VOLUME 41 APRIL 30, 1976 NUMBER 9 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

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; Jane U. Lutick, Production 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 Photocopy	$2.50	$3.00	$3.50
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., 24×, negative, silver halide. Orders must state photocopy or microfiche if both are available. Full bibliographic citation including names of all authors and prepayment are required. Prices are subject to change.

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

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

Editorial Department
American Chemical Society
20th and Northampton Sts.
Easton, Pa. 18042
(215) 258-9111

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

JOCEAH 41(9) 1487–1674 (1976)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry

VOLUME 41, NUMBER 9 APRIL 30, 1976

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

THE JOURNAL OF Organic Chemistry®

VOLUME 41, NUMBER 9

APRIL 30, 1976

Introduction and Extension of Ethynyl Group Using 1,1-Dichloro-2,2-difluoroethylene. A Convenient Route to Lithium Acetylides and Derived Acetylenic Compounds[1a]

Kunio Okuhara

Government Industrial Research Institute, Nagoya,[1b] Japan

Received June 2, 1975

Applicability of the following two-step reaction sequence was examined for conversion of organolithium and -magnesium compounds into lithium acetylides having two more carbon atoms: RLi or RMgBr + CF_2=CCl_2 → RCF=CCl_2, RCF=CCl_2 + n-C_4H_9Li → RC≡CLi. The reaction of RLi with CF_2=CCl_2 was accompanied by formation of RCl as a result of the Cl–Li exchange to a widely varying extent depending on the nature of R. Between butyllithium and CF_2=CCl_2, only the Cl–Li exchange was observed, and the formation of 2,2-dichloro-1-fluorovinyllithium confirmed. The conversion of RCF=CCl_2 into lithium acetylides proceeded with great ease in yields presumed to be nearly quantitative in typical cases. The resulting acetylides were treated with CF_2=CCl_2, and compounds of the type RC≡CCF=CCl_2 were isolated in overall (from RH or RBr) yields up to 69% where R is phenyl, substituted phenyl (o-CH_3O, p-CH_3O, p-CH_3, p-Cl, p-Br, m-CF_3), 1-naphthyl, 2-furyl, 2-thienyl, and ferrocenyl. In some cases RC≡CH and RC≡CCO_2H were also isolated. For example, 2-ethynylthiophene was prepared from thiophene in an overall yield of 63%. Previously unreported 2-ethynylbenzothiazole was also obtained. Stepwise extension of the terminal acetylenic bond is possible in a similar method as illustrated in the synthesis of $C_6H_5(C{\equiv}C)_nCF{=}CCl_2$ (n = 2, 3, 4) from $C_6H_5(C{\equiv}C)_{n-1}CF{=}CCl_2$ and n-$C_4H_9(C{\equiv}C)_2CF{=}CCl_2$ from n-$C_4H_9C{\equiv}CCF{=}CCl_2$. An efficient preparative method of 1,1,1,2-tetracholoro-2,2-difluoroethane, from which CF_2=CCl_2 is obtained by dechlorination, is described.

During the course of a study of nucleophilic reactions of fluorochloro olefins, we encountered a reaction which seemed to have a potential synthetic utility for acetylenic compounds. Thus, when β,β-dichloro-α-fluorostyrene was treated with phenyllithium, the expected fluorochlorostilbene was not detected. Instead, the formation of lithium phenylacetylide was indicated. As the starting compound was obtained from phenyllithium[2] or from phenylmagnesium bromide[3] on treatment with 1,1-dichloro-2,2-difluoroethylene (**1**), the whole transformation is represented by the following sequence:

$$C_6H_5Li\ (C_6H_5MgBr) \rightarrow C_6H_5CF{=}CCl_2 \rightarrow C_6H_5C{\equiv}CLi$$

This suggested a general two-step conversion of organolithiums **4** or Grignard reagents **5** into lithium acetylides **7** having two more carbon atoms. By a combination of existing methods an equivalent transformation generally requires many steps, though somewhat similar conversion of RMgBr into RC≡CCl using dichloroacetylene is reported.[4] Therefore, it was decided to examine the applicability of the proposed sequence to various R groups. This sequence may be compared with a recently reported two-step conversion of aldehydes into the corresponding acetylides having one more carbon atom.[5]

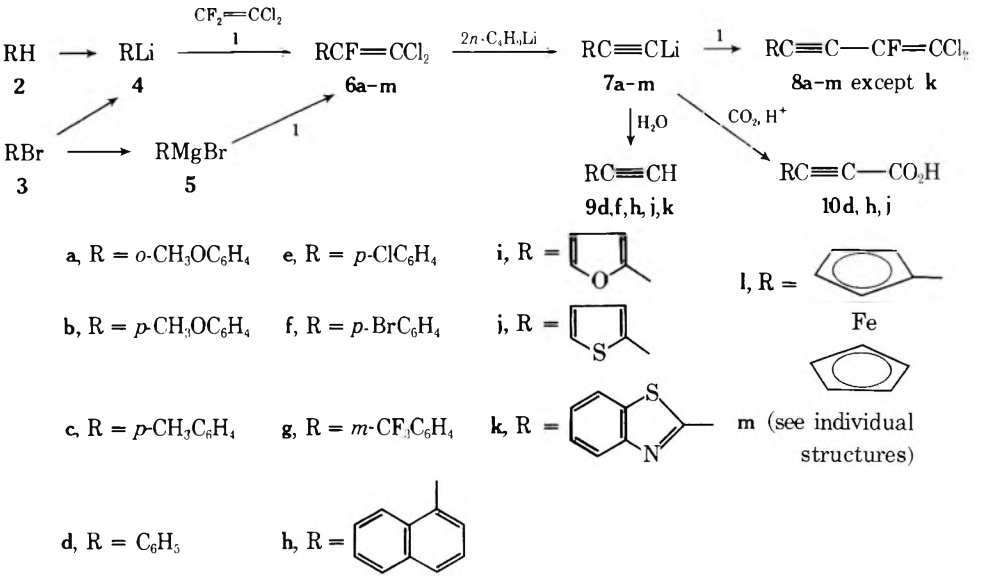
$$RCHO \rightarrow RCH{=}CBr_2 \rightarrow RC{\equiv}CLi$$

The results described herein indicate that the proposed sequence is a convenient synthetic route to some types of acetylenic compounds as well as a useful method for the stated conversion. It was also found that a similar method can be used for conversion of a lithium acetylide into the corresponding lithium acetylide having an extra conjugated acetylenic bond.

Results and Discussion

Reaction of Organolithium Compounds with CF_2=CCl_2. Lithium compounds **4** were prepared from RH (**2**) and RBr (**3**) and added to ether solutions containing excess **1** (Scheme I). The reactions occurred typically at −30 °C. For completion of the reaction the mixtures were allowed to warm to 0 °C or refluxed for up to 4 h. The inverse addition method was used, except for **4l** and **4m**, in order to minimize the possibility of reaction of the initially formed **6** with **4**. The yields of **6** obtained by distillation (in some cases by crystallization) are given in Table I. When **4** was prepared by Li–Br exchange from the corresponding bromo compounds (**3**) using butyllithium, it was necessary to keep the preparations cold in order to avoid the formation of RC_4H_9-n.[6] The preparation of p-methoxyphenyllithium (**4b**) from p-bromoanisole (**3b**) is complicated by the formation of 2-methoxy-5-bromophenyllithium.[7] From these complications and from the formation of side products

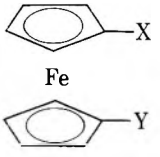
Scheme I



(RCl), the route via **4** is considered inferior to the route via Grignard reagents **5** where bromo compounds **3** are used to prepare **6b–h**. On the other hand, the preparation of **4** by lithiation[8] and subsequent treatment with **1** is considered satisfactory as a route to **6a, 6i, 6j,** and **6k.**

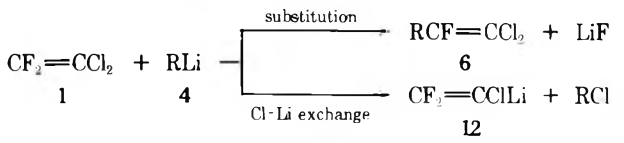
2-Benzothiazolyllithium (**4k**) is reported to be unstable above −35 °C.[9] Hence **1** was added to a solution of **4k** at −70 °C, and the resulting mixture allowed to warm slowly. The yield of **6k** was very low. However, it was found that the yield is greatly increased if the temperature is rapidly raised. This finding and subsequent experiments led to the procedure described in the Experimental Section.

Mixtures from lithiation of ferrocene in ether with butyllithium contained unchanged ferrocene, ferrocenyllithium (**4l**),[10,11] 1,1′-ferrocenediyldilithium (**4m**),[12,13] and a relatively large amount of unchanged butyllithium. Hence treatment with **1** afforded complex mixtures, from which **6l** was obtained as a red oil and **6m** as red crystals. Isolation of **6l** was more difficult since vaccum distillation could not be performed.[14]



4m, X = Y = Li
6m, X = Y = CF=CCl2
7m, X = Y = C≡CLi
8m, X = Y = C≡C—CF=CCl2
11, X = Cl; Y = CF=CCl2

The side reaction observed is a Cl–Li exchange distinct from the substitution with elimination of lithium fluoride for the main reaction:



For example, chlorobenzene and *p*-chlorotoluene were isolated in 13% yield each besides a 60% yield of **6d** and 58% yield of **6b.** When **4h** was prepared from 1-bromonaphthalene (**3h**) with lithium in ether and treated with **1**, the isolated yields (based on **3h**) were as follows: naphthalene, 15%; 1-chloronaphthalene, 24%; **6h**, 31%.[15] These chloro compounds (RCl) could arise from secondary reactions of **6** with **4.** However, chloroacetylene **13** and acetylene **9** (from **7** by hydrolysis), the coproducts of these possible reactions, were not detected though carefully sought by gas chromatography in each case.

$$6 + 4 \longrightarrow \underset{13}{RC{\equiv}CCl} + RCl$$

$$13 + 4 \longrightarrow 7 + RCl$$

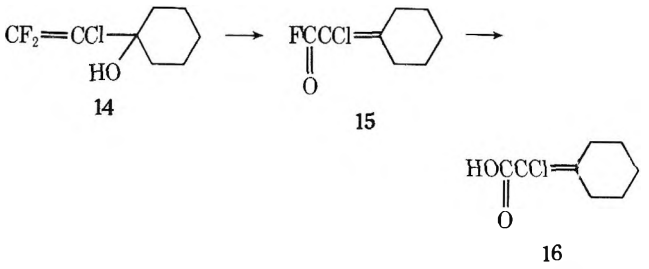
Hence the present author sees no probable way of formation of RCl other than from the Cl–Li exchange between **1** and **4.**[16] Further, the formation of 1-chloro-2,2-difluorovinyllithium (**12**) was shown in the case of the reaction with phenyllithium (**4d**)[17] as well as in the case of the reaction with butyllithium (vide infra). Therefore, it seems reasonable to conclude that the chloro compounds (RCl) were formed from the reactions of **1** and **4.**[16] In the cases of the reactions with **4l** and **4m** there were some indications of formation of chloroferrocene and 1-chloro-1′-(2,2-dichloro-1-fluorovinyl)ferrocene (**11**). However, these products were not isolated. It is not certain either whether these were formed directly from **1.** On the other hand, no evidence of formation of the products of the Cl–Li exchange was found in the cases of the reactions of **4i** and **4j.** From isolated yields of **6** and RCl and from GC peak area ratios, the following order of increasing proportion of the Cl–Li exchange can be presented:

$$\mathbf{4i, 4j} < \mathbf{4g, 4e} < \mathbf{4d, 4c, 4a} < \mathbf{4h} < n\text{-}C_4H_9Li$$

As a rough trend it is suggested that the smaller the extent of delocalization of the negative charge in the reagent the higher the proportion of the exchange. The importance of the steric factor is also suggested from the relatively high proportion of Cl–Li exchange in the reaction of 1-naphthyllithium (**4h**). If other factors are equal, a reagent having factors of higher steric hindrance would give a higher proportion of the Cl–Li exchange.

The reaction observed between **1** and butyllithium was Cl–Li exchange, and no evidence was found of formation of the substitution product (n-$C_4H_9CF{=}CCl_2$) or a secondary product derived from this compound. The formation of 1-chloro-2,2-difluorovinyllithium (**12**) was confirmed by isolation of the cyclohexanone adduct **14** in 62% yield. The adduct was unstable and decomposed to cyclohexylidenechloroacetyl fluoride (**15**) after standing for 1 day at room tem-

perature. The corresponding acid (16) was isolated on further standing.



14 15 16

Decompositions of this type are described in the literature.[18,19] The above results also indicate that 1 is a good source of 12, previously obtained from 1-chloro-2,2-difluoroethylene with *N,N*-dipropyllithium amide.[20]

The exact fate of CF_2=CClLi (12) in the presence of excess 1 is not known, though the final product, an undistillable, dark-colored substance, is thought to have the structure $-(CF{=}CCl)_n-$. In the presence of excess butyllithium, however, 12 was found to be converted into 1-hexynyllithium (17) after an exothermic reaction.

$$1 \rightarrow 12 \rightarrow \underset{17}{n\text{-}C_4H_9C{\equiv}CLi} \rightarrow \underset{18}{n\text{-}C_4H_9C{\equiv}CCF{=}CCl_2}$$

The reaction mixture yielded 18 on treatment with 1. It should be noted that, although the reactions of 1 with excess butyllithium and with excess phenyllithium (4d) give similar acetylides (17 and 7d), the courses of formation of these are quite different from each other.

Reaction of Grignard Reagents with CF_2=CCl_2. Grignard reagents 5 were prepared in ether from the corresponding bromo compounds (3), 1 was added, and the resulting mixtures were refluxed for 7–20 h (not necessarily continuous). The yields of 6 isolated by distillation are included in Table I. No side product was found except small amounts of coupling compounds (e.g., biphenyl), probably formed during the preparations of 5. The inverse addition method was not required. Higher product yields, the absence of side products (RCl), and simplicity in experimental procedure make this route (via 5) generally preferable to the route via 4 when a bromo compound (3) is to be used for the synthesis of 6.

The reactions of alkylmagnesium bromides with 1 were found to be complex and have not yet been studied well, though preliminary experiments indicated compounds of the type RCF_2CCl_2H as the main products (ca. 25% yield where R = *n*-C_4H_9).

Reaction of RCF=CCl_2 with *n*-Butyllithium. Although, originally, the conversion of 6d into 7d was discovered using phenyllithium as reagent, butyllithium was used for such purposes throughout in the present study. The reactions seemed to proceed well at −50 °C and at even lower temperatures, though in some cases higher (subzero) temperatures were used from solubility considerations. There was observed no evidence of formation of side products. The resulting mixtures containing lithium acetylides (7) were treated with 1, and compounds of the type RC≡CCF=CCl_2 (8) were isolated (Table I). However, compound 8k could not be obtained although 2-ethynylbenzothiazole (9k) was isolated in 52% yield after hydrolysis of 7k. The reactions between lithium acetylides (7) and 1 were slow below 20 °C and conducted under refluxing conditions for 2–7 h. In many cases the yields of formation of 7 from 6 were suspected to be practically quantitative. Quantitative formation of ethynylbenzene (9d) from 6d was confirmed by determinations by gas chromatography in duplicate experiments, in each of which butyllithium (2 equiv plus) was added to an ethereal solution of 6d containing *n*-nonane as internal standard until the peak due to chloroethynylbenzene (13d) disappeared. Isolated yields of 9 and 10 are given in Table II.

The reactions of 6 except 6k, 6l, and 6m with butyllithium can be monitored by gas chromatography. Each reaction mixture obtained after addition of approximately 1 equiv of butyllithium was found to contain the unchanged starting material (6), an intermediate, and acetylene 9 (after hydrolysis) besides butyl chloride. The intermediate is almost certainly a chloroethynyl compound (13)[21] though only chloroethynylbenzene (13d) was isolated and confirmed. In such a mixture the peak area of 13 (the total areas of the three components taken as 100%) was 70–85%

Table I. Isolated Yield[a,b] of RCF=CCl_2 (6) and RC≡CCF=CCl_2 (8)

R	Starting compd (2 or 3)	Yield[c] of 6, % Via RLi (4)[e]	Via RMgBr (5)	Yield[d] of 8, %
a	Anisole	41 (2*)		80 (2)
b	*p*-Bromoanisole	32	76 (7)	76 (6*)
c	*p*-Bromotoluene	58	74 (12*)	80 (7*)
d	Bromobenzene	60 (2)	85 (12*)	80 (6)
e	*p*-Bromochlorobenzene	56	70 (14*)	87 (6)
f	*p*-Dibromobenzene		50 (21**)	79 (2*)
g	*m*-Bromo-α,α,α-trifluorotoluene	56	67 (20*)	81 (5*)
h	1-Bromonaphthalene	31	82[f] (16*)	84 (6)
i	Furan	53 (4)		79 (5)
j	Thiophene	81 (4)		84 (5)
k	Benzothiazole	59		0
l	Ferrocene	19 (2)		61 (5)
m	Ferrocene	39 (2)		22 (6)

[a] Based on charged starting material. [b] Total refluxing times (h) with 1 in ether are indicated in parentheses; continuous (unmarked), with one overnight interruption in 2 days (*), with two overnight interruptions in 3 days (**). Where no parenthesized figure is given, the reaction mixture was hydrolyzed without refluxing. [c] Overall yield from 2 or 3. [d] Overall yield from 6. [e] Organolithiums 4 were obtained by reaction with ethereal butyllithium except that 4c, 4d, and 4h were obtained by reaction with cut pieces of lithium. See ref 15 for 4h. [f] Benzene used as cosolvent.

Table II. Yield[a] of RC≡CH (9) and RC≡CCO_2H (10) Obtained from RCF=CCl_2 (6)

Compd	Yield, %		Bp, °C (mm)	n^{20}D or [mp, °C]
9d	77	100[b]	50–52 (30)	1.5483
9f	58[c]	97[b]		[61–65]
9h	44[d]	97[e]	105–106 (4)	1.6500
9j	78		55–56 (30)	1.5849
9k	52			[42–43]
10d	84			[136.5–138.5]
10h	77			[137–139]
10j	72			[130–133] dec

[a] Isolated yield unless otherwise stated. Overall yield from 6. [b] Determined yield by gas chromatography. [c] Yield obtained as crystals. [d] A red balsamlike material, believed to be mainly a polymer of 9h, remained in the distillation pot. The weight corresponded to 96% of the weight of isolated 9h. [e] Yield of di(1-naphthyl)butadiyne, mp 176–178 °C, obtained after treatment of crude 9h with cupric acetate hydrate in pyridine; mp 177.5–178.5 °C (90%) after recrystallization from benzene.

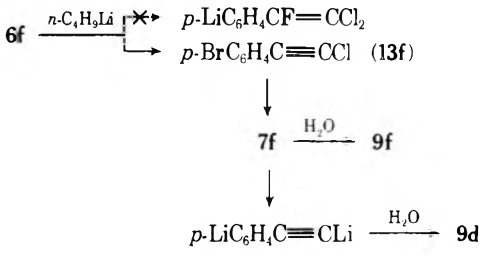
where R is phenyl or a substituted phenyl, about 55% where R is 2-furyl or 2-thienyl, and approximately 20% where R is 1-naphthyl. Some of these chloroethynyl compounds (**13**) may have only a limited stability under GC conditions. Chloroethynylferrocene (**13l**) was not detected by GC although its existence was indicated by ir. The isolated yield of **13d** was 61%. It appears that the values of k_1 and k_2 defined by the following reactions are comparable.

$$6 + n\text{-}C_4H_9Li \xrightarrow{k_1} \underset{\mathbf{13}}{RC{\equiv}CCl} + LiF + n\text{-}C_4H_9Cl$$

$$\mathbf{13} + n\text{-}C_4H_9Li \xrightarrow{k_2} 7 + n\text{-}C_4H_9Cl$$

Specifically, for the reaction where R is phenyl the ratio k_1/k_2 was calculated to be 12 from a determined composition (**6d**, 13%; **13d**, 78%; **7d**, 9% determined as **9d**).[22]

The reaction of **6f** with butyllithium is interesting in that both the Br–Li exchange and the Cl–Li exchange[23] are possible. The Cl–Li exchange occurred exclusively unless excess butyllithium was used. The determined yield of *p*-bromoethynylbenzene (**9f**) was 97%. In the gas chromatogram the remaining 3% was accounted for by the presence of **13f** and **9d** (resulting from the dilithium compound).



When butyllithium had been added to an equimolar mixture of bromobenzene and β,β-dichloro-α-fluorostyrene (**6d**) until chloroethynylbenzene (**13d**) was almost undetectable (<1%), the conversion of bromobenzene was at most 5%. This means that the rate of the Cl–Li exchange with **6d** is at least 10^3 times the rate of the Br–Li exchange with bromobenzene (considering k_1/k_2 = 12 for **6d**). These facts indicate the great ease with which the Li–Cl exchange[23] occurs between **6** and butyllithium.[24]

Among the substitution in **1**, the Cl–Li exchange in **1**, and the Cl–Li exchange[23] in **6**, similarities are notable in the transition states or intermediates, in each of which a (partial) negative charge is stabilized by β-fluorine and also by α-chlorine.[25]

$$4 + 1 \longrightarrow RCF_2\bar{C}Cl_2$$

$$n\text{-}C_4H_9Li \text{ or } 4 + 1 \longrightarrow CF_2{=}\bar{C}Cl$$

$$n\text{-}C_4H_9Li \text{ or } 4 + 6 \longrightarrow RCF{=}\bar{C}Cl$$

The stabilizing effect of fluorine toward a negative charge at the β position has been recognized, though the mechanism of the stabilization is not unanimous.[26]

Extension of Terminal Acetylenic Bond. A formal extension of the reaction sequence shown in Scheme I gives the reaction sequence shown in Scheme II. The applicability of this sequence was demonstrated using phenyl compounds as examples. Thus treatment of **8d** with butyllithium followed by refluxing the resulting mixture with **1** afforded **19** in 84% yield. Similarly, **20** and **21** were obtained from **19** and **20**, respectively, in the yields given above. These compounds are all crystalline, and the structures are confirmed by ir, uv, ^{19}F NMR, and mass spectroscopy as well as by F and Cl elemental analysis data. The change in uv with increase in n is also consistent with the trend known for series of conjugated polynes.

Compound **22** was similarly obtained in 78% yield from

Scheme II

$$R(C{\equiv}C)_{n-1}Li \longrightarrow R(C{\equiv}C)_{n-1}CF{=}CCl_2 \longrightarrow R(C{\equiv}C)_nLi$$

or

$$R(C{\equiv}C)_{n-1}CF{=}CCl_2 \longrightarrow R(C{\equiv}C)_nLi \longrightarrow R(C{\equiv}C)_nCF{=}CCl_2$$

19, R = C_6H_5; n = 2 (84%)
20, R = C_6H_5; n = 3 (76)
21, R = C_6H_5; n = 4 (33)
22, R = n-C_4H_9; n = 2 (78)

18, which in turn was prepared from 1-hexyne by lithiation followed by treatment with **1**. The method of extension of the terminal acetylenic bond is thus shown to be applicable where R is alkyl as well as where R is aryl whereas the method of introduction of the ethynyl group is not applicable at present where R is alkyl.

Synthetic Merits. It appears that the present method is most suited for the preparation of lithium acetylides (substituted ethynyllithiums) to be allowed to react further as such. Compounds of the type $RCF{=}CCl_2$ are as effective precursors of lithium acetylides as are the corresponding terminal acetylenes in that the conversion with butyllithium (and probably with other reagents) can be performed under very mild conditions and, unless other portions of the molecules are susceptible to attack by the reagent, in practically quantitative yield. Instead of RC≡CH, more stable $RCF{=}CCl_2$ is isolated, purified, and stored until it is converted directly into the lithium acetylide, though 2 equiv of butyllithium are required. The presence of butyl chloride (2 equiv) and lithium fluoride, which are formed as coproducts in the present route, is not expected to cause a serious detrimental effect in transformation to most derivatives. The use of a lower alkyllithium (in place of butyllithium) may be desirable in some cases.

Where RLi and/or RMgBr are easily obtainable, the present method is suited even for the preparation of terminal acetylenes though R is restricted to be aryl at present. For example, 2-ethynylthiophene (**9j**) was prepared in the present study from thiophene in two steps in an overall yield of 63%. This method seems to be simpler than any of the previously reported ones: via 2-acetylthiophene,[27] via 2-vinylthiophene,[28b] via 2-iodothiophene,[29] via 5(2-thienyl)-2-oxazolidone.[30] Another example is the preparation of 1-ethynylnaphthalene (**9h**) via the Grignard reagent from easily available 1-bromonaphthalene. A previous synthesis of **9h** from another easily obtainable intermediate, 1-chloromethylnaphthalene, needed a considerable number of steps.[31] Though 1-acetylnaphthalene can be converted into **9h** in two steps (action of PCl_5 followed by dehydrochlorination), availability of pure 1-acetylnaphthalene, unlike that of 2-acetylnaphthalene, is not high. Acetylene **9h** may also be prepared in a good overall yield from 1-naphthaldehyde by Corey's method.[5]

Previous methods of extension of the terminal acetylenic bond by one or more acetylenic bonds are almost exclusively by Cu(I)-catalyzed unsymmetrical coupling followed by elimination of the protective group.[32–34] For example, $Et_3SiC{\equiv}CBr$ was used in Cadiot–Chodkiewicz coupling to prepare $Ar(C{\equiv}C)_nSiEt_3$, from which $Ar(C{\equiv}C)_nH$ (n = 2, 3) was generated by hydrolysis.[33] For such stepwise extension of terminal conjugated acetylenic bonds or more specifically for the preparation of monosubstituted butadiynes and hexatriynes, the present method seems to be useful. The lithium acetylides of terminal conjugated polyacetylenes are probably most easily obtainable by the present method. However, some derivatives (e.g., carboxylic acid) to be obtained from such lithium acetylides are also

Table III. Physical Properties of Compounds Having 2,2-Dichloro-1-fluorovinyl Group[a-c]

Compd	Bp, °C (mm)	n^{20}D or [mp, °C]	νC=C,[d] cm^{-1}	^{9}F NMR,[e] ppm
6a	87–91 (5)	1.5523	1660	10.9
6b	121–123 (10)	[25–26]	~1640	17.3
6c	126–126.5 (30)	1.5605	~1640	17.6
6d[f]	123–126 (60)	1.5625	1638	17.7
6e	132–133 (29)	[36–37]	~1630	18.6
6f	113–115 (10)	[40–40.5]	1637	18.7
6g	126 (60)	1.4970	~1640	19.3
6h	99–103 (1)	[45–46.5]	1648	6.9
6i	105–107 (80)	1.5418	~1640	34.4
6j	125 (48)	1.5981	1634	20.9
6k		[81–83]	1624	24.9
6l		[g]	1644	17.9
6m		[84–85]	1636	19.4
8a		[56–57]	1622	23.2
8b	123–125 (6)	[39–40]	1625	23.2
8c	103–105 (5)	1.6032	1623	23.5
8d	111 (10)	1.6043	1623	23.9
8e		[69–70]	1623	24.3
8f		[79–80]	1623	24.4
8g	112–113 (9)	1.5407	1624	25.0
8h		[37.5–38.5]	1620	23.7
8i	104–105 (20)	1.5910	1623	25.5
8j	105–106 (9)	1.6385	1618	24.2
8l		[80.5–82]	1627	21.9
8m		[122–123]	1622	23.1
18	96 (30)	1.4849	1623	22.0
22	106–108 (8)	1.5559	1612	24.9
19	~160 (4)	[65–66]	1609	25.7
20		[56–57.5]	1608	26.8
21		[67.5–68.5]	1604	27.4

[a] Satisfactory analytical results (≤±0.3% for F and ≤±0.4% for Cl) were obtained for all new compounds listed in the table. [b] A strong band assignable to νC–F appeared at 968–988 cm^{-1} for each of the compounds listed in the table. For **6h, 8g,** or **8i,** an additional peak, somewhat less strong and probably not due to νC–F, appeared at 956–966 cm^{-1}. [c] The νC≡C band for each of **8a–m** (except **k**) appeared at 2195–2205 cm^{-1}. The band for **8i** was accompanied by a somewhat stronger band at 2180 cm^{-1}. The νC≡C bands (cm^{-1}) for other compounds follow: **18,** 2225; **22,** 2230, 2150 (weak); **19,** 2200; **20,** 2165, 2100 (weak), 2200 (weak); **21,** 2125, 2170 (weak), 2200 (weak). [d] Neat for liquid and in KBr pellet for crystals. For **6** the intensity of the vinyl νC=C is generally low. [e] 20% solution in benzene (upfield relative to external CF_3CO_2H). CF_3 chemical shift −15.0 ppm for **6g** and −15.1 ppm for **8g.** [f] Bp 101 °C (12 mm) reported in ref 2; bp 89–89.9 °C (10.5 mm) and n^{26}D 1.5596 reported in ref 3. [g] Difficult to measure n^{20}D; n^{30}D 1.6416.

obtainable directly by Cadiot–Chodkiewicz coupling as well as by dehydrohalogenation reactions.

The 2,2-dichloro-1-fluorovinyl group has spectroscopic features advantageous for characterization. In mass spectra of **6** and **8** the parent peaks, confirmed easily by the characteristic relative intensities of isotope (Cl) peaks, were generally the strongest peaks, and fragments derived from the parents by loss of one and two chlorines, respectively, were also clearly observed except for ferrocene derivatives. Structural correlation of ^{19}F NMR chemical shift and of νC=C frequency, as seen in Table III, may be useful for such purposes. Anomalies for **6a** and **6h** probably originate from steric repulsion by the methoxy group and by the peri hydrogen, respectively.

During the course of this investigation the following three cases have been noted as potentially hazardous: (1) distillation in one-flask preparation of **9j,**[35] (2) distillation stated in ref 14, (3) exothermic reaction described under the heading of "Reaction of CF_2=CCl_2 with Excess Butyllithium" in the Experimental Section. The toxicity of **1** may be inferred to be comparable to those of chloroacetyl chloride, methyl acrylate, etc.,[36] or to be intermediate between those of methyl dichloroacetate and methyl chloroacetate.[37]

Experimental Section

All melting and boiling points are uncorrected. ^{19}F NMR spectra were recorded on a Hitachi R-20BK using trifluoroacetic acid as external standard. Uv spectra were recorded on a Perkin-Elmer 202. Ir spectra were recorded on a Hitachi EPI-G3. Mass spectra were obtained on a Hitachi RMU-7. GC works were performed using a 4-m column of Silicon-DC 550. GC peak area ratios were obtained by weighing papers under curves. Quantitative analysis by GC was made on the basis of the assumed proportionality in peak height using reference solutions in each of which the ratio of the internal standard to the compound to be determined was equal or almost equal to that for the solution to be analyzed. Merck alumina (activity II–III) was used for elution chromatography. All reactions of organolithium and -magnesium compounds were conducted under an atmosphere of nitrogen using a T-tube for nitrogen inlet and outlet. Sodium-dried ether was exclusively used as reaction solvent except that benzene was added as cosolvent for the reaction of **5h** with **1.** Each stock solution (ca. 600 ml, ca. 520 g) of butyllithium was prepared from 1 mol of butyl bromide at about −20 °C, stored in a brown bottle at −20 °C, and used generally within a few months. The amount of butyllithium in a solution taken from a stock solution is expressed by the nominal amount calculated by weight assuming 100% yield from butyl bromide. 1,1-Dichloro-2,2-difluoroethylene (**1**) was obtained by dehalogenation of 1,1,1,2-tetrachloro-2,2-difluoroethane,[38] which was prepared as described below, with zinc in ethanol, distilled twice from phosphorus pentoxide under nitrogen, stored in brown bottles at −20 °C, and used generally within several months after each preparation. Refluxing with **1** (bp 19 °C) was conducted using a condenser circulated with ice water. Refluxing was discontinued overnight if indicated, for example, as "refluxed for 20 h in 2 days".

1,1,1,2-Tetrachloro-2,2-difluoroethane (Precursor of 1).[39] A mixture of 1,1,2-trichloro-1,2,2-trifluoroethane (500 g, 2.67 mol; Daiflon S3, equivalent of Freon 113) and aluminum chloride (30 g, 0.22 mol; powdered reagent usable directly, granular reagent usable after brief grind) was refluxed for 3 h with vigorous mechanical stirring. Upon discontinuation of stirring and external heating, refluxing ceased temporarily but was resumed in a few minutes by the heat of isomerization ($CF_2ClCFCl_2 \rightarrow CF_3CCl_3$). After the refluxing became milder, the mixture was slowly stirred, and 1,1,2,2-tetrachloro-1,2-difluoroethane (1027 g, 5.04 mol; Daiflon S2, equivalent of Freon 112) was added at such a rate that the internal temperature was kept between 40 and 60 °C. Slow stirring was continued for an additional 50 min around 50 °C, external heating being applied toward the end of this period. Water (20 ml) was added with vigorous stirring, and the liquid portion of the resulting mixture, while warm, was transferred to a still pot by decantation. Fractional distillation afforded 1,1,1-trichloro-2,2,2-trifluoroethane, bp 45–47 °C (388 g, 2.07 mol), and 1,1,1,2-tetrachloro-2,2-difluoroethane, bp 92–93 °C (1019 g, 5.00 mol). The results were essentially reproducible in more than 20 such preparations though in some cases the yield of the tetrachlorodifluoroethane was reduced to about 900 g by disproportionation ($3CF_2ClCCl_3 \rightarrow 2CF_3CCl_3 + CCl_3CCl_3$). In no case was unisomerized 1,1,2,2-tetrachloro-1,2-difluoroethane detected (^{19}F NMR).

Work-up procedures were performed by conventional methods of hydrolysis by ice plus hydrochloric acid (procedure A) or by ice or water (procedure B) followed by extraction in ether. Reaction mixtures resulting from magnesium compounds were satisfactorily worked up by the procedure A. On the other hand, when a reaction mixture containing lithium fluoride was shaken with an aqueous solution, phase separation was generally difficult or incomplete unless lithium fluoride was removed by suction filtration. The filtration was performed only with some difficulty in many cases, particularly in the procedure B and for larger scale experiments. In some cases of the work-up procedure B, a limited amount of water was added to the active reaction mixture, and the resulting mixture refluxed for 10 min–2 h as an attempt to reduce this difficulty. After cooling, filtration was performed, or only a rough separation was achieved by decantation. The ether solutions were dried over

Na_2SO_4, after washing with aqueous sodium bicarbonate in the cases of the procedure A. Aliquots were withdrawn and reserved. The remaining solution was generally evaporated using a rotary film evaporator. The fraction (e.g., 0.90) of the solution actually subjected to the isolation procedure is necessary for yield calculation and given as "÷0.90" at the place where the yield of the main product is described. The amounts withdrawn for monitoring the reactions are neglected.

β,β-Dichloro-α-fluoro-o-methoxystyrene (6a). Anisole (0.75 mol) was lithiated with butyllithium under refluxing conditions for a total of 12 h, and the resulting mixture added to a solution of **1**. The yields of anisole, o-chloroanisole, and **6a** isolated by distillation were 15, 4, and 41%, respectively (excluding mixed fractions). The yields of these compounds determined by GC with a reserved aliquot after addition of n-tetradecane as internal standard were 21, 19, and 52%, respectively.

1-(2,2-Dichloro-1-fluorovinyl)naphthalene (6h). To magnesium ribbons (13.0 g, 0.53 g-atom) were added small portions of 1-bromonaphthalene (103.5 g, 0.500 mol) and ether (300 ml). After the reaction was initiated by scratching magnesium surfaces with a glass rod in twisting motions, the remaining portions were added over a period of 45 min with mechanical stirring. The resulting mixture was further refluxed for 30 min by external heating and diluted with benzene (100 ml). Upon addition of **1** (115 g, 0.87 mol) a mildly exothermic reaction occurred. Refluxing was maintained for 2 h without heating and for a total of an additional 14 h in 2 days by external heating. Work-up (A) and fractional distillation afforded 94.7 g (÷0.96, 82%) of **6h,** bp 99–103 °C (1 mm), which crystallized upon seeding. A sample recrystallized from ethanol melted at 45–46.5 °C: mass spectrum *m/e* (rel intensity) 240 (M^+ for 2 ^{35}Cl, 23), 205 (50), 170 (100), 102 (14). Without benzene cosolvent the reaction rate was less than half.

2-(2,2-Dichloro-1-fluorovinyl)thiophene (6j). To a stirred, ice-cooled solution of thiophene (79.8 g, 0.95 mol) in ether (100 ml) was added ethereal butyllithium (600 ml, 1.00 mol). The resulting solution was refluxed for 30 min and added to a solution of **1** (150 g, 1.13 mol) in ether (100 ml) over a period of 30 min at −20 to −30 °C. After 4 h of refluxing 147 g (÷0.97, 81%) of **6j,** bp 125 °C (48 mm), was obtained as the sole product: mass spectrum *m/e* (rel intensity) 196 (M^+ for 2 ^{35}Cl, 100), 161 (33), 126 (47), 117 (18), 81 (15).

2-(2,2-Dichloro-1-fluorovinyl)benzothiazole (6k). Benzothiazole (67.6 g, 0.50 mol) was added dropwise to a stirred solution (500 ml) of butyllithium (0.50 mol) in ether over a period of 74 min, during which time the internal temperature was kept between −70 and −75 °C by strong cooling with dry ice–acetone. Soon after the addition was complete, the resulting mixture was poured into an ice-cooled, stirred solution of **1** (125 g, 0.94 mol) in ether (200 ml). The temperature rose quickly to 23 °C and began to descend in a few minutes. The ice bath was removed, and the resulting mixture stirred for an additional 10 min and worked up (A). Concentration of the resulting solution followed by filtration and washing with ethanol afforded 70 g (÷0.96, 59%) of **6k,** mp 80–81.5 °C. The analytical sample, mp 81–82.5 °C, obtained after chromatography followed by recrystallization from ethanol was almost colorless: mass spectrum *m/e* (rel intensity) 247 (M^+ for 2 ^{35}Cl, 100), 212 (3), 177 (16), 168 (13), 146 (5), 108 (33), 82 (15), 69 (40).

(2,2-Dichloro-1-fluorovinyl)ferrocene (6l). An ether solution (800 ml) containing ferrocene (50.0 g, 0.269 mol) and butyllithium (0.34 mol) was left standing for 24 h at room temperature and cooled in a dry ice–acetone bath with mechanical stirring. To the resulting orange-red slurry was added **1** (88 g, 0.66 mol) in several portions keeping the internal temperature below −50 °C. From the product mixture obtained after 2 h of refluxing, work-up (A), and passage through an alumina (215 g) column as benzene solution, were removed orange crystals (19.7 g) of ferrocene. The rest of the material, which contained **6l** (83%), **11** (4%), and **6m** (13%) according to ^{19}F NMR, was steam distilled (vacuum distillation could not be performed[14]): fractions 1–2 (1 l. of H_2O), 10.2 g, ferrocene, **6l** (97%), **11** (3%); fractions 3–18 (9.6 l. of H_2O), 15.4 g, **6l** (95%), **11** (3.5%), **6m** (1.5%); residue, 9.6 g, **6l** (40%), **11** (8%), **6m** (52%).

Ferrocene (4.5 g, total 48.4%) was isolated as crystals from fractions 1–2. The total weight of the fractions 3–18 (containing practically no ferrocene) corresponds to 19% yield of **6l** based on the initially used ferrocene and to 37% yield based on the unrecovered ferrocene. The analytical sample of **6l** was obtained by a repeated steam distillation of selected fractions obtained from similar runs. Samples of **6l** obtained from chromatography had a tendency to be changed into an amorphous solid on standing whereas ones obtained in early stages of steam distillation were stable and remained as a red oil. The persistent impurity is thought to have the structure **11**. The ^{19}F NMR signal of this compound appeared between those of **6l** and **6m**. In mass spectra of samples of **6l** containing this compound, small peaks consistent as the isotopic parent peaks of **11** were observed. Mass peaks of almost pure **6l** follow: *m/e* (rel intensity) 298 (M^+ for 2 ^{35}Cl, 90), 171 (85), 153 (47), 152 (65), 123 (100).

1,1′-Bis(2,2-dichloro-1-fluorovinyl)ferrocene (6m). An ethereal solution (500 ml) containing ferrocene (25.0 g, 0.134 mol) and butyllithium (0.34 mol) was left standing for 86 h at room temperature and cooled in a dry ice–acetone bath with stirring. After addition of **1** (61 g, 0.46 mol) the mixture was carefully allowed to warm to 18 °C in 1.5 h (exothermic around −30 °C), refluxed for 2 h, and worked up (A). The resulting solution was concentrated and steam distilled (600 ml of condensed water) to give 5.8 g of crude ferrocene. The warm hexane solution of the residue was passed through a short alumina (138 g) column. The eluate (440 ml) was concentrated to ca. 100 ml and cooled to −20 °C giving **6m** (20.1 g) as red crystals, mp 83–84.5 °C. The second crop (1.0 g, mp 78–79 °C) increased the total yield to 39% (÷0.97). The compound was recrystallized from ethanol, mp 84–85 °C, *m/e* 410 (M^+ for 4 ^{35}Cl). The material recovered from the mother liquor was steam distilled (350 ml of H_2O), and the residue (11.9 g) chromatographed to give **6l** (5.3 g, 14%), which was, however, unstable (see the last part of the description for **6l**).

1,1-Dichloro-2-fluoro-4-phenyl-1-buten-3-yne (8d). To a stirred, cooled solution of **6d** (38.2 g, 0.200 mol) in ether (100 ml) was added ethereal butyllithium (260 ml, 0.45 mol) over a period of 2 h at −60 °C. The temperature was allowed to rise to 0 °C in 1 h, **1** (50 g, 0.38 mol) was added, and the resulting mixture was refluxed for 6 h and worked up (B). Fractional distillation afforded 32.6 g (÷0.95, 80%) of **8d:** bp 111 °C (10 mm); *m/e* (rel intensity) 214 (M^+ for 2 ^{35}Cl, 100), 179 (14), 160 (3), 144 (62). The ir spectrum of the sample was indistinguishable from that of **8d** obtained in 76% yield from ethynylbenzene (1.00 mol) after treatment with butyllithium and refluxing with **1** for 9 h.

***p*-Bromoethynylbenzene (9f).** The ir (KBr) agreed with a published one[40] except that our spectrum was devoid of three weak bands (4.32, 9.92, 12.35 μ). Mass spectrum *m/e* (rel intensity) 182 (M^+ for ^{81}Br, 99), 180 (M^+ for ^{79}Br, 100), 101 (65). Lit.[41] mp 63 °C.

2-Ethynylthiophene (9j). To a stirred, cooled solution of **6j** (59.1 g, 0.300 mol) in ether (100 ml) was added ethereal butyllithium (380 ml, 0.68 mol) over a period of 2 h at −40 to −60 °C. Work-up (A) and fractional distillation afforded 23.7 g (÷0.94, 78%) of **9j,** bp 55–56 °C (30 mm), $n^{20}D$ 1.5849 [lit.[27] bp 31–33 °C (3 mm), $n^{20}D$ 1.5886; lit.[28b] bp 40 °C (12 mm), $n^{20}D$ 1.5851; lit.[30] bp 54–60 °C (20 mm)].

2-Ethynylbenzothiazole (9k). To a stirred, cooled slurry of **6k** (12.4 g, 0.050 mol) in ether (150 ml) was added ethereal butyllithium (70 ml, 0.114 mol) over a period of 40 min at about −50 °C. The solution obtained after work-up (B) was dried over Na_2SO_4 and evaporated. Steam distillation of the residual oil (7.3 g) afforded 3.46 g (÷0.84, 52%) of **9k,** mp 39–41 °C. The compound, upon standing in the absence of solvent, had a tendency to be converted into fiberlike crystals: mp 42–43 °C; mass spectrum *m/e* (rel intensity) 159 (M^+, 100), 108 (19), 70 (20); ir (KBr) 3420 (≡CH), 2105 cm^{-1} (C≡C).

Anal. Calcd for C_9H_5NS: C, 67.89; H, 3.17; N, 8.80. Found: C, 67.94; H, 3.02; N, 8.89.

In a similar run where the whole mixture obtained after hydrolysis was directly subjected to steam distillation, the yield of **9k** was considerably lower, the major compound in later distilled fractions being 2-methylbenzothiazole, confirmed by comparison of the ir with that of an authentic sample. Apparently, **9k** was converted (via hydration followed by decarbonylation) into 2-methylbenzothiazole during the steam distillation probably by the catalytic action of lithium hydroxide or fluoride.

Phenylpropiolic Acid (10d). To a stirred solution of **6d** (19.1 g, 0.100 mol) in ether (100 ml) was added ethereal butyllithium (130 ml, 0.217 mol) around −50 °C. Pieces of dry ice (ca. 50 g) were added to the reaction mixture in several portions over a period of 30 min, initially the temperature being kept below −20 °C by cooling. After addition of 120 ml of water, the whole mixture was shaken vigorously and filtered in order to remove lithium fluoride. The aqueous layer was separated, washed with ether, and acidified (aqueous HCl). Filtration followed by drying afforded 12.2 g (84%) of **10d,** mp 133–136 °C. The identity of a recrystallized sample, mp 136.5–138.5 °C, from carbon tetrachloride was confirmed by its undepressed mixture melting point with an authentic sample (mp 137–138 °C).

Chloroethynylbenzene (13d) was obtained in 61% yield from 0.30 mol of **6d** and 0.31 mol of butyllithium, bp 70 °C (20 mm), n^{20}D 1.5794 [lit.[25a] bp 65 °C (10 mm), n^{20}D 1.5783]. The ir spectrum was identical with a reported one.[42]

Reaction of CF_2=CCl_2 with Butyllithium Followed by Addition to Cyclohexanone. To a stirred, well-cooled solution of **1** (20 g, 0.15 mol) in ether (100 ml) were added ethereal butyllithium (65 ml, 0.102 mol) over a period of 25 min and then a solution of cyclohexanone (9.8 g, 0.10 mol) in ether (30 ml) over a period of 20 min. A dark blue mixture resulted. The internal temperature was maintained around −70 °C during these additions and allowed to rise gradually to 17 °C in 1.7 h. The crude product obtained after work-up (B) followed by brief rotary evaporation indicated an AB pattern (4.7, 8.0 ppm, J = 22 Hz) in ^{19}F NMR. Fractional distillation was performed using a packed column washed with aqueous alkali with a small amount of potassium carbonate powder added in the still pot. 1-(1-Chloro-2,2-difluorovinyl)cyclohexanol (**14**), bp 68–72 °C (8 mm) (12.4 g, 62%), was obtained in three fractions, the first two of which were contaminated with a small amount of cyclohexanone (lit.[20] bp 72–75 °C). The fractions decomposed in succession within a few hours after standing in stoppered flasks for 1 day at room temperature. When the decomposition occurred in each flask, the stopper was expelled and the content became hot generating an irritating fume (presumed to be HF). These observations and the change in ir, disappearance of the 1728-cm^{-1} peak (CF_2=CCl–), and appearance of an 1800-cm^{-1} peak (acyl fluoride), are consistent with the transformation to **15**. The decomposed liquid samples changed to crystals of cyclohexylidenechloroacetic acid (**16**) upon further standing for several months. After recrystallization from hexane a total of 5.2 g (29%) of **16**, mp 101–102 °C, was collected: mass spectrum m/e (rel intensity) 176 (M^+ for ^{37}Cl, 9), 174 (M^+ for ^{35}Cl, 31), 68 (100); ir (KBr) 2900 (carboxylic OH, br), 1690 (C=O), 1618 cm^{-1} (C=C).

Anal. Calcd for $C_8H_{11}O_2Cl$: C, 55.02; H, 6.35; Cl, 20.3. Found: C, 54.80; H, 6.16; Cl, 20.1.

Reaction of CF_2=CCl_2 with Excess Butyllithium. To a stirred, cooled solution (600 ml) of butyllithium (1.00 mol) in ether was added a solution of **1** (42 g, 0.32 mol) in ether (50 ml) over a period of 30 min at −40 °C. A 1-ml portion of the reaction mixture boiled as soon as it was withdrawn to a vial. The remaining mixture was intended to be warmed slowly by adjusting the efficiency of cooling (dry ice–acetone bath). However, the temperature rise was uncontrollably rapid above −20 °C, the mixture boiled, and a partial content (estimated 100 ml) was lost from the top of the Dimroth condenser, circulated with ice-cooled water. GC indicated the formation of 1-hexyne and butyl chloride. After addition of **1** (103 g, 0.77 mol) the resulting mixture was refluxed for a total of 10 h in 2 days and worked up (B). Fractional distillation afforded **18**, bp 96–97.5 °C (30 mm), which was identical in ir and GC with the compound obtained as described below. The yield (30.3 g) corresponds to 49% based on the initially added **1**.

1,1-Dichloro-2-fluoro-1-octen-3-yne (18) was obtained in 78% yield from 0.62 mol of 1-hexyne after treatment with butyllithium followed by refluxing with **1** for 23 h in 3 days: mass spectrum m/e 194 (M^+ for 2 ^{35}Cl).

1,1-Dichloro-2-fluoro-6-phenyl-1-hexene-3,5-diyne (19). To a stirred solution of **8d** (43.0 g, 0.200 mol) in ether (80 ml) was added ethereal butyllithium (250 ml, 0.45 mol) over a period of 1.4 h at −50 °C. After 1 h the olefin **1** (50 g, 0.38 mol) was added, and the resulting mixture refluxed for 2 h and worked up (B). Recrystallization from ethanol afforded 40.2 g (84%) of **19**, mp 64–65 °C. Purified samples were colorless: mp 65–66 °C; bp ca. 160 °C (4 mm); mass spectrum m/e (rel intensity) 238 (M^+ for 2 ^{35}Cl, 43), 203 (24), 184 (5), 168 (100).

1,1-Dichloro-2-fluoro-10-phenyl-1-decene-3,5,7,9-tetrayne (21). A solution of **20** (26.3 g, 0.100 mol) was added to ethereal butyllithium below −60 °C, and the resulting mixture refluxed with **1** for 1 h. A considerable amount of carbon powderlike materials was formed. Work-up (B), chromatography, and recrystallization from ethanol afforded 9.6 g (33%) of **21**, mp 67–68 °C. Although this sample turned black in several months, recrystallization from ethanol, after removal of carbonaceous materials by filtration, regenerated beautiful, deep yellow needles, mp 67.5–68.5 °C, which showed only a slight change in appearance during storage at ambient temperature for 20 months (in the dark): mass spectrum m/e (rel intensity) 286 (M^+ for 2 ^{35}Cl, 85), 253 (51), 251 (41), 216 (100).

Uv absorption maxima are given in terms of λ, nm (log ε). **6d:** 207 (4.10), 256 (4.13). **8d:** 207 (4.20), 217 (4.16), 223 (4.14), 236 (4.00), 273 (4.28), 284 (4.36), 290 (shoulder), 301 (4.28). **19:** 208 (4.40), 218 (4.42), 231 (4.44), 253 (4.53), 265 (4.49), 274 (shoulder), 291 (4.29), 309 (4.44), 330 (4.39). **20:** 205 (4.45), 224 (4.41), 251 (4.65), 264 (4.86), 274 (4.78), 291 (4.77), 300 (shoulder), 320 (4.36), 343 (4.49), 369 (4.35). **21:** 209 (4.52), 277 (4.89), 292 (5.06), 301 (shoulder), 315 (4.88), 325 (shoulder), 349 (4.32), 376 (4.37), 407 (4.16). **18:** 236 (4.17), 241 (shoulder), 247 (4.13). **22:** 215 (4.49), 222 (4.53), 248 (3.84), 262 (4.15), 278 (4.35), 294 (4.29).

Registry No.—**1**, 79-35-6; **2a**, 100-66-3; **2i**, 110-00-9; **2j**, 110-02-1; **2k**, 95-16-9; **2l**, 102-54-5; **3b**, 104-92-7; **3c**, 106-38-7; **3d**, 108-86-1; **3e**, 106-39-8; **3f**, 106-37-6; **3g**, 402-43-7; **3h**, 90-11-9; **4** (R = C_4H_9), 109-72-8; **4a**, 31600-86-9; **4b**, 14774-77-7; **4c**, 2417-95-0; **4d**, 591-51-5; **4e**, 14774-78-8; **4f**, 22480-64-4; **4g**, 368-49-0; **4h**, 14474-59-0; **4i**, 2786-02-9; **4j**, 2786-07-4; **4k**, 39582-59-7; **4l**, 1271-15-4; **4m**, 33272-09-2; **6a**, 342-57-4; **6b**, 395-34-6; **6c**, 58228-99-2; **6d**, 394-99-0; **6e**, 58229-00-8; **6f**, 58229-01-9; **6g**, 401-06-9; **6h**, 58229-02-0; **6i**, 58229-03-1; **6j**, 58229-04-2; **6k**, 58229-05-3; **6l**, 58281-24-6; **6m**, 58281-25-7; **8a**, 58229-06-4; **8b**, 58229-07-5; **8c**, 58229-08-6; **8d**, 58229-09-7; **8e**, 58229-10-0; **8f**, 58229-11-1; **8g**, 58229-12-2; **8h**, 58229-13-3; **8i**, 58229-14-4; **8j**, 58229-15-5; **8l**, 58281-26-8; **8m**, 58281-27-9; **9d**, 536-74-3; **9f**, 766-96-1; **9h**, 15727-65-8; **9j**, 4298-52-6; **9k**, 40176-80-5; **10d**, 637-44-5; **10h**, 4843-42-9; **10j**, 4843-44-1; **13d**, 1483-82-5; **14**, 27258-83-9; **15**, 58229-16-6; **16**, 58229-17-7; **18**, 58229-18-8; **19**, 58229-19-9; **20**, 58229-20-2; **21**, 58229-21-3; **22**, 58229-22-4; 1,1,1,2-tetrachloro-2,2-difluoroethane, 76-11-9; 1,1,2-trichloro-1,2,2-trifluoroethane, 76-13-1.

References and Notes

(1) (a) Presented, in part, at the 28th Semiannual Meeting (April 1973, in Tokyo) and at the 30th Semiannual Meeting (April 1974, in Osaka) of the Japan Chemical Society. (b) Hirate Machi, Kita-ku, Nagoya, Japan.
(2) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).
(3) P. Tarrant and D. A. Warner, *J. Am. Chem. Soc.*, **76**, 1624 (1954).
(4) E. Ott and W. Bossaller, *Chem. Ber.*, **76**, 88 (1943).
(5) E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 3769 (1972).
(6) H. Gilman and F. W. Moore, *J. Am. Chem. Soc.*, **62**, 1843 (1940).
(7) H. Gilman, W. Langham, and A. L. Jacoby, *J. Am. Chem. Soc.*, **61**, 106 (1939); R. G. Jones and H. Gilman, *Org. React.*, **6**, 349 (1951).
(8) J. M. Malian and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).
(9) H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, **71**, 2328 (1949).
(10) R. A. Benkeser, D. Goggin, and G. Schroll, *J. Am. Chem. Soc.*, **76**, 4025 (1954).
(11) S. I. Goldberg, L. H. Keith, and T. S. Prokopov, *J. Org. Chem.*, **28**, 850 (1963).
(12) D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. Ind. (London)*, 1388 (1957).
(13) R. A. Benkeser and J. L. Bach, *J. Am. Chem. Soc.*, **86**, 890 (1964).
(14) In the first two experiments attempted separations of **6l** by vaccum distillation resulted in sudden exothermic decompositions of the whole contents of the still pots when most of unchanged ferrocene had distilled and **6l** began to distill.
(15) Naphthalene was found to be formed during the preparation of **4h**; higher temperatures favored the formation of naphthalene. In the run stated above, **4h** was prepared at about 20 °C. No substantial difference in the GC peak area ratio (0.71) of 1-chloronaphthalene/**6h** was observed with various preparations of **4h** obtained from **3h** with lithium or with butyllithium.
(16) With the reservation that a small portion of the RCl could arise from reaction of RLi with **12** and/or with its chlorine-containing derivatives, such as FC≡CCl.
(17) A product mixture obtained from reaction of **1** with **4d** at −60 °C followed by treatment with cyclohexanone contained **6d** and **14** (the cyclohexanone adduct of **12**) in an approximate ratio of 10:1 (5:1 integrated intensity ratio in ^{19}F NMR).
(18) R. N. Sterlin, R. D. Yatsenko, and L. L. Knunyants, *Khim. Nauka Prom.*, **3**, 540 (1958); *Chem. Abstr.*, **53**, 4195 (1959).
(19) (a) P. Tarrant, P. Johncock, and J. Savory, *J. Org. Chem.*, **28**, 839 (1963); (b) F. G. Drakesmith, R. D. Richardson, O. J. Stewart, and P. Tarrant, *J. Org. Chem.*, **33**, 286 (1968).
(20) H. G. Viehe and S. Y. Delavarenne, U.S. Patent 3 506 728 (1970).
(21) The reaction between chloroethynylbenzene and butyllithium is reported: H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **67**, 1420 (1945). See also ref 34.
(22) For the consecutive reactions A → B → with common reagent Y, the following differential equations can be assumed where k_1 and k_2 are the rate constants for A and B, respectively.

$$dA/dt = -k_1AY^n$$

$$dB/dt = k_1AY^n - k_2BY^n$$

Division of the latter equation by the former and integration give the following equation where A_0 is the initial concentration of A (B absent initially):

$$\log [(1 - k_2/k_1)B/A + 1] + (1 - k_2/k_1) \log (A/A_0) = 0$$

This equation is satisfied when k_2/k_1 is approximately 1/12.1 for the values A_0 = 1, A = 0.13, B = 0.78.

One of the referees criticized this calculation as the reversibility of the reaction of **13** and butyllithium is not considered. However, the relative importance of the reverse reaction is so small that the reaction can

be treated as practically irreversible in such a calculation.
(23) The most probable or most easily comprehensible course of RC≡CCl is a Cl–Li exchange followed by elimination of LiF. However, RCF=C-ClLi may or may not be formed at all. Hence the term "Cl–Li exchange" for these reactions is only tentative in the strict sense of the word.
(24) The reactions of halogeno olefins of other types (e.g., RCH=CHCl) with organolithiums to form acetylenic compounds have been described: M. Schlosser and V. Ladenberger, *Chem. Ber.*, **100**, 3901 (1967); G. Köbrich, *Angew. Chem.*, **77**, 75 (1965); G. Köbrich and P. Buck, "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 2. See also ref 5.
(25) Such considerations lead to the suspicion that the Cl–Li exchange reactivities of the chlorines in **6** would be greater than those of the respective chlorines of the corresponding trichlorovinyl compound. In a competitive experiment α,β,β-trichlorostyrene was converted into chloroethynylbenzene at 2.2 times the rate for **6d**. However, which of the chlorines of α,β,β-trichlorostyrene is preferentially exchanged is not clear.
(26) Previously the stabilization was explained by hyperconjugation by fluorine. However, this mechanism has been criticized: A. Streitwieser, Jr., and D. Holtz, *J. Am. Chem. Soc.*, **89**, 692 (1967); A. Streitwieser, Jr., A. P. Marchand, and A. H. Pudjaatmaka, *ibid.*, **89**, 693 (1968); D. Holtz, *Chem. Rev.*, **71**, 139 (1971).
(27) A. Vaitiekunas and F. F. Nord, *J. Org. Chem.*, **19**, 902 (1954).
(28) L. Brandsma "Preparative Acetylenic Chemistry", Elsevier, Amsterdam, 1971: (a) p 97; (b) p 117.
(29) R. E. Atkinson, R. F. Curtis, D. M. Jones, and J. A. Taylor, *J. Chem. Soc. C*, 2173 (1969).
(30) T. B. Patrick, J. M. Disher, and W. J. Probst, *J. Org. Chem.*, **37**, 4467 (1972).
(31) D. Bertin, *C. R. Acad. Sci.*, **229**, 660 (1949); *Chem. Abstr.*, **44**, 2969*i* (1950).
(32) P. Cadiot and W. Chodkiewicz, "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, pp 622–625.
(33) R. Eastmond and D. R. M. Walton, *Tetrahedron*, **28**, 4591 (1972).
(34) The formation of $C_6H_5(C{\equiv}C)_2Cl$ from the reaction between $C_6H_5C{\equiv}CMgBr$ and dichloroacetylene is also reported: H. G. Viehe, *Chem. Ber.*, **92**, 3064 (1959).
(35) The applicability of a one-flask procedure for the present method was tested in the case of the preparation of 2-ethynylthiophene. To a solution of thiophene (0.3 mol) was added successively ethereal butyllithium, **1** (in four portions over 12 min keeping the internal temperature between −40 and 5 °C), and ethereal butyllithium (at −50 °C), refluxing being conducted after the first and the second additions. On distillation of the product mixture obtained after work-up, exothermic decomposition of the pot residue, though not vigorous, occurred after 2-ethynylthiophene (53% yield, bp 35–37° at 10 mm) came out.
(36) C. P. Carpenter, H. F. Smyth, Jr., and U. C. Pozzani, *J. Ind. Hyg. Toxicol.*, **31**, 343 (1949); *Chem. Abstr.*, **44**, 3140*h* (1950).
(37) T. R. Torkelson, C. D Kary, M. B. Chenoweth, and E. R. Larsen, *Toxicol. Appl. Pharmacol.*, **19**, 1 (1971); *Chem. Abstr.*, **75**, 46979c (1971).
(38) W. T. Miller, Jr., E. W. Fager, and P. H. Griswald, *J. Am. Chem. Soc.*, **72**, 705 (1950).
(39) The results of related studies together with discussion of mechanistic implication of the stirring effect will be presented elsewhere.
(40) "Sadtler Standard Infrared Spectra", Sadtler Research Laboratories, Philadelphia, Pa., Midget ed, no. 7604 (sample source: Philadelphia College of Pharmacy and Science).
(41) A. D. Allen and C. D. Cook, *Can. J. Chem.*, **41**, 1084 (1963).
(42) R. D. McLachlan, *Spectrochim. Acta, Part A*, **26**, 919 (1970).

Alkylation–Reduction of Carbonyl Systems. VII. Synthesis of α-Cyclopropyl Aromatic Hydrocarbons by Cyclopropylation–Reduction of Aromatic Aldehydes and Ketones. Parameters of Cyclopropyl α, β, and γ Carbon-13 Shieldings in Cyclopropyl Aromatic Hydrocarbons

Stan S. Hall,* Chin-Kang Sha,[1] and Frank Jordan

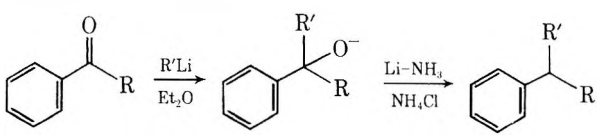
Carl A. Olson Chemistry Laboratories, Newark College of Arts and Sciences, Rutgers University, Newark, New Jersey 07102

Received October 15, 1975

α-Cyclopropyl aromatic hydrocarbons are conveniently prepared, in excellent yields, from aromatic carbonyl compounds by tandem cyclopropylation–reduction. By this procedure cyclopropyl benzyl alkoxides, generated in situ by cyclopropylation, are reduced by lithium–ammonia–ammonium chloride to the corresponding cyclopropyl aromatic hydrocarbons. Examples include cyclopropyl(4-*tert*-butyl)phenylmethane (**8**) from 4-*tert*-butylbenzaldehyde (**1**), 1-cyclopropyl-1-phenylethane (**9**) from acetophenone (**2**), 1-cyclopropylindan (**10**) from indanone (**3**), dicyclopropylphenylmethane (**11**) from cyclopropyl phenyl ketone (**4**), cyclopropyldiphenylmethane (**12**) from benzophenone (**5**), and 1-cyclopropyl-1,3-diphenylpropane (**13**) from benzylideneacetophenone (**6**). Cyclopropylation–reduction of phenyl vinyl ketone (**7**), in contrast, yielded 3-cyclopropyl-1-phenylpropane (**14**) via 1,4 addition. Carbon magnetic resonances were assigned to the cyclopropyl aromatic hydrocarbons. A comparison of the chemical shifts with those of model compounds possessing a hydrogen in place of the cyclopropyl group allowed the estimation of the following cyclopropyl substituent parameters: 17 ± 3.7 ppm (eight values) for α, 6.1 ± 1.3 ppm (five values) for β, and −1.6 ± 0.8 ppm for the γ position (four values). These shielding parameters are smaller but in the same direction as those for a phenyl group. Those compounds possessing a chiral or prochiral center adjacent to the cyclopropyl group exhibit chemical shift nonequivalence of the cyclopropyl methylene carbons.

Synthesis. This laboratory has been exploring the potential applications of tandem alkylation–reduction of aromatic carbonyl systems as a convenient method of preparing aromatic hydrocarbons.[2] The method involves the lithium–ammonia–ammonium chloride reduction of benzyl alkoxides generated in situ by alkylation. Since the entire sequence is performed in the same reaction vessel without the isolation or purification of intermediates, the total synthesis consumes only a few hours and the isolated yield of the product is usually excellent.

The introduction of a cyclopropyl group at the α position in an aromatic hydrocarbon is a very difficult task using classical procedures. After cyclopropylation of the requisite aromatic carbonyl system, for example, the α-cyclopropyl group would not be expected to survive the dehydration[3]–hydrogenation[4] sequence.[5] On the other hand, our tandem alkylation–reduction procedure, using in this case cyclopropyllithium and an aromatic carbonyl compound, offered a potential method of preparing α-cyclopropyl aromatic hydrocarbons.



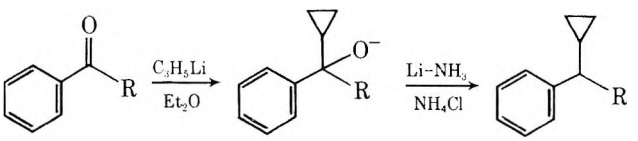


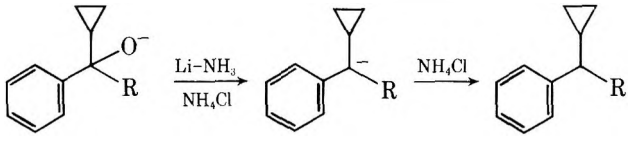
Table I. Cyclopropylation–Reduction of Aromatic Carbonyl Compounds

Carbonyl compd	Cyclopropylation–reduction product	% yield Analytical[a]	% yield Isolated[b]
4-*tert*-Butylbenzaldehyde (1)	Cyclopropyl(4-*tert*-butyl)phenylmethane (8)	99	98
Acetophenone (2)	1-Cyclopropyl-1-phenylethane (9)	90	82
Indanone (3)	1-Cyclopropylindan (10)	85	79
Cyclopropyl phenyl ketone (4)[c]	Dicyclopropylphenylmethane (11)	99	97
Benzophenone (5)	Cyclopropyldiphenylmethane (12)	99	98
Benzylideneacetophenone (6)	1-Cyclopropyl-1,3-diphenylpropane (13)	93	91
Phenyl vinyl ketone (7)	3-Cyclopropyl-1-phenylpropane (14)	60	51[d]

[a] Analyzed by GLC (% of volatiles). [b] Isolated by filtration column chromatography. [c] Owing to the low solubility of 4 in Et_2O, THF was used as the cosolvent. [d] The yield is low because of the presence of polar and higher molecular weight material (polymerization of phenyl vinyl ketone) that was efficiently removed by filtration chromatography.

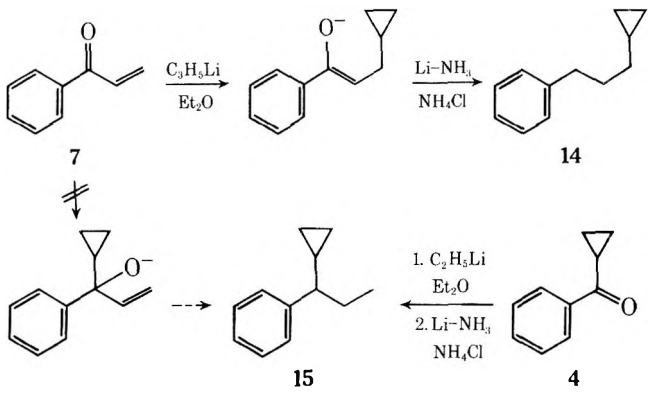
The general procedure adopted for this study was to generate a cyclopropyl benzyl alkoxide in a metal–ammonia reaction vessel[6] by the addition of the aromatic carbonyl compound to cyclopropyllithium, prepared in situ from cyclopropyl bromide and excess lithium, in ether. Ammonia is subsequently distilled into the vessel and then the resulting dark blue mixture is cautiously quenched with ammonium chloride. Table I is a listing of the aromatic carbonyl systems that were subjected to this procedure. Cyclopropylation–reduction of the aromatic aldehyde and ketones 1–5 afforded the corresponding α-cyclopropyl aromatic hydrocarbon in excellent isolated yields.

Since the α-cyclopropyl group does survive these reduction conditions, one significant mechanistic conclusion is possible. During the reduction sequence, from cyclopropyl benzyl alkoxide to product, the intermediate cyclopropyl benzyl anion protonates *exclusively* at the benzylic position.[7]



The cyclopropylation–reduction of the α,β-unsaturated aromatic ketones 6 and 7 requires some additional comments. The saturated product 13 from benzylideneacetophenone (6) was expected since benzylidene benzyl alkoxides are reduced to benzyl alkoxides in lithium–ammonia.[2c] The cyclopropylation–reduction of phenyl vinyl ketone (7)[8] resulted in exclusive 1,4 addition of the cyclopropyllithium yielding 3-cyclopropyl-1-phenylpropane (14) after reduction. Since we were somewhat surprised by this result, the expected product from 1,2 addition and subsequent reduction (1-cyclopropyl-1-phenylpropane, 15) was prepared by ethylation–reduction of cyclopropyl phenyl ketone (4).[9] See Scheme I.

Scheme I



This synthetic study demonstrates that tandem cyclopropylation–reduction of aromatic carbonyl systems is an extremely simple and efficient procedure for the synthesis of α-cyclopropyl aromatic hydrocarbons, compounds that have been heretofore unavailable or difficult to prepare.

Carbon-13 Studies. The structural analysis of organic compounds can be greatly facilitated by carbon magnetic resonance (^{13}C NMR) techniques. Essential to such analysis is the establishment of characteristic substituent chemical shifts. While such shifts for alkyl and phenyl groups (as well as for a number of other functional groups) are well documented,[10] to our knowledge no such values are available for the cyclopropyl substituent in hydrocarbons. The synthesis of cyclopropyl aromatic hydrocarbons in our laboratories made available a unique series of compounds whose ^{13}C NMR spectra we here report. Based on the comparison of the ^{13}C NMR chemical shifts of these compounds with models in which the cyclopropyl group is replaced by hydrogen, one can estimate the α, β, and γ cyclopropyl substituent shielding parameters.

Table II presents the results on the cyclopropyl hydrocarbons and the corresponding model compounds. Distinction between methyl, methylene, and methine carbons was achieved by the off-resonance decoupling technique. Spectra in the gated decoupling plus mode (corresponding to no decoupling but retaining the nuclear Overhauser enhancement) were also collected for compounds 10, 13, and 14. The only dubious assignment arose in the β and γ carbons of compound 14 (both complex multiplets). These assignments were made by comparisons with the other cyclopropyl compounds. For clarity, the resonances of the aliphatic, cyclopropyl, and phenyl regions will be discussed separately.

Aliphatic Carbons. The data in Table II presents the aliphatic carbon positions as 1, 2, and 3 from the phenyl ring. Table III summarizes the effect of cyclopropyl substitution on the chemical shifts. Clearly, the α and β effects are deshielding and the γ effect is weakly shielding. The α effects appear to fall roughly into two groups: 19 ± 1.5 ppm (compounds 9, 10, 11, 14, and 16) and 15 ± 1.7 ppm (compounds 11, 12, 13, and 15) or overall 17 ± 3.7 ppm. Since the compounds in the latter group have bulky substituents attached to the benzylic carbon (especially compounds 11 and 12), the lower α effects in this group may reflect the sterically induced polarization of the valence electrons caused by the sterically compressed system. This shielding effect opposes the deshielding electronic effect of the cyclopropyl group. Such shielding has been observed for sterically perturbed carbon atoms in other spatially crowded molecules.[11]

The β effects appear to be more uniform: 6.1 ± 1.3 ppm. In the molecules exhibiting both α and β effects, those that

Table II. Carbon-13 Chemical Shifts of Cyclopropyl Aromatic Hydrocarbons and Model Compounds[a]

Compd	Aromatic				Aliphatic			Cyclopropyl		
	C_i	C_p	C_o[b]	C_m[b]	C_1	C_2	C_3	CH	CH_2	CH_2
Cyclopropylphenylmethane (16)[c]	142.1	125.8	128.3	128.3	40.4			11.9	4.7	4.7
1-Cyclopropyl-1-phenylethane (9)	147.4	125.9	127.0	128.2	47.7	21.6		18.5	4.6	4.3
Dicyclopropylphenylmethane (11)	145.9	125.9	127.7	128.0	53.7			16.6	4.6	2.8
Cyclopropyldiphenylmethane (12)	145.1	126.0	128.1	128.1	55.7			16.7	5.3	5.3
1-Cyclopropylindan (10)	147.4[d]		126.4	124.4	50.1[e]	32.7		15.8	4.1	2.3
	144.2		126.0	123.9	31.5					
1-Cyclopropyl-1,3-diphenylpropane (13)	145.5[f]	126.0	127.6	128.2	50.4[g]	38.2		17.7	5.5	3.6
	142.5[h]	125.6	127.6	128.2	33.7					
3-Cyclopropyl-1-phenylpropane (14)	142.8	125.6	128.2	128.3	35.9	31.5	34.4	10.8	4.4	4.4
1-Cyclopropyl-1-phenylpropane (15)	145.9	125.8	127.6	128.1	52.8	29.6	12.2	17.3	5.6	3.5
Toluene (17)	137.7	125.3	128.2	129.0	21.3					
Ethylbenzene (18)	144.1	125.6	127.8	128.3	29.0	15.6				
n-Propylbenzene (19)	142.6	125.7	128.2	128.5	38.2	24.7	13.9			
Isopropylbenzene (20)	148.8	125.8	126.4	128.3	34.2	24.0				
Diphenylmethane (21)	141.0	126.0	128.4	128.9	41.9					
Indan (22)[i]	143.9		125.9	124.2	32.3	25.3				
1,3-Diphenylpropane (23)	142.2	125.7	128.3	128.3	35.4	32.9				

[a] The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. [b] No attempt was made to discern the ortho and meta carbons. [c] Prepared by the lithium–ammonia–ammonium chloride reduction of cyclopropyl phenyl ketone [S. S. Hall and C.-K. Sha, *Chem. Ind. (London)*, in press]. [d] C_4 = 126.0, C_5 = 123.9, C_6 = 124.4, C_7 = 126.4, C_8 = 147.4, C_9 = 144.2. [e] C_1 = 50.1, C_2 = 32.7, C_3 = 31.5. [f] 1-Phenyl group. [g] C_1 = 50.4, C_2 = 38.2, C_3 = 33.7. [h] 3-Phenyl group. [i] Data taken from L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, N.Y., 1972, p 342.

Table III. Shielding Effect of the Cyclopropyl Group on Aliphatic Carbons

	δ[a] (cyclopropyl aromatic hydrocarbon)	δ[a] (model aromatic hydrocarbon)	Δ, ppm[b]
α effects	40.4 (16)	21.3 (17)	19.1
	47.7 (9)	29.0 (18)	18.7
	53.7 (11)	40.4 (16)	13.3[c]
		21.3 (17)	19.1[d]
	55.7 (12)	41.9 (21)	13.8
	50.1 (10)	32.3 (22)	17.8
	50.4 (13)	35.4 (23)	15.0
	34.4 (14)	13.9 (19)	20.5
	52.8 (15)	38.2 (19)	14.6
β effects	21.6 (9)	15.6 (18)	6.0
	32.7 (10)	25.3 (22)	7.4
	38.2 (13)	32.9 (23)	5.3
	31.5 (14)	24.7 (19)	6.8
	29.6 (15)	24.7 (19)	4.9
γ effects	31.5 (10)	32.3 (22)	−0.8
	33.7 (13)	35.4 (23)	−1.7
	35.9 (14)	38.2 (19)	−2.3
	12.2 (15)	13.9 (19)	−1.7

[a] The chemical shift values are expressed in δ values (parts per million relative to a Me_4Si internal standard). [b] Positive values indicate deshielding by cyclopropyl; negative values indicate shielding. [c] Represents the α effect of the second cyclopropyl group. [d] Represents the α effect of the first cyclopropyl group.

yield low α parameters (compounds **13** and **15**) also yield low β parameters. The γ effects of the cyclopropyl group are small and, in contrast, shielding: -1.6 ± 0.8 ppm.

It is instructive to compare the effects of phenyl,[12] cyclopropyl, and alkyl groups:[13] 23, 17, and 9 ppm for α; 9.5, 6.1, and 9.4 ppm for β; and −2.0, −1.6, and −2.5 ppm for γ parameters, respectively. All three functional groups shield the 3-carbon position and deshield the 1- and 2-carbon positions. As can be seen, the substituent effect of the cyclopropyl group is consistently smaller than that of the phenyl group.

Successive replacement of cyclopropyl groups for hydrogens, in this study, indicates an α effect of 19.1 ppm (toluene, **17**, to cyclopropylphenylmethane, **16**) for the first and an α effect of 13.3 ppm (cyclopropylphenylmethane, **16**, to dicyclopropylphenylmethane, **11**) for the second. Similar trends and magnitudes have been previously observed in alcohols.[14] Successive replacement of hydrogens by cyclopropyl groups indicated an α effect of 17.9 ppm (methanol to cyclopropylcarbinol) for the first and an α effect of 14.7 ppm (cyclopropylcarbinol to dicyclopropylcarbinol) for the second with neat liquids. These comparisons are probably excellent examples of the effect of steric compression shielding discussed previously. The differences between the first and the second α effect in the two comparisons reflect the shielding caused by the sterically induced polarization of the valence electrons[11] when introducing the second cyclopropyl group. Since the α carbon is more sterically perturbed in dicyclopropylphenylmethane (**11**) than in dicyclopropylcarbinol, this shielding is larger.

Cyclopropyl Carbons. The most interesting features of the cyclopropyl resonances are that usually they are the most highly shielded and that in all cases in which the benzylic carbon is chiral two distinct methylene resonances are observed. The differences between these anisochronous methylene carbons range from ca. 0.3 to 2.1 ppm. This phenomenon, common in proton magnetic resonance, was first documented in ^{13}C NMR in chiral isopropylalkylcarbinols and chiral alkanes containing an isopropyl group.[15] Chemical shift nonequivalence of the cyclopropyl methylene carbons is also evident in dicyclopropylphenylmethane (**11**). This nonequivalence is presumably due to the presence of the prochiral benzylic center.[16] The methine carbon in the

cyclopropyl group is quite susceptible to substituent effects. As can be seen in Table II, its position ranges from 10.8 to 18.5 ppm.

Phenyl Carbons. The ipso phenyl carbon (C_i) and the para carbon (C_p) resonances could be rather unequivocally assigned. The ipso carbon resonance is invariably deshielded by the cyclopropyl group (a β effect at C_i) by ca. 3.8 ± 0.6 ppm (seven cases available). No attempt was made in this study to discern the ortho (C_o) and meta (C_m) carbon resonances. In many cases they coincided.

Experimental Section[17]

General Comments. The entire reaction sequence was performed under a static argon (prepurified) atmosphere, which is connected by a T tube to the assembly and to a soda lime drying trap that is connected in series to an oil bubbler, and is operated at a moderate flow rate throughout the synthesis. All glassware was oven dried and cooled to room temperature in a large box desiccator, and then quickly assembled. Anhydrous ether was used directly from freshly opened containers. Tetrahydrofuran (THF) was freshly distilled under nitrogen from $LiAlH_4$. Lithium wire (0.32 cm, high purity, Foote Mineral Co.) was wiped free of oil, cut into small pieces, and rinsed in petroleum ether just prior to use. Cyclopropyl bromide (99%, Aldrich Chemical Co.) was used without further purification. Anhydrous ammonia was distilled, through a tower of potassium hydroxide pellets, directly into the reaction vessel. Gas chromatography (GLC) analyses were performed on 100 × 0.4 cm (i.d.) glass columns, packed either with 4% silicone gum rubber UCC-W-982 (methylvinyl) supported on 80–100 mesh HP Chromosorb W (AW, DMCS) or with 3% silicone gum rubber OV-17 (methylphenyl) supported on 80–100 mesh HP Chromosorb W, using a 40 ml/min carrier gas flow rate, with a Hewlett-Packard Model 7610A (flame detector) chromatograph. Purification of the product by column chromatography was accomplished on chromatographic grade activated alumina (80–325 mesh, Matheson Coleman and Bell) by elution with petroleum ether. Evaporative distillations, sometimes necessary for microanalyses, were performed in a Kügelrohr oven. The assigned structure of each product is consistent with the spectral data. Satisfactory composition analyses on all products were submitted to the Editor. The cyclopropylation–reduction of 4-*tert*-butylbenzaldehyde (1) is described, in detail, to illustrate the general procedure.

Cyclopropylation–Reduction of 4-tert-Butylbenzaldehyde (1). Cyclopropyl(4-*tert*-butyl)phenylmethane (8). Into a metal–ammonia reaction vessel containing a stirred mixture of 280 mg of lithium (40 mg-atoms, ca. 25 pieces) in 2 ml of anhydrous ether that was cooled by an ice bath was slowly added a solution of 605 mg (5 mmol) of cyclopropyl bromide in 3 ml of ether. The reaction mixture slowly turned black. After the mixture was stirred at 0–5 °C for 1.5 h, it was cooled to ca. −70 °C (dry ice–acetone bath) and then a solution of 405 mg (2.5 mmol) of 4-*tert*-butylbenzaldehyde (1) in 5 ml of ether was slowly added. The mixture was stirred for 1 h at −70 °C and then diluted with 10 ml of ether. Ammonia (ca. 40 ml) was carefully, to prevent excessive splattering, distilled into the mixture and the cooling bath removed. After 20 min ca. 4 g of ammonium chloride was cautiously added[18] (ca. 15 min) to discharge the blue color and then the ammonia was allowed to evaporate. After the residue had been partitioned between brine and ether, the organic phase was dried ($MgSO_4$), filtered, concentrated at water aspirator pressure at 30–40 °C, and then analyzed (GLC). Following column chromatography 461 mg (98%) of cyclopropyl(4-*tert*-butyl)phenylmethane (8) was obtained as a colorless oil: ir (film) 3090, 3020, 2980, 2930, 1465, 1370, 1275, 1020, 820 cm^{-1}; NMR (60 MHz, CCl_4) δ 7.26 (2 H, d, J = 9 Hz), 7.10 (2 H, d, J = 9 Hz), 2.48 (2 H, d, J = 7 Hz), 1.29 (9 H, s), 1.12–0.61 (1 H, m), 0.61–0.30 (2 H, m), 0.30–0.04 (2 H, m); mass spectrum m/e (rel intensity) 188 (M^+, 14), 173 (100), 147 (46), 145 (26), 132 (26), 131 (34), 117 (26), 115 (17), 91 (31), 55 (66), 41 (31).

1-Cyclopropyl-1-phenylethane (9): NMR (60 MHz, CCl_4) δ 7.10 (5 H, apparent s), 2.17–1.73 (1 H, m), 1.30 (3 H, d, J = 6 Hz), 1.18–0.60 (1 H, m), 0.60–0.33 (2 H, m), 0.33–0.04 (2 H, m); mass spectrum m/e (rel intensity) 146 (M^+, 11), 131 (63), 118 (61), 117 (75), 105 (100), 104 (32), 91 (72), 79 (24), 77 (28).

1-Cyclopropylindan (10): NMR (100 MHz, $CDCl_3$) δ 7.60–7.32 (1 H, m), 7.32–7.03 (3 H, m), 3.10–2.59 (2 H, m), 2.59–2.24 (1 H, m), 2.24–1.88 (1 H, m), 1.84–1.53 (1 H, m), 1.10–0.65 (1 H, m), 0.65–0.06 (4 H, m); mass spectrum m/e (rel intensity) 158 (M^+, 25), 130 (100), 129 (44), 117 (96), 115 (54), 91 (19), 51 (17), 39 (29).

Dicyclopropylphenylmethane (11): NMR (100 MHz, $CDCl_3$) δ 7.23 (5 H, s), 1.41 (1 H, t, J = 8.5 Hz), 1.20–0.90 (2 H, m), 0.61–0.03 (8 H, complex m); mass spectrum m/e (rel intensity) 172 (M^+, 1), 143 (59), 129 (100), 115 (28), 104 (99), 91 (52), 77 (29), 51 (41), 39 (69).

Cyclopropyldiphenylmethane (12): NMR (60 MHz, CCl_4) δ 7.16 (10 H, apparent s), 3.20 (1 H, d, J = 9.3 Hz), 1.62–0.90 (1 H, m), 0.82–0.43 (2 H, m), 0.43–0.07 (2 H, m); mass spectrum m/e (rel intensity) 208 (M^+, 3), 180 (73), 179 (36), 165 (33), 152 (12), 115 (17), 104 (100), 91 (24), 77 (17), 51 (24), 39 (25).

1-Cyclopropyl-1,3-diphenylpropane (13): NMR (60 MHz, CCl_4) δ 7.18 (5 H, apparent s), 7.11 (5 H, apparent s), 2.70–2.30 (2 H, m), 2.30–1.45 (3 H, m), 1.14–0.68 (1 H, m), 0.68–0.06 (4 H, complex m); mass spectrum m/e (rel intensity) 236 (M^+, 12), 208 (2), 207 (3), 195 (1), 193 (2), 145 (6), 132 (35), 131 (56), 117 (56), 104 (19), 91 (100).

3-Cyclopropyl-1-phenylpropane (14): NMR (100 MHz, $CDCl_3$) δ 7.38–6.98 (5 H, m), 2.62 (2 H, t, J = 7.5 Hz), 1.72 (2 H, apparent quintet, J = 7.5 and 7.1 Hz), 1.23 (2 H, quartet, J = 7.1 Hz), 0.86–0.50 (1 H, m), 0.50–0.29 (2 H, m), 0.29 to −0.06 (2 H, m); mass spectrum m/e (rel intensity) 160 (M^+, 23), 131 (30), 117 (30), 104 (40), 91 (100), 77 (10), 65 (16), 51 (13), 41 (30), 39 (23).

1-Cyclopropyl-1-phenylpropane (15):[9] NMR (100 MHz, $CDCl_3$) δ 7.50–6.95 (5 H, m), 2.05–1.40 (3 H, m), 0.82 (3 H, t, J = 7 Hz) superimposed on 1.1–0.67 (1 H, m), 0.67–0.04 (4 H, complex m); mass spectrum m/e (rel intensity) 160 (M^+, 10), 131 (100), 119 (12), 117 (38), 104 (28), 91 (78), 77 (12), 51 (12), 41 (12), 39 (12).

Carbon-13 Studies. All spectra were recorded on a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer at 25.2 MHz in the pulse Fourier transform mode. Sample tubes (10 mm) contained about 1.5 ml of $CDCl_3$ solution of ca. 1 M hydrocarbon. A 45° pulse was used for an average of 500 scans per sample to achieve satisfactory signal-to-noise ratios. Chemical shifts were recorded by the Texas Instrument JEC-100 computer system against both internal tetramethylsilane (1% Me_4Si) and the center peak of the $CDCl_3$ triplet. The chemical shifts quoted are thought to be accurate to better than ±0.1 ppm. Eight thousand data points were employed with a spectral width of 250 ppm. Exponential window with a −5 setting was employed to improve the signal-to-noise ratio along with a Systematic Noise Reduction device supplied by the JEOL Co., Cranford, N.J. A noise (broad band proton) decoupled spectrum was first collected for all compounds. Next off-resonance decoupling was employed on selected compounds to assure unequivocal assignments. On three compounds spectra were also run without decoupling (in the Gated Decoupling plus mode to retain the nuclear Overhauser enhancement) to allow observation of long-range coupling patterns.

Acknowledgments. The authors wish to thank Dr. F. Scheidl, Hoffmann-La Roche Inc., Nutley, N.J., for the microanalyses.

Registry No.—**1**, 939-97-9; **2**, 98-86-2; **3**, 83-33-0; **4**, 3481-02-5; **5**, 119-61-9; **6**, 4452-11-3; **7**, 768-03-6; **8**, 58249-45-9; **9**, 16510-30-8; **10**, 58249-46-0; **11**, 5689-20-3; **12**, 5746-99-6; **13**, 58280-91-4; **14**, 58249-47-1; **15**, 58249-48-2; **16**, 1667-00-1.

References and Notes

(1) Taken in part from the Master of Science Thesis of C.-K.S. submitted to the Graduate School, Rutgers University, Oct 1975.
(2) (a) Part VI: S. S. Hall, F. J. McEnroe, and Ho-Jane Shue, *J. Org. Chem.*, **40**, 3306 (1975); (b) S. S. Hall and F. J. McEnroe, *ibid.*, **40**, 271 (1975); (c) S. S. Hall, *ibid.*, **38**, 1738 (1973); (d) S. S. Hall and S. D. Lipsky, *ibid.*, **38**, 1735 (1973).
(3) (a) J. C. Martin and R. J. Arhart, *J. Am. Chem. Soc.*, **93**, 4327 (1971); (b) H. Hart and P. A. Law, *ibid.*, **84**, 2462 (1962).
(4) (a) P. N. Rylanders, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967, pp 468–472; (b) S. Sarel and E. Breuer, *J. Am. Chem. Soc.*, **81**, 6522 (1959).
(5) Alternatively, one might consider the Simmons–Smith reaction that then introduces the problem of preparing the required β,γ-unsaturated aromatic hydrocarbon.
(6) For a useful general discussion of metal–ammonia experimental techniques see M. Smith in "Reduction", R. L. Augustine, Ed., Marcel Dekker, New York, N.Y., 1968, pp 98–105.
(7) For a discussion of the proposed mechanism of the reduction of a benzyl alkoxide to an aromatic hydrocarbon see (a) S. S. Hall, S. D. Lipsky, and G. H. Small, *Tetrahedron Lett.*, 1853 (1971); (b) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971). The intermediate cyclopropyl benzyl anion, as well as the corresponding radical intermediate, might be expected to cleave the cyclopropyl ring.
(8) Prepared by the phenylation of acrolein; followed by Jones oxidation of

the benzyl alcohol. Since the ketone rapidly polymerizes, the alcohol should be oxidized and the product ketone **7** distilled and used immediately.
(9) The general ethylation–reduction procedure used was the same as is described in the Experimental Section for compound **8**, except that ethyllithium was generated in situ, from freshly distilled ethyl bromide and excess lithium, in ether. Yield of **15**: 98% (isolated).
(10) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 55–127.
(11) (a) W. R. Woolfenden and D. M. Grant, *J. Am. Chem. Soc.*, **88**, 1496 (1966); (b) D. M. Grant and B. V. Cheney, *ibid.*, **89**, 5315 (1967).
(12) Reference 10, p 98.
(13) Reference 10, p 58.
(14) G. A. Olah, P. W. Westerman, and J. Nishimura, *J. Am. Chem. Soc.*, **96**, 5348 (1974).
(15) J. I. Kroschwitz, M. Winokur, H. J. Reich, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 5928 (1969).
(16) W. B. Jennings, *Chem. Rev.*, **75**, 307 (1975).
(17) The ir spectra were determined with a Beckman Model IR-10 infrared recording spectrophotometer. The ^{1}H NMR spectra were determined at 60 MHz with a Varian Associates Model T-60 NMR spectrometer or with a Hitachi Perkin-Elmer Model R-24A NMR spectrometer, and at 100 MHz with a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. ^{1}H NMR samples were run with and without Me_4Si. The mass spectra were determined with an AEI Model MS-30 mass spectrometer (70 eV) to which was interfaced a Pye Unicam Model 104 gas chromatograph.
(18) The ammonium chloride is most conveniently introduced by attaching a glass bulb tube filled with the salt to a side arm by means of tygon tubing. When the ammonium chloride is to be added, the bulb is raised and tapped gently to smoothly introduce the quenching agent. Should this step start to become violent, the addition and sometimes even the vigorous stirring should be momentarily stopped to avoid an eruption.

The Electronic Effect of Substituted Methyl Groups. A Carbon-13 Nuclear Magnetic Resonance Study

William Adcock*[1] and B. D. Gupta

School of Physical Sciences, Flinders University, Bedford Park, S.A. Australia

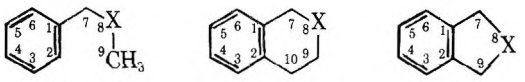
William Kitching

Department of Chemistry, University of Queensland, Brisbane, Australia

Received November 12, 1975

The ^{13}C NMR spectra of a large number of stereochemically well-defined model compounds possessing heteroatoms have been obtained and assigned. An analysis of the data provided the following conclusions: (1) hyperconjugative π-polarization is an important component of the net electronic effect of $-CH_2X$ groups in the neutral ground state; (2) polar field effects play an important role in determining aryl ^{13}C chemical shifts; and (3) the γ shielding effect of second-row heteroatoms is a very general phenomenon.

In order to assess the relative importance of the possible modes of action of substituents in unsaturated systems (polar and π-electron effects) it is necessary to study a series of stereochemically well-defined model systems in which the capacity for the transmission of the electronic effects may be varied systematically. Recently, ^{19}F NMR studies[2,3] have shown that model systems **1**, **2**, and **3** are of value in this regard



1 **2** **3**

since here the CX σ bond is constrained to a varying degree to the nodal plane of the adjacent π system, thus allowing the possible assessment of the relative importance of polar (field-inductive and σ-inductive), π-inductive (inductomesomeric), and mesomeric or resonance (hyperconjugation) effects of substituted methyl groups (vide infra).

In an earlier paper[4] we described a ^{13}C chemical shift study of systems **1**, **2**, and **3** [where X = $Si(CH_3)_2$] which helped to confirm our previous conclusions[2] regarding the importance of metallohyperconjugation in the neutral ground state. Here we report an extension of our ^{13}C NMR studies of these systems to situations where X is an electronegative element or group (NH, NCH_3, CO, O, CF_2, S, and SO_2). The basic objectives in this investigation were threefold. Firstly, we wanted to substantiate our recent proposals[3] regarding the electronic behavior of $-CH_2X$ substituents where X is electronegative: namely, that hyperconjugative electron withdrawal involving the CX σ bond is an important mode of interaction of these groups in the neutral ground state. Secondly, we wanted to examine the effect of pure polar contributions (field-inductive or electrostatic-field effects) on aryl ^{13}C chemical shifts. Previously, this has been prevented because of the difficulty of separating polar and π-electron effects in unsaturated systems where the substituent (X) is directly attached to the substrate, as well as a lack of suitable model compounds with well-defined stereochemistry.

Finally, we wished to assess further the generality of a phenomenon recently reported by Eliel and co-workers.[5] Their ^{13}C NMR studies of a series of model alicyclic systems indicate that a carbon atom located anti or gauche to a second-row heteroatom in the γ position generally resonates at a significantly higher field than an analogous nucleus anti or gauche to a methyl or methylene group, or to a third-row heteroatom. Furthermore, it was also observed that the incremental upfield shift for the anti carbon was generally greater than that for the gauche carbon. A ^{13}C NMR study of systems **2** and **3** should indicate whether this effect can also be transmitted to aromatic carbon centers which are γ disposed to an externally located heteroatom.

Experimental Section

^{13}C Spectra. A Bruker Scientific, Inc. WH-90 Fourier transform spectrometer operating at 22.625 MHz was used to record the spectra. All samples were prepared in deuteriochloroform (0.5–1.0 M) with Me_4Si as an internal reference.

Chemicals. Most of the compounds were known and thus were synthesized by well-established literature procedures: 1-phenylpropan-2-one,[6] benzyldimethylamine,[7] benzyl methyl sulfide,[8] benzyl methyl sulfone,[8] 2-indanone,[9] 1,3-dihydroisobenzofuran,[10] 1,3-dihydroisoindole,[11] *N*-methyl-1,3-dihydroisoindole,[11] 1,3-dihydrobenzo[*c*]thiophene,[12] 1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide,[12]

2-tetralone,[13] 1,2,3,4-tetrahydroisoquinoline[14] (and *N*-methyl derivative[15]), isochroman,[16] and isothiochroman.[17] The latter compound was oxidized to 1,2,3,4-tetrahydro-2-thionaphthalene 2,3-dioxide (mp 164–165 °C) utilizing the procedure outlined for 1,3-dihydrobenzo[c]thiophene.[12] Geminal difluoro derivatives of systems **1**, **2**, and **3** (X = CF_2) were synthesized from the corresponding ketones employing diethylaminosulfur trifluoride as the fluorinating agent.[18] Except for 6- or 7-fluoro-2-methyl-1,2,3,4-tetrahydroisoquinoline, all the necessary aryl fluorine analogues of **1**, **2**, and **3** were available from other studies.[3,6,18] 6-Fluoro-2-butyl-1,2,3,4-tetrahydroisoquinoline was prepared from 4-fluoro-*o*-2-bromoethylbenzyl bromide and *n*-butylamine in acetone as described previously for the *N*-methyl analogue.[3] The *n*-butyl derivative was employed rather than the methyl analogue because it was easier to prepare in good yields.

Benzyl ethyl ether, *n*-propylbenzene, indan, and tetralin were commercially available.

Results

Since our recent ^{13}C NMR studies of various phenyl derivatives,[4,19] particularly benzocycloalkenes,[20] demonstrated convincingly that fluorine substitution is an effective and relatively simple strategy for ^{13}C spectral assignments in such systems, and since all the necessary fluorine analogues of **1**, **2**, and **3** were available from previous investigations,[3,6,18,21] we adopted this approach in order to unambiguously assign the aromatic region of the ^{13}C spectra of systems **1**, **2**, and **3**.

Fluorine substitution in the phenyl ring manifests itself in two important ways. Firstly, there is observed a characteristic regular pattern of ^{13}C–^{19}F coupling constants in the aromatic region of the proton-decoupled spectrum, ^1J ($\simeq$245 Hz) $\gg$ ^2J ($\simeq$18–20 Hz) > ^3J ($\simeq$6–9 Hz) > ^4J ($\simeq$1.5–4 Hz). In addition, coupling is generally observed ($^4J_{^{13}C-^{19}F} \simeq 2$ Hz) to any meta disposed external carbon center which is in a preferred "zigzag" array. A consideration of these data, together with signal intensities and the observed chemical shift patterns previously reported[4,20] for 5-fluoroindan and 6-fluorotetralin, leads to the assignments listed in Table I for the aromatic carbons of the various fluorine derivatives of **1**, **2**, and **3**. The assignments listed (Table I) for the aliphatic carbons were relatively straightforward for most of the compounds, being based essentially on the known α and β effects of the various elements or substituent groupings.[22] However, it should be noted that for many of the bicyclic derivatives (6, 8, 12, 16, and 19–22) the expected coupling ($^4J_{^{13}C-^{19}F}$) to the meta disposed external carbon center, which would have immediately identified that particular carbon, was not resolved. Thus, the listed assignments for C_7 and C_9 (entries 6, 8, and 12) and C_7 and C_{10} (entries 19 and 20) could possibly be reversed. Unfortunately, the α and β shifts of sulfur[5,22] are such that the chemical shifts of C_7 and C_{10} in entries 19 and 20 are fairly similar. Incomplete spectra are listed for entries 9, 13, and 18 because of the limited amounts of these compounds which remained from our previous investigations.[3,18,21] No concerted effort was made to observe the remaining carbon resonances since they were not crucial for assigning the spectra of the unfluorinated analogues.

Secondly, fluorine substitution induces a regular and pronounced effect on the ^{13}C chemical shifts which is an added benefit with regard to the use of fluorine as an assignment strategy. The carbon bearing fluorine is quite deshielded (by >30 ppm), whereas carbons ortho to fluorine experience quite large upfield shifts ($\simeq$14 ppm). Carbons para to fluorine are also shielded by a lesser amount ($\simeq$5 ppm) whereas meta carbons appear to be always deshielded (1–2 ppm). A consideration of this information, together with the data listed in Table I, leads to the assignments tabulated in Table II for systems **1**, **2**, and **3**. The assignments for the asterisked carbons are insecure and could possibly be reversed. It is of interest to note that although the aromatic carbons for entries 18–22 could be readily assigned on the data from one appropriately substituted fluorine derivative, two such derivatives were required for the confident assignments listed for entries 23 and 24. Here many of the aromatic carbons absorb over a narrower range.

The spectra for **2** and **3** where X = $Si(CH_3)_2$, which have been previously reported (measured as concentrated solutions in cyclohexane at 15.18 MHz),[4] were reexamined in DCl_3 (0.5 M) as solvent and are also listed in Table II (entries 16 and 25).

Discussion

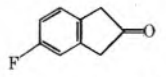
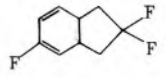
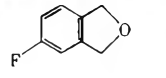
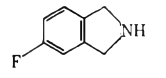
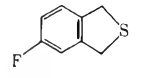
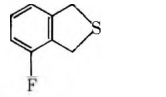
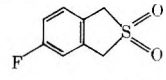
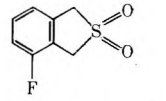
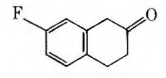
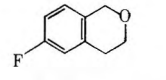
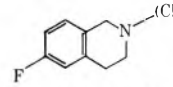
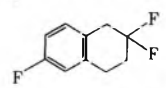
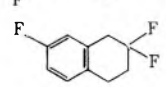
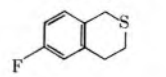
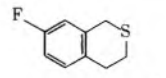
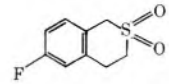
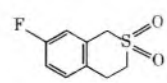
It is well known that a manifold of factors determine the magnitude of carbon chemical shifts.[22,23,24] However, by confining comparisons of chemical shifts to a closely related series of compounds and, at the same time, to those carbons reasonably remote from the site of substitution such that steric, neighboring group, and bond order effects are not important, the ^{13}C nucleus can be employed as a sensitive and reliable monitor of charge density fluctuations. This fact is clearly exemplified by a number of successful empirical and theoretical correlations which have clearly established that para (or C_4) ^{13}C SCS[27] of monosubstituted benzenes accurately reflect the charge density at that position.[24–26] Recent studies have shown that this close relationship between ^{13}C SCS and charge density is also strongly adhered to at para (or C_4) sites remote from the substituent in disubstituted benzenes.[19] However, various attempted correlations of meta (or C_3, C_5) carbon chemical shifts, which absorb over a narrow range and appear to be only marginally influenced by the electronic effect of a substituent, are much less satisfactory.[24–26] Although meta carbon chemical shifts are of limited value, they do assist in substantiating mesomeric phenomena, particularly for weak polar substituents,[28] since it is generally observed that any substituent exercising a significant resonance component clearly effects a chemical shift differential between the meta and para carbon sites.

Thus, in the present context of trying to assess the relative importance of hyperconjugation (σ–π interactions involving the CX σ bond) vs. π-inductive effects of $-CH_2X$ groups from the ^{13}C chemical shifts of **1**, **2**, and **3**, as well as the significance of polar field effects on aryl carbon chemical shifts, the relevant carbon centers are C_4 and $C_{3,5}$ in **1**, C_4 and C_5 in **2**, and $C_{4,5}$ in **3**. Since our recent ^{13}C NMR studies of benzocycloalkenes[20] indicated clearly that the $C_{4,5}$ chemical shifts in these systems are not very sensitive to ring size effects, we were confident that effects related to strain should not cloud the interpretation of the C_4 and C_5 chemical shifts of **2** and **3** for most of the substituents (X). However, our previous studies[4] of **2** and **3**, where X is a large third-row element [$Si(CH_3)_2$], suggested the possibility that structural factors may complicate the interpretation of the chemical shifts in terms of pure electronic phenomena where X = S or SO_2 in **2** and **3**. We shall return to this point below.

The parent systems employed for computing the ^{13}C SCS[27] of the relevant carbon centers in 1, 2, and 3 are *n*-propylbenzene (**1**, where X = CH_2), tetralin (**2**, where X = CH_2), and indan (**3**, where X = CH_2), respectively. It is then assumed, as a first approximation, that these ^{13}C SCS are reasonable monitors of the electronic behavior of the CX σ bond. This postulate is based essentially on two reasonable assumptions: (1) that the effects of CH and CC hyperconjugation are indistinguishable in the ground states of neutral molecules;[29] and (2) that the extent to which CH_2 can undergo hyperconjugative electron release from its CH bonds is the same for similar groups (X) in each particular system.

Before considering the relative ^{13}C SCS of these various carbon centers (listed in Table III), it is pertinent to discuss the structural features inherent in these model systems which allow a definitive decision to be made on the involvement of the CX σ bond in the electronic behavior of a $-CH_2X$ substituent. From an examination of Dreiding molecular models

Table I. Carbon-13 Assignments[a,b] of Fluorine-Substituted Derivatives of Systems 1, 2, and 3

Registry no.	Entry	Compd	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
459-03-0	1	*p*-FC_6H_4-$CH_2C(=O)CH_3$	130.4 (3.7)	131.2 (8.5)	115.5 (22)	162.0 (244.1)	115.5 (22)	131.2 (8.5)	49.7	205.9	29.2	
58325-14-7	2	*p*-$FC_6H_4CH_2CF_2CH_3$	129.8 (broad)	132.1 (8.8)	115.5 (20.6)	162.6 (245.6)	115.5 (20.6)	132.1 (8.8)	43.8 (26.5)	123.5 (239.7)	22.8 (27.9)	
702-11-4	3	*p*-$FC_6H_4CH_2N(CH_3)_2$	134.9 (broad)	130.5 (8.6)	115.0 (22)	162.1 (245.5)	115.0 (22)	130.5 (8.6)	63.6		45.2	
7116-50-9	4	*p*-$FC_6H_4CH_2OCH_3$	134.1 (broad)	129.6 (8.6)	115.3 (22)	162.5 (244.5)	115.3 (22)	129.6 (8.6)	74.0		58.0	
5925-83-7	5	*p*-$FC_6H_4CH_2SO_2CH_3$	124.1 (broad)	132.5 (7.3)	116.1 (22)	163.2 (250.2)	116.1 (22)	132.5 (7.3)	60.2		39.1	
57584-69-7	6		133.5 (broad)	139.9 (8.8)	112.3 (22.1)	162.3 (245.6)	114.6 (22.1)	126.4 (7.5)	43.4	214.3	44.3 (broad)	
57584-73-3	7		133.3 (broad)	139.8 (10.3)	112.1 (23.5)	162.8 (244.1)	114.8 (22.1)	126.2 (8.8)	41.8 (25.0)	131.5 (250)	42.1 (26.5)	
57584-70-0	8		134.8 (broad)	141.7 (10.3)	108.4 (23.6)	162.9 (244.1)	114.4 (23.5)	122.2 (8.8)	73.1		73.4	
57584-71-1	9				109.7 (22.0)		114.0 (23.5)	123.4 (10.3)				
55831-05-5	10		136.1 (broad)	142.9 (7.4)	111.5 (22.1)	162.1 (245.6)	113.8 (22.1)	125.5 (8.8)	37.1		37.8 (2.9)	
58325-15-8	11		144.4 (7.3)	127.7 (18.3)	159.1 (246.6)	113.1 (20.7)	128.8 (7.3)	120.2 (3.6)	38.2		33.9	
55831-03-3	12		127.2 (broad)	133.4 (8.8)	113.3 (22.1)	162.6 (248.6)	116.3 (23.5)	127.9 (8.8)	56.3		57.0 (broad)	
58325-16-9	13					115.3 (19.5)	130.5 (7.3)	121.7 (3.6)	56.9 (2.4)		53.0	
29419-15-6	14		135.5 (7.9)	132.4 (3.1)	129.0 (7.9)	113.5 (21.4)	161.7 (248.8)	114.9 (22.0)	44.8 (1.20)	209.2	38.1	27.7
50396-63-9	15		130.6 (3.1)	135.4 (7.3)	115.3 (20.8)	161.5 (244.1)	113.2 (22.0)	125.9 (7.9)	67.7		65.0	28.5 (1.2)
58325-17-0	16[c]		130.7 (broad)	136.5 (6.1)	114.8 (19.5)	161.5 (245.5)	112.7 (22)	127.9 (8.6)	58.3		55.8	29.4
57584-67-5	17		127.6 (broad)	136.4 (8.8)	115.0 (22.1)	161.8 (244.1)	113.8 (22.1)	130.6 (8.4)	37.5 (27.2)	123.1 (239.7)	30.8 (25.0)	27.1 (5.9)
57584-68-6	18				130.0 (8.8)	114.0 (20.7)		115.4 (22.1)	38.1 (27.2)		31.1 (25.0)	26.3 (5.9)
50396-75-3	19		130.8 (≃2.0)	138.9 (7.4)	115.8 (22.1)	161.5 (245.6)	112.9 (22.1)	129.1 (8.8)	28.7		25.9	30.6
50396-76-4	20		136.9 (7.4)	132.4 (2.9)	130.6 (8.8)	113.4 (20.6)	161.0 (245.6)	114.3 (20.6)	29.2		26.5	29.7
50396-79-7	21		124.5 (≃2.0)	135.7 (7.4)	115.9 (22.1)	162.6 (248.6)	114.8 (22.1)	131.7 (8.8)	54.4		49.3	28.4
50396-80-0	22		130.8 (7.4)	129.3 (2.9)	130.8 (7.4)	115.7 (20.6)	161.7 (245.6)	116.6 (22.1)	54.6		49.7	28.4

[a] Chemical shifts referenced to Me_4Si (±0.1 ppm). Positive values indicate decreased shielding relative to Me_4Si. [b] Values in parentheses are $^{13}C-^{19}F$ couplings in hertz. The carbon numbering system is as shown on the structural formulas in the introduction. This system is for convenience only and bears no relation to the numbering system employed for the systematic naming of these compounds. [c] Chemical shifts for the *N*-butyl group are as follows. $-CH_2{}^aCH_2{}^bCH_2{}^cCH_3{}^d$: a, 50.6; b, 29.4; c, 20.8; d, 14.1.

Table II. Carbon-13 Assignments[a,b] of Systems 1, 2, and 3

Registry no.	Entry	Compd	Carbons									
			C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}
103-65-1	1	$PhCH_2CH_2CH_3$	142.7	128.3*	128.5*	125.7	128.5*	128.3*	38.2	24.7	13.9	
103-79-7	2	$PhCH_2C(=O)CH_3$	134.5	129.5	128.7	126.9	128.7	129.5	50.7	205.8	29.1	
58325-18-1	3[c]	$PhCH_2CF_2CH_3$	134.1 (4.4)	130.5	128.7	127.5	128.7	130.5	44.5 (26.5)	123.7 (238.2)	22.8 (28.0)	
103-83-3	4	$PhCH_2N(CH_3)_2$	139.0	129.0	128.2	127.0	128.2	129.0	64.4		45.3	
539-30-0	5	$PhCH_2OCH_2CH_3$	138.8	127.6	128.3	127.4	128.3	127.6	72.7		65.7	15.2
766-92-7	6	$PhCH_2SCH_3$	138.3	128.8*	128.3*	126.8	128.3*	128.8*	38.2		14.7	
3112-90-1	7	$PhCH_2SO_2CH_3$	128.4	130.6	129.1	129.1	129.1	130.6	61.2		39.1	
496-11-7	8	3, X = CH_2	144.1	144.1	124.4	126.0	126.0	124.4	32.9	25.4	32.9	
496-12-8	9	3, X = NH	141.9	141.9	122.1	126.4	126.4	122.1	52.9		52.9	
3474-87-1	10	3, X = NCH_3	140.8	140.8	122.0	126.5	126.5	122.0	60.9		60.9	42.1
615-13-4	11	3, X = C=O	137.8	137.8	124.8	127.2	127.2	124.8	43.8	214.5	43.8	
54265-06-4	12	3, X = CF_2	137.8 (4.4)	137.8 (4.4)	124.9	127.6	127.6	124.9	42.8 (26.5)	131.5 (250)	42.8 (26.5)	
496-14-0	13	3, X = O	139.4	139.4	121.0	127.2	127.2	121.0	73.5		73.5	
2471-92-3	14	3, X = S	140.4	140.4	124.6	126.6	126.6	124.6	38.0		38.0	
2471-91-2	15	3, X = SO_2	131.5	131.5	126.1	128.9	128.9	126.1	57.0		57.0	
2474-87-6	16[d]	3, X = $Si(CH_3)_2$	142.2	142.2	129.2	125.6	125.6	129.2	21.3		21.3	
119-64-2	17	2, X = CH_2	137.1	137.1	129.1	125.4	125.4	129.1	29.5	23.3	23.3	29.5
530-93-8	18	2, X = C=O	133.0	136.3	127.7	126.3*	126.2*	127.0	44.4	209.2	37.5	27.8
58325-19-2	19	2, X = CF_2	132.1 (broad)	134.2	128.6	126.7*	126.5*	129.2	38.1 (27)	123.1 (239.7)	31.1 (25)	27.0 (5.9)
91-21-4	20	2, X = NH	136.1	134.8	129.2	125.8*	125.6*	126.1	48.2		43.8	29.1
1612-65-3	21[e]	2, X = NCH_3	136.0	134.8	128.5	125.9*	125.4*	126.3	57.9		52.8	29.2
493-05-0	22	2, X = O	135.0	133.2	128.8	126.3*	125.9*	124.3	67.8		65.2	28.3
4426-75-9	23	2, X = S	135.0	136.7	129.1	126.7	126.1	127.6	29.1*		26.3	30.4*
18436-01-6	24	2, X = SO_2	129.0	133.5	129.0*	128.7*	127.7	130.0	55.1		49.9	28.0
5136-93-6	25[d]	2, X = $Si(CH_3)_2$	138.2	141.7	129.5	124.9	126.3	127.9	20.9		11.7	29.6

[a] Chemical shifts referenced to Me_4Si (±0.1 ppm). Positive values indicate decreased shielding relative to Me_4Si. Asterisked assignments could be reversed. [b] The carbon numbering system is as shown on the structural formulas in the introduction. [c] Values in parentheses are $^{13}C-^{19}F$ couplings in hertz. [d] Chemical shift for $Si(CH_3)_2$, −2.4 ppm (16) and −2.1 ppm (25). [e] Chemical shift for NCH_3, 46.0 ppm.

Table III. ^{13}C Substituent Chemical Shifts (SCS)[a]

Substituent X	System 1[b]		2[c]		3[d]
	$C_{3,5}$	C_4	C_4	C_5	$C_{4,5}$
CO	+0.2	+1.2	+0.9	+0.8	+1.2
CF_2	+0.2	+1.8	+1.3	+1.1	+1.6
NH			+0.4	+0.2	+0.4
NCH_3	−0.3	+1.3	+0.5	+0.0	+0.5
O	−0.2	+1.7	+0.9	+0.5	+1.2
S	−0.2	+1.1	+1.3	+0.7	+0.6
SO_2	+0.6	+3.4	+3.3	+2.3	+2.9

[a] Positive values imply a downfield shift relative to the appropriate standard. [b] Relative to C_3 (or C_5) and C_4 in *n*-propylbenzene. [c] Relative to C_4, C_5 in tetralin. [d] Relative to C_4, C_5 in indan.

it is readily seen that the geometries of the bicyclic systems **2** and **3** are considerably more constrained than those of the monocyclic analogues **1** in which the $-CH_2X$ group can be assumed to undergo free rotation. In system **2**, where X = CH_2, CO, CF_2, NH, NCH_3, or O, the alicyclic ring is conformationally mobile, there being two freely interconvertible conformations in which the dihedral angle (θ) (angle between the C_1C_7X plane and the plane of the aromatic ring) is $\simeq 25 \pm 5°$ for CH_2, CF_2, NH, or NCH_3; $\simeq 15 \pm 5°$ for O; and $\simeq 0°$ for CO. However, where X = S or SO_2 the models cannot be maintained in a half-chair-like conformation but prefer a rigid half-boat arrangement in which the dihedral angle (θ) is approximately $65 \pm 5°$. A consequence of the half-boat arrangement is that the benzylic hydrogens are eclipsed with H_3 and H_6 whereas they are staggered in the half-chair. This leads to "perilike" nonbonding interactions which appear to have a significant influence on the chemical shifts of remote carbon positions (vide infra). It is important to note that our previous deductions[2,4] from Dreiding models regarding the half-boat conformation of **2**, where X = $Si(CH_3)_2$, have subsequently been vindicated by x-ray crystallographic studies.[30]

For system **3**, the models indicate essentially a coplanar situation where the CX σ bond lies in the nodal plane of the adjacent π system, i.e., the dihedral angle (θ) is zero. Interestingly, recent structural studies[31] on **3**, where X = $SiPh_2$, indicate the possibility of substantial deviations ($\simeq 30°$) away from coplanarity of the C_7XC_9 plane with respect to the aromatic ring.

Important consequences follow from this systematic variation of the geometrical relationship between the CX σ bond and the adjacent aromatic ring within model systems **1**, **2**, and **3**. First, if hyperconjugation is important, and if we neglect electrostatic-field effects, then according to the specific stereoelectronic requirements of this mechanism[29,32] (an approximate cosine dependence on the appropriate dihedral angle, $\cos 90° - \theta$) the relative magnitude of this interaction as monitored by the ^{13}C SCS should be C_4 (system **1**) > C_4 (system **2**) > $C_{4,5}$ (system **3**) where X = CO, CF_2, NH, NCH_3, or O. However, where X = S or SO_2, the order of ^{13}C SCS could be somewhat perturbed (**1** $\simeq$ **2** > **3** or **2** > **1** > **3**), depending on the magnitude of the effective dihedral angle in the monocyclic analogue **1**. In addition, if hyperconjugation is significant then a chemical shift differential should be observed between C_4 and $C_{3,5}$ in system **1**, and C_4 and C_5 in system **2**. This should be particularly pronounced in the latter system where $\cos 90° - \theta$ is significant (X = S or SO_2), and marginally so where X = CF_2, NH, NCH_3, or O.

If, on the other hand, the π-inductive effect[29] (no angular dependence) is more important than hyperconjugation in effecting π-polarization of the adjacent aromatic ring, then the electrical effect of the CX σ bond should be similar in all

systems for a particular substituent, i.e., in terms of the relevant ^{13}C SCS, C_4 (system 1) $\simeq$ C_4 (system 2) $\simeq$ $C_{4,5}$ (system 3). However, since the π-inductive effect is indistinguishable from mesomeric phenomena in the way it polarizes a π system,[29] a chemical shift differential should still be observed between C_4 and $C_{3,5}$ in system 1, and C_4 and C_5 in system 2, as mentioned above for hyperconjugation.

Second, since the CX σ bonds lie in the plane of the ring system in system 3, σ–π conjugation should play no role here in determining the chemical shifts. Hence, perturbations of the chemical shift at $C_{4,5}$ can only be induced by a significant electrostatic-field or π-inductive effect. According to recent proposals,[33] the effect of an electric field emanating from a polar substituent (dipole or pole) on aryl ^{13}C chemical shifts can be interpreted on the basis of *nonlocalized* polarization (the π-inductive effect is a localized polarizing phenomenon) of the adjacent π-electron system such that significant electron density variations only occur at the terminal carbon centers. Since the π electrons should be polarized toward a positive charge, the polar field effect from electronegative elements or groups (X) will decrease the electron density at C_4 in system 1, C_4 and C_5 in system 2, and $C_{4,5}$ in system 3, and thus lead to more positive ^{13}C SCS at these remote probe sites. Intuitively, one would also expect that this π-polarization phenomenon should be dependent on the component of the electric field in the plane of the aromatic ring and, therefore, be most pronounced when the lines of force emanating from a dipolar group are constrained to operate in the plane of the aromatic ring, i.e., as in system 3. An examination of molecular models indicates that in system 2 the dipole or group moments for the strong polar substituents (excluding X = N or S) lie in a plane which makes a distinct angle (ϕ) with the plane containing the aromatic ring: for X = CO or CF_2, $\phi \simeq 40 \pm 5°$; and for X = SO_2, $\phi \simeq 65 \pm 5°$. Only where X = O in system 2 does the plane containing the dipole almost coincide with the molecular plane ($\phi \simeq 15 \pm 5°$). Thus, a distinction between polar field and π-inductive effects can be made on the following basis. If the electrostatic-field effect predominates (neglecting hyperconjugation) then the relative magnitude of the ^{13}C SCS should be $C_{4,5}$ (system 3; cos ϕ = 1) > C_4 and C_5 (system 2; cos ϕ = 0.766) where X = CO or CF_2; $C_{4,5}$ (system 3; cos ϕ = 1) $\simeq$ C_4 and C_5 (system 2; cos ϕ = 0.966) where X = O; and $C_{4,5}$ (system 3; cos ϕ = 1) $\gg$ C_4 and C_5 (system 2; cos ϕ = 0.423) where X = SO_2.

If, on the other hand, the π-inductive effect is more important, then the ^{13}C SCS of C_5 in system 2 should be small for all the groups and the magnitude of the C_4 SCS in all the systems, which should parallel the polarity of the CX σ bond, will be similar for a particular substituent.

Since the direction and magnitude of the resultant dipole in system 1 depends upon the various rotamer populations in an unknown way, the data from this system are of little value for defining unambiguously polar field effects. However, it should be noted that if hyperconjugation is highly significant then the relative magnitude of the C_4 SCS for 1 and 3 should be 1 $\gg$ 3. This should be particularly pronounced for weak polar groups (X = N or S).

We have already mentioned that the size of X markedly influences the geometry of system 2 and, according to our previous ^{13}C NMR studies on 2 where X = $Si(CH_3)_2$, the ^{13}C SCS at remote sites in this system. Thus, it is informative at this stage to reevaluate the ^{13}C SCS data from 2 (and 3), where X = $Si(CH_3)_2$, in the light of recent structural studies[30,31] on these systems as well as the now-established importance of metallohyperconjugation in the ground state of neutral molecules.[19] This should provide a firm basis for interpreting the data from system 2 where X = S or SO_2 and thus allow the data for these groups to be discussed within the general framework. Based on tetralin and indan as the parent systems, the ^{13}C SCS (ppm) for C_4 and C_5 in 2 (entry 25, Table II) and $C_{4,5}$ in 3 (entry 16, Table II) are −0.5, +0.9, and −0.4, respectively. Two aspects of this data deserve notice with regard to the validity of these systems as models for investigating electronic phenomena. First, the SCS at C_5 in 2 implies fairly strong electron withdrawal by the CSi σ bond, a result which is clearly contrary in magnitude and direction to expectations based on the established weak polar character of this bond[19b,34] (a value of ca. *zero* was expected). Second, the hyperconjugative effect of the C–Si bond, as monitored by the C_4 SCS, is approximately the same in both systems yet a simple cosine dependence of the σ–π interaction implies that the interaction in 2 should be approximately 2.6 times that in 3.[35] We believe that these anomalous results are a manifestation of structural factors due to "perilike" nonbonding interactions (vide supra) in the half-boat form of 2 which do not occur in the parent system (tetralin).

If we assume that this structural factor affects the chemical shifts equally at the C_4 and C_5 probe sites, then the most realistic measure of the σ–π interaction of the CSi σ bond in system 2 is the difference between the ^{13}C SCS at C_4 and C_5, i.e., −1.40 ppm. Based on a simple cosine dependence,[35] the maximum effect of the $-CH_2Si(CH_3)_3$ group in the phenyl ring in terms of a ^{13}C SCS is then computed to be −1.75 ppm. The experimental value[4] of −1.50 ppm is in excellent agreement with this prediction given that the relevant effective dihedral angle in benzyltrimethylsilane is ca. 30° (based on the value determined for benzyltrimethylstannane from carbon–tin coupling constants[19]). The calculated value for 3, where X = $Si(CH_3)_2$, is −0.5 ppm, which is also in excellent agreement with the experimental result (−0.4 ppm). Thus, it is clear from this analysis that although the ^{13}C SCS at C_4 and C_5 in the half-boat arrangement of 2 may be unreliable monitors of electrical phenomena in an absolute sense, their difference provides a sound measure of hyperconjugative interactions. Since similar structural factors will perturb the chemical shifts at C_4 and C_5 in system 2 when X = S or SO_2, then based on the relatively weak polar character of the CS σ bond, the fact that the dipole moment is considerably out of plane of the aromatic ring ($\phi = 65 \pm 5°$) and the chemical shift at C_5 for silatetralin (entry 25, Table II), the ^{13}C SCS at C_5 in 2 where X = S should be approximately zero. It follows then that a correction factor of −0.7 ppm should be applied to the ^{13}C SCS for C_4 and C_5 in system 2 where X = S or SO_2 (Table III) in order to provide approximate values that can be validly compared with the other groups.

Examination of the data listed in Table III indicates quite clearly that the ^{13}C SCS of the appropriate carbon centers for a large variety of groups (X) in 1, 2, and 3 provide a distinct pattern consistent only in terms of angular dependent electronic mechanisms.[36] It can be seen that in general the electron-withdrawing ability of the CX σ bond in the various systems is in the order C_4 (system 1) > $C_{4,5}$ (system 3) > C_4 (system 2) and $C_{4,5}$ (system 3) > C_5 (system 2). Furthermore, the differential between C_4 and C_5 in 2 is most significant when the dihedral angle is substantial (X = S or SO_2). Based on our proposed criteria (vide supra), we believe that only combined significant hyperconjugative and polar field effects can account for these observations. However, it is important to stress that since our arguments are based on geometries deduced from molecular models it is impossible to estimate accurately the relative magnitude of the inherent hyperconjugative abilities of the various CX bonds. The qualitative order deduced from the data in Table III is S ~ SO_2 ~ N > O > CF_2 > CO, which is in line with predictions from the ^{19}F NMR studies.[3,18,21] The importance of similar hyperconjugative interactions in several other connections has been described elsewhere.[3,37]

Unfortunately, it is not possible to distinguish from NMR

experiments such as those described here whether the σ–π interactions involve charge redistribution with associated charge transfer.

Perhaps the most important aspect of the data in Table III is the pronounced influence of polar field effects on aryl ^{13}C chemical shifts. Note the significant SCS for the very polar groups (CO, CF_2, O, and SO_2) in system **3** where structural factors should preclude hyperconjugative interactions.[38] This was somewhat surprising since in most discussions of aryl ^{13}C SCS (remote carbon sites) it is tacitly assumed that mesomeric phenomena are overwhelmingly more important than field effects. Apart from the fact that no suitable studies had been performed on well-defined model systems, this situation seems to have arisen essentially from two well-established correlations:[22-25] (1) para ^{13}C SCS (monosubstituted benzenes) correlate better with σ_p^+ (66% resonance) than σ_p (53% resonance); and (2) para ^{13}C SCS (monosubstituted benzenes) correlate as well with CNDO/2 calculated π-charge densities as they do with total charge densities. More recently, an empirical analysis by Schulman et al.[39] has led to the conclusion that mesomeric effects are 41 times greater than field effects in their effect on aromatic ^{13}C chemical shifts.

An approximate estimate of the relative importance of field vs. mesomeric effects on aryl ^{13}C chemical shifts can be obtained from the ^{13}C SCS for system **3** where X = CF_2 (+1.6 ppm; Table III) and the para SCS (+3.2 ppm; CCl_4)[25] for the CF_3 substituent in trifluoromethylbenzene. If we make the very reasonable assumption that the SCS of the former is a minimum value for the electric field contribution to the total electronic effect by the latter substituent at the para position in trifluoromethylbenzene, then by utilizing the σ_I and σ_R^0 values for the CF_3 substituent (0.45 and 0.08, respectively)[40] it can be readily shown that mesomeric effects are approximately five times greater than field effects in their effect on aromatic ^{13}C chemical shifts. Interestingly, a correlative analysis by the Taft dual substituent parameter (DSP) equation of para ^{13}C SCS derived from monosubstituted benzenes leads to a similar conclusion.[41]

Two final features of the data listed in Table III, which reflect on the way polar field effects perturb the ^{13}C chemical shifts of remote aromatic carbon sites,[42] are worthy of note. First, it can be seen that the formally meta C_5 position in system **2** is significantly more affected by the electric field of the strong polar substituents than the meta position in system **1**. This confirms that only the chemical shifts of the terminal carbon positions of the aromatic ring are markedly effected by electric field induced π-polarization. Second, it is clear from the larger $C_{4,5}$ SCS in system **3** compared to C_5 (and C_4) in **2** (particularly for X = SO_2) that electric field induced π-polarization is more efficient when the lines of force emanating from the dipole (or pole) are constrained to operate in the plane of the aromatic ring.

The shielding effects of carbon nuclei oriented anti (or syn) to the γ heteroatoms in systems **2** and **3** are given in Table IV. It should be noted that whereas the γ effects of NH, NCH_3, O, and S are referenced with respect to methylene, O in CO and F in CF_2 are referenced with respect to hydrogen. However, since the γ effect of methylene should be small in the configurations described here, all the values can be considered referenced to a common standard, hydrogen. A careful scrutiny of Dreiding molecular models indicates that the anti coplanar arrangement is well defined in system **3** where X = NH, NCH_3, O, CO, or S. Although there are minor deviations away from exact coplanarity where X = NH, NH_3, O, or CO in system **2** for the anti (and syn) arrangement, coplanarity is completely destroyed where X = S since here the fused ring adopts a half-boat configuration. Where X = CF_2, both fluorines are out of plane by approximately 50° in the anti arrangement of **3**, but in system **2**, the quasi-equatorial fluorine is almost coplanar for the anti arrangement and roughly so for the syn.

Table IV. γ Shielding Effects (ppm)[a] of Heteroatoms in Systems 2 and 3

Substituent X	System 2 Anti	System 2 Syn	System 3 Anti
NH	−3.0[b]	−2.3[d]	−2.3[f]
NCH_3	−2.8[b]	−2.3[d]	−2.4[f]
O	−4.8[b]	−3.9[d]	−3.4[f]
S	−1.5[b]	−0.4[d]	+0.2[f]
CO	−4.1[c]	−1.7[e]	−6.3[g]
CF_2	−5.0[c]	−2.5[e]	−6.3[g]

[a] Negative values imply an upfield shift relative to the appropriate standard. [b] Relative to C_6 in tetralin. [c] Relative to C_1 in tetralin. [d] Relative to C_2 in tetralin. [e] Relative to C_{10} in tetralin. [f] Relative to $C_{3,6}$ in indan. [g] Relative to $C_{1,2}$ in indan.

Inspection of the data in Table IV clearly reveals that second-row heteroatoms (N, O, F) in systems **2** and **3** cause significant upfield shifts in the resonance of anti- and syn-coplanar carbon nuclei, the effect being more pronounced for the anti than the syn conformational array. Furthermore, the anti γ effect of a third-row element (S) is almost negligible (X = S; system **3**). These observations are clearly in line with the recent observations reported by Eliel and co-workers[5] from a ^{13}C NMR study of a large number of alicyclic derivatives. Thus, the generality of this phenomenon has clearly been extended since all the anti carbon centers in **2** and **3** are part of an adjacent aromatic framework, i.e., sp^2 hybridized carbon centers. The larger anti effects observed in **3** for O in CO and F in CF_2 as compared to the same effects in **2** is not surprising since the chemical shifts of the C_1 and C_2 carbon centers in the former system are expected to be more sensitive[20b] (hybridization effects) to the nature of X in the smaller fused ring. Further, the significantly smaller anti effect for O in **3** as compared to **2** could be a consequence of complicating strain effects in the former system.[29b]

Although we do not wish to rehash in detail on the possible origin of the shielding γ anti effect, since this has been adequately discussed by the previous workers,[5] we would like to comment briefly on the favored proposal, namely, direct hyperconjugative transfer of charge from the free-electron pairs on the heteroatom to the trans γ atom. Eliel et al.[5] failed to point out that CNDO/2 calculations[43] indicate that the donation of the free electrons on a heteroatom by this mechanism in a σ-bonded framework go preferentially to the β and not the γ position, the latter being positively charged. In valence bond terminology, a no-bond resonance structure can be drawn to represent this. More recently, experimental evidence has been presented[44] which appears to support the computational result. Unfortunately, the myriad effects determining the chemical shifts of carbon sites proximate to substituents[22,23,24] preclude any disentanglement of the hyperconjugative mechanism at the β position by ^{13}C NMR. Thus, although we believe that hyperconjugative transfer of charge is likely to be important in an indirect way (relay of charge from the β to the γ position), other mechanisms must also be contributing (field effects[5] and 1,3-back-lobe interactions[5]) which are impossible to specify in any sort of quantitative and predictable way. Interestingly, the anti γ effect for O in SO_2 (system **3**), where a very polar ^+S–O^- bond is involved, is −8.9 ppm (referenced with respect to $C_{1,2}$ in system **3** where X = S).

Acknowledgments. We thank the University of Adelaide and Monash University for the use of their NMR facilities and

are grateful to Dr. D. Doddrell (Griffith University) for assistance with the recording of some of the ^{13}C NMR spectra.

References and Notes

(1) Author to whom correspondence should be addressed at the School of Physical Sciences, Flinders University, Bedford Park, S.A. 5042, Australia.
(2) W. Adcock, S. Q. A. Rizvi, and W. Kitching, *J. Am. Chem. Soc.*, **94**, 3657 (1972).
(3) W. Adcock, M. J. S. Dewar, and B. D. Gupta, *J. Am. Chem. Soc.*, **95**, 7353 (1973).
(4) S. Q. A. Rizvi, B. D. Gupta, W. Adcock, D. Doddrell, and W. Kitching, *J. Organomet. Chem.*, **63**, 67 (1973).
(5) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Miller, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975), and references cited therein.
(6) W. Adcock, P. D. Bettess, and S. Q. A. Rizvi, *Aust. J. Chem.*, **23**, 1921 (1970).
(7) E. L. Eliel, T. N. Ferdinand, and M. C. Hermann, *J. Org. Chem.*, **19**, 1963 (1954), and references cited therein.
(8) T. Thomson and T. S. Stevens, *J. Chem. Soc.*, 69 (1932).
(9) J. E. Horan and R. W. Schiessler, *Org. Synth.*, **41**, 53 (1961).
(10) J. Entel, C. H. Ruof, and H. C. Howard, *J. Am. Chem. Soc.*, **74**, 443 (1952).
(11) J. Bornstein and J. E. Shields, *Org. Synth.*, **47**, 110 (1967); **48**, 65 (1968); and references cited therein.
(12) J. A. Oliver and P. A. Ongley, *Chem. Ind. (London)*, 1024 (1965).
(13) A. Rosowski, J. Battaglia, K. K. N. Chen, and E. J. Modest, *J. Org. Chem.*, **33**, 4288 (1968).
(14) N. H. Cromwell and D. J. Cram, *J. Am. Chem. Soc.*, **65**, 305 (1943).
(15) E. Wedekind and R. Oechslen, *Ber.*, **34**, 3987 (1901).
(16) S. Siegel and S. Coburn, *J. Am. Chem. Soc.*, **73**, 5494 (1951).
(17) F. G. Holliman and F. G. Mann, *J. Chem. Soc.*, 37 (1945).
(18) Details will be published elsewhere: W. Adcock, B. D. Gupta, and T. C. Khor, *Aust. J. Chem.*, to be published.
(19) (a) W. Adcock, B. D. Gupta, W. Kitching, D. Doddrell, and M. Geckle, *J. Am. Chem. Soc.*, **96**, 7360 (1974); (b) W. Adcock, B. D. Gupta, W. Kitching, and D. Doddrell, *J. Organomet. Chem.*, **102**, 297 (1975).
(20) (a) W. Adcock, B. D. Gupta, T. C. Khor, D. Doddrell, D. Jordan, and W. Kitching, *J. Am. Chem. Soc.*, **96**, 1595 (1974); (b) W. Adcock, B. D. Gupta, T. C. Khor, D. Doddrell, and W. Kitching, *J. Org. Chem.*, accepted for publication.
(21) W. Adcock and B. D. Gupta, *J. Am. Chem. Soc.*, **97**, 6871 (1975).
(22) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(23) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(24) G. J. Martin, M. L. Martin, and S. Odiot, *Org. Magn. Reson.*, **7**, 2 (1975).
(25) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972), and references cited therein.
(26) G. A. Olah, P. W. Westerman, and D. A. Forsyth, *J. Am. Chem. Soc.*, **97**, 3419 (1975), and references cited therein.
(27) Defined as the difference (ppm) between the ^{13}C chemical shift of the uubstituted compound and that of the appropriate carbon in the parent hydrocarbon. Positive signs imply deshielding, negative signs shielding.
(28) (a) C. D. Schoeffer, Jr., and J. J. Zuckermann, *J. Organomet. Chem.*, **55**, 97 (1973); (b) D. Doddrell, K. G. Lewis, C. E. Mulquiney, W. Adcock, W. Kitching, and M. Bullpitt, *Aust. J. Chem.*, **27**, 417 (1974); (c) M. Bullpitt, unpublished work.
(29) M. J. S. Dewar, "Hyperconjugation", Ronald Press, New York, N.Y., 1962.
(30) (a) P. J. P. Vidal, J. Lapasset, and J. Falgueirettes, *Acta Crystallogr., Sect. B*, **28**, 3137 (1972); (b) P. J. P. Vidal and J. Falgueirettes, *ibid.*, **29**, 2833 (1973).
(31) P. J. P. Vidal and J. Falgueirettes, *Acta Crystallogr., Sect. B*, **29**, 263 (1973).
(32) $\sigma-\pi$ conjugation should be most favored when the CCX plane is orthogonal to the ring and vanishes when the C–X bond lies in the plane of the ring; see (a) R. S. Mulliken, *J. Chem. Phys.*, **7**, 339 (1939); R. S. Mulliken, C. A. Rieke, and W. G. Brown, *J. Am. Chem. Soc.*, **63**, 41 (1941); (b) M. J. S. Dewar, *ibid.*, **74**, 3345 (1952). The resonance integral β^θ is given approximately by $\beta^\theta \simeq \beta^0 \cos\theta$, where θ is the angle of twist.
(33) (a) G. K. Hamer, I. R. Peat, and W. F. Reynolds, *Can. J. Chem.*, **51**, 897 (1973); (b) W. F. Reynolds, I. R. Peat, M. H. Freedman, and J. R. Lyerla, *ibid.*, **51**, 1857 (1973); (c) D. A. Dawson and W. F. Reynolds, *ibid.*, **53**, 373 (1975); (d) J. G. Batchelor, J. H. Prestegard, R. J. Cushley, and S. R. Lipsky, *J. Am. Chem. Soc.*, **95**, 6358 (1973), and references cited therein; (e) J. G. Batchelor, *ibid.*, **97**, 3410 (1975), and references cited therein.
(34) (a) W. Hanstein, H. J. Berwin, and J. G. Traylor, *J. Am. Chem. Soc.*, **92**, 7476 (1970), and references cited therein; (b) C. G. Pitt, *J. Organomet. Chem.*, **61**, 49 (1973).
(35) The appropriate dihedral angles for **2** and **3**, where X = $Si(CH_3)_2$, are ca. 40 and 70°, respectively (see ref 2, 4, 30, and 31).
(36) The overall ^{13}C SCS pattern is very similar to the ^{19}F SCS results previously observed utilizing the fluorine nucleus at the relevant carbon sites (see ref 3, 18, and 21). Although there is no exact linear correspondence between the ^{13}C and ^{19}F SCS, this was not unexpected since the determining balance between mesomeric and polar field effects of each substituent for both probes are quite different. Plots of the data indicate quite reasonable linear correspondence between the ^{13}C SCS of C_4 (system **1**), C_4 (system **2**), and $C_{4,5}$ (system 3) and the corresponding fluorine data.
(37) (a) It is of interest to note that according to the ^{13}C SCS (C_4) in system **1** [or para ^{19}F SCS in system **1** (ref 2 and 3)] the electron-withdrawing effect of the weak polar CN σ bond (X = NCH_3, Table III) is similar in magnitude but opposite in sign to the electronic effect of the weak polar CSi σ bond (X = $Si(CH_3)_2$ which is now accepted as being due to hyperconjugative electron donation. (b) M. Bullpitt, W. Kitching, D. Doddrell, and W. Adcock, *J. Org. Chem.*, accepted for publication. (c) P. Beltrame, P. L. Beltrame, P. Caramella, G. Cellerino, and R. Fantechi, *Tetrahedron Lett.*, 3543 (1975).
(38) (a) The relative magnitude of the $C_{4,5}$ SCS in system 3 are approximately in accord with expectations based on dipole moment values (ref 38b and 38c) for the various polar bonds in some simple system: tetramethylenesulfone (4.7 D); tetrahydrofuran (1.7 D); difluoromethane (1.93 D); formaldehyde (2.17 D); dimethylamine (1.03 D). (b) "Handbook of Chemistry and Physics", 54th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1973. (c) A. L. McClellan, "Tables of Experimental Dipole Moments", W. H. Freeman, San Francisco, Calif., 1963.
(39) E. M. Schulman, K. A. Christensen, D. M. Grant, and C. Walling, *J. Org. Chem.*, **39**, 2686 (1974).
(40) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
(41) S. K. Dayal and R. W. Taft, *J. Am. Chem. Soc.*, **95**, 5595 (1973).
(42) (a) Although attempts to quantitatively estimate electric field shifts have been presented (ref **22**, 33d, 33e, and 42b), we have adopted a purely qualitative approach to our data since the limits of expectation for electric field calculations are not good (approximately a factor of 2–3). The main difficulty lies in estimating the variation of the field effect with distance since the distance dependence of electric fields within molecules may not be simple. Further, the effective dielectric constant term also presents severe problems. (b) G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1683 (1975), and references cited therein.
(43) J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967).
(44) S. A. Holmes and T. D. Thomas, *J. Am. Chem. Soc.*, **97**, 2337 (1975).

The Palladium(II)-Catalyzed Olefin Carbonylation Reaction. IV. Carbon-13 Nuclear Magnetic Resonance Analysis of the Reaction Products

D. E. James[1] and J. K. Stille*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242

Received August 15, 1975

Carbon-13 NMR spectra of the acyclic and alicyclic diester and β-methoxy ester products from the palladium(II)-catalyzed olefin carbonylation reaction are reported. Substituent effects were derived for the carbons of an alkyl chain containing two carbomethoxyl functions which demonstrate the importance of the steric environment on carbon-13 chemical shifts.

Carbon-13 nuclear magnetic resonance spectrometry (^{13}C NMR) is one of the most powerful techniques available for the study of the structure of organic molecules. This usefulness is based, in part, on empirical correlations of carbon-13 shieldings and molecular structure.[2,3] In general, the effects of various substituents on the ^{13}C shieldings of neighboring carbons are found to be additive within families of compounds. Consequently, the positions of ^{13}C absorptions for related compounds may often be predicted with good precision in a wide variety of systems and can be valuable for signal assignments in the analysis of complex spectra.

Generally, ^{13}C shielding parameter sets have been derived from the results for a series of monosubstituted compounds, while the combined effects in di- and polysubstituted systems, with few exceptions,[4,5] have not been studied in detail. In this paper, we report the results of a ^{13}C NMR study of a series of acyclic and alicyclic diesters and β-methoxy esters obtained from the transition metal catalyzed carbonylation reaction of olefins.[5,6]

Experimental Section

All diesters and β-methoxy esters were obtained from the palladium(II)-catalyzed carbonylation reaction of olefins.[6,7] Isolation and purification of the individual products were effected by preparative vapor phase chromatography. The carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were measured on a Bruker HX-90E pulse Fourier transform NMR spectrometer equipped with an SPX high-power amplifier, a broad band decoupler, and a Model B-NC 12 computer. The spectrometer was operated at 22.63 MHz with a 4-μs pulse duration (flip angle 30°), a 2-s pulse repetition time, and an acquisition time of 0.819 s. Because of the small amounts of material available in most cases, the sample was placed in a 5-mm sample tube held concentrically inside the standard 10-mm sample tube and surrounded by deuterium oxide. In this way the sample was concentrated and a greater portion of computer memory was allotted to sample instead of deuteriochloroform. Spectra were taken on neat or chloroform-*d* solutions and were calibrated with tetramethylsilane as the internal reference. Several spectra taken on neat and 50% solutions in chloroform-*d* solutions of the same compound showed no solvent shift effects. Multiplicities and couplings were obtained directly from undecoupled spectra. Chemical shift assignments are based on multiplicities and the general pattern of shielding effects of substituents.[2,3]

Results and Discussion

The carbon-13 chemical shift data for the acyclic diester products obtained from the palladium(II)–copper(II)-catalyzed carbonylation of selected α-olefins[6,7] are listed in Table I. The assignment of individual signals in the spectra of the diesters is unambiguous and is based on off-resonance decoupling experiments and on the general pattern of shielding effects of substituents (vide infra). The aliphatic carbons of the diester molecules studied absorb over a wide range, 10.7–58.9 ppm. The methoxyl carbons of the ester functions are slightly deshielded with respect to methanol (~+2.3 ppm) absorbing at an average value of 51.6 ± 0.4 ppm. Interestingly, in only two cases were the chemical shifts of two nonequivalent methoxyl functions in the same molecule not accidentally overlapping.

