. E. Lowenthal, *Tetrahedron Lett.*, 5333 (1966).

(4) Cf. H. O. House, C. B Hudson, and E. J. Racah, *J. Org. Chem.*, 37, 989 (1972).

(5) (a) W. G. Dauben and W. W. Epstein, *J. Org. Chem.*, 24, 1595 (1959); (b) F. H. Marquardt, *J. Chem. Soc. B*, 1242 (1966); (c) C. Fayat and A. Foucaud, *C. R. Acad. Sci., Ser. B*, 263, 860 (1966); (d) L. J. Bellamy, "Advances in Infrared Group Frequencies", Methuen, England, 1968, pp 128–131; (e) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy", 2d ed, Academic Press, New York, N.Y., 1975, pp 297–298.

(6) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated MgSO$_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The ^{1}H NMR spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60-A NMR spectrometer and the ^{13}C NMR spectra were determined at 100 MHz with a JEOL Fourier transform spectrometer, Model PFT-100. The chemical shift values are expressed in δ values (ppm) relative to a Me$_4$Si internal standard. The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-7 or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or reactive organometallic intermediates were performed under a nitrogen atmosphere.

(7) The esterification procedure of J. L. Marshall, K. C. Erickson, and T. K. Folsom [*Tetrahedron Lett.*, 4011 (1970)] was used.

(8) This slow addition of a solution of the diacid was necessary to minimize formation of a by-product resulting from protonation of the initially formed carbanion before the CH$_3$I was added.

(9) (a) P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 924 (1964); (b) J. A. Faust, L. H. Jules, and M. Sahyun, *J. Am. Pharm. Assoc.*, 45, 514 (1956).

(10) (a) R. B. Moffett [*Org. Synth.*, 34, 65 (1954)] reports bp 92–93 °C (34 mm) and n^{25}D 1.5497 for the imine 37a. (b) The imine 37a is reported to have NMR peaks (CCl$_4$) at δ 8.24 (CH=N) and 3.45 (CH$_3$) by D. Y. Curtin, E. J. Grubbs, and C. J. McCarty, *J. Am. Chem. Soc.*, 88, 2775 (1966). (c) This imine 37a has an ir band at 1645 cm^{-1} [F. H. Suydam, *Anal. Chem.*, 35, 193 (1963)] with a uv maximum (EtOH) at 246 nm (ε 19 400) [P. Brocklehurst, *Tetrahedron*, 18, 299 (1962)].

(11) The initial characterization of this ester was performed in our laboratories by Dr. Thomas M. Bare.

(12) C. Graebe and E. Gfeller, *Ber.*, 25, 652 (1892).

(13) T. A. Geissman and V. Tulagin, *J. Am. Chem. Soc.*, 66, 716 (1944).

(14) Since both esters 32b and 33b undergo partial decomposition under the conditions of our GLC analysis, we regard these yields as minimum values.

Crown Ether Catalyzed Synthesis of Dialkylvinylidenecyclopropane Derivatives[1]

Tadashi Sasaki,* Shoji Eguchi, Masatomi Ohno, and Fumiyasu Nakata

Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

Received January 20, 1976

In the phase-transfer catalyzed synthesis of dimethylvinylidenecyclopropanes from 3-chloro-3-methyl-1-butyne (1a) and olefins in the presence of 51% aqueous potassium hydroxide, the effect of crown ethers as the catalyst was examined in comparison with quaternary ammonium salts such as benzyltriethylammonium chloride. Crown ethers such as dibenzo-18-crown-6, dicyclohexyl-18-crown-6, and 18-crown-6 were found to be more effective catalysts than quaternary ammonium salts. Application of this method to the synthesis of some new dimethyl- and pentamethylenevinylidenecyclopropane derivatives has been described.

Recently it has been reported that the phase-transfer catalyzed generation of dimethylvinylidenecarbene can be carried out effectively by using appropriate quaternary ammonium salts such as benzyltriethylammonium chloride (BTAC)[2,3] and tricaprylylmethylammonium chloride (Aliquat-336)[4,5] as the catalyst. This method provides a facile synthesis of dimethylvinylidenecyclopropanes from 3-chloro-3-methyl-1-butyne (1a)[2–4] or 1-bromo-3-methyl-1,2-butadiene[5] and appropriate olefins compared to the noncatalyzed method.[6] However, quaternary ammonium salts are not always satisfactory catalysts. For example, the yields of dimethylvinylidenecyclopropanes are much lower for olefinic substrates having hydrophilic or potentially hydrophilic functions such as hydroxyl, ester, and pyridyl groups.[2a] As shown in this paper, certain crown ethers, which are powerful complexing agents for alkali metal cations, and provide highly reactive and unsolvated anions,[7,8] may be more effective or at least as effective catalysts as quaternary ammonium salts in the phase-transfer catalyzed synthesis of dialkylvinylidenecyclopropanes.[9,10]

Results and Discussion

The Catalytic Effect of Crown Ethers on Dimethylvinylidenecyclopropanation of Styrene.

In order to compare the catalytic effect of crown ethers with quaternary ammonium salts, dimethylvinylidenecyclopropanation of styrene was investigated under two-phase reaction conditions by using 18-crown-6 and BTAC as the catalyst. The reaction was carried out by slow addition of 1a (10 mmol) in benzene (5 ml) to a vigorously stirred mixture of 51% aqueous potassium hydroxide (30 ml), benzene (5 ml), and styrene (30 mmol) in the presence of the catalyst (0.7 mmol). The product 2[6] was analyzed on GLC at appropriate times.[11] The results are shown in Figure 1. From these data it is clear that 18-crown-6 is a more effective catalyst than BTAC at all temperatures examined. Even at 45 °C, 18-crown-6 was effective, in contrast to BTAC,[2a] although the product 2 decomposed rapidly at this temperature. Hence, it seems most convenient to carry out the reaction at 25 °C (i.e., around room temperature), at which temperature the optimum yield of 2 was obtained after 5–7 h.

The catalytic effect of several other crown ethers was examined at 20–25 °C as summarized in Table I. Except for 15-crown-5 and dibenzo-24-crown-8, the three 18-crown-6 ethers gave better results than BTAC. Such ring-size effect of crown ethers as the catalyst may be attributable to the stability difference of metal–polyether complexes.[7b]

Table I. Dimethylvinylidenecyclopropanation of Styrene with Various Crown Ethers [a]

Catalyst	Yield of 2, %[b]
15-Crown-5	56.4
18-Crown-6	63.5
Dibenzo-18-crown-6	63.0
Dicyclohexyl-18-crown-6	69.0
Dibenzo-24-crown-8	10.3
BTAC	61.0[c]

[a] Reactions were carried out by method A (see Experimental Section) at 20–25 °C for 9 h. [b] Isolated yield. [c] See ref 2a.

Application of Crown Ether Catalyzed Dialkylvinylidenecyclopropanation to Various Olefins. The above dimethylvinylidenecyclopropanation with crown ethers as the catalyst was applied to various olefinic substrates and the results are summarized in Table II and Chart I.

Chart I

la, R = CH₃

b, R,R = (CH₂)₅

12a, R = CH₂CH(CH₃)₂

b. R = CH₂CH(CH₂)₃CH₃
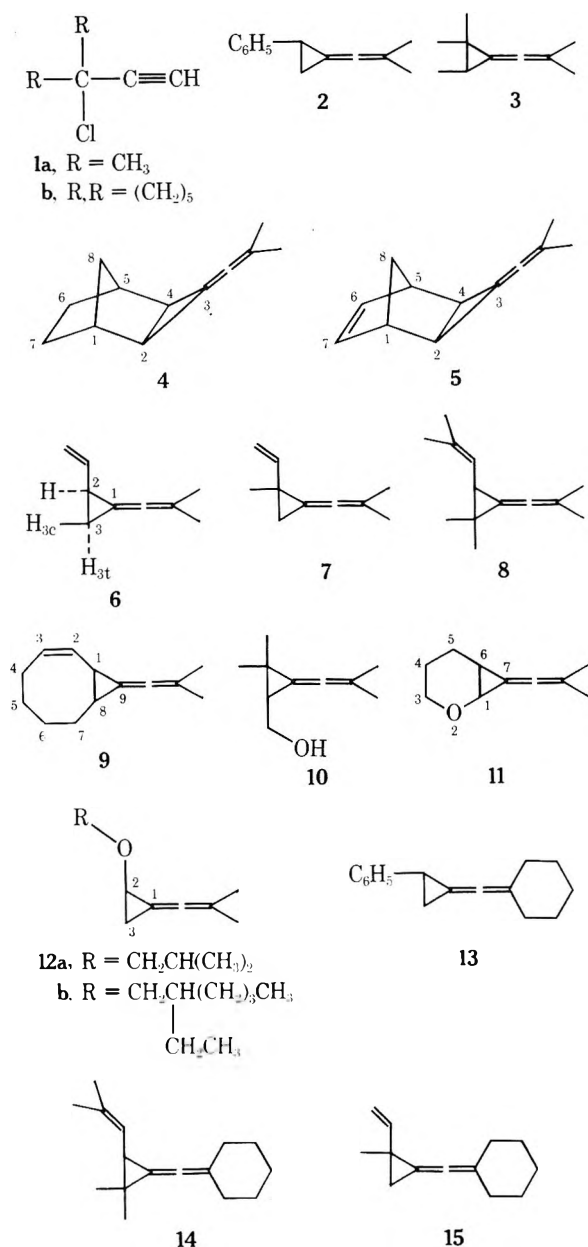
The products 3, 7, 8, and 10 were identified by comparison of spectral (ir and NMR) data, GLC retention times, and *n*D values with those of authentic samples.[2a,6] The yields of these
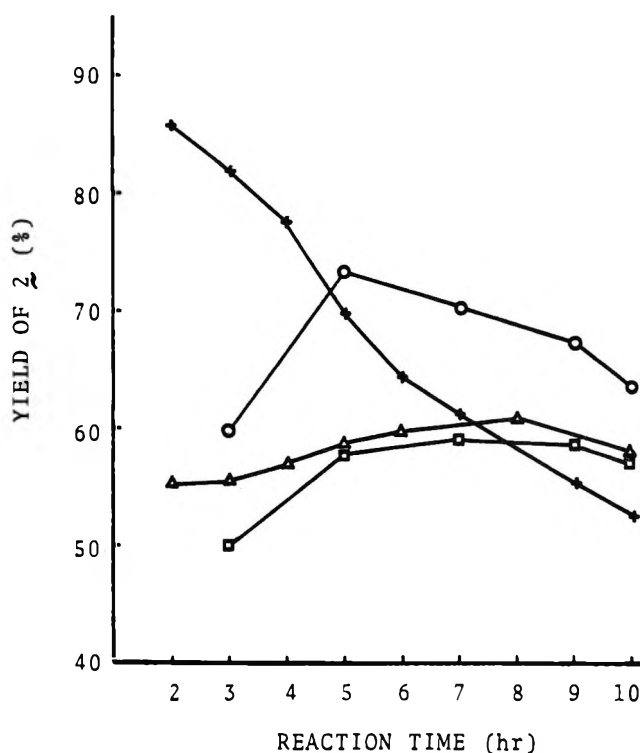
Figure 1. The yield of 2 as a function of reaction time (addition time of 1a, 2 h was involved) under the phase-transfer catalyzed conditions, in which the catalyst and reaction temperature are -×-, 18-crown-6 (45 °C); -O-, 18-crown-6 (25 °C); -Δ-, 18-crown-6 (5 °C); -□-, BTAC (20–25 °C).

adducts were all improved considerably (10–30%) compared to those of BTAC-catalyzed reactions (see the yields in parentheses in Table II) under similar conditions.

The reaction of 1a with norbornene and norbornadiene afforded adducts 4 and 5, respectively, in only modest yields. The structural assignments were based on spectral and analytical data (Table III) as well as analogy to the mode of unsaturated carbene addition to those substrates.[12] In NMR spectra, appearance of the characteristic AB quartet signals at δ 0.96 (4) and 1.26 (5) supported the assigned exo configuration.

Butadiene afforded adduct 6 at −78 °C by using powdered KOH (method B in Table II) instead of aqueous KOH (method A). It should be noted that method B is obviously useful for low-boiling substrates such as butadiene, and also for hydrophilic or potentially hydrophilic substrates such as prenol or prenol acetate (Table II). However, application of method B to 4-vinylpyridine resulted in a rapid polymerization of the substrate.

Reaction of 1,3-cyclooctadiene as a cyclic conjugated olefin gave adduct 9 but in a lower yield than obtained with acyclic dienes.

Vinyl ethers such as dihydropyran, isobutyl and 2-ethylhexyl vinyl ethers as electron-rich olefins afforded the corresponding adducts 11, 12a, and 12b, respectively, in better yields than cyclohexene (26%) and 1-hexene (12%).[6]

Pentamethylenevinylidenecarbene from 1b was also successfully trapped by styrene, 2,5-dimethyl-2,4-hexadiene, and isoprene (method A) affording adducts 13, 14, and 15, respectively, in moderate yields.[13] All of these adducts were characterized by analysis and spectral data (Table III).

The above results indicate that crown ethers, especially dicyclohexyl-18-crown-6, are useful catalysts for dialkylvinylidenecyclopropanation of olefins with 1a or 1b in the presence of potassium hydroxide.

Table II. Crown Ether Catalyzed Dialkylvinylidenecyclopropanation of Various Olefins

Olefin[g]	Precursor	Method[a] (cat.)[b]	Reaction temp, °C	Product[h]	Yield, %[c]	Bp, °C (mm)	nD (temp, °C)
2-Methyl-2-butene	1a	A (DC-18)	20–25	3[d]	37.0 (23.0)[d]		
Norbornene	1a	A (DC-18)	20–25	4	18.8	75–77 (30)	1.5280 (21)
Norbornadiene	1a	A (DC-18)	20–25	5	17.7	60–62 (10)	1.5534 (22)
Butadiene	1a	B (DC-18)	−78	6	58.0	60–62 (25)	1.5199 (19)
Isoprene	1a	A (DC-18)	8–10	7[e]	38.5 (26.0)[e]		
2,5-Dimethyl-2,4-hexadiene	1a	A (DC-18)	20–25	8[e]	59.0 (28.5)[e]		
1,3-Cyclooctadiene	1a	A (18-C)	20–25	9	11.7	46–47 (0.23)	1.5482 (19)
Prenol	1a	B (DB-18)	20–25	10[f]	48.0 (45.0)[f]		
Prenol acetate	1a	B (DC-18)	20–25	10[f]	46.0 (14.5)[e]		
Dihydropyran	1a	A (DB-18)	20–25	11	37.8	65–66 (11)	1.5312 (19)
Isobutyl vinyl ether	1a	A	20–25	12a	35.2	62–63 (10)	1.4842 (19)
2-Ethyl-1-hexyl vinyl ether	1a	A (DC-18)	20–25	12b	64.9	70–74 (0.15)	1.4690 (16)
Styrene	1b	A (DC-18)	20–25	13	39.5	93–95 (0.23)	1.5921 (18)
2,5-Dimethyl-2,4-hexadiene	1b	A (DC-18)	20–25	14	36.5	84–87 (0.30)	1.5350 (17)
Isoprene	1b	A (18-C)	20–25	15	31.5	60–62 (0.25)	1.5430 (20)

[a] For detailed procedure of method A and B, see Experimental Section. [b] DC-18 = dicyclohexyl-18-crown-6; 18-C = 18-crown-6; DB-18 = dibenzo-18-crown-6. [c] Isolated yield. [d] See ref 6. [e] See ref 2a. [f] See R. W. Mills, R. D. H. Murray, and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 133 (1973). [g] Registry no. are, respectively, 513-35-9, 498-66-8, 121-46-0, 106-99-0, 78-79-5, 927-97-9, 1700-10-3, 556-82-1, 1191-16-8, 110-87-2, 109-53-5, 103-44-6, 100-42-5, 1111-97-3. [h] Registry no. are, respectively, 6209-75-2, 59055-13-9, 59055-14-0, 59055-15-1, 59055-16-2, 59055-17-3, 54492-86-3, 59055-18-4, 59055-19-5, 59055-20-8, 59055-21-9, 16069-36-6, 17455-13-9, 14187-32-7.

Table III. Spectral and Analytical Data of Dialkylvinylidenecyclopropane Derivatives

Compd	Ir, cm^{-1} (neat)	NMR chemical shift, δ (CCl$_4$, 60 MHz)	Formula	Anal.	% C	% H
4	2020, 1450, 1005, 820	2.44 (bs,[a] 2 H, H$_1$ and H$_5$), 0.96 (AB q,[b] 2 H, H$_8$ × 2), 2.0–1.2 (m, 12 H, other H)	C$_{12}$H$_{16}$	Calcd Found	89.94 90.06	10.06 9.94
5	3060, 2010, 1450, 1105, 700	6.24 (t, J = 1.5 Hz, 2 H, H$_6$ and H$_7$), 2.98 (m, 2 H, H$_1$ and H$_5$), 1.73 (m, 8 H, H$_2$, H$_4$, and vMe$_2$[c]), 1.20 (AB q,[d] 2 H, H$_8$ × 2)	C$_{12}$H$_{14}$	Calcd Found	91.08 90.97	8.92 9.03
6	3080, 2015, 1630 1445, 980, 900	5.85–4.7 (m, 3 H, CH=CH$_2$), 2.29 (d,d,d[e] 1 H, H$_2$), 1.75 (s. 6 H, vMe$_2$[c]), 1.88–1.55 (m, 1 H, H$_{3t}$), 1.29 (d,d,[f] 1 H, H$_{3c}$)	C$_9$H$_{12}$	Calcd Found	89.94 89.93	10.06 10.07
9	3020, 2018, 1641, 1455, 670	5.8–5.1 (m, 2 H, CH=CH), 1.72 (s, 6 H, vMe$_2$[c]), 2.7–1.05 (m, 10 H, other H)	C$_{13}$H$_{18}$	Calcd Found	89.59 89.66	10.41 10.34
11	2008, 1435, 1100 770	3.95 (d, J = 7.0 Hz, 1 H, H$_1$), 3.46 (m, 2 H, H$_3$ × 2), 1.79 and 1.73 (each s, each 3 H, vMe$_2$[c]), 2.2–1.: (m, 5 H, other H)	C$_{10}$H$_{14}$O	Calcd Found	79.95 80.01	9.39 9.34
12a	3050, 2020, 1450 1180, 1080	3.73 (t, J = 4.5 Hz, 1 H, H$_2$), 3.22 (d, J = 6.0 Hz, 2 H, OCH$_2$), 2.1–1.65 (m, 7 H, vMe$_2$[c] and CHMe$_2$), 1.55 (d, J = 4.5 Hz, 2 H, H$_3$ × 2), 0.88 (d, J = 6.0 Hz, 6 H. CHMe$_2$)	C$_{11}$H$_{18}$O	Calcd Found	79.46 79.59	10.92 10.79
12b	3050, 2010, 1445, 1170, 1070	4.2–3.6 (m, 1 H, H$_2$), 3.6–3.1 (m, 2 H, OCH$_2$), 2.1–1.7 (m, 7 H, vMe$_2$[c] and CH), 1.65–0.6 (m, 16 H, other H)	C$_{15}$H$_{26}$O	Calcd Found	81.02 80.84	11.79 11.97
13	3060, 3035, 2020 1603, 755, 690	7.08 (m, 5 H, C$_6$H$_5$), 2.81 (d,d, J = 8.0 and 5.0 Hz, 1 H, H$_2$), 2.55–2.0 (m, 4 H, C=CCH$_2$ × 2), 2.0–1.3 (m, 8 H, other H)	C$_{16}$H$_{18}$	Calcd Found	91.37 91.47	8.63 8.53
14	2015, 1660, 1455, 850, 770	4.88 (bd,[g] J = 7.5 Hz, 1 H, C=CH), 1.28 and 1.15 (each s, each 3 H, C=CMe$_2$), 2.5–1.4 (m, 17 H, other H)	C$_{16}$H$_{24}$	Calcd Found	88.82 88.65	11.18 11.35
15	3085, 3045, 2020, 1635, 990, 895	5.85–4.63 (ABX m, 3 H, CH=CH$_2$), 2.30 (bs,[a] 4 H, C=CCH$_2$ × 2), 1.32 (s, 3 H, Me), 1.9–1.4 (m, 7 H, other H)	C$_{13}$H$_{18}$	Calcd Found	89.59 89.67	10.41 10.33

[a] bs = broad s. [b] J = 9.8 Hz, Δδ/J = 2.308. [c] vMe$_2$ = C=C=CMe$_2$. [d] J = 9.8 Hz, Δδ/J = 2.231. [e] J$_{H_2,H_{3c}}$ = 5.0, J$_{H_2,H_{3t}}$ = 7.0. J$_{H_2,HC=C}$ = 8.0 Hz, [f] J$_{H_2,H_{3c}}$ = 5.0, J$_{H_{3c},H_{3t}}$ = 6.8 Hz. [g] bd = broad d.

Experimental Section[14]

General Procedure for Crown Ether Catalyzed Synthesis of Dialkylvinylidenecyclopropane Derivatives. Method A. In a 100-ml three-necked flask fitted with a dropping funnel and a mechanical stirrer, a mixture of 51% (w/w) aqueous potassium hydroxide (30 ml), benzene (5 ml), appropriate crown ether (0.5–0.7 mmol), and an olefinic substrate (30 mmol) was vigorously stirred under nitrogen. While stirring was continued, 3-chloro-3-methyl-1-butyne[15] (1a, 1.03 g, 10.0 mmol) or 1-chloro-1-ethynylcyclohexane[15] (1b, 1.43 g, 10.0 mmol) in benzene (5 ml) was added slowly to the mixture over 2 h. After the addition was completed, the mixture was stirred for a further

5–7 h. The diluted mixture with water (120 ml) was extracted with *n*-hexane or ether (4 × 30 ml). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to afford crude product which was purified by distillation under reduced pressure (Table II).

Method B. Instead of aqueous KOH in method A, powdered solid KOH was used. As an example, the reaction of butadiene is described. To a magnetically stirred and cooled (−78 °C) mixture of powdered KOH (85% purity, 4.20 g, 63.6 mmol), dicyclohexyl-18-crown-6 (0.27 g, 0.72 mmol), and butadiene (6.50 g, 120 mmol) was added 1a (2.06 g, 20.0 mmol) slowly over 2 h under nitrogen. After stirring was continued for a further 15 h at the same temperature, the mixture was allowed to warm to room temperature in order to remove the excess butadiene and an oily residue was purified by distillation to afford 6 (1.40 g, 58.0%). Analytical and physical data of all new compounds are summarized in Tables II and III.

References and Notes

(1) Studies on Reactions of Isoprenoids. 22. Part 21: T. Sasaki, S. Eguchi, and T. Ogawa, *J. Am. Chem. Soc.*, **97**, 4413 (1975).

(2) (a) T. Sasaki, S. Eguchi, and T. Ogawa, *J. Org. Chem.*, **39**, 1927 (1974); (b) T. Sasaki, S. Eguchi, and T. Ogawa, *Heterocycles*, **3**, 193 (1975).

(3) M. Makosza, personal communication.

(4) S. Julia, D. Michelot, and G. Linstrumelle, *C. R. Acad. Sci., Ser. C*, 1523 (1974).

(5) T. B. Patrick, *Tetrahedron Lett.*, 1407 (1974).

(6) H. D. Hartzler, *J. Am. Chem. Soc.*, **83**, 4990 (1961); H. D. Hartzler, *ibid.*, **83**, 4997 (1961).

(7) For recent reviews, see (a) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); (b) J. J. Christensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974).

(8) K. H. Wong, G. Konizer, and J. Smid, *J. Am. Chem. Soc.*, **92**, 666 (1970); M. J. Maskornick, *Tetrahedron Lett.*, 1797 (1972).

(9) For examples of application of crown ether to phase-transfer catalyzed reactions, see (a) D. Landini, F. Montanari, and F. M. Pirisi, *J. Chem. Soc., Chem. Commun.*, 879 (1974); (b) C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974); (c) D. J. Sam and H. E. Simmons, *ibid.*, **96**, 2252 (1974); etc.

(10) For application of crown ether to generation of dihalocarbene, see (a) R. A. Moss and F. G. Pilkiewicz, *J. Am. Chem. Soc.*, **96**, 5632 (1974); (b) M. Makosza and M. Ludwikow, *Angew. Chem., Int. Ed. Engl.*, **13**, 665 (1974).

(11) The yield of 2 was finally corrected by the isolated yield after distillation.

(12) For the exo adducts of isopropylidene- and cyclohexylidenecarbenes to norbornadiene, see (a) R. Bloch, F. Leyendecker, and N. Toshima, *Tetrahedron Lett.*, 1025 (1973); (b) M. S. Newman and M. C. V. Zwan, *J. Org. Chem.*, **39**, 761 (1974). For the endo isomer, see (c) P. J. Stang and M. G. Mangum, *J. Am. Chem. Soc.*, **97**, 3854 (1975).

(13) For di-*tert*-butylvinylidenecyclopropanation, see H. D. Hartzler, *J. Am. Chem. Soc.*, **93**, 4527 (1971).

(14) Boiling points are uncorrected. NMR spectra were recorded on a JEOL C-60HL spectrometer at 60 MHz, and ir spectra with a Jasco IRA-1 spectrometer. GLC analysis were performed with a JEOL 20K gas chromatograph on a 1-m Silicone SE-30 and/or Apiezon grease L column. Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer.

(15) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, **79**, 2142 (1957).

Phosphonic Acid Chemistry. 1. Synthesis and Dienophilic Properties of Diethyl 2-Formylvinylphosphonate and Diethyl 2-Formylethynylphosphonate[1a,b]

A. J. Rudinskas* and T. L. Hullar

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

The synthesis of the title compounds, 5 and 11, was accomplished from diethyl 3,3-diethoxy-1-propyn-1-ylphosphonate (6). A reported synthesis of diethyl 3,3-diethoxy-1-propen-1-ylphosphonate (4) from PCl$_5$ and ethyl allyl ether was investigated and found not to give 4 as claimed. The isomeric phosphonyl dichloride (17) and the isomeric vinylphosphonates, 18 and 19, were obtained instead. The dienophiles, 5, 11, dimethyl acetylenedicarboxylate (7), and propiolaldehyde (8), were treated with isoprene and the order of reactivity for these dienophiles was found to be 5 > 7 > 11 > 8. The resultant cycloadducts 21 and 23 were obtained in good yield and the structure of 23 was established unambiguously by conversion to the known xylenylphosphonic acid (28). This latter compound and its isomer (30) were prepared using photochemical Arbuzov reaction methods. The increased dienophilic reactivity of 5 and 11 as compared to 7 and 8, respectively, was in accord with published data that the diethyl phosphonyl group exerts an activating effect on the dienophilic character of an olefin.

A number of phosphorus-containing dienes[2] and dienophiles[3–5] have been synthesized and investigated for their ability to undergo Diels–Alder reactions. The dienophilic character of 1[6] was reported to be less than that of α,β-unsaturated carbonyl and nitrile compounds. More recently, Diels–Alder reactions have been reportedly carried out with 2, generated in situ, from 4[7,8] and with 3.[9] The compound 3 was reported to react exothermically with cyclopentadiene.

The present communication describes further Diels–Alder studies, involving the dienophiles 5 and 11 (the pure cis isomer of 2) and their synthesis from 6. The dienophile 5 is shown to be more reactive toward isoprene than 11, 7, and 8. The communication also presents evidence that the reported synthesis of 4, which was used to generate 2, in situ, for Diels–Alder reactions was in error. Compounds 11 and 5 were of interest because of their potential usefulness in the preparation of new and novel alicyclic analogues of pyridoxal phosphate.[1a]

R—CH=CHPO(OC$_2$H$_5$)$_2$

1, R = H
2, R = CHO
3, R = CN
4, R = CH(OC$_2$H$_5$)$_2$

R—C≡CPO(OC$_2$H$_5$)$_2$

5, R = CHO
6, R = CH(OC$_2$H$_5$)$_2$

CH$_3$OOCC≡CCOOCH$_3$

7

HC≡CCHO
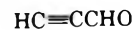
8

Synthesis. The synthesis of 5 was done from 6, whose preparation has been described.[1a] The acetal 6 was hydrolyzed with 97% HCOOH to give 5 in quantitative yield. The compound was isolated by fractional distillation and proved to be a stable, colorless liquid which when stored for several months at 0 °C under N$_2$ showed no decomposition.

The synthesis of 11 was done from 6 also. Catalytic hydrogenation of 6 using 5% Pd/CaCO$_3$, poisoned with quinoline, gave a mixture of acetals 9 and 10, from which the cis isomer

Chart I

$$6 \xrightarrow{\text{HCOOH}} \text{OCH}-\text{C}\equiv\text{C}-\text{PO(OC}_2\text{H}_5)_2$$
$$5$$

(structure **9**) $(C_2H_5O)_2PO$, $CH(OC_2H_5)_2$, $C=C$, H, H — **9**

(structure **10**) $(C_2H_5O)_2PO$, H, $C=C$, H, $CH(OC_2H_5)_2$ — **10**

(structure **11**) $(C_2H_5O)_2PO$, CHO, $C=C$, H, H — **11**

(structure **12**) $(C_2H_5O)_2PO$, H, $C=C$, H, $CH=NNH-$ —$\langle\rangle$— NO_2 / NO_2 — **12**

(structure **13**) $(C_2H_5O)_2PO$, $CH(OC_2H_5)_2$, $C=C$, D, D — **13**
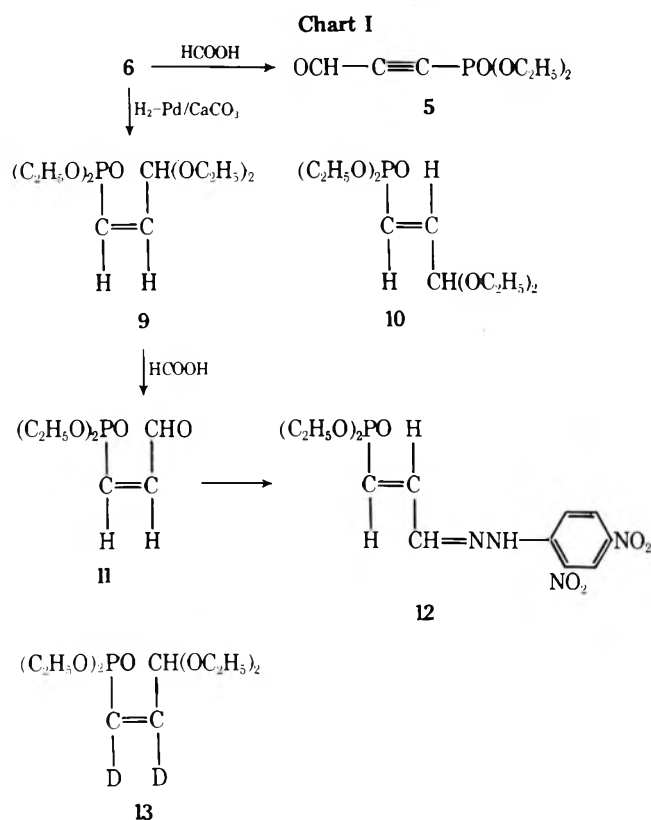
9 was isolated by distillation in 60% yield. Formolysis of pure 9 using 97% HCOOH gave a mixture of cis and trans aldehydes from which cis-11 was isolated in 60% yield by distillation. Compound 11 was characterized by ir and NMR, elemental analysis, and by its conversion to a *trans*-dinitrophenylhydrazone (DNPH) 12.

GLC analysis of the reduction reaction mixture, obtained by the reduction of 6 in C_5H_5N solution with 10% Pd/CaCO₃, revealed the presence of 6, 9, and 10 in 20, 70, and 8.3% yields, respectively. These GLC results were confirmed by the TLC isolation of 6, 9, and 10 in 19, 55, and 8% yields, respectively. The structure of the isomeric trans acetal 10 was established by ir and NMR and was supported by synthesis from pure 9. Formolysis of 9 gave crude 11, which when refluxed with C_2H_5OH, $CH(OC_2H_5)_3$, and HCOOH gave 9 and 10 in 13 and 23% yields, respectively. These compounds were isolated by TLC and exhibited ir and NMR spectra the same as those of 9 and 10 obtained from reduction of 6.

The deuterated acetal 13 was prepared by hydrogenation of 6 with deuterium. The compound was isolated in the same manner as was 9 and had the same TLC mobility as 9. The mass spectrum of 13 showed no molecular ion, but the mass fragmentation pattern was similar to that of 9 and was consistently 2 mass units higher than that for 9.

The stereochemistry of 9–13 was established by NMR. The

chemical shift and proton coupling constants for 9–13 are summarized in Table I. The *cis*-vinylphosphonate geometry was assigned 9 because of the larger coupling constant, $J_{bx} = 50$ Hz, that was observed for this compound as compared to that found in 10 ($J_{bx} = 21$ Hz). This result is in accord with published findings[10–12] that *cis*-vinylphosphonates have larger coupling constants ($J_{bx} = 30$–50 Hz) than do *trans*-vinylphosphonates ($J_{bx} = 10$–30 Hz). The stereochemical assignment of a cis geometry to 9 and a trans geometry to 10 was also supported by chemical shift data of the acetal *methine* protons of 9, 10, and 13. These protons were considerably more deshielded in 9 and 13 (by 1.22 and 1.1 ppm) than the acetal methine proton found in 10. The γ protons in cis olefins are known[13,14] to resonate at lower field than the corresponding ones in the trans isomer.

The crude formolysis product 11 was found to show two NMR aldehyde absorptions, one at 9.33 ppm (d), the other at 11.1 ppm (d) in the ratio of 1:9. The lower field absorption was attributed to *cis*-11. The coupling constants obtained for 12 were consistent with a trans geometry for the compound, indicating that an isomerization of the double bond had occurred during hydrazone formation.

Reaction of PCl₅ with 14 and 20. During the preparation of 9, the reported[7,8] synthesis of 4 of unspecified geometry was repeated to better establish the structure of 9 and 10. The synthesis was found to give products completely different from those claimed.[7,8] Thus 14 reacted with PCl₅ to give a

Chart II

$$(C_2H_5O)_2CHCH=CH_2$$
$$20$$
$$\downarrow \text{PCl}_5$$

$$C_2H_5OCH_2CH=CH_2 \xrightarrow{\text{PCl}_5} \text{(complex)} \xrightarrow{\text{SO}_2} //\to$$
$$14 \qquad\qquad 15 \qquad Cl_2POCH=CHCCl(OC_2H_5)$$
$$16$$
$$\downarrow$$

(structure **17**) Cl_2PO, H, $C=C$, ClH_2C, OC_2H_5 — **17**

(structure **18**) $(C_2H_5O)_2CH$, H, $C=C$, $(C_2H_5O)_2PO$, H — **18**

(structure **19**) $(C_2H_5O)_2PO$, H, $C=C$, $C_2H_5OCH_2$, OC_2H_5 — **19**
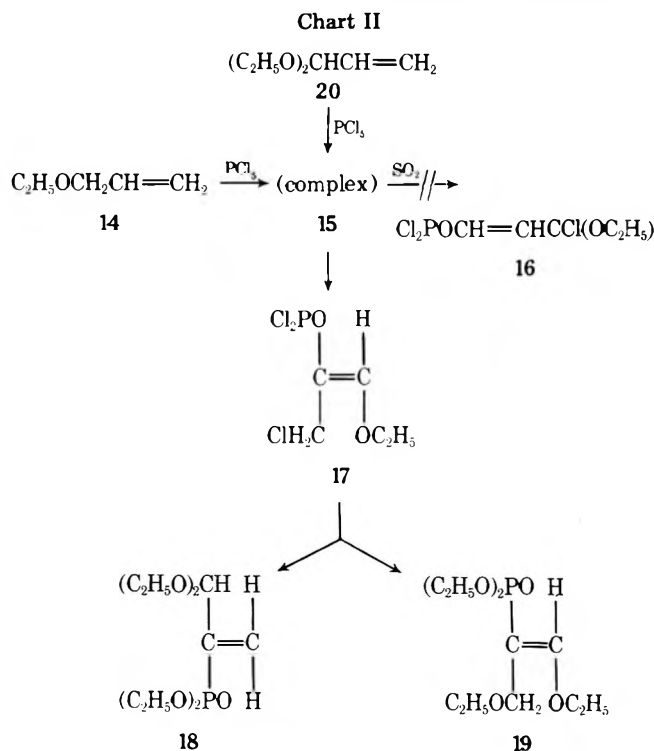
Table I. Chemical Shifts and Coupling Constants of Vinyl and α-Methine Protons of 9, 10, 11, 12, and 13

$$CH_c-CH_b=CH_a-P_x$$
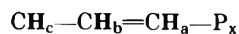
Compd (solvent)	Chemical shifts, ppm			Coupling constants, Hz					
	a	b	c	ab	ac	bc	ax	bx	cx
9 (CDCl₃)	5.90	6.57	5.93	13	~1	7.5	18	50	~2.5
(C₆D₆)	5.68	6.53	6.30						
10 (CDCl₃)	6.20	6.80	5.13	18	~1	3.5	21	21.5	Not detn
(C₆D₆)	6.23	6.85	5.08						
13 (C₆D₆)			6.18						
11 (C₆D₆)	6.27	6.29	11.10	13		7	11	52	
12 (CDCl₃)	7.36	6.16	7.83	16.8		8.8	20.5	17.2	Not detn

Table II. NMR Chemical Shifts and Coupling Constants for 17, 18, and 19

Compd	Solvent		
	C_6D_6	$CDCl_3$	
17[a]	0.73	1.43	t, J = 7 Hz, CH_3
	3.33	4.33	q, J = 7 Hz, CH_2O
	4.02	4.33	d, J = 27 Hz, CH_2Cl
	7.12	7.46	d, J = 10 Hz, CH=C
18	1.13	1.25	t, J = 7 Hz, CH_3
		1.35	t, J = 7 Hz, CH_3
	3.52	3.63	AB q, J = 7 Hz, CH_2O
	4.05	4.15	2 q, J = 7, 8 Hz, CH_2OP
	5.32	5.13	m, J = 0.6, 0.8, 4 Hz, CH
	6.30	6.24	2 m, J = 0.8, 2.4, 22 Hz, CH=C
	6.35	6.28	2 m, J = 0.6, 2.4, 43 Hz, CH=C
19	0.85		3 t, J = 7 Hz, CH_3
	1.07		
	1.20		
	3.44		q, J = 7 Hz, CH_2O
	4.08		2 q, J = 7, 8 Hz, CH_2OP
	4.28		d, J = 18 Hz, CH_2O
	7.28		d, J = 10 Hz, CH=C

[a] The reported spectrum[15] run on a 40-MHz Ya MR-5535 spectrophotometer was listed as 1.35 (t), 4.00 (q), 3.91 (d, J = 23 Hz), and 6.85 ppm (d, J = 12 Hz). No solvent was indicated.

Table III. Diels–Alder Reaction of Isoprene with Various Dienophiles

Compd	Percentage yields		
	Neat[a]	0.5 M benzene[b] solution	Reported
5	c	62	86
7	58	12	90[d]
8	63	2[e]	76[f]
11	55	7 (61[g])	86[h]

[a] No solvent, allowed to react for 70 h at room temperature. [b] Both reactants were present in 0.5 M concentrations in the reaction solution and were allowed to react under nitrogen for 70 h at room temperature. [c] Reaction was too violently exothermic and caused the carbonization of the reaction contents when reactants were mixed neat at room temperature. [d] Reported by V. F. Kucheron and N. Ya. Grigor'eva;[22] obtained by heating 7 with isoprene in benzene solution, 4 h at 130–140 °C. [e] The 2% yield represents the residue after removal of the volatiles which by NMR was predominantly the cycloadduct. [f] Reported by Petrov and Sopov;[23] obtained by heating 8 for 5 h at 110 °C in a bomb in toluene. [g] The yield obtained by heating 11 with isoprene in benzene solution in a Parr bomb for 19 h at 100 °C. [h] Reported by Tsivunin et al.;[7] obtained by heating 4, water, concentrated HCl, and isoprene at 100 °C for 10 h.

complex (15) which precipitated from solution. However, treatment of this complex 15 with SO_2 gave a product in the reported yield which (vide infra) was 17 and not 16 as claimed.[7] The ir spectrum of 17 was remarkably similar to that published for 16. The published spectrum differed from that observed for 17 only in the presence of an additional ir absorption at 13.3 μ. The product 17 was treated with NaOEt in Et_2O in the manner described for the synthesis of 4 to give two vinylphosphonates (proved to be 18 and 19) in 8.5 and 34.5% yields, respectively, and no 4. The compound 17 was known[15] and the reported synthesis of 17 from 20 and PCl_5 was also repeated so that the structure of 17 could be established in a definative manner. Acreolin diethyl acetal (20) was found to react with PCl_5 to give 17 which was the same as 17 obtained above from 14 and PCl_5 (as judged by ir and NMR).

The NMR spectra of 17, 18, and 19 are presented in Table II. The reported NMR spectrum of 17 was found to be at variance with that observed by the present authors. Differences in the chemical shift and coupling constants were observed. Although the chemical shift differences can probably be attributed to solvent effects (present spectra were run in C_6D_6 and $CDCl_3$ while the reported spectrum appears to have been run neat since no solvent was specified), the differences in the coupling constants (especially the vinyl proton one) are more difficultly explainable and may be due to experimental error (published spectrum run on a 40-MHz spectrophotometer).[15]

The NMR spectra listed in Table II for 17, 18, and 19 are in complete accord with the structures assigned these compounds. The cis stereochemistry of the vinyl proton–phosphorus atom assigned 17 and 19 is supported by the small vinyl proton–phosphorus coupling constant ($^3J_{PH}$ = 10 Hz). A trans stereochemistry would require a larger coupling constant ($^3J_{PH}$ = 30–50 Hz).[10-12] The presence of two vinyl proton–phosphorus coupling constants in 18, one large ($^3J_{PH}$ = 43 Hz), the other small ($^3J_{PH}$ = 22 Hz), is consistent with the vinyl methylene structure assigned this compound. Spin decoupling (irradiation of the acetal methine proton) was used to determine the vinyl proton coupling constant ($^2J_{HH}$ = 2.4 Hz) and to provide proof that the smaller coupling constants ($^4J_{HH}$ = 0.6 and 0.8 Hz) were due to allylic coupling with the

acetal methine proton. The allyl proton–phosphorus coupling constants ($^3J_{PH}$ = 27 and 18 Hz in 17 and 19, respectively) are in the expected range[10,16] and also support the structural assignments of 17 and 19. The unusually small acetal methine–phosphorus proton coupling constant ($^3J_{PH}$ = 4 Hz) in 18 is due to stereochemistry. The coupling constant ($^3J_{PH}$) has been reported[10,16] to vary as a function of the dihedral angle ϕ (the angle formed by the intersection of the planes $H_{acetal}C_1C_2$ and C_1C_2P), and was reported to be 14.5–20 Hz for ϕ = 0°, 7–9 Hz for ϕ = 30°, 5–7 Hz for ϕ = 60°, 0.5 Hz for ϕ = 90°, 5.5–8.6 Hz for ϕ = 120°. The small coupling ($^3J_{PH}$ = 4 Hz) observed for the acetal methine proton in 18 would therefore suggest that this proton spends a considerable amount of time in a conformation which has a dihedral angle ϕ > 60° < 120°.

The structural assignment of 18 is also supported by a correct elemental analysis and by mass spectrometry. The mass spectrum of 18 exhibited three principal modes of fragmentation, all of which were consistent with structure 18. The mass spectrum showed (a) a progressive loss of fragments C_2H_5O (m/e 221), C_2H_4 (193), C_2H_4 (165) (this fragmentation pattern was supported by the metastable ions, m/e 168.5, 141, and 113.5); (b) the formation of fragments $CH(OC_2H_5)_2$, $CH(OC_2H_5)OH$, $CH(OH)_2$, the transformation $CH(OC_2H_5)_2$ → $CH(OC_2H_5)OH$ being supported by a metastable ion (m/e 54.6); (c) the formation of phosphorus-containing fragments such as $HPO(OC_2H_5)_2$, $PO(OC_2H_5)_2$, $PO(OH)OC_2H_5$. The above fragmentation pattern is clearly consistent with the structure of 18 and is similar to the isomeric product (9).

The reported[7,8] synthesis of 4 had also indicated that this compound reacted in dilute aqueous HCl with isoprene at 100 °C to give the Diels–Alder adduct, formulated as 21, and characterized by its DNPH 22. The compound 21 was prepared from 11 by reaction with isoprene and was converted to 22 which was found to have a different melting point from that reported.[7]
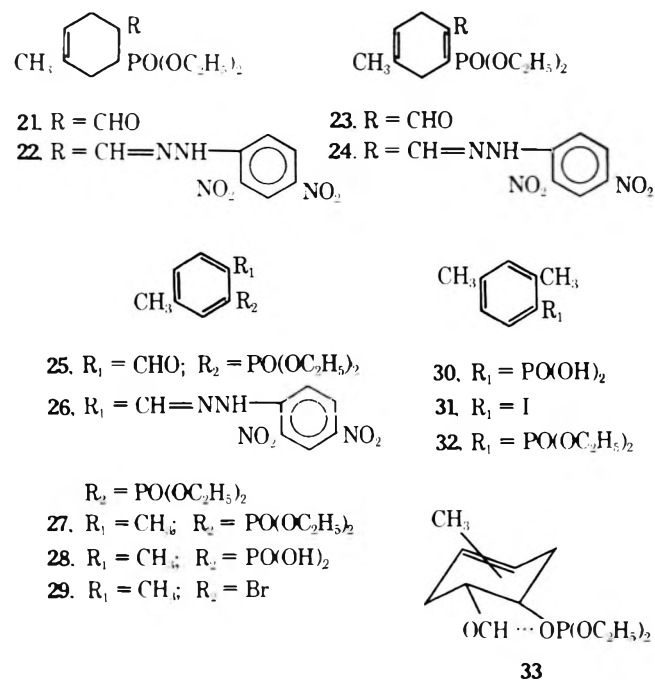
Diels–Alder Reactions. The Diels–Alder reactions of 5 and 11 with isoprene were examined and compared to those of 7 and 8. The results are summarized in Table III.

A violent exothermic reaction occurred when 5 was mixed neat with isoprene. The heat of the reaction carbonized the contents of the flask. In benzene solution, however, 5 reacted

with isoprene to give **23** in 62% yield (room temperature, 70 h).

The structure of **23** was established by conversion into the known **28**. The cycloadduct **23** (Chart III) was dehydrogenated

Chart III

21. R = CHO
22. R = CH=NNH—⟨NO₂, NO₂⟩

23. R = CHO
24. R = CH=NNH—⟨NO₂, NO₂⟩

25. R₁ = CHO; R₂ = PO(OC₂H₅)₂
26. R₁ = CH=NNH—⟨NO₂, NO₂⟩
R₂ = PO(OC₂H₅)₂
27. R₁ = CH₃; R₂ = PO(OC₂H₅)₂
28. R₁ = CH₃; R₂ = PO(OH)₂
29. R₁ = CH₃; R₂ = Br

30. R₁ = PO(OH)₂
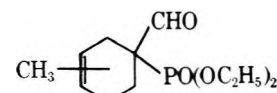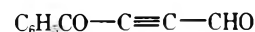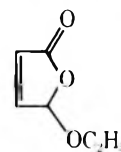**31.** R₁ = I
32. R₁ = PO(OC₂H₅)₂

33

with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give **25** in 56% yield. This compound was characterized by its 2,4-dinitrophenylhydrazone **26**, because distillation of **25** always resulted in some decomposition. Catalytic hydrogenolysis of **25** gave **27** in a near-quantitative yield. The product was converted into **28** using the Rabinowitz method[17] of dealkylation of phosphonate esters. The melting point of phosphonic acid **28** was identical with that reported[18] for **28**. An authentic sample of **28** was prepared from **29** by photolysis[19] of this compound in triethyl phosphite solution at 2537 nm. The compound **27** was isolated in 66% yield and converted into **28** by hydrolysis with refluxing HCl. The product thus obtained was identical in all respects, ir, NMR, melting point, and mixture melting point, with that obtained by transformation of **23**. The known[20] isomeric phosphonic acid **30** was prepared in the same way[19] from **31** and was shown to be different from **28**, obtained by degradation.

The aldehyde **11** reacted with isoprene neat at room temperature *without* the evolution of heat to give **21** in 55% yield. The reaction carried out in benzene solution at room temperature yielded **21** in only 7% yield, but required heating at 100 °C for 19 h to give 61% yield. The position of the methyl group in this cycloadduct was not established. The NMR spectrum of **21**, obtained from the reaction done at 100 °C in benzene solution, showed two broad aldehyde absorptions, one at 10.1 ppm. the other at 9.67 ppm, in a ratio of 1:3. The lower field absorption was attributed to **33** in which the phosphorus and aldehyde groups could assume a coplanar geometry, and would be capable of interacting to give a lower field resonance for the aldehyde proton.[21] The cycloadduct gave a single 2,4-DNPH **22** which had a different melting point from that reported[7] for **22**.

The reaction of **7** and **8** with isoprene gave the known cycloadducts, **34**[22] and **35**.[23] The yield of the adducts from **7** and **8** was low (12 and 2%, respectively) when the reactions were carried out at room temperature in benzene solution. In the case of **8** some polymerization was observed which probably lowered the yield of **35**, because of the long reaction time.

Discussion

The formation of **17** from the reaction of PCl₅ and **14** can be explained in terms of the reaction scheme, **14** → **36** → **37** → **38** → **17**. In this scheme PCl₅ is postulated to react with **14** to give the α-halo ether **36** which undergoes an allylic rear-

CH₂=CH—CHClOC₂H₅
36

ClCH₂CH=CHOC₂H₅
37

ClCH₂—CH—PCl₃⁺PCl₆⁻
        HCClOC₂H₅
38
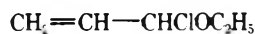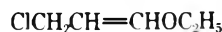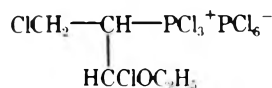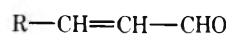
R—CH=CH—CHO
41. R = CHO
42. R = COCH₃
43. R = COC₂H₅
44. R = COOH
45. R = COOCH₃
46. R = COOC₂H₅

39

C₆H₅CO—C≡C—CHO
40

47

rangement to **37**. The product (**37**) then reacts with PCl₅ (PCl₄⁺PCl₆⁻) to give the adduct **38**, which when treated with SO₂ gives **17**. The above reaction scheme is supported by the known[24] ability of PCl₅ to react with vinyl ethers to give after workup the corresponding vinyl ether phosphonic acid derivatives. Also similar reaction mechanisms proceeding through α-halo ethers have been proposed to explain the formation of vinylphosphonate products from reactions of ethers, acetals, and ketals with PCl₅.[25-28]

The experimental results presented in this paper, as (a) the isolation of **17** in place of **16** in the reported yield, (b) the close similarity of the ir spectrum of **17** with that reported for **16**, and (c) the inability to obtain the same physical characteristics (melting point) for the 2,4-DNPH (**22**) reportedly used to characterize the cycloadduct (**21**) derived from **4** (in this case the cycloadduct **21** was prepared from the well-characterized **11**) are strongly indicative of erroneous structural assignment for **16**. Structural data as ir, molecular rotation, elemental analysis, the ability to undergo transformation to a product with a molecular formula C₁₁H₂₃O₅P (assigned structure **4**), and the ability of the latter (**4**) to react in a Diels–Alder manner with isoprene under acidic conditions are not sufficient to distinguish between the isomeric compounds **16** and **17**. The reported cycloadduct may in fact be **39**.

The findings presented in this communication on the dienophilic reactivity of **5** and **11** confirm the previously reported observations[3-6] that the introduction of a phosphonyl group into olefins enhances their dienophilic character. The results in Table III allow a rough qualitative ordering of the dienophilic reactivity of these compounds: **5** > **7** > *cis*-**11** > **8**. The observation that *cis*-**11** is less reactive than **5** is consistent with published findings[29] that cis olefin dienophiles are usually less reactive than their acetylene counterparts. Since analogues of **5** in which the diethyl phosphonyl moiety of **5** has been replaced by CHO, COR, COOR, or CN are for the most part unknown or, as in the case of **40**, the Diels–Alder reactions have been done under different conditions and with different dienes, a more precise evaluation of the activating ability of the diethyl phosphonyl group cannot be made at this time. In the case of **40**, the compound was reported to react with cyclopentadiene,[30] neat at room temperature, to give good yield of adduct. These reaction conditions suggest that

40 may be more similar in its reactivity to **11**, than to **5**, which would be expected to react violently with cyclopentadiene in the light of the present findings with isoprene.

A similar situation exists with analogues related to **11**. Many of these compounds (**41–46**) have been prepared but only a few[31] (**44, 45,** and the pseudoester **47**) have been studied for the Diels–Alder reaction and these under reaction conditions not strictly comparable to the ones used in this study for **5** and **11**. The dienophilic reactivity of esters of **44** was reported[31] to be comparable with those of maleic acid.

Experimental Section

The melting points were taken on a Fisher-Johns melting point block and are uncorrected. The infrared spectra were determined in KBr disks for solids and as smears on NaCl plates for liquids, using a Perkin-Elmer 237 grating spectrophotometer. The NMR spectra were determined in the solvents indicated using Varian A-60 and T-60 spectrophotometers. The chemical shifts are reported in parts per million (ppm) downfield from the internal standard tetramethylsilane. Mass spectra were obtained on a Hitachi Perkin-Elmer RMV-6D mass spectrophotometer. GLC analyses were performed on Varian Aerograph Hi Fi and Model 90 gas chromatographs using analytical columns specified. Elemental analyses were performed by Galbraith Laboratories, Nashville, Tenn.

Diethyl 2-Formylethynylphosphonate (5). A solution of 25.63 g (0.1 mol) of **6** in 125 ml of 97% HCOOH was heated at 60 °C for 0.5 h. The HCOOH was evaporated under reduced pressure and the remaining traces of acid removed by azeotroping with toluene. Distillation of the residue yielded 18.0 g (97%) of **5**: bp 83–91 °C (0.02 Torr); ir (neat) 4.50, 5.94, 7.98, 9.75 μ; NMR (CCl$_4$) δ 1.40 (t, J = 7 Hz, CH$_3$), 4.16 (2 q, J = 7, 9 Hz, CH$_2$OP), 9.3 (s, CHO); mass spectrum m/e 191 (0.17, M + 1), 190 (0.17, M), 163 (25), 161 (17), 147 (16), 145 (19), 135 (100), 134 (48), 133 (38), 118 (18), 117 (59), 89 (28), 82 (27), 81 (32), 70 (29), 65 (33), metastable ions m/e 111.5, 101.5, 61.5, 35.5.

Anal. Calcd for C$_7$H$_{11}$O$_4$P: C, 44.21; H, 5.83; P, 16.27. Found: C, 44.09; H, 5.85; P, 16.23.

Diethyl 3,3-Diethoxy-1-*cis*-propen-1-ylphosphonate (9). A mixture of 1.32 g of **6**, 0.0314 g of 5% Pd/CaCO$_3$, and 20 ml of EtOH containing 0.0088 g of quinoline was hydrogenated at atmospheric pressure until a theoretical amount of H$_2$ was taken up. The catalyst was filtered, and the EtOH was evaporated under reduced pressure to yield a residue which was distilled giving 0.778 g (60%) of **9**, bp 99–101 °C (0.008 Torr). An analytical sample of **9** was prepared by preparative TLC using silica gel G plates and EtOAc as the developing solvent. In this way 0.454 g of pure **9** was obtained: bp 100 °C (0.01 Torr); ir (neat) 6.06, 7.98, 9.45, 9.72, 10.35 μ; NMR (C$_6$D$_6$) δ 1.07 (t, J = 7 Hz, CH$_3$), 1.15 (t, J = 7 Hz, CH$_3$), 3.63 (AB q, J = 7 Hz, CH$_2$O), 3.90 (2 q, J = 7, 9 Hz, CH$_2$OP), 5.68 (m, J = 1, 13, 18 Hz, POCH=C), 6.53 (m, J = 7.5, 13, 50 Hz, POCH=CH), 6.30 [m, J = 1, 2.5, 7.5 Hz, CH(OR)$_2$]; NMR (CDCl$_3$) δ 1.23 (t), 1.35 (t), 3.74 (AB q), 4.13 (2 q), 5.9 (m), 5.93 (m), 6.57 (m); mass spectrum m/e 265 (0.5, M + 1), 237 (58), 221 (98.9), 209 (18), 193 (34), 181 (46), 165 (30), 163 (25), 153 (39), 147 (48), 137 (51), 136 (17), 135 (78), 129 (43), 120 (23), 119 (100), 109 (12), 103 (37), 82 (24), 81 (24), 75 (25), metastable ions m/e 184.5, 168.5, 156.5, 141, 113.5.

Anal. Calcd for C$_{11}$H$_{23}$O$_5$P: C, 49.62; H, 8.74; P, 11.63. Found: C, 49.75; H, 8.57; P, 11.40.

Diethyl 3,3-Diethoxy-1-*trans*-propen-1-ylphosphonate (10). A solution of 0.52 g of **9** in 5 ml of HCOOH (97%) was heated at 60 °C for 15 min. The HCOOH was evaporated under reduced pressure to yield an oil which by GLC was free of starting material. This oil was dissolved in 1.6 g (2 ml) of anhydrous EtOH and 7.2 g (8 ml) of triethyl orthoformate containing a drop of HCOOH and was heated at reflux for 70 min. The solvents were evaporated under reduced pressure and the residue was submitted to preparative TLC on silica gel GF plates using EtOAc to develop the chromatograms. Three TLC fractions were obtained, two of which were isolated: **9** (0.07 g, 13.4%) and **10** (0.12 g, 23%). The third fraction appeared to be unreacted aldehyde. GLC of the crude reaction mixture before TLC indicated the presence of three components in the ratio of 1:1:1.

For **10**: ir (neat) 6.07, 7.97, 9.49, 9.77, 10.37 μ; NMR (C$_6$D$_6$) δ 1.13, 1.21 (2 t, J = 7 Hz, CH$_3$), 3.88 (AB q, J = 7 Hz, CH$_2$O), 4.08 (2 q, J = 7 Hz, CH$_2$OP), 5.08 [t, J = ca. 3 Hz, CH(OEt)$_2$], 6.23 (m, J = 1, 18, 21 Hz, PCH=C), 6.85 (m, J = 3.5, 18, 21.5 Hz, PC=CH; NMR (CDCl$_3$) δ 1.3 (t), 1.4 (t), 3.7 (AB q), 4.22 (2 q), 5.13 (t), 6.20 (m), 6.80 (m).

Analysis of the Reaction Mixture Obtained from the Reduction of 6. A mixture of 1.05 g of **6** and 0.01 g of 10% Pd/CaCO$_3$ in 10 ml of C$_5$H$_5$N was hydrogenated at atmospheric pressure. The hy-

drogenation was stopped after 1 equiv of H$_2$ had been absorbed. The catalyst was filtered and the C$_5$H$_5$N evaporated under reduced pressure. The residue was submitted to preparative TLC on silica gel GF plates using EtOAc to develope the chromatograms. Three fractions were isolated and were identified as **6** (0.2 g, 19%), **9** (0.58 g, 55%), and **10** (0.08 g, 8%). GLC analysis of the crude reaction mixture on a 4-ft UCW 3.8% column indicated a 20:70:8.3 product distribution of the three components. The ir, GLC, TLC, and NMR data were those obtained previously for these compounds.

Diethyl 2-Formylvinylphosphonate (11) and Its 2,4-DNPH (12). A solution of 3.98 g (0.15 mol) of **9** in 37 ml of 97% HCOOH was kept at room temperature for 30 min and heated for 10 min at 70 °C. The HCOOH was evaporated under reduced pressure and the residue was distilled to give 2.04 g (70%) of **11**, bp 70–74 °C (0.06 Torr). Redistillation through a 15-cm Vigreux column yielded 1.75 g (60%) of **11**: bp 62–66 °C (0.07 Torr); ir (neat) 5.86, 6.19, 7.95, 9.50, 9.74, 10.25 μ; NMR (C$_6$D$_6$) δ 1.03 (t, J = 7 Hz, CH$_3$), 3.9 (2 q, J = 7, 8 Hz, CH$_2$OP), 6.27 (m, J = 11, 13 Hz, POCH=CH), 6.29 (m, J = 7, 13, 52 Hz, PO-CH=CH), 11.10 (d, J = 7 Hz, CHO).

Anal. Calcd for C$_7$H$_{13}$O$_4$P: C, 43.76; H, 6.82; P, 16.12. Found: C, 43.57; H, 6.68; P, 16.30.

A solution of 1.45 g (0.0076 mol) of **11** in 30 ml of 2,4-DNPH reagent[32] was allowed to stand for 5 min at room temperature. Water (6 ml) was added and the solution kept for 30 min at room temperature to allow complete crystallization of the hydrazone. The mixture was filtered to yield 1.82 g of crude **12** which was recrystallized from EtOH to yield pure **12**: mp 160.5–161.5 °C; ir (KBr) 6.21, 6.28, 6.37, 6.55, 6.65, 8.0, 9.51, 9.67 μ; NMR (CDCl$_3$) δ 1.37 (t, J = 7 Hz, CH$_3$), 4.17 (2 q, J = 7, ca. 8.5 Hz, CH$_2$OP), 6.16 (overlapping d, J = 17.2, 16.8 Hz, POCH=CH), 7.25 (m, J = 8.8, 16.8, 20.5 Hz, POCH=CH), 7.85 (d, J = ca. 9 Hz, CH=N), 7.95 (d, J = ca. 9.5 Hz), 8.35 (2 d, J = ca. 2.5, 9.5 Hz), 9.13 (d, J = ca. 2.5 Hz), 11.28 (bs, NH); NMR (C$_6$D$_6$) δ 1.13 (t), 4.0 (2 q), 5.87 (2 d), 6.40 (2 bm), 6.92–7.13 (olefin H), 7.25 (d), 7.80 (2 d), 8.78 (d), 10.55 (bs).

Anal. Calcd for C$_{13}$H$_{17}$N$_4$O$_7$P: C, 41.93; H, 4.60; N, 15.05; P, 8.32. Found: C, 42.02; H, 4.45; N, 14.93; P, 8.17.

Diethyl 3,3-Diethoxy-1-*cis*-propen-1-ylphosphonate-*1,2-d$_2$* (13). This was obtained by hydrogenation of **6** using D$_2$, 5% Pd/BaSO$_4$, and C$_5$H$_5$N as the solvent. GLC of the product on a 15% SE-30 (5 ft × 0.125 in. column) at 170 °C indicated it to be a mixture of at least two substances. The product was purified in the same way as that described for the nondeuterated material, cf. **9**: ir (neat) 6.18, 7.95, 9.4, 9.70, 10.30 μ; NMR (C$_6$D$_6$) δ 1.11, 1.15 (2 t, J = 7 Hz, CH$_3$), 3.95 (2 q, J = 7, 9 Hz, CH$_2$OP), 3.65 (AB q, J = 7 Hz, CH$_2$O), 6.18 [s, CH(OEt)$_2$]; mass spectrum m/e 239 (40.9), 224 (15), 223 (80), 222 (20), 211 (13), 195 (33), 194 (10), 193 (12), 167 (27), 165 (26), 164 (8), 155 (25), 149 (44), 148 (13), 139 (75), 138 (33), 137 (77), 136 (20), 135 (10), 131 (31), 130 (10), 129 (16), 123 (12), 122 (28), 121 (100), 120 (30), 111 (25), 110 (15), 109 (16), 103 (39), 100 (12), 94 (16), 93 (26), 87 (16), 84 (11), 83 (28), 82 (53), 81 (46), 75 (30).

3-Chloro-1-ethoxy-1-propen-2-ylphosphonyl Dichloride (17). **Method A.** Using the method of Tsivunin[7] a solution of 50 g (0.59 mol) of **14** in 335 ml of C$_6$H$_6$ was treated with 241 g of PCl$_5$ to give, after workup and distillation, 60 g (42%) of **17**: bp 147–152 °C (5 Torr) [lit.[7] yield 41%, bp 134–135 °C (4 Torr)]; ir (neat) 6.20, 7.9, 8.15 μ; NMR (C$_6$D$_6$) δ 0.73 (t, J = 7 Hz, CH$_3$), 3.33 (q, J = 7 Hz, CH$_2$O), 4.02 (d, J = 26 Hz, CH$_2$Cl), 7.12 (d, J = 10 Hz, OCH=C). The literature ir spectrum for the product formulated as **16** was essentially identical with that found for **17**, except for an additional ir absorption at 13.3 μ.

Method B. Using the method of Moskva[15] a solution of 12 g (0.09 mol) of **20** in 80 ml of C$_6$H$_6$ was treated with 42 g of PCl$_5$ to give after workup and distillation **17**, bp 133.5–135 °C (6 Torr). The ir and NMR spectra of this product were identical with those obtained in method A. The literature NMR [δ 1.35 (t), 3.91 (d, J = 23 Hz), 4.00 (q), 6.85 (d, J = 12 Hz)] differed in its shift values and its coupling constants from that of **17** prepared and observed by the present authors.

Diethyl 1,3-Diethoxy-1-*cis*-propen-2-ylphosphonate (19) and Diethyl 1,1-Diethoxy-2-propen-2-ylphosphonate (18). This was prepared according to the procedure described by Tsivunin[7] for the preparation of **4**. Thus 14.2 g (0.06 mol) of **17** was treated with 12.5 g of NaOEt (prepared from EtOH and NaH) in 75 ml of ether. The mixture was processed as described[7] and the solution distilled to give 12.7 g of crude product, bp 83–101 °C (0.02 Torr). Careful repeated fractional distillation yielded two products.

For **18**: bp 46–48 °C (0.85 Torr); 1.36 g (8.5%) yield; ir (neat) 3.32, 3.40, 3.43, 7.95, 9.45, 9.74, 10.35 μ; NMR (C$_6$D$_6$) δ 1.13 (t, J = 7 Hz, CH$_3$), 3.5 (m, J = 7 Hz, CH$_2$O), 4.05 (2 q, J = 7, 9 Hz, CH$_2$OP), 5.31 [m, J = 0.6, 0.8, 4 Hz, CH(OEt)$_2$], 6.28 (2 m, J = 0.6, 2.4, 43.2 Hz, POC=CH), 6.33 (2 m, J = 0.8, 2.4, 22.0 Hz, POC=CH); mass spec-

trum m/e 266 (0.1), 221 (40), 193 (60), 165 (30), 137 (88), 135 (10), 119 (37), 109 (11), 103 (100), 81 (23), 75 (48), 65 (18), 55 (20), metastable ions m/e 168.5, 141, 113.5, 54.6.

Anal. Calcd for $C_{11}H_{23}O_5P$: C, 49.62; H, 8.71; P, 11.63. Found: C, 49.40; H, 8.74; P, 11.51.

For 19: bp 115–117 °C (0.9 Torr) [lit. bp 148–149 °C (7 Torr)]; 5.5 g (34.5%) yield; ir (neat) 3.38, 3.43, 3.48, 3.53, 6.15, 8.05, 8.30, 9.15, 9.50, 9.75, 10.45 μ; NMR (C_6D_6) δ 0.83, 1.07, 1.20 (3 t, J = 7 Hz, CH$_3$), 3.44 (q, J = 7 Hz, CH$_2$O), 4.08 (2 q, J = 7, 8 Hz, CH$_2$OP), 4.28 (d, J = 18 Hz, CH$_2$OEt), 7.28 (d, J = 10 Hz, CH=C).

Diethyl 5-Methyl-2-formyl-1,4-cyclohexadien-1-ylphosphonate (23) and Its 2,4-DNPH (24). A solution of 5.0 g (0.026 mol) of 5 and 2.11 g (0.031 mol, 2.64 ml) of isoprene in 50 ml of C_6H_6 was kept for 70 h at room temperature. Evaporation of the volatiles under reduced pressure and distillation of the residue yielded 4.2 g (62%) of 23, bp 100–118 °C (0.04 Torr). Redistillation of the liquid through a 15-cm Vigreux column yielded 3.28 g of 23: bp 98–103 °C (0.02 Torr); ir (neat) 5.94, 6.18, 8.15, 9.6, 9.7, 9.95, 10.5 μ; NMR (CDCl$_3$) δ 1.35 (t, J = 7 Hz, CH$_3$), 1.73 (s, CH$_3$), 2.97 (s, CH$_2$ C=C), 4.18 (2 q, J = 7, 7.75 Hz, CH$_2$OP), 5.46 (s, CH=C), 10.67 (s, CHO); mass spectrum m/e 258 (6), 257 (12), 230 (24), 229 (85), 201 (37), 184 (12), 183 (32), 173 (80), 169 (17), 155 (18), 120 (35), 119 (29), 109 (12), 93 (62), 92 (36), 91 (100), metastable ions m/e 204.5, 176.5, 148.5, 139, 46.5.

Anal. Calcd for $C_{12}H_{19}O_4P$: C, 55.80; H, 7.41; P, 11.99. Found: C, 55.77; H, 7.35; P, 11.79.

Treatment of 0.95 g (0.0037 mol) of 23 with 10 ml of 2,4-DNPH reagent[32] gave 0.8 g of hydrazone. Recrystallization of the solid from EtOH yielded an analytical product: mp 150–152 °C; ir (KBr) 6.18, 6.29, 6.37, 6.60, 6.65, 7.43, 7.50, 8.03, 9.42, 9.80, 10.40 μ; NMR (C_6D_6) δ 1.11 (t, J = 7 Hz, CH$_3$), 1.60 (s, CH$_3$), 3.05 (m, CH$_2$C=C), 4.00 (m, J = 7, 8 Hz, CH$_2$OP), 5.4 (s, HC=C), 7.31 (d, J = 9 Hz), 7.84 (2 d, J = 3, 9 Hz), 8.78 (d, J = 3 Hz), 9.55 (s, CH=N), 11.0 (bs, NH); NMR (CDCl$_3$) δ 1.4 (t), 1.8 (bs), 3.13 (m), 4.16 (2 q), 5.53 (bs), 7.9 (d), 8.29 (2 d), 9.12 (d), 9.32 (bs), 11.23 (bs).

Anal. Calcd for $C_{18}H_{23}N_4O_7P$: C, 49.31; H, 5.28; N, 12.78; P, 7.06. Found: C, 49.19; H, 5.16; N, 12.53; P, 6.89.

Diethyl 5-Methyl-2-formylphenylphosphonate (25) and Its 2,4-DNPH (26). A solution of 4.2 g (0.016 mol) of 23 and 3.7 g (0.016 mol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 50 ml of C_6H_6 was stirred under N$_2$ for 42 h. The precipitate was filtered and the solution concentrated to yield a residue. Distillation yielded 2.34 g (55.7%) of 25 (considerable superheating was required to vacuum distill the product): ir (neat) 3.3, 5.9, 6.24, 7.95, 9.57, 9.75, 10.25 μ; NMR (CCl$_4$) δ 1.33 (t, J = 7 Hz, CH$_3$), 2.5 (bs, CH$_3$), 4.2 (2 q, J = 7, 8 Hz, CH$_2$OP), 7.36 (bd, J = 8 Hz, aromatic H), 7.52 (bd, J = 12 Hz), 7.85 (2 d, J = 6, 8 Hz), 10.63 (d, J = 2 Hz, CHO).

A solution of 1.29 g (0.005 mol) of 25 and 1.15 g of DDQ in 50 ml C_6H_6 was stirred under N$_2$ for 42 h. The precipitate was filtered and the solution concentrated to yield an oily residue. This was treated with 20 ml of 2,4-DNPH reagent.[32] The solution was heated at 50 °C for 1–2 min, then left overnight at room temperature. The precipitate was filtered and recrystallized from EtOH to yield an analytical sample: mp 169–171 °C; ir (KBr) 6.16, 6.26, 6.31, 6.60, 7.4, 7.5, 8.03, 9.76, 10.23 μ; NMR (CDCl$_3$) δ 1.37 (t, J = 7 Hz, CH$_3$), 2.47 (s, CH$_3$), 4.18 (2 q, J = 7, 8 Hz, CH$_2$OP), 7.45 (d), 7.72 (d, J = 8, 14 Hz), 8.06 (d, J = 9.5 Hz), 8.33 (2 d, J = 2, 9.5 Hz), 8.4 (d), 8.9 (bs, NH), 9.08 (d, J = 2 Hz), 11.30 (s, b, NH).

Anal. Calcd for $C_{18}H_{21}N_4O_7P$: C, 49.54; H, 4.87; N, 12.84; P, 7.09. Found: C, 49.36; H, 4.77; N, 12.74; P, 7.05.

Diethyl 2,5-Dimethylphenylphosphonate (27). Method A. A solution of 4.45 g (0.017 mol) of 25 in 90 ml of EtOH containing 0.89 g of 5% Pd/C was hydrogenated at an initial pressure of 50 psi until a theoretical amount of H$_2$ was absorbed. The catalyst was filtered, the solvents evaporated, and the residue distilled to give 27, bp 92–94 °C (0.025 Torr), in an almost quantitative yield. GLC using a 15% SE-30 column, 5 ft × 0.125 in., indicated the presence of a second component, but the concentration appeared to be <8%: ir (neat) 6.20, 8.0, 9.55, 9.75, 10.42 μ; NMR (neat) δ 1.27 (t, J = 7 Hz, CH$_3$), 2.28 (s, CH$_3$), 2.56 (s, CH$_3$), 4.12 (2 q, J = 8 Hz, CH$_2$OP), 7.25 (m), 7.81 (d, J = 14.8 Hz); mass spectrum m/e 242 (29), 186 (35), 185 (14), 170 (17), 169 (15), 168 (15), 167 (14), 133 (21), 105 (29), 104 (17), 103 (15), 90 (10), 76 (18), 31 (34), 28 (10), 27 (100).

Method B. A solution of 37 g (0.2 mol) of 2-bromo-p-xylene and 166 g of triethyl phosphite was placed in a quartz vessel. The solution was degassed by passing argon through it for 5 min. Photolysis was done using a Rayonet-Srinivasin-Griffin photochemical reactor RPR-100 with 16 lamps of 2537-nm wavelength. Distillation of the reaction solution yielded 32 g (66%) of 27, bp 99–103 °C (0.04 Torr). The ir and NMR spectra were the same as those obtained for the product derived from 23.

2,5-Dimethylphenylphosphonic Acid (28). Method A. A solution of 1 g of 27 (obtained by degradation) in 10 ml of TMSCl was heated in a Parr bomb for 6 days at 100 °C. Evaporation of the volatiles yielded a residue that was dissolved in EtOH. The EtOH was film evaporated and the process of dissolution and evaporation was repeated again. The solid was recrystallized from H$_2$O to give 28: mp 179–180 °C (lit.[18] mp 179–180 °C); ir (KBr) broad absorption band λ_{max} at 3.5 and 4.4, 6.18, 6.35, 8.0, 9.1, 9.92, 10.75, 12.2, 14.0, 14.35 μ; NMR (CD$_3$COCD$_3$) δ 2.33 (s, CH$_3$), 2.58 (s, CH$_3$), 7.15 (m, aromatic, 2 H), 7.61 (bd, J = 14 Hz, o-H), 10.63 (s, POH).

Method B. A mixture of 5 g (0.02 mol) of synthetic 27 and 20 ml of HCl was heated at reflux for 10 h. The reaction mixture was cooled and the crystalline solids filtered to yield 3.3 g of 28, mp ca. 170 °C. Recrystallization from H$_2$O yielded 28, mp 179–180 °C; mixture melting point with the product obtained from the degradation of 23 showed no melting point depression. The ir and NMR spectra of the two products were also identical.

Diethyl 2,4-Dimethylphenylphosphonate (32) and 2,4-Dimethylphenylphosphonic Acid (30). A solution of 2.51 g (0.01 mol) of 31 and 8.52 g (0.05 mol) of triethyl phosphite was placed in a quartz test tube and degassed by flushing with Ar for 5 min. Photolysis at 37 °C for 24 h using a Rayonet Srinivasin-Griffin photochemical reactor RPR-100, using 16 lamps of 2537 nm, yielded upon distillation 2.6 g (100%) of 32, bp 89 °C (0.005 Torr). This material was contaminated with a small amount of impurity which was visible in the NMR and could not be removed by distillation or acid washing (0.1 M HCl): ir (neat) 6.23, 8.0, 9.54, 9.75, 10.40 μ; NMR (C_6D_6) δ 1.07 (t, J = 7 Hz, CH$_3$), 2.07 (s, CH$_3$), 2.63 (s, CH$_3$), 4.00 (2 q, J = 7, 8 Hz, CH$_2$OP), 6.91 (bd, J = 5 Hz), 8.13 (2 d, J = 8, 14 Hz). GLC using 15% SE-30 column indicated this compound to be different from the product obtained in the previously described Diels–Alder degradation schema.

Anal. Calcd for $C_{12}H_{19}O_3P$: C, 59.50; H, 7.91; P, 12.79. Found: C, 59.89; H, 7.60; P, 13.66.

A mixture of 1.0 g (0.0041 mol) of 32 and 10 ml of concentrated HCl was refluxed for 9 h to give 0.24 g (31%) of 30, recrystallized from H$_2$O, mp 194 °C (lit.[20] mp 194 °C).

Diethyl 6-Formyl-3-methyl-3-cyclohexen-1-ylphosphonate (21) and Its 2,4-DNPH (22). Method A. A solution of 3.6 g (0.019 mol) of 11 and 1.36 g (0.02 mol) of isoprene was heated in a Parr bomb at 100 °C for 19 h. Distillation of the reaction solution yielded 3.0 g (61%) of 21: bp 109–112 °C (0.07 Torr) [lit.[7] yield 86%, bp 129–130 °C (2 Torr)]; ir (neat) 5.78, 8.0, 9.48, 9.75, 10.4 μ (lit.[7] ir 5.78, 6.12 μ); NMR (C_6D_6) δ 1.10 (t, J = 7 Hz, CH$_3$), 1.53 (s, CH$_3$), 1.76–3.0 (m, cyclohexene H hump), 4.0 (2 q, J = 7, 8 Hz, CH$_2$OP), 5.28 (bs, CH=C), 9.67, 10.1 (ratio 3:1) (bs, CHO).

A solution of 1.0 g of 21 and 16 ml of 2,4-DNPH reagent[32] was allowed to stand at room temperature for several hours. The solvent was evaporated and the residue crystallized on standing. Recrystallization from EtOH yielded 22: mp 155–156 °C; ir (KBr) 6.15, 6.30, 6.56, 6.64, 7.42, 7.78, 8.19, 9.45, 9.55, 9.68, 10.24 μ; NMR (CDCl$_3$) δ 1.33 (t, J = 7 Hz, CH$_3$), 1.73 (s, CH$_3$), 2.0–3.1 (m, cyclohexene protons), 4.13 (2 d, J = 7, 8 Hz, CH$_2$OP), 5.47 (bs, CH=C), 7.61 (d, J = 2.4, 9.6 Hz), 7.9 (d, J = 9.6 Hz), 8.03 (2 d, J = 2.4, 9.6 Hz), 9.33 (d, J = 2.4 Hz), 11.23 (bs, NH).

Anal. Calcd for $C_{18}H_{25}N_4O_7P$: C, 49.09; H, 5.72; N, 12.72; P, 7.03. Found: C, 48.96; H, 5.83; N, 12.60; P, 7.00.

Method B. A solution of 3.84 g (0.02 mol) of 11 and 1.36 g (0.02 mol) of isoprene was kept neat at room temperature under N$_2$ for 70 h. Distillation of the reaction mixture yielded 2.85 g (55%) of 21, bp 108–111 °C (0.07 Torr). The product by NMR appeared to be 1:1 mixture of two isomers which were isomeric in the CHO absorption.

Method C. A solution of 3.84 g (0.02 mol) of 11 and 1.36 g (0.02 mol) of isoprene in 40 ml of C_6H_6 was kept at room temperature for 70 h. Distillation gave 3.5 g of unreacted 11, bp 72–86 °C (0.25 Torr). The residue weighing 0.38 g (7%) was found to be 21, as indicated by NMR and GLC.

Dimethyl 5-Methyl-1,4-cyclohexadiene-1,2-dicarboxylate (34). Method A. A solution of 1.95 g (0.014 mol) of 7 and 1.02 g of isoprene was kept neat at room temperature for 70 h. Distillation of the reaction mixture yielded 0.46 g of 7, bp 78–80 °C (3 Torr) [lit.[33] bp 98 °C (20 Torr)], and 1.71 g (58%) of 34: bp 129–132 °C (3.5 Torr) [lit.[22] bp 122.5–124 °C (3 Torr)]; ir (neat) 5.8, 6.04, 7.9 μ; NMR (CDCl$_3$) δ 1.73 (s, CH$_3$), 2.97 (bs, CH$_2$ C=C), 3.81 (s, CH$_3$O), 5.47 (bs, J = ca. 1 Hz, CH=C).

Method B. A solution of 3.9 g (0.027 mol) of 7 and 2.04 g (0.03 mol) of isoprene in 60 ml of C_6H_6 was kept at room temperature for 70 h. Distillation of the reaction mixture yielded 3.32 g of 7, bp 78 °C (3.1 Torr) [lit.[33] bp 98 °C (20 Torr)], and 0.69 g (12%) of 34, bp 128 °C (3.4 Torr) [lit.[22] bp 122.5–124 °C (3 Torr)].

4-Methyl-1,3-cyclohexadiene-1-carboxaldehyde (35). Method A. A solution of 1.4 g (0.026 mol) of propiolaldehyde[34] and 1.8 g (0.026 mol) of isoprene was kept neat at room temperature for 70 h. Distillation of the reaction mixture yielded 2.0 g (63%) of **35**, bp 84–87 °C (10 Torr) [lit.[23] bp 95.5–96 °C (20 Torr)].

Method B. A solution of 2.8 g (0.052 mol) of **8** and 3.6 g (0.053 mol) of isoprene in 100 ml of Et₂O was kept at room temperature for 70 h. The volatiles were removed in vacuo and the residue weighing 0.34 g was distilled to give 0.14 g of **35**, bp 84–86 °C (11 Torr) [lit.[23] bp 95.5–96 °C (20 Torr)].

Registry No.—**5**, 58983-02-1; **6**, 58983-03-2; **7**, 762-42-5; **8**, 624-67-9; **9**, 58983-04-3; **10**, 58983-05-4; **11**, 58983-06-5; **12**, 58983-07-6; **13**, 58983-08-7; **14**, 557-31-3; **17**, 58983-09-8; **18**, 58983-10-1; **19**, 58983-11-2; **20**, 3054-95-3; **21**, 58983-12-3; **22**, 58983-13-4; **23**, 58983-14-5; **24**, 58983-15-6; **25**, 58983-16-7; **26**, 58983-17-8; **27**, 58983-18-9; **28**, 58983-19-0; **31**, 4214-28-2; **32**, 58983-20-3; **34**, 58983-21-4; PCl₅, 10026-13-8; triethyl phosphite, 122-52-1; isoprene, 78-79-5.

References and Notes

(1) (a) Paper in a series on Phosphonic Acid Chemistry. For previous paper in these studies (Pyridoxal Phosphate 5), see A. J. Rudinskas and T. L. Hullar, *J. Med. Chem.*, in press. (b) Supported in part by Grant AM-10234 from the U.S. Public Health Service. (c) On leave serving as Commissioner of Environmental Quality, Erie County, N.Y.
(2) C. E. Griffin and W. M. Daniewski, *J. Org. Chem.*, **35**, 1691 (1970).
(3) W. M. Daniewski and C. E. Griffin, *J. Org. Chem.*, **31**, 3236 (1966).
(4) D. Seyferth and J. D. H. Paetsch, *J. Org. Chem.*, **34**, 1483 (1969).
(5) E. C. Ladd, U.S. Patent 2 611 784 (Sept 23, 1952); *Chem. Abstr.*, **47**, 9355 (1953).
(6) A. N. Pudovik and M. G. Imaev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 916 (1952).
(7) V. S. Tsivunin, G. Kh. Kamai, and V. V. Kormachev, *Zh. Obshch. Khim.*, **36**, 1663 (1966).
(8) V. V. Kormachev, V. S. Tsivunin, N. A. Koren, A. A. Kutuev, and G. N. Kletsko, *Zh. Obshch. Khim.*, **39**, 2256 (1969).
(9) A. N. Pudovik, G. E. Yastrebova, V. I. Nikitina, and Yu. Yur Samitov, *Zh. Obshch. Khim.*, **38**, 292 (1968).
(10) B. I. Ionin and T. N. Timofeeva, *Russ. Chem. Rev. (Engl. Transl.)*, **41**, 390 (1972).
(11) A. A. Petrov, B. I. Ionin, and V. M. Ignatyev, *Tetrahedron Lett.*, 15 (1968).
(12) T. N. Timofeeva, V. M. Ignatyev, B. I. Ionin, and A. A. Petrov, *Zh. Obshch. Khim.*, **39**, 2446 (1969).
(13) D. J. Frost and J. Barzilay, *Recl. Trav. Chim. Pays-Bas*, **90**, 705 (1971).
(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Elmsford, N.Y., 1969, p 222.
(15) V. V. Moskva, L. A. Bashirova, T. V. Zykova, and A. I. Razumov, *Zh. Obshch. Khim.*, **40**, 2764 (1970).
(16) C. Benezra, *J. Am. Chem. Soc.*, **95**, 6890 (1973).
(17) R. Rabinowitz, *J. Org. Chem.*, **28**, 2975 (1963).
(18) J. Weller, *Ber.*, **21**, 1492 (1888).
(19) R. Obrycki and C. E. Griffin, *J. Org. Chem.*, **33**, 632 (1968).
(20) J. Weller, *Ber.*, **21**, 1718 (1888).
(21) In the case of some isomeric 2-methyl-1,3-butadien-1-ylphosphonates the lower field absorption of the γ proton in the cis isomer has been attributed to hydrogen bond formation between the phosphonyl oxygen and the proton: T. N. Timofeeva, L. N. Mashlyakovskii, B. I. Ionin, and A. A. Petrov, *Zh. Obshch. Khim.*, **39**, 1048 (1969); T. N. Timofeeva, B. I. Ionin, and A. A. Petrov, *ibid.*, **39**, 354 (1969).
(22) V. F. Kucheron and N. Ya. Grigoreva, *Zh. Obshch. Khim.*, **31**, 447 (1960).
(23) A. A. Petrov and N. P. Sopov, *Zh. Obshch. Khim.*, **25**, 517 (1955).
(24) B. A. Arbuzov, V. S. Vinogradova, N. A. Polezhaeva, and A. K. Shamsutdinova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 675 (1963).
(25) A. A. Petrov, M. A. Raksha, and V. L. Vinogradov, *Zh. Obshch. Khim.*, **36**, 715 (1966).
(26) V. V. Moskva, V. M. Ismailov, and A. I. Razumov, *Zh. Obshch. Khim.*, **40**, 1489 (1971).
(27) V. V. Moskva, G. F. Nazvanova, T. V. Zykova, and A. I. Razumov, *Zh. Obshch. Khim.*, **41**, 1489 (1971).
(28) V. V. Moskva, G. F. Nazvanova, T. V. Zykova, and A. I. Razumov, *Zh. Obshch. Khim.*, **41**, 1493 (1971).
(29) J. Sauer, H. Wiest, and A. Mielert, *Chem. Ber.*, **97**, 3183 (1964).
(30) T. Y. Shen and M. C. Whiting, *J. Chem. Soc.*, 1772 (1950).
(31) K. Alder and F. Farina, *An. R. Soc. Esp. Fis. Quim.*, Ser. B, **54**, 689 (1958); see subsequent papers also.
(32) The reagent consisted of 2 g of 2,4-dinitrophenylhydrazine in 50 ml of MeOH saturated with 3.5 g of HCl gas.
(33) I. Hedbron, A. H. Cook, H. M. Bernbury, and D. H. Hey, "Dictionary of Organic Compounds", Vol. 1, 4th ed, Oxford University Press, London, 1965, p 20.
(34) J. C. Sauer, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 813.

Electron Impact Induced Fragmentations and Rearrangements of Aliphatic, Heterocyclic Phosphine Oxides[1]

George L. Kenyon,*[2a,3] Dolan H. Eargle, Jr.,[2a] and Charles W. Koch[2b]

Department of Pharmaceutical Chemistry, University of California, San Francisco, California 94143, and Department of Chemistry, University of California, Berkeley, California 94720

Common electron impact induced fragmentations and rearrangements of 1-ethylphospholane 1-oxide (1), 1-ethylphosphorinane 1-oxide (2), 1-phosphabicyclo[2.2.1]heptane 1-oxide (3), and 1-phosphabicyclo[2.2.2]octane 1-oxide (4) were investigated, and the nature of the fragments were compared with those resulting from similar decompositions of trimethylphosphine oxide (5), triethylphosphine oxide (6), quinuclidine (7), and quinuclidine N-oxide (8). Details of ethylene loss from and concomitant rearrangement of 1 were investigated using specifically deuterium-labeled derivatives. Possible structures for some of the major fragments and rearrangement products are proposed.

Reports of the consequences of electron impaction upon carbonyl-containing organic compounds abound in the chemical literature.[4] In contrast, only a few reports have appeared concerning analogous studies on phosphoryl-containing organic substances; mass spectral studies on the simplest class within this series, aliphatic phosphine oxides, have been even scarcer,[5–8] and these reports have dealt almost exclusively with acyclic phosphine oxides. No systematic studies of the mass spectral behavior of aliphatic, heterocyclic phosphine oxides have appeared up to this time.

We have recently synthesized monocyclic and bicyclic phosphine oxides containing five- and six-membered rings, namely compounds 1–4.[9] In order to confirm these structural
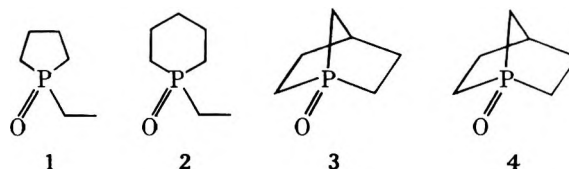
assignments, these compounds were subjected to electron impaction and the ions generated analyzed.[9] In this paper we present much more detailed observations on the fragmentations of 1–4. Particular attention has been given to molecular rearrangements induced by electron impaction. The fragmentation patterns of trimethylphosphine oxide (5), trieth-

Table I.   Major Mass Peaks in the Electron-Impact Spectra of 1—4[a]

Species	Fragment lost	Rel intensity, %			
		1 (132)[e]	2 (146)	3 (130)	4 (144)
M (parent ion)		25.6	51.0	100.0*[b]	100.0*
M − 1	H	15.9	17.8	24.9*	16.1*
M − 15	CH_3	2.0	d	6.2*	17.5*
M − 28	C_2H_4	100.0*	100.0*	91.6*	52.4*
M − 42	C_3H_6	d	24.7	d	1.6*
M − 56	C_4H_8	25.0*	88.9*[c]	2.6*[c]	14.4[c]
M − 68	C_5H_8	d	13.2*[c]	d	d

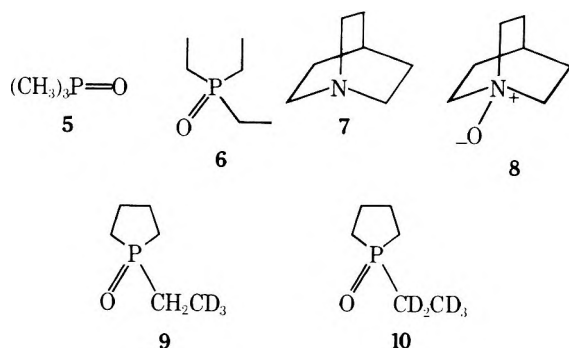[a] Complete listings of fragments lost, their relative intensities and metastable transitions (where observed) for compounds examined in this study appear in the microfilm edition of this volume of the journal (see paragraph at end of paper regarding supplementary material). [b] Asterisk denotes confirmation by observation of metastable peak. [c] Metastables were found which indicated that these fragments were derived from other than [M] ·+. [d] Less than 2% of the base peak. [e] Compound (mol wt).

ylphosphine oxide (6), quinuclidine (7), and quinuclidine N-oxide (8), and specifically deuterated compounds 9 and 10
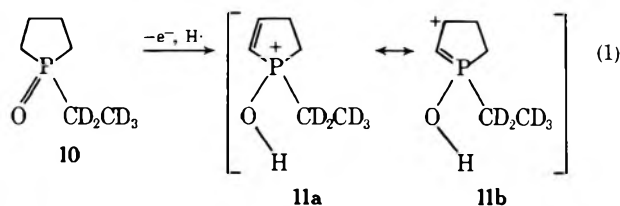

also have been examined in this study for purposes of comparison and mechanistic elucidation. Of the compounds 1–4, 4 is of potential interest pharmacologically because of its close structural relationship to the quinuclidine moiety of the antimalarial quinine.

Results and Discussion

Complete listings of peaks found, their relative intensities and metastable transitions (where observed) for compounds 1–10 appear in the microfilm edition of this volume of the journal (see paragraph at end of paper regarding supplementary material). Table I summarizes the major peaks observed in the electron-impact mass spectra of heterocyclic phosphine oxides 1–4. All four compounds gave relatively strong parent ions; indeed, parent ions are the base peaks for the bicyclic phosphine oxides 3 and 4. Phosphine oxides of this type also exhibit great thermal stability; for example, bicyclic phosphine oxide 4 melts with no apparent decomposition between 291 and 293 °C and may be recovered in high yield after heating for 1 month at 152 °C in 2 N HCl in a sealed tube.[10]

Prominent peaks also appear at M − 1 in all four cases. In order to shed light on the nature of the M − 1 peak, using compound 1 as a specific example, the electron-impact spectrum of compound 10, perdeuterated on the ethyl group, was examined. Once again a strong M − 1 peak appeared (35.0% of the base peak; see eq 1) whereas the M − 2 peak was only 6.4% of the base peak.

It is possible that a deuterium isotope effect may be oper-

ating to discriminate against the loss of a deuterium from the perdeuterated ethyl group of 10. Owing to the relatively high energies involved in the electron impact process, however, such deuterium isotope effects are, when they have been determined in similar cases, generally rather small (~1–4%).[11,12]

This experiment, which is depicted in eq 1, establishes that the hydrogen which is lost in this specific case must come largely from the ring. Our conclusion is based in part on the assumption that major amounts of H/D scrambling between the ethyl side-chain group and the ring do not occur. This assumption will be examined more quantitatively later in the discussion. Also, that the M − 2 peak is relatively small suggests that deuterium loss from the side chain is minor.

Resonance structures 11a and 11b are reasonable representations of the M − 1 peak. Such phosphonium ions as 11a are the well-known protonation products derived from phosphine oxides;[13] also, having the double bond conjugated in this way imparts some secondary carbonium ion character to the structure. The fact that trimethylphosphine oxide (5) has no β hydrogens and no detectable M − 1 peak is consistent with the proposed structure for the M − 1 fragment. Also, the idea leads correctly to the prediction that triethylphosphine oxide (6) should have a relatively weak M − 1 peak since, although it has β hydrogens available, the corresponding resonance hybrid representative of its M − 1 peak would have primary rather than secondary carbonium ion character.

Compounds 1, 2, and triethylphosphine oxide (6) all give base peaks corresponding to M − 28 (M − C_2H_4). In the case of compound 1, for example, this corresponds for the most part to the rearrangement shown in eq 2. Although this type of
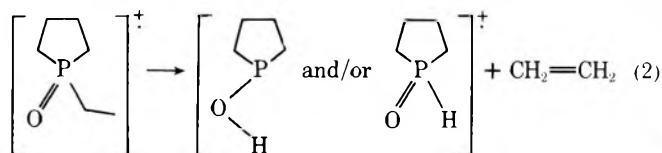
rearrangement has been noted before in the electron impact induced fragmentation of alkyl-substituted phosphine oxides,[7,8] the origin of the hydrogen which remains with the phosphorus-containing fragment has not been previously examined. In order to examine this question, specifically deuterated compounds 9 and 10 were synthesized. Table II shows comparisons among the relative intensities of the pertinent fragments of 1, 9, and 10. Interpretation of the data in Table II is complicated by the fact that the large M − 1 peak (see above) in each case also fragments in an analogous fashion to that shown in eq 2, giving rise in the case of compound 1, for example, to a strong peak at M − 29. The data of Table II are consistent with the conclusion that *either* an α or a β hydrogen (or deuterium) may migrate to the phosphorus-containing fragment in the course of the rearrangement. In the case of compound 9 at least, α-hydrogen migration dominates;

Table II. Comparison of M − Ethylene Peaks in the Electron-Impact Induced Fragmentations of 1, 9, and 10

Compd	Rel intensity, %[a]			
	103	104	105	106
1	32.8	(100.0)	5.1	0
9	52.9	(100.0)	33.8	10.5
10	50.7	22.8	(100.0)	10.5

[a] The relative intensities for these particular m/e values were normalized to make the largest peak for each compound 100%.

Table III. Evidence for Deuterium Migration into the Ring from the Side Chain in the Electron-Impact Induced Fragmentation of 10

Fragment	Rel intensity, %[a]	
	1	10
$[C_3H_5]^+$	5.3	20.6
$[C_3H_4D]^+$	0	6.1
$[C_4H_7]^+$	7.7	25.7
$[C_4H_6D]^+$	0	6.6

[a] Relative intensities are reported relative to the base peak in the spectrum of each compound.

this may be reflecting a slight discrimination against β-hydrogen migration owing to operation of a deuterium isotope effect.[11,12]

Another complicating factor in the interpretation of the spectra of 9 and 10 relative to that of 1 is the fact that some H/D scrambling is occurring upon electron impaction. To look at this possibility, fragments of 1 and 10 which have the highest probability of arising *only* from the carbons and hydrogens in the ring were chosen for examination (see Table III). It may be concluded from examination of this data that some deuteriums of 10 are migrating into the ring positions. This suggests that some of the β deuteriums on the ethyl group of 9 may also be migrating to the α positions of this ethyl group, accounting for some of the distribution of deuteriums in the fragments listed in Table II.
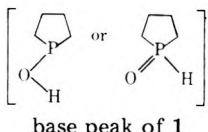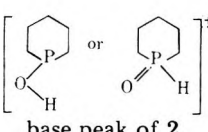
The complications which arise in interpreting the data in Table II are similar to those which were found by those investigating which hydrogen is preferentially abstracted by the carbonyl oxygen in the course of the McLafferty rearrangement.[4] That is, some hydrogens (or deuteriums) which remain with the carbonyl fragment in the McLafferty rearrangement of carboxylic acid esters may come from the α, β, γ, or δ positions.[14,15] Again, only small deuterium-isotope effects appear to be operating.[15] Also, some H/D scrambling reportedly occurs in the McLafferty rearrangement of partly deuterated aliphatic ketones.[16]

Some of the M − 28 peak for 1 is undoubtedly arising from cleavage of C_2H_4 from the ring, rather than from the ethyl group. The evidence for this is that although the base peak of 10 is at m/e 105 (corresponding to loss of C_2D_4), a strong peak at m/e 109 (51.6% relative intensity) also appears, which corresponds to loss of C_2H_4.

Table IV shows comparisons among the fragmentations of the base (M − 28) peaks in both 1 and 2. It can be seen that, as in the parent ions themselves, loss of a single hydrogen from these M − 28 peaks is a common process, preceding the loss of many simple fragments. In the case of compounds 9 and 10 many of the fragments corresponding to those shown in Table IV are accompanied by corresponding peaks containing one or more deuteriums, whose relative intensities confirm the notion of H/D scrambling discussed above.

Bicyclic phosphine oxides 3 and 4 show large fragments corresponding to M − 28 (loss of C_2H_4), and each also shows

Table IV. Comparisons among Decompositions of M − 28 (Base) Peaks of 1 and 2[a]

[a] See footnote a, Table I. [b] Asterisk denotes confirmation by observation of metastable peak.

fragments corresponding to M − 15 (loss of CH_3). The relatively large peak (17.5% relative intensity of the base peak) for loss of CH_3 from 4 was quite unexpected. In order to examine the generality of loss of CH_3 from structures of this type, the electron-impact spectra of both quinuclidine (7) and quinuclidine N-oxide (8) were examined.

The electron-impact spectrum of 8, isoelectronic with phosphine oxide 4, was quite different in character from that of 4. Loss of oxygen, a phenomenon observed previously in the electron-impact mass spectra of amine N-oxides,[17] is the predominant process. Consequently, a closer parallel to the character of the fragmentation of 4 was found in the fragmentation of quinuclidine (7) itself. Indeed many of the peaks observed in the electron-impact mass spectrum of 8 may be shown to be coming from the molecular ion of 7 which is formed from 8 by loss of oxygen. Significantly, the spectrum of 7 shows relatively large peaks corresponding to M − 15 (18.9% relative intensity), M − 28 (29.4%), and M − 29 (34.1%).

In order to account for these observations the following possibility is presented. The molecular ions of both 4 and 7 could be isomerizing via hydrogen shifts into one or more of the structures 4a–d and 7a–d shown below. By analogy to the electron-impact fragmentation of 1 [and the M − 1 peaks of 1 (see Table IV)], 4, for example, would be expected to show relatively large peaks corresponding to the loss of C_2H_4 from 4a or 4b, and to the loss of CH_3 from 4c or 4d. In an analogous

4, X = P=O
7, X = N

4a   4b   4c   4d
7a   7b   7c   7d
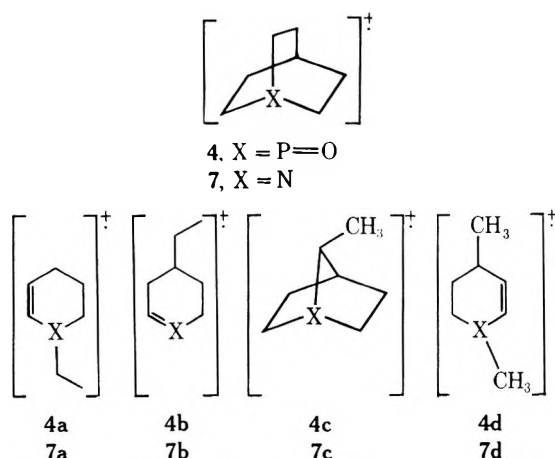
fashion, bicyclic phosphine oxide 3 might rearrange into one or more of the following structures (3a–d). Again these iso-

3a   3b   3c   3d
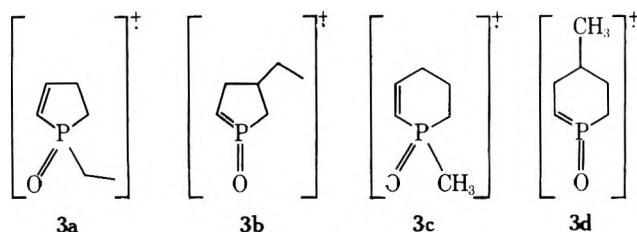
meric rearrangment products may be the parents of at least portions of the M − 15 and M − 28 fragmentation peaks.