Absorptions which were assigned to the carbonyl function ranged from 169.3 to 177.0 ppm. The lower field values were observed for malonic esters while the higher field values were obtained from adipic esters. The data, in addition, suggest that a terminal carboxyl carbon is shielded compared to an internal carboxyl carbon by an average of 2.5 ppm. This is probably the result of a slight deshielding influence that an additional β-carbon–carbon bond exerts at the internal carboxyl carbon.

Another interesting aspect of these data is the occurrence of magnetic nonequivalence. Thus, the ^{13}C NMR data for the *dl* and meso diastereoisomers of dimethyl 2,3-dimethylbutanedioate (**1** and **2**, respectively) demonstrate the effect of the presence of two asymmetric centers in the molecule. All carbons, including the ester carbonyl and methoxyl, have different chemical shifts for the two diastereomers. Carbon-13 NMR is therefore useful for detecting mixtures of diastereomers. In all, three diesters studied were found to be diastereomeric mixtures. These spectra were somewhat unusual in that several carbons which might be expected to give two signals were accidentally equivalent while in other cases carbons two or three bonds removed from the asymmetric center were nonequivalent.

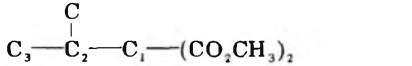
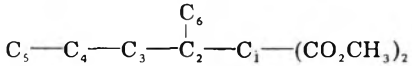
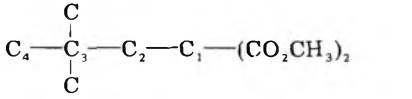
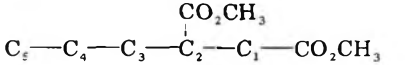
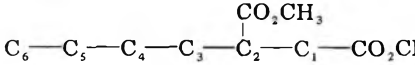
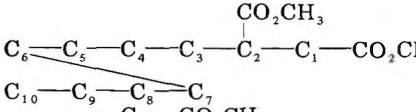
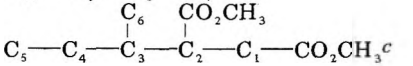
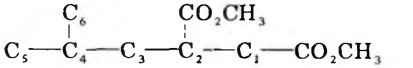
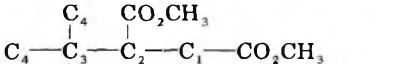
The substituent effects for the linear diesters given in Table I were determined by two methods. The change in chemical shift with respect to the parent alkane, $\Delta\delta = \delta_{obsd} - \delta_{RH}$, is given in parentheses. A second comparison was determined by calculating the chemical shift difference of the diester and the corresponding hydrocarbon wherein methyl groups take the place of ester functions. These calculations, $\Delta\delta = \delta_{obsd} - \delta_{RCH_3}$, are given in brackets. Thus the chemical shift of dimethyl *n*-propylsuccinate was compared with those of pentane and 3-methylhexane, respectively. The chemical shift data for the parent and methyl-substituted hydrocarbons were taken directly from the literature.[8,9] Positive values in Table I indicate downfield shifts while negative values indicate upfield shifts.

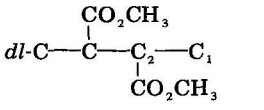
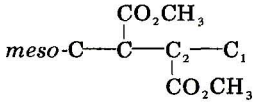
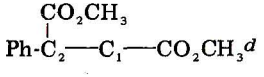
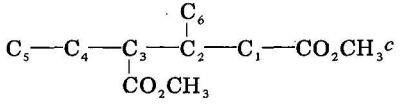
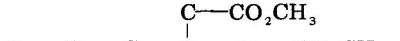
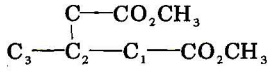
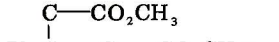
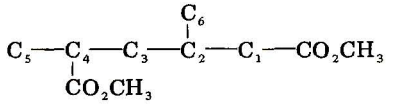
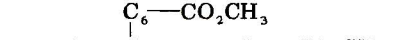
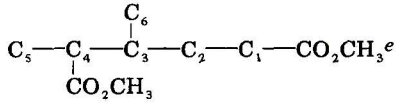
The substituent effects of the carbomethoxyl group derived from a series of terminal aliphatic monoesters by comparison with the parent alkane are α, +20; β, +3; γ, −2.5; δ, +0.8.[3,10] When compared with the methyl-substituted parent alkane, the effects are determined as α, +11.35; β, −6.90; γ, −0.10.[11] The shielding effects derived from the branched dimethyl esters in this study are complicated, however, by the fact that the observed change in chemical shift is usually the result of not one, but two substituents. The data suggest that these shielding effects are quite dependent upon steric and conformational differences. Although the general trends are qualitatively similar for all compounds studied, often large quantitative differences occur which are dependent upon substitution at or near a particular carbon. For instance, comparison of the $\delta_{obsd} - \delta_{RH}$ values for a carbon $\alpha\beta$ to two ester groups (i.e., for succinic esters) demonstrates that the terminal carbons are more highly deshielded than the internal carbons. An average substituent effect of 21.7 ± 0.9 was the value for terminal carbons (C1) and 17.7 ± 1.6 for internal carbons (C2). For all acyclic diesters studied, the average deshielding effect for a terminally substituted carbomethoxyl group averaged 4.0 ppm larger than the corresponding effect of an internal ester substituent. The average deshielding at a carbon $\alpha\beta$ to two carbomethoxyl groups calculated for 16 carbon atoms by comparison with the parent alkane was 19.5 ppm with a standard deviation of 2.2 ppm. Thus computation of diester shielding effects in this manner is subject to rather large errors.

Shielding effect calculations based on the chemical shift difference $\delta_{obsd} - \delta_{RCH_3}$, however, were found to give more consistent results. Substituent effects calculated by this method are listed in Table II. In general, the standard deviation is within 1.0 ppm or less of the average value for a given disubstitution pattern. Comparison with the parent alkane yields a substituent effect in which two bulky ester functions have replaced two hydrogens. This method gives satisfactory results for terminal monoesters but leads to large deviations for the branched diesters. The reliability of the calculations in which the carbomethoxyl groups have replaced methyl groups is probably based upon conformational and rotational restrictions of the diester which are more closely related to those of the dimethyl-substituted alkane (RCH_3) than to those of the parent alkane (RH). The enhanced accuracy of this method is therefore probably the result of a greater accountability for steric perturbations.

The importance of the steric environment on ^{13}C shielding effects at a particular carbon is often reflected in these data. For instance, the $\beta\gamma$ substituent effect is determined for all such carbons to be −4.6 ± 1.7 ppm. A $\beta\gamma$ carbon occurs in both succinic and glutaric esters and as either a secondary or tertiary carbon. When the secondary $\beta\gamma$ carbons are separated from the tertiary $\beta\gamma$ carbons to generate

Table I. Carbon-13 Chemical Shifts in Diesters[a]

Registry no.		Chemical shift, ppm							
		C1	C2	C3	C4	C5	C6	Ester CH_3	Carbonyl(s)
51122-91-9		58.9 (+34.6) [+24.9]	29.0 (+3.8) [−5.0]	20.4 (−3.9) [+1.2]				52.2	169.3
39520-20-2		57.8 (+35.3) [+25.0]	33.4 (+5.6) [−5.1]	36.9 (−4.9) [+0.2]	20.1 (−0.6) [−0.6]	14.0 (−0.1) [0.0]	17.1 (−5.5) [+2.0]	52.0	169.5
58219-43-5		48.8 (+29.9) [+23.1]	42.1 (+5.6) [+11.2]	30.5 (+0.2) [−0.4]	29.2 (+0.5) [−0.7]			52.3	170.3
23143-72-8		36.2 (+22.5) [+6.7]	41.5 (+18.9) [+7.5]	34.6 (+0.1) [−4.4]	20.6 (−2.0) [+0.4]	14.0 (+0.3) [+0.1]		51.4	172.1,175.0
4136-86-1		36.0 (+22.1) [+6.3]	41.3 (+18.4) [+6.6]	31.7 (−0.3) [−4.8]	29.2 (−2.8) [−0.5]	22.5 (−0.4) [−0.8]	13.8 (−0.1) [−0.3]	51.6	172.3,175.3
56425-00-4		35.9 (+21.8)	41.3 (+18.3)	29.4 (−3.0)	27.0 (−2.9)	29.5 (−0.8)	29.5 (−0.8)	51.7	172.5,175.5
58219-44-6 58219-55-9		33.6 31.5 (+22.3) (+20.2) [+6.0] [+5.7]	45.8 45.6 (+16.5) (+16.3) [+6.3] [+7.1]	37.2 36.6 (+0.5) (−0.1) [−2.3] [−1.9]	27.4 27.1 (−1.9) (−2.2) [−0.2] [+1.3]	11.8 (+0.5) [0.0]	16.4 15.9 (−2.2) (−2.7) [+0.6] [+2.1]	51.5	172.8,174.8
58219-45-7		36.4 (+22.3) [+6.5]	39.6 (+18.9) [+7.5]	41.6 (−0.2) [−5.0]	26.2 (−1.6) [+0.8]	22.8 (+0.3) [−0.4]	22.3 (−0.2) [+0.1]	51.4	171.9,175.2
58219-46-8		32.6 (+14.1) [+8.2]	51.6 (+15.1) [+6.2]	32.6 (+2.3) [−0.4]	27.8 (−0.9) [+0.7]			51.2	173.0,174.6

29913-52-8		13.6 (+0.6) [−5.6]	41.7 (+16.9) [+7.7]					51.6	175.5
29800-12-2		14.9 (+1.9) [−4.3]	42.6 (+17.8) [+8.6]					51.7	175.0
15463-92-0		37.7 (+20.9)	47.1 (+17.8)					51.8 52.3	171.9,173.4
36162-68-2 58267-04-2		39.3 39.0 (+16.8) (+16.5) [+11.7] [+13.2]	32.4 (+4.6) [−7.1] [−6.1]	52.5 52.2 (+10.7) (+10.4) [+13.0] [+13.7]	22.8 22.4 (+2.1) (+1.7) [−4.8] [−3.4]	12.1 (−2.0) [+0.3]	17.6 17.1 (−5.0) (−4.5) [+1.8] [+3.3]	51.3 51.1	173.1,175.4 175.1
58219-47-9		38.7 (+16.1) [+13.1]	32.2 (+4.4) [−8.4]	36.7 (−5.1) [+1.3]	20.0 (−0.7) [0.0]	14.0 (0.1) [−0.1]		51.3	172.9
19013-37-7		40.6 (+16.3) [+11.2]	27.7 (+2.5) [−9.1]	20.0 (−4.3) [+1.3]				51.3	172.6
19006-47-4		38.3 (+14.1)	40.4 (+1.5)					51.5	172.0
4819-15-2		41.6 (+19.1) [+11.7]	28.6 (+0.8) [−3.5]	40.9 (−0.9) [−5.7]	37.5 (+16.8) [+12.1]	17.3 (+3.2) [−5.4]	19.7 (−2.9) [+0.7]	51.2	173.0,177.0
26933-03-9		31.5 (+20.2) [+11.5]	28.5 (−0.8) [−6.9]	36.0 (−0.7) [−4.6]	26.0 (−3.1) [+0.6]	10.7 (−0.6) [+0.1]	38.2 (+19.2) [+12.6]	51.5	173.5,174.1
58219-48-0		32.0 31.8 (+20.7) (+20.5) [+11.3] [+11.1]	29.9 28.9 (+0.6) (−0.4) [−6.7] [−7.8]	35.7 35.2 (−1.0) (−1.5) [−2.8] [−3.3]	44.4 44.1 (+15.1) (+14.8) [+11.6] [+11.3]	14.0 12.4 (+2.7) (+1.1) [−4.9] [−6.5]	16.8 15.8 (−1.8) (−3.1) [+1.7] [+0.7]	51.4	173.7,176.4 176.3

[a] δ_C, parts per million from Me_4Si, $\Delta\delta = (\delta_{obsd} - \delta_{RH})$ in parentheses, $\Delta\delta = (\delta_{obsd} - \delta_{RCH_3})$ in brackets. [b] δ_C = 29.4, C = 32.0, C = 22.8, and C = 12.2. [c] Diastereomeric mixture. [d] δ_C aromatic = 127.8, 128.9, and 137.8. [e] δ_C aromatic = 127.0, 127.2, 128.7, and 142.7.

Table II. Carbon-13 Shielding Effects in Linear Diesters[a]

Substitution	Shielding effect	No. of measurements	Standard deviation
$\alpha\alpha$	+25.0	2	0.1
$\alpha\beta$	+6.9	14	0.9
$\alpha\gamma$	+12.7	6	1.0
$\alpha\delta$	+11.5	7	0.3
$\beta\beta$	−7.4	7	2.3
$\beta\gamma$[b]	−4.6	15	1.7
$\beta\gamma'$	−5.7	9	1.2
$\beta\gamma''$	−3.1	6	1.0
$\beta\delta$	−4.1	2	1.0
$\beta\epsilon$	−5.6	3	0.8
$\gamma\gamma$[b]	+1.5	6	1.0
$\gamma\delta$	+0.7	11	0.6
$\gamma\epsilon$	+0.3	1	
$\delta\delta$	0.0	1	
$\delta\epsilon$	−0.3	7	0.4
$\epsilon\epsilon$	−0.1	1	

[a] A carbon α to two ester functions is referred to as $\alpha\alpha$, a carbon α to one ester function and β to another is referred to as $\alpha\beta$, etc. [b] Substituent effects in which a *tert*-butyl group is involved are not included in these calculations.

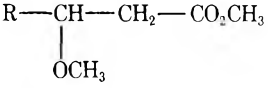
two new parameters, $\beta\gamma'$ and $\beta\gamma''$, the standard deviation is reduced to 1.2 and 1.0 ppm, respectively. A significant standard deviation (2.3 ppm) is observed also for the $\beta\beta$ carbons. Although this substitution pattern occurs for malonic and glutaric esters, no single substitution difference is readily apparent which simply explains the large range in values derived for this substituent effect. Another example of the importance of steric effects is related to the shielding effects calculated from compounds containing a *tert*-butyl group. Nearly all carbons in these molecules showed deviation from generally observable behavior. Often the deviation was so large that the substituent effect was excluded from the calculations of standard substituent effects (Table II).

There are several significant features to the correlations listed in Table II. All diester shielding effects are based upon a comparison with the shielding effects of two methyl groups. The data demonstrate that a carbon α to an ester function is strongly deshielded compared with the methyl analogue. Slight deshielding is also observed for a γ carbon while a significant shielding effect at the β carbon is noted. The effects at the δ and ϵ carbons are quite small. Another aspect of these shielding correlations concerns additivity relationships. Interestingly, the diester ^{13}C shielding effects when calculated in this manner cannot be reduced to simple mono-substituent relationships. Thus, from the $\alpha\alpha$ relationship a value of 12.5 ppm ($\alpha\alpha/2 = \alpha$) may be established for a single α-substituent effect. Using the relationship $\alpha\beta - \alpha = \beta$, then yields a β-substituent effect of −5.6 ppm. A $\beta\beta$ shielding effect ($2\beta = \beta$) of −11.2 is therefore calculated from this relationship which is compared to an observed value of −7.4 ppm. Therefore, when derived by comparison with the dimethyl-substituted alkane, the ^{13}C shielding of two ester functions must be considered as a unit effect rather than as the summation of two separate effects.

The shielding effects given in Table II can be used to predict the chemical shifts of carbons in other diester molecules. The chemical shifts for the appropriate dimethyl-substituted compound are obtained, the relative position of each carbon to the two ester functions is determined, and the shielding effect value is added to the chemical shift of the carbons of the parent compound. If the shifts for the methyl-substituted material are unavailable, an estimate may be obtained by empirical correlations.[8] Thus, the chemical shifts for the ten aliphatic carbons of dimethyl octylsuccinate were determined as shown in Table III. Significantly, the calculated value for each carbon is within 0.9 ppm of the observed value.

In order to test the accuracy of this method, the chemical shifts for 93 carbons from 15 diester molecules were derived by addition of appropriate parameters (Table II) to the calculated chemical shift[8] for each appropriate carbon of the dimethyl-substituted alkane. The standard error of estimation for a calculated chemical shift for the diesters was 1.0 ppm. The agreement between the computed values using this method and the experimental values was excellent. In 81% of the cases, the difference between experimental and predicted values was less than 1.0 ppm. In 87% of the cases, the difference between predicted and experimental values was less than 1.5 ppm and less than 2.0 ppm for 93% of the cases. Importantly, deviations greater than 2.0 ppm were often the result of large deviation in the computation of the chemical shift of the alkane.

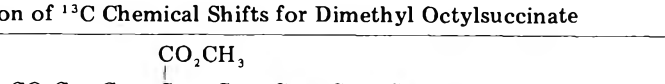
The ^{13}C chemical shift and shielding effect data for nine β-methoxy esters are given in Table IV. Assignments are based upon off-resonance decoupling experiments and are consistent with the general pattern of substituent effects. Of the aliphatic backbone, those carbons α (C2) to the methoxyl function absorb the farthest downfield, 79.5 ± 2.9 ppm. The chemical shift of C2 of the β-methoxy esters is extremely dependent upon the nature of its alkyl substituent, R.



The chemical shift determined from the isomeric 3-methoxyheptanotes is 78.2 ppm for R = *n*-butyl, 81.6 ppm for R = *sec*-butyl, 86.3 ppm for R = *tert*-butyl, and 76.4 ppm for R = isobutyl. These results demonstrate the deshielding effect of β-methyl substituents (R = *sec*-butyl and *tert*-butyl) and the shielding effect of γ-methyl substituent (R = isobutyl). Interestingly, however, methyl substitution at C1 (Table IV) has little effect on chemical shift.

The absorptions assigned to the methoxyl of the ester group averaged 51.2 ± 0.2 ppm and were little changed from similar carbons of the linear diesters. The ether methoxyl carbons for the aliphatic compounds studied absorbed

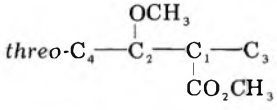
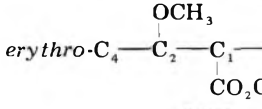
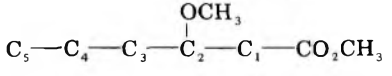
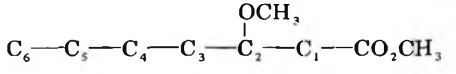
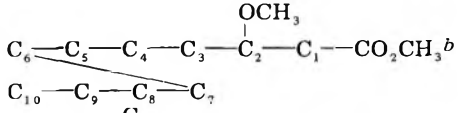
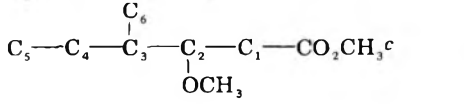
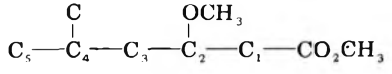
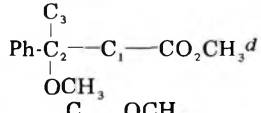
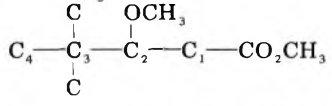
Table III. Calculation of ^{13}C Chemical Shifts for Dimethyl Octylsuccinate



	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
RCH_3[a]	29.6	34.6	37.0	27.0	30.2	30.0	29.7	32.4	22.7	13.9
Substituent effect	+6.9	+6.9	−5.7[b]	+0.7	−0.3	0.0	0.0	0.0	0.0	0.0
Calculated	36.5	41.5	31.3	27.7	29.9	30.0	29.7	32.4	22.7	13.9
Observed	35.9	41.3	29.4	27.0	29.5	29.5	29.4	32.0	22.8	14.2
Difference	−0.6	−0.2	−1.9	−0.7	−0.4	−0.5	−0.3	−0.4	+0.1	+0.4

[a] Calculated chemical shifts[8]. [b] $\beta\gamma'$ substituent effect.

Table IV. Carbon-13 Chemical Shifts in β-Methoxy Esters[a]

Registry no.		Chemical shift, ppm C1	C2	C3	C4	C5	C6	Ether CH_3	Ester CH_3	C=O
39788-67-5		45.4 (+20.6) [+11.4]	78.4 (+53.6) [+44.4]	12.1 (−0.9) [−7.1]	15.7 (+2.7) [−3.5]			56.5	51.3	175.2
39788-68-6		45.8 (+21.0) [+11.8]	78.2 (+53.4) [+44.2]	12.5 (−0.5) [−6.7]	16.9 (+3.9) [−2.3]			56.5	51.3	175.2
54905-29-2		39.6 (+25.9) [+10.1]	78.1 (+55.5) [+43.8]	37.1 (+2.6) [−1.9]	18.8 (−3.8) [−1.4]	14.2 (+0.5) [+0.3]		56.8	51.1	171.8
51664-88-1		39.6 (+25.7) [+9.9]	78.2 (+55.3) [+43.5]	34.4 (+2.4) [−2.1]	27.8 (−4.2) [−1.9]	23.2 (+0.3) [−0.1]	14.1 (+0.2) [0.0]	56.8	51.1	171.6
58219-49-1		39.5 (+25.4)	78.1 (+55.5)	34.4 (+2.0)	25.4 (−4.5)	29.8 (−0.5)	29.8 (−0.4)	56.9	51.3	172.0
58219-50-4 58219-51-5		36.7 36.0 (+25.4) (+24.7) [+9.1] [+10.2]	81.7 81.5 (+52.4) (+52.2) [+42.2] [+43.0]	38.7 37.9 (+2.0) (+1.2) [−0.8] [−0.6]	25.6 (−3.7) [−2.0] [−0.2]	12.2 (+0.9) [−0.4]	14.3 (−4.3) [−1.5] [+0.5]	57.7 57.3	51.1	172.1 172.0
58219-52-6		39.6 (+25.5) [+9.7]	76.4 (+55.7) [+44.3]	44.2 (+2.4) [−2.4]	25.0 (−2.8) [−0.4]	23.4 22.5 (+0.9) (0.0) [0.2] [0.3]		56.7	51.1	171.5
58219-53-7		47.6 (+23.4)	77.7 (+38.8)	23.0 (−1.2)				50.5	51.3	170.7
58219-54-8		36.2 (+17.7) [+11.8]	86.3 (+49.8) [+40.9]	35.7 (+5.4) [+2.7]	25.9 (−2.8) [−1.2]			60.2	51.6	173.5

[a] δ_C, parts per million from Me_4Si, $\Delta\delta = (\delta_{obsd} - \delta_{RH})$ in parentheses, $\Delta\delta = (\delta_{obsd} - \delta_{RCH_3})$ in brackets. [b] δ C = 29.4, C = 32.1, C = 22.8, and C = 14.1. [c] Diastereomeric mixture. [d] δ_C aromatic = 126.2, 127.4, 128.3, and 143.8.

an average of 57.3 ± 1.2 ppm. The slight deshielding effect of δ methyl substituents is observed for R = *sec*- and *tert*-butyl and a very large shielding effect is noted for a γ-phenyl (50.5 ppm).

The ^{13}C shielding data for the β-methoxy esters are summarized in Table V. Again, because of consistency, the substituent effects were calculated by comparison with the methyl-substituted alkane. The results predictably demonstrate the very large deshielding effect at the carbon α to an oxygen (C2). In fact the ether group causes a 36.7-ppm larger downfield shift than does a carbomethoxyl group. Similarly, the deshielding effect of a β ether oxygen is 3.4 ppm larger than that of a carbomethoxyl group.

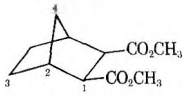
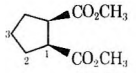
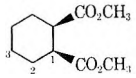
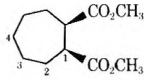
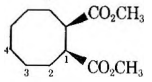
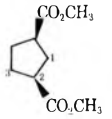
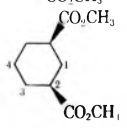
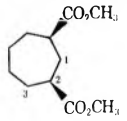
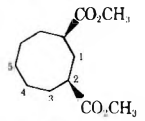
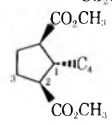
Table V. Carbon-13 Shielding Effects in β-Methoxy Esters

Carbon[a]	Shielding	Deviation
α	+10.3	1.0
β	+43.6	0.8
γ	−1.9	1.0

[a] Position relative to the ester function.

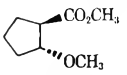
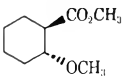
Carbon-13 chemical shift and shielding data for the series of alicyclic diesters and β-methoxy esters obtained from the transition metal catalyzed olefin carbonylation reaction are summarized in Tables VI and VII, respectively. The assignment of individual signals is straightforward and is based on the general pattern of shielding effects, decoupling experiments, and, in certain cases, relative peak in-

Table VI. Carbon-13 Chemical Shifts in Cyclic Diesters[a]

Registry no.		Chemical shift, ppm C1	C2	C3	C4	C5	Ester CH_3	Carbonyl(s)
35436-52-3		51.3 (+21.2)	40.2 (+3.4)	28.9 (−1.2)	36.0 (−2.7)		51.7	173.1
4841-91-2		47.4 (+20.9) [+10.0]	29.1 (+2.6) [−3.9]	24.3 (−2.2) [+1.3]			51.4	174.1
1687-29-2		42.7 (+14.9) [+7.7]	26.4 (−1.4) [−5.7]	24.0 (−3.8) [−0.3]			51.5	173.9
38312-27-5		46.1 (+16.1)	28.3 (−1.1)	26.5 (−2.9)	28.7 (−0.7)		51.4	174.5
54905-31-6		44.2 (+16.4)	26.4 (−1.4)	26.4 (−1.4)	27.1 (−0.6)		51.6	175.0
39590-04-0		33.8 (+7.3) [−10.9]	44.2 (+17.7) [+9.1]	29.5 (+3.0) [−4.5]			51.5	175.3
6998-82-9		31.3 (+3.5) [−14.0]	42.6 (+14.8) [+9.2]	28.6 (+0.8) [−7.4]	25.0 (−2.8) [−2.0]		51.6	175.3
54905-30-5		33.7 (+4.3)	44.3 (+15.0)	31.6 (+2.2)	26.2 (−3.2)		51.4	176.0
54905-32-7		30.5 (+2.7)	43.6 (+15.8)	29.6 (+1.8)	24.1 (−3.7)	26.8 (−1.0)	51.6	176.8
54339-19-4		43.2 (+7.8)	51.9 (+16.5)	29.0 (+3.2)	18.5 (−2.4)		51.5	175.1

[a] δ_C, parts per million from Me_4Si, $\Delta\delta = (\delta_{obsd} - \delta_{RH})$ in parentheses, $\Delta\delta = (\delta_{obsd} - \delta_{RCH_3})$ in brackets.

Table VII. Carbon-13 Chemical Shifts in Cyclic β-Methoxy Esters[a]

Registry no.		Chemical shift, ppm C1	C2	C3	C4	C5	C6	Ether CH_3	Ester CH_3	C=O
54108-60-0		50.3 (+23.8) [+7.8]	85.6 (+59.1) [+43.1]	32.1 (+5.6) [−2.8]	23.5 (−3.0) [+0.3]	28.7 (+2.2) [−6.2]		57.0	51.8	175.9
13640-66-9		50.2 (+22.4) [+10.1]	80.2 (52.4) [+40.1]	30.2 (+2.4) [−6.4]	24.2 (−3.6) [−3.2]	25.0 (−2.8) [−2.4]	28.8 (+1.0) [−7.8]	56.3	51.2	175.1

[a] δ_C, parts per million from Me_4Si, $\Delta\delta = (\delta_{obsd} - \delta_{RH})$ in parentheses, $\Delta\delta = (\delta_{obsd} - \delta_{RCH_3})$ in brackets.

tensities. The absorptions assigned to the carbons of the functional groups are generally similar to the chemical shift ranges for the acyclic systems. The methoxyl group of the ester functions absorbs at an average value of 51.5 ± 0.2 ppm and the ether methoxyl at 56.6 ± 0.5 ppm. Analogously, the absorptions of the carbonyl function for the 1,2-diesters were observed at slightly lower field (174.1 ppm average) than those of the 1,3-diesters (175.9 ppm average).

The shielding results for the alicyclic diesters and methoxy esters also follow the general trends established from the acyclic derivatives, although comparisons with the dimethyl-substituted alkanes can only be made for the cyclopentane and cyclohexane derivatives. Large deviations from predicted values based on acyclic substituent effects may result from conformational effects, intramolecular interactions, and variations in C–C–H and C–C–CO_2R bond angles, all of which are interrelated. The limited amount of information available does not allow a determination of the importance of each of these contributions at the present time.

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this research.

References and Notes

(1) Abstracted in part from the Ph.D. Thesis of D. E. James, University of Iowa, Iowa City, Iowa, May 1975.
(2) G. C. Levy and G. L. Nelson, "^{13}C Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(3) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(4) E. R. Malinowski, T. Vladimiroff, and R. F. Tavares, *J. Phys. Chem.*, **70**, 2046 (1966).
(5) G. E. Maciel, L. Simeral, R. L. Eliot, B. Kaufman, and K. Cribley, *J. Phys. Chem.*, **76**, 1466 (1972).
(6) D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, in press.
(7) D. E. James and J. K. Stille, *J. Am. Chem. Soc.*, in press.
(8) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964).
(9) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).
(10) E. Lippmaa and T. Pehk, *Eesti NSV Tead. Akad. Toim., Keem., Geol.*, **17**, 20 (1968).
(11) J. G. Batchelor, R. J. Cushley, and J. H. Prestegard, *J. Org. Chem.*, **39**, 1698 (1974).

Multiple Regression Analysis of Carbon-13 Chemical Shifts and Carbon-13 Proton Coupling Constants in Ortho-Substituted Aromatics

C. H. Yoder,* F. K. Sheffy, and R. Howell

Department of Chemistry, Franklin and Marshall College, Lancaster, Pennsylvania 17604

R. E. Hess and L. Pacala

Department of Chemistry, Ursinus College, Collegeville, Pennsylvania 19426

C. D. Schaeffer, Jr., and J. J. Zuckerman

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

Received October 17, 1975

Carbon-13 proton coupling constants for off-ring C–H bonds in eight ortho-substituted aromatic systems have been correlated with the divided substituent constants σ_I and σ_R^0. The correlations are in general good and the parameters of the regression equation reveal predominant control by the inductive effect. The influences of hydrogen bonding, steric inhibition of resonance, size of the substituent, and van der Waals forces are discussed. Carbon-13 chemical shifts for off-ring carbons in seven ortho-substituted aromatic systems have also been correlated with σ_I and σ_R^0 but in only a few systems are the correlations good. Attempts to improve the correlations through removal of hydrogen-bonding substituents, variation of σ_R^0 for substituents with possible steric inhibition of resonance, and addition of van der Waals radii, the Q parameter, and $\langle E^2 \rangle$ to the regression equation are discussed.

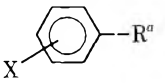
The analysis of the chemical and physical properties of ortho-substituted aromatics is potentially exceedingly complex. In addition to the conventional "through-the-ring" electronic effects, there is the possibility of interaction of the substituent with the ortho site through its electrical field, by van der Waals forces, hydrogen bonding, or dative bonding, or by steric inhibition of resonance as well as other steric effects, to mention just the more easily categorized effects and omitting, obviously, solvation effects. Consequently, it is not surprising that such systems have generally resisted analysis with the Hammett equation. While no one set of ortho-substituent constants has been found to be generally applicable, Charton has correlated reactivities and properties of many ortho-substituted systems with the divided substituent constants σ_I and σ_R^0.[1]

The present study is an attempt to determine what substituent constants or other empirical parameters will correlate successfully with ^{13}C chemical shifts and ^{13}C–^1H coupling constants of off-ring carbons in ortho-substituted benzene derivatives. Since theoretical analyses of ^{13}C–^1H coupling constants point to a heavy dependence upon hybridization and effective nuclear charge,[2] it might be anticipated that correlations with inductive and resonance effects would be successful. Carbon-13 chemical shifts, however, appear to be sensitive to a greater number of factors, such as neighbor anisotropy effects, many of which are still poorly understood.[3]

Experimental Section

Compounds. Most compounds were obtained commercially or prepared by standard procedures. Several, however, were previously unknown. Methyl o-fluorophenyl sulfide, bp 51–55 °C (1.7 mm) (Anal. Calcd for C_7H_7FS: C, 59.12; H, 4.97. Found: C, 59.26; H, 5.04), was prepared by methylation of the thiophenol with methyl iodide. *N,N*-Dimethyl-*o*-trifluoromethylaniline, bp 93 °C (17 mm) (Anal. Calcd for $C_9H_{10}F_3N$: C, 57.14; H, 5.33. Found: C, 56.85; H, 5.33), was obtained by methylation of o-trifluoromethylaniline

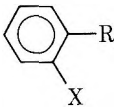
Table I. Coupling Constants, $J(^{13}C-Y) \pm 0.3$ Hz, for



R	Y	X = H	F	Cl	Br	I	CH_3	CN	NO_2	OCH_3	NH_2	$N(CH_3)_2$	CF_3	$COCH_3$
o-$N(CH_3)_2$	^1H	134.5	135.5	135.8			134.1		136.3	134.3	134.2	134.3		
o-$COCH_3$	^1H	127.2	128.4	128.4					128.8	128.0	127.1			
o-SCH_3	^1H	139.2	139.9	139.8	139.4		139.0	140.8		139.1		138.9		
o-CH_2Cl	^1H	150.3	152.7	152.1			150.5		155.4	153.1				
p-$COCH_3$	^1H	127.2	128.4	128.2					128.8	128.0	127.1			
2,6-$(CH_3)_2$	^1H	125.6			127.7	127.65	125.5	127.6	128.7	126.75	125.5	126.4		
o-CF_3	^{19}F	271.7		274.0		273.7		273.7	272.9		271.8	273.6		272.8

[a] 30% in CCl_4.

Table II. Correlations of (J_X-J_H) with σ_I, σ_R^0 for



R	J	ρ_I	ρ_R	λ	C	r	S_{est}	F_{est}	C.L., %	n
CH_3	$^{13}C-^1H$	4.65	0.45	0.10	0.08	0.947	0.44	34.4	99.9	11
OCH_3	$^{13}C-^1H$	2.90	1.15	0.40	0.19	0.975	0.20	58.5	99.9	9
SCH_3	$^{13}C-^1H$	1.95	1.35	0.69	0.06	0.933	0.27	16.7	99	8
CH_2Cl	$^{13}C-^1H$	5.87	0.94	0.16	0.40	0.885	1.13	5.4	90	6
$N(CH_3)_2$	$^{13}C-^1H$	2.80	1.04	0.37	−0.07	0.963	0.27	32.3	99.75	8
CHO	$^{13}C-^1H$	22.86	9.50	0.42	0.40	0.975	1.72	48.7	99.9	8
$COCH_3$	$^{13}C-^1H$	2.58	0.20	0.08	−0.06	0.968	0.22	22.5	97.5	6
$Sn(CH_3)_3$	$^{13}C-^1H$	1.81	1.28	0.71	−0.13	0.958	0.19	22.1	99	7
CF_3	$^{13}C-^{19}F$	3.02	−1.48	−0.49	0.20	0.677	0.77	2.1	75	8
NH_2	$^{15}N-^1H$	12.65	9.96	0.79	0.01	0.931	2.04	9.7	95	6
$Sn(CH_3)_3$	$^{119}Sn-^{13}C$	34.48	−5.05	−0.15	0.28	0.957	3.03	21.8	99	7

with trimethyl phosphate. The preparations of the aryltrimethyltin derivatives were described previously.[4]

Solvents were spectroquality. Chloroform was shaken with alumina to remove ethanol.

Coupling Constants. Carbon-13–proton coupling constants were obtained from the proton satellites on a Varian A-60D NMR spectrometer with the standard sidebanding technique (Hewlett-Packard Model 200CD audiooscillator and 522B electronic counter). Carbon-13–fluorine coupling constants were obtained from ^{13}C spectra.

Chemical Shifts. Natural abundance ^{13}C NMR spectra were recorded on two spectrometers, both operating in the pulsed Fourier transform mode: (1) a modified Varian HA-100D spectrometer, operating at 25.14 MHz, equipped with a Digilab pulse and data system (FTS/NMR-3), described elsewhere,[5] and (2) a Varian XL-100-15 spectrometer operating at 25.21 MHz, equipped with a Varian 620-f computer and data system. Samples run on the XL-100 were contained in 12-mm o.d. tubes, with chloroform-*d* serving as solvent and field–frequency lock material. Compounds studied using the modified HA-100D spectrometer were contained in 8-mm o.d. tubes which held coaxial inner cells containing C_6F_6, the ^{19}F lock substance.

Pseudorandom proton noise decoupling was employed with both spectrometers. All FT spectra were 8K or 16K transforms over spectral widths of 5000 Hz. Ambient probe temperature for both spectrometers was 39 °C.

Carbon chemical shifts were measured in parts per million relative to 5% internal Me_4Si. Positive values are deshielded relative to Me_4Si. Spectra used to obtain both $^{13}C-^1H$ coupling constants and ^{13}C chemical shifts were obtained from 30% solutions (v/v for liquids, w/v for solids) in either carbon tetrachloride or chloroform.

Assignments of carbon resonances were based on proton undecoupled spectra, additivity relationships, and literature values. Though not reported here, assignments were made for all ring carbons and these chemical shift values may be obtained from the authors.

Regression Analyses. Multiple linear regression analyses were accomplished with the stepwise Biomedical computer program BMD02R.[6] In all cases the dependent variable was the difference between the value (either chemical shifts or coupling constants) for the substituted derivative and that of the parent unsubstituted aromatic. All statistical measures of fit except confidence levels were a portion of the output of the program.

Results and Discussion

Coupling Constants. Carbon-13 proton coupling constants for ortho-substituted toluenes, anisoles, benzaldehydes,[7] and trimethylphenylstannanes[8] have been reported previously. Coupling constants for ortho-substituted *N,N*-dimethylanilines, acetophenones, methyl phenyl sulfides, and benzyl chlorides are given in Table I. The coupling constant for the parent compound in each series was subtracted from the values for all members of the series and these substituent-induced values (J_X-J_H) were then correlated with Taft's σ_I, σ_R^0 values[9] by multiple linear regression. Table II contains the parameters for the regression equation

$$J_X-J_H = \rho_I\sigma_I + \rho_R\sigma_R^0 + C \quad (1)$$

where ρ_I and ρ_R express the dependence upon the substituent constants and C is the intercept of the σ_I, σ_R^0 plane with the J_X-J_H axis. The other parameters given in the table include n, the number of substituents correlated; λ, the ratio of ρ_R to ρ_I (see below); r, the multiple correlation coefficient; S_{est}, the standard deviation of the residuals; F_{est}, the F level of the correlation; and C.L., the confidence level derived from F_{est} for the significance of the correlation.[10] An attempt was made to include a basis set of substituents in each correlation and Taft's[9] definition of basis set was adopted for this purpose.

An examination of the confidence levels given in Table II reveals that all but one of the $^{13}C-^1H$ correlations are significant above the 95% confidence level. The use of the F and R values of Swain and Lupton[11] instead of σ_I and σ_R^0 improved the correlations very slightly in a few cases but yielded slightly poorer correlations in others. The use of other resonance parameters,[9] such as $\sigma_{R(BA)}$, σ_R^+, and σ_R^-, led to improved correlations in some cases. For the toluenes, correlations with σ_I and the following σ_R parameters gave the F levels: σ_R^0, 34.4; $\sigma_{R(BA)}$, 35.6; σ_R^+, 34.8; σ_R^-,

37.0. For the benzaldehydes: σ_R^0, 48.7; $\sigma_{R(BA)}$, 51.2; σ_R^+, 43.1; σ_R^-, 54.5. For the anisoles: σ_R^0, 58.5; $\sigma_{R(BA)}$, 38.0; σ_R^+, 28.0; σ_R^-, 91.0. Thus, for these systems σ_R^- gave slightly better correlations for two and an appreciably better correlation for the third. However, because of the heavy weighting of NMR data in the definition of σ_R^0,[9] this measure of the resonance effect was used for all correlations.

Clearly, ^{13}C–^1H coupling constants in ortho-substituted aromatics can be adequately described in terms of σ_I and σ_R^0. As illustrated by the ^{15}N–^1H and ^{119}Sn–^{13}C coupling correlations given in Table II [^{15}N–^1H data (in $CHCl_3$) taken from Axenrod and Wieder;[12] ^{119}Sn–^{13}C data from Schaeffer and Zuckerman[8]] other couplings are apparently also well described by these parameters. This is not the case for the ^{13}C–^{19}F couplings, however. The correlation here is significant at only the 75% confidence level. Schuster reports an excellent correlation (r = 1.000) of four trifluorotoluene couplings with σ_I and σ_R^+ but notes that substituents with a −R resonance effect (e.g., NH_2, NHAc, and OH) lead to deviations from the regression line.[13] The discrepancy is probably due to the presence of different substituents in the sets used for the correlations. Removal of the amino derivative from our set increased the significance of the correlation to the 95% confidence level (ρ_I = 2.88, ρ_R = −2.68, λ = −0.93, r = 0.888, S_{est} = 0.45, F_{est} = 7.5, n = 7).

In an attempt to determine the effect of hydrogen bonding on the significance of the correlations, the value for the amino derivative was removed from the anisole, benzaldehyde, acetophenone, and dimethylaniline sets. After removal of this value the F values and confidence levels are, for anisoles, 145.9, 99.9%; benzaldehydes, 41.9, 99.75%; acetophenones, 44.1, 97.5%; dimethylanilines, 23.4, 99%. Thus, removal of the value for the amino derivative resulted in an improved correlation for the anisoles and acetophenones. Whether the lack of improvement for the other series is a result of an insensitivity of the coupling constant to hydrogen bonding, conformational obstruction to hydrogen bonding (for example, ortho-substituted acetophenones have the carbonyl oriented toward the ortho substituent,[14] whereas the favored conformation for many ortho benzaldehydes has the oxygen away from the substituent[15]), or some other characteristic of these systems that results in a good fit for the NH_2 derivative is not clear.

The effect of steric inhibition of resonance on N-alkyl ^{13}C–^1H coupling constants in 2- and 2,6-disubstituted N-alkylanilines has been reported.[16] The abstraction of an effect due to steric inhibition of resonance with multiple regression analysis is not as straightforward. The dimethylanilines might be expected to yield poor correlations with σ_I and σ_R^0 because of steric inhibition of conjugation of the amino nitrogen with the benzene ring. However, for some substituents (e.g., NO_2), steric inhibition of resonance of the substituent induced by the dimethylamino group is also possible, and conjugation of the substituent and the ortho site with the ring is not independent. In any event, the correlation with σ_I and σ_R^0 for the dimethylanilines is quite good.

The toluenes present a system in which conjugation of only the substituent can be sterically inhibited. In order to test the sensitivity of the correlation to this phenomenon, correlations were performed with σ_R^0 values for the dimethylamino substituent ranging from −0.52 to 0.00. The resultant F levels ranged: σ_R^0 = −0.52, F = 34.4; σ_R^0 = −0.35, F = 36.7; σ_R^0 = −0.25, F = 38.4; σ_R^0 = 0.00, F = 42.5. Thus, a decrease in the resonance contribution (electron release) of the dimethylamino group does result in an increase in the significance of the correlation.

Correlations were also performed for the 2,6-dimethyl series (Table I). With substituents for which steric inhibition of resonance should be minimal (Br, I, CN, NH_2, H, CH_3) the correlation is significant at the 95% level (F_{est} = 13.4, r = 0.948) and the ratio of the ρ_R to ρ_I is low (ρ_I = 4.28, ρ_R = 0.41, λ = 0.096). The addition of the nitro, methoxy, or dimethylamino substituent to this set increases the significance of the correlation, although the correlation coefficient is lower for methoxy (r = 0.947) and dimethylamino (r = 0.925). A decrease in σ_R^0 for $N(CH_3)_2$ to 0.0 increases the F level slightly from 11.8 to 13.3. When all of the substituents are included, the correlation is significant at the 99.75% confidence level (F_{est} = 26.6, r = 0.948) and the ratio of ρ_R to ρ_I is even lower (ρ_I = 4.40, ρ_R = −0.07, λ = −0.016). Thus, the strong dependence on σ_I renders the correlations relatively insensitive to steric inhibition of resonance even in the 2,6-dimethyl system.

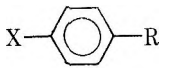
Addition of Other Variables. The possibility that the addition of other variables to the regression equation would improve the correlation of coupling constants was tested with three variables: V, the van der Waals radius; Q, the parameter defined by Hruska, Hutton, and Schaefer[17] and believed to be related to the paramagnetic term in Ramsey's equation[18,19] (and important, therefore, mainly in chemical shifts, see below); and $\langle E^2 \rangle$, presumably a measure of intramolecular dispersion forces (see below). The addition of the third variable was judged to be significant when the confidence level for addition was equal to or greater than 95% as determined by the sequential F test.[10] The correlations with σ_I, σ_R^0, and V were performed on the toluenes, anisoles, and benzaldehydes using Bondi's[20] van der Waals radii for the substituents F, Cl, Br, I, H, and O (radii of OCH_3 assumed to be that of oxygen)[21] and Charton's[21] V_{max} and V_{min} for the CH_3 and NO_2 groups. The correlations of coupling constants with σ_I, σ_R^0, and Q were run for all systems given in Table II, and correlations with σ_I, σ_R^0, and $\langle E^2 \rangle$ were performed for the toluenes and benzaldehydes. The calculations of values of Q and $\langle E^2 \rangle$ are discussed below.

Using the F_{add} criteria for significance, only the σ_I, σ_R^0, V correlation (using either V_{max} or V_{min} for NO_2 and CH_3) for the anisoles (with V_{max}, n = 8, F_{est} = 274, F_{add} = 9.9, confidence level for addition = 95%) and the σ_I, σ_R^0, Q correlation for the toluenes (n = 11, F_{est} = 45.9, F_{add} = 8.1, confidence level for addition = 97.5%) were significant. Hence, it appears that *in general* V, Q, and $\langle E^2 \rangle$ are not significant determinants of variations in ortho coupling constants.

Composition of Electronic Effect. Coupling constants in ortho aromatics are apparently determined, therefore, by inductive and resonance effects. The relative composition of this electronic effect can be expressed in terms of λ, the ratio of ρ_R to ρ_I. The λ values reported in Table II are all less than 1.0, indicating a predominance of the inductive effect for all systems studied. With few exceptions, the lowest values of λ for ^{13}C–^1H couplings appear in those systems that contain the C–H bond directly attached to the ring, e.g., the toluenes and benzyl chlorides. In systems like the anisoles, methyl phenyl sulfides, dimethylanilines, and trimethylphenylstannanes, the methyl group is further removed from the ring, the inductive effect is correspondingly attenuated, and λ is therefore higher. The benzaldehydes and acetophenones are apparently exceptions to these generalizations. In the benzaldehydes, the hydrogen is attached to a carbon capable of conjugation with the ring and λ is, therefore, higher than in the toluenes. The low value for the acetophenones is not easily rationalized.

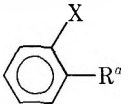
In order to compare the composition of the ortho electronic effect (as manifested by ^{13}C–^1H coupling constants) to that of the para electronic effect, coupling constant data

Table III. Correlations of $(J_X - J_H)$ with σ_I, σ_R^0 for



R	J	ρ_I	ρ_R	λ	C	r	S_{est}	F_{est}	C.L., %	n
CH_3	$^{13}C-^{1}H$	1.94	1.30	0.67	−0.03	0.996	0.062	258.7	99.9	7
OCH_3	$^{13}C-^{1}H$	1.73	2.25	1.30	0.09	0.977	0.188	74.3	99.9	10
CHO	$^{13}C-^{1}H$	7.59	9.29	1.22	−0.70	0.978	0.823	64.4	99.9	9
$COCH_3$	$^{13}C-^{1}H$	0.86	1.55	1.80	0.12	0.957	0.153	27.4	99.75	8
CF_3	$^{13}C-^{19}F$	1.67	3.19	1.91	−0.33	0.970	0.344	39.9	99.9	8
NH_2	$^{15}N-^{1}H$	8.43	13.33	1.58	−0.06	0.992	0.493	151.8	99.9	8
$Sn(CH_3)_3$	$^{119}Sn-^{13}C$	15.10	9.08	0.60	0.37	0.987	0.702	74.8	99.9	7

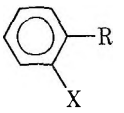
Table IV. ^{13}C Chemical Shifts (±0.05 ppm) for Off-Ring Carbons of



R	X = H	F	Cl	Br	I	CH_3	CN	NO_2	$COCH_3$	OCH_3	NH_2	$N(CH_3)_2$	CF_3
CH_3	21.42	14.36	19.98	22.84	28.04	19.66	20.35	20.25		16.23	17.17	18.33	
OCH_3	54.99	56.03	55.87	55.99	56.16	54.98		56.52	55.48	55.73	55.36		
CHO	192.33	187.15	189.47	191.34		192.61		188.33		189.49	194.13		
$N(CH_3)_2$	40.30			44.01		44.22		42.12		43.06		41.39	45.63
CF_3	124.62		122.77		122.84		122.14	122.07	123.50		125.18	124.33	

[a] 30% in $CDCl_3$.

Table V. Correlations of $(\delta_X - \delta_H)$ with σ_I, σ_R^0 for



R	δ	ρ_I	ρ_R	C	r	S_{est}	F_{est}	C.L., %	n
CH_3	^{13}C	−1.44	7.69	0.44	0.465	3.59	1.1	50	11
OCH_3	^{13}C	2.18	−0.13	0.03	0.966	0.15	48.3	99.9	10
$N(CH_3)_2$	^{13}C	2.24	0.34	2.12	0.347	2.10	0.3	<50	7
CHO	^{13}C	−7.53	−0.04	0.53	0.800	1.69	4.5	90	8
$COCH_3$	^{13}CO	−1.86	3.03	−1.72	0.453	1.59	0.65	<50	8
	$^{13}CH_3$	−4.80	4.55	−1.42	0.708	1.54	2.5	75	8
$Sn(CH_3)_3$	^{13}C	0.85	0.37	0.77	0.342	0.72	0.3	<50	7
CF_3	^{13}C	−4.22	−0.63	0.06	0.955	0.41	25.7	99.75	8
NH_2	^{15}N	2.55	2.06	−0.08	0.837	0.69	3.5	75	6
$Sn(CH_3)_3$	^{119}Sn	28.98	34.50	0.93	0.990	1.74	103.5	>99.9	7

of para-substituted systems were also correlated via eq 1 to σ_I and σ_R^0. Coupling constants for the toluenes,[22] anisoles,[22] and benzaldehydes[23] were reported previously; constants for the acetophenones are listed in Table I. Correlations for $^{13}C-^{19}F$,[14] $^{15}N-^{1}H$,[24] and $^{119}Sn-^{13}C$[8] couplings were also performed. The results of the correlations are given in Table III, from which it is obvious that (a) the correlations are excellent in general, and (b) λ is frequently greater than 1.0 and always higher than that for the ortho correlations. This latter conclusion is easily rationalized on the basis of an increased inductive effect resulting from the increased proximity of substituent and reaction site in the ortho derivatives and supports Charton's[1] conclusion that in general the composition of the ortho and para electronic effects are different.

Chemical Shift Correlations. The off-ring carbon chemical shifts reported in Table IV were correlated with σ_I and σ_R^0 according to the equation

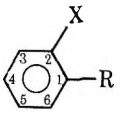
$$\delta_X - \delta_H = \rho_I\sigma_I + \rho_R\sigma_R^0 + C \quad (2)$$

These correlations are tabulated in Table V. Also given there are correlations for ^{13}C shifts of ortho-substituted acetophenones,[25] trimethylphenylstannanes,[8] ^{15}N shifts for anilines (in $CDCl_3$),[12] and ^{119}Sn shifts for trimethylphenylstannanes.[4] For only three systems, the anisoles, trifluorotoluenes, and trimethylphenylstannanes, were the correlations significant above the 95% confidence level. Correlations with σ_I and the other resonance parameters for the toluenes, anisoles, and benzaldehydes produced the following F levels: toluenes, $\sigma_{R(BA)}$, 1.5; σ_R^-, 0.95; σ_R^+, 1.2; anisoles, $\sigma_{R(BA)}$, 43.7; σ_R^-, 47.2; σ_R^+, 48.9; benzaldehydes, $\sigma_{R(BA)}$, 4.5; σ_R^-, 4.5; σ_R^+, 4.9. Thus, for the anisoles and benzaldehydes σ_R^+ led to a slight improvement in the correlations, while for the toluenes $\sigma_{R(BA)}$ provided the best correlation (though differences are small).

The F levels for the correlation of $(\delta_X - \delta_H)$ for the ring carbons with σ_I and σ_R^0 are presented in Table VI. The parameters of eq 2 are given in Table VII for those correlations significant at or above the 95% confidence level. As is apparent from the table, correlations for C(5) are consistently good, while shifts at C(4) and C(6) occasionally afford good correlations. The other ring carbons rarely exhibit good correlations. These trends and the predominance of the resonance effect at C(5), the carbon para to the X substituent, are consistent with previous observations.[26]

The possible influence of hydrogen bonding between the substituent and the reaction site was examined by removal of the amino group from the set of substituents for the ani-

Table VI. F Levels for Correlations of ^{13}C Ring Shifts with σ_I, $\sigma_R{}^{0a}$ and σ_I, $\sigma_R{}^0$, and Q^b for



R		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
CH_3	σ_I, $\sigma_R{}^0$	3.4	1.2	2.1	24.3	18.2	3.5
	σ_I, $\sigma_R{}^0$, Q	11.3	2.2	6.1	0.2	27.5	0.01
OCH_3	σ_I, $\sigma_R{}^0$	7.0	0.4	2.1	1.3	90.5	1.4
	σ_I, $\sigma_R{}^0$, Q	6.8	7.1	6.0	11.4	4.0	3.8
CHO	σ_I, $\sigma_R{}^0$	2.5	1.1	2.1	12.2	44.1	0.7
	σ_I, $\sigma_R{}^0$, Q	5.2	18.5	13.5	0.5	1.1	0.002
CF_3	σ_I, $\sigma_R{}^0$	0.7	0.03	0.6	4.1	17.0	6.2
	σ_I, $\sigma_R{}^0$, Q	0.4	0.1	0.7	1.6	1.9	6.5
$N(CH_3)_2$	σ_I, $\sigma_R{}^0$	1.1	0.5	1.8	0.2	85.2	0.4
	σ_I, $\sigma_R{}^0$, Q	0.05	0.2	0.04	0.05	4.2	1.4
$COCH_3$	σ_I, $\sigma_R{}^0$	1.8	0.3	0.09	0.2	49.2	7.8
	σ_I, $\sigma_R{}^0$, Q	18.1	84.8	1.2	0.4	12.8	0.25
$Sn(CH_3)_3$	σ_I, $\sigma_R{}^0$	1.3	8.8	3.0	36.9	3.9	5.4
	σ_I, $\sigma_R{}^0$, Q	9.1	1.8	1.9	2.6	16.9	12.2

[a] F_{est} for σ_I, $\sigma_R{}^0$ correlations. [b] F_{add} for σ_I, $\sigma_R{}^0$, Q correlations.

Table VII. Correlations of $(\delta_X-\delta_H)$ of Ring Carbons with σ_I, $\sigma_R{}^0$ Significant at or above the 95% Confidence Level

R	Carbon	ρ_I	ρ_R	C	r	S_{est}	F_{est}	C.L., %	n
CH_3	C(4)	2.44	−1.97	0.16	0.927	0.27	24.3	99.9	11
	C(5)	2.17	17.73	0.35	0.906	2.16	18.2	99.75	11
OCH_3	C(1)	−7.67	16.15	−0.42	0.816	3.07	7.0	97.5	10
	C(5)	5.34	20.96	−0.25	0.981	1.11	90.5	99.9	10
CHO	C(4)	1.52	−4.25	−0.70	0.911	0.51	12.2	97.5	8
	C(5)	6.02	21.98	−0.45	0.973	1.48	44.1	99.9	8
CF_3	C(5)	4.29	16.51	−0.19	0.934	2.36	17.0	99	8
	C(6)	3.51	−2.32	0.13	0.844	0.54	6.2	95	8
$N(CH_3)_2$	C(5)	3.18	15.81	−0.36	0.989	0.84	85.2	99.9	7
$COCH_3$	C(5)	−6.03	−21.13	0.48	0.976	1.34	49.2	99.9	8
	C(6)	4.75	3.92	−0.89	0.870	1.06	7.8	97.5	8
$Sn(CH_3)_3$	C(2)	10.80	−52.03	0.09	0.903	7.06	8.8	95	7
	C(4)	2.21	−2.99	0.00	0.974	0.25	36.9	99.5	7

soles, benzaldehydes, and acetophenones. Neither the off-ring or C(5) correlations were improved for the anisoles while both the formyl carbon and C(5) correlations improved (to the 95 and 99.9% confidence levels, respectively) for the benzaldehydes. Only the methyl correlation improved (to the 90% confidence level) for the acetophenones. Thus the relationship between intramolecular hydrogen bonding and the significance of these correlations is uncertain. Moreover, there is in general no parallel between the results obtained for the coupling constant and chemical shift correlations.

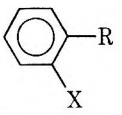
The effect of steric inhibition of resonance on ^{13}C shift correlations was tested by performing the correlation with σ_I and $\sigma_R{}^0$ for the toluenes using values ranging from −0.52 to −0.25 for $\sigma_R{}^0$ for the dimethylamino group. A decrease in the absolute value of $\sigma_R{}^0$ resulted in a slight decrease in F_{est}, and thus there appears to be no evidence that steric inhibition of resonance of the $N(CH_3)$ substituent has resulted in deviation from the correlation plane for the toluenes.

Addition of Other Variables. The possibility of a relation between size of the ortho substituent and ^{13}C chemical shift at the reaction site was tested by addition of the variable V (vide supra) to the regression equation. Correlations to σ_I, $\sigma_R{}^0$, and V were run for the toluenes, anisoles, and benzaldehydes. When either V_{min} or V_{max} was used for CH_3 and NO_2 the addition of V for the off-ring carbons was not significant at the 95% confidence level. For the ring carbons, the addition of V was significant at this level for C(6) of the anisoles and C(4) of the benzaldehydes using V_{max} for $-CH_3$ and $-NO_2$, and C(4) of the toluenes, C(6) of the anisoles, and C(4) of the benzaldehydes using V_{min} for $-CH_3$ and $-NO_2$. *In general*, then, the addition of V to the regression equation is not justified.

The Q parameter, defined by Hruska, Hutton, and Schaefer[17] as P/Ir^3, where P is the polarizability of the C–X bond of the ortho substituent, I is the first ionization potential of the X atom, and r is the C–X bond length, has been applied with some success to proton,[17,27-30] fluorine,[17,27] and carbon[30] shifts in ortho or cis configurations. The parameter has been related to the paramagnetic term in the Ramsey equation.[17] The F levels for the addition of Q to eq 2 for the ring carbons are given in Table VI. The Q values were taken from the compilation of values for ortho substituents based on the proton shifts in various halobenzenes.[29] The Q value for the $N(CH_3)_2$ group was calculated from a least-squares plot of the C(3) proton chemical shifts of 2-substituted chlorobenzenes vs. the Q value of the substituents. The proton shift for 2-dimethylaminochlorobenzene was taken from the work of Goetz, Nerdel, and Rehsc.[31]

The F_{add} values reported in Table VI are significant at the 95% confidence level for the following carbons: toluenes, C(1), C(3), C(5); anisoles, C(1), C(2), C(3), C(4); benzaldehydes, C(2), C(3); trifluorotoluenes, none; dimethylanilines, none; acetophenones, C(1), C(2), C(5); trimethylphenylstannanes, C(5), C(6). Hence, in three out of the seven systems studied the addition of Q is significant at the 95% confidence level (in five out of seven the addition is significant at the 90% confidence level) for the carbon ortho to the substituent and attached to the reaction site, that is, C(1). In three out of seven systems the addition is

Table VIII. Three Parameter (σ_I,σ_R^0, P) Correlations of ($\delta_X - \delta_H$) for Off-Ring Carbons of



R	P	ρ_I	ρ_R	ρ_P	C	r	S_{est}	F_{est}	F_{add}	C.L.$_{add}$	n
CH_3	Q	−4.84	−1.04	2.55	−6.11	0.805	2.57	4.3	8.6	97.5	11
CH_3	$\langle E^2 \rangle$	−4.66	15.84	1.45	−1.72	0.954	1.53	17.0	30.0	99.5	9
CHO	$\langle E^2 \rangle$	−12.06	−0.01	0.83	−1.16	0.986	0.56	35.0	41.1	99	7

significant at the 95% level for the carbon bearing the substituent. In three out of seven systems the addition is significant at the 95% level for the other carbon, C(3), ortho to the substituent. The addition of Q to the regression equation is, therefore, significant for ortho carbons and those attached to the substituent in some cases but certainly not in all. For most correlations for which F_{add} is significant at the 95% level the overall correlation is also significant at that level. The correlations for C(2) and C(3) of the anisoles were significant at lower confidence levels.

Correlations of the off-ring carbons with σ_I, σ_R^0, and Q were also performed. For only one system, the toluenes, was the addition of Q significant at the 95% confidence level. The parameters of this overall poor correlation are given in Table VIII.

Another parameter used to correlate proton,[32] fluorine,[33-35] and carbon[32] chemical shifts is the nonzero time average electric field, $\langle E^2 \rangle$, generated by time dependent dipole moments in neighboring substituents. These van der Waals forces can be estimated by the equation[33,36]

$$\langle E^2 \rangle = \frac{3PI}{r^6} \tag{3}$$

where P is the polarizability of the substituent, I is the first ionization potential, and r is the distance between the reaction site and the substituent. In calculating values of $\langle E^2 \rangle$ we have assumed P to be the polarizability of the bond from the ring to the first atom of the substituent and the bond refractivities given by Smythe[37] were converted to polarizabilities. The ionization potential was assumed to be that of the first atom of the substituent (e.g., O of OCH_3), and r was defined as the distance from a carbon of the ortho site to the center of the bond from the ring to the first atom of the substituent. The distance r was calculated using simple geometry, bond lengths from model compounds,[38] and an angle of 120° for all ring-substituent angles. For the anisoles, r was calculated for two conformations: in one the methyl group is coplanar with the ring and oriented away from the ortho substituent; in the other the methyl group is in a plane perpendicular to the ring. For the acetophenones, the configuration reported by Montaudo et al.[14] was assumed to be constant throughout the series. The distance r for the trimethylphenylstannanes was calculated for the methyl carbon in four conformations. In one, a reflection of the methyl group on the tin–phenyl axis was used as an average position. In a second conformation, the methyl group was assumed to be in the plane of the ring and away from the ortho substituent, while in the third case it was oriented toward the substituent. In the fourth conformation, one methyl group is in the plane of the ring and away from the substituent and r is calculated to one of the other methyl groups (toward the substituent) in that conformation.

The off-ring ^{13}C and ^{119}Sn shifts were then correlated to σ_I, σ_R^0, and $\langle E^2 \rangle$ for the toluenes, benzaldehydes, acetophenones, anisoles (two correlations, one for each conformation), trimethylphenylstannanes (five correlations: four conformations for ^{13}C, one for ^{119}Sn). Of these, only two, the toluenes and benzaldehydes, resulted in a value for F_{add} at or above the 95% confidence level. As is obvious from Table VIII, these correlations are quite good and the addition of $\langle E^2 \rangle$ clearly resulted in a significant improvement.

It appears then that none of the three parameter linear equations employed above can provide satisfactory correlations for a majority of the systems studied. However, the electronic, "paramagnetic", and dispersion effects are not the only factors capable of influencing chemical shifts. A recent review[39] includes, in addition to the factors discussed above, the neighbor anisotropy, steric polarization, electric field, and solvent effects.

While the shielding due to the magnetic field produced by an ortho substituent can be calculated using the point-dipole approximation,[40] the necessary magnetic susceptibilities for the substituents are not accurately known. Moreover, the point-dipole approximation is valid only when the distance between the substituent and the reaction site is greater than the size of the bond or group producing the magnetic field.

The steric polarization effect has been placed on a quantitative basis for gauche 1–4 carbon atoms,[41] but not for the interaction of a carbon atom with a heteroatom in the γ position (some of which have recently been ascribed to hyperconjugative interactions[42]).

The effect of an electric field generated by a polar substituent on a chemical shift at the reaction site can be described by the Buckingham equation[43] and involves two terms, one dependent upon the component of the electric field along the bond direction at the reaction site, the other dependent upon the square of the electric field.

$$\Delta\sigma = -AE_Z - BE^2 \tag{4}$$

Feeney, Sutcliffe, and Walker[32] have assumed that the changes in ^{13}C chemical shifts due to changes in E_Z and E^2 are negligible in a series of halogenated ethanes, owing presumably to the similarity in the magnitudes of the bond dipole moment of the C–X bonds, coupled with the compensating effect of the distance from substituent to the ^{13}C nucleus and the magnitudes of the constants A and B. Carbon-13 shifts in some systems have been rationalized, however, in terms of the electric field model.[39]

The effect of solvent has also not been taken into account. Chloroform is known to produce shifts relative to solvents like CCl_4 or cyclohexane, especially for compounds capable of acceptor hydrogen bonding.[3] The magnitude of these solvent interactions and their variations with substituent is at present impossible to predict.

Thus, it is possible that more accurate quantization of factors such as neighbor anisotropy, solvent effects, etc., will yield improved correlations and understanding of ortho ^{13}C shifts. It seems likely, however, that the ^{13}C shifts of ortho derivatives must be described in terms of a complex mix of factors, the composition of which may vary from substituent to substituent and from system to system.

Carbon-13–proton (and other) couplings, on the other hand, can be described with fair success in terms of only the inductive and resonance substituent parameters.

Acknowledgment. The authors are indebted to the Research Corporation for financial support through a Frederick Gardner Cottrell Grant (C.H.Y. and R.E.H.), the Camille and Henry Dreyfus Foundation (C.H.Y.), the Alexander von Humboldt Foundation for a Senior Scientist Award, and the Technical University of Berlin for a Guest Professorship (J.J.Z.), the Deutsche Forschungsgemeinshaft for a stipend (C.D.S.), and the National Science Foundation for Grant GP-16,554 (J.J.Z.).

Registry No.—*N,N*-Dimethylaniline, 121-69-7; *o*-fluoro-*N,N*-dimethylaniline, 393-56-6; *o*-chloro-*N,N*-dimethylaniline, 698-01-1; *N,N,o*-trimethylaniline, 609-72-3; *N,N*-dimethyl-*o*-nitroaniline, 610-17-3; *o*-methoxy-*N,N*-dimethylaniline, 700-75-4; *N,N*-dimethyl-1,2-benzenediamine, 2836-03-5; *N,N,N',N'*-tetramethyl-1,2-benzenediamine, 704-01-8; acetophenone, 98-86-2; *o*-fluoroacetophenone, 445-27-2; *o*-chloroacetophenone, 2142-68-9; *o*-nitroacetophenone, 577-59-3; *o*-methoxyacetophenone, 579-74-8; *o*-aminoacetophenone, 551-93-9; methyl phenyl sulfide, 100-68-5; methyl *o*-fluorophenyl sulfide, 655-20-9; methyl *o*-chlorophenyl sulfide, 17733-22-1; methyl *o*-bromophenyl sulfide, 19614-16-5; methyl *o*-tolylsulfide, 14092-00-3; methyl *o*-cyanophenyl sulfide, 6609-54-7; methyl *o*-methoxyphenyl sulfide, 2388-73-0; methyl *o*-(dimethylamino)phenyl sulfide, 2388-50-3; benzyl chloride, 100-44-7; *o*-fluorobenzyl chloride, 345-35-7; *o*-chlorobenzyl chloride, 611-19-8; *o*-methylbenzyl chloride, 552-45-4; *o*-nitrobenzyl chloride, 612-23-7; *o*-methoxybenzyl chloride, 7035-02-1; *p*-fluoroacetophenone, 403-42-9; *p*-chloroacetophenone, 99-91-2; *p*-nitroacetophenone, 100-19-6; *p*-methoxyacetophenone, 100-06-1; *p*-aminoacetophenone, 99-92-3; 2,6-dimethylbenzene, 108-38-3; 1-bromo-2,6-dimethylbenzene, 576-22-7; 1-iodo-2,6-dimethylbenzene, 608-28-6; 1,2,6-trimethylbenzene, 526-73-8; 1-cyano-2,6-dimethylbenzene, 6575-13-9; 1-nitro-2,6-dimethylbenzene, 81-20-9; 1-methoxy-2,6-dimethylbenzene, 1004-66-6; 2,6-dimethylaniline, 87-62-7; *N,N*,2,6-tetramethylaniline, 769-06-2; (trifluoromethyl)benzene, 98-08-8; 1-chloro-2-(trifluoromethyl)benzene, 88-16-4; 1-iodo-2-(trifluoromethyl)benzene, 444-29-1; 1-cyano-2-(trifluoromethyl)benzene, 447-60-9; 1-nitro-2-(trifluoromethyl)benzene, 384-22-5; 2-(trifluoromethyl)aniline, 88-17-5; *N,N*-dimethyl-*o*-(trifluoromethyl)aniline, 54672-14-9; *o*-(trifluoromethyl)acetophenone, 17408-14-9; toluene, 108-88-3; *o*-fluorotoluene, 95-52-3; *o*-chlorotoluene, 95-49-8; *o*-bromotoluene, 95-46-5; *o*-iodotoluene, 615-37-2; 1,2-dimethylbenzene, 95-47-6; *o*-methylbenzonitrile, 529-19-1; *o*-nitrotoluene, 88-72-2; *o*-methoxytoluene, 578-58-5; *o*-toluidine, 95-53-4; *N,N*-dimethyl-*o*-toluidine, 609-72-3; anisole, 100-66-3; *o*-fluoroanisole, 321-28-8; *o*-chloroanisole, 766-51-8; *o*-bromoanisole, 578-57-4; *o*-iodoanisole, 529-28-2; *o*-nitroanisole, 91-23-6; 1,2-dimethoxybenzene, 91-16-7; *o*-methoxyaniline, 90-04-0; benzaldehyde, 100-52-7; *o*-fluorobenzaldehyde, 446-52-6; *o*-chlorobenzaldehyde, 89-98-5; *o*-bromobenzaldehyde, 6630-33-7; *o*-methylbenzaldehyde, 529-20-4; *o*-nitrobenzaldehyde, 552-89-6; *o*-methoxybenzaldehyde, 135-02-4; *o*-aminobenzaldehyde, 529-23-7; *o*-bromo-*N,N*-dimethylaniline, 698-00-0; thiophenol, 108-98-5; methyl iodide, 74-88-4; trimethyl phosphate, 512-56-1.

References and Notes

(1) M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971).
(2) M. Barfield and D. M. Grant, *Adv. Magn. Reson.*, **1**, 1 (1965).
(3) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, Chapter 4.
(4) H.-J. Kroth, H. Schumann, H. G. Kuivila, C. D. Schaeffer, Jr., and J. J. Zuckerman, *J. Am. Chem. Soc.*, **97**, 1754 (1975).
(5) C. D. Schaeffer, Jr. and J. J. Zuckerman, *J. Organomet. Chem.*, **55**, 97 (1973).
(6) W. J. Dixon, Ed., "Biomedical Computer Programs", University of California Press, Los Angeles, Calif., 1971.
(7) R. E. Hess, C. D. Schaeffer, Jr., and C. H. Yoder, *J. Org. Chem.*, **36**, 2201 (1971).
(8) C. D. Schaeffer, Jr., and J. J. Zuckerman, *J. Organomet. Chem.*, **99**, 407 (1975).
(9) S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
(10) N. R. Draper and H. Smith, "Applied Regression Analysis", Wiley, New York, N.Y., 1967.
(11) C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, **90**, 4328 (1968).
(12) T. Axenrod and M. J. Wieder, *J. Am. Chem. Soc.*, **93**, 3541 (1971).
(13) I. I. M. Schuster, *J. Magn. Reson.*, **17**, 104 (1975).
(14) G. Montaudo, P. Finocchiaro, and P. Maranigna, *J. Am. Chem. Soc.*, **93**, 4214 (1971).
(15) F. A. Miller, W. G. Fateley, and R. E. Witkowski, *Spectrochim. Acta, Part A*, **23**, 891 (1976).
(16) C. H. Yoder, B. A. Kaduk, and R. E. Hess, *Tetrahedron Lett.*, **42**, 3711 (1970).
(17) F. Hruska, H. M. Hutton, and T. Schaefer, *Can. J. Chem.*, **43**, 2392 (1965).
(18) N. F. Ramsey, *Phys. Rev.*, **78**, 699 (1950).
(19) A. Saika and C. P. Slichter, *J. Chem. Phys.*, **22**, 26 (1954).
(20) A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964).
(21) M. Charton, *J. Am. Chem. Soc.*, 91, 615, 619 (1969).
(22) C. H. Yoder, R. H. Tuck, and R. E. Hess, *J. Am. Chem. Soc.*, **91**, 539 (1969).
(23) C. H. Yoder, C. D. Schaeffer, Jr., and R. E. Hess, *J. Chem. Eng. Data*, **17**, 385 (1972).
(24) T. Axenrod, P. S. Pregosin, J. J. Wieder, and G. W. A. Milne, *J. Am. Chem. Soc.*, **91**, 3681 (1969).
(25) K. S. Dhami and J. B. Stothers, *Can. J. Chem.*, **43**, 479 (1965).
(26) C. D. Schaeffer, Jr., J. J. Zuckerman, and C. H. Yoder, *J. Organomet. Chem.*, **80**, 29 (1974).
(27) T. Schaefer, F. Hruska, and H. M. Hutton, *Can. J. Chem.*, **45**, 3143 (1967).
(28) W. B. Smith and J. L. Roark, *J. Am. Chem. Soc.*, **89**, 5018 (1967).
(29) W. B. Smith, A. M. Ihrig, and J. L. Roark, *J. Phys. Chem.*, **74**, 812 (1970).
(30) W. B. Smith and D. L. Deavenport, *J. Magn Reson.*, 7, 364 (1972).
(31) H. Goetz, F. Nerdel, and K. Rehsc, *Justus Liebigs Ann. Chem.*, **681**, 1 (1965).
(32) J. Feeney, L. H. Sutcliffe, and S. M. Walker, *Mol. Phys.*, **11**, 117 (1966).
(33) N. Boden, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, *Mol. Phys.*, **8**, 133 (1964).
(34) J. W. Emsley, *Mol. Phys.*, 9, 381 (1965).
(35) J. Feeney, L. H. Sutcliffe, and S. M. Walker, *Mol. Phys.*, **11**, 129 (1966).
(36) A. D. Buckingham, H. J. Bernstein, and W. T. Raynes, *J. Chem. Phys.*, **36**, 3481 (1963).
(37) C. P. Smythe, "The Dielectric Constant and Molecular Structure", The Chemical Catalog Co., New York, N.Y., 1931.
(38) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions", The Chemical Society, London, 1958, and Supplement 1, 1965.
(39) G. E. Maciel, "Topics in Carbon-13 NMR Spectroscopy", Vol. 1, G. C. Levy, Ed., Wiley, New York, N.Y., 1974.
(40) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2d ed, Pergamon Press, Oxford, 1969.
(41) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(42) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Wilier, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duck, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(43) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).

Carbon-13 Nuclear Magnetic Resonance Spectra of 9-Thiabicyclo[3.3.1]nonanes

John R. Wiseman,* Herman O. Krabbenhoft, and B. R. Anderson

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48104

Received September 24, 1975

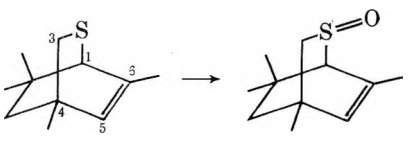
The carbon-13 NMR spectra of a number of sulfides and sulfones in the 9-thiabicyclo[3.3.1]nonane geometry are reported and discussed. Upon conversion of a sulfide to a sulfone, the carbons γ to the oxygen experience upfield shifts; other substituent effects also are described. Incorporation of a 2,3 double bond into the bicyclic nucleus induces an upfield shift of carbon 7 as a consequence of the relief of δ transannular steric interactions. The effects of the configuration of a 2-hydroxyl group on chemical shifts are reported.

Carbon-13 nuclear magnetic resonance spectroscopy has evolved into a very powerful technique for structure elucidation in organic chemistry.[1-3] One of the most useful features of ^{13}C NMR is that steric interactions generate significant shielding or deshielding contributions to the resonance frequency of congested carbon atoms. Because of this sensitive dependence of the carbon chemical shift upon molecular geometry, ^{13}C NMR is especially valuable in conformational analysis.[4] Upon the replacement of a hydrogen atom with a functional group (including alkyl and aryl groups), the carbon bearing the functionality (the α carbon) and the carbon immediately adjacent to the carbon containing the substituent (the β carbon) usually experience downfield shifts. On the other hand, the carbons γ to the substituent usually exhibit upfield shifts. Grant and Cheney[5] have proposed that "the upfield shifts are due to (sterically) induced polarization of charge along the HC^{13} bond" when the γ carbon is in a gauche relationship with the substituent.[6-12] For γ-eclipsed nuclei (such as in cis-disubstituted olefins[13] and ortho-disubstituted aromatics[14]), upfield shifts are also found,[15] presumably for similar steric reasons. While the upfield γ steric argument has been very valuable in assignment of chemical shifts as well as a convenient indicator of spatially proximate groups, it should be employed with care since a substantial amount of data has been presented for δ steric effects which are uniformly downfield.[16-18] Moreover, Eliel et al. recently have demonstrated that appreciable upfield shifts are observed even when the γ carbon and the substituent are in an antiperiplanar arrangement (thus precluding steric effects), but only when the substituent is a second row heteroatom (N, O, F).[19]

We have measured the ^{13}C NMR spectra of 9-thiabicyclo[3.3.1]nonane (1) and a number of its derivatives. In this report we describe the effects on the carbon chemical shifts of these bridged bicyclic substrates as a function of (1) the conversion of a sulfide to a sulfone, (2) the incorporation of a 2,3 double bond into the bicyclo[3.3.1]nonyl geometry, and (3) the configuration of a 2-hydroxyl group.

Results and Discussion

Effect of the Oxidation of Sulfur. For the transformation shown in eq 1, the introduction of an oxygen on sulfur results in the γ-gauche carbon 6 being shielded by 7.1 ppm.[20] Similar γ-gauche steric effects have been reported for trimethylene sulfites,[21] 1,4-oxathiane,[22] and the parent thiane system.[23]



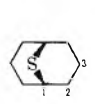
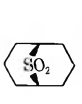
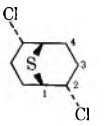
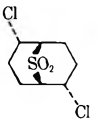
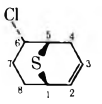
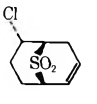
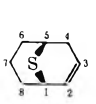
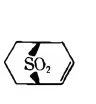
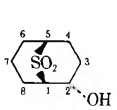
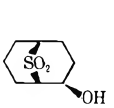
δ_{C-6} = 142.7 δ_{C-6} = 135.6 (1)

The ^{13}C chemical shifts for the 9-thiabicyclo[3.3.1]nonanes we have studied are listed in Table I. Assignments were made in the following manner. The shieldings of the parent sulfide 1 and sulfone 2 were apparent from relative peak intensities and the splitting patterns observed in coupled spectra; the assignments are unambiguous. For the 2,6-dichlorides (3 and 4) the known[24] effects of an endo 2-chloride in the bicyclo[3.3.1]nonane system were employed in conjunction with coupled spectra to assign the signals to the proper carbons.[25] With our data for compounds **1–4**, along with other information for various bicyclo[3.2.1]oct-2-enes,[26] chemical shift assignments for the carbons of the unsaturated sulfides and sulfones **5–8** followed in a straightforward way. In accord with the results of Stothers et al.,[26] the lower field olefinic resonance is assigned to olefinic carbon 2, adjacent to the bridgehead. In all cases, coupled spectra were obtained in order to distinguish positively between the methylene and methine carbon atoms.

From the data assembled in Table I, the substituent parameters of transforming a sulfide to a sulfone in the 9-thiabicyclo[3.3.1]nonane system can be derived; they are summarized in Table II. The effect on the bridgehead carbons (β effect) is 20.0 ppm, a value virtually identical with that reported for the 2-thiabicyclo[2.2.2]octane system.[24] The deshielding direction of the β effect reflects the greater electron-withdrawing inductive nature of the sulfonyl moiety compared to the sulfide group. The γ effects are shielding (presumably owing to gauche steric interactions) and are dependent upon the proximity of any chlorine atoms in the molecule. For the aliphatic γ carbon atoms *without an α or γ chlorine* (γ aliphatic effect *type I*) the sulfonyl oxygen produces upfield shifts of about −2.4 ppm; this effect is in close agreement with that found for the conversion of 1,4-oxathiane to 1,4-oxathiane 4,4-dioxide.[22] γ carbons *with a γ chlorine* (γ aliphatic effect *type II*) experience upfield shifts of about −6.6 ppm upon oxidation to the dioxide. Aliphatic carbons *with an α chlorine* (γ aliphatic effect *type III*) are shielded by approximately −5.1 ppm as a result of the sulfide to sulfone transformation. The olefinic γ carbons are shifted to higher field by 8.5 ppm; a similar shielding has been observed for the 2-thiabicyclo[2.2.2]octene system.[20] At the present time we are unable to offer a satisfactory explanation for the effect of chlorine on the γ aliphatic effects of types II and III. The δ aliphatic effect is −2.5 ppm; similar δ oxidation effects have been reported for the production of thiane 1-oxide[23] from thiane,[19] as well as for the conversions of hydrocarbons to ketones in the bicyclo[3.3.1]nonyl,[24,27] bicyclo[3.2.1]octyl,[26] and adamantyl[11,28] systems. The δ olefinic effect (1.6 ppm) is in substantial agreement with previous results.[20]

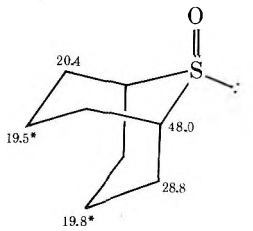
In order to gain some insight of the effect of monooxida-

Table I. ^{13}C Chemical Shifts for Various 9-Thiabicyclo[3.3.1]nonanes[a]

Carbon	 1	 2	 3	 4	 5	 6	 7	 8	 16	 17
1	33.2	53.2	37.3	56.7	31.4	52.5	33.6	54.2	58.6	58.6
2	32.1	29.4	62.4	58.0	129.9	121.3	130.3	121.8	69.2	72.3
3	21.6	19.2	32.5	30.3	127.5	129.9	129.0	129.8	28.2	28.6
4	32.1	29.4	28.3	22.0	34.2	27.1	35.3	32.6	25.2	25.9
5	33.2	53.2	37.3	56.7	38.9	58.4	32.8	52.5	51.9	52.7
6	32.1	29.4	62.4	58.0	64.4	57.9	30.6	28.2	29.2	28.6
7	21.6	19.2	32.5	30.3	25.7	26.0	18.0	14.7	18.6	17.4
8	32.1	29.4	28.3	22.0	28.8	27.1	32.8	31.1	28.2	26.8

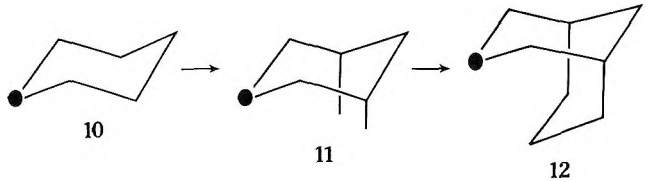
[a] In parts per million from internal Me_4Si for $CDCl_3$ solutions.

tion, the bicyclic sulfoxide **9** was also studied; its chemical shifts are shown with its structure. The coupled spectrum



permits an unequivocal assignment for the bridgehead carbons. The other assignments were based upon the data for thiane 1-oxide[23] and 1,4-oxathiane 4-oxide.[22] For the carbons of the ring in which the oxygen is axial, and γ and δ effects are −11.7 and −2.1 ppm; these values are very similar to those found for thiane 1-oxide (−12.3 and −1.8 ppm, respectively).[19,23] For the carbons of the ring in which the oxygen is equatorial, the γ and δ effects are −3.3 and −1.8 ppm; the corresponding values for the monocyclic model are −4.5 and −1.8 ppm, respectively.[19,23] The γ-gauche effect is a result of steric interactions similar to those exhibited in the sulfide to sulfone transformations described above, although the magnitude is substantially greater for the sulfoxide.[22] The γ-anti effect is not unlike those reported by Eliel[19] and may have the same origin. The β effect (14.8 ppm) is substantially less than those in the parent thiane system (15.9 ppm for axial oxygen and 23.0 ppm for equatorial oxygen).

Effect of Incorporating a 2,3 Double Bond into the 9-Thiabicyclo[3.3.1]nonane System. Introduction of two axial methylene groups onto a six-membered ring in a 1,3 fashion (**10** → **11**) should bring about an upfield shift of the



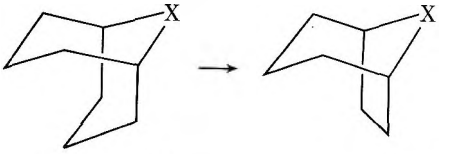
unsubstituted γ carbon by approximately 10 ppm[6-12] as a consequence of the γ-gauche steric effect. Tying the methylene groups together with another methylene unit provides the bicyclo[3.3.1]nonane geometry (**11** → **12**) and adds a deshielding increment to the chemical shift of the carbon atom under consideration as a result of the δ steric effect. From the data collected in Table III, the overall effect on the chemical shift of the designated carbon for the conversion of a (hetero)cyclohexyl substrate into a (9-hetero)bicyclo[3.3.1]nonyl derivative is approximately −5.3 ppm, which implicates a δ steric shift of about 4.7 ppm (a value in good agreement with other reported δ shifts[16-18]).

Table II. Substituent Parameters for Sulfide to Sulfone Conversion

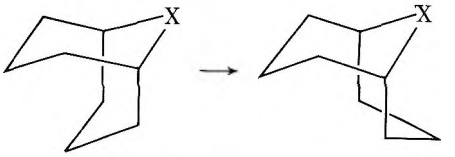
Parameter[a]	Occurrences[b]	Δδ, ppm	Range	Standard deviation
β	*c*	+20.0	19.4 to 21.1	0.7
γ aliphatic I	*d*	−2.4	−1.7 to −2.7	0.5
γ aliphatic II	*e*	−6.7	−6.3 to −7.1	0.6
γ aliphatic III	*f*	−5.4	−4.4 to −6.5	1.5
γ olefinic	*g*	−8.6	−8.5 to −8.6	0.1
δ aliphatic	*h*	−2.6	−2.2 to −3.3	0.6
δ olefinic	*i*	+1.6	0.8 to 2.4	1.1

[a] See text for explanation of types. [b] The number of independent measurements, N, is used to calculate the mean and standard deviation for each effect. [c] 1 → 2, C-1, 5; 3 → 4, C-1, 5; 5 → 6, C-1, 5; 7 → 8, C-1, 5; N = 6. [d] 1 → 2, C-2, 4, 6, 8; 7 → 8, C-4, 6, 8; N = 4. [e] 3 → 4, C-4, 8; 5 → 6, C-4; N = 2. Not included is value of −1.7 for 5 → 6, C-8. [f] 3 → 4, C-2, 6; 5 → 6, C-6; N = 2. [g] 5 → 6, C-2; 7 → 8, C-2; N = 2. [h] 1 → 2, C-3, 7; 3 → 4, C-3, 7; 7 → 8, C-7; N = 3. Not included is value of +0.3 for 5 → 6, C-7. [i] 5 → 6, C-3; 7 → 8, C-3; N = 2.

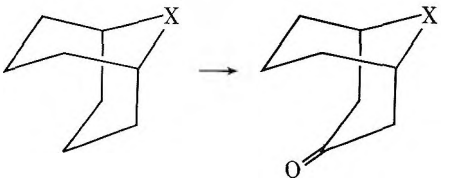
Elimination of the transannular interaction inherent in the chair–chair conformation of the bicyclo[3.3.1]nonane nucleus should remove the δ steric component of the encumbered carbons and induce an upfield shift. There are at least four ways of eliminating or reducing the transannular (δ) steric interaction in bicyclo[3.3.1]nonanes: (1) conversion of the [3.3.1]nucleus to the [3.2.1]nucleus[18a,26,27,30] (eq 2); (2) alteration of the chair–chair to chair–boat equilibrium in favor of the latter[18,31] (eq 3); (3) transformation of a 3-methylene group to a 3-keto group[18,27] (eq 4); and (4) incorporation of a 2,3 double bond into the bicyclic nucleus (eq 5). Table IV contains examples pertinent to the first three types of modifications (eq 2–4). As can be seen, each



(2)

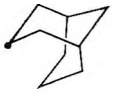
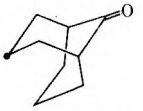
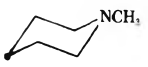
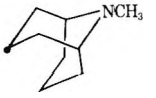
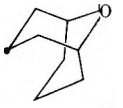
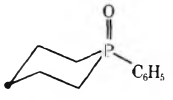
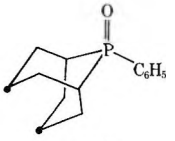
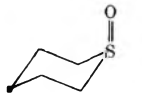
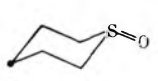
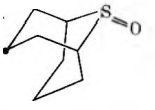


(3)



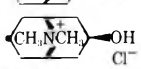
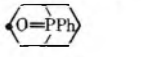
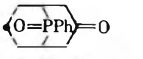
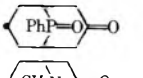
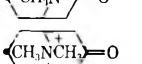
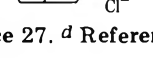
(4)

Table III. Effect on the Chemical Shift of Designated Carbons for the Conversion of (Hetero)cyclohexanes to (9-Hetero)bicyclo[3.3.1]nonanes[a]

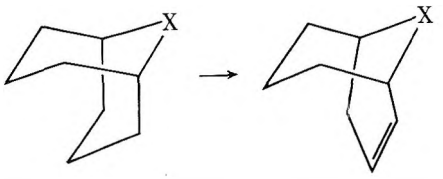
Cyclohexyl compd	Chemical shift[b]	Bicyclononyl compd	Chemical shift[b]	Δδ
	27.7[c]		22.8[d]	−4.9
	24.1[c]		20.7[d]	−3.4
	26.6[c]		20.4[e]	−6.2
	25.1[c]		18.8[d]	−6.3
	27.0[f]		21.6[g] 20.9[g]	−5.4 −6.1
	26.5[h]		21.6[d]	−4.9
	24.7[i]		19.5[j]	−5.2
	24.7[i]		19.8[j]	−4.9

[a] Chemical shifts of carbons denoted by ●. [b] In parts per million from Me_4Si. [c] Reference 1. [d] Reference 27. [e] Reference 18a. [f] Reference 29. [g] Reference 18b. [h] Reference 19. [i] Reference 23. [j] This work.

Table IV. Modification of Bicyclo[3.3.1]nonanes to Relieve Transannular Interactions[a]

Entry	Bicyclo-[3.3.1]-nonane	Chemical shift[b]	Modified compd	Chemical shift[b]	Δδ
1		22.8[c]		19.1[d]	−3.7
2		20.7[c]		17.4[d]	−3.3
3		20.4[e]		15.9[f]	−4.5
4		19.8[e]		14.5[e]	−5.3
5		18.2[e]		13.0[e]	−5.2
6		21.6[f]		18.2[f]	−3.4
7		20.9[f]		17.1[f]	−3.8
8		20.4[e]		16.1[e]	−4.3
9		18.4[e]		14.8[c]	−3.6

[a, b] See Table III. [c] Reference 27. [d] Reference 26. [e] Reference 18a. [f] Reference 18b.



(5)

transformation produces an upfield shift of the sterically relieved carbon. Until now, there have been no examples of the type of transformation indicated in eq 5; our data are summarized in Table V and are in accord with our prediction.

Table V. Effect of Incorporation of a 2,3 Double Bond into the 9-Thiabicyclo[3.3.1]nonane Nucleus[a]

Saturated compd	Chemical shift[b]	Unsaturated compd	Chemical shift[b]	Δδ
	21.6		18.2	−3.4
	19.2		14.7	−4.5
	30.8[c]		26.0	−4.8

[a, b] See Table III. [c] Reference 27.

It is of interest to point out the significance of the larger Δδ values found for the 3-hydroxy-9-methyl-9-azabicyclo-[3.3.1]nonane system (Table IV, entries 4 and 5) compared to those found for all other examples of transannular steric relief (−5.3 ppm vs. about −3.9 ppm, respectively). The additional 1.4 ppm upfield shift found for the granatanol derivatives can be attributed to the γ-gauche steric interaction between the endo hydrogen on carbon 7 and the endo hydrogens at carbons 2 and 4 (see structure **13**).[18]

13

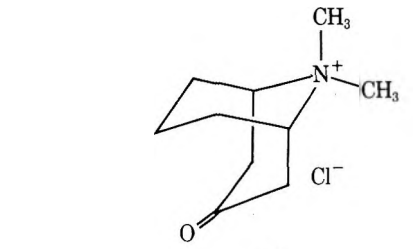
Of additional significance is the resonance position of the carbonyl carbon of pseudopelletierine methochloride (Table IV, entry 9). Jones and Hassan have demonstrated that the chemical shift of the carbonyl carbon of the methiodide of *N*-methyl-4-piperidone is solvent dependent: in dimethyl sulfoxide carbon 4 resonates at 201.7 ppm, a value typical for carbonyl carbons;[1] on the other hand, in water carbon 4 absorbs at 101.7 ppm, indicating that the carbonyl group exists as the hydrate.[31] For the pseudopelletierine derivative **14** the carbonyl carbon resonates at 193.7 ppm in water;[27] thus hydrate formation is insignificant because of steric interactions of the endo hydroxyl group in conformation **15a** or the exo hydroxyl group in conformation **15b**.

Effect of the Configuration of a 2-Hydroxyl Group. We have previously described the effects of the configuration of a 3-hydroxyl substituent in the 9-azabicyclo-[3.3.1]nonane and 9-phosphabicyclo[3.3.1]nonane systems on the chemical shifts of the various carbon atoms.[18] Also of interest are the effects of the configuration of a 2-hydroxyl group. Thus, we measured the ^{13}C NMR spectra of the hydroxyl sulfones **16** and **17**; Tables I and VI contain

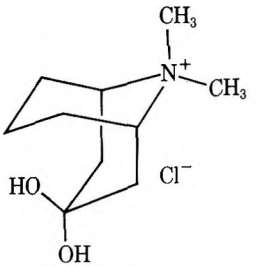
Table VI. ^{13}C Substituent Parameters for 2-Hydroxyl-9-thiabicyclo[3.3.1]nonane 9,9-Dioxides

Compd	Δδ for carbon position[a]							
	1	2	3	4	5	6	7	8
16 (endo OH)	5.4	39.8	9.0	−4.2	−1.3	−0.2	−0.6	−1.2
17 (exo OH)	5.4	42.9	9.4	−3.5	−0.5	−0.8	−1.8	−2.6

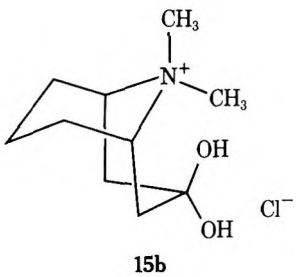
[a] Δδ values are differences in chemical shifts (in parts per million) observed upon introduction of 2-hydroxyl group into parent sulfone 2.



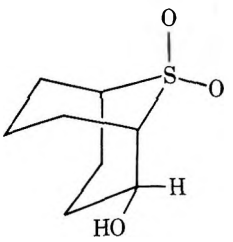
14



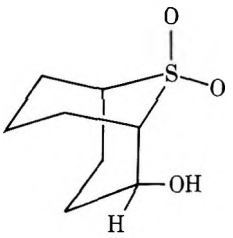
15a



15b



16



17

the pertinent chemical shift information. Assignments were made on the basis of the well-documented substituent effects of hydroxyl groups,[1,19] splitting patterns of coupled spectra, and with the aid of the other sulfone data obtained in the present investigation. Since the completion of our study, a report on the configurational effects of a 2-hydroxyl group in the bicyclo[3.3.1]nonan-2-one system has appeared;[24] our data are completely compatible with those reported, but will not be elaborated here in view of the extensive discussion in the published account.[24]

Experimental Section

^{13}C NMR spectra were measured at 25.15 MHz with a JEOL JNM PS-100 spectrometer interfaced with a Nova 1200 computer operating in the 8K mode. "Coupled spectra" were run fully coupled rather than off-resonance decoupled. All of the 9-thiabicyclo[3.3.1]nonane derivatives were run in deuteriochloroform with Me_4Si as internal standard. In all cases 10-mm tubes were employed, and the sample concentrations were on the order of 0.5 M. With the exception of **17**,[32] all of the 9-thia substrates were prepared and purified according to literature procedures: **1**,[33] **2**,[33] **3**,[33] **4**,[33] **6**,[34] **7**,[34] **8**,[34] **9**,[33] and **16**.[34]

Acknowledgment. This work was supported by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Registry No.—**1**, 281-15-2; **2**, 6522-45-8; **3**, 10502-30-4; **4**, 6522-46-9; **5**, 6522-22-1; **6**, 58703-11-0; **7**, 13334-79-7; **8**, 6435-90-1; **16**, 58240-76-9; **17**, 58240-77-0.

References and Notes

(1) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972.
(2) G. C. Levy and G. L. Nelson, "^{13}C Nuclear Magnetic Resonance for Organic Chemists", Interscience, New York, N.Y., 1972.
(3) E. Breitmaier and W. Voelter, "13-C NMR Spectroscopy", Verlag Chemie, Weinheim/Bergstr., Germany, 1974.
(4) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8**, 1 (1974).
(5) D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1967).
(6) (a) D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.*, **89**, 6612 (1967); (b) *ibid.*, **94**, 5318 (1972); (c) *ibid.*, **96**, 1827 (1974); (d) D. K. Dalling, D. M. Grant and E. G. Paul, *ibid.*, **95**, 3718 (1973).
(7) (a) D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **86**, 2984 (1964); (b) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).
(8) M. Christl, H. J. Reich, and J. D. Roberts, *J. Am. Chem. Soc.*, **93**, 3463 (1971).
(9) (a) E. Lippmaa, T. Pehk, J. Paasivirta, N. Belikova, and A. Plate, *Org. Magn. Reson.*, **2**, 581 (1970); (b) J. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970); (c) J. B. Stothers, C. T. Tan, and K. C. Teo, *Can. J. Chem.*, **51**, 2893 (1973).
(10) E. Lippmaa, T. Pehk, and J. Paasivirta, *Org. Magn. Reson.*, **5**, 277 (1973).
(11) (a) T. Pehk, E. Lippmaa, V. V. Sevostjanova, M. M. Krayushkin, and A. I. Tarasova, *Org. Magn. Reson.*, **3**, 783 (1971); (b) G. E. Maciel, H. C. Dorn, R. L. Greene, W. A. Kleschick, M. R. Peterson, Jr., and G. H. Wall, Jr., *Org. Magn. Reson.*, **6**, 178 (1974); (c) A. S. Murakhovskaya, A. U. Stepanyants, E. I. Bagrii, T. Yu. Frid, K. I. Zimina, and P. I. Sanin, *Neftekhimiya*, **14**, 220 (1974).
(12) D. Zimmermann, R. Ottinger, J. Reisse, H. Cristol, and J. Brugidou, *Org. Magn. Reson.*, **6**, 346 (1974).
(13) (a) D. E. Dorman, M. Jautelat, and J. D. Roberts, *J. Org. Chem.*, **36**, 2757 (1971); (b) G. J. Arbuscato, P. D. Ellis, and T. T. Tidwell, *J. Chem. Soc., Chem. Commun.*, 988 (1972); (c) P. P. Nicholas, C. J. Carman, A. R. Tarpley, Jr., and J. H. Goldstein, *J. Phys. Chem.*, **76**, 2877 (1972); (d) J. W. de Haan and L. J. M. van de Ven, *Org. Magn. Reson.*, **5**, 147 (1973); (e) D. G. Garratt and T. T. Tidwell, *ibid.*, **6**, 87 (1974).
(14) (a) W. R. Woolfenden and D. M. Grant, *J. Am. Chem. Soc.*, **88**, 1496 (1966); (b) N. K. Wilson and J. B. Stothers, *J. Magn. Reson.*, **15**, 31 (1974); (c) A. Kiewiet, J. de Wit, and W. D. Weringa, *Org. Magn. Reson.*, **6**, 461 (1974); (d) N. Platzer, J.-J. Basselier, and P. Demersman, *Bull. Soc. Chim. Fr.*, 905 (1974); (e) T. Sato, T. Takemura, and M. Kainosho, *J. Chem. Soc., Chem. Commun.*, 97 (1974).
(15) K. Tori, M. Ueyama, T. Tsuji, H. Matsumura, and H. Tanida, *Tetrahedron Lett.*, 327 (1974).
(16) J. I. Kroschwitz, M. Winokur, H. J. Reich, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 5927 (1969).
(17) (a) S. H. Grover, J. P. Guthrie, J. B. Stothers, and C. T. Tan, *J. Magn. Reson.*, **10**, 227 (1973); (b) J. B. Stothers and C. T. Tan, *Can. J. Chem.*, **52**, 308 (1974); (c) S. H. Grover and J. B. Stothers, *ibid.*, **52**, 870 (1974).
(18) (a) J. R. Wiseman and H. O. Krabbenhoft, *J. Org. Chem.*, **40**, 3222 (1975); (b) *ibid.*, **41**, 589 (1976).
(19) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(20) H. J. Reich and J. E. Trend, *J. Org. Chem.*, **38**, 2637 (1973).
(21) G. W. Buchanan, J. B. Stothers, and G. Wood, *Can. J. Chem.*, **51**, 3746 (1973).
(22) (a) W. H. Szarek, D. M. Vyas, A.-M. Sepulchre, S. D. Gero, and G. Lukacs, *Can. J. Chem.*, **52**, 2041 (1974); (b) D. M. Frieze and S. A. Evans, *J. Org. Chem.*, **40**, 2690 (1975).
(23) G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1683 (1975).
(24) A. Heumann and H. Kohlshorn, *Tetrahedron*, **31**, 1571 (1975).
(25) Spectral data for sulfide **3** have already been presented: J. A. J. M. Vincent, P. Schipper, Ae. de Groot, and H. M. Buck, *Tetrahedron Lett.*, 1989 (1975).
(26) J. B. Stothers, J. R. Swenson, and C. T. Tan, *Can. J. Chem.*, **53**, 581 (1975).
(27) H. O. Krabbenhoft, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1974.
(28) G. E. Hawkes, K. Herwig, and J. D. Roberts, *J. Org. Chem.*, **39**, 1017 (1974).
(29) G. A. Gray and S. E. Cremer, *J. Org. Chem.*, **37**, 3458, 3470 (1972).
(30) E. Wenkert, J. S. Bindra, C.-J. Chang, D. W. Cochran, and F. M. Schell, *Acc. Chem. Res.*, **7**, 46 (1974).
(31) A. J. Jones and M. M. A. Hassan, *J. Org. Chem.*, **37**, 2332 (1972).
(32) The synthesis of compound **17** will be described in a subsequent report.
(33) E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966).
(34) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966).

Benzobicyclo[3.3.1]non-2-enes. I. Synthesis and Proton Magnetic Resonance Studies of 7-Substituted 1,3,5,5-Tetramethyl-4′-chlorobenzobicyclo[3.3.1]nonenes†

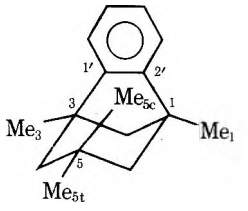
Bernard L. Shapiro* and Michael J. Shapiro‡

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received October 23, 1975

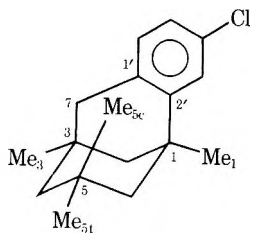
A new family of benzobicyclo[3.3.1]non-2-enes was prepared by the acid-catalyzed ring closure of *trans*-3-(*p*-chlorobenzyl)-1,3,5,5-tetramethylcyclohexanol. The benzobicyclic hydrocarbon so formed was readily converted to a series of compounds endo and exo substituted at C-7, the benzylic methylene carbon. The endo and exo alcohols and bromides all undergo rearrangements to yield a benzobicyclo[3.3.1]nona-2,8-diene and a benzobicyclo[3.2.1]nona-2,6-diene. In the benzobicyclo[3.3.1]non-2-enes, the high-field proton chemical shifts (δ_H 0.05–0.36) of Me_{5c} (the C-5 methyl group syn to the aromatic moiety) are primarily dependent upon aromatic ring current effects. The shifts in a particular derivative are also affected significantly by the nature and stereochemistry of the substituent at the benzylic methylene carbon; substitution results in both upfield and downfield shifts. The methyl ^1H NMR substituent effects in the benzobicyclo[3.3.1]nonene systems compare well with those which occur in the superficially similar adamantane ring system, and this is taken to imply that the steric interactions inherent in both systems are similar, i.e., the cyclohexane ring in the benzobicyclo[3.3.1]nonenes is chairlike in shape.

Previous and current work in this laboratory has been concerned with the synthesis and NMR studies of benzobicyclo[3.2.1]octenes such as **1**.[1]



1

This family of compounds has proven interesting for a variety of NMR spectral studies, particularly those concerning the perpendicular diamagnetic shielding associated with aromatic substituents (the so-called "ring current" effect).[2] In compound **1**, the proton resonance of Me_{5c} occurs at an unusually high field, δ −0.15, owing to this methyl being in the shielding region of the aromatic ring current.[1] Several chlorinated derivatives of **1** also show proton shifts similar to that of the parent hydrocarbon.[3] In naphtho analogues of **1**, the Me_{5c} resonance appears at even higher fields, the range observed being δ −0.32 to −0.41, depending on the particular case.[1] As an extension of these studies, a new family of chlorobenzobicyclo[3.3.1]nonenes such as **2** and derivatives have been synthesized and are now reported.



2

Two theories concerning "ring current" effects have been proposed: the classical theory of Johnson and Bovey[2a] and the quantum mechanical theory of McWeeny.[2b] An extension of McWeeny's theory to include protons above the plane of the aromatic ring has recently been presented by Haigh.[2c] Predictions of the chemical shifts of protons in the plane of the aromatic ring have met with considerable success.[2d] However, the same method does not predict the chemical shifts of protons located above the ring with useful accuracy, as the chemical shifts are greatly underestimated.[2e] Part of the problem associated with such calculations involves a lack of experimental data on model compounds of well-defined geometries.

Since both the ring systems of **1** and **2** are essentially rigid, they can serve as suitable models for calculations of "ring current shifts". In addition, the benzobicyclo[3.3.1]nonene ring system **2** is strain-free (as judged from molecular models as well as from aromatic ring coupling constant data) in virtue of the additional carbon atom "inserted" between C-3 and the aromatic ring (as in **1**). Therefore, these benzobicyclo[3.3.1]nonenes allow the study of perpendicular ring currents in systems which are not affected by any possible ring strain. (The possible effects of ring strain on aromatic ring current shifts remain to be assessed.) In this new family of compounds, these perpendicular ring current effects are also studied at slightly different geometrical positions relative to the aromatic moiety of **1**.

Other reasons for the preparation and study of this series of compounds include (1) the investigation of the effect that substitution at the benzylic carbon (C-7) has upon the chairlike nature of the cyclohexyl ring; (2) the examination of the magnitude and direction of the shifting effect of other group (and bond) anisotropies, such as those of bromine and hydroxyl; and (3) the applicability of ^{13}C NMR substituent effects. This latter area will be reported separately, the present paper being confined to a discussion of the synthesis, characterization, and ^1H NMR studies of this new class of compounds.

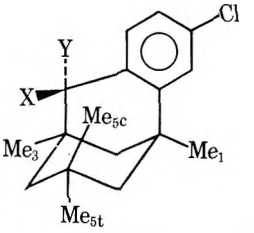
Synthesis. It was decided to study the 4′-chlorobenzobicyclo[3.3.1]non-2-enes rather than the unhalogenated analogue in order to obtain spectra whose aromatic proton patterns would be more conveniently analyzed, as well as to enhance desirable crystallinity in the compounds. No substantial ring current shift changes are introduced by the chlorine, as assessed by a less extensive study of the unchlorinated analogue.

The synthetic route used to obtain the parent compound of this family of benzobicyclo[3.3.1]nonenes, **2**, is outlined in Scheme I. A two-step procedure was employed to prepare ketone **4** since the direct, copper(I)-catalyzed conjugate addition of *p*-chlorobenzylmagnesium chloride to iso-

† Taken in part from the Ph.D. Dissertation of M. J. Shapiro, Texas A&M University, 1974.

‡ Predoctoral Fellow of The Robert A. Welch Foundation.

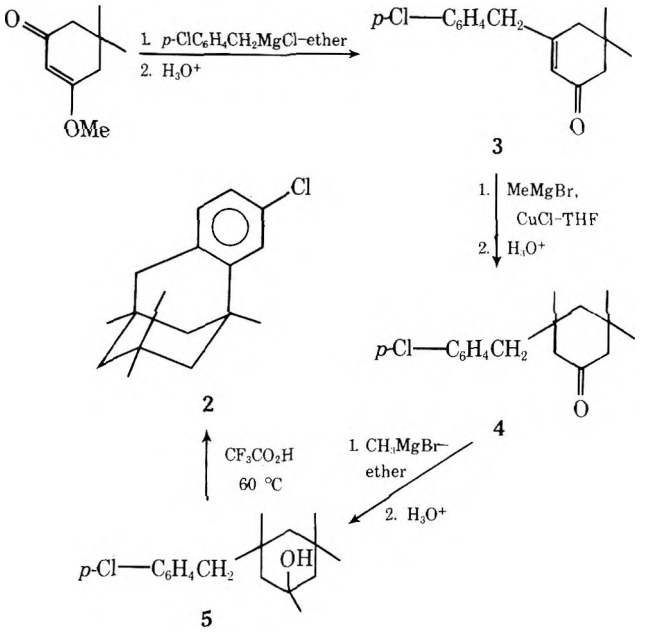
Table I. Proton Chemical Shifts (δ_H) for the Methyl Groups of the Benzobicyclo[3.3.1]non-2-enes[a]



Compd	X	Y	$\delta_{Me_{5c}}$	$\delta_{Me_{5t}}$	δ_{Me_3}	δ_{Me_1}	δ_X	δ_Y
2	H	H	0.30	0.82	1.01	1.30	2.72	2.61
6	Br	H	0.36	0.88	1.30[b]	1.32[b]		5.02
7	H	Br	0.12	0.84	1.30[b]	1.35[b]	5.30	
8	Br	Br	0.25	0.92	1.56	1.34		
9	H	OH	0.11	0.82	1.02	1.30	4.40	
10	OH	H	0.23	0.88	1.10	1.30		4.44
11	CO		0.29	0.90	1.11	1.38		
12	OMe	OMe	0.05	0.89	1.26[b]	1.30[b]	3.67	3.00
13	OH	Me	0.22	0.89	1.03	1.30		1.42

[a] Values refer to 5% w/v solutions in carbon tetrachloride. [b] Assignments in same row may be reversed; see text.

Scheme I

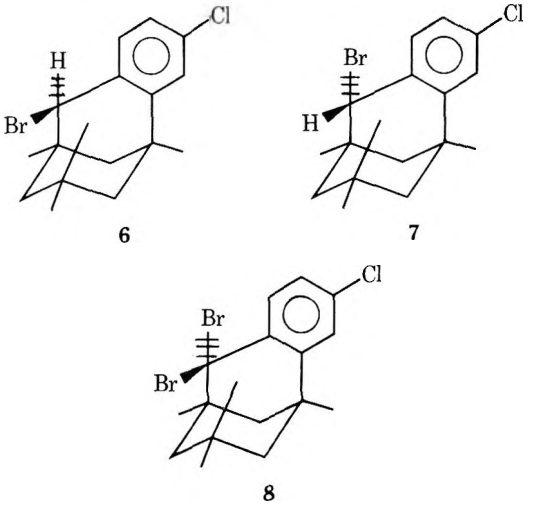


phorone does not proceed in adequate yield (in either diethyl ether or tetrahydrofuran as solvents). It was found that the direct copper(I)-catalyzed conjugate addition of methyl Grignard to 3 proceeded in markedly superior yield (50%) when tetrahydrofuran (THF) was used as a solvent rather than diethyl ether (yield 11%). This parallels the dramatic improvement in the yield of conjugate addition product of phenylmagnesium bromide and isophorone rather than the disappointing, negative results which obtain when THF is used in an analogous α-naphthyl Grignard addition to the same substrate.[4] The nature of this solvent effect remains, for the time being, obscure.

Addition of methylmagnesium bromide to 4 yielded a single tertiary alcohol 5, mp 52–54 °C. The isomer formed is the alcohol which is expected by minimal steric interaction in the transition state (i.e., the alcohol having an axial hydroxyl and an equatorial benzyl moiety), especially since the starting ketone has been shown via lanthanide-induced shift (LIS) data to be in a conformation where the benzyl group is equatorially disposed.[5] No trace (i.e., <1%) of the other alcohol isomer could be found. The lack of the other alcohol isomer is noteworthy in view of the results obtained when methylmagnesium bromide is added to the 3-aryl-3,5,5-trimethylcyclohexanones. In several such cases, *both* isomers are invariably produced in comparable yields.[6] The stereochemical implications of the present observation with 4 are under investigation.

The parent benzobicyclononene, 2, was prepared by the acid-catalyzed cyclization of alcohol 5, similarly to the method previously used to prepare the benzobicyclo[3.2.1]octenes.[1] It was found that excellent yields (ca. 80%) of the bicyclic hydrocarbon 2 could be obtained by adding the neat alcohol to trifluoroacetic acid heated to 60 °C.

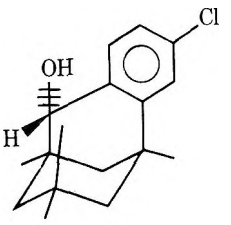
Compound 2 was found to be very susceptible to bromination at the benzylic methylene group (C-7). Thus, reaction with 1.2 molar equiv of bromine in carbon tetrachloride yielded a mixture of two monobrominated products, 6 and 7, and the *gem*-dibromo compound 8, as shown below. The relative yields were 65, 30, and 5%, respectively.



The dibromo compound, 8, could be produced exclusively either by brominating a mixture of 6 and 7 or by adding an excess of bromine to 2. In any event, 8, mp 142–144 °C, is easily isolated by crystallization, but 6 and 7 could not be obtained separately in pure condition. (Spectral data for these compounds, then, were obtained on mixtures of the two isomers.) Unsuccessful attempts to effect this separation included distillation, crystallization, and column, thin layer, and gas chromatographies.

In the case of column chromatography the mixture of monobromo compounds reacted on the alumina (or other)

column to yield an alcohol analogue, mp 133–134 °C, shown to be the exo isomer **9**, as well as two olefinic hydrocarbons (vide infra). The exo nature of the hydroxyl moiety in **9** is demonstrated by the NMR and LIS results presented below. The endo-hydroxyl isomer is probably formed on the column also, but is not isolated for reasons discussed below.



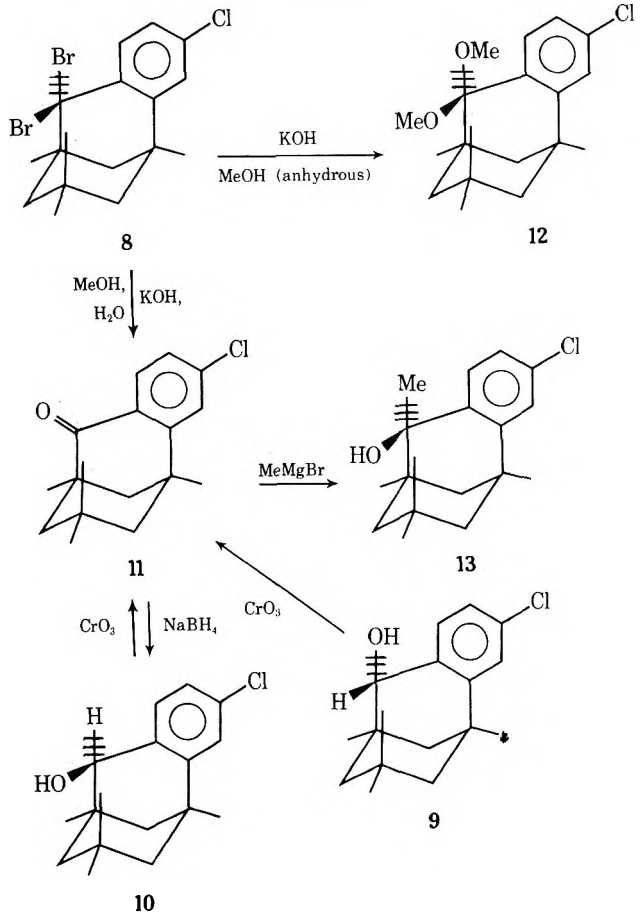
9

The isomeric endo alcohol, **10**, mp 102–104 °C, was prepared in quantitative yield by the sodium borohydride reduction of the corresponding ketone **11**, mp 74–75 °C, which itself was obtained in high yield by the acidic, aqueous methanol hydrolysis of **8**. When anhydrous conditions were maintained in the methanolysis of **8**, the dimethoxy ketal **12**, mp 79–80 °C, was obtained.

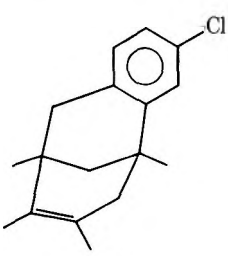
The exo–endo isomeric relationship of the two alcohols **9** and **10** was established by oxidation to the same ketone, **11**. In addition, a single tertiary methyl alcohol **13**, mp 79–80 °C, analogous to **10**, was formed on the addition of methyl Grignard to **11**. Only the one isomer is formed, as expected for steric reasons.

The structures of these benzobicyclo[3.3.1]non-2-ene derivatives are demonstrated by these and other chemical interrelations as summarized in Scheme II, as well as by the detailed ^1H NMR studies that follow and the ^{13}C NMR results to be presented anon.

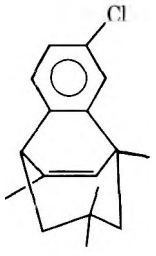
Scheme II



As mentioned above, all attempts to isolate the separate monobromo compounds **6** and **7** by column chromatography yielded two olefinic bicyclic hydrocarbons, **14** and **15**, shown to derive from either of the alcohols **9** and **10**. The same two olefins arise when either alcohol **9** or **10** is treated with *p*-toluenesulfonic acid in refluxing benzene.



14



15

The structures of olefins **14** and **15** are readily assigned on the basis of the mechanisms outlined in Scheme III, and by a detailed analysis of their observed NMR spectral properties.

The first step in the formation of **14** from the initially formed carbonium ion **16**, giving ion **17**, finds close analogy in the work of Berson et al.[7] The conversion of ion **17** to olefin **14** via ion **18**, as well as the ring expansion of ion **16** to olefin **15**, are, of course, completely unexceptional. The involvement of a carbonium ion intermediate in these reactions is further substantiated by the results of the treatment of **9** or **10** with trifluoroacetic acid, whereby the same mixture of epimeric trifluoroacetates is obtained.

The absence of alcohol **10** in the products of the chromatographic decomposition, then, is probably due to its carbonium ion forming much more rapidly owing to steric relief in the transition state. Similar results are observed on the dehydration of axial and equatorial cyclohexanols.[8]

Results and Discussion

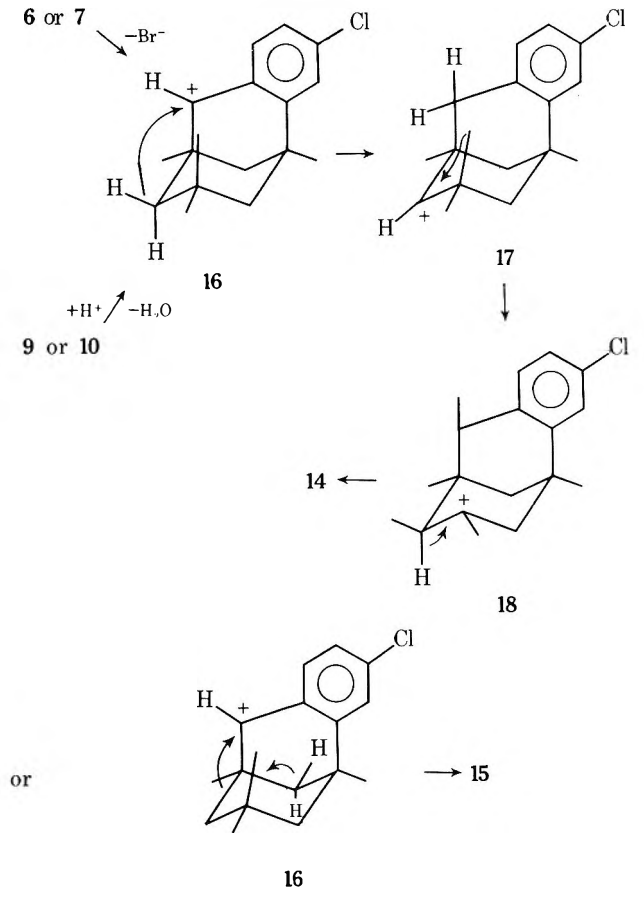
In this section are presented the methyl proton chemical shifts, along with data for the benzylic protons, and that for selected aromatic shifts. The cyclohexane-ring methylene proton shifts were not obtainable because of extensive overlap with each other and the very small shifts between the different proton types. Similar problems precluded the presentation of the aromatic proton shifts in most of the cases other than those cited herein. The methyl and benzyl proton chemical shifts for the benzobicyclo[3.3.1]non-2-enes are summarized in Table I.

The methyl proton resonances at highest and lowest fields are readily assigned to Me_{5c} and Me_1 by analogy with the data of the benzobicyclo[3.2.1]octenes and their precursors.[1] The high-field and low-field nature of these methyl shifts arise respectively from the "out-of-plane" diamagnetic and the "in-plane" paramagnetic ring current effects.[2]

The two remaining methyl group shifts, found at essentially normal positions, may be assigned by a consideration of substituent effects involving C-7. Regardless of the detailed weight of the different factors involved (vide infra), a substituent at C-7 would have a much greater effect on the resonance of Me_3 than it would have on Me_{5t}, for reasons of proximity. The other assignments in Table I, then, are based on the essential consistency of one methyl resonance (δ 0.84–0.92), which is then assigned to Me_{5t}. Because of the small shift differences observed for the Me_1 and Me_3 resonances in **6**, **7**, and **12**, the assignments may be reversed for these compounds.

On the basis of the methyl shift assignments of Table I, the interesting variation of the Me_{5c} chemical shift with the nature and orientation of the C-7 substituent may be ex-

Scheme III



amined. Of particular interest are the isomeric bromides **6** and **7** and the isomeric alcohols **9** and **10.**

The use of lanthanide-induced shifts (LIS) permitted the assessment of the orientation of the hydroxyl function in the two isomeric benzobicyclo[3.3.1]nonene alcohols **9** and **10.** Lanthanide shift reagent (LSR) binding is expected to be more facile in the exo case **9** because the binding site is more accessible sterically. Therefore, the LIS observed in the exo alcohol should be larger than that observed for otherwise comparable protons in the endo case, **10.** In Table II are presented the LIS, as λ values (slopes, in parts per million) for the methyl and benzyl proton types of **9, 10,** and **13.** Although detailed analyses of LIS curves were not performed for these compounds, insight into the benzyl substituent stereochemistry can be obtained by simple examination of λ values, the initial slopes of the LIS doping curves.[6] These semiquantitative experiments have been shown to be valid to explore stereochemical relationships. A larger λ value has the significance of greater LSR binding—for the same functional group (here, hydroxyl)—thus affording a direct, albeit qualitative, assessment of steric hindrance at the binding site.

Of special interest is the LIS observed for H_7, which is equidistant from the binding site in **9** and **10.** It was found that the LIS for this proton was substantially larger in one isomer (**9**) than in the other (**10**). Also, the Me_1 and Me_3 λ values were larger in the compound having the larger H_7 λ value. The compound having the larger λ value for H_7, Me_1, and Me_3 is thus the exo isomer **9.** Conversely, the consistently smaller λ values observed for the other isomer support its configurational assignment as the more hindered endo alcohol, as indicated in structure **10.** Further support for these configurational assignments is found in the λ-value data for the tertiary alcohol analogue of **10,** viz., **13.** For **13,** which must surely have the endo hydroxyl configuration on mechanistic grounds, the λ values resemble those of **10** much more closely than those of **9,** at least for the larger Me_1 and Me_3 λ values. These conclusions derived from the LIS data are consistent with the chemical origin of these compounds, e.g., an endo alcohol is expected upon reduction of ketone **11,** via transfer of a hydride ion from the less hindered side of the molecule. Confirming the LIS and chemical results, the isomer **9,** assigned as exo, shows a singlet H_7 (benzylic) resonance as compared to **10,** assigned as endo, which shows a doublet signal for H_7 owing to slow exchange occurring in the more sterically hindered hydroxyl function.

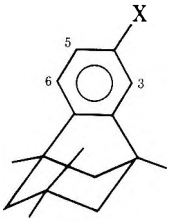
Table II. λ Values (Slopes, ppm) for Methyl and Benzyl Protons of 9, 10 and 13[a]

Compd	Me_1	Me_3	Me_{5c}	Me_{5t}	H_{X_7}
9	0.50	1.36	0.55	0.31	3.54
10	0.30	0.87	0.61	0.23	2.42
13	0.33	0.82	0.44	0.33	1.93[b]

[a] Values refer to $Eu(fod)_3$-doped solutions in carbon tetrachloride. [b] Me_7 (benzylic methyl group).

Assuming the stereochemical nature of the alcohols to be correctly assigned and that hydroxyl and bromine are grossly similar in aspects such as electronic and steric effects, the endo and exo structures (**6** and **7**, respectively) can be assigned for the bromo compounds on the basis of the proton chemical shift of Me_{5c}, i.e., the compound having the higher field methyl resonance is the exo isomer.

The *aromatic proton chemical shifts and coupling constants* for two representative benzobicyclo[3.3.1]nonenes, **2** and **8**, were obtained with the aid of the computer program ITRCL. (ITRCL is a two-part iterative computer program similar to LAOCN3,[9] and is available as part of the Nicolet 1085 data system in our JEOL PFT-100 Fourier transform spectrometer system.) These δ and *J* values are summarized in Table III, along with the data for similar benzobicyclo[3.2.1]octenes, **1** and **19.**



1, X = H
19, X = Cl

A detailed study of the aromatic coupling constants and chemical shifts for most of the other benzobicyclo[3.3.1]nonenes could not be performed owing to insufficient separation of the chemical shifts which in some cases led to deceptively simple spectra, while in other cases, too many unresolvable line frequencies were obtained. From the coupling constant data for **2** and **8** there is no evidence for ring strain in the bicyclo[3.3.1]nonenes analogous to that sometimes manifest in strained systems like the benzobicyclo[3.2.1]octenes (cf. studies of Cooper and Manatt[10a] and Castellano and Kostelnik[10b]). However, even in such strained systems as **1** and **19,** coupling constants are markedly substituent dependent, one chlorine serving to effect substantial changes which render the observed values near normal.

Evaluation of the Chemical Shift Data. As must obviously be the case, the proton chemical shift data in Table I serve to confirm that the benzobicyclo[3.3.1]nonenes all have essentially the same skeletal structure. The problem, then, is how to account for the considerable variation ob-

Table III. Chemical Shifts (δ_H) and Coupling Constants for 1, 2, 8, and 19

	δ_H			
	2	8	19[a]	1[b]
3	7.24	7.09	6.92	6.93
4				7.06
5	7.03	7.19	7.06	7.06
6	6.86	7.98	6.92	6.93
	Coupling constants, Hz			
$^3J(3,4)$				7.406
$^4J(3,5)$	2.309	2.248	1.993	1.117
$^5J(3,6)$	0.253	0.302	0.464	0.662
$^3J(4,5)$				7.497
$^4J(4,6)$				1.117
$^3J(5,6)$	8.241	8.636	7.873	7.406

[a] B. L. Shapiro and G. R. Sullivan, unpublished data. [b] Taken from the Ph.D. Dissertation of M. J. Gattuso, Texas A&M University, 1970.

served for $\delta_{Me_{5c}}$ with the nature and/or orientation of the substituent at the benzylic carbon, C-7. For instance, not only is there a substantial difference, 0.12 ppm, in the proton chemical shift for Me_{5c} in **9** and **10** but it is particularly noteworthy that the Me_{5c} resonance in both of these compounds have Me_{5c} shifts at *higher* fields than that of the parent compound **2**, by 0.19 and 0.07 ppm, respectively.

It is convenient to assess the changes in the Me_{5c} chemical shift in terms of the operation of one or more of the three factors of eq 1

$$\Delta\delta_{obsd} = \Delta\delta_E + \Delta\delta_A + \Delta\delta_G \quad (1)$$

where $\Delta\delta_E$, $\Delta\delta_A$, and $\Delta\delta_G$ are respectively the changes in the chemical shift due to electric field effects, anisotropy effects, and geometry effects. The first two of these effects are intended to have their usual connotations.

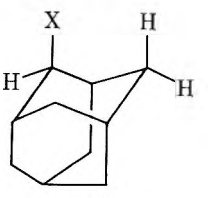
By "geometry effect" we mean the change in shift due to Me_{5c} having its position relative to the aromatic ring altered because of a change in steric crowding, here, because of the substituent at C-7. Since an upfield shift in the Me_{5c} resonances is observed, it is assumed that this alteration would be in a direction which places Me_{5c} closer to the face of the aromatic ring. An examination of Dreiding models indicates that a modest variability in the position of this methyl group due to a flexing of the cyclohexane ring is not energetically prohibitive.

In order to facilitate the discussion of the factors in eq 1; the endo and exo isomer pairs **6** and **7** and **9** and **10** will be discussed separately. Let us consider the exo isomers **7** and **9** first since it appears that their Me_{5c} chemical shifts can be the more easily understood. Of the three factors mentioned above, the "geometry effect" should be absent, because the exo nature of the substituent introduces no new steric interactions vis-à-vis Me_{5c}. In addition, since the C–O and C–Br bonds point away from Me_{5c}, the electric field effect is probably small. By process of elimination, this leaves some anisotropic effect (either atom or bond anisotropies) to be considered.

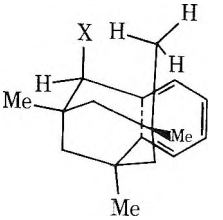
Anomalous shifts to higher field caused by the incorporation of an electronegative atom for hydrogen in a molecule are not without precedent, and have important structural implications. Several examples exist, dating from the earliest days of NMR, and although not completely understood, this effect has been attributed to the anisotropy of the substituent.[11] Schleyer found that the chemical shifts of protons in the δ positions of 1-substituted adamantanes are anisotropy controlled, i.e., a plot of substituent electronegativity vs. δ_{obsd} follows the order of the substituent atom anisotropies, that is, shifts to higher field with increasing electronegativity.[12] Similar shifts have been noticed in 2-substituted adamantanes.[13] The $\Delta\delta_H$ value (where $\Delta\delta_H = \delta_X - \delta_2$, negative values indicating upfield shifts) observed for the methylene protons at the δ positions in 1-hydroxyadamantane (−0.14 ppm) and 1-bromoadamantane (−0.05 ppm)[12] compare well with that found in **9** (−0.19 ppm) and **7** (−0.18 ppm), respectively. The bond pathway is different for the 1-substituted adamantane system than for **7** and **9**, but the spatial relationships between the exo substituent and the protons whose resonances are affected are similar in both types. Since anisotropic field effects are transmitted through space, one might expect that the chemical shift change for these systems would be similar, as is observed.

In any event, if anisotropy and electric field effects are important, then one should be able to predict the chemical shift of Me_{5c} using the additivity of substituent effects as, for example, in a dihydroxy-substituted compound. Although this particular molecule does not exist, a very similar compound, viz., the dimethyl ketal **12**, is in hand. Here the chemical shift of Me_{5c} is δ 0.05 and compares to a remarkable degree with the predicted value of δ 0.04. This value is arrived at by adding the $\Delta\delta_H$ values for **9** and **10** and adding this number to the chemical shift observed for Me_{5c} in **2**. Similarly, using the monobromo compounds to predict the shift of Me_{5c} for the dibromo compound **8**, one obtains δ 0.14 vs. δ 0.25 observed. Although the predicted value in this example is not as accurate as the first case, it is in the right direction. Perhaps the discrepancy can be at least in part accounted for by effective anisotropy changes arising from interactions between the two large and polarizable bromine atoms.

The observed shifts of the Me_{5c} resonance in the endo isomers **6** and **10** are much more difficult to evaluate because all three factors, geometry, anisotropy, and electric field effects, may play an important role. Here, the endo substituent is close in space to Me_{5c}. Thus, the position in space of Me_{5c} might be somewhat altered, causing $\Delta\delta_G$ to become important. However, since the Me_{5c} chemical shift in the endo bromo compound **6** is at lower field than that observed in both the endo hydroxy compound **9** and the parent compound **2**, the "geometry effect" is probably unimportant in these endo-substituted compounds also. A good model to assess the remaining two factors in eq 1 can be found in 2-hydroxyadamantane. Here an x-ray crystallographic study has shown that the hydroxyl function does not perturb the adamantane skeleton.[14] For comparison with the benzobicyclo[3.3.1]nonenes, one is particularly interested in the induced shift changes at the γ protons. As shown in the figure below, the *spatial* relationship between these protons and the functional group is very similar to that found (on a time-averaged basis) for the Me_{5c} protons in the endo-X bicyclo[3.3.1]nonenes. It was found that a



20



6, X = Br
10, X = OH

downfield shift was induced for the endo γ proton (syn to the substituent X) in the 2-substituted adamantane **20**, while for the corresponding exo proton an upfield shift is observed.[13] If we make the crude but simplifying assump-

tion that the protons of the methyl group Me_{5c}, in the endo-substituted benzobicyclo[3.3.1]nonenes, are in analogous position to the endo proton of **20** one-third of the time and in analogous position to the exo proton of **20** two-thirds of the time, then one should be able to predict (using the data for 2-substituted adamantanes[13]) the chemical shift of Me_{5c} in the endo benzobicyclononenes. Doing so, one obtains a chemical shift for Me_{5c} of δ 0.62 for **6** and δ 0.17 for **10**. The direction predicted for the induced shifts of both of these compounds is consistent with that observed, although the magnitude of the change clearly indicates at least the operation of additional factors. In **10** then, the anisotropic field effect is probably more important than the electric field effect (deshielding) and hence an upfield shift is observed. The situation in **6** is probably reversed with the electric field effect dominating. Final analysis concerning the nature of the $\Delta\delta_{Me_{5c}}$ awaits structure determinations by x-ray crystallography, so as to permit assessment of the possible importance of the $\Delta\delta_G$ factor of eq 1.

^{1}H NMR Chemical Shifts and Assignments for Benzobicyclononene Derivatives. The methyl proton chemical shifts of **14** and **15** are given in Table IV.

Table IV. Proton Chemical Shifts (δ_H) for the Methyl Groups of 14 and 15

	Me_{5c}	Me_{5t}	Me_3	Me_1	Other
14			1.12	1.34	1.54 (Me_4 and Me_5)
15	0.15	0.80	1.80	1.42	

Assignments for the methyl protons in **14** were made by comparison with **2**, i.e., Me_1 and Me_3 are in analogous positions to Me_1 and Me_3 in **2** and should have similar proton chemical shifts. The remaining doubly intense methyl resonance, δ 1.54, is assignable to the two olefinic methyl groups Me_4 and Me_5.

A similar procedure was used to assign methyl groups in **15**. Here, Me_1, Me_{5c}, and Me_{5t} are in analogous positions to the three methyl groups in **2**, and are readily assigned. The remaining methyl resonance at δ 1.80 is therefore assigned to the olefinic methyl group Me_3. The lower field resonance observed for this olefinic resonance as compared to those found in **14** is consistent with this methyl being near the edge of the aromatic ring.

Experimental Section

Capillary melting points were determined on a Mel-Temp melting point apparatus. All boiling and melting points reported below are uncorrected. Infrared spectra were determined with a Beckman Model IR 8 infrared recording spectrophotometer, calibrated by means of the 1603-cm^{-1} absorption of a polystyrene film. Microcombustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

All NMR spectra were run on a Varian HA-100 nuclear magnetic resonance spectrometer in the frequency sweep mode at an ambient probe temperature of 30 °C. Shifts were measured on carefully precalibrated chart paper and were estimated to be accurate to ±0.01 ppm or better.

The LAOCN3 and ITRCL analyses were carried out on samples vacuum degassed by means of several liquid nitrogen freeze–thaw cycles. Spectral parameters were obtained on an IBM 360-65 digital computer in the double-precision mode or a Nicolet 1085 data system to a root mean square error of less than 0.05 Hz.

The mass spectral data were obtained with a Consolidated Electronics Corp. Model 21-110B mass spectrometer, operated by Mr. G. Gabel of the Texas A&M University Department of Biochemistry.

3-(*p*-Chlorobenzyl)-5,5-dimethyl-2-cyclohexen-1-one (3). To 24.0 g (1 g-atom) of magnesium shavings in 200 ml of anhydrous ether was slowly added 170.0 g (1.05 mol) of *p*-chlorobenzyl chloride (Aldrich Chemical Co.) dissolved in 250 ml of ether. After all the magnesium had reacted, 100 g (0.67 mol) of dimedone methyl ether (DME) in 100 ml of ether was added slowly. The reaction mixture became very viscous and yellow in color. Stirring was continued overnight and the yellowish solution was hydrolyzed with 6 N hydrochloric acid. The solvent was removed and the crude product distilled. The fraction boiling at 130–144 °C (0.25 Torr) was collected and proved to be greater than 90% pure **3**, the impurity being *p,p'*-dichlorobibenzyl, yield 94.0 g (0.36 mol, 54%). This material was used without further purification. Recrystallization from hexane afforded pure material as needles: mp 84–85 °C; ir (CCl_4) 1660 cm^{-1} (C=O stretch); NMR (10% in CCl_4) δ (methyls) 0.94, δ (benzylic H) 3.22, δ (olefinic H) 5.80; mass spectrum *m/e* (rel intensity) 248 (74, M^+), 192 (100), 157 (50), 129 (50), 67 (32).

Anal. Calcd for $C_{15}H_{17}OCl$: mol wt, 248.906788. Found: mol wt, 248.907774.

3-(*p*-Chlorobenzyl)-3,5,5-trimethylcyclohexanone (4). Addition of *p*-Chlorobenzylmagnesium Chloride to Isophorone. To a flamed-out, 1000-ml, three-necked flask, equipped with a mechanical stirrer, condenser, and dropping funnel, and swept with a slow stream of nitrogen, were added 12.0 g (0.5 g-atom) of magnesium shavings and 300 ml of anhydrous ether. A solution of 80.0 g (0.5 mol) of *p*-chlorobenzyl chloride in 100 ml of ether was added dropwise with vigorous stirring over a period of 1 h. An additional 10 g of the benzyl chloride was added to allow all of the magnesium turnings to react. The reaction mixture was allowed to reach room temperature, 1.0 g (1 mol %) of freshly prepared cuprous chloride was added, and the resulting black solution stirred for 30 min. The reaction mixture was cooled by means of a dry ice–chloroform bath (maintained at ca. −40°), and stirred for 30 min. Isophorone (69.0 g, 0.5 mol) in 100 ml of dry ether was added dropwise, while maintaining the cooling bath. After addition of the isophorone was complete, the reaction mixture was stirred for an additional 4 h and allowed to reach room temperature and stirring continued overnight. The solution at this time was still black in color. (It has been our experience that when this black color is absent, the reaction did not proceed in the desired manner.)

Hydrolysis was effected by the slow addition of a saturated aqueous ammonium chloride solution to the stirred mixture. The ether layer was decanted and the residue washed several times with 50-ml portions of ether; the combined ether extracts were dried and the solvent removed in vacuo. The resulting yellow oil was distilled through a short Vigreux column at reduced pressure until the head temperature reached 120 °C (0.05 Torr) to remove the diene by-products. Chromatography of the remaining crude material (ca. 75% pure) on neutral alumina afforded 10.0 g (0.036 mol, 7.6%) of pure **4**.

The above synthetic procedure was also performed using tetrahydrofuran (THF) as the solvent. Analysis of the reaction product indicated that only *p,p'*-dichlorobibenzyl was formed from the coupling of the Grignard reagent.

Addition of Methylmagnesium Bromide to 3. The Grignard reagent was prepared by the standard method starting with 12.0 g (0.5 g-atom) of magnesium shavings in 200 ml of dry ether, to which methyl bromide was bubbled in until all the magnesium had reacted. [When commercially available methylmagnesium bromide (Alpha Chemical Co.) was used, the overall yield of **4** was reduced by one-half.] To the stirred solution was added 3 mol % of freshly prepared cuprous chloride. The reaction mixture was cooled in an ice–methanol bath (ca. −10 °C) for 1 h and then 70.0 g (0.28 mol) of **3** dissolved in ether was added dropwise with stirring. The reaction mixture was allowed to reach room temperature and stirred for an additional 36 h. Hydrolysis using cold dilute hydrochloric acid, separation of the organic layer, and evaporation in vacuo yielded a viscous yellow oil.

The crude reaction product was distilled at 0.025 Torr until the head temperature reached 110 °C, to remove dienes. The residue was chromatographed on neutral alumina, the ketone eluting in 25% benzene–hexane solution, yield 8.3 g (0.028 mol, 11.3%).

The above procedure was modified using THF as the solvent and 10 mol % of cuprous chloride, which was added *very slowly* owing to a vigorous reaction. An orange color appeared on the surface of the reaction mixture upon contact with the cuprous chloride but this color did not persist. Work-up in the usual fashion resulted in **4** being produced in 50% yield. This dramatic increase in yield is consistent with the observation (H. L. Pearce, in this laboratory) that the copper-catalyzed addition of phenylmagnesium bromide to isophorone using THF as the solvent proceeds in 95% yield while in ether only 30–40% yields are obtained.[4] Ir (CCl_4) 1710 cm^{-1} (C=O stretch); NMR (5% in CCl_4) δ (methyls) 0.98,

1.03, 1.06, δ (methylene H) 1.51, 1.64, 1.94, 2.07, 2.19, 2.47, 2.64, δ (aromatic H) 7.01, 7.20; mass spectrum: *m/e* (rel intensity) 264 (8, M^+), 139 (43), 125 (90), 83 (70), 55 (100).

Anal. Calcd for $C_{16}H_{21}OCl$: mol wt, 264.128088. Found: mol wt, 264.127473.

***trans*-3-(*p*-Chlorobenzyl)-1,3,5,5-tetramethylcyclohexan-1-ol (5).** To 60 ml of 3 M ethereal methylmagnesium bromide (commercially obtained solution) was added 4.0 g (0.015 mol) of **4** in 50 ml of ether. The reaction mixture was stirred at room temperature for 24 h, heated at gentle reflux for an additional 24 h, and hydrolyzed with a saturated ammonium chloride solution. After the ether layer was decanted, the solid residue was dissolved by addition of cold dilute hydrochloric acid and the organic layer extracted into ether. This was necessary since the solid residue was found to contain considerable amounts of product. The crude product (4.2 g, 0.015 mol) was dissolved in hexane and colorless crystals were deposited upon cooling, 2.6 g (9.3 mmol, 62% isolated), mp 52–54°: ir (CCl_4) 3610 cm^{-1} (OH stretch); NMR (5% in CCl_4) δ (methyls) 0.87, 1.25, 1.27, 1.27, δ (benzylic H) 2.38; mass spectrum *m/e* (rel intensity) 280 (2, M^+), 265 (6), 136 (100), 97 (95), 43 (67).

Anal. Calcd for $C_{17}H_{25}OCl$: mol wt, 280.159820. Found: mol wt, 280.160242.