The possibility that the hypothetical rearrangements shown above are thermal processes, not induced by electron impaction, was examined as follows. Electron-impact mass spectra for both 4 and 7 were examined as a function of inlet temperature. The relative ratios of peaks (e.g., M vs. M − 15) did not change appreciably over a wide temperature range. Thus, these processes are electron-impact induced. In contrast, the ratio of [M]/[M − 16] for quinuclidine *N*-oxide (8) decreased continuously as the inlet temperature was raised; this confirms the idea that loss of oxygen from such amine *N*-oxides is a thermal process.[17]

Experimental Section

Methods. Electron-impact mass spectra of 1–6 were obtained using either a Consolidated Model 21-103C or a Consolidated Model 21-110B double-focusing, high-resolution spectrometer at the University of California, Berkeley, and the corresponding spectra of 9 and 10 were observed at the University of California, San Francisco, using an Associated Electrical Industries MS-12 mass spectrometer coupled to an Infotronics Model 2400 gas–liquid chromatograph (GLC). Electron-impact spectra for 7 and 8 were measured using this same spectrometer with direct injection. Chemical ionization mass spectra were measured at the University of California, San Francisco, using an Associated Electrical Industries MS-902 mass spectrometer with isobutane as reagent gas. ^{1}H NMR spectra were taken using a Varian A-60 spectrometer using Me$_4$Si as an external standard. Melting points are uncorrected.

Materials. 1-Ethylphospholane 1-oxide (1), 1-ethylphosphorinane 1-oxide (2), 1-phosphabicyclo[2.2.1]heptane 1-oxide (3), and 1-phosphabicyclo[2.2.2]octane 1-oxide (4) were all prepared as described previously.[9] Both trimethylphosphine oxide (5) and triethylphosphine oxide (6) were obtained from K and K Laboratories Inc., Hollywood, Calif.

1-(Ethyl-*2,2,2*-d_3) phospholane 1-oxide (9) and 1-(ethyl-d_5)-phospholane 1-oxide (10) were prepared as follows. The appropriately deuterium-labeled sample of ethanol (BioRad Laboratories, Richmond, Calif.) (1.42 ml, 0.024 mol) was added over 15 min to an ice-cold, stirred solution of 5.0 g (0.026 mol) of freshly distilled *p*-toluenesulfonyl chloride in 10 ml of dry pyridine. The mixture was stirred at 0 °C for 3 h, diluted with 100 ml of ice-cold 6 N HCl, and then extracted with ligroin (bp 30–60 °C). The ligroin extract was washed with 5% NaOH solution and dried over Na$_2$CO$_3$. After removal of solvent, 2.20 g (0.011 mol, 46% yield) of appropriately deuterated

ethyl *p*-toluenesulfonate remained. Ethyl-*2,2,2*-d_3 *p*-toluenesulfonate gave the following NMR spectrum (neat): δ 2.02 (s, 3 H), 3.7 (s, 2 H), 7.02 (d, 2 H, *J* = 8 Hz), 7.47 (d, 2 H, *J* = 8 Hz). The NMR spectrum of ethyl-d_5 *p*-toluenesulfonate measured under identical conditions was the same except that the singlet at δ 3.7 was missing. All peaks were matched with those of ethyl *p*-toluenesulfonate itself.

The appropriately deuterated samples of diethyl ethylphosphonate were prepared by adapting the previously reported procedure of Harvey et al.[18] To a very dry, 100-ml, three-necked flask fitted with a drying tube and two pressure-equalized dropping funnels was added 0.30 g (0.012 mol, 10% molar excess) of NaH (as a 57% mineral oil suspension, Alfa Inorganics) in 30 ml of dry tetrahydrofuran (THF). This and all other solutions used in this portion of the synthesis were flushed with dry N$_2$ at all stages. In one funnel was placed 5 ml of dry THF and freshly distilled diethyl phosphonate (Aldrich, 1.54 g, 0.011 mol) added by syringe to the solvent. Into the other funnel was placed 5 ml of THF and appropriately deuterated ethyl tosylate (2.29 g, 0.011 mol). The diethyl phosphonate solution was slowly added to the dry ice–methanol-cooled, stirred solution in the flask, and stirring was continued for 0.5 h. Very little foaming occurred. The tosylate solution was then slowly added to the solution at room temperature and allowed to stir for an additional 72 h. At this time 20 ml of H$_2$O and 30–40 ml of ligroin were added to the solution. This mixture was filtered and the ligroin extracts separated. The aqueous extract was itself extracted with CHCl$_3$ (50 ml), and, after drying over Na$_2$SO$_4$ and evaporation of the CHCl$_3$ by a stream of N$_2$, yielded 0.472 g of deuterated diethyl ethylphosphonate. Diethyl ethyl-*2,2,2*-d_3-phosphonate showed the following NMR spectrum (CDCl$_3$): δ 1.0 (t, 6 H, *J* = 7 Hz), 1.5 (d, 2 H, *J* = 20 Hz), 3.8 (m, 4 H). Diethyl ethyl-d_5-phosphonate had the same NMR spectrum (CDCl$_3$) except that the doublet at δ 1.5 was missing.

The deuterated final products, 9 and 10, were prepared according to the procedure of Wetzel and Kenyon,[9] but miniaturized as follows. To a 100-ml flask, purged with N$_2$ and containing a solution of freshly distilled 1,4-dibromobutane (Eastman, 0.35 g, 1.62 mmol) in 25 ml of THF, was added 0.77 g of NaAlH$_2$(C$_2$H$_5$)$_2$ (0.15 mmol, a 25% solution in toluene, Ethyl Corp., Baton Rouge, La.) in 5 ml of THF and the appropriately deuterated diethyl ethylphosphonate (0.27 g, 1.63 mmol) also in 5 ml of THF. Transfer of the NaAlH$_2$(C$_2$H$_5$)$_2$ solution was carried out using an N$_2$-filled syringe. Stirring was continued for 3 days. The final CHCl$_3$ extract was evaporated leaving 88 mg of a mixture of products. This mixture was separated only by use of the GLC–MS system described above, and the appropriate GLC peak (identified by comparison with the retention time for authentic, nonlabeled 1) was chosen for mass spectral display.

1-Azabicyclo[2.2.2]octane 1-oxide (quinuclidine *N*-oxide, 8) was prepared by the procedure below which was adapted from that reported by Craig and Purushothaman.[19] An attempt to synthesize this compound by the previously reported method[20] was unsuccessful in our hands.

To an ice-cold, stirred solution of 0.198 g (1.34 mmol) of quinuclidine hydrochloride (Aldrich) in 5 ml of CHCl$_3$ was added over a 5-min period 0.278 g (1.34 mmol) of 85% *m*-chloroperbenzoic acid (Aldrich). A precipitate formed soon after the addition which in turn redissolved in about 1 h. The solution was stirred for 12 h at 25 °C. The resulting product mixture was applied to a column of basic alumina (50 × 1.7 cm) which had been prepared with ligroin, and a primary elution was made with CHCl$_3$ to expel unreacted quinuclidine. The quinuclidine *N*-oxide was then eluted with 5% MeOH–CHCl$_3$ (v/v). The benzoic acid remained on the column. After removal of solvent 0.116 g (68% yield) of quinuclidine *N*-oxide remained as a very hygroscopic solid, mp 120 °C dec. Accurate mass measurement of its mass spectral parent ion (M + 1) confirmed its composition: calcd for C$_7$H$_{14}$NO$^+$, 128.1075; found, 128.1094. NMR (CDCl$_3$) peaks appeared at δ 2.03 (m, 7 H, β and γ hydrogens), 3.45 (m, 6 H, α hydrogens). Quinuclidine *N*-oxide hydrochloride was prepared by passing excess, dry HCl gas through a CHCl$_3$ solution of quinuclidine *N*-oxide; NMR (CDCl$_3$) peaks appeared at δ 2.25 (m, 7 H, β and γ hydrogens), 3.95 (m, 6 H, α hydrogens), 4.75 (s, 1 H, OH). For comparison, NMR spectra of both quinuclidine (7) and quinuclidine hydrochloride were measured under the same conditions. Quinuclidine (7) had NMR (CDCl$_3$) peaks at δ 1.56 (m, 7 H, β and γ hydrogens), 2.95 (m, 6 H, α hydrogens). Quinuclidine hydrochloride had NMR (CDCl$_3$) peaks at δ 2.00 (m, 7 H, β and γ hydrogens), 3.41 (m, 6 H, α hydrogens), 5.12 (s, 1 H, NH).

Supplementary Material Available. Two tables, one giving comprehensive listings of relative intensities of peaks observed (and, in some cases, accurately mass-measured) and another listing metastable transitions which have been observed in these studies (23 pages). Ordering information is given on any current masthead page.

References and Notes

(1) A preliminary account of this work was presented at the Pacific Conference on Chemistry and Spectroscopy, Los Angeles, Calif., Oct 1975.
(2) (a) Department of Pharmaceutical Chemistry, University of California, San Francisco, Calif. (b) Department of Chemistry, University of California, Berkeley, Calif.
(3) Recipient of a Career Development Award, AM 00014, from the National Institute of Arthritis, Metabolism and Digestive Diseases.
(4) For a review, see M. M. Bursey and M. K. Hoffman in "Mass Spectrometry, Techniques and Applications", G. W. Milne, Ed., Wiley-Interscience, New York, N.Y., 1971, pp 373–417.
(5) M. Halmann and Y. Klein in "Advances in Mass Spectroscopy", Vol. 3, Elsevier, Amsterdam, 1966, p 267.
(6) F. Seel and K. D. Velleman, *Chem. Ber.*, **104**, 2972 (1971).
(7) Y. Kashman and E. Benary, *Tetrahedron*, **28**, 4091 (1972).
(8) R. G. Gillis and J. L. Occoclowitz in "Analytical Chemistry of Phosphorus Compounds", M. Halmann, Ed., Wiley-Interscience, New York, N.Y., 1972, pp 295–331.
(9) R. B. Wetzel and G. L. Kenyon, *J. Am. Chem. Soc.*, **96**, 5189 (1974).
(10) R. B. Wetzel and G. L. Kenyon, *J. Am. Chem. Soc.*, **96**, 5199 (1974).
(11) S. Meyerson, H. M. Grubb, and R. W. Vander Haar, *J. Chem. Phys.*, **39**, 1445 (1965).
(12) A. G. Harrison, E. G. Jones, S. K. Gupta, and G. P. Nagy, *Can. J. Chem.*, **44**, 1967 (1966).
(13) P. Haake, R. D. Cook, and G. H. Hurst, *J. Am. Chem. Soc.*, **89**, 2650 (1967).
(14) F. W. McLafferty and M. C. Hamming, *Chem. Ind. (London)*, 1366 (1958).
(15) C. Djerassi and C. Fenselau, *J. Am. Chem. Soc.*, **87**, 5756 (1965).
(16) A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *Chem. Commun.*, 1269 (1968).
(17) F. Dagne and N. Castagnoli, Jr., *J. Med. Chem.*, **15**, 840 (1972).
(18) R. G. Harvey, T. C. Meyers, H. J. Jacobson, and E. V. Jensen, *J. Am. Chem. Soc.*, **79**, 2612 (1957).
(19) J. C. Craig and K. K. Purushothaman, *J. Org. Chem.*, **35**, 1721 (1970).
(20) E. E. Mikhlina, V. Y. Vorobeva, S. S. Bobyleva, and L. N. Yakhontov, *Khim. Farm. Zh.*, 15 (1969); *Chem. Abstr.*, **72**, 66779d (1970).

Meta Bridging Reactions of Electron-Deficient Aromatics. 3. Isomeric Bridging of Di-, Tri-, and Tetranitronaphthalenes to 2- and 3-Benzazocines

Raymond R. Bard and Michael J. Strauss*

Chemistry Department, University of Vermont, Burlington, Vermont 05401

The preparation of a series of 2- and 3-benzazocines is described which utilizes a one-step meta-bridging reaction of polynitronaphthalenes. The mode of bridging depends on the number of nitro groups in the aromatic substrate. A detailed chemical shift analysis is used to assign product structure. Evidence is presented which shows that the precursor of meta-bridged products in benzenoid systems is not a carbon bonded anionic σ complex as previously reported.

We recently reported the novel meta-bridging reactions[1] of electron-deficient benzenes and naphthalenes with amidines.[2] The initial products of such reactions are σ complexes[3-5] which in certain instances undergo intramolecular cyclization to give meta-bridged products.[6] The reaction is a useful synthesis of 1,5-methano-3-benzazocines (6,7-benzomorphans), potentially useful narcotic antagonists.[7,8] Several of the 3-benzazocine amidinium nitronates which we have prepared (vide infra) are long-acting narcotic antagonists in mice.[9] We present here a detailed product study involving reactions of deuterium labeled napthalenes which provides evidence for isomeric modes of bridging. This work allows a more definitive assignment of product structures and provides additional evidence to substantiate the way in which meta bridging occurs.

Our previous work[2] resulted in the isolation of only two types of adducts, **1** and **3**, from the reaction of amidines with *sym*-trinitrobenzene (TNB), 1,3-di- and 1,3,6,8-tetranitro-

3a (as zwitterion or salt)   **1b**

2b

3b (as zwitterion or salt)

1a   **2a**
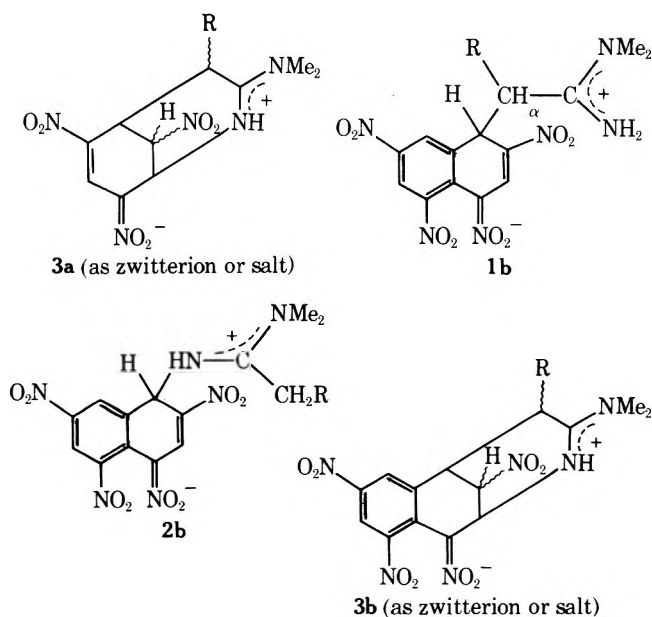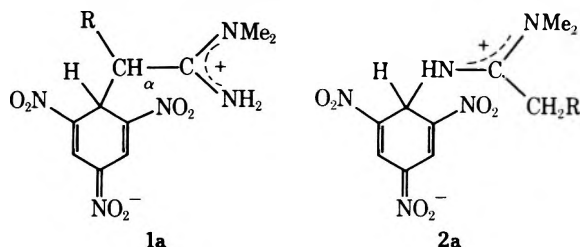
naphthalene (DNN and TETNN). When R in the starting amidine was alkyl only adducts like **1** were obtained, with *no evidence for cyclized products like* **3**. The adducts **1** could not be induced to cyclize under a variety of conditions in which the amidine:aromatic ratio was varied. Interestingly, when R
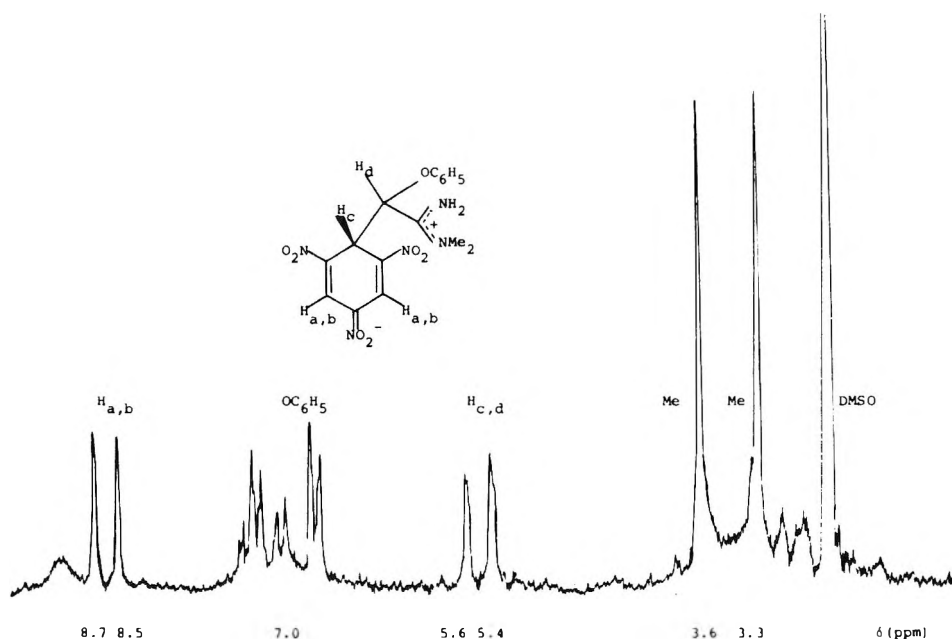
Figure 1.

was phenyl *only cyclized products like* **3** *were obtained.*

We presumed that when R = phenyl the adducts **1** were precursors of **3**, the aromatic side chain facilitating cyclization by acidification of H_α.
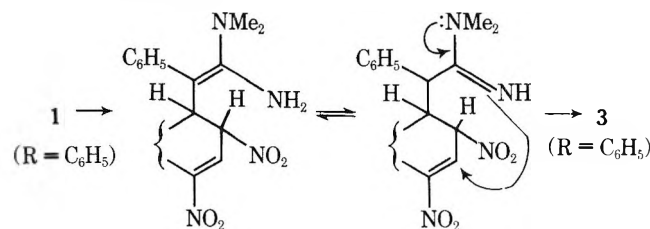
The results presented here are concerned with α-phenoxy-*N,N*-dimethylacetamidine, which reacts more slowly than the α-phenyl analogues, aromatics of intermediate reactivity, 1,3,6-tri- and 1,3,8-trinitronaphthalene (TNN), as well as 1-deuterated 2,4-di- and 2,4,5,7-tetranitronaphthalenes. These experiments have allowed us to distinguish isomeric modes of addition, a dramatic change in reactivity in going from di- and tri- to tetranitronaphthalenes, and also provide indirect evidence for intermediate complexes like **2** in meta-bridging reactions of amidines.

Mixing α-alkyl-*N,N*-dimethylacetamidine with TNB, DNN, or TETNN in Me$_2$SO produces solutions which instantaneously exhibit visible spectra characteristic of the carbon-bonded anionic σ complexes **1**,[2–5] isolated as the final products. On the other hand, with α-phenyl-*N,N*-dimethylacetamidine such solutions instantaneously exhibit spectra characteristic of isolated bridged adducts like **3**.[2] Only with a very large excess of aromatic do such solutions show transient spectra characteristic of C-bonded complexes like **1**.

After attempting such reactions with many different types of α-substituted amidines we were finally able to isolate both the pure crystalline adduct **5a** and the meta-bridged product **6** from a Me$_2$SO solution of α-phenoxy-*N,N*-dimethylacetamidine and TNB. Our intent was to study cyclization of the isolated σ complex **5a**.

Addition of 2 equiv of α-phenoxy-*N,N*-dimethylacetamidine (**4**) to 1 equiv of TNB in Me$_2$SO yields a solution with absorption maxima at 470, 510, and 570 nm. The 510-nm maximum is characteristic of the nitropropene nitronate function in **6**,[2,6] and the 470- and 570-nm maxima are characteristic of the C-bonded complex **5a**.[2,4,6] Workup and fil-

tration of the recrystallized product affords **6** as the α-phenoxy-*N,N*-dimethylacetamidinium salt, which can be converted to the zwitterion **3a** (R = C$_6$H$_5$O) by addition of triethylammonium chloride (see Experimental Section). Upon standing, the filtrate obtained from the workup and recrystallization of **6** deposits well-formed crystals of the addition complex **5a**. The ^{1}H NMR spectrum of purified **5a** is shown in Figure 1. *Most surprisingly, all attempts to induce cyclization of* **5a** *to* **6** *with excess amidine in* Me$_2$SO *failed.*

The only reasonable alternative route to **6** is through the N-bonded addition complex **5b**. If in fact **5b** is a precursor of **6** it is present in very low concentrations as there is no evidence
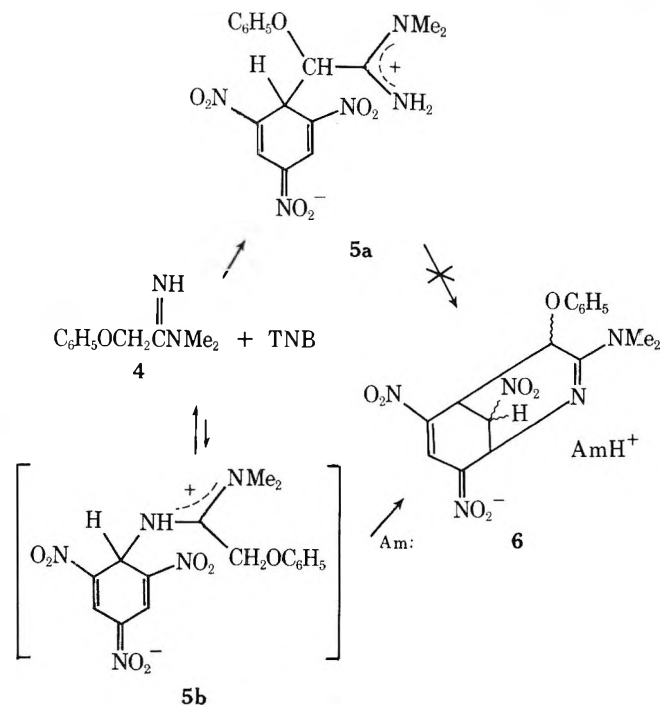
for it in the visible or ^{1}H NMR spectra of the reaction solution. We had previously assumed that the complex **1b**, analogous to **5a**, was the precursor of meta-bridged naphthalene adducts like **3b**. If this is not the case the possibility of isomeric bridged adducts resulting from reaction of polynitronaphthalenes and amidines must be considered, since either of the ring systems

7 or 8 could result depending on whether initial C or N attack occurs at C-1 or C-3.

7   8
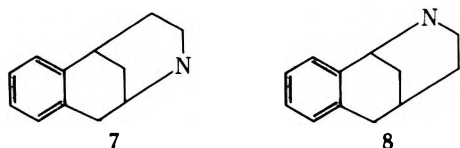
Attempts to isolate addition adducts and/or meta-bridged products from the reaction of polynitronaphthalenes and α-phenoxy-*N*,*N*-dimethylacetamidine failed. In ethanol reaction does not occur at a significant rate and in Me₂SO a complex mixture was obtained with evidence for nitrite displacement products with TETNN. In Me₂SO DNN gave only a red tar which decomposed to starting materials on workup. The problem of substantiating possible isomeric addition was approached by reaction of the more reactive α-phenyl-*N*,*N*-dimethylacetamidine with the deuterium-labeled substrates 9, 9a, and 10. In addition polynitronaphthalenes of increasing electrophilicity 11–14 were treated with this amidine in both ethanol and Me₂SO solutions. TNB-d_3 was prepared by heating TNB in NaOD/DMF solution. The prepa-
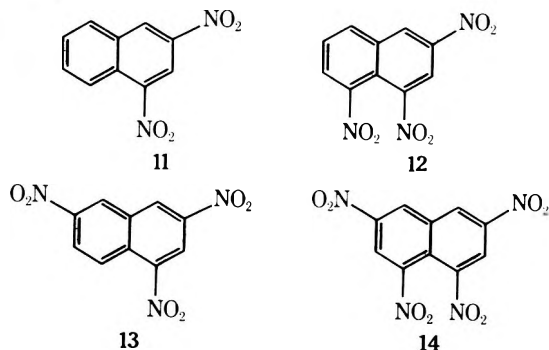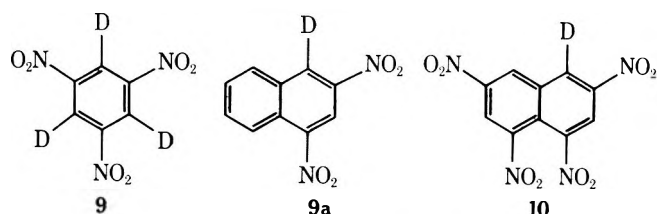
9   9a   10

11   12

13   14
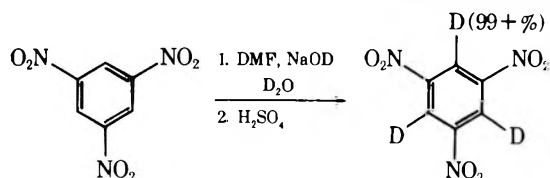
ration of 1-deuterio-2,4-dinitronaphthalene was achieved by dehalogenation of 1-chloro-2,4-dinitronaphthalene in molten deuteriobenzoic acid containing electrolytic copper dust in a procedure similar to that described for the preparation of DNN.[10] Nitration of this C-1 deuterated DNN with fuming nitric acid afforded the C-1 deuterated TETNN. The 1,3,6-
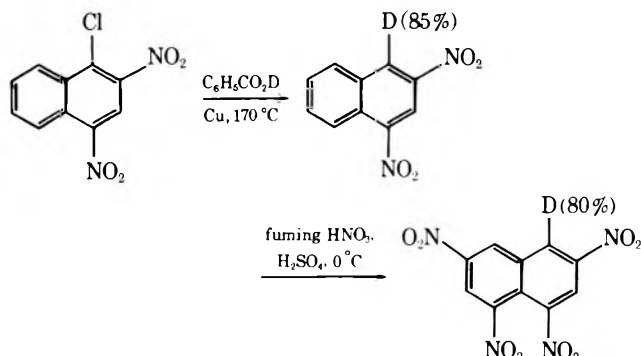
trinitronaphthalene 13 was prepared from 1,8-naphthalic anhydride by nitration and decarboxylation to 2,7-dinitronaphthalene. Nitration of this compound at room temperature afforded 13. The 1,3,8-trinitronaphthalene 12 was prepared

13

12
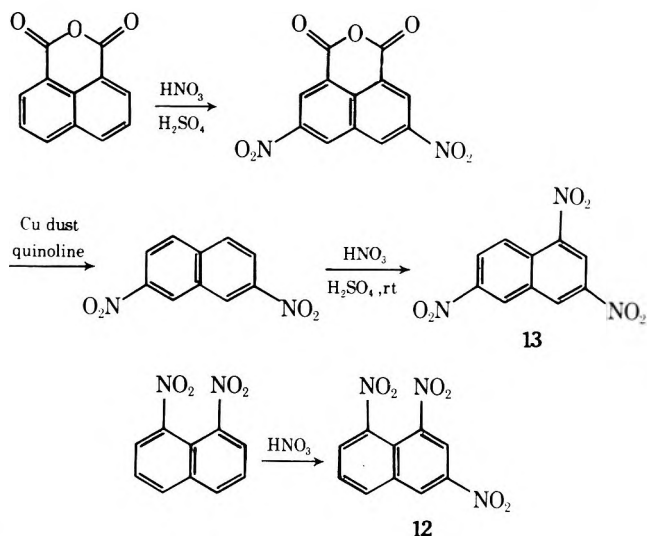
by mononitration of the commercially available 1,8-dinitronaphthalene.

The amidines were prepared from appropriate nitriles via the imidate salts which were treated with dimethylamine.[2]
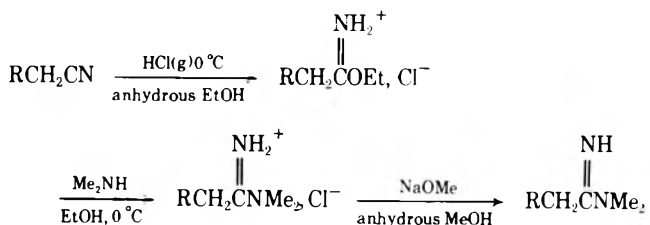
Each of the aromatics was treated with 2 equiv of amidine in Me₂SO or ethanol. In most instances the bicyclic adducts were isolated, purified, and analyzed correctly for 2:1 adducts of amidine and aromatic. They were converted to zwitterions by addition of triethylammonium chloride. Dramatic changes in reactivity were observed in going from 11 to 14 with a complete change in the mode of bridging from 8 to 7 as the number of nitro groups on the substrates increased. A summary of the results for reactions of the naphthalenes is shown in Table I.

The critical point in distinguishing the 2-benzazocines 15, 16b, and 17b from their 3-benzazocine isomers 16a, 17a, and 18 is a correct assignment of the two bridgehead protons H-1 and H-2 (Table III). Our previous assignments for these protons were incorrect, since we based them on changes in chemical shift which occur when the salts 18a and 19 are converted to the zwitterions 18c and 21. We assumed that those protons closest to amidine functionality would shift farthest downfield on conversion of salts to zwitterions. In fact, we have been able to show from deuterated analogues and decoupling experiments (vide infra) that the bridging CHNO₂ proton H-3 shifts farthest downfield (Tables II and III). In addition, we previously were unable to obtain both 2-benzazocine and 3-benzazocine isomers from a single aromatic substrate. The trinitronaphthalenes which *do yield* both isomers have allowed a comparative spectral analysis which is quite definitive.

Complete ¹H NMR absorptions for the TNB salts and zwitterionic adducts with α-phenyl- and α-phenoxy-*N*,*N*-dimethylacetamidine are recorded in the Experimental Section. There is no difficulty in assigning protons except for those bonded to sp³ carbon of the bicyclic framework. Since

Table I. Reaction of Electron-Deficient Naphthalenes with α-Phenyl-*N*,*N*-dimethylacetamidine

Solvent		15a	17a (AmH⁺)
Me₂SO	X = Y = H	15a	
EtOH	X = Y = H	No reaction	
Me₂SO	X = H; Y = NO₂	17b	17a
EtOH	X = H; Y = NO₂	No reaction	
Me₂SO	X = NO₂; Y = H	6b	
EtOH	X = NO₂; Y = H		16a
Me₂SO	X = Y = NO₂		18a
EtOH	X = Y = NO₂	Nitrite displacement products	

Table II. Chemical Shifts of Protons Bonded to sp³ Carbon on Bicyclic Amidine–TNB Adducts[a]

Compd	Structure	H_1	H_2	H_3	H_4
19		5.74 (br)	3.96 (under CH₂ of AmH⁺)	4.83 (dd)	4.22 (s)
20				4.84 (s)	4.26 (s)
21		5.96 (dd)	4.17 (br)	5.38 (d)	4.79 (br)
22		5.71 (brd)	4.40 (m)	5.40 (dd)	5.30 (d)
23		5.95	4.56	5.76 or 5.81	5.76 5.81

[a] δ (ppm) downfield from internal Me₄Si. All solutions are saturated (Me₂SO).

the latter assignments are critical in distinguishing isomeric benzazocine products, a summary of H-1–H-4 chemical shifts is listed in Tables II and III. Splitting patterns for the meta-bridged TNB adducts are also noted in Table II. The solubility of the meta-bridged naphthalenes (benzazocines) was in most instances not sufficient for well-resolved splitting patterns, and only the chemical shifts are recorded in Table III (except for 15b and 18b).

The adduct 19 has four single proton absorptions between δ 4 and 6 for H-1–H-4, Table II. Although the absorption at δ 3.96 cannot be observed directly, the amidinium cation methylene (also at ~δ 3.96) integrates for three protons rather than two, indicating overlap with one proton. The high- and

low-field absorptions are absent in the adduct 20 prepared from TNB-d_3 and can thus be assigned to the bridgehead protons H-1 and H-2. There is no problem with cation overlap in this case. The low-field absorption is assigned to H-1 (δ 5.74) adjacent to electronegative nitrogen and the remaining upfield absorption (δ 3.96) to H-2. This assignment is supported by comparative shift values in the phenoxy adduct 22 (vide infra). The two remaining absorptions at δ 4.83 and 4.22 are assigned to H-3 and H-4, respectively, based on the double-doublet splitting pattern for H-3 which becomes a singlet in the deuterated adduct 20. The splitting pattern and the chemical shift of δ 4.8 are quite similar to CHNO₂ absorptions and splitting patterns in carbocyclic analogues of 19 which we have de-

Table III. Chemical Shifts of Protons Bonded to sp³ Carbon on the Bicyclic Amidine–Naphthalene Adducts[a]

Compd	Structure	H₁	H₂	H₃	H₄
15a	(structure)	5.32	4.23	4.75 (br)	4.68
15b	(structure)	5.32 (15%)	4.23	4.75 (d, J = 3 Hz)	4.68
16b	(structure)	5.26	4.16	4.80	4.52
17b	(structure)	5.32	3.95	5.08	4.86
16a	(structure)	3.79	6.32	4.88	4.44
17a	(structure)	3.77	6.42	4.90	4.29
18a	(structure)	4.0 (overlaps AmH⁺ CH₂)	6.26 (dd)	4.97	4.49
18b	(structure)	(residual H under AmH⁺ CH₂)	6.26 (d, J = 4 Hz)	4.97 (d, J = 4 Hz)	4.47
18c	(structure)	4.38	6.44	5.47	5.11
18d	(structure)	4.38 (60%)	6.44	5.47	5.11

[a] Same as Table II.

scribed previously.[11] The remaining singlet at δ 4.22 is thus H-4. Drieding models of 19 show that the H-2–H-4 dihedral angle is close to 90° ($J_{2,4} \simeq 0$ Hz) and a singlet for H-4 is thus not unexpected.

The H-1–H-4 assignments in 19 are supported by analogous absorptions for the phenoxy adduct 22, which gave a particularly well-resolved spectrum which could be decoupled. The

lowest field bridgehead absorption in 22 at δ 5.71 (H-1) is essentially the same value as H-1 in 19 as expected. Irradiation of the double doublet (H-3) at δ 5.40 causes the poorly resolved H-1 doublet to collapse to a singlet, whereas irradiation of H-1 causes H-3 to collapse to a doublet. The largest shift difference for all the H-1–H-4 protons in going from 19 to 22 is that of H-4 which shifts from δ 4.22 in 19 to δ 5.30 in 22, in accord with

C-4 oxygen functionality in the latter. Irradiation of the high-field multiplet at δ 4.40 (H-2) collapses H-3 to a doublet and H-4 to a singlet. Irradiation of H-3 and H-4, simultaneously, collapses H-2 to a broad singlet.

The same shift differences observed between the phenyl and phenoxy salts 19 and 22, are observed in their zwitterionic forms. It is interesting to note that H-3 and H-4 shift farther downfield in going from the salts to zwitterions than do the bridgehead protons H-1 and H-2.

The naphthalene adducts 15–18 also have four single proton absorptions between δ 4.5 and 6.5, Table III. The similarities in chemical shifts for H-1–H-4 in each benzazocine series should be noted. The adducts 15–18 are extremely insoluble compounds and well-resolved spectra were very difficult to obtain except in certain instances, i.e., 15b, 18a, and 18b. Because of this, assignments are made on the basis of chemical shift comparisons between structural isomers (i.e., 16a and 16b; 17a and 17b), deuterated analogues, and comparisons with the bridged benzene adducts 19–23.

The low-field and high-field absorptions for all the naphthalene adducts 15–18 can again be assigned to the bridgehead protons H-1 and H-2. Consider first the 2-benzazocines 15a, 16b, and 17b. The low-field absorption for H-1 is similar in all these adducts and is also closest to the chemical shift for H-1 in the related benzene adduct 19. When 15a is prepared from 1-deuterio-2,4-dinitronaphthalene (85% D), the absorption at δ 5.32 is diminished to 15% of unity which substantiates nitrogen bonding at this α position. In the deuterated analogue 15b the broad 5.32 absorption in 15a sharpens to a clear doublet ($J = 3$ Hz) and the other bridgehead proton at high field (δ 4.23) integrates for one proton. This is definitive evidence for the 2-benzazocine ring system 8. The H-3 and H-4 protons in 15a are assigned to the δ 4.75 and 4.68 absorptions.

Reaction of 1,3,6- and 1,3,8-trinitronaphthalenes with α-phenyl-*N,N*-dimethylacetamidine afforded two different isomers in *each* case (Table I). The isomers 16b and 17b have proton absorptions in the δ 4.5–5.5 region almost identical with those of the 2-benzazocine 15. The other isomers, 16a and 17a, have quite different absorptions in this region, with the high- and low-field assignments for H-1 and H-2 reversed (based on the deuterated tetranitro analogue 18b, vide infra). These latter compounds have absorptions quite similar to the single product 18a obtained from the reaction of 1,3,6,8-TETNN with α-phenyl-*N,N*-dimethylacetamidine in Me$_2$SO. Reaction of this aromatic with amidine in ethanol solution yields only nitrite displacement products.[12] We have previously assigned structure 18a to the product isolated from Me$_2$SO, but because of the incorrect assignment for 15,[2] we wished to confirm the structural assignment. Based on chemical shift correlations, it is notable that all the H-1–H-4 absorptions for 16a, 17a, and 18a show significant similarities, i.e., for H-1, δ 3.8, 3.8, 4.0; H-2, δ 6.3, 6.4, 6.3; H-3, δ 4.9, 4.9, 5.0; H-4, δ 4.4, 4.3, 4.5. An unequivocal confirmation of the mode of bridging for 18a, and thus the TNN analogues 16a and 17a, was obtained from the C-1 deuterated TETNN adduct prepared from α-deuterated TETNN. In the deuterated salt 18b the broad, poorly resolved multiplets for H-2 and H-3 in 18a became two coupled doublets at δ 6.26 and 4.97 ($J = 4$ Hz). Since H-1 overlaps with the methylene absorption of the amidinium cation, a direct reduction in the one-proton integral for this absorption could not be observed. The H-1 and methylene integration (3 protons in 18a) was slightly less in 18b, however. Only 80% deuterated TETNN precursor could be prepared (see Experimental Section), and since this aromatic is symmetrical meta bridging yields a 50:50 mixture of the adducts 18e and 18b.

The absorption for H-5 in 18b is in fact diminished in intensity by 40%, confirming that 18b is actually a 50:50 mixture with 18e. In order to observe the diminished intensity of H-1

18b

18e
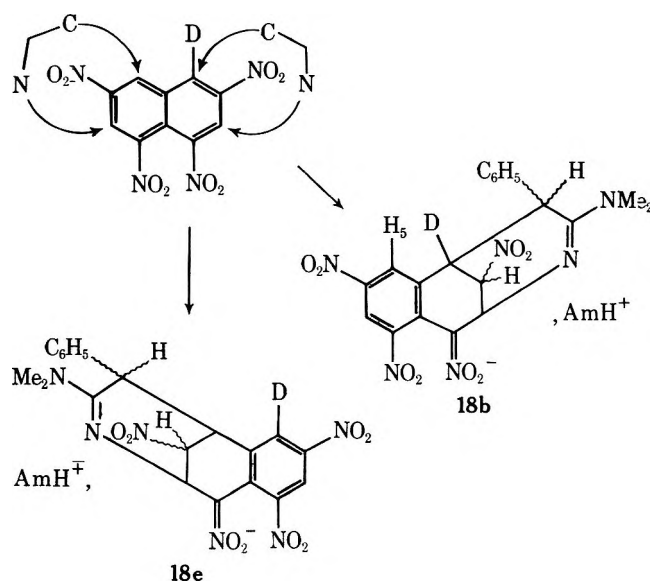
direc⁻ly, the salts 18a and 18b were converted to their respective zwitterions by reaction with triethylammonium chloride in ethanol. The H-1 absorption in 18d is not obscured and a clear 40% reduction in intensity for H-1 in 18d relative to 18c is observed. It is therefore evident that nitrogen is bonded to carbon bearing this low-field proton, and the ring structure 8 is thus established for 18 as well as the trinitro analogues 16a and 17a.

The above product analysis for bridged naphthalene products formed in Me$_2$SO solution shows that under identical conditions a change in the mode of bridging occurs as the number of nitro groups in the substrate increases. If nitrogen-bonded σ complexes are direct precursors to bridged complexes in the naphthalene series, as seems to be the case in the conversion of 5b to 6 in the case of TNB, then the following mechanistic scheme seems plausible in Me$_2$SO.

C-4 complex

C-2 complex
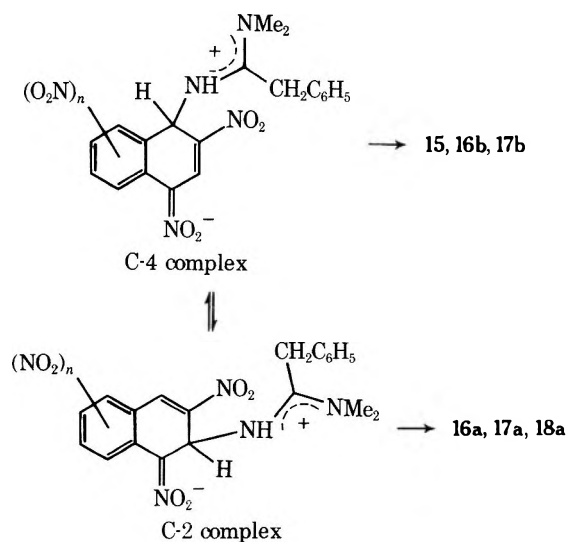
Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were run on JEOL C-60-HL and MH-100 spectrometers with Me$_4$Si as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 uv–visible spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 237B infrared spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and G. I. Robertson Laboratories, Florham Park, N.J.

Nitroaromatics. 1,3-DNN, TNB, and 1,3,6,8-TETNN were prepared and/or purified as reported previously.[2] 1,3,8-TNN was prepared by the method of Ward and Johnson.[13] 1,3,6-TNN was prepared in three steps from naphthalic anhydride. The anhydride was con-

verted to 3,6-dinitronaphthalic anhydride by the method of Hodgson, Ward, and Bell.[14,15] Conversion of the dinitroanhydride to 2,7-dinitronaphthalene was effected in refluxing quinoline with electrolytic copper.[14] The procedure described by Hodgson and Ward for mononitration of 2,7-dinitronaphthalene[16] was modified. A solution of 0.4 ml of nitric acid (d 1.42) in 1.6 ml of sulfuric acid (d 1.84) was added dropwise to a stirred suspension of 1.2 g of dinitroaromatic in 6.2 ml of sulfuric acid (d 182) at 5 °C. After addition was complete the temperature was kept at 20 °C for 24 h. The mixture was then poured on cracked ice and the resulting precipitate was filtered, washed with water, and vacuum dried over P_2O_5. Recrystallization from benzene gave 0.72 g of product, mp 184–185 °C.

Deuterionitroaromatics. TNB-d_3 was prepared by a procedure similar to that reported by Buncel and Symons.[17] A solution of 1.0 g of TNB, 45 ml of DMF, and 5 ml of 0.1 M NaOD in D_2O was heated at 95 °C for 1 h. The solution was then poured on an ice–water mixture containing 1 ml of concentrated sulfuric acid. The resulting yellow solid was filtered, washed with water, and dried in a vacuum desiccator over P_2O_5. After recrystallization from ethanol and drying under vacuum at 80 °C for 3 h 0.71 g (70%) of product was obtained, mp 121 °C. Deuteration was greater than 99% as determined by ^{1}H NMR.

1-Deuterio-2,4-dinitronaphthalene was prepared using a procedure reported by Smith[18] for the preparation of 1,3-DNN. A mixture of 1.0 g of 1-chloro-2,4-dinitronaphthalene and 2.5 g of deuteriobenzoic acid was heated to 160 °C. Small portions of electrolytic copper dust were then added to the stirring molten mixture until 1.0 g was added. After reaction was complete, the mixture was cooled and added to 70 ml of 10% NaHCO$_3$, and the solid was pulverized until the effervescence ceased. The residue was placed in a Soxhlet extractor and extracted with 200 ml of acetone for 24 h. The acetone extract was evaporated and the remaining solid was recrystallized from ethanol. After drying under a vacuum at 80 °C, the crystals were sublimed under a vacuum at 100 °C to give 0.5 g of product (58%) with 85% incorporation of deuterium as determined by ^{1}H NMR.

1-Deuterio-2,4,5,7-TETNN was prepared by the procedure of Ward and Johnson[13] using 1-deuterio-2,4-dinitronaphthalene instead of 1,3-DNN. Deuteration was determined to be 80% by ^{1}H NMR.

Amidines. α-Phenyl-N,N-dimethylacetamidine was prepared as reported previously.[2] α-Phenoxyacetonitrile and α-phenoxy-N,N-dimethylacetamidine hydrochloride were prepared by the method of Djerassi and Scholz.[19] The free amidine was prepared by dissolving the salt in ethanol and adding 1 equiv of sodium ethoxide. The ethanol was evaporated, leaving a viscous oil which was dissolved in ether. This solution was filtered to remove sodium chloride and petroleum ether was added to the filtrate until it became turbid. Cooling at 0 °C resulted in crystallization of the free base, mp 174–175 °C.

Reaction of α-Phenoxy-N,N-dimethylacetamidine with TNB. A solution of 0.54 g of TNB and 0.90 g of the amidine in 50 ml of ethanol was kept at room temperature for 12 h. The resulting orange crystals were filtered and vacuum dried at 70 °C for 4 h, yielding 0.63 g (45%) of **22**: mp 132–134 °C; λ_{max} (Me$_2$SO) 307 and 590 nm; ^{1}H NMR (Me$_2$SO-d_6) δ 9.16 (2 H, NH, br), 7.61 (4 H, aromatic H, m), 7.34 (6 H, aromatic H, m), 5.71 (H$_1$, br d), 5.40 (H$_3$, dd), 5.30 (H$_4$, d), 5.19 (2 H, cation methylene, s), 4.40 (H$_2$ m), 3.24 (6 H, NCH$_3$, s), 2.82 (6 H, NCH$_3$, s). Anal. Calcd for C$_{26}$H$_{31}$N$_7$O$_8$: C, 54.83; H, 5.49; N, 17.21. Found: C, 54.65; H, 5.49; N, 17.35.

The filtrate from the above reaction mixture was reduced to half its volume and was kept at room temperature for 24 h. The resulting red crystals were filtered and vacuum dried at 70 °C for 3 h to give 0.42 g (42%) of the σ complex **5a**, ^{1}H NMR (Me$_2$SO-d_6) shown in Figure 1. Anal. Calcd for C$_{16}$H$_{17}$N$_5$O$_7$·0.5CH$_3$CH$_2$OH: C, 49.28; H, 4.87; N, 16.90. Found: C, 49.40; H, 5.01; N, 16.70.

Preparation of 19, 20, 21, and 23. The adduct **19** was prepared from TNB and α-phenyl-N,N-dimethylacetamidine as reported previously.[2] In preparing **20**, the procedure for **19** was followed except that TNB-d_3 was used instead of TNB. The average yield in several preparations was 78%. The adduct **20** had mp 133–135 °C, λ_{max} (Me$_2$SO) 309 and 509 nm, and ^{1}H NMR absorptions at δ 7.50 (10 H, aromatic H, m), 4.84 (H$_3$, s), 4.26 (H$_4$, s), 4.07 (cation methylene, s), 3.16 (6 H, NCH$_3$, s), and 2.65 (6 H, NCH$_3$, s).

The zwitterionic adduct **21** was prepared by reaction of **19** with triethylammonium chloride as described previously.[2] In a similar fashion the adduct **22** (vide supra) was converted to **23**. Thus, a solution of 0.34 g of **22** in 50 ml of anhydrous methanol and 0.082 g of triethylammonium hydrochloride in 20 ml of anhydrous methanol were mixed at 0 °C. After standing for 3 h the resulting orange precipitate was filtered, washed consecutively with methanol and ether, and vacuum dried at 80 °C for 4 h to give 0.21 g (90%) of **23**: mp 142.5–143.5 °C; λ_{max} (Me$_2$SO) 305 and 495 nm; ^{1}H NMR (Me$_2$SO-d_6) δ 8.45 (1 H, nitropropene nitronate, s), 7.58 (5 H, aromatic H, m), 5.95

(H$_1$, br), 5.81, 5.76 (H$_3$, H$_4$, m), 4.56 (H$_2$, br), and 2.98 (6 H, NCH$_3$, s). Anal. Calcd for C$_{16}$H$_{17}$N$_5$O$_7$: C, 49.11; H, 4.38; N, 17.90. Found: C, 48.88; H, 4.61; N, 17.69.

Preparation of 15a and 15b. The preparation of **15a** was carried out as described previously.[2,20] The deuterated adduct **15b** was prepared in an analogous fashion using 1-deuterio-2,4-dinitronaphthalene as the aromatic substrate. The purified adduct had mp 110–113 °C; λ_{max} (Me$_2$SO) 350 nm; ^{1}H NMR (Me$_2$SO-d_6) δ 9.10 (1 H, aromatic H peri to nitronate, d), 7.48 (10 H, aromatic H, m), 6.96 (3 H, aromatic H, m), 5.32 (0.15 H, H$_1$, br), 4.75 (H$_3$, d), 4.68 (H$_4$, s), 4.23 (H$_2$, br), 4.11 (2 H, cation methylene, s), 3.06 (6 H, NCH$_3$, s), and 2.58 (6 H, NCH$_3$, s).

Preparation of 16a. saturated solution of **13** (0.43 g) in ethanol was mixed with a solution of 0.53 g of α-phenyl-N,N-dimethylacetamidine in 5 ml of ethanol. After standing at room temperature for 24 h, the resulting orange crystals were filtered, washed with cold ethanol, and vacuum dried at 70 °C for 4 h to yield 0.58 g of product (59%): mp 143.5–145 °C; λ_{max} (Me$_2$SO) 305 and 526 nm; ^{1}H NMR δ 9.14 (1 H, peri to nitronate, d), 8.38 (1 H, peri to bridgehead, d), 7.93 (1 H, nitroaromatic H, dd), 7.45 (10 H, aromatic H, m), 6.32 (H$_2$, br dd), 4.88 (H$_3$, br dd), 4.44 (H$_4$, br d), 4.03 (2 H, cation methylene, s), 3.79 (H$_1$, m), 3.12 (6 H, NCH$_3$, s), 2.60 (6 H, NCH$_3$, s). Anal. Calcd for C$_{30}$H$_{33}$N$_7$O$_6$: C, 61.32; H, 5.66; N, 16.67. Found: C, 61.62; H, 5.79; N, 16.58.

Preparation of 16b. A solution of 0.91 g of α-phenyl-N,N-dimethylacetamidine in 0.5 ml of Me$_2$SO was added to a solution of 0.67 g of **13** in 1 ml of Me$_2$SO at 60 °C, and the temperature was kept at 60 °C for 1 h. The mixture was then cooled to 25 °C and was kept at this temperature for 24 h. The mixture was then stirred in ether until a red powder precipitated. This was filtered and stirred with fresh anhydrous ether for 2 h. After filtration and vacuum drying at room temperature for 5 h, a ^{1}H NMR spectrum showed that the product was a 70:30 mixture of **16b** and **16a**. Pure **16b** was obtained by mixing a saturated solution of the powder in methanol with 1 equiv of triethylammonium hydrochloride in the minimum amount of ethanol. The zwitterionic form of **16b** which precipitated from this solution was filtered, dried under vacuum, and reconverted to **16b** by addition of 1 equiv of the amidine in ethanol. After filtering and drying **16b** was recovered in 40% yield: mp 136.5–138.5 °C; λ_{max} (Me$_2$SO) 319 and 522 nm; ^{1}H NMR (Me$_2$SO-d_6) δ 9.17 (1 H, peri to nitronate, d), 8.07 (1 H, peri to bridgehead, d), 7.95 (1 H, nitroaromatic H, dd), 7.38 (10 H, aromatic H, m), 5.26 (H$_1$, m), 4.80 (H$_3$, m), 4.72 (H$_4$, br d), 4.16 (H$_2$, m), 4.02 (2 H, cation methylene, s), 3.12 (6 H, NCH$_3$, s), 2.61 (6 H, NCH$_3$, s). Anal. Calcd for C$_{30}$H$_{33}$N$_7$O$_6$·0.5CH$_3$CH$_2$OH: C, 60.97; H, 5.94; N, 16.06. Found: C, 61.10; H, 6.00; N, 16.00.

Formation of 17a and 17b. A solution of 0.93 g of α-phenyl-N,N-dimethylacetamidine in 0.5 ml of Me$_2$SO was added to a stirring solution of 0.65 g of **12** in 1 ml of Me$_2$SO at 60 °C. After 1 h the mixture was cooled to room temperature and was allowed to stand for 24 h. The resulting viscous oil was stirred with anhydrous ether until a purple powder precipitated. This was filtered and stirred with fresh ether. After filtration and drying under vacuum at 60 °C for 3 h a ^{1}H NMR spectrum of the product (Me$_2$SO-d_6) showed evidence for a ~50:50 mixture of the two isomers: δ 7.53 (13 H, aromatic H, m), 6.42 (H$_2$ in **17a**, br), 5.32 (H$_1$ in **17b**, m), 5.08 (H$_3$ in **17b**, m), 4.9 (H$_4$ in **17b**, H$_3$ in **17a**), 4.29 (H$_4$ in **17a**, br), 4.07 (3 H, cation methylene and H$_2$ in **17b**, br), 3.77 (H$_1$ in **17a**, br), 3.09 (6 H, NCH$_3$, s), 2.61 (6 H, NCH$_3$, s).

Isolation of Pure 17b. A 0.2-g sample of the mixture of **17a** and **17b** was dissolved in the minimum amount of ethanol. Cooling to 0 °C resulted in an orange precipitate which when filtered and dried yielded 0.07 g of pure **17b**: mp 167–169 °C; ^{1}H NMR δ 7.42 (10 H, aromatic H, m), 7.12 (3 H, nitroaromatic H, m), 5.32 (H$_1$, m), 5.08 (H$_3$, m), 4.86 (H$_4$, m), 4.04 (2 H, cation methylene, s), 3.95 (H$_2$, m), 3.13 and 3.62 (12 H, NCH$_3$, two singlets).

Preparation of 18a and 18c. Both **18a** and **18c** were prepared as reported previously.[2]

Preparation of 18b and 18d. The adduct **18b** was prepared by a procedure analogous to that used for **18a** with **10** as the aromatic substrate. Purified **18b** had mp 88–91 °C; λ_{max} (Me$_2$SO) 348 and 553 nm; ^{1}H NMR δ 8.58 (0.6 H, α nitroaromatic H, d), 8.33 (1 H, β nitroaromatic, br s), 7.40 (10 H, aromatic H, m), 6.26 (H$_2$, d), 4.97 (H$_3$, d), 4.47 (H$_4$, s), 4.0 (2.6 H, cation methylene and residual H$_1$), 3.16 (6 H, NCH$_3$, s), 2.61 (6 H, NCH$_3$, s).

The zwitterionic adduct **18d** was prepared by adding a twofold excess of triethylammonium hydrochloride in ethanol to 0.2 g of **18b** in 20 ml of ethanol. After about 30 min the resulting orange precipitate was filtered, washed with ethanol, and vacuum dried at 60 °C to give a 67% yield of **18d**: mp 152–155 °C; λ_{max} 350 and 522 nm; ^{1}H NMR δ 8.81 (0.6 H, α nitroaromatic H, br), 8.49 (1 H, β nitroaromatic H, s),

7.64 (10 H, aromatic H, m), 6.44 (H$_2$, br), 5.47 (H$_3$, br), 5.11 (H$_4$, br s), 4.38 (0.6 H, residual H$_1$, br), 2.98 (3 H, NCH$_3$, s), 2.59 (3 H, NCH$_3$, s).

Comments on Standardization of Chemical Shift Values. In our previous report on the ^{1}H NMR spectra of several of these bicyclic adducts,[2] i.e., 18a and 18c, in addition to incorrect assignment of the protons H$_1$–H$_4$, we had some difficulty due to nonlinearity of the field on the C-60 HL. This problem was corrected and standards of known chemical shift were used to calibrate all spectra reported here.

Registry No.—5a, 59054-73-8; 10, 59054-74-9; 11, 606-37-1; 12, 2364-46-7; 13, 59054-75-0; 14, 28995-89-3; 15a, 59054-77-2; 15b, 59054-79-4; 16a, 59054-81-8; 16b, 59054-83-0; 17a, 59054-85-2; 17b, 59054-87-4; 18a, 59054-89-6; 18b, 59054-91-0; 18c, 59054-88-5; 18d, 59054-90-9; 19, 59054-92-1; 20, 59054-94-3; 21, 56776-21-7; 22, 59054-97-6; 23, 59054-95-4; TNB, 99-35-4; TNB-d_3, 14702-07-9; α-phenoxy-N,N-dimethylacetamidine, 59054-96-5; α-phenyl-N,N-dimethylacetamidine, 56776-16-0; 1-deuterio-2,4-dinitronaphthalene, 59054-98-7.

References and Notes

(1) M. J. Strauss, Acc. Chem. Res., **7**, 181 (1974).
(2) R. R. Bard and M. J. Strauss, J. Am. Chem. Soc., **97**, 3789 (1975).
(3) C. F. Bernasconi, MTP Int. Rev. Sci.: Org. Chem., Ser. One, **3**, 33 (1973).
(4) M. J. Strauss, Chem. Rev., **70**, 667 (1970).
(5) E. Buncel, A. R. Norris, and K. E. Russell, Q. Rev., Chem. Soc., **22**, 123 (1968).
(6) M. M. Strauss, H. F. Schran, and R. R. Bard, J. Org. Chem., **38**, 3394 (1973).
(7) M. C. Braude, L. S. Harris, E. L. May, J. P. Smith, and J. E. Villarrel, Adv. Biochem. Psychopharmacol., **8**, 1 (1973); N. B. Eddy and E. L. May, "Synthetic Analgesics", B, Pergamon Press, Oxford, 1966.
(8) D. C. Palmer and M. J. Strauss, Chem. Rev., in press.
(9) This antagonist testing was carried out at NIH by Dr. Robert Willette and at the Department of Pharmacology, Medical College of Virginia, by Dr. William Dewey.
(10) W. T. Smith, J. Am. Chem. Soc., **71**, 2855 (1949).
(11) M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Connor, J. Org. Chem., **35**, 383 (1970).
(12) R. R. Bard and M. J. Strauss, unpublished results.
(13) E. R. Ward and C. D. Johnson, J. Chem. Soc., 4314 (1961).
(14) H. H. Hodgson and E. R. Ward, J. Chem. Soc., 590 (1945).
(15) F. Bell, J. Chem. Soc., 1952 (1952).
(16) H. H. Hodgson and E. R. Ward, J. Chem. Soc., 533 (1946).
(17) E. Buncel and E. A. Symons, Can. J. Chem., **44**, 771 (1966).
(18) W. T. Smith, J. Am. Chem. Soc., **71**, 2855 (1949).
(19) C. Djerassi and C. R. Scholz, J. Am. Chem. Soc., **69**, 1688 (1947).
(20) The structure for this compound in ref 2 is incorrectly assigned as a 3-benzazocine rather than the correct 2-benzazocine as reported here.

Synthesis of Specific Polychlorinated Dibenzofurans[1]

Allan P. Gray,* Vito M. Dipinto, and I. J. Solomon

Chemistry and Chemical Engineering Research Division, IIT Research Institute, Chicago, Illinois 60616

A number of tri- through pentachlorodibenzofuran (DBF) derivatives have been synthesized by specific methods at a high level of purity, characterized, and identified. A diazotization–cyclization process carried out under novel conditions, in tetrachloroethylene with isoamyl nitrite as the diazotizing agent, has been found relatively convenient and general for the synthesis of these compounds. Cyclization of an o,o'-biphenol ditosylate derivative under mild conditions has also proved useful. Chlorination of DBF beyond the dichloro stage led to complex mixtures of polychloro derivatives, many of which have been identified. Separation of certain of the isomeric and homologous products has been achieved by high-pressure liquid chromatography.

Certain polychlorinated dibenzofurans (DBF), like their close dibenzo-p-dioxin (DD) relatives, have been shown to be extremely toxic trace contaminants of the environment. Along with their DD counterparts, polychlorinated DBF derivatives have been detected and identified in manufactured polychlorophenols[2,3] and thus may appear in a variety of industrial chemical products. The DBF compounds are ubiquitous contaminants of polychlorobiphenyls obtained from various sources[4-7] and the toxicity of these widely used materials has been considered largely attributable to the DBF impurities.[4,8,9] The toxicity of the polychloroDBF derivatives appears to parallel that of their DD analogues, certain of the DBF compounds being extremely toxic to mammals, causing chloracne and producing extensive, irreversible liver damage.[10,11] In the case of the DD derivatives, toxicity is strikingly dependent on the position and number of chloro substituents, peak toxicity being associated with the 2,3,7,8-tetrachloro homologue (2,3,7,8-tetraCDD), one of the most toxic compounds known.[11-13] A corresponding dependence of toxicity on chloro substituents is suspected for the DBF analogues, and in this connection it is noteworthy that 3,4,3',4'-tetrachloroazoxybenzene, a new chemical process intermediate responsible for outbreaks of chloracne and porphyria, has been found to have a parallel toxicologic profile.[11,14]

It is thus of clear importance to investigate these compounds further, to increase understanding of their toxicologic properties and of the relationship of structure to toxicity, and

to refine our techniques for detecting and identifying these environmental artifacts. To these ends, we have carried out specific syntheses of a number of polychlorinated DD[1,15,16] and DBF homologues and isomers at a high level of purity, and have identified and characterized the products and made them available for toxicity studies. The present report deals with the synthesis of DBF derivatives.

At the outset, three classic approaches presented themselves as possible routes to desired, polychloroDBF's, viz., (a) electrophilic chlorination of DBF itself; (b) diazotization and cyclization of substituted o-phenoxyanilines; and (c) cyclization of substituted o,o'-biphenols or their derivatives[17,18] (Scheme I). As Kende et al.[19,20a] have also found in work reported while this investigation was in progress, the most

Scheme I
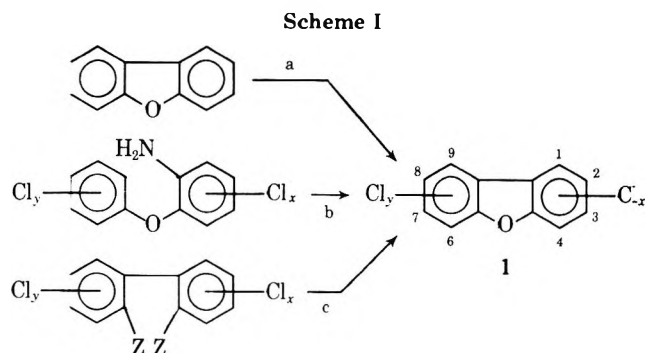
versatile and generally applicable, albeit low-yielding, route to these compounds proved to be via b, the diazotization and cyclization of suitably substituted o-phenoxyanilines. We have found, however, that this process is in general difficult to carry out with chlorinated o-phenoxyanilines under the usual, aqueous conditions, and have developed a more satisfactory method for effecting the reaction.

Required starting materials for this process were prepared in two steps: condensation of an appropriately substituted potassium phenolate with an o-chloronitrobenzene followed by reduction of the nitro group. It was found best to carry out the first, condensation step, by heating an intimate mixture of the reactants at 110–120 °C in the absence of solvent,[19,20a] under which conditions better yields of cleaner product were obtained. This was particularly true when a p-chloro as well as an o-chloro substituent was present on the nitrobenzene. In such cases, the desired o-nitrodiphenyl ether was the major product in the absence of solvent, whereas in the presence of a high dielectric solvent (dimethyl sulfoxide or dimethyl-acetamide) the reverse was true, the p-nitro isomer predominated and, in addition, more significant amounts of trimeric products formed as a result of displacement of both chloro substituents or (to a minor extent) of one chloro substituent and the nitro group. Thus (Scheme II), in the absence of sol-

Scheme II

2 + 3 $\xrightarrow[\text{reflux}]{\text{DMA}}$ **4,** 9% + **5,** 35% + **(7 + 8),** 37%

+ recovered starting materials

6 + 3 $\xrightarrow[110°\text{C}]{\text{Me}_2\text{SO}}$ **9,** 12% + **10,** 42% + trimers + starting materials

(Compositions of crude product mixtures as determined by GLC–mass spectrometric analysis).

vent at 110 °C, potassium p-chlorophenolate (2) reacted with 2,4,5-trichloronitrobenzene (3) to give the ortho-substituted diphenyl ether 4 as the major product whereas in DMA at reflux the para isomer 5 predominated. Similarly, potassium 2,3,5-trichlorophenolate (6) reacted primarily at the ortho position of 3 in the absence of solvent at 110 °C but the reverse was true in Me₂SO at the same temperature. The compositions of crude product mixtures were determined by GLC–mass spectrometric analysis. The ortho and para isomeric ether products were distinguished on the basis of their subsequent behavior in the DBF cyclization step. It appears possible to explain these results on the grounds that the close ion pairs likely to be involved in the absence of solvent would favor ortho substitution, whereas a high dielectric solvent would stabilize separated ions, permit greater separation of charge in the transition state, and thereby encourage para substitution.[20b]

Reduction of the chlorinated o-nitrodiphenyl ethers to the corresponding phenoxyanilines was carried out uneventfully in good yield with hydrazine and Raney nickel. It was found unnecessary to remove any minor amount of p-nitro isomer before reduction since the resultant p-phenoxyaniline could not be cyclized to a DBF derivative.

Polychloro-o-phenoxyanilines in general proved to be essentially nonbasic and very poorly soluble. These attributes generally precluded carrying out the diazotizations in aqueous mineral acids. The compounds could be diazotized in aqueous acetic acid but even here solubilities of the order of 1 g or less per liter of 75–80% acetic acid made the process most inconvenient, particularly since the resultant solution of the diazonium salt had then to be poured into boiling 1 N sulfuric acid containing a copper catalyst. We therefore sought an organic medium in which diazotization could be effected by means of isoamyl nitrite, with minimal intervention of side reactions of the diazonium salt with the solvent. Benzene could not serve as the solvent since it would be expected to react preferentially with the diazonium salt.[21] A number of solvents were evaluated on a test tube scale, by treating solutions of a small amount of o-phenoxyaniline, viz., 2-(p-chlorophenoxy)-4,5-dichloroaniline or 2-(3,4-dichlorophe-noxy)-5-chloroaniline, with isoamyl nitrite, heating until gas evolution ceased, and then analyzing the reaction solutions by GLC and mass spectrometry. The results obtained with various solvents were as follows. Carbon tetrachloride afforded low yields of triCDBF and large amounts of tri- and tetra-chlorodiphenyl ethers as well as other products indicative of interfering reactions with solvent; aliphatic solvents (n-heptane, tetrahydrofuran, tert-butyl alcohol, glacial acetic acid, trifluoroacetic acid) gave 0–20% triCDBF and up to 80% tri-chlorodiphenyl ethers, suggesting solvent-mediated reductive cleavage of the diazonium salt; basic solvents (pyridine, acetonitrile) largely yielded recovered starting aniline, suggesting reaction of the solvent with the isoamyl nitrite; nitrobenzene gave a complex mixture of unidentified products; tetrachloroethylene afforded the most promising results, yielding ca. 50% of triCDBF and lesser amounts of trichlorodiphenyl ether.

Tetrachloroethylene has thus far proved to be the solvent of choice for the reaction. In this solvent with isoamyl nitrite as the diazotizing agent, the diazotization and cyclization processes could be conveniently carried out in one pot, simply by heating solutions of the reactants at concentrations of the order of 1–2 g of aniline per 100 ml for 5–6 h at 80 °C.

The DBF usually, but not always, was the primary product by either procedure representing 40–50% of the crude material. Largely owing to losses suffered during purification, however, isolated yields of DBF products were very low (ca. 5%) with either the aqueous acetic acid or tetrachloroethylene procedure. Surprisingly, the principal by-product (30–40%
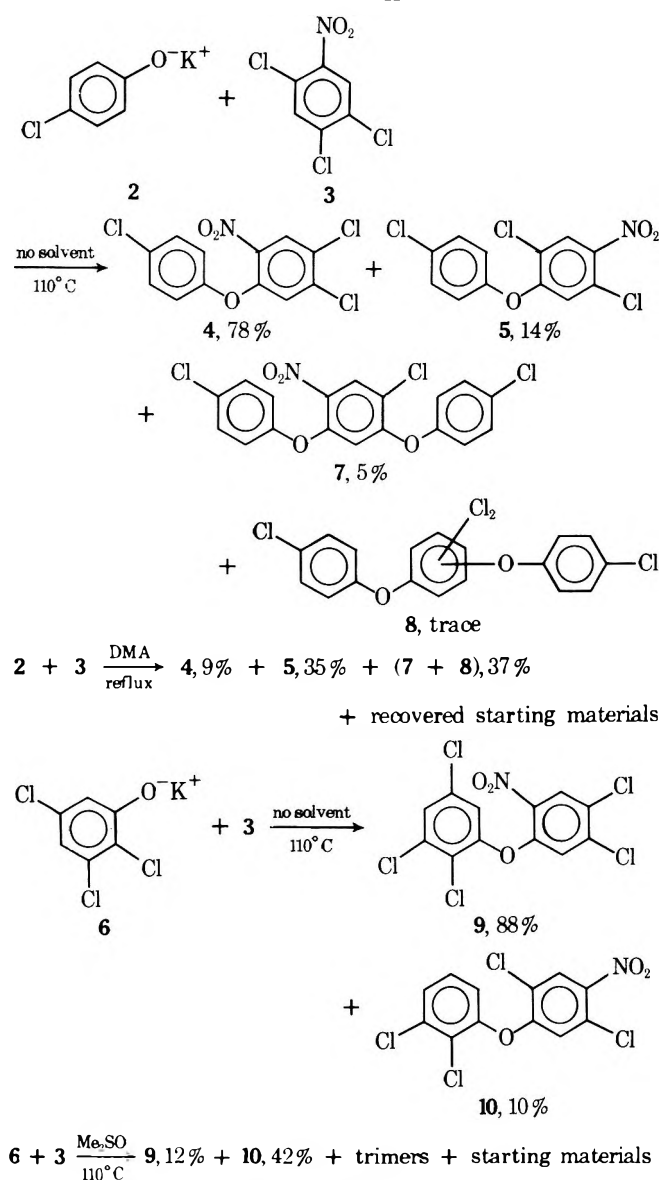
of the crude mixture) was the corresponding diphenyl ether resulting from reduction of the diazonium salt rather than, at least in the case of the aqueous medium, the expected *o*-phenoxyphenol. Quite to the contrary, no evidence for the formation of phenolic by-products could be obtained. Diphenyl ether products could generally be removed by column chromatography. A minor by-product, representing ca. 5% of the crude reaction product from the aqueous acetic acid procedure or up to 10% in tetrachloroethylene, observed in those instances where only one of the ortho positions on the phenoxy substituent of the aniline was open and the other bore a chloro substituent, was an isomer of the expected polychloroDBF. Isomer formation may result from attack of the phenyl cation at the chlorine-bearing ring position, forcing migration of the chloro substituent. Although the isomers were not isolated and their structures were not determined, their identity as polychloroDBF isomers was established by GLC–mass spectrometric analysis. Direct GLC comparison did indicate that the isomeric DBF's produced in the formation of the two pentaCDBF derivatives, 1d and 1e, were different from each other and from the isolated DBF products. Analysis of ^{1}H NMR spectra permits us to be confident that the isolated, major DBF products were the expected isomers derived from direct cyclization without rearrangement. A second minor by-product, occurring only in the tetrachloroethylene medium and representing 10–20% of the crude reaction product from this medium, was identified by GLC–mass spectral analysis as a trichloroethenyl derivative of the chlorinated diphenyl ether, tentatively formulated as 12, and presumably resulted from attack of the phenyl cation on the solvent. These results are illustrated in Scheme III.
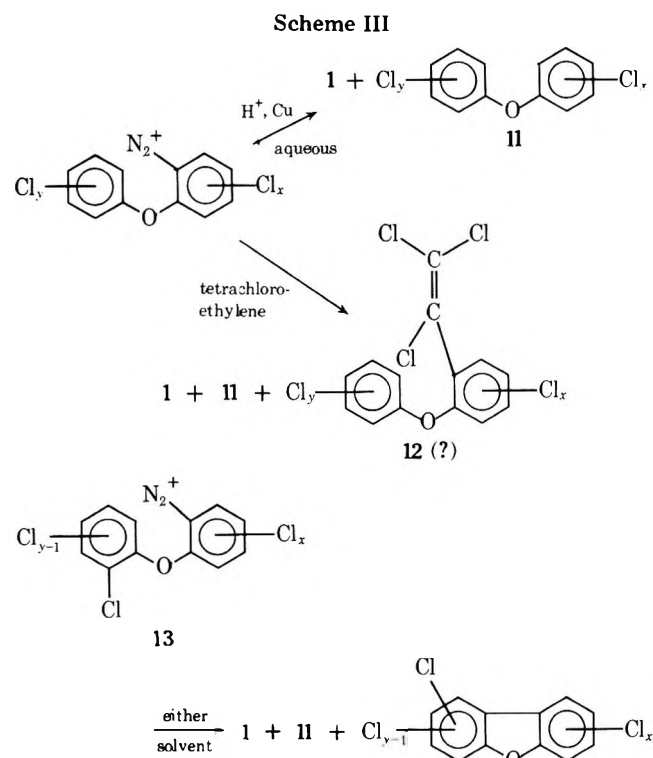
Scheme III

PolyCDBF's prepared according to Scheme III:

1a, 2,3,8-tri[24]

b, 2,4,6-tri

c, 2,3,6,8-tetra[24]

d, 1,2,4,7,8-penta

e, 1,3,4,7,8-penta

It may be noted that generalizations enunciated earlier with respect to the effect of the position of a single substituent on

the course of the cyclization, namely that no direct ring closure to a 1-monosubstituted DBF had been successful[17] and that to form a 4-substituted DBF, the substituent must be attached to the aniline rather than the phenoxy nucleus,[17,22] do not apply when several chloro substituents are present. Thus, 1b was prepared from 2-(2,4-dichlorophenoxy)-3-chloroaniline and 1c from 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline. The 1-substituted compounds, 1d and 1e, were prepared from 2-(2,3,5-trichlorophenoxy)- and 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, respectively.

In this connection, it is significant that an attempt to prepare 2,3,7-triCDBF (1f) by cyclization of 2-(*m*-chlorophenoxy)-4,5-dichloroaniline (14) afforded predominantly what is presumed to be the 1-substituted isomer, 2,3,9-triCDBF (1g) (eq 1). The composition of the crude product mixture was determined by GLC; 1f was identified by spiking with material
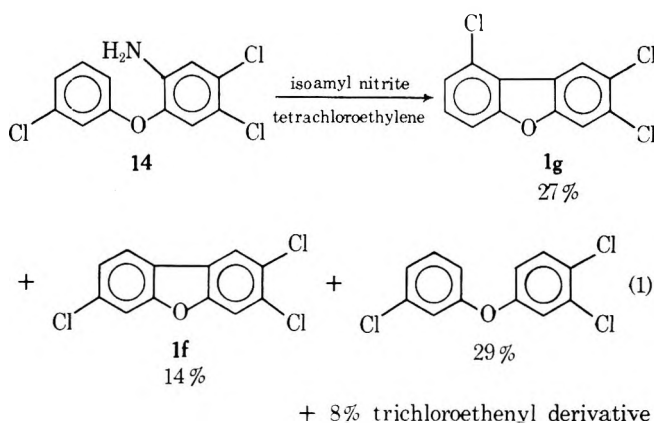
prepared by monochlorination of 3,7-diCDBF (vide infra). A small amount of 1g was isolated by column chromatography; the structural assignment was supported by its ^{1}H NMR spectrum which showed a singlet for the deshielded H_1 proton at δ 8 5.

2,4,6,8-TetraCDBF (1h)[25] was prepared via route c, cyclization of an o,o'-biphenol derivative, since the requisite 2,3,5-trichloronitrobenzene was not readily available for use in route b and since chlorination of 1b gave a complex mixture of products (vide infra). Although o,o'-biphenol itself, simply on being heated, with or without the aid of an acid dehydrating agent (e.g., phosphorus pentoxide, zinc chloride), is cyclized to DBF in excellent yield,[17,18,23] 4,6,4',6'-tetrachloro-2,2'-biphenol proved to be refractory. Subjection of the tetrachlorobiphenol, prepared by chlorination of biphenol with sulfuryl chloride[26] or chlorine, to various acid reagents including zinc chloride and phosphorus pentoxide gave largely recovered starting material under relatively mild conditions or, under more drastic conditions, large amounts of decomposition products accompanied by small amounts of 1h, which was indicated to be present in the crude reaction mixtures by GLC but which could not be isolated.

Since 2,2'-diacetoxybiphenyls, so long as they bear at least two nitro substituents ortho and/or para to the acetoxy functions (bromo substituents can be present but cannot serve in place of nitro), are readily converted to DBF derivatives by heating under basic conditions in admixture with barium carbonate,[27] it appeared possible that by use of a better leaving group such as tosylate a similar cyclization of the tetrachlorobiphenol could be effected. This has indeed proved to be the case. Treatment of the ditosylate (15) with potassium hydroxide, preferably in dimethylacetamide solution under surprisingly mild conditions at 105–110 °C, afforded 1h in reasonable yield (eq 2).

2,3,7,8-TCDBF (1i) was prepared essentially as described by Kende et al.[19,20] from benzidine-2,2'-disulfonic acid following a reaction sequence based on route c.

$$\text{15} \xrightarrow{\text{KOH}} \text{1h} \tag{2}$$
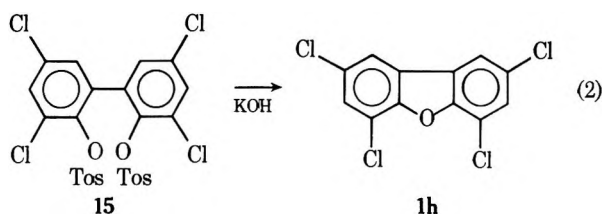
Route a proved to be of little value for the preparation of discrete polychloroDBF derivatives. As might have been expected based on its behavior in other electrophilic substitution reactions,[17,18,28,29] chlorination of DBF beyond the 2,8-dichloro stage led to complex mixtures of products. Whether chlorination was carried out in glacial acetic acid or a chlorocarbon solvent with or without ferric chloride plus iodine catalyst, reaction first led cleanly to 2,8-diCDBF (**1j**) and then to mixtures of isomers of more highly chlorinated products.

Chlorination of DBF in glacial acetic acid at 70 °C and stopping reaction when products of tetrachlorination predominated afforded a crude product mixture with the composition shown in Scheme IV determined by GLC–mass

Scheme IV

$$\text{DBF} \xrightarrow[\text{AcOH, 70 °C}]{\text{Cl}_2}$$

1i
41 %

+

1k
21 %
pairs of doublets δ 7.4, 7.6

+ 6.5% two other tetraCDBF's
+ 25% triCDBF isomers
+ 6% pentaCDBF isomers

$$\xrightarrow{\text{recrystallize}} \quad \begin{array}{cc} \text{1i} & + & \text{1k} \\ 50\% & & 50\% \end{array}$$
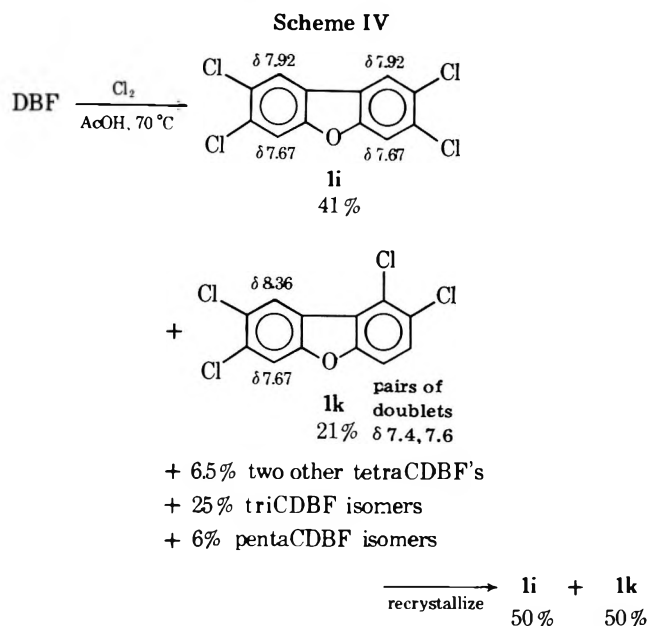
spectrometric analysis. Recrystallization afforded a 1:1 mixture of **1i** and 1,2,7,8-tetraCDBF (**1k**), characterized by analysis of the ^{1}H NMR spectrum. Separation of the two isomers has been accomplished by high-pressure liquid chromatography (HPLC). The formation of so much **1k**, which requires substitution at the 1 position, was quite unexpected based on earlier experience.[17,18,28,29]

Chlorination of **1j** in chloroform containing catalytic amounts of ferric chloride and iodine again to the tetrachloro level afforded a product mixture, the composition of which as determined by GLC–mass spectral analysis and comparison with products synthesized by alternate routes is shown in Scheme V. A recent report of the selective halogenation of alkylbenzenes adsorbed on molecular sieves[30] made it of interest to see if selective chlorination could be similarly achieved. Adsorption of **1j** on molecular sieves did indeed modify the outcome of the chlorination but, as can be seen (Scheme V), in no way improved selectivity. It is most notable that introduction of molecular sieves resulted in the formation of significantly more **1h** (all substituents ortho or para to the ether oxygen) and only a trace of **1i**.

Since chlorination of DBF first goes preferentially to the 2,8 positions (para to the oxygen), it is not surprising that, as reported,[19,20] chlorination of 3,7-diCDBF (**1l**) gives predom-

Scheme V

$$\text{1j} \xrightarrow[\text{CHCl}_3]{\text{Cl}_2} \text{1a}$$
17 %

+ two other triCDBF's + **1k** +
12 %

1c
30 %

+ **1i** + **1h** + 3 pentaCDBF's
12 % 23 %

$$\text{1j} \xrightarrow[\text{molecular sieves}]{\text{Cl}_2, \text{CHCl}_3} \quad \begin{array}{ccc} \text{recovered 1j} & + & \text{3 triCDBF's} & + & \text{1h} \\ 22\% & & 26\% & & 19\% \end{array}$$

+ **1k** + **1c** + **1i** + 4 penta- + 3 hexaCDBF's
10% 0.2% 21%
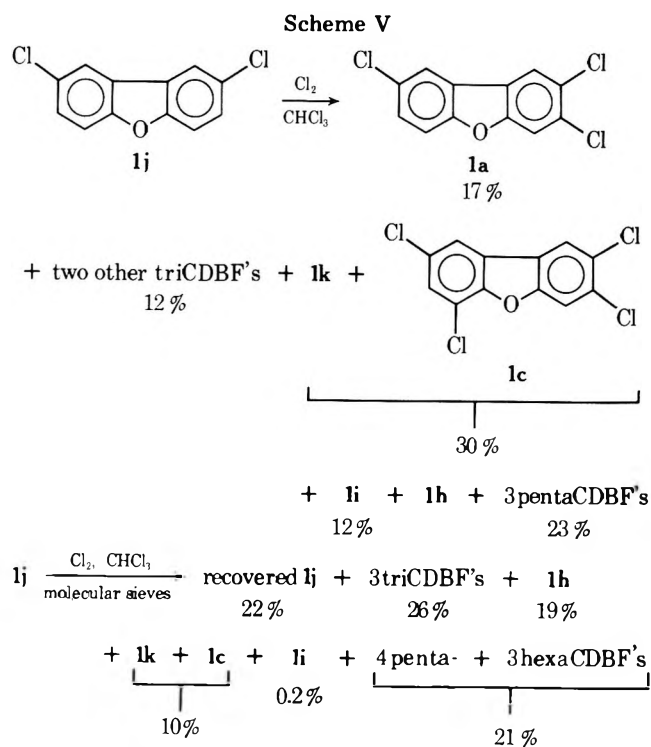
inantly **1i** (Scheme VI). The process could not be stopped cleanly at the monochlorinated stage and, although **1f** was

Scheme VI

1l $\longrightarrow$ **1f** $\longrightarrow$ **1i**

1b $\longrightarrow$ **1h** + complex mixture of other products
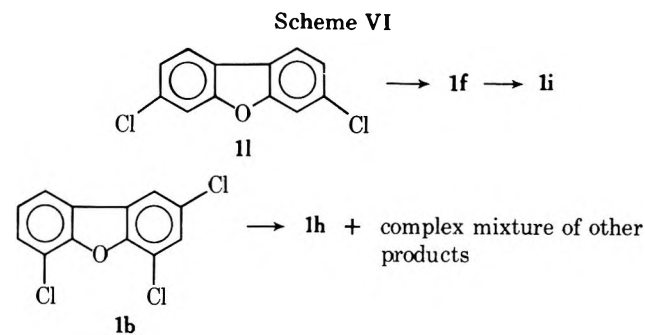
formed by this means, it proved difficult to purify. Isolation of **1f** was finally accomplished by HPLC. In the light of these observations, it appeared reasonable to expect primary introduction of a chloro substituent at the 8 position of **1b** and the clean formation of **1h**. Chlorination of **1b** in either chloroform or acetic acid, however, led to complex mixtures of products containing no more than 20–30% **1h**. The behavior of **1b** is in sharp contrast to that of corresponding nitro analogues; thus, nitration of 4,6-dinitroDBF affords an excellent yield of 2,4,6-trinitroDBF which in turn on further nitration overwhelmingly yields the 2,4,6,8-tetranitro derivative.[28] Explanation would appear to lie in the fact that nitro is a meta-directing substituent which reinforces the influence of the ether oxygen when placed in the 2, 4, and 6 positions, whereas chloro is an ortho-directing substituent which reinforces the influence of the ring oxygen when in the 3 and 7 positions but which counters this influence in the 2, 4, and 6 positions.

GLC data on polyCDBF derivatives are given in Table I. It may be noted that chloro substitution ortho to the ring oxygen, that is in the 4 and 6 positions, tends to decrease retention time.

In sum, use of tetrachloroethylene as a reaction medium and isoamyl nitrite as the diazotizing agent has made the diazotization and cyclization of chlorinated *o*-phenoxyanilines a reasonably convenient and general, if still low-yielding, route to specific chlorinated DBF derivatives.

Table I. GLC Data on Chlorinated Dibenzofurans

No.	CDBF	RT, min[a]	R_{RT}[b]	R_{RT}[c]
1a	2,3,8-Tri	4.5	0.92	1.00
1b	2,4,6-Tri	4.3	0.87	0.88
1c	2,3,6,8-Tetra	7.3	1.52	1.47
1d	1,2,4,7,8-Penta	11.6	2.4	1.66
1e	1,3,4,7,8-Penta	12.0	2.5	1.51
1f	2,3,7-Tri	4.7	0.91	0.92
1g	2,3,9-Tri	4.3	0.87	0.65
1h	2,4,6,8-Tetra	6.0	1.35	1.22
1i	2,3,7,8-Tetra	8.2	1.75	1.83
1k	1,2,7,8-Tetra	7.5	1.59	1.27

[a] Retention time in minutes, Dexsil 300 isothermal at 250 °C. [b] Relative retention time vs. dieldrin; Dexsil 300, isothermal at 250 °C. [c] Relative retention time vs. dieldrin, 1% Apolar 10C, isothermal at 200 °C.

Experimental Section

Caution: Certain of these compounds have been found to be highly toxic and should be handled with extreme care. Work was performed in glove boxes in an isolated toxic laboratory facility. Exhaust air was filtered. All wastes were incinerated. Contact with these compounds can cause chloracne and irreversible liver damage.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance (¹H NMR) spectra were determined with a Varian A-60D spectrometer and are given in parts per million (δ) downfield from tetramethylsilane; ir spectra with a Perkin-Elmer 21 instrument, and uv spectra with a Cary 14; GLC-mass spectra were determined at 70 eV with a Hitachi Perkin-Elmer RMU-6D spectrometer linked in tandem to a gas chromatograph. GLC data were obtained with a Varian Aerograph 1200 or 1440 gas chromatograph, hydrogen flame ionization detector, helium flow rate 40 ml/min; 2 m × 0.32 cm columns packed with Dexsil 300, Apolar 10C or 1% DEGS. Each compound was checked on at least two columns. GLC data are given in Table I. High-pressure liquid chromatography (HPLC) was carried out with a Du Pont 830 instrument. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Micro-Tech Laboratories, Inc., Skokie, Ill. Analytical data are in accord with structural assignments. Percent purity is based on averaged GLC response data.

2,3,8-Trichlorodibenzofuran (1a). Heating an intimate mixture of 36.7 g (0.22 mol) of the dry potassium salt of *p*-chlorophenol (2) and 49.7 g (0.22 mol) of 2,4,5-trichloronitrobenzene (3) at 105-110 °C (bath temperature) for 18 h gave, after workup, 32% of material indicated by GLC to consist of 78% 4, 14% 5, 2.7% recovered 3, and 5.5% 7 plus 8.

Treatment of 20.0 g (0.063 mol) of the crude product with 11.8 g (0.2 mol) of hydrazine hydrate (85%) in boiling ethanol containing a catalytic amount of Raney Ni[32] afforded, after workup, 8.6 g (47%) of material containing (GLC) 87% of 2-(*p*-chlorophenoxy)-4,5-dichloroaniline and 4.6% of the isomeric aniline.

The crude aniline, 6.9 g, was extracted with approximately 8 l. of 80% acetic acid, and the resultant solution in 1-l. portions was cooled in an ice bath and treated with an aqueous solution of sodium nitrite. The solution of the diazonium salt was then poured in portions into boiling 1 N sulfuric acid containing a catalytic amount of copper[33] and the reaction mixture was boiled for 2.5 h, cooled, and extracted with chloroform. Drying and removal of the chloroform and recrystallization of the combined residues from isooctane afforded orange-red material which was chromatographed on alumina[34] and eluted with hexane-benzene (95:5). Recrystallization of the chromatographed product from chloroform yielded 289 mg (4.5%) of 1a, colorless crystals, 99.4% pure (GLC), impurities being 0.2% diphenyl ether and 0.4% trimeric material; mp 189-191 °C; ¹H NMR (CDCl₃) δ 7.95 (s, 1, H₁), 7.68 (s, 1, H₄), 7.84 (t, 1, J = 1.25 Hz, H₉), 7.48 (d, 2, J = 1.4 Hz, H₆ + H₇); ir (CHCl₃)[31] 1606, 1472, 1455, 1392 (aromatic), 1104 (C-O-C), 872 (isolated CH bend), 814 cm⁻¹ (C-Cl); uv (CHCl₃) 256 nm (ϵ 33 000), 302 (29 000), 313 (21 000); mass spectrum m/e 274 (28), 272 (80), 270 (100), 209 (15), 207 (23), 137 (14), 136 (10), 135 (11).

Anal. Calcd for C₁₂H₅Cl₃O: C, 53.08; H, 1.86. Found: C, 53.04; H, 1.97.

1a was also prepared in similar yield from the phenoxyaniline by the isoamyl nitrite-tetrachloroethylene procedure described in the following example.

1,2,4,7,8-Pentachlorodibenzofuran (1d). An intimate mixture of 9.4 g (0.04 mol) of potassium 2,4,5-trichlorophenolate and 9.1 g (0.04 mol) of 3 was heated for 18 h at 105-110 °C (bath temperature). Two recrystallizations of the crude product from methanol yielded 8.57 g (55%) of 2-(2,4,5-trichlorophenoxy)-4,5-dichloronitrobenzene indicated to be 92% pure by GLC. Treatment of the nitro compound, 8.57 g (0.022 mol), with hydrazine and Raney nickel[32] in boiling 95% ethanol yielded 4.75 g (60%) of 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, 92% pure by GLC.

A solution of 4.75 g (0.013 mol) of the aniline and 2.42 g (0.021 mol) of isoamyl nitrite (commercial or freshly prepared material was equally satisfactory) in 250 ml of tetrachloroethylene was heated to the point at which vigorous gas evolution began. The heat was removed and, after the vigorous gas evolution had subsided (in about 5 min), the reaction mixture was heated at 80 °C (bath temperature) for 6 h during which slow gas evolution continued. Prolonged heating at higher temperatures gave large amounts of resinous materials. At lower temperatures, the reaction proceeded too slowly. The final reaction mixture was indicated by GLC-mass spectral analysis to contain 35% of 1d, 12% of an isomeric pentaCDBF, 30% of pentachlorodiphenyl ether isomers, and 13% of a presumed pentachloro-(trichloroethenyl)diphenyl ether derivative resulting from reaction with the solvent. The reaction mixture was evaporated to dryness in vacuo and the residue was washed with hexane, chromatographed on silica gel,[35] and eluted with hexane. Recrystallization of the chromatographed product from chloroform afforded 271 mg (6%) of 1d as colorless needles, mp 234-235 °C, indicated to be 98% pure by GLC: ¹H NMR (CDCl₃) δ 8.46 (s, 1, H₁), 7.78 (s, 1, H₄), 7.65 (s, 1, H₇); uv (CHCl₃) 256 nm (ϵ 27 000), 266 (41 000), 297 (48 000); mass spectrum m/e 344 (24), 342 (71), 340 (100), 338 (64), 277 (22), 275 (19), 203 (26), 173 (17), 138.5 (17), 137.5 (15).

Anal. Calcd for C₁₂H₃Cl₅O: C, 42.34; H, 0.89; Cl, 52.08. Found: C, 42.52; H, 1.10; Cl, 52.36.

2,3,6,8-Tetrachlorodibenzofuran (1c). A mixture of 1 equiv of potassium 2,4-dichlorophenolate and 2 equiv of 3 (because it proved more difficult to remove trimeric material than 3 from the reaction product) was heated at 105-110 °C for 6 h, cooled, and extracted with chloroform. The chloroform solution was washed with dilute alkali, dried, and evaporated, and the residue was recrystallized from methanol to give a 34% yield of 2-(2,4-dichlorophenoxy)-4,5-dichloronitrobenzene, 92% pure by GLC. Treatment of 2.0 g (5.7 mmol) of the product with hydrazine and Raney nickel in boiling ethanol afforded 1.77 g (79%) of 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline, indicated to be 97% pure by GLC.

A solution of 10.9 g (0.036 mol) of the aniline and 6.9 g (0.059 mol) of isoamyl nitrite in 700 ml of tetrachloroethylene was heated at 80 °C (bath temperature) for 6 h. Vigorous gas evolution occurred during the first 5 min. The course of the reaction was followed by GLC. The reaction mixture was concentrated in vacuo and the residue was chromatographed on alumina and eluted with hexane-benzene (95:5). Recrystallization of the eluted product from chloroform yielded 382 mg (3.7%) of 1c as colorless needles: 98.5% pure (GLC); mp 202-203 °C; ¹H NMR (CDCl₃) δ 7.99 (s, 1, H₁), 7.78 (s, 1, H₄), 7.77 (d, 1, J = 1.9 Hz, H₉), 7.53 (d, 1, J = 1.9 Hz, H₇); ir (CHCl₃) 1656, 1606, 1481, 1430, 1394, 1113, 879 (isolated aromatic CH bend), 866, 854 cm⁻¹ (CCl); uv (CHCl₃) 250 nm (ϵ 43 000), 260 (52 500), 285 (27 400), 297 (32 000), 314 (14 100); mass spectrum m/e 308 (48), 306 (100), 304 (80), 243 (39), 241 (41), 171 (56), 153 (23), 132 (18), 86 (25), 85 (34).

Anal. Calcd for C₁₂H₄Cl₄O: C, 47.11; H, 1.32; Cl, 46.34. Found: C, 47.00; H, 1.42; Cl, 46.57.

1c was less conveniently prepared in comparable yield by the aqueous acetic acid-sodium nitrite procedure.

2,4,6-Trichlorodibenzofuran (1b). Heating a mixture of 45.1 g (0.22 mol) of potassium 2,4-dichlorophenolate and 43.0 g (0.22 mol) of 2,3-dichloronitrobenzene at 105-110 °C for 23 h afforded after workup 42.5 g (59%) of 2-(2,4-dichlorophenoxy)-3-chloronitrobenzene at a 98% level of purity (GLC). Treatment of 42 g of this with hydrazine and Raney nickel afforded 27.6 g (73%) of 2-(2,4-dichlorophenoxy)-3-chloroaniline, 96% pure (GLC).

A solution of 27.6 g (0.096 mol) of the aniline and 18.0 g (0.15 mol) of isoamyl nitrite (Eastman) in 950 ml of tetrachloroethylene was heated at 80 °C for 6 h. GLC-mass spectrometric analysis indicated the reaction mixture to contain only 19% of 1b, 70% trichlorodiphenyl ether, 3% tetrachlorodiphenyl ether, and 7% of the presumed trichloroethenyl-diphenyl ether derivative.

With freshly prepared isoamyl nitrite under somewhat more dilute conditions, 15.0 g (0.052 mol) of the aniline and 9.7 g (0.083 mol) of freshly prepared isoamyl nitrite in 750 ml of tetrachloroethylene, the reaction mixture was found to contain (GLC) 28% of 1b, 55% trichloro- and 6.5% tetrachlorodiphenyl ether, and 11% of the trichlo-

roethenyl derivative. Thus, the proportion of **1b** was increased, but it remained a minor product; the amount of trichloroethenyl derivative was also increased. GLC after silylation indicated no detectable amounts of phenolic products present.

Removal of solvent under reduced pressure from the first reaction solution left a dark orange oil which was chromatographed on alumina. Elution with hexane yielded a white solid which was chromatographed on silica gel and eluted with hexane to give 1.9 g (7% of **1b**: 98.5% pure (GLC); mp 116–117 °C; ^{1}H NMR (CDCl$_3$) δ 7.78 (d, 1, J = 2 Hz, H$_1$), 7.50 (d, 1, J = 2 Hz, H$_3$), 7.79 (m, 1, H$_9$), 7.36 (m, 2, H$_7$ + H$_8$); mass spectrum *m/e* 274 (36), 272 (96), 270 (100), 209 (15), 207 (23), 137 (14), 136 (10), 135 (11).

1,3,4,7,8-Pentachlorodibenzofuran (1e). Heating a mixture of equimolar quantities of potassium 2,3,5-trichlorophenolate (**6**) and **3** at 105–110 °C afforded a 30% yield of material indicated by GLC analysis to contain 88% of **9** and 10% of the isomeric ether **10**. Treatment of the crude product with hydrazine and Raney nickel in boiling 95% ethanol afforded 87% of 2-(2,3,5-trichlorophenoxy)-4,5-dichloroaniline, indicated to be 91% pure by GLC.

A solution of 12.0 g (0.034 mol) of the aniline and 6.6 g (0.056 mol) of isoamyl nitrite in 700 ml of tetrachloroethylene was heated at 80 °C for 6 h. The crude oily reaction product was indicated by GLC–mass spectral analysis to contain 55% of **1e**, 20% pentachlorodiphenyl ether, 5% of the isomeric pentaCDBF (not identical with **1d** or its rearrangement product), and 12% of the trichloroethenyl derivative of the pentachlorodiphenyl ether. Purification of this material proved exceedingly difficult and entailed inordinately large losses of product owing to the more than usual difficulty in separating **1e** from its diphenyl ether relative. The crude product was first chromatographed on alumina and the material eluted with hexane–benzene (95:5) was twice chromatographed on silica gel and eluted with hexane. Repeated recrystallization of the eluant from chloroform and then three times from dioxane afforded 30.4 mg of **1e**, indicated by GLC to be 98.7% pure and to contain 1.3% of the corresponding diphenyl ether: ^{1}H NMR (CDCl$_3$) δ 8.30 (s, 1, H$_9$), 7.73 (s, 1, H$_6$), 7.46 (s, 1, H$_2$); ir (CHCl$_3$) 1596, 1435, 1413, 1361, 1100, 883 (isolated aromatic CH bend), 856 cm^{-1} (CCl); uv (CHCl$_3$) 263 nm (ϵ 27 000), 272 (40 000), 297 (48 000), 320 (18 000); mass spectrum *m/e* 344 (22), 342 (63), 340 (100), 338 (70), 277 (18), 205 (22), 171 (15), 170 (24), 169 (16), 138.5 (15).

Similar results were less conveniently realized by the aqueous acetic acid–sodium nitrite procedure.

2,4,6,8-Tetrachlorodibenzofuran (1h). Chlorine was slowly bubbled through a solution of 16.0 g (0.086 mol) of *o,o′*-biphenol in 350 ml of chloroform for 26 h to give 29 g of a white precipitate indicated by GLC to contain 77% of 4,4′,6,6′-tetrachloro-2,2′-biphenol and 19% of trichloro material. Two recrystallizations of the crude product from benzene followed by six recrystallizations from hexane yielded 17.0 g (61%) of 4,4′,6,6′-tetrachloro-2,2′-biphenol, mp 176–177 °C, 97% pure (GLC).

A solution of 1.0 g (3.1 mmol) of the tetrachlorobiphenol and 1.2 g (6.3 mmol) of *p*-toluenesulfonyl chloride in 10 ml of anhydrous pyridine was allowed to stand for 19 h at room temperature. The reaction mixture was diluted with water and extracted with benzene. The benzene solution was washed with dilute alkali and water, and then dried and evaporated to yield 2 g (100%) of crude ditosylate (**15**), mp 164–173 °C, colorless needles from hexane, mp 183–184 °C.

Anal. Calcd for C$_{26}$H$_{18}$Cl$_4$O$_6$S$_2$: Cl, 22.43; S, 10.14. Found: Cl, 22.19; S, 10.01.

To a solution of 2.0 g (3.2 mmol) of crude **15** in 10 ml of DMA was added 0.44 g (7.9 mmol) of powdered potassium hydroxide. The reaction mixture was heated with stirring for 1 h at 100–105 °C (bath temperature) and concentrated in vacuo. The solid residue was extracted with chloroform and the chloroform solution was washed with 10% sodium hydroxide solution and water, dried, and evaporated to dryness. Two recrystallizations of the residual solid from chloroform afforded 283 mg (29%) of **1h** as colorless needles: mp 198–200 °C; 99% pure (GLC); ^{1}H NMR (CDCl$_3$) δ 7.74 (d, 2, J = 3 Hz, H$_1$ + H$_9$), 7.52 (d, 2, J = 3 Hz, H$_3$ + H$_7$); ir (CHCl$_3$) 1600, 1490, 1439, 1379, 1176, 870 cm^{-1}; uv (CHCl$_3$) 257 nm (ϵ 17 000), 294 (18 600), 310 (5800), 323 (5800); mass spectrum *m/e* 308 (55), 306 (100), 304 (86), 243 (21), 241 (22), 171 (22), 153 (22), 152 (18), 121.5 (15), 120.5 (14).

Anal. Calcd for C$_{12}$H$_4$Cl$_4$O: C, 47.04; H, 1.28. Found: C, 47.04; H, 1.28.

2,3,7,8-Tetrachlorodibenzofuran (1i). This was prepared essentially as described by Kende et al.[19,20] Heating 244 g (0.71 mol) of benzidine-2,2′-disulfonic acid in 1300 g of 50% aqueous sodium hydroxide in a stainless steel bomb at 280 °C for 50 h yielded 17.5 g (9%) of 3,7-diaminodibenzofuran dihydrochloride, free base mp 148–150 °C (lit. mp 152 °C).

To a stirred solution at 0 °C of 17.2 g (0.064 mol) of 3,7-diaminoDBF

dihydrochloride in 1 l. of 25% hydrochloric acid was added, dropwise, a solution of 10.1 g (0.15 mol) of sodium nitrite in 100 ml of water. Stirring was continued for 1 h, after which the cold solution was poured in portions into a boiling suspension of freshly prepared cuprous chloride in 450 ml of water (prepared by adding an aqueous solution of 9.8 g of sodium metabisulfite and 5.9 g of sodium hydroxide to a warm aqueous solution of 45.4 g of copper sulfate and 12.3 g of sodium chloride). The reaction mixture was heated at reflux for 2 h, cooled, and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid and salt water, dried, and evaporated to give 17.6 g of brown, solid residue which was chromatographed on silica gel and eluted with hexane. Recrystallization of the chromatographed product from hexane gave 7.9 g (53%) of 3,7-diCDBF (**11**), >98% pure by GLC.