1,3,5,5-Tetramethyl-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (2). To 100 ml of trifluoroacetic acid (TFA) heated to 60 °C was slowly added 40.0 g (0.17 mol) of **5**, resulting in a homogenous solution. (The reaction of **5** at room temperature proceeds very slowly.) The temperature was maintained for 1 h and the TFA was removed in vacuo. The crude product was chromatographed on neutral alumina and distilled at 112 °C (0.025 Torr) to yield 35.8 g (0.14 mol, 80%) of pure **2** as a pale yellow liquid: ir (CCl_4) 2950, 2900 cm^{-1} (CH stretch); NMR (5% in CCl_4) δ (methyls) 0.30, 0.82, 1.01, 1.30, δ (benzylic H) 2.61, 2.72; mass spectrum *m/e* (rel intensity) 262 (8, M^+), 191 (100), 156 (33), 141 (41), 115 (22).

Anal. Calcd for $C_{17}H_{23}Cl$: mol wt, 262.14871. Found: mol wt, 262.14819.

1,3,5,5-Tetramethyl-7,7-dibromo-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (8). To 11.1 g (0.042 mol) of **2** in 50 ml of carbon tetrachloride, maintained at 50 °C, was added 18.2 g (0.12 mol) of bromine. The reaction mixture was allowed to stir overnight. After removal of the solvent and the excess bromine in vacuo, 16.7 g (0.04 mol, 95% yield) of crystals were deposited. Recrystallization from hexane afforded pure **8**: mp 142–144 °C; ir (CCl_4) 2950 cm^{-1} (CH stretch); NMR (5% in CCl_4) δ (methyls) 0.25, 0.92, 1.34, 1.56; mass spectrum *m/e* (rel intensity) 341 (100), 339 (85), 285 (45), 283 (38), 203 (92), 190 (73). A molecular ion peak for this compound could not be obtained even at low ionization voltages (cf. ref 15). The molecular weight determination was based upon the parent minus bromine peak (339). To this exact mass value was added the molecular weight of bromine for comparison with the calculated value.

Anal. Calcd for $C_{17}H_{21}Br_2Cl$: mol wt, 417.96706. Found: mol wt, 417.96851.

1,3,5,5-Tetramethyl-7(*endo*- or *exo*-)bromo-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (6 and 7). An analogous procedure used to prepare **8** was used to prepare these compounds starting with 800 mg (3.1 mmol) of **2** and 1.2 molar equiv of bromine. The small amount of **8** (ca. 50 mg) which was formed was removed by crystallization from hexane, leaving 1.0 g (2.9 mmol) of crude product, ca. 70:30 mixture of **6** and **7**, respectively. All attempts at separating these compounds were unsuccessful. These attempts included chromatography on acidic, neutral, and basic alumina, silica gel, and Florisil, gas chromatography, and short-path distillation: NMR (10% in CCl_4) δ (methyls) 0.36, 0.88, 1.30, 1.35 (**6**); 0.10, 0.84, 1.30, 1.35 (**7**), δ (benzylic H) 5.30 (**6**); 5.02 (**7**).

1,3,5,5-Tetramethyl-7-keto-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (11). The above compound was prepared by the hydrolysis of 4.0 g (9.6 mmol) of **8** with excess aqueous KOH–methanol solution. This reaction mixture was heated for 2.5 h. The organic material was extracted into methylene chloride and the solvent removed in vacuo, yielding **11** quantitatively. An independent synthetic preparation involved the Jones oxidation[16] of either **9** or **10**. Recrystallization from hexane yielded colorless crystals: mp 74–75 °C; ir (CCl_4) 1690 cm^{-1} (C=O stretch); NMR (5% in CCl_4) δ (methyls) 0.29, 0.90, 1.11, 1.38; mass spectrum *m/e* (rel intensity) 276 (100, M^+), 261 (40), 243 (30), 206 (30), 191 (15).

Anal. Calcd for $C_{17}H_{21}OCl$: mol wt, 276.128069. Found: mol wt, 276.128088.

1,3,5,5-Tetramethyl-7-*endo*-hydroxy-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (10). To 2.75 g (9.8 mmol) of **11** in 50 ml of absolute ethanol was added an excess of sodium borohydride. The solution was stirred overnight and then diluted with an equal amount of water. The reaction mixture was extracted by ether and the solvent removed in vacuo to yield 2.64 g (9.5 mmol, 95%) of **10**. Recrystallization from hexane yielded colorless crystals: mp 102–104 °C; ir (CCl_4) 3620 cm^{-1} (OH stretch); NMR (5% in CCl_4) δ (methyls) 0.23 0.88, 1.10, 1.30, δ (benzylic H) 4.44; mass spectrum *m/e* (rel intensity) 278 (100, M^+), 245 (85), 243 (76) 207 (45), 181 (90), 139 (32).

Anal. Calcd for $C_{17}H_{23}OCl$: mol wt, 278.14362. Found: mol wt, 278.14421.

1,3,5,5-Tetramethyl-7,7-dimethoxy-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (12). To 4.0 g (9.5 mmol) of **8** in 150 ml of anhydrous methanol was added 3.0 g (0.05 mol) of fresh potassium hydroxide pellets and the resulting mixture refluxed for 25 h. Half of the methanol was removed in vacuo and replaced by an equal amount of water. The organic material was extracted by three 100-ml additions of CCl_4. The solvent was dried and removed in vacuo. Crystallization from anhydrous methanol gave 1.0 g (3.1 mmol, 33%) of crystalline **12**: mp 79–80 °C; ir (CCl_4) 2950 (CH stretch), 1150 cm^{-1} (OCH_3 stretch); NMR (5% in CCl_4) δ (methyls) 0.05, 0.89, 1.26, 1.30, 3.00, 3.67; mass spectrum *m/e* (rel intensity) 291 (100), 276 (30), 225 (27). See discussion concerning mass spectrum of compound **8**.

Anal. Calcd for $C_{19}H_{27}O_2Cl$: mol wt, 322.16522. Found: mol wt, 322.16299.

1,3,5,5-Tetramethyl-7-*exo*-hydroxy-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (9). This compound (108 mg) was isolated from the chromatography of 800 mg of a mixture of **6** and **7** on alumina by elution with a benzene–methanol solution. Recrystallization from hexane afforded crystals: mp 133–134 °C; ir (CCl_4) 3580 cm^{-1} (OH stretch); NMR (5% in CCl_4) δ (methyls) 0.11, 0.82, 1.02, 1.30, δ (benzylic H) 4.40; mass spectrum *m/e* (rel intensity) 278 (100, M^+), 245 (62), 243 (50), 207 (60), 181 (75), 139 (30).

Anal. Calcd for $C_{17}H_{23}OCl$: mol wt, 278.14362. Found: mol wt, 278.14339.

1,3,5,5,7-Pentamethyl-7-*endo*-hydroxy-4′-chloro-1′,2′-benzobicyclo[3.3.1]non-2′-ene (13). To 0.105 mol of methylmagnesium bromide solution was added 2.0 g (7.3 mmol) of **11** and the reaction mixture allowed to stir for 3 h. Hydrolysis in the usual manner and removal of the ether yielded 2.1 g (7.2 mmol) of crude product. This material was dissolved in hexane and upon cooling 0.90 g (3.5 mmol, 47%) of crystals was isolated, mp 79–80 °C. The remaining 1.2 g of viscous oil was chromatographed on alumina, but decomposed into unidentified material. Ir (CCl_4) 3570 cm^{-1} (OH stretch); NMR δ (methyls) 0.22, 0.89, 1.03, 1.30, 1.42; mass spectrum *m/e* (rel intensity) 292 (2, M^+), 277 (100), 221 (15), 203 (10), 43 (23).

Anal. Calcd for $C_{18}H_{25}OCl$: mol wt, 292.159385. Found: mol wt, 292.158804.

1,3,4,5-Tetramethyl-4′-chloro-1′,2′-benzobicyclo[3.3.1]nona-2′,4-diene (14). To 50 mg (0.18 mmol) of **9** (**10** may also be used) in 30 ml of dry benzene was added 50 mg of *p*-toluenesulfonic acid. The reaction mixture was refluxed for 4 h and neutralized with a saturated sodium bicarbonate solution. The organic layer was removed and washed with another portion of the base. After removal of the solvent, the crude product was dissolved in hexane and placed in the freezer, upon which time crystals were deposited: yield 42 mg (0.16 mmol, 89%) of pure **14**, mp 99–101 °C; ir (CCl_4) 2950, 2900 cm^{-1} (CH stretch); NMR (5% in CCl_4) δ (methyls) 1.12, 1.34, 1.54, 1.54; mass spectrum *m/e* (rel intensity) 260 (96, M^+), 245 (100), 191 (66), 153 (30), 135 (19).

Anal. Calcd for $C_{17}H_{21}Cl$: mol wt, 260.133178. Found: mol wt, 260.133759.

1,3,6,6-Tetramethyl-4′-chloro-1′,2′-benzobicyclo[3.2.2]nona-2′,2-diene (15). This compound (ca. 1 g) was isolated as a colorless liquid from the chromatography of 3.3 g of a mixture of **6** and **7** on alumina: ir (CCl_4) 2870 cm^{-1} (CH stretch); NMR (5% in CCl_4) δ (methyls) 0.15, 0.80, 1.43, 1.80, δ (benzylic H) 3.02; mass spectrum *m/e* (rel intensity) 260 (15, M^+), 245 (33), 190 (100), 189 (80), 175 (50), 152 (50).

Anal. Calcd for $C_{17}H_{21}Cl$: mol wt, 260.13318. Found: mol wt, 260.13350.

Acknowledgments. The authors wish to acknowledge the generous financial support for this research provided by The Robert A. Welch Foundation, Houston, Texas. The authors also wish to thank Professors K. E. Harding and P. S. Mariano for helpful discussions.

Registry No.—**2**, 58240-96-3; **3**, 58240-97-4; **4**, 58240-98-5; **5**, 58240-99-6; **6**, 58241-00-2; **7**, 58267-55-3; **8**, 58241-01-3; **9**, 58341-82-5; **10**, 58249-35-7; **11**, 58241-02-4; **12**, 58241-03-5; **13**, 58241-04-6; **14**, 58241-05-7; **15**, 58241-06-8; *p*-chlorobenzyl chloride, 104-83-6; dimedone methyl ether, 4683-45-8; isophorone, 78-59-1; methyl bromide, 74-83-9.

References and Notes

(1) B. L. Shapiro, M. J. Gattuso, and G. R. Sullivan, *Tetrahedron Lett.*, 223 (1971).
(2) (a) C. E. Johnson and F. A. Bovey, *J. Am. Chem. Soc.*, **79**, 1012 (1958); (b) R. McWeeny, *Mol. Phys.*, **1**, 311 (1958); (c) C. W. Haigh, R. B. Mallion, and E. A. G. Armour, *ibid.*, **18**, 751 (1970); (d) C. W. Halgh and R. B. Mallion, *Org. Magn. Reson.*, **4**, 203 (1972); (e) P. I. Rose, *ibid.*, **5**, 187 (1973).
(3) B. L. Shapiro and G. R. Sullivan, unpublished results.
(4) B. L. Shapiro and H. L. Pearce, unpublished results.
(5) M. J. Shapiro, Ph.D. Dissertation, Texas A&M University, 1974.
(6) B. L. Shapiro, M. D. Johnston, Jr., and M. J. Shapiro, *J. Org. Chem.*, **39**, 796 (1974).
(7) J. A. Berson, R. G. Bergman, G. M. Clarke, and D. Wege, *J. Am. Chem. Soc.*, **90**, 3238 (1968).
(8) G. Vavon, *Bull. Soc. Chim. Fr.*, **49**, 937 (1931).
(9) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3862 (1961).
(10) (a) M. A. Cooper and S. L. Manatt, *J. Am. Chem. Soc.*, **92**, 1605 (1970); (b) S. Castellano and R. Kostelnik, *Tetrahedron Lett.*, 5211 (1967).
(11) (a) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 762 (1961); (b) A. A. Bothner-By and J. A. Pople, *Annu. Rev. Phys. Chem.*, **16**, 43 (1965).
(12) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).
(13) (a) F. W. van Deursen and P. K. Korver, *Tetrahedron Lett.*, 3923 (1967); (b) F. W. van Deursen and J. Bakker, *ibid.*, 4593 (1971).
(14) R. A. Alden, J. Kraut, and T. G. Taylor, *J. Am. Chem. Soc.*, **90**, 74 (1968).
(15) J. H. Beynon, R. A. Saunders, and A. E. Williams, "The Mass Spectra of Organic Molecules", American Elsevier, New York, N.Y., 1968, p 388.
(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Zero Bridge Cleavage and a Neighboring Hydroxyl Group Effect in the Oxymercuration of Bicyclo[3.1.0]hexanes

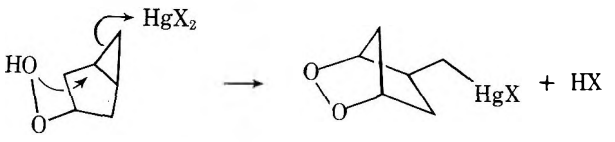
Robert G. Salomon* and Robert D. Gleim

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

Received September 9, 1975

Cleavage of the zero bridge is a major pathway in the oxymercuration of all bicyclo[3.1.0]hexanes examined. Though a 3-acetoxy substituent has no effect on the competition between peripheral and bridge C–C bond cleavage, a cis or trans 3-hydroxyl group markedly promotes the latter. Thus, oxymercuration–acetylation–demercuration of *cis*-3-hydroxybicyclo[3.1.0]hexane (**3b**) gives mainly *cis*-1,3-diacetoxycyclohexane (83%). The intermediate mercurial from zero bridge cleavage of **3b** gives *cis*-1,3-diacetoxy-*cis*-5-chlorocyclohexane upon reaction with chlorine in pyridine. Hence, the electrophilic addition leading to zero bridge cleavage involves inversion of stereochemistry at the center of electrophilic attack as well as at the center of nucleophilic attack.

This study of the oxymercuration of bicyclic cyclopropanes is part of our general examination of the utility of oxymercuration reactions for the total synthesis of prostaglandin endoperoxides.[1] These biological precursors of prostaglandins are base-sensitive derivatives of 2,3-dioxabicyclo[2.2.1]heptane. Peroxymercuration of olefins[2] or cyclopropanes[3] which can be performed under neutral or mildly acidic conditions is especially attractive for the synthesis of base-sensitive secondary alkyl peroxides. Since inversion of configuration at the site of nucleophilic attack is strongly favored for oxymercuration of cyclopropanes,[18] intramolecular peroxymercuration of **1** is expected to lead to **2** by cleavage of a peripheral C–C bond of the three-membered ring. Moreover, oxymercuration of bicyclo[3.1.0]hexane is reported to result in the desired cleavage of a peripheral rather than bridge C–C bond of the three-membered ring.[4] However, we now report that cleavage of the bridge bond is a major pathway for oxymercuration of bicyclo[3.1.0]hexanes. We have also uncovered a novel neighboring group effect on the electrophilic cleavage of a cyclopropane. Thus, some substituents promote almost exclusive cleavage of the zero bridge in bicyclo[3.1.0]hexanes. Moreover, these bridge cleaving oxymercurations are stereospecific and provide an effective new route for the stereospecific synthesis of polysubstituted cyclohexanes.



1 **2**

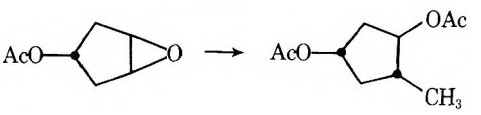
Results

A. Syntheses of Oxymercuration Substrates and Products. Bicyclo[3.1.0]hexane (**3a**),[5] *cis*-3-hydroxybicyclo[3.1.0]hexane (**3b**),[6] and *cis*-3-hydroxybicyclo[4.1.0]heptane (**3c**)[7] were prepared by Simmons–Smith methylenation of the corresponding olefins. Acetylation of **3b** gave the acetate (**3d**). *trans*-3-Hydroxybicyclo[3.1.0]hexane (**3f**)[6] was

X=H or OH
n=1 or 2

3a, X = Y = H; n = 1
b, X = OH; Y = H; n = 1
c, X = OH; Y = H; n = 2
d, X = OAc; Y = H; n = 1
e, X, Y = O; n = 1
f, X = H; Y = OH; n = 1

obtained from the cis epimer (**3b**) by oxidation to the ketone (**3e**) with chromium trioxide–pyridine complex in methylene chloride followed by reduction with aluminum isopropoxide in 2-propanol. *cis*-1,3-Diacetoxycyclohexane (**4b**) and *trans*-1,3-diacetoxycyclohexane (**4c**) were prepared by acetylation of the commercially available diols. 1,3-Diacetoxy-4-methylcyclopentane (**5b**) was prepared by



6 **5b**

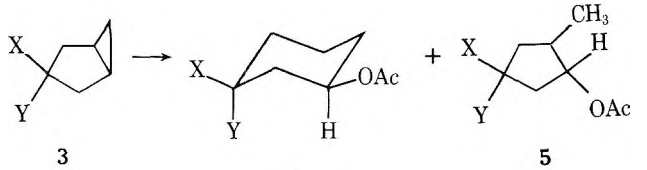
Table I. Product Distributions from Oxymercuration–Acetylation–Demercuration of Bicyclo[3.1.0]hexanes

Reactant	Product yields, % Relative 4a[b]	4b[b]	4c[b]	5	Overall
3a (H,H)[a]	63			37 (a)[b]	95
3b (OH,H)		92	1[c]	8 (b)[b]	91
3d (OAc,H)		59	2[c]	39 (b)[b]	68
3f (H,OH)		5[c]	88	7 (c)[b]	58

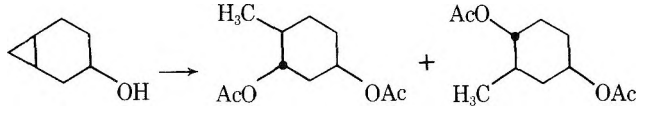
[a] (X,Y). [b] a(H,H), b(OAc,H), c(H,OAc). [c] Maximum yield estimated by GC analysis of acetate mixture; not isolated.

reaction of lithium dimethylcuprate with *trans*-1-acetoxy-3,4-epoxycyclopentane (**6**)[8] followed by acetylation of the product hydroxy acetate.

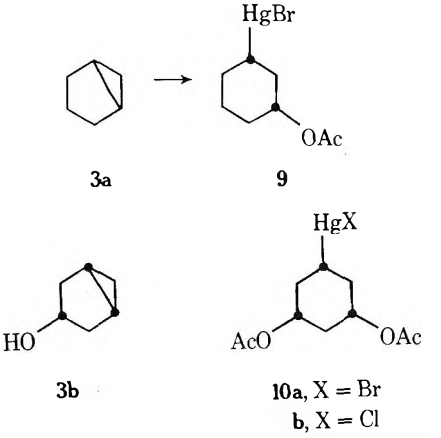
B. Oxymercuration Reactions. Oxymercuration–Acetylation–Demercuration. Levina et al.[4] reported that oxymercuration of bicyclo[3.1.0]hexane (**3a**) with aqueous mercuric acetate gives, after treatment with KBr, a single crystalline product (60%) with an elemental composition $C_6H_{11}OBrHg$ which was assumed to be 1-bromomercurimethyl-2-hydroxycyclopentane. However, the moderate material balance vitiates the conclusion that electrophilic cleavage of the three-membered ring occurs regiospecifically at the peripheral rather than bridge C–C bond. We now report that acetylation of the crude oxymercurial from **3a** with acetic anhydride in pyridine followed by demercuration with aqueous sodium borohydride gives a mixture of two acetates in 95% overall yield. These are cyclohexyl acetate (**4a**) and 2-methylcyclopentyl acetate (**5a**). The relative yields of these products as well as those from similar treatment of the substituted bicyclic cyclopropanes **3b, 3d,** and **3f** are given in Table I. Similar treatment of *cis*-3-hydroxybicyclo[4.1.0]heptane (**3c**) gives a 4:6 mixture of two

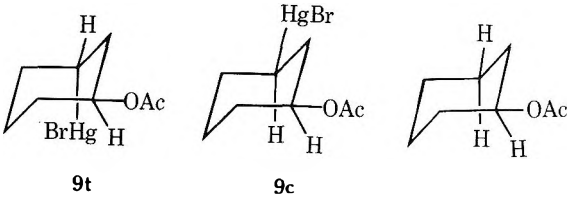


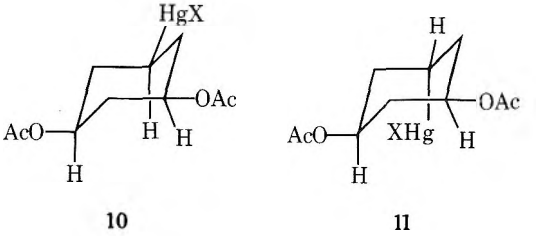
diacetates **7** and **8** in 98% yield. The structures indicated for these diacetates are assumed since a trans relationship between the methyl and vicinal acetate groups is expected from the proclivity for inversion of configuration at the site of nucleophilic attack in oxymercuration of cyclopropanes.[2c] The remaining acetate is assumed to be cis to the methyl group since the progenitors of these groups, the methylene of the cyclopropyl ring and the original hydroxyl group, were cis.



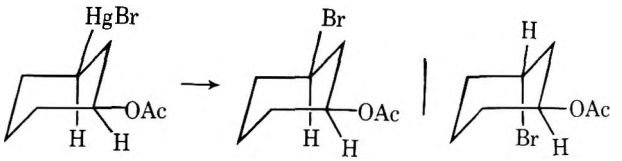
Isolation of Cyclohexyl Mercurials from 3a and 3b. In order to provide further evidence for bridge cleavage in the oxymercuration of bicyclo[3.1.0]hexanes, mercurials from zero bridge cleavage of bicyclo[3.1.0]hexane (**3a**) and *cis*-3-hydroxybicyclo[3.1.0]hexane (**3b**) were isolated. The crude organomercuric acetate product mixtures were converted into the respective organomercuric halides by reaction with potassium halide. Crystallization of the organomercuric halide mixtures from chloroform–ether gave isomerically pure samples of *cis*-1-acetoxy-3-chloromercuricyclohexane (**9**) and *cis*-1,3-diacetoxy-*cis*-5-halomercuricyclohexanes (**10**) from **3a** and **3b,** respectively. These structural assignments are based on an analysis of the ^1H NMR spectra of the halides obtained by reaction of the mercurials with halogen under conditions favoring complete retention of configuration.[9] Thus, *trans*-3-bromomercuricyclohexyl acetate (**9t**) will favor a conformation with an axial bromomercuri group and an equatorial acetoxy group since the *A* values for these groups are *A* = 0[10] and 0.7,[11] respectively. The C-1 proton resonance of the trans isomer will be shifted downfield from the chemical shift observed for the corresponding proton in the cis isomer (**9c**) owing to deshielding by the axial bromomercuri group.[12] Since only a single resonance is observed for this proton in the oxymercuration product, it follows that this product is only a single isomer. The similarity of the chemical shift for this proton (δ4.90) to that of the corresponding proton in cyclohexyl acetate (δ 4.80) suggests structure **9c** for the oxymercuration product. This assignment is confirmed below. Similarly, *trans*-5-halomercuricyclohexyl *cis*-1,3-diacetate (**11**) will favor a conformation with an axial halomercuri group and equatorial acetoxy groups. Again only a single resonance is found for the protons at C-1 and C-3. This suggests that the oxymercuration products are isomerically pure. The choice of structure **10** rather than **11** for the oxymercuration product is supported by further transformations outlined below.







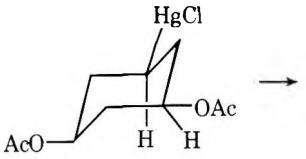
Reaction of **9c** with bromine in pyridine gives *cis*-3-bromocyclohexyl acetate (**12c**) with retention of the configuration at C-3.[9] The chemical shift of the C-1 proton resonance is δ 4.66 compared to δ 4.80 for cyclohexyl acetate. The corresponding proton in *trans*-3-bromocyclohexyl acetate (**12t**) is expected to absorb at considerably lower field



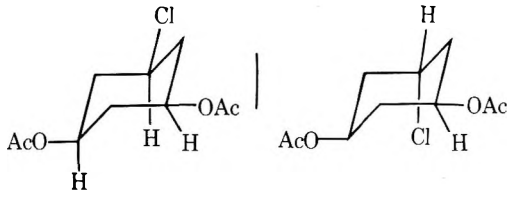
9c 12c 12t

owing to deshielding of the bromo group[13] for which A = 0.4.[11]

Reaction of *cis*-5-chloromercuri-*cis*-1,3-cyclohexyl diacetate (**10b**) with chlorine in pyridine gives *cis*-5-chloro-*cis*-1,3-cyclohexyl diacetate (**13c**) with retention of the configuration at C-5.[9] The chemical shift of the C-1 and C-3 pro-



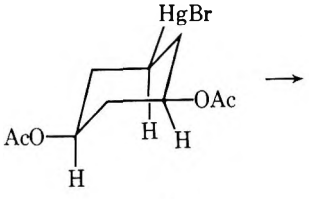
10b



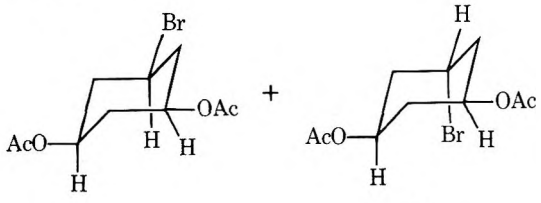
13c 13t

ton resonance is δ 4.75 compared to δ 4.70 in *cis*-1,3-cyclohexyl diacetate, and δ 4.80 for cyclohexyl acetate. The corresponding protons in *trans*-5-chloro-1,3-cyclohexyl diacetate are expected to absorb at considerably lower field owing to deshielding by the chloro group.[13]

Unexpectedly, reaction of *cis*-5-bromomercuricyclohexyl diacetate (**10a**) with bromine in pyridine gives an equal mixture of *cis*- and *trans*-5-bromo-1,3-cyclohexyl diacetates (**14c** and **14t**) with loss of configurational integrity at



10a

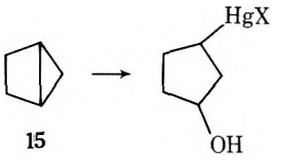


14c 14t

C-5. We have no explanation for this lack of stereospecificity. Though nonstereospecific reactions of mercurials with halogen are common, such reactions with pyridine as solvent generally are stereospecific.[9] The chemical shifts of the C-1, C-3, and C-5 ^{1}H NMR absorptions in **14c** and **14t** are clearly discernible from the spectrum of the mixture. The C-1 and C-3 proton resonances in **14c** occur at δ 4.4–5.0 compared to δ 4.75 in **13c**, δ 4.70 in *cis*-1,3-cyclohexyl diacetate, and δ 4.80 for the C-1 proton resonance in cyclohexyl acetate while the corresponding proton resonance for **14t** is at considerably lower field (δ5.24) owing to deshielding by the neighboring bromo group. Furthermore, the C-5 proton absorption in **14t** occurs at δ 4.4–5.0 which is considerably downfield from the corresponding absorption (δ 3.93) in **14c** in accord with the fact that equatorial proton resonances are about 0.45 ppm downfield from the corresponding axial proton resonances for cyclohexyl derivatives.[14]

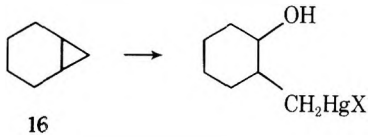
Discussion

A. Regioselectivity of Cyclopropane Cleavage in Bicyclo[3.1.0]hexanes. *Electrophilic cleavage of the cyclopropane ring of bicyclo[3.1.0]hexane* (**3a**) *is not regiospecific.* Thus, Markownikoff addition with cleavage of a peripheral cyclopropyl C–C bond of **3a** accounts for only 37% of the oxymercuration products. The major product (**4a**) arises by anti-Markownikoff oxymercuration with cleavage of the zero bridge bond of the cyclopropyl ring. While this behavior is unusual for oxymercuration of cyclopropanes in general,[15] it is precedented for reactive cyclopropanes in strained systems. Thus, bicyclo[2.1.0]pentane (**15**) undergoes exclusively anti-Markownikoff oxymercuration with rupture of the highly reactive zero bridge bond of the three-membered ring.[4] In contrast, oxymercuration of bicy-



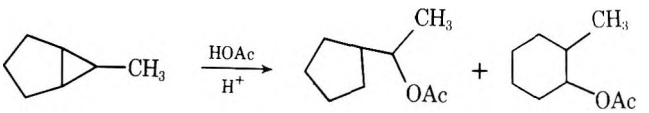
15

clo[4.1.0]heptane (**16**) results in exclusive Markownikoff addition with rupture of the peripheral C–C bond of the three membered ring.[4] Clearly, the extent of zero bridge



16

cleavage in oxymercuration of bicyclic cyclopropanes parallels the degree of ring strain in these molecules. The nonregiospecific, borderline behavior of bicyclo[3.1.0]hexane (**3a**) observed in the present study is consistent with the behavior of the derivatives of **3a** in other electrophilic addition reactions. Acid-promoted acetolysis of 6-methylbicyclo[3.1.0]hexanes (**17**) is nonregiospecific involving cleavage of both bridge and peripheral C–C bonds of the three-membered ring in similar yields.[16] Lead tetraacetate[17] and thal-



17

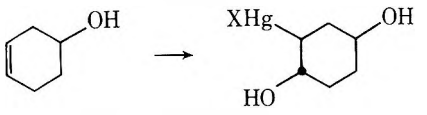
lium triacetate[17b] cleave the three-membered ring of bicyclo[3.1.0]hexane (**3a**) nonregiospecifically while they regiospecifically cleave the zero bridge of bicyclo[2.1.0]pentane (**15**).

B. Stereoselectivity of Electrophilic Addition to the Zero Bridge in Bicyclo[3.1.0]hexanes. The carbon center undergoing nucleophilic attack generally undergoes inversion of stereochemistry during oxymercuration of cyclopropanes.[18] The data in Table I show that nucleophilic attack during zero bridge cleavage of **3b**, **3d**, and **3f** involves almost exclusive inversion stereochemistry.

Cyclopropanes can undergo attack by electrophiles with either inversion or retention of configuration at the carbon to which the electrophile becomes attached.[18] The differ-

ence in energy for retention vs. inversion is small. In the present work, the mercurials **9** and **10** resulting from zero bridge cleavage in **3a** and **3b** were isolated in good yields by crystallization from the reaction product mixtures. The mercurials are each a single isomer. The formation of minor amounts of isomeric mercurials cannot be ruled out since the material balance is not quantitative. Nevertheless the addition of the electrophile involves predominant, if not exclusive, inversion of configuration at the carbon undergoing electrophilic attack. In the case of **3a,** we assume that addition of the nucleophile involves inversion of configuration at carbon. The cis relationship of the mercuribromide and acetate substituents in the bridge cleaved product (**9**) establishes an inversion pathway for attack by the electrophile.

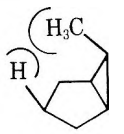
C. Neighboring Group Effect in Electrophilic Cleavage of Cyclopropanes. The influence of substituents in determining the stereochemistry of electrophilic addition during oxymercuration of *olefins* is well known.[19] Thus, cyclohexenes with polar (Lewis base) substituents in the 4 position undergo stereospecific and position specific oxymercuration.[19a] The mercuric group always adds to the 2 position from the same side of the ring as the original substituent while the nucleophile adds to the 1 position trans to the mercury. The stereoselectivity observed was attrib-



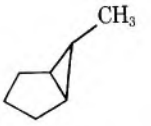
uted to a combination of two factors: preferential diaxial opening of an initial mercurinium ion through a chairlike transition state and preferential formation of a cis mercurinium ion owing to coordinative stabilization by the polar substituent. The position specificity is generally held to result from an inductive effect of the substituent. A similar, though less pronounced,[19c] substituent effect was reported for the oxymercuration of cyclohexenes with polar substituents in the 3 position.[19b] The importance of a coordinative interaction between polar substituent and mercury in directing mercuration has been questioned.[19f,g] Such an interaction in the oxymercuration of cyclohex-2-enols is either very small or nonexistent and the directing effect of hydroxyl substituents in these systems can be accounted for by their effect on conformational equilibria. This conclusion cannot be extrapolated to all unsaturated alcohols. In particular the operation of a product-determining coordinative interaction between substituents and mercury in oxymercuration of cyclohex-3-en-1-ols is not doubted.

In the present study a novel effect of a neighboring hydroxyl group was uncovered in which the substituent moderates the reaction pathway in oxymercuration of cyclopropanes. Thus, cleavage of the three-membered ring during oxymercuration of bicyclo[3.1.0]hexane (**3a**) occurs nonregiospecifically. Rupture of the zero bridge is slightly favored over rupture of a peripheral C–C bond. The reaction pathway is *not* changed by an acetate substituent in the 3 position (i.e., **3d**). In contrast, a hydroxyl group in the 3 position profoundly alters the reaction pathway. Both *cis*- and *trans*-bicyclo[3.1.0]hexan-3-ol (**3b** and **3f**) exhibit an unusually high proclivity toward anti-Markownikoff electrophilic addition resulting in selective cleavage of the zero bridge bond of the bicyclic cyclopropanes during oxymercuration.

The endo methyl substituent in **17n** increases the ring strain in this bicyclic cyclopropane relative to **17x,** which has an exo methyl substituent. The direct relationship between the extent of zero bridge cleavage and ring strain was invoked to account for the greater proportion of zero bridge cleavage during acid-promoted acetolysis of **17n** relative to that found for **17x.**[16]



17n



17x

The cis 3-hydroxyl group in **3b** might cause an increase in ring strain compared to **3a.** However, such increased ring strain cannot account for the greater proportion of zero bridge cleavage during oxymercuration observed for **3b** relative to **3a.** A similar increase in ring strain should result from the cis 3-acetoxy group in **3d.** However, no increase in the extent of zero bridge cleavage is observed for oxymercuration of **3d** compared with **3a.** Furthermore, the trans 3-hydroxyl group in **3f** also promotes zero bridge cleavage relative to **3a.** However, no increase in ring strain is expected in **3f** compared to **3a.**

The hydroxyl group in **3b** and **3f** may exert its influence on the reaction pathway through coordination with the electrophile as postulated for the influence of the hydroxyl group in oxymercuration of cyclohex-3-en-1-ols. Or the hydroxyl group may interact with the attacking nucleophile by hydrogen bonding. It is not clear why such interactions with *either* a cis or trans hydroxyl group would promote zero bridge cleavage. A satisfactory explanation of the mechanistic basis of this novel neighboring hydroxyl group effect must await further study.

Conclusion

Oxymercuration–acetylation of hydroxylated bicyclic cyclopropanes gives good to excellent yields of diacetoxy mercurials. Cleavage of the zero bridge is a major pathway for all of the bicyclo[3.1.0]hexyl compounds examined. An acetoxy substituent in the 3 position has little effect on the competition between cleavage of the zero bridge and the peripheral cyclopropyl C–C bonds. In sharp contrast, a 3-hydroxy substituent promotes almost exclusive cleavage of the zero bridge, and the electrophilic addition involves predominant double inversion. Oxymercuration of bicyclo[3.1.0]hexanes is thus a useful reaction for the stereospecific synthesis of polysubstituted cyclohexanes. The effect of a neighboring hydroxyl group does not extend to the next larger homologue. A 3-hydroxy substituent does not lead to zero bridge cleavage of bicyclo[4.1.0]heptane.

Experimental Section

General. Analytical gas–liquid phase chromatography was performed with a Varian Model 1400 flame ionization detector chromatograph utilizing a 15 ft × 0.125 in. column containing 15% FFAP (Free Fatty Acid Phase) on Chromosorb P at 190° (column 1). Preparative GLC was performed with a Varian Model 202B instrument utilizing a 10 ft × 0.25 in. column containing 10% DEGS (diethylene glycol succinate) on 60/80 Chromosorb P at 180 °C (column 2) or a 10 ft × 0.25 in. column containing 10% FFAP on 60/80 Chromosorb P at 180 °C (column 3). Proton magnetic resonance spectra were recorded with a Varian A-60A or HA-100 FT spectrometer with tetramethylsilane as internal standard (except for mercurials) and $CDCl_3$ as solvent unless indicated otherwise. Mass spectra were determined with a Du Pont Model 21-094 GC–MS with computer analysis. Boiling points are uncorrected. Melting points were measured with a Thomas-Hoover capillary melting point apparatus. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Materials. Bicyclo[3.1.0]hexane (**3a**),[5] *cis*-3-hydroxybicyclo[3.1.0]hexane (**3b**),[6] *trans*-3-hydroxybicyclo[3.1.0]hexane (**3f**),[6] *cis*-3-hydroxybicyclo[4.1.0]heptane (**3c**),[7] and *trans*-6-oxabicyclo[3.1.0]hexan-3-ol acetate (**6**)[8] were prepared by reported procedures.

***cis*-3-Acetoxybicyclo[3.1.0]hexane (3d).** The cis alcohol **3b**[6]

(1.2 g, 12.2 mmol) was treated with acetic anhydride (3.68 g, 720 mmol) and pyridine (2 ml). The resulting solution was heated at 60 °C for 6 h and then stirred overnight at room temperature. The mixture was diluted with ether (50 ml) and washed with cold saturated aqueous $NaHCO_3$ and cold 10% HCl. The ether solution was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give a colorless oil (1.7 g, 98%): ^1H NMR δ 0.40 (m, 2 H), 1.30 (m, 2 H), 2.00 (s, 3 H), 1.80–2.50 (m, 4 H), 5.20 (t, 1 H, J = 6.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 43 (74), 79 (57), 80 (100), 81 (97), 140 (22).

***cis*-1,3-Diacetoxycyclohexane (4b).** A commercial mixture of isomeric 1,3-cyclohexanediols (Aldrich) was acetylated as for **3d** above. A sample of the pure cis isomer was obtained from the resulting mixture of acetates by preparative GLC (column 3): ^1H NMR δ 2.0 (s, 6 H, OAc), 1.10–2.40 (m, 8 H, C-2, 4, 5, 6), 4.70 (m, 2 H, C-1, 3). Relative retention times of the cis and trans isomers are 1.2 and 1.0, respectively. Reduction of this diacetate with lithium aluminum hydride in ether afforded a diol which was identical (^1H NMR) with authentic *cis*-1,3-cyclohexanediol.[20]

***trans*-1,3-Diacetoxycyclohexane (4c).** This was also isolated from the above mixture: ^1H NMR δ 1.5–2.9 (m, 8 H, C-2, 4, 5, 6), 2.0 (s, 6 H, OAc), 5.10 (m, 2 H, C-1, 3).

Oxymercuration–Acetylation–Demercuration of Bicyclo[3.1.0]hexane (3a). To mercuric acetate (2.39 g, 7.50 mmol) was added **3a** (600 mg, 7.31 mmol) and water (7 ml). The mixture was magnetically vigorously stirred in a stoppered flask for 24 h at room temperature. The water was removed in vacuo (2.5 mm) and the residual colorless oily solid was acetylated with an excess of acetic anhydride in pyridine (10:1 anhydride:mercurial) at ambient temperature over 24 h. Volatiles were removed in vacuo (2 mm) and the residual oil was reduced with $NaBH_4$ (1 g) in water (10 ml) over 24 h. The product was extracted into ether (3 × 17 ml). The extract was washed with cold 10% HCl followed by saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered. Solvent was removed by distillation leaving a mixture of acetates (0.97 g, 98%). Analysis of the mixture by GLC (column 1) revealed two components in a ratio of 37:63 with relative retention times 1.00 and 1.36, respectively. The products were separated by preparative GLC (column 2). The component of longer retention time was identified as cyclohexyl acetate by NMR spectrum and GLC retention time: ^1H NMR δ 2.0 (s, 3 H, OAc), 1.1–2.35 (10 H), 4.80 (m, 1 H, C-1). The minor component, **2-methylcyclopentyl acetate (5a),** was characterized as follows: ^1H NMR δ 0.90 (d, 3 H, J = 6.5 Hz, methyl), 2.0 (s, 3 H, OAc), 1.30–2.20 (7 H), 4.65 (m, 1 H, C-1).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found for **5a:** C, 67.77; H, 10.16.

Oxymercuration–Acetylation–Demercuration of *cis*-Bicyclo[3.1.0]hexan-3-ol (3b). A mixture of mercuric acetate (1.69 g, 5.30 mmol) and **3b**[6] (500 mg, 5.10 mmol) in water (3 ml) was vigorously magnetically stirred at room temperature for 3 h. Water was then removed in vacuo (1 mm) to give 2.24 g of crude oily mercurial. This product was acetylated with acetic anhydride (1.1 ml, 50 mmol) and pyridine (4 ml, 50 mmol) by stirring at room temperature for 2 days. Volatile components of the resulting mixture were removed in vacuo (1 mm) and the residual oil was reduced with sodium borohydride (1.5 g) in water by stirring for 3 h at room temperature. The products were extracted into ether (3 × 20 ml). The combined extracts were washed with aqueous 10% HCl and then saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and filtered, and solvents were removed by rotary evaporation to give a mixture of acetates (0.92 g, 90%); GLC analysis (column 1) indicated three components with relative retention times 1.00, 1.27, and 1.55 in a ratio of 7.6:1.4:91.0, respectively. The two major components were isolated by preparative GLC (column 3) and identified as **4b** (91% component) and **5b** (8% component): ^1H NMR δ 1.10 (d, 3 H, J = 6.4 Hz, methyl), 1.2–2.5 (5 H), 2.03 (s, 6 H, OAc), 4.84 (m, 1 H), 5.20 (m, 1 H). The minor component, which has a GLC retention time (column 1) identical with that of an authentic sample of **4c,** was not isolated.

Oxymercuration–Acetylation–Demercuration of *cis*-Bicyclo[3.1.0]hexan-3-ol Acetate (3d). A mixture of mercuric acetate (2.58 g, 8.0 mmol) and **3d** (1.10 g, 7.85 mmol) in water (3 ml) was vigorously stirred at room temperature for 20 h. Volatile components of the mixture were then removed in vacuo (2 mm). The residue was acetylated and demercurated as for **3b** above to give a mixture of acetates (1.1 g, 68%) consisting of three components (GLC analysis on column 1) in a ratio of 39:2:59. The two major components were isolated by preparative GLC (column 3) and identified as **4b** (59% component) and **5b** (39% component). The minor component, which has a GLC retention time (column 1) identical with that of an authentic sample of **4c,** was not isolated.

Oxymercuration–Acetylation–Demercuration of *trans*-Bicyclo[3.1.0]hexan-3-ol (3f). A mixture of mercuric acetate (488 mg, 1.55 mmol) and **3f**[6] (147 mg, 1.50 mmol) in water (2 ml) was vigorously magnetically stirred at room temperature for 20 h. The water was removed in vacuo (2 mm) and the residue acetylated and demercurated as for **3b** above to give a mixture of acetates (175 mg, 58%) consisting of three components in a ratio of 7:88:5. The minor component, which has a GLC retention time (column 3) identical with that of **4b,** was not isolated. The other two components were isolated by preparative GLC (column 3) and identified by ^1H NMR comparison with authentic samples. The major product (88% component) is **4c** and the third product (7% component) is **5c.**

***cis*-4-Methyl-*trans*-1,3-cyclopentyl Diacetate (5b).** Methyllithium (75 mmol) in ether (51 ml) was added dropwise under nitrogen at 0 °C to a mechanically stirred suspension of CuI (7 g, 37 mmol) in ether (340 ml). After stirring for 0.5 h, a clear gray solution was obtained. *trans*-6-Oxabicyclo[3.1.0]hexan-3-ol acetate (**6**,[8] 2.6 g, 18.7 mmol) was added in one portion. The resulting mixture was stirred at 0 °C for 12 h. Ice-cold aqueous 10% HCl was then added dropwise. The organic phase was separated, washed with saturated aqueous sodium bicarbonate and then saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue was acetylated with acetic anhydride in pyridine to give crude **5b** (1.2 g) as a yellow oil. Pure **5b** was obtained by preparative GLC (column 2): ^1H NMR δ 1.10 (d, 3 H, J = 6.5 Hz, methyl), 1.2–2.5 (5 H), 2.03 (s, 6 H, OAc), 4.85 (m, 1 H), 5.20 (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 43 (100), 80 (66), 81 (25), 140 (36), 200 (1).

Oxymercuration–Acetylation–Demercuration of *cis*-Bicyclo[4.1.0]heptan-3-ol (3c). A mixture of mercuric acetate (1.47 g, 4.60 mmol) and **3c**[7] (500 mg, 4.47 mmol) in water (3 ml) was vigorously stirred magnetically. After 2 min the reaction mixture had become homogeneous and the mixture was stirred for an additional 1.5 h at room temperature. Volatile components of the reaction mixture were removed in vacuo (1 mm) and the residue was acetylated and demercurated as for **3b** above to give a mixture of acetates (0.94 g, 98%) consisting of two components in a ratio of 59:41 with relative GLC retention times of 1.00 and 1.24, respectively (column 2). Pure samples were obtained by preparative GLC (column 2, 185 °C) of diacetate I (59% component) and diacetate II (41% component). Diacetate I: ^1H NMR δ 0.94 (d, 3 H, J = 5 Hz, methyl), 1.3–2.5 (7 H), 2.07 (2 s, 6 H, acetate methyls), 4.80 (m, 1 H, α to OAc), 5.17 (m, 1 H, α to OAc).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found for I: C, 61.52; H, 8.57. Diacetate II: ^1H NMR δ 0.94 (d, 3 H, J = 5 Hz, methyl), 1.0–2.2 (7 H), 2.00 (s, 3 H, OAc), 2.05 (s, 3 H, OAc), 4.1–5.0 (2 H, α to OAc).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found for II: C, 61.57; H, 8.62.

***cis*-3-Bromomercuricyclohexyl Acetate (9).** Acetylated mercurial was prepared from bicyclo[3.1.0]hexane (**3a,** 17.3 mmol) as described above. Chromatography of this product on 80–200 mesh silica gel (40 g) afforded a light yellow oil which was treated with a twofold excess of KBr in water. The reaction mixture was extracted with ether and the extract dried ($MgSO_4$) and filtered, and solvent was removed by rotary evaporation. The oily, semisolid residue was triturated with cold ether (10 ml) to leave white, crystalline **9** (42%): mp 120.5–123.5 °C; ^1H NMR δ (CH_2Cl_2 as internal standard) 1.5–2.3 (8 H, C-2, 4, 5, 6), 2.10 (s, 3 H, OAc), 2.85 (m, 1 H, C-3), 4.90 (m, 1 H, C-1).

Anal. Calcd for $C_8H_{13}O_2HgBr$: C, 22.79, H, 3.11. Found for **9:** C, 22.88; H, 3.08.

Reduction of the oily residue, obtained from concentration of the ether extract from the above trituration, with aqueous sodium borohydride gave mainly 2-methylcyclopentyl acetate (**5a,** 32%).

***cis*-5-Bromomercuri-*cis*-1,3-cyclohexyl Diacetate (10a).** Acetylated mercurial was prepared from *cis*-bicyclo[3.1.0]hexan-3-ol (**3b,** 5.1 mmol) as described above. Treatment with a twofold excess of KBr in water gave a white, crystalline precipitate which was collected by filtration with suction. The solid was dissolved in chloroform. The solution was dried ($MgSO_4$), filtered, and concentrated. Crystallization of the residue from chloroform–ether gave **10a** as white needles: mp 141–142 °C (56%); ^1H NMR δ (CH_2Cl_2 as internal standard) 1.84–2.25 (6 H, C-2, 4, 6), 2.10 (s, 6 H, OAc), 2.64 (q, 1 H, J = 4 Hz, C-5), 5.00 (quintet, 2 H, J = 4 Hz, C-1, 3).

Anal. Calcd for $C_{10}H_{15}O_4HgBr$:C, 25.04; H, 3.13. Found for **10a:** C, 25.16; H, 2.83.

***cis*-5-Chloromercuri-*cis*-1,3-cyclohexyl Diacetate (10b).**

Acetylated mercurial from **3b** was treated with a twofold excess of NaCl in water in analogy with the preparation of **10a** above. It was characterized by the near identity of its NMR spectrum with that of **10a**: ^{1}H NMR δ ($CHCl_3$ as internal standard) 1.50–2.27 (5 H, C-2, 4, 6), 2.12 (s, 6 H, OAc), 2.60 (q, 1 H, J = 4.5 Hz, C-5), 5.06 (quintet, 2 H, J = 3.7 Hz, C-1, 3).

3-Bromocyclohexyl Acetate (12). A solution of 3-bromomercuricyclohexyl acetate (**9**, 1.0 g, 2.38 mmol) in anhydrous pyridine (4 ml) was treated dropwise with a solution of bromine (0.64 g, 4 mmol) in pyridine (2 ml) at −40 °C. After the resulting mixture was stirred for 10 min, it was allowed to warm to 25 °C and then stirred for 1.5 h. Pyridine was removed by rotary evaporation and the oily solid residue was taken up in ether (50 ml). The solution was washed with saturated aqueous $NaHCO_3$ and then with saturated aqueous $CuSO_4$, dried ($MgSO_4$), and concentrated by rotary evaporation. The NMR spectrum of this crude material indicated almost pure **12**. A pure sample was obtained by preparative GLC (column 2): 100 MHz ^{1}H NMR δ 1.0–2.4 (8 H, C-2, 4, 5, 6), 2.03 (s, 3 H, OAc), 3.95 (tt, 1 H, J = 4, 14 Hz, C-3), 4.66 (tt, 1 H, J = 4, 11 Hz, C-1); mass spectrum (70 eV) m/e (rel intensity) 43 (92), 61 (11), 81 (100), 162 (7), 221 (63), 223 (58).

***cis*-5-Chloro-*cis*-1,3-cyclohexyl Diacetate (13c).** A solution of chlorine (1.5 ml of 1.75 M) in CCl_4 was added dropwise to a solution of *cis*-5-chloromercuri-*cis*-1,3-cyclohexyl diacetate (**10b**, 385 mg, 0.89 mmol) in pyridine (8 ml) at −40 °C under nitrogen. The resulting mixture was stirred at −40 °C for 1 h, then allowed to warm to room temperature and stirred for an additional 1 h. Solvents were removed by rotary evaporation and the residue was taken up in ether (50 ml). The solution was washed with saturated aqueous $NaHCO_3$ and then with saturated aqueous $CuSO_4$, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give **13c** (121 mg, 58%): ^{1}H NMR δ 1.45 (d, 2 H, J = 11.5 Hz, C-4, 6), 1.85 (d, 2 H, J = 11.5 Hz, C-4, 6), 2.05 (s, 6 H, OAc), 2.1–2.8 (m, 2 H, C-2), 3.84 (tt, 1 H, J = 4, 12 Hz, C-5), 4.75 (tt, 2 H, J = 4.3, 12 Hz, C-1, 3); mass spectrum (70 eV) m/e (rel intensity) 43 (100), 79 (40), 96 (49), 97 (23), 114 (13), 138 (13), 139 (21), 174 (17), 234 (12), 236 (4).

Bromination of *cis*-5-Bromomercuri-*cis*-1,3-cyclohexyl Diacetate (10a). A solution of bromine (0.64 g, 4 mmol) in pyridine (2 ml) was added to a solution of **10a** (1.5 g, 3.14 mmol) in pyridine (6 ml) at −40 °C under an atmosphere of dry nitrogen. After completion of the addition the solution was warmed to room temperature and stirred for 2.5 h. Pyridine and other volatiles were removed in vacuo (4 mm) and the oily residue was taken up in ether (100 ml). The solution was washed with saturated aqueous $NaHCO_3$ and then saturated aqueous $CuSO_4$, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. This material was passed through a column of 80–200 mesh silica gel (10 g) with chloroform as eluting solvent. Removal of solvent by rotary evaporation gave a mixture of isomeric 5-bromo-*cis*-1,3-cyclohexyl diacetates (68%): ^{1}H NMR δ 1.3–2.8 (6 H, C-2, 4, 6), 2.00 (s, 6 H, OAc), 3.93 (tt, 0.5 H, J = 4, 12 Hz, C-5 in *cis*-5-bromo), 4.4–5.0 (1.5 H, C-1, 3 in *cis*-5-bromo and C-5 in *trans*-5-bromo), 5.24 (tt, 1 H, J = 4.5, 7.5 Hz, C-1, 3 in *trans*-5-bromo); mass spectrum (70 eV) m/e (rel intensity) 41 (28), 43 (100), 61 (36), 67 (23), 69 (31), 79 (58), 83 (39), 176 (31), 178 (29), 218 (30), 220 (31), 279 (25), 281 (25).

Acknowledgment. This work was supported by Grant GM-21249 from the Division of General Medical Sciences of the National Institutes of Health. We thank Dr. Mary Salomon for important suggestions.

Registry No.—**3a**, 285-58-5; **3b**, 694-43-9; **3c**, 40213-64-7; **3d**, 58268-46-5; **3f**, 694-44-0; **4b**, 832-09-7; **4c**, 26688-53-9; **5a**, 40991-94-4; **5b**, 58268-47-6; **5c**, 58311-28-7; **6**, 25494-20-6; **7**, 58268-48-7; **8**, 58268-49-8; **9c**, 58268-50-1; **10a**, 58268-51-2; **10b**, 58268-52-3; **12c**, 58268-53-4; **13c**, 58268-54-5; **14c**, 58268-55-6; **14t**, 58268-56-7; acetic anhydride, 108-24-7; *cis*-1,3-cyclohexanediol, 823-18-7; *trans*-1,3-cyclohexanediol, 5515-64-0; mercuric acetate, 1600-27-7; cyclohexyl acetate, 622-45-7.

References and Notes

(1) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 899 (1973), and references cited therein.
(2) (a) D. H. Ballard, A. J. Bloodworth, and R. J. Bunce, *Chem. Commun.*, 815 (1969); (b) V. I. Sokolov and O. A. Reutov, *Zh. Org. Khim.*, **5**, 174 (1969); (c) E. Schmitz, A. Rieche, and O. Brede, *J. Prakt. Chem.*, **312**, 30 (1970); (d) D. H. Ballard and A. J. Bloodworth, *J. Chem. Soc. C*, 945 (1971); (e) A. J. Bloodworth and I. M. Griffin, *J. Organomet. Chem.*, **66**, C1 (1974).
(3) V. I. Sokolov and O. A. Reutov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **7**, 1634 (1969).
(4) R. Ya. Levina, V. N. Kostin, and T. K. Ustynyuk, *J. Gen. Chem. USSR (Engl. Transl.)*, **30**, 383 (1960).
(5) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958).
(6) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961).
(7) J. H.-H. Chan and B. Rickborn, *J. Am. Chem. Soc.*, **90**, 6406 (1968).
(8) R. Steyn and H. Z. Sable, *Tetrahedron*, **25**, 3579 (1969).
(9) F. R. Jensen and L. H. Gale, *J. Am. Chem. Soc.*, **82**, 148 (1960); **81**, 1261 (1959).
(10) F. R. Jensen and L. H. Gale, *J. Am. Chem. Soc.*, **81**, 6337 (1959).
(11) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **4**, 761 (1965).
(12) C. P. Casey, G. M. Whitesides, and J. Kurth, *J. Org. Chem.*, **38**, 3406 (1973).
(13) A. Hassner, J. E. Kropp, and G. J. Kent, *J. Org. Chem.*, **34**, 2628 (1969).
(14) H. Booth, *Prog. Nucl. Magn. Reson. Spectrosc.*, **5**, 237 (1969).
(15) C. H. DePuy, *Top. Curr. Chem.*, **40**, 73 (1973).
(16) R. T. La Londe and A. D. Debboli, Jr., *J. Org. Chem.*, **35**, 2657 (1970).
(17) (a) S. Moon, *J. Org. Chem.*, **29**, 3456 (1964); (b) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Am. Chem. Soc.*, **87**, 2602 (1965).
(18) C. H. DePuy, W. C. Arney, Jr., and D. H. Gibson, *J. Am. Chem. Soc.*, **90**, 1830 (1968); A. DeBoer and C. H. DePuy, *ibid.*, **92**, 4008 (1970); C. H. DePuy and R. H. McGirk, *ibid.*, **96**, 1121 (1974); F. R. Jensen, D. B. Patterson, and S. E. Dinizo, *Tetrahedron Lett.*, 1315 (1974).
(19) (a) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959); (b) S. Moon and B. H. Waxman, *Chem. Commun.*, 1283 (1967); (c) M. R. Johnson and B. Rickborn, *ibid.*, 1073 (1968); (d) S. Moon, C. Ganz, and B. H. Waxman, *ibid.*, 866 (1969); (e) M. R. Johnson and B Rickborn, *J. Org. Chem.*, **34**, 2780 (1969); (f) J. Klein and R. Levene, *Tetrahedron Lett.*, 4833 (1969); (g) P. Chamberlain and G. H. Whitham, *J. Chem. Soc. B*, 1382 (1970).
(20) H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962).

Stereochemistry of Reactions of Silacyclobutanes

B. Gary McKinnie, Norman S. Bhacca, Frank K. Cartledge,* and Jack Fayssoux

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

Received July 31, 1975

Preparations and separations of geometric isomers and structural assignments based on NMR spectra are described for a number of 1-substituted 1,2-dimethylsilacyclobutanes. The stereochemical course for a number of reactions of these derivatives has been determined. There is a decided bias toward retention in the strained ring system even for reactions that are inversions in unstrained organosilanes; nevertheless, inversion can be observed to occur. Mechanistic possibilities are discussed, and an unusual temperature dependence of stereochemical outcome for Br_2 cleavage of an aryl–silicon bond is described.

In recent years considerable attention has been devoted to stereochemical studies of reactions at nonmetal atoms incorporated in strained cyclic systems. Such studies have been particularly important in development of a comprehensive rationalization of the relations between stereochemistry and mechanism in substitution reactions at four-coordinate phosphorus,[1] and recently unusual stereochemical outcomes for reactions at carbon atoms in small rings

Table I. Stereochemistry of Reactions of 1,2-Dimethyl-1-silacyclobutanes

Rxn no.	Compd[a]	*Z*:*E* ratio[b]	Reagent	Product	*Z*:*E* ratio	Predominant stereochemistry
1	R_3SiCl (1)	40:60	$LiAlH_4$	SiH (2)	59:41	Retention
	R_3SiCl (1)	22:78	$LiAlH_4$	SiH (2)	80:20	
2	R_3SiCl (1)	30:70	ZnF_2	SiF (3)	30:70	
	R_3SiCl (1)	50:50	ZnF_2	SiF (3)	30:70	Nonstereospecific
3	R_3SiF (3)	30:70	$LiAlH_4$	SiH (2)	68:32	Retention
4	R_3SiOMe (4)	30:70	$LiAlH_4$	SiH (2)	75:25	Retention
5	R_3SiCl (1)	15:85	*p*-$MeOC_6H_4MgBr$	SiC_6H_4OMe-*p* (5)	15:85	Retention
	R_3SiCl (1)	50:50	*p*-$MeOC_6H_4MgBr$	SiC_6H_4OMe-*p* (5)	50:50	
6	R_3SiCl (1)	50:50	*p*-MeC_6H_4MgBr	SiC_6H_4Me-*p* (6)	50:50	
7	$R_3SiC_6H_4OMe$-*p* (5)	50:50	HF	R_3SiF (3)	30:70	Nonstereospecific
8	R_3SiH (2)	95:5	CCl_4–Bz_2O_2	SiCl (1)	6:94	Retention
	R_3SiH	2:98	CCl_4–Bz_2O_2	SiCl (1)	95:5	
9	R_3SiH (2)	80:20	CBr_3H–Bz_2O_2	SiBr (7)	30:70	Retention
	R_3SiH (2)	2:98	CBr_3H–Bz_2O_2	SiBr (7)	90:10	

[a] R_3Si equals 1,2-dimethyl-1-silacyclobutane. [b] Isomeric ratios for R_3SiH were determined by GLC, all others from relative intensities of the Si-Me absorptions in the NMR spectra.

have been both predicted[2] and observed.[3] We now wish to report the results of a number of transformations taking place at Si atoms in the strained silacyclobutane system.

Dubac and Mazerolles have reported the stereochemistry of a number of reactions of 2-methyl- and 3-methyl-1-silacyclobutanes, all reactions that were stereospecific being proposed to occur with retention of configuration.[4] However, similar reactions in nonstrained systems also occur with retention.[5a,b] The only stereochemical study in a strained cyclic system of a reaction that occurs with inversion in nonstrained systems is the reduction of 1-chloro-1-α-naphthyl-1-silaacenaphthene.[6] Sommer and co-workers observed retention of configuration in its reduction with $LiAlH_4$ and postulated that the stereochemical crossover is associated with angle strain at Si. In a preliminary communication we have reported a similar result in the silacyclobutane ring system.[7]

Results

A convenient route for synthesis of 1-substituted 1,2-dimethyl-1-silacyclobutanes is through the chloro derivative (1). The preparation of 1 from (3-chlorobutyl)dichloromethylsilane was reported by Dubac and Mazerolles to lead to a 36:64 mixture of the *E* and *Z* isomers, respectively.[1a] We reported that a 60:40 mixture of (*E*)-1 and (*Z*)-1 was obtained.[7] The activity of the magnesium (ours being activated by the method of Damrauer[8]) may account for this difference. Further study of the reaction revealed that an 85:15 mixture of (*E*)-1 and (*Z*)-1 was actually formed which underwent isomerization on distillation at atmospheric pressure (probably owing to traces of ether at high temperature[9]) leading to the 60:40 mixture. Indeed, attempted separation of an 85:15 mixture of 1 by spinning-band distillation led to an approximately 50:50 mixture of the two isomers. The isomerization on distillation accounts for the various ratios of isomers used through this work and for the apparent enrichment of a mixture in (*E*)-1 previously reported by this group.[7]

Table I gives the results of the stereochemistry of eight reactions of 1-substituted 1,2-dimethyl-1-silacyclobutanes. The observation of predominant retention of configuration in the reduction of the chloro and fluoro derivatives (reactions 1 and 3) is contrary to the "normal" stereochemistry of inversion in these reactions; however, there has been a recent report of retention in a fluorosilacyclohexane with fused aromatic rings,[5c] and racemization has also been reported to occur in reduction of 2-fluoro-2-α-naphthyl-2-sila-1,2,3,4-tetrahydronaphthalene.[5b] Although only one isomeric ratio of the fluoro derivative 3 was available for reduction, it is apparent that the reaction is stereospecific since the equilibrium ratio of 2 is known to be a 46:54 mixture of the *Z* and *E* isomers, respectively, from isomerization of both isomers in DMF containing KCN.[10] If the reaction were nonstereospecific the equilibrium ratio of 2 would be a likely result, although any ratio is possible if epimerization of starting materials or intermediates is possible. In the latter event, the reaction is unlikely to appear to be stereospecific. By similar reasoning the reduction of the methoxy derivative 4 (reaction 4) is presumed to be stereospecific.

Table II. Stereochemistry of Bromination of 1-*p*-Anisyl-1,2-dimethyl-1-silacyclobutane

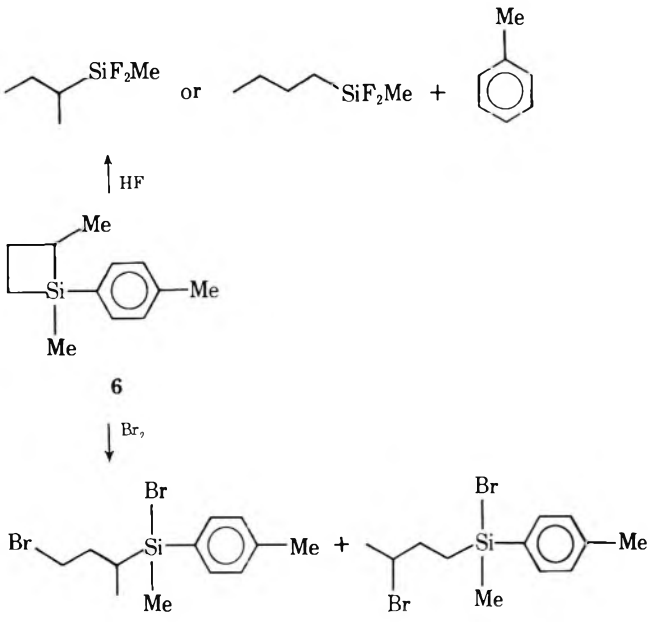
(*E*)-5:(*Z*)-5 ratio	Solvent	Temp, °C	Product ratio (*E*)-7:(*Z*)-7
50:50	CCl_4	−23	50:50
85:15	CCl_4	−23	45:55
50:50	Hexane–ether	−98	30:70
85:15	Hexane–ether	−98	20:80
50:50	CCl_4	~25	70:30
85:15	CCl_4	~25	74:26

The retention of configuration observed in the displacement of chloride ion with *p*-anisylmagnesium bromide (reaction 5) is contrary to the stereochemistry normally observed in the reaction of Grignard reagents with chlorosilanes.[12] However, aryl Grignards often fail to react with the sterically hindered chlorosilanes used in stereochemical studies[12] and thus little is known of these reactions. One chlorosilane has been shown to give predominant (56%) retention of configuration when treated with phenylmagnesium bromide.[13]

The reaction of 1 with zinc fluoride (reaction 2) (represented in Table I as being nonstereospecific) may have occurred stereospecifically, the product then undergoing isomerization induced by halide ion. Evidence for the product ratio representing an equilibrium mixture was formation of the same ratio in both preparations (reactions 2 and 7) and by the failure to observe a change in the ratio when 3 was dissolved in neat methanol. Methanol has previously been shown to give racemization of chiral fluorosilanes.[14]

The desilylation of 5 with anhydrous HF (reaction 7) represents the first reported cleavage of an aryl group from a silacyclobutane in competition with the ring opening normally observed with strong nucleophilic and electrophilic reagents.[15] Ring-opened products were the only ones observed in reaction of 1-*p*-tolyl-1,2-dimethyl-1-silacyclobutane (6) with both HF and bromine (Scheme I). Some ring

Scheme I



opening was also observed in the reaction of the anisyl derivative, **5**, with HF. However the only product obtained in reaction of **5** with bromine was 1-bromo-1,2-dimethyl-1-silacyclobutane (**7**). The results of stereochemical studies of this reaction are shown in Table II. Under the reaction conditions neither **5** nor **7** are isomerized at appreciable rates. The equilibrium mixture of (*Z*)-**7** and (*E*)-**7** at room temperature is 44:56 as demonstrated by isomerization with hexamethylphosphoric triamide.[16] Although inversion of configuration is probably the "normal" stereochemistry of desilylations with bromine,[17] racemization has been observed.[18]

Structural Assignments. The structures of the hydride derivatives (*Z*)-**2** and (*E*)-**2** were assigned from ^1H and ^{13}C chemical shifts. In many substituted cycloalkanes substituents exert an influence on the chemical shifts of protons on an adjacent carbon that is stereospecific and greater when the substituent and proton are cis to one another than when they are trans.[19] Methyl groups generally show the effect of shielding cis protons on adjacent carbons,[20] and in the *E* isomer of **2**, shielding of the proton on Si by the cis C_2-Me gives rise to a resonance at substantially higher field (δ 4.42) than the Si-H of the *Z* isomer (δ 4.75). Also the Si-Me and C_2-Me protons appear at higher field (slightly but consistently) in the *Z* isomer where they are cis to one another. The proton on C_2 could not be resolved from the other ring protons so that no useful coupling constant data are available nor could a nuclear Overhauser effect be determined. The stereochemical assignments were confirmed by ^{13}C chemical shifts for which a reasonably close analogy to the present system exists in a study of methyl-substituted phosphetanes.[21] Steric interaction between the methyl groups of the *Z* isomer of **2** gives rise to resonances at higher field for both the Si-Me (δ −7.0) and the C_2-Me (δ 15.6) relative to the Si-Me (δ −2.3) and C_2-Me (δ 17.3) of the *E* isomer. This high-field shift is also observed for the C_2 resonance of the *Z* isomer.

By reasoning similar to that applied to the hydrides, the structures of all other derivatives were assigned from the ^1H chemical shifts of the Si-Me. In each case, the *E* isomer, where the Si-Me is cis to the C_2-Me, gives rise to a resonance at higher field than the *Z* isomer (Table III). The structures of the fluoride derivatives were confirmed by ^{19}F NMR. The Si-F of the *Z* isomer of **3** where it is cis to the C_2-Me appears at a higher field than the Si-F of the *E* isomer. In both aryl derivatives, **5** and **6**, the C_2-Me of the *Z* isomer where it is cis to the aryl group appears at substantially higher field than the C_2-Me of the *E* isomer. Such diamagnetic anisotropic shifts are well known[19,22] and have previously been observed in phenyl-substituted cyclic silanes.[14c] The structures of the chloride and bromide derivatives were confirmed by stereospecific synthesis from the hydride isomers (reactions 8 and 9). Since these reactions proceed through a silyl radical intermediate,[23] they can be presumed to occur with retention of configuration.

Only in the case of the methoxide isomers are the structural assignments questionable. In the isomer of **4** assigned the *Z* structure from the chemical shifts of the Si-Me groups, the SiOMe which is presumably cis to the C_2-Me gave rise to a resonance at lower field than the SiOMe of the *E* isomer. The structural assignments of **4** made here are the same as those proposed by Dubac and Mazerolles[4a,4c] and are consistent with chemical evidence. The reduction of **4** undoubtedly occurs with retention of configuration since similar reactions of other alkoxysilanes occur with retention.[5]

Table III. NMR Spectra of Derivatives of 1,2-Dimethyl-1-silacyclobutane[a]

Compd	Si-Me	C_2-Me	Si-H	Si-F[b]	SiOMe
SiCl *E*	0.59	1.12			
SiCl *Z*	0.65	1.15			
SiH *Z*	0.28	1.05	4.75		
SiH *E*	0.32	1.11	4.42		
SiF *E*	0.25	1.05		137.6	
SiF *Z*	0.32	1.05		154.7	
SiOMe *E*	0.10				3.40
SiOMe *Z*	0.15				3.48
SiBr *E*	0.67				
SiBr *Z*	0.73				
SiC_6H_4OMe *E*	0.55	1.18			
SiC_6H_4OMe *Z*	0.57	1.03			
SiC_6H_4Me *E*	0.50	1.14			
SiC_6H_4Me *Z*	0.52	0.98			

[a] Complete spectra, solvents, and reference compounds are given in the Experimental Section. [b] ^{19}F NMR.

Discussion

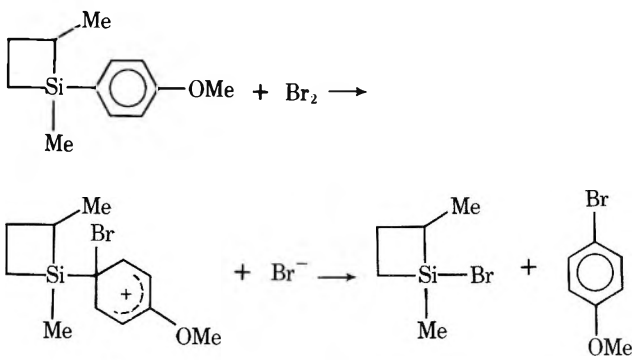
A simple rationalization of the stereochemistry of reactions 1 and 3–5 is possible. "Normal" (SN2-Si)[5a,24] attack on the back side of Si (relative to the leaving group) occurs with the same stereochemical constraints which are normal for SN2 attack on carbon, namely, the entering and leaving groups are apical and the other substituents equatorial. Attack on one of the other three faces of the approximate tetrahedron about silicon (flank attack)[25] leads preferentially to retention of configuration. Flank attack can be induced by coordination of the leaving group to some portion of the entering group (SNi-Si)[5a,26] or, as in the angle strain cases, by the inability of the substituents about Si to occupy their normal equatorial positions in the SN2-Si transition state because of prohibitive increases in angle strain.

An attractive rationalization of the bias toward retention in the silacyclobutane reactions would be formation of a pentacoordinate intermediate by axial entry of the nucleophile. Conversion of the first intermediate to other pentacoordinate intermediates can occur by turnstile rotation or Berry pseudorotation.[1] A single turnstile rotation (TR) followed by loss of the leaving group would result in retention of configuration. The same mechanism was postulated for the recently observed retention reaction of a cyclobutane[3] and has been applied numerous times in phosphorus chemistry.[1] Furthermore, by analogy to arguments applied for

phosphetanes,[27] the strained silacyclobutane ring might be expected to favor formation of extracoordinate intermediates and would be expected to span an axial and an equatorial position in a trigonal bipyramid.

That this stereochemical rationalization is not a complete description of what can occur in small rings is abundantly clear from previous observations of inversions or nonstereoselectivity occurring in four-membered P[28a] and S[28b] rings as well as the present observation of temperature-dependent stereochemical outcome in the bromination of the anisyl derivatives (**5**) in which inversion is occurring at low temperature. The latter reaction presumably proceeds through a σ complex[29] (Scheme II); however, the

Scheme II



15

actual situation cannot be so simple as Scheme II implies since the reaction in nonpolar solvents is second order in Br_2.[30] The occurrence of inversion could be explained on the basis of five-coordinate intermediates using an argument similar to that advanced by Emsley[28] and assigning a high equatoriophilicity to the benzenonium ion group in intermediate **15**. This explanation would allow the four-membered ring to retain its preferred axial–equatorial placement in a trigonal bipyramid. A second scheme allowing inversion would be equatorial entry–equatorial departure (perhaps synchronously, perhaps through an intermediate) retaining the ring bonds axial–equatorial. The possibility of equatorial attack must be taken seriously for Si, and also for other nonmetals, following the work of Corriu.[31] A third possibility for inversion would be apical placement of both entering and leaving groups, forcing the ring bonds to be diequatorial. In the five-coordinate hexafluoroacetone adducts of 1-substituted phosphetanes, free energies of activation have been measured for a pseudorotation which places the four-membered ring bonds diequatorial.[32] The activation free energy varies with the substituent but is in the range of 10–20 kcal/mol. If these figures can be considered to approximately represent the free-energy difference between trigonal bipyramids which have four-membered ring bonds axial–equatorial and those where the bonds are diequatorial, then the latter can certainly be generally considered unfavorable, but nevertheless energetically accessible.

We cannot at present distinguish among these possibilities, nor do any of them afford a ready explanation of the temperature dependence of the stereochemical results. Competing mechanistic pathways which show different temperature dependencies in their rates, combined with normal temperature dependence of the compositions of equilibrium mixtures, can certainly lead to a very complex overall picture. The results are suggestive of a need for temperature-dependency studies in other stereochemical investigations.

Experimental Section

Unless otherwise stated, all reactions were run in three-neck round-bottom flasks equipped with a magnetic stirrer, reflux condenser, addition funnel, and thermometer. All glassware was flame dried and flushed with nitrogen prior to conducting the experiment under an atmosphere of nitrogen. All distillations were through a 7-cm Vigreux column unless stated otherwise. Commercial anhydrous ether was used as supplied. Methanol was dried over 3 Å molecular sieves; carbon tetrachloride over 4 Å molecular sieves. Nuclear magnetic resonance (NMR) spectra were obtained routinely on a Varian A-60A, Varian HA-100, or Varian CFT-20. Infrared (ir) spectra were recorded using a Perkin-Elmer Model 137. A Perkin-Elmer Model 900 equipped with a flame ionization detector was used for routine gas–liquid partition chromatography (GLC). Preparative GLC was carried out using a Perkin-Elmer Model F-21. GLC–mass spectra were obtained on a Perkin-Elmer 990 GLC interfaced through a Biemann-Watson separator to a Hitachi Perkin-Elmer RMS-4 mass spectrometer. Mass spectra were taken at 70 eV and are reported as *m/e* (rel abundance).

Dichloro(3-chlorobutyl)methylsilane[33] and 1-methoxy-1,2-dimethyl-1-silacyclobutane[4a,4c] (**4**) were prepared as previously reported.

1-Chloro-1,2-dimethyl-1-silacyclobutane (1). In a 1-l. three-neck flask equipped as usual was placed 21.9 g (0.900 g-atom) of 40-mesh magnesium powder and 600 ml of ether. 1,2-Dibromoethane (3 ml) was added and the mixture refluxed for 15 min. To this activated magnesium was added dropwise 61.7 g (0.300 mol) of (3-chlorobutyl)dichloromethylsilane in 40 ml of ether over an 8-h period with refluxing. Refluxing was continued for 3 days and stirring at room temperature for 5 days.

The reaction mixture was filtered under nitrogen and the residue washed twice with ether. The solvent was removed by rapid distillation and the remaining liquid distilled to give 25.5 g (63% yield) of **1**: bp 61–65 °C (92–93 mm) [lit.[4a] bp 62–64 °C (110 mm)]; NMR (100 MHz) ($CDCl_3$, internal $CHCl_3$) δ 0.59 (s) and 0.65 (s) (total, 3 H), 1.12 (d) and 1.15 (d) (total, 3 H), 1.0–2.0 (m, 4 H), and 2.45 (m, 1 H). Relative intensities of 85:15 were observed for the singlets at δ 0.59 and 0.65, respectively. MS *m/e* 134 (13), 119 (6), 108 (35), 106 (100), 92 (86), 78 (63), 63 (47), and metastables at 66.3, 64.7, and 57.3.

If the solvent was removed by slow distillation and the product distilled at 760 mm (bp 121–123 °C) a 75% yield was obtained of a 60:40 mixture of (*E*)-**1** and (*Z*)-**1**, respectively.

Keeping the reaction vessel in a cold bath at 4–6 °C during addition of the silane and for 4 days, plus 7 days at 8–10 °C failed to increase the isomeric ratio above 85:15.

Attempted spinning band distillation of **1** at 760 mm resulted in isomerization to a 47:53 mixture of the two isomers. Spinning band distillation at 150 mm (bp 81–82 °C) failed to separate the isomers.

1,2-Dimethyl-1-silacyclobutane (2) (Reaction 1). In a 250-ml three-neck flask equipped as usual was placed 125 ml of ether and 2.30 g (0.242 g-atom of H) of crushed lithium aluminum hydride. To this stirred mixture was added 23.1 g (0.172 mol) of a 60:40 mixture of (*E*)-**1** and (*Z*)-**1**, respectively, in 30 ml of ether at a rate sufficient to maintain refluxing. Refluxing was continued 0.5 h after addition was complete.

After filtering, the reaction mixture was added to 150 ml of ice water containing 30 g of ammonium chloride. The ether layer was washed once with 1 M aqueous ammonium chloride and twice with water, and dried over magnesium sulfate. Distillation gave 10.1 g (59% yield) of **2**, bp 84–87 °C [lit.[4b] bp 85–87 °C (748 mm)].

Analysis by GLC using a 16 ft × 0.125 in. column of 15% Apiezon L on 60–80 mesh Chromosorb W at 85 °C showed an impurity, 10%, retention time of 4.2 min, and the two isomers, (*E*)-**2** and (*Z*)-**2**, retention times of 4.7 and 5.3 min, 37 and 53% respectively (*Z*:*E* ratio of 59:41). Similarly reduction of a 78:22 mixture of (*E*)-**1** and (*Z*)-**1** gave an 80:20 mixture of (*Z*)-**2** and (*E*)-**2** as determined by GLC analysis of the reaction mixture.

The isomers were separated by preparative GLC on a 64 × 0.75 in. column of 10% Apiezon L on 60–80 mesh Chromosorb W operating at a temperature of 85 °C with a nitrogen flow rate of 270 ml/min. The *E* and *Z* isomers had retention times of 6.4 and 7.2 min, respectively. Attempted spinning band distillation of **2** resulted in polymerization. NMR (100 MHz) ($CDCl_3$, internal Me_4Si) **2a:** δ 0.28 (d, J = 4 Hz, 3 H), 1.05 (d, 3 H), 0.76–1.95 (m, 4 H), 2.45 (m, 1 H), and 4.75 (m, 1 H). **2b:** δ 0.32 (d, J = 4 Hz, 3 H), 1.11 (d, 3 H), 0.58–1.87 (m, 4 H), 2.40 (m, 1 H), and 4.42 (m, 1 H). ^{13}C NMR ($CHCl_3$) **2a:** δ −7.0 (Si-Me), 9.0 (C_4), 15.6 (C_2-Me), 20.4 (C_2), and 29.6 (C_3). **2b:** δ −2.3 (Si-Me), 9.0 (C_4), 17.3 (C_2-Me), 23.1

(C_2), and 28.4 (C_3). Ir (film) 2900 s, 2100 s, 1450 m, 1400 w, 1250 s, 1180 w, 1130 m, 1060 m, 970 m, 920 s, 890 s, 855 s, and 730 cm^{-1} s; mass spectrum *m/e* 100 (10), 85 (14), 72 (100), 58 (45), 43 (45), and a metastable at 51.8.

1,2-Dimethyl-1-fluoro-1-silacyclobutane (3) (Reaction 2). In a 50-ml one-neck flask were placed 15.33 g (114 mmol) of a 70:30 mixture of (*E*)-1 and (*Z*)-1, respectively, and 9.0 g (87 mmol) of anhydrous zinc fluoride. The flask was equipped with a magnetic stirrer and set for distillation. Distillation gave a fraction, bp 85–112 °C, which was combined with 9.0 g (87 mmol) of fresh zinc fluoride and redistilled, the fraction bp 80–85 °C being collected. Redistillation of this fraction from 1.0 g of fresh zinc fluoride gave 9.21 g (68% yield) of **3**: bp 83–84 °C; NMR (CCl_4, internal benzene) δ 0.25 (d, J = 8 Hz) and 0.32 (d, J = 8 Hz) (total of 3 H), 1.05 (m, 3 H), and 0.83–2.25 (m, 5 H); estimated relative intensities were 70:30 for doublets at δ 0.25 and 0.32, respectively. ^{19}F NMR ($CFCl_3$, solvent as reference) δ 137.6 (m) and 154.7 (m) (relative intensities of 75:25, respectively); MS *m/e* 118 (7), 103 (6), 90 (94), 77 (77), 76 (100), 63 (50), 62 (92), 47 (83), and metastables at 42.8 and 50.2. Anal. Calcd for $C_5H_{11}FSi$: C, 50.79; H, 9.38; Si, 23.78. Found: C, 50.59; H, 9.40; Si, 23.60.

A similar preparation using a 50:50 mixture of (*E*)-1 and (*Z*)-1 gave a 70:30 mixture of (*E*)-3 and (*Z*)-3 as determined by NMR.

Reduction of 1,2-Dimethyl-1-fluoro-1-silacyclobutane (Reaction 3). In an 8-ml vial equipped with a magnetic stirrer were placed 45.6 mg (4.94 mg-atoms of H) of $LiAlH_4$ and 5 ml of ether. After equipping with a septum 0.50 g (4.2 mmol) of a 70:30 mixture of (*E*)-3 and (*Z*)-3 was added via syringe and the mixture stirred for 15 min. GLC–mass spectrometry analysis showed that (*Z*)-3 and (*E*)-3 were formed in a 68:32 ratio.

Reduction of 1,2-Dimethyl-1-methoxy-1-silacyclobutane (Reaction 4). In an 8-ml vial were placed 6.5 mg (0.73 mg-atoms of H) of $LiAlH_4$ and 2.0 ml of ether. Through a septum 52 mg (0.40 mmol) of a 70:30 mixture of (*E*)- and (*Z*)-1,2-dimethyl-1-methoxy-1-silacyclobutane was added via syringe and the mixture stirred for 0.5 h. GLC–mass spectrometry analysis showed that (*Z*)-2 and (*E*)-2 were formed in a 75:25 ratio.

1,2-Dimethyl-1-(*p*-anisyl)-1-silacyclobutane (5) (Reaction 5). To a solution of 26.9 g (0.200 mol) of a 50:50 mixture of (*E*)-1 and (*Z*)-1 in 100 ml of ether was added with stirring the top layer of a solution of *p*-anisylmagnesium bromide obtained from 39.0 g (0.208 mol) of *p*-bromoanisole and 7.0 g (0.287 g-atom) of magnesium turnings in 350 ml of ether. The lower layer was then added dropwise and the mixture stirred for 2 h under reflux.

The reaction mixture was hydrolyzed in 300 ml of ice water containing 20 g of ammonium chloride. The ether layer was washed once with water and dried over magnesium sulfate. After the solvent was removed, the remaining liquid was distilled, the fraction bp 80–86 °C (0.5 mm) was collected and redistilled to give 26.7 g (65% yield) of a 50:50 mixture of (*E*)-5 and (*Z*)-5, bp 72–76 °C (0.3 mm). NMR (CH_2Cl_2, solvent as reference) (100 MHz) δ 0.55 (s) and 0.57 (s) (total 3 H) (ca. 50:50), 1.03 (d, J = 7 Hz) and 1.18 (d, J = 7 Hz) (total 3 H), 0.94–2.00 (m, 4 H), 2.55 (m, 1 H), 3.82 (s), and 3.83 (s) (total 3 H), 6.99 (m, 2 H), and 7.59 (m, 2 H); ir (film) 2900 s, 1600 s, 1480 s, 1270 s, 1240 s, 1180 m, 1130 w, 1110 s, 1040 m, 965 w, 915 w, 870 w, 850 m, and 780 cm^{-1} m; mass spectrum *m/e* 206 (14), 191 (2), 178 (32), 164 (100), 151 (61), 135 (37), 134 (38), 121 (22), 119 (19), and metastable at 109.5. Anal. Calcd for $C_{12}H_{18}OSi$: C, 69.84; H, 8.79; Si, 13.61. Found: C, 69.91; H, 8.90; Si, 13.74.

Similarly, reaction of 4-methoxyphenylmagnesium bromide with an 85:15 mixture of (*E*)-1 and (*Z*)-1, respectively, gave an 75% yield an 85:15 mixture of (*E*)-5 and (*Z*)-5, respectively.

1,2-Dimethyl-1-(*p*-tolyl)-1-silacyclobutane (6) (Reaction 6). To 30.0 g (0.223 mol) of a 50:50 mixture of (*E*)-1 and (*Z*)-1 in 100 ml of ether was added dropwise a solution of *p*-tolylmagnesium bromide prepared from 42.0 g (0.245 mol) of 4-bromotoluene and 8.0 g (0.33 g-atom) of magnesium turnings in 400 ml of ether. After stirring under reflux for 1 h the mixture was hydrolyzed by addition to 35 g of ammonium chloride in 500 ml of ice water. The ether layer was washed once with water and dried over magnesium sulfate. After the solvent was removed, the remaining liquid was distilled to yield 29.0 g (68% yield) of a 50:50 mixture of (*E*)-6 and (*Z*)-6, bp 73–75 °C (1.0 mm): NMR (CH_2Cl_2, solvent as reference) δ 0.50 (s) and 0.52 (s) (total 3 H) (ca. 50:50), 0.98 (d, J = 7 Hz) and 1.14 (d, J = 7 Hz) (total 3 H), 0.95–1.93 (m, 4 H), 2.37 (broad s, 3 H), 2.31–2.61 (m, 1 H) 7.24 (m, 2 H), and 7.56 (m, 2 H); ir (film) 2900 s, 1600 m, 1450 m, 1400 w, 1250 s, 1180 w, 1130 m, 1110 s, 970 m, 920 w, 870 m, 850 s, and 780 cm^{-1} s; mass spectrum *m/e* 190 (16), 175 (1), 162 (45), 148 (100), 135 (67), 134 (45), 133 (73), 131 (22), 119 (59), 105 (20), 93 (20), and metastables at 138.1 and 110.8. Anal. Calcd for $C_{12}H_{18}Si$: C, 75.71; H, 9.53; Si, 14.76. Found: C, 75.52; H, 9.43; Si, 15.00.

Reaction of 5 with HF (Reaction 7). In a dry polyethylene test tube equipped with a polyethylene stopper was placed 5.8 g of a 50:50 mixture of (*E*)-5 and (*Z*)-5. Anhydrous HF was bubbled through the neat compound for 2 h followed by nitrogen for 1 h. Distillation gave a fraction, 0.91 g, bp 78–83 °C, the NMR spectrum of which showed chemical shifts characteristic of (*E*)-3 and (*Z*)-3 (ca. 70:30, respectively) and approximately an equal amount of the product obtained from reaction of 6 with HF.

Stereospecific Preparations of 1-Chloro-1,2-dimethyl-1-silacyclobutane from 1,2-Dimethyl-1-silacyclobutane (Reaction 8). In a 25-ml one-neck flask equipped with a condenser were placed 2.16 g (21.6 mmol) of 95% isomerically pure (*Z*)-2, 17 ml (175 mmol) of dry carbon tetrachloride, and 0.05 g of benzoyl peroxide. The mixture was held at 80 °C for 1 h, an additional 0.05 g of benzoyl peroxide added, and the mixture heated at 80 °C for 1 h longer. Analysis of the reaction mixture by NMR showed a 94:6 ratio of (*E*)-1 and (*Z*)-1. Distillation gave 1.63 g (56% yield) of 94% isomerically pure (*E*)-1, bp 59–61 °C (89–90 mm).

Similarly, reaction of 0.178 g of 98% (*E*)-2, 1.0 ml of carbon tetrachloride, and 0.02 g of benzoyl peroxide in an NMR tube at 80 °C for 1 h gave >95% pure (*Z*)-2, as determined by NMR analysis of the reaction mixture.

Stereospecific Preparation of 7 from 2 (Reaction 9). In a dry NMR tube were placed 0.02 g of benzoyl peroxide, 1.0 ml (2.89 g, 11.4 mmol) of CBr_3H, and 78 mg (0.78 mmol) of an 80:20 mixture of (*Z*)-2 and (*E*)-2. The mixture was then held at 80 °C for 0.5 h. Analysis by NMR revealed that (*E*)-7 and (*Z*)-7 were formed in a 70:30 ratio, respectively.

Similarly, a 2:98 ratio of (*Z*)-2 and (*E*)-2 gave respectively (*E*)-7 and (*Z*)-7 in a 10:90 ratio.

Reaction of 6 with HF. In a dry polyethylene test tube equipped with a polyethylene stopper was placed via syringe 1.7 g of 6. Anhydrous HF was bubbled through 6 for 3 h by use of a stainless steel needle. After standing overnight nitrogen was bubbled through the solution for 1 h. The reaction mixture was analyzed directly: NMR (CCl_4, external Me_4Si) δ 0.28 (t), 0.60–1.80 (m), 2.31 (s), and 7.10 (s), the latter two chemical shifts characteristic of toluene; MS parent mass 138. The product probably was sec-butyl- and/or *n*-butyldifluoromethylsilane.

A similar reaction was stopped before all starting material was consumed. NMR analysis showed that no 3 was present.

Reaction of 6 with Bromine. To 4.40 g (23.2 mmol) of 6 in 10 ml of CCl_4 held in an ice bath was added 3.7 g (23.2 mmol) of bromine in 10 ml of CCl_4. After addition was completed the solvent was removed by distillation under reduced pressure and the product distilled to give 4.5 g (55% yield) of a clear liquid tentatively identified as a 2:1 mixture of bromo(3-bromobutyl)methyl(*p*-tolyl)silane and bromo(3-bromo-1-methylpropyl)methyl(*p*-tolyl)silane: bp 105–135 °C (0.9 mm); NMR (CCl_4, internal Me_4Si) δ 0.76 (s), 0.87–2.10 (m), 1.66 (d), 2.33 (s), 3.38 (m), 4.20 (m), 7.12 (d), and 7.46 (d).

1-Bromo-1,2-dimethyl-1-silacyclobutane (7). In a one-neck 100-ml flask equipped with a magnetic stirrer and addition funnel were placed 10.4 g (50.5 mmol) of a 50:50 mixture of (*E*)-5 and (*Z*)-5 and 20 ml of carbon tetrachloride. Bromine (8.10 g, 50.5 mmol) in 15 ml of carbon tetrachloride was added dropwise with stirring while keeping the flask in a dry ice–acetone bath at −50 to −55 °C. Distillation gave 7.50 g (83% yield) of a 50:50 mixture of (*E*)-7 and (*Z*)-7: bp 70–71 °C (68 mm); NMR (CCl_4, internal benzene) δ 0.67 (s) and 0.73 (s) (total 3 H) (50:50), 1.06 (d, 3 H), and 0.97–2.78 (m, 5 H); mass spectrum *m/e* 180 (15), 178 (16), 165 (6), 163 (6), 152 (100), 150 (100), 138 (89), 136 (89), 124 (66), 122 (66), 109 (56), 107 (55), 99 (8), 90 (68), 76 (66), and 62 (57). Anal. Calcd for $C_5H_{11}BrSi$: C, 33.52; H, 6.19; Si, 15.69. Found: C, 33.64; H, 6.25; Si, 15.55.

Similarly, reaction of an 85:15 mixture of (*E*)-5 and (*Z*)-5 led to a 64% yield of a 45:55 mixture of (*E*)-7 and (*Z*)-7, respectively.

Reaction of 5 with Bromine at −98 °C. In a 100-ml three-neck flask equipped with a mechanical stirrer, addition funnel, and thermometer were placed 5.48 g (26.6 mmol) of an 85:15 mixture of (*E*)-5 and (*Z*)-5 and 50 ml of ether. The flask was placed in a methanol–liquid nitrogen slurry (−98 °C) and 4.25 g (26.6 mmol) of bromine in 10 ml of dry hexane was added dropwise over a 1-h period. The mixture was stirred for 2 h as it warmed slowly to −78 °C. Analysis by NMR showed only a trace of starting material present and that (*E*)-7 and (*Z*)-7 were formed in ca. a 20:80 ratio respectively.

Similarly, reaction of a 50:50 mixture of (*E*)-5 and (*Z*)-5 gave a

30:70 ratio of (*E*)-7 and (*Z*)-7.

Reaction of 5 with Bromine at Room Temperature. In a dry NMR tube was placed via syringe 0.50 ml of a 2.0 M solution of **5** in CCl_4 (*E*/*Z* ratio of 85:15). To this solution was added via syringe 0.50 ml of a 2.0 M solution of Br_2 in CCl_4. The Br_2 color disappeared immediately. Analysis of the reaction mixture by NMR immediately after reaction showed that a 74:26 ratio of (*E*)-7 and (*Z*)-7, respectively, were formed and all starting material was consumed.

Similarly, a 50:50 mixture of (*E*)-5 and (*Z*)-5 gave a 70:30 ratio of (*E*)-7 and (*Z*)-7, respectively.

Acknowledgment. We wish to thank the National Science Foundation and the Louisiana State University Council on Research for financial assistance and the Cities Service Oil Co. for a fellowship for B.G.M. ^{13}C NMR spectra data were obtained by Miss Barbara Ervine of Varian Associates during the visit of the CFT-20 mobile laboratory on the Louisiana State University campus.

Registry No.—(*E*)-1, 52516-83-3; (*Z*)-1, 52516-84-4; (*E*)-2, 40726-02-1; (*Z*)-2, 40726-01-0; (*E*)-3, 53477-23-9; (*Z*)-3, 53477-24-0; (*E*)-4, 35741-84-5; (*Z*)-4, 35741-83-4; (*E*)-5, 58241-19-3; (*Z*)-5, 58241-20-6; (*E*)-6, 58241-21-7; (*Z*)-6, 58241-22-8; (*E*)-7, 58241-23-9; (*Z*)-7, 58241-24-0; 1,2-dibromoethane, 106-93-4; (3-chlorobutyl)dichloromethylsilane, 18145-84-1; *p*-bromoanisole, 104-92-7; 4-bromotoluene, 106-38-7; HF, 7664-39-3; carbon tetrachloride, 56-23-5; CBr_3H, 75-25-2; bromine, 7726-95-6; bromo(3-bromobutyl)methyl(*p*-tolyl)silane, 58241-25-1; bromo(3-bromo-1-methylpropyl)methyl(*p*-tolyl)silane, 58241-26-2.

References and Notes

(1) (a) F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968); (b) F. Ramirez, *ibid.*, **1**, 168 (1968); (c) K. Mislow, *ibid.*, **3**, 321 (1970); (d) I. Ugi and F. Ramirez, *Chem. Br.*, **8**, 198 (1972); (e) R. F. Hudson and C. Brown, *Acc. Chem. Res.*, **5**, 294 (1972); (f) P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, *Agnew. Chem., Int. Ed. Engl.*, **12**, 91 (1973); (g) R. Luckenbach, "Dynamic Stereochemistry of Pentaco-ordinated Phosphorus and Related Elements". George Thieme Verlag, Stuttgart, 1973.

(2) W.-D. Stohrer, *Chem. Ber.*, **107**, 1795 (1974).

(3) T. ElGomati, D. Lenoir, and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, **14**, 59 (1975); see also H. Yamanaka, T. Yagi, K. Teramura, and T. Ando, *Chem. Commun.*, 380 (1971); C. W. Jefford, U. Burger, M. H. Laffer, and T. Kabengele, *Tetrahedron Lett.*, 2483 (1973); J. T. Groves and K. W. Ma, *ibid.*, 909 (1974). See, however, T. Vergnani, M. Karpf, L. Hoesch, and A. S. Dreiding, *Helv. Chim. Acta*, **58**, 2524 (1975); C. A. Maryanoff, F. Ogura, and K. Mislow, *Tetrahedron Lett.*, 4095 (1975).

(4) (a) J. Dubac, P. Mazerolles, and B. Serres, *Tetrahedron Lett.*, 525 (1972); (b) *ibid.*, 3495 (1972); (c) *Tetrahedron*, **30**, 749 (1974); (d) *ibid.*, **30**, 759 (1974).

(5) (a) L. Sommer, "Stereochemistry, Mechanism and Silicon", McGraw-Hill, New York, N.Y., 1965; (b) R. Corriu and J. Massé, *Bull. Soc. Chim. Fr.*, 3491 (1969); (c) J. D. Citron, *J. Organomet. Chem.*, **86**, 359 (1975).

(6) L. Sommer and D. Roark, *J. Am. Chem. Soc.*, **95**, 969 (1973).

(7) B. G. McKinnie, N. S. Bhacca, F. K. Cartledge, and J. Fayssoux, *J. Am. Chem. Soc.*, **96**, 2637, 6819 (1974).

(8) R. Damrauer, R. Davis, M. Burke, R. Karn, and G. Goodman, *J. Organomet. Chem.*, **43**, 121 (1972).

(9) R. Corriu, M. Leard, and J. Masse, *Bull. Soc. Chim. Fr.*, 2555 (1968).

(10) This reaction appears to be specific for silacyclobutanes since the analogous silacyclopentane failed to isomerize at an appreciable rate.[11]

(11) J. M. Wolcott and F. K. Cartledge, unpublished results.

(12) R. Corriu and G. Royo, *J. Organomet. Chem.*, **40**, 229 (1972).

(13) R. Corriu and J. P. Masse, *Chem. Commun.*, 1373 (1968).

(14) (a) L. Sommer and P. Rodewald, *J. Am. Chem. Soc.*, **85**, 3898 (1963); (b) L. H. Sommer and D. L. Bauman, *ibid.*, **91**, 7045 (1969); (c) K. Tamao, M. Ishikawa, and M. Kumada, *Chem. Commun.*, 73 (1969).

(15) R. Damrauer, *Organomet. Chem. Rev. Sect. A*, 67 (1972).

(16) (a) R. Corriu and M. Henner-Leard, *J. Organomet. Chem.*, **64**, 351 (1974); (b) R. Corriu and M. Henner, *ibid.*, **74**, 1 (1974).

(17) (a) C. Eaborn and O. Steward, *J. Chem. Soc.*, 521 (1965); (b) L. H. Sommer, K. W. Michael, and W. D. Korte, *J. Am. Chem. Soc.*, **89**, 868 (1967).

(18) R. W. Bott, C. Eaborn, and P. W. Jones, *J. Organomet. Chem.*, 6, 484 (1966).

(19) H. Booth, *Prog. Nucl. Magn. Reson. Spectrosc.*, **5**, 149 (1969).

(20) (a) F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 747 (1962); (b) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 741 (1962); (c) H. Booth, *Tetrahedron*, **22**, 615 (1966); (d) R. C. Fort and P. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).

(21) G. A. Gray and S. E. Cremer, *J. Org. Chem.*, **37**, 3458 (1972).

(22) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, N.Y., 1969, p 64.

(23) (a) H. Sakurai, M. Murakami, and M. Kumada, *J. Am. Chem. Soc.*, **91**, 519 (1969); (b) L. Sommer and L. A. Ulland, *J. Org. Chem.*, **37**, 3878 (1972).

(24) L. H. Sommer, G. A. Parker, N. C. Lloyd, C. L. Frye, and K. W. Michael, *J. Am. Chem. Soc.*, **89**, 857 (1967).

(25) (a) C. Eaborn, "Organosilicon Compounds", Butterworths, London, 1960; (b) L. H. Sommer and O. F. Bennett, *J. Am. Chem. Soc.*, **79**, 1008 (1957).

(26) L. H. Sommer, J. McLick, and C. M. Golino, *J. Am. Chem. Soc.*, **94**, 669 (1972).

(27) T. Koizumi and P. Haake, *J. Am. Chem. Soc.*, **95**, 8073 (1973).

(28) (a) D. J. H. Smith and S. Trippett, *Chem. Commun.*, 855 (1969); J. R. Corfield, R. K. Oram, D. J. H. Smith, and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 713 (1972); K. E. DeBruin, A. D. Padilla, and M. T. Campbell, *J. Am. Chem. Soc.*, **95**, 4681 (1973); J. Emsley, T. B. Middleton, and J. K. Williams, *J. Chem. Soc., Dalton Trans.*, 633 (1974); (b) R. Tang and K. Mislow, *J. Am. Chem. Soc.*, **91**, 5644 (1969).

(29) C. Eaborn in "Organometallic Compounds of the Group IV Elements", A. MacDiarmid, Ed., Vol. I, Part 1, Marcel Dekker, New York, N.Y., 1968, p 407.

(30) R. A. Benkeser and A. Torkelson, *J. Am. Chem. Soc.*, **76**, 1252 (1954).

(31) R. Corriu, C. Guerin, and J. Masse, *J. Chem. Soc., Chem. Commun.*, 75 (1975).

(32) R. K. Oram and S. Trippett, *J. Chem. Soc., Chem. Commun.*, 554 (1972).

(33) M. A. Mamedov, I. M. Akhmedov, M. M. Guseinov, and S. I. Sadykhzade, *Zh. Obshch. Khim.*, **35**, 461 (1965).

Stereospecific Synthesis of 6,*c*-10-Dimethyl(*r*-5-*C*¹)spiro[4.5]dec-6-en-2-one and Its Conversion into (±)-α-Vetispirene[1]

Drury Caine,* Anibal A. Boucugnani, Sam T. Chao, J. Byron Dawson, and Paul F. Ingwalson

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

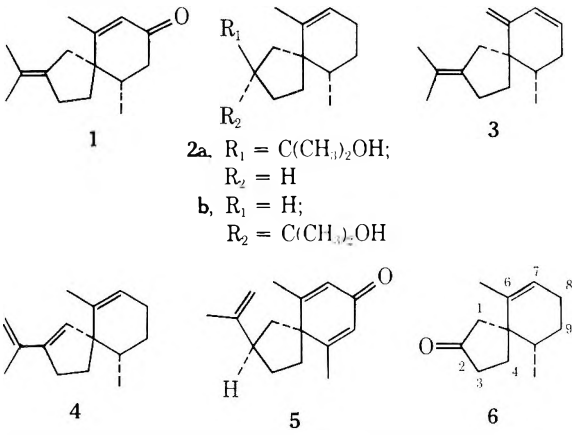
Received November 5, 1975

A stereospecific synthesis of the spiro enone **6** and its conversion into (±)-α-vetispirene is described. The photochemical rearrangement of the methoxy dienone **7** was employed as a key step to establish the spiro[4.5]decane ring system.

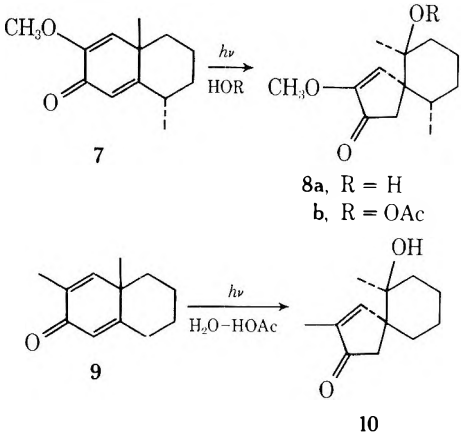
Interest in the synthesis of spirovetivane sesquiterpenes has been aroused since Marshall and co-workers reported that β-vetivone is a member of this group rather than a hydroazulene derivative as originally reported.[2] Recently, total syntheses of (±)-β-vetivone (**1**),[2c,3a-e] (−)-β-vetivone,[3f] (±)-hinesol (**2a**),[3e,4a] (±)-agarospirol (**2b**),[5] (−)-agarospirol,[3f] (±)-β-vetispirene (**3**),[3e,4b,6] and (±)-α-vetispirene (**4**)[3e,4b] have been reported.[7] In addition, relay syntheses of anhydro-β-rotunol (**5**)[8] from β-rotunol[9] and from nootkatone[10] have appeared. Several general approaches to the spiro[4.5]decane ring skeleton of these compounds also have been published.[11]

An attractive approach to various spirovetivane sesquiterpenes appeared to involve the synthesis of the spiro[4.5]dec-6-en-2-one **6** having the carbonyl group in the five-

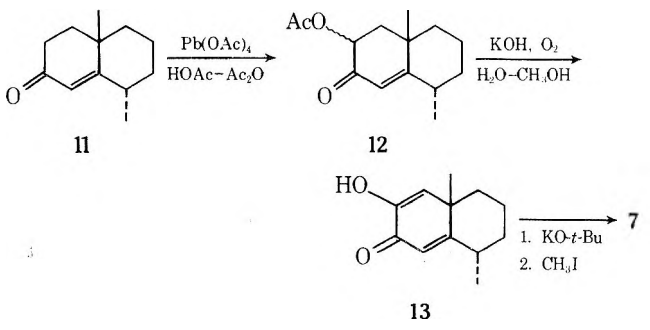
membered ring in the proper position for introduction of an appropriate three-carbon side chain. In this paper we report the stereospecific synthesis of **6**[12] and its ready conversion into (±)-α-vetispirene (**4**).[13]



The route to **6** involved photochemical rearrangement of the 2-methoxy cross-conjugated cyclohexadienone **7** as a means of establishing the spiro[4.5]decane system. Kropp has shown that the 2-methyl dienone **9** yields largely the spiro hydroxy ketone **10** on irradiation in aqueous acetic acid.[14] It

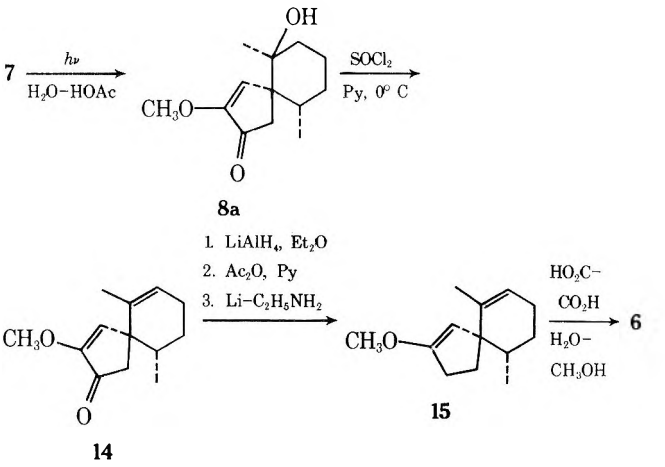


was anticipated that a methoxyl substituent would exert an influence similar to that of a methyl substituent on the course of the photochemical rearrangement and that **7** would also yield spiro[4.5]decane derivatives, e.g., **8**, on irradiation in protic solvents.[15] The synthesis of **6** from **8** would then require (1) the appropriate manipulation of the 2-methoxy-1-en-3-one system to obtain the ketone function at C-2, and (2) the introduction of the 6,7 double bond via an elimination reaction involving the C-6 oxygen function. The methoxy dienone **7** was prepared from the octalone **11**.[16] Treatment of **11** with lead tetraacetate in acetic acid containing acetic anhydride yielded the acetoxy enone **12** (as a mixture of C-2 epimers) in 44% yield.[17] Compound **12** was hydrolyzed and air oxidized to the 2-hydroxy dienone **13** which was methylated by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol followed by addition of methyl iodide to produce **7** in 60% yield.[18]



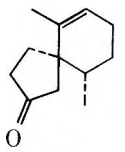
Two somewhat different routes were employed for the conversion of **7** into **6**. The first of these is shown in Scheme I. Irradiation of a 1% solution of **7** in 45% aqueous acetic acid

Scheme I



for 5 h using a 450-W Hanovia high-pressure mercury lamp housed in a quartz probe followed by chromatography of the crude photolysis mixture on silica gel afforded the spiro hydroxy ketone **8a** in 28% yield. The spectral properties of the product were consistent with the assigned structure. They were quite similar to those reported for **10**[14a] if the expected changes resulting from introduction of the C-10 methyl group and substitution of the methoxyl group for the C-2 methyl group were taken into account. In addition to **8a**, significant quantities of unchanged starting material and the hydroxy dienone **13** were isolated. The yield of **8a** was not improved by the use of a Pyrex probe to house the Hanovia lamp or by carrying out the irradiation with a Hanau NK6/20 lamp which emits most of its light at 2537 Å. The use of longer irradiation periods led to the isolation of increased quantities of **13**, which apparently is produced by light-catalyzed hydrolysis of the enol ether function of **7**.[19]

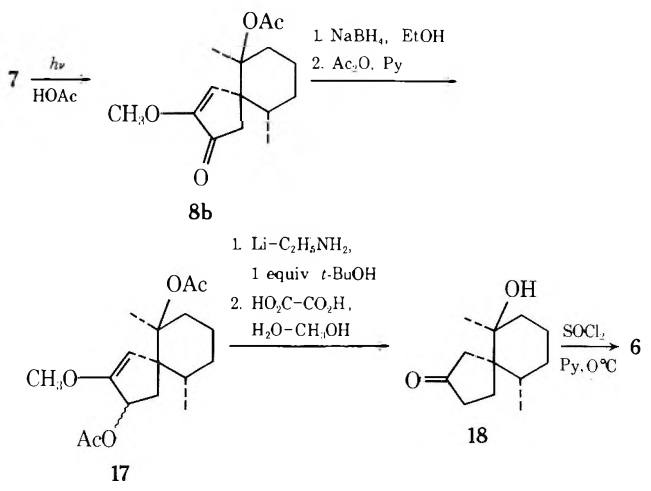
On treatment of **8a** with thionyl chloride in pyridine at 0 °C, the spiro dienone **14** was isolated as the exclusive product in 36% yield. Compound **14** was converted into the enol ether **15** (82% overall yield) by reduction of the carbonyl group with lithium aluminum hydride in ether (inverse addition), acetylation of the resulting mixture of allylic alcohols with acetic anhydride in pyridine, and reductive cleavage of the epimeric mixture of allylic acetates with lithium in ethylamine.[20,21] Examination of models of the allylic anion that would be expected to be involved as an intermediate in the reductive cleavage reaction indicates that protonation at the 3 position leading to **15** should be more favorable sterically than protonation at the 1 position which would yield the corresponding 2,3 isomer. Hydrolysis of **15** with oxalic acid in aqueous methanol afforded **6** in quantitative yield. The product showed ir absorption (film) at 1742 cm^{-1} for a cyclopentanone and lower frequency bands in locations similar to those reported by Marshall and Johnson[2c] for the enone **16**, the epimer of **6** having the 1-methylene group and the 10-methyl group trans. The NMR spectrum (CCl_4) of **6** showed a doublet (J = 6 Hz) at δ 0.93 for the 10-methyl group, a doublet (J = 1.5 Hz) at δ 1.65 for the 6-methyl group, and broad absorption ($W_{1/2}$ ca. 8 Hz) at δ 5.38 for the C-7 olefinic proton. Interestingly, the 1-methylene protons of **6** appear to have almost identical chemical shifts for they give rise to a "singlet" at δ 2.15 at 60 MHz. This absorption appeared as two closely spaced peaks (separation <1 Hz) at 100 MHz and could be attributed to peaks 2 and 3 of an AB quartet centered at δ 2.15. In contrast, the 1-methylene protons of **16** appear as a well-separated AB quartet.[2c]



16

Although the above route proved to be a feasible approach to **6**, the low yields obtained in the photolysis and dehydration steps prompted investigation of another pathway which is shown in Scheme II. The conversion of **7** into a spirocyclic

Scheme II

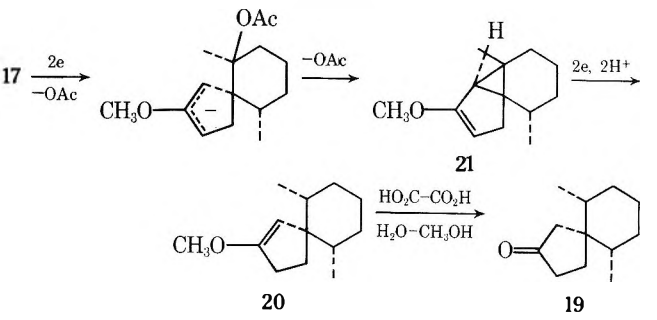


system proceeded much more smoothly when the irradiation was carried out in glacial rather than aqueous acetic acid. The absence of water eliminated the hydrolysis of **7** to **13** and the efficiency of the photochemical rearrangement process was improved significantly as well. Thus the acetoxy ketone **8b** was obtained in 89% yield when a dilute solution of the dienone in glacial acetic acid was irradiated for 3 h using a 450-W Hanovia lamp housed in a Pyrex probe. Again, the spectral properties of **8b** clearly supported the assigned spirocyclic structure.

Although in the conversion of photoproduct **8a** into **6** the 6,7 double bond was introduced as the first step in the sequence, it appeared that a more efficient approach from **8b** would first involve modification of the A ring and then introduction of the B ring double bond as the last step in the sequence. Thus **8b** was converted into a mixture of epimeric diacetates **17** in 81% yield by reduction with sodium borohydride in anhydrous ethanol followed by acetylation of the epimeric mixture of hydroxy acetates with acetic anhydride in pyridine. Treatment of **17** with lithium in ethylamine containing 1 equiv of *tert*-butyl alcohol at −78 °C followed by hydrolysis of the crude reduction mixture with oxalic acid in aqueous methanol gave the hydroxy ketone **18** in 45% yield. A mixture of saturated ketones containing mainly cis-dimethyl compound **19**, which has been obtained as a degradation product of β-vetivone,[2c] was also isolated from this sequence. This product apparently arose from the enol ether **20** which could have been produced by *O*-alkyl cleavage of the tertiary acetate group. *O*-Alkyl cleavage reactions of tertiary acetates have been observed previously in metal–ammonia reductions.[22] However, in this case the pathway shown in Scheme III which involves the formation and reductive cleavage of the vinyl cyclopropane **21** provides a plausible mechanism for the conversion of **17** into **20.**

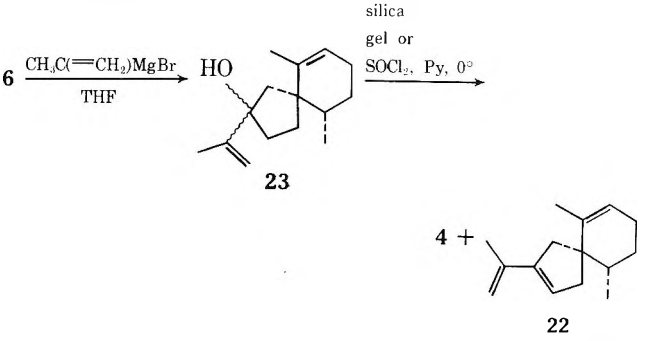
The enone **6** was prepared in ~65% yield by dehydration of **18** with thionyl chloride in pyridine at 0 °C.[23] Despite the occurrence of the side reaction involving hydrogenolysis of the tertiary acetate group in the reduction step, the overall yield

Scheme III



of **6** from **7** by the sequence shown in Scheme II was about 20%. This was more than twice the yield of **6** that was obtained by the route shown in Scheme I.

In order to prepare (±)-α-vetispirene (**4**) from the spiro enone **6** it was necessary to introduce an isopropenyl group at C-2 and to form the 1,2 double bond. It was found that this conversion could be accomplished directly by treatment of **6** with isopropenylmagnesium bromide in dry THF followed by chromatography of the crude reaction mixture on silica gel (Grace, grade 950, mesh size 60–200). In this way the desired natural product **4** and the isomeric triene **22** were obtained in an approximately 3:2 ratio in 35% yield from **6**. Alternatively, if the crude reaction mixture from the Grignard addition step was chromatographed on silica gel that had been prewashed with acetone a mixture of epimeric alcohols having spectral properties consistent with the structure **23** was isolated in approximately 40% yield. This mixture was dehydrated to give a 3:2 mixture of **4** and **22** either on being stirred in a hexane solution with unwashed silica gel or by reaction with thionyl chloride in pyridine at 0 °C.



The isomeric trienes were separated by preparative GLC using a Carbowax column. (±)-α-Vetispirene was eluted first from the column and it exhibited uv, ir, and NMR spectral properties identical with those of the authentic material.[24] The spectral properties of the triene **22** (see Experimental Section) were completely in accord with the assigned structure.

The intermediate spiro ketone **6** clearly has utility for the synthesis of other members of the spirovetivane family and studies along these lines are in progress.

Experimental Section[25]

***trans*-4a,8-Dimethyl-3-acetoxy-3,4,5,6,7,8-hexahydro-2(4a*H*)-naphthalenone (12).** To a solution of 72.6 g (0.41 mol) of **11**[16] in 800 ml of glacial acetic acid containing 60 ml of acetic anhydride was added 300 g (0.68 mol) of lead tetraacetate. The reaction mixture was heated at 60 °C with stirring under nitrogen for 36 h. Approximately 700 ml of acetic acid was then removed by distillation at reduced pressure using a water aspirator and 200 ml of water was added to the residue. The mixture was extracted with three 150-ml portions of ether and the combined ether extracts were neutralized by cautious addition of solid sodium bicarbonate until the evolution of carbon dioxide ceased. The ethereal solution was then washed with two 100-ml portions of water and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo gave a yellow oil which on dis-

tillation under reduced pressure gave 31.0 g of a mixture of 11 and the corresponding cross-conjugated dienone, *trans*-4a,8-dimethyl-5,6,7,8-tetrahydro-2(4a*H*)-naphthalenone, bp 80–120 °C (0.25 mm), and 42.8 g (44%) of **12** as a mixture of the 3α and 3β isomers: bp 120–140 °C (0.25 mm); uv max (95% EtOH) 242 nm (ϵ 12 600); ir ($CHCl_3$) 1720 (acetate), 1691 (α,β-unsaturated ketone), and 1615 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.05 (m, 3 H, 8-CH_3's), 1.25 (s, 2 H, 4a-CH_3), 1.42 (s, 1 H, 4a-CH_3), 2.03 (s, 3 H, 3-OAc), 5.25 (broad t, 1 H, 3α- and 3β-H), and 5.62 ppm (broad s, 1 H, 1-H).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.15, H, 8.53. Found: C, 70.89, H, 8.40.

***trans*-4a,8-Dimethyl-3-methoxy-5,6,7,8-hexahydro-2(4a*H*)-naphthalenone (7).** To a solution of 42.8 g (0.18 mol) of **12** in 300 ml of methyl alcohol was added a solution of 30.0 g (0.54 mol) of potassium hydroxide in 100 ml of water. While a slow stream of oxygen was being passed through the solution, it was stirred for 24 h at room temperature. Approximately 200 ml of methyl alcohol was removed by distillation in vacuo, and 150 ml of water was added to the residue. The aqueous phase was washed with three 50-ml portions of ether and acidified with dilute hydrochloric acid. The acidic mixture was extracted with three 75-ml portions of ether and the combined ether extracts were washed with a saturated solution of sodium chloride and dried over sodium sulfate. The ether was removed in vacuo to give 33.2 g (96%) of crude *trans*-4a,8-dimethyl-3-hydroxy-5,6,7,8-tetrahydro-2-(4a*H*)-naphthalenone (**13**). Recrystallization of this material from ether–hexane gave an analytical sample: mp 100.5–101.5 °C; uv max (95% EtOH) 250 nm (ϵ 14 000) and 288 (3350); NMR (CCl_4) δ 1.17 (d, J = 6 Hz, 3 H, 8-CH_3), 1.28 (s, 3 H, 4a-CH_3), 5.90 (s, 1 H, 4-H), 6.12 (d, J = 1.7 Hz, 1-H), and 6.45 ppm (broad s, 1 H, OH).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.85; H, 8.43.

The crude product (33.0 g) from above was dissolved in 200 ml of *tert*-butyl alcohol and a solution of potassium *tert*-butoxide in *tert*-butyl alcohol (prepared from 28.5 g of potassium and 1 l. of *tert*-butyl alcohol) was added in a thin stream with stirring under nitrogen. The mixture was stirred for 2 h at room temperature and 142.0 g of methyl iodide was added. The mixture was stirred for 1 h at room temperature and then heated at reflux for 30 min. Approximately 500 ml of *tert*-butyl alcohol was removed by distillation and the residue was diluted with 700 ml of water and extracted with four 100-ml portions of ether. The combined ether extracts were washed with one 50-ml portion of 10% aqueous sodium hydroxide and dried over anhydrous sodium sulfate. Removal of the solvent in vacuo afforded an oil which solidified on standing. Recrystallization from ether–hexane gave 23.0 g (64%) of **7**: mp 82.5–83.0 °C; uv max (95% EtOH) 251 nm (ϵ 11 300) and 285 (3300); ir ($CHCl_3$) 1655 (α,β-unsaturated ketone), 1635 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.10 (d, J = 6 Hz, 3 H, 8-CH_3), 1.25 (s, 3 H, 4a-CH_3), 3.57 (s, 3 H, 3-OCH_3), 5.74 (s, 1 H, 4-H), and 5.90 ppm (d, J = 1.7 Hz, 1-H).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69, H. 8.79. Found: C, 75.44; H, 8.61.

Irradiation of 7. A. In Aqueous Acetic Acid. A solution of 12.0 g of **7** in 1.5 l. of 45% aqueous acetic acid was irradiated for 5 h using a 450-W Hanovia lamp housed in a Pyrex probe. A stream of nitrogen was bubbled through the solution for 10 min prior to and during the entire irradiation period. The solvent was removed by lyophilization and the residue was chromatographed on 240 g of silica gel. Elution with 300 ml of each of hexane and 5, 10, 20, and 30% ether–hexane yielded only traces of material and further elution with 300 ml each of 40 and 50% ether–hexane gave 1.23 g of **13**. Elution with 900 ml each of 60 and 70% ether–hexane gave oily products having no clearly defined spectral characteristics while elution with 1200 ml of 80% ether–hexane gave 2.35 g of **7**. Finally, elution with 1 l. of ether and 600 ml of 50% methanol–ether gave 2.93 g (28%, based upon unrecovered starting material) of **8a**: bp 120–125 °C (bath temperature) (0.05 mm); uv max (95% EtOH) 258 mm (ϵ 8300); ir ($CHCl_3$) 1711 (conjugated cyclopentenone), 1626 (conjugated C=C), 1460, 1381, and 1351 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (d, J = 6 Hz, 3 H, 10-CH_3), 1.05 (s, 3 H, 6α-CH_3), 2.16 and 2.72 (AB quartet, J_{AB} = 19.5 Hz, 2 H, 4-CH_2), 3.75 (s, 3 H, 2-OCH_3), and 6.33 ppm (s, 1 H, 1-H).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.94, H, 8.93. Found: C, 69.38, H, 8.70

B. In Glacial Acetic Acid. A solution of 1.00 g (0.0049 mol) of **7** in 290 ml of glacial acetic acid (freshly distilled from molecular sieves) was irradiated with a 450-W Hanovia lamp for 3 h using a Pyrex probe. The solution was agitated with a stream of nitrogen for 10 min prior to and during the entire irradiation period. The solution was washed into a 500-ml round-bottom flask with benzene and frozen, and the solvents were removed by lyophilization to leave light tan crystals. Recrystallization from ether gave 1.15 g (89%) of **8b** as white crystals: mp 123–124 °C; ir ($CHCl_3$) 1720 (ester C=O), 1710 (conjugated cyclopentenone), 1626 (conjugated C=C), 1460, 1370, 1255, 1222, 1169, 1128, 1024, 977, 940, and 755 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (d, J = 6.5 Hz, 3 H, 10-CH_3), 1.37 (s, 3 H, 6-CH_3), 2.03 (s, 3 H, 6-OAc), 2.16 and 2.69 (AB quartet, J_{AB} = 19.5 Hz, 2 H, 4-CH_2), 3.77 (s, 3 H, 2-OCH_3), and 6.22 (s, 1 H, 1-H).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.67; H, 8.27. Found: C, 67.52; H, 8.35.

6,*c*-10-Dimethyl-2-methoxy(*r*-5-*C*^{1})spiro[4.5]dec-1,6-dien-3-one(14).[26] While the temperature was maintained below 7 °C with an ice–salt bath, 8 ml of thionyl chloride was added slowly to a solution of 2.26 g (0.101 mol) of **8a** in 40 ml of pyridine with stirring under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. It was then cooled below 20 °C and 5 ml of water was added dropwise with stirring while the temperature was maintained below 20 °C. An additional 50 ml of water was added and the mixture was extracted with three 50-ml portions of ether. The combined ethereal extracts were washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulfate. The ether was removed in vacuo to give 0.76 g (36%) of **14**: bp 110–115 °C (bath temperature) (0.05 mm); uv max (95% EtOH) 256 nm (ϵ 7900); ir ($CHCl_3$) 1712 (conjugated cyclopentenone), 1632 (conjugated C=C), 1380, 1349, and 982 cm^{-1}; NMR (CCl_4) δ 0.90 (d, J = 6 Hz, 3 H, 10-CH_3), 1.52 (broad s, 3 H, 6-CH_3), 2.20 and 2.32 (AB quartet, J_{AB} = 19 Hz, 2 H, 4-CH_2), 5.52 (m, 1 H, 7-H), and 6.22 (s, 1 H, 1-H); mass spectrum (70 eV) *m/e* 206 (M^+); exact mass calcd, 206.1307; found, 206.1351.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.48; H, 8.60.

2-Methoxy-6,*c*-10-dimethyl(*r*-5-*C*^{1})spiro[4.5]deca-1,6-dienone (15).[26] A solution of 0.152 g (0.004 mol) of lithium aluminum hydride in 10 ml of anhydrous ether was added dropwise with stirring under nitrogen to a solution of 0.298 g (0.0014 mol) of **14** in 30 ml of ether at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and for 1 h at room temperature. A saturated aqueous solution of sodium potassium tartrate was then added dropwise with stirring until no new precipitate was produced on the introduction of fresh reagent. The reaction mixture was filtered with suction and the filter cake was washed with ether. The ethereal filtrate and washings were dried over anhydrous sodium sulfate. The solvent was removed in vacuo to yield 0.281 g (93%) of an oil. The spectral properties of this material showed that it was a ca. 1:1 mixture of C-3 epimers of 3-hydroxy-2-methoxy-6,*c*-10-dimethyl(*r*-5-*C*^{1})spiro[4.5]deca-1,6-diene:[26] ir ($CHCl_3$) 3590 (OH) and 1649 cm^{-1} (C=C); NMR (CCl_4) δ 0.80 and 0.88 (pair of d's, J = 6 Hz, 3 H, 10-CH_3's), 1.30 and 1.47 (pair of d's J = 1.5 Hz, 3 H, 6-CH_3's), 3.60 (s, 3 H, 2-OCH_3), 4.33 (s, 1 H, 1-H), 4.58 (broad t, J = 5 Hz, 1 H, 3-H's), and 5.32 ppm (broad s, 1 H, 7-H); exact mass calcd, 208.146; found, 208.142.

A solution of 0.511 g (0.0025 mol) of the above mixture of alcohols in 20 ml of dry pyridine was treated with 3.7 g of acetic anhydride and stirred at room temperature under nitrogen for 24 h. Water (4 ml) was added and stirring was continued for 1.5 h at room temperature. Forty milliliters of water was then added and the mixture was extracted with two 50-ml portions of ether. The ethereal solution was washed with aqueous sodium bicarbonate and saturated sodium chloride solutions and dried over sodium sulfate. Removal of the solvent in vacuo gave 0.566 g (92%) of a colorless oil. The spectral properties of this material showed that it was a ca. 1:1 mixture of the C-3 epimers of 3-acetoxy-2-methoxy-6,c-10-dimethyl(*r*-5-*C*^{1})spiro[4.5]deca-1,6-diene.[26] This material showed ir ($CHCl_3$) 1726 (OAc), 1648 (C=C), 1366, and 1025 cm^{-1}; NMR (CCl_4) δ 0.85 and 0.90 (pair of d's, J = 6 Hz, 3 H, 10-CH_3's), 1.52 and 1.60 (pair of d's, J = 1.5 Hz, 3 H, 6-CH_3's), 1.97 (s, 3 H, 3-OAc), 3.58 (s, 3 H, 2-OCH_3), 4.55 (s, 1 H, 1-H), 5.36 (m, 1 H, 7-H), and 5.40 and 5.56 ppm (pairs of t's, 1 H, 3-H's); exact mass calcd, 250.157; found, 250.150.

A solution of 0.40 g (0.0057 g-atom) of lithium in ca. 20 ml of dry ethylamine was added dropwise with stirring under nitrogen to a solution of 0.316 g (0.0013 mol) of the above mixture of allylic acetates in 20 ml of dry ethylamine at 16 °C. The addition was continued until the blue color of the metal–amine solution persisted for ca. 20 s after the introduction of a fresh drop of reagent. Then 1 g of ammonium chloride was added immediately. The ethylamine was allowed to evaporate and the residue was washed with 200 ml of ether. Removal of the ether gave 0.24 g (99%) of **15** as a yellow oil, bp 85–90 °C (bath temperature) (0.5 mm), which contained greater than 95% one component on GLC (column A).[25] Compound **15** showed the following spectral properties: ir ($CHCl_3$) 1645 (C=C), 1450, 1376, and 1352 cm^{-1}; NMR (CCl_4) δ 0.78 (d, J = 6 Hz, 3 H, 10-CH_3), 1.49 (d, J = 1.5 Hz, 3 H, 6-CH_3), 3.45 (s, 3 H, 2-OCH_3), 4.13 (t, J = 1 Hz, 1 H, 1-H), and 5.20 (m, 1 H, 7-H); exact mass calcd, 192.151; found, 192.154.

3,*t*-6-Diacetoxy-2-methoxy-*c*-6,*c*-10-dimethyl(*r*-5-*C*^{1})spiro[4.5]dec-1-ene (17).[26] A solution of 6.04 g (0.023 mol) of acetoxy ketone **8b** and 0.863 g (0.023 mol) of sodium borohydride in 60 ml of absolute ethanol was stirred in a 100-ml round-bottom flask at room

temperature for 48 h. Acetone (5 ml) was added, and the solution was stirred for 2 h. The solvents were removed in vacuo, and 100 ml each of ether and water were added to the residue. The layers were separated, the aqueous layer was extracted several times with 20-ml portions of ether, and the combined organic layers were washed with water and dried. Removal of the solvent in vacuo afforded 5.95 g (98%) of a mixture of C-3 epimers of *t*-6-acetoxy-3-hydroxy-2-methoxy-*c*-6,*c*-10-dimethyl(*r*-5-*C*¹)spiro[4.5]dec-1-ene. Recrystallization from ether gave an analytical sample: mp 89–90 °C; ir ($CHCl_3$) 3420 (OH), 1725 (ester C=O), 1648 (C=C), 1447, 1366, 1250, 1168, 1143, 1061, 1040, 827, and 756 cm^{-1}; NMR ($CDCl_3$) δ 0.70 and 0.85 (pair of d's, J = 6.5 Hz, 3 H, 10-CH_3's); 1.33 and 1.47 (pair of s's, 3 H, 6-CH_3's), 1.99 and 2.01 (pair of s's, 3 H, 6-OAc), 3.67 (s, 3 H, 2-OCH_3), 4.43 and 4.46 (pair of s's, 1 H, 1-H), and 4.57 (m, 1 H, 3-H's); exact mass calcd, 268.167; found, 268.163.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.16; H, 8.96. Found: C, 67.23; H, 9.02.

A solution of 2.78 g (0.0104 mol) of the above mixture in 40 ml of dry pyridine was treated with 8 g (0.078 mol) of acetic anhydride, and the solution was stirred under nitrogen at room temperature for 20 h. The reaction mixutre was then cooled to 0 °C, 16 ml of water was added carefully, and stirring was continued for 2 h. The mixture was then poured into 100 ml of ether, the layers were separated, and the aqueous layer was extracted with 50 ml of ether. The combined organic layers were washed with water and dried, and the solvents were removed in vacuo, leaving 3.3 g of pale yellow oil. Chromatography of this material on 60 g of silica gel using hexane–ether as eluent afforded 2.66 g (83%) of a mixture of 3-epimers of the diacetate **17** (20% ether in hexane): ir (film) 1730 (ester C=O), 1650 (C=C), 1446, 1369, 1245, 1170, 1145, 1033, 943, and 831 cm^{-1}; NMR (CCl_4) δ 0.72 and 0.81 (pair of d's, J = 6 Hz, 3 H, 10-CH_3's), 1.32 and 1.40 (pair of s's, 3 H, 6-CH_3's), 1.93 and 1.97 (pair of s's, 6 H, C-3 and C-6 OAc's), 3.63 (s, 3 H, 2-OCH_3), 4.60 (s, 1 H, 1-H), and 5.47 (pair of d's, J = 4.4 Hz, 1 H, 3-H's).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.81; H, 8.39. Found: C, 65.99; H, 8.36.

***t*-6-Hydroxy-*c*-6,*c*-10-dimethyl(*r*-5-*C*¹)spiro[4.5]decan-2-one (18).**[26] In a 250-ml round-bottom flask equipped with magnetic stirrer, dropping funnel, and dry ice condenser 125 ml of ethylamine (freshly distilled from lithium) was collected under nitrogen. The ethylamine was cooled to −78 °C in a dry ice–acetone bath, and a solution of 1.00 g (0.00323 mol) of **17** and 0.239 g (0.00323 mol) of dry *tert*-butyl alcohol in 25 ml of dry ether was added. Then 0.1355 g (0.0194 g-atom) of lithium was added in small, freshly cut pieces. The mixture was stirred for 1.5 h, until the blue color of the lithium in ethylamine solution persisted. After 5 min of additional stirring, the mixture was filtered through glass wool into a flask containing 1 g of solid ammonium chloride, and the flask and funnel were rinsed with dry ether. The solvents were removed in vacuo, 50 ml each of ether and water were added to the residue, and the layers were separated. The aqueous layer was extracted with 50 ml of ether, the combined organic layers were washed with brine and dried, and the ether was removed to leave 0.64 g of an oil which on the basis of NMR and GLC analysis (column A)[25] appeared to be a 2:1 mixture of the desired hydroxy enol ether resulting from cleavage of the allylic acetoxyl group and the corresponding enol ether resulting from reductive cleavage of both the allylic and tertiary acetoxyl groups. This mixture showed the following spectral properties: ir (film) 3460 (OH), 1649 (C=C), 1460, 1365, 1226, 1036, 920, and 805 cm^{-1}; NMR ($CDCl_3$) δ 0.78 (d, J = 6 Hz, C-6 and C-10 CH_3's), 1.09 (s, C-10 CH_3), 3.61 (s, 3 H, OCH_3), and 4.31 ppm (s, 1 H, vinyl H).

A solution prepared from 0.51 g (0.0024 mol) of the crude mixture from above, 0.11 g (0.00122 mol) of oxalic acid, and 22 ml of 60% aqueous methanol was stirred at room temperature for 30 min. Saturated sodium bicarbonate (12 ml) was added and the mixture was extracted with 50 ml of 1:1 benzene–ether. The organic extracts were washed and dried, and the solvents were removed in vacuo to give 0.466 g of yellow oil. Chromatography on silica gel using hexane–ether as eluent afforded 0.151 g of ca. 4:1 mixture of **19** and the corresponding trans dimethyl ketone. The major component of this mixture was collected by GLC (column B)[25] and exhibited identical spectral properties with those reported for **19** by Marshall and Johnson.[2c]

Further elution with 25% ether in hexane gave 0.227 g (43%) of **18**: ir (film) 3470 (OH), 1735 (C=O), 1476, 1458, 1406, 1378, 1254, 1170, 1072, and 919 cm^{-1}; NMR ($CDCl_3$) δ 0.83 (d, J = 6.5 Hz, 3 H, 10-CH_3), 1.15 (s, 3 H, 6-CH_3), and 2.93 (s, 1 H, 6-OH).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.26; H, 10.37.

6,*c*-10-Dimethyl(*r*-5-*C*¹)spiro[4.5]dec-6-en-2-one (6). A. From 18. A solution of 0.224 g (0.00114 mol) of the hydroxy ketone **18** in 4 ml of dry pyridine was placed in a 10-ml round-bottom flask under nitrogen and was cooled to 0 °C in an ice–salt bath. The solution was then treated with 0.5 ml of thionyl chloride dropwise while the temperature was maintained below 5 °C. After the addition was complete the solution was stirred at 0 °C for 75 min, and 6 ml of water was then added dropwise while the temperature of the reaction mixture was maintained between 5 and 15 °C. The mixture was extracted well with 50 ml of ether, the extracts were washed with brine and dried, and the ether was removed to give 0.124 g (61%) of the ketone **6**. Distillation using a micro-Hickman apparatus afforded an analytical sample: bp 83–85 °C (bath temperature) (0.7 mm); ir (film) 1742 (C=O), 1450, 1407, 1377, 1159, 899, and 799 cm^{-1}; NMR (CCl_4) δ 0.90 (d, J = 6 Hz, 3 H, 10-CH_3), 1.65 (d, J = 1.5 Hz, 3 H, 6-CH_3), 2.15 (AB quartet, J_{AB} = 19 Hz, 2 H, 1-CH_2), and 5.37 (s, $W_{1/2}$ = 8 Hz, 1 H, 7-H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.90; H, 10.11. Found: C, 80.69; H, 10.12.

B. From 15. A solution of 0.260 g (0.0013 mol) of **15** in 10 ml of methanol containing 4 ml of water and 0.051 g (0.0005 mol) of oxalic acid was stirred at room temperature for 30 min. A saturated aqueous solution of sodium bicarbonate (5 ml) was added and the mixture was extracted with three 25-ml portions of 1:1 benzene–ether. The organic extracts were dried over sodium sulfate, and the solvent removed in vacuo to yield 0.253 g (100%) of **6** as a pale yellow oil, bp 85–88 °C (bath temperature) (1 mm), which was greater than 95% one component by GLC (column A)[25] and exhibited the same spectral properties as those recorded above.

(±)-α-Vetispirene (4). To a mixture of 1.37 g (0.057 g-atom) of magnesium in 50 ml of dry THF (freshly distilled from $LiAlH_4$) containing a trace of iodine and 15 drops of carbon tetrachloride was added dropwise with stirring under nitrogen 10.18 g (0.084 mol) of freshly distilled isopropenyl bromide. The rate of addition of the halide was adjusted to maintain gentle reflux of the solution during the addition period. When the addition was complete the reaction mixture was allowed to cool to room temperature and then cooled to 3 °C in an ice bath. A solution of 1.13 g (0.0063 mol) of the spiro enone **6** in 6.0 ml of dry THF was added dropwise with stirring under nitrogen while the temperature of the reaction mixture was maintained below 5 °C. When the addition was complete the reaction mixture was stirred at room temperature for 2 h. An aqueous saturated solution of ammonium chloride (50 ml) was then added dropwise at such a rate that the temperature did not go above 50 °C. When the addition was complete the mixture was cooled to room temperature and extracted with two 100-ml portions of ether. The combined ether extracts were washed with 2% aqueous sodium bicarbonate and a saturated solution of sodium chloride and dried over magnesium sulfate. The ether was removed under reduced pressure and the residue was chromatographed on silica gel (Grace, grade 950, mesh size 60–200). Elution of the column with pentane yielded 0.24 g (35% based upon unrecovered **6**) of a colorless oil which by GLC analysis (column C) was found to be composed of (±)-α-vetispirene (**4**) and the isomeric triene **22** in a 3:2 ratio. Further elution of the column with 5% ether–pentane yielded 0.53 g of the starting ketone **6**. None of the expected mixture of epimeric alcohols **21** resulting from simple addition of the Grignard reagent to the ketone was isolated.

In another run starting with 0.15 g of **6**, the crude reaction product was chromatographed on silica gel that had been prewashed with acetone and the acetone removed from the column by elution with hexane before addition of the sample. Elution of the column with 3% ether–hexane gave 0.06 g (~60% based upon unrecovered **6**) of a mixture of epimeric alcohols (**23**). Further elution of the column with ether–hexane mixture gave 0.07 g of the starting ketone **6**. The mixture of alcohols showed the following spectral properties: ir (film) 3450 (OH), 1638 (C=C), 1450, 1376, 898, and 800 cm^{-1}; NMR (CCl_4) δ 0.90 and 1.00 (pair of d's, J = 1.5 Hz, 3 H, 6-CH_3's), 1.83 [d, J = 0.5 Hz, 3 H, -C(CH_3)=CH_2], 4.73 [m, 1 H, -C(CH_3)=CH_2], 4.99 [m, 1 H, J = 0.5 Hz, -C(CH_3)=CH_2], and 5.26 (broad s, $W_{1/2}$ = 8 Hz, 1 H, 7-H); mass spectrum (70 eV) m/e 220 (M^+), 202 ($M^+ - H_2O$), 187 ($M^+ - H_2O$, CH_3), and 178 ($M^+ - CH_3CH{=}CH_2$).

When a solution of approximately 0.100 g of the mixture of the alcohols **23** in 20 ml of pentane was stirred with 6.0 g of unwashed silica gel for 16 h, GLC analysis of the recovered product revealed that dehydration of **23** to produce a 3:2 mixture of **4** and **22** had occurred.

Thionyl chloride (0.092 ml) was added dropwise with stirring under nitrogen to a solution of 0.09 g (0.0004 mol) of the alcohol mixture **23** in 2 ml of dry pyridine while the temperature was maintained at −5 °C with an ice–salt bath. After the addition was complete the solution was stirred at −5 °C for 35 min. Water (5 ml) was added dropwise with stirring while the temperature was maintained below 0 °C. The reaction mixture was extracted with three 10-ml portions of ether and the combined ethereal extracts were washed with 10 ml of a saturated solution of aqueous sodium chloride and dried over sodium sulfate. Removal of the ether by fractional distillation gave 0.065 g (~80%)

of a colorless oil which by GLC analysis (column C) contained **4** and **22** in a ca. 3:2 ratio.

The isomeric trienes were separated by preparative GLC (column B). (±)-α-Vetispirene was eluted from the column first and the sample exhibited uv, ir, and NMR spectral properties identical with those of an authentic sample.[24] The synthetic compound showed the following spectral properties: uv max (95% EtOH) 238 nm (ε 20 600); ir (CCl_4) 3085, 1774, 1630. 884 (C=CH_2); 3045, 3018, 1660, 1597 (CH=C<, conjugated); 1379, 1200, 1076, 1060, and 841 cm^{-1}; NMR (CCl_4) δ 0.86 (d, $J \simeq 6$ Hz, 3 H, 10-CH_3), 1.54 (d, $J = 2$ Hz, 3 H, 6-CH_3), 1.91 [d, $J = 1$ Hz, 3 H, C(CH_3)=CH_2], ~2.50 (10-line multiplet, 2 H, 3-CH_2), 4.86 (br s, 2 H, =CH_2), 5.32 (m, 1 H, 7-H), and 5.45 (br s, $W_{1/2} = 3.5$ Hz, 1 H, 1-H); mass spectrum (70 eV) *m/e* 202 (M^+). The material was shown to be homogeneous on GLC columns A,[25] C,[25] and D.[25] The triene **22** showed uv max (95% EtOH) 237 nm (ε 16 333); ir (CCl_4) 3090, 1770, 1635, 887 (C=CH_2), 3050, 3025, 1655, 1602 (-CH=C<), 1470, 1455, 1382, 1265, and 976 cm^{-1}; NMR (CCl_4) δ 0.85 (d, $J = 6$ Hz, 10-CH_3), 1.56 (d, $J = 2$ Hz, 3 H, 6-CH_3), 1.88 [br s, 3 H, C(CH_3)=CH_2], 4.82 [br s, 2H, C(CH_3)=CH_2], 5.23 (m, 1 H, 7-H), 5.63 (br s, $W_{1/2} = \sim 6$ Hz, 1 H, 3-H); exact mass calcd, 202.1722; found, 202.1728.