Chlorine was slowly bubbled into a stirred solution at room temperature of 2.0 g (6.5 mmol) of **11** in 150 ml of chloroform containing a few crystals of ferric chloride and iodine, and the reaction was followed by GLC. Chlorination was halted when significant amounts of the difficultly separable pentachloro homologues began to appear. Concentration of the solution left 2.9 g of brown solid residue indicated by GLC and mass spectral analysis to consist of 68% of **1i**, 24% of triCDBF, 4.5% of two other tetraCDBF isomers, and 3% of three pentaCDBF isomers. Six recrystallizations of this material from isooctane afforded 140 mg (5.4%) of **1i**: 98% pure by GLC; mp 227–228 °C; ^{1}H NMR (CDCl$_3$) δ 7.99 (s, 2, H$_1$ + H$_9$), 7.72 (s, 2, H$_4$ + H$_6$); uv (CHCl$_3$), 259 nm (ϵ 15 000), 306 (15 000), 316 (14 000); mass spectrum *m/e* 308 (51), 306 (100), 304 (79), 243 (19), 241 (19), 205 (10), 171 (16), 153 (12), 152 (9), 85 (10).

Anal. Calcd for C$_{12}$H$_4$Cl$_4$O: C, 47.11; H, 1.32. Found: C, 47.22; H, 1.37.

2,3,7-TriCDBF (1f). Chlorine was bubbled slowly through a stirred solution of 1.7 g of **11** in 170 ml of glacial acetic acid at 50 °C (bath temperature) and reaction was followed by GLC. Chlorine introduction was stopped after 2 h and the solution, after being allowed to stand at room temperature overnight, was found to contain (GLC) 23% **11**, 61% **1f**, 2% of a second triCDBF, 11% of three tetraCDBF isomers, and 3% of four pentaCDBF isomers. Chlorination in chloroform proved no more satisfactory. The solution was diluted with water and the precipitate was recrystallized several times from chloroform and chromatographed on silica gel and then on alumina, eluting with hexane containing gradually increasing amounts of benzene. Attempts to effect further purification of the chromatographed material by recrystallization from a variety of solvents proved unavailing. A useful purification was, however, achieved on an analytical scale by HPLC. A solution of 24 mg of impure material (69% **1f**, 30% **11**, and 1% tetraCDBF by GLC) in 800 μl of warm dioxane was injected in 100-μl portions onto a Zorbax ODS column, 0.8 × 25 cm, and eluted with methanol–0.01 M aqueous phosphoric acid, 84:16. Near baseline separation of peaks, with a reasonable retention time of 40–50 min for the **1f** peak, was achieved. The middle peak was collected and the product was recrystallized from chloroform to give 6.8 mg of **1f**: 97% pure by GLC; mass spectrum *m/e* 274 (34), 272 (93), 270 (100), 209 (18), 207 (25), 137 (24), 136 (27), 135 (22), 103.5 (17), 86 (19).

2,3,9-Trichlorodibenzofuran (1g). A solution of 1.0 g (3.5 mmol) of 2-(*m*-chlorophenoxy)-4,5-dichloroaniline (prepared by condensation of potassium *m*-chlorophenolate with **3** followed by hydrazine–Raney nickel reduction of the nitro group) and 0.65 g (5.6 mmol) of isoamyl nitrite in 50 ml of tetrachloroethylene was heated at 80 °C for 6 h. GLC analysis indicated the reaction mixture to contain 29% trichlorodiphenyl ether, 27% **1g**, 14% **1f**, and 8% trichloroethenyl derivative. The solvent was removed in vacuo and the residual orange oil was chromatographed on alumina. The early fractions obtained on elution with hexane contained **1g** and **1f** in a >9:1 ratio. The combined early fractions, 15 mg, composed of (GLC) 71% **1g**, 3% **1f**, and 26% of the reduced diphenyl ether, was chromatographed on silica gel, eluted with hexane, and the eluent (8 mg) was twice recrystallized from chloroform to give 4 mg of **1g**, 95% pure by GLC, containing 3% **1f** and 2% of the diphenyl ether. The structure of **1g** is supported by the ^{1}H NMR spectrum (CDCl$_3$): δ 8.5 (s, 1, H$_1$), 7.85 (s, 1, H$_4$), 7.25–7.8 (m, 3, H$_6$, H$_7$, H$_8$); mass spectrum *m/e* 274 (34), 272 (93), 270 (100), 209 (18), 207 (25), 137 (22), 136 (21), 135 (20), 86 (14).

1,2,7,8-Tetrachlorodibenzofuran (1k). Chlorine was passed through a solution, maintained at 70 °C (bath temperature), of 5.0 g (0.03 mol) of DBF in 150 ml of glacial acetic acid for a period of 50 h to give a reaction mixture indicated by GLC–mass spectral analysis to be composed of 41% **1i**, 21% **1k**, 6.5% of two other tetraCDBF isomers, 25% of triCDBF isomers, and 6% of pentaCDBF isomers. Repeated recrystallization of precipitated material from glacial acetic acid afforded 0.73 g indicated by GLC to consist of 56% **1i** and 43%

1k. The identity of **1i** was confirmed by direct GLC comparison with a sample of the compound prepared by the method of Kende et al. The structural assignment of **1k** was indicated by analysis of the ^{1}H NMR spectrum of the mixture, which also accorded with the presence in the mixture of **1i** and **1k** in a roughly 1:1 ratio. The ^{1}H NMR data are tabulated as follows.

Chemical shift, δ	Proton ratios
8.36	1.9
7.92	4.4
7.67	6.9
7.54	1.6
7.48	1.6
7.33	1.0

The peaks at δ 7.67 and 7.92 are assignable, respectively, to the 4,6 and 1,9 protons of **1i**. The δ 7.33, 7.48, and 7.54 signals taken with a signal buried in the δ 7.67 peak are interpretable as a pair of doublets for the 3,4 protons of **1k**. The signal of the 6 proton of **1k** is also presumably buried in the δ 7.67 peak and the δ 8.36 signal can be assigned to the deshielded 9 proton of this isomer.

A solution of 12 mg of a mixture indicated (GLC) to consist of 5.5% triCDBF, 37% **1k**, 51% **1i**, and 5.5% pentaCDBF in 400 μl of warm dioxane was injected (4 × 100 μl) into the HPLC equipped for recycle with two 0.8 × 25 cm Zorbax ODS columns, at 1100 psi and 55 °C, developing solvent 90% methanol, 10% 0.01 M aqueous phosphoric acid. After one pass through, four nonbaseline separated peaks were observed. The third peak was recycled twice. Collection of the **1k** fraction gave 2 mg indicated by GLC to consist of 96% **1k** and 4% pentaCDBF material: mass spectrum m/e 308 (51), 306 (100), 304 (79), 243 (17), 241 (16), 171 (22), 153 (20), 152 (17), 120.5 (16), 85 (18).

Registry No.—**1a**, 57117-32-5; **1b**, 58802-14-5; **1c**, 57117-37-0; **1d**, 58802-15-6; **1e**, 58802-16-7; **1f**, 58802-17-8; **1g**, 58802-18-9; **1h**, 58802-19-0; **1i**, 51207-31-9; **1k**, 58802-20-3; **2**, 1121-74-0; **3**, 89-69-0; **6**, 58200-72-9; **11**, 58802-21-4; **14**, 58802-22-5; **15**, 58802-23-6; DBF, 132-64-9; 2-(p-chlorophenoxy)-4,5-dichloroaniline, 58802-24-7; potassium 2,4,5-trichlorophenolate, 35471-43-3; 2-(2,4,5-trichlorophenoxy)-4,5-dichloroaniline, 58802-25-8; potassium 2,4-dichlorophenolate, 50884-30-5; 2-(2,4-dichlorophenoxy)-4,5-dichloroaniline, 58802-26-9; 2,3-dichloronitrobenzene, 3209-22-1; 2-(2,4-dichlorophenoxy)-3-chloroaniline, 58802-27-0; 2-(2,3,5-trichlorophenoxy)-4,5-dichloroaniline, 58802-28-1; 4,4′,6,6′-tetrachloro-2,2′-biphenol, 14477-61-3; p-toluenesulfonyl chloride, 98-59-9; o,o′-biphenol, 1806-29-7.

References and Notes

(1) Presented in part at the 9th Annual Conference on Trace Substances in Environmental Health, University of Missouri, Columbia, Mo., June 1975, proceedings in press.
(2) D. Firestone, J. Ress, N. L. Brown, R. P. Barron, and J. N. Damico, *J. Assoc. Off. Anal. Chem.*, **55**, 85 (1972).
(3) J. R. Plimmer, J. M. Ruth, and E. A. Woolson, *J. Agric. Food Chem.*, **21**, 90 (1973).
(4) J. G. Vos, J. H. Koeman, H. L. van der Maas, M. C. ten Noever de Brauw, and R. H. de Vos, *Food Cosmet. Toxicol.*, **8**, 625 (1970).
(5) J. A. G. Roach and I. H. Pomerantz, *Bull. Environ. Contam. Toxicol.*, **12**, 338 (1974).
(6) G. W. Bowes, M. J. Mulvihill, B. R. T. Simoneit, A. L. Burlingame and R. W. Risebrough, *Nature (London)*, **256**, 305 (1975).
(7) G. W. Bowes, M. Mulvihill, M. R. DeCamp, and A. S. Kende, *J. Agric. Food Chem.*, in press.
(8) R. D. Kimbrough, *Arch. Environ. Health*, **25**, 125 (1972).
(9) Panel on Hazardous Trace Substances, *Environ. Res.*, **5**, 249 (1972).
(10) Proceedings of NIEHS Conference on Toxicity of Chlorinated Dibenzo-p-dioxins and Dibenzofurans, *Environ. Health Persp., Exp. Issue 5* (1973).
(11) J. S. Taylor, *Cutis*, **13**, 585 (1974).
(12) B. A. Schwetz et al., in "Chlorodioxins-Origin and Fate", E. H. Blair, Ed., *Adv. Chem. Ser., No. 120*, 55–69 (1973).
(13) A. Poland and E. Glover, *Mol. Pharmacol.*, **9**, 736 (1973).
(14) J. S. Taylor, personal communication.
(15) A. P. Gray, S. P. Cepa, and J. S. Cantrell, *Tetrahedron Lett.*, 2873 (1975).
(16) A. P. Gray, S. P. Cepa, I. J. Solomon, and O. Aniline, *J. Org. Chem.*, following paper in this issue.
(17) W. E. Parham in "Heterocyclic Compounds", Vol. 2, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1951, pp 124–136.
(18) G. M. Badger, "The Chemistry of Heterocyclic Compounds", Academic Press, New York, N.Y., 1961, pp 140–141.
(19) A. S. Kende, J. J. Wade, M. DeCamp, D. Ridge, and A. Poland, Abstracts, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., 1974, No. ORGN-130; manuscript in preparation.
(20) (a) A. S. Kende, personal communication. (b) A reviewer has pointed out that other factors such as a steric effect arising from solvation of the nitro group may also be involved.
(21) J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962).
(22) H. Gilman, M. W. Van Ess, and D. M. Hayes, *J. Am. Chem. Soc.*, **61**, 643 (1939).
(23) N. M. Cullinane and C. G. Davies, *Recl. Trav. Chim. Pays-Bas*, **55**, 881 (1936).
(24) Kende et al.[19,20] report the preparation of **1a** and **1c** by this route using the aqueous acid procedure.
(25) Kende et al.[19,20] have obtained impure **1f** by an alternative route.
(26) D. C. DeJongh and R. Y. Van Fossen, *J. Org. Chem.*, **37**, 1129 (1972).
(27) S. Yamashiro, *Bull. Chem. Soc. Jpn.*, **17**, 10 (1942).
(28) S. Yamashiro, *J. Chem. Soc. Jpn.*, **59**, 945 (1938).
(29) S. Yamashiro, *Bull. Chem. Soc. Jpn.*, **16**, 6, 61 (1941).
(30) J. Van Dijk, J. J. van Daalen, and G. B. Paerels, *Recl. Trav. Chim. Pays-Bas*, **93**, 72 (1974).
(31) For analysis of ir spectra of related CDBF derivatives, see J.-Y. T. Chen, *J. Assoc. Off. Anal. Chem.*, **56**, 962 (1973).
(32) Activated Raney nickel packed under water from Research Organic/Inorganic Chemical Corp., water replaced by 95% ethanol before use.
(33) R. Q. Brewster and T. Groening, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 446.
(34) Alcoa Grade F-20, 80–200 mesh, heated at 150 °C for at least 4 h before use.
(35) Grace Division Chemical, Grade 62, 60–200 mesh, heated at 150 °C for at least 4 h before use.

Synthesis of Specific Polychlorinated Dibenzo-p-dioxins[1]

Allan P. Gray,* Steven P. Cepa, I. J. Solomon, and O. Aniline

Chemistry and Chemical Engineering Research Division, IIT Research Institute, Chicago, Illinois 60616

A number of tri- through heptachlorodibenzo-p-dioxin (DD) derivatives have been synthesized, most at a high level of purity. The most versatile method for the preparation of specific derivatives in reasonable yield has been found to be the condensation of chloro-substituted catechols with chloro-substituted o-chloronitrobenzenes. Reactivity of the nitrobenzene depends on the position and number of chloro substituents and increases in the order 2,5-di- and 2,4,5-tri- < 2,3,5,6-tetra- < 2,3,4,5-tetra- and pentachloronitrobenzene. 4-Chloro- and 4,5-dichlorocatechol afforded good results in this reaction but 3,4,5-tri- and particularly tetrachlorocatechol proved less satisfactory, undergoing extensive decomposition and giving low yields of desired products. The principal by-products, where there is a chloro substituent adjacent to one located ortho or para to the nitro function of the nitrobenzene, are nitropolychloroDD analogues.

Certain polychlorinated dibenzo-p-dioxins (DD) and some structurally related compounds have been demonstrated to be highly toxic trace contaminants of the environment (see our previous papers for leading references[1-3]). They have caused chloracne and porphyria in industrial workers, and are potent inducers of the enzymes aryl hydrocarbon hydroxylase and δ-aminolevulinic acid synthetase.[4,5]
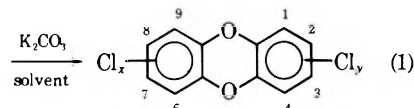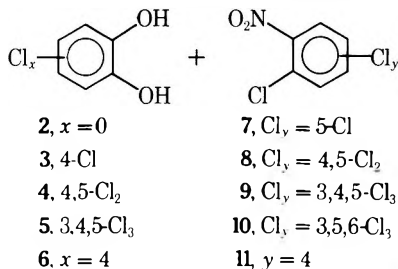
Toxicity is strikingly dependent on the position and number of chloro substituents. Peak toxicity is associated with the 2,3,7,8-tetrachloro homologue (2,3,7,8-tetraCDD), identified as a trace impurity in the herbicide 2,4,5-T and one of the most toxic substances known.[4,5] The 1,2,3,7,8,9-hexachloro analogue (1,2,3,7,8,9-hexaCDD) was identified as the trace contaminant of chicken feed, the so-called chick edema factor, responsible for outbreaks of chick edema disease and the deaths of millions of chickens.[6,7]

In a program aimed at increasing understanding of the nature of the toxicity of these compounds, we have been engaged in the directed synthesis of a number of polychlorinated DD and dibenzofuran (DBF) homologues and isomers at a high level of purity,[1-3] have identified and characterized the products, and made them available for toxicity studies. The present report is concerned with the synthesis of specific polyCDD derivatives.

Chlorinated DD derivatives have generally been prepared by the self-condensation of the alkali metal salts of o-halophenols.[1,2,8,9] Pohland and Yang developed a more attractive approach involving the surprisingly facile condensation of catechol with o-chloropolychloronitrobenzenes in boiling acetone[8] and Kende et al. have condensed catechols at higher temperatures with polychlorobenzenes.[10] These processes have generally afforded mixtures of products and the isolation of pure compounds has proved extremely difficult.[1,2,8-11] It has recently been shown[2,11] that these condensation reactions proceed via Smiles rearrangement, a fact which in large part explains the formation of mixtures of isomeric products in those cases where lack of symmetry makes this possible.

By strategic exploitation of the Smiles rearrangement observed in the phenol condensation process, we were able to isolate both the 1,2,3,6,7,8- and the 1,2,3,7,8,9-hexaCDD (the chick edema factor) isomers in pure form, and identify and characterize the compounds.[2] The occurrence of the rearrangement, however, coupled with the poor yields encountered even under the best conditions made it apparent that this approach had limited value for the synthesis of other desired derivatives. It may be noted that only in a very few instances would the substituents in a phenol be so placed that the product of rearrangement would be identical with that formed by direct self-condensation. A fortuitous example is the synthesis of 2,3,7,8-tetraCDD.[9]

We therefore turned our attention to adaptation of the Pohland and Yang process[8] which, so long as one of the two reactants, either the catechol or the nitrobenzene, has appropriately positioned substituents, the products of rearrangement and of direct condensation will be the same. Thus, the process permits considerably more flexibility (eq 1).

2, x = 0	**7**, Cl$_y$ = 5-Cl
3, 4-Cl	**8**, Cl$_y$ = 4,5-Cl$_2$
4, 4,5-Cl$_2$	**9**, Cl$_y$ = 3,4,5-Cl$_3$
5, 3,4,5-Cl$_3$	**10**, Cl$_y$ = 3,5,6-Cl$_3$
6, x = 4	**11**, y = 4

$$\xrightarrow[\text{solvent}]{K_2CO_3}$$ (1)

1a, 2,3,7-triCDD[12]
b, 1,2,3,7,8-pentaCDD
c, 1,2,4,7,8-pentaCDD
d, 1,2,3,4,7,8-hexaCDD[13]
e, 1,2,3,4,6,7,8-heptaCDD
f, 1,2,3,4,6,7,9-heptaCDD
g, 1,2,3,6,7,9- or 1,2,3,6,8,9-hexaCDD

In this reaction, a chloro substituent ortho to the nitro group and the nitro group of the polychloronitrobenzene are displaced. Pohland and Yang[8] reported the reaction to proceed under surprisingly mild conditions, in boiling acetone, when the reactants were catechol itself (**2**) and either 2,3,5,6-tetrachloro- (**10**) or pentachloronitrobenzene (**11**), but to fail when tetrachlorocatechol (**6**) or 2,3-dichloronitrobenzene were used.

With respect to the catechol, Kende et al.[10] carried out successful condensations of the potassium salts of 4-chloro- (**3**) and 4,5-dichlorocatechol (**4**) with tetrachlorobenzenes and we have had comparable success with the condensation of **3** and **4** with polychloronitrobenzenes. We have also been able to effect similar condensations with 3,4,5-trichlorocatechol (**5**) and with **6**, but these reactants, which have chloro substituent(s) adjacent to a phenolic hydroxyl function, underwent extensive decomposition and afforded extremely poor yields even when precautions were taken to minimize undesired processes.

In regard to the polychloronitrobenzene, we have success-

Table I. GLC Data on Chlorinated Dibenzo-p-dioxins

No.	CDD	RT, min[a,c]	RT, min[a,d]	Rrt[b,c]	Rrt[b,e]
1a	2,3,7-Tri	9.5	2.25	1.00	
1b	1,2,3,7,8-Penta	14		1.72	
1c	1,2,4,7,8-Penta	14	9.1	1.67	
1d	1,2,3,4,7,8-Hexa	14.7		1.9	
1e	1,2,3,4,6,7,8-Hepta	23			7.1
1f	1,2,3,4,6,7,9-Hepta	21.8			6.4
1g	1,2,3,6,7,9- or				
	1,2,3,6,8,9-Hexa	18.2			3.8
1h	1,2,3,6,7,8-Hexa[f]	18.6	16.3	1.95	
1i	1,2,3,7,8,9-Hexa[f]	18.8	19.6	1.99	
1j	1,2,4,6,7,9-Hexa[g]		10.3	1.91	

[a] Retention time in minutes. [b] Relative retention time vs. dieldrin. [c] Dexsil 300, oven program 150–295 °C at 8 °C/min. [d] Apolar 10C (1%), program 150–230 °C at 10 °C/min. [e] Dexsil 300, isothermal at 270 °C. [f] Gray, Cepa, and Cantrell.[2] [g] Or 1,2,4,6,8,9 isomer depending on whether or not the Smiles rearrangement product was isolated. Prepared by the chlorophenolate condensation process as described by Pohland and Yang;[8] 98% pure (GLC) after chromatography on alumina, elution with hexane containing up to 10% benzene, and recrystallization from chloroform; mp 238–240 °C (lit.[8] mp 238–240 °C); ^{1}H NMR (CDCl3) δ 7.24 (s); ir accords with that reported;[17] mass spectrum m/e 396 (9), 394 (38), 392 (94), 390 (100), 388 (53), 331 (8), 329 (17), 327 (26), 325 (18), 266 (10), 264 (23), 262 (19), 196 (17), 195 (16). Anal. Calcd for $C_{12}H_2Cl_6O_2$: C, 36.87; H, 0.52; Cl, 54.52. Found: C, 37.17; H, 0.75; Cl, 54.05.

fully carried out condensations with di- through pentachloronitrobenzenes, those less than tetrachlorinated simply requiring more forcing conditions (e.g., boiling dimethyl sulfoxide or hexamethylphosphoramide[14]). We have found the reactivity of the nitrobenzene to depend on the position and number of chloro substituents and to increase in the order 2,5-dichloro (7) and 2,4,5-trichloro (8) < 10 < 2,3,4,5-tetrachloro (9) and 11.

The principal by-products of these reactions, where the polychloronitrobenzene bore a chloro substituent in an ortho relationship to a 2- or 4-chloro group, were nitropolyCDD derivatives resulting from displacement of the second, adjacent chloro rather than the nitro function. Amounts of these by-products were increased when more vigorous conditions (e.g., boiling dimethyl sulfoxide) were used or when the attempt was made to increase reactivity of the catechol anion by use of a catalytic amount of a crown ether (18-crown-6) in acetonitrile. In any event, these by-products never formed to an extent sufficient to introduce a serious complication and they were readily removed by recrystallization.

Only one of the catechol condensation reactions reported here, reaction of 5 with 10, can lead to an isomeric product via Smiles rearrangement. Indeed, in this instance two hexaCDD isomers, the 1,2,3,6,7,9- and the 1,2,3,6,8,9- (1g), can be expected regardless of whether or not rearrangement takes place, simply on the basis of the orientation of the reactants prior to condensation. GLC–mass spectral analysis of the crude reaction product did in fact reveal the presence of two hexaCDD isomers but the one having the larger retention time represented only a minor component and was easily removed by recrystallization. The purified product contained only a single hexaCDD isomer (plus about 8% of a pentaCDD homologue arising from dichlorocatechol contamination of the starting material). We are not able to say at this point whether the isolated product is 1,2,3,6,7,9- or 1,2,3,6,8,9-HCDD.

In general, the process of eq 1 afforded reasonable yields of pure polyCDD products. GLC data on these products are given in Table I.

Experimental Section

Caution: Certain of these compounds have been found to be highly toxic and should be handled with extreme care. Work was performed in glove boxes in an isolated toxic laboratory facility. Exhaust air was filtered. All wastes were incinerated. Contact with these compounds can cause chloracne and irreversible liver damage.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance (^{1}H NMR) spectra were determined with a Varian A-60D spectrometer and are given in parts per million (δ) downfield from tetramethylsilane; ir spectra with a Perkin-Elmer 21 instrument and uv spectra with a Cary 14; GLC–mass spectra were determined at 70 eV with a Hitachi Perkin-Elmer RMU-6D spectrometer linked in tandem to a gas chromatograph. GLC data were obtained with a Varian Aerograph 1200 or 1440 gas chromatograph, hydrogen flame ionization detector, helium flow rate 40 ml/min; 2 m × 0.32 cm columns packed with Dexsil 300, Apolar 10C, or 1% DEGS. Each compound was checked on at least two columns. GLC data are given in Table I. High-pressure liquid chromatography (HPLC) was carried out with a Du Pont 830 instrument. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Micro-Tech Laboratories, Inc., Skokie, Ill. Analytical data are in accord with structural assignments. Percent purity is based on average GLC response data.

Chlorocatechols. 4-Chlorocatechol (3) and 4,5-dichlorocatechol (4) were prepared essentially as described by Willstätter and Müller.[15]

Treatment of catechol (2) with 1 equiv of sulfuryl chloride in anhydrous ether afforded a 35% yield of 3 indicated by HPLC[16] to be accompanied by a small amount of a contaminant, possibly the 3-chloro isomer.

To an ice-cooled solution maintained under nitrogen of 35.7 g (0.325 mol) of 2 in 150 ml of anhydrous ether was added, dropwise with stirring over a period of 90 min, 58 ml (97 g, 0.72 mol) of sulfuryl chloride. The solution was allowed to warm to room temperature and evaporated under nitrogen to a volume of ca. 75 ml. The crystalline precipitate which formed on standing was collected to afford 22.5 g (39%) of 4 indicated (GLC) to be >97% pure.

The literature method for preparation of 3,4,5-trichlorocatechol (5), chlorination of 2 with chlorine,[15] proved difficult to control and gave considerable amounts of tetrachlorocatechol (6).[15] The following procedure was therefore adopted.

One molar equivalent of sulfuryl chloride was added to a stirred tetrahydrofuran solution of 4, maintained under nitrogen at room temperature, and the reaction was followed by GLC. At the point of 40–45% conversion to 5, significant amounts of 6 began to form and the reaction was stopped. Recrystallization from benzene–hexane yielded 6.5 g of material containing (GLC) 42% of 4 and 58% of 5. This was twice recrystallized from benzene to give 0.7 g (11% yield) of 5 indicated (GLC) to contain 93% 5 and 7% 4.

Passing chlorine through a solution of 4 in glacial acetic acid afforded a 21% yield of 6.

2,3,7-Trichlorodibenzo-p-dioxin (1a). Condensation of 3 with 2,4,5-trichloronitrobenzene (8) or of 4 with 2,5-dichloronitrobenzene (7) failed to take place to any significant extent when the reactions were carried out in boiling acetone containing potassium carbonate,[8] or even in dimethyl sulfoxide solution at 125 °C. Both condensations proceeded smoothly, however, when the reactants were heated at about 180 °C in either dimethyl sulfoxide or hexamethylphosphoramide.[14]

A solution of 2.75 g (0.015 mol) of 96% pure 4 and 2.06 g (0.01 mol)

of 7 in 25 ml of dimethyl sulfoxide containing 5.5 g of potassium carbonate was heated at reflux for 3.5 h. The reaction mixture was taken up in chloroform and washed with water and dilute alkali. The chloroform solution was concentrated and diluted with methanol to give 0.87 g of precipitate indicated by GLC–mass spectral analysis to consist of 96.7% 1a and 3.3% of a dichloro homologue. Recrystallization from chloroform–methanol yielded 0.53 g (17%) of 1a: 99% pure (GLC); mp 162–163 °C;[12] ^{1}H NMR (CDCl3) δ 6.97 (s, 2, $H_1 + H_4$), 6.75–6.95 (m, 3. $H_6 + H_8 + H_9$); ir (CHCl3)[17] 1615, 1575, 1485, 1470, 1375 (aromatic stretch), 1310 (C–O–C stretch), 1295, 1275, 1230, 1110, 1075. 970, 904, 873 (isolated H bend), 860 cm^{-1} (adjacent H bend); uv (CHCl3) 305 nm (ε 5200); mass spectrum m/e 290 (31), 288 (98), 286 (100), 225 (22), 223 (36), 160 (23), 144 (17), 143 (18).

Anal. Calcd for $C_{12}H_5Cl_3O_2$: C, 50.13; H, 1.75; Cl, 36.99. Found: C, 49.86; H, 1.78; Cl, 37.05.

1,2,3,7,8-Pentachlorodibenzo-p-dioxin (1b). An acetone solution of 2.4 g (0.013 mol) of 4 and 2.1 g (0.008 mol) of 2,3,4,5-tetrachloronitrobenzene (9) containing 7.2 g of potassium carbonate was heated at reflux for 5.5 h. The reaction mixture was diluted with water and methanol to give 1.6 g of precipitate indicated by GLC–mass spectral analysis to contain 76% of 1b, the balance being mainly nitropolyCDD materials. Two recrystallizations from chloroform–methanol yielded 0.84 g (29%) of 1b: 98% pure (GLC); mp 240–241 °C; ^{1}H NMR (CDCl3) δ 7.13 (s, 1, H_4), 7.02 (s, 1, H_9), 6.98 (s, 1, H_6); ir (CHCl3)[17] 1565, 1480, 1450, 1380 (aromatic stretch), 1310 (C–O–C stretch), 1115, 955, 915, 875 (isolated CH bend), 838 cm^{-1} (C–Cl stretch); uv (CHCl3) 308 nm (ε 6100); mass spectrum m/e 360 (21), 358 (70), 356 (100), 354 (67), 295 (12), 293 (24), 291 (18), 230 (11), 228 (11).

Anal. Calcd for $C_{12}H_3Cl_5O_2$: C, 40.44; H, 0.85; Cl, 49.73. Found C, 40.09; H, 0.88; Cl, 49.63.

1,2,4,7,8-Pentachlorodibenzo-p-dioxin (1c). Reaction of 4 with 2,3,5,6-tetrachloronitrobenzene (10) proceeded only sluggishly in acetone containing potassium carbonate. After 4 h at reflux, 9% of material was obtained indicated by GLC–mass spectral analysis to contain 82% 1c and 15% nitrotetraCDD products.

A mixture of 5.0 g (0.028 mol) of 4, 7.9 g (0.03 mol) of 10, and 7.7 g (0.056 mol) of potassium carbonate in 100 ml of acetone was heated at reflux for 16 h. Workup yielded 0.67 g of 1c indicated by GLC to be 99% pure and 1.19 g of 97% pure material, combined yield 18.5%. The 99% pure 1c showed mp 205–206 °C; ^{1}H NMR (CDCl3) δ 7.19 (s, 1, H_3), 7.16 (s, 2, $H_6 + H_9$); ir (CHCl3) 1575, 1560, 1475, 1435, 1407, 1104, 870, 838 cm^{-1}; uv (CHCl3) 307 nm (ε 3700); mass spectrum m/e 360 (22), 358 (70), 356 (100), 354 (81), 295 (16), 293 (35), 291 (26), 230 (19), 228 (24), 178 (12), 177 (21).

Anal. Calcd for $C_{12}H_3Cl_5O_2$: C, 40.44; H. 0.85; Cl, 49.73. Found: C, 40.74; H, 0.88; Cl, 49.81.

1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (1d). This compound was prepared in two ways: by condensation of 2 with pentachloronitrobenzene (11) followed by chlorination of the product as described by Pohland and Yang,[8] or, at a higher level of purity, by condensation of 4 with 11. A solution of 0.79 g (4.4 mmol) of 4 and 3.73 g (12.6 mmol) of 11 in 25 ml of acetone containing 2.2 g (15.9 mmol) of anhydrous potassium carbonate was heated at reflux for 5 h. The reaction mixture was poured into water, and the precipitate was collected and washed with hot methanol. The residual solid was recrystallized from chloroform to give 0.75 g (44%) of 1d, 98% pure (GLC), principal impurities being nitropolyCDD analogues: mp 272.5–273 °C (lit.[8] mp 275 °C); ir accords with that reported;[17] uv (CHCl3) 313 nm (ε 4100); mass spectrum m/e 396 (12), 394 (32), 392 (80), 390 (100), 388 (45), 329 (14), 327 (24), 325 (15), 266 (7), 264 (14), 262 (12).

Anal. Calcd for $C_{12}H_2Cl_6O_2$: C, 36.87; H, 0.52; Cl, 54.52. Found: C, 36.78; H, 0.47; Cl, 54.40.

1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (1e). Initial efforts to prepare 1e by monochlorination of 1d were unsuccessful. We therefore turned to the condensation of 6 with 9. Care had to be exercised in this condensation to minimize decomposition of the catechol on the one hand, and to avoid products resulting from reaction at the p-chloro substituent of the nitrobenzene on the other. Although the process was slow, these objectives were found best achieved by running the reaction in acetone.

A solution of 1.51 g (6.1 mmol) of 6 and 1.36 g (5.2 mmol) of 9 in 40 ml of acetone containing 2.76 g (20 mmol) of anhydrous potassium

carbonate was heated at reflux for 90 h. Workup gave 610 mg of material containing (GLC) 30% of 1e. Recrystallization of this from chloroform, isooctane, and then anisole afforded 114 mg (5%) of 1e, 93% pure (GLC). This was chromatographed on alumina and eluted with petroleum ether–benzene (85:15) to give 31.7 mg of 1e: 97% pure (GLC); mass spectrum m/e 430 (18), 428 (51), 426 (73), 424 (100), 422 (43), 365 (12), 363 (21), 361 (23), 359 (14).

1,2,3,4,6,7,9-Heptachlorodibenzo-p-dioxin (1f). A solution of 0.91 g (3.7 mmol) of 6 and 1.66 g (6.4 mmol) of 10 in 80 ml of acetonitrile containing 2.46 g (17.8 mmol) of potassium carbonate was heated at reflux for 150 h. Addition of a catalytic amount of crown ether (18-crown-6) had no significant beneficial effect on the course of the reaction. The reaction mixture was concentrated to dryness, and the residue was washed with water and twice recrystallized from chloroform to give 5.3 mg of 1f indicated by GLC–mass spectral analysis to be 91% pure, the major impurities being two hexaCDD isomers.

1,2,3,6,7,9- or 1,2,3,6,8,9-Hexachlorodibenzo-p-dioxin (1g). A solution of 0.51 g (2.4 mmol) of 5 and 0.87 g (3.3 mmol) of 10 in 50 ml of acetonitrile containing 1.33 g (9.6 mmol) of anhydrous potassium carbonate and a catalytic amount of 18-crown-6 ether was heated at reflux for 24 h. GLC analysis of the reaction solution showed a major and a small second peak in the hexaCDD region. Workup and recrystallization from chloroform resulted in disappearance of the minor peak and yielded 253 mg (27%) of product indicated by GLC to contain 88% of a single hexaCDD isomer, the major impurities being pentaCDD analogues. It is not possible at this point to make even a tentative structural assignment for 1g: mass spectrum m/e 396 (10), 394 (38), 392 (82), 390 (100), 388 (54), 329 (16), 327 (20), 325 (15), 266 (8), 264 (15), 262 (11), 196 (14), 195 (15), 194 (10).

References and Notes

(1) Presented in part at the 9th Annual Conference on Trace Substances in Environmental Health, University of Missouri, Columbia, Mo., June 1975, proceedings in press.
(2) A. P. Gray, S. P. Cepa, and J. S. Cantrell, *Tetrahedron Lett.*, 2873 (1975).
(3) A. P. Gray, V. M. Dipinto, and I. J. Solomon, *J. Org. Chem.*, preceding paper in this issue.
(4) "Chlorodioxins—Origin and Fate", E. H. Blair, Ed., *Adv. Chem. Ser.*, No. 120 (1973).
(5) A. Poland and E. Glover, *Mol. Pharmacol.*, **9**, 736 (1973).
(6) J. C. Wootton and W. L. Courchene, *J. Agric. Food Chem.*, **12**, 94 (1964).
(7) J. S. Cantrell, N. C. Webb, and A. J. Mabis, *Acta Crystallogr., Sect. B*, **25**, 150 (1969).
(8) A. E. Pohland and G. C. Yang, *J. Agric. Food Chem.*, **20**, 1093 (1972).
(9) O. Aniline, ref 4, pp 126–135.
(10) A. S. Kende, J. J. Wade, M. DeCamp, D. Ridge, and A. Poland, *J. Org. Chem.*, **39**, 931 (1974).
(11) A. S. Kende and M. R. DeCamp, *Tetrahedron Lett.*, 2877 (1975).
(12) Kende et al.[10] obtained an impure sample of this compound by condensation of the potassium salt of 4-chlorocatechol with 1,2,4,5-tetrachlorobenzene, mp 153–158 °C.
(13) Pohland and Yang[8] prepared this compound by chlorination of 1,2,3,4-tetraCDD.
(14) Caution: hexamethylphosphoramide has recently been reported to be markedly carcinogenic; see *Chem. Eng. News*, 3 (Feb 2, 1976).
(15) R. Willstätter and H. E. Müller, *Ber.*, **44**, 2182 (1911).
(16) HPLC analysis carried out essentially as described in Du Pont Liquid Chromatography Applications Bulletin No. 74-02 but with Waters C_{18}-μ Bondapak column; initial solvent 10 mM phosphoric acid, gradient of 0–100% methanol in 5%/min linear increments; 500 psi and 40 °C; 254 nm uv detector.
(17) For analysis of ir spectra of related CDD derivaties see J.-Y. T. Chen, *J. Assoc. Off. Anal. Chem.*, **56**, 962 (1973).
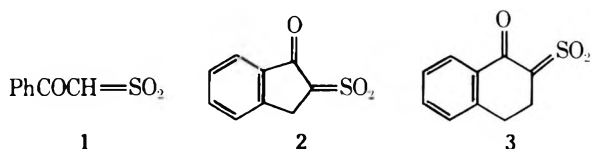
Reactions of α-Ketosulfenes with C,N-Diarylnitrones[1]

Otohiko Tsuge* and Michihiko Noguchi

Research Institute of Industrial Science, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 812, Japan

Benzoylsulfene 1 and two cyclic α-ketosulfenes 2 and 3, generated in situ from the corresponding sulfonyl chlorides and triethylamine, react with nitrones [ArCH=N(O)Ph] to produce the corresponding rearranged adducts, seven-membered cyclic azasultones 5, 11, and 13, accompanied by the formation of by-products, 6, 12 and 14, which arise from the rearranged adducts with the elimination of the benzaldehyde (ArCHO), respectively. An interconversion between 5 and 6 is described, and the stereochemistry of rearranged adduct 5 is also discussed.

In previous papers, it has been reported that benzoylsulfene 1, generated in situ from benzoylmethanesulfonyl chloride and triethylamine, reacts with the C=N bonds of anils,[2] carbodiimides,[3] and ketene imines[4] to give the [2 + 2] and/or [4 + 2] cycloadducts, while simple sulfenes (RCH=SO₂) do not react with the C=N bond.[5] In addition, new cyclic α-ketosulfenes 2 and 3, generated in situ from 2-chlorosulfon-

ylindanone and -1-tetralone, and triethylamine, respectively, added to the C=N bonds of anils to yield the corresponding cycloadducts.[6] These results indicate that the electron-attracting acyl group makes the α-ketosulfene more reactive than simple sulfenes, and the α-ketosulfenes behave as 1,4 and/or 1,2 dipoles.

Recently, Truce and Allison[7] reported that benzoylsulfene 1 and also simple sulfenes reacted with azomethine imines to form a [3 + 2] cycloadduct. The reaction of simple sulfenes with C,N-diarylnitrones proceeds via 1,3 cycloaddition followed by rearrangement to yield seven-membered cyclic azasultones.[8] We now report the reactions of α-ketosulfenes 1–3 with C,N-diarylnitrones.

Results and Discussion

Reaction of Benzoylsulfene 1. When equimolar quantities of C,N-diphenylnitrone 4a and triethylamine were stirred at room temperature in dry dioxane, and a solution of benzoylmethanesulfonyl chloride in dry dioxane was added dropwise in an atmosphere of nitrogen, there was an immediate precipitation of triethylammonium chloride. After the mixture was stirred at the same conditions for 2 h, two crystalline products, 5a and 6, were obtained from the solution. On the basis of its spectral data (Table I) and chemical conversion, 1:1 adduct 5a was assigned to be 4,5-dihydro-3-benzoyl-4-phenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-dioxide, whose ring system is the same as that of the product from simple sulfene and 4a. The stereochemistry of 5a will be described later.

On the other hand, the molecular formula of 6 agreed with that of the compound derived from 5a with the elimination of benzaldehyde. The ir spectrum exhibited strong absorption bands at 1370 and 1165 cm⁻¹ (SO₂), while no bands ascribable to NH and CO absorptions appeared. The NMR spectrum displayed a singlet (2 H) at δ 4.49 in addition to a complicated signal of aromatic protons (9 H). On the basis of the above facts, 6 was assigned to be 4-phenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-dioxide. Further support for this assignment was obtained through chemical conversions. Reduction of 6 with sodium borohydride in ethanol afforded 4,5-dihydro-4-phenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-dioxide (7),[8] which was identical with an authentic sample prepared from

sulfene (CH₂=SO₂) and nitrone 4a. On treatment with hydrochloric acid in boiling ethanol for a long while 6 was converted into o-aminophenol, whereas hydrolyisis of 6 under rather mild conditions afforded o-aminophenyl benzoylmethanesulfonate (8), which on reduction with sodium borohydride gave o-aminophenyl 2-hydroxy-2-phenylethanesulfonate (9). By dehydration 8 easily reverted to 6.

Similarly, the reaction of ketosulfene 1 with C-(p-anisyl)-N-phenyl- (4b), C-(p-chlorophenyl)-N-phenyl- (4c), and C-(p-nitrophenyl)-N-phenylnitrone (4d) gave the corresponding seven-membered cyclic azasultones, 5b–d, and 6 (Scheme I). The yields of 5 and 6 and physical and spectral data of 5 are given in Table I.

Scheme I

a, R = H; b, R = OMe; c, R = Cl; d, R = NO₂
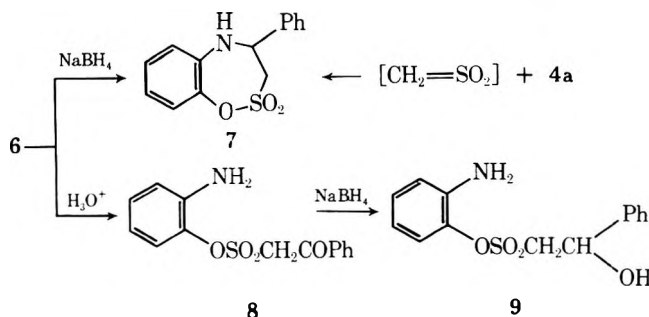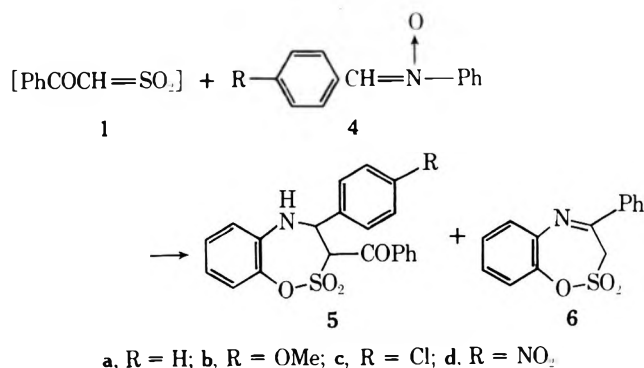
When treated with hydrochloric acid in methanol at room temperature, or chromatographed on acidic alumina, 5a and 5c were converted into 6 along with benzaldehyde and p-chlorobenzaldehyde, respectively. This fact indicates that the formation of 6 in the reaction of 1 with nitrones 4 was derived from the corresponding rearranged adduct 5, and that on conversion of 5 into 6 the benzoyl group at the 3 position in 5 was not involved in the elimination of the benzaldehyde. On treatment with hydrochloric acid under similar conditions, the rearranged adduct 10 which was prepared from phenylsulfene and nitrone 4a was unchanged. It appears that the electron-attracting benzoyl group at the 3 position in 5 enhances the reactivity of the oxathiazepine ring toward hydrolysis.

Table I

$$1 + 4 \longrightarrow \mathbf{5} + \mathbf{6}$$

5   **6**

		Yield, %		Mp, °C	Ir (KBr), cm^{-1}	NMR (CDCl$_3$), δ (*J*, Hz)	Found (calcd), %			M$^+$
	R	5^c	6				C	H	N	*m/e*
a	H	28	8^d	155–156	3380 (NH), 1680 (CO), 1370, 1155 (SO$_2$)	3.7 (1 H, br, NH, exchanged with D$_2$O), 5.27 (1 H, d, H$_a$, *J* = 9.8), 5.81 (1 H, d, H$_b$, *J* = 9.8), 6.8–7.8 (14 H, m, aromatic protons)	66.64 (66.48)	4.24 (4.52)	3.71 (3.69)	379
b	OMe	10	5	154–155.5	3340 (NH), 1690 (CO), 1370, 1165 (SO$_2$)	3.69 (3 H, s, OCH$_3$), 3.8 (1 H, br, NH, exchanged with D$_2$O), 5.21 (1 H, d, H$_a$, *J* = 10), 5.79 (1 H, d, H$_b$, *J* = 10), 6.7–7.9 (13 H, m, aromatic protons)	64.71 (64.54)	4.67 (4.68)	3.52 (3.42)	409
c	Cl	36	6	178–180	3400 (NH), 1675 (CO), 1370, 1155 (SO$_2$)	3.8 (1 H, br, NH, exchanged with D$_2$O), 5.26 (1 H, d, H$_a$, *J* = 9.8), 5.79 (1 H, d, H$_b$, *J* = 9.8), 6.5–7.9 (13 H, m, aromatic protons)	60.94 (60.90)	3.68 (3.87)	3.04 (3.05)	415 413
d	NO$_2$	35	6	200–202 dec	3400 (NH), 1670 (CO), 1370, 1160 (SO$_2$)	5.36 (1 H, d, H$_a$, *J* = 10), 6.3 (1 H, br, NH, exchanged with D$_2$O), 6.75 (1 H, d, H$_b$, *J* = 10), 6.8–8.3 (13 H, m, aromatic protons)^b	59.60 (59.43)	3.74 (3.80)	6.48 (6.60)	424

^{a} 5a, 5b, and 5c, pale yellow needles; 5d, yellow needles. ^{b} Measured in Me$_2$SO-d_6. ^{c} Registry no. are, respectively, 59043-88-8, 59043-89-9, 59043-90-2, 59043-91-3. ^{d} Registry no., 16261-68-0.

As mentioned above, sulfonate 8 was easily converted into 6 by dehydration. The conversion of 5 into 6 might be interpreted as an initial formation of 8 and the benzaldehyde, followed by dehydration of 8 into 6. Thus it was expected that the reaction of 8 with the benzaldehyde would result in the formation of the corresponding rearranged adduct 5. In fact 8 reacted with p-chlorobenzaldehyde in ethanol to give **5c**. Interconversion between 5 and 6 is illustrated in Scheme II.

Scheme II
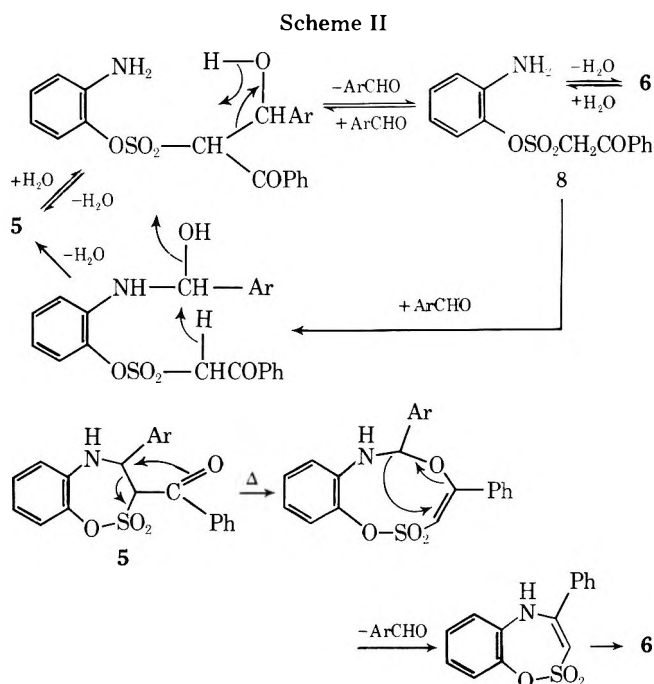
Further, thermolysis of **5a** or **5c** under reduced pressure afforded 6 and the benzaldehyde. Since the thermolysis was performed under anhydrous conditions, water was not involved in the formation of 6 from 5. The exact pathway is not

clear, but we tentatively propose a potential pathway as depicted in Scheme II. Ring expansion of the oxathiazepine ring to the nine-membered cyclic 1,5,2,7-dioxathiazonine ring, followed by elimination of the benzaldehyde, gives 5*H*-1,2,5-oxathiazepine. Subsequent hydrogen shift affords the final product 6.

Although the reaction of methyl-, phenyl-, and bromosulfenes with nitrones 4 which resulted in the formation of seven-membered cyclic azasultones has been reported,[8] no stereochemical aspects are known. The NMR spectra of all 5, as well as azasultone 10, showed a typical ABX pattern for the protons of the oxathiazepine ring. However, the values of vicinal coupling constants J_{AB} in azasultones 5 and 10 are ca. 10 (see Table I) and 3.1 Hz, respectively.

The stereochemistry of **5a** is hereinafter described as a

5a   **7(7-d_2)**   **10**
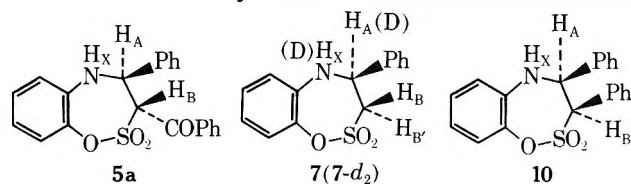
representative example. The measurement of NMR spectra in dioxane indicated that the values of J_{AB} in both 5a and 10 were not changed in the range of 35–90 °C. Thus it seems reasonable to conclude that 5a is the trans azasultone, while 10 is cis. The validity of these trans and cis assignments is also supported by inspection of the NMR spectra of azasultones 7 and 7-d_2 which was prepared by reduction of 6 with sodium borohydride-d_4; the values of coupling constants J_{AB}, $J_{AB'}$, and $J_{BB'}$ in 7 were found to be 10.5, 2.7, and 14.5 Hz, respectively.

It is known that the reaction of sulfenes with diarylnitrones proceeds via 1,3 cycloaddition, followed by rearrangement through a four-membered cyclic transition state to yield an azasultone.[8] Thus the stereochemistry of the azasultone seems to be determined by the stereochemical course of initial 1,3 cycloaddition. Although a concerted [$_\pi4_s + _\pi2_s$] process could

Table II

$$2 + 4 \longrightarrow \quad \text{11} \quad \text{and/or} \quad \text{12}$$

		Yield, %					Found (calcd), %			M+
	R	11c	12	Mp, °C	Ir (KBr), cm⁻¹	NMR (CDCl₃), δ (J, Hz)	C	H	N	m/e
a	H	28	4d	178–179.5	3370 (NH), 1730 (CO), 1380, 1170 (SO₂)	3.94 (1 H, br, NH, exchanged with D₂O), 4.14 (2 H, pseudo s, CH₂), 5.47 (1 H, s, >CH), 6.6–7.6 (13 H, m, aromatic protons)	67.45 (67.51)	4.39 (4.38)	3.54 (3.58)	391
b	OMe	0	30							
c	Cl	31	5	167.5–169	3360 (NH), 1715 (CO), 1370, 1160 (SO₂)	3.87 (1 H, br, NH, exchanged with D₂O), 4.07 (2 H, pseudo s, CH₂), 5.4 (1 H. s, >CH), 6.7–7.7 (12 H, m, aromatic protons)	62.20 (62.04)	3.90 (3.79)	3.38 (3.29)	427 425
d	NO₂	52	3	181.5–183	3350 (NH), 1720 (CO), 1370, 1170 (SO₂)	3.9, 4.34 (each 1 H, d, CH₂, J = 20), 5.42 (1 H, s, >CH), 6.25 (1 H, br, NH, exchanged with D₂O), 6.9–8.2 (12 H, m, aromatic protons)b	60.75 (60.55)	3.71 (3.70)	6.42 (6.42)	436

The table carries the centered heading "Cyclic azasultones 11a" spanning the data columns.

[a] 11a and 11c, colorless prisms; 11d, yellow prisms. [b] Measured in Me₂SO-d₆. [c] Registry no. are, respectively, 59043-92-4, 59043-93-5, 59043-94-6, 59043-95-7. [d] Registry no., 59043-96-8.

conceivably account for cis preference in the geometry of 10, the formation of trans azasultone 5a would be explained by a stepwise process. However, an alternative explanation for the formation of trans azasultone 5a should not be overlooked. Truce and Rach[9] demonstrated the postisomerization of cis cycloadducts obtained from the reaction of benzoyl- and cyanosulfenes with enamines. Several attempts to isolate cis azasultones from the reaction mixtures were unsuccessful. However, since the acidity of the hydrogen atom at the 3 position in the initial cis azasultone is enhanced by the electron-attracting benzoyl group, a base should be capable of catalyzing epimerization to thermodynamically stable trans arrangement via carbanion formation at the 3 position. During the early stages of the reaction triethylamine is in excess, and the postepimerization of initial cis azasultone could be caused by the amine.

Whether the hydrogen atom H_B in 5a is exchanged with deuterium oxide or not was determined by NMR analysis. When a dioxane solution of 5a was treated with deuterium oxide in the presence of excess triethylamine (5.6 molar ratio to 5a) at room temperature for 1 and 2 h, the exchange percentages of the hydrogen atom H_B were found to be about 30 and 50%, respectively. In addition, when a solution of 5a in Me₂SO-d₆ was treated with deuterium oxide at room temperature, the complete exchange occurred in a period of from 3 to 5 h even if the amine was absent.

Reaction of Cyclic α-Ketosulfenes. Next our attention was directed toward the reaction of cyclic α-ketosulfenes 2 and 3 with diarylnitrones 4. The reaction of 2-chlorosulfonyl-indanone with C,N-diphenylnitrone 4a in the presence of triethylamine in tetrahydrofuran afforded a rearranged 1:1 adduct, 4,5-dihydro-2,2-dioxo-4-phenyl-3H-1,2,5-benz[f]-oxathiazepine-3-spiro-2'-indanone (11a) and 12H-indeno-[2,3-c]benz[f]-1,2,5-oxathiazepine 6,6-dioxide (12), mp 236–237 °C dec. Similarly, ketosulfene 2 reacted with nitrones 4c and 4d to yield rearranged 1:1 adducts 11c and 11d, together with small amounts of 12. In the reaction with nitrone 4b, however, 2 gave only 12. Attempts to obtain 11b were not successful. The yields of 11 and 12 and physical and spectral data of 11 are given in Table II.

Hydrolysis of 11c under mild conditions gave 12 and p-chlorobenzaldehyde. The structure of 12 was confirmed by the following evidence. The molecular formula of 12 agreed with that of the compound derived from the rearranged cyclic azasultone 11 with the elimination of the benzaldehyde. The

Scheme III
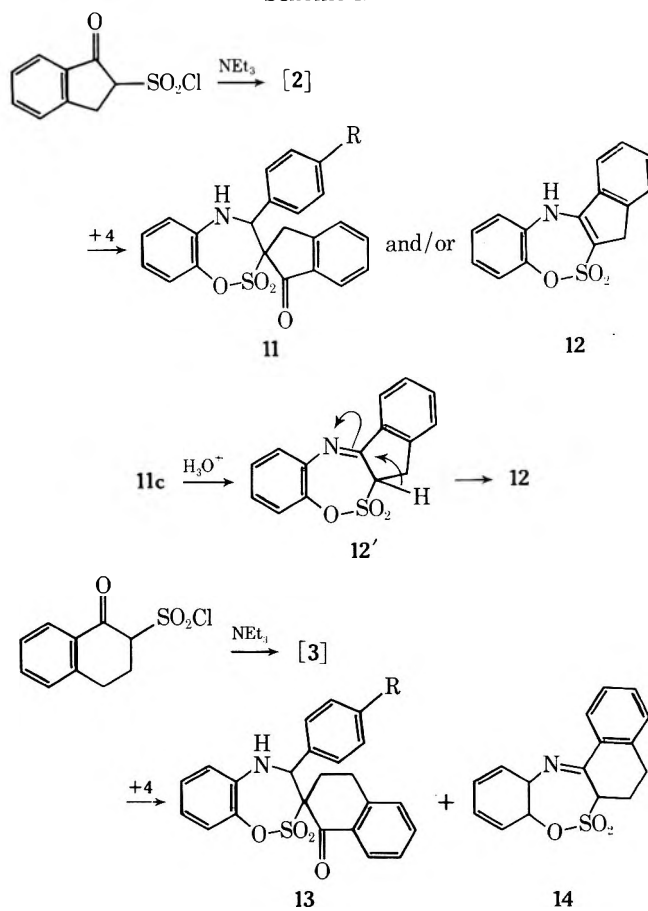
a, R = H; b, R = OMe; c, R = Cl; d, R = NO₂

Table III

$$3 + 4 \longrightarrow \quad 13 \quad + \quad 14$$

		Yield, %		Mp, °C	Ir (KBr), cm^{-1}	NMR (CDCl$_3$), δ (J, Hz)	Found (calcd), %			M$^+$ m/e
	R	13^d	14				C	H	N	

Cyclic azasultones 13^a

	R	13^d	14	Mp, °C	Ir (KBr), cm^{-1}	NMR (CDCl$_3$), δ (J, Hz)	C	H	N	M$^+$ m/e
a	H	23	6^e	178.5–179.5	3400 (NH), 1680, 1670 (CO), 1365, 1150 (SO$_2$)	2.1–3.7 (4 H, m, CH$_2$CH$_2$), 4.1 (1 H, br, NH, exchanged with D$_2$O), 5.97 (1 H, s, >CH), 6.6–8.2 (13 H, m, aromatic protons)	68.41 (68.14)	4.73 (4.72)	3.22 (3.46)	405
b	OMe	13.5	5	146–147	3360 (NH), 1655 (CO), 1365, 1155 (SO$_2$)	2.1–3.9 (4 H, m, CH$_2$CH$_2$), 3.72 (3 H, s, OCH$_3$), 4.0 (1 H, br, NH, exchanged with D$_2$O), 5.91 (1 H, s, >CH), 6.5–8.2 (12 H, m, aromatic protons)	66.07 (66.20)	4.84 (4.86)	3.25 (3.20)	435
c	Cl	30	5	167.5–169	3360 (NH), 1655 (CO), 1365, 1155 (SO$_2$)	1.8–3.6 (4 H, m, CH$_2$CH$_2$), 3.9 (1 H, br, NH, exchanged with D$_2$O), 5.95 (1 H, s, >CH), 6.6–8.2 (12 H, m, aromatic protons)	62.84 (62.82)	4.15 (4.01)	3.15 (3.19)	441 439
d	NO$_2$	26	5	154.5–156	3380 (NH), 1670 (CO), 1350, 1150 (SO$_2$)	2.8–3.3 (4 H, m, CH$_2$CH$_2$), 5.98 (1 H, br, >CH),^{b} 6.4 (1 H, br, NH, exchanged with D$_2$O), 6.5–8.4 (12 H, m, aromatic protons)^c	61.37 (61.33)	4.05 (4.03)	6.19 (6.22)	450

^{a} 13a and 13c, colorless prisms; 13b, yellow needles; 13d, pale yellow prisms. ^{b} Changed to a singlet when treated with D$_2$O. ^{c} Measured in Me$_2$SO-d_6. ^{d} Registry no. are, respectively, 59043-97-9, 59043-98-0, 59043-99-1, 59044-00-7. ^{e} Registry no., 59044-01-8.
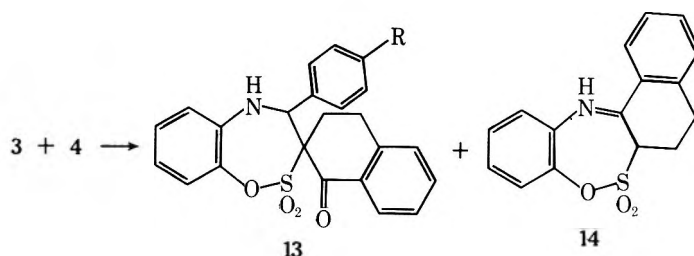
ir and NMR spectra showed the presence of an NH group. Conversion of 11 into 12 by hydrolysis can be understood by a similar pathway to that of hydrolysis of 5 to yield 12′, followed by hydrogen shift (Scheme III).

Similarly, cyclic ketosulfene 3, generated in situ from 2-chlorosulfonyl-1-tetralone and triethylamine, reacted with nitrones 4 to yield the corresponding cyclic azasultones, 4,5-dihydro-2,2-dioxo-4-aryl-3H-1,2,5-benz[f]oxathiazepine-3-spiro-2′-(1′-tetralones) (13), and 5,6-dihydro-7H-naphtho[2,1-c]benz[f]-1,2,5-oxathiazepine 7,7-dioxide (14), mp 195–196 °C. The results and physical and spectral data of 13 are given in Table III.

The molecular formula of 14 agreed with that of the compound derived from the rearranged cyclic azasultone 13 with the elimination of the benzaldehyde, and the ir spectrum did not show NH and CO absorption bands. The NMR spectrum of 14 displayed a double doublet (1 H, J = 6.3 and 3.8 Hz) at δ 4.22, besides methylene (4 H) and aromatic protons (8 H). The above facts support the assigned structure. However, in deuteriochloroform 14 (colorless needles) was partially converted into an isomer 14′, mp 194–195 °C, yellow prisms. In addition, the interconversion between 14 and 14′ was observed in deuteriopyridine by NMR analysis. Thus 14′ can be deduced to be an epimer of 14, but the stereochemistry of 14 and 14′ is not clear.

Experimental Section[10]

Materials. Benzoylmethanesulfonyl chloride, mp 88 °C (lit.[11] mp 87.5–88.2 °C), was prepared according to the method of Truce and Vriesen.[11] 2-Chlorosulfonylindanone, mp 95–98 °C, and 2-chlorosulfonyl-1-tetralone, mp 87–88.5 °C, were prepared from the sulfo-

nation of 1-indanone and 1-tetralone with SO$_3$–dioxane complex, followed by reaction with PCl$_3$.[6]

General Procedure for the Reaction of Benzoylmethanesulfonyl Chloride and Diarylnitrones. The reaction was performed in a nitrogen atmosphere. To a vigorously stirred solution of nitrone 4 (5 mmol) and 0.7 ml (5 mmol) of triethylamine in 30 ml of dry dioxane, a solution of 1.09 g (5 mmol) of benzoylmethanesulfonyl chloride in 30 ml of dry dioxane was added, drop by drop, at room temperature over a period of 1 h. After the addition was complete, the reaction mixture was stirred at the same temperature for 2 h. At this time, the reaction mixture was filtered, resulting in 90–95% yields of triethylammonium chloride. The filtrate was evaporated in vacuo, yielding colored oils which were induced to crystallize by adding 20 ml of methanol. Filtration gave rearranged cyclic azasultone 5. The mother liquor was chromatographed on silica gel using a mixture of benzene and chloroform (3:1) as the eluent to give 4-phenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-dioxide (6), mp 166 °C, as yellow needles.

The yields of products and physical and analytical data of 5 are given in Table I.

6: ir (KBr) 1575 (C=N), 1370, 1165 cm^{-1} (SO$_2$); NMR (CDCl$_3$) δ 4.49 (2 H, s, CH$_2$), 7.4–8.1 (9 H, m, aromatic protons); mass m/e 273 (M$^+$), 209 (M$^+$ − SO$_2$), 196 (M$^+$ − Ph), 104, 103 (PhCN$^+$, base peak), 77.

Anal. Calcd for C$_{14}$H$_{11}$NO$_3$S: C, 61.54; H, 4.06; N, 5.13. Found: C, 61.63; H, 4.06; N, 5.07.

Hydrolysis of Azasultone 5a. A suspension of 0.3 g of 5a in 40 ml of methanol was stirred with 3 ml of concentrated hydrochloric acid at room temperature for 2 h. After the reaction mixture was concentrated in vacuo, a small amount of water was added to the residue, and then the mixture was extracted with benzene. The benzene extract was dried over sodium sulfate, and then evaporated in vacuo. The residue was triturated with 10 ml of methanol to afford 113 mg (53%) of yellow crystals, whose ir spectrum was compatible with that of 6. A solution of 2,4-dinitrophenylhydrazine in ethanol was added to the

mother liquor, yielding 48 mg (21%) of benzaldehyde 2,4-dinitrophenylhydrazone.

Similarly, hydrolysis of 0.15 g of 5c with 2 ml of concentrated hydrochloric acid in 20 ml of methanol for 6 h afforded 36 mg (36%) of 6 and 16 mg (14%) of p-chlorobenzaldehyde 2,4-dinitrophenylhydrazone.

Thermolysis of Azasultone 5c. In a 20-ml flask equipped with a condenser 0.85 g of 5c was placed. The flask was heated at 170–180 °C (bath temperature) under reduced pressure (2 mmHg) for 2 h; during the thermolysis 90 mg (31%) of p-chlorobenzaldehyde adhered to the glass surface. The dark brown residue was triturated with 10 ml of methanol to give yellow crystals, and filtration afforded 0.51 g (91%) of 6. The methanol filtrate was treated with an ethanol solution of 2,4-dinitrophenylhydrazine to give 0.14 g (21%) of p-chlorobenzaldehyde 2,4-dinitrophenylhydrazone.

Similarly, 2.0 g of 5a was pyrolyzed at 165–170 °C (bath temperature) under reduced pressure (3 mmHg) for 20 min; 0.73 g (51%) of 6 and 0.4 g (27%) of benzaldehyde 2,4-dinitrophenylhydrazone were obtained.

Reduction of 6 with Sodium Borohydride. A. A mixture of 0.15 g of 6 and 0.2 g of sodium borohydride in 40 ml of ethanol was stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo, and then 50 ml of water was added to the residue, giving 64 mg (42.5%) of 4,5-dihydro-4-phenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-dioxide (7), mp 158–159 °C (lit.[8] mp 160 °C), which was identical with an authentic sample prepared according to the method of Truce et al.[8] NMR (CDCl₃) δ 3.3–4.1 (3 H, complicated signal, CH₂ and NH), 4.75 (1 H, dd, J = 2.7 and 10.5 Hz), 6.6–7.6 (10 H, m, aromatic protons).

B. A mixture of 50 mg of 6 and 80 mg of sodium borohydride-d₄ in 15 ml of ethanol was stirred at room temperature for 18 h. To the mixture was added 30 ml of water, giving 27 mg (53%) of colorless crystals. Recrystallization from benzene afforded 7-d, mp 160 °C, as colorless prisms: NMR (CDCl₃ + D₂O) δ 3.43, 3.92 (each 1 H, d, J = 14.5 Hz), 6.7–7.6 (10 H, m, aromatic protons).

On the basis of the NMR spectra of 7 and 7-d₂, the assignments of protons were as follows: δ 3.43 (H_B', dd), 3.92 (H_B, dd), 4.75 (H_A, dd), J_{AB} = 10.5, $J_{AB'}$ = 2.7, $J_{BB'}$ = 14.5 Hz.

Hydrolysis of 6. A. A suspension of 0.1 g of 6 in 20 ml of methanol was refluxed with 4 ml of concentrated hydrochloric acid for 4 h. The reaction mixture was evaporated in vacuo to leave yellow crystals. The crystals were treated with aqueous sodium hydrogen carbonate, and then extracted with benzene. The benzene extract was dried over calcium chloride, and evaporated in vacuo at room temperature to give 60 mg (56%) of yellow crystals. Recrystallization from a benzene–petroleum ether (bp 60–80 °C) mixture afforded o-aminophenyl benzoylmethanesulfonate (8), mp 114 °C, as pale yellow needles: ir (KBr) 3460, 3360 (NH), 1680 (CO), 1355, 1160 cm⁻¹ (SO₂); NMR (CDCl₃) δ 4.3 (2 H, br, NH₂, exchanged with D₂O), 4.89 (2 H, s, CH₂, exchanged with D₂O), 6.5–8.2 (9 H, m, aromatic protons); mass m/e 291 (M⁺), 273, 209, 180, 108 (M⁺ − PhCOCH₂SO₂, base peak), 105, 103, 91, 77.

Anal. Calcd for C₁₄H₁₃NO₄S: C, 57.73; H, 4.50; N, 4.82. Found: C, 57.63; H, 4.28; N, 4.78.

B. A suspension of 0.1 g of 6 in 30 ml of ethanol was refluxed with 3 ml of concentrated hydrochloric acid for 18 h. The reaction mixture was evaporated in vacuo, and the residue was treated with aqueous sodium hydrogen carbonate and then extracted with diethyl ether. The ether extract was evaporated in vacuo to give yellow crystals, which on recrystallization from a benzene–petroleum ether (bp 60–80 °C) mixture afforded 22 mg (55%) of o-aminophenol, mp 173–175 °C.

Reduction of Benzoylmethanesulfonate 8. A solution of 0.62 g of 8 in 40 ml of methanol was stirred with 0.2 g of sodium borohydride at room temperature for 2 h. The reaction mixture was evaporated in vacuo to leave a residue, which was triturated with petroleum ether to give 0.18 g (78%) of o-aminophenol. The filtrate was chromatographed on silica gel using a benzene–chloroform mixture as the eluent, giving small amounts of oil (M⁺ m/e 293). A solution of the oil in diethyl ether was treated with hydrogen chloride to give the hydrochloride of o-aminophenyl 2-hydroxy-2-phenylethanesulfonate (9): mp 196–198 °C dec; ir (KBr) 3360 (OH), 3000, 2880, 2620 (NH₃⁺), 1370, 1190, 1150 cm⁻¹ (SO₂).

Dehydration of 8. A solution of 0.1 g of 8 in 12 ml of acetic acid was stirred with 0.5 ml of acetic anhydride at room temperature for 10 h. The mixture was poured into water and filtration gave yellow crystals, which on recrystallization from benzene afforded 80 mg (86%) of 6.

Reaction of 8 with p-Chlorobenzaldehyde. A suspension of 275 mg (0.945 mmol) of 8 in 30 ml of ethanol was stirred with 135 mg (0.96 mmol) of p-chlorobenzaldehyde at room temperature for 14.5 h; the reaction mixture changed to a clear solution. The solution was cooled

in an ice bath to give yellow crystals. Recrystallization from a benzene–petroleum ether (bp 60–80 °C) mixture gave 215 mg (55%) of cyclic azasultone 5c as pale yellow needles.

4,5-Dihydro-3,4-diphenyl-3H-1,2,5-benz[f]oxathiazepine 2,2-Dioxide (10). To a stirred solution of 1.03 g (5.25 mmol) of nitrone 4a and 0.53 g (5 mmol) of triethylamine in 25 ml of dry dioxane, a solution of 1.0 g (5.25 mmol) of benzylsulfonyl chloride in 25 ml of dry dioxane was added, drop by drop, at room temperature over a period of 1 h. After the addition was complete, the reaction mixture was stirred at the same temperature for 30 h. Filtration gave 0.67 g (93%) of triethylammonium chloride, and the filtrate was evaporated in vacuo to leave brown oil, which was triturated with 10 ml of ethanol to give crystals. Recrystallization from ethanol afforded 1.13 g (61%) of 10, mp 220–221 °C, as colorless plates: ir (KBr) 3340 (NH), 1360, 1150 cm⁻¹ (SO₂); NMR (CDCl₃) δ 3.7 (1 H, br, NH, exchanged with D₂O), 4.42, 5.36 (each 1 H, d, CH, J = 3.1 Hz), 6.6–7.7 (14 H, m, aromatic protons); mass m/e 391 (M⁺), 287 (M⁺ − SO₂), 198, 197 (base peak), 196, 120, 104, 93, 91, 77.

Anal. Calcd for C₂₀H₁₇NO₃S: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.24; H, 4.90; N, 4.11.

General Procedure for the Reaction of 2-Chlorosulfonylindanone with Diarylnitrones. The reaction was performed in a nitrogen atmosphere. To a stirred solution of nitrone 4 (5 mmol) and 0.7 ml (5 mmol) of triethylamine in 30 ml of dry tetrahydrofuran, a solution of 1.15 g (5 mmol) of 2-chlorosulfonylindanone in 30 ml of dry tetrahydrofuran was slowly added, drop by drop, under cooling in an ice bath over a period of 1 h. After the addition was complete, the reaction mixture was stirred at room temperature for 5 h. The mixture was filtered, resulting in ca. 80% yield of triethylammonium chloride. The filtrate was evaporated in vacuo, and the residue was chromatographed on silica gel using a benzene–chloroform mixture as the eluent, giving rearranged cyclic azasultone 11 and/or 12H-indeno[2,3-c]benz[f]-1,2,5-oxathiazepine 6,6-dioxide (12), mp 236–237 °C dec, as pale yellow needles.

The yields of products and physical and analytical data of 11 are given in Table II.

12: ir (KBr) 3370 (NH), 1340, 1170 cm⁻¹ (SO₂); NMR (Me₂SO-d₆) δ 3.92 (2 H, s, CH₂), 6.9–8.4 (8 H, m, aromatic protons), 9.77 (1 H, br, NH); mass m/e 285 (M⁺), 221 (M⁺ − SO₂), 220 (base peak), 193, 192, 191.

Anal. Calcd for C₁₅H₁₁NO₃S: C, 63.13; H, 3.89; N, 4.91. Found: C, 62.93 H, 3.82; N, 4.75.

Hydrolysis of Cyclic Azasultone 11c. A suspension of 150 mg of 11c in 20 ml of methanol was stirred with 1 ml of concentrated hydrochloric acid at room temperature for 20 h. The reaction mixture was concentrated in vacuo to one-third of its original volume, and then cooled to give yellow crystals. Recrystallization from acetic acid afforded 38 mg (38%) of 12. The filtrate was treated with a solution of 2,4-dinitrophenylhydrazine in ethanol, giving 22 mg (20%) of p-chlorobenzaldehyde 2,4-dinitrophenylhydrazone.

General Procedure for the Reaction of 2-Chlorosulfonyl-1-tetralone with Diarylnitrones According to the above general procedure for 2-chlorosulfonylindanone, the reaction of 1.22 g (5 mmol) of 2-chlorosulfonyl-1-tetralone with nitrone 4 (5 mmol) in the presence of 0.7 ml (5 mmol) of triethylamine in dry tetrahydrofuran was carried out under a nitrogen atmosphere for 5 h. The products were chromatographed on silica gel using a benzene–chloroform mixture as the eluent, giving cyclic azasultone 13 and 5,6-dihydro-7H-naphtho[2,1-c]benz[f]-1,2,5-oxathiazepine 7,7-dioxide (14), mp 195–196 °C, as colorless needles.

The yields of the products and physical and analytical data of 13 are given in Table III.

14: ir (KBr) 1595 (C=N), 1370, 1170 cm⁻¹ (SO₂); NMR (CDCl₃) δ 2.3–4.0 (4 H, m, CH₂CH₂), 4.22 (1 H, dd, CH, J = 6.3 and 3.8 Hz), 7.2–8.5 (8 H, m, aromatic protons); mass m/e 299 (M⁺), 235 (M⁺ − SO₂, base peak), 234, 221, 220, 218, 206, 191, 179, 178, 127, 120, 117, 116, 115, 64.

Anal. Calcd for C₁₆H₁₃NO₃S: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.01; H, 4.38; N, 4.65.

In chloroform solution the compound 14 was partially converted into an epimer 14', mp 194–195 °C, as yellow prisms: ir (KBr) 1600 (C=N), 1370, 1180 cm⁻¹ (SO₂); mass m/e 299 (M⁺), 235 (M⁺ − SO₂, base peak), 234, 221, 220, 218, 207, 206, 129, 128, 127, 120, 118, 117, 116, 104, 103, 102, 77.

Anal. Calcd for C₁₆H₁₃NO₃S: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.30; H, 4.39; N, 4.69.

Registry No.—1, 32116-82-8; **2**, 59069-51-1; **3**, 59069-52-2; **4a**, 1137-96-8; **4b**, 3585-93-1; **4c**, 5909-74-0; **4d**, 3585-90-8; **7**, 5172-50-9; **8**, 59044-02-9; **9**, 59044-03-0; **10**, 59044-04-1; 2-chlorosulfonylindanone,

51834-39-0; 2-chlorosulfonyl-1-tetralone, 51834-37-8; o-aminophenol, 95-55-6; benzylsulfonyl chloride, 1939-99-7.

References and Notes

(1) Studies of α-Ketosulfenes. 8. Part 7 of this series: O. Tsuge and M. Noguchi, *Chem. Lett.*, 113 (1974).
(2) O. Tsuge and S. Iwanami, *Bull. Chem. Soc. Jpn.*, **43**, 3543 (1970).
(3) O. Tsuge and S. Iwanami, *Nippon Kagaku Zasshi*, **92**, 448 (1971).
(4) O. Tsuge and S. Iwanami, *Org. Prep. Proced. Int.*, **3**, 283 (1971).
(5) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes", Academic Press, New York, N.Y., 1967, p 286. However, it has been recently reported that

phenylsulfene reacted with benzylidenemethylamines to give 1,2-thiazetidine 1,1-dioxides: T. Hiraoka and T. Kobayashi, *Bull. Chem. Soc. Jpn.*, **48**, 480 (1975).
(6) O. Tsuge and M. Noguchi, *Chem. Lett.*, 113 (1974).
(7) W. E. Truce and J. R. Allison, *J. Org. Chem.*, **40**, 2260 (1975).
(8) W. E. Truce, J. W. Fieldhouse, D. J. Vrencur, J. R. Norell, R. W. Campbell, and D. G. Brady, *J. Org. Chem.*, **34**, 3097 (1969).
(9) W. E. Truce and J. F. Rach, *J. Org. Chem.*, **39**, 1109 (1974).
(10) All melting points are uncorrected. NMR spectra were recorded on a Hitachi R-20 NMR spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi RMS-4 mass spectrometer, using a direct inlet and an ionization energy of 70 eV.
(11) W. E. Truce and C. W. Vriesen, *J. Am. Chem. Soc.*, **75**, 2526 (1953).

Concurrent Nitration and Oxygenation of o-Xylene and Hemimellitene with Aroyl Nitrates

Michael E. Kurz* and Eugene Woodby

Department of Chemistry, Illinois State University, Normal, Illinois 61761

Received February 24, 1976

Upon reaction with a series of aroyl nitrates, o-xylene underwent not only nitration but also aroyloxylation to yield dimethylphenyl benzoates comprised primarily of the 3,4 isomer. Nitration ratios were little affected by the nature of the aroyl nitrate substituent suggesting a common nitrating species. The aryl ester product patterns were quite different than those resulting from reaction of o-xylene with aroyl peroxide and either cupric chloride or nitric acid where aroyloxy radical substitution is known to occur. The analogous product situation was observed for hemimellitene. This and other evidence was indicative of a mechanism involving nitronium ion attack at an ipso ring position followed by benzoate trapping of the resultant carbonium ion. The addition product so formed then rearomatized to an aryl benzoate by elimination of nitrous acid analogous to the addition–elimination scheme proposed earlier for acetyl nitrate.
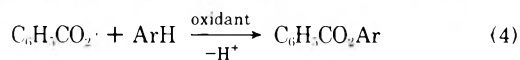
The observation by Fischer and co-workers that o-xylene undergoes not only nitration but also acetoxylation when treated with nitric acid–acetic anhydride[1] has spurred a considerable amount of further investigation into this dual substitution process.[2] The acetate esters have been accounted for by an electrophilic addition–elimination process involving initial nitronium ion attack at the 1 position (ipso attack) to give a phenonium ion (1). This species, which is reluctant to lose either a nitro or methyl group, instead adds a nucleophilic acetate to form a cis–trans pair of 1,4-cyclohexadienes (2 and 3, eq 1), which have been isolated upon careful quenching of the reaction.[3] Upon workup 2 and 3 rearomatize to produce primarily 3,4-dimethylphenyl acetate (eq 2).[3,4]

$$2 \text{ or } 3 \xrightarrow[\text{or } H^+O]{\Delta} CH_3CO_2\text{—}\bigcirc\text{—}CH_3 + HNO_2 \quad (2)$$
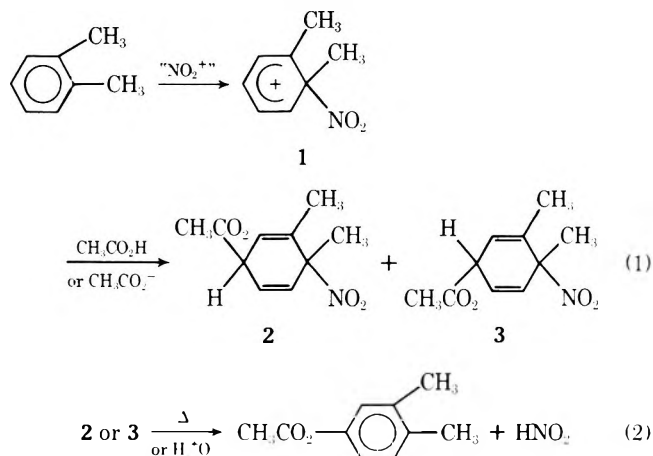
Analogous cyclohexadiene intermediates and the subsequent aryl acetates have been observed in the reactions of acetyl nitrate with hemimellitene,[5] p-xylene,[5] pseudocumene,[2a] toluene,[6] and others.[7] The demonstration of the occurrence of ipso attack has led to critical reinvestigations of

previously reported substitution patterns in the nitration of polyalkylbenzenes.[4,8]

Previous work in this laboratory had demonstrated that dimethylphenyl benzoates are produced in yields ranging from 3 to 14% upon treating o-xylene with benzoyl nitrate under a variety of conditions.[9] However, radical breakdown of benzoyl nitrate to the benzoyloxy and ultimately phenyl radicals (eq 3) had been reported[10] and the former radical is known to substitute on aromatic rings to form aryl benzoates (eq 4) in the presence of suitable oxidants.[11]

$$C_6H_5CO_2NO_2 \longrightarrow NO_2 + C_6H_5CO_2\cdot \longrightarrow C_6H_5\cdot + CO_2 \quad (3)$$

$$C_6H_5CO_2\cdot + ArH \xrightarrow[-H^+]{\text{oxidant}} C_6H_5CO_2Ar \quad (4)$$

Since either a scheme involving benzoyloxy radicals (eq 3 and 4) or an electrophilic ipso nitration process as proposed for acetyl nitrate (eq 1 and 2) seemed to be feasible, we set out to determine which mechanism of benzoate ester formation was applicable in the interaction of a series of para-substituted benzoyl nitrates with o-xylene. The reaction of benzoyl nitrate with hemimellitene was also examined.

Results and Discussion

All of the para-substituted benzoyl nitrates were prepared and used in situ both to ensure a known concentration of the nitrate ester and to reduce the possibility of their hydrolysis. They were prepared from the reaction of silver nitrate and the appropriate para-substituted benzoyl chloride in accordance with the following stoichiometry (eq 5).

$$XC_6H_4COCl + AgNO_3 \xrightarrow[25\,°C]{CH_3CN} XC_6H_4CO_2NO_2 + AgCl \quad (5)$$
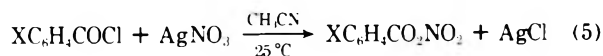
The organic products from the reaction of benzoyl nitrate with o-xylene at room temperature are listed in Table I. Nitration and benzoyloxylation products (nitro-o-xylenes and

Table I.   Reaction of Para-Substituted Benzoyl Nitrates with o-Xylene

Registry no.	p-X-$C_6H_4CO_2NO_2$ X =	Products[a]					
		Nitroxylenes		Dimethylphenyl benzoates		o-Methylbenzyl nitrate[c]	$C_{16}H_{18}$[d]
		Yield	3-/4-	Yield	3-/4-[b]		
39835-12-2	CH$_3$O	20	31/69	5	0/100[e]	4	5
39247-26-2	CH$_3$	23	27/73	17	1/99	5	6
6786-32-9	H[f]	28	32/68	16	5/95[g]	6	5
39835-17-1	Cl	21	36/64	1	0/100[e]	6	5
59104-70-9	F	26	28/72	18	4/96	5	7
39835-16-0	NO$_2$[h]	23	31/69	2	0/100[e]	4	5

[a] Yields are based on moles of product per mole of benzoyl nitrate; other products formed in varying but small amounts (>) included benzyl alcohol, o-tolualdehyde, α-nitroxylene, and dinitroxylene. [b] Some fluctuation in duplicate runs, ±3%, due to small overall yield. [c] Determined by difference in analysis on two columns: the UCW-982 where this product superimposed on 3-nitro-o-xylene and on the OV-225 column on which this product was not eluted. [d] Mixture of suspected trimethyldiphenylmethane isomers; see Experimental Section. [e] No 3 isomer was detected, although owing to the low benzoate yield, a small amount could have gone undetected. [f] Benzoic acid, 70% isolated yield. [g] Average of seven runs with variable (1–16%) ratios of 3 isomer. [h] p-Nitrobenzoic acid, 93% isolated yield.
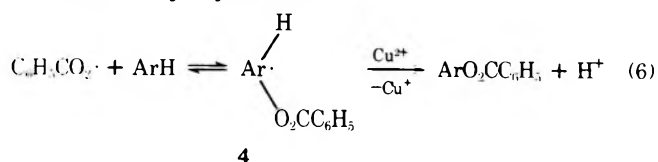
dimethylphenyl benzoates) were found along with various side products: o-methylbenzyl nitrate, isomeric o-xylene dimers, benzoic acids, and small amounts of o-methylbenzaldehyde and dinitro-o-xylenes. The substituted benzoic acids were by-products of the aroyl nitrate decomposition and were not analyzed quantitatively. The presence of dimers (thought to be isomeric trimethyldiphenylmethanes) along with o-methylbenzyl nitrate suggested possible benzylic cation involvement, the origin of which is not clear.

Relatively similar yields and consistent orientation was observed for the nitroxylenes obtained from the variously substituted benzoyl nitrates. A likely common intermediate is the nitronium ion or incipient nitronium ion formed from dinitrogen pentoxide.[9,12]

The products of most significance to our investigation were the dimethylphenyl benzoates. It is not known why there were rather poor yields of these esters with certain of the aroyl nitrates, but there did not appear to be a trend relating aroyl nitrate structure to dimethylphenyl benzoate production. In all reactions nitrogen dioxide fumes were evident above the reaction mixture, and their escape could account for the poor and variable material balance for the nitro entity in the aroyl nitrate.

To try to determine the exact nature of the aroyloxylating species, several systems known to involve aromatic substitution by aroyloxy radicals were studied with o-xylene. Product yields and patterns were compared to those from the aroyl nitrate-o-xylene system.
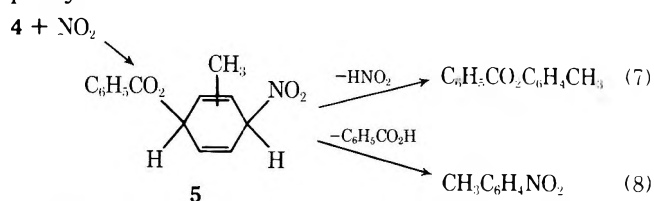
It had been shown that toluene reacts with benzoyl peroxide in the presence of cupric chloride at 60–80 °C to produce tolyl benzoates.[11b,13] Benzoyloxy radicals from peroxide thermolysis or cuprous ion induced breakdown reversibly add to toluene and the resulting σ radical 4 is oxidized to the aryl benzoate by way of a σ carbonium ion (eq 6). A Hammett $\rho\sigma$ treatment indicated that the benzoyloxy, p-methylbenzoyloxy, and p-nitrobenzoyloxy radicals possessed electrophilic properties in this process. The reaction by-products, benzyl chloride, benzyl alcohol, and methylbiphenyls, were attributed to other radicals produced from chain transfer or decomposition of benzoyloxy radicals.[13]

$$C_6H_5CO_2\cdot + ArH \rightleftharpoons Ar\overset{\displaystyle H}{\underset{\displaystyle O_2CC_6H_5}{\big|}} \xrightarrow[-Cu^+]{Cu^{2+}} ArO_2CC_6H_5 + H^+ \quad (6)$$

4

Our general procedure consisted of treating benzoyl peroxide or the para-substituted benzoyl peroxide (nitro-,

methyl-) with o-xylene at reflux in acetonitrile using cupric chloride as catalyst. The products of most significance to this study, the dimethylphenyl benzoates, were formed in yields ranging from 31 to 63% with the three peroxides. Side products resulting from schemes analogous to those reported for toluene[11b,13] included o-methylbenzyl chloride (15–25%), dimethylbiphenyls (10–12%), and small amounts of o-methylbenzyl alcohol and phenyl benzoates.

Previously[11a] the reaction of benzoyl peroxide with toluene in the presence of nitric acid had led to both tolyl benzoates and nitrotoluenes in moderate amounts. Various lines of evidence including an unusual nitrotoluene isomer composition (o-/m-/p = 20/70/10) had led to the proposal of a common intermediate leading to both substitution products. Aroyloxy radical attack onto toluene was suggested as the initial step followed by nitrogen dioxide trapping of the radical intermediate 4 (eq 7, 8) to give a dihydroaromatic derivative 5. This in turn rearomatized by loss of nitrous acid (eq 7) or benzoic acid (eq 8) to give an ester or nitroaromatic, respectively. Previously reported[11a] by-products from toluene included benzaldehyde, benzyl alcohol, benzyl nitrate, and methylbiphenyls.

$$4 + NO_2 \rightarrow$$

$$\begin{array}{l} \xrightarrow{-HNO_2} C_6H_5CO_2C_6H_4CH_3 \quad (7) \\ \xrightarrow{-C_6H_5CO_2H} CH_3C_6H_4NO_2 \quad (8) \end{array}$$

5

Our general procedure consisted of treating benzoyl peroxide or the para-substituted benzoyl peroxide with o-xylene at reflux in acetonitrile using nitric acid as a promoter. Dimethylphenyl benzoates (10–22%) and nitroxylenes (19–24%) were produced presumably by schemes analogous to eq 7 and 8, respectively. Also found with all three peroxide systems were the side products o-methylbenzaldehyde (13–28%), o-methylbenzyl alcohol (10–35%), o-methylbenzyl nitrate (37–71%), o-xylene dimers (6–15%), and dimethylbiphenyls (25–34%) analogous to the earlier reported by-products in the nitric acid–benzoyl peroxide–toluene reaction.[11b]

The nitration and oxygenation products obtained from benzoyl nitrate are compared to those found from benzoyl peroxide with cupric chloride or nitric acid in Table II. Also, included are literature results of the analogous products from acetyl nitrate.[1,4]

It is evident from inspection of the ester product ratios from the various systems that the benzoyloxylating species from benzoyl nitrate possesses considerably more selectivity than

Table II. Comparison of o-Xylene Products from Various Oxygenation Systems

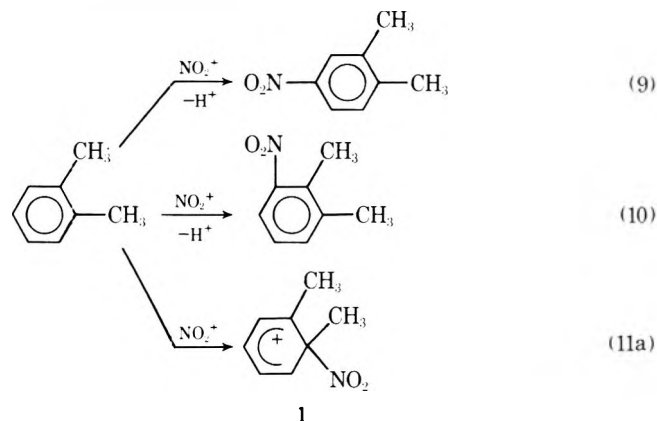|	Products			
	Dimethylphenyl benzoates		Nitroxylenes	
System	Yield	3-/4-	Yield	3-/4-
$C_6H_5CO_2NO_2$	16	5/95	28	32/68
$(C_6H_5CO_2)_2$–$CuCl_2$	31	59/41	—	—
$(C_6H_5CO_2)_2$–HNO_3	17	61/39	19	21/79
$CH_3CO_2NO_2$	36[b]	0/100	37	39/61
$CH_3CO_2NO_2$[a]	39[b]	0/100	34	32/68

[a] See ref 1 and 4. [b] Dimethylphenyl acetates.

Table III. Comparison of o-Xylene Reaction with Substituted Benzoyloxylation Systems

	p-$XC_6H_4CO_2C_6H_3(CH_3)_2$, X =			
	CH_3		NO_2	
System	Yield	3-/4-	Yield	3-/4-
p-$XC_6H_4CO_2NO_2$	17	0/100	2	0/100
$(p$-$XC_6H_4CO_2)_2$–$CuCl_2$	36	58/42	63	56/44
$(p$-$XC_6H_4CO_2)_2$–HNO_3	22	61/39	8	56/44

Table IV. Comparison of Hemimellitene Products from Various Oxygenation Systems

	Trimethylphenyl benzoates		Nitrohemi-mellitenes	
System	Yield	4-/5-	Yield	4-/5-
$C_6H_5CO_2NO_2$	11	17/83	26	78/22
$(C_6H_5CO_2)_2$–$CuCl_2$	63	85/15		
$(C_6H_5CO_2)_2$–HNO_3	4	>98/2	58	45/55
$CH_3CO_2NO_2$[a]	45[b]	21/79	55	84/16

[a] See ref 5. [b] Trimethylphenyl acetates.

Table V. Product Distribution before and after Solvolysis

Products	Direct analysis[a]	After solvolysis with 70% H_2SO_4[b]
3-Nitro-o-xylene	8.9	14.5
4-Nitro-o-xylene	21.6	21.3
3,4-Dimethylphenyl benzoate	10.1	9.3

[a] Benzoyl nitrate and o-xylene reacted in acetonitrile at 25 °C for 48 h; direct GC analysis. [b] Same reaction mixture treated for 10 min at 25 °C with acid, then analyzed by GC.

the benzoyloxy radical involved in the benzoyl peroxide systems. The close similarity (nearly exclusive 4-benzoyloxylation) to the dimethylphenyl acetate pattern observed from acetyl nitrate strongly suggests an analogous reaction pathway to that proposed by Fischer.[3] Initial nitronium ion attack at the 3 or 4 position of o-xylene results in a straightforward nitration product (eq 9, 10). However, ipso nitration (at position 1) forms a σ carbonium ion (1) that is apparently capable of being trapped by benzoate (eq 11) in the same manner noted previously for acetate (eq 1). The cyclohexadiene (6) so produced loses nitrous acid leading to the nearly exclusive production of the 3,4-dimethylphenyl benzoate. The nitration pattern from benzoyl nitrate is virtually identical with that noted previously[1,3,4] for acetyl nitrate with o-xylene lending further support to this mechanism. However, the presence of small and somewhat variable amounts of 2,3-dimethylphenyl benzoates from three of the aroyl nitrate reactions may be indicative of slight competition from radical substitution.

Table III compares aryl esters from the p-methyl- and p-nitrobenzoyl nitrate–o-xylene reactions to the p-methyl- and p-nitrobenzoyl peroxide–o-xylene studies. Again, it is clear that each of these nitrates gives rise to substituted dimethylphenyl benzoates in a manner not involving para-substituted benzoyloxy radical attack, but rather trapping of an initially formed ipso nitration adduct (eq 11).

(9)

(10)

(11a)

1

6

(11b)

Hemimellitene was also treated with benzoyl nitrate and the resulting benzoyloxylation and nitration products compared to those obtained from benzoyl peroxide–cupric chloride and benzoyl peroxide–nitric acid (Table IV). In this case the major trimethylphenyl benzoate was the 5 isomer, in good agreement with what had been noted previously from acetyl nitrate.[5] This predominance of the 5 isomer stood in marked contrast to the pattern observed in the benzoyloxy radical systems[11] where primarily the 4-substituted aryl ester was found. The nitration pattern with benzoyl nitrate was also more consistent with that noted previously for acetyl nitrate.[5]

To date efforts to actually isolate cyclohexadiene intermediates 6 from either o-xylene or hemimellitene by chromatographic workup have been fruitless. However, further indirect evidence for their presence as initial reaction products was indicated by treating the crude reaction mixture from o-xylene–benzoyl nitrate with 70% sulfuric acid. An increase in the proportion of 3-nitro-o-xylene and an accompanying slight decrease in 3,4-dimethylphenyl benzoate was noted compared to directly analyzed reaction product (Table V).[14] This suggested the probable diversion of 6 to the rearranged 3-nitro-o-xylene as was observed previously in the acetyl nitrate system.[4,15]

That the trapping of the initial phenonium ion 1 from ipso attack by carboxylate species appears to be an intermolecular process was demonstrated by a series of competition experiments (Table VI). When equimolar amounts of p-methylbenzoyl nitrate and benzoyl nitrate were treated with o-xylene virtually equal amounts of p-methylbenzoate and benzoate esters were produced. Addition of cupric benzoate to the p-methylbenzoyl nitrate–o-xylene system also led to approximately equal amounts of the two types of benzoates though in much lower yields. Benzoyl nitrate reactions with o-xylene in the presence of excess acetic or trifluoroacetic acid resulted in the repression of the benzoate ester products. In the former

Table VI. Competition Experiments Aroyl Nitrate–*o*-Xylene

p-X-C$_6$H$_4$CO$_2$NO$_2$ X =	Added nucleophile or solvent	Aryl esters, %	
		C$_6$H$_5$CO$_2$C$_6$H$_3$(CH$_3$)$_2$	Other
CH$_3$ and H[a]		7.2	7.3 [*p*-CH$_3$C$_6$H$_4$CO$_2$C$_6$H$_3$(CH$_3$)$_2$]
CH$_3$	Cu(O$_2$CC$_6$H$_5$)$_2$[b]	1.4	1.3 [*p*-CH$_3$C$_6$H$_4$CO$_2$C$_6$H$_3$(CH$_3$)$_2$]
H	CH$_3$CO$_2$H[c]	0.3	19 [4-CH$_3$CO$_2$C$_6$H$_3$(CH$_3$)$_2$]
H	CF$_3$CO$_2$H[c]	1.1	

[a] Equimolar (0.005 mol) ratios. [b] Aroyl nitrate (0.010 mol), cupric benzoate (0.005 mol). [c] Present in approximately a 20-fold molar excess compared to the aroyl nitrate.

Table VII. Authentic Dimethylphenyl Benzoates

Registry no.	3,4-(CH$_3$)$_2$C$_6$H$_3$O$_2$CC$_6$H$_4$X-*p* X =	Mp, °C	Mass spectrum	
			Molecular ion, *m/e*	Base peak, *m/e*
3845-63-4	H	55–57[a]	226	105
59014-71-0	CH$_3$	99–103	240	119
59014-72-1	OCH$_3$	87–89	256	135
59014-73-2	NO$_2$	124–127[b]	271	150
59014-74-3	Cl	79–83	260 (262)[c]	139 (141)[c]
59014-75-4	F	65–67	244	125
	2,3-(CH$_3$)$_2$C$_6$H$_3$O$_2$CC$_6$H$_4$X-*p* X =			
5554-27-8	H	55–57[d]	226	105
59014-76-5	CH$_3$	92–93	240	119
59014-77-6	OCH$_3$	61–62	256	135
59014-78-7	NO$_2$	123–125	271	150
59014-79-8	Cl	105–106	260 (262)[c]	139 (141)[c]

[a] Lit. mp 58.5 °C: R. Granger, H. Orzalesi, and P. Joyeux, *C. R. Acad. Sci.*, **260**, 923–925 (1965). [b] Lit. mp 128 °C, G. Harris, J. R. A. Pollock, and R. Stevens, "Dictionary of Organic Compounds", Vol. 1, Oxford University Press, London, 1965. [c] Isotopic peak. [d] Mixture melting point depression (15 °C) noted upon admixture with the 3,4 isomer.

case the acetate addition–elimination product was formed instead.[16]

The acyl nitrate precursor seemed to be necessary to obtain aryl esters. An attempt to nitrate *o*-xylene at room temperature in the presence of benzoic acid led to no reaction. At elevated temperatures (80 °C) nitration did occur (23% yield, 3-/4- ratio 22/78) but no benzoate esters were detected.

Conclusions

Aroyl nitrates react with certain polymethylbenzenes in a manner analogous to acetyl nitrate resulting in both nitration and aroyloxylation products.

Experimental Section

The chemical reagents used were analyzed by GC where possible and used directly without further purification. The substituted peroxides were synthesized from sodium peroxide and the appropriate acid chloride[17] and analyzed for purity by standard procedures.[18] Authentic 2,3- and 3,4-dimethylphenyl benzoates were prepared from 2,3- and 3,4-dimethylphenol and the appropriate para-substituted benzoyl chloride according to a literature procedure.[19] The esters, most of which have not been reported in the literature, are listed in Table VII.

Synthesis and in Situ Reactions of Aroyl Nitrates with Polymethylbenzenes. General Procedure. The appropriate para-substituted benzoyl chloride (0.020 mol) in acetonitrile (10 ml) was added dropwise to a rapidly stirred solution of silver nitrate (3.4 g, 0.020 mol) in 50 ml of acetonitrile containing *o*-xylene (10 ml, 0.094 mol) or hemimellitene (0.075 mol) at room temperature (25 °C).[7] Silver chloride precipitated immediately, the solution turned yellow, and brown fumes of nitrogen dioxide were evolved. The reaction mixture was stirred for an additional 48 h at this temperature. Iodometric analysis of aliquots from representative reaction mixtures from each aroyl nitrate indicated that less than 10% active oxidizing species (unreacted nitrate or nitrogen oxide species therefrom) remained. The heterogeneous mixture was then filtered in vacuo and the silver chloride dried and weighed to determine the completeness of the benzoyl nitrate formation. Silver chloride recovery ranged from 38 to 96% based on eq 5. Product analyses were made by GC and GC–MS carried out on the filtrate.

On a number of benzoyl nitrate reactions with both *o*-xylene and hemimellitene the acetonitrile solvent was stripped away and the residue containing unreacted aromatic and products was subjected to liquid and column chromatography using silica gel and alumina, respectively. No evidence (NMR, ir, or physical data) could be garnered for the presence of adducts such as 6 among the reaction products.

Reactions of acetyl nitrate with *o*-xylene were performed according to a literature method.[3,4] Careful quenching at −50 °C with anhydrous ammonia followed by workup[6] led to a product mixture which contained the 1,4-cyclohexadienes, **2** and **3**. When a few drops of this mixture were heated in aqueous acetic acid the evolution of brown nitrogen dioxide fumes was clearly evident due to the breakdown of **2** and **3** (eq 2). Similar testing of direct aliquots from various benzoyl nitrate–*o*-xylene reaction mixtures and an acetyl nitrate–*o*-xylene reaction which had been subjected directly to an aqueous wash indicated no nitrogen oxide fumes. Thus it appears that the suspected cyclohexadiene intermediates from benzoyl nitrate systems (**6**) are not very stable, but break down under reaction conditions.

Reactions of Benzoyl Peroxide–Polymethylbenzenes. General Procedure. Cupric chloride (0.2 g, 0.0015 mol) was dissolved with heat and stirring in acetonitrile (50 ml) and the solution transferred to a boiling flask (250 ml) equipped with a condenser. The appropriate para-substituted benzoyl peroxide (0.005 mol) was dissolved in *o*-xylene or hemimellitene (10 ml) and acetonitrile (25 ml) and added to the flask. The solution was then refluxed (~80 °C) for 48 h during which time the mixtures turned green. After cooling, product analysis was performed by GC and GC–MS.

The nitric acid promoted reactions were carried out in similar manner except that the nitric acid (0.010 M, twofold molar excess to the peroxide) was added last and after a 48-h reflux period the reaction mixture had turned a red-brown.