Registry No.—**4,** 51196-11-3; **6,** 58406-60-3; **7,** 58355-87-6; **8a,** 58406-61-4; **8b,** 58384-56-8; **11,** 58407-30-0; 3α-**12,** 58355-88-7; 3β-**12,**58355-89-8; **13,** 58355-90-1; **14,** 58355-91-2; **15,** 58355-92-3; c-3-**17,** 58355-93-4; *t*-3-**17,** 58406-62-5; **18,** 58355-94-5; **22,** 58355-95-6; *c*-3-OH-**23,** 58355-96-7; *t*-3-OH-**23,** 58406-63-6; c-3-hydroxy-2-methoxy-6,*c*-10-dimethyl(*r*-5-C[1])spiro[4.5]deca-1,6-diene, 58355-97-8; *t*-3-hydroxy-2-methoxy-6,*c*-10-dimethyl(*r*-5-C[1])spiro[4.5]deca-1,6-diene, 58406-64-7; 3c-acetoxy-2-methoxy-6,c-10-dimethyl(*r*-5-C[1])spiro[4.5]deca-1,6-diene, 58355-98-9; *t*-3-acetoxy-2-methoxy-6,*c*-10-dimethyl(*r*-5-C[1])spiro[4.5]deca-1,6-diene, 58406-65-8; *t*-6-acetoxy-*c*-3-hydroxy-2-methoxy-*c*-6,*c*-10-dimethyl(*r*-5-C[1])spiro-[4.5]dec-1-ene, 58355-99-0; *t*-6-acetoxy-*t*-3-hydroxy-2-methoxy-*c*-6,c-10-dimethyl(*r*-5-C[1])spiro[4.5]dec-1-ene, 58406-66-9.

References and Notes

(1) (a) This investigation was supported by Public Health Service Research Grants GM 15044 from the National Institute of General Medicine and CA 12193 from the National Cancer Institute. (b) Presented in part at the Agricultural and Foods Division Symposium on the Chemistry of Essential Oils, 166th National Meeting of the American Chemical Society, Chicago, Ill., August 1973.

(2) (a) J. A. Marshall, N. H. Andersen, and P. C. Johnson, *J. Am. Chem. Soc.*, **89,** 2748 (1967); (b) J. A. Marshall and P. C. Johnson, *ibid.*, **89,** 2750 (1967); (c) J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, **35,** 192 (1970); (d) For an excellent review, see J. A. Marshall, S. F. Brady, and N. H. Andersen, *Fortschr. Chem. Org. Naturst.*, **31,** 283 (1974).

(3) (a) A. P. Johnson, International Symposium on Synthetic Methods and Rearrangements in Alicyclic Chemistry, Oxford, July 22–24, 1969, Abstracts, p 13; (b) G. Stork, R. L. Danheiser, and B. Ganem, *J. Am. Chem. Soc.*, **95,** 3414 (1973); (c) K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, *Tetrahedron Lett.*, 4963 (1973); (d) G. Bozzato, J.-P. Bachmann, and M. Pesaro, *J. Chem. Soc., Chem. Commun.*, 1005 (1974); (e) W. G. Dauben and D. J. Hart, *J. Am. Chem. Soc.*, **97,** 1622 (1975); (f) M. Deighton, C. R. Hughes, and R. Ramage, *J. Chem. Soc., Chem. Commun.*, 662 (1975).

(4) (a) J. A. Marshall and S. F. Brady, *Tetrahedron Lett.*, 1387 (1969); *J. Org. Chem.*, **35,** 4068 (1970); (b) K. Yamada, K. Aoki, H. Nagase, Y. Hayakawa, and Y. Hirata, *Tetrahedron Lett.*, 4967 (1973).

(5) M. Mongrain, J. Lafontaine, A. Belanger, and P. Deslongchamps, *Can. J. Chem.*, **48,** 3273 (1970).

(6) P. M. McCurry and R. K. Singh, *Tetrahedron Lett.*, 3325 (1973).

(7) The synthetic approaches reported by Dauben and Hart[3e] and by Yamada and co-workers[3c,4b] are particularly useful since they proceed via intermediates suitable for conversion into a variety of these substances.

(8) Anhydro-β-rotunol in a stress metabolite recently isolated from blight infected potato tubers; see D. T. Coxon, K. R. Price, and B. Howard, *Tetrahedron Lett.*, 2921 (1974).

(9) H. Hikino, K. Atoa, D. Kuwano, and T. Takemoto, *Tetrahedron*, **27,** 4831 (1971).

(10) D. Caine and C.-Y. Chu, *Tetrahedron Lett.*, 703 (1974).

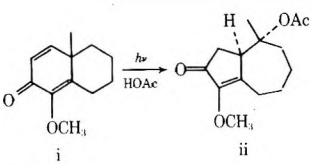
(11) (a) P. C. Mikharji and P. K. Sen Gupta, *Chem. Ind. (London)*, 533 (1970); (b) A. Ogiso, M. Kurabyashi, and H. Nagahori, *Chem. Pharm. Bull.*, **18,** 1283 (1970); (c) P. M. McCurry, Jr., *Tetrahedron Lett.*, 1845 (1971); (d) P. M. McCurry, R. K. Singh, and S. Link, *ibid.*, 1155 (1973).

(12) For a preliminary report describing the synthesis of **6,** see D. Caine and J. B. Dawson, *Chem. Commun.*, 1232 (1970).

(13) α-Vetispirene was first isolated from oil vetiver by Andersen and coworkers; see N. H. Andersen, M. S. Falcone, and D. D. Syrdal, *Tetrahedron Lett.*, 1759 (1970).

(14) (a) P. J. Kropp, *J. Am. Chem. Soc.*, **86,** 4053 (1964). (b) For reviews on the photochemistry of cross-conjugated cyclohexadienones, see P. J. Kropp, *Org. Photochem.*, **1,** 1 (1967); K. Schaffner, *Adv. Photochem.*, **4,** 81 (1966).

(15) (a) We have found that the 4-methoxy dienone i yields the 5/7-fused acetoxy ketone ii on irradiation in glacial acetic acid, and that similar behavior is exhibited by 6/5-fused dienones related to i.[15b] These results, which showed



i ii

that the photochemical behavior of 4-methoxy dienones is similar to that of the corresponding methyl compounds,[15c] provided strong indications that the rearrangement of **7** would proceed in the desired manner. (b) D. Caine and F. N. Tuller, *J. Am. Chem. Soc.*, **93,** 6311 (1971); *J. Org. Chem.*, **38,** 3663 (1973); (c) D. Caine and J. B. Dawson, *J. Org. Chem.*, **29,** 3108 (1964); P. J. Kropp, *ibid.*, **29,** 3110 (1964).

(16) (a) J. A. Marshall and D. J. Schaffer, *J. Org. Chem.*, **30,** 3642 (1965); (b) D. Caine and F. N. Tuller, *ibid.*, **34,** 222 (1969).

(17) E. Seeback and T. Reichstein, *Helv. Chim. Acta*, **27,** 948 (1944).

(18) P. N. Rao and L. D. Axelrod, *J. Am. Chem. Soc.*, **82,** 2830 (1960).

(19) T. N. Huckerly, N. A. J. Rogers, and A. Salter, *Tetrahedron Lett.*, 1113 (1967).

(20) A. S. Hallsworth, H. B. Henbest, and T. L. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(21) For the employment of similar procedure for the conversion of α-methoxy conjugated enones into enol ethers, see ref 15b and R. E. Ireland, D. R. Marshall, and J. W. Tilley, *J. Am. Chem. Soc.*, **92,** 4754 (1970).

(22) P. Blandon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, and G. H. Woods, *J. Chem. Soc.*, 125 (1954).

(23) (a) An exocyclic double bond isomer was reported to be formed as a minor product in the preparation of the spiro enone **16** by dehydration of a spiro hydroxy ketone related to **18** with thionyl chloride in pyridine.[23b] However, in several runs we did not obtain evidence for the formation of the exocyclic double bond isomer of **6** under similar conditions. It is possible that this isomer was formed but was isomerized to **6** or selectively decomposed under our isolation conditions.
Several other methods of dehydration of **18** were investigated. For example, reaction of this hydroxy ketone with (carboxysulfanoyl)triethylammonium hydroxide inner salt methyl ester[23c] in acetonitrile at 40 °C gave a 96% yield of olefinic product. However, examination of the NMR spectrum of this material revealed that it was a ca. 2:1 mixture of **6** and the corresponding exocyclic methylene derivative. Unfortunately, we could not effect the separation of the components of this mixture by distillation or column chromatography on silica gel or alumina. On standing at room temperature in chloroform in the presence of a trace of trifluoroacetic acid the 2:1 mixture of **6** and its isomer was converted into an approximately 8:1 mixture of the two compounds. However, under the reaction conditions acid-catalyzed rearrangement of **6** into the octalone **11**[12] occurred to some extent. Therefore, this method of dehydration was not investigated further. (b) J. A. Marshall and P. C. Johnson, *J. Am. Chem. Soc.*, **89,** 2750 (1967). (c) E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Org. Chem.*, **38,** 26 (1973).

(24) We are grateful to Professor Niels H. Andersen for making copies of the ir, NMR, and uv spectra of natural α-vetispirene available to us.

(25) Melting points and boiling points are uncorrected. Infrared spectra were taken on Perkin-Elmer Model 457 or 137 infrared spectrophotometers. Ultraviolet spectra were taken on a Cary Model 14 or a Beckman DBGT recording spectrophotometer using 1-cm matched quartz cells. NMR spectra were determined at 60 MHz with a Varian A-60 or a Varian T-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-7 or a Varian M-66 spectrometer. Microanalyses were obtained by Galbriath Laboratories, Inc., Knoxville, Tenn., or by Atlantic Microlab, Inc., Atlanta, Ga. Gas–liquid chromatography was carried out using a Perkin-Elmer 881 or an Aerograph A-90-P3 gas chromatograph. The following columns were used: A (6 ft × 0.125 in., 10% Carbowax K-20 on Chromosorb W); B (10 ft × 0.25 in., 20% Carbowax K-20M on Chromosorb W); C (6 ft × 0.125 in., 20% Carbowax K-20M on Chromosorb W); D (6 ft × 0.125 in., 10% SE-30 on Chromosorb W).

(26) For an explanation of the nomenclature used here, see ref 2c, footnote 16d.

Stereochemistry of Diphenylphosphide Displacement at Saturated Carbon. Conformation and Relative Reactivity of Menthyl- and Neomenthyldiphenylphosphine Homogeneous Hydrogenation Complexes

A. M. Aguiar*[1a,b] and C. J. Morrow

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

J. D. Morrison,*[1a] R. E. Burnett, and W. F. Masler

Department of Chemistry, Parsons Hall, University of New Hampshire, Durham, New Hampshire 03824

N. S. Bhacca*[1a]

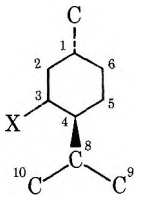
Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

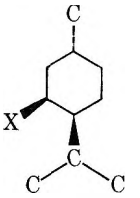
Received June 13, 1975

Menthyl and neomenthyl chloride react with alkali metal diphenylphosphides to produce epimeric, tertiary phosphines with inversion of configuration. The stereochemistry and conformation of the products neomenthyldiphenylphosphine (NMDPP) and menthyldiphenylphosphine (MDPP) were determined by ^{1}H NMR and ^{13}C NMR spectroscopy. Conformational and configurational differences between NMDPP and MDPP are also reflected in their behavior as chiral ligands in asymmetric homogeneous hydrogenation systems. Rh(I) complexes prepared from these epimers showed differences in both activity and the direction and degree of asymmetric induction when used as catalysts for the homogeneous hydrogenation of α-methylcinnamic acid.

In previously reported studies on the chemistry of lithium diphenylphosphide[2] it has been established that vinyl halides undergo stereospecific displacement with retention of configuration to give vinyldiphenylphosphines. Thus, reaction of lithium diphenylphosphide with *cis*- and *trans*-1,2-dichloroethanes leads to *cis*- and *trans*-1,2-vinylenebisdiphenylphosphines, respectively,[3] while *cis*- and *trans*-β-bromostyrenes provide *cis*- and *trans*-β-styryldiphenylphosphines, respectively.[4] Both of these results were established through characterization of the corresponding phosphine oxides. The latter work showed that the displacement occurred with retention of configuration rather than by two successive inversions as would be possible in the former case.

We now wish to report that nucleophilic replacement of halide ion from a saturated carbon by the diphenylphosphide moiety occurs with inversion of configuration at carbon as is found in normal SN2 displacements. Reaction of menthyl chloride (**1**) or menthyl bromide (**2**) with lithium, sodium, or potassium diphenylphosphide provided a compound that has been shown by 220-MHz proton NMR and by ^{13}C NMR to have the neomenthyldiphenylphosphine (NMDPP) structure (**3**). Conversely, treatment of neomenthyl chloride (**4**) with an alkali metal diphenylphosphide gives the epimeric menthyldiphenylphosphine (MDPP, **5**). Oxidation of **3** and **5** with 3% hydrogen peroxide produces the corresponding phosphine oxides **6** and **7**, respectively, and NMR spectra of the oxides confirm the above stereochemical conclusions.





1, X = Cl **7**, X = Ph_2P=O **3**, X = Ph_2P
2, X = Br **8**, X = OH **4**, X = Cl
5, X = Ph_2P **9**, X = H **6**, X = Ph_2P=O

Reaction of the menthyl and neomenthyl halides with lithium diphenylphosphide in refluxing THF solution was found to be quite sluggish when compared with the reaction of an unhindered secondary alkyl halide such as cyclohexyl chloride. Refluxing a mixture of **1** with lithium diphenylphosphide in a 1:1 molar ratio required at least 24 h to completely dissipate the characteristic red phosphide anion color while the reaction of cyclohexyl chloride with lithium diphenylphosphide is complete within 3 h. The reaction time can be reduced to about 12 h if a large excess of the menthyl halide is used.

It is not yet clear if the replacement of a halide bonded to a tetrahedral carbon with inversion of configuration is a general phenomenon. The fact that lithium, sodium, and potassium diphenylphosphide give the same result indicates that the mechanism of replacement is different for vinyl halides than for alkyl halides. This is true because a mixture of products is obtained with sodium diphenylphosphide in the reaction of the vinylenebis dichlorides and β-bromostyrenes. It cannot be definitively concluded that there is a displacement of the alkyl halide by a "diphenylphosphide ion" because potassium diphenylphosphide, with its more ionic metal to phosphorus bond, is not as effective as the sodio compound.

In another report, synthetic procedures for NMDPP and MDPP are detailed for the reaction of sodium diphenylphosphide with the appropriate chloride.[5] The choice of sodium diphenylphosphide was dictated by the results of comparative yield experiments with lithium, sodium, and potassium diphenylphosphide and menthyl chloride. The NMDPP yield ratios were 1:1.55:1.16, respectively, when the reactions were carried out according to a standard procedure.[5]

The orientations of substituents occurring on the cyclohexane rings in **3**, **5**, **6**, and **7** were deduced by ^{1}H NMR and ^{13}C NMR spectroscopy. The line widths of the ^{1}H NMR resonances representing H-3 in **5** and **7** are much greater than those of H-3 in **3** and **6** because the multiplicity occurring in the former absorptions is caused by the spin–spin interactions of axial–axial as well as axial–equatorial protons, whereas in the latter case the fine structure was due to equatorial–axial and equatorial–equatorial couplings. The ^{1}H NMR data therefore indicate that the diphenyl phosphine and the diphenyl phosphine oxide groups occupy equatorial positions in **5** and **7** but axial orientations in **3** and **6**.

Table I. 25.2-MHz ^{13}C NMR Spectral Data for Menthyl and Neomenthyl Compounds

Carbon atoms	5 Menthyl phosphine[a]	3 Neomenthyl phosphine	7 Menthyl phosphine oxide	6 Neomenthyl phosphine oxide	9 Menthane[b]	8 Menthol[b]
1	34.0 (2.5)[c]	27.7 (5.8)	33.6 (13.3)	28.5 (2.5)	36.0	32.2
2	37.9 (1.3)	39.5 (2.5)	36.6 (1.9)	38.6 (0.5)	33.4	45.9
3	38.2 (21.8)	35.8 (19.9)	39.6 (70.5)	37.0 (68.1)	30.2	71.2
4	45.7 (13.1)	50.3 (15.8)	43.8 (3.1)	50.5 (2.4)	44.4	50.7
5	25.9 (8.8)	26.4 (9.8)	25.2 (12.0)	26.0 (1.7)	30.2	23.8
6	35.3	36.3	34.7 (1.3)	36.2	33.2	35.3
7	22.6	22.7	22.6	22.8	22.8	22.6
8	28.5 (20.5)	30.1 (9.6)	28.5 (3.2)	29.9 (2.5)	36.0	26.1
9	15.5 (1.2)	22.4 (1.2)	16.0	22.7	19.3	16.3
10	21.7	21.2 (0.9)	21.8	21.4	19.3	21.3

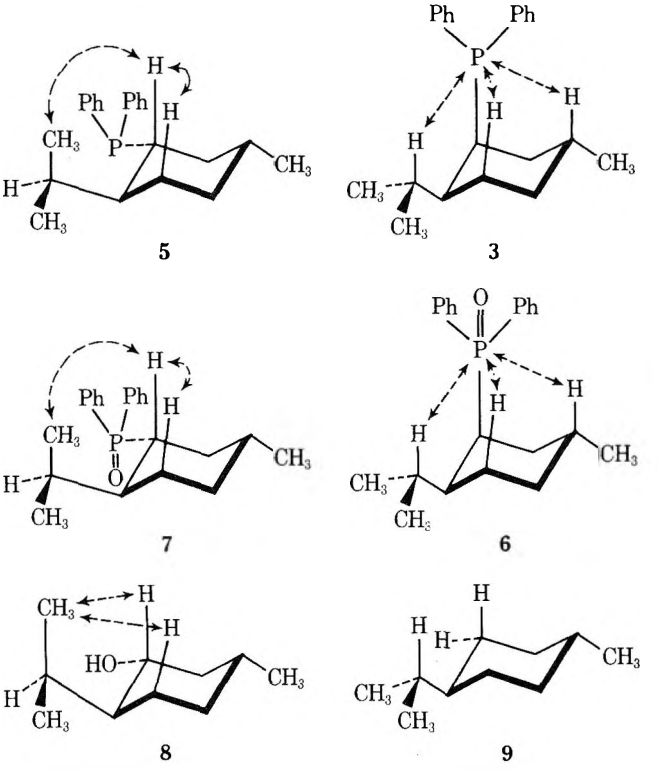
[a] Expressed in parts per million relative to internal Me_4Si. [b] Obtained from J. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 288 (1970), by converting the chemical shift data from (relative to CS_2) to Me_4Si by subtracting their value from 192.8 ppm. [c] The $^{13}C-^{31}P$ coupling constants are recorded in parentheses. J and δ are estimated to be accurate to ±1 Hz or ±0.04 ppm.

^{13}C NMR spectral data not only confirm the above conclusions but also help resolve the location of the isopropyl group at C-4 and the secondary methyl group at C-1 in the four compounds. These latter determinations were achieved by comparing the ^{13}C chemical shifts of carbon atoms occurring in the four compounds with those of menthol (**8**) and methane (**9**) and then correlating the ^{13}C NMR spectral data with the well-known fact that the 1,3-diaxial type steric interaction causes upfield shifts in the resonances of the interacting ^{13}C nuclei. Comparison of the ^{13}C chemical shift of the methyl carbons C-7, -9, and -10 (see Table I) indicates that they are very similar in **5**, **7**, and **8** and, since the orientation of the isopropyl and methyl groups in **8** is known to be equatorial, it is reasonable to assume that these groups in **5** and **2** must also occupy the same positions, namely equatorial. The upfield shifts observed in the resonance positions of C-9, C-5, and C-8 in **5**, **7**, and **8** (see Table I) in relation to the ^{13}C signals of respective carbon atoms in **9** are attributed to the steric interactions as depicted in the structures of **5** and **7** (see Chart I). In **3** and **6** where diphenylphosphine and diphenylphosphine oxide groups at C-3 have axial orientations, steric interactions between C-9 methyl and C-5 axial protons (present in **5**, **7**, and **8**) do not occur and as a result C-9 resonances experience downfield shifts in **3** and **6**. These observations, coupled with the fact that the chemical shifts of C-7 and C-10 in **3** and **6** are very similar (see Table I) to those of the respective carbon atoms in **5**, **7**, and **8**, clearly suggest that the substituents at C-1 and C-4 in **3** and **6** have the same stereochemistry as in **5**, **3**, **7**, and **8**. The variance of the resonance positions of C-1, C-5, and C-8 in **3** and **6** as compared to **5** and **7** (see Table I) is largely due to the various steric interactions represented in the conformational drawings of the respective compounds (see Chart I). The dissimilarity in the chemical shifts of C-3, C-2, and C-4 signals in **3**, **5**, **6**, **7**, and **8** (see Table I) is due to the α and β, effects caused by differences in the electronegativities of the substituents at C-3 as well as the steric interactions shown in Chart I.

The configurational and conformational differences between NMDPP (**3**) and MDPP (**5**) are reflected in their behavior as ligands in homogeneous hydrogenation systems. Previously we reported that NMDPP was effective as a chiral ligand in soluble Rh(I) hydrogenating complexes.[6] Both NMDPP and MDPP have been utilized as ligands in asymmetric hydrosilylations catalyzed by metal complexes.[7] In the latter reaction they induce opposite chiralities.

The reduction of α-methylcinnamic acid was studied in order to evaluate possible differences between these epimeric ligands both with respect to the activity of Wilkinson-type hydrogenation catalysts derived from them and the chiral sense of their asymmetric influence.

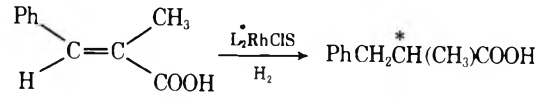
Chart I. Conformational Drawings of Compounds Used in NMR Studies Showing 1,3-Diaxial Type Interactions



In order to promote appreciable reduction in a reasonable period of time extended conditions (higher temperature and pressure) compared to the typical Wilkinson catalyst conditions were used. Extended conditions are necessary to ensure the reduction of more hindered olefinic substrates. To further promote reduction, triethylamine was added to the reaction to convert the substrate to a carboxylate anion which is reduced more rapidly than the free acid.[8] The precise reaction conditions are summarized in Chart II and in the Experimental Section.

In a 24-h period a Rh(I) catalyst (presumably $RhL_2{}^*ClS$ in solution, where L* is the chiral tertiary phosphine ligand and S is a solvent molecule[9]) prepared from NMDPP produced about 1.5 times the amount of reduction of α-methylcinnamic acid as did a similar catalyst system from MDPP (Chart II). The epimeric catalysts produced enantiomeric products and the percent enantiomeric excess (%

Chart II. Comparative Yields and Stereochemistries for Hydrogenations with NMDPP and MDPP Catalysts



L*	24-h yield, %	% ee
NMDPP	100	60 (*R*)
MDPP	67	17 (*S*)

ee = % *R* − % *S* or vice versa) was more than three times greater for the NMDPP catalyst.

The lower activity of the MDPP catalyst may reflect a stronger binding of the ligand to the rhodium in this case as compared to NMDPP. Models suggest that the phosphorus in MDPP is less hindered than that in NMDPP and therefore NMDPP may dissociate more readily to give the coordinately unsaturated intermediate required for catalytic activity.[10] This effect may be accentuated under the relatively high ligand loadings (L*:Rh = 15:1) used in these extended condition experiments.

Experimental Section

Lithium diphenylphosphide was prepared from diphenylphosphinous chloride and lithium metal in dry tetrahydrofuran (THF) solution under a nitrogen atmosphere following the method of Aguiar and Archibald.[2b]

Neomenthyldiphenylphosphine (3).[11] To a nitrogen-filled flask containing a solution of 6.01 g (0.035 mol) of (−)-menthyl chloride in 25 ml of THF was added 17 ml of a solution of lithium diphenylphosphide in THF prepared from 0.030 mol of diphenylphosphinous chloride and 0.12 mol of lithium. The mixture was refluxed for 26 h after which a yellow solution and a white precipitate had replaced the characteristic red color of the lithium diphenylphosphide. The mixture was poured into 50 ml of water and the phosphine was extracted into ether. The ether solution was dried (Na_2SO_4) and evaporated, and the residual oil was kept under nitrogen in a refrigerator for 60 h during which time crystals had separated. These were filtered and washed with methanol, yield 1.16 g (10%). In other preparations the phosphine was vacuum distilled, bp 165–170 °C (0.2 mm), then recrystallized repeatedly from petroleum ether (bp 30–60 °C), ir ν_{max} ($CHCl_3$) 1432 cm^{-1} (no absorptions near 1180 or 1120 cm^{-1}). The phosphine was further characterized as the benzylneomenthyldiphenylphosphonium bromide prepared by reaction of 1.2 g of the phosphine with 6.0 g of benzyl bromide for 14 h at ambient temperature followed by 3 h at reflux. The excess benzyl bromide was removed in vacuo and ether was added to the residue. A white solid formed which was recrystallized from benzene–acetonitrile, mp 220–223 °C, ir ν_{max} ($CHCl_3$) 1437, 1106 cm^{-1}.

Neomenthyldiphenylphosphine Oxide (6). To a nitrogen-filled flask containing 0.016 mol of lithium diphenylphosphide prepared from 0.35 g of lithium and 2.3 ml of diphenylphosphinous chloride in 30 ml of THF was added 2.0 g (0.012 mol) of (−)-menthyl chloride in 15 ml of THF. The solution was refluxed for 24 h until the characteristic red color of the phosphide had dissipated and a yellow solution containing a white precipitate remained. The mixture was poured into 50 ml of 3% hydrogen peroxide and the organic solvent phase was allowed to evaporate. Crystals formed at the phase interface which were filtered off and recrystallized from ethanol. The yield was 1.2 g, 31%. Further recrystallization from hexane–benzene provided the oxide having mp 217–221 °C, ir ν_{max} ($CHCl_3$) 1433, 1175, 117 cm^{-1}.

(*E*)-α-Methylcinnamic Acid.[13] Benzaldehyde (106 g, 1 mol), sodium acetate (82.0 g, 1 mol), and propionic anhydride (160 g, 1.23 mol) were heated at reflux for 35 h. The reaction mixture was then poured onto ice and acidified with hydrochloric acid. The acid solution was extracted with ether. The ether extract was extracted with 2 M sodium hydroxide solution and the basic extract was, in turn, washed with ether and then acidified. The crude product separated as an oil and was extracted into ether. The ether extract was washed with water, dried, and concentrated to give an oil which crystallized on standing. The crude acid was recrystallized from 60–80 °C petroleum ether in three crops, total yield 128.1 g (79%), mp 80–81 °C.

Asymmetric Hydrogenations. A homogeneous catalyst solution was prepared by stirring (30 min) a mixture of $[Rh(COD)Cl]_2$[12] (16.6 mg, 33.7 μmol) and either NMDPP or MDPP (171 mg, 95% phosphine, 5% phosphine oxide, 0.5 mmol phosphine) in 1:1 (v/v) benzene–ethanol (100 ml, freshly deoxygenated with nitrogen) under 3.5 atm of hydrogen. The prereduced catalyst solution was added to a solution of (*E*)-α-methylcinnamic acid (4.05 g, 25 mmol) and triethylamine (0.4 g, 4 mmol) in deoxygenated 1:1 benzene–ethanol (100 ml). The resulting reaction mixture was hydrogenated at 300 psi and 60 ± 5° for 24 h.

Hydrogenation with NMDPP Catalyst. After the reduction period the reaction mixture was evaporated under vacuum and the residue was partitioned between 10% sodium hydroxide (50 ml) and methylene chloride (50 ml). The aqueous layer was separated, washed with ether, and then acidified with hydrochloric acid. The acidified solution was extracted twice with 30-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated to give a crude acid product (3.85 g, 94%). The NMR spectrum was that of 2-methyl-3-phenylpropanoic acid and there were no signals characteristic of unreduced substrate. The crude acid was distilled, bp 99–107 °C (0.4 mm), 3.7 g (90%), $[\alpha]^{19}D$ −16.2 °C (*c* 11.59, benzene), which corresponds to a 60% ee of the *R* isomer based on $[\alpha]^{20}D$ 27.02° for the pure enantiomer.[14]

Hydrogenation with MDPP Catalyst. This reduction was carried out in exactly the same manner as that with NMDPP. The crude acid product (3.9 g) was shown by NMR to contain about 67% 2-methyl-3-phenylpropanoic acid and 33% unreacted α-methylcinnanic acid. The crude acid mixture was distilled, bp 92–94 °C (0.02 nm), to give 1.8 g of a mixture containing 94.4% 2-methyl-3-phenylpropanoic acid and 5.6% starting material. This mixture had $[\alpha]^{21}D$ +4.3° (c 11.08, benzene) which corresponds to 15.9% ee, or 16.8% ee correcting for the amount of achiral starting material present on the assumption that it has only a dilution effect on the rotation.

Acknowledgment. J.D.M., R.E.B., and W.F.M. thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of the portion of this research carried out at the University of New Hampshire. A.M.A. and C.J.M. thank the National Science Foundation and the National Institutes of Health for support of the portion of this work done at Tulane University.

Registry No.—**1**, 16052-42-9; **3**, 43077-29-8; **4**, 13371-12-5; **5**, 43077-31-2; **6**, 43077-30-1; **7**, 43077-32-3; $L_2RhClOEt$, 58191-29-0; (*E*)-α-methylcinnamic acid, 1895-97-2; benzaldehyde, 100-52-7; propionic anhydride, 123-62-6; lithium diphenylphosphide, 58191-08-5; (*R*)-2-methyl-3-phenylpropanoic acid, 14367-67-0; (*S*)-2-methyl-3-phenylpropanoic acid, 14367-54-5.

Supplementary Material Available. ^{13}C NMR figures for compounds **3**, **5**, **6**, and **7** (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Requests for additional information should be directed as follows: concerning phosphide displacements (A.M.A.); NMR data and analysis (N.S.B.); homogeneous hydrogenation experiments (J.D.M.). (b) Department of Chemistry, Rutgers University, Newark, N.J. 07102.
(2) (a) A. M. Aguiar, J. Beisler, and A. Mills, *J. Org. Chem.*, **27**, 1001 (1962); (b) A. M. Aguiar and T. G. Archibald, *Tetrahedron Lett.*, 5541 (1966).
(3) A. M. Aguiar and D. Daigle, *J. Am. Chem. Soc.*, **86**, 2299 (1964).
(4) (a) A. M. Aguiar and D. Daigle, *J. Org. Chem.* **30**, 2826 (1965); (b) *ibid.*, **30**, 3527 (1965).
(5) J. D. Morrison and W. F. Masler, *J. Org. Chem.*, **39**, 270 (1974).
(6) J. D. Morrison, R. E. Burnett, A. M. Aguiar, C. J. Morrow, and C. Phillips, *J. Am. Chem. Soc.*, **93**, 1301 (1973).
(7) Y. Kiso, K. Yamamoto, K. Tamao, and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4373 (1972).
(8) (a) W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *J. Chem. Soc., Chem. Commun.*, 10 (1972); *Chem. Technol.*, 590 (1972) (b) H. B. Kagan and T.-P. Dang, *J. Am. Chem. Soc.*, **94**, 6429 (1972).
(9) R. E. Harmon, S. K. Gupta, and D. J. Brown, *Chem. Rev.*, **73**, 21 (1973).
(10) B. R. James, "Homogeneous Hydrogenation", Wiley, New York, N.Y., 1973, Chapter XI.
(11) The procedure described here is an alternative to the sodium diphenylphosphide reaction described elsewhere.[5] The latter procedure gives higher yields.
(12) J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, 4735 (1957).
(13) L. Edeleano, *Ber.*, **20**, 616 (1887).
(14) R. H. Pickard and J. Yates, *J. Chem. Soc.*, **95**, 1011 (1909).
(15) **Note Added in Proof.** Since completion of our study and its submitted for publication, an article by F. Bohlmann, R. Zeisberg, and E. Klein, *Org. Magn. Reson.*, **7**, 426 (1975), tends to confirm our ^{13}C spectral assignments of the four new compounds.

Structure and Sterochemistry of Phospholene Sulfides from Reaction of Hydrogen Sulfide with Diene–Phosphonous Dihalide Cycloadducts[1]

Courtland Symmes, Jr., and Louis D. Quin*

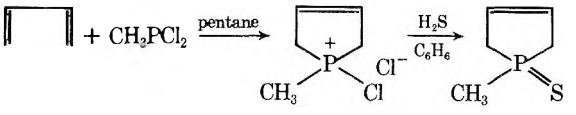
Department of Chemistry, Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received November 4, 1975

The cycloadduct (a 1-halophospholenium halide) from butadiene and methylphosphonous dichloride reacts smoothly with hydrogen sulfide to form 1-methyl-3-phospholene sulfide, rearrangeable with base (in part) or acid (complete) to the isomeric 2-phospholene sulfide. The chloroprene cycloadduct treated with H_2S gave exclusively the 2-phospholene sulfide; the chlorine was replaceable by methoxide ion to form the enol ether, which was easily hydrolyzed to 1-methyl-3-phospholanone sulfide. The piperylene cycloadduct gave exclusively *cis*-1,2-dimethyl-3-phospholene sulfide, and 1-vinylcyclohexene gave a single bicyclic phospholene sulfide shown spectroscopically also to have cis structure. Likewise, 1-(1-bromovinyl)cyclohexene gave a single sulfide stereoisomer, presumably cis. The hydrogen sulfide reaction therefore differs considerably from hydrolysis which gives variable mixtures of cis, trans isomers. ^{13}C NMR spectra of several sulfides were determined; notable is the strong deshielding of the 3 carbon of a 2-phospholene sulfide, possibly a result of delocalization of the π electrons into phosphorus d orbitals.

The McCormack cycloaddition[2] of dienes with trivalent phosphorus halides has provided the major pathway to derivatives of the phospholene ring system for many years. The cycloadducts are generally hydrolyzed to the more stable phosphine oxides as a preliminary step before performing other chemical transformations. McCormack mentioned in one of his patents[3] that phospholene sulfides were formed on addition of hydrogen sulfide to the cycloadducts, but only one example (from $C_6H_5PCl_2$ and isoprene) was given and the literature is devoid of any other mention of this reaction. We have previously examined the double bond[4] and cis, trans isomerism[5] in certain phospholene oxides formed from the McCormack adducts and now have applied our methods to the phospholene sulfides resulting from the hydrogen sulfide reaction. In working with the sulfides, we have found that they have much more desirable properties than the corresponding oxides. They are less polar, and accordingly have solubility in a more useful range of organic solvents. Furthermore, they are nonhygroscopic, and are quite easy to handle. The phospholene sulfides have also recently been approached by another route,[6] the reaction of McCormack-derived phospholene oxides with phosphorus pentasulfide.

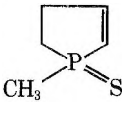
The butadiene–methylphosphonous dichloride adduct, as a slurry in benzene, reacted smoothly with gaseous hydrogen sulfide. A clear solution resulted when the reaction was complete. The solid sulfide (**1**) was recovered in 66% yield after recrystallization. The ^1H NMR spectrum agreed with that



1

reported by Moedritzer;[6] it was very much like that of the oxide,[4] and left no doubt that the double bond was in the 3 position. Thus, the olefinic protons gave a 2 H doublet with the expected large coupling to ^{31}P (28 Hz). As for the hydrolysate of the same cycloadduct,[4] there was no indication of any 2-phospholene isomer in the reaction product.

The double bond of **1** could be rearranged by heating with potassium *tert*-butoxide. The product then consisted of a 1:1 mixture of **1** and 2-phospholene sulfide **2**. The oxide also is

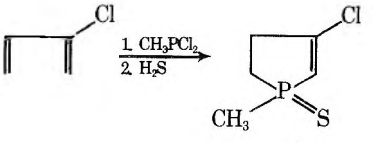


2

reported to give such a mixture with the same base.[6] However, heating **1** in 48% hydrogen bromide (in an unsuccessful attempt to add HBr to the double bond) gave virtually complete rearrangement to **2**.

^{13}C NMR spectra (Table I) of the isomers **1** and **2** reveal an important electronic effect of the thiophosphoryl group on the double bond; in the 2 isomer (**2**), the β-olefinic carbon is deshielded by 19.4 ppm relative to the α carbon. We believe that this is the first instance of the observation of this strong ^{13}C effect for a vinyl phosphine sulfide. The effect is only slightly weaker than that in the corresponding phospholene oxide (23.8 ppm, Table I), and, as pointed out elsewhere,[7] is consistent with diminished electron density on this carbon through delocalization of the π electrons into a phosphorus d orbital. The strong deshielding of all α carbons, as expected from the behavior of noncyclic phosphine sulfides,[8] was observed. The large ^{31}P–^{13}C coupling constants for the α carbons aided greatly in all assignments made in this study.

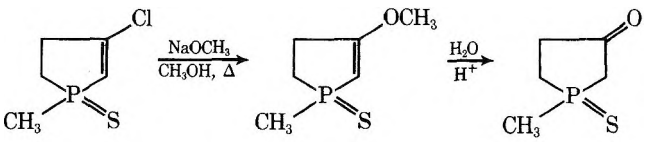
The chloroprene–methylphosphonous dichloride cycloadduct has given varying results on hydrolysis, but generally an isomer mixture rich in the 2-phospholene oxide is obtained.[9] The reaction of this cycloadduct with hydrogen sulfide has been found to be quite specific; *only* the 2 isomer (**3**)



3

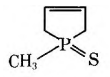
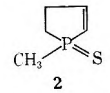
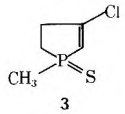
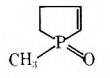
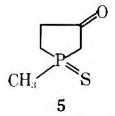
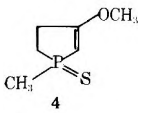
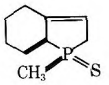
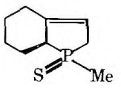
was formed. Again the ^1H NMR spectrum resembled that of the corresponding oxide; the methylene protons had well-separated chemical shifts, and the olefinic proton had weak allylic coupling to the methylenes at C-4, thus appearing as a doublet ($^2J_{PC}$ = 22 Hz) of triplets ($^4J_{HH}$ = 2 Hz).

A valuable property of the 3-chloro-2-phospholene oxide system has been the sensitivity of the chlorine to displacement by methoxide; this provides an enol ether readily hydrolyzed to the 3-keto phospholane oxide.[9] The low electron density of the 3 position of a 2-phospholene sulfide as revealed by the ^{13}C NMR spectrum of **2** suggested that chlorine at this position might be displaceable as it is in the oxide, and this proved to be the case. The enol ether **4** was so obtained and was readily hydrolyzed to the ketone **5**. Spectral examination of



3 **4** **5**

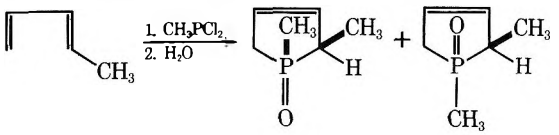
Table I. ^{13}C NMR Spectral Data of Some Phospholene Sulfides[a]

Compd	C-2	C-3	C-4	C-5	PCH_3
 1	38.9 (55)	127.6 (10)	127.6 (10)	38.9 (55)	20.6 (50)
 2	127.9 (75)	147.3 (20)	31.6 (13)	30.3 (45)	22.8 (50)
 3	123.4 (75)	150.0 (40)	36.8 (s)	31.9 (55)	23.7 (50)
	126.9 (92)	150.6 (25)	29.5 (10)	24.5 (68)	17.4 (68)
 5	45.4 (55)	207.4 (15)	37.7 (8)	30.6 (50)	20.4 (52)
 4	91.2 (92)	171.6 (40)[b]	30.4 (s)	29.9 (60)	25.0 (50)
 15	37.6 (55)	117.0 (5)	142.9 (10)	49.5 (55)	16.3 (50)
 14	38.6 (54)	115.2 (5)	143.5 (10)	45.0 (58)	20.9 (49)

[a] Chemical shifts in parts per million downfield from external Me_4Si. Values in parentheses are $^{31}P-^{13}C$ coupling constants in hertz. [b] OCH_3 signal at 57.8 (s).

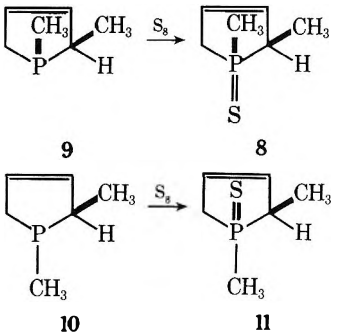
5 showed the absence of detectable amounts of the enol. This is a marked departure from the corresponding oxide, where substantial amounts of enol form are present.[9] It is probable that the greatly reduced hydrogen-bonding ability of sulfur vs. oxygen is largely responsible for this difference; this property has been proposed as an important stabilizing effect in the keto oxide.[9]

The cycloadduct from piperylene on hydrolysis is known to give the 3-phospholene system but as a mixture of cis (6) and trans (7) isomers.[5] When this cycloadduct was treated



6 7

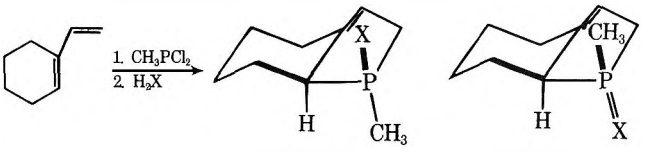
with hydrogen sulfide in the usual way, the product (8) consisted of *only one* stereoisomer; there was no detectable amount of the other isomer by either ^1H or ^{31}P NMR spectroscopy. That sulfide 8 was a 3-phospholene of cis structure was easily established by comparing it to the sulfides formed stereospecifically (retention[10]) on addition of sulfur to the corresponding isomeric phosphines 9 and 10. These had been separated and characterized in previous work.[5] The phosphine known to have the cis structure (9) gave a sulfide identical with 8, while the trans phosphine 10 gave a sulfide (11) of quite different properties.



9 8

10 11

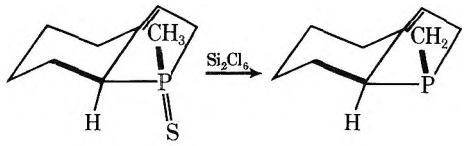
The remarkable stereospecificity of the hydrogen sulfide reaction was observed in another case, that of the cycloadduct from 1-vinylcyclohexene.[11] Again, trans (12) and cis (13) 3-phospholene isomers are possible from this reaction (and are observed in 2:3 ratio on hydrolysis), but only one sulfide isomer was obtained. The assignment of the position of the double bond was straightforward; there was only one olefinic proton in the NMR spectrum. It might be expected that the



12, X = O
14, X = S

13, X = O
15, X = S

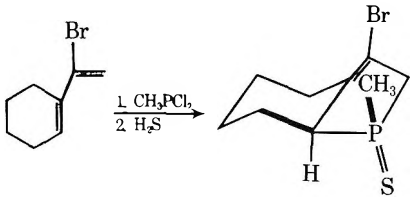
compound would have the cis structure **15**, by analogy to the steric result from the piperylene adduct. This was established by removing sulfur with hexachlorodisilane, a reaction known to occur with retention,[12] which produced a phosphine identical with that of cis structure (**16**). This structure has been



15 **16**

established in another study.[11] This proof was approached from the other direction as well; a trans-rich sample of the phosphine, also available from other work,[11] was treated with sulfur (retention) to form a mixture of sulfides **14** and **15**. The minor product (cis) of the reaction was identical with that obtained from the hydrogen sulfide reaction. Finally, the ^{13}C NMR spectrum (Table I) contained a feature indicative of the isomer structure; as for the oxides,[11] steric crowding in the cis isomer caused its PCH_3 signal to be displaced several parts per million upfield.

The stereospecificity of the hydrogen sulfide reaction was observed in another bicyclic synthesis, that of a 3-bromo derivative (**17**). The reaction product again consisted of a single



17

isomer, to which we feel safe in assigning the cis structure from the previous results.

That only the cis isomer is formed in the hydrogen sulfide reaction is a point of significance with regard to the mechanism of nucleophilic displacement of halogen from the 1-halophospholenium ion. The result does not derive from any instability of the trans isomer in the acidic medium; this point was checked by bubbling H_2S and HCl through a benzene solution of **11** (trans) for 30 min, without effecting any conversion to cis isomer **8**. The only other nucleophilic displacement reaction for which data are available is that of hydrolysis, which can give mixtures dominated by either the cis[5,13] or trans[11] isomers. Even for the same cycloadduct, the experimental conditions play an important role in determining the cis:trans ratio.[5,13] From a recent observation[14] that the cis form of 1-phenyl-2,5-dimethyl-3-phospholene oxide rearranges to trans on standing, possibly through hydration to a pentacovalent dihydroxy form,[15] we suggest that the initially formed oxide on hydrolysis in general may be cis, and that rearrangement to the less crowded trans form occurs to whatever extent is allowed by the reaction conditions. Thus, we propose that the hydrogen sulfide and hydrolysis reactions may proceed by the same kinetically controlled steric pathway, but the product of the former is more indicative of this pathway since it is not prone to rearrange in the medium used.

The 1-halophospholenium ions can exist as cis or trans forms, but NMR spectral data have shown that these rapidly equilibrate through a pentacovalent dihalide.[5,13] The cis preference in sulfide formation would simply imply that one of the equilibrating isomeric halophospholenium ions reacts faster than the other. Whether it is the cis form, involving retention of configuration, or the trans, giving inversion, cannot be ascertained with the data so far at hand. Regardless of the exact steric course, the cis-product preference in this nucleophilic displacement of the cycloadducts now seems established, and the reaction joins two others of the cycloadducts for which a definite steric result can be expected: (1) dehalogenation to the phosphine with magnesium, which gives mostly the trans isomer,[5] and (2) conversion to the oxide with liquid sulfur dioxide, which gives only the cis product.[16]

Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. All manipulations of phosphines were conducted under nitrogen in a glove bag. ^1H NMR spectra were taken with a JEOL MH-100 spectrometer; chemical shifts are relative to internal tetramethylsilane. ^{31}P NMR spectra were obtained on a Bruker HFX-10 system at 36.43 MHz with proton noise decoupling; chemical shifts are referenced to 85% H_3PO_4, with positive shifts upfield, negative downfield. Proton noise-decoupled Fourier transform ^{13}C NMR spectra (Table I) were also obtained on the Bruker spectrometer, at 22.62 MHz, utilizing C_6F_6 in a 3-mm coaxial capillary as an external heteronuclear lock. Chemical shifts are given in parts per million downfield from Me_4Si as zero. Methylphosphonous dichloride was obtained from the Ethyl Corp. Elemental analyses were performed by commercial laboratories.

1-Methyl-3-phospholene 1-Sulfide (1). The cycloadduct (50 g, 0.29 mol) prepared from 1,3-butadiene and methylphosphonous dichloride[4] was washed thoroughly with petroleum ether and suspended in 200 ml of dry benzene. Hydrogen sulfide gas was then bubbled through the stirred suspension until a clear solution resulted (about 45 min). The solution was washed with 200 ml of saturated $NaHCO_3$ solution and then 200 ml of water. The benzene solution was dried ($MgSO_4$) and concentrated on the rotary evaporator. The residual gummy solid was recrystallized from cyclohexane to give 25.1 g of **1** (66%) as colorless plates: mp 45–47 °C (lit.[6] mp 46 °C); ^1H NMR ($CDCl_3$) δ 1.82 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 2.75 (d, $^2J_{PH}$ = 10 Hz, $-CH_2-$), 5.87 (d, $^3J_{PH} \approx$ 28 Hz, $=CH-$); ir (Nujol) 1620 cm^{-1} (C=C); ^{31}P NMR (25% in $CDCl_3$) δ −54.8 (lit.[6] for the same concentration run proton coupled, −52.3).

Anal. Calcd for C_5H_9PS: C, 45.45; H, 6.82; P, 23.48. Found: C, 45.50; H, 6.98; P, 23.34.

1-Methyl-2-phospholene 1-Sulfide (2). A mixture of 1 g (75 mmol) of **1** and 25 ml of 48% HBr was refluxed under N_2 for 8 h. The mixture was neutralized and extracted with chloroform (5 × 75 ml). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Analysis by ^{31}P NMR spectroscopy showed the phospholene oxide composition to be 95% **2**, 5% **1**. Thick layer chromatography on silica gel with ether–petroleum ether (1:1) as eluent gave 0.49 g of pure **2** (49%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.93 (d, $^2J_{PH}$ = 12 Hz, PCH_3), 2.10–2.65 (m, PCH_2CH_2), 2.75–3.15 (m, PCH_2), 6.08–7.28 (complex m, olefinic H); ir (neat) 1600 cm^{-1} (C=C); ^{31}P NMR (25% in $CDCl_3$) δ −65.5 (lit.[6] for the same concentration run proton coupled, −62.5).

Compound **2** also resulted from base-catalyzed rearrangement. To a mixture of 1 g (75 mmol) of **1** in 50 ml of benzene was added 1 g of potassium *tert*-butoxide. The resulting mixture was refluxed for 24 h. The benzene was washed with water (2 × 50 ml), dried ($MgSO_4$), and concentrated to give 0.7 g of a 50:50 mixture of **1** and **2** as determined from the two PCH_3 doublets (δ 1.85 and 1.95, respectively).

3-Chloro-1-methyl-2-phospholene 1-Sulfide (3). The cycloadduct (67 g, 0.33 mol) prepared from methylphosphonous dichloride and chloroprene[9] was washed with petroleum ether and suspended in 250 ml of dry benzene. Hydrogen sulfide was then bubbled through the suspension until all solid had dissolved (2 h). The benzene was washed with 200 ml of saturated $NaHCO_3$ solution and then 200 ml of water. The benzene solution was dried ($MgSO_4$) and concentrated. The resulting solid was recrystallized from ethanol to give 27.1 g of **3** (49%) as white needles: mp 68–69 °C; ^1H NMR ($CDCl_3$) δ 1.91 (d, $^2J_{PH}$ = 14 Hz, PCH_3), 2.22–2.63 (m, PCH_2CH_2), 2.83–3.20 (m, PCH_2), 6.15 (d of t, $^2J_{PH}$ = 22, $^4J_{HH}$ = 1.5 Hz, $>C=CH-$); ir (Nujol) 1610 cm^{-1} (C=C); ^{31}P NMR ($CDCl_3$) δ −58.5.

Anal. Calcd for C_5H_8ClPS: C, 36.04; H, 4.80; P, 18.57. Found: C, 36.03; H, 4.89; P, 18.57.

1-Methyl-3-methoxy-2-phospholene 1-Sulfide (4). To a stirred solution of sodium methoxide prepared from 1.27 g (0.055 g-atom) of sodium and 75 ml of methanol was added 8.6 g (0.05 mol) of chloride **3** in 75 ml of methanol. The resulting solution was refluxed for 15 h. The solution was cooled and neutralized with concentrated hydrochloric acid. The NaCl was filtered off and the solution was concentrated on the rotary evaporator. The residual oil was distilled to give 3.8 g of **4** (47%): bp 118–120 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 1.85 (d,

$^2J_{PH}$ = 12 Hz, PCH_3), 2.00–3.35 (m, 4, methylenes), 3.65 (s, OCH_3), 4.88 (d, $^2J_{PH}$ = 25 Hz, =CH); ir (neat) 1601 cm^{-1} (C=C); ^{31}P NMR ($CDCl_3$) δ −58.7.

1-Methyl-3-phospholanone 1-Sulfide (5). To a mixture of 2 g (12 mmol) of enol ether **4** in 5 ml of water was added 6 drops of 3 N HCl. The stirred mixture was heated at 115 °C for 3.5 h under N_2. The solution was then cooled in ice and the resulting precipitate was filtered off. Sublimation of this solid at 50 °C (0.01 mm) gave 1 g of **5** (57%) as a white powder: mp 80–81 °C; ^1H NMR ($CDCl_3$) δ 1.89 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 2.20–2.98 (m, 4, methylenes); ir (CCl_4) 1720 cm^{-1} (C=O); ^{31}P NMR ($CDCl_3$) −42.4.

Anal. Calcd for C_5H_9OPS: C, 40.54; H, 6.08; P, 20.95. Found: C, 40.74; H, 6.15; P, 20.87.

***cis*-1,2-Dimethyl-3-phospholene 1-Sulfide (8).** The cycloadduct (40 g, 0.22 mol) prepared from methylphosphonous dichloride and *trans*-piperylene was washed with petroleum ether and suspended in 200 ml of dry benzene. Hydrogen sulfide was bubbled through the stirred mixture until all solid dissolved (about 1 h). The benzene was then washed with 200 ml of saturated $NaHCO_3$ solution followed by 200 ml of water. The benzene was dried ($MgSO_4$) and concentrated. The residual solid was recrystallized from ethanol to give 12.5 g of **8** (39%) as white needles: mp 50–51 °C; ^1H NMR ($CDCl_3$) 1.24 (d of d, $^3J_{PH}$ = 18, $^3J_{HH}$ = 7 Hz, C–CH_3), 1.61 (d, $^2J_{PH}$ = 12 Hz), 2.65–3.20 (m, CH_2 and CH), 5.80 (d, $^3J_{PH}$ = 26 Hz, =CH); ir (Nujol) 1615 cm^{-1} (C=C); ^{31}P NMR ($CDCl_3$) δ −63.4.

Anal. Calcd for $C_6H_{11}PS$: C, 49.32; H, 7.53; P, 21.23. Found: C, 49.51; H, 7.70; P, 21.20.

Reaction of the 1,2-Dimethyl-3-phospholenes 9 and 10 with Sulfur. To a solution of 500 mg (4.4 mmol) of the cis isomer (**9**) in 50 ml of dry benzene was added 500 mg of sulfur. The mixture was refluxed for 8 h. The excess sulfur was filtered off and the benzene removed on the rotary evaporator. The residue was recrystallized from ethanol to give 450 mg of **8** (70%), mp 49–50 °C; the ^1H and ^{31}P NMR and the ir spectra were identical with those reported above for compound **8**.

The trans phosphine **10** was treated with sulfur in the same way and gave a different sulfide **11**, mp 42–43 °C. ^{31}P NMR ($CDCl_3$) δ −60.8.

***cis*-1-Methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Sulfide (15).** The cycloadduct (20 g, 0.08 mol) prepared from 1-vinylcyclohexene[11] and methylphosphonous dichloride was washed with petroleum ether and suspended in 150 ml of benzene. Hydrogen sulfide was bubbled through the stirred suspension for 1 h. The clear benzene solution was washed with saturated $NaHCO_3$ solution (200 ml) and water (200 ml). The benzene was dried ($MgSO_4$) and concentrated to an oil that solidified on cooling. Recrystallization from cyclohexane gave 7.8 g of **15** (46%) as white needles: mp 78–80 °C; ^1H NMR ($CDCl_3$) δ 1.65 (d, $^2J_{PH}$ = 12 Hz, PCH_3), 1.2–2.9 (m, CH_2 and CH), 5.42 (d, $^3J_{PH}$ = 29 Hz, =CH); ir (Nujol) 1630 cm^{-1}; ^{31}P NMR ($CDCl_3$) δ −59.9.

Anal. Calcd for $C_9H_{15}PS$: C, 58.06; H, 8.06; P, 16.67. Found: C, 57.87; H, 8.04; P, 16.86.

***cis*-1-Methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole (16).** To a solution of 600 mg (3.2 mmol) of **15** in 50 ml of dry benzene was added 3 ml (56 mmol) of hexachlorodisilane over a 30-min period. The solution was then refluxed for 4 h. The flask was cooled and 15 ml of 30% NaOH solution was added. The layers were separated and the aqueous layer was extracted with benzene (3 × 25 ml). The benzene was dried ($MgSO_4$) and distilled at atmospheric pressure. The residue was distilled at reduced pressure to give 250 mg of **16** (50%) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 0.65 (d, $^2J_{PH}$ = 4 Hz, PCH_3), 0.90–2.65 (m, CH_2 and CH), 5.22 (broad s, =CH); ^{31}P NMR ($CDCl_3$) δ +26.1.

The methiodide was prepared from a small portion of the phosphine by reaction with excess methyl iodide. Recrystallization from ether–methanol gave white crystals, mp 273 °C dec.

Anal. Calcd for $C_{10}H_{18}IP$: C, 40.54; H, 6.08; P, 10.47. Found: C, 40.65; H, 6.13; P, 10.32.

***cis,trans*-1-Methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Sulfide.** To 1 g (6.5 mmol) of a mixture of *cis*- (40%) and *trans*- (60%) 1-methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1*H*-phosphindoles (prepared by the trichlorosilane reduction of the corresponding oxides)[11] dissolved in 25 ml of benzene was added 1 g of sulfur. The resulting solution was refluxed for 12 h. The excess sulfur was filtered off and the benzene was evaporated. The remaining oil solidified and was recrystallized from ethanol to give 680 mg of a mixture of **14** and **15** (56%) as white needles: mp 74–77 °C; ^1H NMR ($CDCl_3$) δ 1.65 (d, $^2J_{PH}$ = 12 Hz, PCH_3), 1.73 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.2–2.9 (m, CH_2 and CH), 5.38 (d, $^2J_{PH}$ = 29 Hz, =CH–); ir (Nujol) 1625 cm^{-1} (C=C); ^{31}P NMR ($CDCl_3$) δ −58.0 (**14**, 65%) and −59.8 (**15**, 35%).

Anal. Calcd for $C_9H_{15}PS$: C, 58.06; H, 8.06; P, 16.67. Found: C, 58.03; H, 8.24; P, 16.40.

3-Bromo-1-methyl-$\Delta^{3(3a)}$-2,4,5,6,7,7a-hexahydro-1*H*-phosphindole 1-Sulfide (17). The cycloadduct (25 g, 81.9 mmol) prepared from 1-(1-bromovinyl)-1-cyclohexene[17] and methylphosphonous dichloride was washed with petroleum ether and suspended in 100 ml of dry benzene. Hydrogen sulfide was bubbled through the stirred suspension for 30 min. The resulting clear solution was then washed with saturated $NaHCO_3$ solution and water (200 ml). The benzene was dried ($MgSO_4$) and concentrated. The gummy residue was recrystallized from ethanol to give 8.3 g of **17** (38%) as white crystals: mp 126–128 °C; ^1H NMR ($CDCl_3$) δ 1.70 (d, $^2J_{PH}$ = 13 Hz, PCH_3), 1.1–3.15 (m, CH_2 and CH); ir (KBr) 1620 cm^{-1} (C=C); ^{31}P NMR ($CDCl_3$) δ −51.4.

Anal. Calcd for $C_9H_{14}BrPS$: C, 40.91; H, 4.92; P, 11.74. Found: C, 40.79; H, 5.15; P, 11.83.

Registry No.—**1**, 52988-60-0; **2**, 52988-61-1; **3**, 58311-81-2; **4**, 58311-82-3; **5**, 58311-83-4; **8**, 58311-84-5; **9**, 2329-12-6; **10**, 2329-00-2; **11**, 58311-85-6; **14**, 58311-86-7; **15**, 58311-87-8; *cis*-**16**, 57065-71-1; **16** methiodide, 57065-73-3; *trans*-**16**, 57065-72-2; **17**, 58311-88-9; 1,3-butadiene, 106-99-0; methylphosphonous dichloride, 676-83-5; chloroprene, 126-99-8; *trans*-piperylene, 2004-70-8; 1-vinylcyclohexene, 2622-21-1; methyl iodide, 74-88-4; 1-(1-bromovinyl)-1-cyclohexene, 57065-75-5.

References and Notes

(1) Supported by U.S. Public Health Service Research Grant CA-05507, National Cancer Institute.
(2) W. B. McCormack, U.S. Patents 2 663 736 and 2 663 737 (1953); for a review, see L. D. Quin, "1,4-Cycloaddition Reactions", J. Hamer, Ed., Academic Press, New York, N.Y., 1967, Chapter 3.
(3) W. B. McCormack, U.S. Patent 2 663 738 (1953).
(4) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).
(5) L. D. Quin, and T. P. Barket, *J. Am. Chem. Soc.*, **92**, 4303 (1970).
(6) K. Moedritzer, *Synth. React. Inorg. Metal-Org. Chem.*, **4**, 119 (1974).
(7) S. G. Borleske, Ph.D. Dissertation, Duke University, 1972.
(8) L. D. Quin, M. D. Gordon, and S. O. Lee, *Org. Magn. Reson.*, **6**, 503 (1974).
(9) (a) L. D. Quin and J. A. Caputo, *Chem. Commun.*, 1463 (1968); (b) L. D. Quin and R. C. Stocks, *J. Org. Chem.*, **39**, 686 (1974).
(10) (a) D. P. Young, W. E. McEwen, D. C. Velez, J. W. Johnson, and C. A. Van der Werf, *Tetrahedron Lett.*, 359 (1964); (b) L. Horner and H. Winkler, *ibid.*, 175 (1964).
(11) C. Symmes, Jr., and L. D. Quin, *J. Org. Chem.*, **41**, 238 (1976).
(12) G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, **91**, 7023 (1969).
(13) S. E. Cremer, F. L. Weltl, F. R. Farr, P. W. Kremer, G. A. Gray, and H. Hwang, *J. Org. Chem.*, **38**, 3199 (1973).
(14) R. C. Stocks and L. D. Quin, manuscript in preparation.
(15) D. Gorenstein, *J. Am. Chem. Soc.*, **94**, 2808 (1972).
(16) A. Bond, M. Green, and S. C. Pearson, *J. Chem. Soc. B*, 929 (1968).
(17) J. C. Traynard, *Bull. Soc. Chim. Fr.*, 19 (1962).

Reactions of 2,2,2-Triphenylethyl p-Toluenesulfonate in Alcohol Solutions in the Presence of Base under High Pressure. Effects of Pressure on SN1- and SN2-Type Reactions

Kang I. Lee[1] and Yoshiyuki Okamoto*

Department of Chemistry, Polytechnic Institute of New York, Brooklyn, New York 11201

Received January 12, 1976

The reactions of 2,2,2-triphenylethyl p-toluenesulfonate (1) with sodium alkoxide in methanol and ethanol solutions were studied at both 1 atm and 5000–5500 atm. In alcohol solution, solvolysis of **1** in the presence of a low concentration of base yielded quantitatively phenyl-migrated products, viz., 1,2,2-triphenylethyl alkyl ether (**2**) and triphenylethylene (**3**). However, it was found that when the concentration of base was increased, the nucleophilic substitution reaction (SN2) competed with the ionization reaction (SN1) and the products were found to be mixtures of **2**, **3**, and 2,2,2-triphenylethyl alkyl ether (**4**). The yield of the unrearranged product **4** was increased accordingly with the base concentration. However, the amount of **4** was found to be decreased by applying pressure to the system. The results indicated that the effect of pressure was greater on the solvolytic reaction than on the nucleophilic substitution reaction. These results were explained in view of different activation volumes. In the solvolytic reactions of **1**, the amount of the rearranged ether product **2** was also found to be increased over the olefin product by the application of pressure. The result was accounted for by the contraction of volume of the system and the favorable structure of the transition state in the formation of the ether as compared to that of the transition state leading to olefin. When the compound **1** was treated with NaOH in water–dioxane solution, the nucleophilic substitution product, 2,2,2-triphenylethanol (**5**), was produced along with triphenylmethane (**6**). The source of compound **6** was found to be a further reaction of **5** with NaOH through a carbon–carbon cleavage process.

In recent years, the use of high pressure for the study of organic chemistry has been increasing.[2] The pressure dependence of the rate constant of a reaction is $(\partial \ln k/\partial p)_T = -\Delta V^{\ddagger}/RT$, where $\Delta V^{\ddagger}$ is the volume of activation. If this volume is negative, i.e., the formation of the transition state complex from the reactants results in overall contraction, the rate constant k will be increased with increasing pressure.[3]

The effect of pressure on the rate of solvolytic and nucleophilic displacement reactions of alkyl halides has been investigated by a number of workers.[4,5] Generally, both reactions were found to be enhanced by applying pressure to the reaction system.

Nucleophilic substitutions (SN2) on neopentyl carbon were found to be notoriously difficult although not impossible under forcing conditions.[6,7] A phenyl group is much bulkier than a methyl group and as a consequence the nucleophilic substitution reaction on the C_1 in the 2,2,2-triphenylethyl system is expected to be much less favored than the same reaction in the neopentyl system. This possibility has never been investigated.

The solvolysis of 2,2,2-triphenylethyl p-toluenesulfonate (**1**) is much faster than a similar solvolysis for neopentyl p-toluenesulfonate, cf. about 7000 times in acetic acid.[8] Compound **1** is a highly substituted system and the relief of steric strain at C_2 in the ionization stage can account for the driving force leading to the enhanced rate. The bridged phenonium ion or the phenyl-rearranged stable tertiary carbonium ion was proposed as the transition state.[8-10] In methanol or ethanol solution **1** was solvolyzed in the presence of a low concentration of sodium alkoxide to yield quantitatively the phenyl-migrated products, viz., 1,2,2-triphenylethyl methyl ether (**2a**) or 1,2,2-triphenyldiethyl ether (**2b**) and triphenylethylene (**3**).[11] However, we have found that when the concentration of RONa was increased, the nucleophilic substitution reaction competed with the ionization reaction. Thus, the products were found to be mixtures of **2**, **3** and either 2,2,2-triphenylethyl methyl ether (**4a**) or 2,2,2-triphenyldiethyl ether (**4b**). The yield of the unrearranged product **4a** or **4b** was increased accordingly with the base concentration.

This system presents an interesting case for the study of the effects of pressure on SN1 and SN2 reactions, because the possibility of backside nucleophilic attack by solvents and normal 1,2 elimination with base are both impossible. Therefore, the solvolysis of **1** was investigated in alcohol containing NaOH or RONa at 1 atm and under high pressure.

Results

Solvolysis of 2,2,2-Triphenylethyl p-Toluenesulfonate (1) in the Presence of Base. Compound **1** was solvolyzed in either dioxane–water or dioxane–alcohol solution in the presence of NaOH or sodium alkoxide in the following manner. The reactants were placed in a Teflon capsule (volume 4 cm^3), which was subsequently heated to 80–100 °C for 20–25 h slightly above 1 atm pressure. When the reactions were carried out in Pyrex vessels, the base was found to react with the glass and the product distributions were found to be different from those found when the reaction was carried out in a Teflon vessel (see Experimental Section). After the solvent was removed under reduced pressure, the solid was treated with H_2O and extracted with ether. The products were then analyzed by GC and characterized by comparison with authentic samples. Typical results are summarized in Table I.

Reactions of 2,2,2-Triphenylethanol (5) with Base. In order to find the source of triphenylmethane (**6**) produced in the reactions with NaOH (see Table I), 2,2,2-triphenylethanol (**5**) was allowed to react with various concentrations of NaOH. The products were analyzed as described above and typical results are summarized in Table II. It was found that **5** reacted further with NaOH to give a carbon–carbon bond cleavage product **6**.[12] The amount of **6** was found to increase with increasing concentrations of NaOH and reaction temperature.

Reactions of 2,2,2-Triphenylethyl p-Toluenesulfonate (1) with Sodium Alkoxide in Alcohol under 1 Atm and High Pressure. In order to avoid complications involving the carbon–carbon cleavage of **5** with NaOH, the reactions of **1** were studied in detail in alcohol solution with the corresponding sodium alkoxide. The reactants were placed in Teflon capsules which were then heated at 80–85 °C for 20–25 h under both 1 atm pressure and also at

Table I. Effects of Base on the Solvolysis of 2,2,2-Triphenylethyl p-Toluenesulfonate (1)[a]

Solvent	Base (mmol)	Temp, °C	Products, % 2	3	4	5	7[b]
Dioxane–water[c]	NaOH (1)	90		55			45
Dioxane–water[c]	NaOH (2)	90		47		17[d]	33
Dioxane–water[c]	NaOH (3)	90		35		30[e]	30
Dioxane–MeOH[f]	MeONa (4)	100	48.2	46.6	5.2		
Dioxane–MeOH[f]	MeONa (8)	100	49.5	37.5	14.0		
Dioxane–EtOH[g]	EtONa (2)	100	37.5	59.5	3.0		
Dioxane–EtOH[g]	EtONa (4)	100	32.4	54.9	12.7		
Dioxane–EtOH[g]	EtONa (8)	100	29.4	37.4	33.2		

[a] Tosylate (0.77 mmol) was used. [b] 1,1,2-Triphenylethanol (7). [c] Dioxane (3 ml) and H_2O (1 ml) were used. [d] 2,2,2-Triphenylethanol (5) was further treated with NaOH to yield 3% triphenylmethane (6). [e] Triphenylmethane produced was ~5%. [f] Dioxane (2 ml) and MeOH (2 ml) were used. [g] Dioxane (2 ml) and EtOH (2 ml) were used.

Table II. Reactions of 2,2,2-Triphenylethanol (5) with NaOH[a]

Run no.	Reaction conditions [NaOH], mol	Temp, °C	Reaction time, h	Triphenylmethane produced, %
9	0.023	80	24	7
11	0.023	100	24	23
13	0.050	100	24	30
15	0.070	100	24	45
17	0.070	130	24	100

[a] The reactions were carried out in Teflon vessels. The initial concentration of 2,2,2-triphenylethanol was 0.004 mol in a mixed solvent system composed of dioxane (50 ml)–methanol (20 ml).

5000–5500 atm using the method previously reported.[13] Control experiments established that 3 was not further reacted under the reaction conditions. The products were isolated as described above and analyzed by GC. Typical results are summarized in Table III.

Discussion

The effect of pressure on the rate of reaction in the liquid phase is known to be controlled by the volume change in the course of formation of the activated complex. Evans and Polanyi[14] suggested that the volume of activation ($\Delta V^{\ddagger}$) should be regarded as the sum of two terms. The structural term $\Delta V_1^{\ddagger}$ is the change in volume of the reacting molecules themselves when they form the transition state, while the solvation term $\Delta V_2^{\ddagger}$ is the accompanying volume change due to interactions of the surrounding molecules with the newly formed charges in the transition state.

Generally, in SN1-type reactions of alkyl halides, the rate-determining step is an ionic process, and $\Delta V^{\ddagger}$ was found to be negative, usually in the order of −15 to −25 cm^3/mol.[15] Since this ionization process implies bond cleavage, one might assume that $\Delta V^{\ddagger}$ is positive. However, at the transition state, charges exert a powerful attractive force on the nearby solvent molecules, and as a result, the molecules in the solvated hull are denser than in the bulk solvent. Thus $\Delta V^{\ddagger}$'s for these kinds of reactions generally have negative values since the $\Delta V_2^{\ddagger}$'s play decisive roles in determining the signs and magnitudes of the $\Delta V^{\ddagger}$'s.

In SN2 reactions such as the reaction of 1 with RONa, there are no additional ions produced or destroyed. In the transition state, the charge is being transferred and is probably dispersed somewhat. A fair number of such reactions have been studied and nearly all have volumes of activation between −5 and −10 cm^3/mol.[16] These negative volumes were accounted for by decreasing the structural volume $\Delta V_1^{\ddagger}$.

The solvolysis rate of 1 in dioxane–ethanol was found to be greatly enhanced by applying pressure. The reaction products were quantitatively the phenyl-rearranged compounds, 2 and 3. The activation volume for this system was found to be about −14 cm^3/mol.[11] The sign and magnitude of this value are similar to those for the solvolysis of alkyl tosylate in which the transition states were suggested to have a large degree of charge delocalization.[17] The structure of the transition state for the solvolytic reaction of 1 may be considered to be a carbonium ion highly stabilized by resonance and in which the charge is dispersed throughout the phenyl rings. Thus, the activation volume appears to be somewhat smaller than those associated with the solvolysis of other alkyl tosylates.

The reaction of 1 in alcohol–dioxane with a high concentration of RONa yielded the phenyl-unrearranged product 4 as well as the rearranged products 2 and 3. The variance of the proportion of the unrearranged product formed with varying base (NaOH and RONa) concentrations over a considerable range suggests that product 4 resulted only from nucleophilic attack of RONa on C_1 (Table I). Since the direct measurement of $\Delta V^{\ddagger}$ for the SN2 reaction of 1 is difficult because of the accompanying solvolytic reaction, the reaction products were isolated and analyzed in order to find the pressure effects on the SN2 reaction.

As has been shown in Table III, the amounts of the rearranged products were increased at the expense of SN2 substitution products by applying pressure on the system, cf. the relative ratio of SN1 to SN2 reactions in ethanol–dioxane with 1 and 2 N sodium ethoxide under 5500 atm were increased respectively three- and fivefold over those under 1 atm. These results indicate that the pressure effect on the SN1 reaction of 1 is more pronounced than on the SN2 reaction. This may be accounted for by the development of a highly ionic character at the transition state for the SN1 reaction and in which the solvation term $\Delta V_2^{\ddagger}$ for this reaction plays a decisive role. Thus, the phenyl-rearranged products were increased by applying pressure.

The amount of ether production in the solvolytic reaction was found to be increased compared to olefin formation by applying pressure to the system; cf., the ratio of ether to olefin formation was increased from 3.3 to 10.5 in methanol with 16 mmol of MeONa and from 0.79 to 1.44 with 8 mmol of EtONa under 5500 atm (Table III). This phenomenon may be accounted for by tight solvation under pressure and probably the oxygen atom of the alcohol is more closely attracted to the carbonium ion under high pressure than it would be at 1 atm. Therefore, the structure of the transition state under high pressure has rather more favorable conditions for ether formation in contrast with

Table III. Effects of Pressure on SN1 and SN2 Reactions of 2,2,2-Triphenylethyl *p*-Toluenesulfonate (1)[a] with Sodium Alkoxide in Alcohol

		Reaction products, %							
		1 atm[b]				5500 atm			
Alcohol	Base (mmol)	2	3	4	SN1/SN2[c]	2	3	4	SN1/SN2[c]
MeOH	MeONa (4)	48.2	46.6	5.2	18.2	50.0	46.2	3.8	25.3
MeOH	MeONa (8)	49.5	37.5	14.0	6.2	52.3	38.7	9.0	10.0
MeOH	MeONa (16)	52.6	15.8	31.6	2.2	79.1	7.5	13.4	6.5
EtOH	EtONa (2)	37.5	59.5	3.0	32.3	62.0	37.0	<1.0	>99.0
EtOH	EtONa (4)	32.4	54.9	12.7	6.7	60.9	34.5	4.6	21.0
EtOH	EtONa (8)	29.4	37.4	33.2	2.0	53.6	37.3	9.2	9.9

[a] Tosylate (0.77 mmol) was used for all reactions. All reactions were carried out at 80–85 °C. [b] The pressure was slightly higher than 1 atm in order to conduct the reaction above boiling points of the solvents. [c] The ratio of SN1 to SN2 reaction products.

Table IV. Reactions of 2,2,2-Triphenylethyl *p*-Toluenesulfonate (1) with Sodium Alkoxide in Methanol or Ethanol in the Pyrex Glass Vessel

			Products, %		
Solvent	Base (mmol)	Temp, °C	2	3	4
Dioxane–MeOH	MeONa (8)	100	50.8	48.1	1.1
Dioxane–MeOH	MeONa (16)	100	54.2	19.4	26.4
Dioxane–EtOH	EtONa (4)	100	33.0	60.5	6.5
Dioxane–EtOH	EtONa (8)	100	36.8	45.0	18.2

olefin formation. In addition, the formation of ether involves the combination of solvent and an ion, and as a result the volume of the system is expected to decrease. On the other hand, the volume for olefin formation remains almost unchanged. Therefore, formation of the substitution product is more favorable than that of the elimination reaction under high pressure.

Experimental Section

Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared absorption spectra were determined on a Perkin-Elmer Model 521 spectrophotometer and were calibrated using 6.23-μ (1603 cm^{-1}) band of polystyrene film. Nuclear magnetic resonance spectra were obtained with Varian A-60 and/or Varian HR-220 spectrometers using Me_4Si as internal standard in chloroform-*d* or carbon tetrachloride. Vapor phase chromatography analyses were performed on an Aerograph A-700 instrument, with a 10% SE-30 silicone rubber on Chromosorb W (80–100 mesh, 10 ft × 0.25 in. aluminum column). In quantitative analyses, areas under the peaks in the chromatogram were measured using either the cut-and-weigh method or with a K and E Model 4236M planimeter.

Materials. 2,2,2-Triphenylacetic acid, triphenylethylene, and 1,1,2-triphenylethanol were purchased from Aldrich Chemical Co., Milwaukee, Wis. Dioxane of reagent grade was purified by distillation and stored over sodium wire. In all cases, NMR and VPC were used to ensure a high degree of purity.

Preparation of 2,2,2-Triphenylethyl *p*-Toluenesulfonate (1). 2,2,2-Triphenylacetic acid was reduced directly with lithium aluminum hydride in THF in the usual manner,[19] producing the ethanol in 45% yield (0.10-mol scale), with mp 105–106 °C after recrystallization from methanol (lit. mp 107 °C). The toluenesulfonate, mp 106 °C, was prepared in 48% yield by the standard procedure.[20] Its NMR spectrum consisted of aromatic peaks between δ 7.0 and 7.6 (m, 19 H), CH_2 peak at δ 4.9 (s, 2 H), and CH_3 peak at δ 2.4 (s, 3 H).

Typical Reaction Procedures of 2,2,2-Triphenylethyl *p*-Toluenesulfonate (1) with Sodium Alkoxide in Methanol or Ethanol Solutions. A mixture of 0.43 g (0.01 mol) of 1 and various concentrations of sodium alkoxide or sodium hydroxide in 2 ml of alcohol and 2 ml of dioxane was prepared in a drybox. The solution thus prepared was placed in a Teflon capsule (1.8 cm i.d., 2 cm long), and the system was pressurized to 5000–5500 atm at 80–85 °C for 20–25 h.[18] The reaction mixture was quenched with H_2O, extracted with ether, and then dried over anhydrous magnesium sulfate. After removal of the solvent on a rotary evaporator, the concentrated product mixture was analyzed by VPC. Retention times of each peak were in good agreement with those of authentic samples, **2**, **3**, and **4**. Compounds **2** and **4** were synthesized by the method of Williamson.[21] Each compound was identified by NMR, ir, and VPC.

In a control experiment, a solution of 2.56 g (0.01 mol) of triphenylethylene (**3**) in 4 ml of 50% absolute ethanol–50% dioxane (v/v), with 8 mmol of sodium ethoxide was placed in a Teflon capsule and subsequently pressurized at 120 °C for 48 h under 5000–5500 atm. NMR and VPC showed the presence only of the starting material **3**.

Typical Reaction Procedures of 2,2,2-Triphenylethanol (5) with Sodium Hydroxide. Compound **5** was treated with 0.023 mol of NaOH at 100 °C for 24 h in a Teflon vessel. Twenty-three percent of triphenylmethane was produced and was identified by NMR.

Reactions of 2,2,2-Triphenylethyl *p*-Toluenesulfonate (1) with Sodium Alkoxide in Methanol or Ethanol in a Pyrex Glass Vessel. When reactions of **1** with various concentrations of sodium ethoxide in methanol or ethanol were done in Pyrex glass vessels, typical results are shown in Table IV. The SN2 product **4** was found to be decreased compared to that of the reaction carried out in a Teflon vessel (see Table I). The result indicated that RONa had reacted with Pyrex glass and decreased the base concentration.

Acknowledgment. We thank Mr. T. Yano for the preliminary experimental work in this investigation.

Registry No.—**1**, 808-85-5; **5**, 896-32-2; NaOH, 1310-73-2; MeONa, 124-41-4; EtONa, 141-52-6; 2,2,2-triphenylacetic acid, 595-91-5.

References and Notes

(1) Abstracted in part from a Dissertation to be submitted by Kang I. Lee to the Department of Chemistry, Polytechnic Institute of New York, in partial fulfillment of the requirements for the degree of Ph.D. (Chemistry).
(2) (a) S. D. Christian, J. Grundnes, and P. Klaboe, *J. Am. Chem. Soc.*, **97**, 3864 (1975); (b) R. C. Neuman, Jr., and E. W. Ertley, *ibid.*, **97**, 3130 (1975); (c) W. J. le Noble and T. Asano, *ibid.*, **97**, 1778 (1975); (d) Y. Okamoto and K. I. Lee, *ibid.*, **97**, 4015 (1975); (e) For recent collection of papers, see Proceedings of the international Conference on High Pressure, Kyoto, Japan, 1974.
(3) (a) M. G. Gonikberg, "Chemical Equilibrium and Reaction Rates at High Pressure", Office of Technical Services, U.S. Department of Commerce, Washington, D.C., 1963, Chapter 3. (b) For review, see W. J. le Noble, *Prog. Phys. Org. Chem.*, **5**, 207 (1967).
(4) K. R. Brower and J. S. Chen, *J. Am. Chem. Soc.*, **87**, 3396 (1965).
(5) K. E. Weale, *Discuss. Faraday Soc.*, **20**, 83 (1955).

(6) Y. Okamoto and T. Yano, *Tetrahedron Lett.*, 4285 (1971).
(7) G. M. Fraser and H. M. R. Hoffmann, *Chem. Commun.*, 561 (1967).
(8) Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1113 (1952).
(9) D. Bethell and V. Gold, "Carbonium Ions, an Introduction", Academic Press, New York, N.Y., 1967, p 245.
(10) (a) H. C. Brown in "The Transition State", *Chem. Soc., Spec. Publ.*, **No. 16**, 155 (1962); (b) H. C. Brown, E. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1248 (1964).
(11) Y. Okamoto and T. Yano, *Tetrahedron Lett.*, 919 (1971).
(12) Similar base-catalyzed reactions have been reported by Cram et al.: (a) D. J. Cram and B. Rickborn, *J. Am. Chem. Soc.*, **83**, 2175 (1961); (b) D. J. Cram, L. K. Gaston, and H. Jager, *ibid.*, **83**, 2183 (1961).
(13) Y. Okamoto and H. Shimizu, *J. Am. Chem. Soc.*, **90**, 6145 (1968).
(14) M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, **31**, 875 (1935).
(15) For example, see ref 3b, p 242, Table V.
(16) J. Koskikallio and E. Whalley, *Can. J. Chem.*, **37**, 783 (1959).
(17) (a) W. J. le Noble and B. L. Yates, *J. Am. Chem. Soc.*, **87**, 3515 (1965); (b) W. J. le Noble, B. L. Yates, and A. W. Scaplehorn, *ibid.*, **89**, 3751 (1967).
(18) The high-pressure apparatus used was described previously: ref 13.
(19) W. G. Brown, *Org. React.*, **6**, 469 (1969).
(20) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).
(21) R. Adams, J. R. Johnson, and C. F. Wilcox, Jr., "Laboratory Experiments in Organic Chemistry", Macmillan, New York, N.Y., 1966, p 200.

Reaction of 1,1-Dibenzoyl-2,2-dimethylhydrazine with Methyl *p*-Toluenesulfonate

Richard F. Smith,* Todd A. Craig, Thomas C. Rosenthal, and Robert F. Oot

Department of Chemistry, State University College of Arts and Science, Geneseo, New York 14454

Received December 11, 1975

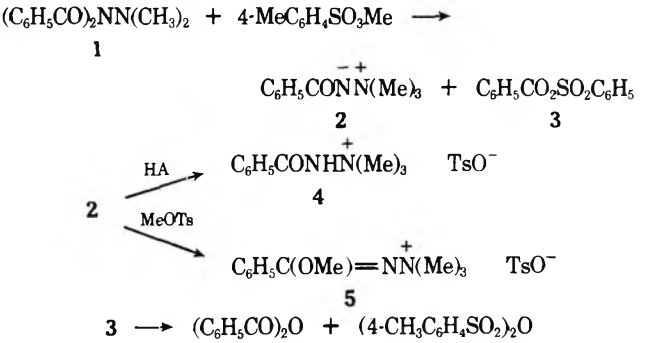
Reaction of 1,1-dibenzoyl-2,2-dimethylhydrazine with 2 equiv of methyl *p*-toluenesulfonate at 120–130 °C afforded a mixture containing 1,1,1-trimethyl-2-benzoylhydrazinium *p*-toluenesulfonate, 1,1,1-trimethyl-2-α-methoxybenzylidenehydrazinium *p*-toluenesulfonate, benzoic anhydride, and *p*-toluenesulfonic acid. The reaction apparently proceeds via the intermediate formation of 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide inner salt [$C_6H_5CO\bar{N}N^+(Me)_3$] and benzoyl *p*-toluenesulfonate.

Hinman has reported that 1,1-dibenzoyl-2,2-dimethylhydrazine (**1**) affords debenzoylated products on reduction with lithium aluminum hydride[1] and hydrogenolysis with Raney nickel.[2] This paper reports additional examples of deacylation reactions of **1**.

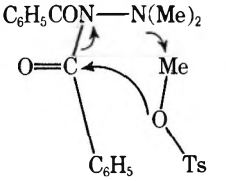
We have found **1** to be unreactive to alkylation with methyl iodide but reaction with 2 equiv of methyl *p*-toluenesulfonate at 120–130 °C afforded a mixture of salts consisting of 1,1,1-trimethyl-2-benzoylhydrazinium *p*-toluenesulfonate (**4**) and 1,1,1-trimethyl-2-α-methoxybenzylidenehydrazinium *p*-toluenesulfonate (**5**). The **4**:**5** ratio varied from 0.4 to 1.5 with the O-methylated material (**5**) predominating when the reaction was conducted on a degassed reaction mixture utilizing methyl *p*-toluenesulfonate that had been freed of acid impurities. Nonionic products were found to consist of benzoic anhydride and *p*-toluenesulfonic acid. Ethyl benzoate and benzoic acid (probably originating from benzoic anhydride) were also isolated when the reaction mixture was worked up in ethanol.

The structure of salt **5** was established by its synthesis from the reaction of 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide inner salt (**2**) with methyl *p*-toluenesulfonate.[3] Salt **4** was recovered unchanged after prolonged treatment with methyl *p*-toluenesulfonate at 120 °C.

The above results suggest that reaction of **1** and methyl *p*-toluenesulfonate initially affords 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide inner salt (**2**) and benzoyl *p*-toluenesulfonate (**3**). Once formed, **2** may then competitively undergo either O-methylation to give **5** or protonation (most likely by *p*-toluenesulfonic acid) to give **4**. The mixed anhydride (**3**) was prepared by the method of Overberger and Sarlo[4] and was found to be thermally unstable. When heated at 120 °C **3** was transformed to benzoic anhydride and *p*-toluenesulfonic acid, which are products also isolated from the reaction of **1** and methyl *p*-toluenesulfonate. The latter results may be accounted for by disproportionation[5] of **3** to *p*-toluenesulfonic anhydride and benzoic anhydride followed by selective hydrolysis of *p*-toluenesulfonic anhydride by moisture.[6]



We have been unable to isolate the aminimide **2** from a reaction involving molar equivalents of **1** and methyl *p*-toluenesulfonate. The latter experiment afforded a mixture consisting of 30% of **5** and 13% of **4** (based on recovered **1**). Thus, the evidence for the intermediacy of **2** must be based on the isolation of its transformation products, **4** and **5**. A possible pathway for the conversion of **1** to **2** may involve a cyclic transition state in which N-methylation and debenzoylation occur in a concerted manner as indicated below.



We have also found that **1** is converted to *n*-butyl benzoate (54%) and 1,1-dimethyl-2-benzoylhydrazine in refluxing 1-butanol.[7]

Experimental Section

Melting points are uncorrected and were determined with a Mel-Temp apparatus. NMR spectra were determined on a Perkin-Elmer R-20 spectrometer utilizing hexamethyldisiloxane as an internal standard.

Reaction of 1,1-Dibenzoyl-2,2-dimethylhydrazine (1) with Methyl *p*-Toluenesulfonate. Identification of 1,1,1-Trimethyl-

2-benzoylhydrazinium p-Toluenesulfonate (4) and 1,1,1-Trimethyl-2-α-methoxybenzylidenehydrazinium Tosylate (5). An ether solution of methyl p-toluenesulfonate was washed with several portions of 10% Na_2CO_3 solution and then dried over $MgSO_4$. A 10% methanolic solution of the ester treated as described above had pH 7.2. The base-treated ester (16.01 g, 0.086 mol) was added to 11.43 g (0.043 mol) of 1,1-dibenzoyl-2,2-dimethylhydrazine (1).[8] The mixture was frozen in liquid nitrogen, evacuated on a mercury diffusion pump, sealed, and heated at 128 °C for 12 h. The dark mixture was added with stirring to 1 l. of dry ether. The ether-insoluble material was dissolved in 50 ml of warm absolute ethanol, decolorized with Darco, and diluted with 600 ml of dry ether. Filtration of the insoluble material afforded 9.98 g of a mixture consisting of 70% of **5** and 30% of **4**, mp 106–109 °C. The composition of the mixture was obtained by comparison of the integrated intensity ratios of the –OMe NMR signal of **5** with the p-methyl signal of the p-toluenesulfonate ion. The $(Me)_3N^+$ signal of **4** appeared as a sharp side peak (δ 3.82) on the $(Me)_3N^+$ signal of **5**.

The salts were efficiently separated by fractional crystallization. In a separate experiment utilizing 10.0 g of **1** and 14 g of unwashed methyl p-toluenesulfonate, the ether-insoluble material was dissolved in 50 ml of absolute ethanol, decolorized, and treated with 100 ml of dry ether. Crude **4** (3.52 g) precipitated as white crystals, mp 171–174 °C. Recrystallization from ethanol–ether afforded white crystals, mp 180–181 °C (lit.[9] mp 179–181 °C). Identity was established by elemental analysis and comparison of the NMR and ir spectra with those of an authentic sample.

The filtrate from the isolation of **4** was diluted with 800 ml of anhydrous ether. The crude methoxy compound (**5**) precipitated as a hygroscopic solid (2.3 g). Recrystallization from ethanol–ether gave white crystals: mp 127–128 °C; NMR ($CDCl_3$) δ 2.20 (s, 3), 3.34 (s, 3), 3.90 (s, 9), 6.95–7.68 (m, 9).

Anal. Calcd for $C_{18}H_{24}N_2O_4S$: C, 59.31; H, 6.64; N, 7.68; S, 8.80; MeO, 8.51. Found: C, 59.15; H, 6.48; N, 7.50; S, 8.78; MeO, 8.25.

The salt obtained above was identical (ir, NMR) with **5** obtained by the following procedure. A mixture consisting of 2.0 g of 1,1,1-trimethyl-2-benzoylhydrazinium hydroxide inner salt (**2**)[10] and 2.2 g of methyl p-toluenesulfonate was heated for 2 h at 120 °C. Dilution with ether gave crude **5** (2.8 g), mp 122–125 °C.

Identification of Nonionic Components. In a separate reaction (17.0 g of methyl p-toluenesulfonate, 12.1 g of **1**, heated for 12 h at 123 °C in an N_2 atmosphere), the filtrate remaining after precipitation of **4** and **5** from ethanol–ether as described above was evaporated to a liquid (9.3 g).

The above mixture was dissolved in 50 ml of chloroform and extracted with two 10-ml portions of 10% Na_2CO_3 solution. Acidification of the aqueous solution afforded 0.6 g of crude benzoic acid (by ir), mp 116–120 °C.

The presence of ethyl benzoate in the liquid mixture remaining after evaporation of the chloroform extracts was demonstrated by NMR and GLC retention time. Distillation of 5.23 g of the mixture afforded 0.8 g of pure ethyl benzoate (by NMR and ir), bp 44 °C (0.25 mm).

A solution consisting of 2.0 g of the crude liquid mixture (obtained from a separate experiment) dissolved in 12 ml of chloroform was extracted with two 10-ml portions of water. Evaporation of the aqueous extract afforded 0.64 g of semisolid hydrated p-toluenesulfonic acid which was identified by its ir and NMR spectra.

The ether-soluble material (6.65 g) from the above reaction was found to consist of a mixture of starting materials (by NMR) and benzoic anhydride. The presence of benzoic anhydride was demonstrated by its R_f value (TLC on silica gel, developing solvent benzene), by hydrolysis to benzoic acid, and by the following procedure. The mixture (6.5 g) was stirred with 20 ml of 10% NaOH for 4 h. The aqueous solution was extracted with chloroform and acidified to precipitate 1.86 g of crude benzoic acid (by ir), mp 97–98 °C. No benzoic acid could be detected (by TLC) prior to hydrolysis.

Thermal Decomposition of Benzoyl p-Toluenesulfonate (3). The crude anhydride (2.0 g) was heated at 124 °C for 12 h in a tube that was purged with nitrogen and stoppered. The dark, tarry residue was treated with chloroform. The chloroform-insoluble material was found to consist mainly of crude hydrated p-toluenesulfonic acid (by NMR and ir). Several minor impurity peaks were noted in the NMR spectrum (Me_2SO-d_6). The chloroform-soluble material was established to be benzoic anhydride (by NMR and ir) which was contaminated with a small amount of p-toluenesulfonic acid.

Reaction of 1,1-Dibenzoyl-2,2-dimethylhydrazine (1) with 1-Butanol. A solution containing 10 g of **1** in 50 ml of 1-butanol was heated under reflux for 12 h. After removal of the excess 1-butanol by distillation at reduced pressure, the residue was extracted with water (4 × 20 ml). The water-insoluble material was diluted with ether and dried ($MgSO_4$). Vacuum distillation of the ether-soluble residue afforded 3.6 g (54%) of pure n-butyl benzoate (by ir), bp 132–133 °C (22 mm). Evaporation of the aqueous washings gave a quantitative yield of 1,1-dimethyl-2-benzoylhydrazine (by ir), mp 104–106 °C (lit.[8] mp 106–107 °C).

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this project.

Registry No.—**1**, 30859-86-0; **3**, 4972-24-1; **4**, 3237-92-1; **5**, 58426-21-4; methyl p-toluenesulfonate, 80-48-8; 1-butanol, 71-36-3; n-butyl benzoate, 136-60-7; 1,1-dimethyl-2-benzoylhydrazine, 1128-86-5.

References and Notes

(1) R. L. Hinman, *J. Org. Chem.*, **21**, 1177 (1956).
(2) R. L. Hinman, *J. Org. Chem.*, **22**, 148 (1957).
(3) For a discussion of the alkylation of aminimides see W. J. McKillip, E. A. Sedor, B. M. Culbertson, and S. Wawzonek, *Chem. Rev.*, **73**, 267 (1973).
(4) C. G. Overberger and E. Sarlo, *J. Am. Chem. Soc.*, **85**, 2446 (1963).
(5) M. H. Karger and Y. Mazur, *J. Org. Chem.*, **36**, 528 (1971).
(6) As noted above, the quantity of **4** (the product resulting from protonation of **2**) was suppressed by utilizing base-washed methyl p-toluenesulfonate.
(7) To account for the formation of a benzamide in the Raney nickel hydrogenolysis of **1**, Hinman[2] has suggested that **1** is initially converted in low yield to ethyl benzoate and 1,1-dimethyl-2-benzoylhydrazine in refluxing ethanol.
(8) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).
(9) S. Wawzonek and R. C. Gueldner, *J. Org. Chem.*, **30**, 3031 (1965).
(10) R. L. Hinman and M. C. Flores, *J. Org. Chem.*, **24**, 660 (1959).

Nucleophilic Displacements on Halogen Atoms. VII.[1] Reactions of α-Halo Sulfones with Sodium Arenesulfinates

Bruce B. Jarvis* and William P. Tong

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received January 12, 1976

A Hammett correlation (using σ^- constants) for the reactions of α-bromo- and α-iodobenzyl phenyl sulfones with sodium arenesulfinates in aqueous dimethylformamide has yielded ρ values of +6.20 and +6.27, respectively. A similar study of the reactions of α-bromo- and α-iodo-*p*-cyanobenzyl phenyl sulfones with substituted sodium arenesulfinates showed that the logarithms of the second-order rate constants gave linear correlations with σ^+ constants to yield ρ values of −2.57 and −1.69, respectively. The order of reactivity in the reactions of sodium benzenesulfinate with the α-halo-*p*-nitrobenzyl phenyl sulfones is $k_{Br} > k_I \gg k_{Cl}$, but α-iodobenzyl phenyl sulfone reacts significantly faster than α-bromobenzyl phenyl sulfone with the nitrogen nucleophile 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN).

The reactions of α-halobenzyl phenyl sulfones with triarylphosphines in aqueous dimethylformamide (DMF) have been investigated in detail.[2,3] This reaction (eq 1) can be characterized as a bimolecular nucleophilic displacement by the phosphine on the halogen atom in **1** to yield a carbanion–halophosphonium ion pair (**3**) which subsequently is rapidly hydrolyzed by water to give the observed products (eq 1).

$$\underset{\mathbf{1}}{ArCHXSO_2Ph} + \underset{\mathbf{2}}{Ar'_3P} \xrightarrow{\text{slow}} \underset{\mathbf{3}}{[ArCHSO_2Ph]^-[Ar'_3PX]^+}$$

$$\xrightarrow[H_2O]{\text{fast}} \underset{\mathbf{4}}{ArCH_2SO_2Ph} + Ar'_3PO + HX \quad (1)$$

Reaction 1 is characterized by several interesting features which distinguish it from normal nucleophilic displacement reactions: (a) k_{Br}/k_I ratios are greater than one;[2-4] (b) the Hammett ρ values associated with the reactions of triphenylphosphine with **1** correlate with σ^- constants and for X = Br and X = I are quite large (ca. +6);[2] (c) the Hammett ρ values associated with **2** in reaction 1 correlate with σ constants and for **1**, Ar = *m*-CNC_6H_4, X = Br and I, the ρ's are ca. −3.[3] These data indicate that this reaction is very sensitive to changes in the substituents on both the nucleophile and the electrophile; this sensitivity was attributed to the high degree of bond making and bond breaking in the transition state of the first step in reaction 1.[2-4]

α-Halo sulfones react with a variety of nucleophiles in protic solvents via nucleophilic attack on the halogen atom to give the reduced sulfones **4**, but to date only triarylphosphines have been studied extensively. We now report on the kinetics of the reactions of the α-halo sulfones **1** with arenesulfinates in aqueous DMF. These reactions (eq 2) follow a pathway similar to eq 1, but in eq 2, the reaction involves nucleophilic displacement on a halogen atom by a sulfur nucleophile.

$$\underset{\mathbf{1}}{ArCHXSO_2Ph} + \underset{\mathbf{5}}{Ar'SO_2^-} \xrightarrow{\text{slow}}$$

$$[ArCHSO_2Ph]^-Ar'SO_2X \xrightarrow[H_2O]{\text{fast}} \mathbf{4} + Ar'SO_3^- + HX \quad (2)$$

Results and Discussion

The reactions of sodium benezenesulfinate (**5**, Ar' = Ph) with the α-halo sulfones were run in 90% (v/v) aqueous DMF, and the rates were measured by titration for liberated halide ion. The kinetic data are given in Tables I and II. The reactions were shown to follow second-order kinetics, first order each in sulfone and benzenesulfinate. The presumed benzenesulfonyl halide intermediates were shown to react under the reaction conditions at rates much greater than those associated with the sulfones **1** (see Experimental Section). The α-chloro sulfones (**1**, X = Cl) reacted considerably slower with sodium benzenesulfinate, and only rate data for α-chloro-*p*-nitrobenzyl phenyl sulfone were determined.

A comparison of the rate data in Table II with those reported earlier for the reaction of **1** with triphenylphosphine in 90% aqueous DMF[2] shows that triphenylphosphine reacts ca. 10^2 times faster with the α-bromo sulfones and ca. 10 times faster with the α-iodo sulfones than does sodium benzenesulfinate. α-Chloro-*p*-nitrobenzyl phenyl sulfone reacts 13 times faster with triphenylphosphine than with sodium benzenesulfinate in 90% aqueous DMF at 25 °C.

Hammett σρ plots of the data in Table II give good correlations with σ^- constants which is consistent with the intermediacy of a carbanion (eq 2) and agrees with the data reported previously for the reactions of **1** with triphenylphosphine.[2] The ρ values for the bromides and iodides for reaction 2 are +6.27 (r = 0.996) and +6.20 (r = 0.997), respectively. They are comparable to those ρ values reported for the reactions of **1** with triphenylphosphine: (Br) ρ = +5.97 and (I) ρ = +6.29.[2] The $\Delta H^{\ddagger}$'s for reaction 2 (see Table II) are about 6–8 kcal/mol higher than the $\Delta H^{\ddagger}$'s associated with reaction 1; however, the $\Delta S^{\ddagger}$'s are about 10–15 eu less negative for reaction 2 than reaction 1. This increase in $\Delta S^{\ddagger}$ for reaction 2 (cf. reaction 1) is expected since in reaction 1 charges are being created in the transition state (hence a high ordering of the polar solvent molecules),[5] whereas in reaction 2, the charge is being dispersed in the transition state.

As in the reactions with triarylphosphines,[2-4] the α-bromo sulfones proved to be more reactive than the α-iodo sulfones toward sodium benzenesulfinate. The absolute difference in reactivity between the bromides and iodides for reactions 1 and 2 are remarkably similar (ca. an order of magnitude) which is surprising in view of the difference in nucleophiles. The diminished reactivity of the iodides (cf. the bromo sulfones) is probably due to the weak sulfur–iodine bond (cf. the significantly stronger sulfur–bromine bond) being formed in the transition state.[6] This implies that the use of a nucleophile in which the incipient nucleophile–iodine bond being formed differs little in strength from the analogous nucleophile–bromine bond might lead to a "normal" order of reactivity, i.e., the iodides reacting faster than the bromides.[7] The bond dissociation energies of the nitrogen trihalides[7] suggest that nitrogen nucleophiles might show a different order of reactivity than the phosphines or the sulfinates. However, since amines are significantly harder bases[8] than phosphines or sulfinates,

Table I. Rate Constants for the Reactions of α-Halobenzyl Phenyl Sulfones, $YC_6H_4CHXO_2Ph$, with Sodium Benzenesulfinate in 90% Aqueous DMF

Registry no.	X	Y	Temp, °C (±0.1°)	$10^3 k_2$, $M^{-1} s^{-1}$
41037-81-4	Br	m-Cl	80.0	0.576 ± 0.049
			90.0	1.29 ± 0.04
			100.0	3.47 ± 0.13
41037-82-5	Br	m-CN	60.0	1.63 ± 0
			70.0	4.20 ± 0.01
			80.0	10.9 ± 0.03
56571-78-9	Br	p-CH_3SO_2	30.0	1.12 ± 0.01
			40.0	3.35 ± 0.12
			50.0	9.67 ± 0.29
41037-83-6	Br	p-CN	20.0	0.840 ± 0.040
			30.0	2.56 ± 0.16
			40.0	7.55 ± 0.01
41037-84-7	Br	p-NO_2	10.0	123 ± 4
			0.0	43.9 ± 1.0
			−10.00	13.4 ± 0.2
41037-86-9	I	m-Cl	70.0	0.194 ± 0.003
			80.0	0.723 ± 0.016
			90.0	1.56 ± 0.02
41037-87-0	I	m-CN	60.0	0.443 ± 0.017
			70.0	1.28 ± 0.01
			80.0	4.47 ± 0.35
58311-76-5	I	p-CH_3SO_2	30.0	0.617 ± 0.03
			40.0	2.05 ± 0.04
			40.0	6.06 ± 0.05
41037-88-1	I	p-CN	30.0	1.01 ± 0.05
			40.0	5.41 ± 0.47
			50.0	10.3 ± 0
41037-89-2	I	p-NO_2	0.0	10.3 ± 1.4
			10.0	33.4 ± 1.5
			20.0	82.4 ± 0.2
7693-38-1	Cl	p-NO_2	80.0	0.833 ± 0.003
			90.0	1.55 ± 0.04
			100.0	4.69 ± 0.07

Table II. Rate Constants and Activation Parameters for the Reaction of α-Halobenzyl Phenyl Sulfones, $YC_6H_4CHXSO_2Ph$, with Sodium Benzenesulfinate in 90% Aqueous DMF at 25 °C

X	Y[a]	k_{25}, $M^{-1} s^{-1}$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
Br	m-Cl	1.16×10^{-6}	22.9 ± 1.2	−12.0 ± 3.3
	m-CN	3.14×10^{-5}	21.6 ± 0.3	−9.7 ± 1.0
	p-SO_2CH_3	6.21×10^{-4}	20.4 ± 0.3	−7.7 ± 1.0
	p-CN	1.49×10^{-3}	19.4 ± 0.4	−9.1 ± 1.4
	p-NO_2	5.41×10^{-1}	15.8 ± 0.3	−9.0 ± 1.0
I	m-Cl	6.84×10^{-7}	25.3 ± 0.3	−5.3 ± 0.7
	m-CN	3.54×10^{-6}	26.4 ± 1.0	+1.9 ± 3.0
	p-SO_2CH_3	3.35×10^{-4}	21.6 ± 0.1	−4.1 ± 0.3
	p-CN	6.27×10^{-4}	22.1 ± 0.5	−1.9 ± 1.5
	p-NO_2	1.37×10^{-1}	16.0 ± 1.1	−9.3 ± 3.7
Cl	p-NO_2	2.15×10^{-6}	22.0 ± 0.2	−14.0 ± 0.9

[a] The σ^- constants used in the Hammett plots are those derived from the ionization of phenols except for the p-CH_3SO_2 group. The σ^- values for the p-CH_3SO_2 group is 0.82 which was obtained from a related study (see ref 1).

typical amines are unreactive in this type of reaction, although some vicinal dihalides may undergo dehalogenation via nucleophilic displacement on an iodine[9] or bromine[10] atom by nitrogen nucleophiles.[11] We have found that the bicyclic amidines such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) are considerably more reactive in reactions involving nucleophilic displacements on halogen atoms than are typical amines; this increased reactivity is probably due to the enhanced polarizability of the bicyclic amidines.[12] The α-iodo sulfones reacted considerably faster than the α-bromo sulfones with DBN. Thus, at ambient temperatures, the reaction of DBN with α-iodobenzyl phenyl sulfone in 90% aqueous DMF was complete within 3 h to give the reduced sulfone 4 (Ar = Ph), while under these conditions, α-bromobenzyl phenyl sulfone gave only recovered starting material. However, at 40° the more reactive α-bromo-m-cyanobenzyl phenyl sulfone did react with DBN to give the reduced sulfone 4. The degree of bond making between the nitrogen and halogen atoms in the transition state for this reaction is no doubt less[9] than the corresponding degree of bond making for the transition states of step one in reactions 1 and 2,[2-4] and this in part accounts for the divergent behavior of DBN vs. the phosphine and sulfinate nucleophiles.[13]

The large positive ρ values associated with the α-bromo and α-iodo sulfones in reaction 2, $Ar'SO_2^- = PhSO_2^-$, are indicative of a carbanion-like transition, i.e., nearly complete carbon–halogen bond cleavage.[2] In order to ascertain the degree of sulfur–halogen bond making in the transition state, a study of the variation of rates with a change in

Table III. Kinetic Data for the Reactions of α-Halo-*p*-cyanobenzyl Phenyl Sulfones, *p*-$NCC_6H_4CHXSO_2Ph$, with Sodium Arenesulfinates, $YC_6H_4SO_2Na$, in 90% Aqueous DMF

X	Y	Temp, °C (±0.1°)	$10^3 k_2$, $M^{-1} s^{-1}$
Br	*p*-Cl	50.0	1.52 ± 0.07
		60.0	3.88 ± 0.14
		70.0	12.4 ± 0.19
Br	*p*-CH_3	20.0	0.510 ± 0.018
		30.0	1.53 ± 0.09
		40.0	4.13 ± 0.18
Br	*p*-$CH_3C(=O)NH$	30.0	10.7 ± 0.6
		40.0	30.6 ± 1.2
		50.0	62.1 ± 1.8
Br	*p*-CH_3O	30.0	9.55 ± 0.08
		40.0	26.7 ± 0.7
		50.0	65.3 ± 1.8
I	*p*-Cl	50.0	1.69 ± 0.01
		60.0	4.17 ± 0.15
		70.0	10.4 ± 0.4
I	*p*-CH_3	20.0	0.346 ± 0.034
		30.0	1.52 ± 0.15
		40.0	5.92 ± 0.17
I	*p*-$CH_3C(=O)NH$	30.0	4.23 ± 0.18
		40.0	12.1 ± 0.2
		50.0	27.5 ± 0.3
I	*p*-CH_3O	20.0	2.24 ± 0.01
		30.0	8.71 ± 0.12
		40.0	21.3 ± 0

structure of the arenesulfinates was undertaken (Tables III and IV). The data in Table IV give good Hammett plots and show significantly better correlations with σ^+ values[14] compared with normal σ^- values: 1 (Ar = *p*-CNC_6H_4; X = Br), $\rho_{\sigma}{}^+ = -2.57$ ($r = 0.999$), $\rho_{\sigma} = -4.18$ ($r = 0.931$);[15] 1 (Ar = *p*-CNC_6H_4; X = I), $\rho_{\sigma}{}^+ = -1.69$ ($r = 0.998$), $\rho_{\sigma} = -2.78$ ($r = 0.945$).[15] These ρ values can be contrasted with those associated with reaction 1 in which the substituents were varied on the ring positions of the triarylphosphines.[3] These latter ρ values (eq 1) are ca. −3 with the one associated with the α-iodo sulfone being slightly larger than the ρ value for the α-bromo sulfone. Where these two systems differ significantly is that for the phosphines (eq 1), the change in rates correlates better with the normal Hammett σ constants, whereas for eq 2 the change in rates with a change in the aryl substituents in the arenesulfinates correlates with σ^+ constants much better than with normal σ values (vide supra).

Hammett $\sigma\rho$ studies of arenesulfinates have consistently shown better correlations with σ constants rather than σ^+ constants. Those studies reported in the literature include bimolecular nucleophilic displacements (SN2 reactions) on carbon[16] and oxygen[17] atoms, Michael additions to acrylonitrile,[18] and correlation of S–O stretching frequencies in the ir spectra of substituted sodium arenesulfinates.[19] In all these studies, the ρ values are ca. −1 indicating that they are not as sensitive to substituent changes as are the reactions we are reporting. Although additional Hammett type studies of SN2 reactions on halogen atoms with arenesulfinate nucleophiles have not been reported, several studies dealing with the reactivity of meta- and para-substituted thioanisoles toward *N*-chloro sulfonamides[20] and molecular bromine[21] (reactions which involve nucleophilic displacement by a sulfur atom on a halogen atom) have been reported. These ρ values were found to be on the order of −3.5 and were derived from a correlation of rates with normal σ constants rather than σ^+ constants. Although the sulfinate anion in these cited studies does not appear to function as an electron-accepting group (via resonance), the sulfonyl group in sulfones under suitable conditions can operate as a strong resonance accepting group.[22] For example, for a series of para-substituted aryl sulfones, the square root of the integrated intensities of the symmetric and asymmetric S–O bond stretching frequencies correlate with σ^+ constants.[23] Since we are suggesting that the transition state for reaction 2 lies very close to complete sulfur–halogen bond formation, it is reasonable that a structure–reactivity correlation might resemble more closely those observed for sulfones (and sulfonyl halides) than those associated with arenesulfinates.

Experimental Section

The syntheses of the α-halo sulfones have been reported previously.[2] The sodium arenesulfinates were prepared by the method of Smiles and Bere[24] and were recrystallized from ethanol. The kinetic procedure followed that reported earlier[2] except that the final concentrations of the sulfones were 0.001 M, and the concentrations of the sodium arenesulfinates ranged from 0.01 to 0.2 M. Aliquots (ca. 5 ml) of sample were quenched with water[25] and titrated against standard silver nitrate solutions using a Sargent-Welch recording titrator Model D equipped with a Corning Silver billet and Sargent calomel electrodes which were interposed by a potassium nitrate–agar salt bridge. Preparative runs for reaction 2 were made for the reactions of α-chloro-, α-bromo-, and α-iodo-*p*-nitrobenzyl phenyl sulfones with sodium benezenesulfinate at ca. 80 °C for 1 half-life. Upon workup, each reaction mixture yielded a solution which was shown by NMR spectroscopy to be a 50:50 mixture of starting α-halo sulfone 1 and reduced sulfone 4. The sulfones were isolated by preparative TLC (silica gel, methylene chloride) and identified by ir, melting point, and mixture melting point.

Reaction of α-Bromo-*m*-cyanobenzyl Phenyl Sulfone with 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN). To a solution of 1.00 g (2.98 mmol) of the α-halo sulfone in 40 ml of 90% aqueous DMF was added 0.40 g (3.22 mmol) of DBN (Aldrich) in 2 ml of 90%

Table IV. Rate Constants and Activation Parameters for the Reaction of α-Halobenzyl Phenyl Sulfones, *p*-$CNC_6H_4CHXSO_2Ph$, with Sodium Arenesulfinates, $YC_6H_4SO_2Na$, in 90% Aqueous DMF at 25 °C

Registry no.	X	Y[a]	k_2, $M^{-1} s^{-1}$	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
14752-66-0	Br	*p*-Cl	7.11×10^{-5}	22.5 ± 1.0	−1.8 ± 0.8
824-79-3		*p*-CH_3	8.89×10^{-4}	18.5 ± 0.4	−10 ± 1.5
15898-43-8		*p*-$CH_3C(=O)NH$	6.95×10^{-3}	16.5 ± 0.6	−13 ± 1.9
6462-50-6		*p*-CH_3O	1.60×10^{-2}	16.9 ± 0.3	−7.7 ± 0.9
873-55-2		*p*-H	1.49×10^{-3}	19.4 ± 0.4	−9.1 ± 1.4
	I	*p*-Cl	1.23×10^{-4}	19.4 ± 0.4	−11 ± 1
		p-CH_3	7.33×10^{-4}	25.3 ± 0.9	12 ± 3
		p-$CH_3C(=O)NH$	2.62×10^{-3}	17.6 ± 0.4	−11 ± 1
		p-CH_3O	4.31×10^{-3}	20.0 ± 0.1	−2.1 ± 0.1
		p-H	6.27×10^{-4}	22.1 ± 0.5	−1.9 ± 1.7

[a] The σ^+ constants used in the Hammett plots are given in ref 14 except for the acetamido group. The σ^+ constant for CH_3CONH is reported by S. Clementi and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 1887 (1973).

aqueous DMF. The solution was heated at 40 °C for 10 h. The addition of water resulted in the formation of a brown precipitate. The precipitate was redissolved in methylene chloride and the solution dried ($MgSO_4$) and decolorized with neutral Norit. Methylene chloride was removed in vacuo and crystallization from methylene chloride–hexane gave 631 mg (83%) of *m*-cyanobenzyl phenyl sulfone. The product identification was made by comparison with an authentic sample.[2]

Reaction of α-Iodo- and α-Bromobenzyl Phenyl Sulfones with DBN. To 200 mg (0.56 mmol) of α-iodobenzyl phenyl sulfone in 6 ml of 90% aqueous DMF at room temperature was added 200 mg (1.01 mmol) of DBN. The reaction was followed by TLC (silica gel, methylene chloride). After 3 h the reaction was complete. Water was added, and the mixture was extracted twice with 20-ml portions of methylene chloride, washed once with water, and dried ($MgSO_4$). The solvent was removed in vacuo. Crystallization from methylene chloride–hexane gave 80 mg (62%) of benzyl phenyl sulfone. Identification was made by comparison with an authentic sample.[2] Under similar conditions, α-bromobenzyl phenyl sulfone gave only recovered starting material.

Reaction of Benzenesulfonyl Halides in Aqueous DMF. Solutions of benzenesulfonyl chloride and benzenesulfonyl bromide (~0.001 M) in 90% aqueous DMF were monitored in a Freas conductivity cell with conductance readings taken with a Barnstead conductivity bridge, Model PM-70CB.[2] The rate of increase in conductivity for the bromide was too fast to follow at 25 °C and crude data for benzenesulfonyl chloride showed that it reacted $>10^3$ times faster than α-chloro-*p*-nitrobenzyl phenyl sulfone reacted with 0.2 M sodium benzenesulfinate in 90% aqueous DMF at 25 °C.

Acknowledgment. Support from the University of Maryland Computer Science Center is gratefully acknowledged.

Registry No.—1,5-Diazabicyclo[4.3.0]non-5-ene, 3001-72-7; α-iodobenzyl phenyl sulfone, 41037-85-8; α-bromobenzyl phenyl sulfone, 15296-88-5.

References and Notes

(1) Part VI: B. B. Jarvis, R. L. Harper, Jr., and W. P. Tong, *J. Org. Chem.*, **40**, 3778 (1975).
(2) B. B. Jarvis and J. C. Saukaitis, *J. Am. Chem. Soc.*, **95**, 7708 (1973).
(3) B. B. Jarvis and B. A. Marien, *Int. J. Sulfur Chem.*, in press.
(4) B. B. Jarvis and B. A. Marien, *J. Org. Chem.*, **40**, 2587 (1975).
(5) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2d ed, Wiley, New York, N.Y., 1961, p 138. For similar activation parameter data associated with the reactions of triphenylphosphine see L. E. Overman, D. Matzinger, E. M. O'Connor, and J. D. Overman, *J. Am. Chem. Soc.*, **96**, 6081 (1974) (displacement on sulfur atoms) and B. A. Sudbury and J. H. Krueger, *Inorg. Chem.*, **13**, 1736 (1974) (displacement on nitrogen atoms).
(6) Although no quantitative bond disassociation energies for the sulfur–halogen bond in sulfonyl halides are available, sulfonyl bromides (see M. Fieser and L. Fieser, "Reagents for Organic Synthesis", Vol. 3, Wiley, New York, N.Y., 1972, p 18) are considerably more stable than sulfonyl iodides [see W. E. Truce and D. L. Heuring, *J. Org. Chem.*, **39**, 245 (1974)].
(7) The energy of atomization per bond in sulfur dihalides is 8.5 kcal/mol greater for sulfur dibromide than for sulfur diiodide: R. T. Sanderson, "Chemical Bond and Bond Energy", Academic Press, New York, N.Y., 1971.
(8) T. L. Ho, *Chem. Rev.*, **75**, 1 (1975).
(9) E. Baciocchi and C. Lillocci, *J. Chem. Soc., Perkin Trans. 2*, 802 (1975).
(10) T. L. Ho and C. M. Wong, *Synth. Commun.*, **5**, 87 (1975).
(11) We take this opportunity to note that dehalogenations are not always as straightforward as they might appear. Some time ago, one of us (B.B.J.) attempted to dehydrohalogenate *meso*-1,2-dibromo-1,2-diphenylethane with sodium ethoxide in ethanol–dioxane cosolvent. Unless the reagent grade dioxane had been purified, this reaction led to *trans*-stilbene as the major product. If the dioxane was purified carefully, the normal product, (*E*)-1,2-diphenylbromoethane, was obtained.
(12) H. Oediger, F. Moller, and K. Eiter, *Synthesis*, 591 (1972).
(13) The order of reactivity for nucleophilic attack on a bromine atom vs. an iodine atom is by no means clear cut. Much of the qualitative data in the literature suggests that the ease of reduction for alkyl halides is RI > RBr, and one quantitative study [M. C. Verploegh, L. Donk, H. J. T. Bos, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **90**, 765 (1971)] has shown that nucleophilic attack by sulfide ion on the halogen atom in 2-(2-thienyl)-1-haloacetylenes occurs much more readily with the iodides than with the bromides. Note that in our study (Table IV) α-bromo-*p*-cyanobenzyl phenyl sulfone reacts faster than the iodo compound with sodium benzenesulfinate, but α-iodo-*p*-cyanobenzyl phenyl sulfone reacts faster than the bromo analogue with sodium *p*-chlorobenzenesulfinate.
(14) O. Exner in "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, p 1.
(15) The correlations with normal σ constants do not include the points for the acetamido group. If these points are included, the fits are considerably worse: (Br) $\rho = -3.76$ ($r = 0.777$) and (I) $\rho = -2.52$ ($r = 0.627$).
(16) B. J. Lindberg, *Acta Chem. Scand.*, **17**, 393 (1963).
(17) B. J. Lindberg, *Acta Chem. Scand.*, **20**, 1843 (1966).
(18) Y. Ogata, Y. Sawaki, and M. Isono, *Tetrahedron*, **26**, 3045 (1970).
(19) B. J. Lindberg, *Acta Chem. Scand.*, **21**, 2215 (1967).
(20) F. Ruff and A. Kucsman, *J. Chem. Soc., Perkin Trans. 2*, 509 (1975).
(21) U. Miotti, G. Modena, and L. Sedea, *J. Chem. Soc. B*, 802 (1970).
(22) (a) G. A. Pagani, *J. Chem. Soc., Perkin Trans. 2*, 1392 (1974); (b) F. de Jong and M. Janssen, *ibid.*, 573 (1972); (c) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952).
(23) N. C. Cutress, T. B. Grindley, A. R. Katritsky, M. Shome, and R. D. Topsom, *J. Chem. Soc., Perkin Trans. 2*, 268 (1974).
(24) S. Smiles and C. M. Bere, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 1. See also ref 16.
(25) Originally the aliquots were quenched with water–acetone–nitric acid (1:1:1); however, electrode response was significantly better with water alone.

Displacement of the Nitro Group of Substituted Nitrobenzenes—a Synthetically Useful Process

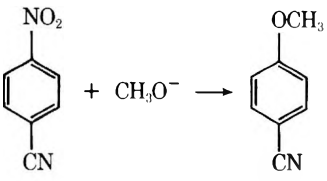
Nathan Kornblum,* Leung Cheng, Robert C. Kerber, Melvin M. Kestner, Barry N. Newton, Harold W. Pinnick, Ronald G. Smith, and Peter A. Wade

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

Received November 20, 1975

Nitrobenzenes substituted by a variety of electron-withdrawing groups readily undergo nucleophilic displacement of the nitro group at 25°C if the reaction is conducted in hexamethylphosphoramide (HMPA). The yields of pure products are excellent.

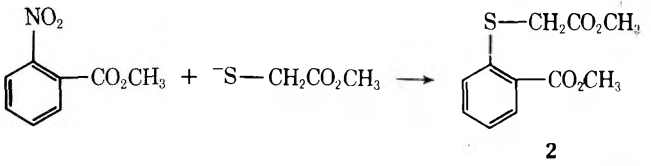
Nucleophilic displacement of a nitro group from a benzene ring carrying only one activating group, e.g., the process of eq 1, has, in the past, rarely been observed.[1] Recently, however, Beck and his colleagues[2] have shown that when a dipolar aprotic solvent (DMF) is employed the displacement of a nitro group by mercaptide ions occurs readily at room temperature and that processes such as that of



(1)

1

eq 2[3] are synthetically very valuable. In 1974 Knudsen and Snyder[4] reported that anions derived from aldoximes are

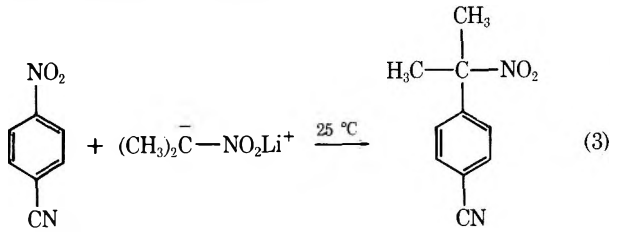


2

(2)

able to replace the nitro group of monosubstituted nitrobenzenes, e.g., *p*-nitrobenzonitrile (1), ultimately giving phenols. Here again the reactions are conducted at room temperature in a dipolar aprotic solvent, dimethyl sulfoxide, and the yields are very good.

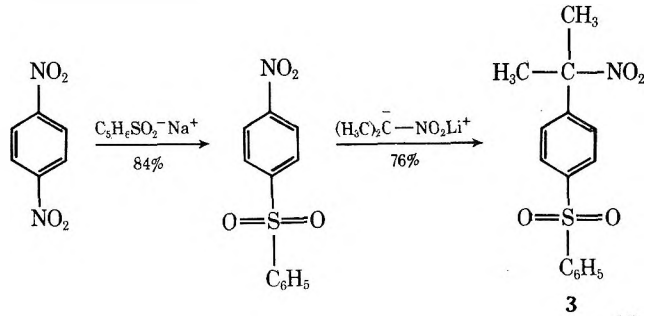
Over the past ten years, in connection with a study of substitution reactions which proceed via radical anion intermediates,[5] a number of otherwise inaccessible compounds have been synthesized in this laboratory from readily available nitroaromatics simply by displacing the nitro group. For example, the reaction of eq 3 is complete in 12 h at 25 °C and gives an 82% yield.



(3)

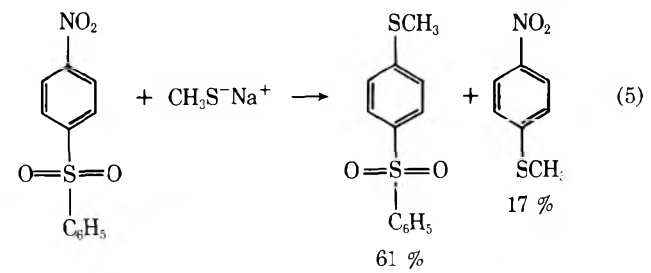
Nitrobenzenes substituted by six different electron-withdrawing groups have been studied and a variety of nucleophiles have been employed. The use of dipolar aprotic solvents makes it feasible to carry out these reactions at 25 °C and, while the matter has not been studied extensively, it appears that these displacements occur most readily in hexamethylphosphoramide (HMPA), less rapidly in Me_2SO, and still less rapidly in DMF. Our results are summarized in Table I; it should be emphasized that the yields given there refer to pure, isolated, products.

A nice example of the value in synthesis of these processes is the two-step conversion of the readily available *p*-dinitrobenzene into the tertiary nitrosulfone 3 in 64% overall yield (eq 4).



3

(4)



(5)

When 4-nitrophenyl phenyl sulfone is treated with the sodium salt of methyl mercaptan the reaction is complete in 15 min and two products are isolated (eq 5). This is the only instance in which two competitive processes were detected.

Experimental Section[6]

The substituted nitrobenzenes employed in this work were commercial products, purified by recrystallization or sublimation. Crystalline, analytically pure salts were used inasmuch as they were available from other studies; it is highly probable that equally good results will be obtained with salts prepared in situ. The various salts were prepared as described in the literature: the lithium salts of 2-nitropropane and 2-nitrobutane,[7] sodium phenoxide,[8] the sodium salt of methyl mercaptan.[9] The sodium salts of thiophenol and benzyl mercaptan were prepared as described for *p*-chlorothiophenol.[7] Commercial sodium benzenesulfinate was recrystallized from ethanol.[10] As noted above, the success of these reactions is, in good part, due to the use of HMPA as the solvent. HMPA should be handled with great care since it has recently been found to cause cancer in laboratory animals [*Chem. Eng. News*, 17 (Sept 29, 1975)].[11]

General Procedure. The synthesis of *p*-cyano-α-nitrocumene (the reaction of eq 3) is illustrative. Under nitrogen, a mixture of 1.48 g (10 mmol) of *p*-nitrobenzonitrile and 1.90 g (20 mmol) of the lithium salt of 2-nitropropane was dissolved in 20 ml of HMPA and the dark red solution was stirred for 12 h at 25 °C after which it was poured into ice water and extracted with benzene. The benzene extract was washed with water and dried, and the solvent was removed under reduced pressure. The orange residue, mp 55–59 °C, 1.78 g, was chromatographed on acid-washed alumina (Merck) and then recrystallized from pentane. In this way 1.56 g (82% yield) of colorless *p*-cyano-α-nitrocumene, mp 59.5–60.5 °C, was obtained:[12] NMR ($CDCl_3$) δ 2.0 (s, 6 H) and 7.6 (m, 4 H).

Anal. Calcd for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.22; H, 5.14; N, 14.71.

4-Benzoyl-α-nitrocumene. 4-Nitrobenzophenone (2.06 g, 9.07 mmol), the lithium salt of 2-nitropropane (4.76 g, 50 mmol), 40 ml of HMPA, and a reaction time of 24 h were employed. Workup gave 2.19 g of a dark orange solid, mp 60–69 °C, which was chromatographed on silica gel and then recrystallized from hexane to give 1.91 g (78% yield) of 4-benzoyl-α-nitrocumene: mp 69.5–70.5 °C; NMR ($CDCl_3$) δ 2.0 (s, 6 H), 7.3–7.9 (m, 9 H); ir (KBr) 6.0 (C=O), 6.52 and 7.55 μ (NO_2).

Anal. Calcd for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.54; H, 5.79; N, 5.33.

4-Phenoxybenzophenone. 4-Nitrobenzophenone (1.18 g, 5 mmol), sodium phenoxide (2.90 g, 25 mmol), and 40 ml of HMPA and a reaction time of 24 h were employed. The crude, an orange oil (1.50 g), when chromatographed on acid-washed alumina, afforded 1.14 g (83% yield) of 4-phenoxybenzophenone, mp 69–70 °C (lit.[13] mp 71 °C).

Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.04; H, 4.99.

4-(Thiobenzyl)benzophenone. Here 1.18 g (5 mmol) of 4-nitrobenzophenone, 0.75 g (5.1 mmol) of the sodium salt of benzyl mercaptan, and 10 ml of HMPA (reaction time 10 min) were employed. The crude product was chromatographed on acid-washed alumina and then recrystallized from methanol. An 82% yield (1.25 g) of 4-(thiobenzyl)benzophenone, mp 83–84 °C (lit.[14] mp 84.5–85.4 °C), was obtained.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.29; S, 10.53. Found: C, 78.93; H, 5.46; S, 10.32.

Ethyl *p*-Ethoxybenzoate. Ethyl *p*-nitrobenzoate (9.8 g, 50 mmol), sodium ethoxide (3.74 g, 55 mmol), and 50 ml of HMPA were employed; reaction time was 30 min. The crude product was a red oil which on distillation through a short column afforded 7.95 g (81% yield) of ethyl *p*-ethoxybenzoate; bp 79–81 °C (0.22 mm) [lit.[15] bp 145–146 °C (13 mm)], $n^{19}D$ 1.5179 (lit.[16] $n\ ^{20}D$ 1.5181). Ir and NMR spectra were identical with those in Sadtler.

Ethyl *p*-(Thiobenzyl)benzoate. Ethyl *p*-nitrobenzoate (0.98 g, 5 mmol), sodium benzyl mercaptide (0.80 g, 5.5 mmol), 10 ml of HMPA, and a 30-min reaction time were employed. Chromatography of the crude product (mp 53–56 °C) on silica gel afforded 1.20 g (88% yield) of ethyl *p*-(thiobenzyl)benzoate, mp 57–58 °C (lit.[17] mp 60 °C).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92; S, 11.77. Found: C, 70.31; H, 5.88; S, 11.53.

4-Carbomethoxy-α-nitrocumene. Methyl *p*-nitrobenzoate (1.81 g, 10 mmol), the lithium salt of 2-nitropropane (4.75 g, 50 mmol), and 33 ml of HMPA were employed; reaction time was 84

Table I. Compounds Synthesized by the Displacement of an Aromatic Nitro Group at 25 °C[a]

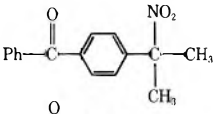
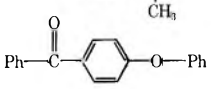
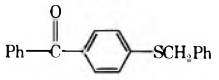
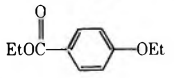
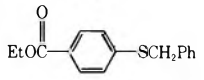
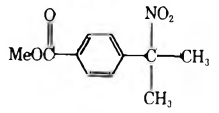
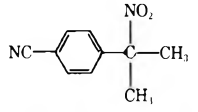
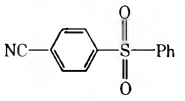
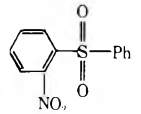
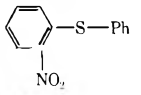
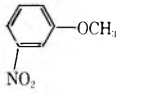
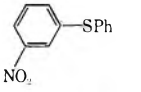
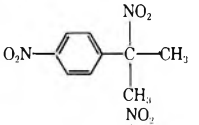
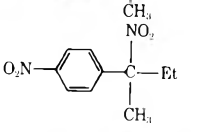
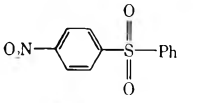
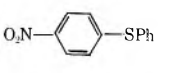
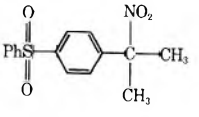
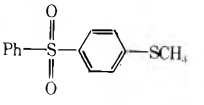
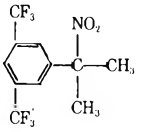
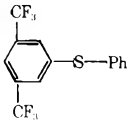
Nitroaromatic employed	Nucleophile employed	Product	Registry no.	Yield, %[b]	Reaction time
4-Nitrobenzophenone	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-79-1	78	24 h
4-Nitrobenzophenone	PhO^-Na^+		6317-73-3	83	24 h
4-Nitrobenzophenone	$PhCH_2S^-Na^+$		26960-79-2	82	10 min
Ethyl *p*-nitrobenzoate	EtO^-Na^+		23676-09-7	31	30 min
Ethyl *p*-nitrobenzoate	$PhCH_2S^-Na^+$		58324-80-4	38	30 min
Methyl *p*-nitrobenzoate	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-81-5	60	84 h
p-Nitrobenzonitrile	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-82-6	82	12 h
p-Nitrobenzonitrile	$PhSO_2^-Na^+$		28525-13-5	67	48 h[c]
o-Dinitrobenzene	$PhSO_2^-Na^+$		31515-43-2	85	1.5 h
o-Dinitrobenzene	PhS^-Na^+		4171-83-9	80	18 h[d]
m-Dinitrobenzene	$CH_3O^-Na^+$		555-03-3	83	16 h
m-Dinitrobenzene	PhS^-Na^+		37984-02-4	88	24 h
p-Dinitrobenzene	$(CH_3)_2\overline{C}-NO_2Li^+$		3276-35-5	75	3 h[e,f]
p-Dinitrobenzene	$CH_3\overline{C}(Et)-NO_2Li^+$		58324-83-7	84	8 h[e]
p-Dinitrobenzene	$PhSO_2^-Na^+$		1146-39-0	84	50 h[e]
p-Dinitrobenzene	PhS^-Na^+		952-97-6	96	24 h[d]
4-Nitrophenyl phenyl sulfone	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-84-8	76	12 h
4-Nitrophenyl phenyl sulfone	$CH_3S^-Na^+$		58324-85-9	61[g]	15 min

Table I (*Continued*)

Nitroaromatic employed	Nucleophile employed	Product	Registry no.	Yield, %[b]	Reaction time
3,5-Bis(trifluoromethyl)-nitrobenzene	$(CH_3)_2\overline{C}-NO_2Li^+$		58324-86-0	70[h]	4 h
3,5-Bis(trifluoromethyl)-nitrobenzene	PhS^-Na^+		58324-87-1	92	6 h[d]

[a] Unless otherwise noted all reactions were carried out in HMPA at 25 °C. [b] Pure, isolated, product. [c] At 80 °C. [d] Reaction probably complete in much shorter time. [e] In Me_2SO. [f] In DMF the reaction requires 65 h. [g] A 17% yield of 4-nitrophenyl methyl sulfide was also isolated. [h] A 5% yield of 3,5-bis(trifluoromethyl)aniline was also isolated.

h. The crude, an orange oil, when chromatographed on silica gel and then recrystallized from pentane afforded 1.34 g (60% yield) of 4-carbomethoxy-α-nitrocumene: mp 50–51 °C; NMR ($CDCl_3$) δ 2.0 (s, 6 H), 3.91 (s, 3 H), 7.5 (d, 2 H), and 8.1 (d, 2 H).

Anal. Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.42; H, 5.98; N, 6.17.

4-Cyanophenyl Phenyl Sulfone. Here 1.04 g (7 mmol) of *p*-nitrobenzonitrile, 5.74 g (35 mmol) of sodium benzenesulfinate, 20 ml of HMPA, and a reaction time of 48 h at 80 °C were employed. Workup gave 1.37 g of a brown solid (mp 115–123 °C) which was passed through a short column of acid-washed alumina and then recrystallized from carbon tetrachloride to give 0.95 g of 4-cyanophenyl phenyl sulfone, mp 125–126° (lit.[18] mp 126 °C). The mother liquor was evaporated to dryness and the residue chromatographed to afford an additional 0.18 g of product, mp 124–125 °C. Total yield of 4-cyanophenyl phenyl sulfone was 67%.

Anal. Calcd for $C_{13}H_9O_2NS$: C, 64.20; H, 3.70; N, 5.76; S, 13.16; mol wt, 243.2. Found: C, 64.31; H, 3.63; N, 5.63; S, 13.42; mol wt, 247.1.

2-Nitrophenyl Phenyl Sulfone. Under nitrogen, a mixture of 2.02 g (12 mmol) of *o*-dinitrobenzene and 2.2 g (13.2 mmol) of sodium benzenesulfinate was dissolved in 20 ml of HMPA. The resulting orange solution was stirred for 1.5 h at 25 °C after which it was poured into ice water. The solid collected (mp 142–145 °C) was recrystallized twice from absolute ethanol to afford 2.67 g (85% yield) of 2-nitrophenyl phenyl sulfone, mp 145–146 °C (lit.[19] mp 145 °C).

2-Nitrophenyl Phenyl Sulfide. *o*-Dinitrobenzene (1.01 g, 6 mmol), sodium thiophenoxide (1.58 g, 12 mmol), 10 ml of HMPA, and a reaction time of 18 h were employed. Chromatography of the crude product (mp 70–74 °C) on acid-washed alumina afforded 1.11 g (80% yield) of 2-nitrophenyl phenyl sulfide, mp 78–79 °C (lit.[20] mp 79 °C).

***m*-Nitroanisole.** *m*-Dinitrobenzene (2.01 g, 12 mmol), sodium methoxide (0.82 g, 15 mmol), and 40 ml of HMPA were employed; reaction time was 16 h. Chromatography of the crude product on silica gel afforded 1.52 g (83% yield) of *m*-nitroanisole: mp 36–37 °C; NMR ($CDCl_3$) δ 3.88 (s, 3 H), 7.10–7.92 (m, 4 H).

3-Nitrophenyl Phenyl Sulfide. *m*-Dinitrobenzene (1.01 g, 6 mmol), sodium thiophenoxide (1.58 g, 12 mmol), 60 ml of HMPA, and a reaction time of 24 h were employed. Chromatography of the brown oil on acid-washed alumina afforded 1.21 g (88% yield) of 3-nitrophenyl phenyl sulfide: mp 40.5–41.5 °C (lit.[21] mp 42.5 °C); NMR ($CDCl_3$) δ 7.18–7.62 m, 7 H), 7.76–8.13 (m, 2 H).

α,*p*-Dinitrocumene. *p*-Dinitrobenzene (10.1 g, 60 mmol), the lithium salt of 2-nitropropane (6.3 g, 66 mmol), and 95 ml of Me_2SO were employed; reaction time was 3 h. Two recrystallizations of the crude product (mp 62–67 °C) from hexane–benzene afforded 9.5 g (75% yield) of α,*p*-dinitrocumene, mp 67–68 °C (lit.[22] mp 69–70 °C).

2-(*p*-Nitrophenyl)-2-nitrobutane. *p*-Dinitrobenzene (97.7 g, 0.582 mol), the lithium salt of 2-nitrobutane (68.7 g, 0.624 mol), and 1 l. of Me_2SO were employed as above (reaction time 8 h). Chromatography of the brown oil on acid-washed alumina afforded 109 g (84% yield) of 2-(*p*-nitrophenyl)-2-nitrobutane, mp 44.5–45.5 °C. A sample was distilled for microanalysis, bp 130–131 °C (0.11 mm).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.53; H, 5.40; N, 12.49. Found: C, 53.43; H, 5.45; N, 12.47.

4-Nitrophenyl Phenyl Sulfone. *p*-Dinitrobenzene (10.5 g, 62.5 mmol), sodium benzenesulfinate (11.3 g, 68.8 mmol), and 100 ml of Me_2SO were employed as above (reaction time 50 h). Two recrystallizations from absolute ethanol afforded 13.82 g (84% yield) of 4-nitrophenyl phenyl sulfone, mp 139–140 °C (lit.[23] mp 140, 142 °C).

4-Nitrophenyl Phenyl Sulfide. *p*-Dinitrobenzene (1.01 g, 6.0 mmol), sodium thiophenoxide (2.38 g, 18 mmol), and 30 ml of HMPA were employed (reaction time 24 h). Chromatography on acid-washed alumina afforded 1.32 g (96% yield) of 4-nitrophenyl phenyl sulfide: mp 52.5–53 °C (lit.[24] mp 54.5, 55 °C); NMR (CCl_4) δ 7.1 (d, 2 H), 7.4 (s, 5 H), 7.9 (d, 2 H).

4-Phenylsulfonyl-α-nitrocumene. To a solution of 4-nitrophenyl phenyl sulfone (13.15 g, 50 mmol) in 100 ml of HMPA, under nitrogen, was added 9.3 g (98 mmol) of the lithium salt of 2-nitropropane. The deep purple solution was stirred at 25 °C for 13 h after which it was poured into water and extracted with benzene. The benzene extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated. Two recrystallizations from absolute ethanol afforded 11.58 g (76% yield) of 4-phenylsulfonyl-α-nitrocumene, mp 117–117.5 °C.

Anal. Calcd for $C_{15}H_{15}NO_4S$: C 59.03; H, 4.92; N, 4.59; S, 10.49. Found: C, 59.13; H, 4.97; N, 4.50; S, 10.41.

4-Thiomethoxyphenyl Phenyl Sulfone. 4-Nitrophenyl phenyl sulfone (1.58 g, 6 mmol), sodium methyl mercaptide (0.428 g, 6.1 mmol), 15 ml of HMPA, and a reaction time of 15 min were employed. Chromatography on silica gel (benzene–ether fractions) followed by recrystallization from absolute methanol afforded 0.96 g (61% yield) of 4-thiomethoxyphenyl phenyl sulfone: mp 110–111 °C (lit.[25] mp 115 °C); NMR ($CDCl_3$) δ 2.42 (s, 3 H), 7.2–8.05 (m, 9 H).

Anal. Calcd for $C_{13}H_{12}O_2S_2$: C, 59.09; H, 4.58; S, 24.23. Found: C, 59.18; H, 4.54; S, 24.21.

From the hexane–benzene fractions of chromatography was isolated 0.172 g (17% yield) of *p*-nitrophenyl methyl sulfide: mp 69–70 °C (lit.[26] mp 71–72 °C); NMR ($CDCl_3$) δ 2.52 (s, 3 H), 7.3 (d, 2 H), 8.12 (d, 2 H).

Anal. Calcd for C_7H_7NS: C, 49.71; H, 4.17; N, 8.28; S, 18.92. Found: C, 49.84; H, 4.28; N, 8.15; S, 19.01.

3,5-Bis(trifluoromethyl)-α-nitrocumene. 3,5-Bis(trifluoromethyl)nitrobenzene (20.5 g, 80 mmol), the lithium salt of 2-nitropropane (8.2 g, 86 mmol), and 100 ml of HMPA were employed; reaction time was 4 h. The crude product was recrystallized from hexane to give 9.7 g of 3,5-bis(trifluoromethyl)-α-nitrocumene, mp 54.5–55 °C. An additional 6.8 g of product was obtained by chromatographing the residue obtained upon evaporation of the mother liquor on acid-washed alumina; total yield was 70%.

Anal. Calcd for $C_{11}H_9F_6NO_2$: C, 43.87; H, 3.01; N, 4.65; F, 37.84. Found: C, 43.98; H, 3.11; N, 4.65; F, 37.80.

3,5-Bis(trifluoromethyl)phenyl Phenyl Sulfide. 3,5-Bis(trifluoromethyl)nitrobenzene (1.03 g, 4 mmol), sodium thiophenoxide (1.06 g, 8 mmol), and 5 ml of HMPA were employed; reaction time was 6 h. Short-path distillation of the orange oil obtained afforded 1.18 g (92% yield) of pale yellow oil, bp 87–89 °C (0.6 mm), $n^{19}D$ 1.5093.

Anal. Calcd for $C_{14}H_8F_6S$: C, 52.17; H, 2.51; S, 9.94; mol wt, 322.2. Found: C, 52.15; H, 2.55; S, 9.81; mol wt, 324.6.

Acknowledgment. Our thanks are due to the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, Eli Lilly and Co., the Hoffmann-La Roche Foundation, and E. I. du Pont de Nemours and Co. for support of this work.

Registry No.—4-Nitrobenzophenone, 1144-74-7; ethyl *p*-nitrobenzoate, 99-77-4; methyl *p*-nitrobenzoate, 619-50-1; *p*-nitrobenzonitrile, 619-72-7; *o*-dinitrobenzene, 528-29-0; *m*-dinitrobenzene, 99-65-0; *p*-dinitrobenzene, 100-25-4; 4-nitrophenyl phenyl sulfone, 1146-39-0; 3,5-bis(trifluoromethyl)nitrobenzene, 328-75-6; 2-nitropropane Li salt, 12281-72-0; sodium phenoxide, 139-02-6; benzylmercaptan Na salt, 3492-64-6; sodium ethoxide, 141-52-6; sodium benzenesulfinate, 873-55-2; sodium thiophenoxide, 930-69-8; sodium methoxide, 124-41-4; 2-nitrobutane Li salt, 35818-95-2; sodium methylmercaptide, 5188-07-8; *p*-nitrophenyl methyl sulfide, 701-57-5.

References and Notes

(1) W. Reinders and W. E. Ringer, *Recl. Trav. Chim. Pays-Bas*, **18**, 326 (1899). A more recent, noteworthy, report is due to J. H. Gorvin [*Chem. Ind. (London)*, **36**, 1525 (1967)] who found that 4-nitrobenzophenone readily undergoes replacement of the nitro group by methoxide (and ethoxide) ion in dipolar aprotic solvents. Still more recently the reaction of sodium phenoxide with 4,4′-dinitrobenzophenone in dipolar aprotic solvents has been described [E. Radlmann, W. Schmidt, and G. E. Nischk, *Makromol. Chem.*, **130**, 45 (1969)]. The fact that certain nitrophthalimides undergo replacement of the nitro group by methoxide ion is also of interest [L. Caswell and T. Kao, *J. Heterocycl. Chem.*, **3**, 333 (1966)].
(2) (a) J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **39**, 3440 (1974); (b) J. R. Beck, *ibid.*, **38**, 4086 (1973); (c) *ibid.*, **37**, 3224 (1972).
(3) Actually, the product of eq 2 is methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate which results upon cyclization of **2**.
(4) R. D. Knudsen and H. R. Snyder, *J. Org. Chem.*, **39**, 3343 (1974).
(5) N. Kornblum, *Angew. Chem., Int. Ed. Engl.*, **14**, 734 (1975).
(6) Our thanks are due to Dr. C. S. Yeh and her associates for the microanalyses.
(7) N. Kornblum, S. D. Boyd, and N. Ono, *J. Am. Chem. Soc.*, **96**, 2580 (1974).
(8) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).
(9) N. Kornblum and A. Scott, to be published.
(10) N. Kornblum, M. M. Kestner, S. D. Boyd, and L. C. Cattran, *J. Am. Chem. Soc.*, **95**, 3356 (1973).
(11) We are indebted to E. I. du Pont de Nemours and Co. for a generous supply of HMPA.
(12) This compound when prepared from *p*-cyanocumyl chloride has mp 60–60.5 °C: R. T. Swiger, Ph.D. Thesis, Purdue University, 1970.
(13) H. Meyer, *Ber.*, **38**, 2492 (1905).
(14) J. B. Baumann, *J. Org. Chem.*, **36**, 396 (1971).
(15) J. Houben and W. Fischer, *Ber.*, **64**, 240 (1931).
(16) Sadtler ir no. 26711; NMR no. 476.
(17) D. F. Elliott and C. Harington, *J. Chem. Soc.*, 1374 (1949).
(18) A. T. Fuller, I. M. Tonkin, and J. Walker, *J. Chem. Soc.*, 637 (1945).
(19) A. A. Levi and S. Smiles, *J. Chem. Soc.*, 1488 (1932).
(20) E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1208 (1926).
(21) D. L. Hammick and R. B. Williams, *J. Chem. Soc.*, 211 (1938).
(22) R. C. Kerber, Ph.D. Thesis, Purdue University, 1965.
(23) (a) Y. Takubo, *J. Pharm. Soc. Jpn.*, **62**, 518 (1942); (b) W. R. Waldron and E. E. Reid, *J. Am. Chem. Soc.*, **45**, 2405 (1923).
(24) (a) H. H. Hodgson and R. Smith, *J. Chem. Soc.*, 1634 (1937); (b) H. Gilman and H. S. Broadbent, *J. Am. Chem. Soc.*, **69**, 2053 (1947).
(25) G. Leandri and M. Pallotti, *Ann. Chim. (Rome)*, **46**, 1069 (1956).
(26) F. Mayer, *Ber.*, **42**, 3050 (1909).

Substitution Reactions of Specifically Ortho-Metalated Piperonal Cyclohexylimine

Frederick E. Ziegler*[1] and Kerry W. Fowler

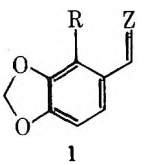
Sterling Chemistry Laboratory, Yale University, New Haven, Connecticut 06520

Received December 2, 1975

The specific ortho metalation of piperonal and 6-bromopiperonal cyclohexylimine is discussed. Typical reactions of the lithio and cuprous organometallics are explored.

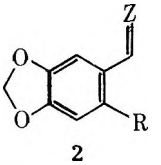
Since the observations of Hauser[2] concerning the stabilizing effect of a neighboring tertiary amine on the stability of ortho-lithiated aryls, this type of reaction has been applied to monosubstituted amides,[3] oxazolines,[4] and imines.[5]. Reiff has observed[5] that when acetophenone cyclohexylimine is treated with *n*-butyllithium (*n*-BuLi) in ether at −78 °C, addition to the imine is the major reaction pathway with minor quantities of dilithioimine derived from metalation at both the methyl group and the ortho position.

We have observed in the instance of piperonal cyclohexylime (**1a**) that reaction with *n*-BuLi in tetrahydrofuran (THF) at 0 °C afforded products of imine addition. When the temperature was lowered to −78 °C, only lithiation at the 2 position (**1b**) was observed, since low-temperature deuteration provided 2-deuteriopiperonal cyclohexylimine (**1d**) with a characteristic ortho-coupling pattern in its NMR spectrum.[6] When 6-bromopiperonal cyclohexylimine (**2e**) was lithiated at −78 °C, the NMR spectrum of the deuterium oxide quenched product indicated that deuteration had occurred exclusively at the 6 position (**2d**). However, when the 6-lithiated imine was allowed to warm to ambient temperature and then quenched with iodine at the same temperature or at −78 °C, only the 2-iodoimine **1f** was observed. Thus, the 2 position of imine **1a** is the site of kinetic and thermodynamic lithiation due to the electron-withdrawing effect of the adjacent oxygen atom. In the latter case, metal–halogen exchange is the kinetic process rather than C-2 deprotonation.[7] The equilibration is thought to be promoted by piperonal cyclohexylimine acting as a proton source. Although a sufficient excess of butyllithium was used in control runs to ensure the metalation of all of the piperonalimine, exchange still occurred. This may imply a disproportionation in which 2 mol of 6-lithiated imine affords 2,6-dilithiated imine and piperonalimine, thereby generating the necessary exchange medium. Alternatively, decomposition (i.e., oxidation and hydrogen abstraction from THF) would also generate piperonalimine.



1

a, R = H; Z = NC_6H_{11}
b, R = Li; Z = NC_6H_{11}
c, R = CuI; Z = NC_6H_{11}
d, R = D; Z = NC_6H_{11}
e, R = Br; Z = NC_6H_{11}
f, R = I; Z = NC_6H_{11}



2

g, R = I; Z = O
h, R = CH_3; Z = O
i, R = $CH_2CH{=}CH_2$; Z = O
j, R = CO_2H; Z = O
k, R = CO_2CH_3; Z = O

Both ortho-lithiated imines were subjected to alkylation with allyl bromide and methyl iodide. The data in Table I under entries A and B indicate that methylation is virtually

Table I

Conditions	Yields,[a] % (% piperonal) 1h	2h	1i	2i
A	61 (0)	79 (1)	61 (12)	57 (31)
B	69 (9)	66 (2)	11 (59)	56 (18)
C	94 (4)[b]	86 (5)	71 (1)[c]	53 (1)[d]
D	61 (15)	66 (9)	62 (5)	61 (3)

A: BuLi (−78 °C); RX (−78 °C, 3 h); warm to room temperature; H_2O; H_3O^+
B: BuLi (−78 °C); RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H_3O^+
C: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); warm to room temperature; H_2O; H_3O^+
D: BuLi (−78 °C); CuI; RX (−78 °C, 3 h); MeOH (−78 °C); warm to room temperature; H_3O^+

[a] Yields are absolute and unless specified are determined by GLC and corrected for differences in thermal conductivity. [b] Sublimed. [c] Distilled. [d] Identified as its semicarbazone.

Table II

Electrophile	Yield, % From 1b	From 2b
D_2O	100[a]	100[a]
I_2	60[b]	64[b]
CO_2	54[b]	43[b]
$ClCO_2Me$	68[b]	6[b,c]

[a] NMR analysis, percent conversion. [b] Isolated. [c] Complex reaction mixture.

complete at −78 °C, while in the allyl bromide alkylation the conversion is not as effective. In the particular case of 2-allylpiperonal (**1i**), the reaction (condition B) is only 11% complete.

When the ortho-lithiated imines were treated with CuI[8] at −78 °C, a green suspension was formed which showed a more pronounced effect on the allyl bromide alkylation yield than in the absence of copper. Although a change in mechanism for the methyl iodide alkylations cannot be inferred from these data, the copper(I)–allyl bromide alkylations suggest oxidative addition[9] as the mode of alkylation. It was observed that upon allowing the cuprous imine **2c** to warm to room temperature followed by treatment with allyl bromide, only a minor amount of the 2-allyl product was obtained, indicating that **2c** is less prone to rearrange than its lithium counterpart, **2b.**

In addition to the alkylation reactions, the lithiated imines could be iodinated, carboxylated, and carbomethoxylated as outlined in Table II.

The direct formation of the 2-lithiated imine **1b** is not a general reaction. Metalation of *m*-methoxybenzaldehyde cyclohexylimine with BuLi at −78 °C gave only addition to the imine. The freely rotating methoxyl group provides sufficient steric inhibition to deprotonation, allowing the imine addition to be the preferred reaction pathway. This difficulty is avoided in the case of piperonalimine since the ether functions are constrained from rotation. Direct metalation of 3,4,5-trimethoxybenzaldehyde failed to result in ortho metalation as was expected, but the lithiated imine could be successfully generated by metal–halogen exchange of the corresponding bromoimine.

Myristicinaldehyde (5-methoxypiperonal) cyclohexylimine, which has both the attributes of piperonal and *m*-methoxybenzaldehyde imines, was metalated to the extent of 60% (deuterium quench) at only one of the two ortho positions. Although the chemical shifts of the two signals could not be assigned with certainty, the selectivity could be observed by internal calibration with the methylenedioxy function and was inferred from the prior results to be the 2 position (adjacent to the methylenedioxy group) as opposed to the 6 position which was metalated.

Experimental Section

Melting points (corrected) were determined on a Fisher-Johns apparatus. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga. NMR spectra were determined on a Joelco Minimar 100-MHz or Perkin-Elmer R-32 90-MHz spectrometer, using Me_4Si (δ) as an internal standard. Gas chromatographic analyses were performed on a Varian 90-P instrument (TC) using a 6 ft × 0.25 in. 20% SE-30 on Anakrom 60/70 SD column. Tetrahydrofuran was distilled from sodium benzophenone ketyl. All glassware was flame dried under N_2. Solutions and solvents were transferred via syringe through serum caps.

Preparation of Cyclohexylimines. The imines were prepared from the aldehydes (1.0 equiv) and cyclohexylamine (1.2 equiv, distilled) in benzene solution by azeotropic removal of water. Recrystallization from methanol or distillation provided the imines in 80–90% yield.

Piperonal Cyclohexylimine (1a): mp 62.5–63.5 °C (lit.[10] 65–66 °C); NMR ($CDCl_3$) δ 1.15–2.0 (10 H, m), 3.15 (1 H, br s, =NCH), 5.92 (2 H, s, OCH_2O), 6.80 (1 H, d, J = 8 Hz, H-5), 7.10 (1 H, dd, J = 1.5, 8 Hz, H-6), 7.38 (1 H, d, J = 1.5 Hz, H-2), and 8.19 (1 H, s, –CH=N–).

6-Bromopiperonal Cyclohexylimine (2e): white needles, mp 127.5–128.5 °C (85% yield); NMR ($CDCl_3$) δ 1.23–1.84 (10 H, m), 3.25 (1 H, br s), 5.97 (2 H, s), 6.97 (1 H, s), 7.52 (1 H, s), and 8.54 (1 H, s).

Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.20; H, 5.20; Br, 25.76; N, 4.52. Found: C, 54.08; H, 5.26; Br, 25.67; N, 4.58.

***m*-Methoxybenzaldehyde Cyclohexylimine:** bp 120–123 °C (0.01 mm); NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.15 (1 H, br s), 3.81 (3 H, s), 6.85–7.05 (1 H, m, aryl), 7.20–7.38 (3 H, m, aryl), and 8.27 (1 H, s).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.28; H, 8.80; N, 6.50.

Myristicinaldehyde Cyclohexylimine: mp 72–73 °C; NMR ($CDCl_3$) δ 1.21–1.93 (10 H, m), 3.15 (1 H, br s), 3.93 (3 H, s), 5.99 (2 H, s), 6.94 (2 H, s), and 8.15 (1 H, s).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94: H, 7.33; N, 5.36. Found: C, 68.85; H, 7.39; N, 5.34.

Typical Metalation Procedure. In a flame-dried flask equipped with a serum cap was placed 2 mmol of imine in 15 ml of THF and the mixture was cooled to −78 °C with a CO_2–acetone bath. To the stirred solution was added a solution of 2.1 mmol of *n*-BuLi–hexane (Alfa-Ventron) over 1 min via syringe through the serum cap. A yellow color appeared upon introduction of the *n*-BuLi. After stirring for 15 min at −78 °C the ortho-metalated imine was ready for further reactions.

2-Deuteriopiperonal Cyclohexylimine (1d). Imine **1b** was treated with 0.2 ml of D_2O and allowed to warm to room temperature. The solution was poured into water, extracted with ether, dried over $MgSO_4$, filtered, and evaporated, providing a crystalline solid **1d.** The NMR spectrum showed the complete disappearance of the δ 7.38 resonance and the loss of meta coupling in the δ 7.10 doublet, indicating quantitative deuteration at C-2.

In a similar fashion **2b** provided **2d** which showed no resonance at δ 7.10 and singlets at δ 6.80 and 7.38 in its NMR spectrum.

2-Iodopiperonal Cyclohexylimine (1f). Iodination. To a solution of the metalated imine **1b** at −78 °C was added dropwise a solution of 762 mg (3.0 mmol) of iodine in 5 ml of THF. The iodine color was immediately discharged upon contact with the solution. The addition was continued until the iodine color persisted. The solution was warmed to room temperature, poured into water, extracted with ether, washed with saturated aqueous Na_2SO_3, dried ($MgSO_4$), filtered, and concentrated. Two crystallizations of the residue from ether–petroleum ether afforded 432 mg (60%) of **1f** as colorless prisims: mp 167–168.5 °C; NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.26 (1 H, br s), 6.04 (2 H, s), 6.75 (1 H, d, J = 8 Hz), 7.55 (1 H, d, J = 8 Hz), and 8.34 (1 H, s).

Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.07; H, 4.52; I, 35.53; N, 3.92. Found: C, 46.85; H, 4.59; I, 35.38; N, 3.97.

Hydrolysis was effected by vigorously stirring 245 mg (0.69 mmol) of imine **1f** in 15 ml of CH_2Cl_2 and 15 ml of 10% aqueous HCl for 2 days. The organic layer was washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated, providing 150 mg of solid. Recrystallization from methanol afforded 93 mg (48%) of **1g** as white needles: mp 135–136 °C; NMR ($CDCl_3$) δ 6.15 (2 H, s), 6.84 (1 H, d, J = 9 Hz), 7.62 (1 H, d, J = 9 Hz), and 9.89 (1 H, s).

Anal. Calcd for $C_8H_5IO_3$: C, 34.81; H, 1.83; I, 45.98. Found: C, 34.84; H, 1.87; I, 45.86.

The 6-lithiated imine **2b** afforded 459 mg (64%) of **2f** as white needles from MeOH: mp 157–157.5 °C; NMR ($CDCl_3$) δ 1.15–2.00 (10 H, m), 3.25 (1 H, br s), 5.99 (2 H, s), 7.26 (1 H, s), 7.53 (1 H, s), and 8.38 (1 H, s).

Anal. Calcd for $C_{14}H_{16}INO_2$: C, 47.07; H, 4.52; I, 35.53; N, 3.92. Found: C, 47.01; H, 4.54; I, 35.44; N, 3.89.

Aldehyde **2g** was formed (vide supra) in 46% yield from imine **2f**: mp 108.5–110.5 °C (MeOH) (lit.[11] 111 °C); NMR ($CDCl_3$) δ 6.08 (2 H, s), 7.31 (1 H, s), 7.34 (1 H, s), and 9.86 (1 H, s).

2-Methylpiperonal (1h) (Method A). To a stirred solution of imine **1b** at −78 °C was added dropwise over 1 min 454 mg (3.2 mmol) of distilled methyl iodide dissolved in 3 ml of THF. The solution was stirred for 3 h at −78 °C and then allowed to warm to room temperature. The reaction mixture was worked up (vide supra) to afford 491 mg of light yellow solid. Hydrolysis provided, upon recrystallization from hexane, aldehyde **1h** in 61% overall yield: mp 73–74.5 °C (lit.[12] 74–75 °C); NMR ($CDCl_3$) δ 2.55 (3 H, s, CH_3), 6.08 (2 H, s), 6.82 (1 H, d, J = 8 Hz), 7.39 (1 H, d, J = 8 Hz), and 10.03 (1 H, s).

Method C. To a stirred solution of metalated imine **2b** at −78 °C was added 381 mg (2.0 mmol) of cuprous iodide (as CuI, Alfa-Ventron) producing after 1 h a gray-green suspension.

After methylation as in method A, the reaction mixture was poured into H_2O, ether was added, and the mixture was shaken and filtered in vacuo through a Celite pad to remove suspended copper salts. The layers were separated and the organic layer extracted twice with ether. The combined organic extracts were washed with 5% NH_4OH, dried ($MgSO_4$), filtered, and concentrated. Hydrolysis afforded a solid which upon sublimation (60 °C, 1 mm) provided a 98% recovery of material (94% **1h**, 4% piperonal by GLC).

The lithiated imine **2b** provided (via method A) **2h** contaminated with piperonal; recrystallization (petroleum ether) afforded product in two crops (79%). Sublimation (55 °C, 1 mm) of the first crop (147 mg) gave 132 mg of pure 6-methylpiperonal (**2h**): mp 86–87.5 °C (lit.[13] 86–87 °C); NMR ($CDCl_3$) δ 2.61 (3 H, s), 6.01 (2 H, s), 6.69 (1 H, s), 7.29 (1 H, s), and 10.18 (1 H, s).

2-Allylpiperonal (1i) (Method C). To the copper reagent **1c** (vide supra) at −78 °C was added 411 mg (3.4 mmol) of allyl bromide and the mixture was stirred for 3 h at −78 °C. After warming to room temperature and workup an oil was obtained. Distillation (bulb to bulb) provided 271 mg (72%) of 2-allylpiperonal (**1i**): bp 122 °C (3 mm); NMR ($CDCl_3$) δ 3.76 (2 H, d, J = 6 Hz), 5.07 (1 H, m, $=CH_2$), 4.94 (1 H, m, $=CH_2$), 6.03 (1 H, m), 6.03 (2 H, s), 6.77 (1 H, d, J = 8 Hz), 7.36 (1 H, d, J = 8 Hz).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.21; H, 5.36.

In a similar fashion 6-allylpiperonal (**2i**) was prepared as a crude oil: NMR ($CDCl_3$, FT) δ 6.02 (2 H, s), 6.71 (1 H, s), 7.31 (2 H, s), and 10.11 (1 H, s). Semicarbazone, mp 193–195 °C (lit.[14] mp 195 °C).

Anal. Calcd for $C_{12}H_{13}N_3O_3$ (semicarbazone): C, 58.29; H, 5.30; N, 16.99. Found: C, 58.34; H, 5.32; N, 17.00.

Methyl 2-Formyl-5,6-methylenedioxybenzoate (1k). To the lithiated imine **1b** at −78 °C was added dropwise 368 mg (3.9 mmol) of freshly distilled methyl chloroformate (from $CaCO_3$) dissolved in 3 ml of THF. The yellow color of the solution was discharged. Upon warming to room temperature, the solution was poured into water, extracted with ether, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The residual oil (644 mg) was preabsorbed on silica gel and eluted from a silica gel column (30/1) with 300 ml of benzene saturated with water, affording 54 mg of oil containing piperonal (GLC). The 5% ether–wet benzene eluent (100 ml) gave 338 mg of solid. Recrystallization from ether–petroleum ether provided the ester **1k** (68%): mp 105.5–106.5 °C; NMR ($CDCl_3$) δ 3.97 (3 H, s), 6.15 (2 H, s), 6.97 (1 H, d, J = 9 Hz), 7.50 (1 H, d, J = 9 Hz), and 10.09 (1 H, s).

Anal. Calcd for $C_{10}H_8O_5$: C, 57.50; H, 3.87. Found: C, 57.76; H, 3.86.

2-Formyl-5,6-methylenedioxybenzoic Acid (1j). To 2 mmol of lithiated imine **1b** was added several chunks of dry ice, the yellow color of the solution being immediately discharged. After warming to room temperature, 15 ml of 10% HCl and 15 ml of ether were added and the mixture stirred overnight. The organic layers were separated, extracted with 10% aqueous KOH, acidified with concentrated HCl in the cold, and thoroughly extracted with ethyl acetate, dried, filtered, and concentrated, providing 211 mg (54%) of acid upon recrystallization from water: mp 164.5–165.5 °C (lit.[15] 155 °C); ir ($CHCl_3$) 1763 cm^{-1} (lactol); NMR (acetone-d_6) δ 3.8 (1 H, br s, lactol –OH, D_2O exchange), 6.22 (2 H, s) 7.1–7.3 (2 H, m, aryl). Methylation with CH_2N_2 provided ester **1k**, mp 103.5–105.5 °C.

In a similar fashion, 2-formyl-4,5-methylenedioxybenzoic acid (**2j**) was prepared from **2b** (43%): mp 165–165.5 °C (lit.[16] 167 °C); ir ($CHCl_3$) 1775 cm^{-1} (lactol); NMR (acetone-d_6) δ 2.9 (1 H, br s, lactol OH, D_2O exchange), 6.21 (2 H, s), 6.60 (1 H, br s, methine), and 7.19 (1 H, s, aryl).

Acknowledgments. We wish to thank the National Cancer Institute, National Institutes of Health (CA 16432-01), and Hoffmann-La Roche for generous support of this work.

Registry No.—**1a**, 58343-42-3; **1b**, 58384-27-3; **1c**, 58384-28-4; **1d**, 58343-43-4; **1f**, 58343-44-5; **1g**, 58343-45-6; **1h**, 58343-46-7; **1i**, 58343-47-8; **1j**, 58343-48-9; **1k**, 58343-49-0; **2b**, 58384-29-5; **2d**, 58343-50-3; **2e**, 58343-51-4; **2f**, 58343-52-5; **2g**, 58343-53-6; **2h**, 58343-54-7; **2i**, 58343-55-8; **2i** semicarbazone, 4518-37-0; **2j**, 51877-66-8; cyclohexylamine, 108-91-8; piperonal, 120-57-0; 6-bromopiperonal, 15930-53-7; *m*-methoxybenzaldehyde, 591-31-1; *m*-methoxybenzaldehyde cyclohexylimine, 58343-56-9; myristicinaldehyde, 5780-07-4; myristicinaldehyde cyclohexylimine, 58343-57-0; allyl bromide, 106-95-6; methyl chloroformate, 79-22-1.

References and Notes

(1) National institutes of Health Career Development Awardee, 1973–1978.
(2) F. N. Jones, M. F. Zinn, and C. R. Hauser, *J. Org. Chem.*, **28**, 663 (1963).
(3) W. H. Puterbaugh and C. R. Hauser, *J. Org. Chem.*, **29**, 853 (1964).
(4) H. W. Gschwend and A. Hamdan, *J. Org. Chem.*, **40**, 2008 (1975); A. I. Meyers and E. D. Mihelich, *Ibid.*, **40**, 3158 (1975).
(5) H. Reiff in "New Methods of Preparative Organic Chemistry", Vol. 6, W. Foerst, Ed., Academic Press, New York, N.Y., 1971, p 48; H. Reiff, Dissertation, University of Heidelberg, 1966.
(6) Although this metalation was complete in 15 min, the metalation of dimethyl piperonalamine occurred exclusively at the 2 position to the extent of 67% in 30 min at −78 °C.
(7) Lithium diisopropylamide (THF, −78 °C) was capable of forming **1b** from **1a** to the extent of 75% (deuteration) in a stoichiometric reaction.
(8) Copper reagents derived from *o*-lithiodimethylbenzylamine have been investigated: G. van Koten and J. G. Noltes, *J. Organomet. Chem.*, **84**, 129 (1975), and earlier papers cited in this series.
(9) J. Halpern, *Acc. Chem. Res.*, **3**, 386 (1970).
(10) F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, **211** (1954).
(11) A. Rilliet and L. Kreitmann, *Helv. Chim. Acta*, **4**, 595 (1921).
(12) W. H. Perkin, Jr., *J. Chem. Soc.*, 907 (1916).
(13) V. N. Eliseva, T. A. Devilskaya, and E. D. Laskina, *Tr. Vses. Nauchno-Issled. Inst. Sint. Nat. Dushistykh Veshchestv*, **5**, 18 (1961); *Chem. Abstr.*, **57**, 11081*c* (1962).
(14) S. Sugasawa and N. Yoshira, *Pharm. Bull.*, **1**, 281 (1953); *Chem. Abstr.*, **49**, 8256*b* (1953).
(15) S. N. Chakravarti, *J. Indian Chem. Soc.*, **20**, 382 (1943).
(16) S. N. Chakravarti, *J. Indian Chem. Soc.*, **17**, 264 (1940).

Chemistry of 2-(Trifluoromethyl)-2-hydroxy-3,3,3-trifluoropropionitrile

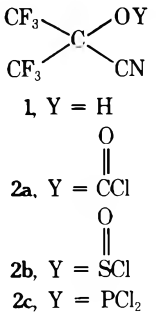
F. Mares* and J. Smith

Chemical Research Center, Allied Chemical Corporation, Morristown, New Jersey 07960

Received September 16, 1975

Pyrolysis of either 1-cyano-1-(trifluoromethyl)-2,2,2-trifluoroethyl chloroformate (**2a**) in an inert atmosphere, or bis[1-cyano-1-(trifluoromethyl)-2,2,2-trifluoroethyl] sulfite (**6**) in an atmosphere of $SOCl_2$ leads to 2-(trifluoromethyl)-2-chloro-3,3,3-trifluoropropionitrile (**9**), which is a potential precursor to perfluoromethyacrylonitrile. Since the sulfite **6** is readily prepared from the cyanohydrin of hexafluoroacetone, the described procedure provides access to perfluoromethacrylic acid derivatives from hexafluoroacetone. Thermal decomposition of sulfite **6** in an inert atmosphere leads to perfluorinated tertiary alkyl derivatives not otherwise available. Possible mechanisms for these reactions are discussed.

When hexafluoroacetone reacts with a nucleophile such as HCN, adducts of type 1 are formed. Substitution of the hydroxy group in cyanohydrin **1** by a halide ion might provide access to bis(trifluoromethyl)ketene and perfluoromethacrylic acid which are now available only from extremely toxic[1] perfluoroisobutene.[2] Unfortunately, owing to the electronic and steric effects, such a nucleophilic substitution is ruled out. It was therefore decided to study the thermal decomposition of chloroformate **2a,** chlorosulfite **2b,** and dichlorophosphite **2c.**



1, Y = H

2a, Y = CCl

2b, Y = SCl

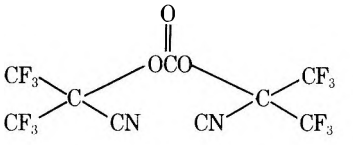
2c, Y = PCl_2

Results and Discussion

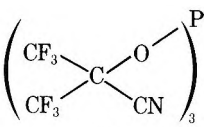
Reaction of Cyanohydrin 1 with Phosgene, Thionyl Chloride, and Phosphorus Trichloride. Cyanohydrin **1** [pK_a (OH) = 4.1][7] failed to react with either of the above chlorides, while methyl 2-hydroxy-2-(trifluoromethyl)-3,3,3-trifluoropropionate (**3**) [pK_a (OH) = 7.7][3] did react partially with $SOCl_2$ and quantitatively with PCl_3. Therefore, it can be concluded that any alcohol with p$K_a \sim 6$ or lower will not react with phosgene, thionyl chloride, and phosphorus trichloride if no base is present.

Addition of the sodium salt of cyanohydrin **1** to an excess of phosgene in ether at −60 °C yielded a mixture of chloroformate **2a** and a smaller amount of carbonate **4.** The products could be separated by distillation. An attempt to prepare chlorosulfite **2b** and dichlorophosphite **2c** in a similar way using excess thionyl chloride or phosphorus trichloride gave quantitative yields of sulfite **6** and phosphite **5** even at −70 °C.

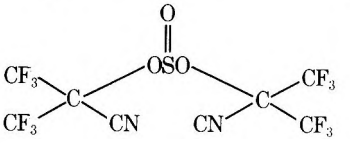
A possible reason for the difference in the reactivity of phosgene as compared with thionyl chloride and phosphorus trichloride may be based on two effects: (a) the anion of cyanohydrin **1** is more strongly electron withdrawing and, therefore, a better leaving group than chloride ion; (b) the oxygen of the cyanohydrin **1** is capable of more extensive (p → d)$_\pi$ dative bonding to sulfur and phosphorus than chlorine. If the first chloride ion in phosgene is displaced by cyanohydrin anion, any further substitution will only exchange one cyanohydrin anion for another one. Therefore, the major product is the chloroformate **2a.** In the case of thionyl chloride or phosphorus trichloride, the introduction of the cyanohydrin group into the molecule will increase the reactivity of the molecule toward further nucleophilic substitution. However, cyanohydrin becomes a poorer leaving group than chlorine since the strength of the O–S or O–P bonds is increased by (p→d)$_\pi$ dative bonding. Therefore, the second chlorine will be replaced more readily than the first chlorine in $SOCl_2$ or PCl_3. As a result only sulfite **6** and phosphite **5** are isolated even if an excess of $SOCl_2$ or PCl_3 is present.



4



5



6

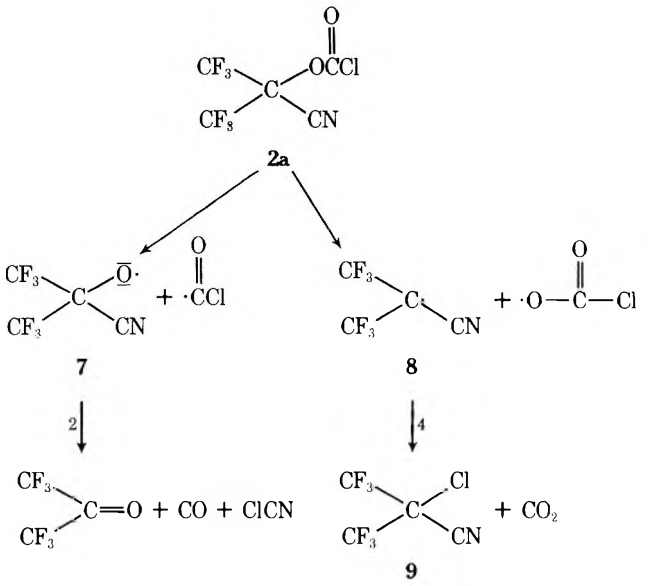
Pyrolysis of Chloroformate 2a. Chloroformate **2a** was pyrolyzed in a flow reactor. A conversion of 40% was achieved only at a temperature of 500 °C and contact time of 51 s. The gaseous products were separated by gas chromatography and identified by infrared and mass spectrometry. The main components were hexafluoroacetone and cyanogen chloride. The minor components were the desired 2-chloro-2-(trifluoromethyl)-3,3,3-trifluoropropionitrile (**9**) and carbon dioxide. The products can be accounted for by two reaction pathways (Scheme I).

The products are formed either by the decomposition of radical **7** (step 2) or by the combination of radicals in step 4.

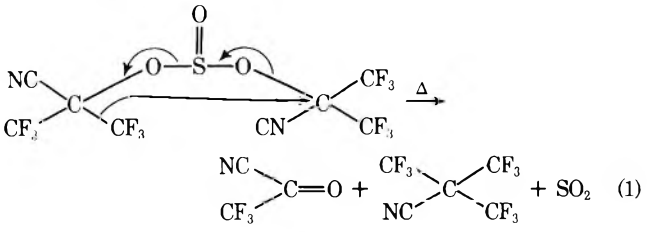
The extremely high temperature required for thermolysis of chloroformate **2a** and the predominant formation of hexafluoroacetone led to the conclusion that in the chloroformate **2a** the strength of the >C–OCOCl bond was greater than the strength of the >CO–COCl bond. In order to avoid formation of hexafluoroacetone, a group Y in **1** with more electron-withdrawing power must be employed. Sulfite **6** was expected to fulfill the requirement.

Pyrolysis of Sulfite 6. Pyrolysis of sulfite **6** was studied at temperatures of 290–410 °C. As before, gaseous products were separated by gas chromatography and analyzed by infrared and mass spectra. The following compounds were identified: hexafluoroacetone, sulfur dioxide, equal molar quantities of perfluoropivalonitrile (**10**) and 2-oxo-3,3,3-trifluoropropionitrile (**11**), and traces of trifluoroacetonitrile and trifluoroacetyl fluoride. The pyrolysis products are stable to 500 °C and are primary products.

Scheme I

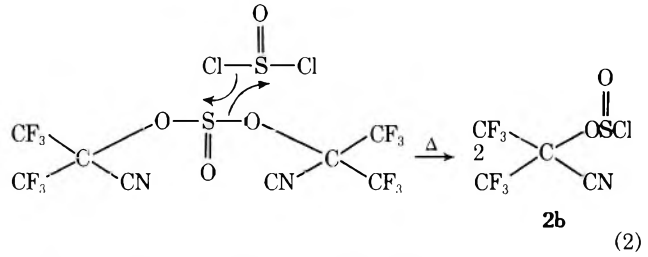


The formation of the main products in pyrolysis of sulfite **6** can be explained either by a radical mechanism (Scheme II) similar to that suggested for pyrolysis of chloroformate **2a** or by a concerted mechanism (eq 1).



(1)

In order to distinguish between the two possible mechanisms, sulfite **6** was pyrolyzed in an excess of thionyl chloride. Thionyl chloride may react with sulfite **6** via a four-center mechanism (eq 2) and form chlorosulfite **2b** at temperatures lower than that necessary for pyrolysis of sulfite **6**. Chlorosulfite **2b** would then decompose immediately to

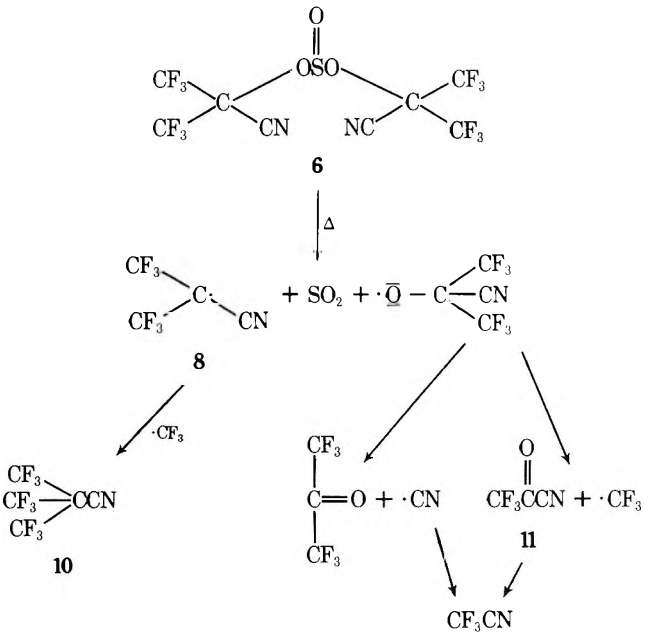


(2)

nitrile **9** via radical **8**. If thionyl chloride does not react with sulfite **6** at temperatures below 300 °C, it will be decomposed[4] into SO_2, SCl_2, Cl_2, and other fragments. Chlorine will then function as a trap for radical **8** (Scheme II). A large excess of thionyl chloride would then give only nitrile **9** and no perfluoropivalonitrile **10**. If the concerted mechanism (eq 1) is the main reaction path for pyrolysis of sulfite **6**, then no, or a very small amount of, nitrile **9** would be expected to form at temperatures above 300 °C.

When a mixture of sulfite **6** and an excess of thionyl chloride was pyrolyzed at temperatures below 300 °C, the sulfite **6** was recovered unchanged. However, substantial decomposition of thionyl chloride to a mixture of sulfur dioxide, sulfur dichloride, and chlorine was observed. When the same mixture of sulfite **6** and thionyl chloride was subjected to pyrolysis at temperatures above 300 °C, hexafluoroacetone, sulfur dioxide, and 2-chloro-2-(trifluo-

Scheme II



romethyl)-3,3,3-trifluoropropionitrile (**9**) were the main products.

Since the thermolysis of sulfite **6** in an excess of thionyl chloride does not occur at temperatures lower than that required for pyrolysis of the same sulfite in an inert atmosphere, the chlorosulfite **2b** can be excluded as the intermediate. No perfluoropivalonitrile was formed in the presence of thionyl chloride; therefore, the concerted mechanism (eq 1) is ruled out and we conclude that the radical path (Scheme II) is responsible for the product formation.

Experimental Section

Gas chromatography was carried out on a 6 ft × 0.25 in. column packed with 207 QF-1 on Chromosorb W at ambient temperature. All mass spectra were obtained on A. E. I. MS 902 using 70 eV electron energy. Interpretation was aided by high-resolution accurate mass measurement.

Sodium Salt of Cyanohydrin 1. The salt was prepared by a procedure similar to that described by Filler and Schure.[3] Sodium cyanide (270 g, 5.5 mol) was suspended in ether (2.5 l.) in a 5-l. flask fitted with a manometer, a mechanical stirrer, and a gas inlet tube. The flask was evacuated until ether started to boil. Hexafluoroacetone was introduced until a pressure of 740 mmHg was achieved. The stirrer was started and the pressure kept constant by adjusting the valve on the container of hexafluoroacetone. When the required amount of hexafluoroacetone (900 g, 5.42 mol) was consumed, the rate of hexafluoroacetone uptake dropped to zero. The solvent was evaporated under vacuum, leaving behind the product (1170 g, 5.42 mol).

2-Hydroxy-2-(trifluoromethyl)-3,3,3-trifluoropropionitrile. The sodium salt of cyanohydrin **1** (53.8 g, 0.25 mol) was suspended in ether (200 ml). Dry HCl (9.1 g, 0.25 mol) was introduced with simultaneous external cooling by ice. The salts were filtered off and the mixture distilled on a 30 TP column. The product, bp 108 °C (lit.[5] 107.5 °C), was obtained in a quantitative yield.

Chloroformate 2a. The synthesis and isolation were carried out in an argon atmosphere. A solution of phosgene (100 g, 1 mol) in ether (400 ml) was cooled to −60 °C and the sodium salt of cyanohydrin **1** (100 g, 0.465 mol) was added in 10 min with vigorous stirring. The stirring was continued for 2 h at −60 °C. The reaction mixture was allowed to warm to room temperature and the salts were filtered off. At this moment the ir showed only one C=O band at 5.5 μ which corresponds to chloroformate **2a**. Distillation of the filtrate afforded three fractions. The first fraction, bp 84 °C (32.1 g), corresponds to chloroformate **2a**: ir 4.4 (w, CN), 5.5 μ (s, C=O); mass spectrum *m/e* 255 ($C_5ClF_6NO_2$) and 220 ($C_5F_6NO_2$). The second fraction (17.2 g), bp 90–125 °C, is a mixture of chloroformate **2a**, cyanohydrin **1**, and carbonate **4**. The third fraction (49.9 g), bp 127–128 °C, mp 48–49 °C, corresponds to carbonate **4**, ir 4.45 (CN, m) and 5.45 μ (C=O, s). Both chloroformate **2a** and

carbonate **4** are hygroscopic and if not stored under inert atmosphere they are hydrolyzed to cyanohydrin **1**.

Sulfite 6. A solution of thionyl chloride (100 ml) in ether (300 ml) was cooled under argon to −60 °C. The sodium salt of cyanohydrin **1** (100 g, 0.465 mol) was added slowly with vigorous stirring. The stirring was continued for 2 h at −60 °C. The reaction mixture was allowed to warm to room temperature. The salts formed were filtered under argon and the filtrate was distilled. Only sulfite **6** (61 g, 60%), bp 139–141 °C, was obtained, ir 4.42 (m, CN), 7.8–8.2 μ [vs, COS(O)OC]. Hydrolysis with 1 equiv of water gave 1 equiv of SO_2 and 2 equiv of cyanohydrin **1**.

[1-(Trifluoromethyl)-1-methylcarboxy-2,2,2-trifluoroethyloxy]dichlorophosphite. A mixture of methyl 2-hydroxy-2-(trifluoromethyl)-3,3,3-trifluoropropionate (19.0 g) and phosphorus trichloride (24.5 g) was refluxed and the disappearance of the O–H bond was followed by ir. After 25 h, the excess of PCl_3 was removed by distillation and the product (quantitative yield) distilled at 171–173°C: ir 3.38 (s, C–H), 5.65 μ (s, C=O); MS *m/e* 326 ($C_5H_3Cl_2F_6O_3P$), 291 ($C_5H_3ClF_6O_3P$), 256 ($C_5H_3F_6O_3P$), 189 ($C_5H_2F_5O_2$).

Pyrolysis. The thermal decomposition of chloroformate **2a** and sulfite **6** was studied in a quartz flow reactor either empty (230 ml) or filled with quartz chips. The empty volume of the reactor was 100 ml. The flow of carrier gas (argon) was 0.5 ml/s. The compounds **2a, 6,** or a mixture of **6** and thionyl chloride were added from a syringe driven by a motor at a constant speed. The products were collected in a trap cooled by a dry ice–acetone mixture at ~−80 °C.

Chloroformate 2a. When chloroformate **2a** (5.0 g) was allowed to react for 15 min at 400 °C, the chloroformate **2a** was recovered unchanged. Under the same conditions, at 500 °C, 3 g (60%) of chloroformate **2a** was recovered. The gaseous compounds were separated into two fractions and then analyzed by gas chromatography. The major fraction (1.2 g) contained hexafluoroacetone: ir 5.5 (m, C=O), 7.5 (m), 7.8–8.3 (vs), 10.35 (s), 12.9 (w), 14.0 μ (s); mass spectra *m/e* 166 (C_3F_6O), 147 (C_3F_5O), and CO_2; ir 2.7 (doublet, m), 4.3 μ (s). The second fraction (0.6 g) contained mainly 2-chloro-2-(trifluoromethyl)-3,3,3-trifluoropropionitrile as shown by GC: ir 4.4 (m, CN), 7.8 (vs), 8.10 (vs), 9.3 (s), 10.55 (s), 13.3 (m), 14.0 μ (s); and mass spectra *m/e* 192 (C_4F_5NCl), 157 (C_4F_5N), 142 (C_3F_3NCl), 123 (C_3F_2NCl). Cyanogen chloride was also present in small quantities, ir 4.6 μ (CN).

Sulfite 6. The thermolysis of sulfite was studied at temperatures of 290–410 °C. As an example the experiment carried out at 330 ± 10 °C in a reactor filled with glass chips is described in detail. Pyrolysis of 17.2 g of sulfite **6** yielded 16.5 g of a mixture from which 12.7 g (73.6% conversion) was volatile products with boiling points lower than 30 °C. The residue (3.8 g) was shown by GC and ir to be the starting sulfite **6**. A small portion of the volatile product was separated by GC into six fractions. Each fraction was collected in an ir cell and analyzed by ir and mass spectrometry. The following components were identified. Trifluoroacetyl fluoride: ir 5.25 (s, C=O), 7.55 (m), 8.0 (s), 8.3 (s), 9.15 μ (s). Trifluoroacetonitrile: ir 4.45 (m, CN), 8.3 μ (vs). Hexafluoroacetone: ir and mass spectrum as above. Perfluoropivalonitrile: ir 4.7 (s, CN), 8.1 (m), 8.7 (s), 9.0 (s), 10.1 μ (m); mass spectrum *m/e* 245 (C_5F_9N). Sulfur dioxide: ir 4.0 (w), 4.3 (vs), 7.3–7.6 (vs), 8.6 (s), 8.8 μ (s); mass spectrum *m/e* 64 (SO_2). 2-Oxo-3,3,3-trifluoropropionitrile: ir 4.55 (m, CN), 5.67 (s, C=O), 7.7 (m), 7.9 (m), 8.15 (vs), 8.45 (vs), 9.85 μ (vs); mass spectrum *m/e* 123 (C_3F_3NO), 104 (C_3F_2NO), 97 (C_2F_3O), 54 (C_2NO). The unused volatile material (10.4 g) was bubbled through distilled water. Pure perfluoropivalonitrile (4.4 g, 71.2%) was isolated, as shown by GC and mass spectra.

Mixture of Sulfite 6 and Thionyl Chloride. The pyrolysis of sulfite **6** in the presence of an excess of thionyl chloride was studied at 400, 350, and 300 °C. At 400 and 350 °C the sulfite conversion was complete. As an example the run at 300 °C is described in detail. In 15 min a mixture of sulfite **6** (11.0 g, 0.025 mol) and thionyl chloride (8.3 g, 0.069 mol) was passed through the reactor. The products (18.0 g) were trapped at −70 °C. The gaseous products (9.2 g) were separated by distillation. The residue (8.8 g) was a mixture of thionyl chloride and sulfite **6**. The gaseous materials were separated by GC into three major peaks of about equimolar quantities and one minor peak (~5% of the third fraction). The fractions were collected in gas infrared cells and analyzed by infrared and mass spectroscopy. The first fraction was shown to be hexafluoroacetone. The second fraction was sulfur dioxide. The third fraction corresponded to 2-chloro-2-(trifluoromethyl)-3,3,3-trifluoropropionitrile (**9**). Hexafluoroacetone and the nitrile **9** were present in a molar ratio of 1:0.84.

Perfluoropivalamide. A crude mixture of products (29.0 g) from pyrolysis of sulfite **6** at 400 °C was introduced into a flask containing 140 ml of concentrated sulfuric acid and heated to 130 °C. The flask was equipped with a dry ice condenser. Reflux was continued for 8 h while the bath was kept at 150 °C. The volatile portions were collected (19.5 g) and analyzed by ir after separation by GC. The volatile portions contained unreacted perfluoropivalonitrile, sulfur dioxide, and traces of trifluoroacetyl fluoride. Hexafluoroacetone and 2-oxo-3,3,3-trifluoropropionitrile were consumed. The residual sulfuric acid solution was distilled, affording 0.5 g of colorless crystals: mp 139 °C; mass spectrum *m/e* 263 ($C_5H_2F_9NO$), 179 (C_4HF_6O), 113 (C_3F_4H), 112 (C_3F_4), 92 (C_2F_2NO), 91 (C_3HF_2O). Both the melting point of 139 °C (lit.[6] mp 138 °C) and the mass spectrum correspond to perfluoropivalamide.

2-Chloro-2-(trifluoromethyl)-3,3,3-trifluoropropionic Acid. The crude volatile products (7.6 g) from pyrolysis of a mixture of thionyl chloride and sulfite **6** were added to concentrated sulfuric acid (80 ml) in a stainless steel container. The reaction mixture was stirred and heated to 180 °C for 30 min. The volatile portions (2.2 g) were collected and shown by GC to contain the unreacted 2-chloro-2-(trifluoromethyl)-3,3,3-trifluoropropionitrile, small amounts of sulfur dioxide, and traces of hexafluoroacetone. Distillation of the residual sulfuric acid yielded hygroscopic, colorless crystals (2.1 g): bp 138–140 °C; mp 67–70 °C; MS *m/e* 186 (C_3HClF_6), 44 (CO_2); 4.30 mequiv CO_2H/g (theory 4.34 mequiv CO_2H/g).

Acknowledgment. We wish to thank E. McCarthy for his assistance with mass spectral measurement and chromatographic separations.

Registry No.—**1**, 677-77-0; 1 Na salt, 6737-59-3; **2a**, 58249-77-7; **2b**, 58249-78-8; **3**, 7594-51-6; **4**, 58249-79-9; **6**, 58249-80-2; **9**, 15056-76-5; **10**, 58249-81-3; **11**, 5882-04-2; sodium cyanide, 143-33-9; hexafluoroacetone, 684-16-2; [1-(trifluoromethyl)-1-methylcarboxy-2,2,2-trifluoroethoxy]dichlorophosphite, 58249-82-4; phosphorus trichloride, 7719-12-2; trifluoroacetyl fluoride, 354-34-7; trifluoroacetonitrile, 353-85-5; sulfur dioxide, 7446-09-5.

References and Notes

(1) J. M. Hamilton, Jr., *Adv. Fluorine Chem.*, **3**, 146 (1963).
(2) (a) I. L. Knunyants, Yu. A. Cheburkov, and M. D. Bargamova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1389 (1963); (b) Yu. A. Charburkov, E. I. Mysov, and I. L. Knunyants, *ibid.*, 1570 (1963); (c) D. C. England and C. G. Krespan, *J. Am. Chem. Soc.*, **88**, 5582 (1966); (d) D. C. England (E. I. du Pont de Nemours and Co.), U.S. Patent 3 362 990 (1968); (e) I. L. Knunyants, Yo. G. Abdugamiev, E. M. Rokhlin, P. O. Okulevich, and N. I. Karpushina, *Tetrahedron*, **29**, 595 (1973).
(3) R. Filler and R. M. Schure, *J. Org. Chem.*, **32**, 1217 (1967).
(4) "Gmelins Handbuch der Anorganishen Chemie", 9th ed, pp 1796–1797.
(5) I. L. Knunyants, E. M. Rokhlin, N. P. Gamberyan, Yu. A. Cherbukov, and Tsin-Yun Chen, *Knim. Nauka Prom.*, **4**, 802 (1959).
(6) Yu. A. Cherkov and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 346 (1967).
(7) The pK_a value was obtained from extrapolation of the pK_a vs. $\Sigma\sigma$ plot using pK_a values for fluorinated tertiary alcohols.[3]

Thermal and Photochemical Behavior of Sterically Hindered *N*-Vinyliminopyridinium Ylides

Akikazu Kakehi,* Suketaka Ito, Takahisa Funahashi, and Yoshio Ota

Department of Industrial Chemistry, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380, Japan

Received November 25, 1975

Thermolyses of sterically hindered *N*-vinylimino-2,6-lutidinium ylides (**3a** and **3b**) afforded 2,6-lutidine, indoles (**5a** and **5b**), oxazoles (**6a** and **6b**), phenylacetates (**7a** and **7b**), and phenylcyanoacetates (**8a** and **8b**) in fairly good yields, while their photolyses gave 2,6-lutidine, a six-membered mesoionic compound (**9**), isonitriles (**10a** and **10b**), and an azirine (**11a**). The reactions of the *N*-ylides (**3a** and **3b**) with ethyl propiolate afforded the rearranged vinylpyridine derivatives (**4a** and **4b**) in 40 and 51% yields, respectively. Structural elucidation of these products was mainly accomplished by their chemical conversions and by comparisons with authentic samples. Some mechanisms for these reactions are also discussed.

Various types of pyridinium *N*-ylides have been synthesized in recent years, and their dipolar[1] and nucleophilic reactivities[1j,2] are well documented. In some reactions of these *N*-ylides, ylidic bond fissions were often observed, and products derived from the resulting reactive species such as carbenes and nitrenes were detected.[3] However, such decomposition of the pyridinium *N*-ylides has been an undesirable side reaction in most cases. Recent interest in azirine chemistry[4] prompted us to investigate the possibility of obtaining vinylnitrene intermediates by this process. In this paper, we wish to report the preparation of *N*-vinyliminopyridinium ylides designed for this purpose and their thermal and photochemical behavior.

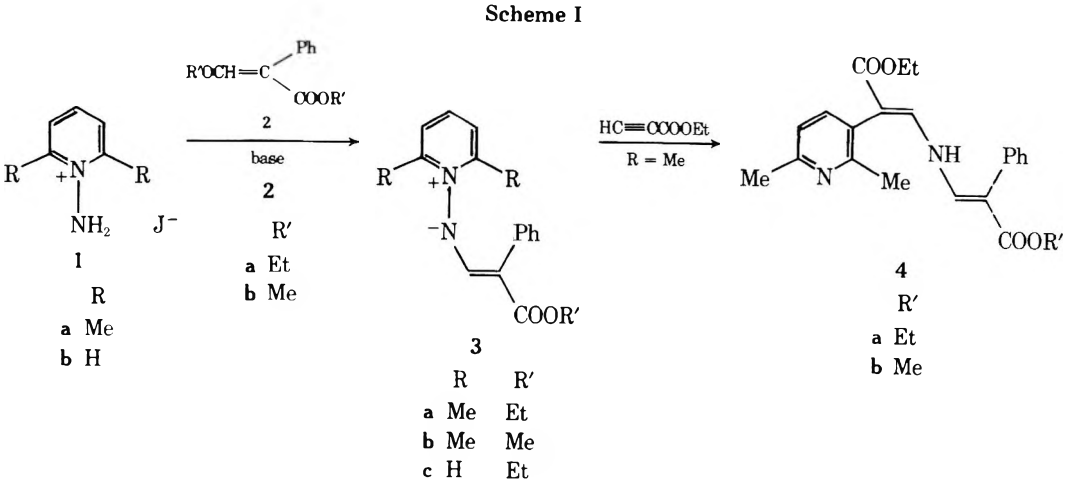
Results and Discussion

Preparation of Pyridinium *N*-Ylides (3a–c). *N*-(3-Alkoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylides (**3a** and **3b**) were prepared from the reactions of 2,6-lutidinium *N*-imine hydriodide (**1a**) with ethyl ethoxy- (**2a**) and methyl methoxymethylenephenylacetate (**2b**). These compounds were selected as models, because the ylide bond might be weakened by steric hindrance of 2 and 6 substituents on the pyridine ring[3b] and the generated vinylnitrene would be trapped intramolecularly by the phenyl and/or the alkoxycarbonyl groups in the N substituent.[3e,5] *N*-Vinyliminopyridinium ylide (**3c**) was similarly prepared from pyridinium *N*-imine hydriodide (**1b**) and ethoxymethylene compound (**2a**) for comparison of its reactivity with those of 2,6-lutidinium ylides (**3a** and **3b**). In order to determine the stereochemistry on the vinyl group in the *N*-ylides **3a–c**, we carried out the reactions of the *N*-ylides **3a** and **3b** with ethyl propiolate and obtained the expected rearranged products (**4a** and **4b**)[6] in 40 and 51% yields, respectively. Since no hydrogen bonding between the amino and the two ester carbonyl groups of the rearranged compounds (**4a** and **4b**) was observed in their ir and NMR spectra (see Experimental Section), the configuration of these groups in the divinylamine moiety was concluded to be both trans. From this, the cis configuration of the iminopyridinium and phenyl groups in the parent *N*-ylides (**3a** and **3b**) was deduced, since this kind of rearrangement of *N*-vinyliminopyridinium ylide has been proposed to proceed with retention of the configuration of the exocyclic *N*-vinyl group.[6a] These results are shown in Scheme I.

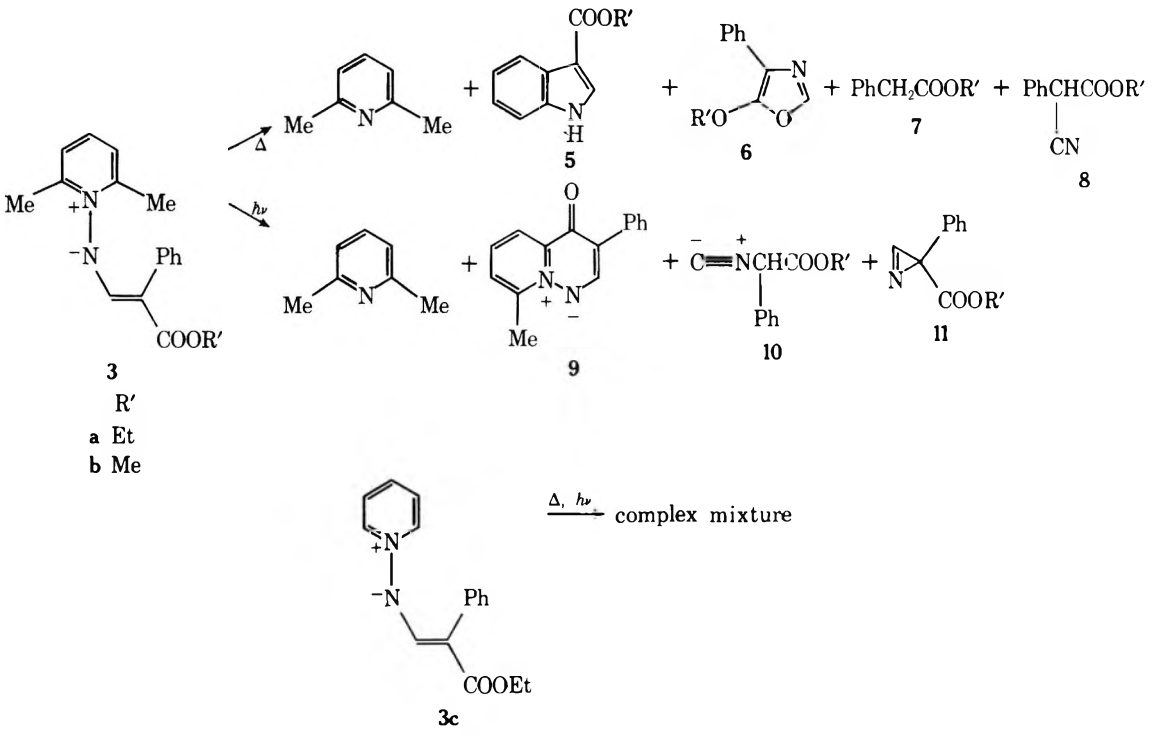
The stereochemical assignment was also supported by the consideration of thermal behavior of these *N*-ylides as will be indicated below.

Thermolysis and Photolysis of *N*-Ylides 3a–c. When *N*-ylides **3a** and **3b** were thermolyzed in refluxing xylene, the smooth generation of expected 2,6-lutidine with disappearance of the *N*-ylides was observed by thin layer chromatography. After evaporation of xylene and 2,6-lutidine from the reaction mixture, separation of the residue gave three types of products, a crystalline compound (**5a**, mp 122–124 °C, 10%, and **5b**, mp 147–148 °C, 7%), and two oily compounds (**6a**, 31% and **7a**, 30%, and **6b**, 32% and **7b**, 2%), respectively (Scheme II). Furthermore, another product (**8a** and **8b**) was detected from the reaction mixture by gas chromatography, but the yields were exceedingly small. On the other hand, photolysis of *N*-ylide **3a** in benzene afforded a crystalline compound (**9**, mp 226–228 °C, 15%), and an oily mixture (**10a** and **11a**, 44%), and that of *N*-ylide **3b** gave only oily product (**10b**, 37%) together with trace amount of compound **9**, except the formation of considerable amounts of 2,6-lutidine. When the *N*-ylides **3a** and **3b** were irradiated in benzene in the presence of a sensitizer such as benzophenone, compounds **10a** and **10b** were obtained exclusively with decreased irradiation time.[3c]

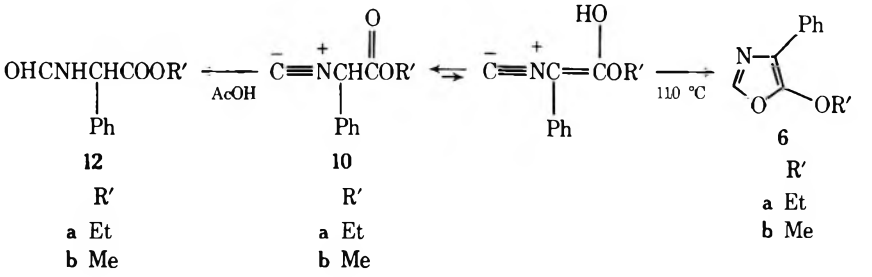
Scheme I



Scheme II



Scheme III



In contrast with *N*-ylides **3a** and **3b**, *N*-ylide **3c**, thermally and photochemically, gave only complex mixtures and isolation of significant product from them was unsuccessful.

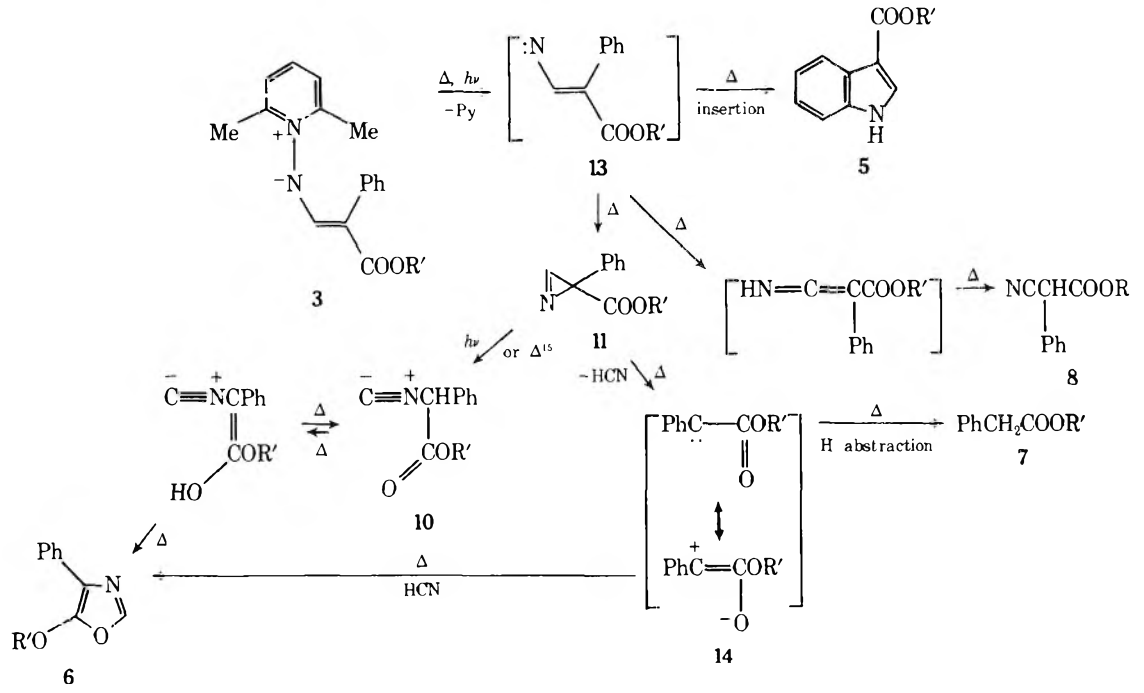
The structures of these compounds (**5**, **6**, **9**–**11**) were determined by their elemental and spectral analyses and by comparisons with authentic samples, and those of compounds **7** and **8** by gas chromatographic identification. Compound **5a**, for example, was assigned to be 3-ethoxycarbonylindole, because the ir spectrum exhibited a secondary amino absorption at 3210 cm^{-1} and a strong carbonyl absorption at 1655 cm^{-1}, and the NMR spectrum showed signals at δ 7.27 (3 H, m), 7.84 (1 H, d), 8.18 (1 H, m), and 9.26 (1 H, br s, NH) attributable to the indole skeleton. The melting points of the products (**5a** and **5b**) were, of course, well coincident with those reported by Peterson et al.[7] Compounds **6a** and **6b** were determined to be 5-alkoxy-4-phenyloxazole derivatives, but not the isomeric isoxazoles, by comparisons with samples prepared in very good yields by isomerization[8] of the corresponding isonitriles (**10a** and **10b**), which were photochemically generated from *N*-ylides **3a** and **3b**. The spectral data of compounds **6a** and **6b** were also completely in accord with those reported in the literature.[9] Compounds **10a** and **10b** showed each one characteristic isonitrile absorption at 2170 cm^{-1} in the ir spectra, and respective singlet signal at δ 5.30 (**10a**) and 5.32 (**10b**) due to exchangeable methine proton by keto–enol tautomerization in the NMR spectra. In addition, conversion of these compounds (**10a** and **10b**) to oxazoles **6a** and **6b** on thermolysis and to formamide derivatives **12a** and **12b** by treatment with acetic acid supported the assignments as ethyl (**10a**) and methyl phenylisocyanoacetate (**10b**) (Scheme III).

Crystalline compound **9** showed a largely shifted carbonyl absorption at 1560 cm^{-1} in the ir spectrum, and only aromatic proton multiplets in the range of δ 7.23–7.98 (9 H) and one methyl proton singlet at δ 2.81 in the NMR spectrum. The presence of the methyl group derived from the 2,6-lutidine moiety exhibited that compound **9** is not a product from ylidic bond fission. Further information for this structure was obtained by its uv spectral inspection: this compound (**9**) has two maximum absorptions in ethanol at 282 (ϵ 4.63 × 10^4) and 332 nm (ϵ 1.29 × 10^4). The former absorption at 282 nm is the same as that at 282 nm (ϵ 2.39 × 10^4) of the *N*-ylide **3a** and also those at 275–290 nm characteristics of various *N*-vinyliminopyridinium ylide structures.[1h,6a] From these results, compound **9** was assigned to be a six-membered mesoionic compound possessing a diazanaphthalene skeleton.[10] Compound **11a** exhibited a singlet signal at δ 9.81 characteristic of the 2-methine proton in the 1-azirine derivative,[11] but several attempts to isolate it were unsuccessful.

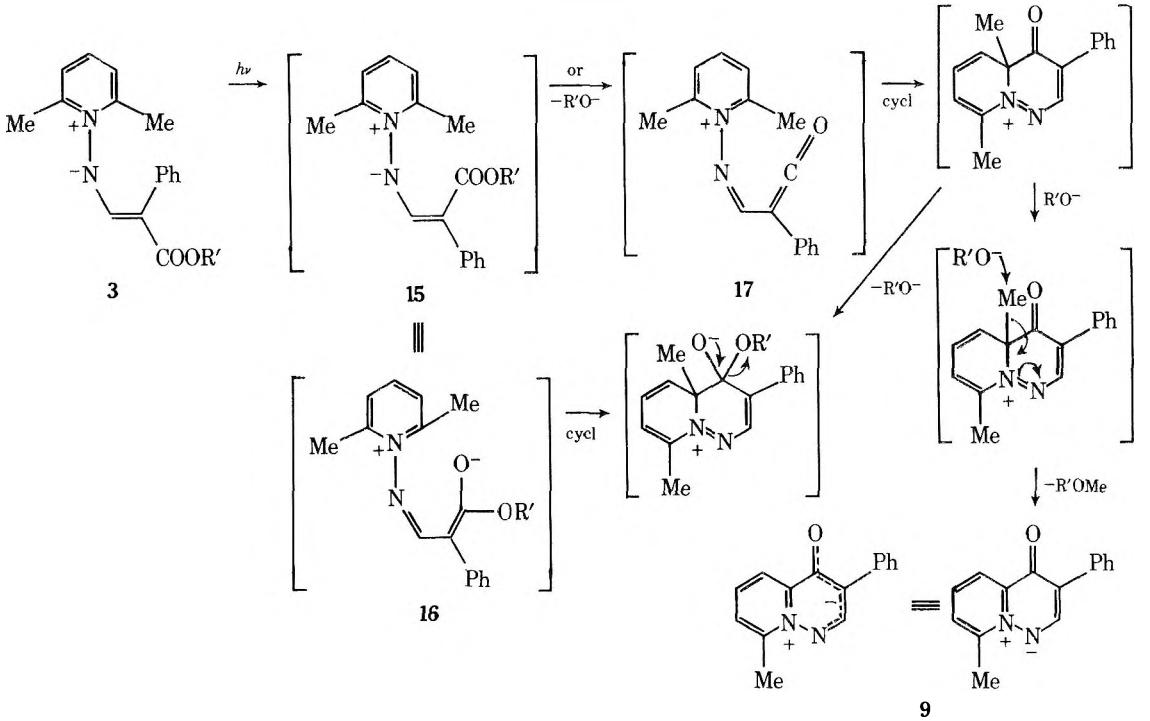
Mechanism. Possible mechanisms for these reactions are summarized in Schemes IV and V.

Except mesoionic compound **9**, all of the products (**5**–**8**, **10**, and **11**) may be formed via vinylnitrene intermediates (**13**) from ylidic bond fission of the *N*-ylides **3a** and **3b**. Indoles **5a** and **5b** should be formed by direct insertion of the nitrenes **13a** and **13b** to the cis-faced aromatic carbon–hydrogen bond rather than ring enlargement of the azirine intermediates **11a**

Scheme IV



Scheme V



and **11b**,[4] because other possible products, isoxazoles, could not be detected in the reaction mixture. Oxazoles **6a** and **6b** seem to be produced via 1,3-dipolar cycloaddition between hydrogen cyanide and alkoxycarbonylphenylcarbenes (**14a** and **14b**), both which were generated by thermal fragmentation of the azirines **11a** and **11b**. Such a fragmentation of 2-unsubstituted 1-azirine[12] and similar cycloadditions of acylcarbenes with nitriles[13] were reported, while thermal preparation of oxazoles via vinylnitrenes and 1-azirines was not. In addition, the isolation of phenylacetates **7a** add **7b** seems to be clear proof of intervention of the carbenes **14**. The formation of nitriles such as compounds **8a** and **8b** has been observed usually in thermal decomposition of vinyl azides possessing an acyl group.[14] The photochemical path of azirine to isonitrile was already established by Hafner et al.[12,15] and facile thermal isomerization of various acyl-substituted isonitriles to oxazoles[8] has been also well known. On the other hand, possible paths of *N*-ylide to mesoionic compound (**9**) may be initiated by photochemical cis–trans isomerization[1h] of the vinyl group of *N*-ylide **3**, and proceeds via cyclization of diazahexatriene component (**16** or **17**) with elimination. Similar mechanisms were proposed for some reactions.[16]

Experimental Section

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 elemental analyzer. The NMR spectra were determined with a JEOL JNM-4H-100 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The chemical shifts are expressed in δ values. The ir and uv spectra were taken with a JASCO DS-301 and a Hitachi EPS-2A spectrophotometer.

Preparation of *N*-Vinyliminopyridinium Ylides (3a–c). Gen-

eral Procedure. A mixture of alkoxyatropate (**2a** or **2b**) and small excess of pyridinium *N*-imine hydriodide (**1a** or **1b**) was stirred with potassium carbonate in ethanol or methanol at room temperature for 2 days. The insoluble substances were removed from the reaction mixture by filtration and the filtrate was concentrated in vacuo. After the separation of the residue by column chromatography (alumina) recrystallization from dichloromethane–ether–*n*-hexane gave pure *N*-ylides **3a–c.**

N-(3-Ethoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylide (**3a**): orange prisms, 73%, mp 107–109 °C; ν (KBr) 1640 and 1525 cm^{-1}; δ ($CDCl_3$) 1.22 (3 H, t, J = 7.0 Hz), 2.64 (6 H, s), 4.11 (2 H, q, J = 7.0 Hz), 6.8–7.7 (8 H, m), and 7.94 (1 H, s); λ_{max} (EtOH) 282 nm (ϵ 2.39 × 10^4).

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.95; H, 6.71; N, 9.50.

N-(3-Methoxycarbonyl-3-phenylvinylimino)-2,6-lutidinium ylide (**3b**): orange prisms, 70%, mp 131–133 °C; ν (KBr) 1630 and 1500 cm^{-1}; δ ($CDCl_3$) 2.60 (6 H, s), 3.60 (3 H, s), 6.8–7.7 (8 H, m), and 7.82 (1 H, s).

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.34; H, 6.52; N, 9.86.

N-(3-Ethoxycarbonyl-3-phenylvinylimino)pyridinium ylide (**3c**): red prisms, 97%, mp 119–121 °C; ν (KBr) 1640 and 1520 cm^{-1}; δ ($CDCl_3$) 1.27 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 6.9–7.6 (8 H, m), 8.1–8.3 (2 H, m), and 8.40 (1 H, s).

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.97; N, 10.60.

Reactions of *N*-Ylides 3a and 3b with Ethyl Propiolate. General Procedure. A mixture of the *N*-ylide (1.5 mmol) and ethyl propiolate (147 mg, 1.5 mmol) was stirred in benzene (25 ml) at room temperature for 2 days. After evaporation of the solvent from the reaction mixture the residue was separated by preparative thin layer chromatography (Merck Kieselgel GF_{254}). Recrystallization of the crude product from dichloromethane–ether–*n*-hexane gave pale yellow plates.

4a: 235 mg (40%); mp 104–106 °C; ν (KBr) 3310, 1680, and 1605 cm^{-1}; δ ($CDCl_3$) 1.22 (6 H, t, J = 7.0 Hz), 2.27 (3 H, s), 2.46 (3 H, s), 4.20 (4 H, q, J = 7.0 Hz), 6.34 (1 H, br t, J = 12.0 Hz, NH), 6.8–7.4 (7 H, m), 7.20 (1 H, d, J = 12.0 Hz), and 7.24 (1 H, d, J = 12.0 Hz).

Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.01; H, 6.82; N, 7.03.

4b: 290 mg (51%); mp 144–145 °C; ν (KBr) 3310, 1680, and 1610 cm^{-1}; δ ($CDCl_3$) 1.19 (3 H, t, J = 7.0 Hz), 2.26 (3 H, s), 2.45 (3 H, s), 3.69 (3 H, s), 4.18 (2 H, q, J = 7.0 Hz), 6.32 (1 H, br t, J = 12.0 Hz, NH), 6.8–7.4 (7 H, m), 7.73 (1 H, d, J = 12.0 Hz), and 7.75 (1 H, d, J = 12.0 Hz).

Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.41; H, 6.40; N, 7.19.

Thermolysis of *N*-Ylides 3a and 3b. *N*-Ylide (1.5 mmol) was thermolyzed in refluxing xylene solution (25 ml) for 30 min and then the reaction mixture was concentrated in vacuo. The separation of the residue by preparative thin layer chromatography afforded the following compounds.

From **3a,** 3-ethoxycarbonylindole (**5a**), 10%, mp 122–124 °C (lit.[7] 119–123 °C), ν (KBr) 3210 and 1655 cm^{-1}, δ ($CDCl_3$) 1.40 (3 H, t, J = 7.0 Hz), 4.37 (2 H, q, J = 7.0 Hz), 7.27 (3 H, m), 7.84 (1 H, d, J = 3.0 Hz), 8.18 (1 H, m), and 9.26 (1 H, br s, NH); 5-ethoxy-4-phenyloxazole (**6a**), 31%, colorless oil, ν (neat) 1645 cm^{-1}, δ ($CDCl_3$) 1.42 (3 H, t, J = 7.0 Hz), 4.29 (2 H, q, J = 7.0 Hz), 7.38 (1 H, s), and 7.1–7.8 (5 H, m); ethyl phenylacetate (**7a**), 30%; and ethyl phenylcyanoacetate (**8a**), trace.

From **3b:** 3-methoxycarbonylindole (**5b**), 7%, mp 147–148 °C (lit.[7] 144–145.6 °C), ν (KBr) 3200 and 1655 cm^{-1}; 5-methoxy-4-phenyloxazole (**6b**), 32%, colorless oil, ν (neat) 1640 cm^{-1}, δ ($CDCl_3$) 4.02 (3 H, s), 7.45 (1 H, s), and 7.2–7.9 (5 H, m); methyl phenylacetate (**7b**), 2%; and methyl phenylcyanoacetate (**8b**), trace.

The structures of these compounds (**5–6**) were determined by comparisons with physical and spectral data of authentic samples and those of compounds **7–8** by gas chromatographic identification.

When *N*-ylide **3c** was treated under the same condition, only a complex mixture was obtained.

Photolysis of *N*-Ylides 3a and 3b. A benzene solution (100 ml) of *N*-ylide (1 mmol) was irradiated under a nitrogen atmosphere with a high-pressure mercury lamp through a Pyrex filter for 2–3 h. The reaction mixture was concentrated in vacuo and then the residue was separated by preparative thin layer chromatography.

From **3a:** diazanaphthalene (**9**), 15%, mp 226–228 °C (from dichloromethane–ether–*n*-hexane), ν (KBr) 1560 cm^{-1}, λ_{max} (EtOH) 282 (ϵ 4.63 × 10^4) and 332 nm (ϵ 1.29 × 10^4), δ ($CDCl_3$) 2.81 (3 H, s), 7.66 (1 H, s), and 7.2–8.0 (8 H, m) (Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.13; H, 5.28; N, 11.78); ethyl phenylisocyanoacetate (**10a**), ca. 34%, colorless oil, ν (neat) 2170 and 1745 cm^{-1}, δ ($CDCl_3$) 1.20 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 5.30 (1 H, s), and 7.36 (5 H, m) (Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.42; H, 5.91; N, 7.20); 3-ethoxycarbonyl-3-phenyl-1-azirine (**11a**), ca. 10%, pale yellow oil, δ ($CDCl_3$) 1.20 (3 H, t, J = 7.0 Hz), 4.16 (2 H, q, J = 7.0 Hz), 7.36 (5 H, m), and 9.81 (1 H, s).[17]

From **3b: 9;** trace, methyl phenylisocyanoacetate (**10b**), 37%, colorless oil, ν (neat) 2170 and 1750 cm^{-1}, δ ($CDCl_3$) 3.73 (3 H, s), 5.32 (1 H, s), and 7.38 (5 H, m).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.22; H, 5.23; N, 7.74.

When the *N*-ylides **3a** and **3b** were irradiated in benzene in the presence of benzophenone (twofold moles), isonitriles (**10a,** 36%, and **10b,** 37%) were obtained exclusively with decrease of irradiation time (ca. 15 min).

In contrast with *N*-ylides **3a** and **3b,** *N*-ylide **3c** gave only a complex mixture on its irradiation.

Thermolysis of Isonitriles 10a and 10b. When isonitriles **10a** and **10b** were heated in refluxing toluene for ca. 5 h, they rearranged to the corresponding oxazoles (**6a** and **6b**) in 89 and 94% yields, respectively. These compounds were identical with those (**6a** and **6b**) prepared by the thermolysis of *N*-ylides **3a** and **3b.**

Hydrolysis of Isonitriles 10a and 10b. Treatment of isonitriles **10a** and **10b** with 99% acetic acid for 1 day afforded the corresponding formamide derivatives (**12a** and **12b**) in 78 and 85% yields.

N-Formylphenylglycine ethyl ester (**12a**): colorless oil; ν (neat) 3240, 1735, and 1670 cm^{-1}; δ ($CDCl_3$) 1.14 (3 H, t, J = 7.0 Hz), 4.14 (2 H, q, J = 7.0 Hz), 5.60 (1 H, d, J = 7.5 Hz), 7.25 (1 H, br, NH), 7.28 (5 H, s), and 8.10 (1 H, d, J = 1.0 Hz).

N-Formylphenylglycine methyl ester (**12b**): colorless needles (from dichloromethane–*n*-hexane); mp 84–85 °C; ν (KBr) 3320, 1730, and 1670 cm^{-1}; δ ($CDCl_3$) 3.64 (3 H, s), 5.58 (1 H, d, J = 7.0 Hz), 7.25 (1 H, br, NH), 7.26 (5 H, s), and 8.09 (1 H, d, J = 1.0 Hz).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.04; H, 5.76; N, 6.92.

Registry No.—**1a,** 36012-28-9; **1b,** 6295-87-0; **2a,** 15937-27-6; **2b,** 6460-86-2; **3a,** 58298-83-2; **3b,** 58298-84-3; **3c,** 58298-85-4; **4a,** 58298-86-5; **4b,** 58298-87-6; **5a,** 776-41-0; **5b,** 942-24-5; **9,** 58298-88-7; **10a,** 39533-31-8; **10b,** 39533-32-9; **11a,** 58298-89-8; **12a,** 34641-48-0; **12b,** 58298-90-1; ethyl propiolate, 623-47-2.

References and Notes

(1) (a) R. Huisgen, R. Grashey, and R. Krischke, *Tetrahedron Lett.*, 387 (1962); (b) T. Okamoto, M. Hirobe, and Y. Tamai, *Chem. Pharm. Bull.*, **11,** 1089 (1963); **14,** 506, 512, 523 (1966); (c) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33,** 2062 (1968); (d) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C,* 481 (1970); (e) Y. Kobayashi, T. Kutsuma, and Y. Sekine, *Tetrahedron Lett.*, 3325 (1972); (f) E. Pojara, *ibid.*, 2585 (1972); (g) Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron,* **28,** 21 (1972); (h) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37,** 3106 (1972); (i) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Jpn.*, **45,** 2050 (1972); (j) *Tetrahedron,* **28,** 4947 (1972); (k) A. Kakehi and S. Ito, *Bull. Chem. Soc. Jpn.*, **47,** 938 (1974).

(2) (a) T. Eicher and A. Hansen, *Tetrahedron Lett.*, 1169 (1967); (b) T. Eicher, E. von Angerer, and A.-M. Hansen, *Justus Liebigs Ann. Chem.*, **746,** 102 (1971); (c) T. Eicher and E. von Angerer, *ibid.*, **746,** 120 (1971); (d) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36,** 2451 (1971); (e) *Tetrahedron,* **28,** 1469 (1972); (f) J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **50,** 584 (1972); (g) C. W. Rees and E. von Angerer, *J. Chem. Soc., Chem. Commun.*, 420 (1972); (h) Y. Sugimura, N. Soma, and Y. Kisida, *Bull. Chem. Soc. Jpn.*, **45,** 3174 (1972); (i) A. Kakehi and S. Ito, *J. Org. Chem.*, **39,** 1542 (1974); (j) A. Kakehi, S. Ito, and T. Manabe, *ibid.*, **40,** 544 (1975).

(3) (a) J. Streith, A. Blind, J.-M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969); (b) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.*, **35,** 426 (1970); (c) J. Streith, J. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, **36,** 2962 (1971); (d) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *J. Chem. Soc., Perkin Trans. 1,* 2089 (1973); (e) Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *ibid.*, 2580 (1973).

(4) There are several reviews about them. See below. (a) F. W. Fowler, *Adv. Heterocycl. Chem.*, **13,** 45 (1971); (b) H. Taniguchi and K. Isomura, *Yuki Gosei Kagaku,* **30,** 280 (1972); (c) J. Anderson and A. Hassner, *Synthesis,* 483 (1975).

(5) (a) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Am. Chem. Soc.*, **89,** 2077 (1967); (b) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970); (c) H. Hemetsberger, D. Knittel, and H. Weidemann, *Monatsh. Chem.*, **101,** 161 (1970); (d) H. Hemetsberger and D. Knittel, *ibid.*, **103,** 194, 205 (1972); (e) K. Isomura, S. Kobayashi, and H. Taniguchi, *Tetrahedron Lett.*, 3499 (1968); (f) G. Smolinsky and C. A. Pryde, *J. Org. Chem.*, **33,** 2411 (1968).

(6) (a) T. Sasaki, T. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972); (b) *J. Org. Chem.*, **36,** 2978 (1971); (c) T. Sasaki, K. Kanematsu, A. Kakehi, and G. Ito, *Bull. Chem. Soc. Jpn.*, **45,** 2050 (1972).

(7) P. E. Peterson, J. P. Wolf, III, and C. Niemann, *J. Org. Chem.*, **23**, 303 (1958).
(8) Formation of oxazole from the corresponding acyl-substituted isonitrile has been well investigated. See I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
(9) T. Miki and T. Matsuo, *Yakugaku Zasshi*, **91**, 1030 (1971).
(10) The benzo analogues of the compound (**9**) were prepared recently by pyrolysis of 2-(2-azidobenzoyl)pyridines. See R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.*, **11**, 125 (1974).
(11) The chemical shift of the 2-methine proton in 1-azirine derivatives is in the range of δ 9.6–10.2. See ref 4b and 5e.
(12) W. Bauer and K. Hafner, *Angew. Chem.*, **81**, 787 (1969).
(13) (a) R. Huisgen, H. Konig, G. Binsch, and H. J. Sturm, *Angew. Chem.*, **73**, 368 (1961); (b) R. Huisgen, *ibid.*, **75**, 604 (1963).
(14) D. Knittel, H. Hemetsberger, R. Leipert, and H. Weidmann, *Tetrahedron Lett.*, 1459 (1970).
(15) However, thermal process of 2-unsubstituted azirine to the corresponding isonitrile was also proposed in the isomerization of indoxazene to benzoxazole. See J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.*, **96**, 2014 (1974).
(16) (a) R. C. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936); (b) H. M. Blatter and H. Lukaszewski, *Tetrahedron Lett.*, 855 (1964).
(17) Contaminated with isonitrile **10a**.

Synthesis of C_7 Alkylated 7-Deaminocephalosporin Derivatives

J. S. Wiering and Hans Wynberg*

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

Received November 24, 1975

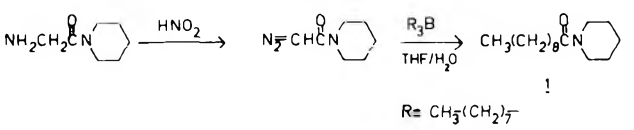
Several 7-alkyl cephalosporins lacking the 7-amino function have been prepared by treatment of the 7-diazo derivatives of cephalosporanic acid *tert*-butyl esters with a variety of trialkylboranes and a dialkylborane. Mixtures of α- and β-substituted cephalosporin *tert*-butyl esters were formed. These were hydrolyzed to the free acids. Biological screening of the free acids (as α and β mixtures) showed little or no antimicrobal activity except for the 7-methyleneadamantyldeacetoxycephalosporanic acid. A new, very mild method of oxidation of the sulfur atom in the cephalosporins was discovered. Sulfoxides were isolated from the alkylation reaction.

In recent years intensive research has been carried out in order to obtain modified cephalosporins with improved properties.[1] Several groups have attempted modifications at the C_7 positions of cephalosporins.[1b,2] As far as we know no cephalosporins[3] are known in which the 7-amino function has been replaced by an alkyl or functionalized alkyl group.[3] By introducing such alkyl groups the lipophilic character of the molecule, and consequently its penetrating ability[4] into the cell wall, changes. The purpose of the research reported here was to synthesize alkylated cephalosporins lacking the amino function at the β-lactam C_7 carbon, and to determine the effect of this change on biological activity.

Results and Discussion

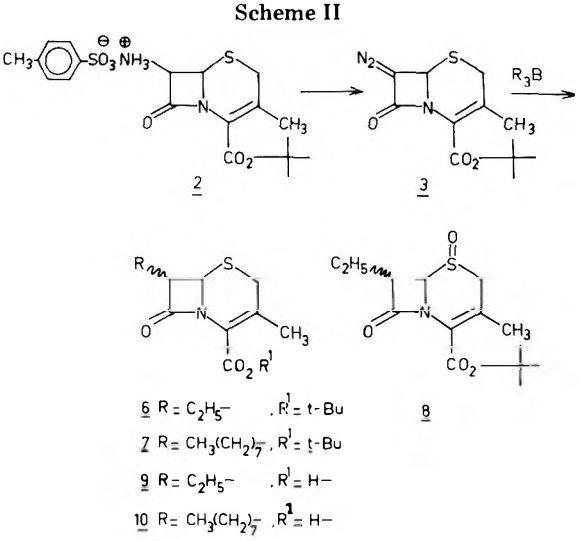
In order to introduce an alkyl side chain at C_7, in fact the replacement of an amino by a methylene group, we made use of the reaction of trialkylboranes with diazo esters,[5a] a reaction which we found to be applicable to diazo amides also. For example, the reaction of trioctylborane with 1-(α-diazoglycyl)piperidine in aqueous tetrahydrofuran gave the amide **1** in almost quantitative yield[6] (Scheme I).

Scheme I



The diazotization of the *p*-toluenesulfonic acid salt of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester (**2**, Scheme II) and 7-aminocephalosporanic acid *tert*-butyl ester (**4**, Scheme IV) was carried out in a mixture of methylene chloride and water.[8] It was possible to isolate the diazo cephem **3** in 80% and **5** in 60–80% yield. Both compounds are yellow, crystalline solids, of which **5** could be obtained analytically pure. The alkylation of **3** with triethyl- and trioctylborane was only successful within a temperature range from −40 to −80 °C (Scheme II). At temperatures higher than −40 °C, no products with intact β-lactam ring were formed. The amount of water was of crucial importance to the course of the reaction.[5] With more than 30 equiv of water, based on diazo cephem **3**, no β-lactam containing products could be isolated. With 20–30 equiv of water, sulfoxide **8** was formed. It could be shown that the latter was not produced during oxidative work-up.

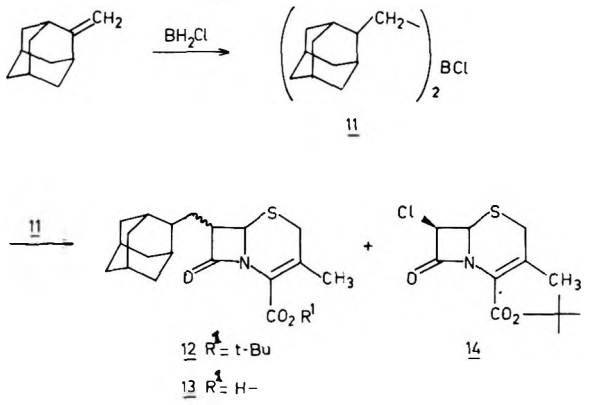
Scheme II



Using minor amounts of water (5–20 equiv) a mixture of **6** and **8** was formed, while alkylation in the presence of 1–5 equiv of water gave the cephem ester **6** as the sole product. The alkylated cephem esters **6** and **7** are both relatively unstable liquids and difficult to purify. Treatment of **6** and **7** with trifluoroacetic acid afforded the acids **9** and **10**, which are stable for a few days at −20 °C.

Diborane reacts with alkenes containing bulky groups to the dialkylborane stage only.[7] Since dialkylmonochloroboranes with bulky alkyl groups react rapidly with diazo esters,[9] we used monochloroborane as reagent to transform methyleneadamantane into the dimethyleneadamantylmonochloroborane **11**. Alkylation of **3** with **11** gave two products **12** and **14**, in the statistical ratio 2:1[10] (Scheme III). The products were separated by repeated chromatography.

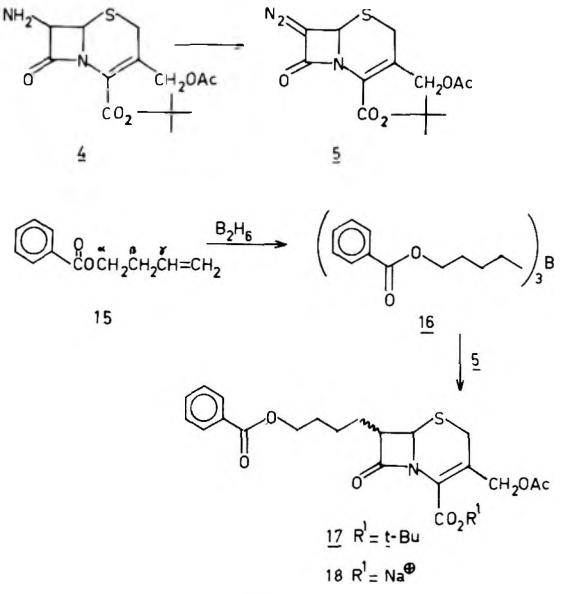
Scheme III



7-*epi*-Chlorodeacetoxycephalosporanic acid *tert*-butyl ester (**14**) was identical with the compound that was formed by treating **3** with hydrochloric acid in tetrahydrofuran. Treatment of **12** with trifluoroacetic acid afforded the acid **13** in 85% yield.

In introducing a functionalized alkyl group at the C_7 position we were restricted in the choice of the appropriate substituted alkenes. First, diborane may react with the double bond, with a functional group in the alkene, or with both.[11] Second, the addition at the double bond is influenced by directing effects caused by the functional group.[12,13] 3-Butenyl benzoate (**15**) was treated with diborane to give tri(4-benzoyloxybutyl)borane (**16**). Reaction of **16** with 7-diazocephalosporanic acid *tert*-butyl ester (**5**) gave the C_7 alkylated cephem ester **17** (Scheme IV). Al-

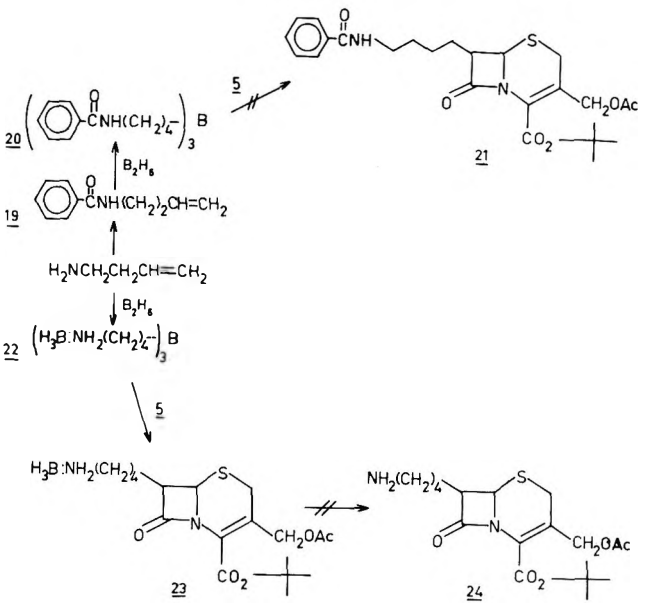
Scheme IV



though alkaline hydrogen peroxide oxidation–hydrolysis[10] of **16** revealed 15% addition of the boron at the γ carbon atom of **15**, no alkylated cephem ester could be detected which was formed by migration of this secondary alkyl group from boron to the C_7 carbon atom. Treatment of the ester **17** with trifluoroacetic acid gave the alkylated cephalosporanic acid **18**, which was isolated as the sodium salt.

The same procedure was not successful for introduction of the *N*-butylbenzamide group (Scheme V). Treatment of diazo cephem ester **5** with 2.5 equiv of tri[4-(*N*-benzoyl)-butylamino]borane (**20**) gave no alkylated cephem ester **21**, but we recovered 50% diazo compound **5**, after separating

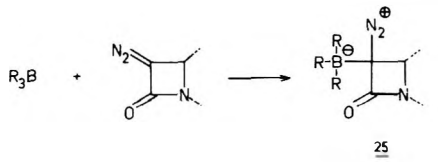
Scheme V



the latter from the alcohols[14] formed during the oxidative work-up from borane **20**. We believe that chelate ring formation between the amide nitrogen and the boron atom in **20** reduces the Lewis acid character of the borane and prevents alkylation.

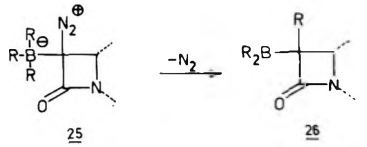
To circumvent this problem an alternative approach was tried, in which the trialkylborane **22** reacts with **5** to give **23**. Aqueous hydrochloric acid in tetrahydrofuran[11] was needed to hydrolyze the amine–boron hydride complex to the free amine; however, no **24** or any other compound with an intact β-lactam ring was formed. Apparently the β-lactam does not survive these hydrolysis conditions. The alkylation of the diazo cephem esters **3** and **5** gave rise to a mixture of two alkylated products with cis and trans configuration at the 6 and 7 position of the β-lactam ring. This ratio could easily be estimated with NMR spectroscopy, by integration of the two doublet signals of the C_6 proton, cis J = 5 Hz and trans J = 2.5 Hz, which are separated by 30 Hz. The data are summarized in Table I. Deblocking of the *tert*-butyl esters with trifluoroacetic acid does not affect this cis–trans ratio. The presence of the Δ_3 cephem nucleus was confirmed by the remaining NMR data.

No detailed study has been published about the mechanism of the reaction of trialkylboranes with diazo compounds, but it appears likely that the reaction involved first a coordination of the borane with the diazo compound to produce the quaternary boron intermediate **25** (eq 1).



(1)

This is followed by loss of nitrogen from **25** with either subsequent or concurrent migration of an alkyl moiety (eq 2).



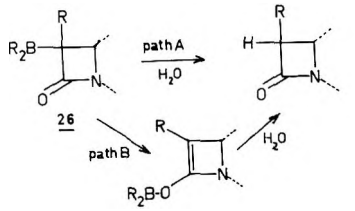
(2)

Hydrolysis of intermediate **26** with water gives the desired product (eq 3, path A). Alternatively, it is possible that in-

Table I

Compd	Yield, %	Cis, %
6	90	33
7	80	30
8	22	33
9	90	33
10	85	30
12	31	6
13	85	6
17	85	~2
18	85	~2

termediate **26** exists in the isomeric enol–borinate form[15] (path B), which is rapidly hydrolyzed to the product.

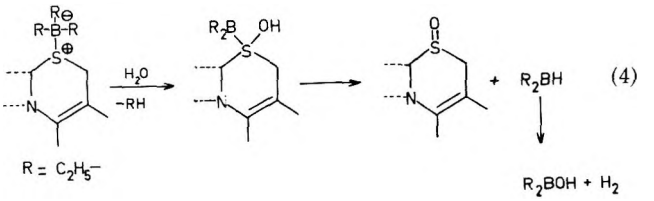


(3)

In cephalosporins the thermodynamically more stable form is the trans-substituted β-lactam ring, probably because the 7 substituents are more crowded in the β than in the α configuration.[16] The α side of the molecule is the least hindered side. Thus the main product in the addition of the trialkylboranes to the diazo cephems **3** and **5** should be the α-substituted alkyl cephalosporin. Neither kinetic nor thermodynamic control appears to be able to influence this result. This is in fact the case. Using trialkylboranes with bulkier alkyl groups (Table I), we found an increasing formation of the trans-substituted cephalosporins. Until now we have been unsuccessful in changing the cis–trans ratio in favor of the cis epimer, the latter in all probability being the configuration which may show biological activity.[17,18]

Formation of the cephem sulfoxide **8** seems to be the first example of oxidation of sulfur with a trialkylborane–water mixture.

We believe that it is the addition complex of sulfur with the trialkylborane that reacts with water (eq 4). Hydrogen gas was shown to be present by GLC.



(4)

The alkylated cephalosporins described here were tested for antimicrobial activity in vitro. The cis–trans mixtures were tested as such, because we were unable to separate the isomers. Only the methyleneadamantyldeacetoxycephalosporanic acid showed a low but definite activity against some gram-positive organism. Minimum inhibitory concentration (MIC) values: *Streptococcus haemolyticus*, 12.5; *Sarcinea lutea*, 6.5; *Haemophilus suis*, 50.

Experimental Section

The ^{1}H NMR spectra were determined on a Varian T60 spectrometer. Chemical shifts are relative to Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 125 or 257 and Unicam Sp200. The mass spectra were obtained on a AEI MS 902 mass spectrometer. Column chromatography was carried out on aluminum oxide "activ neutral" from Merck and silica gel 60–120 mesh from BDH. Merck silica gel PF 254 was used for preparative thin layer chromatography. Melting points are uncorrected. Tetrahydrofuran was freshly destilled from $LiAlH_4$ under a nitrogen atmosphere. We thank the Squibb Institute for Medical Research for a generous supply of 7-ADCA and some financial support to one of us (J.S.W.).

1-Glycylpiperidine. A solution of 9.5 g (3.4 mmol) of 1-(*N*-benzyloxycarbonylglycyl)piperidine[19] in 100 ml of methanol was hydrogenolyzed in the presence of 900 mg of 10% palladium on carbon at room temperature and atmospheric pressure until the uptake of hydrogen had ceased. The solution was evaporated to 25 ml and the catalyst was removed by centrifugation. Evaporation to dryness in vacuo gave 5 g of colorless oil, which was distilled to give 4.6 g (3.2 mmol, 95%) of 1-glycylpiperidine: bp 84–85 °C (3 mmHg); ir (neat) 3400, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.3–1.7 (8 H), 3.2–3.6 (6 H). Anal. Calcd for $C_7H_{14}N_2O$: C 59.07; H, 9.93; N, 19.71. Found: C, 59,13; H, 9.93; N, 19.35.

1-(α-Diazoacetyl)piperidine. A solution of 500 mg (3.52 mmol) of 1-glycylpiperidine in 20 ml of $CHCl_3$ was refluxed during 15 min with 540 mg of isoamyl nitrite and 720 mg of acetic acid. The yellow solution was diluted with 20 ml of $CHCl_3$, cooled, and washed with 5 ml of 1 N H_2SO_4, 5 ml of water, 5 ml of saturated aqueous $NaHCO_3$, and twice with 5 ml of water. After drying (Na_2SO_4) and evaporation to dryness in vacuo, the yellow residue was purified by column chromatography on aluminum monoxide activity III, using ether as eluent. 1-(α-Diazoacetyl)piperidine was isolated as a yellow oil (400 mg, 2.6 mmol, 70%): ir (CH_2Cl_2) 2180, 1600 cm^{-1}; NMR ($CDCl_3$) δ 5.2 (3 H), 3.1–3.4 (4 H), 1.2–1.7 (6 H).

1-Caprylpiperidine (1). To a solution of 0.35 mmol of trioctylborane[20] in 9 ml of dry THF was added 0.1 ml of water and 46 mg (0.30 mmol) of 1-(α diazoacetyl)piperidine. After 3 h at 35 °C 1 ml of 30% hydrogen peroxide was added and the colorless solution was washed with brine solution (3 × 5 ml). GLC analysis indicated 92% yield of **1**. Isolation was carried out with preparative GLC, column 6 ft × 0.5 in. SE-30: n^{20}D 1.4720; ir (CH_2Cl_2) 1630 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H), 1.55 (14 H), 1.65 (6 H); 2.20 (2 H), 3.3 (4 H). Compound **1** was identical in all aspects with an authentic sample.

***p*-Toluenesulfonic Acid Salt of 7-Aminodeacetoxycephalosporanic Acid *tert*-Butyl Ester (2).** To 1.35 g (5 mmol) of 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester[2b] in 50 ml of ether was added a solution of 1.0 g (1.1 equiv) of *p*-toluenesulfonic acid monohydrate in 5 ml of ether and 5 ml of THF. The salt **2** precipitated immediately. After standing in the cold for 1 h the salt was isolated and recrystallized from hot acetonitrile to give 2.1 g (95%) of white salt **2**: mp 175.5 °C dec (preheated block); ir (Nujol) 3200–2600, 1670, 1620, 1650, 1600, 1540 cm^{-1}. Anal. Calcd for $C_{19}H_{26}N_2S_2O_6$: C, 51.56; H, 5.92; N, 6.33; S, 14.49. Found: C, 51.02; H, 5.95; N, 6.06; S, 14.15.

7-Diazodeacetoxycephalosporanic Acid *tert*-Butyl Ester (3). A mixture of 265 mg (0.6 mmol) of compound **2**, 1.5 g of sodium nitrite, 60 ml of $CHCl_2$, and 60 ml of ice water was stirred vigorously and cooled in an ice bath. After 5 min 180 mg (0.95 mmol) of *p*-toluenesulfonic acid monohydrate was added to this mixture gradually over a period of 20 min and stirring was continued for 10 min. The yellow mixture was transferred to an ice-cold separatory funnel and the organic layer was washed twice with 10-ml portions of brine solution. After drying (Na_2SO_4) and evaporation in vacuo to dryness, the residual yellow oil was purified by column chromatography on 6 g of aluminum oxide activity III with CH_2Cl_2 as eluent. Evaporation gave the diazocephem ester **3**, as a yellow oil which solidified: mp 42–43 °C dec; ir (CH_2Cl_2) 2090, 1760, 1700, 1260 cm^{-1}; NMR ($CDCl_2$) δ 5.6 (s, C_6 H), 3.31 (AB q, J = 10 Hz, C_2CH_2), 2.1 (s, CH_3), 1.5 (s, *t*-Bu).

7-Ethyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (6). A three-necked 50-ml flask, equipped with two pressure-equalized dropping funnels and a thermometer, was flushed with nitrogen. The flask was charged with 5 ml of dry THF and cooled to −65 °C. One dropping funnel was filled with a solution of 113 mg (0.40 mmol) of diazo cephem ester **3** in 10 ml of dry THF. The second dropping funnel was filled with 0.8 ml (2 equiv) of 1.008 M triethylborane in THF, 10 ml of THF, and 0.03 ml of water. Both solutions were added at the same rate to the THF over a period of 5 min, keeping the temperature at −65 °C. The solution was allowed to come to −45 °C and 5 drops of 30% hydrogen peroxide was added. When the temperature had reached −15 °C, the mixture was washed in a separatory funnel with brine solution (3 × 7 ml). The almost colorless organic layer was cooled, diluted with 30 ml of CH_2Cl_2, and dried (Na_2SO_4). After evaporation to dryness, the residual oil was purified by column chromatography with 7 g of silica gel, deactivated with 0.8 ml of water, with CH_2Cl_2 as eluent. Evaporation of the first 30 ml gave 110 mg (0.38 mmol, 90%) of oil

6. Preparative thin layer chromatography with CH_2Cl_2–5% ether afforded analytically pure **6**: ir (CH_2Cl_2) 1770, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.84 (d, J = 5 Hz, C_6 H), 4.40 (d, J = 2.5 Hz, C_6 H), 3.30 (AB q, J = 18 Hz, C_2 CH_2), 3.5 (m, C_7 H), 3.08 (m, C_7 H), 2.05 (s, CH_3), 1.85 (m, $-CH_2-$), 1.55 (s, t-Bu), 1.15 (t, J = 7 Hz, CH_3); mass spectrum m/e 283, 255, 228, 199, 158, 157, 140, 139, 57. Anal. Calcd for $C_{14}H_{21}NSO_3$: C, 59.34; H, 7.47; N, 4.94; δ 11.31. Found: C, 58.92; H, 7.45; N, 4.82; δ 11.20. Uv λ_{max} (MeOH) 265 nm (ϵ 6600).

7-Ethyldeacetoxycephalosporanic Acid (9). Compound **6** (85 mg, 0.3 mmol) was stirred with 2.5 ml of trifluoroacetic acid during 5 min at room temperature. Evaporation in vacuo at 10^{-2} mmHg gave a light brown colored residue, which was triturated with dry pentane. After evaporation of the pentane, the solid was taken up in 1 ml of CH_2Cl_2 and dropped into 15 ml of dry ether. This solution was cooled for 30 min at −20 °C. A little brown solid was removed by centrifugation and the supernatant liquid was evaporated. The remaining solid was dissolved in 1 ml of CH_2Cl_2 and added with stirring to 50 ml of dry pentane. Compound **9** (63 mg, 0.27 mmol, 90%) was isolated as a pale yellow, amorphous solid: mp 70–78 °C; ir (CH_2Cl_2) 3600–2500, 1760, 1720, 1630 cm^{-1}; NMR ($CDCl_3$) δ 9.1 (s, COOH), 4.9 (d, J = 5 Hz, C_6 H), 4.45 (d, J = 2.5 Hz, C_6 H), 3.4 (AB q, J = 18 Hz, C_2 CH_2), 3.65 (m, C_7 H), 3.15 (m, C_7 H), 2.2 (s, CH_3), 1.9 (m, $-CH_2-$), 1.1 (~t, $-CH_3$, J = 7 Hz); mass spectrum calcd, m/e 227.061; found, m/e 227.054.

7-Ethyldeacetoxycephalosporanic Acid *tert*-Butyl Ester *S*-Oxide (8). To a solution of 0.4 mmol of triethylborane in 15 ml of dry THF under nitrogen atmosphere was added 0.35 ml of water. The mixture was cooled to −60 °C and 113 mg (0.4 mmol) of diazo cephem ester **3** in 10 ml of dry THF was added over a period of 10 min. The work-up procedure was the same as described for **6**. The isolated colorless oil was submitted to preparative silica gel thin layer chromatography using ether–CH_2Cl_2 (1:2) as eluent. Compound **8** was isolated as an oil (24 g, 0.08 mmol, 20%), which was crystallized from CH_2Cl_2–pentane as a white solid: mp 141–145 °C; ir (CH_2Cl_2) 1780, 1720, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.6 (d, J = 5 Hz), 4.2 (d, J = 2 Hz, C_6 H), 3.1–3.9 (C_2 CH_2, C_7 H), 2.05 (s, CH_3), 1.7–1.9 (m, $-CH_2-$), 1.5 (s, t-Bu), 1.0–1.3 (t, CH_3); mass spectrum calcd, m/e 299.119; found, m/e 299.118. Hydrogen was proved in the gas evolving from the reaction mixture by GLC, column 6 ft × 0.5 in., molecular sieves 5 Å, 80 °C.

7-Octyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (7). The procedure for the preparation of **6** was followed, using trioctylborane as alkylating agent. Compound **7** was isolated in 80% yield after column chromatography on silica gel, deactivated with 10% water. Analytically pure material was obtained by preparative silica gel thin layer chromatography with CH_2Cl_2–5% ether as eluent: ir (CH_2Cl_2) 1770, 1715 cm^{-1}; NMR ($CDCl_3$) δ 4.88 (d, J = 5 Hz, C_6 H), 4.42 (d, J = 2.5 Hz, C_6 H), 3.30 (AB q, J = 18 Hz, C_2 CH_2), 3.5 (m, C_7 H), 3.18 (m, C_7 H), 2.1 (s, CH_3), 1.6 (s, t-Bu), 2.3 (octyl, 12 H), 1.0 (CH_3); mass spectrum m/e 367, 339, 283, 158, 157, 140, 139, 57. Anal. Calcd for $C_{20}H_{33}NSO_3$: C, 65.35; H, 9.05; N, 3.81; S, 8.72. Found: C, 65.04; H, 9.05; N, 3.85; S, 8.51. Uv λ_{max} (EtOH) 267 nm (ϵ 6600).

7-Octyldeacetoxycephalosporanic Acid (10). The procedure for the preparation of **9** was followed. Acid **10** was isolated as an oil in 85% yield: ir (CH_2Cl_2) 1760, 1720, 1630 cm^{-1}; NMR ($CDCl_3$) δ 9.0 (s, COOH), 4.90 (d, J = 5 Hz, C_6 H), 4.45 (J = 2.5 Hz, C_6 H), 3.4 (AB q, J = 18 Hz, C_2 CH_2), 2.2 (s, CH_3), 1.55 (m, $-CH_2-$), 1.3 (octyl, 12 H), 0.9 (CH_3). Determination of the exact mass was not possible, because the molecular ion peak was lacking in the mass spectrum.

7-Methyleneadamantyldeacetoxycephalosporanic Acid *tert*-Butyl Ester (12). A solution of 120 mg (0.43 mmol) of diazo cephem ester **3** in 10 ml of dry ether (distilled from $LiAlH_4$) and a freshly prepared solution of 2 equiv of borane **11** in 10 ml of dry ether were added at the same rate to each other, keeping the temperature at −80 °C. After 5 min 0.06 ml of MeOH was added, followed by about 1.5 ml of triethylamine to neutralize the mixture. After the mixture was allowed to come to −10 °C, the latter was washed with brine solution (3 × 5 ml). The organic layer was dried (Na_2SO_4) and evaporated to dryness in vacuo. By preparative silica gel thin layer chromatography with CH_2Cl_2 as eluent a mixture of **12** and **14** was isolated as an oil (114 mg). Repeated thin layer chromatography of this oil with benzene–acetone (9.75:0.25) gave 54 mg (0.13 mmol, 31%) of compound **12**, crystallized from $CHCl_3$–pentane: mp 160–165.5 °C; ir (CH_2Cl_2) 1760, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.8 (d, J = 5 Hz, C_6 H), 4.35 (d, J = 2 Hz, C_6 H), 3.28 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.8 (methyleneadamantyl), 1.55 (s, t-Bu). Anal. Calcd for $C_{23}H_{33}NSO_3$: C, 68.62; H, 8.01; S, 7.97. Found C, 67.07; H, 8.13; S, 7.99. Mass spectrum exact mass calcd, m/e 403.218; found, m/e 403.218. At the same time 22 mg of compound **14** was isolated as an oil: ir (CH_2Cl_2) 1780, 1710 cm^{-1}; NMR ($CDCl_3$) δ 4.68 (d, J = 1.5 Hz, C_7 H), 4.58 (d, J = 1.5 Hz, C_6 H), 3.3 (AB q, J = 18 Hz, C_2 CH_2), 2.05 (s, CH_3), 1.5 (s, t-Bu); mass spectrum m/e 289/291 (2:1), 233, 235, 205, 207. The spectra of **14** were identical with the spectra of a sample prepared by treating diazo cephem ester **3** (100 mg) with 1 ml of concentrated HCl in 15 ml of THF at 0 °C during 3 min.

7-Methyleneadamantyldeacetoxycephalosporanic Acid (13). Compound **12** (40 mg, 0.22 mmol) was stirred with 0.8 ml of trifluoroacetic acid at room temperature during 5 min. Evaporation gave a light yellow syrup, which was crystallized from CH_2Cl_2–pentane to give 30 mg (0.085 mmol, 85%) of white, crystalline **13**: mp >200 °C dec; (CH_2Cl_2) 1770, 1720 cm^{-1}; mass spectrum exact mass calcd, m/e 347.155; found, m/e 347.157.

7-Diazocephalosporanic Acid *tert*-Butyl Ester (5). 7-Aminocephalosporanic acid *tert*-butyl ester (**4**,[2b] 164 mg, 0.5 mmol) was diazotized in a mixture of 50 ml of CH_2Cl_2 and 50 ml of ice water with 1.5 g of sodium nitrite and 95 mg of p-TSA–H_2O. After 5 min a total amount of 138 mg (0.77 mmol) of p-TSA–H_2O was added over a period of 37 min and stirring was continued for 3 min. The same work-up procedure as described for the synthesis of **3** was followed. Compound **5** (128–141 mg, 64–83%)[21] was isolated as a yellow solid, which was crystallized from CH_2Cl_2–petroleum ether (40:60): mp 99–99.5 °C dec; ir (CH_2Cl_2) 2180, 1765, 1730, 1710, 1635 cm^{-1}; NMR ($CDCl_3$) δ 5.5 (s, C_6 H), 4.83 (AB q, J = 18 Hz, C_2 CH_2), 2.03 (s, CH_3), 1.52 (s, t-Bu). Anal. Calcd for $C_{14}H_{17}N_3O_5S$: C, 49.54; H, 5.05; N, 12.38; S, 9.45. Found C, 49.98; H, 5.12; N, 12.28; S, 9.33.

Tri(4-benzoyloxybutyl)borane (16). To a solution of 422 mg (2.46 mmol) of 3-butenyl benzoate in 4 ml of dry THF was added 4.85 ml (0.85 mmol) of diborane in THF at a temperature of −10 °C. After stirring for 1 h at −10 °C and 30 min at room temperature, the excess of diborane was destroyed with 0.03 ml of water. This solution was used as such for the synthesis of **17**.

7-(4-Benzoyloxybutyl)cephalosporanic Acid *tert*-Butyl Ester (17). The procedure for the synthesis of **6** was followed, except that a solution of **5** was alkylated with borane **16**. Compound **17** was isolated as a colorless oil in 85% yield by preparative silica gel thin layer chromatography with CH_2Cl_2–10% ether as eluent. Despite extensive efforts, **17** could not be obtained in analytically pure form: ir (CH_2Cl_2) 3100, 1770, 1700–1740, 1640, 1600, 1580 cm^{-1}; NMR ($CDCl_3$) δ 7.9–7.4 (aromatic protons), 4.8 (AB q, J = 12 Hz, C_3 CH_2), ~4.55 (d, J = 5 Hz, C_6 H), 4.35 (d, J = 2.5 Hz, C_6 H), 4.25 (~t, $-CH_2O$), 3.32 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.55–1.9 (m, 6 H), 1.5 (s, t-Bu), ~3.6 (m, C_7H), ~3.1 (m, C_7 H); mass spectrum m/e 433 ($M^+ - 56$), 374, 155, 115, 78, 71, 57; uv λ_{max} (95% EtOH) 265 nm (ϵ 7100), 228 (14 000).

Sodium 7-(4-Benzoyloxybutyl)cephalosporanate (18). The same procedure as for the preparation of **9** was followed. From 100 mg (0.20 mmol) of ester **17**, 90 mg of 7-(4-benzoyloxybutyl)cephalosporanic acid was isolated as an amorphous solid: ir (CH_2Cl_2) 3300–2500, 1775, 1750, 1700, 1600, 1580, 1560 cm^{-1}; NMR ($CDCl_3$) δ 7.9–7.4 (aromatic protons), 4.85 (AB q, J = 12 Hz, C_3 CH_2), ~4.55 (d, J = 5 Hz, C_6H), ~4.32 (d, J = 2.5 Hz, C_6 H), 4.25 (t, $-CH_2O$), 3.3 (AB q, J = 18 Hz, C_2 CH_2), 2.0 (s, CH_3), 1.5–2.0 (m, 6 H). Estimation of the exact mass was not possible, because the molecular ion peak was lacking in the mass spectrum. Purification was effected by converting the acid into the sodium salt **18**. The latter was isolated in 85% yield by lyophilization of an aqueous solution of pH 7.5: mp 150 °C dec; uv λ_{max} (H_2O) 230, 260 nm; ir (Nujol) 1770, 1730, 1649–1600, 1580 cm^{-1}.

Registry No.—**1**, 5299-66-1; **2**, 58249-90-4; **3**, 58249-91-5; **4**, 6187-87-7; **5**, 58249-92-6; **6**, 58249-93-7; **7**, 58249-94-8; **8**, 58249-95-9; **9**, 58249-96-0; **10**, 58249-97-1; **11**, 58249-98-2; **12**, 58249-99-3; **13**, 58250-00-3; **14**, 58250-01-4; **15**, 18203-32-2; **16**, 58250-02-5; **17**, 58250-03-6; **18**, 58250-04-7; 1-glycylpiperidine, 5649-08-1; 1-(*N*-benzyloxycarbonylglycyl)piperidine, 3886-37-1; 1-(α-diazoacetyl)-piperidine, 24761-87-3; trioctylborane, 3248-78-0; 7-aminodeacetoxycephalosporanic acid *tert*-butyl ester, 33610-06-9; triethylborane, 97-94-9; 7-(4-benzoyloxybutyl)cephalosporanic acid, 58250-05-8.

References and Notes

(1) (a) E. H. Flynn, "Cephalosporins and Penicillins", Academic Press, New York, N.Y., 1972; (b) *ibid.*, pp 96–105, for details about diazotation of 6-ADA, 7-ACA, and 7-ADCA and the preparation of 7-epi-chlorodeacetoxycephalosporanic acid.

(2) (a) T. Yen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, **38**, 2857 (1973); (b) E. H. W. Bohme, H. E. Applegate, J. B. Ensing, P. T. Funke,

M. S. Puar, and J. E. Dolfini, *J. Org. Chem.*, **38**, 230 (1973); (c) L. D. Cama and B. G. Christensen, *Tetrahedron Lett.*, 3505 (1973); (d) H. E. Applegate, J. E. Dolfini, M. S. Puar, W. A. Husarchyk, B. Toeplitz, and J. Z. Gougatas, *J. Org. Chem.*, **39**, 2794 (1974); (e) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973); (f) H. Yanagiswa, M. Fukusima, A. Ando, and H. Wakao, *Tetrahedron Lett.*, 2705 (1975).

(3) Recently the synthesis of 7-β-phenoxyacetylpenicillanic acid was reported, which showed some antibiotic activity: J. C. Sheehan and Y. S. Lo, *J. Org. Chem.*, **38**, *3227 (1973)*.

(4) G. L. Biagi, M. C. Guerra, A. M. Barbaro, and M. F. Gamba, *J. Med. Chem.*, **13**, 511 (1970).

(5) J. Hooz and S. Linke, *J. Am. Chem. Soc.*, **90**, 6891 (1968). We have no ready explanation for the role which water plays in this reaction, since the reaction proceeds well under anhydrous condition on substrates used by Hooz. The presence of sulfur and the formation of the sulfoxide (8) need to be considered in this respect.

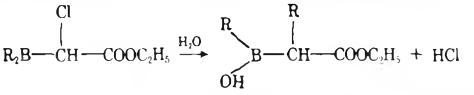
(6) Hydroboration of terminal simple alkenes gives rise to 6% addition of the boron to the 2 and *94%* addition to the 1 position.[7] However, we could not detect any 1-(α-methylnonanoyl)piperidine using GLC and NMR techniques.

(7) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972, Part 5.

(8) The synthesis of benzhydryl 7-diazocephalosporanate has been reported via diazotation of the amine. However, no yield and experimental details were given: L. D. Cama, R. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).

(9) H. C. Brown, M. H. Midland, and A. B. Levy, *J. Am. Chem. Soc.*, **94**, 3662 (1972).

(10) Nucleophilic induced substitution of the chloro substituent, occurring in more simple systems, is apparently not the case here (ref 9).



(11) H. C. Brown and M. K. Unni, *J. Am. Chem. Soc.*, **90**, 2902 (1968).

(12) H. C. Brown and R. L. Sharp, *J. Am. Chem. Soc.*, **90**, 2915 (1968).

(13) H. C. Brown and R. M. Gallivan, Jr., *J. Am. Chem. Soc.*, **90**, 2906 (1968).

(14) The two alcohols *N*-(4-hydroxybutyl)benzamide and *N*-(3-hydroxybutyl)-benzamide were formed in the ratio 89:11, which implied that 11% of the boron had been added to the 2 position of the alkene moiety of **18**.

(15) D. J. Pasto and P. W. Wojtkowski, *Tetrahedron Lett.*, 215 (1970).

(16) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

(17) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969).

(18) R. A. Firestone, N. Schelechow, D. H. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(19) D. M. Brunwin, G. Love, and J. Parker, *J. Chem. Soc. C*, 3756 (1971).

(20) H. C. Brown and G. Zweifel, *Org. React.*, **13**, 1 (1963).

(21) The yield of **5** strongly depends on the purity of the precursor **4** and the rate of addition of the *p*-toluenesulfinic acid to **4**.

Nitrosation of 1-Substituted Aziridines

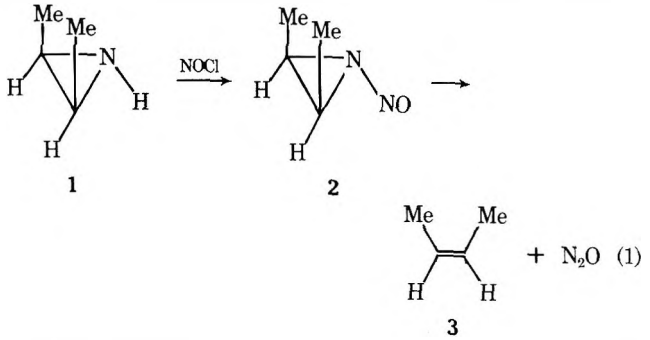
Richard N. Loeppky* and David H. Smith

Department of Chemistry, University of Missouri, Columbia, Columbia, Missouri 65201

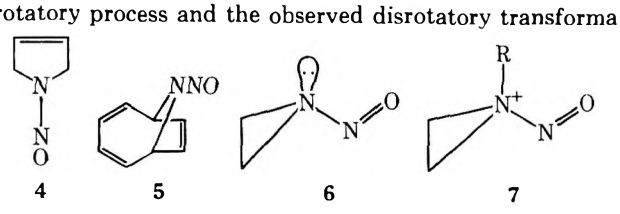
Received May 1, 1975

Three aziridines, (*Z*)-1-butyl-, (*Z*)-1-benzyl-, and (*Z*)-1-(4-chlorophenyl)-2,3-diphenylaziridine, have been prepared and their reaction with nitrous acid in acetic acid studied. The principal product of the *N*-alkylaziridine nitrosation has been assigned the structure of an *N*-alkylnitrosenamine, a new type of compound, on the basis of its chemical and spectroscopic behavior (including high-resolution MS and ^1H and ^{13}C NMR). Acid-catalyzed hydrolysis of (*E*)-1,2-diphenyl-1-(*N*-butyl)nitrosaminoethene gave benzoin in addition to the expected benzyl phenyl ketone. Other products from the nitrosation were benzaldehyde and *threo*-1,2-diphenyl-2-(*N*-butyl)nitrosaminoethyl acetate. The reaction of the *N*-arylaziridine with nitrous acid gave these latter two types of products, and *N*-4-chlorophenylbenzamide among others. Mechanisms which accommodate these findings are discussed.

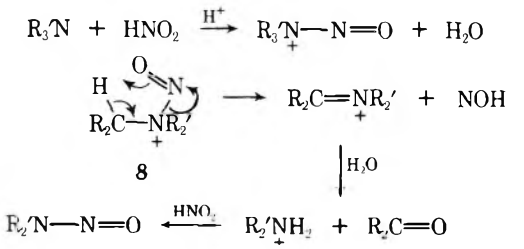
Since the discovery of the facile nitrous oxide extrusion reaction of *N*-nitroso aziridines[1] this transformation (eq 1)



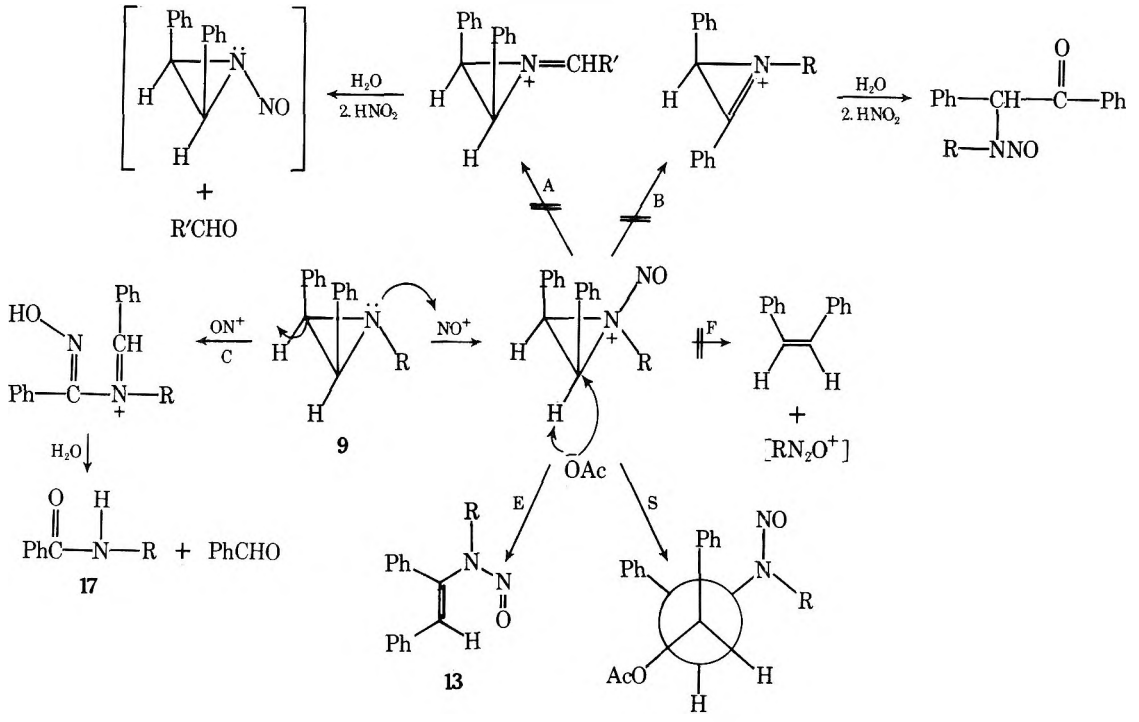
has been of considerable synthetic and theoretical interest.[2-7] Woodward and Hoffmann presented the reaction as an example of a nonlinear cheletropic cycloreversion in explaining the observation of both facile extrusion and retention of stereochemistry.[8] In principle two modes of decomposition are open to the *N*-nitroso aziridines, a linear conrotatory process and the observed disrotatory transformation, although geometric factors allow only this latter mode of decomposition. In order to explain the stability of *N*-nitroso-3-pyrroline **4** and the nitrous oxide adduct of cyclooctatetraene **5** Mock and Isaac[9] have postulated that unlike other nitrosamines the amino nitrogen of *N*-nitroso aziridine exists in a tetrahedral array **6** which uniquely predisposes it to cheletropic fragmentation. Examination of the correlation diagram of Mock and Isaac has led us to consider the fate of the related species **7** where the unshared pair is coordinated with an alkyl or aryl cation. It appears that such a species is capable of facile decomposition to an olefin and [R—N⋯N⋯O$^+$]. A species akin to **7**, the trialkylnitrosammonium ion **8**, has been shown by Smith and Loeppky[10] to lie on the pathway for the nitrosative cleavage of alkyl tertiary amines. This reaction, which has been periodically rediscovered over the past 100 years,[11] proceeds by the mechanism depicted in Scheme I. In this paper we



Scheme I



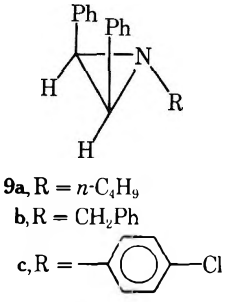
Scheme II



present our studies of the nitrosation of certain 1-alkyl- and 1-aryl-2,3-diphenylaziridines which we presupposed might decompose through a species such as **7** (Scheme II, path F) to give either olefin via RN_2O^+ extrusion or alkyl nitrogen cleavage as depicted in Scheme II, paths A and B. Added impetus to this research has come from concern over the carcinogenic properties of some nitrosamines which can be produced in the stomach from nitrite and secondary or tertiary amines present in foodstuffs or drugs.[12]

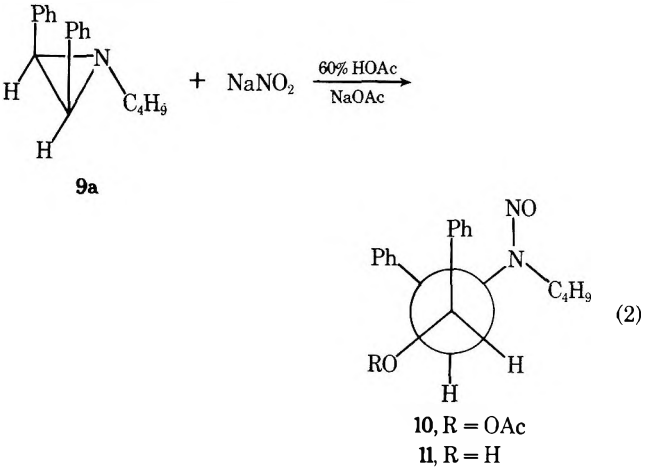
Results

Because of advantages in their handling and purification we chose to utilize 1-substituted 2,3-diphenylaziridines in this study and their synthesis by well-established methods is outlined in the Experimental Section. The general mode of aziridine ring construction utilized in this work involved the ring closure of the appropriate β-chloro secondary amines. This method produced only the *Z*-1-substituted 2,3-diphenylaziridines **9a–c** since the precursors to the corresponding trans aziridines, the erythro β-chloro amines, could not be produced from either of the diastereomeric amino alcohols. A variety of reagents and reaction conditions produced only the threo β-chloro amines.



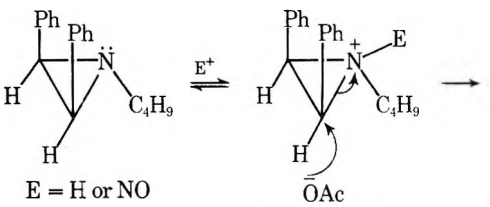
9a, R = *n*-C_4H_9
b, R = CH_2Ph
c, R =

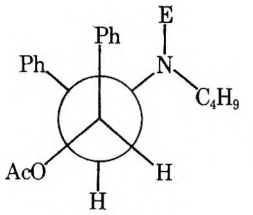
Although 1-unsubstituted aziridines have been nitrosated with NOCl, we initiated our studies with an investigation of the reaction of **9a** with nitrous acid in 60% acetic acid buffered to pH 4 with sodium acetate at 90 °C because these are the conditions which have been employed in the nitrosation of other tertiary amines.[10] The products of this transformation, which were separated and purified by chromatography on alumina, were determined to be *threo*-1,2-diphenyl-2-(*N*-*n*-butyl)nitrosaminoethyl acetate (**10a**) and *threo*-1,2-diphenyl-2-(*N*-*n*-butyl)nitrosaminoethanol (**11**) in 97% combined yield (eq 2). The alcohol **11** was found to arise from the ester **10a** in the course of the work-up procedure. The key to the identity of these products was given by their analyses, spectral data, and independent synthesis, which are given in the Experimental Section.



10, R = OAc
11, R = H

Since the products of this transformation are similar to those expected from the solvolytic ring opening of the aziridine in acetic acid we chose to examine the fate of **9a** in the reaction media in the absence of sodium nitrite. Treatment of **9a** with 60% acetic acid and sodium acetate at pH 4 and 90 °C resulted in its complete conversion to the threo amino acetate **12** (E = H) in 2.5 h as monitored by NMR. This result is not unexpected,[13] and as has been observed for similar cases is found to occur with inversion of configuration at carbon as is depicted in eq 3 where $E^+ = H^+$. The ring opening under nitrosating conditions proceeded slightly more rapidly than it did in the absence of $NaNO_2$. It is therefore possible that the opening is induced by nitrosammonium formation (eq 3, $E^+ = NO^+$) as well as by protona-





(3)

10a, E = NO
12, E = H

tion. It is just as likely, however, that nitrosation occurred after acid-catalyzed ring opening and for this reason we sought conditions which would permit the unambiguous study of aziridine nitrosation.

Our attention was next directed at glacial acetic acid as a suitable solvent for the aziridine and the generation of nitrous acid. We found that **9a** could be recovered quantitatively after dissolution in glacial acetic acid for 2.25 h at 25 °C. While such conditions do not induce aziridine ring opening, the "end of reaction" conditions from the addition of aqueous sodium nitrite are not expected to be as hospitable to the aziridine for they begin to approximate the buffered aqueous acetic acid used previously (eq 4).

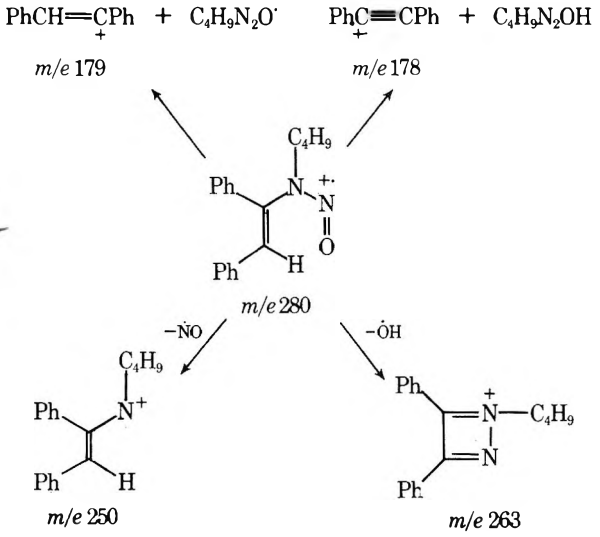
$$2HOAc + 2NaNO_2 \xrightarrow[\Delta]{} H_2O + 2NaOAc + NO_2 + NO \quad (4)$$

By making the extravagant assumption that all of the nitrite added to glacial acetic acid is consumed as shown in eq 4 we prepared a solution of the aziridine in this "end of the reaction" media by adding the appropriate amount of water and sodium acetate and followed the fate of the aziridine by NMR. The half-life of the aziridine under these conditions was 12.75 h and the product isolated after 24 days of reaction was the threo amino acetate **12.**

Since the degradation of the aziridine under these conditions was not rapid we undertook the study of the nitrosation of 3.5% (wt) solution of **9a** in glacial acetic acid. After a reaction time of 2.5 h three products were separated from the reaction mixture (Scheme II, paths C, E, and S). The minor components of this mixture were benzaldehyde (19% yield based on GLC) and the threo nitrosamino acetate **10a** (yield 20%). The major product (yield 62%) of this transformation proved to be a substance of novel structure and unusual properties to which we have assigned the structure of (*E*)-1,2-diphenyl-1-(*N*-butyl)nitrosaminoethene (**13a**). To the extent of our knowledge this is the first nitrosenamine to be reported although allusions to them have been made in the literature.[14,15] Its structure is based on the spectroscopic and chemical data presented below.

The compound **13a** is a white, crystalline solid (mp 91–92 °C), insoluble in acid and base and analyzing for $C_{18}H_{20}N_2O$. The fact that the two phenyl groups and the *n*-butyl group have traversed the reaction course intact was indicated by both the ^1H and ^{13}C NMR spectra of **13a,** the details of which are given in the Experimental Section. The enamine functionality of **13a** was indicated by the ir spectrum (1650 cm^{-1}, w), the uv spectrum (227 nm, ϵ 1.3 × 10^4, and 285 nm, ϵ 1.5 × 10^4) in comparison with spectra of known enamines and enamides[16–20] (223–222 and 278–312 nm), and its ^1H and ^{13}C NMR spectra. The ^1H NMR of **13a** exhibited a nonexchangeable singlet at δ 7.9 which was assigned to the vinyl hydrogen in **13a.** This signal is a full 1

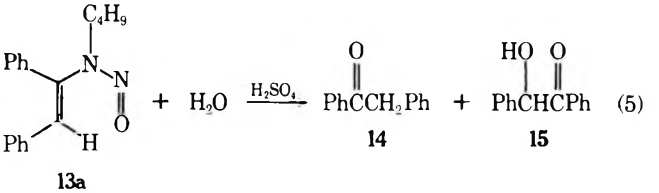
Scheme III



ppm downfield from the vinyl hydrogen of structurally similar enamides[18,19] and this effect is thought to be produced by the deshielding of the nitroso function (vide infra). The ^{13}C NMR of **13a** exhibited eight peaks in the region δ 128.78–148.27 and the lowest field peak was assigned to the nitrogen bearing carbon on the basis of decoupling experiments which showed it to be a quaternary carbon and upon comparison with the spectrum of 1-pyrrolidino-1,2-diphenylethene (C-1, δ 148.64). The nitrosamino functionality was suggested by the intense ir absorption in the region 1300–1500 cm^{-1}, the mass spectrum, which showed peaks due to parent minus OH and parent minus NO, and the ^{13}C spectrum. The nitrogen-bound carbon of **13a** resonates at δ 53.05 which compares favorably with values of δ 59.9 and 50.4 observed for dibutylnitrosamine.[25]

The cis arrangement of the phenyl groups in **13a** is based on its mode of formation (vide infra), the extreme deshielding of its vinyl hydrogen, its uv spectrum in comparison with those of similar compounds,[16–20] and particularly its mass spectrum. High-resolution mass spectrometry of **13a** confirmed the empirical formula and gave as the most significant spectral feature a base peak *m/e* 178 having the formula $C_{14}H_{10}$ assigned the radical cation of diphenylacetylene. This fragment and the second most abundant ion, the stilbene cation (*m/e* 179), are envisioned to arise by the processes shown in Scheme III.[27] All of the peaks found in the mass spectrum of stilbene and diphenylacetylene were found in the mass spectrum of **13a.**[28] The facile McLafferty-type rearrangement of the parent ion to give the diphenylacetylene radical cation is strongly suggestive of the cis ene geometry.

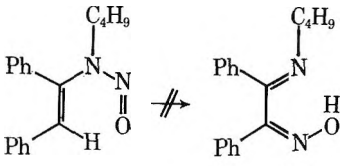
While the extensive spectroscopic data convincingly support the structure assigned to **13a** its reactivity was surprising but none the less corroborative and our cursory investigation of its most interesting chemistry has demonstrated the lack of extensive skeletal rearrangements such as phe-



(5)

nyl migrations. The acid-catalyzed hydrolysis of **13a** gave, in addition to the expected product, benzyl phenyl ketone (**14**), a good yield of benzoin **15.** The chemistry of **13a** dif-

fered from that of other enamides and enamines in other ways as well, since it did not react with Br_2/CCl_4 or H_2/Pt. Furthermore, **13a** failed to give a positive Liebermann's *N*-nitroso test and does not give any indication of isomerizing under acidic or basic conditions to the iminooxime **16** as



13a **16** (6)

does its trans isomer.[15,29] Numerous attempts to synthesize **13a** by independent routes have not yet met with success.[29] Our synthetic efforts have been frustrated by our inability to obtain the precursor erythro β-chloronitrosamine (vide supra).

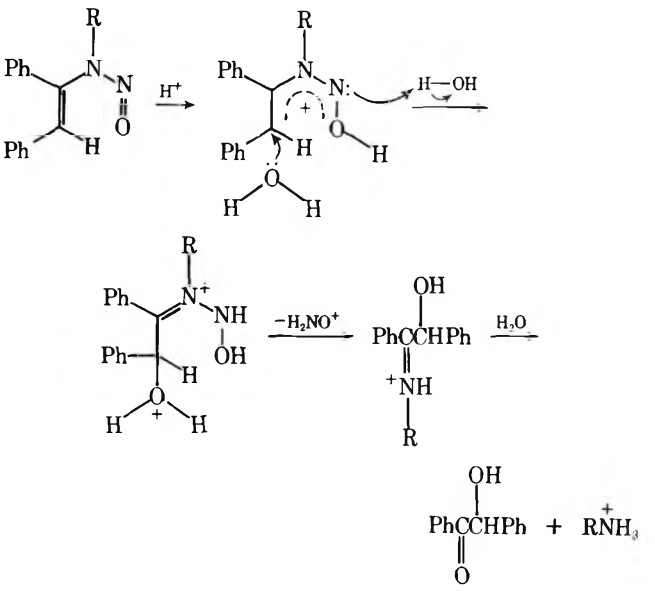
In addition to our investigation of the nitrosation of the *N*-butylaziridine **9a** we also examined the reaction of (*Z*)-1-benzyl-2,3-diphenylaziridine (**9b**) with sodium nitrite in glacial acetic acid. This transformation proceeded in much the same manner as we have described for **14a** to give benzaldehyde (18%), (*E*)-1-*N*-benzylnitrosamino-1,2-diphenylethane (**13b**, 49%), *threo*-1,2-diphenyl-2-*N*-benzylnitrosaminoethyl acetate (**10b**, 18%), and an additional compound characterized as *N*-benzyl-*N*-(1,2-diphenyl-2-acetoxyethyl)ethanamide (**19**, 4%). We have also made a cursory, preliminary investigation of the nitrosation reaction of (*Z*)-1-(4-chlorophenyl)-2,3-diphenylaziridine (**9c**) in glacial acetic acid. Even though our study of this transformation is not completed, it is worth mentioning because it appears to take a course different from the nitrosation of the *N*-alkylaziridines. From a mixture of seven compounds produced in this transformation we have isolated and characterized benzaldehyde, *threo*-1,2-diphenyl-2-*N*-(4-chlorophenyl)nitrosaminoethyl acetate (**10c**), and *N*-4-chlorophenylbenzamide (**17**, R = 4-ClC_6H_4). A preliminary investigation of the reaction of **9a** with nitrosyl chloride has revealed the existence of numerous products and the reaction is under further study.

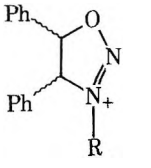
Discussion

Perhaps the most striking feature to arise from our examination of the nitrosation of 1-substituted aziridines is the finding that the reaction proceeds neither by the path (F, Scheme II) taken by their 1-unsubstituted counterparts nor by the route elucidated for the nitrosation of tertiary amines (A and B, Scheme IV). A new mode of tertiary amine nitrosation has been uncovered, and we will now consider the probable origin of the various products. The product whose mode of formation is most easily dealt with is the threo nitrosamino acetate **10**. The production of only the threo diastereomer dictates that this compound be formed from the aziridine with inversion of one of the carbons as is indicated in Scheme II (path S). Even though we found conditions under which the aziridine was nitrosated much more rapidly than it underwent acid-catalyzed ring opening, the observation that this latter process occurs with the same stereochemical result will not permit the conclusion that **10** is formed solely by N-nitrosation followed by nucleophilic ring opening by acetate. The addition of aqueous sodium nitrite to glacial acetic acid produces an environment toward the end of reaction which is more favorable to acid-catalyzed ring opening. We are unable without kinetic data to determine if **10** was formed by nitrosation before or after ring opening.