Identification of Products. Most reaction product mixtures were analyzed on a Finnegan Model 3000 GC peak identifier with a quadrupole mass filter. Mass spectra were obtained at 70 eV for the reaction products eluted from a 6 ft × 0.125 in. stainless steel, 3% OV-1/Chromosorb W column.

GC analyses for the reaction mixtures were made on two dual column instruments (Hewlett-Packard Models 5700A and 5830A) equipped with hydrogen flame ionization detectors. The following 0.125-in. stainless steel columns were used: 2% OV-17/Chromosorb W, 3% UCW-982/Chromosorb W, and 3% OV-225/Chromosorb W.

For all of the systems studied, comparisons between the relative retention times of reaction products and authentic materials on two different columns, and noting peak enhancement upon "spiking" reaction mixtures with authentics comprised one approach for product identification. The mass spectra were used to determine the identities of many of the products (comparison to mass spectra of authentic available products was performed where possible). In this manner 3- and 4-nitro-*o*-xylene and all the benzoic acids and dimethylphenyl benzoates (Table VII) were identified.

o-Methylbenzyl nitrate was determined on the basis of its mass spectrum (molecular ion at *m/e* 167, base peak at *m/e* 91). The product identified as o-xylene dimers consisted of three closely spaced peaks all with similar mass spectra (molecular ion at *m/e* 210, base peak at *m/e* 77). None had the exact retention time of 2,2′-dimethylbibenzyl (mp 57–58 °C, mass spectrum molecular ion at *m/e* 210, base peak at *m/e* 105) synthesized by refluxing di-*tert*-butyl peroxide in excess o-xylene and removing unreacted monomer by distillation under reduced pressure.

To demonstrate unequivocally that the aroyloxy groups were attached to o-xylene at a nuclear position rather than at a side chain in the aryl ester products a concentrated product mixture from a p-methylbenzoyl nitrate–o-xylene run was hydrolyzed with 5% methanolic potassium hydroxide. The basic aqueous extract of the resulting mixture yielded p-methylbenzoic acid and 3,4-xylenol upon acidification (GC analysis), while the original organic portion no longer contained any aryl ester product or any new alcohol product.

All of the hemimellitene products were identified on the basis of their mass spectra and relative GC retention times. 2,3,4-Trimethylphenyl benzoate (mass spectrum molecular ion at *m/e* 240, base peak at *m/e* 105) eluted before 3,4,5-trimethylphenyl benzoate (mass spectrum molecular ion at *m/e* 240, base peak at *m/e* 105). Other products included a chlorohemimellitene (mass spectrum molecular ion at *m/e* 154, M + 2 at *m/e* 156) (structure not determined, but likely an α-chloro isomer[13]) from the cupric chloride–benzoyl peroxide reaction and 4-nitrohemimellitene (mass spectrum molecular ion at *m/e* 165, base peak at *m/e* 119) and 5-nitrohemimellitene (mass spectrum molecular ion at *m/e* 165, base peak at *m/e* 119) from both the benzoyl nitrate and benzoyl peroxide–nitric acid reactions. Also observed from this latter system were a dimethylbenzaldehyde isomer (mass spectrum molecular ion at *m/e* 134), a dimethylbenzyl alcohol isomer (mass spectrum molecular ion at *m/e* 136) and a trimethylbiphenyl isomer (mass spectrum molecular ion at *m/e* 196).

Reaction product yields were determined using phenyl benzoate or carbazole as an internal standard, and comparing product areas

to that of the marker added in known amount. The mean of duplicate analyses in good agreement was used, and response factors were calculated for mixtures of authentic vs. the internal standard and used to correct area ratios to mole ratios. The benzoic acid by-product yields were determined in two cases (Table I) by aqueous base extraction and isolation. Together with the aryl ester products in these two runs the benzoyloxy moiety material balance from the p-nitrobenzoyl nitrate and benzoyl nitrate reactions was 95 and 86%, respectively.

References and Notes

(1) (a) A. Fischer, J. Packer, J. Vaughan, and G. J. Wright, *J. Chem. Soc.*, 3687–3690 (1964); (b) A. Fischer, A. J. Read, and J. Vaughan, *ibid.*, 3691–3701 (1964).
(2) (a) A. Fischer and J. N. Ramsay, *J. Am. Chem. Soc.*, **96**, 1614–1616 (1974); (b) R. C. Hahn and D. L. Strack, *ibid.*, **96**, 4335–4337 (1974); (c) M. W. Galley and R. C. Hahn, *ibid.*, **96**, 4337–4339 (1974).
(3) D. J. Blackstock, A. Fischer, K. E. Richards, J. Vaughan, and G. J. Wright, *Chem. Commun.*, 641 (1970).
(4) P. C. Myhre, *J. Am. Chem. Soc.*, **94**, 7921–7923 (1972).
(5) D. J. Blackstock, J. Cretney, A. Fischer, M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *Tetrahedron Lett.*, 2793–2796 (1970).
(6) A. Fischer and J. N. Ramsay, *J. Chem. Soc., Perkin Trans. 2*, 237–240 (1973).
(7) (a) A. Fischer and A. L. Wilkinson, *Can. J. Chem.*, **50**, 3988–3992 (1972); (b) A. Fischer and D. R. A. Leonard, *ibid.*, **50**, 3367–3372 (1972); (c) A. Fischer, C. C. Greig, A. L. Wilkinson, and D. R. A. Leonard, *ibid.*, **50**, 2211–2216 (1972); (d) A. Fischer and C. C. Greig, *J. Chem. Soc., Chem. Commun.*, 396 (1973); (e) D. J. Blackstock, M. P. Hartshorn, A. J. Lewis, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc. B*, 1212–1213 (1972).
(8) (a) C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc.*, **93**, 3389–3394 (1971); (b) S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 1256–1261 (1971); (c) J. W. Barnett, R. B. Moodie, K. Schofield, and J. B. Weston, *J. Chem. Soc., Perkin Trans. 2*, 648–654 (1975).
(9) M. E. Kurz, L. T. A. Yang, E. P. Zahora, and R. C. Adams, *J. Org. Chem.*, **38**, 2271–2277 (1973).
(10) L. R. Barlow, *Tetrahedron*, **24**, 4913–4915 (1968).
(11) (a) M. E. Kurz, R. L. Fozdar, and S. S. Schultz, *J. Org. Chem.*, **39**, 3336–3342 (1974); (b) M. E. Kurz and M. Pellegrini, *ibid.*, **35**, 990–992 (1970).
(12) (a) V. Gold, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2467–2473 (1950); (b) S. R. Hartshorn, R. B. Moodie, and K. Schofield, *J. Chem. Soc. B*, 2454–2461 (1971).
(13) M. E. Kurz and P. Kovacic, *J. Org. Chem.*, **33**, 1950–1956 (1968).
(14) Addition products such as **2** and **3** break down to aryl esters upon GC analysis (see ref 3 and 4). The corresponding cyclohexadienes (**6**) would be expected to do the same, and appear to be even less stable than **2** or **3** (see Experimental Section).
(15) R. J. Coombes and L. W. Russell, *J. Chem. Soc. B*, 2443–2447 (1971).
(16) Because of the complex equilibria known to exist for acyl nitrate systems (see ref 9, 12a), it is possible that this combination of reagents formed acetyl nitrate which could have been responsible for the products.
(17) C. C. Price and E. Krebs, "Organic Syntheses", Collect. Vol. III, Wiley, New York, N.Y. 1955, pp 649–650.
(18) L. S. Silbert and D. Swern, *J. Am. Chem. Soc.*, **81**, 2364–2367 (1959).
(19) M. E. Kurz, E. M. Steele, and R. L. Vecchio, *J. Org. Chem.*, **39**, 3331–3336 (1974).

Biosynthetic Oxidation and Rearrangement of Vittatine and Its Derivatives[1]

A. I. Feinstein and W. C. Wildman*

Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50011

By the use of appropriately labeled radioactive precursors it is demonstrated that vittatine (**2d**) is a precursor of haemanthamine (**2e**) and montanine (**4a**) in *Rhodophiala bifida*. Evidence is presented to show there is no equilibration of the enantiomeric (−)- and (+)-crinine ring systems in the plants.

Although the Amaryllidaceae alkaloids are almost invariably isolated in optically active form, the family is unique because a given plant may produce two very similar alkaloids possessing enantiomeric nuclei. Thus *Nerine bowde-*

nii W. Wats. contains both crinine (**1**) and (+)-epicrinine (**2a**).[2,3] Several plants contain the optical antipode of **1**, vittatine (**2d**),[4–9] but racemic crinine has never been isolated. Because more oxygenated derivatives of **1** and **2a** have been
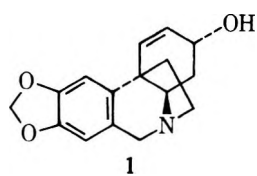
1
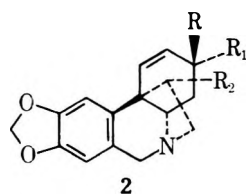
2

a. R_1 = OH; R, R_2 = H
b. R = H; R_1 = OCH_3; R_2 = OH
c. R, R_1 = O; R_2 = H

d. R = OH; R_1, R_2 = H
e. R = OCH_3; R_1 = H; R_2 = OH
f. R = OH, R_1 = H; R_2 = OH
g. R = OCH_3; R_1, R_2 = H

converted either chemically or in vivo into other ring systems (e.g., 3, 4, and 5) it was of interest to follow the pathways of 1 and 2a in the plant to other transformation products.
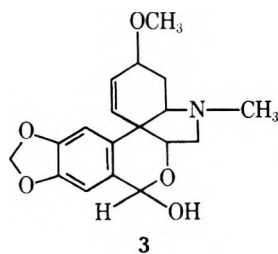
3
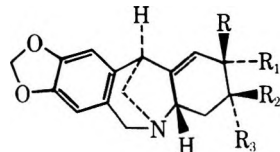
4

a. R = H; R_1 = OCH_3; R_2 = OH; R_3 = H
b. R = OCH_3; R_1 = H; R_2 = OH; R_3 = H
c. R = H; R_1 = OCH_3; R_2 = OCH_3; R_3 = H
d. R = H; R_1 = OH; R_2 = OH; R_3 = H
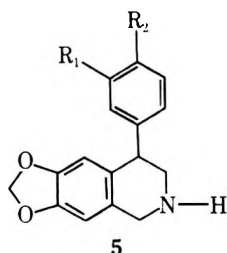
5
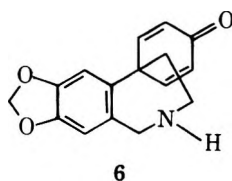
6

It was of biosynthetic importance to determine whether 1 and 2 (and similar alkaloids) could be interrelated in vivo, perhaps through conversion to the symmetrical dienone (6) as an intermediate. (−)-Crinine (1) labeled with tritium in the aromatic ring was fed to *Nerine bowdenii.* After 3 weeks of plant growth, the alkaloids were isolated in the usual manner. All alkaloids derived from the (−)-crinine nucleus were radioactive while the crinamine (2b) and (+)-epicrinine (2a) were inactive. While this preliminary experiment indicated that 1 is not converted to the ring system of 2 in the plant, oxovittatine (2c) might be a more likely precursor of 6 since only β-elimination of the amino function would be required. It could also be rationalized that oxidation of 2a to 2c might, for some reason, be unusually difficult in the plant. The requisite [³H]oxovittatine was readily prepared by the manganese dioxide oxidation of ar-[³H]vittatine. Further oxidation to N-ethylhydrastimide showed that 96% of the label was located in the aromatic ring. An aqueous solution of the tracer was introduced by syringe into eight bulbs of *N. bowdenii.* The alkaloids were isolated after 3 weeks of additional growth in a greenhouse. As expected, lycorine and belladine were inactive. Consistent with previous findings, all alkaloids derived from the nucleus of 1 were nonradioactive. Both cri-

Table I. Incorporation of [³H]Oxovittatine in *N. bowdenii*[a]

Alkaloid	Activity, dpm/mM	Dilution	% inc.
Crinamine	4.64×10^6	3.76×10^3	0.06
(+)-Epicrinine	6.59×10^6	2.63×10^3	0.09

[a] The total activity of the [³H]oxovittatine was 0.88 mCi.

Table II. Incorporation of ar-[³H]Vittatine in *R. bifida*[a]

Alkaloid	Activity, dpm/mM	Dilution	% inc.
Haemanthamine	35.2×10^6	2.8×10^3	0.20
Montanine	4.21×10^6	23.4×10^3	0.06

[a] 1.64 mCi of [³H]vittatine was introduced.

namine (2b) and (+)-epicrinine (2a) were radioactive (Table I) but the low percentage of incorporation leaves doubt whether oxovittatine is on the main biosynthetic route to the crinine-type alkaloids. The radioactive crinamine was degraded to N-ethylhydrastimide which contained, within experimental error, the same specific activity as the radioactive precursor. From the results of these two tracer studies we conclude that there is no evidence that the enantiomeric rings systems of 1 and 2 are interconvertible in the plant.

The alkaloids montanine, coccinine, manthine, and pancracine are based on the 5,11-methanomorphanthridine nucleus (4). The structures assigned to the individual alkaloids were determined by degradation and by partial syntheses which involved the rearrangement of 2b or 2e as the
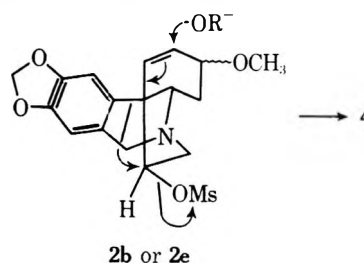
2b or 2e

mesylate to the ring system of 4.[10] In an early attempt to mimic the rearrangement in vivo, ar-[³H]haemanthamine was prepared and fed to blooming *Haemanthus coccineus.* This plant is known to contain haemanthamine (2e), montanine (4a), coccinine (4b), and manthine (4c).[11] The plants were processed after 1 month. No alkaloid related to 4 was found to be radioactive. The C_3 methoxyl group of haemanthamine would appear to be a point of interference in the in vivo rearrangement since 4a and 4b have hydroxyl groups at the equivalent position.

With a supply of ar-[³H]vittatine on hand the experiment was repeated with this precursor using *Rhodophiala bifida* which has been reported to contain haemanthamine, vittatine, 11-hydroxyvittatine (2f), and montanine (4a), among other alkaloids.[12,13] The results given in Table II show that vittatine is a precursor of both haemanthamine and montanine. Both montanine and haemanthamine were converted to N-ethylhydrastimide. The specific activities of the imides were 97 and 96%, respectively, of that found for the isolated alkaloids.

With these results several biosynthetic pathways can be considered for the late-stage elaboration of haemanthamine and montanine (Scheme I). Facts and possible bio-

Scheme I. Proposed Montanine Biosynthesis

(+)-buphanisine ------→ haemanthamine

(2g)   (2e)

vittatine --------→ 11-hydroxyvittatine

(2d)   (2f)

montanine ←---------- pancracine

(4a)   (4d)
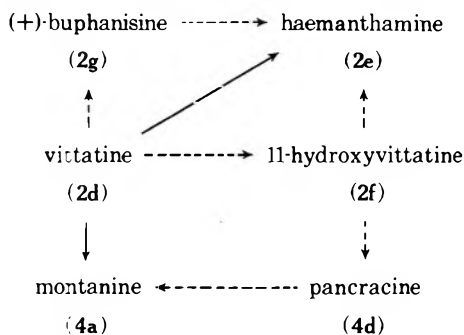
synthetic routes are designated by solid and dashed arrows, respectively. No biosynthetic experiments have been published to establish the nature of the 5,10b-ethanophenanthridine intermediate, unoxidized at C_{11} (8), which leads to haemanthamine (2e). Thus, 2e could be derived either from vittatine by C_{11} hydroxylation followed by C_3 O-methylation or by the reverse process via (+)-buphanisine (2g). Since the latter alkaloid has not been reported to occur in the Amaryllidaceae, and 2f and 4d are known to occur in *R. bifida*, the former route must be considered most likely. We suggest that 11-hydroxyvittatine is the common precursor of both 2e and 4a.

The specific activity of vittatine-derived haemanthamine is substantially higher than that of the montanine isolated from the same experiment. This finding seems to indicate that 11-hydroxyvittatine is converted more efficiently to haemanthamine which only requires the methylation of the hydroxyl function at C_3 of 11-hydroxyvittatine while the formation of montanine involves a rearrangement of the vittatine ring system in addition to the methylation of the oxygen function at C_2.

Experimental Section

Melting points were taken on a Köfler microscope hot stage apparatus and are corrected. Infrared spectra were taken on either a Beckman Model IR-12 or IR-18A recording spectrophotometer in chloroform solution or as a potassium bromide pellet. The proton magnetic resonance spectra were obtained on a Varian A-60 or HA-100 in chloroform-d_1 unless another solvent was indicated. Mass spectra were recorded on an MS-902 mass spectrometer. This spectrometer was purchased on NSF Grant GP 10226. The measurements of radioactivity were made with a Packard Tri-Carb liquid scintillation spectrometer (Model 3002) at ambient temperature. Solutions for counting were either toluene–PPO–POPOP [4.9 g of 2,5-diphenyloxazole (PPO) and 0.1 g of 1,4-bis-2-(5-phenyloxazole) benzene (POPOP) in 1 l. of dry toluene] or Bray's solution.[14] Efficiency of counting tritium was determined for each sample by means of an internal standard of [^{3}H]- or [^{14}C]toluene. Reproducibility of the assays was ±3%.

Preparative-scale layer chromatography used 20 × 20 cm glass plates coated with silica gel (Merck PF 254 + 366) 0.5 mm in thickness. The plates were eluted once with the solvent system specified. The alkaloids were detected by ultraviolet light. The bands of silica gel and alkaloid were removed from the plate and covered with 80–100 ml of 10% aqueous ammonia and the aqueous layer including the silica gel was extracted with chloroform until the aqueous layer gave a negative silico-tungstic acid test. The alkaloids were identified by their TLC behavior, melting point, mixture melting point, and by comparison of their ir spectra with known reference spectra. The alkaloids were purified from chromatographic fractions via recrystallization from appropriate solvents to constant activity. The percent incorporation was calculated as (100 × total activity of isolated alkaloid) divided by (total activity fed). For this purpose, the final constant activity of the alkaloid per milligram was multiplied by the quantity of alkaloid isolated (mg) which was of good chemical purity as determined by TLC, melting point, and ir.

[^{3}H]Vittatine. *O*-Acetylvittatine (50 mg) was tritiated by the catalytic exchange method using aqueous acetic acid containing 10 Ci of tritiated water and 25 mg of prereduced platinum catalyst at 100 °C. The catalyst was removed and the solution was divided into seven parts. One portion was evaporated under reduced pressure. The residue was dissolved in 15 ml of methanol containing 1 ml of 50% sodium hydroxide. After 2 days at 20 °C, the methanol was removed under reduced pressure and the residue was dissolved in 50 ml of water. The aqueous solution was diluted with 35 mg of inactive vittatine and extracted with chloroform. The chloroform solution was washed repeatedly with water in order to remove the remaining labile tritium. Concentration of the dried chloroform extract gave 30 mg of crude tritiated vittatine. The vittatine was recrystallized from acetone to constant activity to give 10 mg, mp 210–211 °C (lit.[15] mp 207–208 °C), 9.89 × 10^{10} dpm/mM. Further dilution with nonradioactive alkaloid gave 800 mg (7.29 × 10^7 dpm/mM) of vittatine which was converted to 2 mg of *N*-ethylhydrastimide,[16] mp 170–171 °C (7.01 × 10^7 dpm/mM).

[^{3}H]-(−)-Crinine was prepared similarly.

[^{3}H]Oxovittatine. A chloroform solution of 57 mg of [^{3}H]vittatine (1.73 × 10^{10} dpm/mM) was oxidized with 350 mg of manganese dioxide. The pure ketone (40 mg, mp 185–187 °C, 1.75 × 10^{10} dpm/mM) was obtained by recrystallization from ether–chloroform.

Incorporation of [^{3}H]Oxovittatine in *N. bowdenii*. An aqueous solution of 30 mg (0.88 mCi) of [^{3}H]oxovittatine (pH 6) was injected into eight growing bulbs. After 3 weeks of growth in a greenhouse, the bulbs (4639 g) were processed for alkaloids.[2] The alkaloid fraction containing chloroform-soluble hydrochlorides (600 mg) was chromatographed on Florisil to give 110 mg of undulatine (mp 151–152 °C) and 128 mg of belladine (as the HCl salt, mp 193–194 °C); both were nonradioactive. The alkaloids forming chloroform-insoluble hydrochlorides (600 mg) afforded 50 mg of inactive lycorine by direct crystallization. The remainder was chromatographed on Florisil to give nonradioactive ambelline, crinamidine, crinine, belladine, and undulatine. The filtrate from the fractions providing ambelline was diluted with 70 mg of crinamine and recrystallized to constant activity, mp 199–200 °C (lit.[17] mp 198–199 °C). The crinine filtrates were diluted with 70 mg of (+)-epicrinine and recrystallized to constant activity, mp 208–209 °C (lit.[17] mp 207–209 °C).

Incorporation of [^{3}H]Vittatine in *R. bifida*. [^{3}H]Vittatine (1.64 mCi, 10 mg) was dissolved in 0.5 ml of water (pH 6) and introduced directly into the *Rhodophiala bifida* bulbs (20 bulbs) with a fine hypodermic needle. The radioactive residue in the vial was dissolved in 0.5 ml of water and injected into six additional bulbs 3 days later. The plants were grown in pots in a greenhouse for 3 weeks after which the bulbs were harvested.

Isolation of Alkaloids from *R. bifida*. The bulbs (437 g) were macerated with 3 l. of 95% ethanol in a Waring Blendor. The mixture was filtered and the filter cake was allowed to stand overnight in 1 l. of 95% ethanol. The solid material was filtered and the filtrates were combined and concentrated under reduced pressure. The resulting residue (5.3 g) was acidified with 2 N hydrochloric acid and filtered to remove the acid-insoluble material. The insoluble material was heated with 2 N hydrochloric acid and refiltered. The filtrates were combined and washed five times with benzene. The benzene extract contained no alkaloidal material and was discarded.

The aqueous acidic solution was made basic (pH 10) with ammonium hydroxide and extracted several times with chloroform. The aqueous solution was then adjusted to pH 12 by the addition of 10% sodium hydroxide and extracted three times with 20% ethanol in chloroform. The organic extracts were combined and concentrated under reduced pressure to give 2.0 g of crude basic material. The basic residue was dissolved in a minimum amount of acetone, and 10 drops of 70% perchloric acid was added followed by enough ether to cause the solution to become turbid. The solution was allowed to stand at 0 °C for 2 h in order to ensure complete precipitation of montanine perchlorate. The product (109 mg) was removed by filtration and recrystallized from acetone to give 100 mg, mp 249–250 °C. The filtrate was dissolved in water, made basic with ammonium hydroxide, and extracted with chloroform. Evaporation of the chloroform gave 1.0 g of a crude residue (1.61 × 10^6 dpm/mM).

A benzene solution of the crude residue was chromatographed on alumina packed in benzene. Elution with 25% chloroform in benzene afforded fractions from which 62 mg of haemanthamine, mp 199–200 °C, was obtained by crystallization from acetone. Elution with 50–75% chloroform in benzene gave fractions rich in montanine from which 91 mg of montanine perchlorate, mp 250–251 °C, was obtained as before. Further elution with chloroform and 1–10% methanol–chloroform solutions gave no characterizable products.

The haemanthamine and montanine perchlorate were recrystallized to constant activity to give a total of 62 mg of haemanthamine, mp 199–200 °C (lit.[11] 203–203.5 °C, 3.52×10^7 dpm/mM), and 200 mg of montanine perchlorate, mp 250–251 °C (lit.[11] mp 249–250 °C, 4.21×10^6 dpm/mM).

Both alkaloids were diluted with inactive alkaloid for oxidative degradation. Haemanthamine (1.5 g, 1.46×10^5 dpm/mM) gave 50 mg of N-ethylhydrastimide, mp 169–170 °C (1.39×10^5 dpm/mM). Oxidation of 1.5 g of montanine (1.31×10^5 dpm/mM) gave 25 mg of imide, mp 169–170 °C (1.27×10^5 dpm/mM).

Registry No.—1, 510-67-8; **2a**, 25375-48-8; **2b**, 639-41-8; **2c**, 59013-69-3; **2d**, 510-69-0; **2e**, 466-75-1; **4a** perchlorate, 58944-40-4; **4a** imide, 3990-41-8; *O*-acetylvittatine, 58944-39-1; undulatine, 6882-09-3; belladine HCl, 58944-41-5; ambelline, 3660-62-6.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of A.I.F., Iowa State University of Science and Technology, June 1967. This work was supported in part by funds from the National Institutes of Health (HL-7503).

(2) F. E. Lyle, E. A. Kielar, J. R. Crowder, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 2620 (1960).
(3) H.-G. Boit and H. Ehmke, *Ber.*, **89**, 2093 (1956).
(4) H.-G. Boit and W. Döpke, *Ber.*, **90**, 1827 (1957).
(5) H.-G. Boit. *Ber.*, **89**, 1129 (1956).
(6) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).
(7) S. Uyeo, K. Kotera, T. Okada, S. Takagi, and Y. Tsuda, *Chem. Pharm. Bull.* **14**, 793 (1966).
(8) H.-G. Boit and H. Ehmke, *Ber.*, **90**, 369 (1957).
(9) S. H. Hung and K. E. Mas, *Yao Hsueh Hsueh Pao*, **11**, 1 (1964).
(10) Y. Inubushi, H. M. Fales, E. W. Warnhoff, and W. C. Wildman, *J. Org. Chem.*, **25**, 2153 (1960).
(11) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 1248 (1955).
(12) W. C. Wildman, C. F. Murphy, K.-H. Michel, C. H. Brown, D. T. Bailey, N. Heimer, and R. Shaffer, *Pharmazie*, **72**, 725 (1967).
(13) W. C. Wildman and C. L. Brown, *J. Am. Chem. Soc.*, **90**, 6439 (1968).
(14) G. A. Bray, *Anal. Biochem.*, **1**, 279 (1960).
(15) H.-G. Boit, *Chem. Ber.*, **89**, 1129 (1956).
(16) E. W. Warnhoff and W. C. Wildman, *J. Am. Chem. Soc.*, **79**, 2192 (1957).
(17) L. H. Mason, E. R. Puschett, and W. C. Wildman, *J. Am. Chem. Soc.*, **77**, 1253 (1955).

Interconversions in the Pluviine–Lycorenine Series[1]

R. D. Harken, C. P. Christensen, and W. C. Wildman*

Department of Chemistry, Iowa State University of Science and Technology, Ames, Iowa 50011

Norpluviine is converted in *Narcissus pseudonarcissus* L. (King Alfred) primarily to alkaloids of the lycorenine type while pluviine undergoes oxidation of the hydroaromatic ring to form unrearranged products in *N. poeticus*. Consistent with our findings on the mechanism of the late stage oxidation of caranine to lycorine, pluviine is converted to galanthine with inversion at C_2. A chemical conversion of lycorine to 7-hydroxylycorine (12–13) has been accomplished. Some spectral and chemical properties of the compound are described.

It was recognized in the original biosynthetic hypothesis of oxidative phenyl–phenyl coupling[2] that alkaloids related to lycorenine (**2b**) could not be derived from a norbelladine-type precursor (1) directly. The well-documented hemiami-
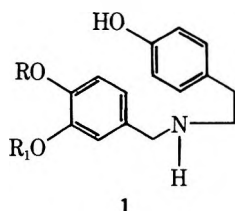
1

a, R = CH_3; R_1 = H (*O*-methylnorbelladine)
b, R, R_1 = H (norbelladine)
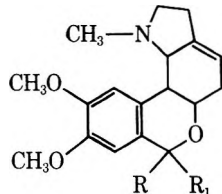
2

a, R, R_1 = O (homolycorine)
b, R = H, R_1 = OH (lycorenine)

nal–hemiacetal interconversion of haemanthidine and pretazettine[3] suggested that a similar process might occur in alkaloids of the lycorine type.[4] Benzylic oxidation of the CH_2 at C_7 would afford **3**; ring opening to form an amino aldehyde followed by hemiacetal formation and methylation could provide derivatives of **2**.

3
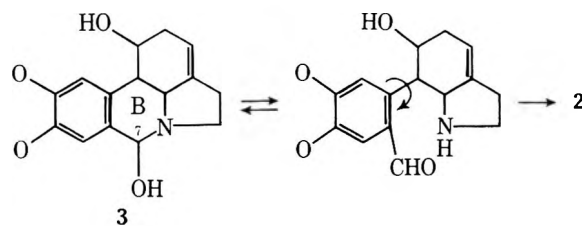
To test the validity of this pathway, [8-³H]norpluviine (**4a**) was prepared by tritium exchange. [8-³H]Pluviine (**4b**) was obtained easily by the action of diazomethane on **4a**. The

4
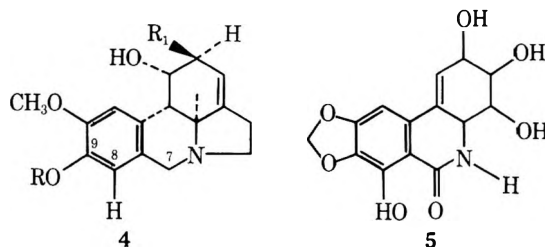
a, R = R_1 = H (norpluviine)
b, R = CH_3; R_1 = H (pluviine)
c, R = CH_3; R_1 = OH (methylpseudolycorine)
d, R = CH_3; R_1 = OCH_3 (galanthine)

5

distribution of the tritium label was determined for radioactive **4b** by oxidation to *m*-hemipinic acid (4,5-dimethoxyphthalic acid) which was converted to the N-ethyl imide. The specific molar activity of the imide was 78% of that found for **4b**, indicating that this percentage of the tritium was located in the aromatic ring. An aqueous solution (pH 6) of 5 mg of

Table I. [8-³H]Norpluviine [a] Feeding to *Narcissus* "King Alfred"

Alkaloid	Activity, dpm/mM	% inc.
Lycorenine	34.9×10^5	0.11
Homolycorine	12.3×10^5	0.018
Pluviine	23.4×10^5	0.029
Methylpseudolycorine	2.46×10^5	0.0023
Galanthine	6.79×10^5	0.017
Narciclasine	0.40×10^5	0.0034

[a] The total activity of [8-³H]norpluviine fed was 0.10 mCi.

Table II. [8-³H]Pluviine [a] Feeding to *Narcissus poeticus*

Alkaloid	Activity, dpm/mM	% inc.
Lycorenine	0	0.00
Galanthine	1.09×10^8	3.26
Methylpseudolycorine	1.35×10^7	0.25
Narcissidine	7.50×10^5	0.021
Lycorine	1.91×10^6	0.14

[a] The total activity of [8-³H]pluviine fed was 0.10 mCi.

Table III. Pluviine Feeding to *Narcissus* "King Alfred"

Alkaloid	Quantity, mg	Specific activity, mCi/mg	Total activity, mCi	³H/¹⁴C ratio
Pluviine	9	0.77×10^{-3} ³H	6.9×10^{-3} ³H	
		0.578×10^{-3} ¹⁴C	5.2×10^{-3} ¹⁴C	1.3
Galanthine	29	0.73×10^{-5} ¹⁴C	2.1×10^{-4}	
		0.75×10^{-5} ³H	2.2×10^{-4}	1.0

a, R, R₁ = CH₂<; R₂ = ³H; R₃ = H
b, R, R₁ = CH₂<; R₂ = OH; R₃ = ³H
c, R, R₁ = H; R₂ = OH; R₃ = H

[8-³H]norpluviine was injected into the flower stalks of King Alfred daffodils. After 18 days, the plants were harvested and the alkaloids were isolated by standard methods. The major alkaloid, haemanthamine, was found to be inactive as expected. Both lycorenine (**2b**) and galanthine (**4d**) were degraded to *N*-ethylhemipinimide which had 79 and 75%, respectively, of the specific molar activity (dpm/mM) of the original [8-³H]norpluviine. Table I summarizes the incorporation data. From these results it is clear that norpluviine is converted much more readily into the rearranged nucleus (**2**) than it is oxidized or simply O-methylated within its own ring system. Most surprising was the observation that the narciclasine (**5**) isolated from this feeding was radioactive. Furthermore, the percent conversion of [8-³H]norpluviine to narciclasine given in Table I must be grossly low, since all tritium at C₈ in the precursor (78%) would have been lost in the transformation. Previous work has indicated that **5** is derived from vittatine[5] and that norpluviine is not converted to narciclasine.[6]

Strikingly different results were obtained when [8-³H]-pluviine (**4b**) was the biosynthetic precursor. The plant host chosen for the study was *Narcissus poeticus* L. since it was readily available and contained lycorenine, pluviine, methylpseudolycorine, galanthine, and narcissidine in isolable amounts. Table II shows that pluviine is an excellent precursor for more highly oxygenated alkaloids of the same nucleus.
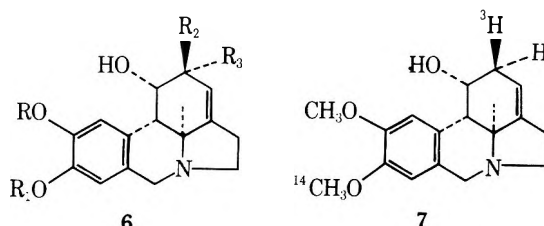
It is most interesting that the lycorenine was completely inactive. It would appear that a free phenolic group at C₉ in **4** promotes the benzylic hydroxylation necessary for rearrangement to the ring system of **2**.[7]

The in vivo conversion of *O,O*-dimethoxy alkaloids to the methylenedioxy related compounds has not been observed before. In this feeding experiment pluviine was converted to lycorine rather efficiently. The mechanism for this transformation probably does not involve a simple O-demethylation at C₉, since this intermediate would be norpluviine, a known precursor of lycorenine (vide supra) which should then be radioactive when isolated.

The stereochemistry of the oxidation process by which C₂ in **4** is converted from a methylene to either a hydroxyl or methoxyl group has been the subject of conflicting results. In the first report[8] [2β-³H]caranine (**6a**) was converted to [2-α-³H]lycorine (**6b**) in *Zephyranthes candida* by hydroxylation with inversion of configuration of the original 2β-³H atom. A

similar mechanism was reported by Bruce and Kirby[9] using both a different biosynthetic precursor and degradative route. A retention mechanism was proposed by Fuganti and Mazza[10] for the oxidation of caranine to lycorine in *Clivia miniata*. Since our initial experiments were with singly labeled material, it was considered of value to repeat the sequence with a doubly labeled precursor. [2β-³H,9-*O*-methyl-¹⁴C]pluviine (**7**) was selected for this purpose.

Lycorine (**6b**, no label) was cleaved to **6c** with boron tribromide. Methylation with diazomethane provided methylpseudolycorine (**4c**) which was converted to [2β-³H]-pluviine by the method used in our [2β-²H]caranine synthesis.[8] [2β-²H]Pluviine was also prepared to determine the label distribution and stereochemistry. Pyrolysis of *O*-acetyl[2β-²H]pluviine provided anhydropseudolycorine with 75% of the deuterium retained. This figure was considered to represent the label at the β-C₂ position since the pyrolysis should proceed by a cyclic cis mechanism. [9-*O*-Methyl-¹⁴C]pluviine (**4b**) was prepared by the methylation of **4a** with [¹⁴C]diazomethane. A combination of these precursors gave doubly labeled material which was crystallized to constant activity and introduced into blooming "King Alfred" daffodils. After 2 weeks, radioactive galanthine was isolated from the plants with 4.1% incorporation into the alkaloid based on ¹⁴C. The carbon–tritium ratio in the isolated galanthine showed a retention of 79% of the tritium (Table III). This result supports our previous work[8] and that of Bruce and Kirby.[9]

To complete our research on the chemistry and biosynthesis of alkaloids related to **2** and **4** it was desirable to attempt a synthesis of a compound related to **3** for chemical and spectral investigation. Although *O,O*-diacetyl-7-oxolycorine (**8**, C=O at C₇) was available by permanganate oxidation of *O,O*-diacetyllycorine (**8**), no chemical reducing agent was found to convert the lactam to the hemiaminal in reasonable yield. A successful route was found in an extension of the work of Mizukami[11] as outlined in Chart I. With cyanogen bromide in chloroform solution **8** provided **9** in greater than 80% yield. The reaction product was not isolated but oxidized with dimethyl sulfoxide–sodium bicarbonate to give **10**. Protection of the aldehyde as the acetal followed by lithium aluminum hydride reduction gave **11b**. This product was unstable and characterized only by ¹H NMR and ir spectra. Acid hydrolysis of **11b** provided a crystalline product which reacted with lithium aluminum hydride to form lycorine (**6b**, R₃ = ¹H). On this basis structure **12** should be assigned to the hydrolysis

Chart I. Interconversions of Lycorine

a. R = CN; R₁ = CH₃CO

b. R, R₁ = H
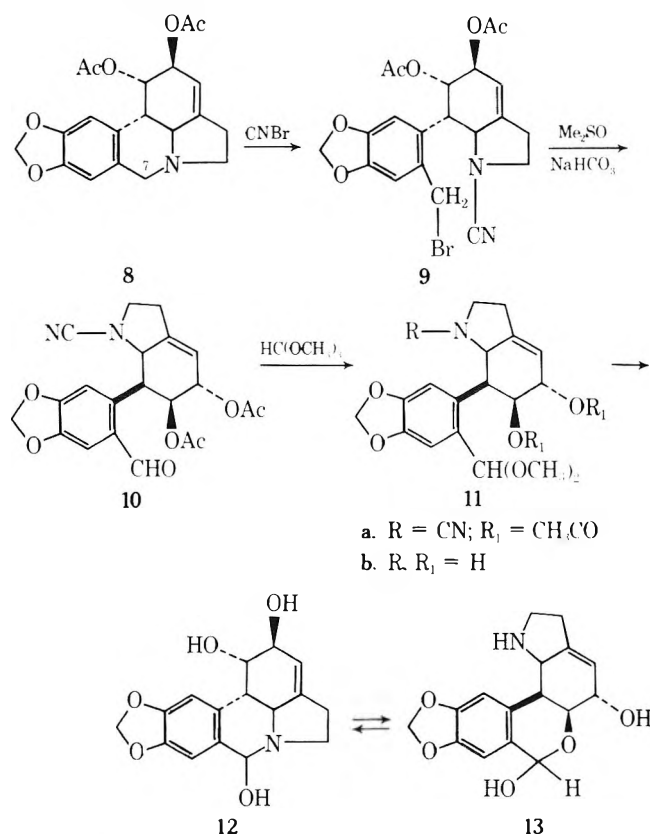
product of **11b** since **13** would be expected to give a dihydroxybenzyl alcohol under these conditions.

Spectral evidence. however, seemed more in accord with **13** for the structure of the hydrolysis product as shown in Table IV. The benzylic proton of **12–13** shows a chemical shift in agreement with model compounds containing the hemiacetal rather than the hemiaminal moiety. Further chemical and spectral studies on this compound are in progress.

Experimental Section

Melting points were taken on a Köfler microscope hot stage apparatus and are corrected. Infrared spectra were taken on either a Beckman Model IR-12 or IR-18A recording spectrophotometer in chloroform solution or as a potassium bromide pellet. The proton magnetic resonance spectra were obtained on a Varian A-60 or HA-100 in chloroform-d_1 unless another solvent was indicated. Mass spectra were recorded on an MS-902 mass spectrometer. This spectrometer was purchased on NSF Grant-GP 10226. The measurements of radioactivity were made with a Packard Tri-Carb liquid scintillation spectrometer (Model 3002) at ambient temperature. Solutions for counting were either toluene–PPO–POPOP [4.9 g of 2,5-diphenyloxazole (PPO) and 0.1 g of 1,4-bis-2-(5-phenyloxazole)benzene (POPOP) in 1 l. of dry toluene] or Bray's solution.[14] Efficiency of counting tritium was determined for each sample by means of an internal standard of [³H]- or [¹⁴C]toluene. Reproducibility of the assays was ±3%.

Preparative-scale layer chromatography used 20 × 20 cm glass plates coated with silica gel (Merck PF 254 + 366) 0.5 mm in thickness. The plates were eluted once with the solvent system specified. The alkaloids were detected by ultraviolet light. The bands of silica gel and alkaloid were removed from the plate and covered with 80–100 ml of 10% HCl for a minimum of 1 h. The acid was neutralized with 10% aqueous ammonia and the aqueous layer including the silica gel was extracted with chloroform until the aqueous layer gave a negative silico-tungstic acid test.

The alkaloids were identified by their TLC behavior, melting point, mixture melting point, and by comparison of their ir spectra with known reference spectra. The alkaloids were purified from chromatographic fractions via recrystallization from appropriate solvents to constant activity. The percent incorporation was calculated as (100 × total activity of isolated alkaloid) divided by (total activity fed). For this purpose, the final constant activity of the alkaloid per milli-

Table IV. Benzylic Proton Chemical Shifts

Compd	Chemical shift(s), δ	Assignment	Ref
12–13	6.02	Hemiacetal	a
Cotarnine	5.39	Carbinolamine	a
6-Hydroxybuphanidrine	5.31	Carbinolamine	12
6-Hydroxypowelline	5.38	Carbinolamine	12
6-Hydroxycrinamine	5.0, 5.6	Carbinolamine	13
Haemanthidine	5.0, 5.6	Carbinolamine	13
Pretazettine	6.06	Hemiacetal	3
Lycorenine	6.04	Hemiacetal	3
6-Hydroxyundulatine	5.20	Carbinolamine	12

ᵃ This work.

gram was multiplied by the quantity of alkaloid isolated (mg) which was of good chemical purity as determined by TLC, melting point, and ir.

[8-¹H]Norpluviine (4a). The material was prepared by New England Nuclear Corp., Boston, Mass., by heating norpluviine in tritiated acetic acid in the presence of a platinum catalyst. A portion of the [8-³H]norpluviine was purified by reprecipitation from aqueous acid solution using solid sodium bicarbonate, and finally by crystallization from methanol. This purification procedure gave 15 mg of [8-³H]-norpluviine, mp 237–239 °C (lit.[15] mp 239–241 °C), with a specific activity of 1.22×10^{10} dpm/mM, 5.51 mCi/mM. The infrared spectrum of this material was identical with the infrared spectrum of authentic norpluviine. Dilution with pure inactive norpluviine resulted in no gain or loss of total activity.

A diluted sample of [8-³H]norpluviine was purified as above to give 29 mg (5.62×10^9 dpm/mM). This material was suspended in 2 ml of methanol and treated with 10 ml of ethereal diazomethane at 25 °C for 6 h. The solvent was removed and the residue resuspended in 2 ml of methanol and treated again with 10 ml of ethereal diazomethane for 4 h. The solution was concentrated and chromatographed on a preparative-scale TLC plate, and eluted with chloroform/methanol/diethylamine (93/2/5). This afforded 20 mg (67%) of crude [8-³H]pluviine which was recrystallized from benzene/hexane (mp 218–219 °C, lit.[15] mp 220–221 °C), 5.68×10^9 dpm/mM, 2.55 mCi/mM. The specific molar activity of [8-³H]norpluviine relative to the specific molar activity of [8-³H]pluviine was 1.01. The infrared spectrum of [8-³H]pluviine was identical with the spectrum of authentic pluviine. Dilution of the sample with inactive pluviine did not alter the total activity.

Conversions to *N*-Ethylhemipinimide. The following oxidation is representative. Pluviine (200 mg, 1.33×10^7 dpm/mM) was dissolved in 30 ml of 10% hydrochloric acid. The solution was adjusted to pH 8 with solid sodium carbonate. A solution of 1.2 g of potassium permanganate was added at room temperature over 35 min. Stirring was continued for 4 h. Sulfur dioxide was passed through the reaction mixture until clear. After acidification to pH 2 with concentrated sulfuric acid and concentration to 50 ml under reduced pressure, the solution was extracted continually with ether for 36 h. Concentration of the ether gave a wet residue that was partitioned between ethyl acetate and 5% sodium bicarbonate solution. The aqueous basic layer was acidified with 50% sulfuric acid to pH 2 and extracted with eight 30-ml portions of ethyl acetate. The organic extract was dried (MgSO₄), filtered, and evaporated to dryness with acetic anhydride. The residue was sublimed at 120 °C (0.1 mm). The sublimate was triturated with 70% ethylamine and resublimed. The product was recrystallized from ethanol to give 11 mg of product, mp 230–231 °C (lit.[16] mp 229–230 °C), 1.04×10^7 dpm/mM. The specific molar activity of the imide relative to that of the [8-³H]pluviine was 0.78.

Feeding Experiments and Isolation of Alkaloids. A typical procedure is as follows. Five milligrams of [8-³H]norpluviine (2.22 × 10⁸ dpm, 0.10 mCi) in 1.1 ml of aqueous HCl solution at pH 6 was injected with fine hypodermic syringe in equal amounts into the flower stalks of 13 blooming *Narcissus pseudonarcissus* L. var. "King Alfred" plants. The plants were allowed to grow for 18 days. The plants (1.47 kg) were processed by grinding in a Waring Blendor using 6 l. of 95% ethanol. The solid material was filtered, covered with 3 l. of ethanol, and allowed to stand overnight. This treatment was repeated twice. The combined ethanolic extracts were concentrated in vacuo to 1.5 l. The aqueous suspension was acidified to pH 4 with 10% tartaric acid. The aqueous solution was washed five times with 200-ml portions of diethyl ether. Three extractions of the aqueous layer with 200-ml portions of 1-butanol yielded, after removal of the butanol,

9.5 g of brown gum. Alkaloid fractions were obtained by extraction of the aqueous layer with six 200-ml portions of chloroform at pH 7, 9, and 12. The combined chloroform extracts yielded 2.6 g of crude alkaloid mixture which was chromatographed on preparative-scale TLC plates eluting with 70/30/1 ethyl acetate/methanol/ammonia to give four fractions (1–4). Fraction 2, R_f 0.7, gave 172 mg of haemanthamine, mp 198–200 °C (lit.[17,18] mp 200–201 °C), that was devoid of tritium activity. The mother liquors and fraction 3 were rechromatographed on plates in 90/10/0.5 chloroform/methanol/ammonia. The lycorenine containing fractions (as determined by analytical TLC) were combined and chromatographed on a column of 600 mg of alumina (Merck). Lycorenine was eluted in ethyl acetate and ethyl acetate/chloroform mixtures. Trituration with acetone yielded 12 mg of impure lycorenine. The material was diluted with 30 mg of nonradioactive lycorenine and recrystallized several times from ethyl acetate to yield 23 mg, mp 197–199 °C (lit.[19] mp 198–200 °C). Constant activity was attained at 1.11×10^4 dpm/mg. The total activity was 0.11 µCi.

Fractions containing homolycorine from the thick layer plate and column chromatography were combined and purified further on preparative-scale TLC plates using chloroform/methanol/acetone (60/20/20) as the solvent system (R_f 0.8). The homolycorine was obtained in trace quantities and was diluted with 40 mg of nonradioactive homolycorine. Recrystallization from ethanol afforded 10 mg of homolycorine, mp 174–176 °C (lit.[20] mp 175 °C) with constant activity of 3.92×10^3 dpm/mg and a total activity of 0.018 µCi.

Column and TLC fractions containing pluviine were combined and further purified via preparative-scale TLC eluting with 60/20/20 chloroform/methanol/acetone (R_f 0.7). Several recrystallizations from acetone gave 8 mg of pluviine, mp 217–219 °C (lit.[21] mp 225 °C). The activity was constant at 8.16×10^3 dpm/mg with a total activity of 0.029 µCi.

By analytical TLC, the mother liquor of pluviine crystallization contained methylpseudolycorine. Dilution with 10 mg of inactive methylpseudolycorine and recrystallization initially from ethanol and then from acetone yielded 7 mg, mp 234–237 °C (lit.[22] mp 234–242 °C). Constant activity was attained at 7.11×10^2 dpm/mg with a total activity of 2.3×10^{-3} µCi.

Fractions rich in galanthine were rechromatographed on preparative-scale TLC plates using 60/20/20 chloroform/acetone/methanol (R_f 0.6). Recrystallization from ethyl acetate/hexane afforded 18 mg of galanthine, mp 135–136 °C (lit.[22] mp 134–136 °C). Radioactivity was constant at 2.14×10^3 dpm/mg. The total activity was 0.017 µCi.

The gum isolated by extraction with butanol was dissolved in 200 ml of chloroform and 50 ml of ethanol and extracted with three 50-ml portions of 15% sodium hydroxide. The combined basic layers were washed with three 50-ml portions of chloroform. These chloroform extracts were added to the initial chloroform/ethanol solution, evaporated to dryness, and dissolved in 10% HCl (150 ml). The acidic solution was extracted with ether, basified to pH 7, and extracted with chloroform. The chloroform extracts were added to the alkaloid fractions. The initial aqueous basic layers were acidified with 20% HCl and extracted four times with 100-ml portions of ethyl acetate. Concentration of the extract gave 0.70 g of material. This material, in ethyl acetate, was chromatographed on a 20-g column of silica gel, packed in ethyl acetate. Narciclasine was eluted with ethyl acetate and recrystallized from acetic acid to give 59 mg of product, dec above 220 °C (lit.[23] mp 232–234 °C). Its activity was constant at 1.29×10^2 dpm/mg. Its total activity was 3.4×10^{-3} µCi.

Methylpseudolycorine (4c). One gram of lycorine was added to a solution of 2 ml of boron tribromide in 25 ml of methylene chloride at −80 °C. After 2 h, the solution was allowed to warm to ambient temperature and the reaction solution was stirred overnight. The solution was evaporated to dryness under reduced pressure and the residue was dissolved in methanol and treated twice with 10 mmol of diazomethane. The crude product was dissolved in chloroform and extracted with 10% sodium hydroxide solution. After the solvent was removed, 4c was recrystallized from ethanol to give 300 mg (28%), mp 233–235 °C (lit.[22] 234–242 °C dec).

[9-Methoxy-¹⁴C]pluviine (4b). Diazomethane (0.6 mmol) was generated from [N-methyl-¹⁴C]-N-nitroso-p-toluenesulfonamide (1.0 mmol) by adding an ethereal solution of the precursor into a solution of ethanolic potassium hydroxide at 60 °C. The labeled diazomethane was distilled into a cold trap at 0 °C containing 100 mg of norpluviine in methanol. The reaction mixture was stirred overnight and evaporated to dryness. The residue was dissolved in chloroform and extracted with 1% sodium hydroxide and the resulting chloroform solution was dried and evaporated to dryness. The labeled pluviine was recrystallized from benzene–hexane, yield 18 mg (17%), mp 225–226 °C.

Methylpseudolycorine α-Epoxide. The synthesis was patterned after the approach of Wildman and Heimer[8] to lycorine α-epoxide. To a mixture of 200 mg of sodium chloride and 150 mg of methylpseudolycorine, 1 ml of phosphorus oxychloride was added. The slurry was heated to 35 °C with stirring; after 5 min, 2 drops of 6 N hydrochloric acid was added, and the reaction mixture was stirred for another 30 min. The reaction mixture was hydrolyzed in ice water and neutralized with sodium hydroxide. The aqueous solution was extracted with ether and evaporated to yield methylpseudolycorine α-epoxide (50 mg) which was contaminated with anhydromethylpseudolycorine; exact mass determination of $[M - 1]^+$ 284.1282 (calcd for $C_{17}H_{19}NO_3$, 284.1287).

The ¹H NMR spectrum of methylpseudolycorine α-epoxide was in good agreement with that found for lycorine α-epoxide when peaks due to anhydromethylpseudolycorine were subtracted.

Anhydromethylpseudolycorine. Galanthine (100 mg) was dissolved in 6 N hydrochloric acid and refluxed for 4 h. The reaction mixture was neutralized and extracted with chloroform to yield anhydromethylpseudolycorine which was recrystallized from ethanol, 75 mg, mp 170–173 °C, recrystallized 176 °C, dec above 230 °C; exact mass determination for $[M - 1]^+$ 266.1178 (calcd for $C_{17}H_{19}NO_2$, 266.1181).

[2β-²H]Pluviine (4a). Methylpseudolycorine α-epoxide (50 mg) was dissolved in 10 ml of dry ether and added to 25 mg of lithium aluminum hydride-²H in dry ether. The reaction mixture was refluxed for 1 h and the excess lithium aluminum hydride was hydrolyzed with wet ether. Saturated sodium potassium tartrate was added and the [2β-²H]pluviine was extracted with chloroform and purified by TLC (R_f 0.6; 6/2/2 chloroform/acetone/methanol), 25 mg (50%); mp 222–225 °C; exact mass determination 288.1594 (calcd for $C_{17}H_{20}^2HNO_3$, 288.1584).

[2β-²H]-O-Acetylpluviine. [2β-²H]Pluviine was dissolved in acetic anhydride–pyridine. After 24 h, the reaction mixture was evaporated to dryness under reduced pressure and the product was sublimed at 160 °C (0.001 Torr), exact mass determination 330.1668 (calcd for $C_{19}H_{22}^2HNO_4$, 330.1690).

Pyrolysis of [2β-²H]-O-Acetylpluviine. The sample was sealed in a Pyrex tube at 0.001 Torr and heated in a 240 °C oven for 45 min. The volatile fraction was shown by MS to contain acetic acid and the nonvolatile fraction contained [2-²H]anhydromethylpseudolycorine.

Feeding of the Doubly Labeled Pluviine. The labeled pluviine (0.77 mCi/mg ³H, 0.58 mCi/mg ¹⁴C, 9 mg) was dissolved in dilute hydrochloric acid and injected into the flower stalks of nine blooming *Narcissus* "King Alfred" plants, which were harvested after 2 weeks. The bulbs and the flower stalks (514 g) were processed. The pH 8 and 10 chloroform extracts were combined and chromatographed on silica gel with 60/20/20 chloroform/acetone/methanol to yield galanthine (29 mg). The identity of the galanthine was confirmed by comparison with an authentic sample. Tracer results are given in Table III.

Addition of Cyanogen Bromide to O,O-Diacetyllycorine. A mixture of 1 g of O,O-diacetyllycorine[24] and 1 g of cyanogen bromide was dissolved in 50 ml of chloroform. After 500 mg of potassium carbonate was added, the solution was refluxed for 6 h. The potassium bromide was removed by filtration and the filtrate was evaporated to dryness. The product (9) was contaminated with the isomer in which the five-membered ring was opened. They were not separated but used for the next reaction, yield 1.2 g, mp 186–187 °C, exact mass determination 476.0602 (calcd for $C_{21}H_{21}N_2O_6Br$, 476.0583).

Me₂SO Oxidation of 9 to 10. To 5 ml of Me₂SO and 500 mg of sodium bicarbonate, 500 mg of 9 was added and the reaction mixture was heated at 120 °C for 1 h. The Me₂SO was removed under reduced pressure and the residue was dissolved in a mixture of chloroform and water. The chloroform layer was removed, dried, and chromatographed on a silica gel column. The undesired isomer of 9 was eluted with chloroform/benzene (3:1) and 10 was eluted with chloroform, giving 420 mg (80%), mp 186–187 °C, exact mass determination 412.1266 (calcd for $C_{21}H_{20}N_2O_7$, 412.1270).

Conversion of the Aldehyde 10 to the Acetal 11a. To a solution of 200 mg of the aldehyde 10 in 1 ml of acidic methanol, 3 ml of methyl orthoformate was added. The solution was refluxed for 3 h. The excess methyl orthoformate and methanol were removed in vacuo and the residue was recrystallized from acetone, 220 mg (95%), mp 81–83 °C, exact mass determination 458.1710 (calcd for $C_{23}H_{26}N_2O_8$, 458.1688).

Acetal 11b. A solution of 11a (100 mg) in dry tetrahydrofuran was added to lithium aluminum hydride (200 mg) and refluxed for 3 h. The excess lithium aluminum hydride was destroyed with saturated sodium potassium tartrate and the organic layer was separated. The aqueous layer was extracted twice with tetrahydrofuran, the organic layers were combined and dried, and the solvent was removed under

reduced pressure to yield 50 mg of amorphous **11b**. High-resolution mass spectra were unobtainable. The infrared spectrum showed the loss of both the acetate carbonyl and the *N*-cyano bands: NMR (CDCl$_3$) δ 7.3 (1 H, s), 7.1 (1 H, s), 5.95 (2 H, s), 5.6 (1 H, s), 5.5 (1 H, s), 3.3 (3 H, s).

Hydrolysis of 11b. A sample (25 mg) of **11b** was dissolved in tetrahydrofuran/water (1:1) and a drop of 6 N hydrochloric acid was added. The solution was warmed on a steam bath and allowed to stand overnight. On evaporation at room temperature the product appeared as a crystalline solid, 10 mg, mp 205–210 °C dec, NMR [CH$_3$CN/D$_2$O (1/1)] δ 7.2 (1 H, s), 7.4 (1 H, s), 6.2 (2 H, s), 6.0 (1 H, s), 5.8 (1 H, s).

Reduction of 10 mg of the solid with 50 mg of lithium aluminum hydride in tetrahydrofuran for 1 h followed by a standard workup gave lycorine (**6b**, R$_3$ = ^{1}H) identified by comparison of its mass spectrum and infrared spectrum with those of authentic lycorine.

Registry No.—**2a**, 477-20-3; **2b**, 477-19-0; **4a**, 517-99-7; **4b**, 548-11-8; **4c**, 476-29-9; **4d**, 517-78-2; **5**, 29477-83-6; **8**, 2492-05-9; **9**, 58958-43-3; **10**, 58944-33-5; **11a**, 58944-34-6; **11b**, 58944-35-7; **12**, 58958-42-2; *N*-ethyl hemipinimide, 27002-36-4; haemanthamine, 466-75-1; lycorine, 476-28-8; methylpseudolycorine α-epoxide, 58944-36-8; anhydromethylpseudolycorine, 58944-37-9; *o*-acetyl-pluviine, 58944-38-0; cyanogen bromide, 506-68-3.

References and Notes

(1) Abstracted in part from the Ph.D. Dissertations of R.E.H., June 1970, and C.P.C., August 1974. This work was supported in part by funds from the National Institutes of Health (HL-7503).
(2) D. H. R. Barton and T. L. Cohen, "Some Aspects of Phenol Oxidation", in "Festschrift Arthur Stoll", Birkhauser, Basel, Switzerland, 1957, pp 117–143.
(3) W. C. Wildman and D. T. Bailey, *J. Am. Chem. Soc.*, **91**, 150 (1969).
(4) A conversion of norpluviine to galanthine has been reported earlier: G. W. K rby and H. P. Tiwari, *J. Chem. Soc. C*, 676 (1966).
(5) C. Fuganti and M. Mazza, *J. Chem. Soc., Chem. Commun.*, 239 (1972).
(6) C Fuganti, J. Staunton, and A. R. Battersby, *Chem. Commun.*, 1154 (1971).
(7) A nonphenolic aromatic ring, however, does not preclude benzylic oxidation and rearrangement to **2**. Caranine is converted to hippeastrine by *Zephyranthes candida* 0.005% incorporation: N. E. Heimer, Ph.D. Dissertation, Iowa State University, Ames, Iowa, 1968.
(8) N. E. Heimer and W. C. Wildman, *J. Am. Chem. Soc.*, **89**, 5265 (1967).
(9) I. T. Bruce and G. W. Kirby, *Chem. Commun.*, 207 (1968); *Chimia*, **22**, 314 (1968).
(10) C. Fuganti and M. Mazza, *J. Chem. Soc., Chem. Commun.*, 936 (1972).
(11) S. Mizukami, *Tetrahedron*, **11**, 89 (1960).
(12) M. R. Slabaugh and W. C. Wildman, *J. Org. Chem.*, **36**, 3202 (1971).
(13) R W. King, C. F. Murphy, and W. C. Wildman, *J. Am. Chem. Soc.*, **87**, 4912 (˜965).
(14) G. A. Bray, *Anal. Biochem.*, **1**, 279 (1960).
(15) G. W. Kirby and H. P. Tiwari, *Chem. Commun.*, 676 (1966).
(16) "Dictionary of Organic Compounds", Vol. 4, Oxford University Press, London, 1965, p 2096.
(17) W. C. Wildman and C. J. Kaufman, *J. Am. Chem. Soc.*, **77**, 1248 (˜955).
(18) H. M. Fales and W. C. Wildman, *Chem. Ind. (London)*, 561 (1958).
(19) H.-G. Boit, *Chem. Ber.*, **87**, 681 (1954).
(20) T. Kitagawa, W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1066 (1955).
(21) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 163 (1956).
(22) H. M. Fales, L. D. Giuffrida, and W. C. Wildman, *J. Am. Chem. Soc.*, **78**, 4145 (1956).
(23) F. Piozzi, C. Fuganti, R. Mondelli, and G. Ceriotti, *Tetrahedron*, **24**, 1119 (1968).
(24) A. Hunger and T. Reichstein, *Helv. Chim. Acta*, **36**, 824 (1953).

Crystal Structure and Absolute Configuration of Astrocasine Methobromide

W. M. Bright[1]

Chemistry Department, Georgetown University, Washington, D.C. 20007

H. A. Lloyd and J. V. Silverton*

Laboratory of Chemistry, NHLI, National Institutes of Health, Bethesda, Maryland 20014

The determination of the crystal structure of the methanol-solvated methobromide of astrocasine, (C$_{21}$H$_{29}$N$_2$O)$^+$Br$^-$·CH$_3$OH, confirms the molecular structure proposed by one of us and the absolute configuration was found to be the same as that of the biogenetically related alkaloid, astrophylline. Crystal data: orthorhombic, $P2_12_12_1$, a = 7.654 (1), b = 8.678 (1), c = 32.589 (3) Å, Z = 4, d_x = 1.342 g/cm^3, d_m = 1.34 (1) g/cm^3, x-ray intensity data were collected with an automatic diffractometer out to sin θ/λ = 0.624 Å^{-1} (3451 observed and 552 "unobserved" reflections.) The structure was solved using the heavy atom and "phase correction" methods. A final R factor of 3.1% (based on observed reflections) resulted.

Several new alkaloids[2-4] were isolated a few years ago from *Astrocasia phyllanthoides Robinson and Millspaugh*, a shrub belonging to the Euphorbiaceae family and growing in Central America.

A structure (I) was advanced[2] for the predominant alkaloid,

I   II
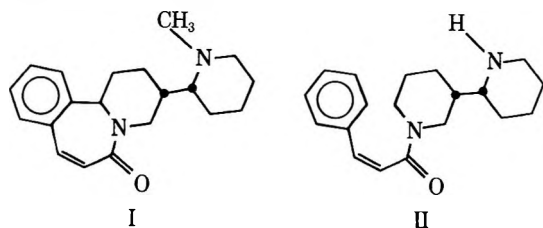
astrocasine (C$_{20}$H$_{26}$N$_2$O, mp 171–172 °C) based mostly on spectral data (ir, uv, NMR, MS) and on a partial degradation. Later[3] the isolation of astrophylline (C$_{19}$H$_{26}$N$_2$O) from the same plant and its characterization as *N-cis*-cinnamoyl-3(*S*)-[2'(*R*)-piperidyl]piperidine (II) provided strong support

for structure I. Astrophylline was the first *cis*-cinnamoyl alkaloid reported in nature and astrocasine is simply its cyclic analogue.

More recently[4] *N*-methylastrophylline, C$_{20}$H$_{28}$N$_2$O, and astrocasidine, C$_{20}$H$_{24}$N$_2$O, related to astrocasine but possessing an additional double bond conjugated with the aromatic ring, were also found in *A. phyllanthoides*.

Two alkaloids related to astrophylline, orensine and isoorensine, had been identified earlier in several *Adenocarpus* species (Leguminosae) by Ribas et al.[5] and both had been assigned *N-trans*-cinnamoyl tetrahydroanabasine skeletons; however, a later revision[6] indicated that isoorensine was the *cis*-cinnamoyl isomer of orensine.

A possible biogenetic pathway for demethylastrocasine and isoorensine,[4] postulating tautomerism of a charged intermediate, has been proposed as a variant of the scheme of Schütte et al.[7] for orensine.

Since the proposed structure for astrocasine contained a new and unique heterocyclic ring system, it seemed worth-

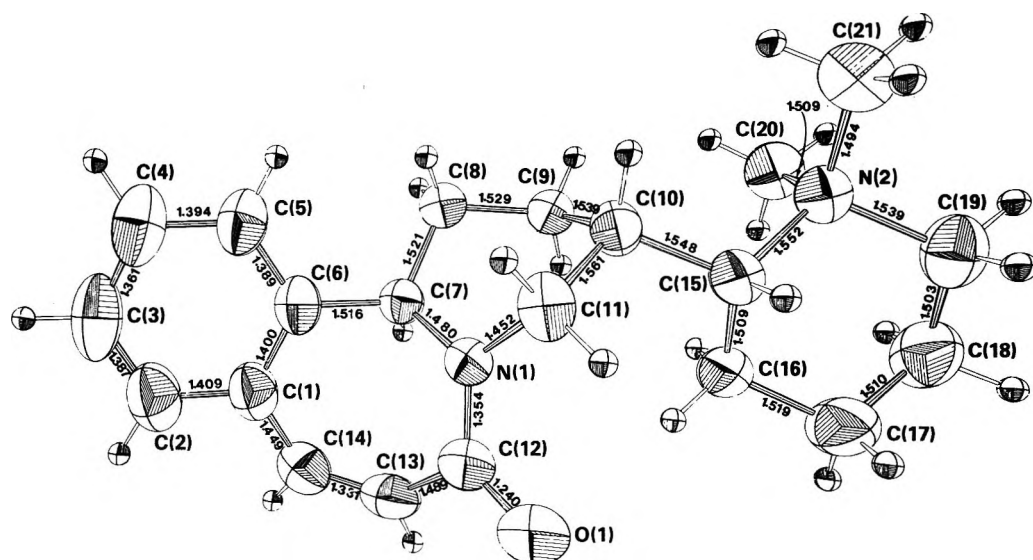**Figure 1.** Crystal conformation and bond lengths of the astrocasine ion (thermal ellipsoids correspond to 50% probability). All bond lengths shown have esd's in the range of 0.003 to 0.006 Å. Hydrogen atom sizes are arbitrary.
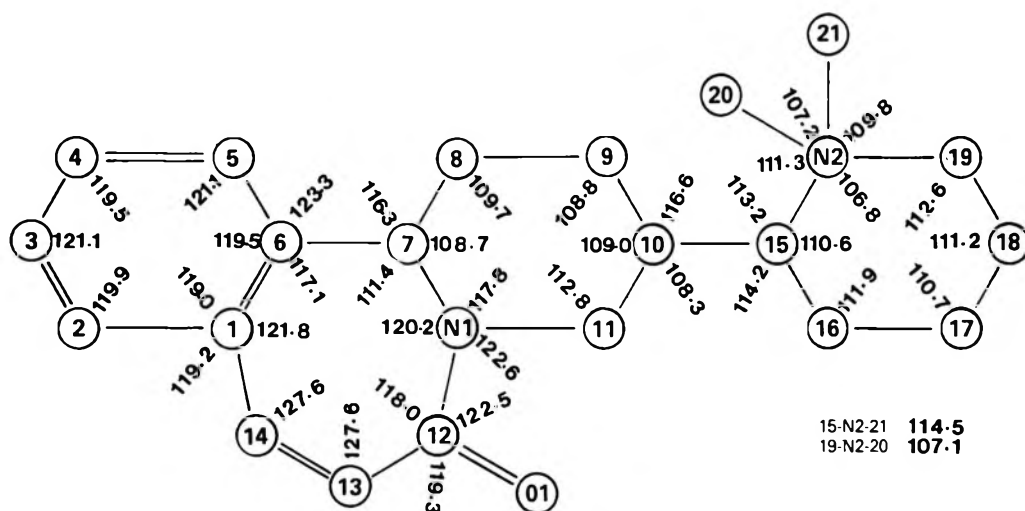

15-N2-21 **114·5**
19-N2-20 **107·1**

Figure 2. Bond angles in the cation. All angles have esd's ≤0.3°.

while to carry out an x-ray study and learn more about the structure, the conformational preferences, and the absolute configuration of this compound.

Discussion

A. Packing of Ions in the Crystal. The astrocasine cation has the three fused rings in a roughly planar conformation with the attached piperidine ring approximately parallel to the rest of the molecule. Most interionic contacts exceed van der Waals distances with only two values being less than 3.5 Å: C(8)–C(13), related by a, has a length of 3.47 Å and C(4)––C(11), related by the screw axis parallel to b, has a length of 3.43 Å. The packing is shown in Figure 4.

The packing of the cations is somewhat different from that which could be expected for un-ionized molecules in that they lie roughly on planes parallel to (010) and are not inclined to screw axes. Electrostatic forces between anions and cations presumably control the packing to a large extent since each bromide ion lies between two quaternary nitrogen atoms (related by the b translation) at distances of 4.239 and 4.880 Å and is also at a distance of 4.405 Å from another ionized nitrogen atom (related by the a screw axis to the first). The solvent molecules occupy spaces between the ions and appear to be held by O–H $\cdots$ Br hydrogen bonds of length 3.269 Å.

The thermal parameters of the solvent molecule indicate that the oxygen atom, despite being hydrogen bonded, is vibrating more than the carbon atom. However, the carbon atom is fairly close to several hydrogen atoms in astrocasine ions and may be held by van der Waals forces. The experiment of reversing the atomic types was tried and led to unrealistic thermal parameters. It is also not impossible that there is some positional disorder since the ease of loss of solvent molecules from the crystal indicates that the forces holding them are weak. The other thermal parameters appear consistent with the packing; the least vibrating parts of the astrocasine ion are those near the ionized nitrogen atom which is presumably held by the ionic forces. The phenyl ring has the largest thermal parameters and it can be seen from Figures 1 and 4 that its maximum vibration is in the ring plane which is in the direction where van der Waals forces are weakest.

B. Molecular Structure and Conformation. The piperidine ring containing the ionized nitrogen atom adopts a reasonably good chair conformation as may be seen from the torsion angles (Figure 3). The ring angle at N(2) is smaller than the tetrahedral angle but the average angle at the other atoms is 111.4° and the average torsion angle is 57.2° which may be compared with the corresponding angles of 111.1 and 55.8° given as best values for cyclohexane by Bucourt and Hainaut.[8] The C–N bond lengths show the expected expan-
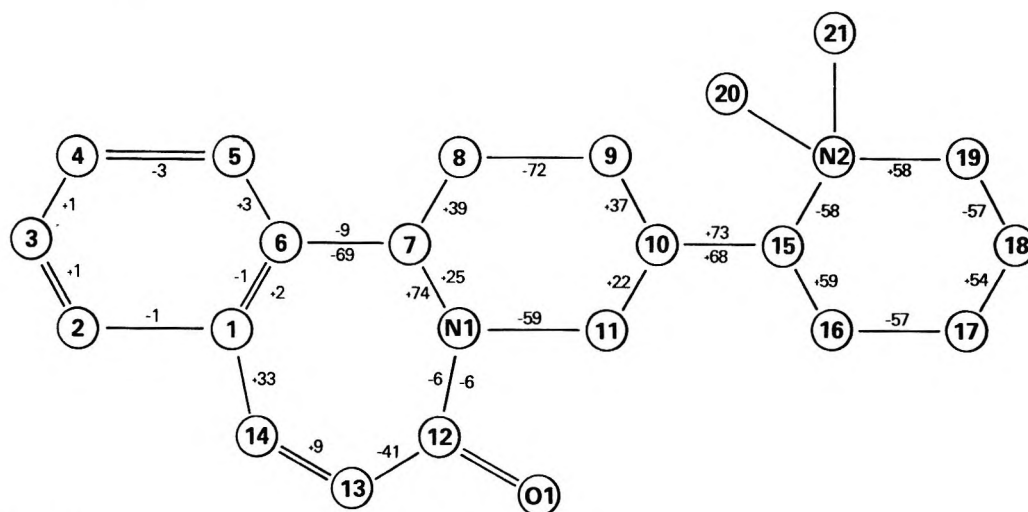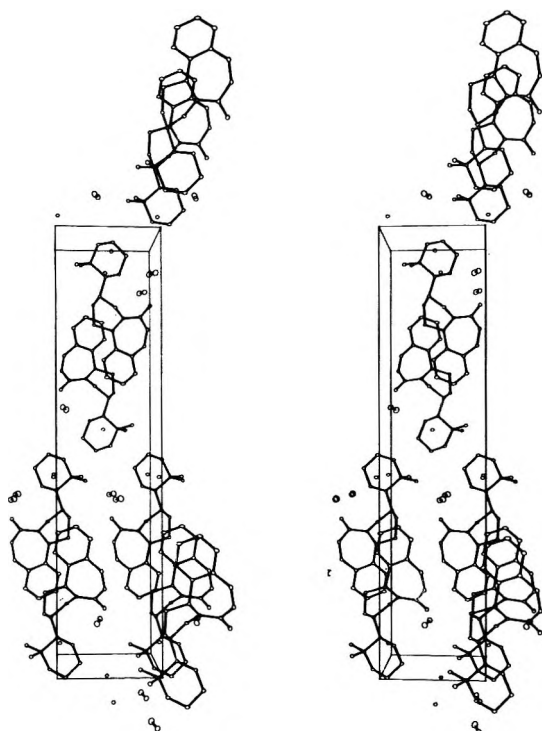
Figure 3. Torsion angles.[22]

Figure 4. Packing diagram. The direction of projection is down a.

sion[9] from the standard un-ionized length[10] of 1.47 Å. The C–C bonds of the piperidine ring do not differ significantly in length (average 1.510 Å) but are all slightly shorter than the usual alkane C–C length of 1.54 Å.

In the rest of the cation, bond lengths are, within the esd's, essentially normal[10] except for the rather long C(10)–C(11) bond [1.561 (4) Å]. The long bond may result from strain introduced by the planar conformation at N(1). The single bond C(13)–C(12) has a length of 1.489 (5) Å, probably indicating some conjugation between the carbonyl carbon C(12) and the doubly bonded C(13) despite the torsion angle of −41°. The bond C(1)–C(14) has a length of 1.449 (5) Å and the conjugation may be greater corresponding to the smaller torsion angle (33°) of the bond. In the amide, the N(1)–C(12) bond is a little longer than the standard value of 1.322 Å but some strain may be present since N(1) is a bridgehead atom in a seven-member ring system.

The seven-membered ring adopts the boat conformation as may readily be seen by comparing the pattern of signs of torsion angles with those given by Bucourt.[11] The conformation is different from the corresponding cycloheptane conformation because of the restriction of rotation about the bonds C(1)–C(6), C(13)–C(14), and N(1)–C(12) and the ring, unlike that of cycloheptane, is essentially rigid. Since the rigidity of the C(1)–C(6) bond forces C(1) and C(6) to be on the same side of the plane of atoms C(7), C(14), and C(13) the adoption of the boat conformation is necessary.

Given the conformation of the seven-membered ring, the torsion angles on either side of the bond N(1)–C(7) have the same sign and thus the fused piperidine ring must adopt a "flexible", i.e., boat or twist-boat, conformation.[12] The pattern of torsion angles indicates the twist-boat conformation. There are two possible twist-boat conformations, but, with the one opposite to that observed, the hydrogen atoms on C(5) and C(19) would be too close to each other.

Experimental Section

The data for astrocasine methobromide were collected first with Mo Kα x-radiation by the stationary-crystal stationary-counter method using a Picker diffractometer. The structure was solved by the heavy atom and "phase correction"[14] methods. Direct phasing by means of the bromine contribution did not give a recognizable picture since the bromine coordinates are very close to ($\frac{1}{2},\frac{1}{2},\frac{1}{2}$) and thus electron density maps phased by the bromine alone have almost exact mmm symmetry. Refinement by block diagonal least-squares methods resulted in an R factor of 9.8%. The results were judged unsatisfactory because of high standard deviations in bond lengths and angles, probably caused by decomposition of the crystal and resolution problems attributable to the long c axis of the crystal.

The data were then recollected on an Enraf-Nonius CAD-4 diffractometer using Cu Kα radiation. Because a determination of the absolute configuration was desired, both hkl and $\bar{h}kl$ were measured

Table I. Atomic Parameters for the Heavier Atoms ($\times 10^4$)[a]

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br (1)	5284 (1)	−5032 (1)	−4459 (1)	68 (1)	58 (1)	61 (1)	−7 (1)	1 (1)	−3 (1)
C (1)	2252 (4)	−6480 (3)	−2705 (1)	71 (2)	64 (2)	54 (2)	9 (2)	−16 (1)	−13 (1)
C (2)	1923 (5)	−6291 (4)	−3127 (1)	100 (3)	84 (2)	60 (2)	24 (2)	−27 (2)	−19 (2)
C (3)	3210 (6)	−5692 (3)	−3381 (1)	133 (3)	66 (2)	47 (2)	18 (2)	−13 (2)	−10 (1)
C (4)	4820 (5)	−5329 (3)	−3232 (1)	128 (3)	50 (2)	54 (2)	−1 (2)	13 (2)	−4 (1)
C (5)	5170 (4)	−5535 (3)	−2816 (1)	94 (2)	52 (1)	49 (1)	−9 (1)	10 (2)	−5 (1)
C (6)	3901 (4)	−6091 (3)	−2551 (1)	65 (2)	48 (1)	47 (1)	1 (1)	−6 (1)	−7 (1)
C (7)	4239 (3)	−6421 (2)	−2101 (1)	39 (1)	49 (1)	44 (1)	−1 (1)	1 (1)	−4 (1)
C (8)	6136 (3)	−6363 (3)	−1963 (1)	42 (1)	70 (2)	48 (1)	−3 (1)	1 (1)	−8 (1)
C (9)	6220 (3)	−6308 (3)	−1494 (1)	39 (1)	64 (2)	48 (1)	3 (1)	−2 (1)	−8 (1)
C (10)	5627 (3)	−4702 (2)	−1351 (1)	48 (1)	47 (1)	42 (1)	−9 (1)	−4 (1)	−2 (1)
C (11)	4107 (4)	−4138 (2)	−1633 (1)	69 (2)	42 (1)	47 (1)	2 (1)	−9 (1)	2 (1)
C (12)	1454 (3)	−5628 (3)	−1791 (1)	43 (1)	75 (2)	62 (2)	15 (1)	−6 (1)	−7 (1)
C (13)	619 (3)	−6835 (4)	−2050 (1)	41 (2)	93 (2)	81 (2)	−2 (2)	−8 (1)	−11 (2)
C (14)	900 (4)	−7122 (4)	−2445 (1)	55 (2)	90 (2)	74 (2)	−3 (2)	−20 (2)	−20 (2)
C (15)	5025 (3)	−4561 (2)	−899 (1)	46 (1)	42 (1)	43 (1)	1 (1)	−8 (1)	−1 (1)
C (16)	3570 (3)	−5650 (3)	−783 (1)	50 (2)	58 (2)	46 (1)	−2 (1)	1 (1)	1 (1)
C (17)	2838 (4)	−5291 (4)	−360 (1)	63 (2)	90 (3)	56 (2)	1 (2)	10 (1)	5 (2)
C (18)	4272 (4)	−5294 (4)	−42 (1)	79 (2)	95 (3)	42 (1)	6 (2)	4 (1)	2 (2)
C (19)	5736 (4)	−4232 (3)	−162 (1)	76 (2)	66 (2)	40 (1)	15 (2)	−10 (1)	−9 (1)
C (20)	7924 (4)	−3460 (3)	−672 (1)	60 (2)	57 (2)	69 (2)	−12 (1)	−17 (1)	−7 (1)
C (21)	7417 (4)	−6175 (3)	−557 (1)	61 (2)	53 (2)	64 (2)	15 (1)	−14 (2)	−4 (1)
C (S)	9377 (7)	−4003 (6)	−3943 (2)	128 (5)	117 (4)	146 (4)	−18 (4)	−36 (4)	−6 (3)
O (S)	9012 (5)	−5650 (5)	−3998 (1)	132 (3)	179 (4)	188 (4)	20 (3)	−45 (3)	50 (3)
O (1)	543 (2)	−4852 (3)	−1554 (1)	53 (1)	116 (2)	84 (1)	31 (2)	−4 (1)	−29 (1)
N (1)	3194 (2)	−5398 (2)	−1833 (1)	45 (1)	52 (1)	43 (1)	5 (1)	−3 (1)	−7 (1)
N (2)	6532 (2)	−4644 (2)	−582 (1)	49 (1)	44 (1)	45 (1)	3 (1)	−8 (1)	−3 (1)

[a] Esd's are given parenthetically and refer to the last figure quoted. The temperature factor used had the form $\exp - 2\pi^2 \cdot (\Sigma_i \Sigma_j U_{ij} a_i{}^* a_j{}^* h_i h_j)$.

Table II. Hydrogen Atom Parameters[a]

Atom	x/a	y/b	z/c	B
1	−989	−786	−257	8.1
2	−920	−651	−325	8.5
3	−698	−551	−366	8.6
4	−420	−488	−341	8.2
5	−363	−532	−270	7.0
6	−619	−747	−205	5.4
7	−327	−734	−205	6.1
8	−327	−549	−208	6.1
9	−457	−706	−137	6.2
10	−260	−648	−139	6.2
11	−339	−398	−139	5.8
12	−673	−351	−146	6.2
13	−542	−340	−183	6.2
14	−28	−747	−191	7.5
15	−548	−348	−87	5.6
16	−736	−562	−98	6.0
17	−594	−670	−77	6.0
18	−804	−603	−28	7.2
19	−768	−426	−36	7.2
20	−621	−499	+22	7.7
21	−527	−635	−1	7.7
22	−471	−318	−16	6.8
23	−337	−427	+5	6.8
24	−257	−243	−68	6.5
25	−116	−348	−46	6.5
26	−153	−368	−94	6.5
27	−200	−640	−81	6.7
28	−174	−617	−33	6.7
29	−345	−697	−50	6.7

[a] Positional coordinates are multiplied by 10^3.

and also used in the refinement. Crystals were mounted approximately along the a axis but, in order to minimize double reflection, were misaligned by about 5° on each goniometer arc. The orientation matrix was determined by the diffractometer. Three standard reflections were measured periodically and, since a significant linear decrease in intensity was observed during data collection, three scaling groups were used. Within each group, the drop in intensities of the standard reflections was about 3%.

Scattering factors for carbon, nitrogen, and oxygen[15] and the bromide ion[16] were taken from the "International Tables for X-Ray Crystallography" and, for bonded hydrogen, from Stewart, Davidson, and Simpson,[17] and calculations were carried out using the XRAY72 system.[18]

Using the previously obtained atomic positional and thermal parameters, the structure was refined for several cycles using a Peterson and Levy[19] type weighting scheme by block diagonal least-squares methods. The function minimized was $\Sigma w \Delta^2$. A difference synthesis showed significant peaks for all hydrogen atoms except for one methyl hydrogen atom, those bonded to the aromatic ring, and those of the solvent molecule. The relatively large thermal parameters of the atoms concerned may explain the difficulty experienced in locating their attached hydrogen atoms but the positions of the missing atoms were calculated where possible. Subsequent refinement to convergence was carried out using a full matrix least-squares approach, and a final R factor of 3.1%[20] resulted (based on observed reflections). Hydrogen atom parameters were not refined but were set at chemically reasonable values consistent with the difference map. Atomic parameters are given in Tables I and II, bond lengths in Figure 1,[21] bond angles in Figure 2, and torsion angles[22] in Figure 3. (The C–O bond length in the solvent molecule is 1.467 (7) Å.)

The absolute configuration was determined by selecting the 23 Friedel pairs of reflections which had the highest significant differences in the observed structure factors and comparing those values with the calculated dispersion-corrected structure factors. Twenty-two of the pairs were consistent with the configuration indicated in I and Figure 1. The anomalous dispersion correction for bromine, with Cu Kα x-radiation, is only ca. 1.5e and thus the observed differences in Friedel pairs are relatively small and absorption errors can account for the single discrepancy. It might also be noted that, at an R factor of ca. 6.5%, the ratio of the R factors for the two configurations also indicated that configuration I was correct.

References and Notes

(1) The work described in the paper was submitted in partial fulfillment of the requirements for the Ph.D. degree (Georgetown University, 1974).

(2) H. A. Lloyd, *Tetrahedron Lett.*, 1761 (1965).
(3) H. A. Lloyd, *Tetrahedron Lett.*, 4537 (1965).
(4) H. A. Lloyd, *An. R. Soc. Esp. Fis. Quim.*, **68**, 769 (1972).
(5) I. Ribas and M. R. Mendes, *An. R. Soc. Esp. Fis. Quim.*, **51**, 55 (1955).
(6) M. Rico, A. Vidal, and I. Ribas, *An. R. Soc. Esp. Fis. Quim.*, **64**, 613 (1968).
(7) H. R. Schütte, K. L. Kelling, D. Knöfel, and K. Mothes, *Phytochemistry*, **3**, 249 (1964).
(8) R. Bucourt and D. Hainaut, *Bull. Soc. Chim. Fr.*, 1366 (1965).
(9) G. Birnbaum, *Acta Crystallogr.*, **23**, 526 (1967).
(10) O. Kennard, "International Tables for X-Ray Crystallography", Vol. III, C. H. Macgillavry and G. D. Rieck, Ed., Kynoch Press, Birmingham, England, 1968, p 275.
(11) R. Bucourt, *Top. Stereochem.*, **8**, 190 (1974).
(12) R. Bucourt, *Top. Stereochem.*, **8**, 173 (1974).
(13) J. V. Silverton, G. W. A. Milne, P. E. Eaton, K. Nye, and G. H. Temme, *J. Am. Chem. Soc.*, **96**, 7429 (1974).
(14) J. Hoppe and J. Gassmann, *Acta Crystallogr., Sect. B*, **24**, 97 (1968).
(15) "International Tables for X-Ray Crystallography", Vol. III, Kynoch Press, Birmingham, England, 1962.
(16) "International Tables for X-Ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974.
(17) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **53**, 205 (1970).
(18) J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, The X-Ray System, Version of June 1972, Technical Report TR-192, Computer Science Center, University of Maryland, 1972.
(19) S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **11**, 70 (1957).
(20) Structure factor table is available from authors, if desired.
(21) C. K. Johnson, ORTEP, Oak Ridge National Laboratory Technical Report-3794, 1965.
(22) The sign convention for torsion angles is that of W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

Structures of Norditerpene Lactones from *Podocarpus* Species

Satish K. Arora, Robert B. Bates,* and Paul C. C. Chou

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Wolfango E. Sanchez L.[1] and Keith S. Brown, Jr.

Centro de Pesquisas de Produtos Naturais I.C.B., Universidade Federal do Rio de Janeiro, Ilha do Fundão, Rio de Janeiro ZC-32, Brazil, and Instituto de Química and Departamento de Zoologia, Instituto de Biologia,[2] Universidade Estadual de Campinas, C.P. 1170 Campinas, São Paulo 13.100, Brazil

M. Neil Galbraith

CSIRO, Division of Applied Organic Chemistry, P.O. Box 4331, Melbourne, Victoria 3001, Australia

Received January 12, 1976

The crystal structure of sellowin B bromohydrin acetate ($C_{20}H_{21}O_7Br$) has been determined. The space group is $P2_1$ with cell dimensions $a = 10.060$ (5), $b = 6.127$ (4), $c = 16.037$ (6) Å, $\beta = 96.02$ (2)°, and $Z = 2$. The structure, solved using MULTAN and refined to $R = 0.053$, indicates sellowin B and related compounds to be 2,3-β rather than 1,2-α epoxides. Earlier chemical results are interpreted in light of the new structure.

In recent years, many norditerpene dilactones showing important biological activities have been isolated from *Podocarpus* species, ancient gymnosperms growing in scattered parts of the southern hemisphere.[3] These compounds are usually highly polar and hydrophilic, heavily oxygenated, and chemically refractory, in spite of the presence of the lactones and (usually) epoxide groups. The small number of interpreted reactions reported[4-7] includes almost exclusively simple functional group derivatization (alcohol to acetate or ketone) and unexpected transformations of the molecules.

Perhaps due to this refractory response to usual chemical reagents, and to unusual spectral characteristics of the compounds as well, recent x-ray analyses have revised the majority of the published structures[3] in the group. Thus, inumakilactone A, long supposed to possess a 1,2-α epoxide in ring A,[6] was shown by x-ray analysis to be in fact a 1,2-β epoxide (1).[8] This structural modification affected, by extension, the accepted constitutions of at least ten other compounds isolated from eight *Podocarpus* species in three continents and New Zealand, including the most widely distributed member of the group, nagilactone C (2).[3,7,8] By x-ray analysis of its *p*-bromobenzoate, podolactone A was shown to possess a 2,3-β epoxide (3)[9] rather than the 1,2-α group widely accepted.[3,10] By extension, at least five additional lactones from three *Podocarpus* species are subject to a similar modification. The present paper confirms that the structure of one of these five, from the Brazilian *P. sellowii*, likewise must be modified from a 1,2-α epoxide to a 2,3-β epoxide. Thus, no ring A epoxide in the series remains with its originally proposed structure, and interpretations of the chemistry of this group in these compounds[4,5] must be revised. Even a ring A alcohol, nagilactone

A, was definitively assigned stereochemistry (4) only after an x-ray analysis.[11] It is also possible that a ring A olefin, podolactone D, could possess a 2,3 rather than a 1,2 double bond; unfortunately, this olefin does not react with peracid to form an epoxide,[12] and the reverse deepoxidation in nagilactone C (2) gave complete saturation of the ring,[4] though in the absence of a neighboring hydroxyl group olefin formation might be favored. The presence of a 2,3 double bond in podolactone D is rendered more probable by the x-ray study[13] which shows the closely related podolide (5) to contain this structural feature.

Reaction of sellowin B (published structure 6)[3,4,14] with *N*-bromoacetamide under forcing conditions, in an attempt to functionalize the double bond and thereby give entry to a three-carbon side chain, gave exclusively a hygroscopic ring A bromohydrin, mp 204–208 °C, which was directly acetylated to a beautifully crystalline bromohydrin acetate. This compound was selected for x-ray analysis over the less satisfactorily crystalline tribromide (olefin dibromide + epoxide bromohydrin) produced by direct bromination of sellowin B.

X-ray analysis of the bromohydrin acetate revealed it to possess structure 7, with the conformation depicted in Figure 1. Figure 2 gives bond lengths and bond angles, Figure 3 packing in the unit cell, Table I atomic coordinates, and Table II torsion angles for the rings in the molecule. The torsion angles reveal that rings A, B, and C approximate chair, 1,2-diplanar (sofa), and 1,3-diplanar conformations.[15] The torsion angles involving the acetate group are C2–C3–O17–C17 (124.7°), C4–C3–O17–C17 (−108.4°), C3–O17–C17–C21 (−174.8°), and C3–O17–C17–O18 (4.0°).
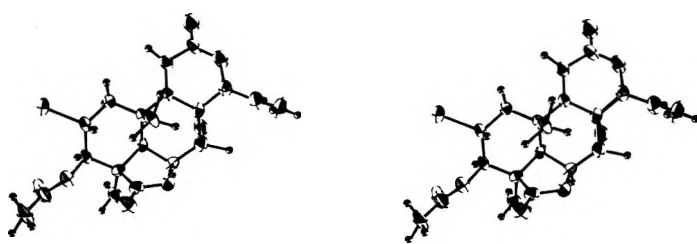
Figure 1. Stereoscopic view of the molecule. Hydrogen atoms are depicted as spheres, and other atoms as 50% probability ellipsoids.

The constitution revealed by the x-ray study of the bromohydrin acetate (**7**) leaves no doubt that the correct structure for sellowin B is **8**, identical with the published structure in all details except for the position and configuration of the ring A epoxide. This corresponds, however, to the modification required in podolactone A (**3**)[9] which can be extended to podolactone C (**9**) because of the extremely close similarity of chemical shifts and coupling constants for the ring A protons in the NMR spectra of the two compounds,[12] and because the two lactones coexist in *P. neriifolius.*

By arguments similar to the above, the revised ring A structure can be extended from sellowin B (**6**) to sellowin A (**10**) and also hallactone B (**11**)[16] which is obtained by oxidation of podolactone C (**9**).[12] The NMR spectra of the latter compound in Me₂SO and pyridine, however, are more suggestive of the presence of at least one β proton on the epoxide;[3] this may be simply another case of the unusual spectral characteristics of these compounds, which seem to obey few of the rules derived from observations on less polar natural products with more scattered functional groups.

The direction of opening of the epoxide ring in sellowin B (**8**) to give after acetylation bromoacetate **7** violates the axial attack rule, and is probably the result of unfavorable steric interactions (C18 methyl group with bromine, C20 methyl group with the developing hydroxyl group) in the transition state leading to the unobserved bromohydrin. The observed
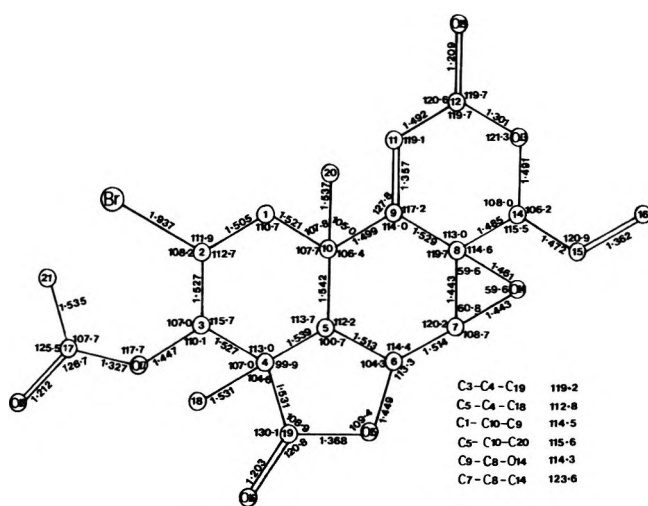
Figure 2. Bond lengths (Å) and bond angles (deg) in the molecule, with standard deviations in Br–C, C–C, and C–O lengths of 0.007, 0.008, and 0.009 Å, respectively, and in Br–C–C, C–C–C, and C–C–O angles of 0.4, 0.5, and 0.5°, respectively.

Figure 3. Stereoscopic view of a unit cell, *b* axis projection, *a* axis horizontal.

<div align="center">Scheme I</div>

sellowin B + trifluoroacetic acid

m/e 203

Table I. Fractional Coordinates ($\times 10^4$ for Nonhydrogens and $\times 10^3$ for Hydrogens) and Estimated Standard Deviations

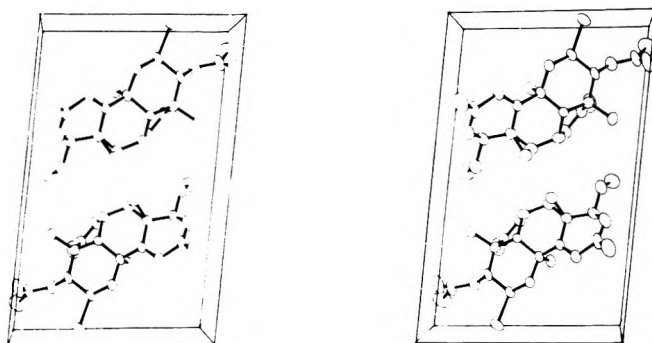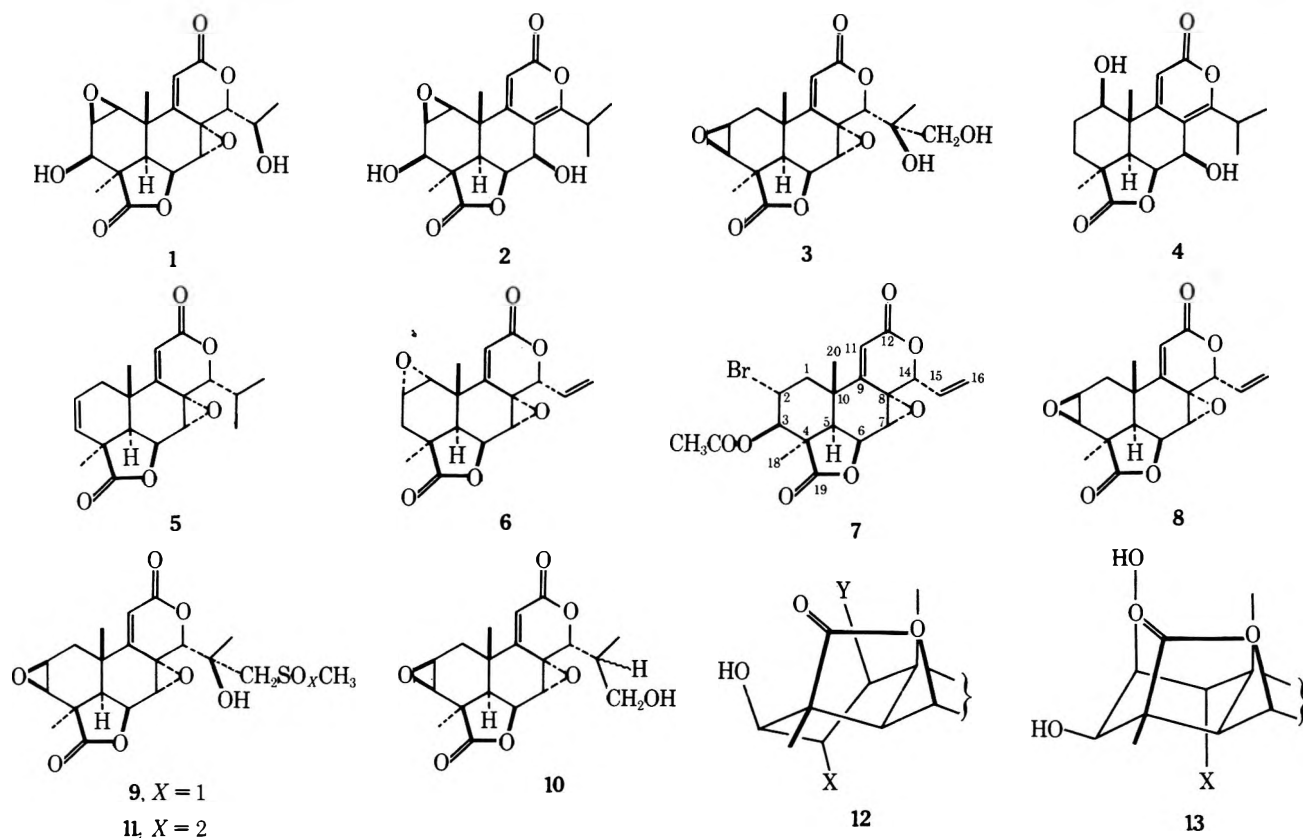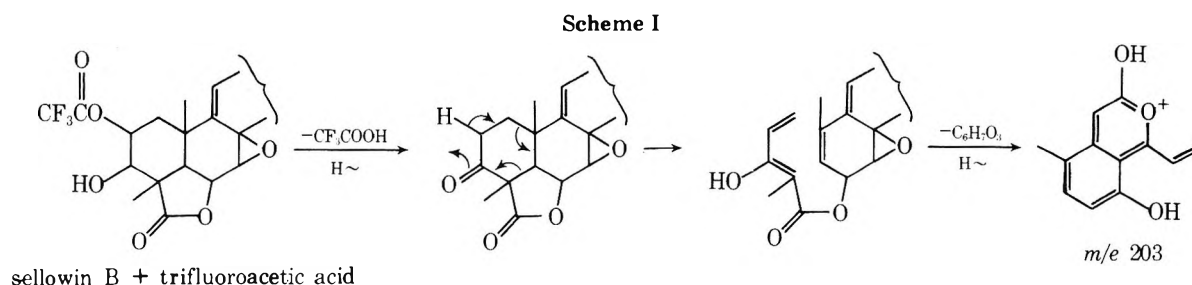| Atom	x/a	y/b	z/c
Br	3479 (1)	1755 (5)	9892 (1)
C1	4982 (6)	1764 (13)	8473 (4)
C2	3939 (6)	456 (13)	8859 (4)
C3	2656 (6)	174 (11)	8269 (4)
C4	2844 (6)	−424 (10)	7365 (4)
C5	4040 (5)	746 (11)	7039 (4)
C6	4197 (7)	−573 (13)	6258 (4)
C7	5536 (8)	−303 (17)	5920 (4)
C8	6573 (6)	993 (11)	6371 (4)
C9	6370 (5)	1889 (12)	7239 (3)
C10	5317 (6)	715 (11)	7661 (4)
C11	7281 (6)	3353 (11)	7582 (4)
C12	8332 (6)	4168 (11)	7070 (5)
O13	8616 (5)	3059 (9)	6420 (3)
C14	8002 (7)	882 (10)	6219 (4)
C15	8253 (7)	389 (17)	5351 (6)
C16	8831 (10)	−1530 (21)	5158 (6)
C17	637 (7)	−970 (19)	8769 (6)
C18	1520 (6)	50 (15)	6835 (4)
C19	3170 (6)	−2788 (12)	7155 (5)
C20	5909 (6)	−1555 (13)	7875 (4)
C21	64 (12)	−2897 (27)	9228 (7)
O14	5690 (5)	1950 (12)	5686 (3)
O15	3927 (5)	−2799 (9)	6494 (3)
O16	8903 (6)	5871 (10)	7243 (4)
O17	1868 (5)	−1480 (11)	8633 (3)
O18	57 (6)	722 (17)	8581 (5)
O19	2814 (6)	−4470 (10)	7448 (5)
H1C1	572 (8)	160 (16)	893 (5)
H2C1	446 (8)	316 (16)	829 (5)
HC2	438 (6)	−133 (11)	893 (4)
HC3	204 (6)	145 (13)	823 (4)
HC5	387 (8)	209 (17)	680 (5)
HC6	351 (10)	−0 (22)	582 (6)
HC7	605 (6)	−114 (12)	531 (4)
HC11	739 (8)	379 (14)	818 (5)
HC14	824 (7)	−27 (14)	651 (4)
HC15	823 (8)	142 (19)	487 (4)
H1C16	885 (9)	−124 (18)	449 (6)
H2C16	882 (8)	−269 (15)	561 (5)
H1C18	154 (6)	−42 (12)	642 (4)
H2C18	120 (6)	195 (11)	678 (4)
H3C18	76 (8)	−63 (16)	697 (5)
H1C20	515 (6)	−272 (13)	821 (4)
H2C20	695 (9)	−124 (18)	811 (6)
H3C20	628 (6)	−239 (12)	741 (4)
H1C21	30 (9)	−460 (20)	920 (5)
H2C21	102 (9)	−299 (20)	916 (5)
H3C21	54 (7)	−266 (16)	975 (5)

Table II. Endocylic Torsion Angles (deg)

Ring	Bond	Angle	Ring	Bond	Angle
A	C1–C2	−57.1	C	C8–C9	30.5
	C2–C3	44.5		C9–C11	6.1
	C3–C4	−38.2		C11–C12	−19.9
	C4–C5	45.5		C12–O13	−5.6
	C5–C10	−57.5		O13–C14	40.8
	C10–C1	63.0		C14–C8	−51.4
B	C5–C6	−41.3	γ-Lactone	C4–C5	37.9
	C6–C7	4.6		C5–C6	−38.2
	C7–C8	6.0		C6–O15	23.0
	C8–C9	19.9		O15–C19	2.3
	C9–C10	−53.8		C19–C4	−26.2
	C10–C5	65.8			

coupling constants[5] must be represented by either **12** or **13** (X = Br, Cl, or OH; Y = OH). **13**, the product of axial attack, fits the observed ^{1}H NMR constants, but so does **12** (Y = OH) provided that it remains predominantly in the twist-boat conformation.