The elimination of acetic acid from the nitrosamino acetate **10** provides an appealing path for the formation of the *N*-nitrosoenamine **13**. We must argue against this route for the formation of **13**, however, because the subjection of **10a** to the reaction and work-up conditions for the formation of **13a** did not produce **13a**. Furthermore, we were unable to induce the formation of **13a** from **10a** by either pyrolysis or elimination catalyzed by sodium acetate or stronger bases. Indeed, the anti elimination of acetic acid from **10a** would produce the trans nitrosenamine. A more reasonable path for the formation of **13a** is depicted in Scheme II, path E. The nitrosenamine stereochemistry is indicative of its formation by a simple, acetate-induced E-2 type ring opening of the nitrosammonium ion **7**. An alternate route involves a ring expansion of uncertain stereochemistry to **18** and would surely lead to other products as well.

Scheme IV





18

The details of the origin of the benzaldehyde in these reactions is a subject of current research in our laboratories but we will make few observations here. We presume that each aziridine taking the aldehyde cleavage route produces a single molecule of benzaldehyde. With this assumption our material balance is 96% for the reaction of **9a**. There may be more than one nitrogenous product from this pathway. The only clue we have to the origin of benzaldehyde comes from the nitrosation of **9c** which gave the benzamide **17** as well. A possible path to these products is given in Scheme II, path C. Nitrosation is envisioned to occur at the aziridine C–C bond assisted by the nitrogen unshared pair. The resulting α-nitroso iminium salt isomerizes and hydrolyzes in the media to the observed products. There are, of course, alternative routes.

Our data and the preceding analysis of the 2,3-diphenylaziridine nitrosation lead us to conclude that less than 20% of the reaction proceeds via C-nitrosation and 82% of the aziridine is consumed by N-nitrosation. The nitrosammonium ion so produced is destroyed stereospecifically in a classical elimination (76%)–substitution (24%) competition. Although we have not followed the relative product yields

Table I. Physical Properties of Aziridines and Their Precursors

Series		Mp or bp, °C	Yield, %	Registry no.
		Amino Ketones		
a	*n*-Butyl HCl[a]	226–228	90	7253-85-2
c	*p*-Chloro-phenyl	164–165.5	91	58268-09-0
		Amino Alcohols (Erythro)		
a	*n*-Butyl	131–133	78, 86	58268-10-3
c	*p*-Chloro-phenyl	109–110	96	58268-11-4
b	Benzyl	154–156	92	58268-12-5
a	*n*-Butyl (threo)	60.5–61.5	85	58268-13-6
		Amino Chlorides (Threo)		
a	*n*-Butyl HCl[b]	214–215	69	58268-14-7
c	*p*-Chloro-phenyl HCl	140	53	58268-15-8
b	Benzyl HCl	175–177	35	58268-16-9
		Aziridines (Cis)		
9a	*n*-Butyl[c,e]	126–127 (0.1 mm)	90	58268-17-0
9c	*p*-Chloro-phenyl	89–90.5	73	58268-18-1
9b	Benzyl[d]	52.5–53.5	76	42136-65-2

[a] Free base is an oil. [b] Anal. Calcd: C, 66.67; H, 7.15; N, 4.32. Found: C, 66.75; H, 7.13; N, 4.23. [c] Anal. Calcd: C, 86.00; H, 8.42; N, 5.57. Found: C, 86.21; H, 8.40; N, 5.59. [d] Anal. Calcd: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.50; H, 6.82; N, 4.86. [e] n^{20}D 1.5510.

(10 and 13) of this competition as a function of time it is well known that where elimination and substitution reactions are in competition elimination can be favored by the employment of stronger base. As acetic acid is diluted with water the acetate ion becomes a weaker base and this may explain why nitrosenamine formation is favored in the medium having the higher acetic acid content.

Our study of 1-substituted aziridine nitrosation is not far enough advanced to determine why the reaction did not take paths A, B, or F of Scheme II. Phenyl substitution on the aziridine ring certainly aids the processes observed whereas intramolecular elimination (Scheme II, paths A or B) is not expected to be facile in small rings and is particularly impeded if NO and H are not syn to one another.

Finally we must comment on the unusual chemical properties of the nitrosenamine. Although our work on these substances is far from complete the hydrolysis of **13a** reveals a mode of reaction which has not previously been reported for enamines or enamides. The formation of benzoin upon acidic hydrolysis requires that this oxidation be accompanied by the reduction of the nitrogen-containing fragment. Although we have not isolated a nitrogen-bearing fragment from the hydrolysis mixture as yet a plausible mode of benzoin formation is depicted below. The reaction is perceived to occur by nucleophilic attack of water on the alkenyl carbon which is assisted by protonation on the nitroso oxygen and fission of the N–N bond (Scheme IV). It has been demonstrated that the most nucleophilic site (and presumably the most basic site as well) in nitrosamines is the nitroso oxygen[30] and this fact accompanied by the well-known resistance of nitrosamines to hydrolysis and the elimination of NO as NO^- or NOH accounts for the predominance of the benzoin-forming reaction path. The formation of benzyl phenyl ketone by the more usual mode of enamine hydrolysis requires protonation on carbon and acceptance of the positive charge by the amino (amide) nitrogen and must be preceded in enamide hydrolysis by the amide hydrolysis to generate the secondary enamine which then hydrolyzes. The specific nature of this hydrolysis is being further explored.

In conclusion our initial studies of aziridine nitrosation have demonstrated a new mode of tertiary amine nitrosation which warrants further investigation. We have discovered an enamine with unusual properties and further exploration will allow us to evaluate its synthetic utility and provide us with an understanding of its reactivity.

Experimental Section

Boiling points and melting points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were taken on a Perkin-Elmer 237B grating infrared spectrometer and NMR spectra were taken on a Varian A-60 or a Bruker HX90 spectrometer. ^{13}C NMR spectra were measured by pulse FT spectroscopy utilizing a Nicolet 1083 computer, and all chemical shifts are referenced to internal Me_4Si. GLC was performed on a Microtek 2000 GCR using a 20% SE column on Chromosorb W with anisole as an internal standard. TLC was performed with Eastman silica gel plates with fluorescent indicator and developed with a solution of 5% ethyl acetate in petroleum ether "F", unless otherwise noted. Uv spectra were taken of cyclohexane solutions on a Cary 15 uv–visible spectrometer. Mass spectra were recorded on a CEC 21-110 mass spectrometer at 70 eV utilizing perfluorokerosene in the peak matching.

Synthesis of Aziridines. Aziridines were prepared by the methods given below for *n*-butyl series. Their physical properties and those of their precursors are given in Table I.

Method A. *erythro*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol. *erythro*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol was prepared from *trans*-stilbene oxide according to the method of Lutz, Freek, and Murphey[31] to give a 78% yield: mp 131–133 °C (lit.[13] 134–135 °C); NMR ($CDCl_3$) δ 7.15 (s, 10, phenyl), 4.82 (d, 1, –NCHPh, J = 5.5 Hz), 3.88 (d, 1, PhCHOH, J = 5.5 Hz), 2.48 (t, 1.6, $-NCH_2-$, J = 6.5 Hz), 0.62–1.70 (m, 7.4, $-CH_2CH_2CH_3$).

Method B. To 41.17 g (0.136 mol) of α-(*N*-*n*-butylamino)benzyl phenyl ketone hydrochloride in 300 ml of ethanol was added dropwise 4.6 g (0.121 mol, 0.484 equiv) of sodium borohydride in 125 ml of ethanol. The mixture was refluxed for 2 h, cooled, and poured into an excess of water. The crystals were collected and recrystallized from ethanol to give 31.14 g (82%) of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol: mp 132.5–134 °C (lit.[31] 134–135 °C); NMR identical with that of the *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol prepared by method A.

α-(*N*-*n*-Butylamino)benzyl Phenyl Ketone. α-(*N*-*n*-Butylamino)benzyl phenyl ketone was prepared according to the literature method and collected as the hydrochloride (56%), a white solid: mp 226–228 °C (lit.[31] 184–186 °C); ir (Nujol) (as the hydrochloride) 2375 (NH) and 1690 cm^{-1} (ketone); NMR ($CDCl_3$) (as the free base) δ 6.9–8.3 (m, 10, phenyl), 5.39 (s, 0.6, NH, exchangeable in D_2O), 4.15 (s, 1.1, PhCHC=O), 2.3–3.8 (m, 1.8, $-NHCH_2-$), 0.6–2.0 (m, 7.3, $-CH_2CH_2CH_3$).

***threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol.** *threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethanol was prepared by the literature method[31] and collected in 58% yield as the hydrochloride, mp 184–185 °C (lit.[31] 181–182 °C). Shaking a portion of the hydrochloride with 10% sodium carbonate solution followed by extraction with ether, concentration, and recrystallization from 30–60 °C petroleum ether gave the free base, mp 60.5–61.5 °C (lit.[31] 63–64 °C).

***threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethyl Chloride.** This amino chloride was prepared by a method following that of Taylor, Owen, and Whittaker.[32] A 300-ml single-neck round-bottom flask fitted with a magnetic stirrer was charged with 31.1 g (0.116 mol) of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol in 104 ml of dry chloroform. Phosphorus pentachloride (28 g, 0.13 mol) was added slowly to the stirred mixture. A strongly exothermic reaction ensued. The resulting mixture was cooled and the precipitate was collected. Recrystallization of the crude product from ethanol gave 32.7 g (87.5%) of a white solid as the hydrochloride: mp 214–215 °C; ir 3400 cm^{-1} (weak, –NH); NMR ($CDCl_3$) δ 7.08 (s, 10, phenyl), 4.95 (d, 1, PhCHN–, J = 9.5 Hz), 4.03 (d, 1,

Table II. Nitrosation of Aziridines. Experimental Details

Expt. no.	Compd	Wt, g (mol)	Solvent (ml)	Wt., g $NaNO_2$ (H_2O, ml)	Temp, °C	Reaction time, h	% yield of **10**	% yield of **13**	% yield of PhCHO	Other products (% yield)
1	**9a**	27 (0.11)	60% HOAc[a] (500)	69 (100)	90	2.5	10	10		**12** (88)
2	**9a**	8 (0.032)	HOAc (216)	22 (30)	25	2.5	20.2	62.1	19.2	
3	**9b**	2.54 (8.9×10^{-3})	HOAc (61)	6.15 (8)	25	2	18%	49	18	**19** (4)
4[b]	**9c**	5 (0.0164)	HOAc (120)	12 (20)	25	2	Undetd		19	**17** (?)

[a] 68 g of sodium acetate added. [b] 31% starting material recovered.

PhC**H**Cl, J = 9.5 Hz), 2.3–3.1 (m, 2, $-NCH_2-$), 0.7–1.7 (m, 7.5, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{18}H_{23}NCl_2$: C, 66.67; H, 7.15; N, 4.32. Found: C, 66.75; H, 7.13; N, 4.23.

Hydrolysis of *threo*-1,2-Diphenyl-2-(*N*-*n*-butylamino)ethyl Chloride. The hydrolysis of the chloride was undertaken in order to establish unequivocally its stereochemistry and that of the aziridine **9a**. The hydrochloride (5.2 g, 0.016 mol) was placed in a 500-ml single-neck round-bottom flask fitted with a condenser, and 350 ml of a saturated sodium hydrogen carbonate solution was added. The mixture was refluxed for 16 h, cooled, and washed four times with ether. The ethereal extracts were combined, dried, and concentrated. The resulting solid was recrystallized from ethanol to give a white solid in good yield, mp 131–134 °C, undepressed by addition of an authentic sample of *erythro*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol.

(*Z*)-1-*n*-Butyl-2,3-diphenylaziridine (9a). Following the method of Taylor, Owen, and Whittaker,[32] a 3-l. three-neck round-bottom flask was fitted with a reflux condenser and a mechanical stirrer and 129 g (0.40 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl chloride hydrochloride was placed therein. After the addition of 2.12 l. of 22% alcoholic potassium hydroxide, the stirred reaction mixture was heated at reflux for 1.5 h, then cooled and poured into 3 l. of water. The resulting mixture was extracted with ether and concentrated and the resulting wet oil taken up in benzene and dried. The benzene solution was filtered, concentrated, and distilled in vacuo, giving 86.5 g (86.6%) of a colorless liquid: bp 114–116 °C (0.1 mm); mp 32.0–35.5 °C; $n^{25}D$ 1.5510; ir (neat) 3040, 2945, 1615, 1505, 1460, 1420, 1380, 1030, 760, 700 cm^{-1}; NMR δ 7.05 (s, 10, phenyl), 2.78 (s, 2, PhC**H**–), 2.6 (t, 1.6, $-NCH_2-$, J = 6.5 Hz), 0.65–2.00 (m, 7.4, $-CH_2CH_2CH_3$). The NMR spectrum was not temperature dependent down to −50 °C.

Nitrosation of Aziridines. The general procedure for the nitrosation of the aziridine involved its dissolution in the acidic solvent and stirring while a 10 M excess of saturated sodium nitrite solution was added dropwise and the solution stirred at the prescribed temperature for the time noted along with quantities in Table II.

Work-up involved pouring the reaction mixture into twice the volume of water followed by extraction with five portions of $CHCl_3$, drying, and removal of the $CHCl_3$ after analysis for benzaldehyde. GC analysis for benzaldehyde was performed by adding a known quantity of anisole to a known volume of the reaction mixture and the determination of the benzaldehyde yield was made from the corresponding peak areas via a calibration curve. The reaction mixture or a weighed portion thereof was chromatographed on silica gel by eluting with 20% ethyl acetate–petroleum ether. The details of product characterization are given below for each experiment.

Experiment 1. Nitrosation of 9a. The $CHCl_3$ solution was subjected to GC analysis and the presence of a trace of butanal found, which was confirmed by its conversion to its 2,4-dinitrophenylhydrazone, mp 118–122 °C (lit.[33] 123 °C). Column chromatography gave *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosoamino)ethyl acetate (**10a**, 10%): mp 135–136.5 °C; Liebermann nitroso test[34] positive; ir (CCl_4) no –OH, or –NH, 1750 cm^{-1} (ester carbonyl), 1470, 1439, 1280, and 1030 (weak, possibly associated with N–NO);[35] NMR ($CDCl_3$) δ 7.30 (s, 10, phenyl), 6.70 (d, 1, PhC**H**N–NO, J = 10.5 Hz), 5.80 (d, 1, AcOC**H**Ph, J = 10.5 Hz), 2.90–4.10 (broad m, 2, $-CH_2N-NO$), 1.94 (s, 3, acetate), and 0.65–1.70 (m, 7, $-CH_2CH_2CH_3$).

Synthesis of 10a. A 100-ml single-neck round-bottom flask fitted with a magnetic stirrer and drying tube was charged with 3.7 g (0.012 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethanol and 22.4 ml of freshly distilled acetyl chloride. The mixture was allowed to stir for 24 h at room temperature. The resulting crystals were filtered off and recrystallized from acetonitrile to give 3.15 g (74.5%) of product as the hydrochloride: mp 190.5–191.5 °C; ir (Nujol) 2700 (NH·HCl), 1750 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 7.40 (m, 10, phenyl), 6.45 (d, 1, PhC**H**OAc, J = 10 Hz), 4.30–4.80 (d, 1, PhC**H**NH·HCl, J = 10 Hz), 2.92 (m, 1.6, $-CH_2NH\cdot HCl$), 2.39 (s, 3, acetate), 0.65–2.30 (m, 7.4, $-CH_2CH_2CH_3$).

A 50-ml test tube equipped with a magnetic stirrer was charged with 0.153 g (0.00044 mol) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate hydrochloride and 1.3 ml of water. Sodium nitrite (0.4 g) in 1.3 ml of water was added in portions while stirring continued.[36] The mixture was stirred at room temperature for 1.5 h, then diluted with water and extracted with ether. The ethereal solution was dried overnight (sodium sulfate), then filtered and stripped of solvent at room temperature to give 0.14 g (30%) of *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate as white crystals: mp 136.5–137.5 °C; mmp with **10a** (expt 1) 135–136 °C; Liebermann nitroso test positive.

Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.65; H, 7.12; N, 8.14. Found: C, 70.36; H, 7.34; N, 8.09.

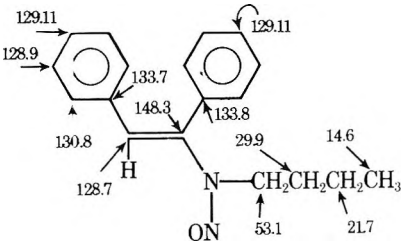
threo-1,2-Diphenyl-2-(*N*-*n*-butylnitrosamino)ethanol (**12**): 7.27 g; mp 79.0–79.2 °C; Liebermann nitroso test positive; ir (CCl_4) 3400 (–OH), no carbonyl, 1480, 1440, 1285, and 1030 cm^{-1} (weak, possibly associated with N–NO); NMR ($CDCl_3$) δ 7.21 (s, 10, phenyl), 5.64 (d, 0.94, PhC**H**N–NO, J = 9 Hz), 5.11 (d, 0.94, PhC**H**OH, J = 9 Hz), 2.77–4.11 (m, 2.98, $-CH_2N-NO$), 0.50–1.56 (m, 7.1, $-CH_2CH_2CH_3$).

Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.54; H, 7.51; N, 9.36. Found: C, 72.70; H, 7.44; N, 9.40.

Conversion of 12 to 10a. *threo*-1,2-Diphenyl-2-(*N*-*n*-butylnitrosamino)ethanol (**12**), isolated from the reaction of **9a** with nitrous acid, was converted to *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate (**10a**) as follows:[37] 1.0 g of the nitrosamino alcohol was added to 10 ml of dry pyridine in a 50-ml one-neck round-bottom flask fitted with a reflux condenser. Four grams of freshly distilled acetic anhydride was added through the condenser and the solution was refluxed for 5 min. The mixture was cooled and poured into 30 ml of ice water. The solid was filtered off, washed with 2% hydrochloric acid solution, and recrystallized from ethanol to give a white solid, mp 139–140 °C, mixture melting point with **10a** 139–140 °C.

Experiment 2. Nitrosation of 9a in Glacial Acetic Acid. Chromatography of 9.44 g of reaction mixture provided the following compounds.

13a: 5.79 g (62.1% of crude product mixture); mp 91.5–92.5 °C; ir (CCl_4) no –NH, –OH, carbonyl, 1479, 1439, 1290, 1041 cm^{-1} (weak, may be associated with N–NO); NMR ($CDCl_3$) δ 7.90 [s, 0.965, HC=C(Ph)N–NO, 6.82–7.55 (m, 10, phenyl, 3.60 (t, 1.93, $-CH_2N-NO$, J = 7 Hz), 0.70–1.95 (m, 7.21, $-CH_2CH_2CH_3$); ^{13}C NMR assignments are given below in parts per million relative to



Me_4Si = 0; uv 227 nm (ϵ 1.3 × 10^4), 285 (1.5 × 10^4); Br_2/CCl_4, no color loss; $KMnO_4$, slow reaction; Liebermann nitroso test, negative. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.97; H, 7.10; N, 9.83.

Mass spectrum *m/e* (rel intensity): 281 (9), 280 (40), 279 (4.6), 264 (5), 263 (3), 262 (3), 250 (3), 237 (7), 224 (2), 221 (3), 208 (2), 207 (2), 206 (2), 196 (4), 195 (8), 194 (8), 193 (9), 180 (12). 179 (73), 178 (100), 177 (18), 176 (15), 175 (5), 174 (13), 169 (6), 167 (37), 166 (5), 165 (10), 159 (5), 153 (5), 152 (19), 151 (9), 132 (10), 131 (53), 126 (3), 119 (5), 118 (13), 115 (13), 105 (11), 104 (25), 103 (7), 102 (3), 91 (9), 89 (6), 77 (14), 76 (6), 63 (3), 57 (5), 51 (10), 39 (5). Precise mass data (formula, observed mass, calculated mass): $C_{18}N_{20}N_2O$, 280.1565, 280.1576; $C_{13}H_{11}$, 167.085658, 167.086071; $C_{12}H_8$, 152.061113, 152.062597; $C_8H_7N_2$, 131.060125, 131.060920; C_7H_6N, 104.049648, 104.050022.

10a: 1.91 g (20.2%); mp 136–137 °C; mixture melting point with *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate undepressed.

Benzaldehyde. An aliquot of the original chloroform extract was examined by GC for volatile compounds and benzaldehyde was found in 19.2% yield, based on the starting aziridine using the method previously given. Treatment of the extract with 2,4-dinitrophenylhydrazine gave benzaldehyde 2,4-dinitrophenylhydrazone, mp 235–236 °C (lit.[38] 237 °C).

Experiment 3. Nitrosation of 9b in Acetic Acid. Chromatography gave *threo*-1,2-diphenyl-2-(*N*-benzylnitrosamino)ethyl acetate (**10b**): mp 121.5–121.9 °C; ir (Nujol) no –OH, –NH, 1723, 1733 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 6.88–7.45 (m, 15, phenyl), 6.70 (d, 1.08, PhC**H**N–NO, J = 10.5 Hz), 5.40 (d, 1.08, PhC**H**OAc, J = 10.5 Hz), 5.31 (d, 0.75, PhCH_2N–NO, J = 15 Hz), 1.92 (s, 2.66, acetate).

Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.57; H, 6.05; N, 7.33.

(*E*)-1,2-Diphenyl-1-(*N*-benzylnitrosamino)ethene (**13b**): 1.38 g (4.4 × 10^{-3} mol, 49%); mp 97.5–98 °C; ir (Nujol) no –NH, –OH, or carbonyl, 1474, 1440, 1305 cm^{-1} (possibly associated with N=O); NMR ($CDCl_3$) δ 7.95 [s, 0.78, **H**C(Ph)=C(Ph)N(R)NO], 6.78–7.47 (m, 15, phenyl), 4.80 (s, 1.69, PhCH_2N–NO).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.41; H, 5.91; N, 8.83.

Benzaldehyde assayed by the previous method, yield 18%.

19: tentatively identified by its spectra as *N*-benzyl-*N*-(1,2-diphenyl-2-acetoxyethyl)ethanamide: 0.15 g; ir (neat oil) 3375 (weak, broad), 1730, 1685 cm^{-1} (carbonyl); NMR ($CDCl_3$) δ 7.07–8.19 (m, phenyl), 6.94 (s), 6.91 (d, J = 10.5 Hz), 5.22 (d, J = 10.5 Hz), 5.08 (d, J = 15 Hz), 3.90 (d, J = 15 Hz), 2.20 (s), 1.71 (s).

Experiment 4. Nitrosation of 9c in Acetic Acid. 1-(*4*-Chloro)phenyl-2,3-diphenylaziridine (5.0 g, 0.0164 mol) was nitrosated in glacial acetic acid in the usual manner. A solid was filtered from the reaction mixture and the supernatant liquid extracted in chloroform as before. The odor of benzaldehyde was noted as is the usual case in these reactions. The solid filtered off proved to be unreacted starting material (1.55 g, 31%) (NMR identical, mixture melting point undepressed, 86.5–88.5 °C, mp of starting material 87–88 °C). GC assay for benzaldehyde showed the yield of this compound to be 19.1%.

threo-1,2-Diphenyl-2-(*N*-4-chlorophenylnitrosamino)ethyl acetate (**10c**) was observed (same R_f as the authentic compound).

N-4-Chlorophenylbenzamide (**34**) was isolated: mp 183.5–184 °C; ir (Nujol) 3330 (–NH), 1645 cm^{-1} (amide); mixture melting point 184–187 °C (lit.[39] 192 °C); TLC R_f identical.

Control Reaction of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine with Hot Buffered 60% Aqueous Acetic Acid. A solution of 1.5 g of the aziridine **9a** in 29 ml of 60% aqueous acetic acid buffered to pH 4–5 with sodium acetate was heated to 90 °C on a steam bath in a 100-ml three-neck round-bottomed flask fitted with a condenser, mechanical stirrer, and dropping funnel. At 90 °C, 5.6 ml of water was added slowly through the dropping funnel. At the end of 1 h, all of the aziridine had disappeared (TLC). Heating was continued for a total of 2.5 h. Work-up was performed as in the nitrosation reaction. The product was an oil, *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate: 1.88 g; ir (neat) 3325 (–OH or –NH), 1750 (ester carbonyl, weak), and 1630 cm^{-1}, identical with the spectrum for *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate; NMR δ 7.29 (d, 10, phenyl), 5.45 (d, 0.46, J = 7.5 Hz), 5.00 (d, 0.46, J = 7.5 Hz), 4.58 (d, 0.40, J = 8.5 Hz), 3.61 (d, 0.40, J = 8.5 Hz), 2.81–3.22 (m, 1.03), 2.26–2.70 (m, 0.91), 2.03 (s, 1.84, acetate), 0.48–1.92 (m, 7.75, $-CH_2CH_2CH_3$).

Reaction of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine with Glacial Acetic Acid. The fate of the aziridine **9a** in glacial acetic acid at room temperature was monitored by following the changes in the aziridine ring protons in the NMR. The peak corresponding to the ring protons was unchanged and undiminished after a 1-h period.

In a separate experiment, 1.0 g of the aziridine **9a** was dissolved in 25 ml of glacial acetic acid and stirred for 2.5 h at room temperature. Following the standard work-up, ir and TLC demonstrated the product to be unchanged starting material. No ring-opening products were observed and 1.0 g of the aziridine was recovered.

Lifetime Study of (*Z*)-1-*n*-Butyl-2,3-diphenylaziridine under Conditions Corresponding to the End of the Nitrosation Reaction in Glacial Acetic Acid. A solution corresponding to that obtained after the total decomposition and loss of nitrous acid under the glacial acetic acid nitrosating conditions was prepared by mixing 2.61 g of sodium acetate, 3.24 g of water, and 20.8 g of glacial acetic acid. Under the conditions of the reaction 0.8 g of the aziridine should be added but this is too little to allow the ring protons to be seen conveniently in the NMR spectrum. Instead, 1.25 g of the aziridine was added to give a satisfactory NMR signal. The aziridine dissolved slowly. The ^1H NMR was followed for 13 h and the ratio of the integrated intensities of the phenyl to aziridine ring protons obtained.

Table III. Kinetics of Solvolysis of 9a under "End of the Reaction Conditions"

Time, min	Ratio[b]	Time, min	Ratio[b]
10	10:1.68	125	10:1.27
20	10:1.52	150	10:1.17
50	10:1.62	765	10:1.02
75	10:1.34		

[a] As followed by ^1H NMR at 35 °C. [b] Aromatic to aziridine ring hydrogens.

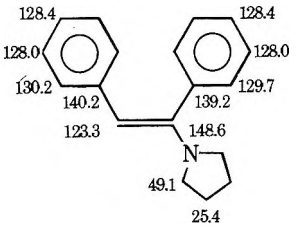
The portion of the reaction mixture that was not used for the NMR study was allowed to stand for 24 days, at which time the now lavender solution was neutralized with 10% sodium carbonate solution and subjected to the standard work-up. The oily product possessed the following spectral properties: ir (neat) 3370 (–OH or –NH), 1735 (ester), 1620 cm^{-1} (amine); NMR ($CDCl_3$) δ 6.83–7.50 (m, 10, phenyl), 5.42 (d, 0.75, PhC**H**N, J = 7.5 Hz), 5.02 (d, 0.75, PhC**H**OAc, J = 7.5 Hz), 3.00 (m, 1.27 NCH_2–), 2.01 (s, 2.2, acetate), 0.45–1.58 (m, 7.3, $-CH_2CH_2CH_3$).

Stability of 13a and 10a under the Reaction Conditions. (*E*)-1,2-Diphenyl-1-(*N*-*n*-butylnitrosamino)ethene (**13a**, 0.5 g) was placed in 13.5 ml of glacial acetic acid and treated with 2.37 g of sodium nitrite in 1.87 g of water, added all at once. The solution was stirred for 2 h, then given the standard work-up to yield 0.5 g of unchanged starting material, mp 88–89 °C.

Similarly, 0.5 g of *threo*-1,2-diphenyl-2-(*N*-*n*-butylnitrosamino)ethyl acetate (**10a**) was treated to the reaction conditions above with 0.47 g of unchanged starting material isolated at the end of 2 h, mp 133–135 °C.

Hydrolysis of (*E*)-1,2-Diphenyl-1-(*N*-*n*-butylnitrosamino)ethene (13a) in Acidic Dioxane. The *N*-nitrosenamine **13a** (1.0 g, 0.0036 mol) was taken up in a solution of 45.5 ml of dioxane, 22.5 ml of water, and 3.0 ml of concentrated sulfuric acid and refluxed for 47 h. The reaction mixture was poured into excess water and extracted into ether. The ether extract was spotted on freshly prepared silica gel TLC plates and run against starting material, benzoin, and benzyl phenyl ketone in 5% ethyl acetate–petroleum ether F. The TLC showed no spots due to **13a** and only those of benzoin (R_f 0.065), benzyl phenyl ketone (R_f 0.325), and **13a** (R_f 0.45). After drying the ether was stripped to give a solid–oil mixture. Removal of the solid and recrystallization from ethanol gave benzoin (0.25 g, 37%), mp 129–130 °C (lit.[40] 129.5–130.5 °C). The oil and the stripped filtrate from the crystallization were chromatographed on silica gel to give benzyl phenyl ketone which was identified as its 2,4 dinitrophenylhydrazone, mp 198–199 °C (lit.[41] 204 °C).

Synthesis of 1,2,Diphenyl-1-pyrrolidinoethene. This enamine was prepared from benzyl phenyl ketone and pyrrolidine by the method of Dulou et al.[17] and its properties agreed with those reported for it: ir C=C, 1610 cm^{-1}; uv 227 nm (ϵ 1.25 × 10^4), 312 (1.98 × 10^4); ^1H NMR >C=CH– δ 5.32; ^{13}C NMR assignments given below.



Registry No.—**10a**, 58268-19-2; **10b**, 58268-20-5; **10c**, 58268-21-6; **12**, 58268-22-7; **13a**, 58268-23-8; **13b**, 58268-24-9; **19**, 58268-25-0; **34**, 2866-82-2; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate HCl, 58268-26-1; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate, 58268-27-2; 1,2-diphenyl-1-pyrrolidinoethane, 58268-28-3.

References and Notes

(1) H. Euler, *Chem. Zentralbl.*, **74**, 1165 (1903).
(2) H. Euler, *Justus Liebigs Ann. Chem.*, **330**, 280 (1903).
(3) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83**, 4417 (1961).
(4) W. Rundel and E. Muller, *Chem. Ber.*, **96**, 2528 (1963).
(5) R. D. Clark and G. K. Helmkamp, *J. Org. Chem.*, **29**, 1316 (1964).
(6) G. Drefahl, K. Ponsold, and B. Schoenekker, *Chem. Ber.*, **97**, 2014 (1964).
(7) R. M. Carlson and S. Y. Lee, *Tetrahedron Lett.*, 4001 (1969).
(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 159.
(9) W. L. Mock and P. A. H. Isaac, *J. Am. Chem. Soc.*, **94**, 2749 (1972).
(10) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89**, 1147 (1967).
(11) G. E. Hein, *J. Chem. Educ.*, **40**, 181 (1963).
(12) W. Lijinsky, L. Keefer, E. Conrad, and R. Van de Bogart, *J. Natl. Cancer Inst.*, **49**, 1239 (1972).
(13) N. H. Cromwell, G. V. Hudson, R. A. Wankel, and P. J. Vanderhorst, *J. Am. Chem. Soc.*, **75**, 5385 (1953); G. J. Buist and H. J. Lucas, *ibid.*, **79**, 6157 (1957).
(14) J. D. McCown, Ph.D. Thesis, University of Iowa, 1968.
(15) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **14**, 15 (1975).
(16) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 3705 (1965).
(17) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).
(18) R. Huisgen, E. Funke, H. Gotthardt, and H. L. Panke, *Chem. Ber.*, **104**, 1532 (1971).
(19) R. W. Hoffmann and K. R. Eicken, *Chem. Ber.*, **102**, 2987 (1969).
(20) G. P. Rizzi, *J. Org. Chem.*, **35**, 2069 (1970).
(21) J. Collin, *Bull. Soc. R. Sci. Liege*, **23**, 201 (1954).
(22) S. S. Dubou anc A. M. Khokhlova, *Zh. Obshch. Khim.*, **34**, 1961 (1964).
(23) G. Schroll, R. G. Cooks, P. Klemmensen, and S. O. Luwesson, *Ark. Kemi*, **28**, 413 (1967).
(24) T. Axenrod and G. W. A. Milne, *Chem. Commun.*, 67 (1968).
(25) J. W. ApSimon and J. D. Cooney, *Can. J. Chem.*, **49**, 1367 (1971).
(26) P. S. Pregosin and E. W. Randall, *Chem. Commun.*, 399 (1971).
(27) A detailed interpretation of the mass spectrum of **13a** may be obtained by writing the principal author.
(28) A. A. Polyakova et al., *Zh. Org. Khim.*, **3**, 836 (1967).
(29) R. N. Loeppky, R. Christiansen, and D. H. Smith, unpublished results.
(30) S. Hunig, G. Buttner, J. Cramer, L. Geldern, H. Hansen, and E. Lucke, *Chem. Ber.*, **102**, 2093 (1969).
(31) R. E. Lutz, J. A. Freek, and R. S. Murphey, *J. Am. Chem. Soc.*, **70**, 2015 (1948).
(32) T. W. J. Taylor, J. S. Owen, and D. Whittaker, *J. Chem. Soc.*, 206 (1938).
(33) "Tables for the Identification of Organic Compounds", C. D. Hagman, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p 68.
(34) R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 142.
(35) R. N. Haszeldine and B. J. H. Mattison, *J. Chem. Soc.*, 4172 (1955).
(36) R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 142.
(37) Reference 36, p 254.
(38) Reference 33, p 71.
(39) Reference 34, p 329.
(40) Reference 33, p 101.
(41) Reference 33, p 97.

The Configuration[1] of Nicotine. A Nuclear Magnetic Resonance Study

Jerry F. Whidby and Jeffrey I. Seeman*

Philip Morris Research Center, P.O. Box 26583, Richmond, Virginia 23261

Received July 29, 1975

Radiofrequency irradiation of the *N*-methyl group in nicotine at pD values of 11.0, 5.0, and 0.8 caused nuclear Overhauser enhancements (NOE) of the pyridyl protons and the C-2′ and C-5′ protons on the pyrrolidine ring. However, irradiation of the *N*-methyl group at 3.13 ppm of nicotine in trifluoroacetic acid solution (TFA) did not cause an NOE on the pyridyl protons but rather on the C-2′ and C-5′β protons. In TFA, the rate of deprotonation of nicotinium diacid salts is slow compared to the NMR time scale, and the peak at 3.13 ppm is attributed to the nicotinium salt in which the *N*-methyl group is trans to the pyridine ring. A second singlet at 2.82 ppm is attributed to the nicotinium salt in which the *N*-methyl group is cis to the pyridine ring. These assignments were established by NMR studies in mixtures of TFA–TFA-*d*. These results are interpreted in terms of nitrogen protonation–deprotonation–pyramidal inversion equilibria and the complexities of NOE studies on configurationally mobile systems. The rates of inversion and proton relaxation are considered. It is estimated that nicotine-free base exists with its *N*-methyl group preferentially (90.9 ± 0.9%) trans to the pyridine ring by gas-phase kinetic quenching experiments.

The configuration[1] of nicotine and nicotine acid salts has been a topic of concern for many years.[2-9] Nicotine structural analysis indicates two unknown features: the orientation of the *N*-methyl group and the relative position of the pyridine and pyrrolidine rings. Experimental determination of these two structural parameters is complicated by the likelihood of low energy barriers to change.[10] We now report the results of our studies which show that the preferred (>90%) configuration of the *N*-methyl group in nicotine is 1′ (*R*) (i.e., trans to the pyridine ring) under a variety of experimental conditions.

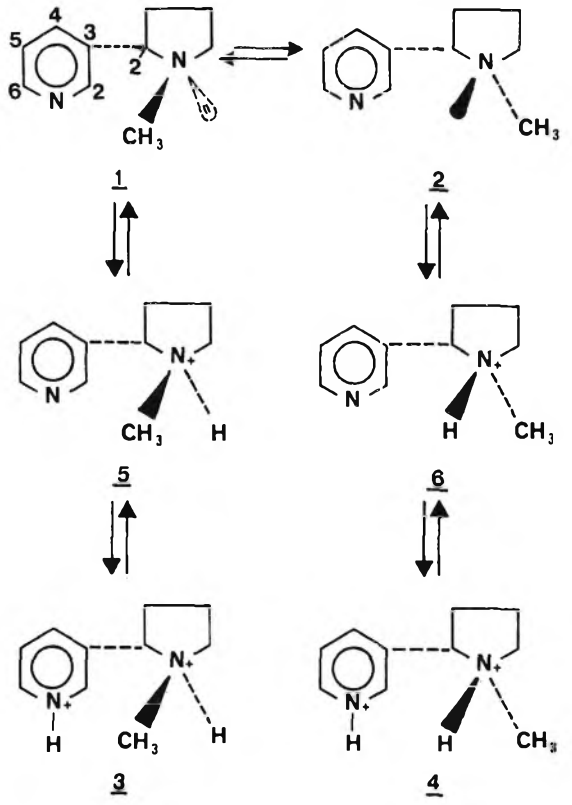
Recently, Chynoweth, Ternai, Simeral, and Maciel[8] concluded on the basis of their NMR studies of nicotine in $CDCl_3$ and D_2O "that the N-methyl group is preferentially on the same side of the pyrrolidine ring as the pyridine ring". That conclusion[8] contrasted with perturbative configuration interaction calculations performed by Pullman, Courriere, and Coubeils,[7a] which indicated that 1 (see Scheme I) was approximately 4 kcal/mol more stable than **2**.[11] Other investigators[2-4] based their configurational assignments on (1) steric evaluations using space-filling models or (2) demethylation studies of nicotine *N*′-oxide. Any conclusion based on these latter two criteria meets with severe criticism.[12] Finally, Koo and Kim[5] have reported the x-ray analysis of a crystal of nicotine dihydriodide in which the *N*-methyl group was in a trans configuration with respect to the pyridine ring (cf. **3**). However, the crystalline sample was undoubtedly prepared under conditions in which the equilibria shown in Scheme I were operative, and it is theoretically possible that a minor component, or one of a number of components, crystallized. In addition, conclusions based on x-ray data of a solid cannot necessarily be applied to the conformation or configuration of the same molecule in solution, especially if protonation–deprotonation reactions are occurring in solution.[14]

Table I. NOE Studies of Nicotine[c]

Sample description	Figure	Position irradiated, ppm	Proton irradiated[d]	Position observed, ppm	Proton observed	% enhancement[e]
pD 11.0[a]	1	2.16	N-CH_3 of	8.52	2,6	10.8
			1 ⇄ 2	7.98	4	10.0
pD 5.0[a]	2	2.88	N-CH_3 of	8.69	2,6	5.9 (4)[b]
			5 ⇄ 6		4	10.9 (10)[b]
pD 0.8[a]	3	2.98	N-CH_3 of	9.00	2,4,6	8.1
			3 ⇄ 4	4.00	5′α	5
				3.58	5′β	5
Trifluoroacetic acid-*d*	4	3.13	N-CH_3 of	9.36	2,4,6	0
			3[d]	4.90	2′	13
				4.28	5′α	3
				3.58	5′β	11
22% DCl	*f,g*	3.13	N-CH_3 of	9.36	2,4,6	0
			3[d]	4.90	2′	12.5
				4.28	5′α	3
				3.58	5′β	11

[a] Acidity was adjusted with D_2SO_4 in D_2O. [b] Data from ref 8. [c] See Experimental Section for instrumental details. [d] See text for discussion of assignments. [e] Enhancements reported are based on total number of protons in the multiplet observed and not on the number of protons expected to be enhanced. [f] Essentially identical with Figure 4. [g] Similar results were found with concentrated DCl.

Scheme I



Note that rotation of one ring with respect to the other effectively interchanges the spatial orientation of H_2 and H_4 with respect to the pyrrolidine ring.

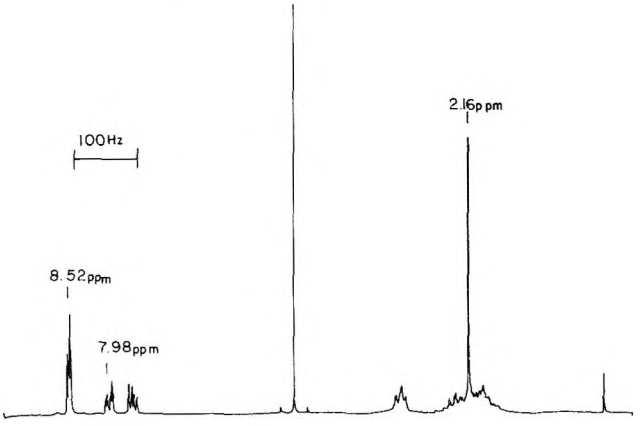


Figure 1. NMR spectra of nicotine, pD 11, at 100 MHz.

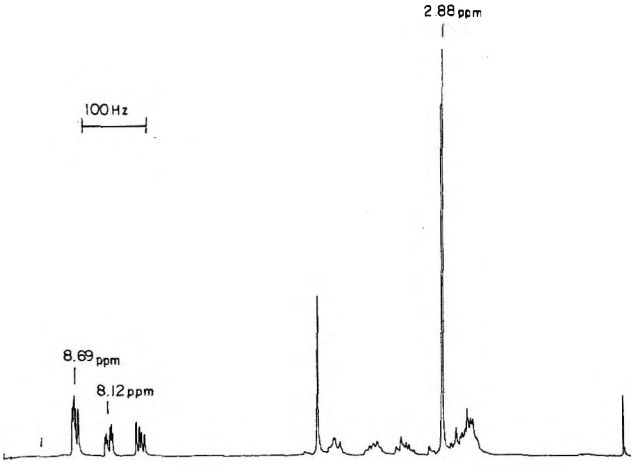


Figure 2. NMR spectra of nicotine, pD 5.0, 100 MHz. At this pD, only the pyrrolidine nitrogen is protonated.

Results and Discussion

A knowledge of the intramolecular distance between the *N*-methyl group and the pyridine ring would be sufficient to uniquely determine the cis–trans nature of the *N*-methyl group in nicotine. Recently, the intramolecular nuclear Overhauser effect (NOE) has been utilized to determine intramolecular distances between atoms.[15] This technique measures an area change of the NMR signal of one atom when a second radiofrequency field is applied at the resonance frequency of another atom. Since the magnitude of the area increase is strongly dependent on the intramolecular distance between the atoms involved ($1/r^6$ dependency), structural information is often obtainable.

Ternai et al.[8] attempted to utilize the intramolecular NOE data from nicotine to determine structural information. Table I summarizes their results and includes our data as well (see Figures 1–4). At pD ≥0.8, irradiation of the *N*-methyl group clearly results in a substantial NOE signal enhancement of the 2- and 4-pyridyl protons. Molecular models indicate that

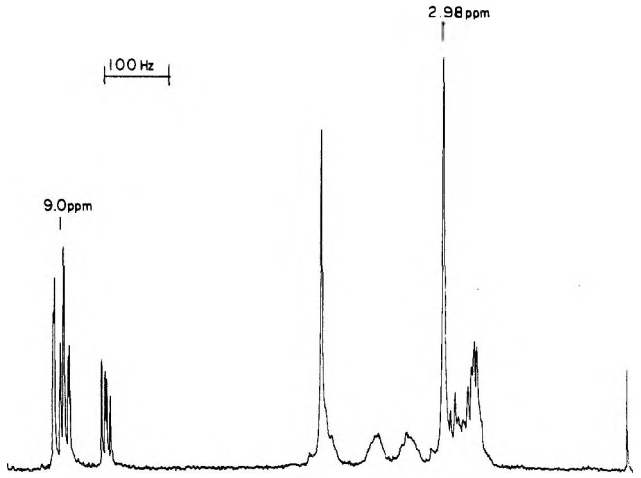


Figure 3. NMR spectra of nicotine, pD 0.8, at 100 MHz. At this pD, both nitrogens are protonated but deprotonation is extremely rapid compared to the NMR time scale.

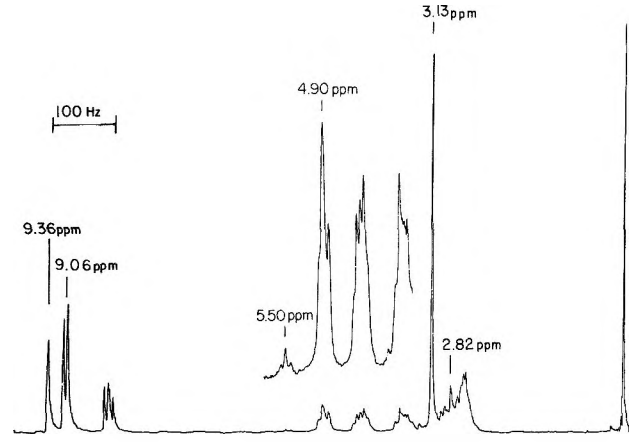
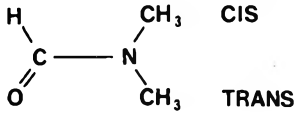


Figure 4. NMR spectra of nicotine in trifluoroacetic acid-*d* at 100 MHz. In this solvent, both nitrogens are protonated and deprotonation is slow compared to the NMR time scale.

only in **2** is the methyl group of nicotine-free base sufficiently close to the pyridine ring protons to cause an NOE. These considerations led Ternai et al.[8] to conclude that **2** is the predominant stereoisomer of nicotine-free base in solution.

However, for systems in which conformational or configurational equilibria are possible, the rate of interchange must be considered. This was elegantly demonstrated by Saunders and Bell,[16] who considered the NOE of dimethylformamide (**7**). At 90 °C, the two methyl signals are separated by 0.15



7

ppm; however, NOE studies showed that irradiation of each signal independently resulted in equal enhancements (28%) of the formyl proton. It is expected that the methyl group cis to the formyl proton should show an NOE and that the trans methyl group is too distant to cause an enhancement. Indeed, at 31 °C, the NOE for the trans methyl was almost zero, but as the temperature was raised the enhancement increased to the limiting value of 28%. This phenomenon is explained by (1) spin saturation of the trans methyl group; (2) temperature-dependent rotation about the amide linkage, thereby effectively interchanging methyl groups; and (3) spin–spin interaction and NOE enhancement. Thus, in a mobile system, the observation of an NOE is not sufficient evidence on which to base conformational or configurational preference.[15,16]

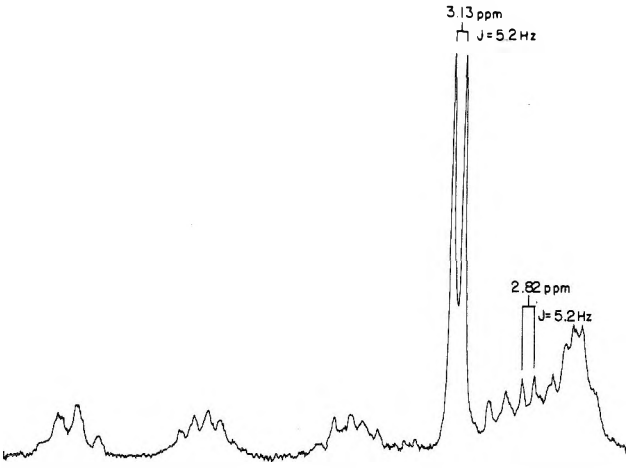
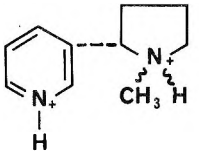


Figure 5. NMR spectra of nicotine in trifluoroacetic acid at 100 MHz.

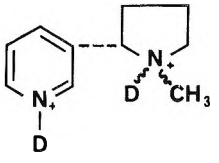
These considerations indicate that the observed NOE enhancements of nicotine discussed above (see Table I, pD ≥0.8) could be a phenomenological effect of a conformationally or configurationally mobile system. We, therefore, investigated the NOE of nicotine at various acidities since it is well known[17] that the rate of deprotonation and nitrogen inversion can be markedly decreased by increasing acid concentration.

The NMR of nicotine in trifluoroacetic acid-*d* (TFA-*d*) is shown in Figure 4. In this solvent, the rates of deprotonation (**4** → **6** → **2** and **3** → **5** → **1**) have been slowed considerably. Indeed, careful inspection of Figure 4 reveals a singlet at 2.82 ppm which can be attributed to the methyl group in **4** in addition to a singlet at 3.13 ppm for the methyl group in **3**. Accumulation of multiple repetitive scans of nicotine in TFA-*d* allows the observation of a multiplet at 5.50 ppm which corresponds to the proton at C-2′ of **4** in addition to a multiplet at 4.90 ppm for the C-2′ proton in **3**.[24]

To establish that the resonance at 2.82 ppm is due to the methyl group in **4**, the NMR of nicotine was run in TFA (Figure 5) and in mixtures of TFA-*d* and TFA (Figure 6). The methyl group of **8** should appear as a doublet while the methyl group of **9** should be a singlet. The combination of **8** and **9** in



8



9

solution produces a triplet (the combination of a singlet and a doublet) at 3.13 ppm and a triplet at 2.82 ppm (Figure 6) in which the ratio of the doublet area to the singlet area is equal to the ratio of TFA to TFA-*d* (see Figure 6).[24]

Thus, increasing the acidity of the nicotine solution effectively freezes out, relative to the NMR time scale, the two diastereomeric nicotine acid salts, **3** and **4**. The similarities of this to the often utilized variable-temperature NMR experiments are readily apparent.

Table I shows the results of NOE experiments performed on the nicotine–strong acid mixtures. Irradiation of the *N*-methyl group singlet at 3.13 ppm resulted in no area enhancement in the pyridyl proton region, indicating that the methyl group at 3.13 ppm is trans to the pyridine ring, i.e., this methyl group is from **3**. However, large NOE (>11%) were observed for two of the three protons α to the prrrolidine nitrogen (4.90 and 3.58 ppm) when the 3.13-ppm singlet was irradiated.

The multiplet at 4.90 ppm was assigned to the C-2′ proton of **3** using both decoupling experiments and chemical shift

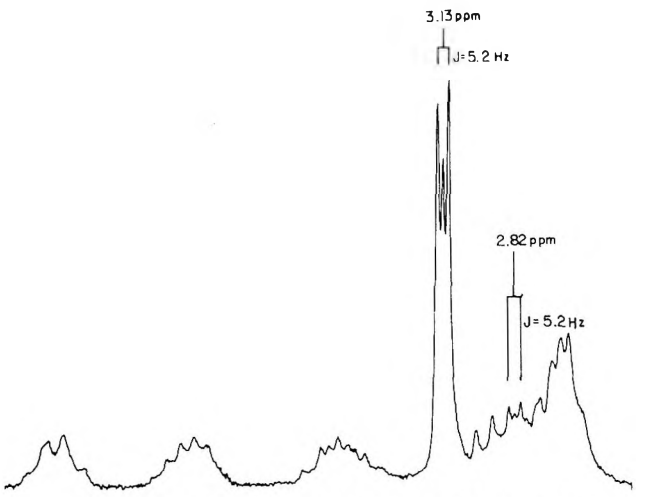


Figure 6A. NMR spectra of nicotine in 2.5:1 trifluoroacetic acid–trifluoroacetic acid-*d* at 100 MHz.

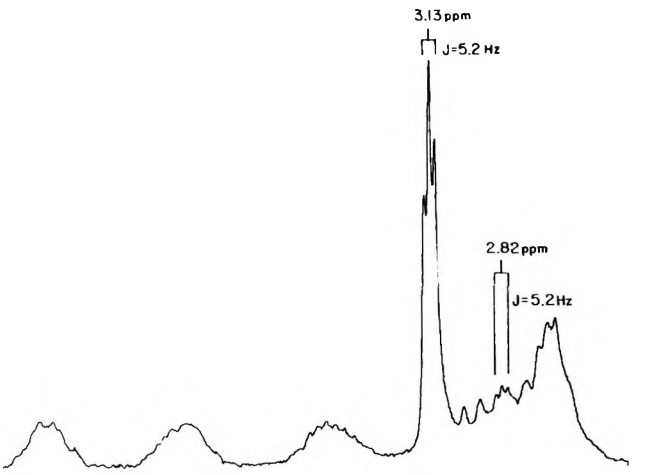
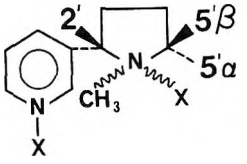


Figure 6B. NMR spectra of nicotine in 1:1 trifluoroacetic acid–trifluoroacetic acid-*d* at 100 MHz.

evaluations. When a decoupling frequency was applied to the C-3′ and C-4′ proton region, the multiplet at 4.90 ppm was simplified to a doublet with a coupling constant of 8.8 Hz due to coupling with the proton on the protonated nitrogen (H–C–N–H coupling). Under these decoupling conditions, multiplets at 3.58 and 4.28 ppm approximated somewhat complex ABM patterns due to geminal coupling and H–C–N–H coupling. The signal at 3.58 ppm was assigned to the C-5′β proton



X=H,D or nitrogen lone pair

10

(cf. **10**) because of the observed NOE. Furthermore, quantitative NMR shift analysis of nicotine with increasing acid concentration confirm these assignments. The observation of an NOE for the C-2′ and C-5′β protons and the failure to observe an NOE for the pyridyl or C-5′α protons confirm the assignment of the 3.13-ppm singlet as the resonance from the methyl group of **3**.

An NOE enhancement in the pyridyl protons was observed when the minor methyl group singlet at 2.82 ppm was irradiated, but evaluation of this NOE is hampered since the pyrrolidine resonances appear in the 2.5–3.2-ppm region and an NOE would be expected from these protons on the pyridyl protons.

Further confirmation of the trans configuration of the major isomer can be obtained by considering the relative chemical shifts of the large (3.13 ppm) and small (2.82 ppm) methyl groups and the large (4.90 ppm) and small (5.50 ppm) C-2′ protons in the **3**–**4** mixture. Examination of space-filling models reveals that in the cis orientation, the methyl group is much closer to the face of the pyridine ring than in the trans orientation in which the methyl group appears to be almost antiperiplanar to the pyridine ring. The anisotropic magnetic field generated by the circulating π electrons in the aromatic ring would therefore be expected to shield the cis methyl group near the face of the pyridine ring, resulting in an upfield shift for that methyl group.[18a] In fact, this is observed for the smaller methyl group, i.e., the methyl group in **4**. A similar argument can be made for the relative positions of the C-2′ proton and the *N*-methyl group, since it is established that a methyl group is capable of shielding protons in close proximity to itself.[18b] Comparing **3** and **4**, the methyl group is closer to the C-2′ proton in **3** than in **4**, and the C-2′ proton of **3** would be expected to be upfield relative to the C-2′ proton of **4**.

The NOE experiments in strong acid were also performed in 22% DCl and 38% DCl (see Table I). The results obtained in these solvents were essentially identical with the NOE found (or not found) in TFA. These duplicate experiments were necessary to evaluate the possible complications of TFA as solvent in NMR relaxation studies. It is known[19] that the ^{19}F dipoles of the solvent TFA are large and could provide a competing relaxation mechanism for the pyridine ring protons, thereby short-circuiting any excess polarization of these protons produced by saturating the *N*-methyl group. However, the similarity of the results in the nonfluorinated solvents and the observation of NOE for some of the protons in TFA-*d* mitigate against this complication.

These results reemphasize the importance of considering rate processes in NOE measurements involving systems possessing configurational or conformational mobility. In the case at hand, saturation of the *N*-methyl resonance will result in an NOE for the pyridine protons only if these protons are relaxed to a significant extent by the methyl protons. For nicotine, an NOE would be observed even if the methyl group spends only a very small portion of its time in the cis orientation, given the simultaneous condition that relaxation by other mechanisms is insufficient to completely relax the methyl group when it is trans to the pyridine ring.[15]

This explanation applies when nitrogen inversion is rapid relative to $1/T_{1,\text{trans}}$ for the methyl proton, otherwise the methyl protons would have sufficient time to return to spin equilibrium. This is the case for nicotine in neutral, basic, or mildly acidic solutions. For example, we have determined that $1/T_{1,\text{trans}}$ is 0.75 s^{-1} in concentrated DCl solution. Proton relaxation rates are commonly slow. We have attempted to freeze out nicotine using low-temperature NMR techniques, but even at −145 °C (in CF_2Cl_2) we observed no line broadening of the *N*-methyl group. Nitrogen atomic inversion is well known to be a very facile process,[17a] and E_a for related *N*-alkyl pyrrolidines have been found to be less than 12 kcal/mol, and should be even more facile a process for nicotine owing to steric acceleration of inversion.[17a] The fact that the acidity of the nicotine medium must be very high in order to slow down the **3** $\rightleftarrows$ **4** interconversion (see above) is indicative of an exceedingly low E_a.[20]

At the other extreme, the observation of two methyl groups and two C-2′ protons in the nicotine–TFA-*d* solutions clearly indicates that the deprotonation–inversion–protonation processes have been slowed down considerably. However, the

observation of two sets of signals is not inherently sufficient to make transfer of spin saturation inefficient. The time scales for NOE and collescence phenomenon are different. Coalescence is related to the frequency difference of the protons in their different orientations while NOE phenomena are related to the T_1 of these protons.[16]

We have evaluated the low inversion rate conditions in four fashions. First, when the nicotine–DCl mixture is irradiated at 4.90 ppm, corresponding to the C-2′ proton in **3**, no decrease in the area of the multiplet at 5.50 ppm corresponding to the C-2′ proton of **4** was observed. Thus, spin saturation is not transferred under these conditions from **3** to **4**. Apparently, the relaxation time is short enough *not* to allow transfer of saturation.

Second, when the nicotine–DCl mixture was irradiated at 3.13 ppm (cf. above), only the C-2′ and C-5′β protons were enhanced. The C-5′α proton did not show an NOE. If the deprotonation–inversion–protonation processes were occurring with an overall rate of the same order of magnitude of the rate of relaxation, an NOE would have been expected for all three of these protons (cf. experiments of nicotine pD 0.8).

Third, when a sample of nicotine is treated with 1:1 D_2SO_4–TFA-*d*,[21] a mixture of diastereomers **9** is formed. Subsequent treatment with 1:1 H_2SO_4–TFA allows a crude determination of the deprotonation–inversion rate by an analysis of the rate of transformation of **9** → **8**. After 120 h, no NMR evidence for the formation of **8** was observed. Under these conditions, the deprotonation–inversion rate is many orders of magnitude slower than $1/T_{1,\text{trans}}$.

Fourth, when a crystalline sample of isomerically pure *trans*-nicotine dihydriodide (**3**)[14] was dissolved in concentrated DCl, H–D exchange at the pyrrolidine nitrogen was observed by following the disappearance of the doublet and appearance of the singlet at 3.13 ppm, i.e., **8** → **9**. This H–D exchange was essentially complete after 1 h. However, even after 4 h, *cis*-nicotine dideuterioiodide was not formed under these conditions, as judged by the absence of both the C-2′ proton at 5.50 ppm and the *N*′-methyl group at 2.82 ppm. Upon addition of D_2O to this solution (to form approximately 22% DCl), a significant quantity (~10%) of **4** formed within 15 min. Thus, in concentrated DCl, a solvent less acidic than either TFA, sulfuric acid, or TFA–sulfuric acid mixtures used above, the nicotinium salt is capable of deprotonation to form the amine followed by reprotonation *without* nitrogen inversion. This is not unexpected as the rate constant for nitrogen inversion is slower than the rate constant for protonation.

Thus, the accumulated evidence proves that **3** and **4** formed in the nicotine–concentrated DCl or TFA mixtures have rates of deprotonation and inversion sufficiently less than their respective $1/T_1$'s, thereby satisfying the conditions necessary for the NOE studies at low interconversion rates.

The ratio of **3**:**4** can be used to determine the ratio of **1**:**2** if protonation to form **3** and **4** occurs faster than deprotonation and inversion.[22] Kinetically controlled protonation conditions can be met since (1) protonation can be made effectively irreversible by adjusting the acidity of the solution and (2) by quenching the amine with acid in the gas phase. The former criterion has been demonstrated in TFA-*d*–D_2SO_4 by measuring the conversion of **9** → **8**. The latter condition removes the objection of reversible protonation at the interface of the acidic and basic phases during the mixing process.

A dilute stream of nicotine vapor in argon was mixed with hydrogen chloride gas. A solid, crystalline mass of nicotine dihydrochloride **8** was formed at the region of mixing and this was treated with D_2SO_4–TFA-*d* (1:20) under anhydrous conditions. The failure to observe **9** after 20 h proves that the deprotonation–inversion processes do not interfere with this analysis. Careful integration of the C-2′ protons of **3** and **4** allowed determination of the ratio **3**:**4** = **1**:**2** = 10:1. Thus, nicotine in the vapor phase is 90.9 ± 0.9% **1**.

The relative concentrations of **1**–**6** (cf. Scheme I) under various conditions may well be important in the evaluation of the chemical behavior of nicotine. However, this work is also pertinent to the conformational and configurational analysis of many other alkaloid bases which possess a substituted nitrogen atom capable of facile pyramidal inversion.[23] Spectroscopic techniques are well geared to solving the complex questions of conformational and configurational analysis, but caution is the keynote in any such analysis.

In summary, we have demonstrated (1) that nicotine exists 90% in the 1′ (*R*) configuration; and (2) that the use of the NOE for determining nitrogen configuration must be evaluated under slow inversion conditions relative to the appropriate relaxation conditions.[24]

Experimental Section

The NMR spectra of nicotine (5% v/v) at various acidities were recorded on a Varian XL-100 operating at 100 MHz. The spectrometer was operated in the pulse Fourier transform mode, using a Digilab data system (FTS/NMR-3) and pulse unit. The samples used for the NOE measurements were thoroughly degassed by at least five freeze–pump–thaw cycles. The power from the decoupler was held at a minimum since the pyrrolidine proton resonances were close to the *N*-methyl resonance. The pD of the D_2O–nicotine solutions was determined on a Corning Digital 110 line operated pH meter standardized with NBS buffer solutions.

Acknowledgment. The authors gratefully acknowledge the encouragement of Dr. T. S. Osdene during the course of this work. Helpful discussions with Drs. W. F. Gannon, E. B. Sanders, and T. P. Pitner are also acknowledged with pleasure.

Registry No.—**1**, 58407-29-7.

References and Notes

(1) (a) Although seemingly a matter of semantics, the orientation of the *N*-methyl group relative to the pyridine ring in nicotine is properly described in terms of configurational rather than the uniformly used conformational label. Even though no bonds are broken in the nitrogen inversion process, a net change in configuration results. Conformation usually connotes "one of the infinite number of momentary arrangements of the atoms in space that result from the rotation about single bonds",[1b] and the pyramidal inversion process is more complicated than a simple rotational process. However, configuration involves the three dimensional arrangement in space of the atoms around a chiral center, in this case the nitrogen atom.[1c] There are numerous examples of misnomer in the current literature involving nitrogen conformational and configurational terminology. Two molecules which differ *only* by the process of nitrogen pyramidal inversion are properly termed configurational isomers. (b) E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 87. (c) *ibid.*, p 124.
(2) J. C. Craig, N. Y. Mary, N. L. Goldman, and L. Wolf, *J. Am. Chem. Soc.*, **86**, 3866 (1964).
(3) T. R. Simpson, J. C. Craig, and W. D. Kumler, *J. Pharm. Sci.*, **56**, 708 (1967).
(4) L. B. Kier, *Mol. Pharmacol.*, **4**, 70 (1968).
(5) (a) C. H. Koo and H. S. Kim, *Daehan Kwahak Kwoejee*, **9**, 134 (1965); *Chem. Abstr.*, **65**, 6431e (1966); (b) C. Chothia and P. Pauling, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 477 (1970).
(6) M. Ohashi, I. Mor shima, and T. Yonezawa, *Bull. Chem. Soc. Jpn.*, **44**, 576 (1971).
(7) (a) B. Pullman, P. Courriere, and J. L. Coubeils, *Mol. Pharmacol.*, **7**, 397 (1971); (b) B. Testa and P. Jenner, *ibid.*, **9**, 10 (1973); (c) R. J. Radna, D. L. Beveridge, and A. L. Bender, *J. Am. Chem. Soc.*, **95**, 3831 (1973).
(8) K. R. Chynoweth, B. Ternai, L. S. Simeral, and G. E. Maciel, *Mol. Pharmacol.*, **9**, 144 (1973).
(9) M. S. Cushman, Ph.D. Thesis, University of California, San Francisco, 1973.
(10) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970), and references cited therein.
(11) The free energy difference, $\Delta F°$, at 25 °C of 4 kcal/mol implies that for an equilibrium of isomers, the more stable isomer is present to the extent of almost 99.9%.
(12) For example, in the demethylation studies on nicotine *N*′-oxide, no mention of the possibility of diastereoisomerism was considered.[2] Indeed, two nicotine *N*′-oxides are known.[13]
(13) A. H. Beckett, P. Jenner, and J. W. Gorrod, *Xenobiotica*, **3**, 557 (1973).
(14) We have found that treatment of nicotine in ether with an excess of dry hydrogen iodide led to a heavy white precipitate which gave colorless needles when crystallized from methanol. The NMR spectrum of this material in TFA-*d* indicates that it is pure **3** dihydriodide. J. Seeman and J. F. Whidby, unpublished results.

(15) (a) R. A. Bell and J. K. Saunders, *Top. Stereochem.*, **7**, 1 (1973); (b) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, N.Y., 1971.
(16) J. K. Saunders, and R. A. Bell, *Can. J. Chem.*, **48**, 512 (1970).
(17) (a) J. B. Lambert, *Top. Stereochem.*, **6**, 19 (1971); (b) V. K. Pogorelyi and I. P. Gragerov, *Russ. Chem. Rev.*, **39**, 875 (1970); (c) D. Eustace and E. Grunwald, *J. Am. Chem. Soc.*, **96**, 7171 (1974).
(18) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1972, p 94; (b) E. Breuer and D. Meiumad, *J. Org. Chem.*, **38**, 1601 (1973), and references cited therein.
(19) Reference 15b, p 31.
(20) (a) W. R. Morgan and D. E. Leyden, *J. Am. Chem. Soc.*, **92**, 4527 (1970); (b) M. Saunders and F. Yamada, *ibid.*, **85**, 1882 (1963).
(21) For a discussion of the Hammett acidity function for this solvent, see H. H. Hyman and R. A. Garber, *J. Am. Chem. Soc.*, **81**, 1847 (1959).
(22) (a) M. J. T. Robinson, *J. Chem. Soc., Chem. Commun.*, 844 (1975); (b) P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *ibid.*, 825 (1974), and references cited therein; (c) J. McKenna, *Tetrahedron*, **30**, 1555 (1974).
(23) For an early excellent use of this technique, see G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959).
(24) **Noted Added in Proof.** We have prepared nicotine-*3',3',4',4',5',5'-d*$_6$. NMR analysis of this substance in TFA-*d* substantiates our assignments for **3** and **4** (see Figures 4–6).

Novel Synthesis of Imidazole Derivatives from 1-Phenyl-1,2-propanedione and Methylguanidine

Tamio Nishimura* and Koji Kitajima

Department of Chemistry, School of Hygienic Sciences, Kitasato University, Asamizodai, Sagamihara-shi, Japan

Received December 2, 1975

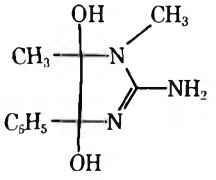
The reaction of 1-phenyl-1,2-propanedione (I) with methylguanidine (II) at −10 °C yielded 2-amino-4,5-dihydroxy-1,5-dimethyl-4-phenylimidazoline (IIIa) in methanol and 2-amino-4,5-dihydroxy-1,4-dimethyl-5-phenylimidazoline (IIIb) in ethanol. Catalytic hydrogenation of the reaction mixture of I and II in methanol produced 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc). IIIa and IIIb were converted to 2-amino-5-chloromethyl-1-methyl-4-phenyl- and 2-amino-4-chloromethyl-1-methyl-5-phenylimidazoles (Va and Vb) by concentrated hydrochloric acid treatment. Va and Vb produced 2-amino-1,5-dimethyl-4-phenyl- and 2-amino-1,4-dimethyl-5-phenylimidazoles (VIa and VIb) by catalytic hydrogenation and 2-amino-5-ethoxymethyl-4-phenyl- and 2-amino-4-ethoxymethyl-5-phenylimidazoles (VIIa and VIIb) by ethanolysis. 2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) was obtained by hydrolysis of Va in dilute hydrochloric acid.

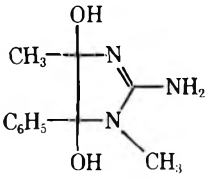
We have previously reported that 2-(disubstituted amino)-4-methyl-5-phenyl-4*H*-imidazoles, produced in good yields by the reaction of 1-phenyl-1,2-propanedione with 1,1-disubstituted guanidines in methanol at −10 °C, are useful as intermediates for synthesizing various 2-(disubstituted amino)imidazoles.[1] We have now explored the synthesis of 2-amino-1-methyl- and 2-methylaminoimidazoles by the application of this method to methylguanidine.

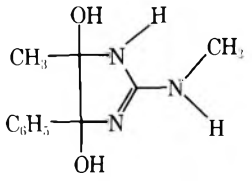
The reaction of 1-phenyl-1,2-propanedione (I) and methylguanidine (II) in methanol at −10 °C yielded a white powder, mp 54.5–55 °C dec (A-1), with molecular formula $C_{11}H_{15}N_3O_2{\cdot}CH_3OH$. This material showed absorption bands at 1650 and 1570 cm^{-1}, which may be assigned to a 4*H*-imidazole ring.[1] When the reaction mixture was hydrogenated in the presence of Pt catalyst without isolation of A-1, 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc) was obtained. The NMR spectrum of VIc exhibited a doublet for the *N*-methyl protons due to coupling with the proton on the same nitrogen atom. Ir and mass spectral and elemental analyses were consistent with this structure. Accordingly, one of the possible structures for A-1 was 2-methylamino-4*H*-imidazole (IV) but this structure was inconsistent with the observed mass spectral fragmentation pattern. The mass spectrum of A-1 lacked the $M^+ - C_6H_5CN$ fragment ion characteristic for 2-(disubstituted amino)-4*H*-imidazoles.[1] The abundant ions in the mass spectrum of A-1 were those of *m/e* 105 (22%, $C_6H_5C{\equiv}O^+$) and 104 (59%, $C_6H_5C{\equiv}N^+H$). Neither ion is conspicuous in 2-(disubstituted amino)-4*H*-imidazoles[1] but the former ion is abundant in 2-alkyl-4,5-dihydroxyimidazolines.[2] The mass spectral behavior of the latter compound is consistent with the fact that they are liable to decompose to starting materials.[3,4] The above spectral evidence strongly suggests 4,5-dihydroxyimidazoline (IIIc) as the structure of A-1; however, additional evidence did not support this structure, but rather the structure IIIa. Measuring NMR and uv spectra of A-1 was impossible because of quick decomposition of A-1 in the usual solvents, although they are obvious methods of establishing the structure of A-1.

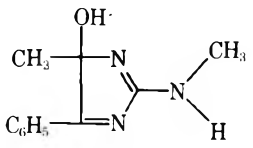
Reaction of I and II in ethanol rather than methanol unexpectedly gave a different unstable compound, mp 45–47 °C dec (B-1). The abundance (86%) of the *m/e* 105 ion in the mass spectrum of B-1 together with elemental and ir analysis suggests either IIIa or IIIb as its structure. The structures of A-1 and B-1 were unraveled from the following series experiments. Treatment of B-1 hydrochloride (prepared by treating B-1 with a small amount of concentrated hydrochloric acid at −10 °C) with concentrated hydrochloric acid at room temperature gave a new compound B-2 as colorless prisms, mp 251 °C dec. The ir, NMR, and mass spectral and elemental analyses of B-2 were consistent with 1-methylimidazole Va or Vb. Treatment of A-1 with concentrated hydrochloric acid at −10 °C and then at room temperature precipitated colorless needles, mp 238–240 °C dec (A-2). On the basis of elemental and spectral data, A-2 was determined to be Va or Vb but isomeric to B-2. The NMR spectrum of A-2 showed an NCH_3 absorption at δ 3.73, which is consistent with that reported for the 1-methyl protons in 1-methylimidazoles (δ 3.42–4.05).[5] The chemical shift of *N*-methyl protons on the 2-amino nitrogen in 2-(disubstituted amino)imidazoles is reported to be δ 2.96–3.30.[1] Moreover, the ir spectrum of A-2 showed a medium peak at 1540 cm^{-1} (δ NH_2).

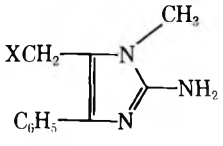
Hydrogenation of A-1 in the presence of Pt catalyst yielded pale yellow prisms, mp 225 °C dec (A-3). Similar treatment of B-2 afforded yellow plates, mp 226–227 °C dec (B-3). The NMR NCH_3 proton signals for these substances were consistent with the 1-methylimidazole structure. However, in their mass spectra, the relative intensity of the *m/e* 118 ($C_6H_5C{\equiv}N^+CH_3$) fragment ion was 8.3% in B-3 but only 1.2% in A-1. On the other hand, the *m/e* 56 ($CH_3C{\equiv}N^+CH_3$) ion was observed (13%) in A-3 but not in B-3. On the basis of these observations, it was established that A-3 is 2-amino-1,5-dimethyl-4-phenylimidazole (VIa) and B-3 is 2-amino-1,4-

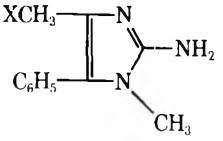

IIIa

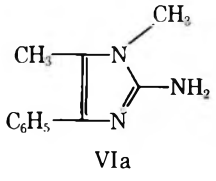

IIIb

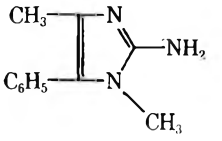

IIIc

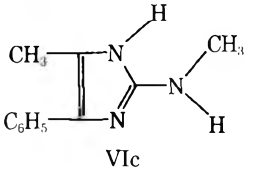

IV


Va, X = Cl
VIIa, X = OC_2H_5
VIIIa, X = OH


Vb, X = Cl
VIIb, X = OC_2H_5

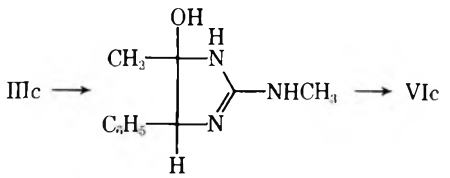

VIa


VIb


VIc

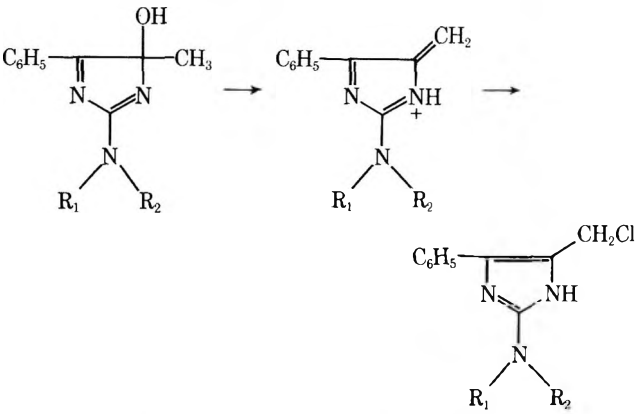
dimethyl-5-phenylimidazole (VIb). This is the first synthesis of two isomeric 1-substituted 2-aminoimidazoles having two different substituents at the 4 and 5 positions. From the foregoing discussions it is concluded that A-2 is 2-amino-5-chloromethyl-1-methyl-4-phenylimidazole (Va) and B-2 is 2-amino-4-chloromethyl-1-methyl-5-phenylimidazole (Vb). Accordingly A-1 is 2-amino-1,5-dimethyl-4,5-dihydroxy-4-phenylimidazoline (IIIa) rather than IIIc and B-1 is 2-amino-1,4-dimethyl-4,5-dihydroxy-5-phenylimidazoline (IIIb).

IIIa is stable at room temperature for 1 month, but IIIb easily decomposes to a brown oil within 2–3 h. This might be ascribed to the strain of the ring due to the steric interaction between the 1-CH_3 and 5-phenyl groups. Though 4*H*-imidazole (IV) was not isolated in these experiments, the existence of IV in the reaction mixture is beyond doubt, since hydrogenation of said mixture gave the corresponding reduced compound VIc. It could arise via a benzylic alcohol hydrogenolysis and dehydration of IIIc. However, the formation of VIc

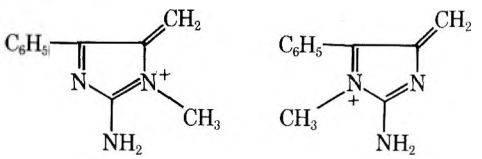


via this route is not probable on the basis of the fact that 2-methoxy-, 2-alkyl-, and 2-aryl-4,5-dihydroxy-4(5)-methyl-5(4)-phenylimidazolines are not amenable to hydrogenation.[6] Interestingly, IIIa was converted to IIIb when suspended in ethanol at −10 °C and similarly IIIb suspended in methanol yielded IIIa. The experimental results described above indicate that the reaction products IIIa, IIIb, IIIc, and IV exist in equilibrium in the reaction mixture of I with II. IIIa and IIIb may be the primary products because of low solubility in their respective reaction solvents.

We have previously reported that a plausible mechanism for the formation of 4(5)-chloromethylimidazoles by the reaction of 2-(disubstituted amino)-4-hydroxy-4*H*-imidazoles with concentrated hydrochloric acid is the formation of protonated diazafulvene followed by nucleophilic attack of chloride ion at the 6 position of the diazafulvene.[1]



The mechanism of formation of Va and Vb from IIIa and IIIb is analogous to the one mentioned above, since protonation and dehydration of IIIa and IIIb may produce cations IIIa′ and IIIb′


IIIa′ IIIb′

It is known[7,8] that 4(5)-chloromethylimidazoles are highly reactive and their hydrolysis proceeds through an intermediate carbonium cation (protonated diazafulvene) rather than a neutral diazafulvene. Va and Vb were also highly reactive and heating in ethanol at 60 °C in a short time easily gave the corresponding 5(4)-ethoxymethylimidazoles (VIIa and VIIb). Hydrolysis of Va with dilute hydrochloric acid afforded 5(4)-hydroxymethylimidazole (VIIIa) in good yield but VIIIb was not obtained in the case of Vb. Hydroxymethyl compound VIIIa changed to Vb by treatment with concentrated hydrochloric acid.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were obtained on a Hitachi spectrophotometer EPI-G_2 as KBr tablets and the following abbreviation were used: s = strong; m = medium; v = very; sh = shoulder. NMR spectra were obtained on a Varian T-60 (60 MHz) spectrometer or Hitachi R-24 (60 MHz) spectrometer in the solvent indicated. Chemical shifts are reported relative to Me_4Si. The mass spectra were determined on a Japan Electron Optics JMS-OIS high-resolution mass spectrometer operating with an ionizing energy of 70 eV by the direct inlet procedure.

1-Methylguanidine (II). 1-Methylguanidine hydrosulfate ($\frac{1}{2}H_2SO_4$)[9] (0.265 g, 3 mmol) was dissolved in a solution of 0.112 g (2.8 mmol) of sodium hydroxide in 10 ml of methanol, the precipitated sodium sulfate was filtered off, and the filtrate was concentrated to dryness under reduced pressure. The residue was extracted with 6 ml of 2-propanol and the extract was concentrated to dryness under reduced pressure to give 0.187 g (92%) of II, hygroscopic needles, mp 123–125 °C.

2-Amino-4,5-dihydroxy-1,5-dimethyl-4-phenylimidazoline (IIIa). A. A solution of 0.365 g (5 mmol) of II in 7 ml of methanol

and a solution of 0.740 g (5 mmol) of 1-phenyl-1,2-propanedione (I) in 3 ml of methanol were cooled at about −10 °C (bath temperature) and mixed. The mixture was stirred at this temperature for 10 min. The resulting precipitates were collected, washed twice with 1 ml each of cold methanol, and dried over phosphorus pentoxide under reduced pressure for 1 day to give a white powder, 0.920 g (72%): mp 54.5–55 °C dec; ir 3650 (w, OH), 3250 (vs, NH), 1650 and 1573 (vs and s, imidazoline ring or NH_2), 1115 (s, C–O), 763 and 698 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 203 (37, $M^+ - H_2O$), 188 (100, $M^+ - H_2O - CH_3$), 148 (9, $C_6H_5COCOCH_3^+$), 105 (22, $C_6H_5C{\equiv}O^+$), 104 (59, $C_6H_5C{\equiv}N^+H$), 57 (84, $CH_3NHC{\equiv}N^+H$), 43 (25, $CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}CH_3OH$: C, 56.90; H, 7.56; N, 16.59. Found: C, 57.16; H, 7.56; N, 16.98.

B. A solution of 0.22 g (0.7 mmol) of IIIb in 2 ml of cooled methanol was allowed to stand for 30 min at about −10 °C. The resulting precipitates were collected and dried under reduced pressure for 3 h to give 0.05 g (28%) of IIIa. Its ir spectrum was identical with that of IIIa.

2-Amino-4,5-dihydroxy-1,4-dimethyl-5-phenylimidazoline (IIIb). A. A solution of 0.365 g (5 mmol) of II in 6 ml of ethanol and a solution of 0.740 g (5 mmol) of I in 2 ml of ethanol were cooled at about −10 °C (bath temperature) and mixed. The mixture was maintained at this temperature for 30 min. The resulting precipitates were collected, washed with 10 ml of cold ethanol and then with 10 ml of cold ether, and dried over phosphorus pentoxide under reduced pressure for 1 h below 25 °C to give colorless needles, 0.925 g (64%): mp 45–47 °C dec; ir 3220 (s, NH), 1680, 1640, and 1595 (s, s, and vs, imidazoline ring), 1585 (vs, ring or NH_2), 1130 (s, C–O), 760 and 700 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 203 (46, $M^+ - H_2O$), 188 (100, $M^+ - H_2O - CH_3$), 148 (7, $C_6H_5COCOCH_3^+$), 105 (86, $C_6H_5C{\equiv}O^+$), 104 (66, $C_6H_5C{\equiv}N^+H$), 103 (25, $C_6H_5C{\equiv}N^+$), 57 (75, $CH_3NHC{\equiv}N^+H$), 43 (29, $CH_3C{\equiv}O^+$).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}\frac{3}{2}C_2H_5OH$: C, 57.91; H, 8.43; N, 14.47. Found: C, 57.30; H, 8.05; N, 14.34.

B. A suspension of 0.20 g (0.8 mmol) of IIIa in 7.3 ml of cooled ethanol was allowed to stand for 4 h at about −10 °C. The resulting precipitates were collected and dried over silica gel for 3 h in an evacuated glass tube kept in a refrigerator to give 0.06 g (21%) of IIIb. Its ir spectrum was identical with that of IIIb.

IIIb HCl. To 1.01 g (3.5 mmol) of IIIb cooled at about −10 °C was added 1.8 ml of cooled concentrated hydrochloric acid and the reaction mixture maintained at this temperature for 30 min. The resulting precipitates were filtered, washed with 0.5 ml of cold concentrated hydrochloric acid, and dried over phosphorus pentoxide under reduced pressure for 1 day at room temperature to give 0.36 g (40%) of a white powder: mp 111 °C sinter, 126 °C dec; ir 3300 and 3200 (vs sh and vs, NH and OH), 1685 and 1620 (vs and m, imidazolinium ring), 1590 (s, NH_2 or imidazolinium ring), 1140, 1120, and 1100 (m, m, and s, C-O), 750 and 695 cm^{-1} (s and s, C_6H_5); mass spectrum *m/e* (rel intensity) 148 (30, $C_6H_5COCOCH_3^+$), 105 (100, $C_6H_5C{\equiv}O^+$), 77 (74, $C_6H_5^+$), 73 (10, $HN{=}C(NH_2)NHCH_3^+$), 43 (25, $CH_3C{\equiv}O^+$); NMR (CD_3OD) δ 1.00 (s, 3, CH_3), 2.83 (s, 3, NCH_3), 7.38 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{15}N_3O_2{\cdot}HCl$: C, 51.26; H, 6.25; N, 16.30. Found: C, 51.02; H, 5.97; N, 16.29.

2-Amino-5-chloromethyl-1-methyl-4-phenylimidazole (Va) Hydrochloride. A. To IIIa (1.26 g, 5 mmol) cooled at about −10 °C was added 5.3 ml of cooled, concentrated hydrochloric acid and the mixture stirred for 2–3 min at this temperature. Then the reaction mixture was allowed to stand for 1 h at room temperature. The resulting precipitates were collected on a glass filter, washed three times with 0.7 ml each of concentrated hydrochloric acid, and dried over phosphorus pentoxide to yield 1.14 g (82%) of Va $HCl{\cdot}H_2O$, colorless needles: mp 238–239 °C dec; ir 3370, 3300, and 3150 (s, s, and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1280 (m, CH_2Cl), 650 cm^{-1} (m, C–Cl); NMR (CF_3COOD) δ 3.73 (s, 3, CH_3N), 4.66 (s, 2, CH_2Cl), 7.60 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}N_3Cl{\cdot}HCl{\cdot}H_2O$: C, 47.83; H, 5.47; N, 15.21. Found: C, 47.80; H, 5.83; N, 15.30.

B. A solution of 25 mg (0.1 mmol) of VIIIa HCl in 0.1 ml of concentrated hydrochloric acid was kept for 10 min at room temperature. The resulting precipitates were collected and dried over phosphorus pentoxide under reduced pressure for 1 day to give 18 mg (66%) of Va $HCl{\cdot}H_2O$, colorless needles, mp 240 °C dec.

2-Amino-4-chloromethyl-1-methyl-5-phenylimidazole (Vb) Hydrochloride. A solution of 0.358 g (1.3 mmol) of IIIb HCl in 0.7 ml of concentrated hydrochloric acid was kept for 20 min at room temperature. The resulting precipitates were collected on a glass filter, washed twice with 0.1 ml each of concentrated hydrochloric acid, and dried over phosphorus pentoxide under reduced pressure for 1 day to give 0.24 g (67%) of Vb HCl, colorless plates: mp 249–250 °C dec; ir 3280 and 3100 (s and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1270 (s, CH_2Cl), 770 and 700 (s and s, C_6H_5), 670 cm^{-1} (s, CCl); NMR (CF_3COOD) δ 3.45 (s, 3, NCH_3) 4.47 (s, 2, CH_2Cl), 7.20–7.78 (m, 5, C_6H_5).

Anal. Calcd for $C_{11}H_{12}N_3Cl{\cdot}HCl$: C, 51.18; H, 5.08; N, 16.28. Found: C, 51.18; 5.28; N, 16.29.

2-Amino-1,5-dimethyl-4-phenylimidazole (VIa) Hydrochloride. Phenylimidazole Va hydrochloride ($\frac{1}{2}H_2O$) (5.34 g, 20 mmol) obtained by drying Va $HCl{\cdot}H_2O$ at 100 °C in vacuo for 2 h was hydrogenated in 80 ml of dry DMF in the presence of 0.53 g of PtO_2 at room temperature. After completion of the hydrogenation, the catalyst was filtered off, and the solvent was removed by vacuum distillation. The resulting residue was dissolved in 80 ml of water, and a small amount of insoluble substance was filtered off. The filtrate was concentrated to dryness under reduced pressure and dried over phosphorus pentoxide in vacuo for 2 days to give a hygroscopic, yellowish powder. The powder was dissolved in a small amount of 15% methanol in chloroform, and the solution was charged onto a column (made of 175 g of 200 mesh Wako-gel 55 mm diameter) and then eluted with the same solvent mixture. After the fastest yellowish band (110 ml) had been removed, a faintly yellow main band (about 500 ml) was collected, the solvent was removed, and the residue was dried over phosphorus pentoxide under reduced pressure for 1 day to yield 2.64 g (58%) of crude VIa HCl, a hygroscopic, yellowish powder. The powder was dissolved in 21 ml of ethanol and after 40 ml of ether was added the solution was allowed to stand for 5 h at room temperature to give 1.79 g (40%) of VIa HCl, yellowish prisms, mp 223–225 °C dec. One recrystallization from etaanol and ether gave an analytical sample, yellowish prisms: mp 225 °C dec; ir 3100 (vs, NH_2), 1680 (vs, imidazolium ring), 1560 (m, NH_2), 775 and 700 cm^{-1} (s and m, C_6H_5); NMR ($CDCl_3$ + Me_2SO-d_6) δ 2.28 (s, 3, C–CH_3), 3.52 (s, 3, NCH_3), 7.20–7.70 (m, 7, C_6H_5 and NH_2); mass spectrum *m/e* (rel intensity) 187 (100, M^+), 172 (15, $M^+ - CH_3$), 144 (11, $M^+ - NCNH_2 - H$), 131 (12, $M^+ - HN{=}C{=}NCH_3$), 130 (12, $M^+ - HN{=}C{=}NCH_3 - H$), 103 (14, $C_6H_5CN^+$), 56 (13, $CH_3C{\equiv}NCH_3^+$).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.06; H, 6.31; N, 18.78. Found: C, 58.87; H, 6.03; N, 18.60. Use of Va $HCl{\cdot}H_2O$ instead of Va $HCl{\cdot}\frac{1}{2}H_2O$ decreased the yield to 30% (crude), because of the formation of VIIIa. Attempted complete dehydration of Va $HCl{\cdot}H_2O$ resulted in decomposition of Va.

2-Amino-1,4-dimethyl-5-phenylimidazole (VIb) Hydrochloride. Phenylimidazole Vb hydrochloride (0.426 g, 1.6 mmol) in 20 ml of THF was hydrogenated in the presence of 0.04 g of PtO_2 at room temperature. After completion of the hydrogenation, 10 ml of methanol was added and the catalyst filtered off. The filtrate was evaporated to dryness and allowed to stand for 1 day at room temperature. To the crystalline residue was added 8 ml of THF and the resulting crystals were collected, washed twice with 1 ml each of THF, and dried over phosphorus pentoxide under reduced pressure for 1 day to give 0.292 g (81%) of VIb HCl, yellowish plates, mp 227–231 °C. One recrystallization from ethanol and ether gave an analytical sample, yellowish plates: mp 228–230 °C dec; ir 3100 (vs, NH_2), 1675 (vs, imidazolium ring), 1560 (m, NH_2), 775 and 715 cm^{-1} (m and s, C_6H_5); NMR ($CDCl_3$) δ 2.15 (s, 3, C–CH_3), 3.47 (s, 3, NCH_3), 7.10–7.45 (m, 5, C_6H_5), 7.53 (s, 2, NH_2); mass spectrum *m/e* (rel intensity) 187 (100, M^+), 172 (25, $M^+ - CH_3$), 144 (13, $M^+ - NCNH_2 - H$), 131 (20, $M^+ - HN{=}C{=}NCH_3$), 130 (13, $M^+ - HN{=}C{=}NCH_3 - H$), 103 (8, $C_6H_5CN^+$).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.06; H, 6.31; N, 18.78. Found: C, 58.93; H, 6.15; N, 18.59.

2-Methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc) Hydrochloride. A solution of II (0.14 g, 2 mmol) in 10 ml of methanol and a solution of I (0.29 g, 2 mmol) in 10 ml of methanol were cooled to about −10 °C (bath temperature) and then mixed. The solution was hydrogenated in the presence of 100 mg of PtO_2 while cooling with ice–water. Immediately after completion of the hydrogenation, 0.1 ml of concentrated hydrochloric acid was added to the reaction mixture, the catalyst filtered off, and the filtrate evaporated to dryness under reduced pressure at about 30 °C. The residue was dissolved in 2 ml of ethanol and about 50 ml of ether added until white opacity was observed in the solution. The mixture was kept for 2 weeks in a refrigerator to give 0.19 g (37%) of VIa HCl, colorless needles, mp 185–186 °C. One recrystallization from ethanol and ether in the same manner as above yielded pure VIa HCl: mp 188.5–189 °C; ir 2950 (vs, NH), 1675, 1655, 1625, and 920 cm^{-1} (vs, s sh, m sh, and m, imidazolium ring); NMR ($CDCl_3$) δ 2.40 (s, 3, CH_3), 3.16 (d, J = 5 Hz, 3, CH_3NH), 6.93 (broad q, J = 5 Hz, 1, CH_3NH).

Anal. Calcd for $C_{11}H_{13}N_3{\cdot}HCl$: C, 59.05; H, 6.30; N, 18.78. Found: C, 58.77; H, 6.04; N, 18.86.

2-Amino-5-ethoxymethyl-1-methyl-4-phenylimidazole (VIIa)

Hydrochloride. A solution of 55 mg (0.2 mmol) of Va HCl·H_2O in 10 ml of ethanol was warmed at 60 °C for 5 min and the mixture was concentrated to about 2 ml under reduced pressure. To the concentrate was added 3 ml of ether and the solution was allowed to stand for 1 day. The resulting precipitates were collected by filtration, washed with 5 ml of ether, and dried over phosphorus pentoxide under reduced pressure to give 45 mg (80%) of VIIa HCl·H_2O, colorless needles: mp 119 °C dec; ir 3350 and 3150 (vs and vs, NH_2), 1680 (vs, imidazolium ring), 1540 (m, NH_2), 1095 (vs, C–O–C), 770 and 700 cm^{-1} (m and s, C_6H_5); NMR (CF_3COOD) δ 1.36 (t, J = 7 Hz, 3, OCH_2CH_3), 3.75 (s, 3, NCH_3), 4.70 (s, 2, $CH_2OC_2H_5$), 4.85 (q, J = 7 Hz, 2, OCH_2CH_3), 7.60 (s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (16, M^+), 186 (100, $M^+ - OC_2H_5$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·H_2O: C, 54.63; H, 7.05; N, 14.70. Found: C, 54.58; H, 7.24; N, 14.48.

2-Amino-4-ethoxymethyl-1-methyl-5-phenylimidazole (VIIb) Hydrochloride. In the same manner as VIIa 0.258 g (1 mmol) of Vb HCl gave 0.150 g (57%) of VIIb, pale yellow needles, mp 164 °C effervescence, 246–250 °C dec. Two recrystallization from ethanol and ether afforded colorless plates: mp 171 °C effervescence, 249 °C dec; ir 3260 and 3100 (s and vs, NH_2), 1675 (vs, imidazolium ring), 1540 (m, NH_2), 1100 (s, C–O–C), 775 and 700 cm^{-1} (m and s, C_6H_5); NMR ($CDCl_3$) δ 1.18 (t, J = 7 Hz, 3, OCH_2OH_3), 3.50 (q, J = 7 Hz, 2, OCH_2CH_3), 3.55 (s, 3, NCH_3), 4.28 (s, 2, $CH_2OC_2H_5$), 7.10–7.70 (broad s, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 231 (44, M^+), 186 (100, $M^+ - C_2H_5O$), 103 (23, $C_6H_5C{\equiv}N^+$), 45 (76, $CH_3CH{=}O^+H$).

Anal. Calcd for $C_{13}H_{17}N_3O$·HCl·½H_2O: C, 56.43; H, 6.91; N, 15.14. Found: C, 56.88; H, 6.53; N, 15.23.

2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) Hydrochloride. Compound Va HCl·H_2O (0.552 g, 2 mmol) was dissolved in 6.0 ml of 2% hydrochloric acid at 60 °C. After standing for 1 day in a refrigerator, the precipitates were collected and washed twice with 0.3 ml each of 2% hydrochloric acid to give 0.373 g (72%) of VIIIa HCl, pale pink needles, mp 70 °C sinter, 96 °C. One recrystallization from 2% hydrochloric acid gave colorless needles: mp 70 °C sinter, 102 °C; ir 3300 and 3120 (vs and vs, NH_2), 1675 (vs, imidazolium ring). 1555 (m, NH_2), 1025 or 1000 (s and s, C–O), 785 and 710 cm^{-1} (s and s, C_6H_5); NMR (Me_2SO-d_6) δ 3.60 (s, 3, NCH_3), 4.46 (s, 2, CH_2OH), 5.50 (broad, about 1, CH_2OH), 7.50 (s, 5, C_6H_5), 7.80 (s, 2, NH_2).

Anal. Calcd for $C_{11}H_{13}N_3O$·HCl·2H_2O: C, 47.91; H, 6.57; N, 15.24. Found: C, 47.02; H, 6.20; N, 15.52.

Registry No.—I, 579-07-7; II, 471-29-4; II ½H_2SO_4, 598-12-9; IIIa, 58325-27-2; IIIb, 58325-28-3; IIIb HCl, 58325-29-4; Va HCl, 58325-30-7; Vb HCl, 58325-31-8; VIa HCl, 58325-32-9; VIb HCl, 58325-33-0; VIc HCl, 58325-34-1; VIIa HCl, 58325-35-2; VIIb HCl, 58325-36-3; VIIIa HCl, 58325-37-4.

References and Notes

(1) T. Nishimura, K. Nakano, S. Shibamoto, and K. Kitajima, *J. Heterocycl. Chem.*, **12**, 471 (1975).
(2) Unpublished observations. Relative intensity of acetyl ion was 100% in the mass spectrum of 4,5-dihydroxy-4,5-dimethyl-2-phenylimidazoline.
(3) O. Diels and K. Schleich, *Ber.*, **49**, 1711 (1916).
(4) J. B. Ekeley and A. R. Ronzio, *J. Am. Chem. Soc.*, **59**, 1118 (1937).
(5) M. R. Grimett, *Adv. Heterocycl. Chem.*, **12**, 148 (1970).
(6) Unpublished observations.
(7) R. A. Turner, C. F. Huchner, and C. R. Scholz, *J. Am. Chem. Soc.*, **71**, 2801 (1949).
(8) T. C. Bruice and J. L. Herz, *J. Am. Chem. Soc.*, **86**, 4109 (1964).
(9) H. Toku, Y. Sakabe, S. Mogi, and T. Nishimura, *Kitasato Arch. Exp. Med.*, **44**, 213 (1971).

Analogues of Sparteine. II. Synthesis of *N*-Monoalkylbispidines and *N,N'*-Dialkylbispidines

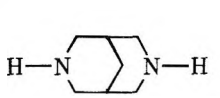
Edward E. Smissman† and Peter C. Ruenitz*

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66045

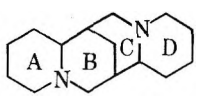
Received August 26, 1975

The structural and physiochemical similarity of the bicyclic diamine bispidine (**1**) to the antiarrhythmic–oxytocic agent sparteine (**2**) prompted the development of synthetic routes to bispidines containing substituents on one or both nitrogens, for studies directed toward elucidation of optimum molecular characteristics required for sparteine-like bioactivity. Condensation of N-substituted 4-piperidones with benzylamine and formaldehyde, followed by modified Wolff–Kishner reduction of the resulting diamino ketones (**8**) furnished hydrogenolytically labile intermediates (**11**) which were converted to *N*-alkylbispidines (**12**). Alkylation of these last compounds by formation and reduction of amides (**15**) or by selective alkylation of the secondary amine functions afforded several *N,N'*-dialkylbispidines (**3**).

Investigations concerning the synthesis and reactivity of the bicyclic amine bispidine (**1**) have been reported by a number of groups.[1] Although bispidine itself is not naturally occurring, the bispidine moiety constitutes the B and C rings of the C-15 lupine alkaloid sparteine (**2**).[2] As a result, both compounds have similar physical properties: they are strong bases[3] and form complexes with certain divalent metal cations.[1b,4]

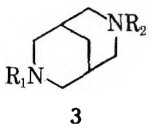


1



2

Sparteine has been shown to affect muscular activity, especially the myocardium (heart) and myometrium (uterus).[5] Its chemical and physical similarity to bispidine prompted our efforts to develop facile synthetic routes to *N*-alkylbispidines (**3**, R_2 = H) and *N,N'*-dialkylbispidines (**3**) for pharmacologic studies.



3

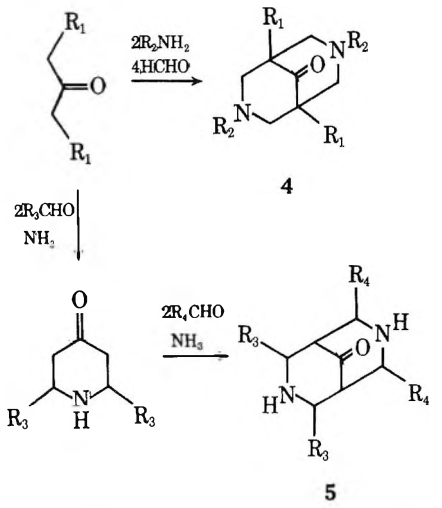
Bispidine was originally prepared in six steps from pyridine-3,5-dicarboxylic acid ester.[1a] Difficulties encountered in attempted conversion of **1** to **3** ($R_1 = R_2 = CH_3$)[1e] and the number of steps required prompted us to investigate alternate routes for preparation of **3**.

The syntheses of various 1,5-dicarboalkoxybispidinones[6] and 1,5-diarylbispidinones[7] (**4**) and 2,4,6,8-tetraarylbispidinones[8] (**5**) via Mannich condensations have been reported (Scheme I). Reductive removal of the carbonyl group in the N-substituted condensation products (e.g., **4**, R_1 = H, or **5**, $R_3 = R_4$ = H) would constitute a two-step synthesis of **3**. Alternatively, formation of **4** (R_1 = $COOC_2H_5$) followed by hy-

† Professor Smissman died on July 14, 1974.

* Address correspondence to School of Pharmacy, The University of Georgia, Athens, Ga. 30602.

Scheme I

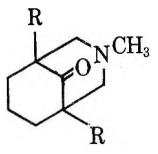


4

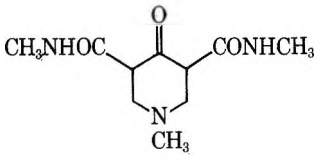
5

R_1 = aryl, $COOC_2H_5$; R_2 = aryl, alkyl; R_3 = aryl; R_4 = aryl

drolysis and decarboxylation would furnish the intermediate diamino ketones which could then be reduced to the desired compounds. [Decarboxylation of the related base (**6a**) in boiling 20% HCl gave amino ketone **6b** in 67% yield.[9]] How-



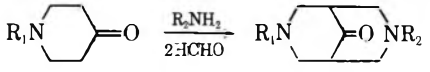
6a, R = $COOC_2H_5$
b, R = H



7

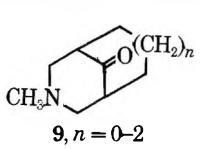
ever, condensation of acetonedicarboxylic acid ester with formaldehyde and methylamine (Scheme I, R_1 = $COOCH_3$; R_2 = CH_3) afforded a small amount of the piperidone **7** accompanied by polymeric products; the respective bicyclic diamine **4** was not detected. Use of acetone itself in this condensation failed to give any tractable products. In contrast, the condensation of *N*-methyl-4-piperidone with paraformaldehyde and methylamine furnished diamino ketone **8a** in low yield (Scheme II).[10] Comparable yields of some closely

Scheme II



8a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$
c, $R_1 = n$-C_4H_9; $R_2 = CH_2C_6H_5$

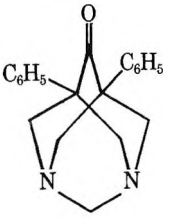
related bicyclic amino ketones (**9**) have been obtained utilizing analogous double Mannich condensations starting with cy-



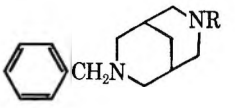
9, n = 0–2

cloalkanones instead of *N*-methyl-4-piperidone.[11] The use of benzylamine as the primary amine (Scheme II, R_2 = $CH_2C_6H_5$) resulted in a decrease in reaction time and more satisfactory yields of bicyclic amino ketones **8b,c** without the production of significant amounts of other condensation products. This is consistent with earlier work which showed that benzylamine reacts more readily with formaldehyde and ketones than do most primary amines.[12,13]

Amino ketones **8a,b** failed to react with carbonyl reagents, and reacted with hydrazine only under vigorous conditions. This relative inertness may be due to an amide-like character of these compounds. The 1,3-diazadamantanone **10** is of similar reactivity for this postulated reason.[14] Amino ketones **8a,b** were, however, reduced without difficulty under modified Wolff–Kishner conditions[15] to give bicyclic amines **11a,b.**



10

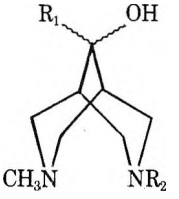


11a, R = CH_3
b, R = n-C_4H_9

12a, R = CH_3
b, R = n-C_4H_9

Hydrogenolytic removal of the benzyl groups in **11a,b** utilizing 10% palladium on carbon[16] afforded the *N*-monoalkylbispidines **12a,b.**

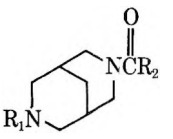
Attempted catalytic debenzylation of bridge-substituted bispidine **8b** gave amino alcohol **13,** and similar treatment of **14**[17] gave only the product of C–O bond cleavage.[18] This suggested that *N*-benzylbispidines are adsorbed exo prior to C–N bond fission, as expected from inspection of molecular models of these compounds.



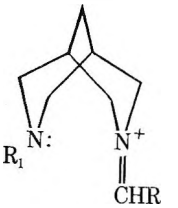
13, $R_1 = R_2 = H$
14, $R_1 = C_6H_5$; $R_2 = CH_2C_6H_5$

The *N*-alkylbispidines **12a,b** were converted to the N,N′-disubstituted analogues by (a) acylation followed by lithium aluminum hydride reduction of the resulting amides or (b) selective alkylation of the secondary amine groups.

It had been anticipated that hydride reduction of *N*-acyl-*N*′-alkylbispidines (**15**), prepared readily from the appropriate *N*-alkylbispidines and acid chlorides or anhydrides, would not constitute a feasible approach owing to the demonstrated susceptibility of the probable reduction intermediates, immonium ions **16,** to cyclization.[1c] Reductive alkylation of **12a,b** was not attempted for this reason. However, *N*-benzoyl-*N*′-*n*-butylbispidine (**15c**) was reduced with $LiAlH_4$ to afford **11b** cleanly in 83% yield. Less favorable results were obtained in the reductions of amides **15a,b** with $LiAlH_4$. Reduction of **15b** gave a mixture of products containing the desired diamine and a substantial amount of deacylated starting material (**12a**). Reduction of formamide **15a** gave a low yield of diamine ac-



15a, $R_1 = CH_3$; R_2 = H
b, $R_1 = R_2 = CH_3$
c, $R_1 = n$-Bu; $R_2 = C_6H_5$



16

Table I. Products of Alkylation of Amide Anions of *N*-Alkylbispidines

Anion of	Alkyl halide	Yield, %	EIMS, *m/e* M	EIMS, *m/e* B	Monoacid salts Mp, °C	Crystn solvent	Ref	Registry no.
12a	CH_3I	100	154	58	227–229 dec[a]	Ethanol	10, 22	14789-40-3
12a	C_2H_5Br	74	168	58	189–190[a]	Acetone	23, *d*	
12a	n-C_4H_9Br	100			129–131[b]	Ethyl acetate–ether	*d*	
12a	c-$C_6H_{11}CH_2Br$	75	236	58	163.5–166 dec[c]	Acetone	*d*	
12b	n-C_4H_9Br	100			94.5–95.5[a]	Ethyl acetate–petroleum ether	*d*	

[a] Perchlorate salt. [b] Hydrobromide salt. [c] Hydrochloride salt. [d] Elemental analysis agreed within 0.4% in carbon, hydrogen, and nitrogen.

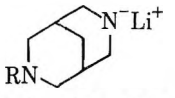
Table II. Proton Magnetic Resonance Spectral Analysis of *N,N'*-Dialkylbispidines[a]

R_1, R_2			
C_2H_5, CH_3	n-C_4H_9, CH_3	c-$C_6H_{11}CH_2$, CH_3	n-C_4H_9, n-C_4H_9
1.00, 3 H, t (7)	0.9, 3 H, t (6)	0.83–1.91, 15 H, m	0.93, 6 H, t (6)
1.45, 2 H, t (3)	1.15–1.60, 8 H, m		1.17–1.63, 10 H, m
1.75, 2 H, m		2.08, 2 H, d (6)	1.82, 2 H, m
2.15, 3 H, s	2.1, 3 H, s	2.15, 3 H, s	
2.2, 4 H, dd (10.5, 4)	2.1–2.45, 6 H, m	2.2–2.8, 8 H, m	2.1–2.3, 8 H, m
2.3, 2 H, q (7)			
2.7, 4 H, dd (10.5, 3)	2.5–2.9, 4 H, m		2.68, 4 H, dd (10, 3)

[a] Spectra were taken using benzene as solvent. Chemical shifts are in parts per million relative to internal tetramethylsilane.

companied by several impurities. Diborane reduction[19] of **15c** proceeded with complete reaction of starting material. However, the borane–amine complex that had formed could not be readily decomposed.[20]

Since it appeared that *N,N'*-dialkylbispidines could not be synthesized from alkyl amides **15** without complications, an alternate method was used to prepare these compounds. Treatment of **12a** or **12b** with an equimolar amount of methyllithium in the cold[21] generated amide anions **17**, which



17, R = CH_3, n-C_4H_9

reacted readily with various alkyl halides to afford *N*-*n*-butyl-*N'*-alkylbispidines and *N*-methyl-*N'*-alkylbispidines (**3**) in 74–100% yields (Tables I and II).

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were taken on Beckman IR 10, IR 33, and Perkin-Elmer 727 spectrophotometers. Nuclear magnetic resonance spectra (NMR) were obtained using Varian A-60A and T-60 spectrometers with tetramethylsilane as internal standard. Electron impact mass spectra (EIMS) were recorded using Finnegan 1015 and Varian CH5 spectrometers, at 70 eV unless otherwise indicated. Elemental analysis were obtained on a Hewlett-Packard 185 C, H, N analyzer, and from Midwest Microlab, Inc., Indianapolis, Ind. Analytical gas–liquid chromatography (GLC) was performed with a F & M 810 gas chromatograph using dual column flame ionization detection; carrier gas helium (55 ml/min); detector gases hydrogen (55 ml/min), compressed air (250 ml/min); columns 6 ft × 0.125 in. stainless steel containing Dowfax 9N9 KOH supported on 80–100 mesh acid-washed DMCS-treated HP Chromosorb G; instrument temperatures, injection port (210 °C), detector (225 °C), oven (125–170 °C isothermal). The GLC–EIMS experiment was conducted using the columns and conditions described above, on a Varian Aerograph 1700 gas chromatograph interfaced with the Varian CH5 mass spectrometer.

Free bases were prepared from salts by partitioning the salt between ether and 10% aqueous sodium hydroxide. In the case of water-insoluble salts (perchlorates of aromatic ring containing bispidines) ethanol was added to the mixture to increase the rate of equilibration.

Perchlorate salts were prepared by treating ice-cold ethereal solutions of the amines with excess 70% perchloric acid–ethanol (1:1); the resulting precipitates were filtered and washed with ether. This method afforded diperchlorate salts, except in the case of the aromatic-ring-containing bispidines which yielded monoperchlorates. Monoperchlorates (and other monoacid salts) were prepared by the procedure of Leonard and co-workers.[3]

Workup of Organic Extracts. Unless otherwise stated, solutions were dried with anhydrous sodium sulfate, filtered, and concentrated at a rotary evaporator using a Buchler water aspirator at water bath temperatures of 40 °C or less.

***N*-Benzyl-*N'*-alkylbispidinones (8b,c). A. General Procedure.** The synthesis of *N*-benzyl-*N'*-methylbispidinone (**8b**) is typical. To a suspension of 45 g (1.5 mol) of paraformaldehyde in 500 ml of methanol was added 21.5 g (0.2 mol) of benzylamine in 100 ml of methanol, which had previously been neutralized with 12 g (0.2 mol) of glacial acetic acid. A solution of 22.5 g (0.2 mol) of *N*-methyl-4-piperidone (freshly distilled) in 100 ml of methanol was neutralized with 12 g (0.2 mol) of glacial acetic acid and added in increments to the magnetically stirred contents of the reaction flask over a period of 5 days. After stirring for an additional 15 days, the solvent was distilled in vacuo and the residual oil partitioned between 250 ml of water and 200 ml of chloroform. The chloroform was removed and discarded and the aqueous phase was reextracted with 100 ml of chloroform which was also discarded. To the aqueous phase was added 100 ml of ice-cold 20% aqueous sodium hydroxide, and the resulting suspension was extracted with five 200-ml portions of ether. The combined extracts gave 21.6 g (44%) of an amber oil which crystallized on standing. A small amount of this material was placed in a microsublimator and evacuated at 20 mm (70 °C) for 48 h. The product was collected (15 mg) as white crystals: mp 60–61 °C; ir (KBr) 3.24 (w, aromatic CH), 3.38 (s), 3.56 (s, Bohlmann bands), 5.76 (s), 5.83 (s, C=O), 6.85, 7.41, 9.17, 9.62, 13.7, 14.5 μ; NMR ($CDCl_3$) δ 2.3 (s, 3, NCH_3), 3.5 (s, 2, NCH_2Ph), 7.2 (s, 5, C_6H_5), 2.2–3.2 (m, 10, remaining protons); EIMS *m/e* 244 (M), 58 (B).

The monoperchlorate salt was precipitated from ether, washed with water, and crystallized from acetone–ethyl acetate, mp 110–112 °C.

Anal. Calcd for $C_{15}H_{21}ClN_2O_5 \cdot H_2O$: C, 49.66; H, 6.39; N, 7.71. Found: C, 49.30; H, 6.53; N, 7.30.

B. *N*-Benzyl-*N'*-*n*-butylbispidinone (8c) was prepared in 38% yield by the above procedure. It could not be induced to crystallize: ir (CCl_4) 3.24 (w), 3.40 (s), 3.62 (s), 5.71 (s), 5.83 μ (shoulder); NMR (CCl_4) δ 0.92 (t, J = 6 Hz, 3, CCH_3), 1.06–1.67 (m, 6, CCH_2CH_2C), 2.23–3.33 (m, 12, NCH_2 and bridgehead CH), 3.47 (s, 2, NCH_2Ph), 7.30 (s, 5, C_6H_5).

Catalytic Debenzylation of 8b. To a solution of 2.5 g (10 mmol) of **8b** in 20 ml of glacial acetic acid containing 1 ml of 70% aqueous perchloric acid was added 0.2 g of 10% palladium on carbon. The suspension was stirred under 1 atm of hydrogen for 8 h, filtered, and the filtrate concentrated, giving 2.5 g of **13** as a cream-colored powder. The free base was prepared from 0.3 g of this salt: ir (NaCl) 3.03 μ (s, broad, NH and OH), no absorption between 5.7 and 5.9 μ; NMR (CCl_4) δ 2.1 (s, 3, NCH_3), no peaks are seen further than 3.1 ppm downfield.

Attempted Synthesis of 1,5-Dicarbomethoxy-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (4). The method for the preparation of **6a** from 1,3-dicarbethoxycyclohexan-2-one was used,[24] starting instead with acetonedicarboxylic acid dimethyl ester and twice the molar quantities of methylamine and formaldehyde. The crude product, analyzed by GLC–EIMS, consisted primarily of the starting keto diester accompanied by a small quantity of monoamino ketodiamide **7** (*m/e* 229).

***N*-Benzyl-*N'*-alkylbispidines (11a,b). A. General Procedure.** The reduction of amino ketone **8b** to give *N*-benzyl-*N'*-methylbispidine (**11a**) is typical. A magnetically stirred solution of 50 g (1 mol) of hydrazine hydrate, 49 g (0.2 mol) of **8b**, and 500 ml of triethylene glycol, maintained under nitrogen, was heated to 60 °C, and 50 g of 85% potassium hydroxide (pellets) was added. The yellow solution was stirred and refluxed (145 °C) for 4 h; then a Dean-Stark trap was inserted, and 59 ml of distillate was removed. The cooled contents of the reaction flask were poured into 50 ml of cold water, and the mixture was extracted with four 50-ml portions of ether. The combined extracts afforded 35.9 g (78%) of an amber liquid. Treatment of 2 g of this base with excess perchloric acid furnished the monoperchlorate of **11a**, white plates from acetone–ethyl acetate, 0.4 g, mp 145–147 °C.

Anal. Calcd for $C_{15}H_{23}ClN_2O_4$: C, 54.46; H, 7.01; N, 8.47. Found: C, 54.19; H, 6.97; N, 8.23.

The free base was prepared from this salt as a colorless oil: ir (neat) 3.25 (w, aromatic, CH), 3.40 (s), 3.58 (s, Bohlmann bands), 6.70, 6.85, 7.30, 7.84, 8.85, 9.01, 9.40, 10.0, 13.5, 13.9, 14.5 μ; NMR ($CDCl_3$) δ 1.45 (t, J = 3 Hz, 2, CH_2 bridge), 1.90 (m, 2, bridgehead CH), 2.2–2.6 (m, 4, *exo*-NCH), 2.75 (dd, J_1 = 11 Hz, J_2 not resolved, 4, *endo*-NCH), 3.40 (s, 3, NCH_2Ph), 7.3 (s, 5, C_6H_5); EIMS *m/e* 230 (M), 58 (B).

B. *N*-Benzyl-*N'*-*n*-butylbispidine (11b). This was prepared in 68% yield from **8c** by use of the general procedure. The monoperchlorate salt crystallized from water–methanol, mp 142–143 °C.

Anal. Calcd for $C_{18}H_{29}ClN_2O_4$: C, 57.99; H, 7.83; N, 7.51. Found: C, 57.67; H, 8.03; N, 7.46.

This salt was converted to the free base: ir (CCl_4) 3.24 (w), 3.40 (s), 3.62 μ (s, trans bands); NMR (CCl_4) δ 0.95 (t, J = 6 Hz, 3, CCH_3), 1.20–1.67 (m, 6, CCH_2CH_2C and CH_2 bridge), 1.85 (m, 2, bridgehead CH), 2.28 (m, 6, *exo*-NCH and NCH_2 of *n*-Bu), 2.73 (d, J = 10 Hz 4, *endo*-NCH), 3.40 (s, 2, NCH_2Ph), 7.03 (s, 5, C_6H_5); EIMS *m/e* 272 (M), 58 (B).

Catalytic Debenzylation of 11a,b. A. *N*-Methylbispidine (12a). A suspension of 5 g of 10% palladium on carbon in 30 ml of 85% acetic acid was stirred under 1 atm of hydrogen until uptake ceased. This suspension was then added to a solution of 33.9 g (0.24 mol) of *N*-benzyl-*N'*-methylbispidine in 120 ml of 85% acetic acid. The mixture was shaken under 50 psi of hydrogen until uptake ceased—5 h at ambient temperature. The catalyst was filtered and the solvent was removed at the oil pump. The residual oil was ice cooled and 110 ml of ice-cold 10% aqueous sodium hydroxide was added. The mixture was extracted with four 200-ml portions of ether. The combined extracts afforded 20.05 g (97%) of a mobile yellow liquid: bp 97–99 °C (28 mm); ir (neat) 3.11 (w, NH), 3.45 (s), 3.57 μ (s); NMR (C_6H_6) δ 1.33 (m, 2, CH_2 bridge), 1.50 (m, 2, bridgehead CH), 1.98 (s, 3, NCH_3), 2.18 (d, J = 11 Hz, 2, *exo*-NCH adjacent to NCH_3), 2.75 (d, J = 11 Hz, 2, *endo*-NCH adjacent to NCH_3), 2.93 (m, 4, NCH_2 adjacent to NH); EIMS *m/e* 140 (M), 44 (B). The monoperchlorate separated from ethanol–benzene–Skellysolve B as fine white crystals, mp 200–205 °C.

Anal. Calcd for $C_8H_{17}ClN_2O_4$: C, 39.92; H, 7.12; Cl, 14.73; N, 11.64. Found: C, 40.12, H, 7.37; Cl, 14.66; N, 11.62.

B. *N*-*n*-Butylbispidine (12b). This was synthesized from 29.6 g (0.109 mol) of **11b** in 100% yield via the method described in A. Distillation furnished the pure compound, a water-white, mobile liquid: bp 62–68 °C (0.2 mm); ir (CCl_4) 2.98 (w, NH), 3.41 (s), 3.63 (s), 6.90, 7.78, 9.09, 10.6 μ; NMR (C_6D_6) δ 0.92 (t, J = 6 Hz, 3, CCH_3), 1.33 (m, 6, CCH_2CH_2C and CH_2 bridge), 1.58 (m, 2, bridgehead CH), 2.13 (m, 4, *exo*-NCH adjacent to *N*-*n*-Bu, and $NCH_2C_3H_7$), 2.87 (dd, J_1 = 11 Hz, J_2 not resolved, 2, *endo*-NCH adjacent to *N*-*n*-Bu), 3.00 (m, 4, NCH_2 adjacent to NH); EIMS *m/e* 182 (M), 58 (B). Addition of saturated ethanolic picric acid to a cold ethereal solution of this base afforded the monopicrate which separated at once as fine yellow needles: mp 98–100 °C (softening at 80 °C).

Anal. Calcd for $C_{17}H_{25}N_5O_7$: C, 49.63; H, 6.13; N, 17.02. Found: C, 49.74; H, 6.30; N, 16.67.

Hydrogenolysis of 3-Methyl-7-benzyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonan-9-ol (14). A solution of 390 mg (1 mmol) of **14** in 40 ml of ethanol was adjusted to pH 3 with ethanolic hydrogen chloride and shaken with 0.1 g of 10% palladium on carbon for 22 h. The catalyst was then filtered and the solvent was removed in vacuo. The residue was partitioned between 5 ml of 10% aqueous sodium hydroxide and 25 ml of ether. The aqueous phase was extracted with an additional 25-ml portion of ether, and the combined extracts were worked up to give 0.25 g (79%) of a yellow oil: NMR ($CDCl_3$) δ 3.53 (s, 2, CH_2Ph), 7.2 (m, 10, C_6H_5). Use of 80% aqueous acetic acid as the reaction solvent resulted in no change in the appearance of the NMR spectrum of the product.

Preparation of *N,N'*-Dialkylbispidines by Selective Alkylation of *N*-Alkylbispidines. A solution of 6 mmol of **12a** or **12b** in 10 ml of dry tetrahydrofuran, magnetically stirred under nitrogen, was cooled to −10 °C and an equimolar amount of ethereal methyllithium (1.3–1.6 M) was added. After stirring for 2 min, a solution of 6 mmol of the appropriate alkyl halide in 5 ml of dry tetrahydrofuran was added dropwise to the brown reaction solution. Completion of addition discharged the color, and after warming to room temperature and stirring for 2 h, the reaction solution was concentrated in vacuo, and the product was worked up with ether and 5% aqueous sodium hydroxide. Characterization of compounds prepared by this method is summarized in Tables I and II.

Synthesis and Reduction of *N*-Acyl-*N'*-alkylbispidines (15a–c). Treatment of *N*-methylbispidine with acetic–formic anhydride[25] or acetic anhydride in dry chloroform under routine conditions gave **15a** and **15b**, respectively. *N*-*n*-Butylbispidine gave **15c** on treatment with benzoyl chloride. Purity of ca. 100% was confirmed by GLC; the ir spectra exhibited strong amide carbonyl absorbtion.

Reduction was carried out as follows. The amide (1–2 mmol) was dissolved in 2–3 ml of tetrahydrofuran. The resulting solution, magnetically stirred and maintained under nitrogen, was treated with 2–3 ml of a ca. 10% solution of lithium aluminum hydride in tetrahydrofuran. The suspension was refluxed for 17–24 h, after which time the excess hydride was destroyed with saturated aqueous ammonium chloride and wet tetrahydrofuran. Filtration and concentration gave the crude products which were analyzed by GLC. Amide **15c** gave a product in 83% yield and >95% purity whose ir and NMR spectra were identical with those of a known sample of bicyclic amine **11b**. Reduction of **15b** resulted in a 90% yield of a product containing eight parts of *N*-ethyl-*N'*-methyl-, one part of *N*-methylbispidine, and one part of an unidentified substance. The identities of *N*-ethyl-*N'*-methyl- and *N*-methylbispidine were verified by simultaneous GLC with authentic samples. The formamide **15a** furnished only 29% of a mixture containing six parts of *N,N'*-dimethylbispidine, one part of *N*-methylbispidine (retention times coincided with those of authentic samples), and a total of three parts of two unknown components.

Acknowledgments. The assistance of Mr. R. Drake, Mr. J. Haug, and Ms. K. Widiger in obtaining mass spectral and elemental analyses data is gratefully acknowledged, as is the assistance of Ms. Deborah Smith (NSF Undergraduate Research Participant, summer, 1973) in the preparation of some of the compounds reported herein. This research was sponsored by training grant GM 1341 from the National Institutes of Health, Department of Health, Education, and Welfare.

Registry No.—**3** (R_1 = C_2H_5; R_2 = CH_3) $HClO_4$, 14789-41-4; **3** (R_1 = *n*-C_4H_9; R_2 = CH_3) HBr, 58324-88-2; **3** (R_1 = CH_2-c-C_6H_{11}; R_2 = CH_3) HCl, 58324-89-3; **3** (R_1 = R_2 = *n*-C_4H_9) $HClO_4$, 58324-91-7; **8b**, 58324-92-8; **8b** $HClO_4$, 58324-93-9; **8c**, 58324-94-0; **11a**, 58324-95-1; **11a** $HClO_4$, 58324-96-2; **11b**, 58324-97-3; **11b** $HClO_4$, 58324-98-4; **12a**, 58324-99-5; **12a** $HClO_4$, 58325-00-1; **12b**, 58325-01-2; **12b** picrate, 58375-24-9; **13**, 58904-53-3; **14**, 58325-03-4; **15a**, 58325-04-5; **15b**, 58374-89-3; **15c**, 58325-05-6; CH_3I, 74-88-4; C_2H_5Br, 74-96-4; *n*-

C_4H_9Br, 109-65-9; c-$C_6H_{11}CH_2Br$, 2550-36-9; benzylamine, 100-46-9; *N*-methyl-4-piperidone, 1445-73-4; acetic–formic anhydride, 2258-42-6; acetic anhydride, 108-24-7; benzoyl chloride, 98-88-4.

References and Notes

(1) (a) F. Galinovsky and H. Langer, *Monatsh. Chem.*, **86**, 449 (1955); (b) H. Stetter and H. Hennig, *Chem. Ber.*, **88**, 789 (1955); (c) H. Stetter and R. Merten, *ibid.*, **90**, 868 (1957); (d) V. Galik and S. Landa, *Collect. Czech. Chem. Commun.*, **38**, 1101 (1973); (e) E. E. Smissman and J. A. Weis, *J. Heterocycl. Chem.*, **5**, 405 (1968); (f) J. A. Weis, Ph.D. Thesis, The University of Kansas, Lawrence, Kans., 1968.

(2) Reviews of the chemistry of sparteine: (a) R. K. Hill in "The Chemistry of the Alkaloids", S. W. Pelletier, Ed., Van Nostrand-Reinhold, Princeton, N.J., 1970, p 418; (b) W. Dopke, "Einfuhrung in die Chemie der Alkaloids", Akademie-Verlag, Berlin, 1968, p 74; (c) F. Bohlmann and D. Schumann in "The Alkaloids", Vol. 9, R. H. F. Manske, Ed., Academic Press, New York, N.Y., 1967, pp 201–207; (d) N. J. Leonard, *ibid.*, Vol. 7, 1960, pp 289–295.

(3) N. J. Leonard, P. D. Thomas, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 1552 (1955).

(4) G. Fraenkel, B. Appleman, and J. G. Ray, *J. Am. Chem. Soc.*, **96**, 5113 (1974); (b) H. Nozaki, T. Aratani, T. Toraya, and R. Noyori, *Tetrahedron*, **27**, 905 (1971); (c) M. Guetté, J. P. Guetté, and J. Capillon, *Tetrahedron Lett.*, 2863 (1971); (d) R. A. Kretchmer, *J. Org. Chem.*, **37**, 2744 (1972); (e) M. Carmack, E. Boschmann, and L. M. Weinstock, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, No. INOR 67.

(5) References to the pharmacology of sparteine: (a) J. Senges, R. Rüdel, and E. Schmid-Wiedersheim, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **274**, 348 (1972); (b) I. Rosenblum, and A. A. Stein, *J. Pharmacol. Exp. Ther.*, **144**, 138 (1964); (c) M. Ohta, and T. Narahashi, *ibid.*, **187**, 47 (1973).

(6) C. Mannich and F. Veit, *Chem. Ber.*, **68**, 506 (1935).

(7) (a) Z.-Y. Kyi and W. Wilson, *J. Chem. Soc.*, 1706 (1951); (b) S. Chiavarelli, G. Settimj, and H. M. Alves, *Gazz. Chim. Ital.*, **87**, 109 (1957); *Chem. Abstr.*, **52**, 15519*d* (1958); (c) S. Chiavarelli and G. Settimj, *Gazz. Chim. Ital.*, **88**, 1234, 1246 (1958); *Chem. Abstr.*, **53**, 22008*a*, 22009a (1959).

(8) (a) S. Chiavarelli, G. Settimj, and F. M. Rabagliati, *Gazz. Chim. Ital.*, **90**, 311 (1960); *Chem. Abstr.*, **55**, 13435*h* (1961); (b) V. Baliah and R. Usha, *Indian J. Chem.*, **10**, 319 (1972); (c) Z. Kafka, V. Galik, and M. Safar, *Collect. Czech. Chem. Commun.*, **40**, 174 (1975).

(9) H. O. House and H. C. Müller, *J. Org. Chem.*, **27**, 4436 (1962); see also ref 11.

(10) E. E. Smissman, P. C. Ruenitz, and J. A. Weis, *J. Org. Chem.*, **40**, 251 (1975).

(11) H. O. House, P. P. Wickham, and H. C. Müller, *J. Am. Chem. Soc.*, **84**, 3139 (1962).

(12) C. Mannich and O. Hieronimus, *Chem. Ber.*, **75B**, 49 (1942); *Chem. Abstr.*, **37**, 1125 (1943).

(13) Use of primary amines in the Mannich reaction: (a) F. F. Blicke, *Org. React.*, **1**, 303–341 (1942); (b) B. B. Thompson, *J. Pharm. Sci.*, **57**, 715 (1968).

(14) T. Sasaki, S. Eguchi, T. Kiriyama, and Y. Sakito, *J. Org. Chem.*, **38**, 1648 (1973).

(15) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(16) (a) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, N.Y., 1967, p 463; (b) L. Birkofer, *Chem. Ber.*, **75B**, 429 (1942); (c) W. H. Hartung and R. Simonoff, *Org. React.*, **7**, 263 (1953).

(17) Prepared by addition of amino ketone **8b** to ethereal phenyllithium, followed by aqueous workup.

(18) Selective N-debenzylation of compounds related to **14** has been achieved under similar conditions: (a) P. M. Carabateas and L. Grumbach, *J. Med. Pharm. Chem.*, **5**, 913 (1962); (b) N. J. Harper, C. F. Chignell, and G. Kirk, *J. Med. Chem.*, **7**, 726 (1964).

(19) (a) H. C. Brown and P. Heim, *J. Org. Chem.*, **38**, 912 (1973); (b) H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).

(20) Borane–tertiary amine complexes have in some cases been shown to be relatively stable to hydrolysis: L. T. Murray, Ph.D. Thesis, Purdue University, Lafayette, Ind, 1963; *Diss. Abstr.*, **24**, 5003 (1964).

(21) The procedure used is a modification of that used to prepare lithium diisopropylamide: H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

(22) J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968).

(23) This compound was reportedly prepared by Mannich condensation using ethylamine as the primary amine (cf. Scheme II), followed by Wolff–Kishner reduction.[22] Difficulties experienced in repeating the Mannich condensation in these laboratories[10] serve to indicate that the reported melting point (241–243 °C) may actually be that of a related bicyclic amine.

(24) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1379 (1959).

(25) L. I. Krimen, *Org. Synth.*, **50**, 1 (1970).

Reactions of Cytidine with 7-Bromomethylbenz[*a*]anthracene, Benzyl Bromide, and *p*-Methoxybenzyl Bromide. Ratio of Amino to 3 Substitution[1]

Robert Shapiro* and Shian-Jan Shiuey

Department of Chemistry, New York University, New York, New York 10003

Received November 18, 1975

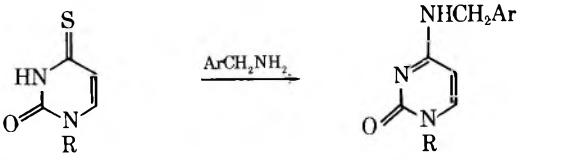
Alkylation of cytidine in dimethylacetamide by 7-bromomethylbenz[*a*]anthracene (**1**), benzyl bromide, and *p*-methoxybenzyl bromide afforded the 3-substituted cytidines in good yield. The identity of these products has been confirmed by spectroscopic studies and chemical transformations. Deamination of 3-(benz[*a*]anthryl-7-methyl)cytidine by nitrous acid or sodium bisulfite afforded the corresponding uridine derivative, which was also prepared from uridine and **1**. Alkylation of cytidine by the above halides in aqueous solution led to the formation of 3- and N^4-substituted products. The structure of the latter was established by unequivoval synthesis from 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine and the appropriate benzylic amines. The alkylation reactions in aqueous solution went in low overall yield. 3-Substitution of cytidine predominated in the case of benzyl bromide, and N^4 substitution with *p*-methoxybenzyl bromide, while both types of product were formed in almost equal amounts with **1**. Substitution at N^4 of cytidine appears to be correlated with the ability of the reagent to accommodate a positive charge, which leads to thermodynamic rather than kinetic control of the reaction.

Alkylation of the heterocyclic bases of the nucleic acids generally proceeds most rapidly at the pyridine-type ring nitrogen atoms. The most reactive positions in nucleosides are the 7 position of guanosine, 1 position of adenine, and 3 position of cytosine. Similar results are obtained in single stranded nucleic acids.[2,3] One striking exception to this rule was reported by Dipple and co-workers in studies with the carcinogenic alkylating agent, 7-bromomethylbenz[*a*]anthracene.[4] Alkylation by this reagent in dimethylacetamide was in accord with the usual pattern described above. In aqueous solution, however, alkylation of nucleosides and polynucleotides proceeded mainly on the amino group of guanine, adenine, and possibly cytosine. The possible importance of amino group alkylation to carcinogenesis was pointed out by the above authors. More recently, another author has suggested that amino group substitution is a significant process in the reaction of another carcinogen, *N*-acetoxy-*N*-acetyl-2-aminofluorene, with DNA.[5]

We have further investigated the reactions of cytidine with 7-bromomethylbenz[*a*]anthracene (**1**) and with benzyl bromide and *p*-methoxybenzyl bromide. One objective was to confirm the structure of the reaction product formed by **1** in an aqueous solution and in dimethylacetamide. The position of substitution on alkylation of a nucleic acid component is usually assigned on the basis of ultraviolet spectroscopy.[2] This technique is inapplicable in reactions in-

volving 1 because the reagent has its own very strong ultraviolet absorption. We have used this opportunity to demonstrate other methods of structure determination. Another purpose of this study was to understand more about the factors that direct a particular alkylating agent to the amino group of a nucleic acid component, rather than to a pyridine-type ring nitrogen. Cytidine was selected as a model in this study because of its simplicity—it contains just one of each type of reactive site.

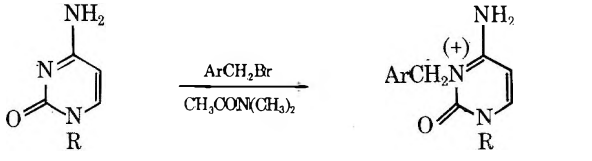
Syntheses of N^4- and 3-Substituted Cytidines. It was desirable to have authentic samples of N^4-substituted cytidines as reference compounds. These compounds were prepared by reaction of 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine (**2**)[6] with benzylamine, *p*-methoxybenzylamine, and 7-aminomethylbenz[*a*]anthracene. In the case of the synthesis of **3c**, a subsequent treatment with ammonia was necessary to complete the removal of the *O*-benzoyl groups. It was also possible to prepare **3a** directly from cytidine by bisulfite-catalyzed transamination with benzylamine. This procedure failed in the case of **3c**.



2, R = 2′,3′,5-tri-*O*-benzoyl-β-D-ribofuranosyl

3, R = β-D-ribofuranosyl
a, Ar = C_6H_5
b, Ar = *p*-$CH_3OC_6H_4$
c, Ar = 7-benz[*a*]anthryl

The preparation of 3-benzylcytidine (**4a**) by direct reaction of cytidine with benzyl bromide in dimethylacetamide had previously been reported.[8] The assignment of structure was based largely on ultraviolet spectroscopic properties. We now found that the reaction of cytidine with *p*-methoxybenzyl bromide went similarly to give a compound with properties closely comparable to those of **4a**. We assigned the structure 3-*p*-methoxybenzylcytidine (**4b**) to this product. The reaction product of cytidine with 7-bromomethylbenz[*a*]anthracene[4] could not be characterized by ultraviolet spectroscopy, for reasons discussed above. It differed in its properties from the authentic sample of **3c**, prepared as described above.



R = β-D-ribofuranosyl

4a, Ar = C_6H_5
b, Ar = *p*-$CH_3OC_6H_4$-
c, Ar = 7-benz[*a*]anthryl

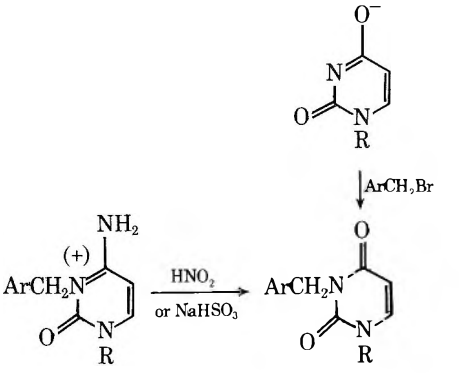
To demonstrate a chemical method for distinguishing ring- from amino-substituted product, applicable when reference compounds are not available, the following transformations were run. Deamination of **4c** was successful, using either nitrous acid[9] or sodium bisulfite.[10] The product retained the benzanthryl residue, and was also preparable by the reaction of 7-bromomethylbenz[*a*]anthracene with uridine. It was assigned structure **5**.

The assignment of **4c** and **5** as 3-substituted nucleosides was further supported by the following evidence. Their NMR spectra show the retention of H-5 and H-6. Compound **4c** migrated as a cation upon paper electrophoresis at pH 7. The infrared spectra of **4a–c** were quite similar in the carbonyl region, all three compounds containing a band at 5.75–5.8 μ, not present in **2a–c**. The absorbance due to the CH_2 group in the NMR spectra of **4a–c** was about 0.6–0.75 τ further downfield than the corresponding absorbance in **3a–c**. An additional structural possibility, not completely excluded by this evidence, is O-2 substitution in **4c** and **5**. Reaction at this position of cytosine has no precedent in nucleic acid chemistry, however,[2] and this structure is quite unlikely as a major reaction product.

Table I. Yield of Substituted Cytidine Derivatives[a]

Alkylating agent	Position substituted	Solvent, % Dimethylacetamide	Solvent, % Aqueous buffer
Benzyl bromide	3	95	0.62
	N^4	0	0.09
p-Methoxybenzyl bromide	3	83	0
	N^4	0	0.14
7-Bromomethylbenz[*a*]anthracene	3	51	0.18
	N^4	1.1	0.14

[a] The conditions (temperature, reactant ratio) used in the aqueous reactions differed from those in dimethylacetamide. See the Experimental Section for complete details.



4c

5, R = β-D-ribofuranosyl; Ar = 7-benz[*a*]anthryl

Product Distribution on Alkylation in Dimethylacetamide and Water. With authentic samples now available as reference compounds, it was possible to study the relative yields of 3- vs. N^4-substituted cytidine upon alkylation of cytidine in dimethylacetamide, and in a buffered aqueous solution, pH 5.5. With our technique, we were able to detect as little as 0.1% yield of a product. The results are presented in Table I. It can be seen that the total yield of products was good in the reactions conducted in dimethylacetamide. In water, however, the yield of alkylated products was less than 1%, which undoubtedly is due to competition by the solvent for the alkylating agent. These results are comparable to those recently reported for alkylation of cytidine by ethyl methanesulfonate and diethyl sulfate in aqueous solution.[11]

The results of the alkylation study in dimethylacetamide with all three bromides was generally in accord with observation previously reported.[4] The sole new feature was that a small amount of N^4 substitution (relative to 3 substitution) was observed in the case of 7-bromomethylbenz[*a*]anthracene. The results in aqueous solution provide a striking contrast. The introduction of a methoxyl group into the para position of benzyl bromide altered the product distribution from 7:1 in favor of 3 substitution to exclusive (within the limits of our technique) N^4 substitution. The case of bromomethylbenz[*a*]anthracene fell in between

these extremes, with 3 substitution slightly ahead of N^4 substitution. This contrasts with the results of Dipple et al.,[4,12] who suggested that amino substitution was the principal reaction, at the nucleoside level as well as with nucleic acids.

Some studies were also performed on the methylation of cytidine in an organic solvent, and aqueous buffer. This was done to compare our results with those of other workers, who generally have not observed monoalkylation at N^4, except in strongly alkaline solution. In fact, even when a large excess of dimethyl sulfate was used, no N^4-methylcytidine was detected. 3-Methylcytidine was obtained in 77% yield in dimethylformamide, and in 64% yield in an aqueous buffer, under these conditions.

The results of Sun and Singer[11] on the ethylation of cytidine should be considered in connection with our results. The ratio of 3- to N^4-substituted product was about 20:1 in dimethyl sulfoxide, and 5.5:1 in neutral aqueous solution.

We wished to consider the possibility that the N^4-substituted products observed by us were formed by intramolecular Dimroth rearrangement[13] of the 3-substituted products. This process has been observed when 3-substituted cytosines were heated in alkali,[14] or in a mixture of acetic anhydride and acetic acid.[15] This process seemed unlikely in our case, as it would also have been expected in the methylation reaction, where no amine-substituted product was observed. In fact, no rearrangement was observed when **4b** and **4c** were allowed to stand under the aqueous reaction conditions. At 85%, pH 4.7, a small amount of rearrangement to **3b** and **3c** was observed. The major product, under those conditions, was cytidine. This formation of cytidine suggested that the rearrangement observed was not Dimroth, but by an intermolecular path, similar to that produced on heating 3-benzylhypoxanthine.[16]

It is apparent that the conditions which favor substitution on the amino group relative to the ring nitrogen in cytidine are those which favor the development of a positive charge on the alkylating agent: stabilization of the developing carbonium ion (compare *p*-methoxybenzyl bromide to benzyl bromide) and an aqueous rather than a less polar solvent. As suggested by Dipple and co-workers,[4] this first-order process resembles acylation. The thermodynamically more stable amino-substituted product is formed. The neutral product formed after 3 substitution is in the less stable amino tautomeric form of cytidine.

Our results provide additional information on the factors that control amino group substitution in nucleosides. The biological significance of this event remains undetermined.

Experimental Section

Melting points are uncorrected. Ultraviolet spectra were determined on a Cary 15 spectrophotometer, infrared spectra with a Perkin-Elmer Model 137 spectrophotometer, and NMR spectra with a Varian XL-100 instrument using tetramethylsilane (τ 10.00) as standard. Mass spectra were determined at 70 eV with Varian M-66 and CEC 21-110B spectrometers. Thin layer chromatography was performed on Avicel mecrocrystalline cellulose TG-101 (FMC Corp.) and on precoated silica gel plates (E. Merck). Plates were visualized with a uv lamp equipped with a short-wavelength filter. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Preparation of N^4-Benzylcytidine (3a). A. From 2′,3′,5′-Tri-*O*-benzoyl-4-thiouridine. A mixture of 228 mg (0.396 mmol) of 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine[6] (**2**) and 2.26 ml (24.0 mmol) of benzylamine in 6 ml of absolute ethanol was heated for 22 h at 100 °C in a sealed vial. The solvents were then removed under vacuum, and 40 ml of water was added to the resulting heavy liquid. The aqueous layer was extracted repeatedly with benzene, then freeze dried to afford a light yellow solid. This product was worked up by preparative TLC in methanol–benzene (3:7). The major band (R_f 0.20) afforded 111 mg of a light yellow glass. This material was dissolved in methanol–2-propanol (2:3) and filtered. The solvents were evaporated, and the solid triturated with ether to afford 40 mg (29%) of an amorphous solid, which could not be crystallized: λ_{max} (pH 2) (ϵ) 285 nm (16 400), λ_{max} (pH 7) 238, 273 nm; NMR (CD_3OD) τ 2.07 (1 H, d, J = 8 Hz, H_6) 2.71 (5 H, s, C_6H_5), 4.00–4.20 (2 H, m, H_5, $H_{1'}$), 5.42 (2 H, s, CH_2), 5.78–6.08 (3 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.10–6.30 (2 H, m, $H_{5'}$); ir (KBr) 6.03, 6.36, 6.60 μ; mass spectrum *m/e* calcd for $C_{16}H_{19}N_3O_5$, 333.1325; found, 333.1303.

Anal. Calcd for $C_{16}H_{19}N_3O_5 \cdot H_2O$: C, 54.70; H, 6.03; N, H.95. Found: C, 55.39; H, 5.65; N, 11.99.

B. Preparation of 3a from Cytidine. Cytidine (48.6 mg, 0.20 mmol), benzylamine (0.44 ml, 4.0 mmol), and 5 ml of aqueous sodium bisulfite were combined. The pH was adjusted to 7.2 with 6 N NaOH, and the final volume of solution was brought to 12.5 ml by addition of water. The solution was heated at 45 °C for 138 h. The pH was adjusted to 10.7 by addition of concentrated NH_4OH, and the solution was stirred for 10 min. The solvents were evaporated to give a white powder. The powder was dissolved in water, and the solution was absorbed onto 100 ml of cation exchange resin (Dowex A.G. 50W-X8), H^+ form. The column was washed with water and then eluted with 1.5 N NH_4OH. The purity of fractions was checked by TLC on cellulose in acetonitrile–0.1 M NH_4Cl (9:1) (R_f 0.13 for cytidine, 0.67 for **3a**). Earlier fractions were contaminated with cytidine, later fractions with a fluorescent impurity. The pure middle fractions were evaporated to afford 17.3 mg (26%) of **3a** as a glass. The R_f (above) of **3a** and NMR were identical with those of the product prepared by another route.

N^4-(*p*-Methoxybenzyl)cytidine (3b). The first procedure listed above for **3a** was employed, starting from 230 mg (0.40) mmol of 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine and 3.28 ml (25.2 mmol) of *p*-methoxybenzylamine. After preparative TLC on silica in methanol–benzene (3:7), the product (R_f 0.37) was recrystallized from ethanol–ethyl acetate to yield 67 mg (44%) of a solid: λ_{max} (pH 2) (ϵ) 283 nm (16 600); λ_{max} (pH 7) 273 nm; NMR (CD_3OD) τ 2.10 (1 H, d, J = 8 Hz, H_6), 2.76 (2 H, d, J = 8 Hz, aromatic), 3.16 (2 H, d, J = 8 Hz, aromatic), 4.06–4.20 (2 H, m, H_5, $H_{1'}$), 5.50 (2 H, s, CH_2), 5.78–6.08 (3 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.10–6.28 (5 H, m, OCH_3, $H_{5'}$); ir (KBr) 6.03, 6.36, 6.60 μ; mass spectrum *m/e* 231 (base + H^+), 121 ($CH_3OC_7H_6^+$).

Anal. Calcd for $C_{17}H_{21}N_3O_6 \cdot H_2O$: C, 53.53; H, 6.08; N, 11.02. Found: C, 53.79; H, 6.09; N, 10.50.

N^4-(Benz[a]anthryl-7-methyl)cytidine (3c). A mixture of 115 mg (0.20 mmol) of 2′,3′,5′-tri-*O*-benzoyl-4-thiouridine[6] (**2**) and 257 mg (1 mmol) of 7-aminomethylbenz[a]anthracene[4] in 8 ml of absolute ethanol was heated for 42 h at 100 °C in a sealed vial. The solvent was evaporated and the residue was dissolved in 8 ml of methanol. Dry ammonia gas was passed through the solution at 25 °C for 3 h. The suspension was filtered and washed with methanol. The filtrate was concentrated and worked up by preparative TLC on silica in methanol–benzene (3:7). The product (R_f 0.45) was triturated with ethyl acetate, washed with ether, and recrystallized from ethanol–water to yield 44 mg (45%) of light yellow crystals: mp 175–177 °C; λ_{max} (MeOH) (ϵ) 260 nm (38 700), 270 (52 800), 280 (88 700), 291 (106 000), 319 (5100), 335 (8600), 351 (12 300), 369 (7900), 388 (900); NMR (CD_3OD) τ 0.6–2.6 (12 H, m, H_6 + aromatic), 4.05 (1 H, d, J = 3 Hz, $H_{1'}$), 4.20 (1 H, d, J = 8 Hz, H_5), 4.55 (2 H, s, CH_2), 5.60–6.60 (5 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$); ir (KBr) 6.01, 6.40, 6.62 μ.

Anal. Calcd for $C_{28}H_{25}N_3O_5 \cdot H_2O$: C, 67.05; H, 5.43; N, 8.38. Found: C, 66.95; H, 5.35; N, 8.28.

3-Benzylcytidine Hydrobromide (4a). This compound was prepared by the method of Brookes et al.[8] and had its melting point and uv in accord with those listed: NMR (CD_3OD) τ 1.47 (1 H, d, J = 8 Hz, H_6), 2.65 (5 H, s, C_6H_5), 3.71 (1 H, d, J = 8 Hz, H_5), 4.10 (1 H, d, J = 2 Hz, $H_{1'}$), 4.67 (2 H, s, CH_2), 5.73–6.03 (3 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.04–6.21 (2 H, m, $H_{5'}$); ir (KBr) 5.75, 6.01, 6.46 μ.

3-*p*-Methoxybenzylcytidine Hydrobromide (4b). To a suspension of cytidine (243 mg, 1 mmol) in 4 ml of dry dimethylacetamide was added 605 mg (3 mmol) of *p*-methoxybenzyl bromide.[17] The mixture was heated in a sealed tube at 32 °C for 72 h. To the mixture were added acetone (8 ml), ethyl acetate (80 ml), and then ether, to the point where the solution became cloudy. The solution was allowed to stand at 25 °C for 16 h. The gummy solid which deposited was triturated with ether, then worked up by preparative TLC on cellulose in 2-propanol–water (8:2). The product (R_f 0.66) was purified by recrystallization from ethanol–ethyl acetate to yield 228 mg (51%) of **4b**: mp 176–177°; λ_{max} (pH 2) (ϵ) 280 nm (13 500); λ_{max} (pH 11.5) 268 nm; NMR (CD_3OD) τ 1.47 (1 H, d, J = 8 Hz, H_6), 2.69 (2 H, d, J = 8 Hz, aromatic), 3.07 (2 H, d, J = 8 Hz, aromatic), 3.73 (1 H, d, J = 8 Hz, H_5), 4.08 (1 H, d, J = 2 Hz,

$H_{1'}$), 4.75 (2 H, s, CH_2), 5.70–6.04 (3 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 6.05–6.33 (5 H, m, OCH_3 at 6.23, $H_{5'}$); ir (KBr) 5.75, 6.03, 6.50, 6.60 μ.

3-(Benz[*a*]anthryl-7-methyl)cytidine Hydrobromide (4c). This compound was prepared by the method of Dipple et al.[4] from 300 mg (1.23 mmol) of cytidine and 450 mg (1.4 mmol) of 7-bromomethylbenz[*a*]anthracene.[18] Purification of the product was performed by preparative TLC on cellulose with 1-butanol–water (86:14). The yield of recrystallized product was 242 mg (35%): mp 177–179 °C (lit.[4] 177–179 °C); λ_{max} (MeOH) (ϵ) 260 nm (37 100), 270 (45 400), 281 (74 100), 292 (89 000), 320 (5800), 336 (8300), 353 (9800), 370 (7400), and 388 (2500); NMR (Me_2SO-d_6 + D_2O) τ 0.36–2.46 (12 H, m, aromatic and H_6), 3.50 (1 H, d, J = 8 Hz, $H_{5'}$), 3.92 (2 H, s, CH_2), 4.62 (1 H, d, J = 3 Hz, $H_{1'}$), 5.96–6.46 (5 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$); ir (KBr) 5.80, 6.00, 6.52 μ.

Preparation of 3-(Benz[*a*]anthryl-7-methyl)uridine (5) from 4c. A. Nitrous Acid. Sodium nitrite (560 mg, 8.12 mmol) was added over 30 min at 25 °C to a solution of 70 mg (0.124 mmol) of **4c** in 7 ml of aqueous acetic acid. The reaction mixture was stirred at 5 °C for 16 h. The precipitate that appeared was filtered and washed with water. This product was separated from contaminating starting material by preparative TLC on cellulose using 1-butanol–water (86:14), and recrystallized from absolute ethanol to give 21 mg (35%) of **5**: no sharp melting point; λ_{max} (MeOH) 260, 270, 280, 291, 321, 336, 352, 369, and 388 nm; NMR (Me_2SO-d_6) τ 0.4–2.60 (12 H, m, aromatic + H_6), 3.96 (2 H, s, CH_2), 4.13 (1 H, d, J = 8 Hz, H_5), 4.36 (1 H, d, J = 3 Hz, $H_{1'}$), 4.60–5.20 (3 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$), 5.90–6.60 (5 H, m, $H_{5'}$ + OH); ir (KBr) 5.82, 6.05 μ; mass spectrum *m/e* 484 (M^+); TLC on silica, R_f 0.41 (methanol–benzene, 3:7), 0.26 (acetone); TLC on cellulose, R_f 0.69 (2-propanol–water, 8:2).

Anal. Calcd for $C_{28}H_{24}N_2O_6 \cdot H_2O$: C, 66.92; H, 5.22; N, 5.58. Found: C, 66.57; H, 4.80; N, 5.71.

B. Sodium Bisulfite. A suspension of 10 mg (0.017 mmol) of **4c** in 2.5 ml of 2.26 M $NaHSO_3$ solution, pH 5.0, was stirred at 37 °C for 22 h. The pH was adjusted to 11.5 by addition of Na_2HPO_4 and NaOH, and the reaction mixture stirred for an additional 1 h. The pH was then adjusted to 1 by addition of 6 N HCl, and a stream of nitrogen was passed through to remove sulfur dioxide. NaOH was added, to change the pH to 7, and the precipitate, which contained starting material and product, was filtered. The work-up by preparative TLC was conducted in the same manner as in the nitrous acid reaction. The R_f values and uv spectrum of the product were identical with those of the product in the nitrous acid reaction. The yield (estimated spectrophotometrically) was 53%.

Preparation of 3-(Benz[*a*]anthryl-7-methyl)uridine (5) from Uridine. To a suspension of 20 mg (0.41 mmol) of sodium hydride (50% dispersion in oil) in 1 ml of dry dimethylformamide was added 100 mg (0.41 mmol) of uridine. The mixture was heated under N_2 for 3 h at 70 °C, and 158 mg (0.49 mmol) of 7-bromomethylbenz[*a*]anthracene in 2 ml of dry dimethylformamide was added. The reaction mixture was stirred under N_2 at 70 °C for 20 h, and the solvents were evaporated under vacuum. The residue was worked up by preparative TLC on silica in methanol–benzene (3:7). A crude yield of 87 mg (44%) of yellow, partly crystalline material, R_f 0.48, was obtained. A pure sample, identical in ir (KBr) and R_f with **5** preprared from **4c**, was obtained.

Reaction of Cytidine with Benzylic Bromides in Aqueous Buffer. Product Distribution Studies. To 100 mg (0.41 mmol) of cytidine dissolved in 45 ml of 0.01 M sodium acetate buffer, pH 5.5, was added 0.5 mmol of either benzyl bromide (as a solution), *p*-methoxybenzyl bromide (as a solution), or 7-bromomethylbenz[*a*]anthracene (as a suspension, in 5 ml of acetone), over a 30-min period. The reaction mixtures were stirred at room temperature for 7 days and then freeze dried. The resulting powders were extracted in methanol and worked up by preparative thin layer chromatography: on cellulose in 2-propanol–water (8:2) for the benzyl bromide reaction, on cellulose in acetonitrite–0.1 M NH_4Cl (9:1) for the *p*-methoxybenzyl bromide reaction, and on silica with methanol–benzene (3:7) for the 7-bromomethylbenz[*a*]anthracene reaction. The following are the R_f values of the marker compounds run to locate the products: **4a**, 0.45; **3a**, 0.78; **4b**, 0.25; **3b**, 0.42; **4c**, 0.25; **3c**, 0.48. The identity of each compound was confirmed by its uv spectrum and R_f on TLC in a different solvent system.

Reaction of Cytidine with Benzylic Bromides in Dimethylacetamide. Product Distribution Studies. Cytidine (20 mg, 0.8 mmol) and an approximately twofold excess of each of the benzylic halides were allowed to react for 24 h at 38 °C in dry dimethylacetamide. The reaction mixtures were worked up by preparative TLC following the procedures used in the aqueous reactions.

Reaction of Cytidine with Dimethyl Sulfate in Dimethylformamide. To a suspension of 400 mg (1.64 mmol) of cytidine in 4 ml of dry dimethylformamide was added 1.6 ml (16 mmol) of dimethyl sulfate. The mixture was heated for 45 min at 40 °C. On addition of 10.4 ml of methanol and 25 ml of ethyl acetate, a precipitate appeared. The melting point, R_f, and uv spectrum of this substance were identical with those reported for 3-methylcytidine methosulfate,[19] yield 450 mg (77%). The mother liquor was concentrated under vacuum, neutralized with dilute ammonia, and worked up by preparative TLC on cellulose in 1-butanol–water–concentrated NH_4OH (86:14:1). A number of weak bands were observed by uv, but none corresponded in R_f to an authentic marker of N^4-methylcytidine.[7]

Reaction of Cytidine with Dimethyl Sulfate in Aqueous Buffer. To a solution of 50 mg (0.21 mmol) of cytidine in 4 ml of 0.05 M sodium acetate buffer, pH 5.5, was added 0.4 ml (4.3 mmol) of dimethyl sulfate. The reaction mixture was stirred at 25 °C for 1 h, with occasional addition of NaOH to maintain the pH at 5.0. The reaction mixture was examined by TLC on cellulose in 1-butanol–water–concentrated NH_4OH (86:14:1). Spots were observed that were identified by R_f and uv as 3-methylcytidine (R_f 0.34, yield 64%) and unreacted cytidine (R_f 0.15). No spot corresponding in R_f to a marker of N^4-methylcytidine was observed.

Registry No.—**1**, 24961-39-5; **2**, 15049-50-0; **3a**, 58343-13-8; **3b**, 58343-14-9; **3c**, 58343-15-0; **4a**, 22423-32-1; **4b**, 58343-16-1; **4c**, 58343-17-2; **5**, 58343-18-3; benzylamine, 100-46-9; cytidine, 65-46-3; *p*-methoxybenzylamine, 2393-23-9; 7-aminomethylbenz[*a*]anthracene, 58343-19-4; *p*-methoxybenzyl bromide, 2746-25-0; uridine, 58-96-8; benzyl bromide, 100-39-0; dimethyl sulfate, 77-78-1.

References and Notes

(1) This investigation was supported by Grants GP-27366 from the National Science Foundation and GM-20176 from the National Institute of General Medical Sciences, National Institutes of Health. Robert Shapiro holds a Research Career Development Award (GM-50188) from the National Institute of General Medical Sciences.
(2) B. Singer, *Prog. Nucleic Acid Res. Mol. Biol.*, **15**, 219 (1975).
(3) R. Shapiro, *Ann. N.Y. Acad. Sci.*, **163**, 624 (1969).
(4) A. Dipple, P. Brookes, D. S. Mackintosh, and M. P. Rayman, *Biochemistry*, **10**, 4323 (1971).
(5) E. Kriek, *Biochim. Biophys. Acta*, **355**, 177 (1974).
(6) J. J. Fox, D. VanPraag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *J. Am. Chem. Soc.*, **81**, 178 (1959).
(7) R. Shapiro and J. M. Weisgras, *Biochem. Biophys. Res. Commun.*, **40**, 839 (1970).
(8) P. Brookes, A. Dipple, and P. D. Lawley, *J. Chem. Soc. C*, 2026 (1968).
(9) R. Shapiro and S. H. Pohl, *Biochemistry*, **7**, 448 (1968).
(10) R. Shapiro, R. E. Servis, and M. Welcher, *J. Am. Chem. Soc.*, **92**, 422 (1970).
(11) L. Sun and B. Singer, *Biochemistry*, **13**, 1905 (1974).
(12) A. Dipple and K. V. Shooter, *Biochim. Biophys. Acta*, **374**, 392 (1974).
(13) D. J. Brown in "The Pyrimidines", Supplement I, A. Weissberger and E. Taylor, Ed., Wiley, New York, N.Y., 1970, p 287.
(14) H. Mizuno, H. Okuyama, H. Hayatsu, and T. Ukita, *Chem. Pharm. Bull.*, **12**, 1240 (1964).
(15) T. Ueda and J. J. Fox, *J. Org. Chem.*, **29**, 1770 (1964).
(16) J. A. Montgomery, H. J. Thomas, and K. Hewson, *Chem. Ind. (London)*, 1596 (1965).
(17) H. Stephens and C. Weizmann, *J. Chem. Soc.*, **105**, 1152 (1914).
(18) A. Dipple and T. A. Slade, *Eur. J. Cancer*, **6**, 417 (1970).
(19) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 1348 (1962).

9(10→19)Abeo Steroids. Total Synthesis of *abeo*-Estradiol, *abeo*-Estradiol 3-Methyl Ether, and 17α-Ethynyl *abeo*-Estradiol 3-Methyl Ether

Elie Abushanab,* Daw-Yuan Lee, and William A. Meresak

Department of Medicinal Chemistry, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island 02881

William L. Duax

Medical Foundation of Buffalo, Buffalo, New York 14203

Received September 11, 1975

9(10→19)Abeo steroids combine structural features of both normal and 19-nor steroids. Starting with the known seco steroid (1) the total synthesis of the title compounds is described. Stereochemical assignments in 9(10→19)*abeo*-estradiol (13) and its 3-methyl ether (9) are made by x-ray analysis of the 17-ketone (11).

One of the outstanding classes of oral contraceptives are the 19-nortestosterone derivatives. These are used in combination with estrogens and the formulated drugs suffer from side effects.[1] Steroidal estrogens are known to have postcoital antifertility effect, which could not be separated from the estrogenic activity in primates.[2] The 9(10→19)abeo steroids[3] represent a hybrid between normal and 19-nor steroids combining structural features of both types. It is hoped that abeo estrogens would retain the antifertility properties acting as modified estrogens with reduced hormonal effects. To that end the preparation of abeo analogues of estradiol was undertaken and the results are reported here.

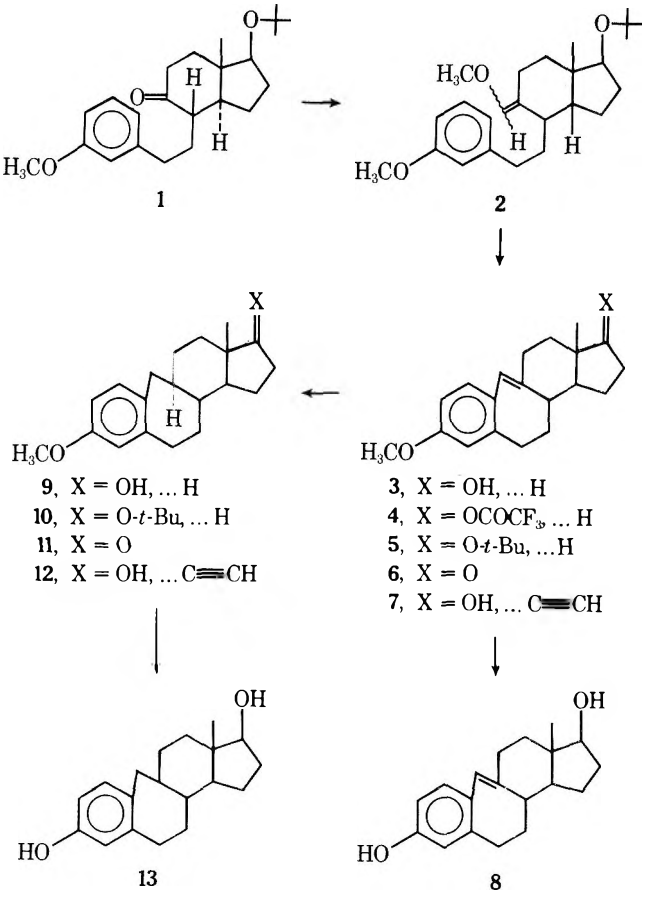
The two synthetic approaches reported[4-7] for the abeosteroid nucleus are not general and do not lend themselves to preparing various types of abeo estrogens for biological evaluation. Both methods start with naturally occurring steroids where the 19-methyl group is functionalized and is subsequently incorporated into ring B by a rearrangement. Our total synthetic approach started with the known optically active seco steroid (1)[7,8] (Scheme I). Condensation of this ketone with the ylide derived from methoxymethylenetriphenylphosphonium chloride resulted in the formation of the enol ether (2) which consisted of a mixture of two geometric isomers as evidenced by the methoxy group signals in the ^{1}H NMR spectrum. Cyclization of 2 to the abeo-steroid nucleus was effected either by trifluoroacetic acid or *p*-toluenesulfonic acid. While the former furnished a mixture of the 17β-alcohol (3) and its trifluoroacetic ester (4), the latter furnished the uncleaved 17-*tert*-butyl ether (5).

Evidence for the cyclized structure rested upon spectral data as well as elemental analysis. The ultraviolet spectrum had a maximum similar to that reported for substituted styrenes.[9] In addition, the aromatic pattern in the ^{1}H NMR spectrum was similar to related steroid structures.[10] These data rule out cyclization at the position ortho to the methoxy group.

Oxidation of the alcohol (3) with chromic acid and 3,5-dimethylpyrazole[11] furnished the corresponding 17-ketone (6). This upon treatment with lithium acetylide-ethylenediamine complex[12] in dioxane gave the corresponding 17α-ethynyl derivative (7). Boron tribromide treatment of 5 resulted in the estratetraene (8).

Catalytic hydrogenation of 3 over palladium on charcoal resulted in the uptake of 1 mol of hydrogen and furnished a mixture of two isomeric compounds at C-9; the major isomer was suspected to be the 9α isomer (9) by analogy with results obtained on the steroid nucleus.[7] However, when 3 was reduced with sodium in liquid ammonia[13] a single product was isolated which was identical with the major isomer obtained earlier. Similarly, reduction of 5 furnished the corresponding dihydro compound (10) as the only product in good yield.

Scheme I



Confirmation of the stereochemistry at C-9 came from x-ray analysis of the 17-keto derivative (11) (vide infra). Treatment of 11 with lithium acetylide–ethylenediamine complex gave 17α-ethynyl 9(10→19)*abeo*-estradiol methyl ether (12). 9(10→19)*abeo*-Estradiol was obtained by simultaneous cleavage with boron tribromide of the 3-methyl and 17-*tert*-butyl ethers in compound 10.

X-Ray Analysis of Compound 11. Single crystals were grown by evaporation of a petroleum ether–ethanol solution. The crystal data follow: space group $P2_1$, a = 13.424 Å, b = 8.847 Å, c = 7.172 Å, β = 91.26°, V = 851.5 Å^3. The intensities of 2619 diffraction spectra were measured, of

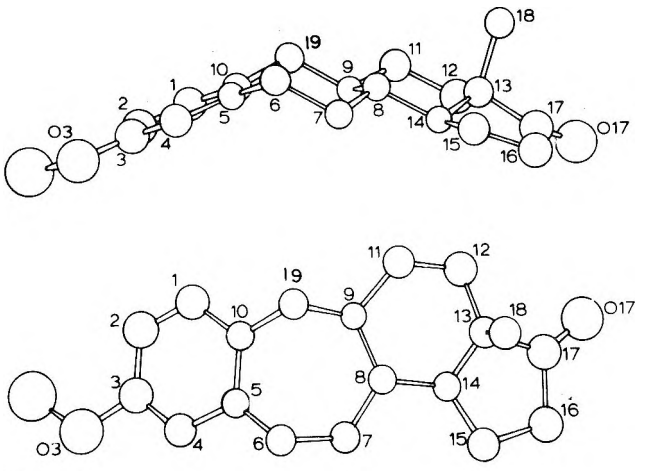


Figure 1.

which 1036 had intensity greater than twice the background. The crystal structure was solved by direct methods.[14,15] The structure was refined by full-matrix least-squares techniques and all hydrogen atoms were located in Fourier difference syntheses. The final reliability index (R) was 5.7%. The α configuration of the hydrogen substituent at C-9 was unambigously defined as illustrated in Figure 1. A complete structure report will be published elsewhere.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Optical rotations were obtained on a Perkin-Elmer 141 polarimeter. ^{1}H NMR spectra were determined on a Varian A-60 or on a JEOLCO C-60-HL spectrometer using $CDCl_3$ and Me_4Si. Mass spectral fragmentations were obtained from either a Perkin-Elmer RMV-6E or CEC 24-104 mass spectrometer. Microanalyses were performed by Microanalysis, Inc., Marshallton, Del. Compounds **2**–**13** had acceptable carbon and hydrogen analyses. All evaporations were carried out in vacuo using a water aspirator and solutions were dried over anhydrous magnesium sulfate. Column chromatography utilized Brinkmann silica gel 60 (70–230 mesh ASTM).

(1*S*,3a*S*,4*S*,7a*S*)-1-*tert*-Butoxy-5-methoxymethylene-4-[2-(3-methoxyphenyl)ethyl]-7a-methylhexahydroindan (2). Methoxymethylenetriphenylphosphonium chloride (2.5 g, 7.3 mmol) was suspended in anhydrous ether (100 ml) under a stream of nitrogen. The suspension was cooled to −35 °C and phenyllithium (1.7 M, 4.23 ml) was introduced. A red color was formed instantly. After stirring at that temperature for 0.5 h, an ether solution (15 ml) of the ketone **1** (1.12 g, 3.0 mmol) was introduced and the reaction mixture was allowed to stir at −35 °C for 0.5 h, after which it was allowed to warm up to room temperature. Water (50 ml) was then added and the organic layer was separated and dried. The residue obtained after evaporation was placed on a dry silica gel column. Hexane elution furnished the product as an oil (0.98 g, 80%): NMR δ 0.98 (3 H, s), 3.2–3.5 (1 H, m), 3.53–3.56 (3 H, singlets), 3.78 (3 H, s), 5.83 (1 H, m), 6.66–7.42 (4 H, m).

(+)-17β-Hydroxy-3-methoxy-9(10→19)*abeo*-estra-1,3,5(10),9(19)-tetraene (3) and 3-Methoxy-17β-trifluoroacetoxy-9(10→19)*abeo*-estra-1,3,5(10),9(19)-tetraene (4). The enol ether (**2**, 110 mg, 0.28 mmol) was dissolved in trifluoracetic acid (1.0 ml) and the resulting dark solution was allowed to stand at room temperature for 0.5 h. Water (10 ml) was added and the solution was neutralized with aqueous sodium hydroxide. Ether extraction gave a gum (98 mg) whose thin layer chromatographic analysis (ether–hexane, 4:6) showed two spots, the upper minor compound (R_f 0.9) and a lower major spot (R_f 0.3). The pure compounds were obtained by column chromatography eluting with a 1:1 mixture of ether–hexane and collecting 10-ml fractions. Fraction 2 contained compound **4** (20 mg, 17%): mp 168–170 °C; NMR δ 1.0 (3 H, s), 4.5–5.0 (1 H, m), 3.78 (3 H, s), 6.3 (1 H, m), 6.5–7.1 (3 H, m).

Fractions 3–7 contained the parent alcohol **3** (80 mg, 95%): mp 90–92 °C; $[\alpha]^{25}$D + 3.85° (c 0.26, $CHCl_3$); NMR δ 0.83 (3 H, s), 3.33–3.75 (1 H, m), 3.7 (3 H, s), 6.18 (1 H, m), 6.52–7.1 (3 H, m); uv (EtOH) λ_{max} 270 nm (log ϵ 4.29).

In later experiments the reaction mixture was treated with 10% aqueous methanolic sodium hydroxide with subsequent isolation of the alcohol **3** only.

(+)-17β-*tert*-Butoxy-3-methoxy-9(10→19)*abeo*-estra-1,3,5(10),9(19)-tetraene (5). To a solution of **2** (5.07 g, 13 mmol) in benzene (100 ml) was added a catalytic amount of p-toluenesulfonic acid (100 mg) and the solution was refluxed for 0.5 h. The reaction mixture was evaporated to dryness and the residue was dissolved in ether (300 ml). The ether solution was washed once with water, dried, and evaporated to dryness to give a yellowish gum (4.2 g, 90%). The analytical sample was obtained from methanol: mp 66–69 °C; $[\alpha]^{25}$D +45.63° (c 1.03, $CHCl_3$); NMR δ 0.87 (3 H, s), 1.11 (9 H, s), 4.5–5.0 (1 H, m), 3.7 (3 H, s), 6.18 (1 H, m), 6.52–7.1 (3 H, m).

(+)-3-Methoxy-9(10→19)*abeo*-estra-1,3,5(10),9(19)-tetraen-17-one (6). 3,5-Dimethylpyrazole (580 mg) was added to a suspension of chromic acid (600 mg) in methylene chloride (40 ml), and the mixture was stirred at room temperature, under nitrogen, for 15 min. To this solution was added the alcohol **3** (617 mg, 2 mmol) dissolved in methylene chloride (10 ml) and the resulting mixture was stirred at room temperature for 0.5 h. Evaporation of the organic solvent was followed by ether extraction. The concentrated extract was passed through a short silica gel column (5% ether–hexane) to give a gum (415 mg, 70%). The analytical sample was obtained from ether–hexane; mp 154–156 °C, $[\alpha]^{25}$D +156.00° (c 0.605, $CHCl_3$).

(+)-17α-Ethynyl-3-methoxy-9(10→19)*abeo*-estra-1,3,5(10),9(19)-tetraen-17-ol (7). To a saturated solution of acetone-free acetylene in dioxane (20 ml) was added, with stirring, lithium acetylide–ethylenediamine complex (1.1 g) followed by a solution of the ketone **6** (207 mg, 0.7 mmol) in anhydrous dioxane (10 ml). During the addition and for 2 h thereafter a stream of acetone-free acetylene was passed through the reaction mixture. Stirring was then continued in a closed system for 2 days. An aqueous solution of ammonium chloride was added slowly and the aqueous layer was extracted with ether several times. The combined extracts were dried and evaporated to dryness to give a brown semisolid (150 mg) which gave the analytical sample upon crystallization from methanol–water: mp 167–169 °C; $[\alpha]^{25}$D +37.140° (c 0.14, $CHCl_3$); ir (KBr) 3500 (OH), 3340 cm^{-1} (C≡CH); mass spectrum m/e 322 (M^+), 296 ($M^+ - C_2H_2$), 187.

(+)-9(19)-Dehydro-9(10→19)*abeo*-estradiol (8). A solution of compound **5** (360 mg, 1.0 mmol) in methylene chloride (10 ml) was cooled in a dry ice–acetone bath and was treated with boron tribromide (0.4 mg). The reaction mixture was gradually warmed up to room temperature and was stirred at this temperature for 1 h. Water was added and the organic layer was separated, dried, and evaporated to dryness to give a gum which consisted of a mixture of two compound (TLC). The lower spot was isolated by dry column chromatography (ether–hexane, 1:1) (153 mg, 54%). The analytical sample was obtained from acetone–hexane: mp 224–230 °C; $[\alpha]^{25}$D +60.11° (c 0.18, MeOH); mass spectrum m/e 284 (M^+), 266 ($M^+ - H_2O$), 145.

(+)-9(10→19)*abeo*-Estradiol 3-Methyl Ether (9). A solution of the alcohol **3** (1.65 g, 5.5 mmol) in methanol (200 ml) was hydrogenated over 10% palladium on charcoal (0.5 g) in a Parr apparatus at 40 psi overnight. Filtration of the catalyst and evaporation gave a solid (1.4 g) which consisted of a mixture of two compounds. Column chromatography of the residue using ether–hexane (1:1) furnished the major compound (783 mg), mp 119–120 °C.

The same compound was obtained by hydrolysis of the *tert*-butyl ether **10** with trifluoracetic acid as described for the preparation of **3**: $[\alpha]^{25}$D +23.14° (c 0.60, $CHCl_3$); NMR δ 0.83 (3 H, s), 3.5–3.7 (1 H, m), 3.78 (3 H, s), 6.52–7.3 (3 H, m).

(+)-17β-*tert*-Butoxy-3-methoxy-9(10→19)*abeo*-estra-1,3,5(10)-triene (10). A solution of compound **5** (211 mg, 0.6 mmol) in dry tetrahydrofuran (40 ml) was added with stirring to a solution of sodium (138 mg, 6 mmol) in liquid ammonia (100 ml). After stirring for 5 min, an additional amount of sodium (138 mg) was added and the stirring was continued for 0.5 h. Ammonium chloride (1.0 g) was added in small portions. After evaporation of ammonia, water (15 ml) was added and the solution was extracted with ether. Evaporation of the dried ether extract gave a crystalline residue (218 mg, 100%). Recrystallization from methanol gave the analytical sample: mp 122–126 °C; $[\alpha]^{25}$D +52.69° (c 0.99, $CHCl_3$); mass spectrum m/e 356 (M^+), 300 ($M^+ - C_4H_8$); NMR δ 0.76 (3 H, s), 1.11 (9 H, s), 3.0–3.3 (1 H, m), 3.75 (3 H, s), 6.52–7.1 (3 H, m).

(+)-9(10→19)*abeo*-Estrone 3-Methyl Ether (11). Jones reagent (1 ml) was added dropwise to a cooled solution of the alcohol **9** (157 mg, 0.52 mmol) in acetone (30 ml). Stirring was continued

for another 20 min. Evaporation of acetone was followed by partitioning the residue between chloroform and water followed by the usual work-up. Filtration of the residue on a silica gel column (1:1 ether–hexane) gave the compound (62 mg, 40%): mp 152–153 °C; $[\alpha]^{25}D$ +120.47° (c 1.07, $CHCl_3$); NMR δ 0.92 (3 H, s), 3.73 (3 H, s), 6.52–7.1 (3 H, m).

(+)-17α-Ethynyl-9(10→19)*abeo*-estradiol 3-Methyl Ether (12). The procedure employed here is essentially the same as that described for the preparation of **7**. Thus the ketone **11** (570 mg, 1.9 mmol) was treated with lithium acetylide–ethylenediamine complex (3.0 g) in anhydrous dioxane (15 ml). The product was obtained from methanol–water (315 mg, 51%): mp 154–156 °C $[\alpha]^{25}D$ +5.52° (c 1.31, $CHCl_3$); NMR δ 0.93 (3 H, s), 2.5 (1 H, s), 3.8 (3 H, s), 6.55–7.1 (3 H, m).

(+)-9(10→19)*abeo*-Estradiol (13). Although this compound was prepared from the alcohol **9**, direct hydrolysis of compound **10** gave better yields. Thus, under similar reaction conditions to those reported for the preparation of **8**, compound **10** (48 mg, 0.13 mmol) was treated with boron tribromide (0.1 ml) in methylene chloride (5 ml). The work-up furnished a residue (29 mg, 78%) which gave the analytical sample upon crystallization from methanol: mp 234–238 °C; ir (KBr) 3550, 3250 cm^{-1}; mass spectrum *m/e* 286 (M^+).

Acknowledgment. This work was supported by a contract from the National Institutes of Child Health and Human Development, NO1-HD-2-2709. We are grateful to Drs. Gabriel Saucy and Noal Cohen of Hoffmann-La Roche for providing us with generous gifts of valuable intermediates. The able technical assistance of Mr. August J. Zabbo is also acknowledged.

Registry No.—**1**, 53016-36-7; **2**, 58281-62-2; **3**, 58281-63-3; **4**, 58281-64-4; **5**, 58281-65-5; **6**, 58281-66-6; **7**, 58281-67-7; **8**, 58281-68-8; **9**, 58281-69-9; **10**, 58281-70-2; **11**, 58281-71-3; **12**, 58281-72-4; **13**, 58281-73-5; methoxymethylenetriphenylphosphonium chloride, 4009-98-7.

References and Notes

(1) R. Doll and M. P. Vessey, *Br. Med. Bull.*, **26**, 33 (1970).
(2) J. P. Bennett, "Chemical Contraception", Columbia University Press, New York, N.Y. 1974, pp 101–107.
(3) The use of the prefix abeo in the rest of the paper refers to 9(10→19) abeo.
(4) S. M. Kupchan and E. Abushanab, *Tetrahedron Lett.*, 3075 (1965).
(5) S. M. Kupchan, E. Abushanab, K. T. Shamasundar, and A. W. By, *J. Am. Chem. Soc.*, 89, 6327 (1967).
(6) F. Kohen, L. K. Lala, W. VanBever, and R. E. Counsell, *Chem. Commun.*, 347 (1969).
(7) F. Kohen, W. VanBever, and R. E. Counsell, *J. Org. Chem.*, **35**, 2272 (1970).
(8) N. Cohen, B. L. Banner, W. F. Eichel, D. R. Parrish, G. Saucy, J. M. Cassal, W. Meier, and A. Furst, *J. Org. Chem.*, **40**, 681 (1975).
(9) U. Eder, G. Hatfer, J. Ruppert, G. Sauer, and R. Wiechert, German Offen. 2 253 088 (1974).
(10) D. E. Bays, R. C. Cookson, and S. MacKenzie, *J. Chem. Soc. B*, 215 (1967); W. E. Bachmann and J. Controulis, *J. Am. Chem. Soc.*, **73**, 2636 (1951).
(11) Varian NMR Spectra Catalogue, Spectrum No. 343.
(12) E. J. Corey and G. W. J. Fleet, *Tetrahedron Lett.*, 4499 (1973).
(13) T. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965).
(14) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughs, B. J. McLoughlin, J. Sidall, and H. Smith, *J. Chem. Soc.*, 5072 (1963).
(15) G. T. DeTitta, J. W. Edmonds, D. A. Langs, and H. Hauptman, *Acta Crystallogr., Sect. A*, in press.
(16) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

Agaridoxin, a Mushroom Metabolite. Isolation, Structure, and Synthesis

Albert Szent-Gyorgyi

Laboratory of the Institute for Muscle Research, Marine Biological Laboratory, Woods Hole, Massachusetts 02543

Rack H. Chung, Michael J. Boyajian, and Max Tishler*

Wesleyan University, Middletown, Connecticut 06457

Byron H. Arison, Erwin F. Schoenewaldt, and James J. Wittick

Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

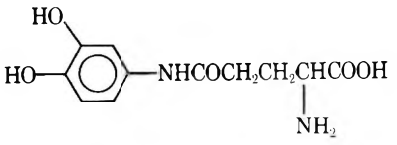
Received November 4, 1975

Agaridoxin, a strongly autoxidizable substance, was isolated from the common mushroom *Agaricus campestris*. Its structure was established, largely by NMR, mass spectroscopy, uv spectroscopy, and polarography, to be 3,4-dihydroxy-(γ-L-glutamyl)anilide (**1**). This metabolite was synthesized starting with the reaction between 3,4-(isopropylidenedioxy)aniline (**5**) and *N*-phthaloylglutamic anhydride (**6**). The resulting substituted phthalimide (**7**) was converted into (γ-L-glutamyl)-3,4-(isopropylidenedioxy)anilide (**9**) by treatment with hydrazine in ethanol. Removal of the isopropylidene protecting group by use of boron trichloride gave agaridoxin in good yield.

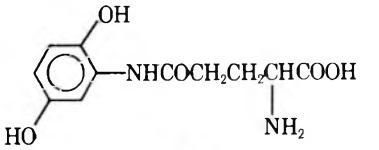
The isolation of 4-hydroxy(γ-L-glutamyl)anilide from the gill tissue of *Agaricus bisporus*,[1] its enzymatic conversion to the sulfhydryl enzyme inhibitor, *N*-(γ-L-glutamyl)amino-3,4-benzoquinone,[2] and the direct isolation of the quinone from this mushroom have recently been described. We wish to report the isolation, identification, and confirmatory synthesis of the putative intermediate, 3,4-dihydroxy(γ-L-glutamyl)anilide (**1**), obtained from the very closely related species *Agaricus campestris*. Our interest in **1** resulted from a long and continual search by one of us (A.S.-G.) for compounds with low electron affinity[3] which would autoxidize readily and would be expected to suppress cell division. Since we observed that aqueous extracts of *Agaricus campestris* (var. *bifidis*) autoxidized rapidly, the isolation of the substance responsible for this reaction was undertaken. The autoxidation was markedly promoted by manganese salts with the development of a red color, a reaction used to follow the isolation of the mushroom factor. We now wish to report on the isolation, identification and synthesis of this substance which we named agaridoxin.

Agaridoxin was isolated from a methanol extract of the powdered mushroom by treating with lead acetate, separating from insolubles, concentrating to dryness, and subjecting the residue in aqueous solutions to Sephadex G10 chromatography.

Primary identification studies led us to believe that agaridoxin was a dihydroxy(γ-glutamyl)anilide represented by **1** or **2**. This conclusion was based on NMR, gas–liquid chro-

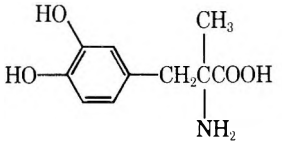


1

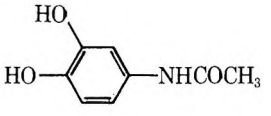


2

matography–mass spectrographic analysis, ir, and elemental analyses. The NMR spectral parameters of agaridoxin in D_2O (Varian HA-100 spectrometer) are listed in Table I. Signals at δ 3.82, 2.57, and 2.24 indicated the presence of a $>CHCH_2CH_2$–moiety. The suspicion that this grouping represented a glutamyl residue was virtually confirmed when it was observed that the methine signal exhibited a pH dependency typical of the α proton in amino acids. The ir spectrum showed a sharp absorption at 3380 cm^{-1} indicating a peptide linkage. The aromatic resonances between δ 6.81 and 7.02 indicated a 1,2,4-trisubstituted system having one or more electron-donating substituents. Two of these were tentatively considered to be hydroxyls on the basis of the chemical shifts of the aromatic protons and the ease of autoxidation shown by the compound. Since the disposition of the hydroxyl groups would not be definitively assigned from the NMR spectrum, we resorted to comparisons of the polarographic and uv spectrographic behavior of agaridoxin with those of the model compounds L-3,4-dihydroxy-α-methylphenylalanine (**3**) and 3,4-dihydroxyacetanilide (**4**) and *p*-hydroquinone. Polarograms of agaridoxin and the model compounds in pH 5 acetate buffer are shown in Table II. Clearly, agaridoxin resembles 3,4-dihydroxyacetanilide in its oxidation properties. The uv comparison of agaridoxin and **4** in Table III confirms assignment of the hydroxyl groups in the 3,4 positions.



3



4

The combined gas–liquid chromatography and mass spectrometry was carried out on the tetratrimethylsilyl derivative of agaridoxin which was prepared by heating a mixture of **1** and bis(trimethylsilyl)trifluoroacetamide in acetonitrile at 105 °C for 15 min. Only one component was observed on the gas chromatogram. This component gave a mass spectrum with strong signals at *m/e* 614 [M^+, corresponding to the molecular weight of the tetratrimethylsilyl (TMSi) derivative of **1** with fragmentation peaks at *m/e* 497 (CO_2TMSi), 396 [$CH(CO_2TMSi)NHTMS$)] and the base peak *m/e* 383 [M − 231, loss of $CH_2{=}C(CO_2TMSi)NHTMSi$], and 571 ($M^+ - CH_3CO$), fragments expected to be lost from TMSi derivatives of amino acids.

Confirmation of the glutamyl moiety was obtained from the acid hydrolysate of agaridoxin (6 N HCl, 111 °C, 20 h) by Spinco analysis. Thin layer chromatography in two systems showed glutamic acid to be the sole ninhydrin-positive amino acid in the molecule. The acid hydrolysate, passed through a column of Pittsburg OL Carbon to remove aromatics, was compared by optical rotatory dispersion with a sample of L-glutamine that had been similarly hydrolyzed and treated. The ORD curves were essentially identical. Thus, agaridoxin contains a glutamine moiety with the natural L configuration and is 3,4-dihydroxy(γ-L-glutamyl)anilide (structure **1**).

Table I. NMR Parameters and Assignments for Agaridoxin (in D_2O)

δ^a	Multiplicity[b]	Assignment
7.02	(d) (J = 2.0)	Aromatic
6.89	(d) (J = 8.5)	Aromatic
6.81	(d,d) (J = 8.5, 2.0)	Aromatic
3.82	(t) (J = 6.0)	CH
2.57	(t) (J = 7.5)	$CH_2C{=}O$
2.24	(q) (J = 6.0, 7.5)	CH_2C

[a] Relative to internal DSS. [b] d = doublet, t = triplet, q = quartet.

Table II. Polarographic Data for 1, 3, 4, and Hydroquinone

Compd	$E_{1/2}$, V vs. SCE
3	0.24
Agaridoxin	0.18
4	0.18
p-Hydroquinone	0.13

Table III. Uv Data for 1 and 4

	λ_{max}, nm	ϵ	λ_{max}', nm	ϵ'	ϵ'/ϵ
1	285	4240	248	9670	2.28
4	285	3460	246	8100	2.34

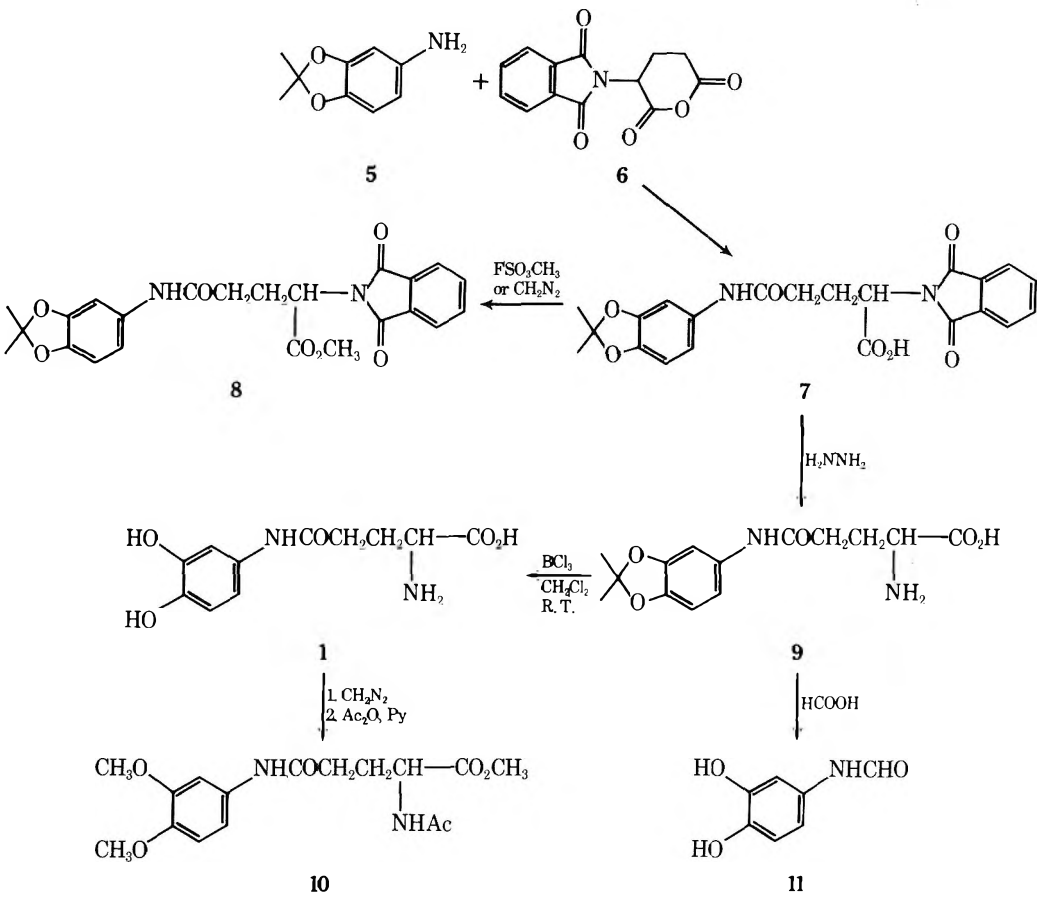
The synthesis of agaridoxin involves the formation of a peptide bond between the γ-carboxyl group of glutamic acid and the amino group of 4-aminopyrocatechol. This scheme entails the usual problems of peptide synthesis: protection of some functional groups, peptide formation, and removal of the protective groups. The starting materials of our successful synthesis were isopropylidene-3,4-dioxyaniline (**5**) and the anhydride of *N*-phthaloyl-L-glutamic acid (**6**) and the scheme that we employed is outlined in Scheme I. The anhydride **6** was prepared by acetic anhydride[4] treatment of *N*-phthaloyl-L-glutamic acid which in turn was prepared from *N*-carboethoxyphthalimide and L-glutamic acid by the elegant method of Nefkens, Tesser, and Nivard,[5] a sequence shown by them to take place without significant racemization.

The reaction of *N*-phthaloyl-DL-glutamic anhydride with various nucleophilic reagents has been extensively investigated,[4-7] and the results indicate that cleavage of the anhydride ring to form γ derivatives is a general occurrence. Thus, the condensation of the aniline **5** and the anhydride **6** in ether at room temperature provided **7** in 90% yield. Treatment of this acid **7** with methyl fluorosulfonate or diazomethane yielded a methyl ester **8**, which gave a three-proton singlet at δ 3.70 in the NMR spectrum. In addition, the character of the compound was further verified by the appearance of the corrected molecular ion (*m/e* 438) in the mass spectrum as well as by its elemental analysis.

Removal of the phthaloyl group was accomplished by boiling an ethanol solution of hydrazine hydrate[6] and the phthaloyl acid **7** for 2 h. The amino acid **9** was readily separated from the reaction mixture in 71% yield.

Removal of the isopropylidene protecting group by treatment with acidic, aqueous, or alcoholic medium is generally a facile process. However, this process could not be applied in our case, owing to the sensitive amide group. Ordinary conditions for hydrolysis of the acetal group also brought about cleavage of the amide portion of the molecule. It is worthy of note that *N*-formylaminopyrocatechol was obtained

Scheme I



when the amino acid **9** was refluxed with 97% formic acid for 0.5 h, and that even at room temperature the amide group was cleaved. Success was finally achieved by use of boron trichloride, a reagent proving to be a useful Lewis acid,[8,9] and superior in some instances to boron trifluoride and boron tribromide. The latter two reagents gave intractable mixtures in our case.

Selective cleavage of aromatic methyl ethers with boron trichloride has been utilized by several workers.[10-12] Likewise, the use of boron trichloride as a reagent for the cleavage of cyclic acetals of hexitols has been studied.[13] However, removal of an isopropylidene group with this reagent has not been reported.

Amino acid **9** on treatment with boron trichloride in methylene chloride at room temperature followed by workup with minimum air exposure yielded agaridoxin in 80% yield. The synthetic product was identical in physical properties, including spectral behavior, with the natural substance. In addition, the *N*-acetyl dimethoxy methyl ester **10** obtained by treating the synthetic agaridoxin with diazomethane followed by reaction with acetic anhydride and pyridine was identical with the compound obtained from the natural agaridoxin by the same sequence of reactions.

It is interesting to note that while agaridoxin showed no antitumor activity in our animal tests γ-L-glutaminyl-4-hydroxybenzene and γ-L-glutaminyl-3,4-benzoquinone were recently found to have interesting biological activities.[14] They appear to be involved in the initiation and maintenance of dormancy of the mushroom spores and to possess modest bactericidal action against a variety of microorganisms.

Experimental Section

Melting points were determined with a Mel-Temp apparatus and are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer 137 spectrophotometer; only bands characteristic of the functional groups present are reported. The nuclear magnetic resonance (NMR) spectra were obtained with a Varian Model A-60 and HA-100 spectrometer. Tetramethylsilane was employed as the internal reference, except where noted. Ultraviolet (uv) spectra were taken on a Perkin-Elmer 202 spectrophotometer. GLC–mass spectra were carried out on a LKB 9000 instrument and the polarography was done with a Melabs Pulse Polarographic Analyzer, Model CPA3.

Except where noted solvents were reagent grade and were used as received. In all work-up procedures, the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

Isolation of Agaridoxin (1). Fresh mushrooms, *Agaricus campestris*, were frozen by storage in a deep freeze refrigerator, pulverized using a hammer–mincer, and dropped directly into methanol (90 l. for 45-kg lots) containing 0.1% formic acid. The brei was homogenized by agitation and the solid was then separated on a drum centrifuge lined with a wire net and cheese cloth. To the somewhat turbid filtrate, 2 l. of 50% lead acetate was added and the precipitate was allowed to settle overnight.

The supernatant was clarified on a Sharples supercentrifuge, and the sediment filtered on a large Büchner funnel. The combined clear filtrates were concentrated at reduced pressure to 4.5 l. on a thin-film evaporator and further concentrated on a flash evaporator to 1 l. Three volumes of methanol were added to the aqueous concentrate and the resulting solution stored overnight at 0 °C. The supernatant was decanted, and the sediment filtered and washed with methanol. To the combined filtrates and washings was added 500 ml of 50% lead acetate and enough sodium hydroxide to bring the pH of the liquid to 8.5. The precipitate was quickly separated on a laboratory model Sharples and the pH of the liquid adjusted to 3–4 with sulfuric acid. After storage at 0 °C overnight, the clear liquid was concentrated to a sticky gum. To eliminate excess acid (acetic and formic), the residue was stored in a vacuum desiccator containing NaOH pellets. Eventually the dried material was dissolved in a small volume of water and passed twice through a Sephadex G10 column. The active material was contained in the fourth void volume. The elution was followed by adding 1 drop of 0.1 M manganese acetate solution to 0.5-ml samples and then neutralizing the solution with sodium bicarbonate. The developing red color indicated the presence of agaridoxin. The eluate was concentrated and the solid residue was recrystallized by dissolving in a minimum of water and adding several volumes of

methanol, mp 218–221 °C. About 3 g was obtained from 1 ton of mushrooms.

Agaridoxin was obtained as a grayish-white powder which darkened on storage in air. It gives a beautiful blue color with ferric chloride. NMR data are summarized in Table I; ir, sharp absorption at 3380 cm^{-1} (CONH–), broad band 3200–2400 cm^{-1}, multiple absorption 1650–1500 cm^{-1}. The hydrochloride showed absorption at 1720 cm^{-1} (COOH) and bands at 1640–1660 and 1510 cm^{-1} (CONH–); polarographic and uv data are summarized in Tables II and III. For mass spectral studies a sample was silylated (0.5 mg heated in a mixture of 50 μl of bis(trimethylsilyl)trifluoroacetamide and 50 μl of acetonitrile at 105 °C for 15 min) and examined by combined gas–liquid chromatography and mass spectrometry with the LKB Model 9000 instrument; GLC operating conditions, 6 ft × 3.5 mm i.d. glass spiral column, 2% SE-30 stationary phase on 100–120 mesh acid-washed and silanized Gas Chrom T, 180 °C, 25 ml/min flow rate; MS operating conditions, 70 eV ionizing potential, 270 °C ion source temperature, 50-μA filament current, 3.5-kV accelerating potential; MS data in discussion section.

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.52; N, 11.03. Found: C, 51.59; H, 5.58; N, 10.92.

3,4-Dihydroxyacetanilide.[15] A solution of 4-nitropyrocatechol (4.49 g, 32.2 mmol) in 50 ml of absolute ethanol was hydrogenated at 40 psig over 0.25 g of 5% Pd/C. Hydrogenation was complete in 1 h. The mixture was filtered from the catalyst and evaporated in vacuo to an oily residue. Acetic anhydride (3.64 ml) was added to the residue and allowed to stand for 1 h at room temperature. The reaction mixture was quenched by addition of 3 ml of water, evaporated to an oil in vacuo, and dissolved in 30 ml of water containing 0.2 g of Na_2SO_3 to yield 4.3 g (80%) of dark but well-formed crystals. Recrystallization from 25 ml of water containing 0.4 g of Na_2SO_3 and using 0.6 g of Darco G-60 for decolorization yielded 2.768 g (51.5% overall yield) of 3,4-dihydroxyacetanilide (mp 171–173 °C with softening at 167 °C) with satisfactory elemental analysis. The NMR spectrum confirmed the absence of *O*-acetate and the aromatic portion of the spectrum was superimposable on that of agaridoxin.

***N*-Phthaloyl(γ-L-glutamyl)-3,4-(isopropylidenedioxy)anilide (7).** To a partially dissolved solution of 26 g (0.1 mol) of *N*-phthaloyl-L-glutamic anhydride[4,5,16] (**6**) in 500 ml of absolute ether was added dropwise a solution of 17 g (0.1 mol) of 3,4-(isopropylidenedioxy)aniline[17] (**5**) in dry ether at room temperature. The mixture was stirred at room temperature for 40 min. The yellowish solid was filtered and recrystallized from ethyl acetate and dimethoxyethane to give 32 g (76%) of pale yellow solid: mp 132–134 °C; NMR ($CDCl_3$–NMe_2SO-d_6, 1:1) δ 1.6 (6 H, s), 2.45 (4 H, m), 4.95 (1 H, m), 6.75 and 7.1 (3 H, m), and 7.87 (4 H, s).

Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.27; H, 15.15; N, 6.61.

***N*-Phthaloyl(γ-L-glutamyl)-3,4-(isopropylidenedioxy)anilide Methyl Ester (8).** Equimolar amounts of the acid **7** and methyl fluorosulfonate were refluxed for 1 h in ethanol. Following the work-up, a quantitative yield of ester **8** was obtained. Recrystallization from benzene gave a yellow solid: mp 148–149 °C; NMR ($CDCl_3$) δ 1.6 (6 H, s), 2.5 (4 H, m), 3.75 (3 H, s), 6.9 (1 H, s), 6.4 and 7.1 (3 H, m), and 7.75 (4 H, narrow multiplet); mass spectrum (70 eV) *m/e* 438 (parent).

(γ-L-Glutamyl)-3,4-(isopropylidenedioxy)anilide (9). To a solution of 7.58 g (0.179 mol) of purified phthaloyl acid **7** in 300 ml of absolute ethanol was added 1 g (0.2 mol) of hydrazine hydrate at room temperature. The reaction mixture was refluxed for 2 h, and ethanol was removed on a rotary evaporator. The white residue was taken up in 60 ml of 5% HCl at ice bath temperature and after standing for 30 min, the solid *N,N'*-phthaloyl hydrazide was separated by filtration. The filtrate was made alkaline with ammonium hydroxide solution at 0 °C to give 3.75 g (71%) of amino acid **9**, mp 185–191 °C. An analytical sample was recrystallized from water–methanol: mp 194–195 °C; mass spectrum (based on trisilylated compound of amino acid **5**) *m/e* (rel intensity) 510 (7), 495 (13.4), 393 (42.5), 292 (39), 279 (100), 164 (17), 116 (22.8), 73 (74).

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.52; H, 6.03; N, 10.07.

3,4-Dihydroxy-*N*-formylaniline (11). A mixture of 400 mg (1.36 mmol) of amino acid acetal **9** and 7 ml of 97% formic acid was refluxed for 0.5 h. The mixture was allowed to cool and was then poured over crushed ice. Thorough extraction with ethyl acetate and concentration in vacuo yielded 116 mg (55%) of *N*-formyl product as a grayish solid which became crystalline on triturating with ethyl acetate: mp 182–183 °C; NMR (Me_2SO-d_6) δ 6.7 (2 H, m), 7.24 (1 H, s), 8.3 (2 H, m), 9.5 (1 H, s); mass spectrum (70 eV) *m/e* (rel intensity) 153 (100), 125 (50), 79 (35); uv λ_{max} (H_2O) 285 nm (ε 3650) and 247 (8960).

Agaridoxin (3,4-Dihydroxy-(β-L-glutamyl)anilide, 1). Boron trichloride (tenfold excess) was bubbled into methylene chloride (50 ml) at 0°C. To this solution was added in portions 1 g (0.0034 mol) of acetal **9**. The suspension was stirred for 4 h at room temperature. Most of the excess boron trichloride was then removed by blowing nitrogen gas into the reaction flask. Finally, solvent was removed on a rotary evaporator until a completely dry white residue remained in the flask. Methanol was added at 0 °C and was removed in vacuo at room temperature. The darkish residue was taken up in 95% ethanol and basified with triethylamine or ammonium hydroxide solution. The solvent was then removed under reduced pressure at room temperature and the residue was triturated with 95% ethanol to yield 690 mg (80%) of agaridoxin as a grayish solid (mp 215–219 °C). This was recrystallized by dissolving in a minimum amount of water containing 100 mg of sodium bisulfite, adding an equal volume of methanol, and chilling in a refrigerator giving a grayish solid: mp 220–221 °C, mixture melting point with natural unchanged; NMR (D_2O, DSS as internal reference) δ 2.24 (2 H, q), 2.57 (2 H, t), 3.82 (1 H, t), 6.81 (1 H, dd), 6.89 (1 H, dd), 7.02 (1 H, d); uv λ_{max} (H_2O) 285 nm (ε 4240) and 248 (9670).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.87, H, 5.49; N, 10.79.

The NMR of the synthetic preparation was identical with that of the natural product. The NMR spectrum of a 1:1 mixture of the two solutions was indistinguishable from the individual curves.

***N*-(4-Acetylamino-4-carbomethoxybutyryl)-3,4-dimethoxyaniline (10).** To 200 mg of agaridoxin solid was added methanolic hydrogen chloride at 0 °C. Solvent was then completely removed in vacuo at room temperature. The residue was taken up in methanol and treated with excess diazomethane at 0 °C. The solvent was evaporated and the residue stirred with acetic anhydride and pyridine at room temperature for 10 h. After removal of the excess acetic anhydride and pyridine, the product was dissolved in ethyl acetate and washed first with 5% HCl and then saturated $NaHCO_3$ solution. Drying and evaporation of ethyl acetate provided a thick oil. The white solid product was obtained by crystallization from a minimum amount of ethyl acetate at freezer temperature: mp 169–171 °C; NMR ($CDCl_3$) δ 2.05 (3 H, s), 2.25 (4 H, m), 3.7 (3 H, s), 3.83 (6 H, s), 6.8 (3 H, m). A sample prepared from natural agaridoxin was identical in all respects with the synthetic product.

Acknowledgments. The authors thank the following at Merck Sharp & Dohme Research Laboratories: Mr. Richard N. Boos and his staff for microanalyses, Mr. Jack L. Smith and Mr. Robert W. Walker for mass spectrographic and infrared spectra, and Mr. Carl Homnick for Spinco analysis.

Registry No.—**1**, 58298-77-4; **4**, 37519-14-5; **5**, 6324-89-6; **6**, 25830-77-7; **7**, 58298-78-5; **8**, 58298-79-6; **9**, 58298-80-9; **10**, 58298-81-0; **11**, 58298-82-1; 4-nitropyrocatechol, 3316-09-4; acetic anhydride, 108-24-7.

References and Notes

(1) R. F. Weaver, K. V. Rajagopalan, P. Handler, D. Rosenthal, and P. W. Jeffs, *J. Biol. Chem.*, **246**, 2010 (1971).
(2) R. F. Weaver, K. V. Rajagopalan, P. Handler, and W. L. Byrne, *J. Biol. Chem.*, **246**, 2015 (1971).
(3) For review see A. Szent-Gyorgyi, *Life Sci.*, **15**, 863 (1975).
(4) F. E. King and D. A. A. Kidd, *Nature (London)*, **162** (1948); *J. Chem. Soc.*, 3315 (1949).
(5) G. H. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **79**, 688 (1960).
(6) F. E. King, B. S. Jackson, and D. A. A. Kidd, *J. Chem. Soc.*, 243 (1951).
(7) J. C. Sheehan and W. A. Bolhofer, *J. Am. Chem. Soc.*, **72**, 2469 (1950).
(8) W. Gerrard and M. Lappert, *Chem. Rev.* **58**, 1081 (1958).
(9) H. Steinberg, "Organoboron Chemistry", Vol. 1, Interscience, New York, N.Y., 1964, Chapter 12.
(10) F. Dean, J. Goodchild, L. Houghton, J. Martin, R. Morton, B. Parton, A. Price, and M. Somvichen, *Tetrahedron Lett.*, 4135 (1966).
(11) R. Molyneux, *Chem. Commun.*, 318 (1975).
(12) W. Gerrard and M. Lappert, *J. Chem. Soc.*, 1486 (1952).
(13) T. Bonner and N. Saville, *J. Chem. Soc.*, 2851 (1960).
(14) F. S. Vogel, S. J. McGarry, L. A. K. Kemper, and D. G. Graham, *Am. J. Pathol.*, **76**, 165 (1975).
(15) This preparation is included since we feel that it is germane to our study. 3,4-Dihydroxyacetanilide has been mentioned previously, but its synthesis has not been described; C. R. Creveling, N. Morris, H. Schimizu, H. Ong and J. Daly, *Mol. Pharmacol.*, **8**, 398 (1972).
(16) Prepared from *N*-phthaloyl-L-glutamic acid with $[\alpha]^{29}D$ 49.5° (*c* 1, in dioxane) corresponding with published values.[5] The specific rotation of *our N*-phthaloyl-L-glutamic anhydride (**6**), $[\alpha]^{25}D$ −44.1° (c 3, dioxane), also agreed with published data[5] including J. W. Clark-Lewis and J. S. Fruton, *J. Biol. Chem.*, **207**, 481 (1954).
(17) J. Boeseken and G. Sloof, *Proc. Acad. Sci. Amsterdam*, **35**, 1250 (1932); R. W. Balsiger, R. W. Fischer, R. Hirt, and E. Giovannini, *Helv. Chim. Acta*, **36**, 708 (1953).

One-Electron Redox Reactions of Water-Soluble Vitamins. II. Pterin and Folic Acid

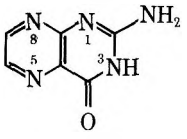
P. N. Moorthy[1] and E. Hayon*

Pioneering Research Laboratory, U.S. Army Natick Laboratories, Natick, Massachusetts 01760

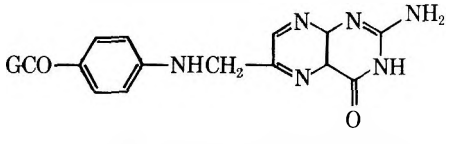
Received July 29, 1975

Using the fast reaction technique of pulse radiolysis and kinetic absorption spectrophotometry, the one-electron reductions of pterin (Pt), 3-methylpterin (3-Me-Pt), and folic acid (FH) were studied in aqueous solutions, over the pH range 0–14. The hydrated electron and the acetone ketyl radical were used as reducing agents. The reaction rate constants of e_{aq}^- with these compounds were $1–3 \times 10^{10}$ M^{-1} s^{-1}. The reaction rate constants of the $(CH_3)_2\dot{C}OH$ radical with these compounds were markedly dependent on pH and the dissociation constants of the molecules. The intermediates formed from the one-electron reduction of these pterins have characteristic absorption spectra in the uv and visible regions. These spectra are dependent upon pH and from the change in absorbance with pH at fixed wavelengths, the ionization constants of the free radicals were derived. For pterin, for example, the $\cdot PtH_4^{2+}$, $\cdot PtH_3^+$, $\cdot PtH_2$, $\cdot PtH^-$, and $\cdot Pt^{2-}$ species are postulated with pK_a (radical) values of 2.3, 6.6, 8.1, and 10.3, respectively. Furthermore, over certain pH ranges, the spectra of some of the intermediates change with time. This change was found to be due to protonation reactions by H^+, pterin, and $H_2PO_4^-$, with rate constants of $\sim 2.1 \times 10^{10}$, 7.2×10^8, and 3.1×10^8 M^{-1} s^{-1}, respectively. The N_3 proton in pterin was shown to be involved in the protonation reaction of the intermediates, since 3-methylpterin could not protonate the initial transient species formed. Schemes of reactions are suggested to interpret the nature of the transient species observed. These results are discussed and compared to recent work on the one-electron reduction of aromatic nitrogen heterocyclic compounds.

Pteridines, in particular the 2-amino-4-hydroxy derivatives (pterin), are widely distributed in biological systems. Folic acid,[2–4] a vitamin of the B group, is converted in vivo



pterin



folic acid [G = NHCH(COO⁻)CH_2CH_2COOH]

through a series of enzymic transformations into a coenzyme form. The folic acid coenzymes catalyze reactions concerned with the metabolism of nucleic acids and proteins. A deficiency of folic acid leads to the failure to synthesize the purines and thymine required for DNA synthesis.

In aqueous solutions the folate ion exists[5] in an unfolded extended conformation. However, at high concentrations and temperature (not the conditions used in this work) folate ions are involved in intermolecular association consisting of a vertical stacking interaction.

Pterin and folic acid can easily be reduced by a variety of reducing agents to the corresponding dihydro and tetrahydro derivatives in the pyrazine ring of the molecule. The coenzyme form of folic acid is the 5,6,7,8-tetrahydrofolic acid. Free-radical intermediates have been suggested[6–8] both in the chemical oxidation of reduced pterins by air, H_2O_2, or Fe^{3+} and in the enzymic oxidation of reduced pterin by phenylalanine hydroxylase.

No systematic investigations appear to have been carried out on the nature of the radical intermediates produced from the one-electron reduction of pterin and folic acid (or the one-electron oxidation of the reduced pterins). Presented below are the results obtained on the one-electron reduction in water of pterin, 3-methylpterin, and folic acid by hydrated electrons, e_{aq}^-, the acetone ketyl radical, $(CH_3)_2\dot{C}OH$, and other donor radicals. The fast reaction technique of pulse radiolysis and kinetic absorption spectrophotometry was used to monitor and study the free-radical intermediates produced.

Experimental Section

The pulse radiolysis experimental set-up and conditions used have been described elsewhere.[9–11]

The radiation chemistry of water produces e_{aq}^-, hydroxyl radicals, and H atoms

$$H_2O \text{ —}\sim\!\!\rightarrow e_{aq}^- (2.8), OH (2.8), \text{ and } H (0.6)$$

where the numbers in parentheses are the G values (yields of radicals produced per 100 eV of energy absorbed). In part I of this series[11] details and explanations have been given for the choice of the experimental conditions used. Briefly, one-electron reduction by e_{aq}^- was carried out in aqueous solutions containing ~1.0 M *tert*-butyl alcohol and saturated with argon. The β alcohol radical produced[9] from this alcohol was found not to interfere with the observations reported below. One-electron reduction by electron transfer from the $(CH_3)_2\dot{C}OH$ radical was carried out in 1–2 M isopropyl alcohol in solutions saturated with N_2O gas.

$$OH + (CH_3)_2CHOH \rightarrow (CH_3)_2\dot{C}OH + H_2O \quad (1)$$

$$e_{aq}^- + N_2O \rightarrow N_2 + OH + OH^- \quad (2)$$

$$e_{aq}^- + H^+ \rightarrow H \quad (3)$$

$$H + (CH_3)_2CHOH \rightarrow H_2 + (CH_3)_2\dot{C}OH \quad (4)$$

In acid solutions, e_{aq}^- are converted to H atoms which generate $(CH_3)_2\dot{C}OH$ radicals, reactions 3 and 4. Similar reactions were employed to generate other donor radicals in water.

All the chemicals used were the highest purity research grade available commercially, and were obtained from Calbiochem. Aldrich, and Sigma Chemicals. The reagents used were obtained from Baker & Adamson, Mallinckrodt, and Eastman Chemicals. Solutions were buffered with $HClO_4$, KOH, and various amounts of phosphates and tetraborate. The concentrations of buffer and substrate used were strictly controlled, since these affected the protonation reactions of the free-radical intermediates produced.

The stability in acid and basic solutions of the compounds used was checked in every case. The transient optical absorption spectra presented below were corrected for depletion of the substrate at the appropriate wavelengths and pH. The extinction coefficients derived were based on the G values for e_{aq}^- and OH, and the KCNS radiation dosimetry.[9]

Results and Discussion

The reaction rate constants of e_{aq}^- with pterin (PtH), 3-methylpterin (3-Me-Pt), and folic acid (FH) in aqueous solutions were determined by monitoring the decay kinetics of e_{aq}^- at 700 nm. From the pseudo-first-order decays, the second-order rate constants were determined and are given in Table I. These rates are close to being diffusion controlled as was found for pyrimidines,[12,13] pyrazine,[13] and various aromatic diazines.[13]

Table I. Reaction Rate Constants of e_{aq}^- with Pterin, Folic Acid, and Related Compounds in Water[a]

Registry no.	Compd	pK_a	pH	Ionic form	$k(e_{aq}^- + S)$, M^{-1} s^{-1} [b]
2236-60-4	Pterin, PtH	2.27, 7.92	6.5	PtH	2.5×10^{10}
			11.5	Pt^-	1.9×10^{10}
941-90-2	3-Methylpterin, 3-Me-Pt	2.27	7.7	3-Me-Pt	2.9×10^{10}
59-30-3	Folic acid, FH	~2.3, 8.26	6.0	FH	2.2×10^{10}
			12.0	F^-	1.1×10^{10}
91-18-9	Pteridine, Pt	4.1	6.0	Pt	3.0×10^{10} [c]

[a] Determined in presence of ~0.5 M *t*-BuOH by monitoring decay kinetics of e_{aq}^- at 700 nm. [b] Values to ±10%. [c] At pH 6.0, 78% present in water as pteridine.

Table II. Rate Constants of Electron Transfer Processes to Pterin and Folic Acid by Various Electron Donors in Water

System	pH	Ionic form	Electron donor[a]	k(electron transfer), M^{-1} s^{-1} [f]
Pterin, PtH	0.8	PtH_2^+	$\dot{C}H_2OH$[b]	9.0×10^7
	7.0	PtH	$\dot{C}H_2OH$[e]	$\ll 10^7$
	13.0	Pt^-	$\dot{C}H_2O^-$	6.0×10^8
	7.0	PtH	$CH_3\dot{C}HOH$[b]	3.7×10^7
	13.0	Pt^-	$CH_3\dot{C}HO^-$	1.2×10^9
	0.8	PtH_2^+	$(CH_3)_2\dot{C}OH$	2.0×10^9
	7.0	PtH	$(CH_3)_2\dot{C}OH$	4.5×10^8
	9.4	Pt^-	$(CH_3)_2\dot{C}OH$[e]	$\ll 10^7$
	13.0	Pt^-	$(CH_3)_2\dot{C}O^-$	1.5×10^9
	7.0	PtH	$\cdot CO_2^-$	4.6×10^8
	9.5–13.0	Pt^-	$\cdot CO_2^-$ [e]	$\ll 10^7$
3-Methylpterin, 3-Me-Pt	0.8	3-Me-PtH^+	$\dot{C}H_2OH$[c]	6.0×10^7
	6.3	3-Me-Pt	$CH_3\dot{C}HOH$[d]	3.2×10^7
	0.8	3-Me-PtH^+	$(CH_3)_2\dot{C}OH$	1.9×10^9
	7.0	3-Me-Pt	$(CH_3)_2\dot{C}OH$	2.9×10^8
Folic acid, FH	~0.5	FH_2^+	$(CH_3)_2\dot{C}OH$	1.1×10^9
	6.0	FH	$(CH_3)_2\dot{C}OH$	4.0×10^8
Pteridine, Pt	6.0	Pt	$\dot{C}H_2OH$	3.6×10^8

[a] ~100% electron transfer was found, unless stated otherwise. [b] ~40% electron transfer. [c] ~45% electron transfer. [d] ~55% electron transfer. [e] No electron transfer observed under experimental conditions used. [f] The k values where partial electron transfer occurs were calculated as described in ref 14.

Pterin and folic acid undergo keto–enol tautomerism with a consequent small reduction in alkaline solution of the reaction rate constants with e_{aq}^- (Table I). This reduction in the rate is less than that observed[12] for the enol form of the pyrimidines, and may simply be due to a lower encounter rate for like-charged reactants. These results suggest that the pyrazine ring in pterin and folic acid can be effectively reduced by e_{aq}^-.

Pteridine is unstable in aqueous solution and undergoes partial covalent hydration (~22% at the pH of the experiment). The rate constant given in Table I is the overall value for the mixture of the anhydrous and hydrated forms.

The reaction rate constants of $(CH_3)_2\dot{C}OH$ (and other organic radicals) with pterins were determined by following the formation kinetics of the radical intermediates produced from this electron transfer reaction at the appropriate wavelengths. The rate constants were found, Table II, to be dependent on the state of protonation and the nature of the substituents in pterin.

The efficiencies for the one-electron reduction of substrates by $(CH_3)_2\dot{C}OH$ and the rate constants for this reaction have recently been interpreted, in a number of systems, on the basis of the redox potentials of the substrates and the kinetic potential[14] of the $(CH_3)_2\dot{C}OH$ radical, $E_k^{01} = -0.82$ V. The E^{01} values in the literature for pterin (PtH) are −0.39 and −0.57 V for the PtH and Pt^- forms, respectively.[15] These values have to be more negative (~−0.8 and ~−1.0 V for PtH and Pt^-, respectively), if one is to interpret the data in Table II on the basis of the redox potentials of the donors and acceptors.

Pterin. The one-electron reduction of pterin (PtH, $pK_a^1 = 2.27$, $pK_a^2 = 7.92$) by e_{aq}^- in 2.5×10^{-4} M aqueous solutions forms short-lived free radicals which absorb in the visible and uv regions of the spectrum, Figure 1. At pH 5.2, a transient species (T_1) with maxima[16] at ~355 and ~440 nm is produced immediately after the 30-ns electron pulse. This transient absorption changes with time and at ~5 μs after the pulse a species (T_2) with λ_{max} ~ 258, 328, and 448 nm is observed. It can be noted that for the T_2 transient the band in the visible region is red shifted and that in the uv region is blue shifted, with respect to the corresponding bands of the T_1 transient. Similar changes are found on reaction of e_{aq}^- with pterin at pH 7.2, Figure 1 (b) and Table III. At pH 9.2 and 11.7 only one transient absorption is observed at each pH, Figure 1 (c), at the time resolution (τ ~0.2 μs) available.

In neutral solutions at pH 7.2, the transient species formed by electron transfer from the $(CH_3)_2\dot{C}OH$ radical were found to be identical with the T_2 species formed from the reaction of e_{aq}^- with pterin. In acid solutions, e_{aq}^- react very fast with protons, reaction 3. Therefore, one-electron reduction of pterin at pH 0.35 was brought about by the reaction of $(CH_3)_2\dot{C}OH$ with PtH_2^+. Figure 2 and Table III give the results.

The changes in the optical absorption of the transient species T_1 and T_2 with pH have been titrated at fixed wavelengths. The titration curves are shown in Figure 3. Ionization constants for the T_1 radicals of ~6.5 and ~8.4, and pK_a values of 2.3, 6.6, 8.1, and 10.3 for the T_2 radicals (see Table III), were found.

The time dependence for the change from the T_1 to the T_2 species (whenever both species were observed under the experimental conditions used) was found to depend on the presence and concentration of proton donors, HA:

Table III. Absorption Maxima, Extinction Coefficients, Ionization Constants, and Decay Kinetics of the Radicals Produced by Reaction of e_{aq}^- with Pterin and Folic Acid in Water

Substrate[a]	pH	Ionic form	Transient	λ_{max}, nm	ϵ, mM^{-1} cm^{-1}	$2k$, M^{-1} s^{-1}	pK_a (radical) T_1	pK_a (radical) T_2 (or T)
Pterin, PtH	0.35	PtH_2^+	T[b]	260, 320, 350, 450	22.0, 4.0, 4.2, 4.4	1.1×10^8 [b]		2.3
(2.27, 7.92)	5.2	PtH	T_1	~355, ~440	4.3, 1.6		~6.5	
			T_2	~258, 328, 448	19.5, 4.7, 3.5	5.4×10^8 [b]		6.6
	7.2	PtH + Pt^-	T_1	~355, ~440	4.3, 1.4		~8.4	
			T_2	255, 325, 460	21.4, 4.6, 2.1	1.8×10^8 [b]		8.1
	9.2	Pt^-	T	~252, 355, 480	22.0, 5.5, 2.3	1.0×10^8		10.3
	11.7	Pt^-	T	~252, 358, 435	14.0, 4.8, 1.6	5.5×10^7 [c]		
3-Methyl-	0.35	3-Me-PtH^+	T[b]	335, 460	3.9, 3.5	6.1×10^7 [b]		3.1
pterin,	5.2	3-Me-Pt	T_1	~372	5.4		~7.6	
3-Me-Pt			T_2	~457, <355	3.0	1.6×10^8 [b]		7.7
(2.27)	8.3, 9.2	3-Me-Pt	T_2	365	5.4	6.3×10^7 [b]		
Folic acid,	0.5	FH_2^+	T[b]	≤260, 465	28.0, 4.2	8.1×10^6 [b]		~1.0
FH	5.2	FH	T_1	~278, 360, ~440	25.0, 6.2, 1.9		~6.5	
(~1.6,[d] 8.26)			T_2	~278, 360, 460	25.0, 5.5, 3.7	4.4×10^7 [b]		~6.6
	7.2	FH	T_1	280, 355	22.0, 6.4			
			T_2	350, 435	5.6, 2.5	1.1×10^8 [b]		~8.0
	9.4	F^-	T_1	~258, ~290, 365	23.0, 23.0, 7.7		~8.4	
			T_2	~258, ~290, 360	23.0, 23.0, 7.0	5.7×10^7		~10.3
	11.9	F^-	T	255, 290, 365, ~440	21.5, 22.5, 7.2, 2.6	3.0×10^7 [b]		

[a] Values in parentheses are pK_a of the substrate. [b] Transient produced by electron transfer from $(CH_3)_2\dot{C}OH$. [c] At pH 13.0 by electron transfer from $(CH_3)_2\dot{C}O^-$. [d] Spectrophotometrically determined in this work.

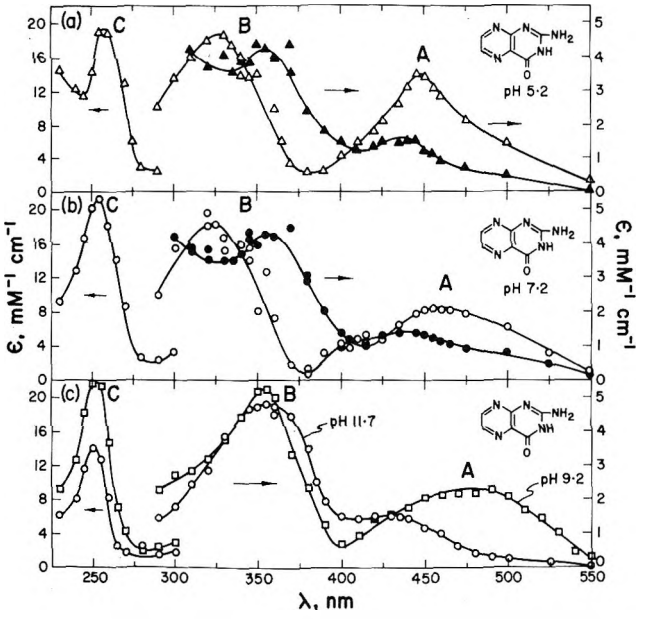


Figure 1. Absorption spectra of transient species (T_1 and T_2) produced from the one-electron reduction of pterin by e_{aq}^- in water. Bands A and B were determined in solutions containing 2.5×10^{-4} M pterin (~5×10^{-5} M used for determining bands C), 0.5 M *t*-BuOH, 2 mM buffer (see text), and argon (1 atm). Dark symbols represent initial transient T_1 (absorbance read ~0.5 μs after the pulse) and open symbols are for transient T_2 (absorbance read at ~5 μs after the pulse): (a) at pH 5.2, (b) at pH 7.2. and (c) at pH 9.2, □, and pH 11.7, ○. Total dose ~4.0 krad/pulse.

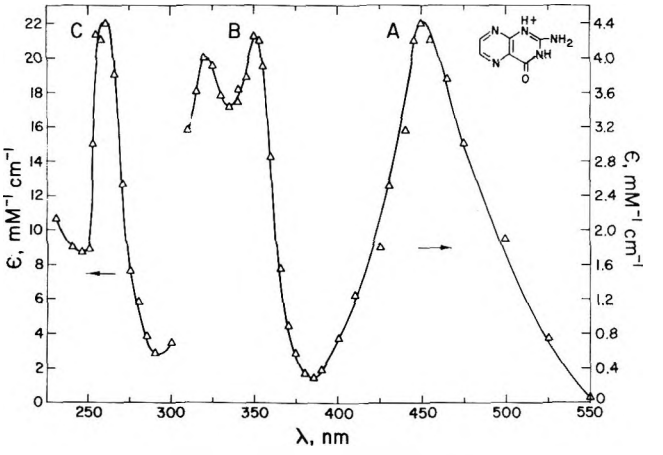


Figure 2. Absorption spectra of transient species produced from the one-electron reduction of pterin by $(CH_3)_2COH$ radicals at pH 0.35. Aqueous solutions contained 2.5×10^{-4} M pterin (~5×10^{-5} M for band C), 1.0 M isopropyl alcohol and argon (1 atm). Total dose ~1.3 krad/pulse.

$$T_1 \xrightarrow{HA} T_2 \qquad (5)$$

The presence of H^+, $H_2PO_4^-$ buffer, and pterin itself was found to accelerate reaction 5. Figure 4 shows the results for protonation of T_1 by pterin, and Table IV the rate constants for various proton donors. The $k(T_1 + HA \rightarrow T_2 + A^-)$ rate constants in solutions containing more than one proton donor were determined by multilinear regression analysis, using a Hewlett-Packard calculator Model 9830. Protonation of T_1 radicals by H^+ gave k_5 ~2.1×10^{10} M^{-1} s^{-1}, while for $H_2PO_4^-$ $k_5 = 3.1 \times 10^8$ M^{-1} s^{-1}.

Evidence that the $>N_3H$ group in pterin itself can act as the proton donor can be seen from the absence of protonation when 3-methylpterin was used instead (see Figure 4 and Table IV), under otherwise identical experimental conditions. This is probably the first time that it has been clearly demonstrated that a substrate can act as a proton donor to a radical species. Similar results[17] have been obtained for the protonation of the corresponding T_1 radical from lumazine.

Based on the above results (and the results given below for 3-methylpterin) the following scheme of reactions is tentatively suggested for a complex molecule such as pterin (and, below, for 3-Me-Pt and FH) with at least four different reactive sites for reduction. Other schemes consistent with the experimental facts can also be written. The one given below was chosen on the basis that pyrazines are known[13] to be readily reduced, and the reduced forms of pterins are in the pyrazine ring.

Based on ESR data, Ehrenberg et al.[6] have inferred that the free-radical species produced by reduction of pterins in

Table IV. Rate Constants for Protonation of Electron Adducts (T_1 Transients) of Pterin and Folic Acid by Various Proton Donors in Water

System	λ monitored, nm	Proton donor, HA	$k(T_1 + HA)$, $M^{-1} s^{-1}$ [a]
Pterin, PtH	455	H_3O^+	$\sim 2.1 \times 10^{10}$
	455	$H_2PO_4^-$	3.1×10^8
	455	PtH	7.2×10^8
	460	H_2O	$\sim 3.0 \times 10^3$
3-Methyl-pterin, 3-Me-Pt	460	H_3O^+	2.2×10^{10}
	460	$H_2PO_4^-$	3.8×10^8
	460	3-Me-Pt	0
	460	H_2O	$\sim 3.0 \times 10^3$
Folic acid, FH	465	H_3O^+	5.9×10^{10}
	465	$H_2PO_4^-$	1.0×10^8
	465	FH	1.5×10^8
	465	H_2O	$\sim 4.0 \times 10^3$

[a] Rate for the first (lowest pH) T_1 species, determined by multilinear regression analysis of observed protonation rates at different concentrations of H_3O^+, $H_2PO_4^-$, and substrate.

acidic media is a pyrazyl dihydro radical cation ($\cdot PtH_3^+$). In the time scale employed for ESR experiments, only longer lived species, e.g., the T_2 species, would be present. Hence, we have postulated the T_2 species to be primarily pyrazyl radicals. The scheme presented below takes into consideration the possibility that the initial site for the one-electron reduction of pterins may be in the pyrimidine part of the molecule, giving the T_1 species, as was previously shown[18] for the one-electron reduction of pyrimidines.

Ionization Constants of the T_2 Species. The first protonation of pyrazine occurs at $pK_a = 0.65$, while in pterin the fusion of the isocytosine ring shifts it to a $pK_a = -3$. The dihydro cation radical of pyrazine was found[13] to have a $pK_a = 10.5$, and the base-weakening effect of the isocytosine ring can be expected to shift the pK_a of the pyrazyl radical in pterin to lower pH values. The $pK_a = 6.6$ for the $\cdot PtH_3^+$ radical is attributed to this step. The pK_a (radical) values of 2.3 and 8.1 are close to those of the parent molecule, and are therefore attributed to the same ionization steps as in pterin.

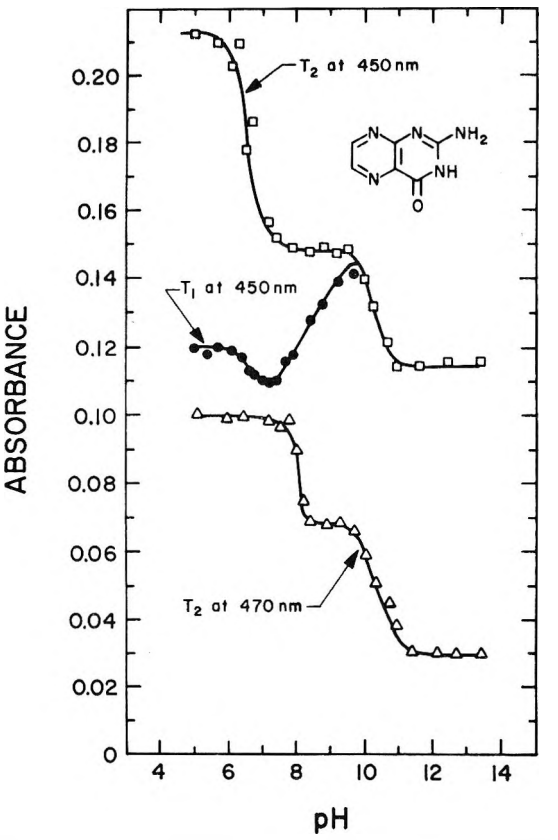
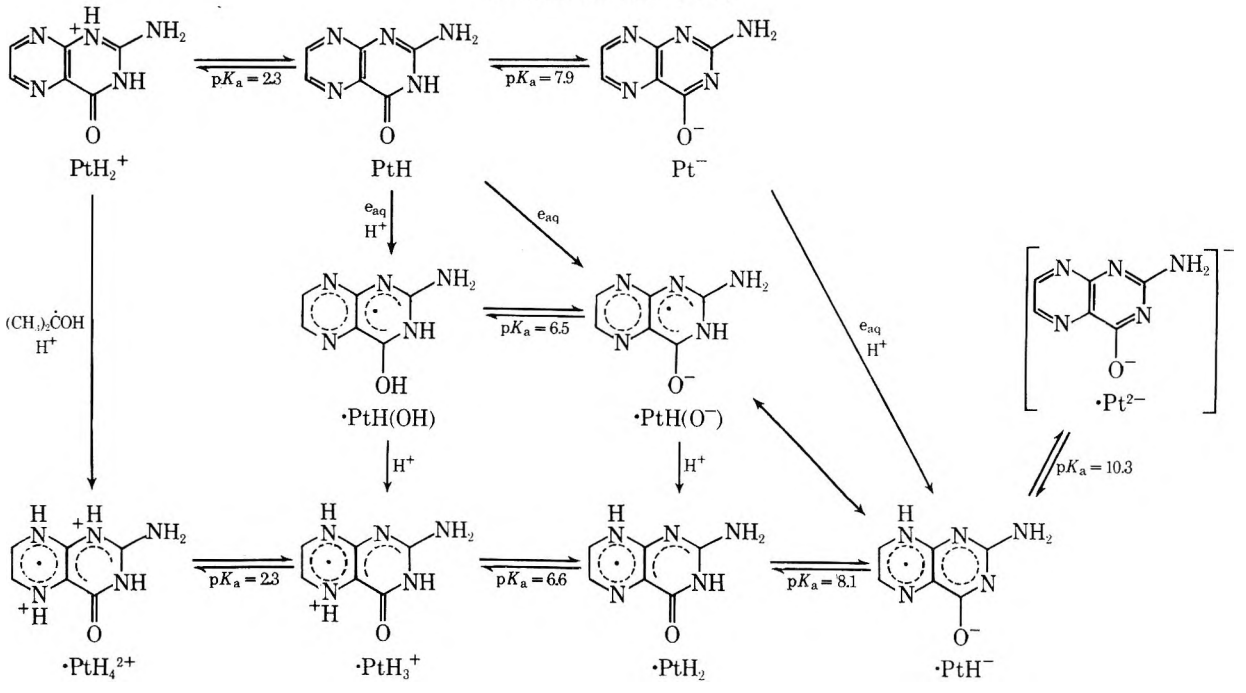


Figure 3. Dependence upon pH of the absorbance of the transient species T_1 and T_2 monitored at 450 and 470 nm. Solutions contained 2.5×10^{-4} M pterin, 0.5 M *t*-BuOH, and argon (1 atm). Total dose ~15 krad/pulse.

The $pK_a = 10.3$ for the $\cdot PtH^-$ radical to give species $\cdot Pt^{2-}$ is tentatively suggested, and is consistent with the absence of a pK_a (radical) = 10.3 in the case of 3-methylpterin; see below.

Ionization Constants of the T_1 Species. In the pH range 5.2–7.2, the addition of an electron to PtH is postulated to occur in the pyrimidine ring to give the ketyl radical and radical anion (see Scheme I). The pK_a ~6.5 is close

Scheme I. Pterin (PtH)



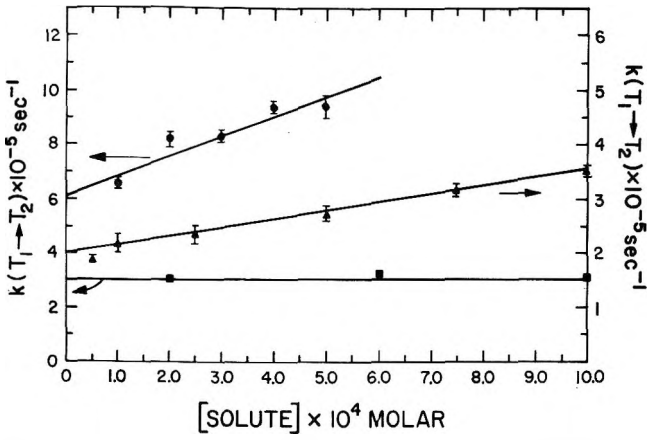


Figure 4. Dependence of the rate of protonation of T_1 species to form T_2 species upon the concentration of (a) pterin, ●, 0.5 M *t*-BuOH, 1 mM $H_2PO_4^-$, pH 6.3; (b) 3-methylpterin, ■, 0.5 M *t*-BuOH, 0.2 mM $H_2PO_4^-$, pH 5.1; and (c) folic acid, ▲, 1.0 M *t*-BuOH, 1 mM $H_2PO_4^-$, pH 6.3.

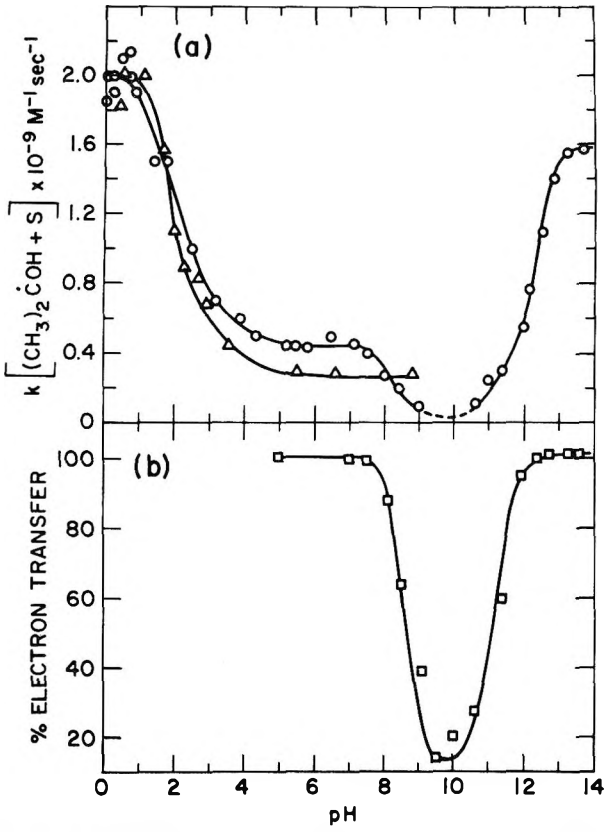


Figure 5. Dependence upon pH of the electron transfer reaction of $(CH_3)_2\dot{C}OH$ radicals to pterin and 3-methylpterin in water: (a) rate constants for electron transfer to pterin, ○, and 3-methyl pterin, △; (b) percentage efficiency for electron transfer to pterin. Solutions contained 2.5 × 10^{-4} M solutes, 1.0 M isopropyl alcohol, argon (1 atm), and total dose ~2 krad/pulse.

to those of similar radicals derived from various pyrimidines[18] and guanine.[19]

Reactivity toward $(CH_3)_2\dot{C}OH$ Radicals. Figure 5 (a) shows that the rate constant for the reaction of $(CH_3)_2\dot{C}OH$ radicals with pterin is strongly dependent on pH and the state of protonation of pterins and the acetone ketyl radicals. Apparent pK_a values are observed in Figure 5 (a) which reflect the pK_a = 2.3 and 7.9 for PtH_2^+ and PtH, and pK_a ~ 12.2 the ionization constant of the $(CH_3)_2\dot{C}OH$ radical.[20] Figure 5 (b) demonstrates that the percentage efficiency for electron transfer from $(CH_3)_2\dot{C}OH$ radicals to the Pt^- form of pterin is almost zero, indicating that the

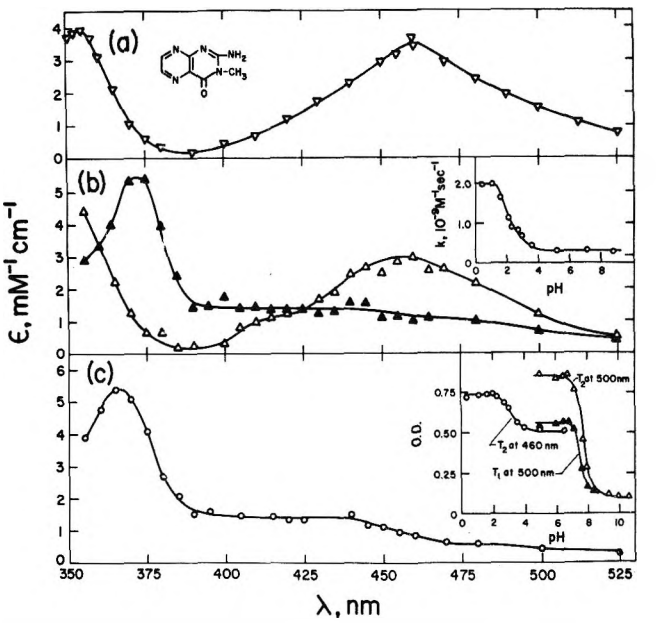


Figure 6. Absorption spectra of transient species (T_1 and T_2) produced from the one-electron reduction of 3-methylpterin in water. Solutions contained 5.0 × 10^{-4} M 3-Me-pterin, 0.5 M *t*-BuOH (or 1.0 M isopropyl alcohol), 2 mM buffer, and argon (1 atm). Dark symbols represent initial transient T_1 (absorbance read ~0.5 μs after the pulse) and open symbols represent T_2 transients (absorbance read at ~5 μs after the pulse). (a) reduction by $(CH_3)_2\dot{C}OH$ radicals, pH 0.35, 1.2 krad/pulse; (b) reduction by e_{aq}^- at pH 5.2 (~4 krad/pulse). Insert, dependence upon pH of the rate of electron transfer from $(CH_3)_2\dot{C}OH$ radicals to 3-Me-Pt, N_2O-saturated solutions (1.2 krad/pulse); (c) reduction by e_{aq}^- at pH 8.3 (~4 krad/pulse). Insert, dependence upon pH of the absorbance of T_2 at 460 nm, produced by electron transfer from $(CH_3)_2\dot{C}OH$ (1.2 krad/pulse); and of T_1 and T_2 transients at 500 nm, produced from reaction with e_{aq}^- (~6 krad/pulse).

redox potential of Pt^- is much more negative than the kinetic potential[14] E_k^{01} = −0.82 V of $(CH_3)_2\dot{C}OH$. The kinetic potentials of the $(CH_3)_2\dot{C}O^-$ and $CH_3\dot{C}HO^-$ radicals are <−1.0 V and explain the 100% transfer from these radicals to Pt^-.

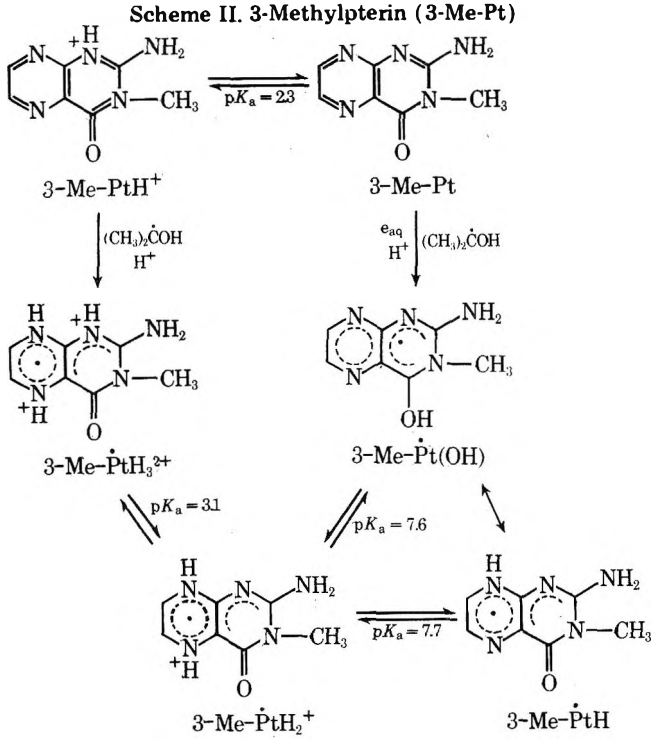
3-Methylpterin. 3-Methylpterin (pK_a = 2.3) was found to be unstable at pH >11.0. One-electron reduction of this compound was brought about by e_{aq}^- and acetone ketyl radicals. The $(CH_3)_2\dot{C}OH$ radicals were found to reduce 3-Me-Pt and 3-Me-PtH^+ with 100% efficiency, and reaction rate constants of 2.9 × 10^8 and 1.9 × 10^9 M^{-1} s^{-1}, respectively (see Tables I and II), were obtained.

The absorption spectra of the free-radical intermediates produced at pH 0.35, 5.2, and 8.3 are shown in Figure 6. At pH 5.2, an initial (T_1) transient species is observed whose spectrum changes with time to give a second (T_2) transient species. The change from the T_1 to the T_2 species is accelerated in the presence of good proton donors. Table IV shows the rate constants for this protonation reaction by H_3O^+ and $H_2PO_4^-$. No protonation by 3-Me-Pt itself occurred, supporting the statement made above for pterin that the N_3H hydrogen in pterin is a proton donor.

The changes with pH for the absorbances of these radicals at fixed wavelengths are shown in Figure 6 and Table III. pK_a values of ~7.6 for the T_1 species and 3.1 and 7.7 for the T_2 species have been observed.

Scheme II shows the reactions suggested to occur in this system. The initial (T_1) species observed at pH 5.2 is ascribed to a ketyl radical—3-Me-$\dot{P}t$(OH)—which on protonation to give the T_2 species forms predominantly a pyrazyl type of radical, 3-Me-$\dot{P}tH_2^+$. Since this molecule cannot undergo keto–enol tautomerism, ionization of the above radical is suggested to form 3-Me-$\dot{P}tH$. Further ionization

Scheme II. 3-Methylpterin (3-Me-Pt)



of the latter radical presumably occurs at pH > 11.0, a pH region which could not be examined owing to the instability of 3-Me-Pt itself.

Folic Acid. The reactivity of folic acid toward the one-electron reducing agents is quite similar to that of pterin; see Tables I and II. The spectral and physicochemical properties of the free-radical intermediates produced are

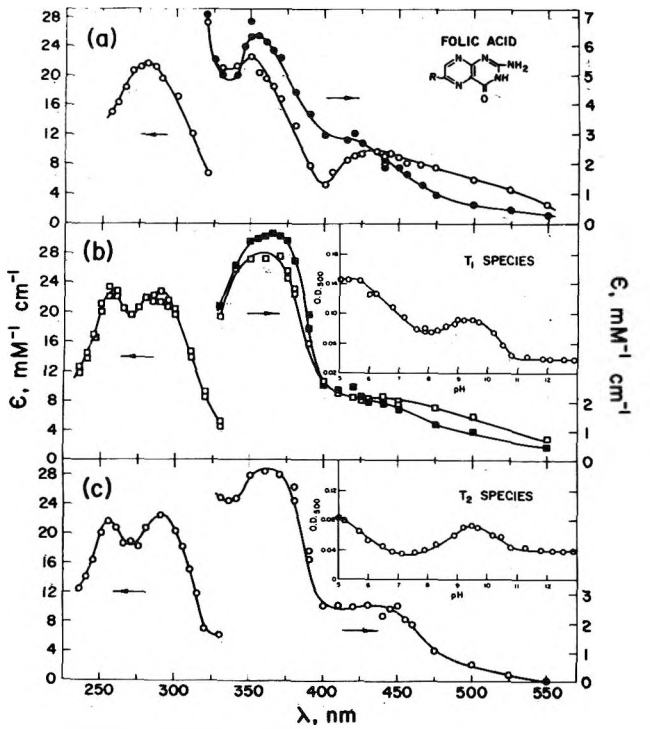


Figure 7. Absorption spectra of transient species (T_1 and T_2) produced from the one-electron reduction of folic acid by e_{aq}^- in water. Solutions contained 2.0×10^{-4} M folic acid (5.0×10^{-5} M at $\lambda <$ 320 nm), 0.5 M *t*-BuOH, 2 mM buffer, and argon (1 atm). Dark symbols represent T_1 species (absorbance read at ~0.5 μs) and open symbols represent T_2 species (absorbance read at ~5 μs): (a) at pH 7.2; (b) at pH 9.4, insert, change in absorbance of T_1 species with pH; and (c) at pH 11.9, insert, change in absorbance of T_2 species with pH. Total dose ~4 krad/pulse.

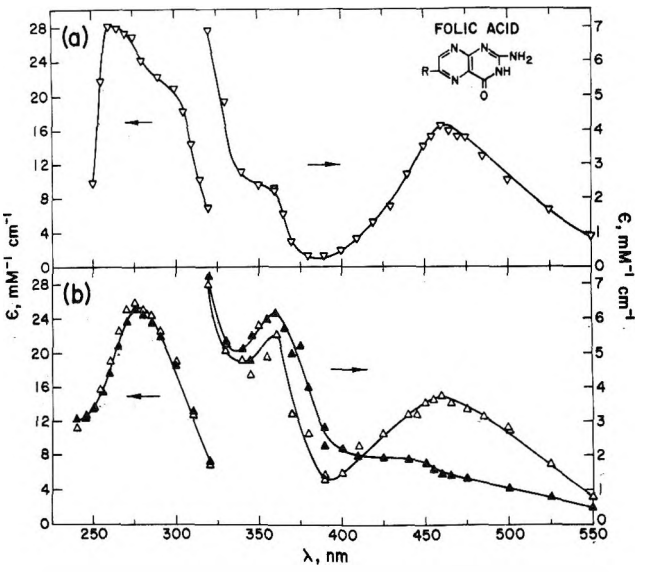


Figure 8. Absorption spectra of transient species (T_1 and T_2) produced from the one-electron reduction of folic acid in water. Solutions contained 2.0×10^{-4} M folic acid (5×10^{-5} M at $\lambda <$ 360 nm). (a) 1.0 M isopropyl alcohol, pH 0.5, argon (1 atm), and 1.5 krad/pulse. Dark symbols represent T_1 species (absorbance read at ~0.5 μs) and open symbols represent T_2 species (absorbance read at ~5 μs).

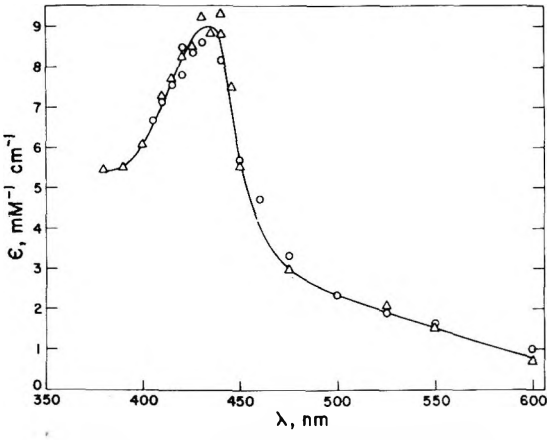


Figure 9. Absorbance spectra of transient species produced from the reaction of OH radicals with folic acid (10^{-4} M, N_2O-saturated aqueous solution) at pH 5.1, △, and pH 10.5, ○. Total dose ~7 krad/pulse.

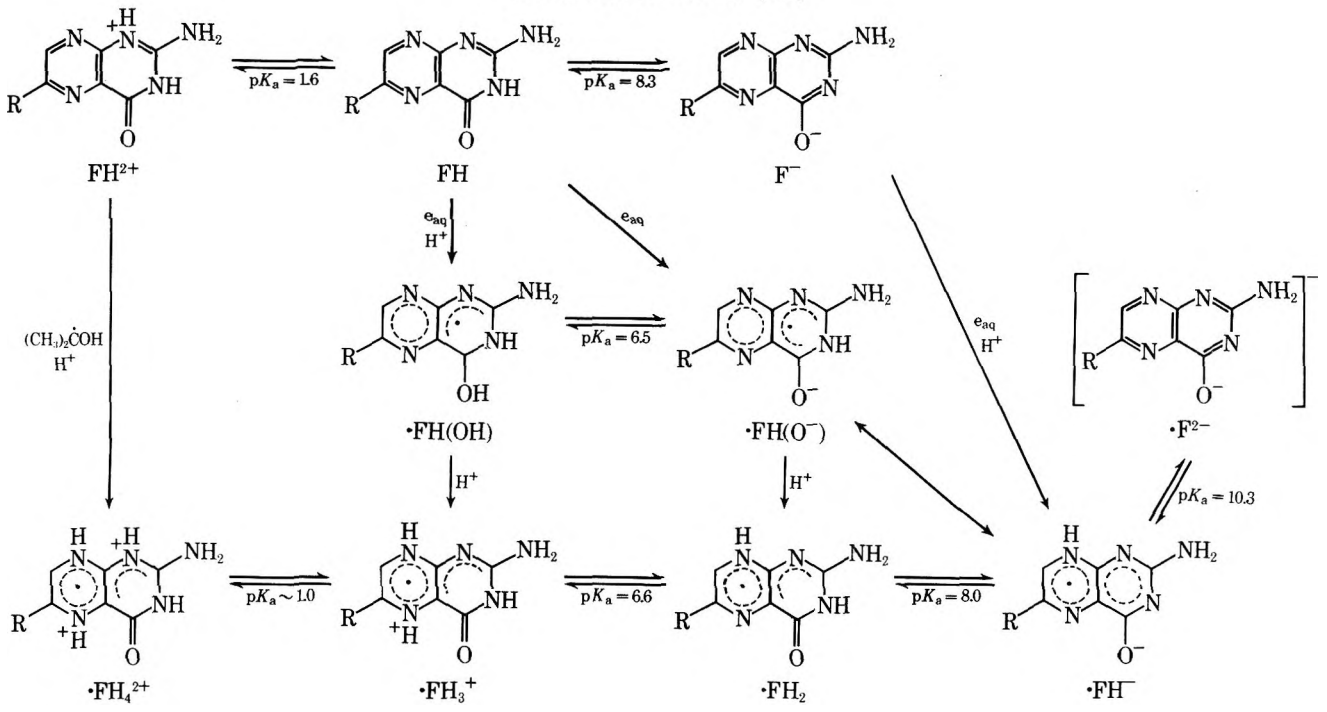
also similar to those observed from pterin (Figures 7 and 8 and Table III). This is not surprising since the side chain at the C_6 position is not expected to have a strong influence on the reduction or spectral characteristics of the transient species formed.

At pH 5.2, 7.2, and 9.4, the absorption spectra of the initial (T_1) transient species formed change with time. Protonation of T_1 gives rise to the T_2 species formed at a later time after the pulse. Table IV shows the rate constants for the protonation of the T_1 species formed at pH 5.2 by H_3O^+, $H_2PO_4^-$, and folic acid itself. These rate constants are somewhat different from those observed for pterin. No explanation is presently available.

The scheme of reactions tentatively suggested for folic acid is shown in Scheme III. The nature of the radical intermediates and their ionization constants are similar to those for pterin.

Reaction with OH Radicals. The reaction of hydroxyl radicals with aromatic compounds is less specific than that of e_{aq}^-—addition to the ring can occur at various positions. The reaction rate constants of OH radicals with folic acid

Scheme III. Folic Acid (FH)



at pH 5.1 and 10.5 were determined by monitoring the formation kinetics of the transient species produced from this reaction, Figure 9. The k (OH + FH) = 9.6×10^9 M^{-1} s^{-1} at pH 5.1 and k (OH + F^-) = 1.2×10^{10} M^{-1} s^{-1} at pH 10.5. No change was observed in the absorption spectra of this intermediate from pH 5.1 to 10.5 (Figure 9). The OH radicals presumably add at the pyrimidine, pyrazine, and *p*-aminobenzoic acid rings. In addition some abstraction of an H atom from the glutamic acid side chain may occur. The radicals decay by second-order kinetics with $2k$ = 2.9×10^8 M^{-1} s^{-1} at pH 5.1 and $2k$ = 6.0×10^7 M^{-1} s^{-1} at pH 10.5.

Conclusions

The nature of the free-radical intermediates formed from the one-electron reduction of pterin, 3-methylpterin, and folic acid in water at different pH values have been suggested. Schemes of reactions have been proposed.

These intermediates decay by second-order kinetics, with rate constants that range from $\sim 10^7$ to $\sim 5 \times 10^8$ M^{-1} s^{-1}; see Table III. Disproportionation reactions of these free radicals presumably occur with the formation of the corresponding dihydropyrazine derivatives. No transient spectra were observed from the decay of the T_2 species (or T species when no T_1 species were observed).

The intermediates formed appear to be good reducing agents. For example, the $\cdot PtH^-$ and $\cdot Pt^{2-}$ radicals have been found to reduce anthraquinone 2,6-disulfonate (E^{01} = −0.184 V) with efficient formation of the $\cdot AQ^-$ radical anion, with $k \sim 10^9$ M^{-1} s^{-1} for the electron transfer process.

Acknowledgment. We are very grateful to Dr. D. J. Brown at the Australian National University for a gift of 3-methylpterin.

References and Notes

(1) Chemistry Division, Bhabha Atomic Research Center, Trombay, Bombay, India.
(2) W. Shive in "Comprehensive Biochemistry", Vol. 11, M. Florkin and E. H. Stotz, Ed., American Elsevier, New York, N.Y., 1963, p 82.
(3) B. Pullman and A. Pullman, "Quantum Biochemistry", Interscience, New York, N.Y., 1963.
(4) R. L. Blakley in "The Biochemistry of Folic Acid and Related Pteridines", North-Holland Publishing Co., Amsterdam, 1969.
(5) Y.-F. Lam and G. Kotowycz, *Can. J. Chem.*, **50**, 2357 (1972).
(6) A. Ehrenberg, P. Hemmerich, F. Muller, T. Okada, and M. Viscontini, *Helv. Chim. Acta*, **50**, 411 (1967).
(7) D. J. Vonderschmitt and K. G. Scrimgeour, *Biochem. Biophys. Res. Commun.*, **28**, 302 (1967).
(8) P. Hemmerich, *Proc. R. Soc. London, Ser. A*, 302, 335 (1968).
(9) M. Simic, P. Neta, and E. Hayon, *J. Phys. Chem.*, **73**, 3794 (1969).
(10) J. P. Keene, E. D. Black, and E. Hayon, *Rev. Sci. Instrum.*, **40**, 1199 (1969).
(11) U. Brühlmann and E. Hayon, *J. Am. Chem. Soc.*, **96**, 6169 (1974).
(12) E. J. Hart and M. Anbar, "The Hydrated Electron", Wiley-Interscience, New York, N.Y., 1970.
(13) P. N. Moorthy and E. Hayon, *J. Phys. Chem.*, **78**, 2615 (1974).
(14) P. S. Rao and E. Hayon, *J. Am. Chem. Soc.*, **96**, 1287 (1974); **97**, 2986 (1975).
(15) M. Brezina and P. Zuman, "Polarography in Medicine, Biochemistry and Pharmacy", Interscience, New York, N.Y., 1958; L. Meites, "Polarographic Techniques", Interscience, New York, N.Y., 1967; I. M. Kolthoff and J. J. Lingane, "Polarography", Interscience, New York, N.Y., 1958.
(16) Another absorption band at λ <310 mm is produced but cannot be accurately determined, since at these wavelengths the correction for solute depletion is considerable compared to the absorption of the free radical. The same problem exists at other pH values and for other pterins, and will not be commented upon again.
(17) P. N. Moorthy and E. Hayon, *J. Phys. Chem.*, **79**, 1059 (1975).
(18) E. Hayon, *J. Chem. Phys.*, **51**, 4881 (1969).
(19) P. N. Moorthy and E. Hayon, *J. Am. Chem. Soc.*, **97**, 3345 (1975).
(20) K. D. Asmus, A. Henglein, A. Wigger, and G. Beck, *Ber. Bunsenges, Phys. Chem.*, **70**, 756 (1966).

A J_- Acidity Function for Solutions of Sodium Hydroxide in Water–Ethanol and Water–Dimethyl Sulfoxide Mixtures

Theodorus J. M. Pouw[1] and Petr Zuman*

Department of Chemistry, Clarkson College of Technology, Potsdam, New York 13676

Received November 10, 1975

The addition of hydroxyl ions to substituted benzaldehydes according to the reaction ArCHO + OH^- ⇄ ArCH(OH)O^- is used to establish J_- acidity scales in water–ethanol and water–Me_2SO mixtures containing sodium hydroxide as a base. Both in water–ethanol and in water–Me_2SO mixtures the pK values of the addition reaction are linearly correlated with the Hammett substituent constants. The reaction constant ρ is independent of the solvent composition, confirming that substituted benzaldehydes form a suitable set of J_- indicators for hydroxide solutions in water–ethanol and water–Me_2SO mixtures of different composition. J_- scales, representing J_- as a function of the sodium hydroxide concentration, are only slightly affected by the presence of ethanol up to 90 vol %. Similarly the J_- value of 0.01 or 0.1 M sodium hydroxide shows only a very small increase on increasing the ethanol content from 90 to 98 vol %. The effect of Me_2SO is much more pronounced especially at concentrations higher than 80 vol %, but this effect is very much smaller than that of the Me_2SO percentage on H_- values based on proton abstraction from anilines.

Basicity scales for strongly alkaline aqueous solutions of alkali metal and quaternary ammonium hydroxides seem to be reasonably well established both for reactions involving dissociation of protons[2] (H_-) and for reactions which result in addition of hydroxyl ions[3] (J_-).

In organic solvents, the acidity function H_-, based on hydrogen ion abstraction from neutral indicator acids, in solutions of alkali metal alkoxides in various alcohols,[2] and the acidity J_- function (denoted as H_R^-), based on additions of methoxides and ethoxides to neutral indicator acids, in dimethyl sulfoxide–methanol and ethanol mixtures[4] have been reported. These scales involve arbitrary choice of water as the solvent for determination of the dissociation constant of the anchoring acid.

For mixtures of organic solvents with water, the available information[2] is derived only from reactions involving dissociation of hydrogen ion, leading to acidity function H_-. Measurements for solutions containing a constant concentration of a base and a varying ratio of water and the organic solvent were carried out using sodium alkoxides as bases in mixtures of water and alcohols[5] as well as tetramethylammonium hydroxide as the base in mixtures of water with pyridine,[6] tetramethylenesulfone,[6] and dimethyl sulfoxide.[6,7] When 0.005 M sodium ethoxide was used, a relatively modest increase of the value of H_- (from 11.74 to 13.35) was observed[5] on increasing the ethanol concentration from 0 to 100 mol %. In solutions containing 0.011 M tetramethylammonium hydroxide and increasing dimethyl sulfoxide (Me_2SO) concentration, the increase in the value of H_- was found to be much more dramatic, from 12.0 in water to 26 in 99.5 mol % Me_2SO. The increase in the value of H_- with Me_2SO concentration was smaller at concentrations below 85 mol %, but very steep at higher Me_2SO concentrations.[7]

Substituted benzaldehydes have been proved to be a useful series of acid–base indicators for reactions involving addition of hydroxide ions in strongly alkaline aqueous media,[3] and it seemed logical to extend their use to solutions of sodium hydroxide in water–ethanol and water–Me_2SO mixtures. In the first case, it was of interest whether the competition between addition of hydroxide and ethoxide ions will be reflected in the dependence of the J_- function on ethanol concentration. In the case of water–Me_2SO mixtures, it was considered of importance to investigate whether the radical change at higher Me_2SO concentrations, observed for H_- values and attributed to changes in solvation of the hydroxide ion, will be observed for the addition reaction as well.

In addition to determination of the J_- function at constant sodium hydroxide concentration (0.01 M) and varying ethanol or Me_2SO content, measurements were carried out which made possible the definition of acidity function J_- in solutions containing fixed percentages of the organic solvent component and varying concentrations of sodium hydroxide. Such scales provide the possibility of preparing solutions of known J_- in mixtures containing a given concentration of the organic component and thus seem to be of practical importance (e.g., for electroanalytical measurements). They have rarely been reported, even for the H_- function.

Furthermore, equilibrium constants K_2 for the formation of the adduct corresponding to the reaction

$$\mathrm{ArCHO} + \mathrm{OH^-} \rightleftharpoons \mathrm{ArCH(OH)O^-} \qquad (1)$$

were determined by the overlap procedure in solutions containing fixed concentrations of the organic component and the effect of solvent composition on the Hammett reaction constant ρ was followed.

Experimental Section

Most of the benzaldehydes employed were obtained from Aldrich Chemical Co., Milwaukee, Wis. Purity was checked chromatographically and by measurement of boiling or melting points. The few benzaldehydes the purity of which proved to be unsatisfactory were recrystallized from ether or ethanol solutions.

Two sets of 0.01 M stock solutions of the benzaldehydes were prepared, one in absolute ethanol and one in Me_2SO, to be used for the experiments in water–ethanol and water–Me_2SO mixtures, respectively. Both Me_2SO (Baker Chemical Co.) and ethanol were used without purification.

Sodium hydroxide stock solutions were prepared of three different concentrations, viz., 0.1, 1.0, and 10 M. The 0.1 and 1.0 M solutions were obtained by diluting Baker reagent grade Dilut-it standardized solutions. The 10 M solution was prepared by dilution of 50% "Baker Analyzed" sodium hydroxide (18.86 M). Carbonate-free water was used for all dilutions and the solutions were protected from contact with air.

Uv spectra were recorded with a Unicam-SP-800-A (Pye Unicam, Cambridge, England) recording spectrophotometer, using matched quartz cells (10 mm optical path).

All solutions used for the measurement of spectra were prepared by mixing adequate volumes of the hydroxide and benzaldehyde stock solutions together with an appropriate amount of water and ethanol or Me_2SO. All these solutions were made up to a total volume of 10 ml.

In the majority of cases, the absorbance at 250–280 nm was measured in solutions containing 1×10^{-4} M of the benzaldehyde studied. In solutions containing higher concentrations of Me_2SO, these benzenoid absorption bands were overlapped by a cutoff due to solvent absorption. In those cases, the absorbance corresponding to n–π^* transition of the carbonyl group at 290–310 nm was measured. Because of the lower extinction coefficient of this absorption band, measurements were then carried out in 5×10^{-4} M benzaldehyde solutions.

Table I. pK_2 Values for Substituted Benzaldehydes in Water–Ethanol Mixtures

Registry no.	Benzaldehyde	σ_x[a]	1% EtOH pK_2	10% EtOH pK_2	10% EtOH Δ[b]	50% EtOH pK_2	50% EtOH Δ[b]	90% EtOH pK_2	90% EtOH Δ[b]
555-16-8	*p*-NO_2[c]	+0.78	−1.05	−1.26	0.21	−1.28	0.23	−1.84	0.79
10203-08-4	3,5-diCl[c]	+0.74	−0.91	−0.97	0.06				
99-61-6	*m*-NO_2[c]	+0.71	−0.81	−1.11	0.30	−1.06	0.25	−1.11	0.30
24964-64-5	*m*-CN[c]	+0.68	−0.64	−0.79	0.15	−0.85	0.21	−0.95	0.31
105-07-7	*p*-CN[c]	+0.66	−0.84	−1.01	0.17			−1.25	0.41
6287-38-3	3,4-diCl	+0.60	−0.19						
455-19-6	*p*-CF_3	+0.55	−0.32	−0.46	0.14	−0.68	0.36	−0.88	0.56
454-89-7	*m*-CF_3	+0.41	−0.07						
587-04-2	*m*-Cl	+0.37	+0.12	−0.26	0.38	−0.05	0.17	−0.46	0.58
456-48-4	*m*-F	+0.34	+0.22	−0.03	0.25	0.00	0.22	−0.41	0.63
104-88-1	*p*-Cl	+0.23	+0.54	+0.27	0.27	+0.27	0.27	−0.11	0.65
58325-13-6	*p*-COO^-	+0.13	+0.38						
591-31-1	*m*-OCH_3	+0.11	+0.76	+0.55	0.21				
459-57-4	*p*-F	+0.06	+0.09					+0.43	0.56
100-52-7	H	0.00	+1.05					+0.48	0.57
620-23-5	*m*-CH_3	−0.07	+1.18						
104-87-0	*p*-CH_3	−0.17	+1.48						
123-11-5	*p*-OCH_3	−0.27	+2.04						
38144-52-4	*m*-O^-	−0.71	+2.12						

[a] Hammett substituent constants.[18] [b] Δ = pK_2 (H_2O) − pK_2 (solvent mixture). [c] pK_2 values of these compounds were obtained by extrapolation of a [log ($C_{ArCH(OH)O^-}/C_{ArCHO}$) − log C_{NaOH}] vs C_{NaOH} plot to C_{NaOH} = 0.

Table II. pK_2 Values for Substituted Benzaldehydes in Water–Me_2SO Mixtures

Benzaldehyde	10% Me_2SO pK_2	10% Me_2SO Δ[a]	50% Me_2SO pK_2	50% Me_2SO Δ[a]	80% Me_2SO pK_2	80% Me_2SO Δ[a]	90% Me_2SO pK_2	90% Me_2SO Δ[a]
p-NO_2[b]	−1.14	0.0.9	−1.29	0.24	−2.03	0.98	−2.35	1.30
m-NO_2[b]	−0.94	0.13						
m-CN[b]	−0.90	0.26						
p-CN[b]	−0.92	0.08	−1.10	0.26	−1.67	0.83	−2.18	1.34
p-CF_3	−0.43	0.11	−0.67	0.35	−1.27[c]	0.95	−1.64[c]	1.32
m-Cl	0.00	0.12	−0.21	0.33	−1.21[c]	(1.33)		
m-F			−0.09	0.32				
p-Cl	+0.49	0.06	+0.28	0.26				
m-OCH_3	+0.64	0.12						
H	+0.86	0.19						
m-CH_3	+1.20	(−0.02)						

[a] Δ = pK_2 (H_2O) − pK_2 (mixed solvent). [b] For these compounds, pK_2 was found by extrapolation of the [log ($C_{ArCH(OH)O^-}/C_{ArCHO}$) − log C_{NaOH}] plot. [c] Determined in 5 × 10^{-4} M benzaldehyde solutions.

The ionization ratios $C_{ArCH(OH)O^-}/C_{ArCHO}$ needed were calculated from experimentally accessible absorbancies, using expression 2

$$C_{ArCH(OH)O^-}/C_{ArCHO} = (A_0 - A)/(A - A_R) \quad (2)$$

where A_0 is the absorbance of the benzaldehyde solution at such a hydroxyl ion concentration or in a buffer of such a pH that no addition of OH^- to benzaldehyde occurs and A_R is the residual absorbance in a solution where all of the benzaldehyde is present as the anion $ArCH(OH)O^-$. A is the absorbance at the given OH^- concentration. Unless otherwise stated, the values of A, A_0, and A_R were measured at the wavelength of maximum benzenoid absorption (250–280 nm). The value of A_R was usually obtained by an extrapolation procedure.

Values of $C_{ArCH(OH)O^-}/C_{ArCHO}$ for each benzaldehyde derivative were measured at 10–15 different sodium hydroxide concentrations in solutions containing fixed ethanol or Me_2SO concentrations ranging from 1 to 90 vol %. Since spectra obtained in the presence of 1% ethanol were indistinguishable from spectra recorded in purely aqueous solutions, it was possible to use absorbancies obtained in 1% ethanolic solutions for the calculation of pK_2 (H_2O) values. Ionization ratios were also determined in benzaldehyde solutions containing a constant concentration of sodium hydroxide (0.01 M) and an ethanol or Me_2SO content which was varied between 1 and 98 vol %.

The addition of ethanol appears to have an appreciable influence on the absorptivity of substituted benzaldehydes. Generally the molar absorptivity decreases by about 40% when increasing the ethanol content of the solution from 1 to 90 vol %. Moreover, there is a slight shift of both the benzenoid and the carbonyl band to shorter wavelengths. These changes must be taken into consideration when absorbancies in solutions containing varying concentrations of ethanol are compared. No such effects were observed in the study of solutions containing varying amounts of Me_2SO.

Unless otherwise stated spectra were time independent over the 3–5 min needed for recording the spectra.

Results

pK_2 Values. Attention has been paid first to the values of equilibrium constant K_2 of substituted benzaldehydes in individual mixed solvents with reference to a standard state in those particular solvents. For this purpose, ratios of $C_{ArCH(OH)O^-}/C_{ArCHO}$ were determined in each solvent mixture as a function of hydroxide concentration. For benzaldehydes with electronegative substituents, the value of the equilibrium constant K_2 defined as

$$K_2 = (C_{ArCH(OH)O^-}/C_{ArCHO}C_{OH^-}) \times (f_{ArCH(OH)O^-}/f_{ArCHO}f_{OH^-}) \quad (3)$$

can be obtained by extrapolation of the plot of [log ($C_{ArCH(OH)O^-}/C_{ArCHO}$) − log C_{NaOH}] against concentration of sodium hydroxide to C_{NaOH} = 0 (i.e., μ = 0).

For benzaldehydes with higher pK_2 values, the overlap procedure[8] can be used. Values obtained by both procedures in the individual solvent mixtures are summarized in Tables I and II.

Table III. J_- of Solutions of NaOH in H_2O–EtOH

$J_- \equiv 14 + pK_2$ (as determined in water) + log C_{ROH^-}/C_R

C_{NaOH}	J_- (1% EtOH)	J_- (10% EtOH)	J_- (50% EtOH)	J_- (90% EtOH)
0.01	11.91			
0.05	12.74			
0.1	13.07	13.20	13.57	13.41
0.2	13.45	13.66	13.73	13.92
0.3	13.68	13.80	13.86	14.14
0.4	13.89	13.94	14.00	14.27
0.5	13.97	14.04	14.14	14.41
0.6	14.04	14.12	14.22	14.53
0.7	14.10	14.20	14.28	14.60
0.8	14.18	14.22	14.34	14.67
0.9	14.24	14.30	14.40	14.73
1.0	14.28	14.34	14.48	14.77
1.32				14.95
1.5	14.52	14.56	14.70	
1.89				15.15
2.0	14.69	14.72	14.80	
2.5	14.85	14.92	14.96	
3.0	14.95	15.06	15.16	
3.5	15.08	15.22		
4.0	15.20	15.38		
4.5	15.32	15.50		
5.0	15.47	15.62		
6.0	15.69			
7.0	15.69			
8.0	16.16			
9.0	16.34			
10.0	16.54			
11.0	17.20			
12.0	17.45			

In every solvent system studied, pK_2 values above a certain limit (dependent on the solvent system) could not be measured owing to either limited solubility of sodium hydroxide or changes of the spectra with time indicating competitive processes at high organic solvent concentrations.

Variations in the differences, Δ, between pK_2 (H_2O) and pK_2 (mixed solvent) for each individual solvent composition are relatively small (Tables I and II), indicating that reaction 1 for different substituted benzaldehydes is almost equally influenced by the change in solvent composition. This fact, together with the existing evidence[3] that for aqueous hydroxide solutions substituted benzaldehydes form a suitable set of J_- indicators, proves that it is indeed justified to use substituted benzaldehydes also for the establishment of J_- scales in water–ethanol and water–Me_2SO mixtures.

J_- for Hydroxide Solutions in Aqueous Ethanol. From the pK_2 (H_2O) values and values of log $C_{ArCH(OH)O^-}/C_{ArCHO}$ at a given C_{OH^-} in a given solvent mixture, it is possible to calculate J_- values for the solvent mixture under consideration using the definition

$$J_- \equiv pK_w + pK_2\,(H_2O) + \log \frac{C_{ArCH(OH)O^-}}{C_{ArCHO}} \qquad (4)$$

where pK_w is the autoprotolytic constant of water. This definition expresses J_- values with reference to a standard state in pure water and therefore basicities of sodium hydroxide solutions in mixed solvents can be compared to basicities of sodium hydroxide solutions in water by J_- values.

Calculated values (Table III) of J_- in ethanol–water mixtures show a dependence on sodium hydroxide concentration (Figure 1) resembling that in water.

To investigate the influence of ethanol concentrations higher than 90 vol % on the values of the J_- function, two series of measurements were carried out in which the sodium hydroxide concentration was kept constant at 0.01 and 0.1 M,

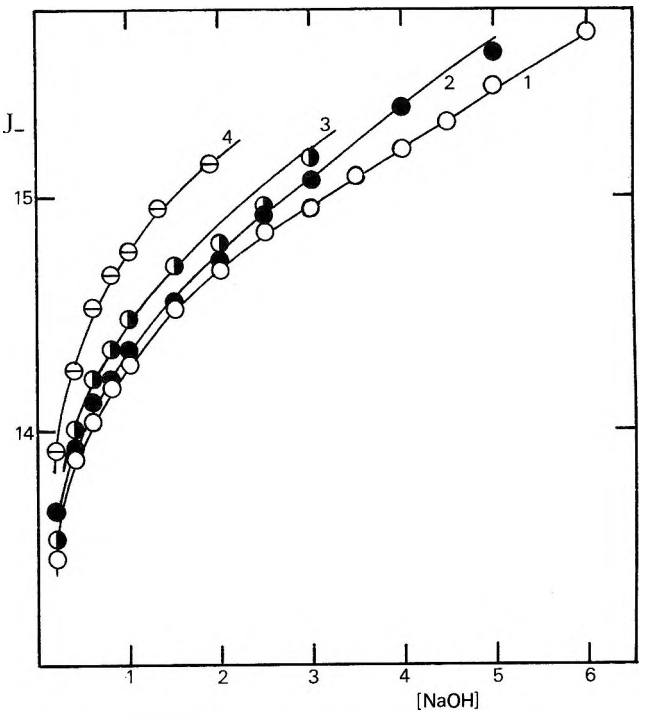


Figure 1. Dependence of the J_- acidity function on sodium hydroxide concentration in water–ethanol mixtures of different composition: curve 1 (○), 1 vol % EtOH; curve 2 (●), 10 vol % EtOH; curve 3 (◑), 50 vol % EtOH; curve 4 (⊖), 90 vol % EtOH.

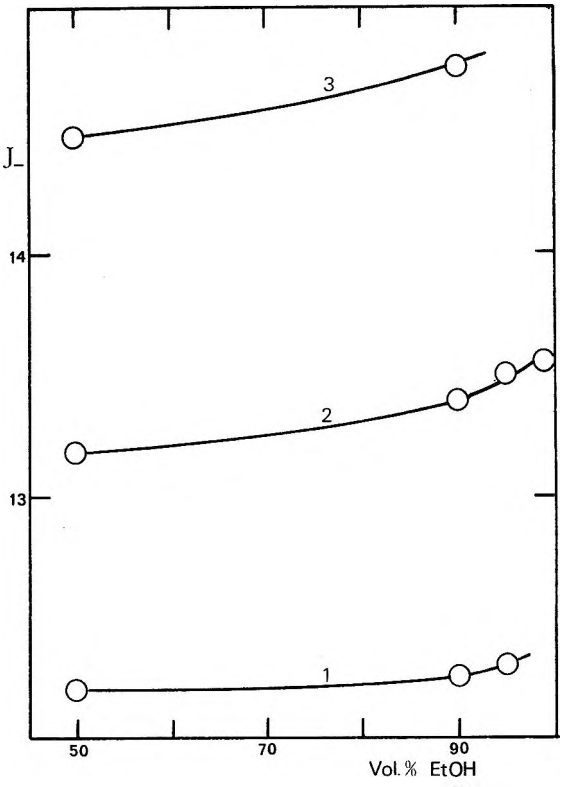


Figure 2. Influence of ethanol on the J_- value of 0.01 M (curve 1) and 0.1 M (curve 2) sodium hydroxide. The two points of curve 3 are taken from Figure 1 for 1 M sodium hydroxide.

respectively, and the concentration of ethanol changed, using *p*-nitrobenzaldehyde (for the 0.01 M NaOH solutions) and *m*-trifluoromethyl- and *m*-chlorobenzaldehyde (for the 0.1 M NaOH solutions) as indicators. After correction for medium effects caused by ethanol, the slight decrease in benzenoid absorption observed resulted in a small increase in J_- with increasing ethanol concentration (Figure 2), paralleling the

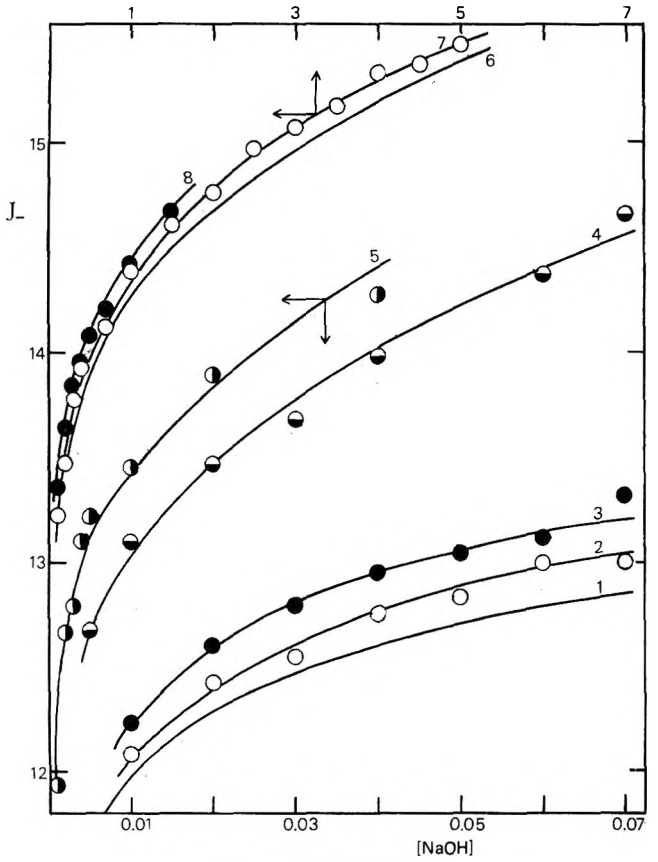


Figure 3. Dependence of the J_- acidity function on sodium hydroxide concentration in water–Me_2SO mixtures of different composition. Curves 1 and 6: aqueous solutions. Curves 2 and 7 (○): 10 vol % Me_2SO. Curves 3 and 8 (●): 50 vol % Me_2SO. Curve 4 (◒): 80 vol % Me_2SO. Curve 5 (◑): 90 vol % Me_2SO. The [NaOH] scale on top of the figure refers to curves 6, 7, and 8, the one on the bottom to curves 1, 2, 3, 4, and 5.

trend calculated for 1 M sodium hydroxide solutions from Figure 1.

J_- for Hydroxide Solutions in Aqueous Me_2SO. J_- values for solutions containing fixed amounts of Me_2SO and varying sodium hydroxide concentrations were determined (Table IV) using eq 4 and show a similar trend for all Me_2SO concentrations investigated (Figure 3).

The effect of Me_2SO contents above 90 vol % was studied in mixtures where the sodium hydroxide concentration was kept constant at 0.01 M and the Me_2SO content varied. *p*-Nitro-, *p*-cyano-, *p*-trifluoromethyl-, *m*-chloro-, *m*-fluoro-, *p*-chlorobenzaldehydes and *m*-anisaldehyde were used as indicators. At Me_2SO concentrations higher than 90 vol %, some of the spectra (particularly those of *m*-Cl, *m*-F, *p*-Cl, and *m*-OCH_3 benzaldehyde) became time dependent and extrapolation of absorbance measurements to zero time became necessary. Hence, the calculated J_- values displayed a larger average deviation (Table V) at these higher Me_2SO concentrations. Below 80 vol % Me_2SO the average deviation was hardly ever higher than 0.05. The dependence of J_- on Me_2SO concentration was compared with that of H_- (Figure 4).

Discussion

Structural Effects and Solvent. The effect of solvent on the equilibrium of reaction 1 can be first discussed in terms of effects on the susceptibility to substituent effects. The values of pK_2, characterizing this equilibrium, are a satisfactorily linear function of the Hammett constants σ_x as shown by the values of the correlation coefficient *r* (Table VI). The values of reaction constant ρ are practically independent of

Table IV. J_- of Solutions of NaOH in Water–Me_2SO Mixtures

C_{NaOH}	J_- (10% Me_2SO)	J_- (50% Me_2SO)	C_{NaOH}	J_- (80% Me_2SO)	J_- (90% Me_2SO)
0.01	12.08	12.23	0.001		11.93
0.02	12.43	12.60	0.002		12.66
0.03	12.54	12.79	0.003		12.79
0.04	12.75	12.94	0.004		13.10
0.05	12.82	13.04	0.005	12.67	13.22
0.06	12.89	13.11	0.006		13.20
0.07	12.98	13.31	0.007		13.24
0.1	13.22	13.35	0.008		13.24
0.2	13.47	13.63	0.01	13.09	13.45
0.3	13.78	13.84	0.02	13.46	13.89
0.4	13.92	13.95	0.03	13.68	
0.5	13.99	14.07	0.04	13.98	14.27
0.6	14.01	14.19	0.06	14.37	
0.7	14.12	14.21	0.07	14.65	
0.8	14.17	14.25			
0.9	14.24	14.35			
1.0	14.38	14.40			
1.5	14.61	14.67			
2.5	14.76				
2.0	14.97				
3.0	15.07				
3.5	15.17				
4.0	15.33				
4.5	15.37				
5.0	15.46				

Table V. J_- in Water–Me_2SO Mixtures Containing 0.01 M NaOH

% Me_2SO (v/v)	J_-	n^a	Average deviation	Indicators used
50	12.26	2	0.04	*p*-NO_2, *p*-CN
80	12.97	2	0.09	*p*-NO_2, *p*-CN
90	13.48	6	0.13	*p*-NO_2, *p*-CN, *p*-CF_3,[b] *m*-Cl,[b] *m*-F,[b] *p*-Cl
91	13.58	3	0.11	*m*-Cl,[b] *m*-F,[b] *p*-Cl
92	13.77	4	0.16	*P*-CF_3,[b] *m*-Cl,[b] *m*-F,[b] *p*-Cl
93	13.84	3	0.12	*m*-Cl,[b] *m*-F,[b] *p*-Cl
94	13.98	4	0.09	*m*-Cl,[b] *m*-F,[b] *p*-Cl, *m*-OCH_3[b]
95	14.08	4	0.14	*p*-CN, *m*-Cl,[b] *m*-F,[b] *p*-Cl
96	14.28	4	0.11	*m*-Cl,[b] *m*-F,[b] *p*-Cl, *m*-OCH_3[b]
97	14.62	4	0.18	*m*-Cl,[b] *m*-F,[b] *p*-Cl, *m*-OCH_3[b]
98	15.07	3	0.06	*m*-F,[b] *p*-Cl, *m*-OCH_3[b]

[a] Number of measurements. [b] Measurements with these compounds were carried out in 5×10^{-4} M benzaldehyde solution.

the ethanol concentration (Table VI), as was already indicated by the almost constant value of the differences Δ between pK_2 (H_2O) and pK_2 (mixed solvent) for a given composition of the mixed solvent (Table I). The same situation is indicated for Me_2SO mixtures (Table II) by the small variations in Δ for any given solvent composition. The number of accessible pK_2 values was in this case too small to allow a meaningful determination of reaction constants ρ. The structural dependence for various water–ethanol mixtures is thus represented by a set of parallel lines. The shifts between these lines are given by the difference between the pK_2^H values (pK of reaction 1 for the unsubstituted benzaldehyde) in the different solvent mixtures.