The published mass spectral fragmentation schemes for sellowin B (**8**) and derivatives[4] are not substantially changed by the modification in its structure; even the retro-Diels–Alder cleavage of ring A can proceed in identical fashion through an enol, or in slightly modified form through a ketone, as in Scheme I.

Experimental Section

Sellowin B Bromohydrin Acetate (7). Sellowin B (**8**, 70 mg, mp 316–317 °C) in hot acetone (50 ml) was treated with a 2% aqueous solution of N-bromoacetamide (5 ml), agitating for 6 days at room temperature. The reaction mixture was treated with water (10 ml) and the mixture extracted with chloroform (5 × 15 ml), giving after drying (anhydrous Na$_2$SO$_4$) and evaporation a crude product (77 mg). Crystallization from pyridine gave 73 mg (87%) of poorly crystalline, highly insoluble material: mp 204–208 °C; ir (KBr) ν_{max} 3530 (sharp, strong), 1780, 1730, 1670, 1250, 1095, 1070, 1050, 1025, 1000, 973, 890, 765, 700, 600, and 550 cm^{-1}, with many additional weaker sharp peaks giving a pattern much more complex than that of sellowin B; NMR showing all three vinyl protons in a pattern similar to that of sellowin B, but lacking the epoxide proton signals, giving instead new one-proton peaks near δ 3.8 and 4.0. This compound was not further purified, but was directly acetylated in pyridine (6 ml) and acetic anhydride (2 ml) for 12 h at room temperature. Workup with water (10 ml) and chloroform (5 × 8 ml) gave 74 mg, crystallized from methanol to provide 64 mg (79%): mp 241–243 °C; ir (KBr) ν_{max} 1780, 1730 i, 1720, 1215, 1015, 880, 760, 695 cm^{-1}; MS m/e 452/4 (M$^+$), 410/2 (M − CH$_2$CO), 367/9 (410/2 − CO$_2$ + H), 339/41 (367/9 − CO), 331 (M − Br), 313 (331 − H$_2$O), 213 (base peak)[4]; ^{1}H NMR (100 MHz, Py-d_5) δ 6.46 (1 H s, 11-H), 5.97 (1 H septet, J = 8, 10, 17 Hz, 15-H), 5.66 (1 H d, J = 11 Hz, 3α-H), 5.54 (1 H dd, J = 2, 11 Hz, 16-trans-H), 5.40 (1 H dd, J = 3, 10 Hz, 16-cis-H), 5.36 (1 H d, J = 8 Hz, 14-H), 5.23 (1 H dd, J = 1.5, 4 Hz, 6α-H), 4.74 (1 H ddd, J = 5, 11, 12.5 Hz, 2β-H), 3.97 (1 H d, J = 1.5 Hz, 7β-H), 2.68 (1 H dd, J = 5, 12.5 Hz, 1β-H), 2.38 (1 H d, J = 4 Hz, 5α-H), 2.25 (3 H s, OAc), ~2.2 (1 H t?, J ~ 12.5 Hz, 1α-H), 1.47 and 1.29 (2 × 3 H s, 2 C-Me).

Crystal Structure Determination. Oscillation and Weissenberg photographs of a needle 0.2 × 0.2 × 0.4 mm of **7** indicated monoclinic space group $P2_1$. The cell parameters were found by least-squares fitting of the settings for the four angles of ten reflections on a Picker

product results from ring opening to a twist-boat conformation **12** (X = Br; Y = H), which quickly equilibrates to a chair conformation similar to that depicted in Figure 1. The correction in the stereochemistry of inumakilactone A (**1**)[8] also requires modification of the stereochemistry of its 1,2-epoxide ring opening products, which from the reported ^{1}H NMR

FACS-I diffractometer (Cu Kα, λ = 1.54178 Å, graphite monochromator) to be a = 10.060 (5), b = 6.127 (4), c = 16.037 (6) Å, β = 96.02 (2)°, ρc = 1.53 g/ml, and Z = 2. Intensity data were collected using a scintillation counter with pulse-height analyzer, θ–2θ scan, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10^4 counts/s, and a 2° scan range with a dispersion factor allowing for α_1–α_2 splitting at large 2θ values. Of 1620 independent reflections measured, 1591 > $3\sigma(I)$ were considered observed. Lorentz and polarization corrections were applied, but no correction was made for absorption. No significant decrease was observed in the intensities of standards.

The structure was solved using MULTAN.[17] The first E map revealed Br and seven other atoms. The rest of the nonhydrogen atoms were located by difference synthesis. The structure was refined by full matrix least-squares techniques to a final R of 0.053. Anisotropic thermal parameters were assumed for nonhydrogen atoms, and all hydrogen atoms were located and included in the refinement. The scattering factors used were those of Hanson et al.[18] Anomalous scattering factors were used for bromine, but the absolute configuration was not determined and is assumed to be as established earlier.[14] The refinement was based on F_o, the quantity minimized being $\Sigma w(F_o - F_c)^2$. The weighting scheme used was based on counter statistics,[19] with p = 0.04.

References and Notes

(1) Taken in part from Master's Thesis, CPPN, Nov 1973. Departamento de Quimica, Universidade Federal de Paraiba, João Pessoa, Paraiba 58.000, Brazil.
(2) Present address of latter author.
(3) K. S. Brown, Jr., and W. E. Sánchez L., *Biochem. Syst. Ecol.*, **2**, 11 (1974).
(4) K. S. Brown, Jr., and W. E. Sánchez L., *Tetrahedron Lett.*, 675 (1974).
(5) T. Hayashi, H. Kakisawa, S. Itô, Y. P. Chen, and H.-Y. Hsu, *Tetrahedron Lett.*, 3385 (1972).
(6) S. Itô, M. Kodama, M. Sunagawa, T. Takahashi, H. Imamura, and O. Honda, *Tetrahedron Lett.*, 2065 (1968).
(7) Y. Hayashi, S. Takahashi, H. Ona, and T. Sakan, *Tetrahedron Lett.*, 2071 (1968).
(8) J. E. Godfrey and J. M. Waters, *Aust. J. Chem.*, **28**, 745 (1975).
(9) B. J. Poppleton, *Cryst. Struct. Commun.*, **4**, 101 (1975).
(10) M. N. Galbraith, D. H. S. Horn, J. M. Sasse, and D. Adamson, *Chem. Commun.*, 170 (1970).
(11) Y. Hayashi, T. Sakan, K. Hirotsu, and A. Shimada, *Chem. Lett.*, 349 (1972).
(12) M. N. Galbraith, D. H. S. Horn, and J. M. Sasse, *Chem. Commun.*, 1362 (1971).
(13) S. M. Kupchan, R. L. Baxter, M. F. Ziegler, P. M. Smith, and R. F. Bryan, *Experientia*, **31**, 137 (1975).
(14) W. E. Sánchez L., K. S. Brown, Jr., T. Nishida, L. J. Durham, and A. M. Duffield, *An. Acad. Bras. Cienc., Suppl.*, **42**, 77 (1971).
(15) R. Bucourt, *Top. Stereochem.*, **8**, 159 (1974).
(16) G. B. Russell, P. G. Fenemore and P. Singh, *J. Chem. Soc., Chem. Commun.*, 166 (1973).
(17) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970).
(18) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr., Sect. B*, **17**, 1040 (1964).
(19) P. W. R. Corfield, R. J. Deodens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).

Some Chemical Constituents of the Digestive Gland of the Sea Hare *Aplysia californica*

Chris Ireland, Martha O. Stallard, and D. John Faulkner*

Scripps Institution of Oceanography, La Jolla, California 92093

Janet Finer and Jon Clardy[1]

Ames Laboratory—USERDA and Department of Chemistry, Iowa State University, Ames, Iowa 50010

Received August 4, 1975

The digestive gland of the sea hare *Aplysia californica* contains halogenated metabolites which are obtained from its algal diet. We have isolated three halogenated sesquiterpenes, prepacifenol epoxide (1), the diol 5, and the epoxide 6, and two halogenated monoterpenes 7 and 11, which had not been isolated from algae. The structure of the epoxide 6 was elucidated by single-crystal x-ray diffraction analysis, and the remaining four compounds by chemical and spectroscopic techniques.

We previously reported[2] that the chemical constituents of the digestive gland of the herbivorous opisthobranch mollusc *Aplysia californica* (Cooper) were identical with metabolites of the red algae which form a major portion of the sea hare's diet. In a few instances we were able to demonstrate that chemical transformations had occurred within the digestive gland.[3] We found that the sea hare obtained halogenated sesquiterpenes from *Laurencia* sp. and halogenated monoterpenes from *Plocamium* sp. The mixture of halogenated monoterpenes in *Aplysia* was so complex that we chose to investigate these metabolites from *P. cartilagineum*[4] and *P. violaceum*[5] separately. In recent studies of the chemical constituents of the digestive gland of *Aplysia*, we found

compounds which have not been detected in local red algae. We wish to report the structural elucidations of three sesquiterpenes and two monoterpenes.

During 1973 and 1974, we made three collections of *Aplysia californica* at three locations in the vicinity of La Jolla, Calif. Each collection of *Aplysia* was investigated separately, resulting in three digestive gland extracts having different compositions. In the first collection, the major constituents were sesquiterpenes, while the two later collections each contained a different monoterpene as the major component.

A group of 50 *Aplysia* were collected at Sunset Cliffs, San Diego, Calif., during August 1973, and the digestive glands
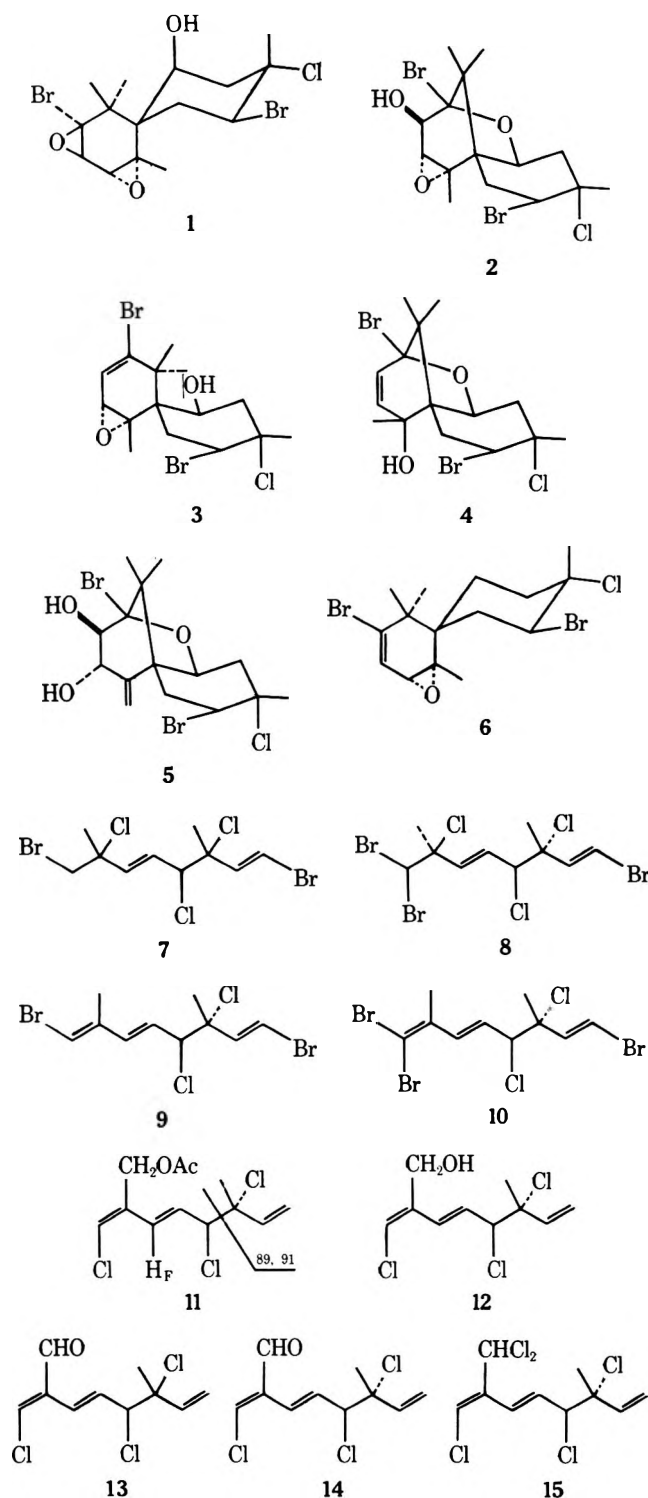
were excised and homogenized in acetone. Chromatography of the ether-soluble material on silica gel led to the isolation of three undescribed crystalline halogenated sesquiterpenes. Prepacifenol epoxide (1),[6] mp 98–99 °C (1% of ether-soluble material), was shown to be an isomer of johnstonol (2), which had previously been isolated from *A. californica* and *L. johnstonii*.[7] The NMR spectrum (220 MHz, CDCl3, Me4Si) of 1 contained signals for four methyl groups at δ 0.95, 1.50, 1.54, and 1.86, two α-epoxy protons at 3.00 and 3.58, one proton α to hydroxyl at 4.00, and an α-bromo proton at 4.64 ppm. The presence of the hydroxyl group was indicated by a band at 3500 cm⁻¹ in the infrared spectrum and a signal in the NMR spectrum at 1.95 ppm which disappeared on D2O treatment. Comparison of the NMR spectrum with those of johnstonol (2) and prepacifenol (3) led to the suggestion of the diepoxide structure for prepacifenol epoxide (1).

Some details of the stereochemistry of prepacifenol epoxide (1) could be deduced from the coupling constants observed in the NMR spectrum. The absence of coupling between the two α-epoxy protons indicated that the epoxide rings were trans to one another. The coupling constants for the proton α to bromine (J = 13.5, 4.0 Hz) and the proton α to hydroxyl (J = 3.5, 3.5 Hz) suggested an equatorial bromine and an axial hydroxyl. This is precisely the stereochemistry which is required if prepacifenol epoxide (1) is to be a precursor to johnstonol (2) in the same way that prepacifenol (3) is related to pacifenol (4).[8]

The structure of prepacifenol (3) had been confirmed by its conversion to pacifenol (4) under mild acid catalysis. In similar manner, prepacifenol epoxide (1) was converted into johnstonol (2) in high yield by treatment with a catalytic quantity of oxalic acid in refluxing methanol for 24 h.

When treated with p-toluenesulfonic acid in benzene, prepacifenol epoxide (1) was converted into the diol 5 in quantitative yield. We had previously encountered the diol 5, mp 172–173 °C, as the most polar product from the chromatography of the ether-soluble material from *Aplysia* (0.05% of ether-soluble material). The diol 5 had also been obtained by Sims et al.[7] by treatment of johnstonol (2) with hydrogen bromide in acetic acid. All spectral data which we have recorded for the diol 5 are completely in accord with the structure proposed by Sims et al.

A third sesquiterpene was obtained from *Aplysia* in low yield (0.1% of ether-soluble material). The epoxide 6, mp 124–125 °C, has the molecular formula C15H21OBr2Cl. The NMR spectrum of 6, which contained an α-epoxy proton at δ 2.95 (J = 3 Hz) coupled to an olefinic proton at 6.23 and an α-bromo proton at 4.68 ppm, was almost identical with the published spectral data for prepacifenol (3). These data, considered in conjunction with the ir spectrum, which lacks a hydroxyl band, strongly suggested that the epoxide 6 differed from prepacifenol (3) only by the absence of the hydroxyl function. Confirmation of this assignment was provided by single-crystal x-ray structure determination.

The epoxide crystallized in space group $P2_12_12_1$ with one molecule per asymmetric unit and unit cell axes a = 12.10 (1) Å, b = 11.593 (6) Å, and c = 11.64 (1) Å. The calculated density of the crystals is 1.59 g/cm³ with one molecule of C15H21OBr2Cl per asymmetric unit. A total of 1344 reflections with θ < 57° were measured on a Syntex P21 four-circle automated diffractometer using Cu Kα radiation (λ = 1.5418 A) and an ω-scan technique with a minimum scan speed of 2°/min. Of these, 1285 of the reflections were judged observed using the criteria [Fo ≥ 3σ (Fo)].

The Patterson map calculated from the data was easily deconvoluted to give the fractional coordinates of the two bromine atoms.[9] Two subsequent electron density map calculations served to locate all remaining nonhydrogen atoms. Refinement of the structure proceeded routinely, giving a final residual index of 0.085. Anisotropic temperature factors were assigned to all nonhydrogen atoms. Included in the final model were 11 nonmethyl hydrogens. These were assigned isotropic temperature factors, and both their positions and temperature factors were held fixed during refinement.

In order to determine the absolute configuration of the molecule, the model was also refined using a complete data set of Friedel pairs and correcting for anomalous scattering by the bromines and chlorines. The original model refined to a residual index of 0.085 while its mirror image refined to a significantly higher residual, 0.088, a statistically significant difference.[10] Figure 1 shows a computer-generated drawing of 6. In general, bond distances and angles agree well with generally accepted values.[11]

A second batch of 24 *Aplysia* was collected at Cardiff, 15 miles north of La Jolla, Calif., in June 1974. The ether-soluble
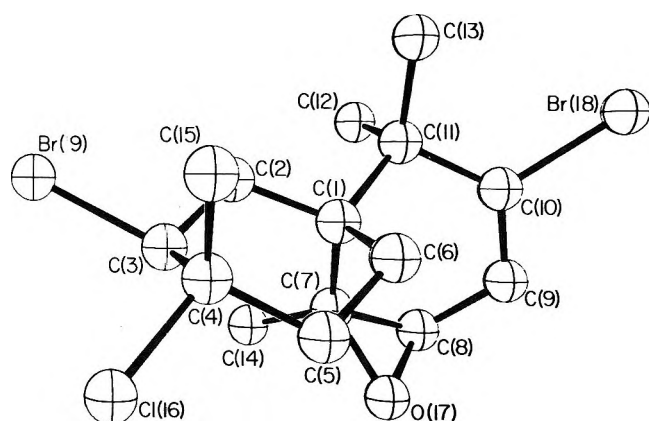
Figure 1. A computer-generated perspective drawing of 6. Hydrogen atoms are omitted for clarity.

material from this sample contained a previously undescribed halogenated monoterpene as the major component (7.5% of ether-soluble material). The monoterpene 7, obtained as an oil which crystallized from ethanol at -10 °C, had the molecular formula $C_{10}H_{13}Br_2Cl_3$. The mass spectrum did not exhibit a molecular ion, the highest peaks being a cluster at m/e 361, 363, 365, 367 due to the $M^+ - Cl$ ion. The mass spectrum also contained a $(C_4H_5BrCl)\cdot^+$ cluster at m/e 167, 169, 171, identical with the base peak of the known monoterpene 8^{12} and assigned to the ion indicated (Figure 2). The NMR spectrum contained two methyl singlets at δ 1.78 and 1.83, an AB quartet at 6.36 and 6.51 ($J = 13$ Hz) assigned to the vinyl bromide group, an AMX system at 4.54 ($J = 8$ Hz), 5.89 ($J = 16$ Hz), and 6.00 ($J = 16, 8$ Hz) assigned to a $-CH=CHCHCl-$ group, and a two-proton singlet at 3.65 ppm. The NMR spectrum of the monoterpene 7 was remarkably similar to that of monoterpene 8, with the notable exception that a one-proton singlet at 5.76 ppm had been replaced by a two-proton singlet at 3.65 ppm. We therefore propose that monoterpene 7 differs from the known monoterpene 8 by replacement of the $-CHBr_2$ group by a $-CH_2Br$ group. The coupling constants exhibited by the vinyl protons indicated that both olefinic bonds were trans.

Despite the persuasive arguments of analogy, it was difficult to assign specific locations for the halogen atoms.[13] However, comparison of the mass spectra of monoterpenes 7 and 8 revealed that the major peaks in both spectra can be rationalized using identical mechanisms (Figure 2) only when the halogen atoms of 7 are arranged as shown. In particular, the peaks at m/e 115, 117 in the spectrum of 7, corresponding to peaks at m/e 193, 195, 197 in the spectrum of 8, strongly suggest that there is a bromine atom at C-8, rather than at C-4 or C-7. The monoterpenes 9 and 10, which are related to 7 and 8, respectively, by loss of the C-8 hydrogen and the C-7 chlorine, have been isolated from *P. cartilagineum*.[4]

Two large *Aplysia* were collected at Casa Cove, La Jolla, Calif., in July 1974. The major component (16% of ether-soluble material) of the digestive gland extract was a halogenated monoterpene acetate 11 (ir 1740 cm^{-1}). The mass spectrum exhibited a strong cluster at m/e 89, 91, which has been assigned to $(C_4H_6Cl)^+$ ion indicated. The uv absorption at 259 nm was indicative of a halogenated diene system similar to that found in a number of the metabolites of *Plocamium cartilagineum*. The NMR spectrum contained a methyl singlet at δ 1.72, an acetoxy singlet at 2.00, the three signals of a vinyl group at 5.23, 5.36, and 6.02, an AMX system at 4.50 ($J = 9$ Hz), 6.02 ($J = 9, 16$ Hz), and 6.68 ($J = 16$ Hz), an AB quartet at 4.67 and 4.74 ($J = 13$ Hz) due to the nonequivalent protons of the $-CH_2OAc$ group, and a one-proton singlet at 6.36 ppm. The spectral data allow only one gross structure to be assigned to the acetate 11.
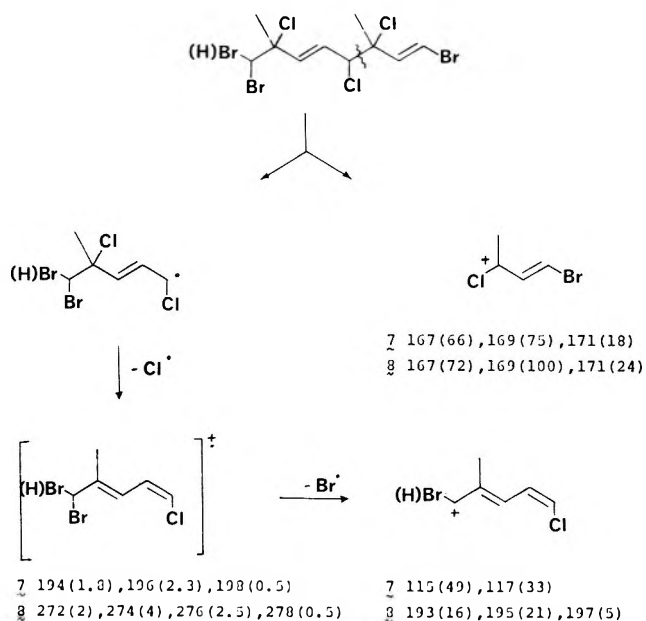
Figure 2. Mass spectral fragmentation of monoterpenes 7 and 8.

Hydrolysis of the acetate 11 with 0.16% methanolic potassium hydroxide solution gave the corresponding alcohol 12 (ir 3600 cm^{-1}) in good yield. The NMR spectrum of the alcohol 12 was similar to that of the acetate 11, except that the signals at δ 4.67 and 4.74 were replaced by a two-proton singlet at 4.31 ppm and the acetoxy singlet was absent.

The assignment of the stereochemistry of 11 and 12 depends on the empirical rules developed for the assignment of stereochemistry for *Plocamium cartilagineum* metabolites using NMR spectral data.[4] The chemical shifts of the methyl signals suggested the erythro configuration at carbons 3 and 4. The chemical shifts of proton H_f (δ 6.68 and 6.70 ppm) indicated that the 7,8 double bond has the E geometry.

While this research was in progress, the gross structure of cartilagineal (13), a metabolite of *Plocamium cartilagineum*, was described.[14] We therefore oxidized the alcohol 12 with manganese dioxide in hexane to obtain the corresponding aldehyde 14. Owing to fairly rapid decomposition[15] of this sample, we were unable to arrange a direct comparison with cartilagineal. The NMR spectrum of the aldehyde 14 contained a methyl singlet at δ 1.74, three signals of the vinyl group at 5.24, 5.40, and 6.05, an AMX system at 4.46 ($J = 9$ Hz), 6.49 ($J = 15$ Hz), and 7.11 ($J = 9, 15$ Hz), a vinyl proton singlet at 7.02, and an aldehyde proton at 9.52 ppm. The chemical shift (9.04 ppm) of the aldehyde proton in cartilagineal (13) differs substantially from that of the aldehyde proton in 14, indicating that the aldehyde 14 could be a stereoisomer of cartilagineal, but it should be noted that the spectra were recorded in different solvents.

Although the new compounds described in this paper are closely related to known algal metabolites, they have not been found in specimens of *Laurencia* and *Plocamium* collected locally. Over 200 samples of *Plocamium cartilagineum* have been collected from various depths and locations. Although all samples contained 8, examination of the gas–liquid chromatography traces and selected GC–mass spectral analyses did not reveal the presence of 7 and 11. The close relationships between 7 and 8 and between 11 and cartilagineal (13) and the pentachloro monoterpene 15, found in *P. cartilagineum*,[4] coupled with the failure to locate the compounds in *P. cartilagineum*, may indicate transformations within the digestive gland. More likely, however, is the possibility of an undiscovered source of halogenated monoterpenes among the red algae which abound in the La Jolla region or the presence of different chemical strains of *P. cartilagineum*.

The isolation of the chamigrenes **1, 5,** and **6** from *Aplysia* but not from local[16] *Laurencia* species shows the value of studying a herbivore rather than the algal species that comprise its diet. The extract from which these compounds were isolated also contained very much larger quantities of pacifenol (**4**) and johnstonol (**2**). In order to have obtained similar quantities of pacifenol (**4**) and johnstonol (**2**) from plant sources, we would have had to expend considerably greater effort. The chamigrenes which occur in small quantities in *Aplysia* could very easily be overlooked when studying a *Laurencia* species.

We wish to suggest that the epoxide **6** is the biosynthetic precursor of prepacifenol (**3**) and is the missing link between the more simple halogenated chamigrenes[17] and pacifenol (**4**) and johnstonol (**2**). Prepacifenol epoxide **1** is the obligatory precursor to johnstonol (**2**). We were rather surprised to find prepacifenol epoxide (**1**) in the digestive gland extract, since the compound is very sensitive to acid-catalyzed conversion to johnstonol (**2**). It is not possible to determine whether the conversion of prepacifenol epoxide (**1**) first to johnstonol (**2**) and then to the diol **5** is simply a chemical reaction controlled by the pH of the digestive gland or is an enzyme-controlled reaction. We have some preliminary evidence that the more polar diol **5** can be transported to the skin of *Aplysia*, where it may be employed as a chemical deterrent.[18]

Experimental Section

Commercially available chemicals were used without further purification unless otherwise stated. All solvents were either spectral grade or redistilled prior to use. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on Varian HR-220 or EM-360 spectrometers; chemical shifts are expressed as values in parts per million relative to tetramethylsilane (0). Infrared spectra were recorded on a Perkin-Elmer 700 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 402 instrument. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. High-resolution mass spectra were measured by Beth Irwin, Department of Chemistry, UCLA.

Collections. *Aplysia californica* were collected intertidally from three different habitats: (1) Sunset Cliffs, August 1973, (2) Cardiff, June 1974, (3) Casa Cove, July 1974. The organisms from the different locations were extracted separately.

Typical Extraction. The *Aplysia* were anesthetized by injection of 10 ml of a saturated magnesium chloride solution 2 cm behind the rhinophores. The *Aplysia* were dissected to remove the digestive gland. The digestive glands were homogenized in acetone in a Waring blender and the resulting suspension was filtered through a pad of Celite to remove the solids. The solids were rehomogenized in acetone and allowed to stand for 18 h. The second suspension was filtered and both extracts were combined. The solvent was evaporated in vacuo, and the residue was partitioned between ether and water. The ether solution was dried over anhydrous sodium sulfate and the solvent removed to obtain a black oil.

Aplysia **Collected at Sunset Cliffs.** The digestive glands of 50 adult *Aplysia* were homogenized and extracted to obtain the ether-soluble oil (32 g). A portion of the oil (30 g) was applied to a 6 × 90 cm column of Silicar CC-7 prepared in distilled hexane. Material was eluted from the column with mixtures of hexane, benzene, and ether, allowing the polarity to gradually increase.

The Epoxide (6). The material (0.390 g) eluted with 40% benzene in hexane was rechromatographed on alumina plates (20 × 20 × 0.15 cm) prepared from EM aluminum oxide PF-254, type E. Development with 20% CH$_2$Cl$_2$ in hexane permitted resolution of two bands. The band of lower R_f yielded pure 7-chloro-3,7-dimethyl-1,4,6-tribromo-1-octen-3-ol[19] (330 mg). The more mobile band solidified on evaporation of solvent and was recrystallized from pentane to give colorless crystals of the epoxide (30 mg): mp 125 °C; NMR (CCl$_4$/Me$_4$Si) δ 1.17 (s, 3 H), 1.20 (s, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 2.05–2.50 (m, 6 H), 2.95 (d, 1 H, J = 3.5 Hz), 4.68 (dd, 1 H, J = 13, 5 Hz), 6.23 (d, 1 H, J = 3 Hz); mass spectrum *m/e* 410, 412, 414, 416 (M$^+$); high-resolution mass measurement M$^+$ 409.9648, C$_{15}$H$_{21}$OBr$_2$^{79}Cl^{35} requires 409.9649.

Prepacifenol Epoxide (1). The material eluted with 50% benzene in hexane (0.5 g) was recrystallized from pentane to yield colorless crystals of prepacifenol epoxide (300 mg): mp 98 °C; ir (CCl$_4$) 3650 cm^{-1}; NMR (CCl$_4$/Me$_4$Si) δ 0.95 (s, 3 H), 1.50 (s, 3 H), 1.54 (s, 3 H), 1.86 (s, 3 H), 1.96 (d, 1 H, J = 6 Hz), 2.09 (d of dd, 1 H, J = 13.5, 4, 1.6 Hz), 2.45 (d, 2 H, J = 3.5 Hz), 2.50 (t, 1 H, J = 13.5 Hz), 3.00 (s, 1 H), 3.58 (s, 1 H), 4.00 (d of dd, 1 H, J = 6.0, 3.5, 1.6 Hz), 4.64 (dd, 1 H, J = 13.5, 4 Hz); mass spectrum *m/e* 442, 444, 446, 448 (M$^+$), 426, 428, 430, 432, (M$^+$ − 0), 424, 426, 428, 430 (M$^+$ − H$_2$O), 407, 409, 411 (M$^+$ − C·); high-resolution mass measurement M$^+$ 441.9548, C$_{15}$H$_{21}$O$_3$Br$_2$^{79}Cl^{35} requires 441.9547.

The Diol (5). The fraction eluted with ether (0.05 g) was rechromatographed on alumina plates (20 × 20 × 0.15 cm) prepared from EM aluminum oxide PF-254, type E. Development with ether allowed resolution of one major band. The solid obtained upon evaporation of solvent was recrystallized from carbon tetrachloride to yield the diol **5** (15 mg): mp 172–173 °C; NMR (CDCl$_3$/Me$_4$Si) δ 0.91 (s, 3 H), 1.39 (s, 3 H), 1.83 (s, 3 H), 4.29 (s, 1 H), 4.55 (dd, 1 H), 4.79 (s, 1 H), 5.07 (dd, 1 H), 5.39 (s, 1 H), 5.58 (s, 1 H).

Conversion of Prepacifenol Epoxide to Johnstonol. Prepacifenol epoxide (20 mg) was dissolved in anhydrous methanol (5 ml) under a nitrogen atmosphere. One crystal of oxalic acid was added, and the solution was refluxed for 24 h. After addition of water (5 ml) the solution was partitioned between ether and 5% sodium bicarbonate solution. The ether layer was dried over sodium sulfate and the solvent evaporated to yield a solid. The solid was recrystallized from carbon tetrachloride to give colorless needles that were identical in every respect with johnstonol.

Conversion of Prepacifenol Epoxide to the Diol 5. A solution of *p*-toluenesulfonic acid (one crystal) in benzene (20 ml) was refluxed for 1 h in a Dean-Stark apparatus to remove any moisture. Prepacifenol epoxide (10 mg) was added, and refluxing was continued for 0.5 h. The cooled solution was washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and evaporated to a solid. The solid was recrystallized from carbon tetrachloride to give the diol **5** as the only product.

Conversion of Johnstonol to the Diol 5. A solution of *p*-toluenesulfonic acid (1 mg) in benzene (20 ml) was refluxed for 1 h in a Dean-Stark apparatus. Johnstonol (30 mg) was added, and refluxing was continued for 0.5 h. The organic layer was washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and evaporated to yield a solid. Recrystallization from carbon tetrachloride gave the diol **5** (28 mg).

Aplysia **Collected at Cardiff.** The digestive glands of 24 adult *Aplysia* were homogenized and extracted as described previously to yield the ether-soluble oil (11 g). A portion of this oil (10 g) was applied to a 2.5 × 30 cm column of Silicar CC-7 prepared in distilled hexane. The material was eluted from the column with mixtures of hexane and benzene of increasing polarity.

trans,trans-1,8-Dibromo-3,7-dimethyl-3,4,7-trichloro-1,5-octadiene (7). The material eluted with 40% benzene in hexane (1.3 g) was rechromatographed on alumina plates (20 × 20 × 0.15 cm) prepared from EM aluminum oxide PF-254, type E. Development with hexane gave a band at R_f 0.3. The resulting oil crystallized on standing and was recrystallized from MeOH to give needles of **7** (0.75 g): mp 20 °C; NMR (CCl$_4$/Me$_4$Si) δ 1.78 (s, 3 H), 1.83 (s, 3 H), 3.65 (s, 2 H), 4.54 (d, 1 H, J = 8 Hz), 5.89 (d, 1 H, J = 16 Hz), 6.00 (dd, 1 H, J = 16, 8 Hz), 6.36 (d, 1 H, J = 13 Hz), 6.51 (d, 1 H, J = 13 Hz); mass spectrum *m/e* 361, 363, 365, 367 (M$^+$ − Cl), 167, 169, 171 (C$_4$H$_5$BrCl$^+$), base peak 91 (C$_7$H$_7$$^+$); high-resolution mass measurement M$^+$ 360.8762, C$_{10}$H$_{13}$Br$_2$^{79}Cl$_2$^{35} (M$^+$ − Cl) requires 360.8760. Anal. Cl/Br ratic 1.68, C$_{10}$H$_{13}$Br$_2$Cl$_3$ requires 1.5.

Aplysia **Collected at Casa Cove.** The digestive glands of two adult *Aplysia* were homogenized and extracted in the manner described previously to yield an ether-soluble oil (6.89 g). A portion of this oil (6 g) was applied to a 2.5 × 30 cm column of Silicar CC-7 prepared in CCl$_4$. Three 200-ml fractions were collected.

7-Acetoxymethylene-3-methyl-3,4,8-trichloro-1,5,7-octatriene (11). The second and third fractions (2 g) were subjected to reverse phase high performance liquid chromatography, using a 4 ft × 0.375 in. c.d. column of Bondapak C$_{18}$/Porosil B (37–75 μ) with 60% CH$_3$CN/H$_2$O eluent. The resulting fractions were extracted with pentane. Combined pentane layers were dried over sodium sulfate and the solvent evaporated in vacuo to yield the acetate **11** (1.0 g): λ$_{max}$ (CCl$_4$) 259 nm; ir 1740 cm^{-1}; NMR (CCl$_4$) δ 1.72 (s, 3 H), 2.0 (s, 3 H), 4.50 (d, 1 H, J = 9 Hz), 4.67 (d, 1 H, J = 13 Hz), 4.74 (d, 1 H, J = 13 Hz), 5.36 (d, 1 H, J = 17 Hz), 6.02 (dd, 1 H, J = 17, 10 Hz), 6.02 (dd, 1 H, J = 16, 9 Hz), 6.36 (s, 1 H), 6.68 (d, 1 H, J = 16 Hz); mass spectrum *m/e* 89, 91 (C$_4$H$_6$Cl$^+$), base peak 43 (C$_2$H$_3$O$^+$); high-resolution mass measurement M$^+$ 296.0138, C$_{12}$H$_{15}$O$_2$Cl$_3$^{35} requires 296.013757.

7-Hydroxymethylene-3-methyl-3,4,8-trichloro-1,5,7-octa-

triene (12). The acetate (75 mg) was dissolved in anhydrous methanol (5 ml) under a nitrogen atmosphere. The solution was cooled to 0 °C using an alcohol–ice bath. Methanolic potassium hydroxide solution (1%, 1 ml) was added and the solution stirred for 1 h. The reaction mixture was poured into ether, then washed with 5% hydrochloric acid. The ether layer was dried over sodium sulfate to a residue. The residue was chromatographed on silica plates (20 × 20 × 0.15 cm) prepared from EM silica gel PF-254 which were developed with 25% ether in hexane to obtain the alcohol 12 (40 mg): R_f 0.25; λ_{max} (CCl$_4$) 260 nm; ir 3600 cm^{-1}; NMR (CCl$_4$/Me$_4$Si) δ 1.75 (s, 3 H), 4.31 (s, 2 H), 4.51 (d, 1 H, J = 9 Hz), 5.26 (d, 1 H, J = 10 Hz), 5.39 (d, 1 H, J = 17 Hz), 6.05 (dd, 1 H, J = 17, 10 Hz), 6.05 (dd, 1 H, J = 16, 9 Hz), 6.32 (s, 1 H), 6.70 (d, 1 H, J = 16 Hz); mass spectrum m/e 165, 167, 169 (C$_6$H$_7$OCl$_2^+$), base peak 129, 131 (C$_6$H$_6$OCl$^+$), 89, 91 (C$_4$H$_6$Cl$^+$); high-resolution mass measurement M$^+$ 254.0031, C$_{10}$H$_{13}$OCl$_3^{35}$ requires 254.0032.

7-Formyl-3-methyl-3,4,8-trichloro-1,5,7-octatriene (14). The alcohol (39 mg) and manganese dioxide were stirred in hexane at room temperature for 24 h. The solution was filtered through Whatman paper to remove solids. The hexane was evaporated in vacuo to a residue. The residue was chromatographed on silica plates (20 × 20 × 0.15 cm) prepared from EM silica gel PF-254. Development with 25% ether in hexane gave the pure aldehyde (15 mg): R_f 0.3; λ_{max} (CCl$_4$) 264 nm; NMR (CCl$_4$/Me$_4$Si) δ 1.74 (s, 3H), 4.46 (d, 1 H, J = 9 Hz), 5.24 (d, 1 H, J = 10 Hz), 5.40 (d, 1 H, J = 16 Hz), 6.05 (dd, 1 H, J = 16, 10 Hz), 6.49 (dd, 1 H, J = 15, 2 Hz), 7.02 (s, 1 H), 7.11 (dd, 1 H, J = 15, 9 Hz), 9.52 (d, 1 H, J = 2 Hz); mass spectrum m/e 252, 254, 256, 258 (M$^+$), 217, 219, 221 (M$^+$ − Cl), 181, 183 (C$_{10}$H$_{10}$OCl$^+$), base peak 89, 91 (C$_4$H$_6$OCl$^+$); high-resolution mass measurement M$^+$ 251.9875, C$_{10}$H$_{11}$OCl$_3^{35}$ requires 251.9875.

Supplementary Material Available. A listing of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Camille and Henry Dreyfus Teacher–Scholar Grant Awardee, 1972–1977, and Fellow of the Alfred P. Sloan Foundation, 1973–1975.
(2) M. O. Stallard and D. J. Faulkner, *Comp. Biochem. Physiol. B*, **49**, 25 (1974).
(3) M. O. Stallard and D. J. Faulkner, *Comp. Biochem. Physiol. B*, **49**, 37 (1974).
(4) J. S. Mynderse and D. J. Faulkner, *Tetrahedron*, **31**, 1963 (1975).
(5) (a) J. S. Mynderse and D. J. Faulkner, *J. Am. Chem. Soc.*, **96**, 6771 (1974); (b) J. S. Mynderse, D. J. Faulkner, J. Finer, and J. C. Clardy, *Tetrahedron Lett.*, 2175 (1975).
(6) Preliminary communication: D. J. Faulkner, M. O. Stallard, and C. Ireland, *Tetrahedron Lett.*, 3571 (1974).
(7) J. J. Sims, W. Fenical, R. M. Wing, and P. Radlick, *Tetrahedron Lett.*, 195 (1972).
(8) J. J. Sims, W. Fenical, R. M. Wing, and P. Radlick, *J. Am. Chem. Soc.*, **95**, 972 (1973).
(9) 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.
(10) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).
(11) Tables of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors will be found in the microfilm edition.
(12) D. J. Faulkner, M. O. Stallard, J. Fayos, and J. Clardy, *J. Am. Chem. Soc.*, **95**, 3413 (1973).
(13) We have isolated, but were unable to fully purify and characterize, a small quantity of a monobrominated monoterpene, C$_{10}$H$_{14}$Cl$_3$Br, having the spectral data expected for structure i: NMR (CDCl$_3$) δ 1.80 (s, 3 H), 1.82

i

(s, 3 H), 3.68 (s, 2 H), 4.62 (d, 1 H, J = 9 Hz), 5.25 (d, 1 H, J = 10 Hz), 5.37 (d, 1 H, J = 15 Hz), 5.96 (m, 2 H), 6.02 (dd, 1 H, J = 15, 10 Hz); mass spectrum m/e (rel intensity) 283, 285, 287, 289 (M − Cl)$^+$, 115 (61), 117, 89 (100), 91.
(14) P. Crews and E. Kho, *J. Org. Chem.*, **39**, 3303 (1974).
(15) The aldehyde 12 undergoes an autocatalytic decomposition, with loss of hydrogen chloride, to give a tetraene (uv 328 nm) which rapidly decomposes to a complex mixture of products.
(16) *Laurencia johnstonii*, the major source of johnstonol (2) and prepacifenol epoxide (1), is found in the Gulf of California. Prepacifenol epoxide (1) has not been isolated from *L. pacifica*, although this local species is known to contain johnstonol (2).
(17) B. M. Howard and W. Fenical, *Tetrahedron Lett.*, 1687 (1975).
(18) M. Stallard, Ph.D. Thesis, University of California, San Diego.
(19) D. J. Faulkner and M. O. Stallard, *Tetrahedron Lett.*, 1171 (1973).
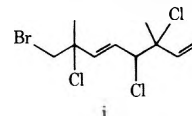
Cyclic Polysulfides from the Red Alga *Chondria californica*

Stephen J. Wratten and D. John Faulkner*

Scripps Institution of Oceanography, La Jolla, California 92093

Received February 12, 1976

The antibiotic activity of the red alga *Chondria californica* is due to a mixture of cyclic polysulfides and their oxidation products. We have identified 1,2,4-trithiolane, 1,2,4,6-tetrathiepane, 1,2,3,5,6-pentathiepane, 1-oxo-1,2,4-trithiolane, 4-oxo-1,2,4-trithiolane, 4-dioxo-1,2,4,6-tetrathiepane, and a 12-membered heterocycle containing eight sulfur atoms.

Cyclic polysulfides are relatively uncommon in nature, but those compounds which have been described have usually exhibited interesting biological activities.[1] Marine organisms have provided two interesting examples of cyclic disulfides. The annelid worm *Lumbriconereis heteropoda* contains nereistoxin (1), a simple compound having insecticidal activity.[2] Two brown algae of the genus *Dictyopteris* have been shown to contain a cyclic disulfide 2, together with acyclic mono-, di-, and trisulfides.[3] Among examples of cyclic polysulfides attributed to terrestrial organisms are two antibiotics, 1,2,3,5,6-pentathiepane (lenthionine, 3) and 1,2,4,6-tetra-

1

2

3

4

5
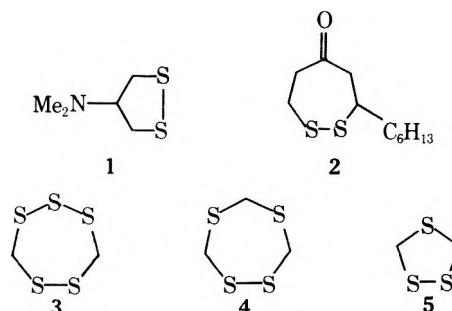
thiepane (4), obtained from the mushroom *Lentinus edodes*.[4,5] We wish to describe the isolation and structural elucidation of seven sulfur-containing heterocycles, including the antibiotics 3 and 4, from the red alga *Chondria californica*.

Fresh *Chondria californica*, collected at Isla San Jose, Mexico, in April 1975, possessed a strong "sulfur" odor. Crude extracts of the alga exhibited antimicrobial activity against *Vibrio anguillarium*. Chromatography of combined extracts of *C. californica* on Florisil afforded column fractions containing three distinct bands of antimicrobial activity, designated A, B, and C in order of increasing eluent polarity.

Careful chromatography of the combined fractions of band A on silica gel plates, using hexane as eluent, afforded two antibacterial components. The minor compound (0.06% of extractable oil) could be sublimed or recrystallized to obtain long needles of 1,2,4,6-tetrathiepane (4), mp 78–79 °C, identical in all respects with a synthetic sample prepared by the method of Morita and Kobayashi.[5] The major component (0.9%), obtained as white crystals, mp 56–57 °C, from 10% dichloromethane in ether, was shown to have identical spectral data with that published for lenthionine (3) (lit. mp 60–61 °C).[4] Vapor phase chromatography showed that the material contained approximately 95% lenthionine (3) contaminated with 1,2,4-trithiolane (5) and traces of two unidentified isomers of tetrathiane ($C_2H_4S_4$). The identities of lenthionine (3) and 1,2,4-trithiolane (5) were confirmed by coinjection of authentic samples.[5]

When the combined fractions of band A were allowed to stand prior to chromatography, a white powder was precipitated. The white powder was recrystallized from 30% chloroform in carbon disulfide to obtain white needles (0.02%), mp 177–178 °C, having the molecular formula $C_4H_8S_8$. The NMR spectrum of the octasulfide consisted of a single signal at δ 4.33 ppm, indicating the presence of four symmetrically arranged methylene groups, each flanked by two sulfur atoms. There are only two structures, 6 and 7, which satisfy these require-

6   7

ments. We favor structure 6, but only on the basis of negative evidence. Structure 7 might be expected to give an ion at *m/e* 96, due to the S_3^+ fragment, which has been observed in the low-resolution mass spectrum of lenthionine (3).[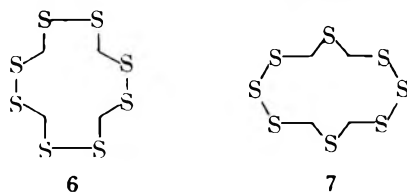4] The major peaks in the low-resolution mass spectrum could be assigned to fragments derived from either structure 6 or structure 7, but the absence of a peak at *m/e* 96 sways the balance in favor of structure 6.

The combined fractions of antibacterial band B were triturated under ether to obtain a solid (17.5%) which crystallized from chloroform as colorless prisms, mp 154–155 °C, having the molecular formula $C_3H_6O_2S_4$. The infrared spectrum contained signals at 1330, 1125, and 1120 cm^{-1} which could be assigned to either sulfone or thiolsulfonate groups.[6] The NMR spectrum consisted of three two-proton singlets at δ 4.18, 4.43, and 4.56 ppm which were assigned to three methylene groups, each flanked by heteroatoms. The data are consistent with two structures, a sulfone 8 and a thiolsulfonate 9. High-resolution mass measurement of the peak at *m/e* 110

8   9
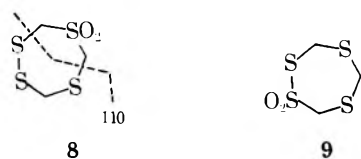
showed that the signal was due to a $CH_2S_3^+$ fragment, which can result from simple cleavage of the sulfone 8 as shown. Thiolsulfonates are reported to react rapidly with mercaptans to obtain a disulfide and a sulfinic acid.[7] The unknown molecule was recovered unchanged after treatment for >12 h with either propyl mercaptan in chloroform or cysteine in aqueous acetone, indicating that it was 4-dioxo-1,2,4,6-tetrathiepane (8).

Careful chromatography of the combined fractions of antibacterial band C allowed the separation of two isomeric compounds 10 and 11, both having the molecular formula

10   11

$C_2H_4OS_3$. The NMR spectrum of the more polar compound 10 (1%), obtained as white needles, mp 76–77 °C, consisted of an AB quartet at δ 3.97 and 4.25 ppm ($J = 12$ Hz) which was assigned to two identical methylene groups in which the geminal protons are nonequivalent, owing to the asymmetry of the sulfoxide group (ir 1105, 1043 cm^{-1}). The NMR spectrum of the less polar compound 11 (0.6%), isolated as an oil, contained two AB quartets at δ 3.99 and 4.64 ($J = 12$ Hz) and 4.40 and 4.73 ppm ($J = 10$ Hz), which were assigned to two different methylene groups in which the geminal protons were again nonequivalent. The infrared spectrum of 11 contained signals at 1120, 1087, and 1065 cm^{-1} which are appropriate for a thiolsulfinate.[8] Reduction of 1-oxo-1,2,4-trithiolane (11) with triphenylphosphine[9] in chloroform at room temperature gave a quantitative yield of 1,2,4-trithiolane (5) identical in all respects with an authentic sample.[5] Under identical conditions, 4-oxo-1,2,4-trithiolane (10) gave less than 10% reduction to 1,2,4-trithiolane (5), a result which is consistent with published data.[10] We were able to synthesize a mixture of the 4-oxo-1,2,4-trithiolane (10) and 1-oxo-1,2,4-trithiolane (11) by oxidation of 1,2,4-trithiolane (5) with sodium periodate in aqueous acetone.[11] The natural and synthetic materials were identical in all respects except for the optical activity.

Although 4-oxo-1,2,4-trithiolane (10) possesses a plane of symmetry, 1-oxo-1,2,4-trithiolane (11) is capable of exhibiting optical activity. We could not detect an optical rotation at 589 nm. However, the circular dichroism spectrum in the range of 200–400 nm exhibited two negative ($[\theta]_{258} -100$, $[\theta]_{341} -130$) and one broad positive ($[\theta]_{300} +20$) Cotton effects having very small molecular ellipticity maxima. We cannot assign an absolute configuration from this data.

By screening the pure compounds, we have shown that the cyclic polysulfides, particularly 4-dioxo-1,2,4,6-tetrathiepane (8), are responsible for the antibiotic activity of *Chondria californica*. Analysis of *C. californica* specimens from La Jolla, Calif., indicated the presence of the same metabolites, suggesting that they occur throughout the range of the alga. We have examined samples of *C. nidifica* and *C. coerulescens* but were unable to detect either antibacterial activity or cyclic polysulfides. A search for terpenoids in *C. californica* yielded only steroids and *trans*-phytol (1%).

Experimental Section

Packard 402 chromatograph, using a 6 ft × 2 mm column packed with 3% SP2250 on Supelcoport.

Collection and Extraction of *Chondria californica*. *Chondria californica* was collected at Isla San Jose (−2 m) in the Gulf of California (24°53′N, 110°35′W) in April 1975. The alga was drained of excess water and frozen immediately. After approximately 1 month, the alga was thawed and homogenized under ethyl acetate (1 l.) in a Waring blender. The solids (500 g) were removed by filtration and extracted with chloroform (2 × 2 l.) in a Soxhlet apparatus. The ethyl acetate filtrate was separated from the aqueous phase and dried over sodium sulfate. All organic extracts were combined and the solvents removed to obtain a viscous green oil (8.1 g, 1.6% of dry weight).

Chromatographic Separations. The combined extracts (8.1 g) were applied to a column of 100–200 mesh Florisil (Floridin) (318 g) and eluted with solvents of increasing polarity from hexane to methanol. Each fraction was screened against *Vibrio anguillarium* to reveal three bands of antibiotic activity. Fractions 3–9 were combined as band A (110 mg), fractions 21–24 were combined as band B (2.511 g), and fractions 27 and 28 were combined as band C (320 mg).

1,2,4,6-Tetrathiepane (4) and 1,2,3,5,6-Pentathiepane (3). The semisolid material of band A was rechromatographed on preparative silica gel GF plates (20 cm × 20 cm × 1.5 mm) using hexane as eluent to obtain two bands at R_f 0.4 (minor) and 0.3 (major). The minor component was extracted and crystallized from *p*-dioxane to obtain colorless needles of 1,2,4,6-tetrathiepane, mp 78–79 °C, identical in all respects with authentic material prepared by the method of Morita and Kobayashi. Yield 5 mg (0.06% of extractable oil); NMR (CDCl₃) δ 4.22 (s, 2 H) and 4.26 ppm (s, 4 H). The major component was extracted and crystallized from 10% dichloromethane in diethyl ether to obtain white crystals of 1,2,3,5,6-pentathiepane (3), mp 56–57 °C (lit. mp 60–61 °C). Yield 75 mg (0.9% of extractable oil); NMR (CDCl₃) δ 4.33 ppm (s, 4 H). Analysis of the sample by GC and combined GC–mass spectrometry showed that the melting point depression was caused by small quantities (<5% total) of two isomers of tetrathiane and 1,2,4-trithiolane (5), identified by coinjection of an authentic sample.[5]

Octasulfide 6 or 7. The combined fractions of band A were allowed to stand as a concentrated oil prior to rechromatography. A white solid which precipitated was collected and recrystallized from 30% chloroform in carbon disulfide to obtain white needles of the octasulfide, mp 177–178 °C. Yield 2 mg (0.025% of extractable oil); NMR (CDCl₃) δ 4.33 ppm (s); mass spectrum *m/e* (rel intensity) 312 (3), 188 (3), 156 (7), 142 (16), 124 (40), 110 (31), 78 (45), 64 (13), 46 (65), 45 (100) with appropriate ³⁴S peaks; high-resolution mass measurement, observed 311.8392, C₄H₈S₈ requires 311.8392.

4-Dioxo-1,2,4,6-tetrathiepane (8). The combined fractions of band B (2.511 g) were triturated under diethyl ether (3 × 50 ml) to obtain a white powder (1.70 g) which was crystallized from chloroform to obtain 4-dioxo-1,2,4,6-tetrathiepane (8) as prisms, mp 154–155 °C. Yield 1.42 g (17.5% of extractable oil); ir (CHCl₃) 1330, 1125, 1120 cm⁻¹; ¹H NMR (CDCl₃) δ 4.18 (s, 2 H), 4.43 (s, 2 H), 4.56 (s, 2 H); ¹³C NMR (Me₂SO-d₆) 43.8, 54.1, 63.3 ppm; mass spectrum *m/e* (rel intensity) 202 (33), 138 (16), 124 (8), 110 (9), 92 (20), 64 (30), 46 (97), 45 (100) with appropriate ³⁴S peaks; high-resolution mass measurement, observed 201.9257, C₃H₆O₂S₄ requires 201.9251, observed 109.9319, CH₂S₃⁺ requires 109.9319.

4-Oxo-1,2,4-trithiolane (10) and 1-Oxo-1,2,4-trithiolane (11). The combined fractions of band C were rechromatographed on preparative silica gel plates using diethyl ether as eluent to obtain two bands, visualized with iodine, at R_f 0.40 and 0.25. The band at R_f 0.25 was extracted to obtain a solid which crystallized from 10% chloroform in hexane to obtain white needles of 4-oxo-1,2,4-trithiolane (10), mp 76–77 °C. Yield 83 mg (1.0% of extractable oil); ir (CDCl₃) 1105, 1043 cm⁻¹; NMR (CDCl₃) δ 3.97 (d, 2 H, J = 12 Hz), 4.25 ppm (d, 2 H, J = 12 Hz); mass spectrum *m/e* (rel intensity) 140 (60), 124 (5), 110 (42), 78 (66), 64 (12), 62 (50), 46 (96), 45 (100) with appropriate ³⁴S peaks; high-resolution mass measurement, observed 139.9422, C₂H₄OS₃ requires 139.9424.

The band at R_f 0.4 was extracted to obtain 1-oxo-1,2,4-trithiolane (11) as an oil. Yield 50 mg (0.6% of extractable oil); ir (CHCl₃) 1120, 1087, 1065 cm⁻¹; uv λmax (ε) 335 (70), 210 (2700); CD (MeOH) [θ]₂₅₈ −100, [θ]₃₀₀ +20, [θ]₃₄₁ −130; NMR (CDCl₃) δ 3.99 (d, 1 H, J = 12 Hz), 4.40 (d, 1 H, J = 10 Hz), 4.64 (d, 1 H, J = 12 Hz), 4.73 ppm (d, 1 H, J = 10 Hz); mass spectrum *m/e* (rel intensity) 140 (44), 124 (10), 110 (22), 94 (26), 78 (20), 60 (36), 46 (77), 45 (100) with appropriate ³⁴S peaks; high-resolution mass measurement, observed 139.9424, C₂H₄OS₃ requires 139.9424.

Synthesis of 4-Oxo-1,2,4-trithiolane (10) and 1-Oxo-1,2,4-trithiolane (11). A solution of sodium periodate (306 mg, 1.33 mmol) in distilled water (2 ml) was added dropwise over 5 min to a cooled (0 °C), stirred solution of 1,2,4-trithiolane (165 mg, 1.33 mmol) in acetone (10 ml). The solution was stirred at 0–5 °C for 3 h and at room temperature for 21 h. The resulting solution was extracted with chloroform (2 × 25 ml), the extracts were dried over magnesium sulfate, and the solvent was evaporated to yield a yellow oil. Chromatography of the oil on preparative silica gel plates gave 4-oxo-1,2,4-trithiolane (10), mp 75–75 °C (50 mg, 27% theoretical), and 1-oxo-1,2,4-trithiolane (11) (49 mg, 26% theoretical).

Reduction of 1-Oxo-1,2,4-trithiolane (11). A solution of 1-oxo-1,2,4-trithiolane (14 mg, 0.1 mmol) and triphenylphosphine (26 mg, 0.1 mmol) in chloroform (1 ml) was stirred under a nitrogen atmosphere at room temperature for 24 h. The solvent was removed and the product mixture examined by NMR and GC. Both analyses indicated a quantitative reduction of 1-oxo-1,2,4-trithiolane to 1,2,4-trithiolane (5), which was not isolated from the mixture with triphenylphosphine oxide.

References and Notes

(1) S. N. Pandeya, *J. Sci. Ind. Res.*, **31**, 320 (1972).
(2) T. Okaichi and Y. Hashimoto, *Agric. Biol. Chem.*, **26**, 224 (1962).
(3) P. Roller, K. Au, and R. E. Moore, *Chem. Commun.*, 503 (1971); R. E. Moore, *ibid.*, 1168 (1971); *J. Chem. Soc., Chem. Commun.*, 326 (1972).
(4) K. Morita and S. Kobayashi, *Tetrahedron Lett.*, 573 (1966).
(5) K. Morita and S. Kobayashi, *Chem. Pharm. Bull.*, **15**, 988 (1967).
(6) S. Ghersetti, *Boll. Sci. Fac. Chim. Ind. Bologna*, **21**, 232 (1963); *Chem. Abstr.*, **61**; 179b (1964); B. G. Boldyrev, L. P. Slesarchuk, E. E. Gatala, T. A. Trofimoya, and E. N. Vasenko, *Zh. Org. Khim.*, **2**, 96 (1966); *Chem. Abstr.*, **64**, 14119d (1966); B. G. Boldyrev, L. P. Slesarchuk, and T. A. Trofimoya, *Khim. Seraorg. Soedin., Soderzh. Neftyakh Nefteprod.*, **8**, 108 (1968); *Chem. Abstr.*, **72**, 54934n (1970).
(7) J. P. Weidner and S. S. Block, *J. Med. Chem.*, **10**, 1167 (1967); T. F. Parsons, J. P. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).
(8) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 3028 (1961); D. Banard, *J. Chem. Soc.*, 4673 (1957).
(9) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 1467 (1961).
(10) S. K. Ray, R. A. Shaw, and B. C. Smith, *Nature (London)*, **196**, 372 (1962); H. H. Szmant and O. Cox, *J. Org. Chem.*, **31**, 1595 (1966).
(11) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962); R. G. Hiskey and M. A. Harpold, *ibid.*, **32**, 3191 (1967).

Pentaketide Metabolites of *Verticillium dahliae*. 3.[1] Identification of (−)-3,4-Dihydro-3,8-dihydroxy-1(2*H*)-naphthalenone [(−)-Vermelone] as a Precursor to Melanin

Robert D. Stipanovic* and Alois A. Bell

U.S. Department of Agriculture, National Cotton Pathology Research Laboratory, P.O. Drawer JF, College Station, Texas 77840

(−)-Vermelone [3,4-dihydro-3,8-dihydroxy-1(2*H*)-naphthalenone] was isolated and identified from culture filtrates of the melanin-deficient *brm-1* mutant of *Verticillium dahliae* fed 1,3,8-trihydroxynaphthalene. (−)-Vermelone was readily dehydrated both chemically and biologically to 1,8-dihydroxynapthalene (1,8-DHN). Since 1,8-DHN oxidizes to a black pigment (melanin), (−)-vermelone is probably the terminal ketone in the biosynthetic pathway from (+)-scytalone to melanin. Thus, the melanin in *V. dahliae* is apparently a polymer composed of oxidized 1,8-DHN subunits.

Recently Bell et al.[2] isolated a series of melanin-deficient mutants from the fungus *Verticillium dahliae*. The mutant *brm-1* (brown microsclerotia) accumulated (+)-scytalone (1)[3] that served as a substrate for natural melanin synthesis in *alm* (albino microsclerotia) mutants.[2,3] When fed to a different brown mutant (*brm-2*), (+)-scytalone (1) was enzymatically dehydrated to 1,3,8-trihydroxynaphthalene (1,3,8-THN, 2) but was not converted to normal black melanin.

We fed 1,3,8-THN (2) to the *brm-1* mutant to determine if 2 would be converted to melanin. However, a new compound 4 was produced in quantity and accumulated without melanin synthesis. Compound 4 was converted to normal black melanin by either *brm-2* or *alm* mutants.[4] Therefore, 4 also appears to be in the biosynthetic pathway leading from (+)-scytalone to melanin. We propose the trivial name (−)-vermelone (derived from *Verticillium* melanin ketone) for 4.

The high-resolution mass spectrum of (−)-vermelone (4) indicated the formula $C_{10}H_{10}O_3$ (*m/e* 178, 98%). Thus 4 was a dihydro derivative of 1,3,8-THN (2). The ir, NMR, and mass spectra of (−)-vermelone (4) and (+)-scytalone (1) were very similar. The ir spectra of both showed hydrogen-bonded carbonyl groups (1635 cm^{-1} for 1 and 1642 cm^{-1} for 4). The NMR spectra confirmed the hydrogen bonded phenolic groups (δ 12.45 for 1 and δ 12.42 for 4). Three aromatic protons appeared in the NMR spectrum of (−)-vermelone (4). Two formed complex doublets at δ 6.75 (*J* = 7.3 Hz) and were coupled to a third aromatic proton (δ 7.45, t, *J* = 7.3 Hz). The methine proton (CHOH) in (+)-scytalone (1) appeared at δ 4.20 whereas that in (−)-vermelone (4) gave a multiplet at δ 4.32. In each compound the methine proton was coupled to four methylene protons; these appeared as complex multiplets at δ 2.75–2.95 in 1 and δ 3.00–3.20 in 4. Thus, the NMR spectrum indicated that vermelone is 3,4-dihydro-3,8-dihydroxy-1(2*H*)-naphthalenone (4).

Fragment ions of (−)-vermelone observed in the high-resolution mass spectrum also agreed with structure 4. (−)-Vermelone (4) was found to readily lose a molecule of water (*m/e* 160, $C_{10}H_8O_2$, 100%) and to undergo a reverse Diels–Alder fragmentation giving CH_2=CHOH and the fragment *m/e* 134 ($C_8H_2O_2$, 98%).

To confirm its structure, we oxidized (−)-vermelone (4) to 2-hydroxyjuglone; 4 also was dehydrated in alkali to give 1,8-dihydroxynaphthalene (1,8-DHN).

The diketone tautomer 3 probably is an intermediate in the conversion of 1,3,8-THN (2) to (−)-vermelone (4). Free-energy calculations[5] for the tautomers 2 and 3 indicated similar thermodynamic stabilities. The ¹H NMR spectrum showed only the 2 tautomer; however, on the surface of an enzyme the predominant tautomer might have been the diketone 3. An alcohol dehydrogenase then could reduce 3 to (−)-vermelone (4).

In the biosynthetic pathway to melanin, (−)-vermelone (4) apparently dehydrates to 1,8-DHN. Allport and Bu'Lock previously showed that 1,8-DHN can be chemically oxidized to a black polymer. When fed to the *alm-1* mutant, (−)-vermelone (4) was dehydrated to a naphthol with chromatographic and spectral properties identical with those of 1,8-DHN Also, the 1,8-DHN like (−)-vermelone (4) was rapidly converted to a black pigment (melanin) by *alm* or *brm-2* cultures.

The *brm-1* mutant lacks the enzyme activity necessary to convert either of the 3-hydroxytetralones (1 or 4) to their corresponding naphthols. This suggests that the same enzyme catalyzes both dehydratase reactions in the conversion of (+)-scytalone to 1,8-DHN.

Experimental Section[10]

Melting points were determined on a Kofler hot stage and are uncorrected. Low-resolution spectra were recorded at 70 eV on a Varian CH-7 mass spectrometer, with a probe temperature of 20 °C and a source temperature of 200 °C. High-resolution mass measurements were made with a CEC 21-110 spectrometer. Peaks above *m/e* 50 and 10% are reported. NMR spectra were recorded on a JEOL MH-100 in $(CD_3)_2CO$ with Me_4Si as an internal standard. Phenolic protons were determined by D_2O exchange. Coupling between protons was determined by spin decoupling techniques. Uv spectra were determined in 95% EtOH or 95% EtOH containing 0.03 M NaOH (EtONa) with a Beckman ACTA-MVI.

Biological Conversion of 1,3,8-Trihydroxynaphthalene (2) to (−)-Vermelone (4) and of 4 to 1,8-Dihydroxynaphthalenone. The mutants *brm-1* and *alm-1* of *Verticillium dahliae* and their growth on potato–carrot–dextrose–agar (PCDA) have been described.[2] Conidia were washed from the outer 1 cm of fungal colonies with sterile distilled water and adjusted to 10^6 conidia/ml. Aliquots (0.2 ml) of the conidial suspension were spread on fresh PCDA in culture dishes (9 cm diameter) and incubated in the dark at 24 °C for 6 days. Compound 2 was prepared from (+)-scytalone (1) by acid dehydration.[3] Excess 2 was stirred under N_2 for 1 h in 0.01 M potassium phosphate buffer (pH 6) containing 1% sucrose. The saturated solution was filtered and added to the 6-day-old cultures of *brm-1* (10 ml/dish), and the cultures were incubated for another 18 h. Solutions were then decanted and each culture dish was rinsed twice with 12 ml of hot (90 °C) water. All aqueous fractions were combined and filtered. Crude metabolites were then prepared as described previously.[3]

Similarly, (−)-vermelone (4) was dissolved in the sucrose–buffer solution at 1 mg/ml, and was added to the *alm-1* mutant for conversion to 1,8-DHN.

Purification of (−)-Vermelone [3,4-Dihydro-3,8-dihydroxy-1(2*H*)-naphthalenone, 4]. (−)-Vermelone (4) was purified by sequential TLC on polyamide developed with 9:1 chloroform–acetone (R_f 0.77), on Silicar TLC-7GF (Mallinkrodt Chemical Co., St. Louis, Mo.) with 50:50:1 ethyl ether–naphtha solvent–formic acid (R_f 0.28), and on Silicar with 9:1 chloroform–acetone (R_f 0.34). Silica gels with zinc silicate phosphor were avoided because they gave poorer resolution. Compound 4 was located on TLC layers as a quenching spot under 254-nm uv light or a yellow fluorescing spot under 365-nm uv
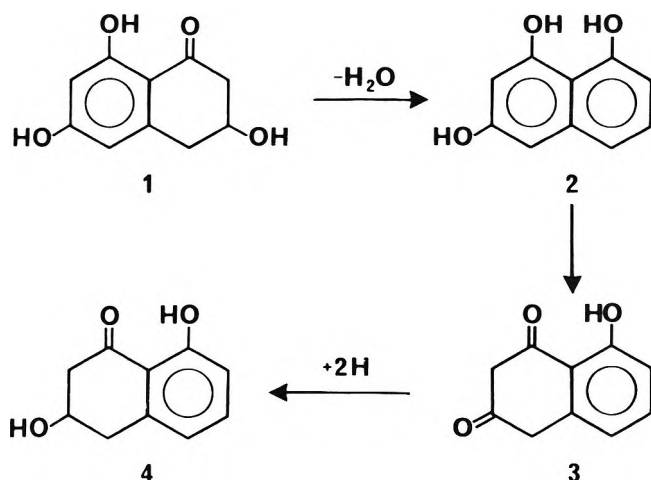
Figure 1. Probable biosynthetic pathway for the conversion of (+)-scytalone (1) to (−)-vermelone (4).

light. Compound **4** also formed a red-brown chelate when chromatograms were sprayed with 1% $FeCl_3$ and a gray spot with DMB reagent (equal volumes of 1% 2,4-dimethoxybenzaldehyde in ethanol and concentrated HCl, freshly mixed). Bands of silica gel containing **4** were scraped from TLC plates, packed in 1-cm chromatography columns, and eluted with ethyl ether.

(−)-Vermelone formed crystals from cyclohexane: mp 91–94 °C; $[\alpha]^{25}D$ −18° (c 0.36, EtOH); MS m/e (%) 178.062345 (98, M$^+$; $C_{10}H_{10}O_3$ requires 178.062980), 161 (20), 160 (100, M − H_2O), 135 (25), 134.037171 (98, M − CH_2=CHOH; $C_8H_6O_2$ requires 134.036770), 132 (44), 131 (20), 107 (13), 106 (62), 105 (32), 104 (28), 103 (16), 78 (54),

77 (44), 63 (13), 52 (19), 51 (31); uv–visible λ_{max} (EtOH) (ϵ) 333.5 nm (4000), 259 (10 600); λ_{max} (EtONa) (ϵ) 374 (5500), 346 (5200), 333 (sh), 266 (sh).

Chemical Conversions of (−)-Vermelone (4). Compound **4** was oxidized with Jones reagent[7] to give a single orange quinone. The R_f values and uv–visible spectra of this quinone agreed with those[1] of synthetic 2-hydroxyjuglone.[8] (−)-Vermelone (4) was dehydrated with 50% aqueous KOH by the methods described for (+)-scytalone.[3] The uv–visible and mass spectra of the phenol obtained from **4** agreed with those of 1,8-DHN synthesized from 8-hydroxy-1-naphthalenesulfonic acid (sodium salt) according to Tanaka et al.[9]

References and Notes

(1) Part 2: R. D. Stipanovic and A. A. Bell, *Mycologia,* in press.
(2) A. A. Bell, J. E. Puhalla, W. J. Tolmsoff, and R. D. Stipanovic, *Can. J. Microbiol.,* in press.
(3) A. A. Bell, R. D. Stipanovic, and J. E. Puhalla, *Tetrahedron,* in press.
(4) Details of bioassay are in ref 3.
(5) S. W. Benson, F. R. Cruickshank, D. M. Golden, G. R. Haugen, H. E. O'Neal, A. S. Rodgers, and R. Walsh, *Chem. Rev.,* **69,** 279 (1969).
(6) D. C. Allport and J. D. Bu'Lock, *J. Chem. Soc.,* 654 (1960).
(7) K. Bowden, I. M. Hielbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.,* 39 (1946).
(8) H. Stetter and H. Heidel, *Chem. Ber.,* **99,** 2172 (1966).
(9) H. Tanaka, Y. Ohne, N. Ogawa, and T. Tamura, *Agr. Biol. Chem.,* **27,** 48 (1963).
(10) Tradenames in this paper are included as a matter of convenience to the reader, and such inclusion does not constitute any preferential endorsement by the U.S. Department of Agriculture.

Maytansinoids. Synthesis of a Fragment of Known Absolute Configuration Involving Chiral Centers C-6 and C-7

William J. Elliott and Josef Fried*

Department of Chemistry and Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois 60637

An efficient, stereocontrolled synthesis is described for compound 2, which represents a fragment corresponding to carbons 5–12 of the maytansinoid ring skeleton. The total yield from (Z)-2-butene-1,4-diol is 78%. The dioxepane 6 has been resolved via the α-phenethylurethane and the absolute configuration of the enantiomers determined by the Horeau method. The specific rotations of all intermediates are reported.

The maytansinoids[1–4] are a group of structurally related ansa macrolides isolated from *Maytenus* and *Colubrina* species, which are of great current interest because of their high antileukemic potency and cytotoxicity. They are characterized by structure **1**, in which R may be CH_3 (maytansine),[1] C_2H_5 (maytanprine),[2] $CH(CH_3)_2$ (maytanbutine),[2] or $CH_2CH(CH_3)_2$ (maytanvaline).[3] 15ξ-Hydroxymaytanbutine (colubrinol)[4] and its acetate have also been described. More recently,[3] maytansine, the most thoroughly investigated representative of this class of compounds, has also been found to possess significant activity against solid murine tumor systems, and it is presently undergoing clinical trials.

Sparked by our interest in the unusual biological properties of these structurally interesting natural products, whose isolated yields from their respective plant sources are in the order of 10^{-4}% or less, we have initiated a synthetic program aimed at the natural products themselves as well as at structurally related substances, which might retain the biological properties of the former. Two groups, Meyers et al.[5–7] and Corey

and Bock,[8] have recently reported on their approaches to this problem. In this paper we wish to describe the synthesis of compound **2**, which represents a fragment corresponding to carbon atoms 5–12 of the maytansinoid ring skeleton. The final intermediate **3** has also been prepared in optically active form of known absolute configuration. The elaboration of this intermediate which contains the chiral centers corresponding to C-6 and C-7 in maytansine in the correct relative configuration seemed to us an appropriate point of departure since such a precursor could in turn direct the development of stereochemistry of all the remaining chiral centers, C-3, C-4, C-5, and C-10. The synthesis of **3**, which follows a plan similar to that of Corey and Bock,[8] and is identical with the latter up to compound **7**, had been completed when that paper appeared. Interestingly, the further utilization of that intermediate proceeds along quite different lines. It was envisioned that the relative stereochemistry at C-6 and C-7 could be created by a methyllithium opening of a suitably protected (Z)-2,3-epoxybutane-1,4-diol. Thereafter the vicinal hydroxyl

1

2, R = H
2a, R = CH$_3$

3

Scheme I
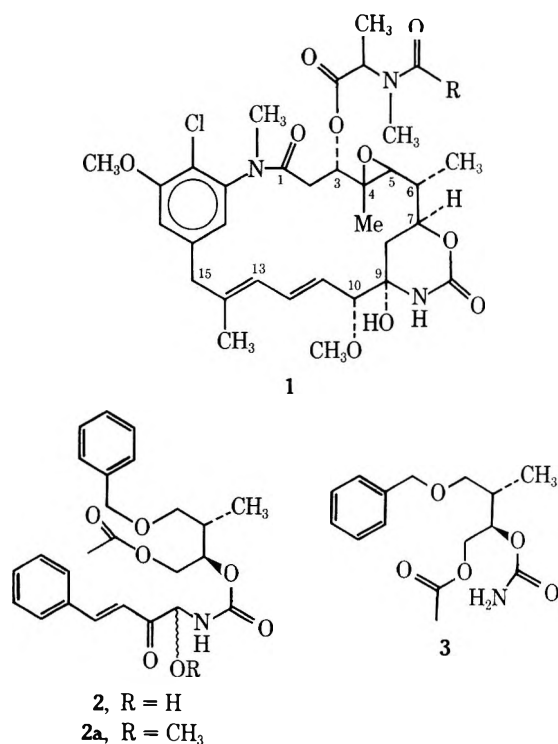
groups could be protected as a ketal, followed by benzylation of the free hydroxyl group. After hydrolysis of the ketal and reaction of the resulting glycol with phosgene, ammonolysis of the cyclic carbonate should produce a hydroxyethyl carbamate, which could be acetylated to produce compound **3**. The expected regioselectivity of carbamate formation was based on previous studies of unsymmetrical 1,3-dioxolane-2-ones.[9,10] A crucial point here is the purity of the required cis-2-butene-1,4-diol, since contaminating trans diol would lead to the undesirable erythro product, thereby creating purification problems. Moreover, the inherent stereospecificity of epoxide ring openings would be wasted on a mixture of the cis and trans epoxides, in that both the (2RS, 3SR) and (2RS,3RS) isomers would result. Since the difficulties in obtaining pure cis-2-butene-1,4-diol are well known,[12] it seemed advantageous to incorporate this compound in a small ring system which would dictate the configuration of the double bond. Theoretical possibilities include 2,5-dihydrofuran, 4,5-dehydro-1,2-dioxane, and a 4,7-dihydro-1,3-dioxepin. This last structure not only fixes the configuration of the double bond, but also contains another advantage: it incorporates the ketal protecting group for the future 1,2-glycol. Since the acetone ketal 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (**4**) had already been prepared in high yield,[13] it was chosen as the starting material.

The synthetic pathway to compound **2** is summarized in Scheme I. Reaction of the dioxepin **4** (prepared according to Monroe[13] in better than 90% yield) with *m*-chloroperbenzoic acid in CH$_2$Cl$_2$ for 6 h at reflux gave the acid-labile epoxide **5** in 99% yield. According to previous work,[11] lithium dimethylcuprate is the reagent of choice for effecting trans opening of epoxides without rearrangement. When the epoxide **5** was treated with 0.52 molar equiv of Me$_2$CuLi in ether, first at −78 °C for 30 min and then at room temperature for 18 h, the enantiomeric pair represented by **6**[14] was produced in 94% yield. This hydroxydioxepane was easily hydrolyzed with aqueous acid, but could be rearranged directly to the dioxolane ring system **7** in 99% yield either by *p*-toluenesulfonic acid catalysis in benzene or more conveniently with a trace of concentrated HCl, followed by distillation through a Vigreux column. The structure of the rearranged product was shown to be **7** rather than the isomeric 2,2,5-trimethyl-4-hydroxymethyl-1,3-dioxane by ^{1}H NMR double resonance
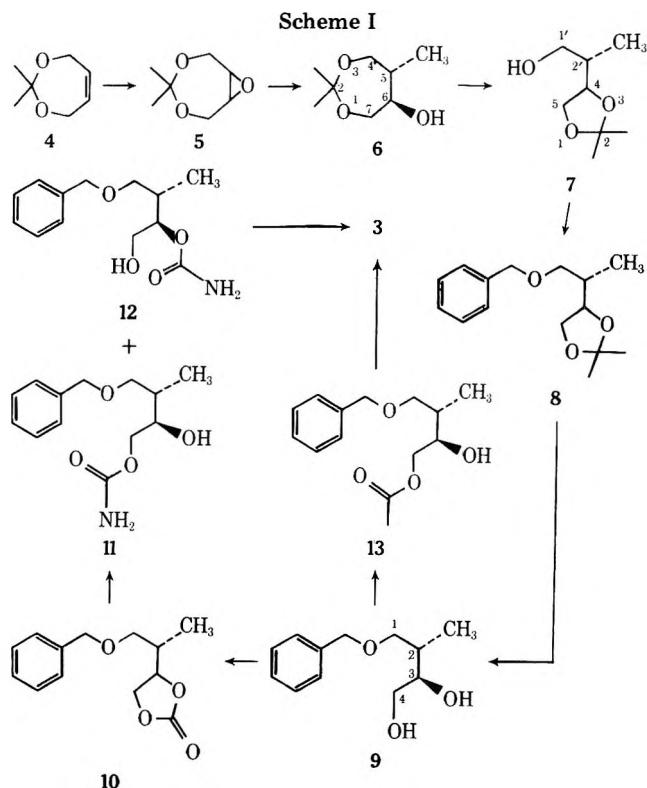
measurements at 270 MHz. Thus, the doublet corresponding to the carbinol hydrogens collapsed upon irradiation of the septet at about δ 2 (CHCH$_3$), consistent with dioxolane structure **7**, but not the dioxane structure. Had the latter been correct, the doublet corresponding to the carbinol hydrogens should have collapsed upon irradiation of a quartet at about δ 3.5 (CHOC). The free alcohol in **7** was benzylated in 91–95% yield by treatment with NaH and benzyl chloride in dimethylformamide. The resulting benzyl ether ketal **8** was then hydrolyzed to the glycol **9** by 1 N HCl in 2:1 acetonitrile–H$_2$O in 91% yield. The benzyl ether glycol **9** was converted to the cyclic carbonate **10** in 70% yield by treatment with phosgene in toluene–pyridine. When **10** was ammonolyzed, two compounds were isolated in a 3:1 ratio. Since the major product had ^{1}H NMR signals at δ 4.11 (AB pattern, 2 H) and 3.99 (X of ABX, 1 H), and showed a doublet at δ 4.73 for the alcohol proton in Me$_2$SO-d_6, while the minor product had ^{1}H NMR signals at δ 4.77 (quartet, 1 H) and 3.72 (broad doublet, 2 H) and a triplet at δ 4.76 for the alcohol proton in Me$_2$SO-d_6, the major and minor products were assigned structures **11** and **12**, respectively. Corroborative evidence was also obtained from the mass spectra and ^{13}C spectra of the two compounds. This finding is at variance with two previous reports,[9,10] in which unsymmetrical 1,3-dioxolane-2-ones were ammonolyzed to give urethanes similar to **12**. Since the major product **11** leads not to **3**, but to an isomer, this route was not considered a viable method for the synthesis of **3**.

When glycol **9** was treated with 0.95 equiv of acetic anhydride for 2 days in pyridine, the monoacetate **13** was formed in about 80% yield, with the starting material comprising the other 20% of the mixture. These could be easily separated by chromatography and **13** characterized. Structure **13**, rather than the isomeric 3-acetoxy structure, was assigned to this substance on the basis of spectral evidence: ^{1}H NMR in CDCl$_3$, which showed an AB pattern at δ 4.09 and an X of ABX at δ 4.01, very similar to that of compound **11**; ^{1}H NMR in Me$_2$SO-d_6, which showed a doublet at δ 4.87 coupled to the quintet at δ 3.76; mass spectrum, which showed a peak at *m/e* 179, corresponding to loss of CH$_2$OAc, and no peak at *m/e* 221, corresponding to loss of CH$_2$OH; and ^{13}C spectra. The 3-acetoxy-4-hydroxy compound was later synthesized by trit-

ylation of **9** in pyridine, addition of acetic anhydride, and detritylation with ethanol. It had all the expected properties, which were different than those of **13**. When monoacetate **13** was treated in benzene with 2 equiv each of NaOCN and CF_3CO_2H,[15] the desired urethane **3**, mp 112–113 °C, was formed in 96% yield after one recrystallization from benzene–ether, identical in all respects with the product obtained by acetylation of the urethane **12**.

In order to effect the linkage of the urethane nitrogen of **3** with the carbon chain extending from C-9 to the aromatic ring, thereby generating the carbinolamide functionality at C-9 and providing at the same time an oxygen function at C-10, we have condensed the urethane **3** with styrylglyoxal to form the adduct **2** in quantitative yield. Carbinolamides of highly electrophilic aldehydes have been known since 1874, when Bischoff[16] condensed chloral hydrate with ethyl urethane under strong acid catalysis. More recently Vail et al.[17] prepared the 1,2-biscarbinolamide of glyoxal and ethyl urethane using a bicarbonate alkaline medium. In contrast to either of these two sets of conditions we have effected the condensation without external catalyst in refluxing benzene. The reversibility of the condensation reaction could be observed when the NMR spectrum of the crystalline adduct was taken in $CDCl_3$ at 270 MHz. Peaks corresponding to free urethane and aldehyde hydrate were identified, which accounted for approximately 5% of the sample. This reversibility could be arrested by conversion of **2** into the methyl ether **2a** in boiling methanol for 5 min. The conditions for both the condensation reaction and the protection of the carbinolamide by methylation are thus compatible with a wide variety of functionality and protecting groups that could be built into the precursor molecules.

In a lengthy synthetic scheme, it is generally accepted that separation of enantiomers, or resolution, is most advantageously carried out at the earliest possible stage. In the case of the above scheme, attempts at resolution of the alcohol **6** seemed most likely to succeed, in that the hydroxyl group to be derivatized is bonded to an asymmetric carbon atom, and compound **6** occupies an early position in the synthetic sequence. Standard attempts at resolution through hemiphthalate esters provided low yields of derivatives, since the acidic carboxyl group catalyzed hydrolysis and decomposition of the acetonide. On the other hand, reaction of the alcohol **6** with $(+)$-(R)-α-phenethylamine isocyanate resulted in conversion to the diastereomeric urethanes, which could be separated by crystallization from hexane–toluene (10:1). The higher melting diastereomer melted at 103–103.5 °C after two or three recrystallizations and had $[\alpha]^{23}$D $-1.9°$,[18] which did not improve upon further crystallization. The lower melting diastereomer could be obtained by chromatography on silica gel; it had mp 74–74.5 °C and $[\alpha]^{23}$D 78.4°. Both diastereomers were judged to be at least 99% pure by FT ^{1}H NMR at 270 MHz. Samples composed of the two diastereomers in a 98:2 ratio displayed two distinct and separate signals at δ 0.98 and 0.93. In pure samples the complete absence of one signal was observed even after a large number of pulses. Reduction of the urethanes with lithium aluminum hydride in refluxing THF for 5 h, followed by nonacidic, nonaqueous workup, gave the parent alcohols having $[\alpha]^{23}$D 43.4° from the lower melting urethane and $[\alpha]^{23}$D $-43.5°$ from the higher melting diastereomer in 96% yield. Esterification of the two antipodes with *rac*-α-phenylbutyric anhydride according to the method of Horeau[19] provided the absolute configuration of (+)-**6** as (5*S*, 6*R*) and that of (−)-**6**[20] as (5*R*,6*S*). The "optical yields" in these reactions were 16.7 and 13.9%, respectively. These were corroborated by the 270-MHz ^{1}H NMR spectra of the isolated esters, which showed, for instance, two signals at δ 2.11 and 1.81 in the ratio of 58:42 corresponding to the diastereomeric hydrogens at C-3 of the butyric esters.

The synthetic sequence leading to **3** was repeated with (−)-**6** to give the following yields and $[\alpha]^{23}$D values:[18] (−)-**7**, 95%, $-5.1°$; (−)-**8**, 95%, $-7.7°$; (−)-**9**, 91%, $-3.7°$; (+)-**13**, 68%, (80% conversion), +4.9°; (−)-**3**, 68%, (75% conversion), $-5.4°$.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were run as a thin film between NaCl plates and solid samples in KBr disks. NMR spectra were determined as solutions in $CDCl_3$ with Me_4Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d. t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. ^{1}H NMR spectra were recorded on a Bruker HX-270 (270 MHz) spectrometer operating in the pulsed Fourier transform mode. ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz in the pulsed Fourier transform mode. Free induction decay data were accumulated and processed with a Nicolet 1089 computer. Mass spectra were determined using a Finnigan 1015 quadrupole mass spectrometer equipped with VPC, gas and solid probe inlets; the data were recorded and processed by a Systems Industries Computer Interface System/150, and plotted as bar graphs. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Melting points are uncorrected. High-pressure liquid chromatography was carried out using Quantum Industries TLC grade silica gel (no binder) in glass columns. Microanalyses were performed by Baron Consulting Co., Orange, Conn. All compounds are racemic unless otherwise specified.

2,2-Dimethyl-4,7-dihydro-1,3-dioxepin (4).[13] 2-Butene-1,4-diol (91% cis, 22.00 g, 250 mmol) was combined with 2,2-dimethoxypropane (55.00 g, 530 mmol) in a 100-ml flask. *p*-Toluenesulfonic acid monohydrate (2 mg) was added and the solution stirred magnetically during distillation at atmospheric pressure. Fractions collected were bp 63–65 °C (MeOH, 50 ml); bp 78–85 °C (excess dimethoxypropane, 13 ml); bp 144–146 °C (product, 28.27 g, 89% yield based on 100% cis diol, 97% based on 91% cis diol). ^{1}H NMR δ 5.67, t, *J* = 1.65 Hz, 2 H (olefinic protons); 4.26, d, *J* = 1.65 Hz, 4 H (CH_2); 1.44, s, 6 H (CH_3). ^{13}C NMR δ 129.5, d (C-5 + 6); 101.9, s (C-2); 61.4, t (C-4 + 7); 24.0, q (methyls). Ir 1381, 1372 (methyls); 1217 (acetonide); 1176, 1086, 1073 (ether C–O); 735, 725 cm^{-1} (olefins). Mass spectrum (10% cutoff) *m/e* 128, 0.05% (M^+); 70, 17% (CH_2=CHCH$_2$CHO$^+$); 59, 88% [$CH_3C(OH)CH_3$]; 43, 100% ($CH_3C≡O^+$); 39, 30%.

4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (5). A solution of 10.00 g (78 mmol) of 2,2-dimethyl-4,7-dihydro-1,3-dioxepin (4) in 50 ml of CH_2Cl_2 was added over a 30-min period to a solution of 18.00 g of 85% pure *m*-chloroperbenzoic acid (89 mmol) in 150 ml of CH_2Cl_2 and the addition funnel rinsed with 50 ml of CH_2Cl_2. The mixture was allowed to reflux for 6 h, and then the flask was cooled to 0 °C to precipitate the *m*-chlorobenzoic acid present. The solid was filtered, and the CH_2Cl_2 solution washed with 2 × 250 ml of 10% K_2SO_3, 3 × 250 ml of saturated $NaHCO_3$, 200 ml of 5% NaOH, and 200 ml of saturated NaCl and dried over $MgSO_4$. Removal of solvent in vacuo left 15 g of slightly yellow oil, which was distilled with a 10-cm Vigreux column. Only one fraction distilled; it had bp 85–88 °C (17 Torr) and weighed 11.10 g (99% yield). ^{1}H NMR δ 4.02, AB of ABX, $|J_{AB}|$ = 14.4, $|J_{AX} + J_{BX}|$ = 39 Hz, 4 H (–CH$_2$–); 3.22, X of ABX, 2 H (epoxide protons); 1.38, s, 3 H (CH_3); 1.32, s, 3 H (CH_3). ^{13}C NMR δ 101.8, s (C-4); 59.9, t (C-2 + 6); 56.1, d (C-1 + 7); 24.4, q (C-4 methyl cis to epoxide); 23.1, q (C-4 methyl trans to epoxide). Ir 1380, 1370 (methyls); 1218 (acetonide); 1086 (ether C–O); 834, 796 cm^{-1} (epoxide). Mass spectrum (10% cutoff) *m/e* 129, 25% (M^+ − CH_3); 99, 12%; 59, 18% [$CH_3C(OH)^+$–CH_3]; 43, 100% ($CH_3C≡O^+$); 31, 11% ($^+CH_2OH$); 29, 12% ($HC≡O^+$).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.59; H, 8.17.

(5*RS*,6*SR*)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (6). Purified cuprous iodide (5.00 g, 26 mmol) and a stirring bar were placed in an oven-dried 250-ml flask, and the flask was evacuated and purged with N_2 (ten times). Dry ether (10 ml) was added by syringe and the flask cooled to −78 °C. Then 40 ml of 1.38 M methyllithium (55 mmol) was added and the solution allowed to stir for 10 min. 4,4-Dimethyl-3,5,8-trioxabicyclo[5.1.0]octane (5, 7.50 g, 52 mmol) was placed in a 25-ml test tube, which was capped, evacuated, and purged with N_2 (ten times). Dry ether (10 ml) was added by syringe and the solution mixed. The epoxide solution was added over 20 min to the cuprate, giving a slight yellow color to the reaction mixture. The solution was kept at −78 °C for 30 min and then allowed to warm to room temperature. After 18 h, no starting material was seen by NMR of an aliquot. The mixture was quenched with 15 ml of MeOH and added to 250 ml of saturated NH_4Cl, followed by extraction with 5 × 250 ml of ether (only first extract is yellow). The ether solution was washed with 250 ml of saturated NaCl and dried over $MgSO_4$, and the

solvent was removed in vacuo. Distillation through a 10-cm Vigreux column afforded 7.82 g of compound boiling at 102–104 °C (13–14 Torr) (94% yield). ^{1}H NMR δ 3.70, d of d, J = 3, 13 Hz, 1 H (C-7 H); 3.68, d of d, J = 3, 13 Hz, 1 H (C-4 H); 3.59, d of d, J = 6, 13 Hz, 1 H (C-7 H); 3.37, d of d, J = 7, 13 Hz, 1 H (C-4 H); 3.31, t of d, J = 6, 3 Hz, 1 H (C-6 H); 3.06, broad s, 1 H (OH); 1.68, sextet of d, J = 7, 3 Hz, 1 H (C-5 H); 1.34, s, 3 H (CH$_3$ of acetonide); 1.32, s, 3 H (CH$_3$ of acetonide); 0.98, d, J = 7 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 101.1, s (C-2); 74.0, d (C-6); 63.4, t (C-7); 62.4, t (C-4); 40.7, d (C-5); 24.6, q (C-2 methyls); 14.6, q (C-5 methyl). Ir broad 3600–3200 (OH); 1381, 1370 (methyls); 1215 (acetonide); 1080 (ether C–O); 850 cm^{-1}. Mass spectrum (10% cutoff) *m/e* 145, 3% (M$^+$ – CH$_3$); 72, 67%; 59, 100% [CH$_3$C(OH)$^+$CH$_3$]; 57, 71%; 43, 95% (CH$_3$C≡O$^+$).

Anal. Calcd for C$_8$H$_{16}$O$_3$: C, 59.98; H, 10.07. Found: C, 59.84; H, 10.01.

Acetate: bp 85–88 °C (4 Torr).

Anal. Calcd for C$_{10}$H$_{18}$O$_4$: C, 59.38; H, 8.97. Found: C, 59.11; H, 8.71.

(2′RS,4SR)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propanol (7). (5RS,6SR)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (6, 4.00 g, 25 mmol) was placed in a 5-ml flask along with 2 drops (30 μl) of concentrated HCl and a stirring bar. The mixture was distilled through a 10-cm Vigreux column, giving only one fraction, bp 112–114 °C (20 Torr), weighing 3.95 g (98% yield). ^{1}H NMR δ 4.12, q, J = 6.5 Hz, 1 H (CHO); 4.03, t, J = 7.1 Hz, 1 H (CHOCH$_2$); 3.71, t, J = 7.9 Hz, 1 H (CHOCH$_2$); 3.66, s, 1 H (OH); 3.53, d, J = 6.3 Hz, 2 H (CH$_2$OH); 1.85, septet, J = 6.5 Hz, 1 H (CH$_3$CH); 1.41, s, 3 H (acetonide CH$_3$); 1.32, s, 3 H (acetonide CH$_3$); 0.96, d, J = 7.5 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 108.5, s (C-2); 78.0, d (C-4); 67.2, t (C-5); 65.2, t (C-1′); 38.2, d (C-2′); 26.4, q (C-2 methyl cis to alkyl group); 25.3, q (C-2 methyl trans to alkyl group); 12.1, q (C-3′). Ir broad 3600–3200 (OH); 1380, 1370 (methyls); 1212 (acetonide); broad 1060–1040 (C–O); 860 cm^{-1}. Mass spectrum (50% cutoff) *m/e* 145, 69% (M$^+$ – CH$_3$); 101, 62% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 85, 94%; 72, 89%; 59, 51% [CH$_3$C(OH)$^+$-CH$_3$]; 57, 59%; 55, 59%; 43, 100% (CH$_3$C≡O$^+$); 41, 70%; 31, 50% (+CH$_2$OH).

Anal. Calcd for C$_8$H$_{16}$O$_3$: C, 59.98; H, 10.07. Found: C, 60.26; H, 9.79.

(2′RS,4SR)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propyl Benzyl Ether (8). Sodium hydride (4.18 g, 55% in oil, 95 mmol) was placed in a 100-ml flask with a stirring bar and washed with 3 × 20 ml of hexane. Freshly distilled (from CaH$_2$) DMF (20 ml) was added, and the flask was sealed with a septum, evacuated, and flushed ten times with N$_2$. (2′RS,4SR)-2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-1′-propanol (7, 7.73 g, 48.2 mmol) was placed in 10 ml of distilled DMF and added dropwise to the stirred NaH suspension by syringe while cooling in an ice bath. The ice bath was removed after all the alcohol had been added, and the solution stirred at room temperature for 30 min. Freshly distilled and degassed benzyl chloride (6.39 g, 50.6 mmol) was dissolved in 10 ml of DMF and this solution added dropwise to the alcoholate solution while cooling in an ice bath. The reaction mixture was then stirred for 48 h at room temperature. For workup 50 ml of ether was added followed by 30 ml of MeOH, to destroy excess hydride, and 150 ml more of ether. The combined ether layers were washed with 5 × 100 ml of H$_2$O (only first H$_2$O layer is yellow) and dried over MgSO$_4$, and the ether was removed in vacuo. Distillation of the slightly yellow residue afforded only one fraction, bp 174–176 °C (19 Torr), weighing 11.52 g (94.4% yield). ^{1}H NMR δ 7.31, m, 5 H (aromatic protons); 4.47, s, 2 H (benzylic protons); 4.03, t, J = 10.8 Hz, 1 H (CHOCH$_2$); 4.01, q, J = 5.2 Hz, 1 H (CHOCH$_2$); 3.68, t, J = 10.8 Hz, 1 H (CHOCH$_2$); 3.36, d, J = 6 Hz, 2 H (CHCH$_2$OCH$_2$); 1.92, septet, J = 7 Hz, 1 H (CH$_3$CH); 1.39, s, 3 H (acetonide CH$_3$); 1.36, s, 3 H (acetonide CH$_3$); 1.01, d, J = 7 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 138.4, s (quaternary phenyl C); 128.3, d (meta C's); 127.4, d (ortho + para C's); 108.1, s (C-2); 78.2, d (C-4); 73.1, t (benzylic C and C-1′); 68.1, t (C-5); 37.2, d (C-2′); 26.6, q (C-2 methyl cis to alkyl group); 25.6, q (C-2 methyl trans to alkyl group); 13.2, q (C-3′). Ir 1385, 1372 (methyls); 1215 (acetonide); 1100, 1058 (ether C–O); 862; 738, 700 cm^{-1} (monosubstituted benzene). Mass spectrum (5% cutoff) *m/e* 235, 5% (M$^+$ – CH$_3$); 101, 10%, (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 91, 100% (PhCH$_2$$^+$); 43, 32% (CH$_3$C≡O$^+$).

Anal. Calcd for C$_{15}$H$_{22}$O$_3$: C, 71.97; H, 8.86. Found: C, 71.70; H, 8.63.

(2RS,3SR)-2-Methylbutane-1,3,4-triol 1-O-Benzyl Ether (9). To 30 ml of 2:1 (v/v) CH$_3$CN–H$_2$O was added 2.6 ml of concentrated HCl, making the solution 1 N HCl. (2′RS,4SR)-2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-1′-propylbenzyl ether (8, 3.56 g) was added and the mixture was stirred for 7 days. The mixture was then poured into 50 ml of saturated NaCl and extracted with 5 × 30 ml of ether. The combined ether layers were washed with 50 ml of saturated NaHCO$_3$ and dried over MgSO$_4$, and the ether was evaporated in vacuo. The residue was distilled, first at 20 mm to remove traces of ether, and then at ~1 Torr, where only one fraction was collected,

having bp 142–147 °C and weighing 2.99 g (91% yield). ^{1}H NMR δ 7.35, m, 5 H (aromatic protons); 4.50, s, 2 H (benzylic protons); 3.73, broad m, 1 H (CHOH); 3.60, br d, 2 H (CH$_2$OH); 3.48, eight-line AB of ABX, $|J_{AB}|$ = 9, $|J_{AX} + J_{BX}|$ = 22 Hz, 2 H (C-1 H$_2$); 2.87, br d, 1 H (CHOH); 2.51, br s, 1 H (CH$_2$OH); 1.96, complex septet, 1 H (CH$_3$CH); 0.96, d, J = 7 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 138.1, s (quaternary phenyl C); 128.3, d (meta C's); 127.6, d (ortho C's); 73.6, d (C-3); 73.1, t (C-1 and benzylic C); 64.8, t (C-4); 36.0, d (C-2); 12.0, q (C-2 methyl). Ir 3600–3200 (OH); 1375 (methyl); 1100, 1060 (ether C–O); 738, 701 cm^{-1} (monosubstituted benzene). Mass spectrum (25% cutoff) *m/e* 210, 2.5% (M$^+$); 179, 8% (M$^+$ – CH$_2$OH); 108, 31%; 107, 51% (+OCH$_2$Ph); 91, 100% (PhCH$_2$$^+$); 65, 35%; 43, 41% (CH$_3$C≡O$^+$); 31, 28% (+CH$_2$OH).

Anal. Calcd for C$_{12}$H$_{18}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.39; H, 8.61.

2′-(1,3-Dioxacyclopent-2-on-4-yl)-1′-propyl Benzyl Ether (10). To a solution of 905 mg (4.3 mmol) of 2-methylbutane-1,3,4-triol 1-O-benzyl ether in 15 ml of pyridine was added 3 ml of a 2.07 M phosgene solution in toluene (6.2 mmol) with vigorous stirring and cooling with an ice bath. After stirring for 1 h at room temperature, the solution was poured into 50 ml of ice–H$_2$O–concentrated HCl (~3:1:1), which was extracted with 5 × 30 ml of ether. The ether layer was washed with 3 × 50 ml of saturated NaHCO$_3$ and dried over MgSO$_4$, and the ether was evaporated. The residue was distilled; only one fraction was collected at bp 164–167 °C (1 Torr) weighing 700.6 mg (69% yield, not optimized). ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 4.68, q, J = 8 Hz, 1 H (CHOCH$_2$); 4.48, t, J = 9 Hz, 1 H (CHOCH$_2$); 4.47, s, 2 H (benzylic protons); 4.26, t, J = 9 Hz, 1 H (CHOH$_2$O); 3.47, d of d, J = 4.5, 9 Hz, 1 H (CHCH$_2$O); 3.33, t, J = 9 Hz, 1 H (CHCH$_2$O); 2.11, m, 1 H (CH$_3$CH); 1.02, d, J = 7 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 155.1, s (C-2); 137.8, s (quaternary phenyl C); 128.5, d (meta C's); 127.8, d (para C); 127.6, d (ortho C's); 79.1, d (C-4); 73.3, t (benzyl C); 71.7, t (C-1′); 68.8, t (C-5); 37.5, d (C-2′); 11.6, q (C-3′). Ir 1812 (carbonate C=O); 1370 (methyl); 1176, 1091, 1066 (C–O); 740; 694 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) *m/e* 236, 0.9% (M$^+$); 235, 1.6% (M$^+$ – H); 159, 10% (M$^+$ – C$_6$H$_5$); 107, 18% (PhCH$_2$O$^+$); 91, 100% (PhCH$_2$$^+$); 68, 23%; 65, 20%; 43, 29%.

Anal. Calcd for C$_{13}$H$_{16}$O$_4$: C, 66.08; H, 6.83. Found: C, 66.26; H, 6.89.

3-Carbamoyl-2-methylbutane-1,3,4-triol 1-O-Benzyl Ether (12) and 4-Carbamoyl-2-methylbutane-1,3,4-triol 1-O-Benzyl Ether (11). To a solution of 1.37 g of 2′-(1,3-dioxacyclopent-2-on-4-yl)-1′-propyl benzyl ether (10) dissolved in 1 ml of dioxane, 5 ml of concentrated NH$_4$OH was added and the solution stirred for 15 h. The reaction mixture was poured into 50 ml of H$_2$O and extracted with 5 × 30 ml of ether. The ether layers were combined, washed with 2 × 100 ml of 10% HCl, 3 × 100 ml of saturated NaHCO$_3$, and 100 ml of saturated NaCl, and dried over MgSO$_4$. The ether was then evaporated, leaving 1.52 g of residue. This was chromatographed on 103 g of silica gel, giving 108.6 mg of 2-methylbutane-1,3,4-triol 1-O-benzyl ether (10, 8.8% yield, eluted with 20% EtOAc in benzene); 854.6 mg of pure 4-carbamoyl-2-methylbutane-1,3,4-triol 1-O-benzyl ether (11, 57.5%, 25% EtOAc in benzene); 278.8 mg of pure 3-carbamoyl-2-methylbutane-1,3,4-triol 1-O-benzyl ether (12, 18.9%, 25% EtOAc in benzene); as well as 181 mg of mixed fractions. An integrated 270-MHz ^{1}H NMR spectrum of the reaction mixture showed the ratio of primary (11) to secondary carbamate (12) to be 73:27. The products isolated were in the ratio 75:25.

Properties of 11: ^{1}H NMR δ 7.30, m, 5 H (aromatic protons); 5.50, br s, 2 H (NH$_2$); 4.45, s, 2 H (benzylic protons); 4.03, AB of ABX, $|J_{AB}|$ = 9 Hz, 2 H (CH$_2$OCONH$_2$); 3.93, X of ABX, 1 H (CHOH); 3.66, br s, 1 H (OH); 3.43, CD of CDY, $|J_{AB}|$ = 10, $|J_{AX} + J_{BX}|$ = 30 Hz, 2 H (CHCH$_2$OCH$_2$); 1.91, m, 1 H (CH$_3$CH); 0.92, d, J = 7 Hz, 3 H (CH$_3$CH). In Me$_2$SO-d_6, a pentet appears at δ 3.81, J ~ 4 Hz, 1 H (CHOH), that is coupled to a signal at δ 4.79, d, J = 5 Hz, 1 H (OH). ^{13}C NMR δ 157.2, s (urethane C=O); 137.9, s, (quaternary phenyl C); 128.4, d (meta C's); 127.7, d (para C); 127.6, d (ortho C's); 73.7, t (benzyl C*); 73.4, t (C-1*); 71.9, d (C-3); 67.8, t (C-4); 35.9, d (C-2); 11.3, q (C-2's methyl). Ir 3600–3200 (OH); 2850 (C–H); 1727–1740 (C=O); 1390 (methyl); 1080 (C–O); 740, 700 cm^{-1} (monosubstituted benzene). Mass spectrum (30% cutoff) *m/e* 254, 0.8% (M$^+$ + 1); 179, 5% (M$^+$ – CH$_2$OCONH$_2$); 147, 50% (M$^+$ – OCH$_2$Ph + 1); 108, 29% (PhCH$_2$OH$^+$); 107, 31% (PhCH$_2$O$^+$); 104, 27% (HO$^+$=CHCH$_2$O-CONH$_2$); 103, 28% (O=CHCH$_2$OCONH$_2$); 92, 44% (PhCH$_2$$^+$ + 1); 91, 100% (PhCH$_2$$^+$); 77, 13% (Ph$^+$); 44, 34% (NH$_2CO^+$).

Anal. Calcd for C$_{13}$H$_{19}$NO$_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.37; H, 7.31; N, 5.79.

Properties of 12: ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 5.04, br s, 2 H (NH$_2$); 4.77, q, J = 5 Hz, 1 H (CHOCONH$_2$); 4.50, s, 2 H (benzylic protons); 3.72, d, J = 4 Hz, 2 H (CH$_2$OH); 3.40, AB of ABX, $|J_{AB}|$ = 9 Hz, 2 H (CHCH$_2$OCH$_2$); 3.24, br s, 1 H (OH); 2.16, septet,

$J \sim 7$ Hz, 1 H (CH$_3$CH); 0.97, d, $J = 7$ Hz, 3 H (CH$_3$CH). In Me$_2$SO-d_6, a signal appeared at δ 4.76, t, $J \sim 5$ Hz, 1 H (OH), that was coupled to a signal at δ 3.46, obscured by H$_2$O peak (CH$_2$OH). ^{13}C NMR δ 157.6, s (urethane C=O); 137.8, s (quaternary phenyl C); 128.4, d (meta C's); 127.7, d (ortho + para C's); 77.7, d (C-3); 73.3, t (benzyl C); 71.9, t (C-1); 63.2, t (C-4); 34.9, d (C-2); 12.9, q (C-2's methyl). Ir 3600–3200 (OH); 2940–2850 (C–H); 1718 (C=O); 1380 (methyl); 1100, 1050, 1020 (C–O); 740, 697 cm^{-1} (monosubstituted benzene). Mass spectrum (30% cutoff) m/e 254, 0.8% (M$^+$ + 1); 223, 0.6% (M$^+$ – CH$_2$OH + 1); 192, 32% (M$^+$ – NH$_2$CO$_2$H); 107, 48% (PhCH$_2$O$^+$); 92, 48% (PhCH$_2^+$ + 1); 91, 100% (PhCH$_2^+$); 44, 32% (CO$_2^+$ or NH$_2$CO$^+$).

Anal. Calcd for C$_{13}$H$_{19}$NO$_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.48; H, 7.47; N, 5.55.

(2RS,3SR)-4-Acetoxy-2-methylbutane-1,3-diol 1-O-Benzyl Ether (13). A solution of 1.00 g (4.7 mmol) of (2RS,3SR)-2-methyl-butane-1,3,4-triol 1-O-benzyl ether (9) in 15 ml of pyridine and 0.44 ml (4.6 mmol) of acetic anhydride was stirred at room temperature for 48 h, and then poured into an ice–H$_2$O–concentrated HCl (3:3:1) mixture. This was extracted with 5 × 30 ml of ether, and the combined ether extracts washed with 2 × 100 ml of 5% HCl and 3 × 100 ml of saturated NaHCO$_3$, dried over MgSO$_4$, and evaporated under reduced pressure. The residue was applied to a high-pressure column chromatographic system and these fractions eluted: 925 mg of product (80% conversion, 96% yield, eluted with 10–15% EtOAc in benzene) and 201 mg of starting material (20%, eluted with 50% EtOAc in benzene). ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 4.50, s, 2 H (benzyl protons); 4.09, AB of ABX, $|J_{AB}| = 10.5$, $|J_{AX} + J_{BX}| = 36$ Hz, 2 H (CH$_2$OAc); 4.01, br X of ABX, 1 H (CHOH); 3.51, complex d, 2 H (CHCH$_2$OCH$_2$); 2.83, br s, 1 H (OH); 2.10, s, 3 H (CH$_3$CO); 2.00, m, 1 H (CH$_3$CH); 0.97, d, $J = 7$ Hz, 3 H (CH$_3$CH). In Me$_2$SO-d_6, a signal appeared at δ 4.87, d, $J \sim 6$ Hz, 1 H (CHOH), that was coupled to a signal at δ 3.76, pentet, $J \sim 5.2$ Hz, 1 H (CHOH). ^{13}C NMR δ 171.1, s (carbonyl C); 138.0, s (quaternary phenyl C); 128.3, d (meta C's); 127.5, d (ortho + para C's); 73.1, t (benzyl C + C-1); 70.6, d (C-3); 67.0, t (C-4); 35.9, d (C-2); 20.8, q (acetate methyl); 11.2, q (C-2 methyl). Ir 3600–3200 broad, (OH); 1745 (acetate C=O); 1380 (methyl); 1242 (C–O–C of acetate); 1095, 1060 (ether C–O); 740, 694 cm^{-1} (monosubstituted benzene). Mass spectrum (3% cutoff) m/e 252, 0.05% (M$^+$); 179, 1.0% (M$^+$ – CH$_2$OAc); 91, 100% (PhCH$_2^+$); 43, 87% (CH$_3$C=O$^+$).

Anal. Calcd for C$_{14}$H$_{20}$O$_4$: C, 66.64; H, 7.99. Found: 66.67; H, 7.72.

When 1.2 molar equiv of acetic anhydride was used, 26% of the diacetate of 9 was isolated by HPLC.

Anal. Calcd for C$_{16}$H$_{22}$O$_5$: C, 65.29; H, 7.53. Found: C, 65.54; H, 7.55.

(2RS,3SR)-4-Acetoxy-3-carbamoyl-2-methyl-1-butanol 1-O-Benzyl Ether (3). A solution of 331 mg (1.31 mmol) of 4-acetoxy-2-methylbutane-1,3-diol 1-O-benzyl ether in 5 ml of CH$_2$Cl$_2$ was added to a 10-ml flask containing 173 mg (2.62 mmol) of NaOCN, and 314 mg (2.62 mmol) of CF$_3$CO$_2$H was added dropwise with very slow stirring. The flask was stoppered and allowed to stir slowly for 2 days. The reaction mixture was then poured into 50 ml of CH$_2$Cl$_2$, to which 50 ml of H$_2$O was added. The H$_2$O layer was extracted with 4 × 25 ml of CH$_2$Cl$_2$ and washed with 2 × 50 ml of 5% HCl and 3 × 50 ml of saturated NaHCO$_3$, and the CH$_2$Cl$_2$ was evaporated, leaving 382 mg of solid, which was recrystallized from ether–benzene to give 371 mg (96%) of white solid with mp 112–113 °C. ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 5.08, m, 1 H (CHO); 4.73, br s, 2 H (NH$_2$); 4.50, s, 2 H (benzylic protons); 4.27, d of d, $J = 3$, 12 Hz, 1 H (CH$_2$OAc); 4.17, d of d, $J = 12$, 15 Hz, 1 H (CH$_2$OAc); 3.38, complex d, 2 H (CHCH$_2$OCH$_2$); 2.11, m, 1 H (CH$_3$CH); 2.06, s, 3 H (CH$_3$C=O); 1.00, d, $J = 7$ Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 170.9, s (acetate C=O); 156.6, s (urethane C=O); 138.1, s (quaternary phenyl C); 128.3, d (meta C's); 127.6, d (ortho + para C's); 73.2, t + d (benzyl C + C-3); 71.8, t (C-1); 64.2, t (C-4); 35.1, d (C-2); 20.8, q (acetate methyl); 12.3, q (C-2-methyl). Ir 3401, 3279 (NH$_2$); 1745 (acetate C=O); 1701 (urethane C=O); 1647 (amide I band); 1235 (C–O–C of acetate); 1050 (ether C–O); 740, 695 cm^{-1} (monosubstituted benzene). Mass spectrum (10% cutoff) m/e 295, 0.09% (M$^+$); 128, 15%; 91, 69% ($^+$CH$_2$Ph); 71, 18%; 68, 32%; 65, 19%; 43, 100% (CH$_3$C=O$^+$).

Anal. Calcd for C$_{15}$H$_{21}$NO$_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.82; H, 6.96; N, 4.48.

(2RS,3SR)-3-Acetoxy-2-methylbutane-1,4-diol 1-O-Benzyl Ether. To a solution of 1.00 g of (2RS,3SR)-2-methylbutane-1,3,4-triol 1-O-benzyl ether in 15 ml of pyridine was added 1.44 g of trityl chloride. The solution was stirred for 48 h at room temperature following which 0.45 ml of acetic anhydride was added, and the solution stirred 2 more days at room temperature. After addition of 50 ml of ether the mixture was washed with 2 × 50 ml of H$_2$O. The H$_2$O layer was extracted with 3 × 50 ml of ether and the combined ether extracts

washed with 2 × 50 ml of 5% HCl and 3 × 100 ml of saturated NaHCO$_3$ and dried over MgSO$_4$. The residue after solvent evaporation was subjected to HPLC on 108 g of slightly acidic silica gel. In addition to trityl compounds, eluted with benzene, there were obtained 345 mg of diacetate (25%, eluted with 5% EtOAc in benzene), 170 mg of 4-acetoxy-2-methylbutane-1,3-diol 1-O-benzyl ether (14%, eluted with 10% EtOAc in benzene), and 673 mg of 3-acetoxy-2-methylbutane-1,4-diol 1-O-benzyl ether (56%, eluted with 15–20% EtOAc in benzene). ^{1}H NMR δ 7.32, m, 5 H (aromatic protons); 4.91, d of t, $J = 4.5$, 6.3 Hz, 1 H (CHOAc); 4.50, AB quartet, $|J_{AB}| = 16.2$ Hz, 2 H (benzylic protons); 3.72, br t, $J \sim 6$, 2 H (CH$_2$OH); 3.42, d of d, $J = 4.8$, 19.5 Hz, 1 H (CH$_3$CHCH$_2$O); 3.34, d of d, $J = 7.4$, 9.5 Hz, 1 H (CH$_3$CHCH$_2$O); 2.69, t, $J \sim 6$ Hz, 1 H (CH$_2$OH); 2.18, m, 1 H (CH$_3$CH); 2.07, s, 3 H (CH$_3$C=O); 0.94, d, $J = 7$ Hz, 3 H (CH$_3$CH). Ir 3600–3200 broad (OH); 1745 (acetate C=O); 1380 (methyl); 1245 (C–O–C of acetate); 1095, 1060 (ether C–O); 740, 694 cm^{-1} (monosubstituted benzene). Mass spectrum (5% cutoff) m/e 235, 0.2% (M$^+$ – OH); 222, 0.3% (M$^+$ – CH$_2$OH + 1); 209, 0.3% (M$^+$ – CH$_3$C=O); 192, 12% (M$^+$ – CH$_3$CO$_2$H); 191, 2.2% (M$^+$ – CH$_3$CO$_2$); 161, 3% (M$^+$ – CH$_2$Ph); 108, 31% (PhCH$_2^+$OH); 107. 17% (PhCH$_2$O$^+$); 91, 100% (PhCH$_2^+$); 65, 14%; 43, 76% (CH$_3$C=O$^+$).

Anal. Calcd for C$_{14}$H$_{20}$O$_4$: C, 66.64; H, 7.99. Found: C, 66.45; H, 7.82.

Preparation of the Carbinolamide 2. To a solution of 57.9 mg (0.2 mmol) of 3-carbamoyl-4-acetoxy-2-methylbutanol 1-O-benzyl ether (3) in 1 ml of hot benzene was added a solution of 32.0 mg (0.2 mmol) of styrylglyoxal[21,22] in hot benzene. The solution was stirred for 48 h under reflux and the solvent evaporated in vacuo. It was replaced with 2 ml of hexane–toluene (10:1) and the mixture kept at –25 °C for 2 days. Crystals (88.0 mg, 98%) having mp 80–82 °C were collected after centrifugation and washing with cold hexane (1 ml). The melting point of these crystals was not changed after a further recrystallization from the same solvent mixture. They may consist of a mixture of diastereomers. ^{1}H NMR δ 7.86, d, $J = 15$ Hz, 1 H (=CHCO); 7.62, d of d, $J = 6$, 2 Hz, 2 H (meta H's of PhCH=); 7.38, br m, 3 H (ortho and para H of PhCH=); 7.27, m, 5 H (PhCH$_2$); 7.03, d, $J = 15$ Hz, 1 H (PhCH=); 6.10, br d $J \sim 6$ Hz, 1 H (OCHNH); 5.75, br d, $J \sim 6$ Hz, 1 H (OCHNH); 5.20, m, 1 H (CHOCONH); 4.78, br m (HOCHNH); 4.47, s, 2 H (CH$_2$Ph); 4.28, m, 2 H (CH$_2$OAc); 3.40. d, $J = 6$ Hz, 2 H (CH$_3$CHCH$_2$O); 2.03, s, 3 H (COCH$_3$); 1.98, m, 1 H (CH$_3$CH); 1.02, d, $J = 6$ Hz, 3 H (CH$_3$CH). The doublet at δ 1.02 is really two doublets (in about a 60:40 ratio) separated by less than 2 Hz at 270 MHz, possibly resulting from this being a diastereomeric mixture. In addition to the peaks reported above, there are present clear peaks at δ 6.98 (styrylglyoxal) and 5.11, 4.90, and 4.49 (urethane 3) comprising roughly 5% of the mixture, possibly resulting from dissociation in the NMR tube. Ir 3400 (NH); broad 3600–3300 (OH); 1745 (OCOCH$_3$); 1701 (CH=CHCO); 1227; br 1064 (C–O–C); 754, 712 cm^{-1} (monosubstituted benzene). Mass spectrum (20% cutoff) m/e 192, 3.1%; 174, 67%; 159, 23%; 131, 100% (PhCH=CHCO$^+$); 99. 23%; 91, 87% (PhCH$_2^+$); 43, 53% (CH$_3$CO$^+$).

Anal. Calcd for C$_{25}$H$_{29}$NO$_7$: C, 65.92; H, 6.42; N, 3.08. Calcd for hemihydrate: C, 64.64; H, 6.51; N, 3.02. Found: C, 64.91, 65.02; H, 6.31, 6.36; N, 3.40, 3.36.

Preparation of the Carbinolamide Methyl Ether 2a. A solution of 40 mg of the carbinolamide 2 in 1 ml of distilled methanol was heated in an oil bath until boiling occurred. The boiling was continued for 1 min and then the excess methanol evaporated in vacuo. This yielded 40.2 mg of a clear oil homogeneous by TLC and NMR. ^{1}H NMR δ 7.86, d, $J = 12$ Hz, 1 H (=CHCO); 7.61, d of d, $J = 6$, 2 Hz, 2 H (meta H's of PhCH=); 7.38, br m, 3 H (ortho and para H of PhCH=); 7.28, m, 5 H (PhCH$_2$); 7.01, d, $J = 12$ Hz, 1 H (PhCH=); 6.32, d, $J \sim 6$ Hz, 1 H (OCHNH); 6.02, br d, $J \sim 6$ Hz, 1 H (OCHNH); 5.20, m, 1 H (CHOCONH); 4.48, s, 2 H (CH$_2$Ph); 4.29, m, 2 H (CH$_2$OAc); 3.50, s, 3 H (CH$_3$O); 3.40, d, $J = 6$ Hz, 2 H (CH$_3$CHCH$_2$O); 2.05, s, 3 H (OCOCH$_3$); 1.98, m, 1 H (CH$_3$CH); 1.02, d, $J = 6$ Hz, 3 H (CH$_3$CH). Ir 3350 (NH); 1730 (OCOCH$_3$); 1689 (PhCH=CHCO); 1215; 1100, 1062 (C–O–C); 750, 712 cm^{-1} (monosubstituted benzene). Mass spectrum (20% cutoff) m/e 338, 19% (M$^+$ – PhCHCHCO); 131, 100% (PhCHCHCO$^+$); 91, 37% (PhCH$_2^+$); 57, 22%; 43, 42% (CH$_3$CO$^+$).

Anal. Calcd for C$_{26}$H$_{31}$NO$_7$: C, 66.51; H, 6.66; N, 2.98. Found: C, 66.23; H, 6.57; N, 3.02.

(–)-(5R,6S)-2,2,5-Trimethyl-6-[(R)-N-α-phenylethylcarbamoyloxy]-1,3-dioxepane and (+)-(5S,6R)-2,2,5-Trimethyl-6-[(R)-N-α-phenylethylcarbamoyoxy]-1,3-dioxepane. Into a flame-dried 100-ml flask containing a stirring bar and 60 ml of freshly distilled hexane was added by syringe 5.63 g (35.2 mmol) of (5RS,6SR)-2,2,5-trimethyl-6-hydroxy-1,3-dioxepane, followed by 4.93 g (33.5 mmol) of (+)-(R)-α-phenethyl isocyanate (Norse Laboratories). The flask was fitted with a reflux condenser and flushed with N$_2$. After 4 days at reflux, TLC showed no isocyanate remaining, and

the solvent was removed in vacuo. The resulting yellow oil was dissolved in 90 ml of hexane + 15 ml of toluene + 1 ml of pyridine and left in the freezer for 5 days, during which time crystallization occurred. After three recrystallizations from hexane–toluene (9:1 to 5:1), there was obtained 2.32 g (22.5%, 45% of theory) of a solid having mp 103–103.5 °C and $[\alpha]^{23}$D −1.96° (c 1.0, CHCl₃). Prior experiments had shown that the rotation of such material does not improve upon further recrystallization. ¹H NMR δ 7.31, m, 5 H (phenyl H); 5.11, br d, 1 H (NH); 4.82, pentet, J ~ 6.6 Hz, 1 H (CHN); 4.42, br m, 1 H (CHO); 3.73, two d, J = 12, 2 Hz, 2 H (one H each from C-4 and C-7); 3.61, d of d, J = 12, 6 Hz, 1 H (C-7 H); 3.40, d of d, J = 12, 5.4 Hz, 1 H (C-4 H); 1.86, m, 1 H (CH₃CHCH₂); 1.49, d, J = 7 Hz, 3 H (CH₃CHN); 1.33, s, 3 H (CH₃CCH₃); 1.31, s, 3 H (CH₃CCH₃); 0.98, d, J = 7 Hz, 3 H (CH₃CHCH₂). ¹³C NMR δ 155.3, s (urethane C=O); 143.9, s (quaternary phenyl C); 128.5, d (meta C's); 127.2, d (para C); 125.9, d (ortho C's); 101.1, s (C-2); 76.4, d (C-6); 62.6, t (C-7); 61.3, t (C-4 of dioxepane); 50.9, d (benzyl C); 38.6, d (C-5 of dioxepane); 24.8, q (methyl of C-2); 24.4, q (methyl of C-2); 22.6, q (methyl β to phenyl); 14.4, q (methyl of C-5). Ir 3322 (NH); 1724 (C=O); 1370, 1380 (methyls); 1233, 1214 (acetonide); 846; 704, 763 cm⁻¹ (monosubstituted benzene). Mass spectrum (10% cutoff) m/e 308, 0.5% (M⁺ + 1); 307, 0.05% (M⁺); 292, 1.8% (M⁺ − CH₃); 250, 10% (M⁺ − CH₂COCH₃); 249, 11% (M⁺ − CH₃COCH₃); 105, 100% (PhCHCH₃⁺); 84, 26%; 77, 10% (Ph⁺); 72, 18%; 58, 56% (CH₃COCH₃⁺); 43, 36% (CH₃C≡O⁺).

Anal. Calcd for C₁₇H₂₅NO₄: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.50; H, 8.00; N, 4.71.

The mother liquors from the first crystallization were chromatographed on silica gel using 1–4% EtOAc in benzene containing 0.1% pyridine, which afforded slight separation of the diastereomers. After four passes through a HPLC column of 108 g silica gel, there was obtained 321 mg (23%, 47% of theory) of the diastereomer melting at 74.5–75.0 °C after crystallization from hexane. This diastereomer had $[\alpha]^{23}$D 78.44° (c 1.0, CHCl₃). ¹H NMR δ 7.31, m, 5 H (phenyl H); 5.20, br d, J ~ 6 Hz, 1 H (NH); 4.82, pentet, J = 6.6 Hz, 1 H (CHN); 4.44, br d of t, 1 H (OCH); 3.78, br d, 2 H (one H each from C-4 and C-7); 3.67, br d of d, J = 12, 5.4 Hz, 1 H (C-7 H); 3.38, d of d, J = 12, 6 Hz, 1 H (C-4 H); 1.80, sextet of d, J = 6.6, 2 Hz, 1 H (C-5 H); 1.48, d, J = 7.2 Hz, 3 H (CH₃CHN); 1.33, s, 3 H (CH₃CCH₃); 1.31, 3 H (CH₃CCH₃); 0.93, d, J = 7.2 Hz, 3 H (CH₃CHCH₂). ¹³C NMR δ 155.2, s (urethane C=O); 143.8, s (quaternary phenyl C); 128.6, d (meta C's); 127.2, d (para C); 125.9, d (ortho C's); 101.2, s (C-2 of dioxepane); 76.3, d (C-6 of dioxepane); 62.6, t (C-7 of dioxepane); 61.2, t (C-4 of dioxepane); 50.8, d (benzyl C); 38.6, d (C-5 of dioxepane); 24.8, q (C-2's methyl); 24.4, q (C-2's methyl); 22.4, q (methyl β to phenyl); 14.5, q (C-5's methyl). Ir 3330 (NH); 1689 (C=O); 1368 (methyls); 1239, 1218 (acetonide); 847; 777, 703 cm⁻¹ (monosubstituted benzene). Mass spectrum (10% cutoff) m/e 292, 2.7% (M⁺ − CH₃); 249, 17% (M⁺ − CH₃COCH₃); 164, 17%; 132, 27%; 130, 23%; 120, 10% (PhCHNHCH₃⁺); 105, 100% (PhCHCH₃⁺); 91, 20% (PhCH₂⁺); 84, 62%; 79, 16%; 77, 18% (Ph⁺); 71, 42%; 59, 65% (CH₃⁺COHCH₃); 43, 42% (CH₃C≡O⁺).

Anal. Calcd for C₁₇H₂₅NO₄: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.18; H, 7.95; N, 4.33.

(−)-(5R,6S)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (Enantiomer of 6). To 1.06 g (31.1 mmol) of lithium aluminum hydride suspended in 20 ml of THF (freshly distilled from LiAlH₄) was added with stirring over a period of 10 min a solution of 1.96 g (6.4 mmol) of (−)-(5R,6S)-2,2,5-trimethyl-6-[(R)-N-α-phenylethylcarbamoyl]-1,3-dioxepane in 10 ml of THF, while cooling in an ice bath. The mixture was then heated at reflux under N₂ for 5 h. The flask was cooled in an ice bath and 2.5 ml of saturated Na₂SO₄ solution added dropwise with stirring. The resulting white precipitate was filtered and washed with 10 × 6 ml of Et₂O. The filtrate was dried over MgSO₄ and evaporated, leaving 1.94 g of a mixture of the alcohol and α-phenethylamine. These were separated by a rapid filtration through silica gel. For this purpose the mixture was dissolved in 5 ml of hexane, applied to 15 g of silica gel, and 45 ml of hexane filtered through and discarded. Elution with 20 ml of ether, followed by 30 ml of EtOAc, afforded 1.03 g of the alcohol. Further elution with EtOAc (50 + 100 ml) eluted only amine in small quantities. The alcohol was distilled in a microstill to give 988.3 mg (96%) of pure (−)-6 having $[\alpha]^{23}$D −43.46° (c 1.0, CHCl₃). The ir, ¹H NMR, and mass spectra of this material were identical with those of the racemate.

Determination of Absolute Configuration of (+)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (6). (+)-(5S,6R)-2,2,5-Trimethyl-6-hydroxy-1,3-dioxepane (32.0 mg, 0.20 mmol) having $[\alpha]^{22}$D = +42.39° (c 1.0, CHCl₃) and 124.0 mg (0.40 mmol) of α-phenylbutyric anhydride²³ were dissolved in dry pyridine to make 1.00 ml of solution. Previous work had established that the reaction is complete in 8 h at room temperature. The reaction mixture was allowed

to remain at room temperature for 16 h after which 50.0 μl of H₂O was added to effect hydrolysis of excess anhydride. After 45 min a rotation was taken of the solution: α_1 2.346°. The solution was removed from the cell, mixed with 100 μl of Et₃N, and a second rotation taken immediately: α_2 2.529°. According to the method of Horeau¹⁹ one obtains $\alpha_1 - 1.1 \alpha_2 = -0.436°$ and thus the alcohol has the "configuration":
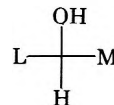
In this case, this translates to 5S,6R for the absolute configuration of the alcohol 6 and 16.7% for the optical yield in the acylation reaction. The ester was isolated by pouring the solution into 20 ml of Et₂O, washing with 2 × 20 ml of NaHCO₃, drying over MgSO₄, and evaporating the solvents. The residue weighed 52.3 mg (86% yield) and had a rotation of 2.426° when dissolved in 1.00 ml of dry pyridine + 50.0 μl of H₂O ([α]²³D 48.7°) and 2.224° when dissolved in 1.00 ml of dry pyridine + 50.0 μl of H₂O + 100 μl of Et₃N ([α]²³D 48.9°). Thus the assumption of little change in [α]D of ester upon addition of Et₃N is correct in this case (cf. ref 19). ¹H NMR δ 7.32, s, + 7.30 (ratio 58:42), s, 5 H (phenyl H); 4.50, d of t, J = 6.6, 3.6 Hz, 1 H (OCH); 3.65, d, J = 4.2 Hz, 1 H (OCHCH₂); 3.59,²⁴ d of d, J = 9.6, 3.0 Hz, and 3.42,²⁴ d of d, J = 12, 7.8 Hz, 1 H (CHCO₂); 3.50,²⁴ d of d, J = 24, 7.2 Hz, 1 H (OCHCH₂O); 3.49,²⁴ d of d, J = 14.4, 12.6 Hz, 1 H (CHCH₂); 3.32,²⁴ d of d, J = 12.6, 7.2 Hz, 1 H (CHCH₂O); 2.11, d of quintets, J = 7.2 Hz, and 1.81, d of quintets, J = 7.2 Hz (ratio 58:42), 2 H (CH₃CH₂); 1.68, d of sextets, J = 7.2, 3.0, 1 H (CH₃CH); 1.32, s, 3 H (CH₃CCH₃); 1.31, s, 3 H (CH₃CCH₃); 0.91, d of d, J = 7.2 Hz, and 0.89, d of d, J = 7.2, 13.6 Hz (ratio 58:42), 3 H (CH₃CH₂); 0.73, d, J = 7.2 Hz, 2 H (CH₃CH). Ir 1730 (C=O); 1370, 1366 (methyl); 1220 (acetonide) 846; 698, 770 cm⁻¹ (monosubstituted benzene). Mass spectrum (10% cutoff) m/e 291, 8% (M⁺ − CH₃); 147, 15% [PhC(CH₂CH₃)=COH⁺]; 119, 100% (PhCHC₂H₅⁺); 91, 46% (PhCH₂⁺); 84, 15%, 59, 18% (CH₃⁺COHCH₃); 43, 12% (CH₃C≡O⁺).

Registry No.—2, 59005-35-5; 2a, 59005-36-6; 3, 59005-37-7; 4, 1003-83-4; 5, 57280-22-5; 6, 59005-38-8; 6 acetate, 59005-39-9; (−)-(5R,6S)-6, 59042-52-3; (+)-(5S,6R)-6, 59042-53-4; 7, 58967-01-4; 8, 59005-40-2; 9, 59005-41-3; 10, 59005-42-4; 11, 59005-43-5; 12, 59005-44-6; 13, 59005-45-7; cis-2-butene-1,4-diol, 6117-80-2; 2,2-dimethoxypropane, 77-76-9; NaOCN, 917-61-3; CF₃CO₂H, 76-05-1; (2RS,3SR)-3-acetoxy-2-methylbutane-1,4-diol 1-O-benzyl ether, 59005-46-8; styrylglyoxal, 6784-05-0; (−)-(5R,6S)-2,2,5-trimethyl-6-[(R)-N-α-phenylethylcarbamoyloxy]-1,3-dioxepane, 59005-47-9; (+)-(5S,6R)-2,2,5-trimethyl-6-[(R)-N-α-phenylethylcarbamoyloxy]-1,3-dioxepane, 59042-54-5; (+)-(R)-δ-phenethyl isocyanate, 33375-06-3.

References and Notes

(1) S. M. Kupchan, Y. Komoda, W. A. Court, G. J. Thomas, R. M. Smith, A. Karim, C. J. Gilmore, R. C. Hattiwanger, and R. F. Bryan, *J. Am. Chem. Soc.*, **94**, 1354 (1972).

(2) S. M. Kupchan, Y. Komoda, G. J. Thomas, and H. P. J. Hintz, *J. Chem. Soc., Chem. Commun.*, 1065 (1972).

(3) S. M. Kupchan, Y. Komoda, A. R. Branfman, R. G. Diley, and V. A. Zimmerly, *J. Am. Chem. Soc.*, **96**, 3706 (1974).

(4) M. C. Wani, H. L. Taylor, and M. E. Wall, *J. Chem. Soc., Chem. Commun.*, 390 (1973).

(5) A. I. Meyers and C. C. Shaw, *Tetrahedron Lett.*, 717 (1974).

(6) A. I. Meyers, D. Horne, C. C. Shaw, L. M. Trefonas, and R. J. Majeste, *Tetrahedron Lett.*, 1746 (1975).

(7) A. I. Meyers and R. S. Brinkmeyer, *Tetrahedron Lett.*, 1749 (1975).

(8) E. J. Corey and M. J. Bock, *Tetrahedron Lett.*, 2643 (1975).

(9) J. D. Malkemus, U.S. Patent 2 627 524; *Chem. Abstr.*, **48**, 712h (1948).

(10) H. Najer, P. Chabrier, and R. Giudicelli, *Bull. Soc. Chim. Fr.*, 1142 (1954).

(11) R. W. Herr, D. M. Wieland, and C. R. Johnson, *J. Am. Chem. Soc.*, **92**, 3812 (1970); R. W. Herr and C. R. Johnson, *ibid.*, **92**, 4979 (1970).

(12) Cf. for instance, *Chem. Zentralbl.*, **2**, 3192 (1939).

(13) R. F. Monroe, U.S. Patent 3 240 702; *Chem. Abstr.*, **64**, 13995c (1966).

(14) The threo stereochemistry established for 6 on mechanistic grounds has been confirmed by converting this compound into threo-3-methylmalic acid, mp 127–128 °C, by benzylation followed by hydrolysis of the acetonide grouping in aqueous HCl, oxidation of the primary alcohol groups with Jones reagent, and debenzylation with Pd/H₂. Y. Izumi, S. Tatsumi, and M. Imaida [*Bull. Chem. Soc. Jpn.*, **39**, 1818 (1966)] reported mp 129

°C for the threo acid and mp 115 °C for the erythro isomer. Stereoisomeric purity of **6** was shown by elution of a single peak on GLC under conditions that separated the (5*RS*,6*SR*) and (5*RS*,6*RS*) isomers, obtained by Collins oxidation of **6** and reduction of the resulting ketone by NaBH₄.

(15) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **28**, 3421 (1963).
(16) C. Bischoff, *Ber.*, **7**, 631 (1874). Cf. also O. Diels and C. Seib, *ibid.*, **42**, 4062 (1909).
(17) S. L. Vail, C. M. Moran, and R. H. Barker, *J. Org. Chem.*, **30**, 1195 (1965).
(18) All rotations in this study were taken in CHCl₃ at concentration 1.0.
(19) A. Horeau, *Tetrahedron Lett.*, 1939 (1971).
(20) Note that (−)-**6** is the enantiomer both of structure **6** as drawn in Scheme I and of the native configuration of maytansine.
(21) M. Miyano, C. R. Dorn, and R. A. Mueller, *J. Org. Chem.*, **37**, 1810 (1972).
(22) Prepared by Y. Y. Chan Leung.
(23) H. Falk and K. Schlögl, *Monatsh. Chem.*, **96**, 276 (1965).
(24) These signals could have coupling constants incorrectly assigned; the chemical shifts and their assignment to individual protons were established by double resonance.

Stereocontrolled Synthesis of α-Multistriatin, an Essential Component of the Aggregation Pheromone for the European Elm Bark Beetle

William J. Elliott and Josef Fried*

Department of Chemistry and The Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Illinois 60637

A practical stereocontrolled synthesis of an 85:15 equilibrium mixture of α- and γ-multistriatin (**1**) in an overall yield of 73% is described. α-Multistriatin is one of the three essential components of the aggregation pheromone of the European elm bark beetle. The dioxolane **3** which is available in 90% yield from (*Z*)-2-butene-1,4-diol in both the racemic and enantiomeric forms is converted as the racemate to the iodide **5** and the latter used in the alkylation of the anion of 3-pentanone. Hydrolytic cleavage of the resulting acetonide **6** furnishes the racemic multistriatins in 80% yield from **3**. The use of optically active **3** in this synthesis should furnish the as yet unknown absolute configuration of the natural pheromone.

The aggregation pheromone for the European elm bark beetle, *Scolytus multistriatus* (Marsham), which is the principal vector of Dutch elm disease in the United States, has recently been characterized as a three-component mixture by Silverstein et al.[1] One of the active components has been named α-multistriatin by these authors and has been assigned structure **1**.[2] The other two components are (−)-4-methyl-

3, R = OH
4, R = tosyl
5, R = I

6

3-heptanol and (−)-α-cubebene (**2**). The first two components are beetle-produced pheromones, the third a host-produced synergist. The possible uses of a mixture of the three as a control of the elm bark beetle makes α-multistriatin an interesting target for chemical synthesis.

Of the two previous syntheses by Silverstein and associates the first, a nonstereospecific approach, served to elucidate and confirm the structure of the molecule; the second was designed to prove its stereochemistry. Although stereocontrolled, it proceeded in less than 2.5% overall yield.[2]

The synthesis reported in this paper yields multistriatin as an 85:15 mixture of α and γ isomers (as does that of Silverstein et al.[2]) in an overall yield of 73% from commercially available (*Z*)-2-butene-1,4-diol. The crucial step is the alkylation of
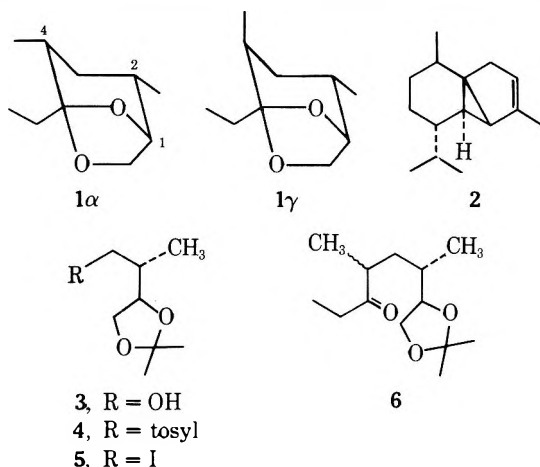
3-pentanone with the iodide **5**, which possesses the correct threo configuration at C-1 and C-2 of both α- and γ-multistriatin.[3] The iodide **5** was obtained in quantitative yield by classical procedures from the dioxolane **3**. The synthesis of the latter in four steps in 90% yield is described in the preceding paper.[4,5] The alkylation reaction of 3-pentanone with the iodide **5** could be accomplished in low yield via the pyrrolidine enamine,[6] or the magnesium salt of the *tert*-butylimine.[7] The preferred method was reaction of the enolate (5 equiv; prepared from the ketone with lithium diisopropylamide) and the iodide in THF for 3 days at room temperature. This method afforded approximately 85% of the mixture of diastereomeric ketones **6**, and 15% of recovered iodide. The acetonide grouping was removed and the molecule cyclized by treatment with 1 N HCl in 2:1 acetonitrile–H₂O for 18 h, which provided multistriatin (**1**) in quantitative yield in an 85:15 ratio of α and γ isomers, shown by ¹H NMR at 270 MHz and GLC to be identical with the equilibrium mixture obtained by Silverstein et al.[2]

That no detectable amounts of the β or δ isomers were formed in this sequence of reactions attests to the stereospecificity of the epoxide opening reaction with dimethyllithium cuprate,[4,5] a key reaction in the synthesis of the dioxolane **3**.

Since this compound has been obtained in optically active form of known absolute configuration,[4] this synthesis also constitutes a total synthesis of optically active α- and γ-multistriatin. Completion of the synthesis with optically active **3** will at the same time establish the as yet unknown absolute configuration of the natural pheromone.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer. Liquid samples were run as a thin film between NaCl plates. NMR spectra were determined as solutions in CDCl₃ with Me₄Si as an internal standard. Chemical shifts are reported in δ, coupling constants (*J*) are reported in hertz; the abbreviations s, d, t, q, and m signify singlet, doublet, triplet, quartet, and multiplet, respectively. ¹H NMR spectra were recorded on a Bruker HX-270

(270 MHz) spectrometer in the pulsed Fourier transform mode. ^{13}C NMR spectra were recorded on a Bruker HX-90E spectrometer operating at 22.63 MHz in the pulsed Fourier transform mode. Free induction decay data were accumulated and processed with a Nicolet 1089 computer. Low-resolution mass spectra were determined using a Finnigan 1015 quadrupole mass spectrometer equipped with VPC, gas and solid probe inlets; the data were recorded and processed by a Systems Industries Computer Interface System/150, and plotted as bar graphs. High-resolution mass spectra were determined on an AEI MS-9 spectrometer fitted with a PDP-8/I computer system for data analysis. High-pressure liquid chromatography was carried out using Quantum Industries TLC grade silica gel (no binder) in glass columns. Separation of multistriatin isomers was carried out using an F and M Model 400 gas chromatograph with a 6 ft × 0.125 in. glass column containing 1.5% Carbowax 20M on 100/120 Chromosorb G at 80 °C.

(2′RS,4SR)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-propyl Tosylate (4). To a solution of 503.5 mg (3.14 mmol) of the acetonide alcohol 3 in 8 ml of pyridine, cooled to 0 °C, was added 1.1996 g (6.3 mmol) of tosyl chloride and the solution stirred at 0 °C for 2 h and then at room temperature for 3 h. Cold H_2O (50 ml) was added and the liquid extracted with 4 × 35 ml of ether. The ether layers were combined, washed with 2 × 35 ml of 5% HCl and 3 × 50 ml of saturated $NaHCO_3$, and dried over $MgSO_4$. Evaporation of the ether gave 978.2 mg (99%) of an oil that was 99% pure by NMR. This material was thermally unstable when kept neat at room temperature, and was therefore used immediately in the next reaction. ^1H NMR δ 7.60, AA′BB′, 4 H (aromatic protons); 4.03, m, 1 H (CHO); 3.95, d, J = 6.5 Hz, 2 H (CH$_2$OTs); 3.91, m, 1 H (OCHCH$_2$O); 3.60, t, J = 6.7 Hz, 1 H (OCHCH$_2$O); 2.45, s, 3 H (CH$_3$Ar–); 1.98, septet, J = 6.5 Hz, 1 H (CH$_3$CH); 1.32, s, 3 H (acetonide CH$_3$); 1.28, s, 3 H (acetonide CH$_3$); 0.95, d, J = 6.5 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 144.8, s (para C); 132.9, s (sulfur-bearing C); 129.9, d (meta C's); 127.9, d (ortho C's); 108.8, s (C-2 of dioxolane); 76.2, d (C-4 of dioxolane); 72.1, t (C-1 of propyl); 67.1, t (C-5 of dioxolane); 36.0, d (C-2 of propyl); 26.2, q (methyl of dioxolane cis to alkyl chain); 25.2, q (methyl of dioxolane trans to alkyl chain); 21.6, q (tosyl methyl); 11.8, q (C-3 of propyl). Ir 1361, 1186 (SO$_2$OR); 971; 820 cm^{-1} (para-disubstituted benzene). Mass spectrum (10% cutoff) m/e 299, 1.9% (M$^+$ – CH$_3$); 172, 65% (TsOH$^+$); 155, 10% (Ts$^+$); 107, 44%; 91, 100% (PhCH$_2$$^+$); 65, 56%; 57, 55% (CH$_3$COCH$_2$$^+$); 43, 14% (CH$_3$C≡O$^+$).

(2′RS,4SR)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-1′-iodopropane (5). A solution of 394.7 mg of the tosylate 4 in 5 ml of distilled acetone and 502.3 mg of NaI was stirred for 18 h, and the resulting precipitate filtered. An additional 201.3 mg of NaI was added, and the mixture stirred for 30 more h, after which it was filtered, and the filtrate poured into 50 ml of H$_2$O and extracted with 4 × 50 ml of ether. The combined layers were washed with 50 ml of 10% Na$_2$SO$_3$ and dried over MgSO$_4$, and the ether was evaporated. The resulting pale yellow oil was distilled at 20 mTorr at 55 °C in a microstill to give 340 mg (99%) of a clear oil. The oil decomposed to a black tar when allowed to remain at room temperature in air for 24 h, or upon heating above 60 °C. It could be stored for at least 6 months in hexane over copper wire. ^1H NMR δ 4.08, m, 1 H (CHOCH$_2$); 4.06, m, 1 H (CH$_2$O); 3.63, m, 1 H (CH$_2$O); 3.26, d of d, J = 6, 12.4 Hz, 1 H (CH$_2$I); 3.03, d of d, J = 7.2, 12.4 Hz, 1 H (CH$_2$I); 1.76, m, 1 H (CH$_3$CH); 1.41, s, 3 H (acetonide CH$_3$); 1.34, s, 3 H (acetonide CH$_3$); 1.09, d, J = 6 Hz, 3 H (CH$_3$CH). ^{13}C NMR δ 108.6, s (C-2 of dioxolane); 78.3, d (C-4 of dioxolane); 66.8, t (C-5 of dioxolane); 38.3, d (C-2 of propane); 26.3, q (methyl of dioxolane cis to alkyl group); 25.2, q (methyl of dioxolane trans to alkyl group); 16.2, q (C-3 of propane); 10.7, t (C-1 of propane). Ir 2950 (CH); 1490, 1480 (methyls); 1205; 1065 (C–O–C); 862 cm^{-1}. Mass spectrum (20% cutoff) m/e 270, 0.02% (M$^+$); 255, 38% (M$^+$ – CH$_3$); 195, 20%; 101, 40% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 43, 100%, (CH$_3$C≡O$^+$). High-resolution MS, calcd for C$_8$H$_{15}$IO$_2$ (M$^+$ – I), 143.1072; found, 143.1077, 143.1065.

(2′RS,4SR)-2′-(2,2-Dimethyl-1,3-dioxacyclopent-4-yl)-4′-ξ-methylhept-5′-one (6). To a dry 25-ml flask were added under N$_2$ 0.7 ml (5.0 mmol) of freshly distilled diisopropylamine, 3 ml of dry THF, and a stirring bar. After cooling to −78 °C, 3.75 ml of a 1.3 M n-BuLi solution was added, and the contents of the flask stirred for 30 min. Then 0.52 ml (4.94 mmol) of freshly distilled diethyl ketone in 5 ml of THF was added and the solution stirred for 0.5 h while

warming to −40 °C. A solution of 270 mg (1 mmol) of the iodide 5 in 5 ml of THF was added and the solution stirred for 3 days at room temperature. The yellow mixture was then poured into 30 ml of saturated NaCl, and the H$_2$O layer extracted with 4 × 20 ml of ether. The ether layers were combined, washed with 2 × 50 ml of 10% HCl and 50 ml of saturated NaHCO$_3$, and dried over MgSO$_4$. The ether was evaporated and the residue of 249 mg was chromatographed on 18.6 g of silica gel. Iodide 5 (38.2 mg, 14%) was eluted with 5% EtOAc in hexane. Thereafter 193.8 mg of the desired ketone 6 (84%) was eluted with 3% EtOAc in hexane. This material was a mixture of two diastereomers as shown by NMR, which could not be separated by GLC. A sample was distilled at 90 °C (bath temperature) at 180 mTorr. ^1H NMR δ 4.01, complex q, 1 H (CHO); 3.87, m, 1 H (CH$_2$O); 3.61, m, 1 H (CH$_2$O); 2.73, m (C-4′ H); 2.65, m, (C-2′ H); 2.49, q, 2 H (C-6′ H$_2$); 1.70, m, 2 H (C-3′ H$_2$); 1.34, s, 3 H (acetonide CH$_3$); 1.26, s, 3 H (acetonide CH$_3$); 1.09, d, J = 7 Hz, 3 H (C-4′ CH$_3$); 1.05, t, J = 7 Hz, 3 H (C-7′); 0.94, d, J = 7 Hz, 3 H (C-1′). The resonance at δ 0.94 is split into two doublets in a 60:40 ratio separated by less than 2 Hz at 270 MHz; the resonance at δ 1.34 is also so split. Ir 2980–2930 (CH); 1748 (CO); 1374 (CH$_3$); 1064 (C–O–C); 875–860 cm^{-1}. Mass spectrum (10% cutoff) m/e 228, 0.04% (M$^+$); 213, 2.7% (M$^+$ – CH$_3$); 101, 23% (2,2-dimethyl-1,3-dioxacyclopent-4-yl ion); 97, 43%; 57, 100% (CH$_3$CH$_2$C≡O$^+$); 43, 66% (CH$_3$C≡O$^+$). High-resolution MS, calcd for C$_{12}$H$_{21}$O$_3$ (M$^+$ – CH$_3$), 213.1491; found, 213.1490.

Anal. Calcd for C$_{13}$H$_{24}$O$_3$: C, 68.38; H, 10.59. Found: C, 68.17; H, 10.31.

(±)-α (and γ-) Multistriatin (2,4-Dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane) (1). To a solution of 150.0 mg (0.66 mmol) of 2′-(2,2-dimethyl-1,3-dioxacyclopent-4-yl)-4′-methylhept-5′-one (6) in 2 ml of CH$_3$CN 1 ml of aqueous 10% HCl was added. The solution was stirred for 18 h at room temperature and then 2 g of NaCl was added to saturation. It was poured into 30 ml of saturated NaCl solution and extracted with 4 × 20 ml of ether. The ether layers were combined and washed with 40 ml of saturated NaHCO$_3$ and dried over MgSO$_4$ and the solvent was removed. This left a clear oil that was distilled in a microstill: 110.2 mg (98%) were collected at bath temperature, 90 °C at 20 Torr. This material was shown to be an 85:15 mixture of α:γ-multistriatin by 270-MHz ^1H NMR and by GLC. The identity of the synthetic material with α-multistriatin was established by the very characteristic NMR, the infrared, and low-resolution mass spectra, all of which were the same as the data published by Silverstein et al.[2] ^1H NMR δ 4.20, m, 1 H (C-1 H); 3.89, d of d, J = 7.0, 0.8 Hz, 1 H (C-7 H); 3.68, d of d, J = 7.0, 5.0 Hz, 1 H (C-7 H); 2.06, m, 1 H; 1.83, m, 1 H; 1.73, q, 2 H (CH$_2$CH$_3$); 1.61, m, 1 H; 0.94, t, J = 7.0 Hz, 3 H (CH$_2$CH$_3$); 0.81, d, 6 H, J = 7 Hz (C-2 and C-4 methyls). Ir 2960–2880 (CH); 1453, 1379, 1361 (CH); 1172, 1124, 1031 (C–O–C); 912, 894 cm^{-1} (ring). Mass spectrum (10% cutoff) m/e 170, 3% (M$^+$); 128, 11%; 57, 100% (CH$_3$CH$_2$C≡O$^+$). High-resolution MS, calcd for C$_{10}$H$_{18}$O$_2$, 170.1307; found, 170.1307.

References and Notes

(1) G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier, and J. B. Simeone, *J. Chem. Ecol.*, **1**, 115 (1975).

(2) W. E. Gore, G. T. Pearce, and R. M. Silverstein, *J. Org. Chem.*, **40**, 1705 (1975).

(3) β- and δ-multistriatin posses the erythro configuration at C-1 and C-2.

(4) W. J. Elliott and J. Fried, *J. Org. Chem.*, preceding paper in this issue.

(5) A similar, independent synthesis of this molecule has recently been reported by E. J. Corey and M. J. Bock, *Tetrahedron Lett.*, 2643 (1975).

(6) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

(7) G. Stork and S. A. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).

Synthesis of Corticosteroid Derivatives Containing the 20β-Ol-21-al Side Chain

Sea-wha Oh and Carl Monder*

Research Institute for Skeletomuscular Diseases, Hospital For Joint Diseases & Medical Center, New York, New York 10035

Received November 25, 1975

A general synthesis of steroids containing the 20β-ol-21-al side chain is described. The ketol side chain was oxidized to 20-oxo-21-al, and treated with hydroxylamine to yield the 20-oxo-21-oxime in good yield. Reduction with sodium borohydride followed by hydrolysis afforded the final product. The procedure is illustrated by the synthesis of 20β-hydroxy-3-oxopregn-4-en-21-al, 17,20β-dihydroxy-3-oxopregn-4-en-21-al, 11β,20β-dihydroxy-3-oxopregn-4-en-21-al, and 11β,17,20β-trihydroxy-3-oxopregn-4-en-21-al.

Kendall et al.[1] proposed in 1934 that the physiologically essential steroid hormone secreted by the mammalian adrenal cortex contained a hydroxy aldehyde side chain. Subsequent studies by Reichstein and his co-workers[2] demonstrated that Kendall had erred in his interpretation of the data, and that the side chain was a ketol. Corticosteroids with the 17-hydroxy aldehyde configuration were as a consequence no longer seriously considered in a physiological context. Recently, as a result of in vivo and in vitro studies of corticosteroid metabolism in humans[3–5] and hamsters,[6] we revived the possibility that 20-hydroxy 21-aldehydes are important metabolic intermediates. In this context we therefore investigated the chemical synthesis of this class of compound.

The synthesis of corticosteroids with the hydroxy aldehyde side chain has been attempted by others.[7–13] In general, the isolation of pure products was troublesome, and the yields were low. Approaches used included selective oxidation of 20,21,22-triols with periodate,[7,8] reduction of 20-oxo-21-al dimethyl acetal and deacetalation,[9,10] and reduction of 20-oxo-21-aldehydes with 20β-hydroxy steroid dehydrogenase.[11]

The procedure we use is illustrated in Scheme I. The formation of aldoxime (3) from keto aldehyde (2) and hydroxylamine hydrochloride was carried out at room temperature using stoichiometric amounts of reactants at neutral pH. The proportion of ethanol to water in the solvent mixture was adjusted to permit the aldehyde to stay in solution, and the product to precipitate out. When ethanol was used in excess, products and reactants stayed in solution, resulting in a decrease in the purity and yield of the product.

Initially, lithium aluminum hydride was employed to reduce the 20-carbonyl group. Attempts to reoxidize the resulting 3-hydroxy group selectively with manganese dioxide were unsuccessful, because the =NOH group at position 21 facilitated the reoxidation of 20-ol as well. Both 3-oxo-4-ene and 20-oxo-21-oxime are electronically equivalent since both are α,β-unsaturated ketones.

With sodium borohydride, reduction (3 → 4) was influenced by temperature and solvent. At ice bath temperatures reduction of the 20-oxo group occurred preferentially. As the temperature rose, selectivity of reduction was directed increasingly to the 3-oxo group. The nature of the solvent had a strong directing effect on the selectivity of the reduction. The 3-oxo group was favored over the 20-oxo group in methanol, ethanol, 2-propanol, tetrahydrofuran, methanol–water mixtures, or tetrahydrofuran–water mixtures. In dimethylformamide–methanol (2/1 v/v), reduction of the 20-oxo group was significantly favored over the 3-oxo group. In this reagent the reaction proceeded more slowly than in other solvents; more sodium borohydride was needed to effect complete reduction. It is probable that the dielectric constant of the medium plays an important role in determining selectivity and reduction rate.

It was found that 17α-hydroxylated steroids were reduced

Scheme I

a. $R_1 = R_2 = H$
b. $R_1 = H; R_2 = H$
c. $R_1 = OH; R_2 = H$
d. $R_1 = R_2 = OH$
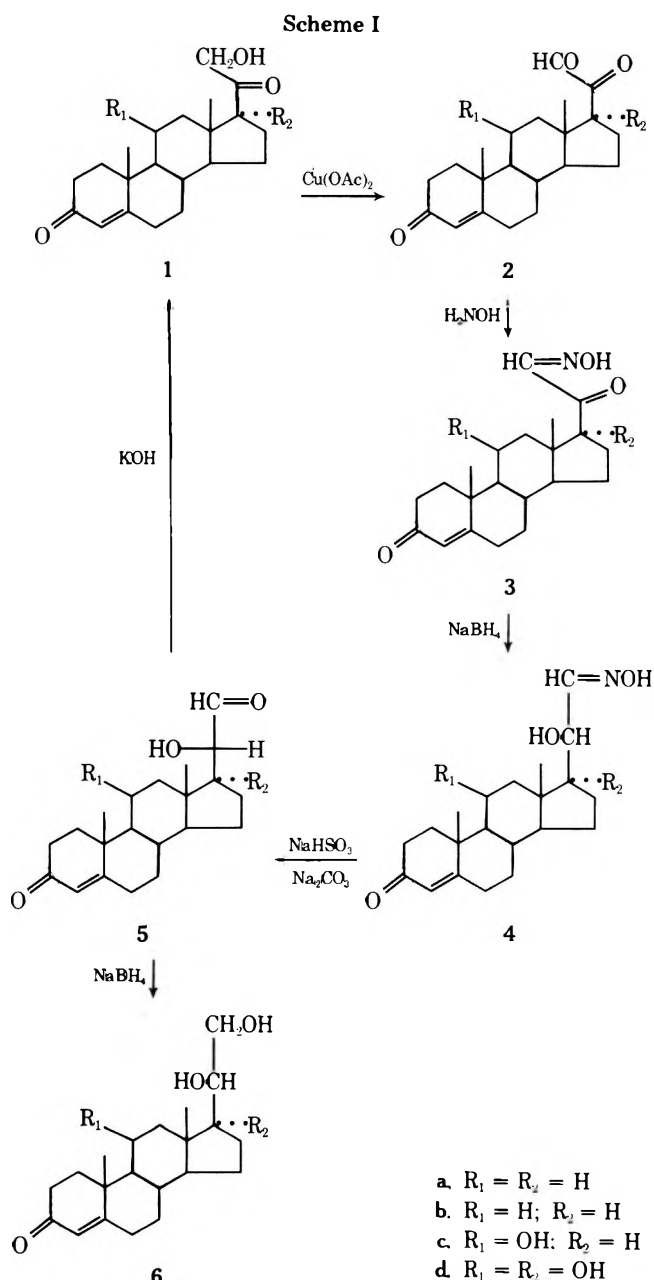
significantly faster than 17-deoxy steroids. For 3,20-dioxopregn-4-en-21-oxime and 11β-hydroxy-3,20-dioxopregn-4-en-21-oxime, a large excess of sodium borohydride was necessary to effect reduction, which required 2–3 h to complete. With 17-hydroxy-3,20-dioxopregn-4-en-21-oxime, the reaction was completed within 1 h and required much less reducing agent. The latter two steroids were reduced with a greater selectivity favoring the 20 position.

Faster reduction at the 3 position in methanol seems to be due to easier accessibility of the borohydride reagent to this exposed position. We propose that the 3 position is shielded by dimethylformamide, and is thus made less accessible to the reagent, but that bulky groups in the region of the D ring permit the selective approach of the borohydride over dimethylformamide to the reactive 20 position. The presence of a 17-hydroxyl group polarizes the 20-oxo group, and increases the reduction rate. The reaction is stereospecific, yielding only 20β-hydroxy enantiomers.

When excess sodium borohydride was decomposed with acetic acid, further reduction took place rapidly which led to undesired products and decreased yield of the hydroxy oxime. Consequently, the product was extracted directly at the completion of the reaction without attempting to destroy residual sodium borohydride.

Hydrolysis of the oximes (4 → 5) was performed by a modification of the method described by Pines et al.[14] We found that it was not possible to cleave the oxime by refluxing the steroid in ethanol–water (1:1) with excess sodium bisulfite as recommended by these authors, since the resulting hydroxy aldehydes were unstable under these conditions. At 45–55 °C, hydrolysis by excess sodium bisulfite proceeds smoothly with little decomposition. It was not possible to decompose the bisulfite adduct with dilute acid, since hydroxy aldehydes are unstable under these conditions. Sodium carbonate readily generated the desired steroidal 20-ol-21-al. In order to minimize decomposition at this stage, all manipulations were performed in an ice bath. If the hydroxy aldehydes remained in aqueous solution or suspension, they rapidly polymerized to intractable materials that were insoluble in ethyl acetate. Therefore, as the free aldehyde was released during sodium carbonate hydrolysis, it was extracted directly into ethyl acetate.

The steroid hydroxy aldehydes are stable as pure, dry products, especially at low temperature. Alkali catalyzes their isomerization to the corresponding ketols. The isomerization of 20β-hydroxy-3-oxopregn-4-en-21-al and 11β,20β-dihydroxy-3-oxopregn-4-en-21-al in base was clean and quantitative. Isomerization of 17,20β-dihydroxy-3-oxopregn-4-en-21-al was slower and less efficient, possibly because the aldehyde is stabilized to some degree by hydrogen bonding with the 17-hydroxy group.
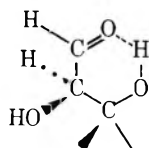
The NMR data show a distinct downfield shift for the 20α proton of the 17-hydroxylated steroids from 4.1 to 4.4 ppm. This deshielding effect is consistent with the more rapid reduction of 17-hydroxy steroids by sodium borohydride. The extreme downfield singlet at 9.7 ppm corresponds to the 21-aldehyde proton. There was no evidence of splitting, and it is tentatively suggested that the 21-H is oriented at right angles to the adjacent proton at position 20. Further explorations of these stereochemical relationships require that the 20α epimer be prepared.

Experimental Section

Corticosteroids were bought from Steraloids, Pawling, N.Y. The 3-methyl-2-benzothiazolone hydrazone hydrochloride (MBTH) was purchased from Aldrich Chemical Co. Hydroxylamine hydrochloride and other reagents were used as purchased without further purification. Prepacked chromatographic columns, size A and B, containing silica gel 60 were purchased from Em Laboratories, Elmsford, N.Y.

Melting Points. Melting points were determined with a Hoover capillary apparatus and are uncorrected. The true melting points are within a degree of those reported.

Absorption Spectra. The ultraviolet spectra were determined in absolute methanol in a Cary Model 15 recording spectrophotometer. Infrared spectra were obtained in KBr pellets with a Perkin-Elmer Model 221 spectrophotometer.

Nuclear Magnetic Resonance. NMR spectra were determined in CDCl₃ solution on Varian A-60A or HA-100 spectrophotometers. Chemical shift data are reported in parts per million downfield from internal tetramethylsilane (δ scale).

Mass Spectrometry. A Du Pont Model 21-492B mass spectrometer with 21-094 computerized data system was used. The mass spectra were recorded at an electron ionizing energy of 70 eV. Source temperature was 210 °C and the range of probe temperature was from room temperature to about 300 °C. Spectra above 100 °C are reported.

MBTH Reaction. About 0.5-mg sample was weighed out and dissolved in 2 ml of ethanol. To 100 or 200 μl of the sample solution was added 0.5 ml of 0.1% MBTH followed by 1.2 ml of 0.1 M glycine buffer (pH 4.0). After total volume was adjusted to 2.5 ml by adding water, the mixture was heated in a boiling water bath for 7 min. When the solution had cooled, 2.5 ml of ethanol was added and absorbancy was determined spectrophotometrically between 200 and 450 nm.

3,20-Dioxopregn-4-en-21-al (2a) from 21-Hydroxypregn-4-ene-3,20-dione (1a). The method of Monder and Furfine[15] was followed with minor modification. To a solution of 3 g (9.10 mmol) of 1a in 250 ml of methanol was added a solution of 0.75 g (4.1 mmol) of cupric acetate in 375 ml of methanol. After standing for 10 min, air was bubbled through the mixture for 30 min. To the clear blue solution, 150 ml of 0.1 M aqueous sodium carbonate containing 1.5 g of EDTA (pH 9.0) was added; most of the methanol was removed under vacuum at 25 °C. Steroid was extracted with 200 ml of ethyl acetate after adding 1200 ml of water. About 100 g of sodium sulfate was dissolved into the water phase which was then extracted with three 150-ml portions of ethyl acetate. The combined solvent extract was washed with 2% sodium bicarbonate in saturated sodium chloride, then with saturated sodium chloride and dried over anhydrous sodium sulfate. Ethyl acetate was evaporated to dryness and the residual product was dissolved in 50 ml of acetone. Crystallization was initiated by carefully adding 300 ml of phosphate buffer (0.001 M, pH 7.5) with a dropper under the surface. The turbid solution was left overnight at 5 °C. Crystals were collected by filtration and washed with water. A second crop was obtained by partial evaporation of solvent. The combined yield was 2.7 g (90%). Chromatographic mobility on thin layer plates and ir spectrum matched exactly those of an authentic sample: mp 90–92 °C dec; λ_{max} (alcohol) 241 nm (ϵ 15 400); MBTH derivative, λ_{max} 374 nm; ir 5.85, 6.02, 8.13, 9.30 μ.

Anal. Calcd for C₂₁H₂₈O₃·H₂O (346.45): C, 72.80; H, 8.73. Found: C, 72.71; H, 8.66.

17-Hydroxy-3,20-dioxopregn-4-en-21-al (2b) from 17,21-Dihydroxypregn-4-ene-3,20-dione (1b). Conversion of 1b to 2b was performed as described for the synthesis of 1a, except that the cupric acetate catalyzed oxidation proceeded for 2 h. Yield was 2.6 g (87%): mp 96–100 °C dec; λ_{max} (alcohol) 241 nm (ϵ 15 400); MBTH derivative, λ_{max} 387 nm; ir 5.80, 6.06 μ.

Anal. Calcd for C₂₁H₂₈O₄·H₂O: C, 69.58; H, 8.34. Found: C, 69.39; H, 8.25.

11β-Hydroxy-3,20-dioxopregn-4-en-21-al (2c) from 11β,21-Dihydroxypregn-4-ene-3,20-dione (1c). Conversion of 1c to 2c was performed as described for the synthesis of 2a except that the cupric acetate catalyzed oxidation proceeded for 60 min. Yield was 2.6 g (87%): mp 113–116 °C dec; λ_{max} (alcohol) 241 nm (ϵ 15 300); MBTH derivative λ_{max} 373 nm; ir 5.84, 6.05, 9.20, 9.60 μ.

Anal. Calcd for C₂₁H₂₈O₄·H₂O: C, 69.58; H, 8.34. Found: C, 69.91; H, 8.70.

11β,17-Dihydroxy-3,20-dioxopregn-4-en-21-al (2d) from 11β,21-Trihydroxypregn-4-ene-3,20-dione (1d). Conversion of 1d to 2d was performed as described for the synthesis of 2a except that the cupric acetate catalyzed oxidation proceeded for 90 min. Yield was 2.4 g (80%): mp 160–162 °C dec; λ_{max} (alcohol) 241 nm (ϵ 15 700); MBTH derivative λ_{max} 386 nm; ir 5.81, 6.06, 9.60 μ.

Anal. Calcd for C₂₁H₂₈O₅·H₂O: C, 66.65; H, 7.99. Found: C, 66.79; H, 8.01.

3,20 Dioxopregn-4-en-21-oxime (3a from 2a). To 500 mg (1.5 mmol) of 2a in 16 ml of 75% aqueous ethanol, 120 mg (1.7 mmol) of hydroxylamine hydrochloride was added and 104 mg (0.8 mmol) of sodium carbonate monohydrate in 1 ml of water was added slowly with stirring. Stirring was continued for 60 min at room temperature. Water (50 ml) was added. The suspension was cooled in an ice bath for 10 min, filtered, and washed with cold water. The collected product was dried in vacuo over P₂O₅. Yield was 510 mg (98%): mp 208–210 °C dec; ir 2.96–3.20 (multiple bands), 3.34, 3.45, 6.0–6.20, 6.8–7.0 (multiple bands), 7.23, 7.33, 7.57, 7.80, 7.88, 8.02, 8.12, 8.26, 8.42, 8.58,

9.00, 9.92 μ.

Anal. Calcd for $C_{21}H_{29}O_3N$: C, 73.49; H, 8.52; N, 4.08. Found: C, 73.36; H, 8.86; N, 4.58.

3,20-Dioxo-17-hydroxypregn-4-en-21-oxime (3b from 2b). To 500 mg (1.5 mmol) of **2b** in 11 ml of 77% aqueous ethanol was added 104 mg (1.5 mmol) of hydroxylamine hydrochloride and 93 mg (0.75 mmol) of sodium carbonate monohydrate in 1 ml of water. The mixture was stirred for 45 min and worked up as for **3a**. Yield was 505 mg (96%): mp 195–197 °C dec; ir 2.92, 3.40,·3.48, 5.9–6.2 (multiple bands), 6.8–7.05 (multiple bands), 7.22, 7.37, 7.52, 7.89, 8.11, 8.22, 8.40 8.90, 9.20, 9.33 μ.

Anal. Calcd for $C_{21}H_{29}O_4N$: C, 70.19; H, 8.13; N, 3.90. Found: C, 69.74; H, 8.28; N, 3.79.

3,20-Dioxo-11β-hydroxypregn-4-en-21-oxime (3c from 2c). To 345 mg (1.0 mmol) of **2c** in 11 ml of 73% aqueous ethanol was added 0.069 g (1.0 mmol) of hydroxylamine hydrochloride and 0.062 g (0.5 mmol) of sodium carbonate monohydrate in 1 ml of water and treated as for **3a**. Yield was 340 mg (94%): mp 184–188 °C dec; ir 2.95–3.20 (multiple bands), 3.48 5.95–6.20 (multiple bands), 6.96, 7.03, 7.26, 7.45, 7.92, 8.16, 8.49, 8.74, 9.02, 9.25, 9.40 μ.

Anal. Calcd for $C_{21}H_{29}O_4N$: C, 70.19; H, 8.13; N, 3.90. Found: C, 70.31; H, 8.22; N, 3.90.

3,20-Dioxo-11β,17-dihydroxypregn-4-en-21-oxime (3d from 2d). To 360 mg (1.0 mmol) of **2d** in 17 ml of 70% aqueous ethanol was added 0.069 g (1.0 mmol) of hydroxylamine hydrochloride and 0.062 g (0.5 mmol) of sodium carbonate monohydrate in 1 ml of water. The mixture was stirred for 1 h and concentrated to 5 ml under vacuum. Water (15 ml) was added and the precipitate was collected by filtration. Yield was 350 mg (93%): mp 202–203 °C; ir 2.90–3.10 (multiple bands), 3.42, 5.87–6.25 (multiple bands), 6.93, 6.98, 7.42, 7.45, 7.87, 8.12, 8.22, 8.42, 8.64, 8.76, 8.99, 9.27, 9.42, 9.65, 9.78 μ.

Anal. Calcd for $C_{21}H_{29}O_5N$: C, 67.18; H, 7.79; N, 3.37. Found: C, 66.76; H, 7.89; N, 3.26.

20-Hydroxy-3-oxopregn-4-en-21-oxime (4a from 3a). To 500 mg (1.5 mmol) of **3a** in 15 ml of dimethylformamide–methanol (2/1 v/v) in an ice bath was added slowly with stirring 125 mg (3.3 mmol) of sodium borohydride in 7 ml of the same solvent. The mixture was stirred in an ice bath for 3 h. Methanol was removed under vacuum. Ethyl acetate was added followed by 85 ml of water and 5 ml of saturated aqueous sodium chloride with vigorous stirring. The ethyl acetate extract was washed twice with water, twice with saturated sodium chloride, and dried with anhydrous sodium sulfate. The ethyl acetate was removed under vacuum. Product was purified on a silica gel column (E. Merck, size B) with chloroform–methanol (97/3 v/v) as eluent. Yield of purified product was 240 mg (48%): mp 203–205 °C; ir 2.92, 3.43, 3.47, 6.05–6.17 (multiple bands), 6.90, 6.98, 7.27, 7.37, 7.50, 7.85, 8.05, 8.12, 8.37, 9.0, 9.40, 9.72, 9.87 μ.

Anal. Calcd for $C_{21}H_{31}O_3N$: C, 73.01; H, 9.05; N, 4.05. Found: C, 72.02; H, 8.97; N, 4.03; m/e 345.230616 (calcd, 345.230404).

11β,20-Dihydroxy-3-oxopregn-4-en-21-oxime (4c from 3c). To 500 mg (1.4 mmol) of **3c** in 16 ml of dimethylformamide (2/1 v/v) was added 140 mg (3.7 mmol) of sodium borohydride in 6 ml of the same solvent. The mixture was stirred for 3 h and worked up as described for **4a**. The product was purified on a silica gel column with chloroform–methanol (96/4 v/v) as developing solvent. The purified yield was 230 mg (46%): mp 65–67 °C dec; ir 2.39, 3.41, 3.47, 6.00–6.25 (multiple bands), 6.85–7.07 (multiple bands), 7.45, 7.57, 7.85, 8.05, 8.13, 8.42, 8.66, 9.40, 9.73 μ.

Anal. Calcd for $C_{21}H_{31}O_4N$: C, 69.8; H, 8.64; N, 3.88. Found: C, 66.3; H, 8.63; N, 3.51; m/e 361.226758 (calcd, 361.225319).

17,20-Dihydroxy-3-oxopregn-4-en-21-oxime (4b from 3b). **3b** (500 mg, 1.4 mmol) in 12 ml of dimethylformamide–methanol (2/1 v/v) was treated with 25 mg of sodium borohydride in 2 ml of the same solvent and stirred for 60 min in an ice bath. The product was purified on a silica gel column with chloroform–methanol (95/5 v/v) as eluent. The purified product was 310 mg (62%): mp 204 °C dec; ir 2.94, 3.39, 3.48, 5.95–6.20 (multiple bands), 6.76–7.05 (multiple bands), 7.26, 7.37, 7.51, 7.89, 8.06, 8.49, 8.94, 9.60, 9.77, 10.05 μ.

Anal. Calcd for $C_{21}H_{31}O_4N$: C, 69.8, H, 8.64; N, 3.88. Found: C, 68.0; H, 8.68; N, 3.47; m/e 361.226226 (calcd, 361.225319).

11β,17,20-Trihydroxy-3-oxopregn-4-en-21-oxime (4d from 3d). **4d** was prepared by following the same method as for **4b**. Yield was 290 mg (58%): mp 85–87 °C; ir 2.92, 3.41, 3.47, 6.0–6.19 (multiple-bands), 6.89, 6.98, 7.24, 7.45, 7.87, 8.13, 8.45, 8.87, 9.48, 9.67, 9.75 μ.

Anal. Calcd for $C_{21}H_{31}O_5N$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.47; H, 8.52; N, 3.31; m/e 377.220502 (calcd, 377.220502).

Purification of products **4a–d** was difficult, since some decomposition to unidentified products occurred, even though the various reduced oximes were well separated. Degradation products were removed by extraction with ethyl acetate after conversion of the oxime to the bisulfite adduct which was then hydrolyzed to the 20-hydroxy 21-aldehyde.

20-Hydroxy-3-oxopregn-4-en-21-al (5a). To 70 mg (0.2 mmol) of **4a** in 30 ml of 50% aqueous ethanol, 700 mg (6.7 mmol) of powdered sodium bisulfite was added. The mixture was stirred for 3 h in a water bath at 50 °C. Ethanol was evaporated thoroughly, then 10 ml of water was added to the residue. The solution was washed with ethyl acetate four times. If a white precipitate insoluble in ethyl acetate developed, more water was added. The washed water layer was cooled to 3 °C. Ethyl acetate (15 ml) and 6 ml of saturated sodium carbonate solution was added with vigorous mixing, which was continued for 10 min. The organic layer was separated and extracted with ethyl acetate once more. The combined extract was washed twice with water and twice with saturated sodium chloride solution, then dried with anhydrous sodium sulfate. Ethyl acetate was removed under vacuum at below 0 °C. The residue was isolated from dichloromethane–hexane. The residual white powder was dried under high vacuum. Yield was 34 mg (51%): mp 140 °C dec; ir 2.92, 3.41, 3.48. 5.80, 6.01, 6.20, 6.90, 6.98, 7.27, 7.30, 7.52, 7.87, 8.07, 8.14, 8.43, 8.95, 9.34, 9.66, 9.86 μ.

Anal. Calcd for $C_{21}H_{30}O_3$·$0.5H_2O$: C, 74.4; H, 9.20. Found: C, 75.0; H, 8.95.

λ_{max} (methanol) 241 nm (ϵ 16 400); MBTH derivative λ_{max} 312 nm (ϵ 26 900); NMR 18-CH_3, 0.88; 19-CH_3, 1.19; 4-H, 5.69; 20-CHOH, 4.06 (multiplet; doublet in D_2O, J = 10 Hz); 21-CHO, 9.65 ppm; mass spectrum m/e 330 (M^+, $C_{21}H_{30}O_3$), 11.4%; 301 [M^+ − (HC=O)], 7.3%; 300 [M^+ − (CHO) − (H)], 3.5%; 299 [M^+ − (CHO) − (2 H)], 100%; 271 [M^+ − (CHO − CHOH)], 47.4%.

17,20-Dihydroxy-3-oxopregn-4-en-21-al (5b). **5b** was prepared from **4b** as described for **5a**. Yield 31 mg (46%): mp 98–101 °C; ir 2.89, 3.38, 3.46, 5.75, 6.05, 6.18, 6.90, 6.97, 7.07, 7.25, 7.37, 7.84, 8.05, 8.12, 8.44 8.90, 9.40, 9.60, 9.82, 10.42, 10.59 μ.

Anal. Calcd for $C_{21}H_{30}O_4$: 72.80; H, 8.70. Found: C, 72.82; H, 8.84.

λ_{max} (methanol) 241 nm (ϵ 15 900); MBTH derivative λ_{max} 312 nm (ϵ 25 100); NMR 18-CH_3, 0.95; 19-CH_3, 1.20; 4-H, 5.72; 20-H, 4.36 (20-HCO–); 21-H, 9.72 ppm (21-HC=O); mass spectrum m/e 346 (M^+, $C_{21}H_{30}O_4$), 16.0%; 317 [M^+ − (HC=O)], 15.2%; 316 [M^+ − (CHO) − (H)], 29.2%; 288 [M^+ − (CHOCHOH) + (H)], 22.2%; 287 [M^+ − (CHOCHOH)], 100%.

11β,20-Dihydroxy-3-oxopregn-4-en-21-al (5c). The same method was followed as for **5a**. Yield 33 mg (49%): mp 138 °C dec; ir 2.92, 3.41, 3.47, 5.81, 6.07, 6.19, 6.90, 7.26, 7.41, 7.86, 8.12, 8.43, 8.68, 11.50 μ.

Anal. Calcd for $C_{21}H_{30}O_4$·$0.25H_2O$: C, 71.90; H, 8.80. Found: C, 71.50; H, 9.03.

λ_{max} (methanol) 241 nm (ϵ 15 100); MBTH derivative λ_{max} 312 nm (ϵ 17 500); NMR 18-CH_3, 1.12; 19-CH_3, 1.46; 4-H, 5.68; 20-H, 4.10 (multiplet); 21-H, 9.71 (21-HC=O); 11-H, 4.32; mass spectrum m/e 346 (M^+, $C_{21}H_{30}O_4$), 8.6%; 317 [M^+ − (HC=O)], 18.0%; 316 [M^+ −(CHO) − (H)], 40.0%; 315 [M^+ − (CHO) − (2 H)], 100%; 270 [M^+ − (CHOCHO) − (H_2O)], 76.4%.

11β,7,20-Trihydroxy-3-oxopregn-4-en-21-al (5d). **5d** was synthesized as described for **5a**. Yield 27 mg (40%): mp 107 °C; ir 2.92, 3.41, 3.46 5.82, 6.05–6.15 (multiple bands), 6.77–7.01 (multiple bands), 7.24, 7.45, 7.85, 8.10, 8.42, 8.62, 8.85, 9.25–9.95 μ (multiple bands).

Anal. Calcd for $C_{21}H_{30}O_5$·$0.25H_2O$: C, 68.73; H, 8.38. Found: C, 68.62; H, 8.52.

λ_{max} (methanol) 241 nm (ϵ 14 900); MBTH derivative λ_{max} 312 nm (ϵ 25 600); NMR 18-CH_3, 1.18; 19-CH_3, 1.45; 4-H, 5.69; 11-H, 4.39; 20-H, 4.39; 21-H, 9.73 (21-HC=O); mass spectrum m/e 362 (M^+, $C_{21}H_{30}O_5$), 28.6%; 333 [M^+ − (HC=O)], 14.7%; 344 [M^+ − (H_2O)], 20.8%; 332 [M^+ − (CHO) − (H)], 11.1%; 314 [M^+ − (CHO) − (H) − (H_2O)], 16.7%; 302 [M^+ − (CHOCHOH) − (H_2O)], 83.5%; 163 [M^+ − (199)], 100%.

Isomerization of 5a–d to Corticosteroids. To 3 mg (0.01 mmol) of **5a–d** was added 0.15 mmol of potassium hydroxide in 0.3 ml of methanol. The solution was stirred for 25 min at room temperature and 0.17 mmol of glacial acetic acid was added. Methanol was evaporated, then steroid was extracted with ethyl acetate after 0.3 ml of water was added. The extract was washed with water, then dried with anhydrous sodium sulfate and solvent was evaporated. Identification of the resulting ketols was made in each case on the basis of infrared spectra and chromatographic mobilities.

Determination of Stereochemistry at C-20. 5a–d (5 mg) were reduced to 20,21-glycol by adding 0.2 mg of sodium borohydride in 0.3 ml of methanol in an ice bath. After 20 min stirring, methanol was evaporated and ethyl acetate and water were added. Ethyl acetate extract was chromatographed with authentic standard on a silica gel coated TLC plate which had been dipped into 0.1 M sodium borate solution (pH 9.0) and dried at 45 °C overnight. R_f values with chlo-

roform–methanol (90:10) as developing solvent were (mobilities of authentic standards in parentheses) **6a**, 0.37, (20α = 0.26; 20β = 0.37); **6b**, 0.47 (20α = 0.37; 20β = 0.47); (chloroform–methanol, 85:15) **6c**, 0.32 (20α = 0.24; 20β = 0.32); **6d**, 0.25 (20α = 0.18, 20β = 0.25).

References and Notes

(1) E. C. Kendall, H. L. Mason, B. F. McKenzie, C. S. Myers, and G. A. Koelsche, *Proc. Staff Meet. Mayo Clin.*, **9**, 245 (1934).

(2) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, p 600.

(3) K. O. Martin and C. Monder, *Biochemistry*, **15**, 576 (1976).

(4) H. L. Bradlow, B. Zumoff, C. Monder, H. J. Lee, and L. Hellman, *J. Clin. Endocrinol. Metab.*, **37**, 811 (1973).

(5) H. L. Bradlow, B. Zumoff, C. Monder, and L. Heilman, *J. Clin. Endocrinol. Metab.*, **37**, 805 (1973).

(6) H. L. Lee and C. Monder, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **36**, 479 (1973).

(7) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **24**, 1140 (1941).

(8) T. Reichstein, U.S. Patent 2 389 325; *Chem. Abstr.*, **40**, 1974 (1946).

(9) W. Schindler, H. Frey, and T. Reichstein, *Helv. Chim. Acta*, **24**, 360 (1941).

(10) D. Taube, R. H. Pettebone, N. L. Wendler, and M. Tishler, *J. Am. Chem. Soc.*, **76**, 4094 (1954).

(11) C. S. Furfine and A. White, *J. Biol. Chem.*, **243**, 1190 (1968).

(12) Soc. pour l'Ind. Chim a Bâle, Swiss Patent 235 507; *Chem. Abstr.*, **43**, 7055h,i (1949).

(13) Schering A.-G., German Patent 870 103; *Chem. Abstr.*, **52**, P15603g (1958).

(14) S. H. Pines, J. M. Chemerda, and M. A. Kozlowski, *J. Org. Chem.*, **31**, 3446 (1966).

(15) C. Monder and C. S. Furfine, *Methods Enzymol.*, **15**, 667 (1969).

Synthesis of Substituted Glycopeptides Containing a 2-Acetamido-2-deoxy-β-D-glucopyranosyl Residue and the Amino Acid Sequence 18–22 of Bovine Pancreatic Deoxyribonuclease A[1]

Hari G. Garg and Roger W. Jeanloz*

Laboratory for Carbohydrate Research, Departments of Biological Chemistry and Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts 02114
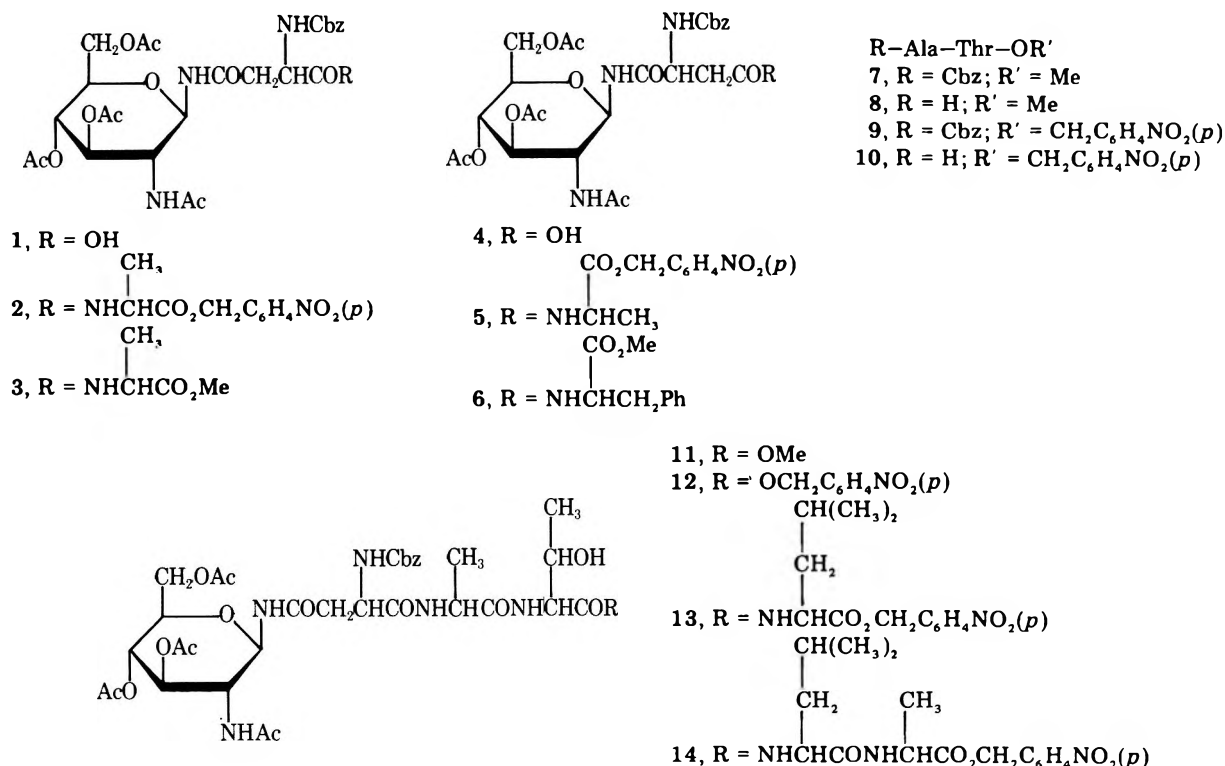
Condensation of 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-4-oyl]-2-deoxy-β-D-glucopyranosylamine (1) with protected L-alanine, L-alanyl-L-threonine, L-alanyl-L-threonyl-L-leucine, and L-alanyl-L-threonyl-L-leucyl-L-alanine derivatives gave glycodi-, -tri-, -tetra-, and -pentapeptides corresponding to the sequences 18–19, 18–20, 18–21, and 18–22 of deoxyribonuclease A.

Glycoproteins containing the 2-acetamido-1-N-(L-aspart-4-oyl)-β-D-glucosylamine carbohydrate–protein linkage include many of the biologically important proteins, such as hormones, enzymes, plasma proteins, etc.[2] The mechanism of the biosynthesis of the carbohydrate chain and its attachment to the protein backbone are not as yet completely elucidated, because of the difficulty in the separation and identification of the final product, in addition to the instability of the possible carbohydrate intermediates. For this reason, a study of the biosynthesis of glycoproteins based on chemically synthesized peptide acceptors and carbohydrate intermediates[3,4] has been undertaken in this laboratory. Glycoproteins from pancreatic tissues were selected because this tissue has been shown to synthesize rapidly the possible intermediates.

In a preceding paper,[3] we have described the synthesis of glycopeptides derived from beef ribonuclease B and in the present paper we describe the synthesis of glycopeptides derived from beef deoxyribonuclease A. This enzyme exists in bovine pancreatic tissue in three forms, A, B, and C, which differ in the carbohydrate composition of the chain attached to Asn-18 as well as in their amino acid sequences.[5-8] In addition, the amino acid sequence Asn-X-Ser, which is generally assumed to be a prerequisite for the linkage of a carbohydrate chain to an asparagine residue,[2] exists at Asn-103, X being Asp-104, but no carbohydrate chain is linked to Asn-103. Thus, biosynthetic experiments with glycopeptides derived from the Asn-18 and Asn-103 regions could give important information on the role played by the amino acid sequence in the formation and structure of the carbohydrate chain. As model glycopeptides, the synthesis of di-, tri-, tetra-, and

pentapeptides related to the sequence 18–22 (Asn-Ala-Thr-Leu-Ala) of deoxyribonuclease A, where a 2-acetamido-2-deoxy-β-D-glycopyranosyl residue is linked to the amide group of the Asn-18 residue, is described.

The present synthesis of the protected glycopeptides Asn (GlcNAc)-Ala (2 and 3), Asn (GlcNAc)-Ala-Thr (11 and 12), Asn (GlcNAc)-Ala-Thr-Leu (13), and Asn (GlcNAc)-Ala-Thr-Leu-Ala (14) is based on the synthesis of the peptide chain, unmasking of the terminal amino group, and condensation with 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl]-2-deoxy-β-D-glucopyranosylamine (1), in a sequence of reactions similar to that described[3] for the synthesis of glycopeptides derived from the region of Asn-34 of beef ribonuclease B. Of the two reagents for peptide synthesis, N-ethyl-5-phenylisoxazolium 3'-sulfonate[9] (WRK) and 2-ethoxy-N-ethoxycarbonyl-1,2-dihydroquinoline[10] (EEDQ), the latter-named reagent was found to be more efficient for the synthesis of N[4]-glycosylasparagine,[1] but less efficient for peptides of high molecular weight.[12] Both reagents were tested for the condensation of the glycopyranosylamine 1 with L-alanine p-nitrobenzyl ester to give crystalline 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanine p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (2) in similar yields. The p-nitrobenzyl ester group, protective of the C-terminal group, is stable under acid conditions and, thus, is useful for elongation of the peptide chain from the N-terminal group. In order to elongate the chain at the C-terminal group, the methyl ester derivatives, which can be easily converted into reactive hydrazides,[14] were selected. Condensation of 1 with L-alanine methyl ester in the presence of the WRK re-

1, R = OH

2, R = NHCHCO$_2$CH$_2$C$_6$H$_4$NO$_2$(p), with CH$_3$

3, R = NHCHCO$_2$Me, with CH$_3$

4, R = OH

5, R = NHCHCH$_3$, with CO$_2$CH$_2$C$_6$H$_4$NO$_2$(p)

6, R = NHCHCH$_2$Ph, with CO$_2$Me

R–Ala–Thr–OR'
7, R = Cbz; R' = Me
8, R = H; R' = Me
9, R = Cbz; R' = CH$_2$C$_6$H$_4$NO$_2$(p)
10, R = H; R' = CH$_2$C$_6$H$_4$NO$_2$(p)

11, R = OMe
12, R = OCH$_2$C$_6$H$_4$NO$_2$(p)

13, R = NHCHCO$_2$CH$_2$C$_6$H$_4$NO$_2$(p), with CH$_2$–CH(CH$_3$)$_2$

14, R = NHCHCONHCHCO$_2$CH$_2$C$_6$H$_4$NO$_2$(p), with CH$_2$–CH(CH$_3$)$_2$ and CH$_3$

agent gave, however, the methyl ester analogue **3** of **2** only in 25% yield.

In order to ascertain whether the alkaline condition of the peptide chain elongation might cause a translocation of the glycosylamine group from C-4 to C-1 of the asparagine moiety, the isomeric glycosylamine of **1**, namely 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl]-2-deoxy-β-D-glucoypyranosylamine (**4**), was condensed with L-alanine p-nitrobenzyl ester and L-phenylalanine methyl ester in the presence of the WRK or EEDQ reagent to give 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-4-oyl-(L-alanine nitrobenzyl ester and L-phenylalanine methyl ester)-1-oyl]-2-deoxy-β-D-glucopyranosylamine (**5** and **6**), respectively. Both **5** and **6** showed properties different from those of the analogue **3** and of the previously synthesized 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-phenylalanine methyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine,[3] respectively, and no transposition products were observed.
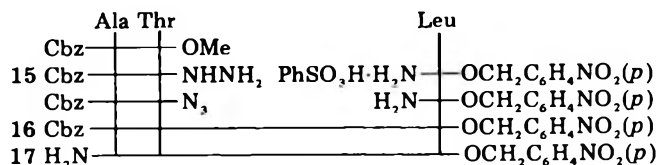
Removal of the protective N-benzyloxycarbonyl group from the methyl[15] and p-nitrobenzyl esters of N-(benzyloxycarbonyl)-L-alanyl-L-threonine (**7** and **9**), obtained by condensation of N-benzyloxycarbonyl-L-alanine with L-threonine methyl or p-nitrobenzyl ester in the presence of dicyclohex-

acarbodiimide, gave the corresponding dipeptides **8** and **10**. These were coupled with **1** in the presence of the WRK reagent to give the crystalline glycotripeptides 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonine methyl and p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (**11** and **12**), in 38 and 30% yields, respectively. These protected glycotripeptides correspond to the amino acid sequence 18–20 of deoxyribonuclease A.

The synthesis of the p-nitrobenzyl ester of the tri- and tetrapeptides N-(benzyloxycarbonyl)-L-alanyl-L-threonyl-leucine (**16**) and N-(benzyloxycarbonyl)-L-alanyl-L-threonyl-L-leucyl-L-alanine (**19**) by coupling N-(benzyloxycarbonyl)-L-alanyl-L-threonine hydrazide (**15**) via the azide derivative with L-leucine p-nitrobenzyl ester and with N-(benzyloxycarbonyl)-L-leucinyl-L-alanine p-nitrobenzyl ester (**18**), after removal of the N-(benzyloxycarbonyl) group, respectively, is illustrated in Schemes I and II. After removal of the protective N-(benzyloxycarbonyl) group, the tripeptide **17** was condensed with **1** in the presence of either the WRK or the EEDQ reagent to give crystalline 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonyl-L-leucine p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (**13**), which corresponds to the amino acid sequence 18–21 of deoxyribonuclease A. In both cases, the yields of **13** were low (19 and 13%, respectively).

A similar condensation of the deblocked tetrapeptide **20**, obtained from **19**, with **1** in the presence of the WRK or EEDQ reagent gave the crystalline, protected glycopentapeptide 2-acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonyl-L-leucyl-L-alanine

Scheme I

	Ala	Thr		Leu
Cbz		OMe		
15 Cbz		NHNH$_2$	PhSO$_3$H·H$_2$N	OCH$_2$C$_6$H$_4$NO$_2$(p)
Cbz		N$_3$	H$_2$N	OCH$_2$C$_6$H$_4$NO$_2$(p)
16 Cbz				OCH$_2$C$_6$H$_4$NO$_2$(p)
17 H$_2$N				OCH$_2$C$_6$H$_4$NO$_2$(p)

Scheme II

	Ala		Thr		Leu		Ala	
				Cbz		OC$_6$H$_4$NO$_2$(p)	H$_2$N	OCH$_2$C$_6$H$_4$NO$_2$(p)
				18 Cbz				OCH$_2$C$_6$H$_4$NO$_2$(p)
				HBr·H$_2$N				OCH$_2$C$_6$H$_4$NO$_2$(p)
Cbz			N$_3$	H$_2$N				OCH$_2$C$_6$H$_4$NO$_2$(p)
19 Cbz								OCH$_3$C$_6$H$_4$NO$_2$(p)
20 H$_2$N								OCH$_2$C$_6$H$_4$NO$_2$(p)
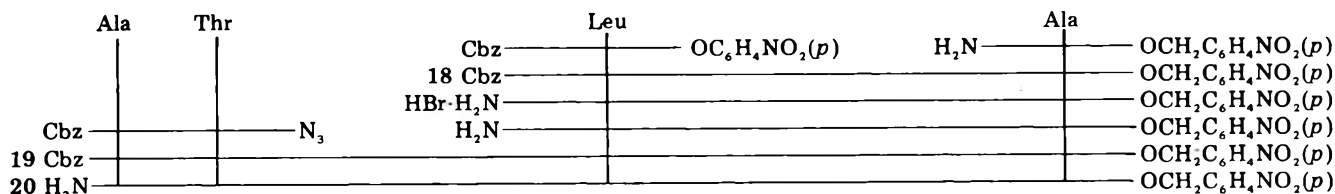
Table I. Amino Acid Composition of the Synthetic Glycopeptides[a]

			Amino acid analysis	
		Theory	Found (GLC)	Found (Beckman)
L-Alanine p-nitrobenzyl ester (2)	L-Asp	1.00	1.00	
	L-Ala	1.00	0.81	
L-Alanine methyl ester (3)	L-Asp	1.00	1.00	
	L-Ala	1.00	1.06	
L-Alanyl-L-threonine methyl ester (11)	L-Asp	1.00	1.00	
	L-Ala	1.00	0.86	
	L-Thr	1.00	0.91	
L-Alanyl-L-threonine p-nitrobenzyl ester (12)	L-Asp	1.00	1.00	1.00
	L-Ala	1.00	0.92	0.93
	L-Thr	1.00	1.04	0.91
L-Alanyl-L-threonyl-L-leucine p-nitrobenzyl ester (13)	L-Asp	1.00	1.00	1.00
	L-Ala	1.00	0.82	0.98
	L-Leu	1.00	0.90	0.98
	L-Thr	1.00	1.00	0.96
L-Alanyl-L-threonyl-L-leucyl-L-alanine p-nitrobenzyl ester (14)	L-Asp	1.00	1.00	1.00
	L-Ala	2.00	2.08	1.89
	L-Leu	1.00	0.99	0.93
	L-Thr	1.00	0.84	0.78

[a] 2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(peptide ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine.

p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (14), corresponding to the amino acid sequence 18–22 of ribonuclease A. The respective yields were 11 and 3%. The low yield of the condensation in the presence of the EEDQ reagent is in agreement with the low yields obtained previously in the synthesis of high molecular weight polypeptides with this reagent.[12]

Experimental Section

General Methods. Melting points were determined with a Mettler FP-2 apparatus and correspond to "corrected melting points". Rotations were determined for solutions in 1-dm semimicrotubes with a Perkin-Elmer No. 141 polarimeter. The N,N-dimethylformamide used was Spectro-reagent grade. Ir spectra were recorded for potassium bromide disks, with a Perkin-Elmer spectrophotometer Model 237. Evaporations were performed in vacuo, the bath temperature being kept below 45 °C. Column chromatography was performed on silica gel Merck (70–325 mesh, E. Merck, Darmstadt, Germany), used without pretreatment; the ratio of the weight of substance to the weight of silica gel was 1:60; the volume of the fractions collected was 2 ml/g of the substance; the ratio was verified by ascending TLC on precoated plates of silica gel (Merck); solvents (v/v) used were A, chloroform–methanol, 19:1; B, chloroform–ethanol, 19:1; C, chloroform–methanol, 14:1; D, chloroform–methanol, 9:1; E, chloroform–ethanol, 14:1; the spots were detected by spraying the plates with 20% sulfuric acid and heating them at 200 °C for a few minutes. The microanalyses were performed by Dr. W. Manser, Zurich, Switzerland.

The amino acid composition of the peptides was determined after hydrolysis by heating the solution for 24 h at 108 °C with hydrochloric acid (ca. 5.8 M, constant boiling point), followed by evaporation in the presence of NaOH pellets. (a) The dry residue was heated with 3 M hydrochloric acid (5 ml) for 1 h at 100 °C, followed by treatment with a 25% solution of trifluoroacetic anhydride in dichloromethane (0.1 ml) for 1 h at 100 °C. GLC analysis of the N-trifluoroacetyl butyl esters was performed on a column of Tabsorb (Regis Chemical Co., Chicago, Ill.) programmed for a rise of 4 °C/min from 75 to 225 °C. (b) The amino acid composition of the residue was determined with a Beckman Spinco Model 117 amino acid analyzer.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanine p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (2). A. To a solution of N-ethyl-5-phenylisoxazolium 3'-sulfonate (63 mg) in acetonitrile (10 ml) at 10 °C was added 1 (0.149 g) and N-methylmorpholine (25 μl) in acetonitrile (20 ml). The reaction mixture was stirred and the ice bath was removed. After 65 min, all compounds were in solution. L-Alanine

p-nitrobenzyl ester hydrobromide[17] (80 mg) in acetonitrile (10 ml) and N-methylmorpholine (25 μl) were added. The mixture was stirred for 24 h at room temperature, and the solvents were removed in vacuo. The residue was dissolved in chloroform, and the solution was successively washed with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and evaporated in vacuo. The residue was crystallized from chloroform–methanol (0.125 g, 62.5%): mp 271–273 °C dec; [α]^{22}D +4.7° (c 0.94, N,N-dimethylformamide); ir 3300 (NH), 1740 (OAc), 1650 (benzyloxycarbonyl group CO), 1580–1680 cm^{-1} (peptide amide I); R_f 0.63 (D), 0.54 (E).

Anal. Calcd for C$_{36}$H$_{43}$N$_5$O$_{16}$: C, 53.93; H, 5.41; N, 8.73; O, 31.93. Found: C, 53.93; H, 5.50; N, 8.78; O, 32.04.

B. A solution of 1 (0.149 g) in tetrahydrofuran–acetonitrile (20 ml) was mixed with L-alanine p-nitrobenzyl ester hydrobromide (80 mg) in the same solvent mixture (1 ml) containing triethylamine (35 μl), and treated with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ, 0.62 g). The mixture was stirred overnight and evaporated in vacuo. The residue was dissolved in chloroform and processed as described in method A. The residue crystallized as long needles from chloroform–methanol (0.13 g, 65%), mp 274–275 °C; ir spectrum and mobility on TLC were identical with those of material obtained by method A.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanine methyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (3). To a solution of N-ethyl-5-phenylisoxazolium 3'-sulfonate (0.125 g) in acetonitrile (20 ml) at 0 °C was added 1 (0.298 g) and N-methylmorpholine (50 μl) in acetonitrile (40 ml). The suspension was treated as described for 2, and a solution of L-alanine methyl ester hydrochloride (70 mg)[16] in acetonitrile (12 ml) and N-methylmorpholine (50 μl) was added. The mixture was treated as described for 2 and the residue was crystallized from hot methanol (85 mg, 25%): mp 268–269 °C dec (sintered at 255–257 °C); [α]^{25}D +7.9° (c 0.94, N,N-dimethylformamide); ir 3300 (NH), 1650 (benzyloxycarbonyl group CO), 1550–1740 cm^{-1} (peptide amide I); R_f 0.58 (C).

Anal. Calcd for C$_{30}$H$_{40}$N$_4$O$_{14}$: C, 52.94; H, 5.92; N, 8.23; O, 32.91. Found: C, 52.86; H, 5.96; N, 8.28; O, 32.91.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-4-oyl-(L-alanine p-nitrobenzyl ester)-1-oyl]-2-deoxy-β-D-glucopyranosylamine (5). A. A solution of 4 (0.15 g)[18] in benzene–ethanol (1:1 v/v, 20 ml) was mixed with a solution of L-alanine p-nitrobenzyl ester hydrobromide (80 mg) in the same solvent mixture (5 ml) containing triethylamine (35 μl), and EEDQ (65 mg) was added. The mixture was stirred overnight and the solvents were removed in vacuo. The residue was washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, evaporated in vacuo, and crystallized from

acetonitrile (95 mg, 47.5%): mp 238–239 °C dec; $[\alpha]^{18}$D −10.4° (c 1.1, N,N-dimethylformamide); ir 3300 (NH), 1740 (OAc), 1650 (benzyloxycarbonyl group CO), 1550–1700 cm⁻¹ (peptide amide I); R_f 0.25 (E).

Anal. Calcd for $C_{36}H_{43}N_5O_{16}$: C, 53.93; H, 5.41; N, 8.73; O, 31.93. Found: C, 53.89; H, 5.72; N, 8.84; O, 31.65.

B. To a clarified mixture of N-ethyl-5-phenylisoxazolium 3'-sulfonate (63 mg), 4 (0.15 g), and N-methylmorpholine (25 μl) in acetonitrile (20 ml) obtained under conditions described for **2** was added a solution of L-alanine p-nitrobenzyl ester hydrobromide (80 mg) containing N-methylmorpholine (25 μl). The mixture was stirred overnight and the solvents were removed in vacuo. The residue was dissolved in chloroform, and the solution was washed, dried, and evaporated as described for **5**. The residue was crystallized from acetonitrile (26 mg, 13%): mp 238.5–239 °C dec; ir spectrum and mobility on TLC were identical with those of the compound obtained by method A.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-4-oyl-(L-phenylalanine methyl ester)-1-oyl]-2-deoxy-β-D-glucopyranosylamine (6). A solution of 4 (0.15 g) in benzene–ethanol (1:1 v/v, 20 ml) was mixed with a solution of L-phenylalanine methyl ester hydrochloride[19] (55 mg) in the same solvent mixture (2 ml) containing triethylamine (35 μl), and EEDQ (65 mg) was added. The mixture was stirred overnight and the solvents were evaporated. The residue was filtered off, washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and crystallized from hot acetonitrile as needles (0.135 g, 71%): mp 263–264 °C dec (sintered at 260 °C); $[\alpha]^{21}$D +1.0° (c 0.8, N,N-dimethylformamide); ir 3300 (NH), 1740 (OAc), 1675 (benzyloxycarbonyl group CO), 1555–1695 cm⁻¹ (peptide amide I); R_f 0.34 (E).

Anal. Calcd for $C_{36}H_{44}N_4O_{14}$: C, 57.14; H, 5.86; N, 7.40; O, 29.60. Found: C, 57.00; H, 5.83; N, 7.38; O, 29.48.

N-(Benzyloxycarbonyl)-L-alanyl-L-threonine p-Nitrobenzyl Ester (9). A solution of L-threonine p-nitrobenzyl ester was prepared by treatment of a solution of N-(benzyloxycarbonyl)-L-threonine p-nitrobenzyl ester[20] (1.94 g) in glacial acetic acid (5 ml) with 30% hydrogen bromide in acetic acid (5 ml), keeping the mixture at room temperature for 1 h and precipitating the resulting hydrobromide with anhydrous ether; the precipitate was rapidly filtered off and treated with triethylamine (0.7 ml) in N,N-dimethylformamide (5 ml). This solution was added to a cooled solution (0 °C) of N-(benzyloxycarbonyl)-L-alanine (1.12 g) and N,N-dicyclohexylcarbodiimide (1.03 g) in dichloromethane–N,N-dimethylformamide (2:1 v/v, 30 ml). This mixture was stirred for 3 h at 0 °C and then at room temperature overnight. The solvents were evaporated and the residue was dissolved in ethyl acetate. The N,N-dicyclohexylurea was filtered off and the filtrate was successively washed with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, and dried with sodium sulfate. After evaporation, the residual syrup crystallized on trituration with hexane. The crystals were recrystallized from ethyl acetate as long needles (1.3 g, 57%): mp 133–134 °C; $[\alpha]^{25}$D −55.5° (c 0.76, N,N-dimethylformamide); ir 3325–3375 (NH), 1660 (benzyloxycarbonyl group CO), 1525–1746 cm⁻¹ (peptide amide I); R_f 0.21 (A).

Anal. Calcd for $C_{22}H_{25}N_3O_8$: C, 57.51; H, 5.48; N, 9.15; O, 27.86. Found: C, 57.60; H, 5.68; N, 9.14; O, 27.66.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonine methyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (11). To a solution of N-ethyl-5-phenylisoxazolium 3'-sulfonate (63 mg), 1 (0.15 g), and N-methylmorpholine (25 μl) in acetonitrile (20 ml), prepared under the conditions described for **2**, was added L-alanyl-L-threonine methyl ester hydrobromide in acetonitrile (10 ml) containing N-methylmorpholine (25 μl). L-Alanyl-L-threonine methyl ester hydrobromide was prepared from N-(benzyloxycarbonyl)-L-alanyl-L-threonine methyl ester[15] (85 mg) by treatment in acetic acid (1 ml) with 30% hydrogen bromide in acetic acid (1 ml) at room temperature for 1 h; subsequent precipitation, and rapid filtration. The mixture was stirred overnight and the solvent evaporated in vacuo. The residue was dissolved in dichloromethane and the solution washed, dried with sodium sulfate, and evaporated as described for **2**. The residue was crystallized from ethyl alcohol (75 mg, 38%): mp 252–254 °C dec (sintered at 247 °C); $[\alpha]^{25}$D +9.4 °C (c 0.54, N,N-dimethylformamide); ir 3300 (NH), 1650 (benzyloxycarbonyl group CO), 1540–1690 cm⁻¹ (peptide amide I); R_f 0.47 (C).

Anal. Calcd for $C_{34}H_{47}N_5O_{16}$: C, 52.23; H, 6.06; N, 8.96; O, 32.75. Found: C, 51.99; H, 6.00; N, 8.67; O, 32.48.

2-Acetamido-3,4,6-tri-O-acetyl-1-N-[N-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonine p-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (12). L-Alanyl-

L-threonine p-nitrobenzyl ester hydrobromide was prepared by treatment of 9 (0.115 g) in glacial acetic acid (2 ml) with 30% hydrogen bromide in acetic acid (2 ml) at room temperature for 1 h, subsequent precipitation with anhydrous ether, and filtration. A solution in acetonitrile (10 ml) containing N-methylmorpholine (25 μl) was added to a solution of N-ethyl-5-phenylisoxazolium 3'-sulfonate (63 mg), 1 (0.15 g), and N-methylmorpholine (25 μl) in acetonitrile (10 ml) prepared as described for **2**. The reaction mixture was stirred for 24 h and the solvents were removed in vacuo. The residue was dissolved in chloroform, and the solution was washed, dried, and evaporated as described for **2**. The residue crystallized from methanol (75 mg, 30%): mp 244.5–245.5 °C dec (sintered 241.5 °C); $[\alpha]^{21}$D −18.0° (c 0.77, N,N-dimethylformamide); ir 3300 (NH), 1740 (OAc), 1640 (benzyloxycarbonyl group CO), 1525–1700 cm⁻¹ (peptide amide I); R_f 0.77 (D).

Anal. Calcd for $C_{40}H_{50}N_6O_{18}$: C, 53.21; H, 5.58; N, 9.31; O, 31.90. Found: C, 53.17; H, 5.66; N, 9.38; O, 31.78.

N-(Benzyloxycarbonyl)-L-alanyl-L-threonine Hydrazide (15). Hydrazine[22] (95%, 0.6 ml) was added to a solution of methyl N-(benzyloxycarbonyl)-L-alanyl-L-threonate[15] (2.0 g) in methanol (10 ml) and the mixture was kept at room temperature overnight. The hydrazide was obtained after evaporation of the solvent and recrystallized from methanol (1.7 g, 85%): mp 208–210 °C; $[\alpha]^{25}$D −37.4° (c 0.53, 0.2 M hydrochloric acid); ir 3250–3275 (NH), 1630 (benzyloxycarbonyl group CO), 1525–1675 cm⁻¹ (peptide amide I).

Anal. Calcd for $C_{15}H_{22}N_4O_5$: C, 53.26; H, 6.56; N, 16.54; O, 23.64. Found: C, 53.08; H, 6.47; N, 16.41; O, 23.69.

N-(Benzyloxycarbonyl)-L-alanyl-L-threonyl-L-leucine p-Nitrobenzyl Ester (16). N-(Benzyloxycarbonyl)-L-alanyl-L-threonine hydrazide (15, 0.85 g) was dissolved in a mixture of concentrated hydrochloric acid (0.25 ml), glacial acetic acid (0.75 ml), and water (6.5 ml), and the solution was cooled to 0 °C. Sodium nitrite (0.175 g) was added with stirring and the syrupy azide formed was extracted with ethyl acetate precooled to 0 °C. The extract was washed with cold water and dried with sodium sulfate. It was added to a precooled solution of L-leucine p-nitrobenzyl ester prepared from a solution of its benzenesulfonic salt[21] (1.06 g) in N,N-dimethylformamide (5 ml) and triethylamine (0.35 ml). After 24 h at 6 °C and several hours at room temperature, the solvents were evaporated. The residue was dissolved in ethyl acetate and washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, and dried with sodium sulfate. The solution was evaporated and the residue dissolved in a small amount of ethyl acetate. The insoluble material was filtered off, and the filtrate crystallized on cooling (0.975 g, 69%): mp 79–80 °C; $[\alpha]^{22}$D −12.3° (c 0.61, N,N-dimethylformamide); ir 3275 (NH), 1630 (benzyloxycarbonyl group CO), 1550–1750 cm⁻¹ (peptide amide I); R_f 0.36 (B).

Anal. Calcd for $C_{28}H_{36}N_4O_9$: C, 58.73; H, 6.34; N, 9.78; O, 25.15. Found: C, 58.63; H, 6.36; N, 9.84; O, 25.22.

N-(Benzyloxycarbonyl)-L-leucyl-L-alanine p-Nitrobenzyl Ester (18). A solution of p-nitrophenyl N-(benzyloxycarbonyl)-L-leucinate[23] (1.93 g) in chloroform (10 ml) was added to a N,N-dimethylformamide solution (5 ml) containing L-alanine p-nitrobenzyl ester hydrobromide[17] (1.52 g) and triethylamine (0.7 ml). The mixture was stirred for 24 h, the solvents were removed, and the residue was dissolved in ethyl acetate. The organic layer was washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, and dried with sodium sulfate. The solvent was evaporated and the syrup crystallized from ethyl alcohol on cooling (1.7 g, 72%): mp 108–109 °C; $[\alpha]^{25}$D −17.3° (c 0.87, N,N-dimethylformamide); ir 3300 (NH), 1630 (benzyloxycarbonyl group CO), 1560–1725 cm⁻¹ (peptide amide I); R_f 0.7 (B).

Anal. Calcd for $C_{24}H_{29}N_3O_7$: C, 61.14; H, 6.20; N, 8.91; O, 23.75. Found: C, 61.14; H, 6.24; N, 8.88; O, 23.89.

N-(Benzyloxycarbonyl)-L-alanyl-L-threonyl-L-leucyl-L-alanine p-Nitrobenzyl Ester (19). N-(Benzyloxycarbonyl)-L-leucyl-L-alanine p-nitrobenzyl ester (18, 0.24 g) was converted into its hydrobromide derivative by dissolving it in glacial acetic acid (1.5 ml) and treating the solution with 30% hydrogen bromide in acetic acid (1.5 ml) for 1 h at room temperature. The hydrobromide was precipitated by anhydrous ether and rapidly filtered off, dissolved in N,N-dimethylformamide (1 ml), and treated with triethylamine (70 μl). The resulting product was condensed with the azide prepared from N-(benzyloxycarbonyl)-L-alanyl-L-threonine hydrazide (15, 0.17 g) in the same manner as described for 16. The mixture was stirred for 20 h, and the solvents were removed in vacuo. The residue was dissolved in ethyl acetate, and the solution was washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and concentrated in vacuo. The residue was crystallized from absolute ethanol as granules

(0.19 g, 60%); mp 187–189 °C dec; $[\alpha]^{22}$D −11.7° (c 0.71, *N,N*-dimethylformamide); ir 3250 (NH), 1660 (benzyloxycarbonyl group CO), 1630–1730 cm^{-1} (peptide amide I); R_f 0.3 (B).

Anal. Calcd for $C_{31}H_{41}N_5O_{10}$: C, 57.85; H, 6.42; N, 10.88; O, 24.85. Found: C, 57.83; H, 6.47; N, 10.86; O, 24.80.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-[*N*-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonyl-L-leucine *p*-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (13). A. A solution of *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (63 mg) in acetonitrile (10 ml) cooled to 0 °C was added to 1 (0.149 g) and *N*-methylmorpholine (25 μl) in acetonitrile (20 ml). The reaction mixture was stirred for 65 min at room temperature until dissolution. A solution of L-alanyl-L-threonyl-L-leucine *p*-nitrobenzyl ester hydrobromide was prepared from 16 (0.143 g) in glacial acetic acid (2 ml) by treatment with 30% hydrogen bromide in acetic acid (2 ml) at room temperature for 1 h, removal of the acids by evaporation in vacuo, washing the residue with anhydrous ether, and drying in a vacuum desiccator. This residue was dissolved in acetonitrile (10 ml) containing *N*-methylmorpholine (25 μl), and the solution was added to the previously described solution. The mixture was stirred for 24 h and the acetonitrile was evaporated in vacuo. The residue was dissolved in chloroform, and the solution was successively washed with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and evaporated in vacuo. The crude material (0.15 g) showed on TLC two major spots [R_f 0.55 and 0.43 (C)] and a few minor spots moving faster. It was purified by column chromatography on silica gel. Chloroform eluted fast-moving products, and successive elution with a linear gradient (1:100 to 3:100, v/v) of methanol–chloroform gave in the earlier fractions 0.21 mg of a compound having R_f 0.53 (C) and then pure 13 [R_f 0.43 (C), 0.56 g]. This was crystallized from acetonitrile–methanol (48 mg, 19%): mp 263–264 °C dec; $[\alpha]^{21}$D −2.0° (c 0.68, *N,N*-dimethylformamide); ir 3285 (NH), 1740 (OAc), 1630 (benzyloxycarbonyl group CO), 1530–1650 cm^{-1} (peptide amide I).

Anal. Calcd for $C_{46}H_{61}N_7O_{19}$: C, 54.38; H, 6.05; N, 9.65; O, 29.92. Found: C, 54.29; H, 6.08; N, 9.63; O, 30.02.

B. A solution of 1 (0.149 g) in tetrahydrofuran (15 ml) was treated with a solution of L-alanyl-L-threonyl-L-leucine *p*-nitrobenzyl ester hydrobromide [prepared from 16 (0.143 g) under the same conditions as described in method A] in acetonitrile (5 ml) containing triethylamine (35 μl) and EEDQ reagent (62 mg). The mixture was stirred overnight at room temperature. The solvents were removed in vacuo and the residue was dissolved in chloroform. The solution was washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and evaporated. The residue was crystallized from acetonitrile–methanol (35 mg, 13%), mp 261–263 °C. The ir spectrum and the mobility on TLC were identical with those of the material obtained by method A.

2-Acetamido-3,4,6-tri-*O*-acetyl-1-*N*-[*N*-(benzyloxycarbonyl)-L-aspart-1-oyl-(L-alanyl-L-threonyl-L-leucyl-L-alanine *p*-nitrobenzyl ester)-4-oyl]-2-deoxy-β-D-glucopyranosylamine (14). A. To a solution of *N*-ethyl-5-phenylisoxazolium 3′-sulfonate (63 mg) in acetonitrile (10 ml) at 0 °C was added 1 (0.149 g) and *N*-methylmorpholine (25 μl) in acetonitrile (20 ml). The reaction mixture was stirred for 65 min at room temperature until dissolution. A solution of L-alanyl-L-threonyl-L-leucyl-L-alanine *p*-nitrobenzyl ester hydrobromide [prepared from 19 (0.161 g), glacial acetic acid (2 ml), and 30% hydrogen bromide in glacial acetic acid (2 ml) under the same conditions as described for 16] in acetonitrile (10 ml) containing *N*-methylmorpholine (25 μl) was added to the previously described solution. The mixture was stirred for 24 h and then the acetonitrile was removed in vacuo. The crude material was dissolved in chloroform, and the solution was successively washed with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and evaporated to give a crude material (33 mg, 12%) that was crystallized from methanol (19 mg): mp 249–251 °C dec (and shrinking at 247 °C); $[\alpha]^{21}$D +6.4° (c 0.72, *N,N*-dimethylformamide); ir 3300 (NH), 1740 (OAc), 1660 (benzyloxycarbonyl group CO), 1530–1700 cm^{-1} (peptide amide I); R_f 0.34 (E) and 0.69 (D).

Anal. Calcd for $C_{49}H_{66}N_8O_{20}$: C, 54.14; H, 6.11; N, 10.30; O, 29.43. Found: C, 54.17; H, 6.18; N, 9.62; O, 29.53.

B. A solution of 1 (0.149 g) in tetrahydrofuran (15 ml) was treated with a solution of L-alanyl-L-threonyl-L-leucyl-L-alanine *p*-nitrobenzyl ester hydrobromide [prepared from 19 (0.161 g) by following the same conditions as described in method A] in acetonitrile (5 ml) containing triethylamine (35 μl) and EEDQ reagent (62 mg). The mixture was stirred overnight at room temperature. The solvents were removed in vacuo and the residue was dissolved in chloroform. The solution was washed successively with 1 M hydrochloric acid, water, 1% sodium hydrogen carbonate, and water, dried with sodium sulfate, and evaporated. The residue crystallized from ethanol–ether (8 mg, 3%), mp 250–252 °C dec, ir identical with that of the product prepared by method A.

References and Notes

(1) Amino Sugars. 101. This is Publication No. 696 of the Robert W. Lovett Memorial Group for the Study of Diseases Causing Deformities, Harvard Medical School at the Massachusetts General Hospital, Boston, Mass. 02114. The work was supported by a research grant from the National Institute of Arthritis and Metabolic Diseases (AM-03864), National Institutes of Health, U.S. Public Health Service. A preliminary communication has been presented; see H. G. Garg and R. W. Jeanloz, Abstracts, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, No. CARB-011.
(2) R. D. Marshall and A. Neuberger in "Glycoproteins", 2d ed, A. Gottschalk, Ed., Elsevier, Amsterdam, 1972. p 453.
(3) H. G. Garg and R. W. Jeanloz, *Carbohydr. Res.*, **32**, 37 (1974).
(4) M. A. E. Shaban and R. W. Jeanloz, *Carbohydr. Res.*, **43**, 281 (1975); C. D. Warren, I. Y. Liu, A. Herscovics, and R. W. Jeanloz, *J. Biol. Chem.*, **250**, 8069 (1975); and references cited therein.
(5) J. Salnikov, S. Moore, and W. H. Stein, *J. Biol. Chem.*, **245**, 5865 (1970).
(6) J. Salnikov, T.-H. Liao, S. Moore, and W. H. Stein, *J. Biol. Chem.*, **248**, 1480 (1973).
(7) T.-H. Liao, J. Salnikov, S. Moore, and W. H. Stein, *J. Biol. Chem.*, **248**, 1489 (1973).
(8) J. Salnikov and D. Murphy, *J. Biol. Chem.*, **248**, 1499 (1973).
(9) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).
(10) D. Belleau and G. Malek, *J. Am. Chem. Soc.*, **90**, 1651 (1968).
(11) D. Dunstan and L. Hough, *Carbohydr. Res.*, **23**, 17 (1972).
(12) J. Meinhoffer, R. Cotton, and E. Atherton, *J. Org. Chem.*, **36**, 3746 (1971).
(13) J. E. Shields, W. H. McGregor, and F. H. Carpenter, *J. Org. Chem.*, **26**, 1491 (1961).
(14) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis", Wiley-Interscience, New York, N.Y., 1966, p 76.
(15) T. Wieland and R. Sarges, *Justus Liebigs Ann. Chem.*, **658**, 181 (1962).
(16) H. Zahn and H. Schüssler, *Justus Liebigs Ann. Chem.*, **641**, 176 (1961).
(17) W. K. Park, R. R. Smeby, and F. M. Bumpus, *Biochemistry*, **6**, 3458 (1967).
(18) H. G. Garg and R. W. Jeanloz, *Carbohydr. Res.*, **23**, 437 (1972).
(19) A product from Aldrich Chemical Co.
(20) L. P. Egan, J. R. Vercellotti, and W. T. Lowry, *Carbohydr. Res.*, **23**, 261 (1972).
(21) E. Schroder and E. Klieger, *Justus Liebigs Ann. Chem.*, **673**, 208 (1964).
(22) A product of Eastman Kodak Co.
(23) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959).

Asymmetric Induction in the Pyrolysis of β-Hydroxy Olefins[1]

H. Kenneth Spencer and Richard K. Hill*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

Received December 12, 1975

Pyrolysis of (R)-(−)-(E)-1,4-diphenyl-3-penten-1-ol (3) at 460 °C leads to benzaldehyde and (R)-(−)-3-phenyl-1-butene, formed in 25.6% enantiomeric excess. While the results support a concerted cyclic reaction, the direction of asymmetric induction is not that expected on the basis of a transition state conformation resembling chair cyclohexane. It is concluded that the chair model is a poor one for thermal reactions involving hydrogen transfer.

Among the large family of concerted thermal organic reactions, the fragmentation of β-hydroxy olefins (eq 1) is one of the earliest discovered,[2] now well-recognized[3] subclassifications. The generality of the reaction was established and the accepted mechanism first proposed by Arnold;[4] the concerted cyclic nature of the process, which may be described as a symmetry allowed suprafacial 1,5-hydrogen migration, has been confirmed by a large body of kinetic[5] and stereochemical[6]

$$R_1—CH{=}CH—CH_2—CR_2R_3 \xrightarrow{\Delta}$$

$$\longrightarrow R_1CH_2CH{=}CH_2 + R_2COR_3 \quad (1)$$

evidence. The reaction is reversible[7] and has been extended to β-hydroxyacetylenes.[8]

A stereochemical feature which this fragmentation shares with a number of [3,3]-sigmatropic rearrangements is the possibility of taking place through a transition state of geometry approximating that of either chair or boat cyclohexane (Chart I). In an elegant example provided by Ohloff,[6b] the

Chart I. Possible Transition State Conformations Resembling Chair and Boat Cyclohexanes

pyrolysis of (+)-terpin-1-en-4-ol to (S)-(+)-2,6-dimethyl-7-octen-3-one (eq 2) is forced to occur via a boat transition

$$(2)$$

state; normally in sigmatropic rearrangements of acyclic molecules free to adopt either conformation, chairlike conformations are preferred, and β-hydroxy olefin pyrolysis has been specifically proposed to involve the chair conformation.[8]

The transition state geometry of reactions occurring via six-membered cyclic transition states may be deduced by following the stereochemistry of reactant and product double bonds, as in Doering and Roth's[9] original investigation of the Cope rearrangement. An alternative method to probe transition-state topology is to trace the direction and magnitude of asymmetric induction with a chiral substrate. This method has been used to show that the Claisen,[10] Cope,[11] amino-Claisen,[12] orthoester, and Eschenmoser rearrangements[13] proceed primarily by chairlike transition states. A further

conclusion that can be drawn from these investigations is that of the two possible chair forms, that conformation which places substituents on saturated carbons of the reactant in equatorial positions is greatly preferred. It is surprising for a six-membered transition state in which all six atoms have at least some sp² character that the rules of cyclohexane conformational analysis should apply so well, but Perrin and Faulkner have shown[14] that it is possible to predict quantitatively the cis/trans ratios of Claisen and Cope products from the axial/equatorial free-energy differences in substituted cyclohexanes.

We report here the application of the asymmetric induction probe to β-hydroxy olefin pyrolysis and the unexpected finding that the results are not in accord with conformational predictions.

Results and Discussion

The substrate selected for this study was the homoallylic alcohol 3, which could easily be prepared by the Julia–Johnson rearrangement[15] of the cyclopropylcarbinol 2. Alcohol 2 was prepared by methyl Grignard addition to the known[16] cyclopropyl ketone 1 (Scheme I) and solvolyzed in dilute formic acid to afford 3. Although two geometric isomers are possible, the product was homogeneous by TLC and VPC, gave a single crystalline phthalate, and showed a single methyl peak in the NMR spectrum. It had been reported[17] that carbinols of type 2 rearrange specifically to that homoallylic alcohol with alkyl groups cis, and this was confirmed by spectroscopic analysis of 3. The uv maximum at 247 nm (log ε 4.19) is consistent with the E configuration, according to Cram's data on the 2-phenyl-2-butenes[18] and related olefin pairs in which the Z isomer absorbs some 8–15 nm lower because of twisting out of coplanarity.[19] Moreover, the chemical shift of the vinyl proton in 3, δ 5.70, is in good agreement with the value calculated by Simon's rules[20] (E, 5.80; Z, 5.36).

The phthalate ester of 3 was resolved with α-phenylethylamine and hydrolyzed to afford both enantiomers of 3. To determine the absolute configuration and optical purity of these samples, each isomer was ozonized to β-hydroxy-β-phenylpropionic acid (4). Based on the maximum rotation,

Scheme I

$[\alpha]$D 21.1° (*c* 2.2, ethanol), reported[21] for **4** and its known (*R*)-(+) configuration,[22] (*R*)-(−)-**3**, $[\alpha]^{25}$D −42.1° (ethanol), is 80.1% optically pure, while (*S*)-(+)-**3**, $[\alpha]^{25}$D 40.3° (ethanol), is 77.7% optically pure.

Pyrolysis was carried out at 460 °C in a Vycor tube packed with glass beads by injecting a toluene or cyclohexane solution of **3** under a positive nitrogen flow and collecting the products at −74 °C. Distillation gave 3-phenyl-1-butene (**5**), further purified by VPC to afford 51–63% of the pure olefin. From the pyrolysis of (*S*)-(+)-**3** the sample of **5** isolated had $[\alpha]^{24}$D 1.09°, while pyrolysis of (*R*)-(−)-**3** gave **5** with $[\alpha]$D −1.26°.

The absolute configuration of **5** has been established as (*R*)-(−), and from the rotation of the optically pure hydrocarbon[23] (6.39°, neat) the optical purities of the dextro- and levorotatory pyrolysis products are calculated to be 17.1 and 19.7%, respectively. These conclusions were confirmed by oxidation of (*R*)-(−)-**5** to (*S*)-(+)-hydratropic acid[24] (**6**) of 20.5% optical purity, based on the maximum rotation recorded[25] of 81.1°.

Pyrolysis of the optically active homoallylic alcohol **3** consequently furnishes olefin **5** with 25.6% retention of optical activity. Three conclusions from this result may be noted.

(1) The retention of appreciable optical activity during the formation of **5** from **3** provides additional evidence that β-hydroxy olefin pyrolysis proceeds (at least partly) through a cyclic transition state in a concerted reaction, as opposed to, e.g., initial homolytic cleavage to a radical pair followed by hydrogen atom transfer. The observed asymmetric induction (a "self-immolative" asymmetric synthesis[26]) requires a chiral transition state in which the original asymmetric center in **3** is not lost before exerting its influence on the creation of the new asymmetric center in **5**. While Ohloff had provided an earlier example[6b] of a self-immolative β-hydroxy olefin pyrolysis, the present case is the first involving a nonrigid, acyclic substrate.

(2) The degree of conservation of optical purity, about 25%, is at first sight low by comparison with optical yields found in other thermal reactions which occur via six-membered cyclic transition states, e.g., 94–96% in the Cope rearrangement[11] and greater than 90% in the orthoester and Eschenmoser rearrangements.[13] However, it is of the same order of magnitude as the few published cases involving *hydrogen* transfer in six-membered transition states: 15% optical yield in the 1,5-intramolecular hydride transfer to carbonium ions;[27] apparently low optical yields in the intermolecular ene reaction.[28] Moreover, those hydride reductions, such as the Meerwein–Ponndorf–Verley and Grignard reductions, which transfer a hydrogen atom in a six-membered cyclic complex containing a metal atom as well also occur with variable but generally low optical yields.[29]

The low optical yield does not necessarily imply a nonconcerted component to the mechanism, but rather that several transition states of small energy differences, leading to products of opposite configuration, are available. It appears that in this case, and possibly the other hydrogen-transfer reactions cited above, the presence of a hydrogen atom in the cycle results in marked lowering of energy differences between puckered transition-state conformations, and perhaps in flattening of these conformations.

(3) The four transition-state conformations for pyrolysis of (*R*)-(−)-**3** resembling chair and boat cyclohexanes are shown below:

7   (*S*)-**5**   9
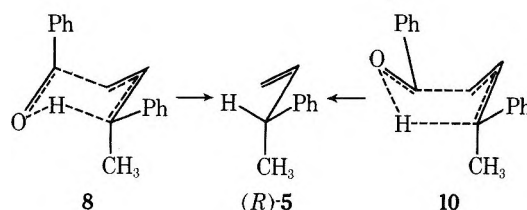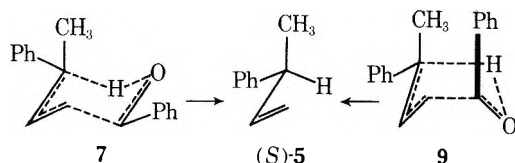
On the basis of the published cases cited earlier, in which product formation seems to be governed by principles of cyclohexane conformational analysis, it would have been anticipated that conformation **7**, a chairlike conformer with equatorial phenyl, would be the preferred transition state, leading to a predominance of the *S* enantiomer of **5**. The observed preference for (*R*)-**5** is the first case of a thermal rearrangement involving a six-membered cyclic transition state in which the direction of asymmetric induction is incorrectly predicted by conformational arguments.

What is responsible for this failure of conformational prediction? It should be noted, first of all, that the energy differences involved are quite small; $\Delta\Delta G^{\ddagger}$ for a reaction giving 25.6% asymmetric induction at 460 °C corresponds to 0.76 kcal/mol. Mislow has cogently warned of the dangers of predicting the direction of asymmetric induction when the energy differences are small and the transition state conformation imperfectly understood.[30] In the present case, the substitution of oxygen and hydrogen for two of the carbon atoms in the cyclohexane model, as well as the ring flattening induced by the sp^2 carbons, conspire to severely weaken the validity of the model. The 1,3-diaxial interactions which are responsible for the normal preference of equatorially substituted cyclohexanes vs. their axially substituted conformers are absent in transition states **7** and **8**, and Dreiding models reveal no obvious preference for either. In any case, the cyclohexane model which has served so well for [3,3]-sigmatropic rearrangements is apparently a poor model for the six-membered cycles involved in thermal hydrogen transfer.

Experimental Section[31]

Methylphenyl(2-phenylcyclopropyl)carbinol (2). The Grignard reagent was prepared in the usual way from 0.9724 g of magnesium turnings and 5.68 g of methyl iodide in 30 ml of ether. To this solution was added an ethereal solution of 7.0 g of 1-benzoyl-2-phenylcyclopropane[16] and the mixture was stirred for 1 h, then heated to reflux for 20 min. The reaction mixture was hydrolyzed with saturated aqueous NH$_4$Cl, the layers separated, and the aqueous layer extracted with ether. The combined ether solutions were washed with water, dried (MgSO$_4$), and distilled, yielding 6.27 g (82%) of **2**: bp 147–155 °C (0.4 mm); ir (neat) 3450, 3000, 1610, 1500, 765, 700 cm^{-1}; NMR (CCl$_4$) δ 7.15 (m, 10 H), 2.60 (br s, 1 H, OH), 1.95 (m, 1 H), 1.4 (s, 3 H), 0.9 (m, 3 H); t_R 21.5 on a 10 ft × 0.125 in. Carbowax column, 160 °C, 80 psi He.

Anal. Calcd for C$_{17}$H$_{18}$O: C, 85.67; H, 7.61. Found: C, 85.92; H, 7.44.

(*E*)-1,4-Diphenyl-3-penten-1-ol (3). A mixture of 2.0 g of **2**, 90 ml of water, 36 ml of dioxane, and 0.81 g of formic acid was heated under reflux for 1.5 h, then cooled and extracted with several portions of ether. The combined extracts were washed with water, dried (MgSO$_4$), and distilled, affording 1.93 g (96%) of **3**: bp 145–160 °C (0.4 mm); ir (neat) 3360, 2980, 1600, 1505, 1060, 765, 705 cm^{-1}; NMR (CDCl$_3$) δ 7.2 (m, 10 H), 5.70 (triplet of quartets, 1 H, *J* = 7.3 and 1.3 Hz), 4.59 (t, 1 H, *J* = 6.5 Hz), 2.9 (s, 1 H, OH), 2.5 (triplet of quartets, 2 H, *J* = 6.5 and 1.15 Hz), 1.85 (s, 3 H); uv (cyclohexane) λ_{max} 247 nm (log ε 4.19); t_R 18.0 on a 5 ft × 0.125 in. Carbowax column, 160 °C, 60 psi He; mass spectrum M$^+$ *m/e* 238.

The hydrogen phthalate was prepared by heating a mixture of **3** (5.88 g), phthalic anhydride (3.67 g), and pyridine (4.1 ml) under reflux for 1.5 h. The mixture was cooled, acidified with 0.1 N HCl, and extracted with ether. The extracts were dried (MgSO$_4$) and concentrated under reduced pressure, leaving 9.54 g of crude product. This was taken up in a small volume of CHCl$_3$ and unreacted phthalic anhydride allowed to crystallize; the residue was crystallized from acetic acid–water (9:1) and then from ethyl acetate. The product (8.15 g, 85%) was collected as colorless prisms: mp 130–131 °C; mmp with

phthalic anhydride (mp 131–132 °C) was 105–112 °C; ir (CCl₄) 3050, 1740, 1700, 1595, 1295, 1135, 705 cm⁻¹; NMR (CDCl₃) δ 12.6 (s, 1 H), 7.3 (m, 14H), 6.15 (t, 1 H, J = 6.8 HZ), 5.75 (t, 1 H, J = 7.2 Hz), 2.9 (m, 2 H), 1.9 (s, 3 H).

Anal. Calcd for C₂₅H₂₂O₄: C, 77.70; H, 5.74. Found: C, 77.82; H, 5.56.

Resolution of Alcohol 3. A mixture of 45.2 g of the above acid phthalate and 14.17 g of (+)-α-phenylethylamine in 500 ml of ether and 250 ml of acetone was brought to reflux, filtered, and kept in the dark for 24 h. The salt (27.6 g, mp 131–136 °C) which had precipitated was collected and recrystallized seven times from acetone–ether at room temperature, affording 22.3 g, mp 142–143 °C, [α]²⁸D −28.0° (c 1.03, ethanol). The salt was decomposed with 1 N HCl and the phthalate extracted into ether. Removal of the ether left the phthalate (16.5 g) as an oil, [α]²⁵D −9.22° (c 7.0, ethanol).

The combined mother liquors from the recrystallization of the amine salt were concentrated to dryness and decomposed with 1 N HCl as above to furnish 24.2 g of crude phthalate, [α]²⁸D 2.66° (ethanol). This was resolved with (−)-α-phenylethylamine (7.69 g) as described above, recrystallizing the salt five times, to give a salt of mp 142–143 °C, [α]²⁵D 26.07° (c 1.12, ethanol), which yielded 18.2 g of oily phthalate, [α]²⁵D 9.05° (c 7.0, ethanol).

A mixture of the levorotatory phthalate (3.24 g) and 0.84 g of NaOH in 70 ml of ethanol and 130 ml of water was heated under reflux for 7 h, cooled, and extracted with ether. The combined extracts were washed with water, dried (MgSO₄), and distilled to yield 1.54 g (77.7%) of (−)-3, [α]²⁵D −42.1° (c 5.69, ethanol).

Hydrolysis of the dextrorotatory phthalate in the same way gave (+)-3, in 97% yield, [α]²⁶D 40.32° (c 6.51, ethanol).

Ozonolysis of 3. A solution of 1.1 g of (−)-3, [α]²⁵D −42.1°, in 25 ml of CH₂Cl₂ was ozonized in a Welsbach Model T-408 ozonator at −74 °C, using an ozone flow rate of 0.16 mol/min for 40 min. The solvent was then removed at reduced pressure, 3.1 ml of 90% HCOOH and 3.0 ml of 30% H₂O₂ were added, and the mixture was heated to reflux for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was taken up in 1 N NaHCO₃ and washed with ether, then acidified with HCl and extracted with ether. Concentration of the extracts left 0.585 g (76%) of **(R)-(+)-β-hydroxy-β-phenylpropionic acid (4):** mp 116–117 °C (lit.²¹ mp 117–118 °C) after crystallization from CHCl₃; ir (KBr) 3000 (br), 1680, 1390, 1260, 1045, 1005, 755, 690 cm⁻¹; NMR (acetone-d₆) δ 7.4 (m, 5 H), 4.8 (t, 1 H), 3.4 (s, 1 H, OH), 2.85 (d, 2 H); [α]²⁴D 16.9° (c 1.73, ethanol); the maximum rotation reported²¹ is 21.1° (c 2, ethanol). The **methyl ester,** bp 120–128 °C (4 mm, Kugelrohr), [α]²⁵D 16.3° (c 2.39, ethanol), lit. [α]D 18.3° (c 4.78, ethanol),²²ᶜ was prepared with ethereal diazomethane.

Ozolysis of the antipode of 3, [α]²⁶D 40.32° (ethanol), by the same procedure gave (S)-(−)-4 in 86% yield, mp 116–117 °C, [α]²⁴D −16.4° (c 3.70, ethanol), methyl ester bp 115–124 °C (2.0 mm, Kugelrohr), [α]²⁵D −16.2° (c 2.1, ethanol).

Pyrolysis of 3. The apparatus used was essentially that described by Bailey and Hewitt³² for ester pyrolysis. A 2 × 100 cm vertical Vycor tube, with an injection port and gas inlet near the top, was heated by a Lindberg tube furnace. The heated zone was packed with glass beads supported by a constantan wire. The bottom of the tube was connected to a condenser connected in turn to three vacuum traps at −74 °C and a gas bubbler. The temperature was controlled by a calibrated external voltage and thermocouple gauges. Before each run the tube was thermally equilibrated at 450–470 °C for 1 h. During a run the rate of nitrogen flow was held constant, and the product gases were condensed in the first and second traps.

A solution of 1.5 g of (S)-(+)-(E)-1,4-diphenyl-3-penten-1-ol in 2 ml of toluene was injected into the tube at 460–465 °C over a period of 30 min. After the tube had cooled, the tube and traps were rinsed with ether; after removal of the solvent, the dark residue was purified by VPC on a 10-ft Carbowax 20M on Chromosorb W 60/80 column at 140 °C 40 psi He. 3-Phenyl-1-butene (5), 0.425 g (51%), was collected at tᵣ 6 min and redistilled: bp 172–180 °C (Kugelrohr); the product showed a single peak on two different VPC columns (5-ft SE-30 column at 150 °C, tᵣ 4; 10-ft SDC 710 column at 150 °C, tᵣ 10), with retention times identical with those of an authentic sample; the ir spectrum was identical with that reported by Cram;²³ NMR (CCl₄) δ 7.10 (s, 5 H), 5.88 (m, 1 H), 4.95 (m, 2 H), 3.32 (m, 1 H), 1.26 (d, 3 H); uv (hexane) λ_max 245 nm (log ε 2.98); mass spectrum M⁺ m/e 132; [α]²⁴D 1.09° (c 1.0, ethanol); reported [α]²²D 6.39° (ethanol).²³

Pyrolysis of the antipode of 3, [α]²⁵D −42.1°, gave (R)-(−)-3-phenyl-1-butene in 62% yield, [α]²⁴D −1.26° (c 5.15, ethanol).

Oxidation of 5. To a vigorously stirred solution of 1.243 g of K₂CO₃ in 100 ml of water was added 0.396 g of (R)-(−)-5, [α]²⁴D −1.26°. A

solution of 5.13 g of NaIO₄ and 0.633 g of KMnO₄ in 100 ml of water was added and the solution adjusted to pH 8.5 with 2 N NaOH. After stirring for 16 h, the solution was extracted with ether. The aqueous layer was acidified with HCl to pH 2.5, NaHSO₃ added to destroy the MnO₂, and the solution extracted with ether. The extracts were dried (MgSO₄), concentrated, and distilled to give 0.319 g (71%) of (S)-(+)-hydrotropic acid (6): bp 119–125 °C (4.2 mm, Kugelrohr); [α]²³D 16.6° (c 1.1, ethanol); reported [α]²⁰D 81.1° (c 3.108, ethanol).²⁵ The ir and NMR spectra were identical with those of an authentic sample.

References and Notes

(1) This project was supported by Research Grant GP-28056 from the National Science Foundation, to whom the authors express their appreciation.
(2) The earliest examples, which include the pyrolysis of ricinoleic acid as well as several studies by Grignard, are summarized by C. D. Hurd, "The Pyrolysis of Carbon Compounds", The Chemical Catalog Co., Reinhold, New York, N.Y., 1929, pp 164, 172.
(3) (a) J. Mathieu and J. Vails, *Bull. Soc. Chim. Fr.*, 1509 (1957); (b) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 571 (1969).
(4) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, **81**, 6443 (1959); **82**, 4918 (1960); *J. Org. Chem.*, **25**, 129 (1960).
(5) G. G. Smith and R. Taylor, *Chem. Ind. (London)*, 949 (1961); G. G. Smith and B. L. Yates, *J. Chem. Soc.*, 7242 (1965); G. G. Smith and K. J. Voorhees, *J. Org. Chem.*, **35**, 2182 (1970); H. Kwart and M. C. Latimore, *J. Am. Chem. Soc.*, **93**, 3770 (1971).
(6) (a) G. Ohloff, *Chem. Ber.*, **93**, 2673 (1960); (b) G. Ohloff, *Angew. Chem., Int. Ed. Engl.*, **9**, 743 (1970).
(7) R. T. Arnold and P. Veeravagu, *J. Am. Chem. Soc.*, **82**, 5411 (1960).
(8) A. Viola and J. H. MacMillan, *J. Am. Chem. Soc.*, **90**, 6141 (1968); A. Viola, J. H. MacMillan, R. J. Proverb, and B. L. Yates, *ibid.*, **93**, 6967 (1971).
(9) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).
(10) H. L. Goering and W. I. Kimoto, *J. Am. Chem. Soc.*, **87**, 1748 (1965).
(11) R. K. Hill and N. W. Gilman, *Chem. Commun.*, 619 (1967).
(12) R. K. Hill and N. W. Gilman, *Tetrahedron Lett.*, 1421 (1967).
(13) R. K. Hill, R. Soman, and S. Sawada, *J. Org. Chem.*, **37**, 3737 (1972).
(14) C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969); D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, **95**, 553 (1973).
(15) M. Julia, S. Julia, and S. Tchen, *Bull. Soc. Chim. Fr.*, 1849 (1961); M. Julia, S. Julia, and J. A. du Chaffaut, *ibid.*, 1735 (1960); S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Am. Chem. Soc.*, **90**, 2882 (1968).
(16) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).
(17) S. Sarel and R. Ben-Shoshan, *Tetrahedron Lett.*, 1053 (1965); M. Julia, S. Julia, B. Stella-Bourdillon, and C. Descoins, *Bull. Soc. Chim. Fr.*, 2533 (1964).
(18) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).
(19) S. W. Ela and D. J. Cram, *J. Am. Chem. Soc.*, **88**, 5777 (1966); R. M. Parkhurst, J. O. Rodin, and R. M. Silverstein, *J. Org. Chem.*, **28**, 120 (1963); J. W. Morgan, Ph.D. Dissertation, Princeton University, 1967; ref 17a.
(20) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
(21) S. G. Cohen and S. Y. Weinstein, *J. Am. Chem. Soc.*, **86**, 725 (1964).
(22) (a) R. Lukes, K. Bláha, and J. Kovár, *Chem. Ind. (London)*, 527 (1958); (b) K. Balenović, B. Urbas, and A. Deljac, *Croat. Chem. Acta*, **31**, 153 (1959); (c) C. Schöpf and W. Wüst, *Justus Liebigs Ann. Chem.*, **626**, 150 (1959).
(23) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952).
(24) H. I. Bernstein and F. C. Whitmore, *J. Am. Chem. Soc.*, **61**, 1324 (1939).
(25) H. S. Raper, *J. Chem. Soc.*, 2557 (1923).
(26) K. Mislow, "Introduction to Stereochemistry", W. A. Benjamin, New York, N.Y., 1965, p 131.
(27) R. K. Hill and R. M. Carlson, *J. Am. Chem. Soc.*, **87**, 2772 (1965).
(28) R. K. Hill and M. Rabinovitz, *J. Am. Chem. Soc.*, **86**, 965 (1964).
(29) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, Chapter 5.
(30) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, Jr., *J. Am. Chem. Soc.*, **87**, 1958 (1965); P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *ibid.*, **90**, 4869 (1968).
(31) Melting points were determined in a Thomas-Hoover oil immersion apparatus and are uncorrected. NMR spectra were recorded on a Varian HA-100 spectrometer by Mr. C. Pape; chemical shifts are reported as δ units, against tetramethylsilane as an internal standard. Ir spectra were recorded on Perkin-Elmer Models 257 and 621 spectrophotometers and uv spectra on a Perkin-Elmer Model 202 spectrometer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter; c is expressed as g/100 ml solution. A Varian Aerograph Model 90P gas chromatograph was used in VPC analyses. Elemental analyses were performed at the University of Georgia.
(32) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).

A Generalized Total π-Energy Index for a Conjugated Hydrocarbon

Jun-ichi Aihara

Department of Chemistry, Faculty of Science, Hokkcido University, Sapporo 060, Japan

A total π-energy index Z^* is defined as $Z^* = |P(i)|$ for a conjugated hydrocarbon, where $P(X)$ is an HMO characteristic polynomial of the compound, and $i = \sqrt{-1}$. It is found that the HMO total π energy E_π is proportional to the logarithm of this index: $E_\pi \approx 6.0846 \log Z^*$. With the use of an analogous π-energy index Z_0^* for the reference structure previously defined by us, the resonance energy RE for the conjugated hydrocarbon can be expressed in the form RE $\approx 6.0846 \log Z^*/Z_0^*$.

Total π energy is one of the key quantities in chemistry of a conjugated hydrocarbon, and is especially important when its thermochemical stability and reactivity are examined.[1,2] So far, molecular orbital theories have provided much of the information concerning the total π energy of the conjugated system.[3] In parallel with this, a considerable amount of effort has been devoted to correlating the total π energy with particular structural features of the conjugated system.[4,5] The problem of prime interest has been to find a formula which would express the total π energy as a function of topological parameters, such as sp^2 carbon atoms, π bonds, and numbers and types of π electron rings. Although in 1974 Gutman verified that no exact topological formulas can exist for the total π energy,[5] this problem does not cease to attract us.

Since 1968, Wilcox et al. have stressed that the algebraic structure count (ASC) and not the number of Kekulé structures plays an essential role in determining stability of a conjugated hydrocarbon.[6] Not a few expressions in terms of the ASC and/or the numbers of sp^2 carbon atoms and π bonds have skillfully been presented to duplicate the total π energy[5,7] and the resonance energy[8] as well for the conjugated hydrocarbon. McClelland attempted to reproduce the total π energy in terms of the Frobenius norm of an adjacency matrix for the conjugated system.[9]. The coefficients of an HMO characteristic polynomial can graph-theoretically be enumerated from the π-electron framework,[10,11] and hence are topological quantities of a different kind. Last year, Hosoya et al. ingeniously showed that these coefficients also reflect the total π energy for most conjugated hydrocarbons.[12] In this paper, I would like to generalize and verify their formula for the total π energy, with its application to a variety of conjugated hydrocarbons. An HMO theory is used in its simplest form. All energies are given in units of β.

Definition of a Generalized Total π-Energy Index Z^*. In general, an HMO secular determinant for a conjugated hydrocarbon can be expanded into a polynomial $P(X)$, which is termed an HMO characteristic polynomial, i.e.,

$$P(X) = \det|EX - A| = \sum_{k=0}^{N} a_k X^{N-k} \qquad (1)$$

Here, A is an adjacency matrix which specifies the connectivity of sp^2 carbon atoms in the compound,[13] and therefore is a square matrix of the same order as the number of sp^2 carbon atoms ($N = 2m$); E is a unit matrix of the same order. The coefficients a_k can readily be evaluated either by enumerating the Sachs graphs[10] or by counting the nonadjacent numbers concerned.[11] The secular variable X is related to an HMO eigenvalue variable ϵ in this manner:

$$X = (\epsilon - \alpha)/\beta \qquad (2)$$

The roots of $P(X) = 0$ are arranged in a decreasing order as

$$X = X_1, X_2, \ldots, X_m, X_{m+1}, \ldots, X_{N-1}, X_N \qquad (3)$$

All these roots are real, and lie in the interval between -3.0

and 3.0[14] The first m roots correspond to the energies of the occupied π molecular orbitals. The π energy of the entire compound E_π is then given by

$$E_\pi = 2 \sum_{k=1}^{m} X_k \qquad (4)$$

Equation 1 is expressed by means of the roots of $P(X) = 0$ as

$$P(X) = \prod_{k=1}^{N} (X - X_k) \qquad (5)$$

Now, let us consider a new quantity Z^* defined as

$$Z^* = |P(i)| = \left| \sum_{k=0}^{N} a_k i^{N-k} \right| \qquad (6)$$

where $i = \sqrt{-1}$. This expression can be rewritten by the use of the roots of $P(X) = 0$ as

$$Z^* = \left| \prod_{k=1}^{N} (i - X_k) \right| = \prod_{k=1}^{N} (|i - X_k|) = \prod_{k=1}^{N} (1 + X_k^2)^{1/2} \qquad (7)$$

The logarithm of Z^* is

$$\log Z^* = \frac{1}{2} \sum_{k=1}^{N} \log(1 + X_k^2) \qquad (8)$$

In order to visualize the physical image of eq 8, we introduce the approximation

$$\log(1 + X^2) \approx h|X| \qquad (9)$$

where h is a quasi-proportionality constant for this relation. The validity of this expression for $|X| \le 3.0$ can straightforwardly be seen from Figure 1. It is especially noteworthy that this approximation holds very well within the same region ($|X| \le 3.0$) as covered by the roots of $P(X) = 0$. The constant h is obtained by equating the following integral I to zero:

$$I = \int_{-3}^{3} \{ \log(1 + X^2) - h|X| \} \, dX \qquad (10)$$

This means that the h is so determined that eq 9 holds best within the same region as covered by the roots of $P(X) = 0$. The h value thus derived is 0.32870. With this approximation, eq 8 can be made linear with respect to every X_k:

$$\log Z^* \approx \frac{h}{2} \sum_{k=1}^{N} |X_k| \qquad (11)$$

On this basis, we defined E_{Z^*} as

$$E_{Z^*} = \frac{2}{h} \log Z^* = 6.0846 \log Z^* \qquad (12)$$

We can show that this quantity is closely related to the HMO total π energy E_π of the conjugated hydrocarbon as follows. The sum of all roots of $P(X) = 0$ always vanishes for any conjugated hydrocarbons. Accordingly as far as the product $X_m \cdot X_{m+1}$ is less than, or equal to, zero,

$$E_\pi = \sum_{k=1}^{N} |X_k| \tag{13}$$

This formula exactly holds for all alternant and most nonalternant hydrocarbons, because the product $X_m \cdot X_{m+1}$ is not positive for them. Then, we arrive at a desired expression for the total π energy:

$$E_\pi \approx E_{Z^*} \tag{14}$$

i.e., for these compounds, the total π energy is said to approximate to E_{Z^*}. The Z^* values and the total π energies thus obtained for 20 typical conjugated hydrocarbons are presented in Table I. The agreement with HMO total π energies is quite satisfactory for all the hydrocarbons investigated.

For nonalternant hydrocarbons with $X_m \cdot X_{m+1} > 0$, eq 13 and 14 no longer hold. Among such rare hydrocarbons are symmetric fulvalenes and fulvadienes, and as-indacene.[15] With the intention of including these exceptions, we might most safely say that, as shown by eq 11, the logarithm of Z^* is linearly related to the sum of the absolute values of all the HMO π orbital energies. The correlation between these two quantities is excellent even for these exceptional compounds. However, as eq 14 holds very well for most conjugated hydrocarbons, we term Z^* a total π-energy index.

Comparison with Hosoya's Total π-Energy Index $\bar{Z}$. An HMO characteristic polynomial $P(X)$ is divided into an even function $S(X)$ and an odd function $A(X)$ with respect to X, namely,

$$P(X) = S(X) + A(X) = \sum_{k=0}^{m} a_{2k} X^{N-2k}$$
$$+ \sum_{k=0}^{m-1} a_{2k+1} X^{N-2k-1} \tag{15}$$

The present index Z^* is rewritten in terms of these functions as

$$Z^* = \{|S(i)|^2 + |A(i)|^2\}^{1/2} \tag{16}$$

On the other hand, Hosoya et al. defined an analogous π-energy index $\bar{Z}$ simply as[12]

$$\bar{Z} = |S(i)| \tag{17}$$
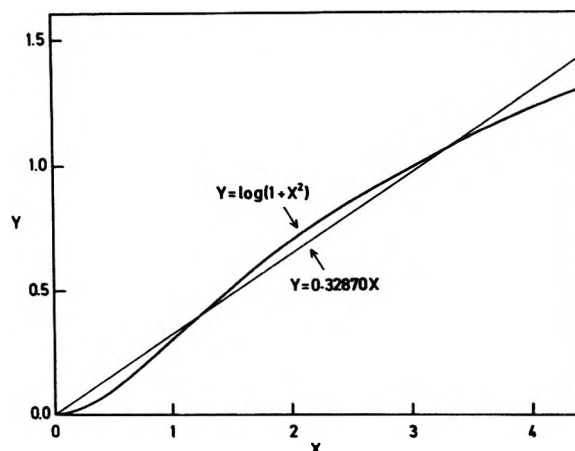
Figure 1. Plots of $Y = \log(1 + X^2)$ and its approximate form $Y = 0.32870X$.

where the contribution from the odd function $A(i)$ is missing. Contrary to Z^*, $\bar{Z}$ is always an integral number. After practicing extensive numerical analysis, they showed that the logarithm of $\bar{Z}$ is approximately proportional to the total π energy of the conjugated hydrocarbon. It is broadly true that, as the contribution from $A(i)$ is relatively small for most hydrocarbons (see Table I), Hosoya's index $\bar{Z}$ is evidently comparable to our index Z^*. However, the mathematical justification for $\bar{Z}$ and the limit of its utility remained obscure. As mentioned in a previous section, the derivation of Z^* has overcome these difficulties. In this sense, our total π-energy index can be considered as a more general index for the HMO total π energy. From a mathematical standpoint, any other topological formula for the total π energy[4–9] is not so straightforward as ours.

For any alternant hydrocarbon, Z^* is an integer, and agrees with $\bar{Z}$ because $A(X) = 0$. Conversely, for any nonalternant hydrocarbon, Z^* is never an integer, and hence disagrees with $\bar{Z}$. The decimal fraction of Z^* obviously comes from $A(i)$. By correlating the coefficients of the HMO characteristic polynomial with corresponding Sachs graphs,[10,11] Z^* can com-

Table I. Total π-Energy Indices and Related Quantities for Typical Conjugated Hydrocarbons

Registry no.	Compd	$|S(i)|$	$|A(i)|$	Z^*	Z_0^*	Estimated total π energy (β)[a]	Estimated resonance energy (β)[b]
1120-53-2	Cyclobutadiene	5	0	5.00	7	4.253 (4.000)	−0.889 (−1.226)
71-43-2	Benzene	20	0	20.00	18	7.916 (8.000)	0.278 (0.273)
629-20-9	Cyclooctatetraene	45	0	45.00	47	10.059 (9.657)	−0.115 (−0.595)
3227-76-7	[10]Annulene	125	0	125.00	123	12.759 (12.944)	0.043 (0.159)
497-20-1	Fulvene	16	2	16.12	15	7.436 (7.466)	0.190 (0.020)
5291-90-7	Dimethylenecyclo-butene	13	0	13.00	15	6.778 (7.208)	−0.378 (−0.163)
250-25-9	Pentalene	54	12	55.32	56	10.605 (10.456)	−0.032 (−0.215)
257-24-9	Heptalene	384	32	385.33	386	15.734 (15.618)	−0.005 (−0.141)
275-51-4	Azulene	149	10	149.34	147	13.229 (13.364)	0.042 (0.151)
267-21-0	s-Indacene	469	108	481.27	457	16.321 (16.231)	0.137 (0.055)
208-96-8	Acenaphthylene	522	52	524.58	466	16.549 (16.619)	0.313 (0.354)
209-86-9	Cyclopent[cd]azu-lene	464	66	468.67	466	16.251 (16.366)	0.015 (0.101)
209-42-7	Aceheptylene	1236	28	1236.32	1220	18.814 (18.911)	0.035 (0.106)
92-52-4	Biphenyl	464	0	464.00	388	16.225 (16.383)	0.473 (0.502)
4026-23-7	Benzocyclobuta-diene	49	0	49.00	57	10.284 (10.381)	−0.400 (−0.393)
259-79-0	Biphenylene	481	0	481.00	477	16.320 (16.505)	0.022 (0.123)
91-20-3	Naphthalene	170	0	170.00	148	13.571 (13.683)	0.366 (0.389)
120-12-7	Anthracene	1440	0	1440.00	1208	19.217 (19.314)	0.464 (0.475)
85-01-8	Phenanthrene	1489	0	1489.00	1233	19.306 (19.448)	0.499 (0.546)
129-00-0	Pyrene	4810	0	4810.00	3888	22.404 (22.505)	0.562 (0.598)

[a] See eq 14; exact values are placed in parentheses. [b] See eq 21; exact values are placed in parentheses.

pletely be assigned to individual π bonds and π-electron rings in the conjugated system. Our expression for the total π energy (eq 14) has a particular advantage in that the total π energy can necessarily be assigned to the individual π bonds and π-electron rings.[16,17] Especially, the coefficients of A(X) are attributed mainly to the odd-membered π-electron rings.[10] Therefore, eq 16 strongly suggests that the existence of such odd-membered rings increases, more or less, the total π energy of the system. It goes without saying that the even-membered rings influence the total π energy to much more extent.[12,16]

Derivation of Dewar-Type Resonance Energy. In a previous paper,[16] we graph-theoretically formulated Dewar's theory of aromaticity.[1,2] We therein proposed an HMO reference polynomial R(X) for a conjugated hydrocarbon defined as

$$R(X) = \sum_{k=0}^{m} (-1)^k p(2k) X^{N-2k} \qquad (18)$$

where N and m bear the same meanings as in eq 1–4. The coefficient $p(2k)$ is indicative of the number of ways in which k π bonds are so chosen from the conjugated system that no two of them are connected to each other.[11] By definition, $p(0)$ = 1. The roots of R(X) = 0 are supposed to represent the energies of the π molecular orbitals which the hydrocarbon would possess if it were absolutely olefinic in nature. The reference energy $E_\pi{}^\circ$, relative to which aromatic stabilization is calculated, can be estimated from the coefficients of this polynomial in the same manner as the actual total π energy, i.e.,

$$E_\pi{}^\circ \approx 6.0846 \log Z_0{}^* \qquad (19)$$

where

$$Z_0{}^* = |R(i)| = \sum_{k=0}^{m} p(2k) \qquad (20)$$

Dewar-type resonance energy has been considered as the best measure of aromaticity available at present.[1,2] It has widely been accepted that it correlates very well with experimental stability for a variety of conjugated systems.[1,2,16] The resonance energy is defined as the difference between the total π energy of the conjugated hydrocarbon and its reference energy.[2,16] These two π energies were shown above to be estimated from eq 14 and 19, respectively. On this basis, the resonance energy RE of this type can now be estimated as

$$RE = E_\pi - E_\pi{}^\circ \approx 6.0846 \log \frac{Z^*}{Z_0{}^*} \qquad (21)$$

The resonance energies thus obtained for the 20 conjugated hydrocarbons, together with their exact resonance energies (A-II resonance energies),[16] are also listed in Table I.

As may easily be seen from this table, the estimated reso-

nance energy is in fairly good agreement with the exact one for all the hydrocarbons investigated. When the absolute value of the resonance energy is small, a discrepancy between these two resonance energies may be large. However, a better agreement is naturally attained as the size of the conjugated system increases. It is especially noteworthy that the sign of the estimated resonance energy is always in accord with that of the exact one. This fact means that aromaticity or antiaromaticity can assuredly be inferred from the sign of the former resonance energy.

As stated before, the coefficients of the HMO characteristic polynomial can manually be enumerated with little difficulty from the geometry of the conjugated system.[10,11] The coefficients of the HMO reference polynomial can more easily be obtained as nonadjacent numbers for the same system.[11] It should hence be emphasized that the total π energy and the resonance energy for a conjugated hydrocarbon, both usually obtained by complicated MO calculations, can accurately be reproduced merely by inspecting the π-electron framework. This implies that the present approach can be employed as a practical and instructive basis for chemistry of a conjugated hydrocarbon.

References and Notes

(1) M. J. S. Dewar and G. J. Gleicher, *J. Am. Chem. Soc.*, **87**, 685, 692 (1965); M. J. S. Dewar and C. de Llano, *ibid.*, **91**, 789 (1969).
(2) B. A. Hess, Jr., and L. J. Schaad, *J. Am. Chem. Soc.*, **93**, 305, 2413 (1971); *J. Org. Chem.*, **36**, 3418 (1971); L. J. Schaad and B. A. Hess, Jr., *J. Am. Chem. Soc.*, **94**, 3068 (1972); *J. Chem. Educ.*, **51**, 640 (1974).
(3) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists", Wiley, New York, N.Y., 1961; L. Salem, "The Molecular Orbital Theory of Conjugated Systems", W. A. Benjamin, New York, N.Y., 1966; M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry", McGraw-Hill, New York, N.Y., 1969.
(4) I. Gutman, *Theor. Chim. Acta*, **35**, 355 (1974).
(5) References in this area are mostly collected in ref 4.
(6) C. F. Wilcox, Jr., *Tetrahedron Lett.*, 795 (1968); *J. Am. Chem. Soc.*, **91**, 2732 (1969); W. C. Herndon, *Tetrahedron*, **29**, 3 (1973); *J. Chem. Educ.*, **51**, 10 (1974).
(7) I. Gutman, N. Trinajstić, and C. F. Wilcox, Jr., *Tetrahedron*, **31**, 143 (1975); C. F. Wilcox, Jr., I. Gutman, and N. Trinajstić, *ibid.*, **31**, 147 (1975).
(8) W. C. Herndon, *J. Am. Chem. Soc.*, **95**, 2404 (1973); W. C. Herndon and M. L. Ellzey, Jr., *ibid.*, **96**, 6631 (1974); W. C. Herndon, *Thermochim. Acta*, **8**, 225 (1973); R. Swinborne-Sheldrake, W. C. Herndon, and I. Gutman, *Tetrahedron Lett.*, 755 (1975); M. Randić, *Tetrahedron*, **31**, 1477 (1975).
(9) B. J. McClelland, *J. Chem. Phys.*, **54**, 640 (1971); I. Gutman, M. Milun, and N. Trinajstić, *ibid.*, **59**, 2772 (1973).
(10) A. Graovac, I. Gutman, N. Trinajstić, and T. Zivković, *Theor. Chim. Acta*, **26**, 67 (1972); I. Gutman and N. Trinajstić, *Top. Curr. Chem.*, **42**, 49 (1973).
(11) H. Hosoya, *Bull. Chem. Soc. Jpn.*, **44**, 2332 (1971); *Theor. Chim. Acta*, **25**, 215 (1972); *Fibonacci Q.*, **11**, 255 (1973).
(12) H. Hosoya, K. Hosoi, and I. Gutman, *Theor. Chim. Acta*, **38**, 37 (1975).
(13) F. Harary, "Graph Theory", Addison-Wesley, Reading, Mass., 1968, Chapter 13.
(14) C. A. Coulson, *Proc. Cambridge Philos. Soc.*, **46**, 202 (1949).
(15) C. A. Coulson and A. Streitwieser, Jr., "Dictionary of π-Electron Calculations", Pergamon Press, Oxford, 1965.
(16) J. Aihara, *J. Am. Chem. Soc.*, **98**, 2750 (1976).
(17) A detailed analysis of the correlation between the geometry of a conjugated system and its total π energy will be published elsewhere.

Determination of the Amino and Imino Tautomer Structures of α-Quinolylamines by Analysis of Proton Magnetic Resonance Spectra

Mona F. Zady and John L. Wong*

Department of Chemistry, University of Louisville, Louisville, Kentucky 40208

The ^{1}H NMR spectra of a series of α-quinolylhydrazones which have been isolated in the α-amino and the α-imino forms are compared. Chemical shift data of the exocyclic N–H, the azomethine C–H, and the salicylidine O–H of the amino tautomers are used to deduce the planarity of the exocyclic amino group which bridges the two π systems of the quinoline nucleus and the salicylaldimine moiety. Quinoline proton assignments in these α-amino compounds are also made with the help of 300-MHz spectra. Likewise, the ^{1}H NMR spectra of the α-imino tautomers are analyzed. Characteristic differences of (1) δN–H, (2) $J_{3,4}$ of the heterocycle, and (3) δH-8 of the quinoline nucleus are useful in determining the α-amino and α-imino tautomer structures of the α-quinolylamines.

Prototropic tautomerization of α- and γ-heteroaromatic amines to the corresponding imino forms has long been a subject of lively interest.[1] The traditional working hypothesis[1] that these imino forms are the rare tautomers is corroborated by a recent SCF MO calculation showing that the free energy barrier for isomerization is 15 kcal mol^{-1} for α-aminopyridine.[2] However, there are no lack of challenges to this view of the imino form. Thus, the broadening of the cytosine H-5 resonance observed in the ^{1}H NMR spectrum of cytosine was attributed to the presence of 15 ± 3% of the abnormal imino form,[3] but this conclusion was later retracted because the line broadening was a spurious observation.[4] While studies of the acid dissociation constants of α- and γ-aminopyridine have indicated[5] that the equilibrium constants for imino ⇌ amino forms are ca. 200 000 and 2000 respectively, a similar study of the dissociation constant of α-aminoquinoline has led to exactly the opposite conclusion, viz., α-aminoquinoline appears to exist in solution predominantly in the imino form.[6] In one ^{1}H NMR study of γ-aminoquinoline,[7] the coupling constant $J_{2,3}$ = 8 Hz was assigned to the H-2 and H-3 olefinic coupling of the γ-imino structure. This was disputed later[8] on the ground that δH-3 of 2-methyl-4-aminoquinoline at 6.50 ppm is similar to δH-3 (6.56) of 2-methyl-4-dimethylaminoquinoline but dissimilar to δH-3 (5.79) of 1,2-dimethyl-4-iminoquinoline. These contradicting and often precarious conclusions point to the need of isolating the imino tautomers for characterization under conditions which would disallow equilibration with the amino forms. Thus, in the special cases where the imino forms are chelated as in a, b, and c of Scheme I, the imino structures are more reassuring. The evidences advanced are (1) $\nu_{C=N}$ 1650 cm^{-1} for a,[9] (2) uv spectrum of b compatible with 2-(N-quinolylamino-1-ethyl)-1-ethylquinolinium iodide,[10] and (3) a broad singlet at δ 10.2 ascribed to the hydrogen bonded N hydrogen of c.[11] However, there has not been a comparison of a series of compounds in both the amino and imino forms under nonequilibrating conditions to decipher their major physical characteristics. In our study[12] of the photochromism of salicylaldehyde α-quinolylhydrazones (Scheme II), we have prepared a series of α-quinolylhydrazones in both the amino and the imino forms. We have now characterized these isomeric structures by the ^{1}H NMR method and found that they are distinguishable by means of (1) the chemical shift of the N hydrogen, (2) the coupling constant of H-3 and H-4 of the quinoline ring, and (3) the change in chemical shifts of the quinoline 8 hydrogen. This paper appears to be the first detailed comparative study of the ^{1}H NMR characteristics of tautomeric heteroaromatic amines in their amino and imino forms.

Results and Discussion

Planarity of the Exocyclic Amino Group. The resonances of N, O, and azomethine hydrogens in the α-quinol-

ylhydrazones shown in Table I permit the deduction of the electronic and stereochemical nature of the amino hydrogen. These absorptions are readily recognizable. The former two signals appear as a broad singlet in Me$_2$SO-d_6 which readily exchange in D$_2$O. The azomethine proton appears as a sharp singlet at lower field from the aromatic region. Using salicylaldehyde phenylhydrazone (2) as a point of departure, the deshielding effect of the quinoline ring as opposed to the benzene ring, viz., Δδ **5,2** is found to be additive of the shift due to both the ring nitrogen, Δδ **3,2**, and the fused benzene ring,

Scheme I

a   b

c

Scheme II

5

5a
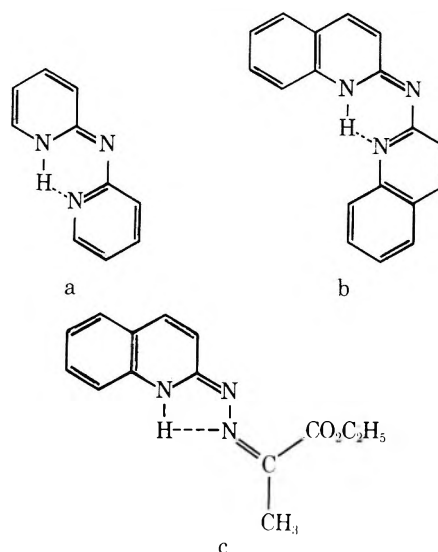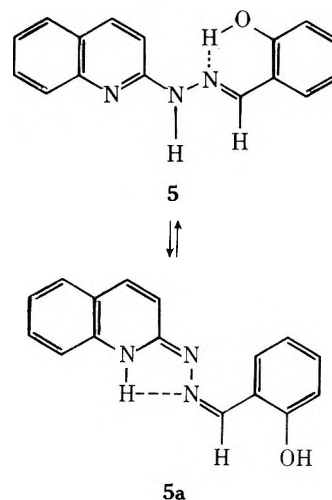
Table I. Comparison of ^{1}H NMR Spectra of α-Quinolylhydrazones and Derivatives in the Amino Form[a]

No.	Compd[b]	Chemical shift, δ			Compd	Comparison (Δδ)		
		N–H	O–H	N=C–H		N–H	O–H	N=C–H
1	Ph—NH—N=CH—C$_6$H$_5$	9.97		7.62				
2	Ph—NH—N=CH—C$_6$H$_4$—2—OH	10.43	10.70	8.27	2,1	0.46		0.65
3	Py—NH—N=CH—C$_6$H$_4$—2—OH	10.73	10.73	8.35	3,2	0.30	0.03	0.08
4	Py—CH$_2$—N=CH—C$_6$H$_4$—2—OH		12.27	8.92	4,3		1.54	0.57
5	Q—NH—N=CH—C$_6$H$_4$—2—OH	11.10	11.10	8.50	5,2	0.67	0.40	0.23
					5,3	0.37	0.37	0.15
6	Q—NH—N=CH—C$_6$H$_5$	10.97		8.33	6,1	1.00		0.71
					5,6	0.13		0.17
7	Q^3—NH—N=CH—C$_6$H$_4$—2—OH	10.75	11.12	8.62	5,7	0.35	−0.02	−0.12
8	Q—NH—N=CMe—C$_6$H$_4$—2—OH	10.58	13.43		5,8	0.52	−2.33	

[a] 60-MHz spectra, 1 M in Me$_2$SO-d_6. [b] Ph = phenyl, Q = 2-quinolyl, Q^3 = 3-quinolyl, Py = 2-pyridyl.

Table II. Quinoline Proton Assignments of α-Quinolylhydrazones and Derivatives in the Amino Form

No.	Compd	Chemical shift, δ						$J_{3,4}$, Hz
		H–3	H–4	H–5	H–6	H–7	H–8	
9	Quinoline[a,b]	7.27	8.00	7.69	7.44	7.62	8.06	8.3
10	2-Aminoquinoline[c]	6.90	7.90	7.48–7.80	7.17	7.51	7.48–7.80	8.8
11	2,7-Dimethylquinoline[d]	7.06	7.81	7.49	7.16		7.68	
5	Q—NH—N=CH—C$_6$H$_4$—2—OH[e]	6.841	8.100	7.604 or 7.537	7.263–7.150	7.604 or 7.537	7.712	8.5
12	Q—NH—N=CH—C$_6$H$_4$—2—OCH$_3$[e]	7.000	8.091	7.580	7.303–7.193	7.544–7.490	7.700	9.0
13	Q—NH—N=CH—C$_6$H$_2$—2—OH—4,6-diOMe[f,g]	7.280	7.983	7.620	7.308	7.581	7.674	8.0
14	Q—NH—N=CH—C$_6$H$_2$—2—OH—3,6-diMe[h,i]	7.15	8.30	7.95–7.37	7.95–7.37	7.95–7.37	7.95–7.37	8.5

[a] See ref 14. [b] H–2 observed at δ 8.81. [c] "Sadtler Indices", Sadtler Research Laboratories, Philadelphia, Pa., 1967, Spectrum No. 6041. [d] R. Pastor, J. Musso, and A. Cambon, *Bull. Soc. Chim. Fr.*, 3009 (1973). [e] 300-MHz spectrum, 1 M in Me$_2$SO-d_6. [f] 300-MHz spectrum, 1 M in CDCl$_3$. [g] The chemical shifts for N–H, O–H, N=C–H (1 M in Me$_2$SO-d_6) are respectively 10.83, 10.83, 8.53. [h] 60-MHz spectrum, 1 M in Me$_2$SO-d_6. [i] The chemical shifts for N–H, OH, N=CH are respectively 11.50, 12.10, 8.65.

Δδ 5,3. This additive effect operates for all the three hydrogens, although the deshielding by the quinoline ring is most pronounced at the amino hydrogen site. Hence, considerable conjugation of the amino lone pair electrons with the ring must exist. This observation is substantiated by the higher field N-hydrogen absorption of the isomeric 3-quinolylhydrazone 7. Here the upfield shift due to the loss of the α-nitrogen effect, Δδ 5,7, is comparable to that between the pyridyl and phenyl hydrazone, Δδ 3,2. The phenolic signal merges with the amino hydrogen of pyridyl and quinolyl hydrazones 3 and 5 as one broad singlet. However, the phenylhydrazone 2 and 3-quinolylhydrazone 7 show two separate singlets for these heteroatom hydrogens. The lower field of the two is attributed to the phenolic group in view of the well-known chelation of salicylaldimines. Such chelation imposes a positive character on the azomethine carbon, hence the extent of chelation is indicated by the shift of the azomethine hydrogen to lower field, e.g., Δδ 2,1. In this respect, Δδ 5,6 being only 23% of that of Δδ 2,1 denotes much weaker chelation strength, a result of decreased azomethine nitrogen basicity via conjugation with the inductively withdrawing quinoline system. When the azomethine hydrogen is replaced by a methyl, chelation is enhanced as displayed by the acetophenone quinolylhydrazone 8 where δOH is shifted 2.33 ppm downfield from that in 5. That the salicylaldimine chelation is sensitive to inductive effects is also shown by Δδ 4,3. Here, replacement of the exocyclic amino group by the methylene has shifted the phenolic OH downfield by 1.54 ppm. Since the quinoline ring exerts pronounced deshielding effect on the amino hydrogen and the salicylaldimine chelation is progressively weakened by the attachment of the hydrazone nitrogen and the quinoline ring, it is probable that the exocyclic amino nitrogen is sp^2 hybridized and planar, thereby bridging the two π systems of the

quinoline nucleus and the salicylaldimine moiety.

Quinoline Proton Assignments in the α-Amino Tautomers. The ^{1}H NMR spectrum of quinoline 9 has been studied extensively.[13,14] The chemical shifts of the ring hydrogens have been assigned and, with the exception of H-8, have been correlated with the charge density on the respective carbon atoms calculated by the extended Huckel method.[13] The deshielding experienced by H-8 relative to its calculated chemical shift has been ascribed to the proximity of the quinoline nitrogen lone pair.[13] The lowest field resonance is assigned to H-2 followed by H-8 and H-4. Placing a substituent on C-2 has a marked effect upon the chemical shifts of H-3, H-4, and H-8. In the case of 2-aminoquinoline 10 and 2,7-dimethylquinoline 11, H-8 resonates at higher field than H-4 while H-3 which is at highest field in the parent quinoline is shielded further by the 2-amino or 2-methyl substituent. The order of absorptions of H-3 and H-4 from the highest to the lowest field is expected from their meta and para relationship to the quinoline nitrogen.[14a]

Analysis of the 2-quinolylhydrazones 5, 12, and 13 using 300-MHz ^{1}H NMR spectra has enabled the assignments of H-3, H-4, and H-8 resonances of the α-amino form (Table II). The assignments for H-3, H-4, and H-8 resonances are in agreement with the literature values for 10 and 11. Exact assignment of H-5, H-6, and H-7 resonances in compounds 5 and 12 could not be accomplished owing to the overlap of resonances from the aryl substituent. For 13 which has a 4,6-dimethoxyphenyl ring, these three resonances are clearly resolved, and are assigned in accordance with the quinoline assignments.[14] Applying the same pattern of assignments to the less resolved 60-MHz spectra of the 3,6-dimethyl derivative 14, H-3 and H-4 can be assigned as shown in Table II.

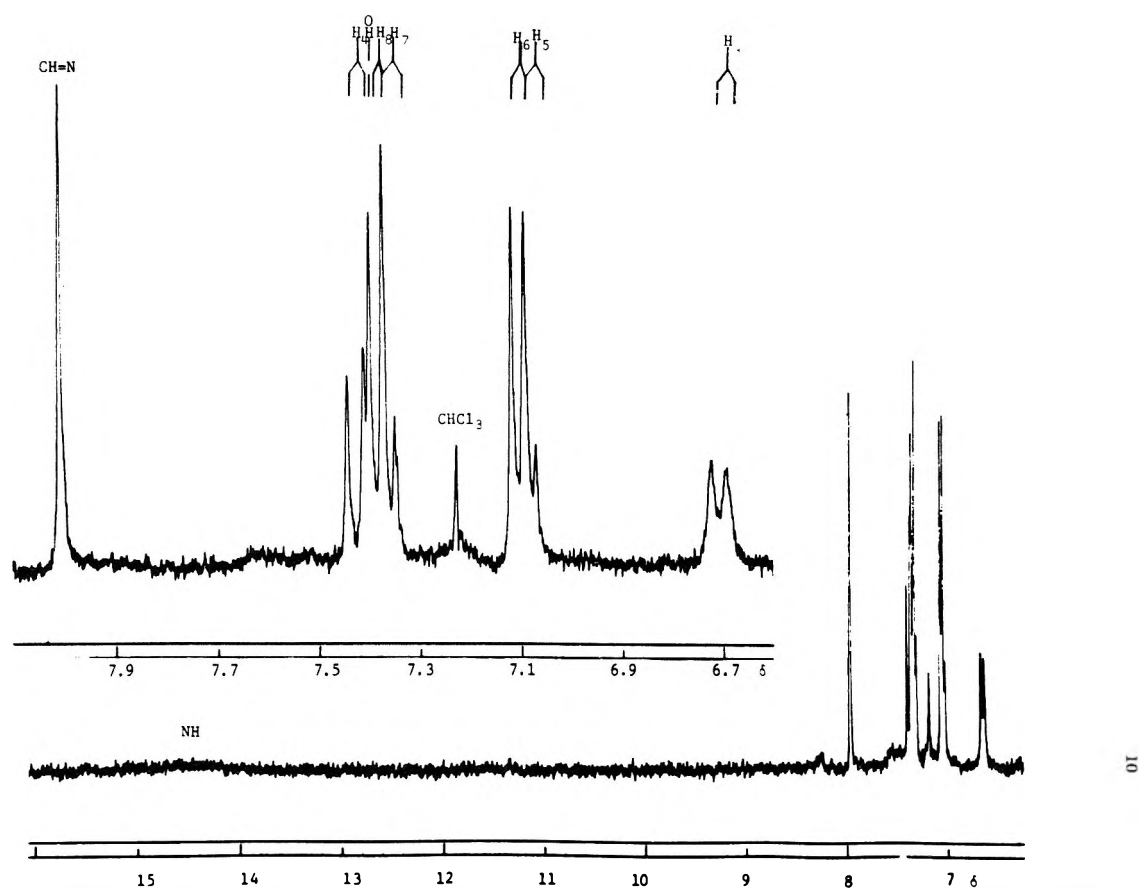**Analysis of the ^{1}H NMR Spectra of α-Iminoquinolines.**

Figure 1a. 300-MHz ¹H NMR spectrum of 13a in the region of δ 6.33–16.0 ppm. Sweep width 5000 Hz (sweep width 1000 Hz).
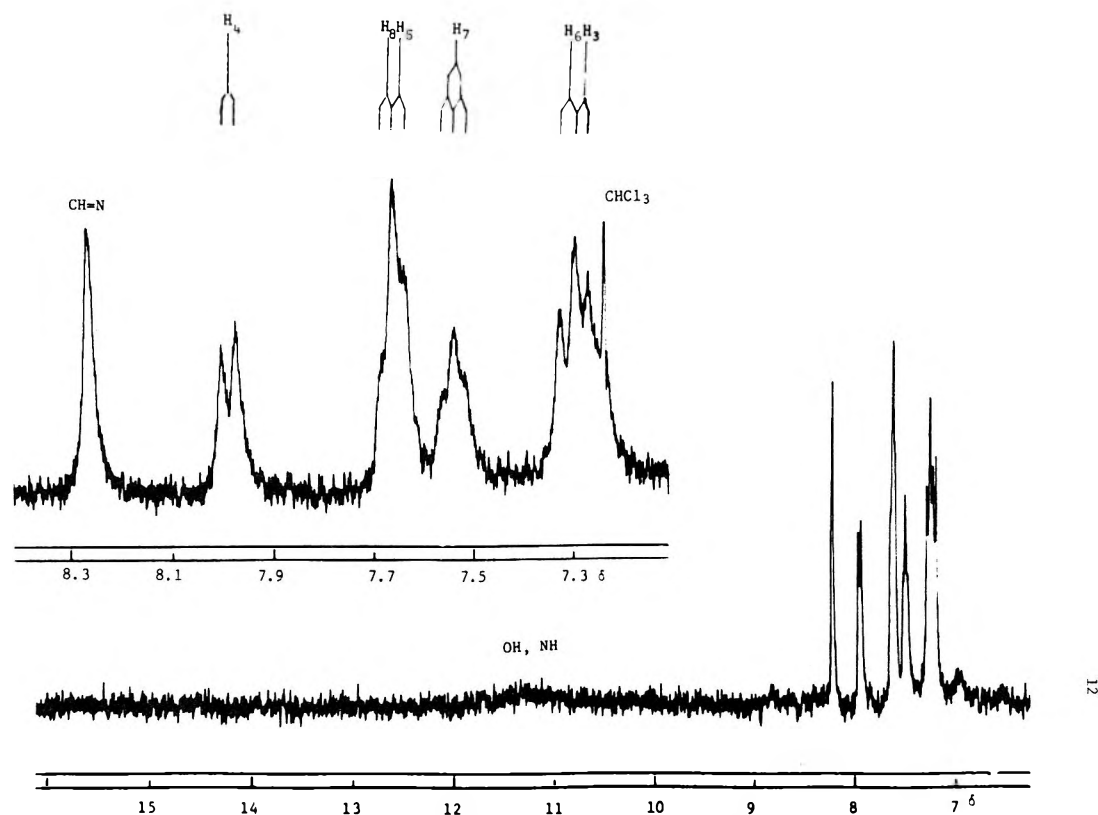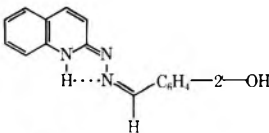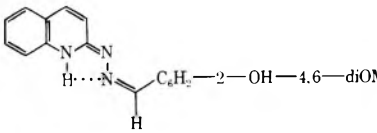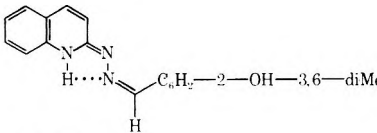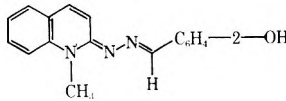

Figure 1b. 300-MHz ¹H NMR spectrum of 13 in the region of δ 6.33–16.0. Sweep width 5000 Hz (sweep width 1000 Hz).

The 300-MHz ¹H NMR spectrum of the α-iminoquinoline **13a** has been analyzed and compared with that of the α-amino compound **13** as shown in Figure 1. As mentioned earlier, the stability of α-imino heteroaromatic compounds is usually dependent upon internal chelation. For the α-iminoquinolylhydrazones such as **5a**, stabilization of the α-imino bond is due to the formation of a new five-membered chelate ring between the quinoline N–H and the hydrazone imino nitrogen

Table III. ¹H NMR Spectra of the Imino Tautomers

No.	Compd	N–H	O–H	N=C–H	H–3	H–4	H–5	H–6	H–7	H–8	$J_{3,4}$ Hz
5a[a]	(quinoline structure) C_6H_4—2—OH	11.80	7.743[b]	7.581	6.892	8.094	7.700–7.125	7.700–7.125	7.700–7.125	7.356	10
13a[c]	(quinoline structure) C_6H_2—2—OH—4.6—diOMe	14.50[d]	7.398[b]	8.017	6.705	7.431	7.110	7.138	7.391	7.418	10
14a[e]	(quinoline structure) C_6H_2—2—OH—3.6—diMe	12.23	f	7.97	7.26	8.00	7.83–7.42	7.83–7.42	7.83–7.42	7.83–7.42	10
15[e]	(N-methyl quinoline structure) C_6H_4—2—OH	11.93		8.63	6.72	7.72	7.60–7.19	7.60–7.19	7.60–7.19	7.60–7.19	10

[a] 300-MHz spectrum, 1 M in $Me_2SO\text{-}d_6$. [b] δ -OH determined by D_2O exchange. [c] 300-MHz spectrum, 1 M in $CDCl_3$. [d] δ N–H 11.30 (1 M in $Me_2SO\text{-}d_6$). [e] 60-MHz spectrum, 1 M in $Me_2SO\text{-}d_6$. [f] Not resolved.

Scheme III

15
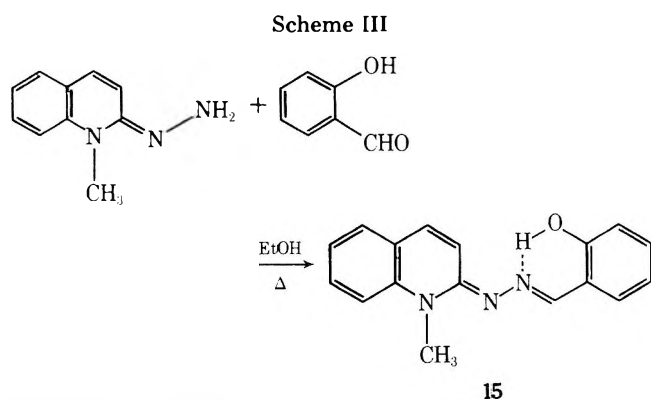
(Scheme II) as evidenced by the chemical shift differences between the azomethine hydrogen and the hydroxyl hydrogen in the α-amino and α-imino forms (Tables II and III). In the case of the amino structure 13, the azomethine hydrogen found at δ 8.53 is 0.51 ppm lower field than that of the imino tautomer 13a, δ 8.02. This is consistent with that observed for E and Z hydrazones where the azomethine hydrogen of the Z form resonates 15–60 Hz higher field than that of the E form.[15] Furthermore, the phenolic hydrogen in the α-amino 13 (δ 10.83) is 3.43 ppm lower field than that of the α-imino 13a (δ 7.40), indicating the loss of intramolecular hydrogen bonding. The actual stabilization of the α-imino bond due to the intramolecularly hydrogen-bonded quinoline N–H can be seen in its lower field resonance. Thus, comparing δN–H of the amino and imino forms (1 M $Me_2SO\text{-}d_6$), the following Δδ are observed: Δδ 5,5a −0.7 ppm, Δδ 13,13a −0.47, and Δδ 14,14a −0.73. In all cases, the imino N–H resonates at lower field. It also appears that these Δδ values are indicative of the stability of the α-imino forms. Hence, from the above Δδ, the stability of 13a should be less than that of the other two α-iminoquinolylhydrazones. Indeed, half-life determination at 56 °C in ethanol for the imino → amino conversion showed 10 h for 5a vs. 8 h for 13a.

The other diagnostic changes in proceeding from an α-aminoquinoline to an α-iminoquinoline are found in the coupling constants $J_{3,4}$ and H-8 resonance. Analysis of the coupling constant $J_{3,4}$ of 2-quinolone derivatives which are

known to exist exclusively as the keto tautomer[3] provides a criterion for the presence of vinylic H-3 and H-4. As an example, the H-3 and H-4 of 6-methoxy-1-methylcarbostyril[16] are observed as doublets at δ 6.60 and 7.49 with a coupling constant of 9.6 Hz consistent with the vinylic assignment. Further confirmation of this criterion was obtained via the synthesis of a hydrazone similar to those of interest to this study which exists exclusively in the α-imino form (Scheme III).[12] As expected, ¹H NMR analysis of both the hydrazine and the product, 15, revealed $J_{3,4}$ = 10 Hz. For the α-imino tautomers 5a, 13a, and 14a, H-3 and H-4 possess similar vinylic character as revealed in Table III by the uniform $J_{3,4}$ of 10 Hz as opposed to $J_{3,4}$ of <9 Hz for their α-amino counterparts.

The applicability of this criterion in the determination of tautomeric forms of α-quinolylamine systems is illustrated by the analysis of the ¹H NMR spectra of α-aminoquinoline and α-hydrazinoquinoline. In the former compound the H-3 and H-4 resonances are observed as doublets at δ 6.90 and 7.90 ($J_{3,4}$ = 8.8 Hz), whereas in the latter they are observed at δ 6.96 and 7.92 ($J_{3,4}$ = 9 Hz). The $J_{3,4}$ values are too low to be associated with vinylic coupling; therefore both the above must exist in the α-amino form. This conclusion has been advanced on the basis of ir analysis, viz., $\nu_{C=N}$ 1622 ± 2 cm⁻¹, which is too low to be associated with an exocyclic imino group.[17]

Our attempt to use the chemical shift values of H-8 to distinguish the α-aminoquinolines from their imino tautomers is also successful. On comparing H-8 of 5a (δ 7.356) and 13a (δ 7.418) with H-8 of the corresponding α-aminoquinolines 5 (δ 7.712) and 13 (δ 7.674), it is apparent that H-8 of the α-imino tautomers is shifted upfield by 0.356 and 0.256 ppm, respectively. The lower field resonance of H-8 in the amino form has been attributed to the deshielding effect of the quinoline nitrogen lone pair. Thus, since the quinoline nitrogen of the α-imino form no longer contains the lone pair electrons in the sp² orbital, the H-8 resonance would be shifted upfield to a value more nearly approximating that calculated by the charge density on C-8. The correlation obtained by Chakrabarty and Hanrahan[13] for the carbon charge density vs. chemical shift of the quinoline ring hydrogens is linear except for H-8. Their calculated shift value of 7.35 ppm for

H-8 of quinoline is in excellent agreement with δH-8 obtained for **5a** and **13a**.

Characteristic Differences between the Amino and Imino Tautomer Structures of α-Quinolylamines. The ^{1}H NMR spectra of the quinolylhydrazones in the amino form differ from that of their α-imino tautomers in three basic features. In all cases, the chemical shift of the N hydrogen in proceeding from an α-amino to an α-imino form is to lower field. These Δδ values are indicative of the relative stability of the α-imino form. There is a vinylic center in the imino tautomers as evidenced by the increase in *J* values of H-3 and H-4 of the heterocycle. Furthermore, a pronounced upfield shift is noted in H-8 of the imino form which is no longer parallel to the nitrogen lone pair. This hydrogen in the α-imino form, unlike that in the amino form, is now correlatable with the charge density on the respective carbon atom.

In this series of α-iminoquinolines, the hydrazone portion stabilizes the α-imino structure from reverting to the α-amino form. The ^{1}H NMR characteristics deduced above pertain to the α-iminoquinoline moiety. Therefore, they should be applicable to other α-quinolylimines which may be stabilized by a different substituent.

Experimental Section

The ^{1}H NMR spectra of the compounds were obtained on a Varian A-60A 60-MHz nuclear magnetic resonance spectrometer. 2,2-Dimethyl-2-silapentane-5-sulfonate (DDS) was used as an internal standard in Me_2SO-d_6 and Me_4Si in $CDCl_3$. The results of the ^{1}H NMR spectral analyses are listed in Tables I–III. The 300-MHz ^{1}H NMR spectra were provided by the NMR Service of the Institute of Polymer Science at the University of Akron. Two 300-MHz ^{1}H NMR spectra for **13** and **13a** are given from δ 6.33 to δ 16.0 in Figure 1.

The preparation and photochromic chemistry of this series of α-quinolyl hydrazones have been described elsewhere.[12]

References and Notes

(1) (a) A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.*, **1**, 403–410 (1963); (b) A. S. Tomcufcif and L. N. Starkee, "Pyridine and its Derivatives", Part III, E. Lingsberg, Ed., Interscience, New York, N.Y., 1962, pp 12–14.

(2) N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Am. Chem. Soc.*, **92**, 2929 (1970).

(3) G. C. Y. Lee and S. I. Chan, *J. Am. Chem. Soc.*, **94**, 3218 (1972).

(4) M. Pieber, P. A. Kroon, J. H. Prestegard, and S. I. Chan., *J. Am. Chem. Soc.*, **95**, 3408 (1973).

(5) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).

(6) S. G. Schulman, *J. Pharm. Sci.*, **60**, 671 (1971).

(7) J. Renault and J. C. Cartron, *C. R. Acad. Sci., Ser. C*, **262**, 1161 (1966).

(8) J. C. Craig and D. E. Pearson, *J. Heterocycl. Chem.*, **5**, 631 (1968).

(9) A. P. Rud'ko, I. N. Chernyuk, Y. S. Rozum, and G. T. Pilyugin, *Ukr. Khim. Zh.*, **34**, 1275 (1968); *Chem. Abstr.*, **70**, 110146e (1969).

(10) H. H. Credner, H. J. Friedrich, and G. Scheibe, *Chem. Ber.*, **95**, 1881 (1962).

(11) H. Reimlinger, W. R. F. Lingier, and R. Merenyi, *Chem. Ber.*, **104**, 2793 (1971).

(12) (a) J. L. Wong and M. F. Zady, *J. Chem. Soc., Chem. Commun.*, 684 (1973); (b) M. F. Zady, F. N. Bruscato, and J. L. Wong, *J. Chem. Soc., Perkin Trans. 1*, 2036 (1975); (c) J. L. Wong and M. F. Zady, *J. Org. Chem.*, **40**, 2512 (1975).

(13) M. R. Chakrabarty and E. S. Hanrahan, *J. Mol. Spectrosc.*, **30**, 348 (1969).

(14) (a) E. Vander Donckt, R. H. Martin, and F. Geerts-Evrard, *Tetrahedron*, **20**, 1495 (1964); (b) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **17**, 558 (1964).

(15) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Am. Chem. Soc.*, **85**, 2326 (1963).

(16) "Sadtler Indices", Sadtler Research Laboratories, Philadelphia, Pa., 1967, Spectrum No. 13687.

(17) C. L. Angyal and R. L. Werner, *J. Chem. Soc.*, 2911 (1952).

Notes

High Pressure Thermal and Photosensitized Dimerizations of 2-Pyrones

W. H. Pirkle,* C. A. Eckert, W. V. Turner,
B. A. Scott, and L. H. McKendry

*School of Chemical Sciences, University of Illinois,
Urbana, Illinois 61801*

Received September 9, 1975

Owing to the synthetic manipulability of the resulting lactones, 2 pyrones have frequently been utilized as dienes and, more recently, as dienophiles[1] in Diels–Alder reactions. In view of their ability to act in both capacities, it is surprising that no Diels–Alder dimers of 2-pyrones have ever been reported. Seyferth[2] has postulated the intermediacy of such a dimer in the conversion of 2-pyrone to *trans*-cinnamic acid. Even earlier, Chavanne[3] reported that protracted heating of 3-acetoxy-2-pyrone or 3-hydroxy-2-pyrone afforded then unidentified $C_{11}H_8O_4$ and $C_9H_6O_3$ compounds, respectively. We have subsequently found these compounds to be 3-acetoxycoumarin and coumarilic acid and note that the formation of these products can also be rationalized as proceeding via Diels–Alder dimers.

It is well known that pressure accelerates Diels–Alder reactions and slows fragmentation reactions such as decarboxylation.[4] Accordingly, several representative 2-pyrones have

been subjected to pressures of up to 7 kbar and moderate temperatures (<100 °C) to determine whether Diels–Alder dimerization of 2-pyrones can thus be effected. Synthesis of such dimers would allow one to determine whether their subsequent chemistry is consistent with their postulated intermediacy in the reactions of Seyferth and Chavanne. Moreover, dimers of suitably functionalized 2-pyrones are potentially useful as precursors of substituted coumarins and isocoumarins. Finally, the comparison of the structures of thermal dimers of 2-pyrones with those of the dimers obtained via photosensitization[5] of the same 2-pyrones would be of interest.

Dimerization of 2-Pyrones. Initially, the thermal dimerization of 2-pyrone was attempted simply by heating neat pyrone at 120 °C for 24 h. This procedure afforded only unreacted 2-pyrone and a tan, insoluble powder melting above 300 °C and presumed to be polymeric. Pressurization of 50% solutions of 2-pyrone in toluene or nitromethane at 7 kbar at 70 °C, in the presence of 1% hydroquinone to scavenge radicals, yields mostly polymer and a minor amount of a dimer, **1**. Identification of this dimer was facilitated by the earlier characterization of two [2 + 4] dimers of 2-pyrone obtained by photosensitization.[5] By means of selective spin–spin decoupling experiments and preparation of the photodimers from each of the four monodeuterated 2-pyrones, these compounds were shown to have structures **2** and **3**.[5] While the ^{1}H NMR spectrum of thermal dimer **1** is not identical with
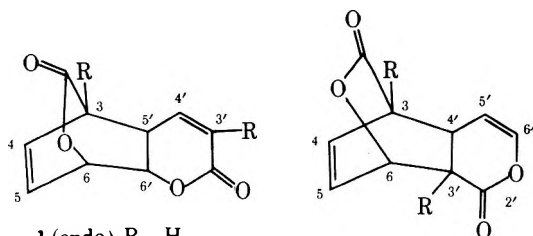
1 (endo), R = H
2 (exo), R = H
4 (endo), R = O-acetyl
6 (exo), R = O-acetyl
7 (exo), R = OH

3 (exo), R = H
5 (exo), R = O-acetyl

that of either of the photodimers, its similarity to that of 2 is such that it is clear that the difference between the two is in the stereochemistry of the ring junctures, the former being endo and the latter exo. The stereochemical assignments of these and subsequently described dimers stem from comparison of their coupling constants with those of several model compounds.[6a-c]

Pressurization of 50% solutions of 3-acetoxy-2-pyrone in either toluene or 2-butanone at up to 7 kbar at ca. 70 °C for ca. 45 h affords a crystalline material identified as endo dimer 4 through comparison of its ^{1}H NMR spectral properties with those of the 2-pyrone [2 + 4] dimers. This dimer can also be obtained by heating neat 3-acetoxy-2-pyrone at 110–120 °C for 70 h.

Irradiation of acetophenone in the presence of 3-acetoxy-2-pyrone affords two dimers which appear to be analogous to those similarly prepared from 2-pyrone. Again, the ^{1}H NMR spectral properties of one photodimer, 5 are very unlike those of the thermal dimer while those of the second, 6, are quite similar with the exception of certain key coupling constants about the ring juncture. Endo and exo structures have been assigned to the thermal dimer 4 and photodimers 5 and 6, respectively.

No dimer could be prepared by pressurization of 3-hydroxy-2-pyrone, methyl coumalate, or 4,6-dimethyl-5-carbethoxy-2-pyrone, although the first yielded an insoluble, high-melting, and presumably polymeric material. However, photosensitization of 3-hydroxy-2-pyrone affords a single dimer, the protons of which differ in chemical shifts, but not in coupling constants, from those of the 3-acetoxy-2-pyrone photodimer 6. This dimer has accordingly been assigned the exo structure 7.

The 2-pyrone photodimer 3, in which the 3,4 double bond of 2-pyrone is the dienophile, has for $J_{3',6}$ a value very near those of $J_{6,6'}$ in photodimers 2 and 6 to which exo geometry has been assigned. It may thus be concluded that photodimer 3 also has the exo configuration. No such comparison can be made for photodimer 5, which lacks the analogous coupling constant. The assignment of exo configuration to 5 follows from the stereochemistry of the other photodimers.

Thermolysis of the Dimers. On being heated at 200 °C both 2-pyrone dimers 1 and 2 yield 2-pyrone and second GLC identical components. In the case of 2, this second component was identified as *cis*-cinnamic acid. Since *cis*-cinnamic acid is known to rearrange to the more stable trans isomer, such rearrangement could plausably occur under Seyferth's original reaction conditions.[2] The other photodimer, 3, slowly decarboxylates in boiling acetonitrile to afford 9,10-dihydroisocoumarin which can be dehydrogenated over palladium to afford isocoumarin. Heated at its melting point, the thermal dimer of 3-acetoxy-2-pyrone reverts completely to monomer; no 3-acetoxycoumarin could be detected by ^{1}H NMR. If this dimer is indeed the 3-acetoxycoumarin precursor in Chavanne's reaction, then, at 200 °C where that reaction is carried out, the equilibrium concentration of the dimer must be quite

small. However, the irreversible decarboxylation of even a minute portion of this dimer could ultimately afford 3-acetoxycoumarin as a major product.

Registry No.—1, 59041-90-6; 2, 21044-75-7; 3, 21044-74-6; 4, 58983-22-5; 5, 58983-23-6; 6, 59091-52-0; 7, 58983-24-7; 2-pyrone, 504-31-4; 3-acetoxy-2-pyrone, 51270-29-2; 3-hydroxy-2-pyrone, 496-64-0; acetophenone, 98-86-2; 3-acetoxycoumarin, 58983-26-9; coumarilic acid, 496-41-3; maleic anhydride, 108-31-6; *cis*-cinnamic acid, 102-94-3; 9,10-dihydroisocoumarin, 58983-27-0; isocoumarin, 491-31-6; 10, 58983-25-8; acetonitrile, 75-05-8.

Supplementary Material Available. Tables of ^{1}H and ^{13}C NMR spectra of the dimers, a discussion of the assignment of endo and exo structures from ^{1}H NMR spectra of model compounds, and experimental procedures (17 pages). Ordering information is given on any current masthead page.

References and Notes

(1) T. Imagawa, N. Sueda, and M. Kawanisi, *Tetrahedron*, **30**, 2227 (1974).
(2) D. L. White and D. Seyferth, *J. Org. Chem.*, **37**, 3545 (1972).
(3) G. Chavanne, *Ann. Chim. (Paris)*, **3**, 535 (1904).
(4) For a recent review on the effects of high pressures on reaction rates, see J. P. McCabe and C. A. Eckert, *Acc. Chem. Res.*, **7**, 251 (1974).
(5) W. H. Pirkle and L. H. McKendry, *Tetrahedron Lett.*, 5279 (1968).
(6) (a) H. Behringer and P. Heckmaier, *Chem. Ber.*, **102**, 2835 (1969); (b) K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1904); (c) C. M. Cumarusti and J. Wolinsky, *J. Am. Chem. Soc.*, **90**, 113 (1968).

A Reaction of α-Pyrone and Nitrosobenzene

Yigal Becker, Samuel Bronstein, Amihai Eisenstadt, and Youval Shvo*

*Department of Chemistry, Tel-Aviv University, Tel-Aviv, Israel*

1,2-oxazine[1,2] and its N-substituted derivatives, such as 2, is an elusive molecular system. Its thermal instability can be understood when bond energies and the antiaromatic character are considered.[3,4] Its chemical reactivity can be rationalized in terms of the available electrocyclic ring opening reaction which may yield an unsaturated imino aldehyde. A controversy has arisen around the structure of several substituted 1,2-oxazines;[5-7] however, the parent system 2 (with N-alkyl or aryl substituents) has neither been prepared nor detected as a transitory species. A very recent attempt to obtain 1-cyclohexyl-1,2-oxazine has failed.[1]

We expected the formation of 2 by a simple 1,4-cycloaddition reaction of nitrosobenzene and α-pyrone with subsequent loss of CO_2 from the intermediate (1) or from its isomeric adduct.

Indeed our experiments show that when α-pyrone and nitrosobenzene are brought into contact (in ether, methylene chloride, or benzene solutions) at 0 °C, the starting materials disappear and CO_2 is evolved. However, the products isolated after chromatography are azoxybenzene (18.8%) and a colorless solid (24%), which was not the anticipated 1-phenyl-1,2-oxazine. Its mass spectrum (M+ *m/e* 266) and elemental analysis ($C_{16}H_{14}N_2O_2$) indicate a formal 2:1 adduct of nitrosobenzene/α-pyrone with the loss of CO_2.

A logical structural candidate (3), or its isomeric adduct, which could have originated from a second 1,4 polar addition of nitrosobenzene and 2, was ruled out on the basis of spectral and chemical properties, which suggest the alternative structure 4.

The ir spectrum (CHCl₃) exhibits intense bands at 3550, 3300 (OH stretching), and 1705 cm⁻¹ (conjugated carbonyl). The NMR spectrum was not very informative inasmuch as the only signals recorded were several sets of multiplets in the
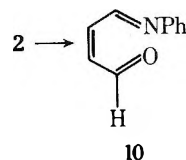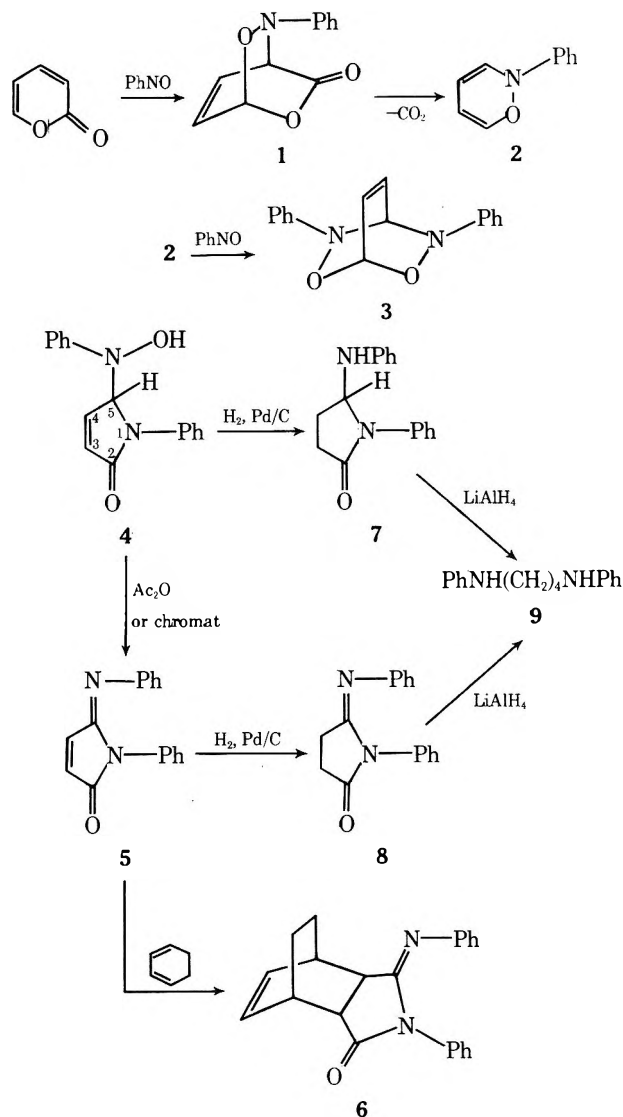
(LiAlH$_4$) of both **7** and **8** led to a single known compound, 1,4-dianilinobutane (**9**).

The structural data and analysis presented in this work leave little doubt regarding the suggested structure for the primary compound isolated from the reaction of α-pyrone and nitrosobenzene (**4**). Unfortunately our idea of the simple reaction scheme had not materialized inasmuch as the desired oxazine could not be isolated nor detected. We cannot at this stage state whether 1-phenyl-1,2-oxazine is an intermediate in the observed reaction. Three possible general routes for the formation of **4** were considered.

1. Skeletal rearrangement of **3**, accompanied by H or hydride shift.

2. Electrophilic substitution of α-pyrone by nitrosobenzene followed by 1,4 addition of nitrosobenzene, elimination of CO_2, and skeletal rearrangement.

3. The imino aldehyde (**10**) can be considered to arise from the electrocyclic ring opening reaction of the oxazine (**2**).

Simple bond energies calculations indicate its thermal stability over **2**. Hydride or H removal of the aldehyde hydrogen of **10** followed by addition of PhNOH (radical or anion) and subsequent cyclization may give rise to **4**.

Experimental Section

Reaction of α-Pyrone and Nitrosobenzene. A solution of 0.90 g (0.00935 mol) of α-pyrone and 2.0 g (0.0187 mol) of nitrosobenzene in chloroform (10 ml) was kept at 0 °C for 5 h under nitrogen; the evolution of CO_2 was noticed and confirmed by sweeping the evolved gas into a saturated Ba(OH)$_2$ solution. The solvent was evaporated and the residual dark oil was chromatographed on Silicar (80 g). Azoxybenzene (0.376 g) was eluted with 1:4 CH$_2$Cl$_2$-petroleum ether mixture. Gradual increase of CH$_2$Cl$_2$ concentration eluted 0.594 g (24%) of **4** homogenous by TLC, crystallized from benzene–petroleum ether: mp 129.5–130 °C; NMR (acetone-d_6) δ 8.9 (1 H, s, exchangeable with D$_2$O), 6–7.7 (13 H, m); uv λ_{max} (EtOH) 280 nm (ϵ 4720), 230 (11 900); ir (CHCl$_3$) 3550 and 3300 (OH free and bonded), 1705 (C=O), 1600 and 1500 cm^{-1} (phenyl); ir (KBr) 3220, 1680 cm^{-1}; mass spectrum m/e 266 (M$^-$), 248 (M$^+$ – H$_2$O).

Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_2$: C, 72.2; H, 5.26; N, 10.5. Found: C, 72.4; H, 5.02; N, 10.5.

Lower yields of **4** resulted when equimolar quantities of α-pyrone and nitrosobenzene were used.

Nitrosobenzene-d_5. Benzene-d_6 was nitrated[8] (76%) and then reduced[9] to give nitrosobenzene-d_5 (37%), mp 65–67 °C, ^{1}H NMR (CHCl$_3$) no detectable signals at 10% concentration.

Reaction of α-Pyrone and Nitrosobenzene-d_5. The reaction and isolation of product were carried out as described above: mp 129.5–130 °C; NMR (acetone-d_6) δ 8.85 (1 H, s, exchangeable), 7.17 (1 H, pair of doublets, J = 6.0 and 1.8 Hz), 6.35 (1 H, pair of doublets, J = 6.0 and 1.2 Hz), 6.50 (1 H, t, $J \simeq$ 1.3 Hz).

1-Phenyl-2-phenyliminomaleimide (5). The crude reaction product of **4** was chromatographed on basic alumina (III) instead of Silicar. With 2:3 CH$_2$Cl$_2$–petroleum ether mixture there was eluted 0.522 g (23%) of **5**, yellow needles: mp 136–137 °C after crystallization from CH$_2$Cl$_2$–petroleum ether; NMR (acetone-d_6) δ 6.7–7.4 (m); uv λ_{max} (EtOH) 377 nm (ϵ 3460), 250 (21 200); ir (CHCl$_3$) 1730 (C=O), 1658 (C=N), 1594, 1500 cm^{-1} (phenyl); mass spectrum m/e 248 (M$^+$).

Anal. Calcd for C$_{16}$H$_{12}$N$_2$O: C, 77.5; H, 4.84; N, 11.3. Found: C, 77.6; H, 4.96; N, 11.1.

An identical substance was obtained by treating **4** with Ac$_2$O.

A mixture of **4** (0.2 g) and 1,3-cyclohexadiene (1 ml) was kept at room temperature for 48 h. The solid which crystallized was chromatographed on basic alumina: 0.16 g (60%) of **6**; mp 185–187 °C; NMR (CDCl$_3$) δ 6.8–7.5 (10 H, m), 6.22 (2 H, m), 3.4 (1 H, dd, J = 10 and 3 Hz), 3.22 (1 H, m), 2.94 (1 H, dd, J = 10 and 2 Hz), 2.5 (1 H, m), 1.1–1.8 (4 H, broad); ir (CHCl$_3$) 1740 (C=O), 1665 (C=N), 1595 and 1500 cm^{-1} (phenyl); mass spectrum m/e 328 (M$^+$).

region δ 6.20–7.80. A singlet (1 H) of an exchangeable proton was recorded at δ 8.0, in agreement with the ir findings. In order to clarify the NMR spectrum we have repeated the reaction using nitrosobenzene-d_5. An AB quartet (J = 6.0 Hz) with further unequal doubling of each branch (J = 1.2 and 1.8 Hz) was clearly evident in the olefin region of the NMR spectrum. This quartet was assigned to the C-3 and C-4 protons of **4**. An additional apparent triplet signal (1 H) (allylic spin coupling) was assigned to the C-5 proton. Although an alternative assignment of the signals is possible, the spectral pattern is in accord with structure **4**.

Compound **4** readily loses a molecule of water either by chromatography on basic alumina or by treatment with Ac$_2$O to yield the yellow maleimide derivative **5**. Besides the correct analysis and the mass spectral data, the phenyl-d_{10} derivative of **5** exhibits a single uncoupled AB quarter (J = 6.0 Hz) in the NMR spectrum, confirming the spectral assignments of **4**. Compound **5** proved to be a dienophile inasmuch as it gave a cycloaddition product (**6**) with cyclohexadiene.

Finally, the structure of **4** has been rigorously established by chemical transformations. Catalytic hydrogenation of **4** (uptake of 2 molar equiv of H$_2$) led to a crystalline product (**7**). Its mass spectrum (M$^+$ m/e 250) and NMR analysis have indicated that both hydrogenation of the double bond and hydrogenolysis of the N–OH bond took place. Similarly, catalytic hydrogenation of **5** (uptake of 1 molar equiv of H$_2$) led to a colorless solid, for which structure **8** has been assigned on the basis of spectral and analytical data. Chemical reduction

1-d₅-Phenyl-2-d₅-phenyliminomaleimide. This compound was prepared from the d_{10}-phenyl derivative of **4**, as described in the above procedure: mp 136–137 °C; NMR (acetone-d_6) δ 7.05 (1 H, d, J = 6.0 Hz), 6.65 (1 H, d, J = 6.0 Hz); mass spectrum *m/e* 258 (M⁺).

5-Anilino-1-phenylpyrrolid-2-one (7). A 50-mg sample of **4** was hydrogenated at room temperature and atmospheric pressure using Pd/C. After 12 h 2 molar equiv of H₂ was absorbed. The residue after evaporation of the solvent was crystallized (EtAc/petroleum ether): 38 mg of colorless crystals; mp 137–139 °C; NMR (CDCl₃) δ 6.4–7.6 (10 H, complex, multiplet), 5.65 (1 H, m), 4.10 (1 H, broad singlet, exchangeable), 1.7–2.8 (4 H, complex multiplet); ir (CHCl₃) 3410 (NH) and 1695 cm⁻¹ (CO); uv λ_{max} (EtOH) 287 nm (ϵ 1700), 245 (12 500); mass spectrum *m/e* 252 (M⁺, $C_{16}H_{16}N_2O$), 160 (M⁺ − C_6H_5NH).

Phenylimino-*N*-phenylsuccinimide (8). **5** (250 mg, 1 mmol) and 50 mg of 10% Pd/C in ethyl acetate (15 ml) was hydrogenated at atmospheric pressure and room temperature. One molar equivalent of H₂ was absorbed after 5 h. The mixture was filtered through Celite, the solvent was evaporated, and the residue was twice crystallized from EtAc/petroleum ether: colorless, prismatic crystals; mp 139–140.5 °C; NMR (CDCl₃) δ 6.70–7.60 (10 H, complex multiplet), 2.70 (4 H, s); ir (CHCl₃) 1780 and 1665 cm⁻¹; mass spectrum *m/e* 250 (M⁺, $C_{16}H_{14}N_2O$).

1,4-Dianilinobutane (9). To a solution of 200 mg of **8** in THF (20 ml) there was added portionwise LiAlH₄ (400 mg). The mixture was refluxed for 4 h, the solvent was evaporated, ether was added, and to the cooled mixture a 20% aqueous NaOH solution was added. The ether was decanted off, and the solid was triturated with portions of chloroform which were combined with the ether phase, dried (K₂CO₃), and evaporated. The residue was distilled with Kugelrohr (0.005 mm). The distillate (148 mg) was crystallized from ether–petroleum ether at 0 °C, crystals, mp 36–37 °C (lit.[10] mp 37 °C).

A 300-mg sample of **7** was reduced as described above, also yielding 1,4-dianilinobutane (65%).

Registry No.—**4**, 58966-81-7; **4** d_{10}-phenyl derivative, 58966-82-8; **5**, 58966-83-9; **5** d_{10} phenyl derivative, 58966-84-0; **6**, 58966-85-1; **7**, 58966-86-2; **8**, 58966-87-3; **9**, 13170-61-1; nitrosobenzene, 586-96-9; α-pyrone, 504-31-4; nitrosobenzene-d_5, 18628-43-8; benzene-d_6, 1076-43-3; 1,3-cyclohexadiene, 592-57-4.

References and Notes

(1) S. Shatzmiller and A. Eschenmoser, *Helv. Chim. Acta,* **56**, 2975 (1973).
(2) R. Gompper and G. Seybold, "Aromaticity, Pseudo-Aromaticity and Anti-Aromaticity", Proceedings of the International Symposium, Jerusalem, 1970, p 215.
(3) R. Breslow, *Angew. Chem., Int. Ed. Engl.,* **7**, 565 (1968).
(4) R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.,* **10**, 572 (1971); P. Gygax, T. K. Das Gupta, and A. Eschenmoser, *Helv. Chim. Acta,* **55**, 2205 (1972).
(5) W. Dilthey, G. Hurtig, and H. Passing, *J. Prakt. Chem.,* **156**, 27 (1940).
(6) J. Rigaudy, G. Cauquis, and J. Baranne-Lafont, *Tetrahedron Lett.,* 1569 (1964).
(7) J. Rigaudy and J. Baranne-Lafont, *Tetrahedron Lett.,* 1375 (1965).
(8) A. Rieker and P. Ziemek, *Z. Naturforsch. B,* **20**, 640 (1965).
(9) A. I. Vogel, "Textbook of Practical Organic Chemistry", 3d ed, Wiley, New York, N.Y., 1966, p 630.
(10) G. Wittig, W. Joos, and P. Rathfelder, *Justus Liebigs Ann. Chem.,* **610**, 180 (1957).

Reaction of Amines with Thiophthalimides. Anomalous Formation of a Thiooxamide[1]

David N. Harpp* and Thomas G. Back

Department of Chemistry, McGill University, Montreal, Quebec, Canada

The reaction of various amines with thiophthalimides (**1**) has been shown to be a useful, general method for the preparation of sulfenamides **2**.[2a,b] The only observed exception to this behavior appears to be in the reaction of primary amines with thiophthalimides which have bulky groups. In these cases the nitrogen nucleophile reacts at the carbonyl carbon to give a ring-opened product (**3**).[2a,c] We have discovered an instance where the reaction of a primary amine with an unhindered thiophthalimide proceeds by an alternate route giving two
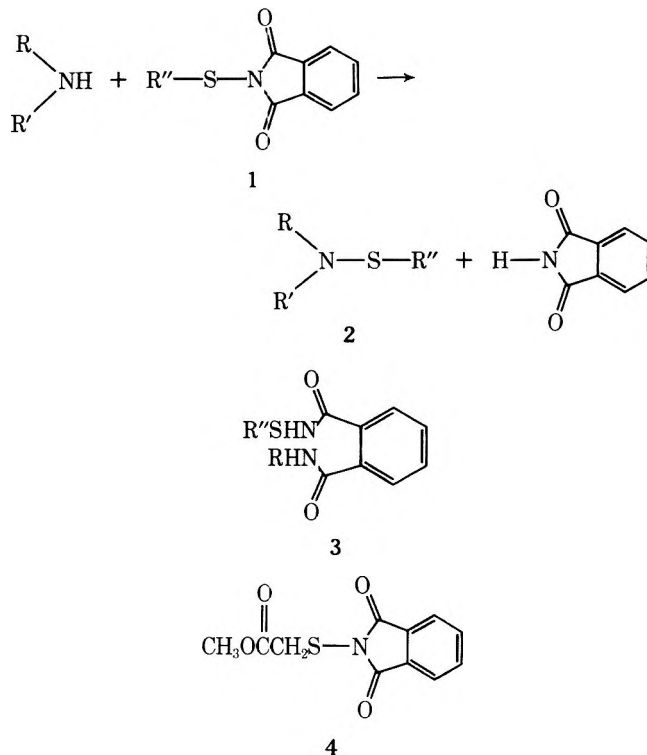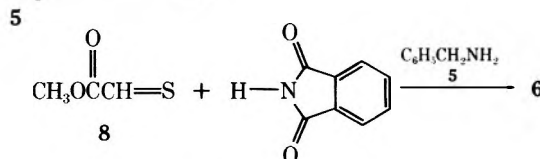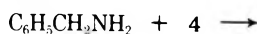

products which can be rationalized by an α-elimination process (vide infra).

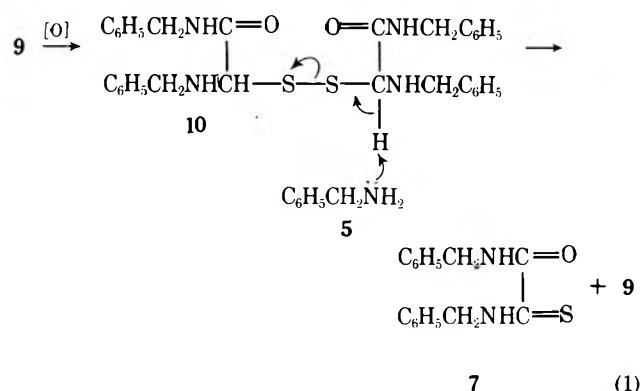Thiophthalimide **4**[3] was treated with 2 equiv of benzylamine (**5**), the by-product phthalimide collected (69%), and the remaining material chromatographed to provide a mixture of unidentified components as well as two pure compounds.

One of the latter products (**6**) was identified as *N*-benzylphthalamide (16% yield) (see Experimental Section). The other substance is a solid, mp 120–122 °C. It shows NMR (CDCl₃) δ 4.40 (d, 2 H), 4.75 (d, 2 H) (J = 6 Hz), 7.2 (s, 10 H), 8.38 (broad, 1 H), 9.71 (broad, 1 H). After treatment with NaOD/D₂O, the two high-field doublets collapsed to singlets and the low-field signals disappeared. Infrared, combustion, and MS analyses are consistent with thiooxamide **7** as the structure.
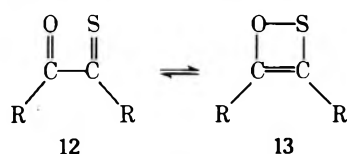
$$
\underset{7}{C_6H_5CH_2NHC\overset{\overset{\displaystyle O}{\|}}{}-C\overset{\overset{\displaystyle S}{\|}}{}NHCH_2C_6H_5}
$$
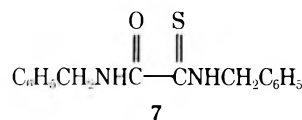
The formation of both **6** and **7** may be envisioned to arise via abstraction of an acidic methylene proton in **4** by benzylamine (**5**), thus eliminating phthalimide and generating the intermediate thioaldehyde **8**.[4a] The latter species probably suffers further attack by the amine, resulting in both amida-
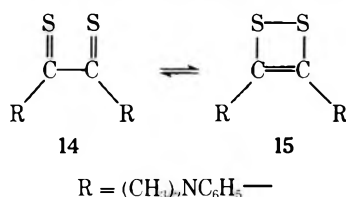
$$9 \xrightarrow{[O]} \begin{array}{c} C_6H_5CH_2NHC{=}O \quad O{=}CNHCH_2C_6H_5 \\ | \qquad\qquad\qquad | \\ C_6H_5CH_2NHCH{-}S{-}S{-}CNHCH_2C_6H_5 \\ \textbf{10} \qquad\qquad\qquad | \\ H \\ \downarrow \\ C_6H_5CH_2NH_2 \\ \textbf{5} \end{array}$$

$$\begin{array}{c} C_6H_5CH_2NHC{=}O \\ | \qquad\qquad + \ \textbf{9} \\ C_6H_5CH_2NHC{=}S \end{array}$$

$$\textbf{7} \qquad (1)$$
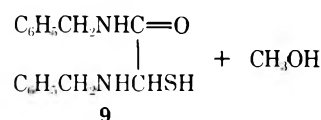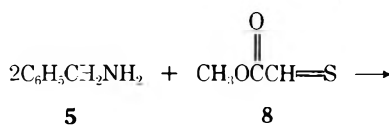
tion and addition to the thione function. The resulting thiol **9** may then be oxidized to the corresponding disulfide **10**,[4b] which in turn undergoes further proton abstraction, thereby displacing mercaptide ion and providing thiooxamide **7** (eq 1).

Compounds containing a thione moiety α to a carbonyl group have rarely been reported in the literature.[4a,7] Recently they have attracted attention[7d,g] because of possible interaction between the oxygen and sulfur atoms as shown below.

$$\begin{array}{c} O \quad S \\ \| \quad \| \\ C{-}C \\ / \qquad \backslash \\ R \qquad R \end{array} \rightleftharpoons \begin{array}{c} O{-}S \\ | \quad | \\ C{=}C \\ / \qquad \backslash \\ R \qquad R \end{array}$$

$$\textbf{12} \qquad\qquad \textbf{13}$$

Although the existence of the 1,2-oxathiete structure **13** has not been firmly established,[7d,g] uv studies on the α-dithione **14** indicate that the corresponding 1,2-dithiete **15** is present in solution.[8,9] The equilibrium between these valence tau-

$$\begin{array}{c} S \quad S \\ \| \quad \| \\ C{-}C \\ / \qquad \backslash \\ R \qquad R \end{array} \rightleftharpoons \begin{array}{c} S{-}S \\ | \quad | \\ C{=}C \\ / \qquad \backslash \\ R \qquad R \end{array}$$

$$\textbf{14} \qquad\qquad \textbf{15}$$

$$R = (CH_3)_2NC_6H_5{-}$$

tomers is affected by changes in solvent polarity, with formation of the cyclic form being favored by nonpolar media. To examine the possibility of a 1,2-oxathiete structure in solutions of **7**, uv spectra were recorded in solvents of disparate polarity. The spectrum in CH_2Cl_2 [λ_{max} 247 nm (ϵ 6800), 303 (6100), and 398 (40)] closely resembeled that reported for *N,N*-dimethylthiooxamide.[10] The spectra of **7** in 1:1 mixtures of ethanol–methylene chloride or cyclohexane–methylene chloride was not measurably different, indicating that an equilibrium of the type **12** ⇌ **13** is not operative to a significant extent.[11]

Experimental Section

Elemental analyses of compounds were obtained on a Hewlett-Packard Model 185 automatic CHN analyzer, or by Organic Microanalyses (Montreal, Canada). Infrared spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer or on a Unicam SP 1000 instrument. A Unicam SP 800 spectrophotometer was used to obtain ultraviolet spectra. NMR spectra were determined on a Varian T-60 instrument. The high-resolution mass spectrum of **7** was recorded by Dr. J. R. Hoyland at the Battelle Memorial Institute (Columbia, Ohio) through the cooperation of Dr. J. P. Snyder, University of Copenhagen.

Reaction of Thiophthalimide 4 with Benzylamine. A solution containing 1.26 g (5 mmol) of thiophthalimide **4** and 1.07 g (10 mmol) of benzylamine in 50 ml of ether was stirred for 2 h at room temperature. After this time, phthalimide was filtered: 0.51 g (69%); mp 228–233 °C (lit.[12] 238 °C). The filtrate was evaporated to dryness to give a sticky, yellow solid which was chromatographed on a dry column of alumina. Elution with methylene chloride gave 0.38 g (27%) of **7**, mp 116–118 °C. Recrystallization from ethanol yielded yellow needles:

Table I. Mass Spectrum of Thiooxamide 7

m/e Measured	m/e Calcd	% of base of peak	Possible structure of ion
284.1030	284.0983	16.6	$C_6H_5CH_2NHCOCSNH{-}CH_2C_6H_5$
193.0460	193.0436	64.7	$C_6H_5CH_2NHCSCONH$
149.0290	149.0299	6.7	$C_6H_5CH_2NCS$
106.0658	106.0657	63.8	$C_6H_5CH_2NH$
91.0561	91.0548	100.0	$C_6H_5CH_2$ or tropylium

mp 120–122 °C (lit.[7c] 118–119 °C); ir (KBr) max 3234, 1664, 1108, 1098, 1066, and 1023 cm^{-1}; mass spectrum, see Table I. Anal. Calcd for $C_{16}H_{16}N_2OS$: C, 67.6; H, 5.7; N, 9.9. Found: C, 67.6; H, 5.7; N, 9.8.

Further elution with ethyl acetate gave a white solid which was recrystallized from chloroform to give 0.21 g (16%) of *N*-benzylphthalamide **6**, mp 180–182 °C. A second recrystallization provided an analytical sample: mp 188 °C; NMR (CDCl$_3$) 4.60 (d, 2 H), 7.4 (m, 11 H), 8.07 ppm (s, 1 H); ir (KBr) 3365, 3300, 3185, 1642, 1595, 1540, 1420, 1095, 798, 750 cm^{-1}. Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.9; H, 5.6; N, 11.0. Found: C, 71.0; H, 5.6; N, 10.7.

While other compounds were produced in low yield, separation into pure components could not be achieved.

References and Notes

(1) Organic Sulfur Chemistry. 20. For part 19 see D. N. Harpp and T. G. Back, *J. Labelled Compd.*, **11**, 95 (1975).

(2) (a) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 4953 (1971); (b) K. S. Boustany, *Chimia*, 396 (1970); (c) K. S. Boustany and J. P. Vander Kooi, *Tetrahedron Lett.*, 4983 (1970).

(3) D. N. Harpp and B. A. Orwig, unpublished results; B. A. Orwig, M.S. Thesis, McGill University, 1971.

(4) (a) A similar intermediate to **8** (a thioaldehyde) has been proposed to account for the formation of thiooxamides in the reaction of carbamoyl thiosulfates with amines; see B. Milligan and J. M. Swan, *J. Chem. Soc.*, 2969 (1959). Compound **6** can be thought to arise by attack of benzylamine on the carbonyl carbon of **4** followed by α-elimination to give thioaldehyde **8** and **6**. Alternatively, however, we have demonstrated that **6** could arise by reaction of phthalimide with benzylamine under the given reaction conditions. (b) The exact nature of the oxidation process by which disulfide **10** is produced is not clear; however, it is well known[5] that thiols are readily converted to disulfides by aerial oxidation in basic media. For example, 2-aminoethanethiol oxidizes spontaneously on exposure to air by virtue of the catalytic effect of its own basic amino group.[6] Hence, it would not be surprising if a similar process occurs in the case of thiol **9** in the presence of benzylamine.

(5) E. E. Reid, "Organic Chemistry of Bivalent Sulfur", Vol. 1, Chemical Publishing Co., New York, N.Y., 1958, Chapter 2.

(6) S. Gabriel and J. Colman, *Chem. Ber.*, **45**, 1643 (1912).

(7) (a) A. Reissert, *Chem. Ber.*, **37**, 3708 (1904); (b) G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 3189 (1956); (c) B. Milligan and J. M. Swan, *ibid.*, 1194 (1961); (d) D. C. Dittmer, G. C. Levy, and G. E. Kuhlman, *J. Am. Chem. Soc.*, **89**, 2793 (1967); (e) F. Becke and H. Hagen, German Patent 1 270 552 (1968); *Chem. Abstr.*, **70**, 11208 (1969); (f) D. C. Dittmer, G. E. Kuhlman, and G. C. Levy, *J. Org. Chem.*, **35**, 3676 (1970); (g) D. C. Dittmer and G. E. Kuhlman, *ibid.*, **35**, 4224 (1970); (h) B. Saville and M. Steer, *J. Chem. Soc., Chem. Commun.*, 616 (1972); (i) K. Thimm and J. Voss, *Tetrahedron Lett.*, 537 (1975).

(8) W. Küsters and P. de Mayo, *J. Am. Chem. Soc.*, **95**, 2383 (1973). A parallel dithiete structure has been proposed (NMR evidence) for dithiooxalmorpholide [3-methylthio-4-(*N*-morpholino)dithiete]: S. Wawzonek and S. M. Heilmann, *J. Org. Chem.*, **39**, 511 (1974). It is of interest that a stable dithiete has been prepared although detailed uv studies were not reported: R. B. Boar, D. W. Hawkins, J. F. McGhie, S. C. Misra, D. H. R. Barton, M. F. C. Ladd and D. C. Povey, *J. Chem. Soc., Chem. Commun.*, 756 (1975).

(9) Recent calculations on several model α-dithiones and α-ketothiones have suggested that ring closure and rupture is thermally forbidden but photochemically allowed: J. P. Snyder, Abstracts of VI International Symposium on Organic Sulfur Chemistry, Bangor, Wales, 1974.

(10) B. Persson and J. Sandström, *Acta Chem. Scand.*, **18**, 1059 (1964); O. Korver, J. U. Veenland, and T. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **84**, 289 (1965).

(11) It is of interest in the mass spectrum of **7** (see main peaks, Experimental Section) that no peak was found corresponding to a loss of SO. Dittmer and Kuhlmann reported a small peak for the loss of SO in the mass spectrum of monothiobenzil ($C_6H_5COCSC_6H_5$).[7g]

(12) J. R. A. Pollock and R. Stevens, Ed., "Dictionary of Organic Compounds," Vol. 5, Eyre and Spottiswoode, London, 1965, p 2741.

Reaction of *tert*-Butyl Hydroperoxide Anion with Dimethyl Sulfoxide. On the Pathway of the Superoxide–Alkyl Halide Reaction[1]

Morton J. Gibian* and Timothy Ungermann

Department of Chemistry, University of California, Riverside, California 92502

Superoxide ion ($O_2\cdot^-$) has been of considerable recent interest because of its biochemical ubiquity (all aerobic cells produce it) and as a species of relatively unexplored chemical reactivity.[2] It has the potential of acting as a redox (oxidizing or reducing) agent, or as a nucleophile (or base). With alkyl halides, it apparently acts in its nucleophilic capacity. Two original studies were of electrochemically generated $O_2\cdot^-$ reacting under slightly basic conditions with the butyl halides;[3] hydroperoxides (by GC) and dialkyl peroxides were reported as respective products in Me_2SO[3a] and DMF.[3b]

Recently, two reports utilizing KO_2 solubilized with crown ether showed that stereochemical inversion occurs at the reacting carbon atom of alkyl halides and tosylates.[4,5] However, San Filippo et al.[4] (using RX:KO_2:18-crown-6 of 3.3:10:1 mole ratio in Me_2SO) found primarily alcohols (some olefin) as the major end products, while Johnson and Nidy[5] (all reagents 1:1:1 using dicyclohexyl-18-crown-6 in benzene, one experiment with 0.1 equiv of crown ether in benzene) found primarily dialkyl peroxides (plus olefin and a little alcohol in some cases). At first it seemed that the reagent ratios (particularly KO_2:RX) might be causing the difference in products, in that the prior workers mentioned that in benzene or HMPA similar products but in lower yield resulted. That is not the case, however, and we report here on the extremely rapid reaction of alkyl hydroperoxide ion, a likely intermediate in the $O_2\cdot^-$ plus alkyl halide reaction, with Me_2SO to give a quantitative (by GC) yield of corresponding alcohol and dimethyl sulfone.

Experimental Section

Solvents were reagent grade, dried over molecular sieve. Distillation of Me_2SO from desiccant did not reduce its water content below that as supplied in Baker Analyzed material. KO_2, from Alfa, was used as obtained after thorough grinding to a fine powder in a dry atmosphere (glove bag). Crown ether (18-crown-6) was synthesized as reported by Gokel et al.,[6] and peroxides were distilled Lucidol products.

All reactions were run at room temperature by adding ground KO_2 or base to solvent with or without crown ether, followed by further grinding and dispersing with a spatula, addition of peroxide, and then vigorous stirring throughout. Several workup procedures were employed. *tert*-Butyl alcohol is not well extracted into organic solvent from Me_2SO/water, even after acidification (*tert*-butyl hydroperoxide is also poorly extracted). For the runs in Me_2SO, the addition of water at the end of a run (whether KOH, K_2CO_3, or KO_2) did not affect the alcohol and peroxide GC peak areas in any case. Apparently the activity of the water in Me_2SO ("dry") is sufficient to keep at least 95% of the OH groups protonated. For the toluene runs 1 equiv (to base) of concentrated HCl was added to terminate reaction, the reaction mixture was thoroughly shaken, and an aliquot was removed for analysis. All analyses were on GC, and product identification was by retention volume.

Results and Discussion

The simplest explanation for the difference in products might have been that in the alcohol-producing study excess KO_2 reacted with product dialkyl peroxide, reducing it to alcohol and forming O_2. However, we found that 0.17 M di-*tert*-butyl peroxide was completely stable when stirred at room temperature in Me_2SO (20 ml) in the presence of 0.05 M 18-crown-6 and 10 mmol of well-dispersed KO_2 for up to a day. This experiment was repeated several times under various conditions, another set being included in Table I.[7]

Since the product in this case is stable, and the same initial inverting $O_2\cdot^-$ displacement very likely occurs in both solvents, an intermediate must be somehow diverted in one of the systems (KO_2/crown ether is stable in Me_2SO for long times).

Pathways involving bimolecular peroxy radical reaction are unlikely for two reasons. First, the concentration of the peroxy radicals vis-à-vis other potential exothermic reactants ($O_2\cdot^-$, RX hydrogens, solvent) is very low, so that even given the high rate constant for recombination it is unlikely to be a major route. Second, such a mechanism fails to account for the dramatic effect of solvent on products.

Alkyl hydroperoxide anion is a second likely intermediate on the route to dialkyl peroxide, being produced by reduction of the initially formed alkyl peroxy radical by $O_2\cdot^-$. The peroxide anion might be intercepted by either excess $O_2\cdot^-$ or solvent rather than participating in a subsequent displacement on halide, and we here report data showing that such a competitive situation is reasonable.

Table I, presenting representative data from a variety of experiments, indicates that in mixtures of *tert*-butyl hydroperoxide, KO_2, and Me_2SO with crown ether the only reaction observed is the base-catalyzed transformation of hydroperoxide and Me_2SO to *tert*-butyl alcohol and dimethyl sulfone. *In toluene, no loss of hydroperoxide occurs with KO_2 or crown ether or both together.* While hydroperoxide itself is stable in Me_2SO crown ether, the addition of just base (K_2CO_3 or KOH) causes a rapid quantitative transformation to alcohol and sulfone (eq 1 and 2).

$$ROOH + B \rightleftharpoons ROO^- + BH^+ \qquad (1)$$

$$BH^+ + ROO^- + (CH_3)_2SO \longrightarrow B + ROH + (CH_3)_2SO_2 \qquad (2a)$$

or

$$ROO^- + (CH_3)_2SO \longrightarrow RO^- + (CH_3)_2SO_2$$
$$RO^- + BH^+ \longrightarrow ROH + B \qquad (2b)$$
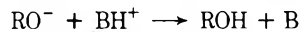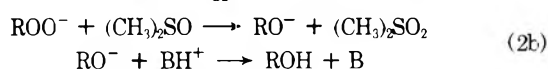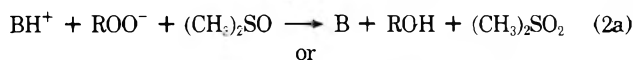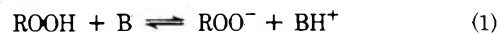
The reaction with KO_2, since it does not occur in 2×10^4 the time in toluene, would seem to be eq 2 in which B is $O_2\cdot^-$ and BH^+ is $HOO\cdot$. The equilibrium in eq 1 would lie far to the left, but at least one of the species on the right is then extremely reactive in Me_2SO and not in toluene.[8] From Table I it is clear that both crown ether and base are required to catalyze the hydroperoxide reaction with Me_2SO. KOH is more effective than K_2CO_3, and KO_2 is apparently more like KOH. Several entries show that crown ether is required to solubilize the base, and that the rate increases as its concentration is raised. Two runs, one with KO_2 and the other with KOH, were found to produce quantitative yields of *tert*-butyl alcohol and dimethyl sulfone.

The analogous oxidation of sulfoxides with H_2O_2 and organic peracids has been known for some time, and involves O atom transfer with formation of a covalent intermediate adduct.[9] It has been shown that two processes can occur:[10] a slower one in neutral or acidic medium (pH independent) that involves attack by H_2O_2 or peracid itself, and a rapid reaction of HO_2^- or peracid anion on sulfur that is dependent on the pK_a involved. Alkyl hydroperoxides have been investigated in neutral and acidic medium, and give oxidation of sulfides to the sulfoxide stage only.[11] With transition metal catalyst sulfones are formed.[12] In a study of the autoxidation of triphenylmethane, Russell and Bemis[13] found that triphenylmethyl hydroperoxide, in a base-requiring process, yielded triphenylmethylcarbinol in 95% yield in Me_2SO (they also found Me_2SO_2), but not in HMPA or DMF.
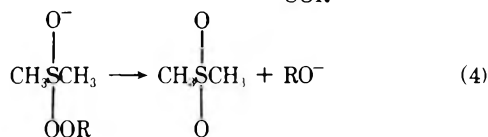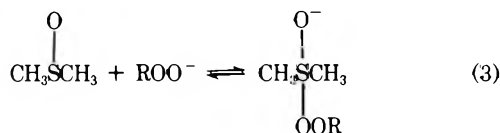
An attractive pathway for the hydroperoxide reaction, based on that for H_2O_2 and peracids, with sulfoxide is shown in Scheme I. Crown ether catalyzes this process by solubilizing the cations. There is a basis for preferring the process in eq 5 over that in eq 4 (or 2a over 2b) because in addition to an excess of base (KO_2, K_2CO_3, KOH) in each reaction in Table I,

Table I. Reaction of *tert*-Butyl Hydroperoxide in the Presence of Various Bases and Crown Ether
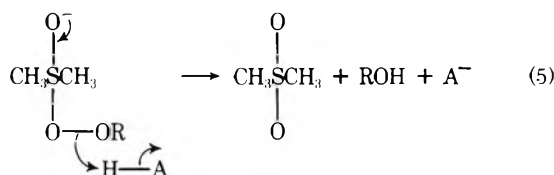
	Solvent[a]	t-BuOOH, M	18-crown-6, M	Base, mmol	Product	Comment
1	Me$_2$SO	0.17, 2.5	.05	None	No reaction	
2	Me$_2$SO	2.5	<0.05	K$_2$CO$_3$ (1.3)	No reaction	1 h
3	Me$_2$SO	2.5	0.5	K$_2$CO$_3$ (1.3)	t-BuOH, ca. 50%	1 h
4	Me$_2$SO	0.17	0.05	KO$_2$ (1.33)	t-BuOH (100%) / Me$_2$SO$_2$ (100%)	<1 min
5	Me$_2$SO	0.17	0.05	KOH (1.33)	t-BuOH (100%) / Me$_2$SO$_2$ (100%)	<1 min
6	Toluene	0.17	0.05	KO$_2$ (1.33)	No reaction[b]	3 days
7	Me$_2$SO	0.17	0.05	K$_2$CO$_3$ (1.33)	t-BuOH, ca. 50%	1 day
8	Toluene[c]	0.5	0.5	K$_2$CO$_3$ (1.0)	No reaction	6 days
9	Me$_2$SO[c]	0.5	0.5	K$_2$CO$_3$ (1.0)	t-BuOH, ca. 30%	6 min
10	Me$_2$SO	0.17[d] (ROOR)	0.05	KO$_2$ (1.33)	No reaction	5 days

[a] 2.0 ml. [b] *tert*-Butyl hydroperoxide recovered quantitatively. [c] Concentrations as in Johnson and Nidy.[5] [d] Di-*tert*-butyl peroxide.

Scheme I

$$CH_3SCH_3 + ROO^- \rightleftharpoons CH_3SCH_3(O^-)(OOR) \quad (3)$$

$$CH_3SCH_3(O^-)(OOR) \longrightarrow CH_3SCH_3(O) + RO^- \quad (4)$$

or

$$CH_3SCH_3(O^-)(O{-}OR)(H{-}A) \longrightarrow CH_3SCH_3(O) + ROH + A^- \quad (5)$$

there is present 1 molar equiv of protium from hydroperoxide.

In our studies with KO$_2$ and crown ether, O$_2$·$^-$ seems to perform the same chemistry with *tert*-butyl hydroperoxide that bases do. This does not eliminate the possibility of an electron transfer path having occurred via a Haber–Weiss type process.[14]

$$ROOH + O_2\cdot^- \longrightarrow RO\cdot + OH^- + O_2$$
$$(\text{or } RO^- + OH\cdot,\ \text{somewhat less exothermic})$$
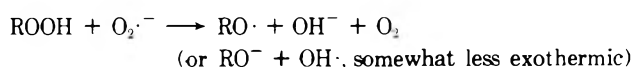
This does not occur in toluene, however, nor with di-*tert*-butyl peroxide, as shown above. It is certainly not likely to occur between ROO$^-$ and superoxide (two anions).

The KO$_2$–crown ether–alkyl halide reaction may be rather complex. The overall mechanism basically proposed by Dietz et al.[3b] is shown in somewhat expanded form in Scheme II.

Scheme II

$$O_2\cdot^- + RX \longrightarrow RO_2\cdot + X^- \quad (6)$$
$$\longrightarrow R(-H) + HO_2\cdot + X^- \quad (7)$$
$$(\text{olefin})$$
$$HO_2\cdot \rightleftharpoons H^+ + O_2\cdot^- \quad (8)$$
$$HO_2\cdot + O_2\cdot^- \longrightarrow HO_2^- + O_2 \quad (9)$$
$$RO_2\cdot + O_2\cdot^- \longrightarrow RO_2^- + O_2 \quad (10)$$
$$RO_2^- + RX \longrightarrow RO_2R + X^- \quad (11)$$
$$(H^+) + RO_2^- + Me_2SO \longrightarrow ROH + Me_2SO_2 \quad (12)$$
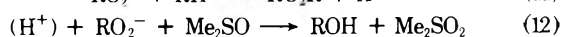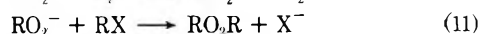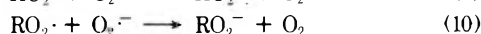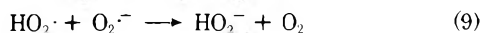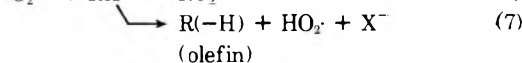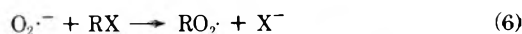
(eq 12 is the sum of eq 3 and eq 4 or 5)

The initial steps (eq 6 and 7) seem well proven by the stereochemical and competitive kinetic data. The HOO· formed in eq 7 may then ionize to superoxide (eq 8) or disproportionate via eq 9. In protic solvent HOO$^-$ can lead to OH·, a very facile oxidizing agent.[15] Equation 10 is the analogue to eq 9 for alkyl

peroxy radical, and is equally exothermic, perhaps diffusion controlled. Finally, the peroxy anion formed in this step can undergo reactions 11 or 12, leading to products.

The displacement of halide by peroxide anion (eq 11) is quite facile,[16] occurring in water with a second-order rate constant roughly 50 times that of attack by hydroxide.[17] The effect of crown ether plus aprotic polar solvent ("naked anions"[18]) should be an enhancement of rate.
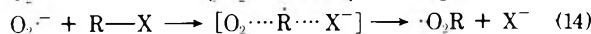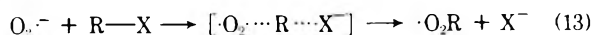
We have performed experiments with *n*-octyl bromide included in the usual reaction medium (Me$_2$SO, 0.17 M *t*-BuOOH, 0.05 M 18-crown-6, 1.33 mmol K$_2$CO$_3$, with 0.17–0.33 M *n*-C$_8$H$_{17}$Br). The *tert*-butyl alcohol was partially depleted by a new product which grew as *tert*-butyl hydroperoxide was lost, and had reasonable retention time for the mixed *tert*-butyl *n*-octyl peroxide. At completion, the relative peak areas indicated a ratio of attack on Me$_2$SO to that on *n*-C$_8$H$_{17}$Br of between 4.1 and 4.8 (small amounts of octene were observed). Thus, the competition between eq 11 and 12 occurs, and favors eq 12 under conditions usually used in these studies.

One other side process that could give rise to alcohol in the superoxide system in Me$_2$SO is attack by ROO· upon solvent to give alcohol and Me$_2$SO$_2$.

$$ROO\cdot + Me_2SO \longrightarrow RO\cdot + Me_2SO_2$$
$$\xrightarrow{X-H} ROH$$
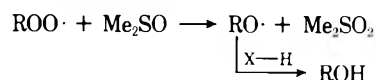
This is analogous to known processes,[19] but does not seem to have been reported for sulfoxides.

While the overall scheme is certainly reasonable and the order of reactivities of a series of halides shows a correlation with normal S$_N$ leaving group abilities (eq 6),[20] the relative rates for different alkyl groups are not very sensitive to structure. Both relative rate comparisons and a direct competitive study agreed that tertiary halides are about as reactive as secondary, these only about fourfold less than primary. This is a quite flat distribution for a real S$_N$2 process,[20] and may indicate a strong contribution of an electron-transfer character (eq 13 vs. 14)

$$O_2\cdot^- + R{-}X \longrightarrow [\cdot O_2 \cdots R \cdots X^-] \longrightarrow \cdot O_2R + X^- \quad (13)$$
$$O_2\cdot^- + R{-}X \longrightarrow [O_2 \cdots \dot{R} \cdots X^-] \longrightarrow \cdot O_2R + X^- \quad (14)$$

or perhaps even the electron-transfer followed by radical coupling mechanism (eq 15).
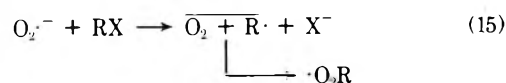
$$O_2\cdot^- + RX \longrightarrow \overline{O_2 + R}\cdot + X^- \quad (15)$$
$$\longrightarrow \cdot O_2R$$

References and Notes

(1) Supported by the National Science Foundation, Grant BMS 71-03481.
(2) I. Fridovich, *Acc. Chem. Res.*, **5**, 321 (1972); I. Fridovich, *Annu. Rev. Biochem.*, **44**, 147 (1975), and references cited therein.
(3) (a) M. V. Merritt and D. T. Sawyer, *J. Org. Chem.*, **35**, 2157 (1970); (b) R. Dietz, E. J. Forno, B. E. Larcombe, and M. E. Peover, *J. Chem. Soc. B*, 816 (1970).
(4) J. San Filippo, Jr., C. I. Chern, and J. S. Valentine, *J. Org. Chem.*, **40**, 1678 (1975).
(5) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975).
(6) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
(7) Primary and secondary dialkyl peroxides are known to react with bases under these usual conditions, but probably too slowly to account for the results in ref 4. See R. Hiatt in "Organic Peroxides", Vol. III, D. Swern, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 1, p 23.
(8) The pK_a values in Me_2SO for the various species under consideration here are not known; in water the values are 4.5, 11.5, and 16 for $\cdot O_2H$, RO_2H, and ROH, respectively. It is not unlikely that this order and approximate relative acidities are maintained in Me_2SO; in acetonitrile the value of $pK_a(H_2O) - pK_a(CH_3CN)$ is quite constant for a series of ionizations involving the same ionizing groups or atoms. A. J. Parker, *Adv. Phys. Org. Chem.*, **5**, 173 (1967).
(9) For a review, see "Dimethyl Sulfoxide", S. W. Jacob, E. E. Rosenbaum, and D. C. Wood, Ed., Marcel Dekker, New York, N.Y., 1971, p 78 ff.
(10) T. M. Santosusso, R. D. Slockett, and D. Swern, *Q. Rep. Sulfur Chem.*, **3**, 187 (1968).
(11) K. R. Hargrave, *Proc. R. Soc. London, Ser. A*, **235**, 55 (1956).
(12) L. Kuhnen, *Angew. Chem., Int. Ed. Engl.*, **5**, 893 (1966).
(13) G. A. Russell and A. G. Bemis, *J. Am. Chem. Soc.*, **88**, 5491 (1966).
(14) Indeed, after submission of this manuscript, evidence for such a process in acetonitrile was presented using the soluble $(CH_3)_4N^+O_2$ salt. As shown above, this does not take place with KO_2-crown ether in toluene. J. W. Peters and C. S. Foote, *J. Am. Chem. Soc.*, **98**, 873 (1976).
(15) C. Walling, *Acc. Chem. Res.*, **8**, 125 (1975).
(16) J. E. McIsaac, Jr., L. R. Subbaraman, J. Subbaraman, H. A. Mulhausen, and E. J. Behrman, *J. Org. Chem.*, **37**, 1037 (1972).
(17) N. A. Radomsky and M. J. Gibian, *J. Am. Chem. Soc.*, **95**, 8713 (1973).
(18) E.g., C. L. Liotta and H. P. Harris, *J. Am. Chem. Soc.*, **96**, 2250 (1974).
(19) S. A. Buckler, *J. Am. Chem. Soc.*, **84**, 3093 (1962). This discusses the well-known reaction for phosphorus compounds.
(20) A. Streitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962.

A Convenient Synthesis of *o*- and *p*-Hydroxy Substituted Phenylacetonitriles and Phenethylamines

Martin A. Schwartz,* Michael Zoda, Baburao Vishnuvajjala, and Ismail Mami

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

During the course of work in isoquinoline alkaloid synthesis,[1] we required relatively large quantities of phenolic β-phenethylamines. The most direct route to these compounds is by high-pressure catalytic hydrogenation[2] or lithium aluminum hydride reduction[3] of the corresponding phenolic β-nitrostyrenes, but both of these procedures gave very variable results in our hands. Since nitriles can be smoothly reduced to amines, we sought a method for preparing phenolic phenylacetonitriles without the usual necessity of blocking the phenolic hydroxyl groups.

Ours and co-workers[4] have reported the conversion of phenolic benzylamines to the corresponding phenolic phenylacetonitriles by direct displacement with cyanide ion, presumably by way of quinone methide intermediates. Based on our previous success in using 4-hydroxybenzyl alcohols as incipient quinone methides,[5] it seemed to us that the more readily available benzyl alcohols would constitute even more convenient precursors to the desired nitriles.

As indicated by the results summarized in Table I, 2- and 4-hydroxybenzyl alcohols were smoothly converted to the nitriles by treatment with sodium cyanide in hot dimethylformamide. The 2-hydroxybenzyl case is particularly noteworthy in view of the poor results previously obtained with the analogous 2-hydroxybenzylamines.[4] Both 3-hydroxy-4-

Table I. Preparation of Phenylacetonitriles and Phenethylamines

$$ArCH_2OH \xrightarrow[\text{DMF, 110 °C}]{\text{NaCN}} ArCH_2C\equiv N \xrightarrow[\text{HCl}]{H_2,\ Pd/C}$$

1 2

$$ArCH_2CH_2NH_2 \cdot HCl$$

3

1 Ar	2 Yield, %	2 Mp, °C	3 Yield, %	3 Mp, °C
4-Hydroxyphenyl	67	69–71[a]		
2-Hydroxyphenyl	60	115–118[b]	87	152–154[c]
4-Hydroxy-3-methoxyphenyl	79	53–56[d]	91	213–216[e]
3-Hydroxy-4-methoxyphenyl	0			
3,4,5-Trimethoxyphenyl	0			

[a] Lit.[6] mp 70–71.5 °C. [b] Lit.[6] mp 120–122 °C. [c] Lit.[7] mp 152 °C. [d] Bp 135–140 °C (0.05 mm) [lit.[4] bp 140–144 °C (0.1 mm)]; a melting point for this compound has apparently not been previously reported. [e] Lit.[2,4] mp 212–214 °C.

methoxybenzyl alcohol and 3,4,5-trimethoxybenzyl alcohol were recovered unchanged under these conditions and under a variety of more vigorous conditions, results that are in consonance with the postulated intermediacy of quinone methides in the substitution reaction.

A similar procedure applied to 2- and 4-acetoxybenzyl acetate has been recently reported.[6]

Experimental Section

Melting points were measured on a Kofler hot stage and are uncorrected. The benzyl alcohols were obtained from Aldrich Chemical Co., or were prepared by $NaBH_4$ reduction of the corresponding benzaldehydes. See Table I for melting points of the products and comparisons with literature values.

4-Hydroxyphenylacetonitrile. A mixture of 2.02 g (16.3 mmol) of 4-hydroxybenzyl alcohol and 965 mg (19.7 mmol) of NaCN in 50 ml of DMF was stirred under nitrogen at 110–130 °C (oil bath) for 20 h. The solution was cooled to room temperature, 10 ml of water was added, and the mixture was basicified with solid NaOH to pH ~10. The solvent was evaporated under vacuum, 25 ml of water was added, and the solution was neutralized with glacial acetic acid (*Caution —* HCN). The mixture was extracted with $CHCl_3$, and the combined organic extracts were washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residual orange oil was subjected to molecular distillation at 75–80 °C (0.04 mm) to afford 1.46 g (11.0 mmol) of the nitrile as a white solid.

2-Hydroxyphenylacetonitrile. The same procedure was followed using 1.01 g (8.15 mmol) of 2-hydroxybenzyl alcohol, 483 mg (9.86 mmol) of NaCN, and 25 ml of DMF, with heating for 7 h. Molecular distillation of the crude product at 75–80 °C (0.02 mm) yielded 647 mg (4.86 mmol) of the nitrile as an off-white solid.

4-Hydroxy-3-methoxyphenylacetonitrile. The same procedure was followed using 30.8 g (0.200 mol) of 4-hydroxy-3-methoxybenzyl alcohol, 11.8 g (0.241 mol) of NaCN, and 500 ml of DMF, with heating for 6 h. Vacuum distillation of the crude product afforded 25.7 g (0.158 mol) of the nitrile as a colorless oil which solidified upon standing in the refrigerator.

2-Hydroxyphenethylamine Hydrochloride. To a solution of 717 mg (5.39 mmol) of 2-hydroxyphenylacetonitrile in 25 ml of 95% ethanol and 1 ml of concentrated HCl was added 275 mg of 10% Pd/C, and the mixture was hydrogenated at 40 psi in a Parr shaker apparatus for 10 h at room temperature. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residual yellow oil was crystallized from ethanol–ether to give 815 mg (4.71 mmol) of the amine hydrochloride as off-white crystals.

4-Hydroxy-3-methoxyphenethylamine Hydrochloride. The above procedure was followed using 10.0 g (0.0613 mol) of 4-hydroxy-3-methoxyphenethylamine Hydrochloride, 10 ml of concentrated HCl, 2.0 g of 10% Pd/C, and 150 ml of 95% ethanol. The residual solid was re-

crystallized from methanol–ethyl acetate to afford 11.3 g (0.0557 mol) of amine salt as off-white crystals.

Registry No.—4-Hydroxyphenylacetonitrile, 14191-95-8; 4-hydroxybenzyl alcohol, 623-05-2; 2-hydroxyphenylacetonitrile, 14714-50-2; 2-hydroxybenzyl alcohol, 90-01-7; 4-hydroxy-3-methoxyphenylacetonitrile, 4468-59-1; 4-hydroxy-3-methoxybenzyl alcohol, 498-00-0; 2-hydroxyphenethylamine HCl, 5136-97-0; 4-hydroxy-3-methoxyphenethylamine HCl, 1477-68-5; NaCN, 143-33-9.

References and Notes

(1) See, for example M. A. Schwartz and I. S. Mami, *J. Am. Chem. Soc.,* **97,** 1239 (1975).
(2) A. Brossi, J. Van Burik, and S. Teitel, *Helv. Chim. Acta,* **51,** 1965 (1968).
(3) F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.,* **72,** 2781 (1950).
(4) J. H. Short, D. A. Dunnigan, and C. W. Ours, *Tetrahedron,* **29,** 1931 (1973).
(5) M. A. Schwartz and S. W. Scott, *J. Org. Chem.,* **36,** 1827 (1971).
(6) H. Hayashi and S. Oka, *Bull. Inst. Chem. Res., Kyoto Univ.,* **52,** 517 (1974).
(7) T. Kondo and S. Tanaka, *J. Pharm. Soc. Jpn.,* **52,** 608 (1932).

Communications

Organoselenium Chemistry. Intra- and Intermolecular Trapping of Selenenic Acids Formed by Selenoxide Elimination. Formation of a Selenium Ylide

Summary: The thermal decomposition of 3,3-dimethyldihydrobenzoselenophene oxide (1) leads to an unstable intermediate selenenic acid, which is trapped intramolecularly to give hydroxyselenides (2 and 3) or intermolecularly with diethylamine or benzyl bromide to give a selenenamide or selenoxide.

Sir: We report here the thermolysis of the selenoxide 1,[1] which exhibits several striking departures from the behavior of re-

1
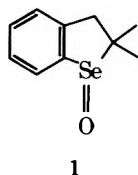
lated sulfur compounds.[3] Compound 1 decomposes at room temperature, rapidly in organic solvents, slowly in aqueous solution, giving the alcohols 2 and 3. Similar results are obtained in acidic (acetic acid–dichloromethane, aqueous HCl) or weakly basic (triethylamine– or 1,8-bis(dimethylamino)-naphthalene–dichloromethane, aqueous Na$_2$CO$_3$) media.

The thermal transformations of 1 are probably initiated by selenoxide syn elimination[4] to selenenic acid 4a. Evidence for

4a, X = OH
 b, X = NEt$_2$
 c, X = CH$_3$
 d, X = ArSeO
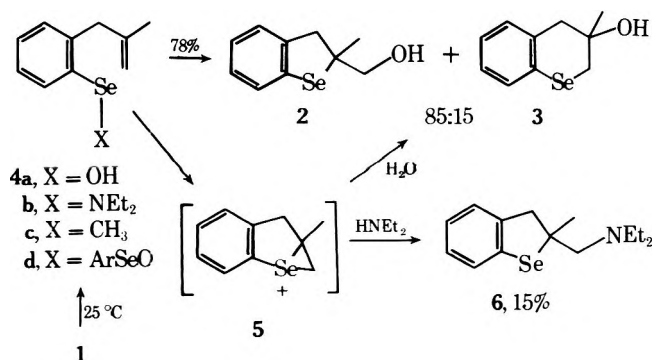
a ring-opened intermediate was obtained by the formation of selenenamide 4b when 1 was decomposed in the presence of excess diethylamine. The selenenamide was characterized spectroscopically,[5] but could not be isolated in pure form. Reduction (LiAlH$_4$) and methylation of 4b gave the stable selenide 4c. N,N-Dialkylbenzeneselenenamides have been prepared previously by trapping of selenenic acids with

amines.[6] Acyclic products were also obtained when decomposition was carried out with strong base and an alkylating agent present (see below). These results are accommodated by a mechanism in which a reactive intermediate (either 4a or, more probably, the selenenic anhydride[7] 4d, RSeOSeR or RSe(O)SeR) is trapped either intramolecularly by the olefin, leading to 2 and 3 via an episelenonium ion (5),[8] or intermolecularly by amine, with both of these processes being more rapid than the normal disproportionation to diselenide and seleninic acid. Diisopropylamine is evidently too hindered to compete effectively with olefin, since in its presence 1 decomposes to 2 and 3 giving no selenenamide. The selenenamide 4b in the presence of excess diethylamine slowly isomerizes to 6 in low yield, presumably by reversible hydrolysis to 4a or 4d, cyclization to 5, and capture by amine.[9]

The behavior of 1 is in sharp contrast to the chemistry observed for related sulfur systems. β-Oxygenated sulfides are formed from sulfenic acids, but only in the presence of electrophiles (typically acetic anhydride or acetic acid).[3c,d] In the present study, products of electrophilic double-bond addition (2, 3, and 6) are observed even under basic conditions.

When the decomposition of 1 is carried out in acidic or basic D$_2$O to test for reversibility of the ring opening, no deuterium incorporation in 2 and 3 could be detected. This demonstrates that the *selenenic acid does not revert to selenoxide* competetively with further transformation. A number of sulfoxide syn eliminations have been shown to be highly reversible under neutral conditions.[3b–h] Even intermolecular olefin additions of sulfenic acids to give sulfoxides can frequently be observed.[3b,h] We have carried out the decomposition of 1 in the presence of ethyl propiolate, phenylacetylene, norbornadiene, or dihydropyran, but have seen no indication of intermolecular reaction with 4a.

Dimethyl acetylenedicarboxylate reacted rapidly with 1. The adduct was not the vinyl selenoxide expected from addition of selenenic acid,[3h] but, rather, the ylide 7 formed by

7
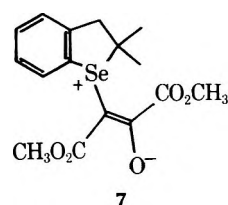
direct reaction with selenoxide 1. Similar ylides have been formed from sulfoxides[10] (although at 100 rather than at 0 °C), as well as from phosphine imides.[11] The much greater rate of

reaction of selenoxides compared with that of sulfoxides is reasonably accounted for by the 4–5 pK_a greater basicity of selenoxides.[12] The spectroscopic and analytic properties of **7** are fully compatible with the proposed structure and with the data obtained for analogous sulfur and phosphorus ylides. In particular, the *gem*-dimethyls are diastereotopic and show ^{77}Se–H and ^{77}Se–^{13}C coupling in the proton and carbon NMR spectra,[13] proving that geometry at selenium is pyramidal, and that the five-membered ring is intact.

Decomposition of **1** in the presence of a strong base and an alkylating agent such as benzyl bromide results in the formation of benzyl selenoxide **8**, presumably by Se alkylation
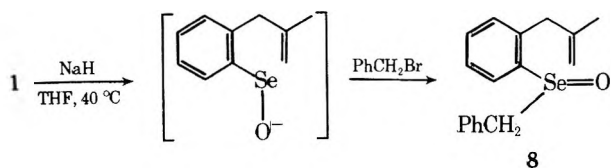
of the selenenate ion.[14] This result suggests that the transformation of halides or sulfonates to olefins could be carried out by a selenenate alkylation–selenoxide elimination sequence, perhaps even in a catalytic fashion.

Only a few selenenic acids with special substitution have been isolated and characterized.[15] The results reported here, together with previous studies of selenenamide chemistry,[6] point to the emergence of significant differences between selenenic acids and their sulfur analogues.

Acknowledgment. The donors of the Petroleum Research Fund, administered by the American Chemical Society, provided support for this work. We thank David Ting for technical assistance.

References and Notes

(1) Prepared by ozonolysis of the selenide, which was prepared from phenyl methallyl selenide by pyrolysis in quinoline.[2]
(2) E. G. Kataev, G. A. Chmutova, A. A. Musina, and A. P. Anastas'eva, *Zh. Org. Khim.*, **3**, 597 (1967); **8**, 1531 (1972).
(3) (a) J. E. Baldwin, G. Hofle, and S. C. Choi, *J. Am. Chem. Soc.*, **93**, 2810 (1971). (b) J. R. Shelton and K. E. Davis, *Int. J. Sulfur Chem.*, **8**, 205 (1973). (c) A. K. Mukerjee and A. K. Singh, *Synthesis*, 547 (1975), and references therein. (d) Y. Makisumi, S. Takada, and Y. Matsukura, *Chem. Commun.*, 850 (1974); R. B. Morin, D. O. Spry, and R. A. Mueller, *Tetrahedron Lett.*, 849 (1969). (e) R. J. Stoodley and R. B. Wilkins, *J. Chem. Soc., Perkin Trans. 1*, 1572 (1974). (f) D. N. Jones and D. A. Lewton, *Chem. Commun.*, 457 (1974); D. N. Jones, *Tetrahedron Lett.*, 2235 (1975). (g) E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3929 (1974). (h) D. H. R. Barton, et al., *J. Chem. Soc., Perkin Trans. 1*, 1187 (1973).
(4) (a) D. N. Jones, D. Mundy, and R. D. Whitehouse, *Chem. Commun.*, 86 (1970); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
(5) Proton NMR: 1.13 (t, *J* = 7 Hz, 6 H), 1.69 (s, 3 H), 3.08 (q, *J* = 7 Hz, 4 H), 3.28 (s, 2 H), 4.59 (br s, 1 H), 4.80 (br s, 1 H), 7.08 (m, 3 H), 7.75 (m, 1 H). Carbon NMR: 14.26, 54.11 (NEt), 22.46 (CH₃), 43.22 (CH₂), 112.73 (CH₂=C), 125.80, 126.59, 128.08, 129.73, 137.03 (q), 137.18 (q), 143.64 (q) (aryl, vinyl C).
(6) H. J. Reich and J. M. Renga, *J. Org. Chem.*, **40**, 3313 (1975).
(7) Sulfenic anhydrides (thiolsulfinates) are formed during the disproportionation of sulfenic acids.[3a,b,9]
(8) H. J. Reich and J. E. Trend, *Can. J. Chem.*, **53**, 1922 (1975); G. H. Schmid and D. G. Garratt, *Tetrahedron Lett.*, 3991 (1975); H. J. Reich, *J. Org. Chem.*, **39**, 428 (1974); K. B. Sharpless and R. F. Lauer, *ibid.*, **39**, 429 (1974).
(9) *N,N*-Dimethylbenzeneselenenamide does not react with cyclohexene under anhydrous conditions.[6]
(10) E. Winterfeldt, *Chem. Ber.*, **98**, 1581 (1965).
(11) E. M. Briggs, G. W. Brown, W. T. Dawson, and J. Tirieny, *Chem. Commun.*, 641 (1975).
(12) The pK_a of selenolane oxide is 3.3 (H. J. Reich, J. E. Trend, unpublished results). The pK_a of thiolane oxide is −1.34 [R. Curci, F. DiFuria, A. Levi, V. Lucchini, and G. Scorrano, *J. Chem. Soc., Perkin Trans. 2*, 341 (1975)].
(13) H. J. Reich and J. E. Trend, *Chem. Commun.*, 57 (1975).
(14) A significant amount of the benzyl selenide is also formed by some reductive process. Selenenic acids have not previously been alkylated. Sulfenic acid anions undergo O or S alkylation depending on alkylating agent: D. R. Hogg and A. Robertson, *Tetrahedron Lett.*, 3783 (1974); G. A. Koppel and S. Kukolja, *Chem. Commun.*, 57 (1975).
(15) (a) H. Rheinboldt and E. Giesbrecht, *Chem. Ber.*, **88**, 666, 1037, 1974 (1955); **89**, 631 (1956). (b) W. Jenny, *Helv. Chim. Acta*, **41**, 317, 326 (1958). (c) D. L. Klayman and J. W. Lown, *J. Org. Chem.*, **31**, 3396 (1966). (d) O.

Behagel and W. Müller, *Chem. Ber.*, **67B**, 105 (1934); **68**, 1540 (1935).
(16) Alfred P. Sloan Fellow, 1975–1977.

Hans J. Reich,*[16] John E. Trend

*Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706*

Received April 2, 1976

1,2-Diamination of 1,3-Dienes by Imido Selenium Compounds

Summary: Solutions thought to contain the selenium diimide species **3** (TsN=Se=NTs) react with 1,3-dienes to produce 1,2-disulfonamides. In the case of 1,3-cyclohexadiene the sulfonamide groups are introduced cis to each other.

Sir: We have reported that aza analogues (**1** and **3**) of both selenium dioxide[1] and sulfur dioxide[2,3] effect allylic amination
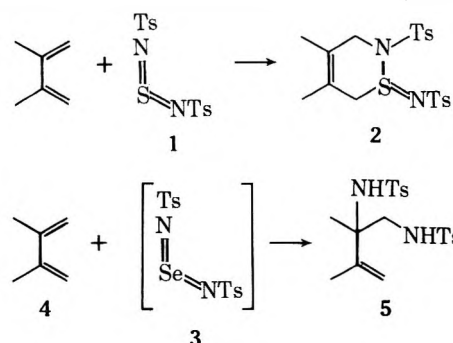
of olefins. Since it is well known that the imides of sulfur dioxide (e.g., **1**) readily undergo cycloadditions with dienes to produce stable [4 + 2] adducts (e.g., **2**),[4] we attempted to trap the putative selenodiimide intermediate **3** as its [4 + 2] adduct with 2,3-dimethylbutadiene (**4**). However, only the vicinal disulfonamide **5** could be isolated. This reaction was found to occur with a variety of 1,3-dienes (Table I), and is envisioned as proceeding through the pathway shown in Scheme I for 1,3-cyclohexadiene (**6**). In support of this path-

Scheme I
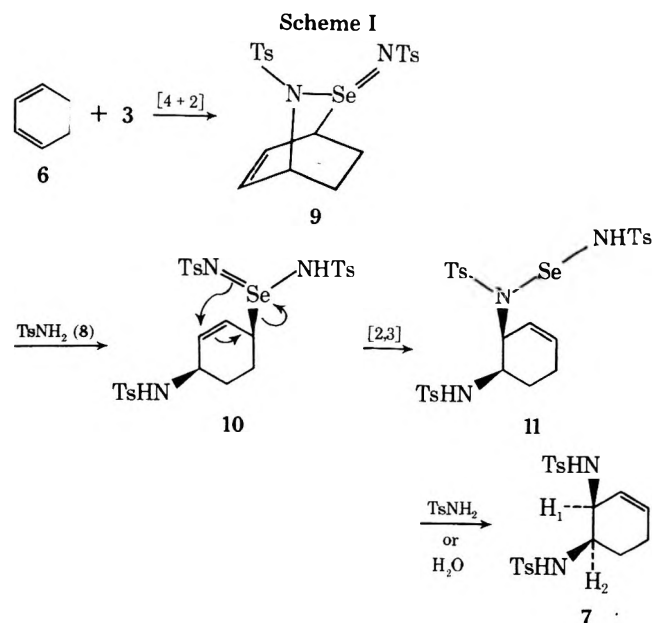
way, hydrogenation (PtO₂, 5 psi H₂ pressure, EtOAc) of the product, disulfonamide **7**,[5a] gave only *cis*-1,2-di(*p*-toluenesulfonamido)cyclohexane.[5b] Exclusive cis stereochemistry

Table I. 1,2-Diamination of 1,3-Dienes[a]

Case	Diene	Equiv of 3	Equiv of TsNH₂ (10)	Products[b]	% yield[c]
1	(structure)	1.1	1.1	—NHTs / —NHTs (136)	68
2	(structure)	1.1	0	—NHTs / —NHTs (136)	4
3	(structure)	2.5	0	—NHTs / —NHTs (136)	61
4	(structure)	3.75	3.75	NHTs / NHTs (158–159)	37
5	(structure)	1.25	1.25	NHTs / NHTs (158–159)	29
6	(structure)	2.5	0	NHTs / NHTs (158–159)	15
7	(structure)	1.1	0	NHTs / NHTs (158–159)	0
8	(structure)	1.1	1.1	NHTs[d] / NHTs (142.5)	40
9	(structure)	1.1	1.1	NHTs 12 (113.5)	52
10	(structure)	1.1	1.1	NHTs / —NHTs (144–145)	26
				TsHN— / TsHN— 8	
11	Ph (structure)	1.1	1.1	Ph NHTs / —NHTs (157)	45
				Ph / TsHN— / TsHN— 8	
12	(structure)	1.1	1.1	NHTs / NHTs (150)	37
				NHTs / —NHTs 4	

[a] All reactions were run on a 10-mmol scale as described in the general procedure. [b] The melting point (°C) appears in parentheses below the structure. [c] In the case of solid products the yields are for recrystallized substances. When no melting point is given, the substance was an oil, and the yield is for chromatographically pure material. [d] The stereochemistry is assumed to be cis by analogy with the 1,3-cyclohexadiene case.

is expected in cyclic systems since all steps must occur on the same face of the molecule. Addition of an equivalent of p-toluenesulfonamide (8) during reagent generation resulted in greatly improved yields of the 1,2-disulfonamides (e.g., cases 1 and 2 in Table I). The p-toluenesulfonamide is presumed to effect cleavage of the seleninolactam 9 to the intermediate 10, which is then able to undergo [2,3] rearrangement[6] leading, via selenium(II) amide 11, to the observed products. In the

absence of nucleophiles such as sulfonamide 8, lactam 9 seems to decompose to a variety of selenium containing compounds. The reagent 3 is generated from anhydrous Chloramine-T which probably always contains traces of p-toluenesulfonamide. This would account for the formation of some vicinal diamide even when sulfonamide is not intentionally added (cases 2, 3, 6, and 7 of Table I).

A seleninolactone analogous to lactam intermediates of type 9 was isolated by Mock upon reaction of dimethylbutadiene 4 with selenium dioxide.[7,8] It seemed likely that under aqueous conditions such lactones should undergo hydrolysis and [2,3] rearrangement to 1,2-diol products in a manner analogous to that proposed for formation of the 1,2-disulfonamides (7) in Scheme I. In support of this reasoning, reaction of cyclohexadiene 6 with 1 equiv of selenium dioxide in aqueous *tert*-butyl alcohol gave *cis*-3,4-dihydroxycyclohexene[9] (22% yield) as the only nonselenium containing organic product.

Even though no diene remains after a few hours, examination of Table I reveals that the yields of disulfonamide are generally only poor to fair. Polar, uncharacterized by-products were formed in most cases; however, these were easily removed by chromatography on alumina. Interestingly, 1,3-cyclooctadiene (case 9) gave the allylic sulfonamide 12 as the only isolated product; in this instance the ene reaction[1] takes precedence over the [4 + 2] cycloaddition.[10]

General Procedure. A silver-gray slurry of the reagent was prepared by stirring a mixture of 1.08 g (13.6 mg-atoms) of powdered selenium metal, 5.69 g (25 mmol) of anhydrous[11] Chloramine-T, and 2.14 g (12.5 mmol) of dry[11] p-toluenesulfonamide in 50 ml of dry[11] methylene chloride under nitrogen for 15 h at room temperature.[12] The diene (10 mmol) was added and stirring was continued overnight. Water (20 ml) was added and, after stirring for 15 min, the dark reaction mixture was poured into 100 ml of 1:1 ethyl acetate/ether and 100 ml of 1:1 4% NaOH/brine. After filtering through Celite, the organic phase was washed twice with 1:1 4% NaOH/brine to remove the residual sulfonamide, then once with brine, and finally was dried (MgSO₄) and concentrated to afford the crude product. The products were isolated by chromatography on 250 g of activity III (6% H₂O) basic alumina using hexane/EtOAc mixtures as eluent. The products were recrystallized from either CHCl₃/hexane or acetone/hexane. All new compounds gave consistent analytical and spectral data.

References and Notes

(1) K. B. Sharpless, T. Hori, L. K. Truesdale, and C. O. Dietrich, *J. Am. Chem. Soc.*, **98**, 269 (1976).
(2) K. B. Sharpless and T. Hori, *J. Org. Chem.*, **41**, 176 (1976).
(3) Kresze has also recently reported the ene reaction of sulfur diimides with olefins [N. Schönberger and G. Kresze, *Justus Liebigs Ann. Chem.*, 1725 (1975)].
(4) G. Kresze and W. Wucherpfennig, *Angew. Chem., Int. Ed. Engl.*, **6**, 149 (1967).
(5) (a) Results from NMR decoupling experiments are consistent with the proposed cis relationship between the sulfonamide groups in 7 ($J_{1,2}$ = 4 Hz in CDCl₃ containing 0.1 N NaOD/D₂O). (b) Its identity was established by comparison with an authentic sample prepared by reaction of *cis*-1,2-diaminocyclohexane [A. I. Smith, U.S. Patent 3 167 586 (1965)] with excess p-toluenesulfonyl chloride in pyridine.
(6) A [2,3]rearrangement of the corresponding sulfur(IV) species is described in ref 2.
(7) W. L. Mock and J. H. McCausland, *Tetrahedron Lett.*, 391 (1968).
(8) Other similar seleninolactones have been isolated recently [D. Arigoni, A. Vasella, K. B. Sharpless, and H. P. Jensen, *J. Am. Chem. Soc.*, **95**, 7917 (1973)].
(9) H. Z. Sable et al., *Tetrahedron*, **26**, 1509 (1970).
the dienophile [O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31**, 3862 (1966)].
(11) Anhydrous Chloramine-T is available from Aldrich (see also ref 1). The p-toluenesulfonamide was dried at 80° under high vacuum for 12 hr. The methylene chloride was passed through neutral activity I alumina and stored over 4Å molecular sieves.
(12) At this time, the exact nature of the reactive species present in the slurry in not known. However, this reagent, formed in the presence of an equivalent of TsNH₂, is different from the reagent (ref 1) formed in the absence of sulfonamide. It seems to form more rapidly, and the resulting suspension

has a silver-gray luster. When cyclohexene was treated with 1.25 equiv of this new reagent, the allylic sulfonamide was obtained in somewhat improved yield (~10% better than using 1.25 equiv of the reagent in ref 1). However, when only 0.63 equiv of this new reagent was employed, it gave the same yield of allylic amide as did 0.63 equiv of the original reagent (ref 1). Further comparisons are needed, but it appears that this modified reagent may also be useful for the allylic aminations of olefins.

K. Barry Sharpless,* Stephen P. Singer

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received February 18, 1976

Preparative Methods for β-Acyl Vinyl Anion Equivalents from Enones or Allyl Sulfides

Summary: The treatment of many α,β-unsaturated aldehydes and ketones with triphenyl thioborate provides the 1,3-bis-(phenylthio)alkene derivatives, the anions of which are shown to be effective β-acyl vinyl anion equivalents.

Sir: We wish to report that a variety of α,β-unsaturated aldehydes and ketones (1) can be converted directly to their 1,3-bis(phenylthio)alkene derivatives (2) by heating in hy-

$$R_2CH=C(R_1)COR_3 \xrightarrow{B(SPh)_3} PhSCH(R_2)C(R_1)=C(SPh)R_3 \quad (1)$$
$$\mathbf{1} \qquad\qquad\qquad \mathbf{2}$$

drocarbon solvents with triphenyl thioborate (eq 1);[1] this reagent is readily prepared from B_2S_3 and thiophenol.[4] Several examples are given in Table I.
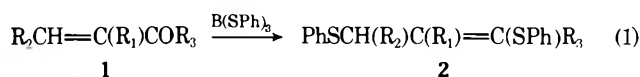
This simple reaction gives a poor yield with acrolein and fails completely with methyl vinyl ketone.[5] Fortunately, the desired products from both reactions can be prepared by alternative routes. That (4, R = H) from acrolein can be prepared from phenyl allyl sulfide (3, R = H; commercially available) by the sequence in Scheme I; as pointed out else-

Scheme I

where,[6] the chlorination is faster with the far less expensive reagent trichloroisocyanuric acid (Chloreal), but N-chlorosuccinimide can be used.[7] The bis(phenylthio) derivative (4, R = Me) of methacrolein can be prepared in a similar fashion; this sequence has been performed on a 20-g scale. The product 7, expected from methyl vinyl ketone (5), can be prepared from the latter by treatment with thiophenol and HCl, followed by elimination of thiophenol from the condensation product (6) by cuprous trifluoromethanesulfonate (triflate)[8] (Scheme II).[9]
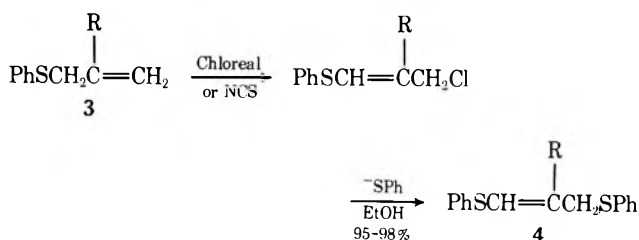
Scheme II
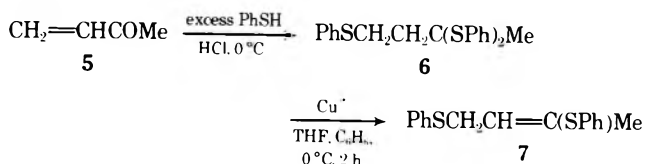
Table I. Reactions of Enones with Triphenyl Thioborate[a]

R_1[b]	R_2[b]	R_3[b]	% yield of **8**[c]
H	$CH_2CH_2CH_2$		78
H	CH_2CH_2		43
$CH_2CH_2CH_2CH_2$		Me	50[d,e]
H	Me	H	66[f]
Me	H	H	70[g]
H	H	H	35
H	H	Me	h

[a] Satisfactory spectral and elemental analyses were obtained on all new compounds. [b] Refers to eq 1. [c] In a typical run, 9.3 mmol of 1 was heated with 6.2 mmol of B(SPh)$_3$ at 50 °C in petroleum ether (60–110 °C) for 15 h; removal of the precipitate by filtration and evaporation of the solvent provide the isolated yields recorded. [d] Reaction performed at 150 °C for 24 h in a sealed tube; no product was obtained at 50 °C. [e] Cis–trans mixture. [f] 75% trans. [g] 50% trans. [h] Only 4-phenylthio-2-butanone produced.

Table II. Reactions of Bis(phenylthio)allyl Anions with Alkyl Halides[a]

$$PhSCH(R_2)C(R_1)=C(SPh)R_3 \xrightarrow[\substack{2.\ RX}]{\substack{1.\ sec\text{-BuLi, THF,}\\ -20\ °C,\ 45\ min}} PhSC(R_2)(R)CR_1=C(SPh)R_3$$

R_1	R_2	R_3	RX	% yield
H	H	H	MeI	98
H	H	H	i-BuI	98
Me	H	H	MeI	94
Me	H	H	n-BuI	98
Me	H	H		94
H	$CH_2CH_2CH_2$[b]		MeI	90
H	Me[b]	H	MeI	98[c]
H	H	Me	MeI	98[c]

See footnote a, Table I. [b] When R_2 is alkyl, HMPA must be present to generate the anion quantitatively. [c] 90% methylation at secondary carbon, 10% at tertiary.

These bis(phenylthio)alkenes have many potential uses but one of the most important derives from the behavior of their lithio derivatives as β-acyl vinyl anion equivalents.[10] The results in Table II indicate that the lithio derivatives can be formed readily and alkylated efficiently. The anion of **8**, derived from cyclohexenone, also added to benzaldehyde and underwent conjugate addition to chalcone in 90 and 95% yields, respectively.

The otherwise unfunctionalized 1,3-bis(phenylthio)alkenes can be hydrolyzed to enones by mercuric chloride in wet acetonitrile as found by Corey[10] for the methylthio analogues; this was demonstrated for **2** (R$_1$ = Me, R$_2$ = n-butyl, R$_3$ = H)[11] and **9**. The ketone **10**, however, gave only a 25% yield of enone and a large quantity of insoluble material by this method. The following procedure, based on our new method of carbonium ion formation,[8] is successful for both **10** and **8**;[13] a solution of 0.20 mmol of **10** and 0.40 mmol of the benzene complex of cuprous triflate in 5 ml of acetonitrile and 0.5 ml of water[14] was heated at reflux for 10 h, cooled, and passed rapidly through a silica column and the solvent evaporated.

Thus, for example, the overall transformations shown in Scheme III have been realized.

It is clear that these techniques will frequently allow the replacement of a β hydrogen of a conjugated enone by an electrophilic substituent.[15] However, as implied by the last two entries in Table II (Scheme IV), in the case of enones

Scheme III

63% overall

9

Scheme IV

PhS(Me)C=CHCH(Me)SPh + PhS(Me)$_2$CCH=CHSPh

9 : 1
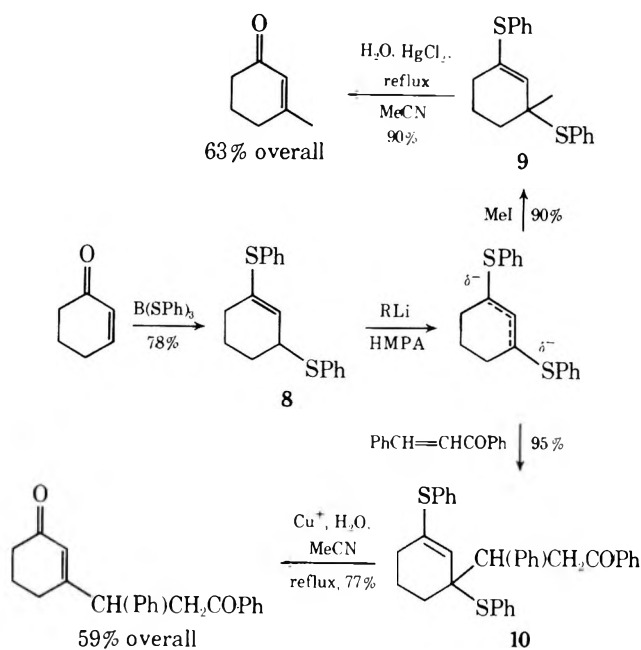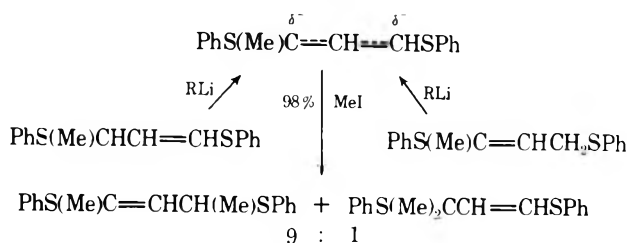
which yield unsymmetrical anions, this procedure will result in a substitutive 1,3-carbonyl transposition[16] in some cases. Presumably, in the case of unsymmetrical anions with different steric requirements at the partially negative carbon atoms, the least hindered of the latter will be alkylated most readily as in Scheme IV. Methods of reversing this regioselectivity and of exploiting the interesting implications of this aspect are now under investigation, as are alternative uses of the 1,3-bis(phenylthio)alkenes.

Acknowledgment. We thank the National Institutes of Health for Grant GM20707 in support of this work. We also thank Mr. Richard Gapinski for technical assistance.

References and Notes

(1) Triethyl thioborate is reported[2] to form a normal thioacetal with α,β-unsaturated aldehydes. In view of the known allylic rearrangements of allylic thioethers,[3] we intended to perform the thermal or Lewis acid catalyzed rearrangements of these unsaturated thioacetals. However, both reactions apparently occur in the same reaction mixture with triphenyl thioborate, presumably because of the Lewis acid behavior of the latter and the superior leaving ability of thiophenoxide.
(2) R. H. Cragg and J. P. N. Husband, *Inorg. Nucl. Chem. Lett.*, **6**, 773 (1970).
(3) H. Kwart and N. Johnson, *J. Am. Chem. Soc.*, **92**, 6064 (1970); Y. Makisumi and T. Sasatani, *Tetrahedron Lett.*, 1975 (1969).
(4) A modification of the literature procedure [J. Brault and J. M. LaLancette, *Can. J. Chem.*, **42**, 2903 (1964)] consisting of heating B$_2$S$_3$ (Alpha) with thiophenol in refluxing benzene for 48 h gives a nearly quantitative yield of triphenyl thioborate as white crystals which can be handled rapidly in air and stored in a desiccator.
(5) The presence of galvinoxyl does not influence this result: G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, and M. Itoh, *J. Am. Chem. Soc.*, **92**, 710 (1970).
(6) A. J. Mura, Jr., D. A. Bennett, and T. Cohen, *Tetrahedron Lett.*, 4433 (1975).
(7) T. B. Stevens, Ph.D. Thesis, Vanderbilt University, 1968.
(8) T. Cohen, G. Herman, J. R. Falck, and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975); T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975).

(9) The same sequence is also successful starting from methacrolein. A subsequent publication will elaborate on eliminations from such tris-(phenylthio) compounds by means of cuprous triflate.
(10) Corey has shown that the lithio derivative of 1,3-bis(methylthio)propene behaves as a synthetic equivalent of the hypothetical β anion of acrolein: E. J. Corey, B. W. Erickson, and R. Noyori, *J. Am. Chem. Soc.*, **93**, 1724 (1971); E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970). See also K. Oshima, H. Yamamoto, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **48**, 1567 (1975); R. G. Carlson and W. S. Mardis, *J. Org. Chem.*, **40**, 817 (1975).
(11) Hydrolysis of this compound was also successful (quantitatively, according to ¹H NMR) using the cupric chloride method[12] but in this case it was necessary to separate the product from diphenyl disulfide.
(12) T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94**, 8641 (1972).
(13) Unpublished work of Richard Gapinski indicates that this method is also successful with a third 1,3-bis(phenylthio)propene which was prepared by a different procedure.
(14) A similar solution can be prepared more easily by adding water to a solution formed by heating cupric triflate and copper metal in acetonitrile: C. L. Jenkins and J. K. Kochi, *J. Am. Chem. Soc.*, **94**, 843 (1972).
(15) The only other method of which we are aware for preparing β-acyl vinyl anion equivalents directly from enones requires four separate operations in some cases and five in others: K. Kondo and D. Tunemoto, *Tetrahedron Lett.*, 1007 (1975).
(16) B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97**, 4018 (1975).
(17) A. W. Mellon Predoctoral Fellow.

Theodore Cohen,* David A. Bennett
Albert J. Mura, Jr.[17]

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Nitrogen Acids. 1. Carboxamides and Sulfonamides

Summary: Measurement of the equilibrium acidities in Me$_2$SO of carbon, nitrogen, and oxygen acids has revealed the expected order, i.e., GOH $\gg$ GNH$_2$ $\gg$ GCH$_3$, when G is Ph, CH$_3$SO$_2$, or F$_3$CSO$_2$, but when G is CH$_3$CO or PhCO the carbon and nitrogen acids have comparable acidities.

Sir: Carboxamides are too weakly acidic to allow equilibrium acidities to be measured in water by ordinary methods. In fact, to our knowledge, no report of an *absolute* acidity measurement for a simple carboxamide has been recorded in the literature in the 48 years since Branch and Clayton reported the equilibrium constant of acetamide in water to be 8.3×10^{-16}.[1,2] Measurements on carboxamides in strongly basic aqueous media by acidity function techniques are made difficult, if not impossible, by hydrolysis, and pK data are scarce for this important class of weak nitrogen acids.[2] We wish to report that absolute equilibrium acidity measurements in dimethyl sulfoxide solution can be made accurately and conveniently for carboxamides, as well as for sulfonamides, by the competitive indicator method developed for carbon acids.[4] These nitrogen acids differ from oxygen acids in this respect, the latter having a strong tendency to undergo hydrogen bonding ("homoconjugation") with their conjugate bases (e.g., RO⁻·⁻·HOR), which makes measurements more difficult.[4,5] The pK's in Me$_2$SO for a few carboxamides and sulfonamides are compared in Table I with those of their carbon and oxygen analogues.

Examination of Table I shows that the pK for dissociation of the N–H bond in acetamide is much higher in Me$_2$SO than in water (25.5 vs. 15.1). This is consistent with results obtained with other acids in which the negative charge in the anion is concentrated on oxygen where it can be stabilized by strong H bonding in water, but not in Me$_2$SO.[4] Judging from preliminary results with *N,N*-dimethylacetamide, the pK for dissociation of the C–H bond in acetamide is above 32 in Me$_2$SO, which places the acidity more than 7 units higher than the pK in water estimated from deuterium exchange rates.[6]

The order of acidities of carbon, nitrogen, and oxygen acids is seen from Table I to be GCH$_3$ $\ll$ GNH$_2$ $\ll$ GOH, when G

Table I.   Comparison of the Equilibrium Acidities of Analogous Carbon, Nitrogen, and Oxygen Acids in Dimethyl Sulfoxide Solution

Acid	pK	Acid	pK	Acid	pK
$PhCH_3$	$\sim 47^a$	$PhNH_2$	30.7^b	PhOH	$16.4,^c \sim 18.5^d$
CH_3COCH_3	26.5^e	CH_3CONH_2	25.5	CH_3COOH	12.6^c
CH_3COCH_2Ph	19.8^f	$CH_3CONHPh$	21.45		
$C_6H_5COCH_3$	24.7^e	$C_6H_5CONH_2$	23.35	C_6H_5COOH	11.1^c
$C_6H_5COCH_2Ph$	17.7^f	$C_6H_5CONHPh$	18.8		
$CH_3SO_2CH_3$	31.1^e	$CH_3SO_2NH_2$	17.5	CH_3SO_2OH	1.62^g
$F_3CSO_2CH_3$	18.8^h	$F_3CSO_2NH_2$	9.7	F_3CSO_2OH	0.31^g

a Estimated by extrapolation. *b* Preliminary value. *c* Reference 11. *d* Z. Margolin, unpublished results. *e* Reference 4. *f* Reference 9. *g* Reference 12. *h* Reference 10.

is Ph, CH_3SO_2, or F_3CSO_2. In these systems there is nearly the same difference in acidity between the carbon and nitrogen acids as between the nitrogen and oxygen acids. The difference is ~15 pK units when G is Ph or CH_3SO_2, and ~9.5 pK units when G is F_3CSO_2. When G is CH_3CO or $PhCO$ the difference in acidities between nitrogen and oxygen acids (12 to 13 pK units) appears to be in line with that expected by analogy with the corresponding acids where G is Ph or CH_3SO_2, but the difference in acidities between the carbon and nitrogen acids is only ~1.5 pK units in each instance. Furthermore, the carbon acids in which a phenyl group has been substituted for a hydrogen atom at the acidic site, i.e., CH_3COCH_2Ph and $C_6H_5COCH_2Ph$, are actually over 1 pK units *more* acidic than their nitrogen analogues, $CH_3CONHPh$ and $C_6H_5CONHPh$. In comparing the acidities of carboxamides to ketones it is clear that some factor is present that negates the intrinsically greater acidity of the N–H bond as compared to the C–H bond. It seems likely that the strong resonance stabilization of the undissociated carboxamide is responsible. Judging from the results with the other carbon, nitrogen, and oxygen acid systems (Table I), the difference in acidities between ketones and carboxamides should be as large as between carboxamides and carboxylic acids or ~7 pK units (half the difference in acidities between the carbon and oxygen acids). If "extra" resonance in the carboxamide is the cause of the much smaller difference actually observed (1.5 pK units), this would require a resonance energy of ~7.5 kcal/mol. It is interesting to note in this connection that the barrier to rotation around the C–N bond in carboxamides is high, ranging from about 14 to 18 kcal/mol at the appropriate coalescence temperatures.[8]

Resonance between the electron pair on nitrogen and the function to which the nitrogen atom is attached no doubt occurs in the undissociated forms of all of the nitrogen acids listed in Table I. Evidently, this resonance in aniline and in the sulfonamides is relatively much weaker than in the carboxamides.

References and Notes

(1) G. E. K. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1680 (1928).
(2) J Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952), measured *relative* acidities of a variety of weak acids in isopropyl alcohol, including some carboxamides. Bowden has converted these to "pK's" by reference to acidities determined by the H_ method in mixed aqueous solvents using diphenylamines as reference standards.[3] The "pK's" estimated in this way with "water as a standard state" must be considered as only rough estimates, however, since it is highly unlikely that the diphenylamine indicators would have the same acidities in aqueous media as in isopropyl alcohol, even if they could be measured in the absence of ion pairing effects.
(3) (a) K. Bowden, *Chem. Rev.*, **66**, 119 (1966); (b) R. B. Homer and C. D. Johnson, "The Chemistry of Amides", J. Zabicky, Ed, Wiley-Interscience, New York, N.Y., 1970, pp 238, 239.
(4) W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 7006 (1975).
(5) I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, *J. Am. Chem. Soc.*, **90**, 23 (1968).
(6) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953). Estimates of pK's based on kinetic acidities must be viewed with considerable caution, however.[7]
(7) F. G. Bordwell, W. S. Matthews, and N. R. Vanier, *J. Am. Chem. Soc.*, **97**, 442 (1975).
(8) J. A. Hirsch, R. L. Augustine, G. Koletar, and H. G. Wolf, *J. Org. Chem.*, **40**, 3547 (1975), and references cited therein.
(9) F. G. Bordwell, J. E. Bartmess, G. E. Drucker, Z. Margolin, and W. S. Matthews, *J. Am. Chem. Soc.*, **97**, 3226 (1975).
(10) F. G. Bordwell, N. R. Vanier, W. S. Matthews, J. B. Hendrickson, and P. L. Skipper, *J. Am. Chem. Soc.*, **97**, 7160 (1975).
(11) I. M. Kolthoff, M. K. Chantooni, and S. Bhowmik, *J. Am. Chem. Soc.*, **90**, 23 (1968).
(12) C. McCallum and A. D. Pethybridge, *Electrochem. Acta*, **20**, 815 (1975)

F. G. Bordwell,* **Donald Algrim**

Department of Chemistry, Northwestern University
*Evanston, Illinois 60201*

Methyl methylthiomethyl sulfoxide (MMTS, FAMSO)

A masked formaldehyde reagent

I. Aldehydes and Acetals

The carbanion derived from **methyl methylthiomethyl sulfoxide (MMTS, FAMSO)** reacts with alkyl halides to give aldehyde dimethylmercaptal S-oxides (1) which are readily hydrolyzed in acid to produce the corresponding aldehydes in excellent overall yields.[1] As an aldehyde equivalent, 1 affords directly the diethyl acetal of the corresponding aldehyde upon treatment with ethyl orthoformate.[1] This scheme has been used successfully to prepare substituted pyridinecarboxaldehydes, whereas other methods fail.[2] This synthesis is especially suitable for labile aldehydes and is superior to the 1,3-dithiane method since the carbanion is easily generated and the hydrolysis of 1 can be accomplished under mild conditions.[1] Homologation of aromatic aldehydes can be achieved using MMTS.[1]
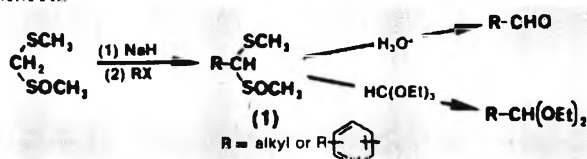
II. α-Hydroxyaldehydes and Derivatives

Treatment of the carbanion of MMTS with ketones leads to the α-hydroxyaldehyde dimethylmercaptal S-oxides (2) which can be similarly hydrolyzed to the corresponding ketones or converted to the ketals.[4] The intermediate 2 can also be formed by $NaBH_4$ reduction of a ketone compound 4 (*vide infra*).[5] Protected hydroxyaldehydes can be produced by methylation or benzylation of 2 followed by treatment with cupric chloride dihydrate in 1,2-dimethoxyethane (DME).
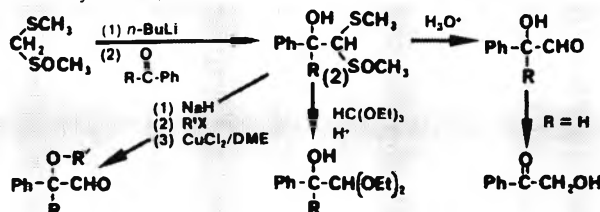

III. Dialkyl Ketones and Cyclic Ketones

In reactions analogous to the aldehyde synthesis, symmetrical dialkyl ketones,[6] substituted cyclobutanones,[7] and other cyclic ketones[8] can be prepared from MMTS.


X = Br or TsO; n=2,3,4,5,6
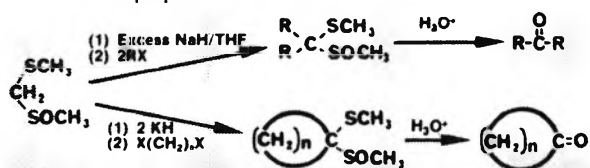
The versatility of this method is further demonstrated by the synthesis of tetrahydro-γ-pyrone from bis(2-chloroethyl) ether (eq A) and the synthesis of 3-cyclopentenone from cis-1,4-dichloro-2-butene (eq B).
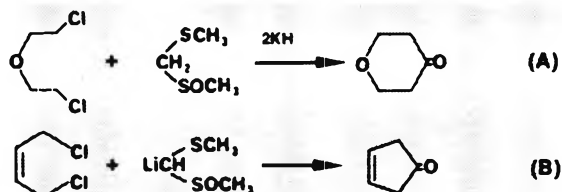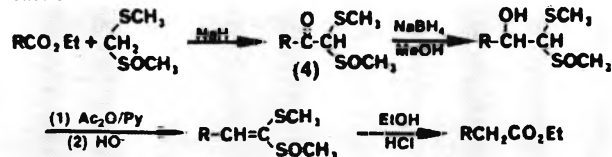

IV. Synthesis of Phenylacetic Acid Derivatives and Homologation of Esters

MMTS and aromatic aldehydes undergo Knoevenagel-type condensation to give 1-methylsulfinyl-1-methylthio-2-arylethylenes (3). Acid-catalyzed ethanolysis of 3 produces ethyl arylacetates in high yields.[9]
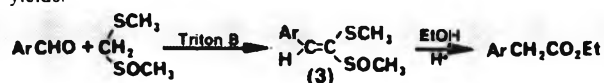

Homologation of esters can be achieved by the following sequence of reactions.[5]

V. Synthesis of α-Amino Acids from Nitriles

The carbanion of MMTS reacts with nitriles to form enaminosulfoxides (5) which, upon treatment with Ac_2O, afford the unusual rearranged product 6. Ester exchange of 6 followed by desulfurization leads to the N-acetylamino acid ester 7.[10] The synthesis of the methyl ester of DL-N-acetyl-5-hydroxytryptophan by this method is a remarkable example.[10]
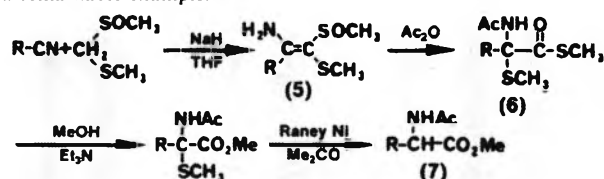
References:
1) *Tetrahedron Lett.*, 3151 (1971); 2) *Chem. Commun.*, 410(1974); 3) *Synthesis*, 385 (1975); 4) *Tetrahedron Lett.*, 2681 (1972); 5) *Chem. Lett.*, 659 (1974); 6) *Synthesis*, 117 (1974); 7) *Tetrahedron Lett.*, 3653 (1974); 8) *ibid.*, 2767 (1975); 9) *ibid.*, 1383 (1972); 10) *J. Amer. Chem. Soc.*, **96**, 1960 (1974).

17,795-4   Methyl methylthiomethyl sulfoxide 50g $25.00
(MMTS, FAMSO)   250g $88.00; 1kg $220.00