Provided that the influence of the water–ethanol composition on the reaction involving addition of hydroxyl ions to benzaldehydes can be characterized by any parameter Y_i (the

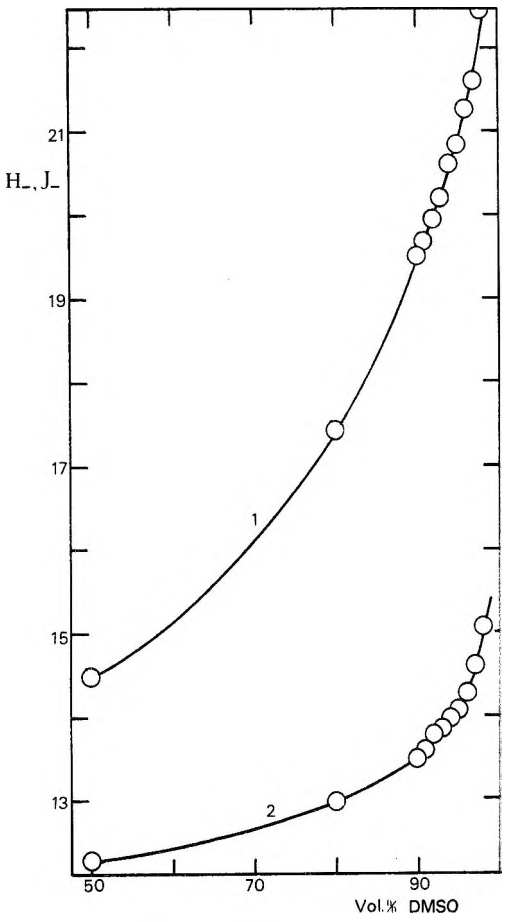


Figure 4. Acidity functions H_- (curve 1) and J_- (curve 2) for water–Me_2SO mixtures containing 0.01 M base (tetramethylammonium hydroxide in case of H_- and sodium hydroxide in case of J_-).

application of Y_- used for benzoic acid dissociations in ethanol–water mixtures[9] might be doubtful), application of the relation $\rho Y_i - \rho Y_0 = C(Y_i - Y_0)$ would indicate that the value of C (0.638 for benzoic acids[9] and −0.573 for anilines[10]) is close to zero for the benzaldehyde reaction (1).

The Validity of the J_- Function. For aqueous sodium hydroxide solutions the validity of the J_- function, describing the basicity of a solution by its ability to add hydroxyl ions to a carbonyl group to form an anion of the geminal diol, has been proved earlier.[3] For all substituted benzaldehydes studied both in water–ethanol and water–dimethyl sulfoxide (Me_2SO), the value of log ($C_{ArCH(OH)O^-}/C_{ArCHO}$) determined from absorbance measurements was found to be a linear function of the J_- function with a slope varying between 0.95 and 1.05 in the region of J_- values where measurements were possible. The Cannizzaro reaction or other consecutive processes did not affect the measurements at 25 °C except in solutions containing the highest concentrations of Me_2SO. Careful measurements with derivatives bearing electronegative substituents did not indicate any evidence for formation of dianions of the geminal diol [$ArCH(O^-)_2$]. Hence it can be concluded that benzaldehydes are simpler indicators than cyanostilbenes,[4] where competition of carbanion formation, even if evidently not predominant, cannot be completely excluded. The behavior of the benzaldehydes is also simpler than that of nitroaromatic compounds where measurements of equilibria leading to the formation of Meisenheimer complexes were complicated by consecutive reactions,[11] by uptake of a second hydroxyl ion,[12a] or by complicated changes in the absorption spectra.[12]

Comparison of Aqueous and Water–Ethanol Solutions. The effect of the presence of ethanol in aqueous solutions of sodium hydroxide is generally speaking, small. This is shown by the similar shape of the dependence of J_- on sodium hydroxide concentration (Figure 1) and by the small differences in J_- values obtained at the different constant ethanol concentrations up to 90 vol % (Table III). Even when the concentration of sodium hydroxide was kept constant (e.g., 0.1 M), the difference between J_- values in 90 vol % ethanol and 98 vol % ethanol was only 0.16 J_- units (Figure 2). In this range of ethanol concentrations, it is necessary to consider the competitive influence of ethoxide ions, the addition of which would result in a decrease of the C_6H_5CO absorbance indistinguishable from the decrease due to hydroxyl ion addition. In 90 vol % ethanol, the ratio of hydroxide and ethoxide concentrations is about 1:1, while in 98 vol % ethanol, it is possible to extrapolate[13] that about 90% of the base will be present as the ethoxide ion.

Table VI. Influence of Ethanol Percentage on the Free Energy Relationship $pK_2 = -\rho\sigma_x + pK_2^H$

% EtOH (v/v)	ρ^a	Std dev in ρ	pK_2^{Hb}	Std dev in pK_2^H	n^c	r^d
1	2.65	0.09	1.08	0.05	18	−0.987
10	2.58	0.17	0.82	0.10	10	−0.984
50	2.84	0.18	0.97	0.11	7	−0.991
90	2.58	0.20	0.52	0.11	10	−0.973

[a] Reaction constant. [b] pK_2 for the unsubstituted benzaldehyde. [c] Number of measurements. [d] Linear correlation coefficient.

The relatively modest increase in the value of the J_- function when increasing the ethanol content of a sodium hydroxide solution from 90 to 98 vol % indicates that either the nucleophilic reactivity of the ethoxide ion under these conditions does not differ substantially from that of the hydroxide ion while solvation of the hydroxide ion and the geminal diol anion is similar to solvation of the ethoxide ion and the hemiacetal anion, or that compensation of effects takes place.

The procedure by which Yagil and Anbar calculated theoretical H_- values[14b] can be applied to the J_- function as well and leads to

$$J_- = 14 + \log C_{OH^-} - n \log C_{H_2O} \qquad (5)$$

where C_{H_2O} is the free water concentration and n can be considered[14a] either as the hydration number of the hydroxide ion or as the difference in hydration numbers between (ArCHO + OH^-) and $ArCH(OH)O^-$. Calculations of J_- with $n = 3$ and $n = 4$ were made for aqueous sodium hydroxide solutions, using for C_{H_2O} the expression $C_{H_2O} = d - 0.001\,(18n + 40)C_{OH^-}$ in which d is the density of the solution (Table VII). Comparison of the calculated values with the experimental J_- values for aqueous sodium hydroxide solutions seems to indicate a change in n with the concentration of sodium hydroxide. In solutions which are 2 M in sodium hydroxide or less, the best agreement between calculated and experimental J_- values if obtained for n larger than 4, between 3 and 5 M for $n = 4$, and between 6 and 8 M for $3 > n > 4$. Although the results for aqueous sodium hydroxide solutions with concentrations between 9 and 11 M also suggest a value of n between 3 and 4, it is more likely that in this concentration range a further dehydration takes place causing an increase in the activity of the OH^- ion. Under those circumstances, it is no longer appropriate to calculate J_- values by formula 5, which only takes into account the mass action effect of the decrease in free water concentration.

An attempt to apply eq 5 to the calculation of J_- values in ethanol–water mixtures containing base, using the expression

Table VII. Theoretical and Experimental Values of J_- for Aqueous NaOH Solutions

C_{NaOH}	J_- (exp)	J_- (theor)$_{n=3}$[a]	J_- (theor)$_{n=4}$[a]
1	14.28	14.08	14.12
2	14.69	14.46	14.58
3	14.95	14.73	14.90
4	15.20	14.95	15.20
5	15.47	15.16	15.51
6	15.69	15.35	15.82
7	15.96	15.56	16.17
8	16.16	15.78	16.58
9	16.34	16.01	17.09
10	16.64	16.27	17.71
11	17.20	16.50	18.61
12	17.45		

[a] J_- (theor) = 14 + log $C_{OH^-} - n \log C_{H_2O}$ where $C_{H_2O} = d - 0.001\,(18n + 40)\,C_{OH^-}$ (d is density of the solution).

$C_{H_2O} = d - 0.001C_{OH} - (18n + 40) - 0.0079x$ (x is the volume percentage of ethanol present), failed especially for the higher ethanol percentages where it led to J_- values considerably higher than actually found. This again indicates that the decrease in free water concentration which takes place on adding increasing amounts of ethanol is largely compensated for by the fact that the ethanol in many respects displays a behavior similar to the water it replaces.

Comparison of Aqueous and Water-Me_2SO Solutions. The increase in J_- with increasing Me_2SO concentration cannot be ascribed to a change in one single physical or chemical property. It is necessary to consider the change in dielectric constant, the effect of hydrogen bonding between Me_2SO and water (particularly at high Me_2SO concentrations), the change in water activity, dispersion interactions, and the effect of Me_2SO on the structure of water and on the hydration of the hydroxide ion. These aspects of the increase in the basicity of solutions containing a constant amount of base with increasing Me_2SO content have been adequately discussed by Dolman and Stewart.[7]

The question which needs some further discussion is why the effect of Me_2SO concentration on the J_- acidity function describing hydroxide ion addition to benzaldehydes is considerably smaller (Figure 4) than the effect on the H_- function obtained from measurements involving proton abstraction from anilines and diphenylamines.

Some idea about the origin of this difference might be obtained by comparing the expression for H_-[14a]

$$H_- = 14 + \log C_{OH^-} - (n + 1) \log a_{H_2O} + \log \frac{f_{HA} f_{OH^-}}{f_{A^-}} \quad (6)$$

with a similar expression which can be derived for the J_- function:

$$J_- = 14 + \log c_{OH^-} - n \log a_{H_2O} + \log \frac{f_{ArCHO} f_{OH^-}}{f_{ArCH(OH)O^-}} \quad (7)$$

From 6 and 7, the difference between H_- and J_- is found to be

$$H_- - J_- = -\log a_{H_2O} + \log \frac{f_{HA}}{f_{A^-}} - \log \frac{f_{ArCHO}}{f_{ArCH(OH)O^-}}$$

Using available information on activity of water in water–Me_2SO mixture,[15] the value $H_- - J_- + \log a_{H_2O}$ is larger than zero, which indicates that the ratio f_{HA}/f_{A^-}, for the H_- indicator acids, is considerably larger than the ratio of $f_{ArCHO}/f_{ArCH(OH)O^-}$ for the benzaldehydes used as J_- indicators. Probably this difference in activity coefficient ratios is due to a larger extent of charge delocalization in the A^- anion compared to the geminal diol anion, which causes an extra stabilization of A^- (manifested by a decrease in f_{A^-}) by dispersion interaction with Me_2SO.

The acidity function J_- (denoted as J_M) for addition of methoxide ions to benzaldehydes[16] increases also much less steeply with base concentration than acidity function obtained for additions of methoxide ion to polynitrobenzenes[17] or α-cyanostilbenes.[4]

The foregoing considerations confirmed that the acidity function approach to the properties of strongly acidic or strongly alkaline media leads to acidity scales which not only depend on the investigated solvent system but also on the nature of the indicators used.

Acknowledgment. One of us (T.P.) is indebted to the Netherlands America Commission for Educational Exchange for financial support by a Fulbright-Hayes grant.

References and Notes

(1) Reactor Centrum Nederland (Afdeling Chemie), Westerduinweg 3, Petten NH, The Netherlands.
(2) K. Bowden, *Chem. Rev.*, **66**, 119 (1966); see also "Solute-Solvent Interactions", J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N.Y., 1969, pp 186–215.
(3) W. J. Bover and P. Zuman, *J. Am. Chem. Soc.*, **95**, 2531 (1973).
(4) D. J. Kroeger and R. Stewart, *Can. J. Chem.*, **45**, 2163 (1967).
(5) K. Bowden, *Can. J. Chem.*, **43**, 2624 (1965).
(6) R. Stewart and J. P. O'Donnell, *Can. J. Chem.*, **42**, 1(81, 1694 (1964).
(7) D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).
(8) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, **54**, 2721 (1932).
(9) E. Grunwald and B. J. Berkowitz, *J. Am. Chem. Soc.*, **73**, 4939 (1951).
(10) B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, **75**, 559 (1953).
(11) (a) C. H. Rochester, *Trans. Faraday Soc.*, **59**, 2820, 2829 (1963); (b) V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1727 (1964).
(12) (a) R. Schaal, *C. R. Acad. Sci.*, **239**, 1036 (1954); (b) V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1710, 1717 (1964).
(13) E. F. Caldin and G. Long, *J. Chem. Soc.*, 3737 (1954).
(14) (a) J. T. Edward and I. C. Wang, *Can. J. Chem.*, **40**, 399 (1962); (b) G. Yagil and M. Anbar, *J. Am. Chem. Soc.*, **85**, 2376 (1963).
(15) B. C. Cox and P. T. McTigue, *Aust. J. Chem.*, **20**, 1815 (1967).
(16) M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2*, 185 (1975).
(17) F. Terrier, *Ann. Chim. (Paris)*, **4**, 153 (1969).
(18) O. Exner, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Ed., Plenum Press, New York, N.Y., 1972, pp 1–69.

Reactions of Delocalized Dicarbanions with Dihalides

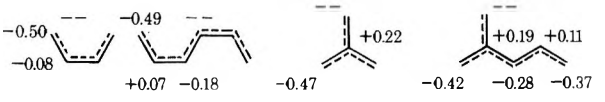
Joseph J. Bahl, Robert B. Bates,* William A. Beavers, and Nancy S. Mills

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

Received August 12, 1975

The reaction of butadiene dianion, hexatriene dianion, 2-methyleneallyl dianion, and 2-methylenepentadienyl dianion with dihalides $X(CH_2)_{1-4}X$ gave, in variable yield, products with three-to seven-membered rings as well as some acyclic products. The predominant cyclic products generally came from initial alkylation at the most negatively charged carbon of the dianion to give the most stable monoanion intermediate, followed by cyclization to give the smallest ring possible. These reactions appear to provide the most convenient route to some of the observed products.

The reaction of a carbanion with an alkyl halide is one of the most commonly used carbon–carbon bond-forming reactions. Recently delocalized dicarbanions **1–4** have been prepared and shown to react in good yield with 2 equiv of alkyl halide.[1] The current study was undertaken to determine the feasibility of treating dianions **1–4** with dihalides to give a series of cyclic hydrocarbons, some of which are currently available only by multistep procedures using unusual starting materials.[2]



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

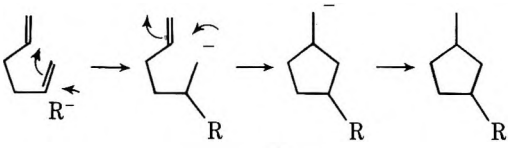
Results

Dianions **1–4** were prepared in 25–90% yield as crystalline dilithium salts solvated with two tetramethylethylenediamine (TMEDA) molecules[3] by metalating the appropriate alkene or diene.[1] Although dianion yields would have been higher if the dianion in the supernatent liquid were included, it was considered desirable to avoid contamination from the intermediate monoanion which remains in solution. The salts of **1** and **3** had not been crystallized previously.

The dihalides used were $ClCH_2Cl$, ICH_2I, and $Br(CH_2)_{2-4}Br$. To favor ring formation over polymerization, high dilution techniques were indicated. After it was determined in one case that simultaneous addition of dilute solutions of the two reactants to a large volume of vigorously stirred solvent[5] gave only slightly better yields than adding a dilute dianion solution to a vigorously stirred 0.1 M dihalide solution, the latter technique was employed.

The products obtained are summarized in Table I. They were isolated by distillation and preparative GC, and characterized by ^1H NMR, mass spectrometry, and in many cases by comparison with authentic samples. The *E* configurations of **8b** and **8c** were demonstrated by oxidation to (*E*)-cyclopentane-1,2-dicarboxylic acid[6] and (*E*)-cyclohexane-1,2-dicarboxylic acid,[7] respectively. The 1,2-divinylcyclopropane isolated must have the *E* configuration as shown in **8a** since it is stable to at least 125 °C, whereas the *Z* isomer Cope rearranges above 0 °C.[8]

During the reactions involving **2** prepared by dimetalating 1,5-hexadiene with *n*-butyllithium, 1-methyl-3-*n*-butylcyclopentane (**14a**) was noted among the products. That this is a minor by-product in the dimetalation step was shown by isolating it in 7% yield from the mother liquors from the preparation of **2**. Similarly, when *tert*-butyllithium was substituted for *n*-butyllithium, 1-methyl-3-*tert*-butylcyclopentane (**14b**) was formed in 7% yield. These reactions may occur as follows, or perhaps with the first two steps concerted:



14a, R = *n*-butyl
b, R = *tert*-butyl

Discussion

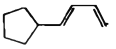
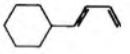
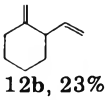
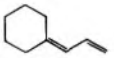
Of the products listed in Table I, **5a–c**, **7a–c**, **8a–c**, **11a–b**, **12a–c**, and **13**, with three- to seven-membered rings, were from the desired reactions. Where total yields of these cyclization products were low, it was not due to the formation of further isomeric cyclization products (e.g., cyclopentene in the first reaction), but to side reactions. Most of the by-products were higher boiling and no doubt arose from two intermolecular alkylations rather than an intermolecular alkylation followed by an intramolecular one; these side reactions could have been lessened by employing higher dilution.

The diethylations of these same four dianions[1] are far from perfect models for these cyclizations, especially in the case of **2**, which gives only 1,4 and 1,6 diethylation, but only 1,2 and 3,4 dialkylation in its cyclic reactions. However, it might be expected that the formation of the *first* carbon–carbon bond would occur with essentially the same distribution over the carbons of the dianion, whereas in the *second* alkylation, the distribution pattern could differ greatly between the intermolecular and intramolecular cases. The diethylation products could in all cases be rationalized by initial attack at an end of the dianion system to give the most stable monoanion intermediate, e.g., pentadienyl anion **15a** from **2**.[1] However, although no 3,4-diethyl-1,5-hexadiene was found in the diethylation of **2**, **8a–c**, the analogous cyclic products, were found in significant amounts and prove that some of the initial alkylation of **2** by a dihalide occurs at carbon 3, the site of *second* highest electron density,[9] giving an ene-allylanion intermediate **15b**. Probably some of the 81% of diethylation products of

15a **15b**

2 which could have come from initial attack at either carbon 1 or 3 similarly came from initial attack at carbon 3 rather than all at 1 as was previously assumed. All of the cyclization products other than **8a–c** can be rationalized as coming from *initial alkylation at the most negatively charged carbon of the dianion to give the most stable monoanion intermediate, followed by cyclization to give the smaller of two possible ring sizes*, i.e., three rather than

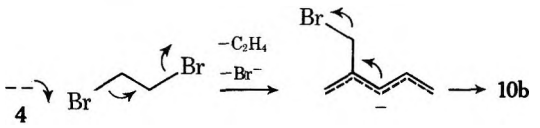
Table I. Isolated Products and Yields

Starting Materials	ICH_2I	$Br(CH_2)_2Br$	$Br(CH_2)_3Br$	$Br(CH_2)_4Br$
1	 5a, 3% 6a, 7%	 6a, 33%	 5b, 8%	 5c, 3%
2	 7a, 20%[a] 6b, 10%	 6b, 61%	 7b, 8%	 7c, 0.6%
	 8a, 8%		 8b, 9%	 8c, 4%
3	 9, 5% 10a, 6%	 10a, 70%	 11a, 96%	 11b, 15%
4	 12a, 14%		 12b, 23%	
	10b, 10%	 10b, 100%	 13, 5%	 12c, 5%

[a] In this case, $ClCH_2Cl$ was used instead of ICH_2I; yields of these products might have been higher with ICH_2I. Other products included chlorobenzene (5%), 2,4,6-octatriene (3%), and 1,3,5-octatriene (2%).

five, four than six, five than seven, six than eight, and seven than nine. **12b** and **13** can arise via competing cyclizations of the same precursor to give the same size ring.

Instead of giving cyclization products, ethylene dibromide (and to a minor extent, the methylene halides) oxidized the dianions, giving two halide ions, 1 mol of ethylene, and, in relatively high yield, **6a, 6b, 10a,** or **10b,** obtained by the loss of two electrons from the dianion. These reactions may proceed by displacement on bromine as indicated below for **4**:



These displacements on bromine occur readily with ethylene dibromide because the leaving group is bromide ion, and most of the time this dihalide is in the anti conformation, favoring this reaction and hindering displacement on carbon. Only the *E* stereoisomer of **6b**[10] was observed, probably reflecting a very large predominance of *E* configuration for the central bond of **2**.[1,4] Dianions are oxidized similarly by I_2, but the yield of **6b** from **2** with I_2 was only 8%, probably because **6b** reacts further with I_2.

The methylene halides are sufficiently acidic to protonate these dianions, especially the very basic **1** and **3**. Yields of diprotonation products from **1–4** were 30, 10, 60, and 15%, respectively. With methylene *chloride*, **4** gave a 25% yield of diprotonation products and virtually no **10b** or **12a**. An unusual product from **3** was 2-methyl-1-butene (**9**), apparently formed by alkylation of the monoanion with methyl iodide formed from methylene iodide.

Among the unexpected products was chlorobenzene, obtained in 5% yield from the reaction of **2** with methylene chloride; this is reminiscent of the formation of biphenyl (77% yield) by heating 3-phenylhexatriene dianion at 60 °C.[11] Other unusual products from the reaction of **2** with methylene chloride were 1,3,5- and 2,4,6-octatrienes (2 and 3%, respectively).

Owing to the shortness of these syntheses and the ease in separating the products (most side reactions lead to higher molecular weight substances readily removed by distillation), these reactions may serve as the most convenient ways of preparing some of these substances. For example, the previous syntheses of **8a**,[12] **8b**,[13] and **8c**[13] each required many steps. **6b** was prepared previously in considerably lower yield by a several-step procedure which gives a mixture of stereoisomers rather than *E* only.[14] **10b** and its thermolysis product 3-methylenecyclopentene may be more readily prepared by the procedure described herein than by earlier methods.[15] **7b, 12a, 12b,** and **12c** have to our knowledge not been prepared previously.

Experimental Section

All solvents and starting alkenes were distilled from either CaH or $LiAlH_4$ and stored under argon over molecular sieves. The gases, (*Z*)-2-butene and isobutylene, were distilled from lecture bottles just prior to use and not further purified. *n*-Butyllithium and *tert*-butyllithium solutions in hexane or pentane were used as received from Alfa Inorganics. Columns for preparative GC were 15–25 ft × 0.25 in., packed with 20% Carbowax 20M on Chromosorb P, and operated at 50–160 °C.

Preparation of Dicarbanions 1–4. Each dianion was prepared and crystallized in 18 × 150 mm test tubes filled with argon and tightly capped with a rubber septum. To these tubes was added 10.0 ml (24 mmol) of 2.4 M *n*-butyllithium. The tubes were cooled in an ice–acetone bath and 3.6 ml (24 mmol) of anhydrous TMEDA was added. Upon warming to room temperature, the white, crystalline 1:1 complex dissolved whereupon 12 mmol of the corresponding precursor alkene was added via syringe. This mixture was set aside at room temperature until crystallization was complete. Just prior to use, the crystallized dianion was purified by removing the supernatent solution by syringe, washing the resi-

due with hexane (optional), and drying in a stream of dry argon. The yield, necessary for the determination of the amount of dihalide to be used, was determined by weighing the dried anion. The precursor, crystallization time, solvent(s), and yield for each dianion follow: **1** [(*Z*)-2-butene; 3–5 weeks; TMEDA; 25–35%];[16] **2** (1,5-hexadiene; overnight; TMEDA or THF or ether; 80–90%); **3** (isobutylene; 3–7 days; TMEDA or THF; 50–70%); **4** (2-methyl-1,4-pentadiene; 2–4 weeks; TMEDA or THF; 30–40%).

Reaction of Dianions 1–4 with Dihalides. To an argon-filled, septum-capped, 250-ml round-bottomed flask equipped with a magnetic stirring bar and cooled by a dry ice–acetone bath was added 30–50 ml of anhydrous solvent and a 10% excess of dihalide. The solvent used depended on the properties of the desired products. For products boiling below 50 °C (**5a, 6a, 9,** and **10a**) dibutyl ether was used. Diethyl ether was suitable for materials boiling above 50 °C, while THF and hexane were used for products with boiling points above 90 °C.

The reaction was conducted with rapid stirring at −78 °C by adding dianion solution dropwise via syringe through the septum cap. Dibutyl ether tended to crystallize at these temperatures but this problem was avoided by either conducting the reaction rapidly or warming to no higher than −50 °C. The product was worked up in different ways depending on the product's boiling point. The low-boiling **5a, 6a, 9,** and **10a** were isolated by fractional distillation through a short Vigreux column, collecting all material until the distillation head temperature exceeded 100 °C. A slow stream of argon swept out further product, which was collected in a series of traps cooled in acetone–dry ice baths. The crude product was further purified by preparative GC. Products boiling above 50 °C were worked up by quenching with 20 ml of water unless the solvent was THF. The organic layer was separated and the aqueous phase was discarded after being extracted with 2 × 15 ml of ether. The combined organic phases were washed with dilute sulfuric acid to extract amines. An emulsion generally formed when the washings became acidic but the problem could be minimized by making the acid wash emulsion slightly basic, separating the aqueous phase and backwashing it with 2 × 15 ml of ether, combining the organic phases and extracting the combined solution with one final 10-ml wash of dilute sulfuric acid. If an emulsion still formed, it was separated by centrifuging. The organic layer was then washed with water, recentrifuged if necessary, and the separated organic layer washed with 5% aqueous sodium bicarbonate. The product solution was dried over sodium hydroxide pellets and filtered into a round-bottomed distillation flask and the solvent was removed by careful fractional distillation through a 3-ft tantalum wire column. When solvent removal was nearly complete, the distillation was interrupted, the residue was cooled and drawn into a syringe, and the material was flash distilled under vacuum. The purified product, free from polymer, was collected in a dry ice cooled trap and was suitable for preparative GC.

If THF was used as the initial solvent, the aqueous workup was avoided since much of the product was carried into the aqueous washes and thereby lost. Instead the crude reaction product was fractionally distilled, removing further THF by periodically adding spectrograde hexane and continuing the distillation until all THF had codistilled. The cooled residue was then diluted with 20 ml of ether and worked up as described in the preceding paragraph.

The structure of **7b** was deduced from its spectral properties:[17] MS *m/e* 122 (m), 107, 93, 79, 67 (base); NMR δ 6.3 (ddd, 1, *J* = 8.5, 9.5, 16.5 Hz), 5.9 (m, 2), 5.0 (dd, 1, *J* = 2.0, 16.5 Hz), 4.9 (dd, 1, *J* = 2.0, 9.5 Hz), 2.4 (m, 1), 1.6 (m, 8).

For **12a**: NMR δ 6.0 (ddd, 1, *J* = 7.0, 9.5, 17.0 Hz), 5.1 (d, 1, *J* = 17.0 Hz), 5.1 (d, 1, *J* = 9.5 Hz), 4.9 (m, 2), 3.7 (m, 1), 2.7 (m, 2), 2.1 (m, 2).

Anal. Calcd for C_7H_{10}: C, 89.29; H, 10.71. Found: C, 89.13; H, 10.57.

For 12b: MS *m/e* 122 (m), 107, 93, 79 (base), 67; NMR δ 6.0 (ddd, 1, *J* = 7.0, 9.0, 18.0 Hz), 5.1 (dd, 1, *J* = 2.0, 9.0 Hz), 5.1 (dd, 1, *J* = 2.0, 18.0 Hz), 4.8 (m, 2), 2.8 (m, 1), 2.3 (m, 2), 1.7 (m, 6).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.36; H, 11.51.

The structure of **12c** was deduced from the similarity of its NMR spectrum to those of **12a** and **12b**.[17] For **12c**: NMR δ 6.0 (ddd, 1, *J* = 6.0, 9.5, 17.5 Hz), 5.1 (d, 1, *J* = 9.5 Hz), 5.1 (d, 1, *J* = 17.5 Hz), 5.0 (m, 2), 3.1 (m, 1), 2.3 (m, 2), 1.8 (m, 8).

Preparation of Compounds 14a and 14b. The reaction was set up as for the preparation of dianion **2**, using *n*-butyllithium for preparing **14a** and *tert*-butyllithium for **14b**. After 12 h at room temperature, the dark red-black liquid was removed by a syringe and quenched into 30 ml of water. The organic layer was separated and treated as above to remove impurities except that the flash distillation was unnecessary. Starting with 1.0 g (12 mmol) of 1,5-hexadiene, the yield of both **14a** and **14b** after preparative GC was 115 mg (7%).

Stereochemistry of 8b and 8c. According to the method of Arai and Crawford,[12] 58.5 mg (0.48 mmol) of **8b** was added to a septum-capped 50-ml Erlenmeyer flask containing a stirring bar, 1.65 g (7.67 mmol) of sodium periodate, 20 mg (0.13 mmol) of potassium permanganate, and 45 ml of water. After 6 days, the reaction was worked up by filtering off the inorganic solids, extracting the organic phase exhaustively with ether, evaporating the ether, and dissolving the solid residue in 1 ml of hot water. In a few days crystals of acid formed which had mp 160–162 °C [lit. for (*Z*)-1,2-cyclopentanedicarboxylic acid, 139–140 °C; (*E*)-1,2-cyclopentanedicarboxylic acid, 162–163 °C].[6] These crystals showed no melting point depression on mixing with an authentic sample of (*E*)-1,2-cyclopentanedicarboxylic acid.

The identical procedure using 65.5 mg (0.48 mmol) of **8c** gave product with mp 223–226 °C [lit. for ((Z)-1,2-cyclohexanedicarboxylic acid, 192 °C; (*E*)-1,2-cyclohexanedicarboxylic acid, 227–229 °C].[6,7]

Acknowledgment. Financial support from the National Science Foundation (GP-38070X) is gratefully acknowledged.

Registry No.—**1,** 53721-70-3; **2,** 53721-71-4; **3,** 53721-69-0; **4,** 53721-72-5; **7b,** 58298-55-8; **12a,** 58298-56-9; **12b,** 19995-92-7; **12c,** 58298-57-0; (*Z*)-2-butene, 590-18-1; 1,5-hexadiene, 592-42-7; isobutylene, 115-11-7, 2-methyl-1,4-pentadiene, 763-30-4; ICH_2I, 75-11-6; $Br(CH_2)_2Br$, 106-93-4; $Br(CH_2)_3Br$, 109-64-8; $Br(CH_2)_4Br$, 110-52-1.

References and Notes

(1) R. B. Bates, W. A. Beavers, M. G. Greene, and J. H. Klein, *J. Am. Chem. Soc.*, **96,** 5640 (1974).
(2) For the preparation of a cyclooctane ring in 25% yield by reaction of a delocalized dianion with a dihalide, see M. P. Cooke, Jr., and R. Goswami, *J. Am. Chem. Soc.*, **95,** 7891 (1973).
(3) Only one carbanion (**2**) is positively known to have this composition,[4] but the others appear to from quenching studies.
(4) S. K. Arora, R. B. Bates, W. A. Beavers, and R. S. Cutler, *J. Am. Chem. Soc.*, **97,** 6271 (1975).
(5) E. J. Corey and E. Block, *J. Org. Chem.*, **31,** 1663 (1966).
(6) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **20,** 1178 (1955); "Dictionary of Organic Compounds", Vol. 2, Oxford University Press, London, 1965, p 728.
(7) D. E. Applequist and N. D. Werner, *J. Org. Chem.*, **28,** 48 (1963).
(8) J. M. Brown, B. T. Golding, and J. J. Stofko, *J. Chem. Soc., Chem. Commun.*, 319 (1973).
(9) The charge calculated on each carbon atom in dianions **1–4** is shown on its formula; an INDO program was used and since hydrogens were included, the sums of charges on carbon do not total 2.
(10) J. C. H. Hwa, P. DeBenneville, and H. Sims, *J. Am. Chem. Soc.*, **82,** 2537 (1960).
(11) R. M. Magid and S. W. Wilson, *Tetrahedron Lett.*, 19 (1971).
(12) M. Arai and R. J. Crawford, *Can. J. Chem.*, **50,** 2158 (1972).
(13) E. Vogel, K. H. Ott, and K. Gajek, *Angew. Chem.*, **71,** 172 (1961).
(14) "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 608.
(15) T. C. Shields, W. E. Billups, and A. R. Lepley, *J. Am. Chem. Soc.*, **90,** 4749 (1968); W. E. Billups, T. C. Shields, W. Y. Chow, and N. C. Deno, *J. Org. Chem.*, **37,** 3676 (1972).
(16) The crystalline form of **1** referred to here is red. In some runs, orange crystals, relatively insoluble, formed first; on longer standing they were replaced by the red solid.
(17) Elemental analyses on **7b** and **12c** were 2–3% low on carbon, presumably owing to partial oxidation on exposure to air.

Carbonyl-Stretching Frequencies in Substituted Phenyl Carboxylates[1]

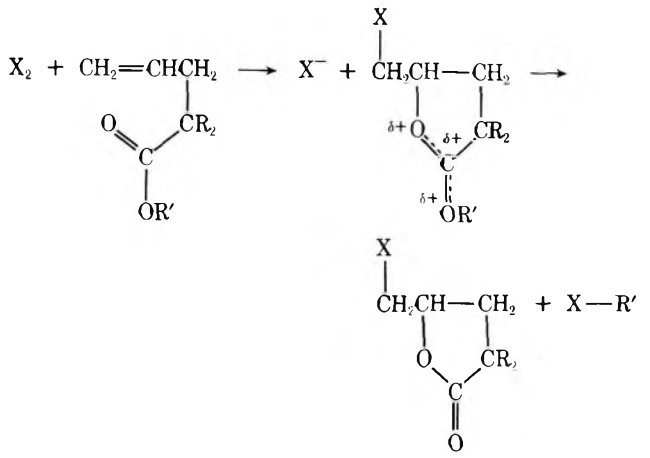
Antonia T. do Amaral[2] and Luciano do Amaral*

Instituto de Química da Universidade de São Paulo, Caixa Postal 20780, São Paulo, SP., Brazil

Received August 12, 1975

The infrared carbonyl-stretching frequencies for para-substituted phenyl allylacetates (set I), para-substituted phenyl diphenylacetates (set II), para-substituted phenyl allyldiphenylacetates (set III), phenyl acetate, phenyl allylphenylacetate, and phenyl propyldiphenylacetate were determined in carbon tetrachloride and chloroform. In the sets studied the values obtained are shown to correlate with Hammett substituent constants for the ring substituent. Using phenyl acetate as the basis for comparison, it was found that increasing the methyl substitution by alkyl or aryl substituents causes lowering of the infrared carbonyl-stretching frequency.

It is known that the γ,δ-unsaturated acids and their derivatives react with electrophilic reagents giving rise to δ-substituted γ-lactones.[3-5]



It was shown in a qualitative way that an increase of electron density on the carbonyl group[6] and/or the presence of substituents at the α position of the carboxylic acids[7,8] increases the rate of the lactonization.

Our infrared investigations were undertaken in order to obtain quantitative information pertinent to the electronic effects on the carbonyl-stretching frequencies of phenyl allylacetates caused by substituents on the para position of the benzene ring and by the substitution at the α position of the carboxylic acids.

Experimental Section

Materials. Allylacetic acid, diphenylacetic acid, and phenyl acetate were obtained commercially and were either redistilled or recrystallized before use. Allyldiphenylacetic acid and phenyl allylphenylacetate (XVII) were synthesized according to known procedures.[5]

Preparation of Para-Substituted Phenyl Allylacetates. *p*-Nitrophenyl allylacetate (I), *p*-bromophenyl allylacetate (II), phenyl allylacetate (III), *p*-methoxyphenyl allylacetate (IV), and *p*-tolyl allylacetate (V) were synthesized according to known procedures.[5] Compound II, yield 79%. Anal. Calcd: C, 52.21; H, 4.35. Found: C, 51.21; H, 4.58. Bp 94–95 °C (0.12 Torr); ir absorption (film) 3100, 1760, 1660, 1600, 1490, 1220, 1015, 840, and 520 cm^{-1}.

Preparation of Para-Substituted Phenyl Diphenylacetates. The diphenylacetic acid (0.10 mol) with 0.20 mol of thionyl chloride were heated until the evolution of gases ceased. After the excess of thionyl chloride was removed by distillation, 0.10 mol of the corresponding phenol was added and the mixture heated for 2–3 h. The product was washed with cold 10% sodium hydroxide solution and water, and extracted with ether; solvent was evaporated. The crude ester was recrystallized from methanol (Table I).

Preparation of Para-Substituted Phenyl Allyldiphenylacetates. *p*-Bromophenyl allyldiphenylacetate (XII), phenyl allyldiphenylacetate (XIII), *p*-methoxyphenyl allyldiphenylacetate (XIV), and *p*-tolyl allyldiphenylacetate (XV) were prepared by the following method. A solution of 11 mmol of n-butyllithium (solution 2 M in hexane) was added to a solution of 12 mmol of isopropylcyclohexylamine (ICA) in 30 ml of THF at −5 °C. The reaction mixture was cooled to −78 °C. A solution of 10 mmol of the ester (*p*-bromophenyl, phenyl, *p*-methoxyphenyl, and *p*-tolyl diphenylacetate) in 10 mmol of THF was added slowly. After 15 min, 10 ml of Me_2SO was added and the solution stirred for 15 min. Allyl bromide (15 mmol) was then added in one portion. After stirring at −78 °C for 2 h and then at room temperature for 2 h followed by distillation of the solvent, the residue was poured into water and extracted with petroleum ether. The ether solution was washed with 10% HCl cold and with water. After removal of the petroleum ether, the crude ester was obtained and distilled or recrystallized from methanol (Table II).

Phenyl *n*-propyldiphenylacetate (XVI) was prepared as above, employing phenyl diphenylacetate and *n*-propyl bromide. Compound XVI, yield 91%, mp 69–70 °C. Anal. Calcd: C, 83.58; H, 7.18. Found: C, 83.60; H, 6.71. Ir absorption (KBr) 3100–2860, 1746, 1595–1590, 1495–1485, 1210, 1100 cm^{-1}; ^1H NMR absorption (CCl_4) 0.67–1.43, 2.20–2.60, 6.67–7.50, and 7.35 ppm. *p*-Nitrophenyl allyldiphenylacetate (XI) was prepared by heating 12 mmol of allyldiphenylacetic acid with 71 mmol of thionyl chloride until the evolution of gases ceased. After the excess of thionyl chloride was removed by distillation, 14 ml of carbon tetrachloride and a solution of 42 mmol of *p*-nitrophenol in 28 ml of pyridine was added. The reaction mixture was kept at room temperature for 5 days. The product was washed with cold 10% cupric sulfate solution and extracted with ether. The ether solution was washed with 10% sodium hydroxide solution and water. The crude ester was obtained by distillation. This was recrystallized from methanol, yield 96%, mp 116–118 °C. Anal. Calcd: C, 73.98; H, 5.13. Found: C, 73.95; H, 5.05. Ir absorption (KBr) 3110–2860, 1759, 1640, 1590–1490, 1550, 1345, 1200, and 885 cm^{-1}; ^1H NMR absorption 3.22, 4.76–5.20, 5.23–6.00, 7.02, 7.32, 8–17 ppm.

Infrared Spectroscopy. Ir spectra (cm^{-1}) were measured in carbon tetrachloride and in chloroform (0.040, 0.060, and 0.080 M) on a Perkin-Elmer Model 457 grating spectrometer. The carbonyl region was scanned slowly, and spectra were recorded in triplicate, at a chart speed of 50 cm^{-1}/min, between 1900 and 1500 cm^{-1}. Calibration and paper alignment difficulties were minimized by recording the 1583.1-cm^{-1} polystyrene band on each spectrum. The transmittance minima given are the average of nine readings (on triplicate runs). The carbonyl absorption band had a symmetric shape that simplified the determination of its position in the spectrum. The standard deviation, S, was calculated for each compound. The carbonyl stretching frequency was not modified significantly dependent on the concentration (examples are shown in Table III). ^1H NMR spectra were recorded on carbon tetrachloride solutions on a Varian Model T-60 spectrometer with an internal Me_4Si reference. Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

Results

Preparation of Esters. Esters from allylacetic acid and diphenylacetic acid were prepared by the usual method of converting the respective acids into their chlorides by reaction with thionyl chloride, followed by reaction with the appropriate phenol.[5] The reaction of the allyldiphenylacetic acid with thionyl chloride, followed by reaction with para-substituted phenol, has produced impure esters of difficult purification, except for the *p*-nitrophenyl allyldiphenylacetate. Esters from that acid have been prepared

Table I. Yield and Characterization of Para-Substituted Phenyl Diphenylacetates Prepared from Diphenylacetic Acid and Para-Substituted Phenols

Compd	Substituent	Yield, %	Mp, °C	Ir[d] ν_{max}, cm^{-1}	^1H NMR,[e] ppm
VI	*p*-Nitro	66	89–91[a]	1762, 1620	5.11, 7.11, 7.27, 8.12
VII[f]	*p*-Bromo	70	61–63	1750, 1590	5.08, 6.87, 7.27, 7.37
VIII	Unsubstituted	91	65–66[b]	1744, 1590	5.16, 6.83–7.40, 7.31
IX[f]	*p*-Methoxy	91	101–102	1751, 1600	3.73, 5.13, 6.67–7.00, 7.30
X	*p*-Methyl	91	76–78[c]	1751, 1600	2.30, 5.12, 6.83, 7.07, 7.30

[a] Lit.[9] 89–90 °C. [b] Lit.[9] 66–67 °C. [c] Lit.[9] 76–78 °C. [d] KBr. [e] Taken in carbon tetrachloride. [f] Satisfactory combustion analytical data for C and H (±0.4%) were reported for these compounds.

Table II. Yield of Allylation of Para-Substituted Phenyl Diphenylacetates, and Characterization of the Para-Substituted Phenyl Allyldiphenylacetates Formed

Compd	Substituent	Yield, %	Mp, °C	Ir[a] ν_{max}, cm^{-1}	^1H NMR,[b] ppm
XII[c]	*p*-Bromo	90	76–77	1759, 1630	3.20, 4.73–5.20, 5.27–6.00, 6.73, 7.27
XIII	Unsubstituted	91	40–42[d]	1753, 1630	3.21, 4.73–5.17, 5.33–6.00, 6.73–7.50
XIV[c]	*p*-Methoxy	97	71–73	1759, 1630	3.20, 3.73, 4.71–5.15, 5.28–6.00, 7.75
XV[c]	*p*-Methyl	93	54–55	1756, 1600	2.30, 3.22, 4.68–5.22, 5.25–6.00, 6.70

[a] KBr. [b] Taken in carbon tetrachloride. [c] Satisfactory combustion analytical data for C and H (0.04%) were reported for these compounds. [d] Lit.[5] 40–42 °C.

Table III. Carbonyl-Stretching Frequencies (cm^{-1}) of Phenyl Allylacetate (III), Phenyl Diphenylacetate (VIII), and Phenyl Allyldiphenylacetate (XIII) in Carbon Tetrachloride and Chloroform, as Function of the Concentration

	III		VIII		XIII	
Concn, M	CCl_4	$HCCl_3$	CCl_4	$HCCl_3$	CCl_4	$HCCl_3$
0.040	1765.3	1753.1	1773.4	1765.4	1754.8	1748.4
	1765.5	1753.7	1774.6	1765.0	1754.2	1748.0
	1765.5	1754.3	1773.8	1765.4	1755.2	1748.4
	1765.3				1755.1	1748.5
0.060	1765.3	1753.5	1773.9	1765.3		
	1765.3	1753.2	1773.9	1765.2		
	1765.4	1753.7	1774.5	1765.1		
	1765.2	1753.4				
0.080	1765.6	1752.8	1773.6	1765.6	1754.8	1748.6
	1765.0	1753.5	1773.9	1765.9	1755.3	1748.8
	1764.9	1753.4	1774.4	1765.3	1755.0	1748.9
	1765.3				1755.0	1748.4
	ν_m 1765.3	ν_m 1753.5	ν_m 1774.0	ν_m 1765.4	ν_m 1754.9	ν_m 1748.5
	S = 0.2	S = 0.4	S = 0.4	S = 0.3	S = 0.3	S = 0.3

by allylation of the para-substituted phenylic esters of the diphenylacetic acid, using as a base lithium isopropylcyclohexylamide.[11] The same method was used to introduce the *n*-propyl radical into the phenyl diphenylacetate. Alkylations were done with excellent yields, obtaining pure monoalkylated esters (Table II).

Infrared Spectroscopy. The position of the carbonyl group absorption band in carbon tetrachloride and in chloroform has been determined for each one of the esters synthesized, viz., set I, *p*-nitrophenyl (I), *p*-bromophenyl (II), phenyl (III), *p*-methoxyphenyl (IV), and *p*-tolyl allylacetates (V); set II, *p*-nitrophenyl (VI), *p*-bromophenyl (VII), phenyl (VIII), *p*-methoxyphenyl (IX), and *p*-tolyl diphenylacetates (X); set III, *p*-nitrophenyl (XI), *p*-bromophenyl (XII), phenyl (XIII), *p*-methoxyphenyl (XIV), and *p*-tolyl allyldiphenylacetates (XV), phenyl propyldiphenylacetate (XVI), phenyl allylphenylacetate (XVII), and phenyl acetate (XVIII).

These determinations were obtained as described in the Experimental Section. Frequency values (cm^{-1}) determined for the three series of esters are shown in Table IV.

As can be seen in Table IV, the electron-attracting groups shift the absorption band to higher frequency values (cm^{-1}), as compared with the unsubstituted compound, in the three series studied. An opposite shift is observed in the compounds with substituent groups that supply electrons. In the three tables it can also be observed that the values of carbonyl absorption frequency determined in carbon tetrachloride are greater than the values determined in chloroform. As usually higher frequencies are found in nonpolar solvents (carbon tetrachloride) than in polar solvents (chloroform), this behavior was to be expected.[11,12]

Inspection of Table V shows that substitution of one hydrogen atom of the methyl group in phenyl acetate by the allyl radical shifts the carbonyl absorption to lower frequency. When two hydrogen atoms are substituted by radicals (phenyl diphenylacetates or phenyl allylphenylacetates), an even greater shift to lower frequency is observed. A still greater shift is observed when all three hydrogen atoms are substituted (phenyl propyldiphenylacetate and phenyl allyldiphenylacetate).

Discussion

Hammett's Equation Application. Freedman[13] determined the absorption frequencies of the carbonyl group in a series of meta- and para-substituted phenyl acetates, in both carbon tetrachloride and chloroform as solvent. He tried to correlate the results with the Hammett σ values, but the points indicated on the graph were scattered, indicating only a tendency of an increase of frequency with σ. To explain the behavior observed with the meta- and para-substituted phenyl acetates, Freedman concluded that the electronic effect was transmitted from the substituent group to the carbonyl by the inductive effect. The resonance effect would not be transmitted, or it would be transmitted with little intensity, owing to the lack of the needed coplanarity. Considering that in the para-substituted phe-

Table IV. Carbonyl Absorption (cm^{-1}) for Para-Substituted Phenyl Allylacetates (Set I), Para-Substituted Phenyl Diphenylacetates (Set II), and Para-Substituted Phenyl Allyldiphenylacetates (Set III)

Substituent	CCl_4		$HCCl_3$	
	ν_m	Δ_ν[a]	ν_m	Δ_ν[a]
Para-Substituted Phenyl Allylacetates				
p-NO_2	1774.4 ± 0.2	9.1 ± 0.3	1762.4 ± 0.4	8.9 ± 0.4
p-Br	1766.9 ± 0.3	1.6 ± 0.4	1756.5 ± 0.3	3.0 ± 0.4
H	1765.3 ± 0.2	0.0	1753.5 ± 0.5	0.0
p-OCH_3	1761.3 ± 0.3	−4.0 ± 0.4	1749.6 ± 0.3	−3.9 ± 0.4
p-CH_3	1762.8 ± 0.2	−2.5 ± 0.3	1752.7 ± 0.2	−0.8 ± 0.3
Para-Substituted Phenyl Diphenylacetates				
p-NO_2	1774.0 ± 0.4	10.3 ± 0.4	1765.4 ± 0.3	9.0 ± 0.4
p-Br	1764.7 ± 0.2	1.0 ± 0.2	1759.7 ± 0.1	3.3 ± 0.2
H	1763.7 ± 0.1	0.0	1756.4 ± 0.2	0.0
p-OCH_3	1762.0 ± 0.4	−1.7 ± 0.4	1754.2 ± 0.6	−2.2 ± 0.6
p-CH_3	1761.6 ± 0.2	−2.1 ± 0.2	1753.7 ± 0.1	−2.7 ± 0.2
Para-Substituted Phenyl Allyldiphenylacetates				
p-NO_2	1760.5 ± 0.4	5.6 ± 0.5	1757.2 ± 0.2	8.7 ± 0.4
p-Br	1755.6 ± 0.1	0.7 ± 0.3	1750.0 ± 0.2	1.5 ± 0.4
H	1754.9 ± 0.3	0.0	1748.5 ± 0.3	0.0
p-OCH_3	1751.3 ± 0.2	−3.6 ± 0.4	1747.2 ± 0.5	−1.3 ± 0.6
p-CH_3	1750.8 ± 0.4	−4.1 ± 0.5	1747.4 ± 0.4	−2.1 ± 0.5

[a] $\Delta_\nu = \nu_m^R - \nu_m^H$.

Table V. Carbonyl Absorptions (cm^{-1}) of α-Substituted Phenyl Acetates, $R_1R_2R_3C-CO_2C_6H_5$

R_1	R_2	R_3	CCl_4		$HCCl_3$	
			ν_m, cm^{-1}	$\Delta\nu$	ν_m, cm^{-1}	$\Delta\nu$
H	H	H	1767.4 ± 0.3	0.0	1765.1 ± 0.3	0.0
H	H	$H_2C{=}CHCH_2$	1765.3 ± 0.2	−2.1 ± 0.4	1753.5 ± 0.5	−11.6 ± 0.6
H	C_6H_5	C_6H_5	1763.7 ± 0.1	−3.7 ± 0.3	1756.4 ± 0.2	−8.7 ± 0.4
H	C_6H_5	$H_2C{=}CHCH_2$	1760.7 ± 0.2	−6.7 ± 0.4	1753.9 ± 0.2	−11.2 ± 0.4
C_6H_5	C_6H_5	$H_3C{-}CH_2CH_2$	1755.8 ± 0.4	−11.6 ± 0.5	1749.2 ± 0.2	−15.9 ± 0.4
C_6H_5	C_6H_5	$H_2C{=}CHCH_2$	1754.9 ± 0.3	−12.5 ± 0.4	1748.5 ± 0.3	−16.6 ± 0.4

nyl acetates there has been a great predominance of the inductive effect, it seemed to us that Hammett's equation might be applied using σ^n values. We calculated the correlation coefficient (r) between the values determined by Freedman for the meta- and para-substituted phenyl acetates in carbon tetrachloride and in chloroform and the values σ^n. We found the value 0.81, which is not satisfactory according to the criterion proposed by Jaffé.[14]

More recently, Cohen and Takahashi[15] determined the carbonyl absorption frequencies of polysubstituted phenyl hydrocinnamates. These authors proposed that the carbonyl electronic density would depend on the electronic effects (inductive and resonance) that the substituting group would exercise on the carbon C-1. So the carbonyl stretching frequency values would be better correlated to the values of σ^o. With the values determined by Cohen and Takahashi, we calculated the correlation coefficients achieved by applying Hammett's equation to the esters *p*-nitrophenyl, *p*-bromophenyl, phenyl, tolyl, and *p*-methoxyphenyl hydrocinnamates, that is, for the esters corresponding to the ones synthesized by us in accordance with the values of σ, σ^n, and σ^o obtaining the values 0.992, 0.997, and 0.998, respectively. We have therefore verified that Hammett's equation fits in perfectly with the values determined by the two authors for the esters mentioned above, using any of the above mentioned σ values.

We could satisfactorily apply Hammett's equation for the carbonyl group absorption frequencies on our three series of esters for σ, as well as for σ^n and σ^o. (See Table VI and Figure 1). Values of σ, σ^n, and σ^o were taken from the compilation of Ritchie and Sager.[16] It can be observed in Table VI that correlation coefficients do not permit a judgment as to which one of the σ value series our results fit best. It can be observed that values of ρ, ρ^n and ρ^o are slightly greater in carbon tetrachloride than in chloroform; this signifies that the sensitivity of the carbonyl absorption frequency to the para groups is a little higher in carbon tetrachloride than in chloroform. This slight difference observed could be attributed to a greater sensitivity of the carbonyl frequency to the substituents in nonpolar solvents.

Effects of the Introduction of Substituting Groups in the α Position of the Acetic Acid Phenylic Esters on the Carbonyl Stretching Frequency. The shift to lower frequency caused by the substitution of the methyl radical hydrogens of the phenyl acetate by alkyl or aryl radicals can have various explanations. (1) An inductive effect due to the radicals. The phenyl group exerts only a small inductive effect (−I). If this effect is significant, the phenyl group's presence in the α position would shift the carbonyl absorption band to higher frequency. The shift in the same direction, but of smaller magnitude, would be observed in the presence of the allyl radical. The propyl radical, on the other hand, exerts a small +I inductive effect causing a shift to the lower frequency values. The observations made do not agree with these considerations. (2) Interaction between the carboxyl group and the double bond of the allyl radical. Conformational analysis of these esters shows that successive introduction of substituents in the α position causes greater stability to the conformation that has the carbonyl group and the double bond closer; this would facilitate a possible interaction between these two groups which would be reflected in the carbonyl absorption position. The more stable conformation in the phenyl *n*-propyl-

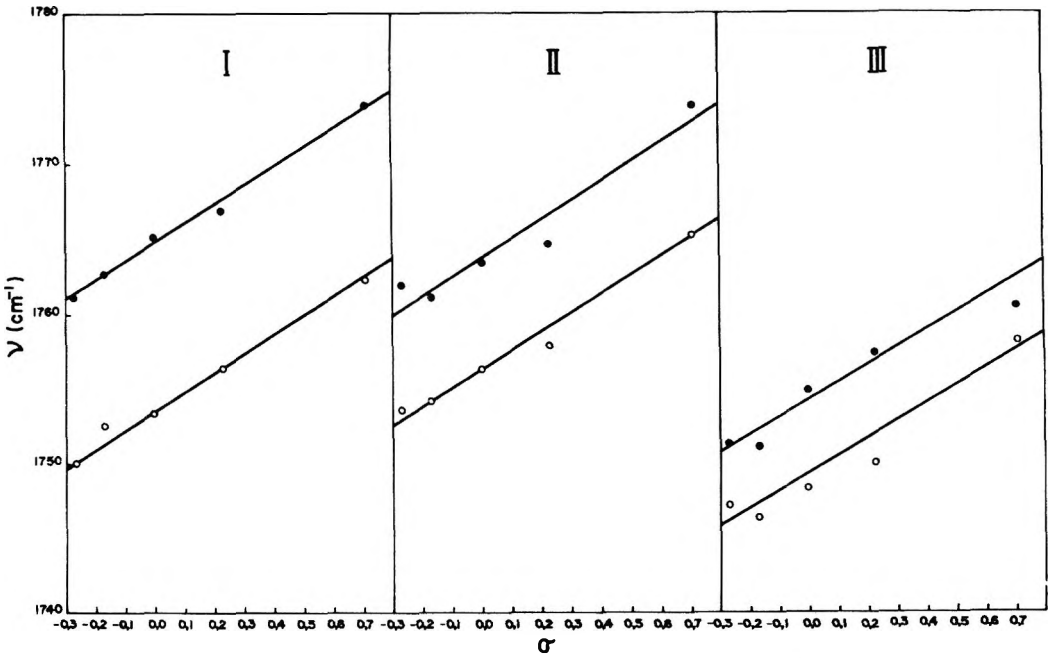


Figure 1. Correlation of carbonyl-stretching frequencies (cm^{-1}) for para-substituted phenyl allylacetates (set I), para-substituted phenyl diphenylacetates (set II), and para-substituted phenyl allyldiphenylacetates (set III) with σ in carbon tetrachloride (●) and in chloroform (○).

Table VI. Correlations between the Carbonyl Absorptions (cm^{-1}) of Para-Substituted Phenyl Allylacetates (Set I), Para-Substituted Diphenylacetates (Set II), and Para-Substituted Allyldiphenylacetates (Set III), and the Hammett Substituent Constants

Best fit linear equation	Solvent	r	ρ^a
Para-Substituted Phenyl Allylacetates			
$\nu = 1764.8 + 12.2\,\sigma$	CCl_4	0.996	12.2
$\nu = 1764.0 + 13.2\,\sigma^n$	CCl_4	0.981	13.2
$\nu = 1764.2 + 13.5\,\sigma^o$	CCl_4	0.986	13.5
$\nu = 1753.6 + 11.5\,\sigma$	$HCCl_3$	0.989	11.5
$\nu = 1753.0 + 12.3\,\sigma^n$	$HCCl_3$	0.967	12.3
$\nu = 1753.2 + 12.7\,\sigma^o$	$HCCl_3$	0.976	12.7
Para-Substituted Phenyl Diphenylacetates			
$\nu = 1763.8 + 11.8\,\sigma$	CCl_4	0.969	11.8
$\nu = 1763.1 + 13.1\,\sigma^n$	CCl_4	0.978	13.1
$\nu = 1763.4 + 13.2\,\sigma^o$	CCl_4	0.970	13.2
$\nu = 1756.6 + 11.4\,\sigma$	$HCCl_3$	0.991	11.4
$\nu = 1755.8 + 12.6\,\sigma^n$	$HCCl_3$	0.995	12.6
$\nu = 1756.1 + 12.9\,\sigma^o$	$HCCl_3$	0.998	12.9
Para-Substituted Phenyl Allyldiphenylacetates			
$\nu = 1753.6 + 9.1\,\sigma$	CCl_4	0.972	9.1
$\nu = 1753.0 + 9.9\,\sigma^n$	CCl_4	0.959	9.9
$\nu = 1753.2 + 10.2\,\sigma^o$	CCl_4	0.968	10.2
$\nu = 1748.7 + 10.1\,\sigma$	$HCCl_3$	0.998	10.1
$\nu = 1748.0 + 11.3\,\sigma^n$	$HCCl_3$	0.989	11.3
$\nu = 1748.3 + 11.4\,\sigma^o$	$HCCl_3$	0.983	11.4

[a] Hammett's ρ value is dimensionless. In this work it has the dimension of cm^{-1} as is common in the literature in spectroscopic comparison (See ref 11 and 15).

diphenylacetate is the one that has the carbonyl and the ethyl radical closer. This *n*-propyldiphenylacetate is saturated and serves as a saturated model to compare with the allyl-substituted esters. However, the position of the carbonyl absorption band of the saturated model is very close to the phenyl allyldiphenylacetate's. These results seem to indicate that there is no interaction between the carboxyl and the vinyl groups, or, if there is some interaction, it has no influence on the carbonyl frequency. These observations agree with those which were established by Leonard and Owens,[17] who observed that transannular interaction between C=C and C=O groups in cyclic ketones is not detected by infrared spectroscopy. (3) The effect of changing angles on adjacent bonds. It has been shown[18] with aliphatic esters that it is not necessary to distort the carbonyl group valency angles in order to accommodate groups linked to it. Bowden et al.[19] suggest that interactions involving the methoxyl group are small even in the methyl propyldiphenylacetate. (4) Mass effect result of the carbonyl substituent in α, as successive substituting groups are introduced into α carbon. The importance of this effect has been suggested by various authors.[18-20] Thus, it has been observed that the carbonyl band position shifts to lower frequency upon deuteration of the methyl acetate.[20] We suggest, then, that shifts of ir band to lower frequency observed in carbonyl groups when hydrogen atoms of the α carbon of the phenyl acetate are substituted can be due a mass effect.

Registry No.—I, 51231-11-9; II, 51231-10-8; III, 51231-09-5; IV, 51231-07-3; V, 51231-08-4; VI, 58241-10-4; VII, 58241-11-5; VIII, 58241-12-6; IX, 58241-13-7; X, 58241-14-8; XI, 58241-15-9; XII, 58241-16-0; XIII, 51231-12-0; XIV, 58241-17-1; XV, 58267-79-1; XVI, 58241-18-2; XVII, 51231-03-9; XVIII, 122-79-2; diphenylacetic acid, 117-34-0; *p*-nitrophenol, 100-02-7; *p*-bromophenol, 106-41-2; phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-methylphenol, 106-44-5; allyl bromide, 106-95-6; *n*-propyl bromide, 106-94-5; allyldiphenylacetic acid, 6966-03-6.

References and Notes

(1) Supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) Abstracted from Ph.D. Thesis of A.T.A.
(3) R. T. Arnold, M. Moura Campos, and K. L. Lindsay, *J. Am. Chem. Soc.*, **75**, 1044 (1953).
(4) L. do Amaral and S. C. Melo, *J. Org. Chem.*, **38**, 800 (1973).
(5) O. A. El Seoud, A. T. dc Amaral, M. Moura Campos, and L. do Amaral, *J. Org. Chem.*, **39**, 1916 (1974).
(6) M. Moura Campos, *An. Acad. Bras. Cienc.* **27**, 405 (1955).
(7) M. Moura Campos, *Chem. Ber.*, **93**, 1075 (1960).
(8) M. Moura Campos and L. do Amaral, *Arch. Pharm. (Weinheim, Ger.)*, **298**, 92 (1965).
(9) J. Wolinski, D. Busa, E. Czerwinska, and W. Zamlynski, *Chem. Anal. (Warsaw)*, **4**, 989 (1959).
(10) R. T. Arnold, W. E. Parham, and R. M. Dodson, *J. Am. Chem. Soc.*, **71**, 2439 (1949).
(11) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy", Aca-

demic Press, New York, N.Y., 1963, pp 192–237 and 572.
(12) L. J. Bellamy, "Advances in Infrared Group Frequencies", Methuen, Great Britain, 1968, pp 123–190.
(13) H. H. Freedman, *J. Am. Chem. Soc.*, **82**, 2454 (1960).
(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(15) L. A. Cohen and S. Takahashi, *J. Am. Chem. Soc.*, **95**, 443 (1973).
(16) C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, 2, 323 (1964).
(17) N. J. Leonard and F. H. Owens, *J. Am. Chem. Soc.*, **80**, 6039 (1958).
(18) K. J. Morgan and N. Unwin, *J. Chem. Soc. B*, 880 (1968).
(19) K. Bowden, N. B. Chapman, and J. Shorter, *Can. J. Chem.*, **41**, 2154 (1963).
(20) B. Nolin and J. R. Norman, *Can. J. Chem.*, **34**, 1382 (1956).

Aromatic Substitution. XXXVIII.[1a] Chloromethylation of Benzene and Alkylbenzenes with Bis(chloromethyl) Ether, 1,4-Bis(chloromethoxy)butane, 1-Chloro-4-chloromethoxybutane, and Formaldehyde Derivatives

George A. Olah,* David A. Beal,[1b] and Judith A. Olah

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

Received November 17, 1975

The chloromethylation of benzene and alkylbenzenes was studied with bis(chloromethyl) ether, 1,4-bis(chloromethoxy)butane, 1-chloro-4-chloromethoxybutane, and formaldehyde derivatives. Relative rate data of chloromethylations compared to benzene as well as isomer distributions were determined. The mechanisms of the reactions are considered in view of the experimental data. Preparative aspects of the novel chloromethylations with 1,4-bis(chloromethoxy)butane and 1-chloro-4-chloromethoxybutane are also discussed.

Since the discovery of the chloromethylation reaction by Grassi-Cristaldi and Maselli,[2] mechanistic studies have centered on establishing the role of formaldehyde in the reaction.[3] It is now generally accepted that the electrophilic reagent in chloromethylations in aqueous or polar solvents (such as glacial HOAc) is the hydroxycarbenium ion (protonated formaldehyde, $CH_2^+{=}OH$).[3,4] Interestingly, however, in our recent work[5] protonated chloromethyl alcohol, $ClCH_2O^+H_2$, was obtained as a stable species, thus indicating its possible significance in chloromethylations.

It was reported by Brown and Nelson[6] that chloromethylation shows high substrate and positional selectivity. The competitive rate between toluene and benzene in chloromethylation with paraformaldehyde, HCl gas, and $ZnCl_2$ in glacial acetic acid solution at 65 °C was found to be 112, with an ortho/para ratio of 0.54. At the same time they claimed that previously reported investigations of chloromethylation reactions,[7] showing low substrate selectivity, while maintaining high positional selectivity, were found to be unreproducible.

We have previously reported[8] that electrophilic aromatic substitution reactions generally can display variable substrate selectivity, not necessarily showing substantial loss of positional selectivity, as evidenced by generally low meta isomer contents observed in substitution of toluene.

We wish to report now related observations of the chloromethylation of benzene and alkylbenzenes with bis(chloromethyl) ether, 1,4-bis(chloromethoxy)butane, 1-chloro-4-chloromethoxybutane, and formaldehyde derivatives. The varied chloromethylations cannot be characterized by a single selected value of substrate and positional selectivity, which can vary widely depending on specific reaction systems and conditions used.

Results and Discussion

Chloromethylation with Bis(chloromethyl) Ether. Since reproducible kinetic data cannot be obtained in heterogeneous systems, it was decided to confine our studies to those chloromethylating agents which displayed good solubility in aromatic hydrocarbons or in a common solvent, thus allowing homogeneous reaction conditions. After preliminary experiments with paraformaldehyde in a number of solvent systems, it was discarded in favor of bis(chloromethyl) ether, which displays good solubility in aromatic hydrocarbons. Bis(chloromethyl) ether has found extensive use in the chloromethylation of aromatic compounds and was generally assumed to generate monomeric formaldehyde in situ, which then reacts analogously to paraformaldehyde or aqueous formaldehyde.[3] Our work shows, however (vide infra), that this is not the real reaction mechanism of chloromethylation with bis(chloromethyl) ether or other halomethyl ethers.

Early in our study it was realized that improved analytical methods were necessary for quantitative analysis of chloromethylated products formed in the reaction mixtures. Previous studies have relied on titrimetric methods, ir spectroscopy, or on analysis after isolating and subsequently converting the chloromethylated products by reduction with $LiAlH_4$ and uv analysis of the resultant methylarenes (utilized for example by Brown and Nelson[6]). We have developed a suitable GLC method to obtain unequivocal data of product compositions, which permits the reaction mixture to be analyzed directly for chloromethylated products (i.e., benzyl chloride and methylbenzyl chlorides). Product compositions could thus be directly determined with an accuracy of better than 1%.

With the choice of chloromethylating agent decided upon and using as solvent excess of neat aromatics, it was then necessary to select a suitable catalyst for the chloromethylation reactions to be studied. In our initial studies, zinc chloride was used because of the general utility it has enjoyed in chloromethylations. Its solubility in aromatic hydrocarbons, however, is poor, and we found that only after the chloromethyl ether was added to a slurry of aromatic hydrocarbon and zinc chloride did the zinc chloride go into solution. Consequently stannic chloride was chosen as a catalyst for the chloromethylation studies. It is a highly soluble catalyst, and generally not so active as to cause secondary reactions (i.e., condensation of chloromethylated products and excess aromatics to give diarylmethanes). Finally, our studies were carried out at 65 °C to allow comparison with the work of Brown and Nelson,[6] which was carried out at this temperature.

A summary of the results of chloromethylation of benzene and methylbenzenes with bis(chloromethyl) ether and stannic chloride catalyst is given in Table I.

Table I. Competitive Chloromethylation of Benzene and Methylbenzenes with Bis(chloromethyl) Ether (BCME)[a]

Registry no.	Substrate	Time, min	$k_{C_6H_5R}/k_{C_6H_6}$[b]	Isomer distribution
71-43-2	C_6H_6		1.0	
108-88-3	$C_6H_5CH_3$	100[c]	16.2	o-, 42%; m-, 3%; p-, 55%
		10[d]	15.5	o-, 44%; m-, 2%; p-, 54%
95-47-6	o-$(CH_3)_2$-C_6H_4	25	31.3	4-Chloromethyl-o-xylene 97% 3-Chloromethyl-o-xylene 3%
108-38-3	m-$(CH_3)_2$-C_6H_4	25	40.1	4-Chloromethyl-o-xylene 10
106-42-3	p-$(CH_3)_2$-C_6H_4	25	24.3	2-Chloromethyl-p-xylene 10

[a] All reactions run at 65 °C with ArH:PhH:BCME:$SnCl_4$ mole ratios of 10:10:1:0.75. [b] From direct GLC analysis (see text and Experimental Section). [c] Shorter reaction times did not yield sufficient product for reliable analysis. [d] Reaction run with $AgBF_5$ in place of $SnCl_4$; BCME/$AgBF_4$ = 1/0.1 (m/m).

The competitive method of kinetic evaluation of relative reaction rates was employed in our studies. The basis of this method lies in assuming that the substituting agent present competes for two aromatic substrates.

It is seen from Table I that the positional (regio-) selectivity is high in the chloromethylation of toluene, with only 2–3% of the meta isomer formed in the reaction. The substrate selectivity over benzene $k_{toluene}/k_{benzene}$ is 15.5–16.2. The ortho/para ratio of 0.77 (assuming no significant ortho steric hindrance) indicates that conjugative stabilization by the methyl group in the transition state is not excessive (vide infra).

It is noted that the chloromethylation of the isomeric xylenes proceeds only modestly faster than that of toluene. Despite the diminishing substrate selectivity behavior of increasingly nucleophilic aromatics, the positional selectivity as shown in the case of o-xylene stays high (97% of 4-chloromethoxy- and 3% of 3-chloromethyl-o-xylene). Thus, no diffusion (or encounter) controlled reaction leading directly in a single step to isomeric products can be involved and it is suggested, as previously discussed,[8] that the reactions proceed through separate consecutive steps defining substrate and positional selectivity.[8] The substrate reactivity of the reactions thus can reach the encounter controlled limit, while regioselectivity stays high.

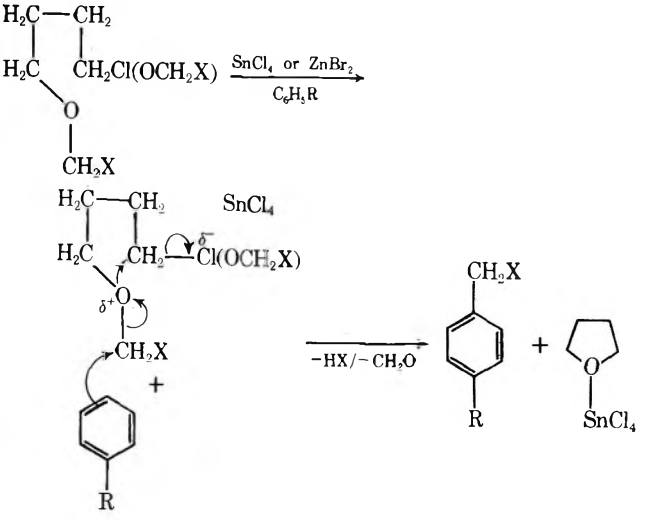
Chloromethylation with 1,4-Bis(chloromethoxy)butane and 1-Chloro-4-chloromethoxybutane. We reported recently preliminary findings to have found in 1-chloro-4-chloromethoxybutane and 1,4-bis(chloromethoxy)butane, respectively, extremely effective new chloromethylating agents of wide utility.[9] At the same time the substantially decreased volatility of these reagents decreases the danger associated with the use of more volatile chloromethyl ethers, which are powerful carcinogens.

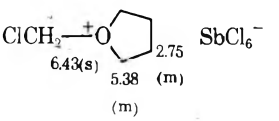
Preparative results of the tin(IV) chloride catalyzed chloromethylation of benzene and methylbenzenes are summarized in Table II (yields of isolated chloromethylarenes are given).

1-Chloro-4-halomethoxybutanes and 1,4-bis(halomethoxy)butanes in their Friedel–Crafts halomethylation reactions act, owing to strong oxygen participation in the developing carbocationic substituting agents, as incipient halomethyltetrahydrofuranonium ions, i.e., reactive Meerwein-type oxonium ions. Tetrahydrofuran formed as by-product of the reaction complexes the Lewis acid catalyst and greatly diminishes formation of diarylmethane by-products. The existence of the corresponding chloromethyltetrahydrofuranonium ion was proven by preparing the novel oxonium ion under stable ion conditions in sulfur dioxide solutions with antimony(V) chloride at −50 °C. The ^1H NMR parameters are as shown.

Table II. Preparative Chloromethylation of Benzene and Methylbenzenes

Arene	% yield of chloromethylarene: With 1,4-bis(chloromethoxy)butane	With 1-chloro-4-chloromethoxybutane
Benzene	43	50
Toluene	53	44
p-Xylene	41	41
m-Xylene	51	55
Mesitylene	60	70





1,4-Bis(chloromethoxy)- and 1-chloro-4-chloromethoxybutane are capable of chloromethylating aromatics under mild conditions, and are well suited for reaction mechanism studies.

The competitive chloromethylation of benzene and alkylbenzenes was carried out, giving results similar to those obtained for bis(chloromethyl) ether. The results obtained are shown in Table III. The most obvious conclusion from comparison of Tables I and III is that the reaction mechanism must be similar in both cases.

An interesting feature of these reactions is that their steric requirements are not as stringent as those of bis(chloromethyl) ether (compare for example yields of 2,3-dimethylbenzyl chloride in Table III vs. Table I).

It may be seen from Table III that the chloromethylation of toluene with bis(chloromethoxy)butane at 65 °C gives an isomer distribution identical with that found at 35 °C, indicating no temperature dependence of the isomeric products, i.e., no isomerization (which would, however, not prevent some

Table III. Competitive Chloromethylation of Benzene and Alkylbenzenes with 1,4-Bis(chloromethoxy)butane

Substrate	Time, min	$k_{C_6H_5R}/k_{C_6H_6}$ [b]	Isomer distribution, % [b]
C_6H_6		1.0	
$C_6H_5CH_3$	25	21.0	o-, 45; m-, 4; p-, 51
	100 [c]	22.2	o-, 43; m-, 3; p-, 54
o-$(CH_3)_2C_6H_4$	12.5	23.6	4-Chloromethyl-o-xylene 94 3-Chloromethyl-o-xylene 6
m-$(CH_3)_2C_6H_4$	12.5	34.5	4-Chloromethyl-m-xylene 100
p-$(CH_3)_2C_6H_4$	12.5	21.5	2-Chloromethyl-p-xylene 100

[a] All reactions run at 65 °C with ArH:PhH:BCMB:$SnCl_4$ = 10:10:1:0.1 (m/m). [b] Determined by GLC. [c] This reaction run at 35 °C.

Table IV. Relative Rate of the Chloromethylation of Benzene and Toluene as a Function of Their Varying Ratios in Competition Experiments

Mole ratio $C_6H_5CH_3/C_6H_6$	Observed product ratios of toluene/benzene	k_T/k_B
1/1	21.0	21.0
1/5	4.1	20.5
1/10	2.4	24.0

isomerization within the arenium ion type intermediates prior to their deprotonation).

A small kinetic hydrogen isotope effect was found in the reaction of bis(chloromethoxy)butane with hexadeuteriobenzene compared to benzene at 35 °C.

$$k_{C_6H_6}/k_{C_6D_6} = 1.4$$

This observation is in line with the absence of primary isotope effects in studied Friedel–Crafts type alkylations.

Competition experiments were also carried out with various toluene/benzene mole ratios. The dependence of the relative rate upon aromatic hydrocarbon concentration is shown in Table IV. These values compare well with each other and indicate first-order dependence in aromatic hydrocarbons.

In the study of the chloromethylations it was observed that change in catalyst concentration has a marked effect on the selectivities of the reactions. Higher catalyst concentrations favor a more reactive reaction system, whereas increasingly smaller amounts of catalyst have the opposite effect. To study this effect a series of reactions were run with benzene and toluene in competition in which the amount of catalyst ($SnCl_4$) used in the reactions was systematically varied. The reactions were sampled at varying intervals, and the relative rate constants, $k_{toluene}/k_{benzene}$, were obtained by extrapolating these measurements to zero time. The data are shown in Table V.

It is apparent from these data that a significant change occurs with changes in catalyst concentration. What was initially a rather low substrate selectivity reaction has become extremely substrate selective. At the same time the ortho/para isomer ratios also show a continuous decrease. This again suggests, as had related work from this laboratory, that the position of the transition state of highest energy in aromatic substitutions is *not* a fixed one, and depending upon reaction conditions it can either lie early (π-complex-like) or late (σ-complex- or arenium-ion-like) on the reaction coordinate. Further, these results suggest that there is a continuum of substrate and positional selectivity and mean that no single selected set of substrate and positional selectivity values can be used to characterize chloromethylation reactions.

Table V. Variation of the Selectivity of Chloromethylation of Toluene and Benzene with Catalyst Concentration

		Chloromethyltoluenes			
10^{-5} M $SnCl_4$	$k_{toluene}/k_{benzene}$	% ortho	% meta	% para	o-/p-
100	21	45	4	55	0.83
68.6	41	37	3	60	0.61
34.3	56	36	2	62	0.58
7.68	317	32.5	1.5	66	0.49

Table VI. Relative Reactivities of Methylbenzenes and Benzene in Chloromethylations at Low (3.84×10^{-5} M) $SnCl_4$ Concentration

Substrate	k^0_{ArH}/k^0_{PhH}
C_6H_6	1
$C_6H_4CH_3$	370
p-$(CH_3)_2C_6H_4$	1 200
o-$(CH_3)_2C_6H_4$	2 700
m-$(CH_3)_2C_6H_4$	27 000

On obtaining these results the question of substrate selectivity in reactive hydrocarbons such as xylenes was also further studied. In view of the seemingly significant substrate discrimination for toluene displayed under low catalyst concentration, these substrates should also show a much enhanced reactivity over benzene. Indeed, in these chloromethylation reactions xylenes could only be compared with benzene via the indirect comparison with toluene, owing to the greatly enhanced reactivity of the xylenes. The results are summarized in Table VI.

It can be seen from these data that the chloromethylation reactions show increasing substrate selectivity with lower catalyst concentration (note m-xylene is 27 000 times more reactive than benzene) with simultaneous decrease of the ortho/para isomer ratio. There is also a decrease of meta substitution (from 4 to 1.5%).

Having observed chloromethylations with chloromethyl ethers which do not always display the high substrate, high positional selectivity characteristics reported by Brown and Nelson,[6] it was also felt necessary to extend our studies to formaldehyde systems to clarify any discrepancies which might exist, and to see if modification of the reaction conditions would vary the substrate selectivity. With regard to the latter point, the work of Ogata and Okano[4] suggested that increasing the acidity of the reaction mixture might accomplish this, since they found a strong dependence of the rate of chloromethylation of mesitylene with aqueous formaldehyde on the Hammett acidity function.

In order to use a source of formaldehyde which is soluble in aromatic solvents and which would not be prone to secondary reactions with chloromethylated products, paraformaldehyde and dialkyl formals were considered unsuitable. The reactions were accordingly carried out with s-trioxane as a source of formaldehyde. Since it was necessary to have a highly soluble proton acid catalyst, a solution of $SnCl_4$ saturated with HCl was used. In some experiments the use of s-tetraoxane was also attempted. This highly soluble cyclic tetramer of formaldehyde has recently become available.[10] However, s-tetraoxane was found to be rapidly depolymerized in the presence of acid and gives via repolymerization insoluble paraformaldehyde.

The repetition of the work of Brown and Nelson[6] was also considered necessary, because it was felt possible that in their pre-gas–liquid chromatography analytical method used they may have encountered difficulties in the analysis of reaction

Table VII. Competitive Chloromethylation of Benzene and Toluene with Formaldehyde Derivatives

Reagent/catalyst (mole ratio)	k_{PhMe}/k_{PhH}[a]	Isomer distribution, %		
		Ortho	Meta	Para
Trioxane/$SnCl_4$[b] (5/1)	63	37	2	61
Trioxane/$SnCl_4$[b] (0.9/1)	7.8	55	5	40
Paraform/$ZnCl_2$[c,d] (6/1)	28.2	43	4	53
Paraform/$ZnCl_2$[d] (6/1)	40.3	40	3	57
Paraform/$ZnCl_2$[e] (6/1)	112	35	2	64

[a] Analysis by GLC. [b] Mole ratio PhMe:PhH:s-trioxane = 12:12:1 at 65 °C (excess aromatic used as solvent). [c] Paraform = paraformaldehyde. [d] From the same reaction; fourth entry subjected to more extensive workup (both run at 65 °C in glacial acetic acid solvent; see text and note *e*). [e] Data of H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).

products, particularly when considering the necessity of indirect uv spectroscopic analysis, after first converting the chloromethylated products to methylarenes by reduction with $LiAlH_4$. To this end their procedure for the competitive chloromethylation of benzene and toluene was repeated. For convenience the quantities of materials and the reaction time were reduced by a factor of 20 (while keeping molar ratios identical) and gaseous HCl was used from a lecture bottle (Matheson). The reaction mixture was divided into two parts for analysis. One part was washed with ice water, dried over $CaSO_4$, and analyzed by the direct GLC analytical method developed in our work for benzyl chlorides and methylbenzyl chlorides (see Experimental Section). The other portion was carried through the identical workup reported by Brown and Nelson: washings with ice water and with 10% aqueous potassium carbonate, extraction of washings with petroleum ether, drying of organic materials over calcium chloride–potassium carbonate, and removal of the petroleum ether and excess hydrocarbon by distillation at atmospheric pressure and at 95 mm. This portion was then analyzed by the same GLC method as used throughout in our work in contrast to Brown and Nelson's method of reducing the benzyl chlorides with $LiAlH_4$ to the corresponding methylbenzenes followed by uv spectroscopic analysis. It was necessary to dilute samples with carbon tetrachloride prior to GLC analysis, but this in no way affected the product composition.

The results of the chloromethylation reactions with formaldehyde derivatives are summarized in Table VII.

Turning first to the reactions with *s*-trioxane, it can be seen that the chloromethylations are indeed highly dependent on acidity (catalyst concentration) of the reaction systems. The fact that increased acidity has decreased the relative rate of reactions (cf. $k_{toluene}k_{benzene}$ = 63 vs. 7.8, with a 5.5-fold decrease in acid concentration) and also causes significant changes in the isomer distribution clearly indicates that at high acidity the reactivity of the system is higher than that observed at low acidity. This is compatible with an equilibrium-controlled increase in the concentration of the hydroxycarbenium or chloromethyloxonium ion, which would be expected to react more rapidly than a formaldehyde–proton acid complex. There is further evidence of this in the ortho/para ratios of the two reactions. In the low acidity reaction the methyl group plays a greater role in stabilizing the arenium-ion- (or σ-complex) -like transition state by conjugation, and the para isomer predominates (*o*-/*p*- = 0.63). This conjugative stabilization is less important in the high-acidity case where in the earlier transition state of aronium ion (or π-complex) nature the electrophile requires less contribution of the aromatic π electrons. As a consequence inductive stabilization predominates and the ortho/para ratio is high (1.38).

While the determination of the isomer distribution in the chloromethylation reactions was accurate (they are considered to be accurate to 1%), it is not possible to exclude some intramolecular isomerization in the arenium type transition states prior to deprotonation. This can be of significance, particularly in reactions with high catalyst concentrations, and affect the results through thermodynamically controlled factors.

Returning to the repetition of the Brown–Nelson experiments, it may be seen that there is less significant difference in the distribution of methylbenzyl chloride isomers from either the simple workup and direct GLC analysis (third entry, Table VII) or the original more elaborate workup (fourth entry, Table VII) or from the results Brown and Nelson reported (fifth entry, Table VII). These differences lie probably within experimental error of the methods used. Clearly, however, the same cannot be said of the relative rates determined from product compositions obtained from the two different workup procedures. The most probable explanation lies in the difficulty of separating chloromethylated products from excess aromatics by distillation without losses of the former, a factor obviously seriously affecting the data of Brown and Nelson. Judging from the difference in $k_{toluene}/k_{benzene}$ between these experiments, the removal of solvent causes some loss of the more volatile benzyl chloride. In fact, when the aromatic hydrocarbon forerun obtained from the Brown–Nelson workup procedure was subjected to GLC analysis, a significant amount of benzyl chloride was found in it. The more benzyl chloride lost, the higher the apparent value of $k_{arene}/k_{benzene}$.

Conclusions

The paucity of mechanistic information about the chloromethylation reaction led previously to somewhat contradictory results. In our studies we have been able to show that a wide range of selectivity exists for chloromethylations with varying reaction conditions and, therefore, no single set of data can characterize all electrophilic chloromethylation reactions. It is clear from our studies that toluene remains predominantly ortho/para directing in all chloromethylations with the change in meta substitution ranging from 1.5 to 5%, with simultaneous substrate selectivity, i.e., k_T/k_B ratio changes ranging from 15 to 320.

Experimental Section

Reagents. Aromatic hydrocarbons were of the highest purity available and were dried over molecular sieves prior to use. Benzene, toluene, alkylbenzenes, and all solvents used were spectral or highest purity grade, dried over molecular sieves. Stannic chloride was ACS reagent quality. Bis(chloromethyl) ether (Eastman Kodak) was obtained in sealed glass ampules (100 g). These ampules were open in a drybox, and the reagent was stored in and dispensed from Teflon bottles. 1,4-Bis(chloromethoxy)butane and 1-chloro-4-chloromethoxybutane were prepared as reported.[9]

Warning! Bis(chloromethyl) ether[11] and 1,4-bis(chloromethoxy)butane are toxic even in small quantities. In addition, bis(chloromethyl) ether has been shown to be a powerful carcinogen.[12] Because of its higher boiling point at atmosphere pressure, 1,4-bis(chloromethoxy)butane is considered a lesser inhalation hazard than bis(chloromethyl) ether, but all chloromethyl ethers (as well as other haloalkyl ethers and difunctional haloalkyl compounds such as haloalkyl tosylates, alcohols, etc) should be stored and dispensed in a fume hood, using rubber gloves and eye protection. Concentrated aqueous NaOH solution was used to hydrolyze material before disposal.

Equipment Used. Flasks and pipets used to contain and dispense the reagents were cleaned with H_2SO_4–$K_2Cr_2O_7$ solution, rinsed with distilled water, and dried in an oven. Kinetic measurements were carried out in thermostated solutions using a Haake F4291 circulating bath fitted with immersion heater and thermoregulator. This bath was capable of maintaining temperature with a precision of better than ±0.1 °C.

Chloromethylation Reactions. Reaction mixtures were prepared in clean glassware in a fume hood. In competitive studies, 0.05 mol of each aromatic was weighed into a flask and to it was added (calibrated Pasteur pipet) 0.005 mol of the reagent under study. The desired volume of a 0.5 M solution of $SnCl_4$ in cyclohexane (1.00 ml = 0.0005 mol of $SnCl_4$) was added and the flask transferred to the constant-temperature bath. After a predetermined heating period to allow the reactants to come to the bath temperature, the similarly prepared and thermostated solution of the chloromethylating agent was than added with good stirring. The mixtures were either quenched after a specified time or periodically sampled, as described previously.

GLC analysis of products (Aerograph 1200 with flame ionization detector) was carried out using the following columns: 15 ft × 0.125 in. in 5% bentone-34 + 1% DC-200, 60/80 mesh Chromosorb W, acid-washed (for separation of benzyl chloride and isomeric methylbenzyl chlorides) and 5 ft × 0.125 in. 5% SE-30, 80/120 mesh silanized acid-washed Chromosorb W (for separating dimethylbenzyl chlorides). Both columns gave good baseline separation allowing quantitative determination of isomers.

Calculation of product concentration was by the relative response method, and competitive rate ratios were determined from product ratios.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No.—BCME, 542-88-1; $SnCl_4$, 7646-78-8; bis-1,4-(chloromethoxy)butane, 13483-19-7; 1-chloro-4-chloromethoxybutane, 3970-17-0; mesitylene, 108-67-8; *s*-trioxane, 110-88-3; paraformaldehyde, 30525-89-4.

References and Notes

(1) (a) Part XXXVII: G. A. Olah and J. Nishimura, *J. Am. Chem. Soc.*, **96**, 2214 (1974). (b) Taken in part from the Ph.D. Thesis of D. A. Beal, Case Western Reserve University, 1973.
(2) G. Grassi-Cristaldi and M. Maselli, *Gazz. Chim. Ital.*, **20**, 477 (1898).
(3) For reviews see G. A. Olah and W. S. Tolgyesi in "Friedel-Crafts and Related Reactions", Vol. II, G. A. Olah, Ed., Wiley-Interscience, New York, N.Y., 1964, pp 659–784; R. C. Fuson and C. H. McKeever, *Org. React.*, **1**, 64 (1942).
(4) M. Ogata and Y. Okano, *J. Am. Chem. Soc.*, **78**, 5423 (1956).
(5) G. A. Olah and S. H. Yu, *J. Am. Chem. Soc.*, **97**, 2293 (1975).
(6) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 6292 (1953).
(7) (a) H. H. Szmant and J. Dudek, *J. Am. Chem. Soc.*, **71**, 3763 (1949); (b) G. Vavon, J. Bolle, and J. Calin, *Bull. Soc. Chim. Fr.*, **6**, 1025 (1939).
(8) For a review see G. A. Olah, *Acc. Chem. Res.*, **4**, 240 (1971), and references cited therein.
(9) G. A. Olah, D. A. Beal, S. H. Yu, and J. A. Olah, *Synthesis*, 560 (1974).
(10) We gratefully acknowledge the gift of a sample of *s*-tetraoxane by Mitsui Toatsu Chemicals, Ltd.
(11) N. I. Sax, Ed., "Dangerous Properties of Industrial Materials", Reinhold, New York, N.Y., 1963, p 696.
(12) B. L. Van Duren et al., *J. Natl. Cancer Inst.*, **43**, 481 (1969); L. Collier, *Environ. Sci. Technol.*, **6**, 930 (1972).

Metathesis Catalysts. V. Competitive Character of Metathesis and Alkylation Reactions Catalyzed by Tungsten Hexachloride–Ethylaluminum Dichloride

Léonard Hocks,* Alfred Noels, André Hubert, and Philippe Teyssie

Laboratoire de Chimie Macromoléculaire et de Catalyse Organique, Université de Liège, Sart Tilman par 4000 Liège, Belgium

Received May 27, 1975

The olefin metathesis catalytic system WCl_6-$EtAlCl_2$ in an aromatic solvent promotes both olefin metathesis and solvent alkylation reactions. The yields of these two competitive reactions strongly depend on the relative concentration of the three compounds of the system (olefin, solvent, catalyst), with a marked dependence on the π donor ability of the aromatic solvent; moreover, our catalytic conditions can promote exclusive formation of monosubstituted benzenes at the thermodynamic equilibrium. The mechanism proposed involves competitive coordination equilibria of the solvent and of the olefin as the key step.

The use of WCl_6–$EtAlCl_2$ as a catalytic system for olefin metathesis reactions has been described by several groups.[1] This catalyst, which is also a strong Lewis acid, can consequently promote a variety of cationic reactions such as prototropic isomerizations,[2] oligomerization of olefins,[3] and alkylation of aromatic solvents.[4]

However, neither the specificity nor the optimal conditions for the competition between metathesis and cationic-like reactions have been thoroughly investigated; it is the goal of this paper to study the parameters which govern this competition between metathesis and alkylation processes.

Experimental Section

All solvent and olefins (*trans*-2-pentene, *trans*-4-octene, 1-octene, and 1-dodecene) were dried over $LiAlH_4$ or CaH_2 before distillation and the operations were conducted under an inert atmosphere (argon).

Ethylaluminum dichloride (Fluka), obtained as a 50% solution in hexane, was diluted (after titration) with the appropriate amount of hexane to obtain 0.2 M solutions.

Tungsten hexachloride (Fluka) was purified by sublimation of the volatile impurities ($WOCl_4$, WO_2Cl_2) before dissolution in the aromatic solvents, respectively benzene; *o*-, *m*-, *p*-xylenes; 1,2,4 and 1,3,5-trimethylbenzenes; and finally *o*-dichlorobenzene. The solutions obtained (0.05 M) are intensively colored: benzene, violet blue; toluene, blue; xylenes, green blue; trimethylbenzenes, green; dichlorobenzene, brown.

The different components were injected into the reaction vessel through a septum, together with an internal VPC standard (cyclooctane or undecane).

The solution of olefin in the suitable aromatic solvent was cooled to 5 °C and the appropriate amount of the aromatic solution of WCl_6 was added, immediately followed by the solution of $EtAlCl_2$ in hexane with a molar ratio Al to W kept equal to 4. After 1 min of reaction time, the system was quenched with water.

Quantitative VPC analysis was performed using a silicone column (20% SE-30 on Chromosorb 80/100) (flame ionization detector) and the yields calculated by comparison with the internal standard.

The different olefins and alkylated products have been identified by comparison with standard products which have been obtained from Fluka or by the following classical reaction sequence: addition of the suitable Grignard reagent on the corresponding α-ketoalkylbenzene gives a tertiary alcohol which is dehydrated on *p*-toluenesulfonic acid to a phenylalkene. Subsequent hydrogenation of the olefin on Raney nickel gives the required phenylalkane.

Moreover, some of the alkylated products have been isolated by preparative GLC and analyzed by mass spectrometry which shows a fragmentation pattern characteristic of alkylbenzenes; for in-

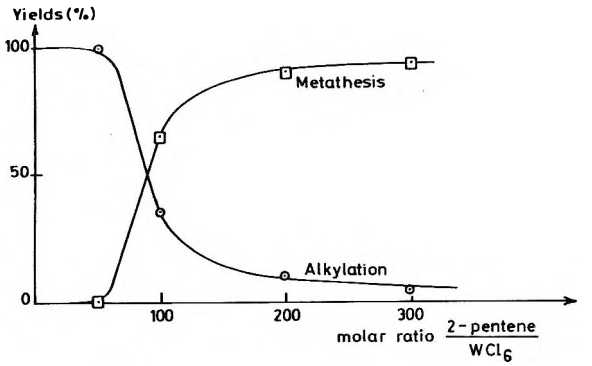


Figure 1. Yields of metathesis and alkylations reactions vs. molar ratio 2-pentene/WCl_6 for a constant molar ratio benzene/WCl_6 = 200.

stance, the 2-, 3- and 4-phenyloctanes have a parent peak at *m/e* 190 ($C_{14}H_{22}$) in addition to groups of peaks differing by 14 (CH_2) mass units.[5]

Results

1. Alkylation–Metathesis Competition in Benzene. We have already observed that the yields of metathesis or alkylated products depend on the ratios benzene to olefin, olefin to catalyst, and benzene to catalyst.[6]

Figure 1 reports the results obtained for a variation of the olefin concentration (with a constant ratio of benzene to catalyst). We have also previously reported[6] the influence of the variations of the concentration of the catalyst (for a constant ratio C_nH_6/olefin) on the relative yields of metathesis and alkylated products. In both cases, S-shaped curves are obtained and Figure 2 sums up the overall situation observed for the C_6H_6–2-pentene system.

It appears that both metathesis and alkylation reactions are competitive over a large range of concentrations, and that alkylation reactions increase with an increase of either the concentration of the catalyst or of the benzene to olefin ratio.

These results are given for a reaction time of 1 min. Longer times slowly increase the yields in alkylated products at the expense of metathesis, as indicated in Table I.

The composition of the mixture remains practically unaltered for several days after quenching with water.

2. Influence of the Nature of the Aromatic Solvent. Besides the relative concentration of the components of the system, the competition between alkylation and metathesis is greatly affected by the π-donor ability of the aromatic molecule used as solvent.[7] Increasing yields in alkylated compounds are observed in going from benzene to toluene, xylenes, and trimethylbenzenes (Table II).

On the other hand, our catalytic system does not alkylate *o*-dichlorobenzene; we then observe the formation of saturated polymers resulting from a cationic polymerization of the olefin, and only traces of alkylated products.

3. Distribution of the Alkylated Products. High concentrations of catalyst and large solvent/olefin ratios thus favor the alkylation of the aromatic solvent. If the latter is large enough, monoalkylated products are exclusively formed, which correspond to a thermodynamic equilibrium as calculated for molar ratio benzene/2-pentene larger than 4.

A similar effect has been noted by Popov[8] with a $NiCl_2$–$EtAlCl_2$ catalytic system although it is not always observed.

(a) $EtAlCl_2$ alone or the mixture WCl_6–$EtAlCl_2$ (the olefin being added to the preformed catalyst in benzene) give mixtures of mono- and polyalkylated benzenes, no change in product with time being observed (Table III, A and B).

(b) With WCl_6 alone at 50 °C or WCl_6–$EtAlCl_2$ (order of addition: benzene, olefin, WCl_6, and finally $EtAlCl_2$) di- and polyalkylated products quickly disappear to give exclusively monoalkylbenzenes (Table III, C, D, and E).

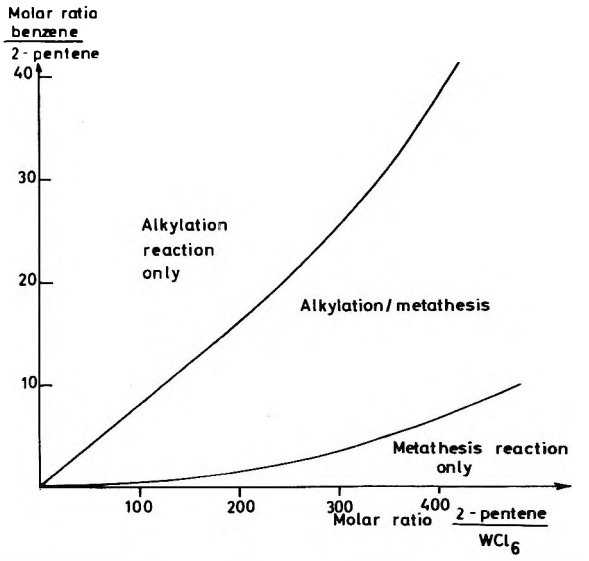


Figure 2. Competitive metathesis and alkylation reactions (after 1 min of reaction time).

Moreover, the thermodynamic distribution between monoalkylated products (in terms of isomers branching) does not depend on the position of the double bond in the original olefin (Table III, D, E).

Under the same catalytic conditions, independently prepared polyalkylbenzenes are quickly transformed to monoalkylbenzenes (Table III, F), but monoalkylbenzenes remain unaffected.

So there is a definite redistribution of polysubstituted benzenes to monoalkylated ones and the kinetics of this transalkylation reaction depend on the molar ratio of aromatic compound to olefin. For a ratio benzene/4-octene = 4, a quantitative formation of monoalkylated products is observed after a few days, but the same result is obtained in a few minutes if the ratio is increased up to 20 (Table III, D, G).

This potentially interesting alkylation redistribution process has been applied to industrial synthesis such as the preparation of monododecylbenzenes (detergent chemistry) and of monoethylbenzene (preparation of styrene). Indeed, 1-dodecene yields monoalkylbenzenes in a few minutes at room temperature (100% yield) when molar ratios benzene/olefin = 20 and olefin/catalyst = 50.

On the other hand, benzene and ethylene (molar ratio = 3, ethylene/catalyst = 50) give polyethylene (25%) and a mixture of mono- and polyethylbenzenes (75%) at room temperature. A few days at 60 °C increase the yield in ethylbenzene up to about 85%, but some diethylbenzenes and polymers remain present.

Discussion

It is well known that the active catalyst resulting from reaction of WCl_6 with $EtAlCl_2$ is a polynuclear species where both tungsten and aluminum atoms are associated via μ-chloride and/or μ-alkyl bonding.[9]

Moreover, the coordination of olefins[10] or of aromatic molecules[11] to tungsten carbonyl complexes or halogenides (WCl_6 and WF_6)[12] has been investigated. It was shown that, at least in the latter case, a rapid exchange process actually takes place.[12b,d]

On the other hand, we have studied the electronic spectra of WCl_6 in aromatic solvents such as, e.g., 1,2,4-trimethylbenzene, which shows three bands: two of these (355 and

Table I. Yields of Metathesis and Alkylation Reactions

$$\frac{\text{2-pentene}}{WCl_6} = 200 \quad \frac{\text{benzene}}{\text{2-pentene}} = 5 \quad \frac{Al}{W} = 4$$

	Metathesis, %			Alkylation, %			
				Monoalkylbenzenes			
Time, min	2-Butene	2-Pentene	3-Hexene	Ph-C_4	Ph-C_5	Ph-C_6	Di- and polyalkylbenzenes
0		100					
5	16	36	16	5	21	4	2
100	15	26	16	6	27	7	4
2400	11	20	12	8	33	11	5

Table II. Relative Yields of Metathesis and Alkylation Reactions in Function of the Aromatic Molecule (Reaction Time 1 min at 5 °C)

		Molar ratios				
Registry no.	Aromatic compd	2-Pentene / WCl_6	Aromatic / WCl_6	Aromatic / 2-pentene	Yields of metathesis, %	Yields of alkylation, %
71-43-2	Benzene	50	200	4	0	100
		100	200	2	65	35
		200	200	1	90	10
		300	200	0.66	94	6
108-88-3	Toluene	100	200	2	0	100
		150	200	1.3	13	87
		200	200	1	67	33
		300	200	0.66	92	8
95-47-6	*o*-Xylene	50	200	4	0	100
		100	200	2	5	95
		200	200	1	42	58
		300	200	0.66	70	30
108-38-3	*m*-Xylene	100	200	2	0	100
		200	200	1	33	67
		400	200	0.5	80	20
		800	200	0.25	94	6
106-42-3	*p*-Xylene	100	200	2	0	100
		200	200	1	52	48
		300	200	0.65	72	28
		400	200	0.5	81	19
		800	200	0.25	96	4
95-63-6	Pseudocumene (1,2,4-trimethylbenzene)	100	200	2	0	100
		200	200	1	1	99
		400	200	0.5	30	70
		800	200	0.25	61	39
108-67-8	Mesitylene (1,3,5-trimethylbenzene)	100	200	2	0	100
		400	200	0.5	24	76
		600	200	0.33	34	66
		1200	200	0.16	67	33

460 nm, ϵ_{355} 6300 and ϵ_{460} 380 l. mol^{-1} cm^{-1}) correspond to electronic transitions of the WCl_6 molecules as observed in an inert solvent[9d,13] and the third one (570 nm, ϵ_{570} 690 l. mol^{-1} cm^{-1}) is assumed to be a charge transfer band from the aromatic molecule to the metal. The formation of such complexes is also supported by the different colors of the aromatic solutions (see Experimental Section).

Moreover, the coordination between the tungsten and the olefinic or aromatic molecules should be strengthened by a lowering of the oxidation state by $EtAlCl_2$[9] [W(VI) is reduced to W(V) or (IV)] owing to an increased back-bonding of the tungsten to the ligands.

The formation of a complex between the tungsten atom and the olefin in an aromatic solution thus involves a competition for the coordination sites of the metal. The relative importance of both tungsten–olefin and tungsten–aromatics complexes depends on the relative stability constants for their formation. This general problem is indeed a very complex one and has been reported by some authors which explains such competition by qualitative HSAB theory.[14]

The evolution of both olefin–tungsten and aromatics–tungsten complexes can respectively give metathesis or alkylation reactions. From a kinetic point of view these two reactions depend on the absolute concentrations and on the partial kinetic orders of the species in solution. Partial kinetic orders for metathesis are difficult to estimate with accuracy but activation energies of 6–8 kcal/mol have been found for this reaction.[15] On the other hand, values of about 10–16 kcal/mol are generally accepted for the alkylation of benzene[16] by secondary carbenium ions; of course, these values are given for quite different experimental conditions and they must be considered only as a crude indication. Nevertheless, a metathesis process should be lower in energy than an alkylation one.

Table III. Alkylation Reactions of Benzene[a]

	Molar ratio benzene/olefin	Molar ratio olefin/catalyst (1)	Time, min	Monooctylbenzenes, % Ph-C^C_{C6}	Ph-C^{C2}_{C5}	Ph-C^{C3}_{C4}	Dioctylbenzenes, %	Polyoctylbenzenes, %
A	30	20	1–1400	23	16	22	29	10
B	20	60	1	27	22	29	20	2
			15	29	22	34	14	1
			1400	29	23	31	16	1
C	30	30	900	42	28	29	1	
D	20	50	0.5	37	28	33	2	
			1	38	27	32	3	
			10	40	27	33		
			1400	44	27	29		
E	20	50	5	50	27	21	2	
			20	48	26	26		
			1400	43	33	24		
F	20	50	0	18	17	20	33	12
			5	23	14	23	31	9
			20	24	21	25	24	6
			190	42	25	33		
			1400	46	27	27		
G	4	50	3	24	16	21	35	4
			45	25	15	21	39	
			1400	37	23	29	11	
			4300	40	25	33	2	

[a] All reactions are performed at room temperature, except for WCl_6 alone for which a temperature of 50 °C is necessary to promote alkylation. Benzene and 4-octene are respectively used as the aromatic substrate and the olefin (except for experiment E where the olefin is 1-octene). (1) Molar ratio olefin/catalyst is calculated from the concentration of olefin and WCl_6 in the system. Nevertheless, for case A, this molar ratio is based on olefin and $C_2H_5AlCl_2$ concentrations. (A) The catalytic system used is $C_2H_5AlCl_2$ alone. (B) Catalytic system: WCl_6–$C_2H_5AlCl_2$ with addition order aromatic + WCl_6 + $C_2H_5AlCl_2$ + olefin. (C) Catalytic system: WCl_6 alone. (D–G) Catalytic system: WCl_6–$C_2H_5AlCl_2$ with addition order aromatic + olefin + WCl_6 + $C_2H_5AlCl_2$.

The mechanism of olefin metathesis reaction probably involves some tungsten–carbene complexes formed by alkylation of the tungsten atom in interaction with the organoaluminum compound. Such tungsten–carbene complex would react with a probably π-coordinated olefin via a four-atom metallocycle.[9a,17]

On the opposite, the coordination of one aromatic molecule on the tungsten complex prevents metathesis and promotes the alkylation reaction through a completely different pathway which would involve electrophilic substitution of aromatics by a secondary carbenium ion[18] and yields mono- and polyalkylated products for which the thermodynamic equilibrium depends on the initial molar ratio aromatic compound/olefin. When this ratio is greater than 4, monoalkylated products are exclusively formed.

The relative yields of metathesis and alkylation reactions thus depend on two parameters: the relative stability constants of the tungsten–olefin or aromatics π complexes and the relative rates of the alkylation and metathesis reactions.

The importance of the thermodynamic stability of the π complexes is strongly supported by the results quoted in Table II which show that the alkylation yields increase with the donor character of the aromatic ligand (for a constant molar ratio of olefin to aromatics), reflecting so the enhancement of the thermodynamic stability of the π complexes. On the other hand, the alkylation yields do not depend on the relative positions of the methyl substituents; for instance, there is almost no change in the relative reactivity of *o*-, *m*-, and *p*-xylenes. Therefore, in opposition to classical cationic alkylation of aromatics which takes place generally through a σ-type mechanism (characterized by a very large substituent effect),[19] our result is in agreement with the formation of a π tungsten–aromatics complex as the rate-determining step for the alkylation reaction.

The WCl_6–$C_2H_5AlCl_2$ system is therefore a very active and very selective catalyst for both metathesis and alkylation reactions: the relative importance of these two competing problems depends on the relative concentrations of the different components in the reaction mixture. Moreover, under the conditions which lead exclusively to alkylation, the WCl_6–$C_2H_5AlCl_2$ catalytic system is also very efficient for reaching rapidly the thermodynamic equilibrium between the different alkylated isomers.

Registry No.—$C_2H_5AlCl_2$, 563-43-9; WCl_6, 13283-01-7; *trans*-2-pentene, 646-04-8; *trans*-4-octene, 14850-23-8; 1-octene, 111-66-0; 1-dodecene, 112-41-4; ethylene, 74-85-1.

References and Notes

(1) (a) N. Calderon, H. Y. Chen, and K. W. Scott, *Tetrahedron Lett.*, 3327 (1967); (b) N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and R. W. Scott, *J. Am. Chem. Soc.*, **90**, 4133 (1968); (c) N. Calderon, E. A. Ofstead, and W. A. Judy, *J. Polym. Sci.*, **5**, 2209 (1967); (d) K. W. Scott, N. Calderon, E. A. Ofstead, W. A. Judy, and J. P. Ward, *Adv. Chem. Ser.*, **91**, 399 (1969); (e) P. Günter, F. Haas, G. Marwede, K. Nützel, W. Oberkirch, G. Pampus, J. Witte, and N. Schön, *Angew. Makromol. Chem.*, **16/17**, 27 (1971).

(2) G. Dall'Asta, G. Stigliani, A. Greco, and L. Motta, *Polym. Prepr.*, **13**, 910 (1972).

(3) G. Dall'Asta and G. Motroni, *Chim. Ind. (Milan)*, **50**, 972 (1968).

(4) (a) V. M. Kothari and J. J. Tazuma, *Chem. Eng. News*, **48**, 39 (1970); (b) V. M. Kothari and J. J. Tazuma, *J. Org. Chem.*, **36**, 2951 (1971); (c) A. Uchida, Y. Hamano, Y. Mukai, and S. Matsuda, *Ind. Eng. Chem., Prod. Res. Dev.*, **10**, 372 (1971); (d) L. Hocks, A. J. Hubert, and P. Teyssié, *Tetrahedron Lett.*, 3687 (1972); (e) V. P. Yur'Ev, G. A. Gailyunas, G. A. Tolstikov, V. I. Khostenko, and S. R. Rafikov, *Dokl. Chem.*, **219**, 844 (1974).

(5) F. W. McLafferty, "Mass Spectrometry", W. A. Benjamin, New York, N.Y., 1966.

(6) L. Hocks, A. J. Hubert, and P. Teyssié, *Tetrahedron Lett.*, 2719 (1973).

(7) L. Hocks, A. J. Hubert, and P. Teyssié, *Tetrahedron Lett.*, 877 (1974).

(8) A. F. Popov, N. N. Korneev, and G. S. Solov'eva, *Sov. Chem. Ind. (Engl. Transl.)*, **48**, 71 (1972).

(9) (a) E. L. Muetterties, *Inorg. Chem.*, **14**, 951 (1975); (b) L. Hocks, *Bull. Soc. Chim. Fr.*, 1893 (1975); (c) W. B. Hughes, *Adv. Chem. Ser.*, **132**, 192 (1974); (d) H. Hocker and F. R. Jones, *Makromol. Chem.*, **161**, 251

(1972); (e) R. J. Haine and G. J. Leigh, *Chem. Soc. Rev.*, **4**, 155 (1975).
(10) (a) I. W. Stolz, G. R. Dobson, and R. K. Sheline, *Inorg. Chem.*, **2**, 1264 (1963); (b) M. Wrighton, G. S. Hammond, and H. B. Gray, *J. Am. Chem. Soc.*, **92**, 6068 (1970); **93**, 6048 (1971); (c) B. T. Manuel and F. G. A. Stone, *Chem. Ind. (London)*, 1349 (1959).
(11) I. W. Stolz, H. Haas, and R. K. Sheline, *J. Am. Chem. Soc.*, **87**, 716 (1965).
(12) (a) H. F. Priest and W. C. Schumb, *J. Am. Chem. Soc.*, **70**, 2291 (1948); (b) H. J. Clase, A. M. Noble, and J. M. Winfried, *Spectrochim. Acta, Part A*, **25**, 293 (1969); (c) J. C. Evans and G. Y.-S. Lo, *J. Mol. Spectrosc.*, **26**, 147 (1968); (d) F. N. Tebbe and E. L. Muetterties, *Inorg. Chem.*, **7**, 172 (1968).
(13) (a) R. A. Walton, P. C. Crouch, and B. J. Brisdon, *Spectrochim. Acta, Part A*, **24**, 601 (1968); (b) C. K. Jorgensen, *Mol. Phys.*, **2**, 309 (1959).
(14) (a) C. K. Jorgensen, *Top. Curr. Chem.*, **56**, 1 (1975); (b) Y. Marcus and I. Eliezer, *Coord. Chem. Rev.*, **4**, 273 (1969).
(15) (a) A. Clark and C. Cook, *J. Catal.*, **15**, 420 (1969); (b) W. B. Hughes, *J. Am. Chem. Soc.*, **92**, 532 (1970); (c) A. J. Moffat and A. Clark, *J. Catal.*, **17**, 264 (1970).
(16) (a) G. A. Olah and P. v. R. Schleyer, "Carbonium Ions", Vol. II, Interscience, New York, N.Y., 1968, pp 774–776; (b) C. R. Smoot and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 2185, 6245 (1956).
(17) (a) C. P. Casey and J. J. Burkhardt, *J. Am. Chem. Soc.*, **96**, 7808 (1974); (b) T. J. Katz and J. M. Ginnis, *ibid.*, **97**, 1592 (1975); (c) R. H. Grubbs, P. L. Burk, and D. D. Carr, *ibid.*, **97**, 3265 (1975); (d) J. L. Herisson and Y. Chauvin, *Makromol. Chem.*, **141**, 161 (1970); (e) J. P. Soufflet, D. Commereuc, and Y. Chauvin, *C. R. Acad. Sci., Ser. C*, **276**, 169 (1973).
(18) (a) H. R. Alul, *J. Org. Chem.*, **33**, 1522 (1968); (b) C. D. Nenitzescu, *Rev. Roum. Chim.*, **9**, 5 (1964).
(19) (a) R. D. Gillion, "Introduction to Physical Organic Chemistry", Addison-Wesley, Reading, Mass., 1970, p 227; (b) J. L. Andrews, *Chem. Rev.*, **54**, 713 (1954); (c) J. Hine, "Physical Organic Chemistry", 2d ed, McGraw-Hill, New York, N.Y., 1962, p 344.

Homoconjugation Interactions between Occupied and Unoccupied Molecular Orbitals. II

Peter V. Alston*

E. I. du Pont de Nemours and Company, Analytical Research Group, Spruance Plant, Richmond, Virginia 23261

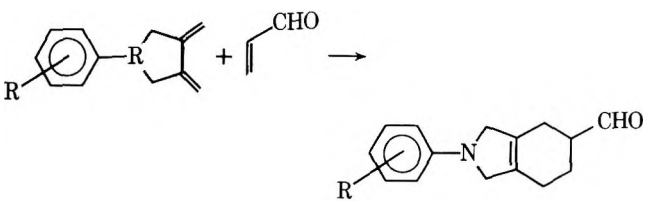
Raphael M. Ottenbrite

Department of Chemistry, Virginia Commonwealth University, Richmond, Virginia 23284

Received August 6, 1975

Perturbation molecular orbital theory is used to explain the homoconjugation interactions in systems in which the respective frontier molecular orbitals of the π moieties are of opposite symmetry. The theory predicts a hypsochromic shift in the uv wavelength maximum for such systems from reference compounds. No cases of unambiguous bathochromic λ_{max} shifts were found in the literature to contrast with the theory's prediction. Inductive effects and hyperconjugation were not the origin of the hypsochromic shifts. The prediction of uv data and photoelectron spectroscopy concerning through-space interactions is compared.

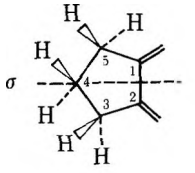
Homoconjugation between nonconjugated π-electron systems has received considerable attention over the last decade.[1] More recently, through-bond and hyperconjugation interactions have been shown to have an important role in certain cases.[1c-e,2] The use of perturbation molecular orbital theory to explain the homoconjugation in systems in which the respective frontier molecular orbitals (MO's) of the π moieties are of the same symmetry was demonstrated by Hofmann et al.[1d,e] Recently, we used the perturbation molecular orbital approach to explain the novel substituent effect in the Diels–Alder reaction between 1-(substituted phenyl)-3,4-dimethylenepyrrolidine, homoconjugated diene, and acrolein.[3] The respective frontier MO's of the π moieties of this exocyclic diene are of opposite symmetry (symmetric or asymmetric) with respect to the plane of symmetry which bisects the molecule. In this paper a general theory for predicting the effect of homoconjugation on the energy separation of the frontier MO's of π moieties whose respective frontier MO's are of opposite symmetry is developed.



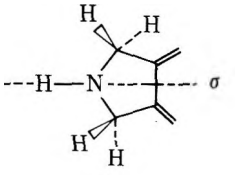
Theory

The fundamentals of perturbation molecular orbital theory are as follows. (1) When two molecular orbitals interact (the molecular orbitals must be of the same symmetry), the lower energy molecular orbital is stabilized and the higher energy molecular orbital is destabilized. (2) The smaller the energy separation between the interacting molecular orbitals, the greater the interaction.

The application of this theory to homoconjugation systems with π moieties, whose respective frontier MO's are of opposite symmetry with respect to the plane of symmetry which bisects the molecule, will be first illustrated by the exocyclic dienes 1,2-dimethylenecyclopentane (**1**) and 3,4-dimethylenepyrrolidine (**2**). The relative energies of the



1



2

frontier MO's of **1** and **2** are determined from orbital interaction diagrams of the CNDO/2 frontier MO's of 2,3-dimethyl-1,3-butadiene with those of methane[4] and ammonia. In **1**, both frontier MO's of methane (4-methylene moiety) interact with the LUMO of the hyperconjugated butadiene (Figure 1). The interaction between the σ^* and the LUMO-butadiene is more important; thus, a small decrease in the LUMO energy of **1** is expected as compared to *cis*-2,3-dimethyl-1,3-butadiene. However, the substitution of a heteroatom as in **2** for the 4-methylene moiety of **1** will replace the above molecular orbital interactions with a single molecular orbital interaction between the nonbonded

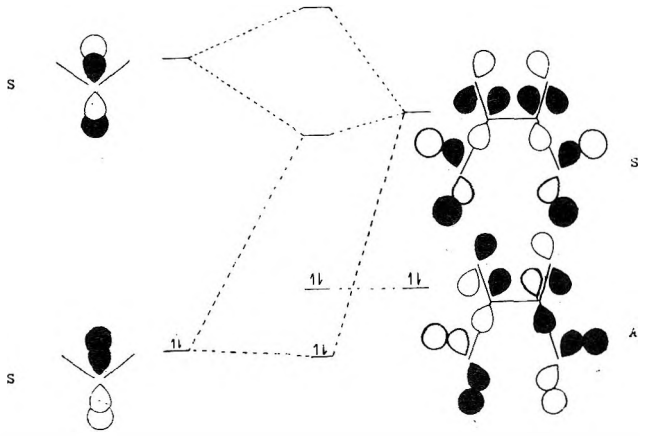


Figure 1. Relative energies of the frontier MO's of 1,2-dimethylenecyclopentane from the interaction of the CNDO/2 frontier MO's of methane and 2,3-dimethyl-1,3-butadiene.

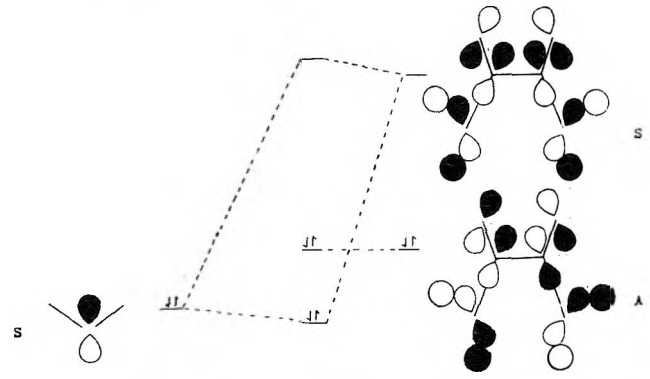


Figure 2. Relative energies of the frontier MO's of 3,4-dimethylenepyrrolidine from the interaction of the CNDO/2 frontier MO's of ammonia and 2,3-dimethyl-1,3-butadiene.

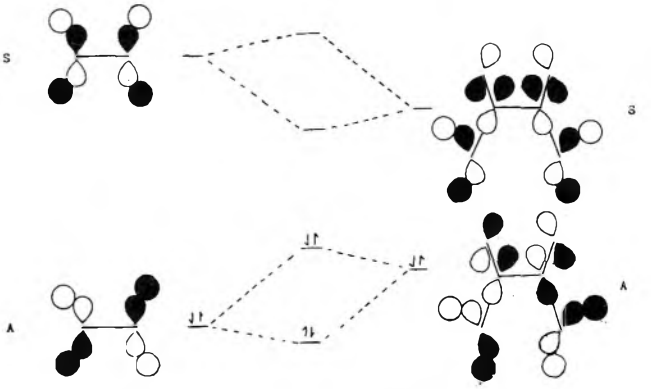


Figure 3. Relative energies of the frontier MO's of 1,2-dimethylenecyclohexane from the interaction of the CNDO/2 frontier MO's of ethane and 2,3-dimethyl-1,3-butadiene.

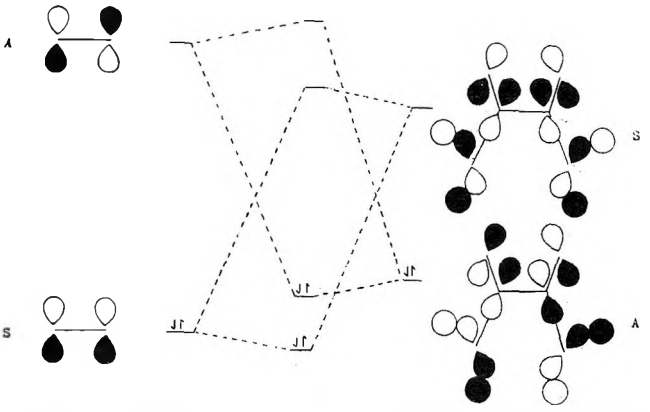
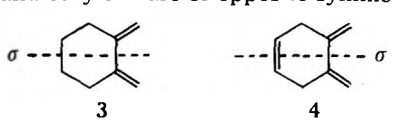


Figure 4. Relative energies of frontier MO's of 1,2-dimethylene-4-cyclohexene from the interaction of the CNDO/2 frontier MO's of ethylene and 2,3-dimethyl-1,3-butadiene.

orbital[5] of the heteroatom and the LUMO of the hyperconjugated butadiene (Figure 2). This MO interaction will raise the LUMO of **2** in energy as compared to *cis*-2,3-dimethyl-1,3-butadiene. Consequently, **2** is predicted to have a greater energy separation between its frontier MO's than is **1**.

To provide additional assurance that the above postulated effect is present, the relative energies of the frontier MO's of these exocyclic dienes were also determined from orbital interaction diagrams of the CNDO/2 frontier MO's of butadiene with those of propane and dimethylamine. The MO interactions between the frontier MO's of these compounds were also such as to produce a greater energy separation between the frontier MO's of **2**. The HOMO of both dimethylamine and propane interacted only with the LUMO of butadiene. This interaction was greater with dimethylamine because its HOMO (−0.498 au) was of considerably higher energy than the HOMO (−0.570 au) of propane. Also, the calculations predict that dimethylamine has one less unoccupied MO than does propane and the absent unoccupied MO corresponds to the LUMO (0.275 au) of propane which by symmetry interacts with the LUMO of butadiene.

Another situation which is encountered frequently is the replacement of an ethane moiety with an ethylene moiety as in 1,2-dimethylenecyclohexane (**3**) and 1,2-dimethylene-4-cyclohexene (**4**). The respective CNDO/2 frontier MO's of ethane[6] and ethylene are of opposite symmetry with respect to a symmetry plane that is perpendicular to and bisects the carbon–carbon bond of the molecule. The HOMO-ethane moiety interacts with the HOMO-hyperconjugated butadiene and the LUMO-ethane moiety interacts with the LUMO-hyperconjugated butadiene in **3**; consequently, the energy separation between the frontier MO's of **3** is expected to be less than that of *cis*-2,3-dimethyl-1,3-butadiene (Figure 3). In **4**, the HOMO-ethylene moiety interacts with the LUMO-hyperconjugated butadiene and the LUMO-ethylene moiety interacts with the HOMO-hyperconjugated butadiene; consequently, the frontier MO energy separation of **4** is expected to be greater than that of *cis*-2,3-dimethyl-1,3-butadiene (Figure 4). Thus, the replacement of an ethane moiety with an ethylene moiety as in **3** and **4** is predicted to increase the energy separation between the frontier MO's of the diene moiety.



3 **4**

CNDO/2 calculations[7] on various model systems predict the above discussed MO interactions. The CNDO/2 calculations were carried out on ethane, ethylene, 1,2-dimethylenecyclohexane, 1,2-dimethylene-4-cyclohexene, methane, water, ammonia, hydrogen sulfide, 2,3-dimethyl-1,3-butadiene, 1,2-dimethylenecyclopentane, 3,4-dimethylenetetrahydrofuran, 3,4-dimethylenepyrrolidine, and 3,4-dimethylenethiophane.

The energy of uv transitions are calculated in SCF methods from eq 1.[8]

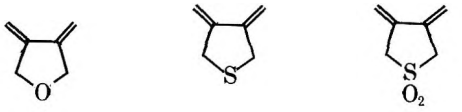
$$\Delta E = \epsilon_j - \epsilon_i - J_{ij} + 2K_{ij} \quad (1)$$

In this expression, ϵ_j and ϵ_i are the energies of an occupied MO and an unoccupied MO, respectively, while J_{ij} and K_{ij} are the coulomb and exchange integrals which account for the difference in electron repulsion in the ground and ex-

cited states. Consequently, homoconjugation of the type discussed can be verified experimentally by hypsochromic λ_{max} shifts from reference compounds if the two-electron effects are smaller or reinforce the one-electron effects.

Results and Discussion

Experimental data in Table I indicate the possibility of a small hypsochromic λ_{max} shift in **5** and **6** from the reference compounds **1** and **7**, while 3,4-dimethylenethiophane (**8**) exhibits a larger λ_{max} shift. Furthermore, when the nonbonded electrons of the sulfur of **8** become bonded in a sulfone group (**9**) and a sulfoxide group (**10**), the expected bathochromic shift is observed.



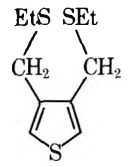
5 λ_{max} 244 nm **8** λ_{max} 240 nm **9** λ_{max} 244 nm

Homoconjugation is also observed in the thiophene system (Table I). A hypsochromic shift of 12 nm is observed for 1*H*,3*H*-thieno[3,4-*c*]thiophene (**11**) from the reference compound, cyclopenta[*c*]thiophene (**12**). When the sulfur heteroatom is oxidized to the sulfone (**13**), the expected bathochromic shift is again observed. However, homoconjugation is not observed with the nitrogen and oxygen heteroatoms, **14** and **15**.

11 λ_{max} 232 nm **12** λ_{max} 244 nm **13** λ_{max} 244 nm

The larger λ_{max} shift observed in the diene and the thiophene moieties that are homoconjugated with sulfur rather than with nitrogen and oxygen is probably due to the greater overlap between the nonbonded π orbital of sulfur and the carbon 2p orbitals of the thiophene and the diene moieties. In support of this hypothesis, Schmidt and Schweig observed by photoelectron spectroscopy a large through-space interaction between the π moieties of 2,5-dihydrothiophene, but none in 2,5-dihydrofuran.[9] Also, the CNDO/2 resonance and overlap integrals at 2.5 and 3.0 Å support this hypothesis (Table II).[10] Experimental ionization potentials of model compounds of the heteroatom moieties rule out the orbital energies as the origin of the larger shifts.[11,12] Also, CNDO/2 calculations predict an interaction between the d orbitals of the sulfur moiety and the frontier MO's of the thiophene and the diene moieties. This additional interaction could also contribute to the larger λ_{max} shifts.

Hyperconjugation and inductive effects could be the origin of the hypsochromic shifts observed in the exocyclic diene and thiophene systems. If they were, an even larger hypsochromic λ_{max} shift would be expected in 3,4-bis(ethylthio)methylthiophene (**16**) from the reference compound



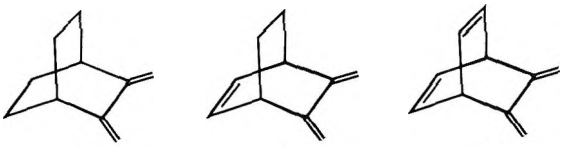
16 λ_{max} 246 nm

12. However, a bathochromic shift is observed. Furthermore, the oxidation of the homoconjugation sulfur to a sulfone gave a bathochromic shift in both systems as would be expected if through-space orbital interactions are the origin of the λ_{max} shifts. Also, the replacement of the methylene group with a heteroatom should give the hypsochromic λ_{max} shifts in every case if hyperconjugation and inductive effects are its origin. This is expected because the overlap between the orbitals of the heteroatoms and the adjacent methylene groups is significant in all cases. The CNDO/2 resonance and overlap integrals at 1.5 Å support this hypothesis (Table II).[10]

The predicted hypsochromic λ_{max} shift was not observed in the cyclohexane system (**3, 4, 17**) because of the nonplanarity of the diene moiety[13] of 1,2-dimethylenecyclohexane whose effect dominates the possible homoconjugation. However, homoconjugation is observed in the analogous bicyclo[2.2.1]heptane system (**18–23**) in which the diene moiety is rigidly held in the cisoid planar conformation.

18 λ_{max} 248 nm **19** λ_{max} 240 nm

In the bicyclo[2.2.2]octane and tricyclo[4.2.2.$0^{2,5}$]decane systems, the hypsochromic shift is small or not present when the diene moiety is homoconjugated with one double bond moiety (**24–28**). However, a 10-nm hypsochromic shift is observed by Butler and Snow[14] when the diene moiety is homoconjugated with two double bond moieties (**29**).



25 λ_{max} 252 nm **24** λ_{max} 252 nm **29** λ_{max} 242 nm

The predicted hypsochromic λ_{max} shift is observed in the bicyclo[4.2.1]nona-2,4-diene and 2,4,7-triene systems. The homoconjugated compounds **32–34** have shorter wavelength maxima than the reference compound, bicyclo[4.2.1]nona-2,4-diene (**30**). Furthermore, the smaller shift

30 λ_{max} 259 nm **31** λ_{max} 257 nm **32** λ_{max} 248 nm

observed when electron-withdrawing groups are attached to the nitrogen heteroatom is expected since these groups lower the energy of the nonbonded orbital of the heteroatom thereby decreasing its interaction with the LUMO of the diene moiety. The homoconjugated compounds **35–38** also have shorter wavelength maxima than the reference compound, bicyclo[4.2.1]nona-2,4,7-triene (**31**). The predicted homoconjugation interaction in the bicyclo[4.2.1]diene system is in contrast to photoelectron data which has been interpreted as indicating no homoconjugation between the π moieties.[15] Furthermore, comparison of the wavelength maxima in compounds **30** and **31** indicates no significant homoconjugation interactions between the π

Table I. Ultraviolet Spectral Data of Homoconjugated and Reference Compounds

No.	Compd	λ_{max}, nm (ϵ)	Solvent	Ref
1	1,2-Dimethylenecyclopentane	243	C_6H_{12}	*a*
		248 (10 500)	Isooctane	*b*
3	1,2-Dimethylenecyclohexane	218 (7602)	No solvent given	*c*
		220 (6375)	95% EtOH	*d*
4	1,2-Dimethylene-4-cyclohexene	216	No solvent given	*e*
		219 (5340)	95% EtOH	*d*
5	3,4-Dimethylenetetrahydrofuran	244 (9820)	Isooctane	*a*
6	1-Methyl-3,4-dimethylenepyrrolidine	245 (8700)	Isooctane	*f*
7	1,2-Dimethylene-3-methylcyclopentane	248 (8510)	Isooctane	*b*
8	3,4-Dimethylenethiophane	240 (6000)	95% EtOH	*g*
9	3,4-Dimethylenethiophane 1,1-dioxide	244 (6680)	95% EtOH	*g*
10	3,4-Dimethylenethiophane 1-oxide	244 (6150)	95% EtOH	*g*
11	1*H*,3*H*-Thieno[3,4-*c*]thiophene	232 (6100)	95% EtOH	*h*
12	Cyclopenta[*c*]thiophene	244 (7370)	95% EtOH	*i*
13	1*H*,3*H*-Thieno[3,4-*c*]thiophene 2,2-dioxide	244 (6400)	95% EtOH	*j*
14	4*H*,6*H*-5-Ethylthieno[3,4-*c*]pyrrole	242.5 (6200); 232.5 (5900)	95% EtOH	*j*
15	1*H*,3*H*-Thieno[3,4-*c*]furan	244 (6600)	95% EtOH	*k*
16	3,4-Bis[(ethylthio)methyl]thiophene	246 (5600)	95% EtOH	*h*
17	1,2-Dimethylene-4-methyl-4-cyclohexene	218 (5340)	95% EtOH	*d*
18	2,3-Dimethylenebicyclo[2.2.1]heptane	248 (10 600)	C_6H_{12}	*a*
		249 (11 510)	No solvent given	*c*
		248 (8900)	EtOH	*l*
19	2,3-Dimethylenebicyclo[2.2.1]hept-5-ene	241 (9560)	95% EtOH	*d*, *m*
		240 (8900)	EtOH	*l*
20	7-Isopropylidene-2,3-dimethylenebicyclo-[2.2.1]hept-5-ene	246 (12 900)	EtOH	*l*
21	7-Isopropylidene-2,3-dimethylenebicyclo-[2.2.1]heptane	250 (1200)	EtOH	*l*
22	2,3-Dimethylenebicyclo[2.2.1]hept-5-ene-7-spiro-1′-cyclopropane	241.5 (9550)	EtOH	*l*
23	2,3-Dimethylenebicyclo[2.2.1]heptane-7-spiro-1′-cyclopropane	247.5 (9300)	EtOH	*l*
24	2,3-Dimethylenebicyclo[2.2.2]octane	247 (10 000)	95% EtOH	*d*
		249 (8390)	No solvent given	*c*
		247 (7600); 252 (7600)	EtOH	*l*
25	2,3-Dimethylenebicyclo[2.2.2]oct-5-ene	253 (6650)	No solvent given	*m*
		246 (8100); 252 (8100)	EtOH	*l*
26	2,3-Dimethylene-5-methyl-8-isopropyl-bicyclo[2.2.2]oct-5-ene	246 (8350)	95% EtOH	*d*
27	9,10-Dimethylenetricyclo[4.2.2.0^{2,5}]deca-3,7-diene	247 (7900)	EtOH	*l*
28	9,10-Dimethylenetricyclo[4.2.2.0^{2,5}]dec-3-ene	249.5 8300)	EtOH	*l*
29	2,3-Dimethylenebicyclo[2.2.2]octa-5,7-diene	242 (9100)	C_6H_{12}	*l*
30	Bicyclo[4.2.1]nona-2,4-diene	259	EtOH	*n*
31	Bicyclo[4.2.1]nona-2,4,7-triene	259 (2691); 268 (2455); 278 sh (1349)	C_6H_{12}	*o*
		257	No solvent given	*p*
32	9-Azabicyclo[4.2.1]nona-2,4-diene	248 (2200)	CH_3CN	*q*
33	*N*-Cyano-9-azabicyclo[4.2.1]nona-2,4-diene	257 (4630)	CH_3CN	*q*
34	*N*-Carbamoyl-9-azabicyclo[4.2.1] nona-2,4-diene	255 (1500)	CH_3CN	*q*
35	9-Azabicyclo[4.2.1]nona-2,4,7-triene	245 (2300)	C_6H_{12}	*q*
36	*N*-Cyano-9-azabicyclo[4.2.1]nona-2,4,7-triene	255	CH_3CN	*r*
37	*N*-Carbamoyl-9-azabicyclo[4.2.1]nona-2,4,7-triene	255 (1980)	CH_3OH	*q*
38	*N*-Carboethoxy-9-azabicyclo[4.2.1]nona-2,4,7-triene	252 (2200)	C_6H_{12}	*q*
39	Bicyclo[4.2.1]nona-2,4,7-trien-9-one	267 (3000); 276 (2800); 320 (630)	CH_3OH	*s*
40	Bicyclo[4.2.1]nona-2,4-dien-9-one	264 (3300); 313 (500)	CH_3OH	*s*

Footnotes to Table I

[a] W. J. Bailey and S. S. Miller, *J. Org. Chem.*, **28**, 802 (1963), and references cited therein. [b] A. T. Blomquist, J. Wolinsky, Y. C. Meinwald, and D. T. Longone, *J. Am. Chem. Soc.*, **78**, 6057 (1956). [c] K. Alder and H. Molls, *Chem. Ber.*, **89**, 1960 (1956). [d] J. M. Garrett, Ph.D. Thesis, University of Texas, Austin, Texas, 1966. [e] C. S. Manuel and E. E. Ryder, *J. Am. Chem. Soc.*, **77**, 66 (1955). [f] Y. Gaoni, *Tetrahedron Lett.*, 2361 (1973). [g] S. Sadeh and Y. Gaoni, *ibid.*, 2365 (1973). [h] H. Wynberg and D. J. Zwanenbury, *J. Org. Chem.*, **29**, 1919 (1964). [i] D. W. H. MacDowell, T. B. Patrick, B. K. Frame, and D. L. Ellison, *J. Org. Chem.*, **32**, 1226 (1967). [j] D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.*, **34**, 333 (1969). [k] D. J. Zwanenburg and H. Wynberg, *J. Org. Chem.*, **34**, 340 (1969). [l] Reference 13. [m] K. Alder, S. Hartung, and O. Netz, *Chem. Ber.*, **90**, 1 (1957). [n] C. W. Jefford and F. Delay, *Helv. Chim. Acta*, **56**, 1083 (1973). [o] H. Tsuruta, K. Kurabayashi, and T. Mukai, *Tetrahedron Lett.*, 3775 (1967). [p] L. G. Cannell, *Tetrahedron Lett.*, 5967 (1966). [q] A. G. Anastassiou and R. P. Cellura, *J. Org. Chem.*, **37**, 3126 (1972). [r] A. G. Anastassiou, *J. Am. Chem. Soc.*, **90**, 1527 (1968). [s] D. I. Schuster and C. W. Kim, *J. Org. Chem.*, **40**, 505 (1975).

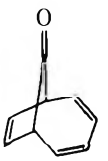
Table II. CNDO/2 Resonance (β) and Overlap (S) Integrals[a]

	$p\pi$, $p\pi$ overlap						$p\sigma$, $p\sigma$ overlap					
r, Å	S_{CN}	S_{CO}	S_{CS}	$-\beta_{CN}$	$-\beta_{CO}$	$-\beta_{CS}$	S_{CN}	S_{CO}	S_{CS}	$-\beta_{CN}$	$-\beta_{CO}$	$-\beta_{CS}$
1.5	0.1573	0.1197	0.2579	3.618	3.112	5.048	0.3094	0.2711	0.3455	7.116	7.049	6.763
2.5	0.0173	0.0108	0.0416	0.398	0.281	0.814	0.0859	0.0589	0.1705	1.976	1.531	3.338
3.0	0.0051	0.0029	0.0144	0.117	0.075	0.282	0.0331	0.0205	0.0804	0.761	0.533	1.574

[a] Resonance integral is in eV.

moieties of **31**. In this case, the uv data and photoelectron data are consistent.[16]

To further demonstrate the usefulness of the uv wavelength maximum method, this approach will be applied to compounds **39** and **40** in which a bathochromic λ_{max} shift is observed when compared respectively to reference compounds, **31** and **30**. This shift must originate from the orbit-



39
λ_{max} 267 nm

40
λ_{max} 264 nm

al interaction of the asymmetric nonbonding π orbital of the oxygen and the asymmetric HOMO of the diene because the other through-space interactions, LUMO-diene with HOMO-carbonyl and LUMO-diene with LUMO-carbonyl, have opposite effects on the HOMO–LUMO diene energy separation.[17] Further, the nonbonded π orbital must be of lower energy than the HOMO of the diene since the shift is bathochromic. Analysis of **39** by photoelectron spectroscopy confirms this rationale.[18]

Conclusion

The theoretical approach presented in this paper accounts for the hypsochromic λ_{max} shifts observed in many homoconjugation systems. In no case was an unambiguous bathochromic λ_{max} shift found in the literature to contrast with the theory's prediction. Inductive effects and changes in hyperconjugation do not appear to significantly alter the frontier orbital separation of the moieties.[19] Also, the detection of through-space interactions appeared to be just as reliable with the uv method as with photoelectron spectroscopy and the uv method has an advantage in that changes in the energy level of unoccupied MO's can be detected. Finally, since the stabilization obtained from the homoconjugation is small (<2 kcal/mol), steric effects will reduce this interaction in some cases.

Acknowledgments. The authors thank the Virginia Commonwealth University Computer Center for a grant of computer time and D. D. Shillady for helpful discussions.

Registry No.—1,2-Dimethylenecyclopentane, 20968-70-1; methane, 74-82-8; 2,3-dimethyl-1,3-butadiene, 513-81-5; 3,4-dimethylenepyrrolidine, 50586-16-8; ammonia, 7664-41-7; 1,2-dimethylenecyclohexane, 2819-48-9; ethane, 74-84-0; 1,2-dimethylene-4-cyclohexene, 54290-41-4; ethylene, 74-85-1.

References and Notes

(1) (a) S. Winstein and F. P. Lossing, *J. Am. Chem. Soc.*, **86**, 4485 (1964); (b) S. Yoneda, Z. Yoshida and S. Winstein, *Tetrahedron*, **28**, 2395 (1972); (c) L. N. Ferguson, "Organic Molecular Structure", Willard Grant Press, Boston, Mass., 1975; (d) R. Hoffmann, E. Heilbronner, and R. Gleiter, *J. Am. Chem. Soc.*, **92**, 706 (1970); (e) R. Hoffmann, *Acc. Chem. Res.*, **4**, 1 (1971).
(2) R. Gleiter, *Angew. Chem., Int. Ed. Engl.*, **13**, 696 (1974).
(3) P. V. Alston and R. M. Ottenbrite, *J. Org. Chem.*, **40**, 322 (1975).
(4) Only the hyperconjugation frontier MO's of methane are used in the orbital interaction diagram because of their greater overlap with the butadiene π MO's.
(5) O. Eisentein, N. T. Anh, Y. Jean, A. Devaquet, J. Cantacuzene, and L. Salem, *Tetrahedron*, **30**, 1717 (1974). The energetic nonequivalence of lone pairs is discussed.
(6) As in the methane case, only the hyperconjugation frontier MO's of ethane are used in the orbital interaction diagram.[4]
(7) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, N.Y., 1970.
(8) T. Fueno and K. Yamaguchi, *J. Am. Chem. Soc.*, **94**, 1119 (1972).
(9) (a) H. Schmidt and A. Schweig, *Chem. Ber.*, **107**, 725 (1974); (b) H. Schmidt and A. Schweig, *Tetrahedron Lett.*, 1437 (1973).
(10) The sulfur moiety is probably ~0.35 Å further from the thiophene and the diene moieties than the nitrogen and oxygen moieties because of the longer carbon–sulfur bond length.
(11) The ionizational potentials[12] of the model compounds are as follows: methane, 12.6 eV; ammonia, 10.2 eV; water, 12.6 eV; hydrogen sulfide, 10.4 eV.
(12) "CRC Handbook of Chemistry and Physics", 53rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1972, p E62.
(13) W. J. Bailey and W. B. Lawson, *J. Am. Chem. Soc.*, **77**, 1606 (1955).
(14) (a) D. N. Butler and R. A. Snow, *Can. J. Chem.*, **50**, 795 (1972); (b) *ibid.*, **52**, 447 (1974).
(15) H. Schmidt, A. Schweig, A. G. Anastassiou, and H. Yamamota, *J. Chem. Soc., Chem. Commun.*, 218 (1974).
(16) P. Bischof, R. Gleiter, and E. Heilbronner, *Helv. Chim. Acta*, **53**, 1425 (1970).
(17) Symmetry of the MO's were determined from the mirror plane which bisects the molecule.
(18) H. Schafer, H. Schmidt, A. Schweig, R. W. Hoffmann, and H. Kurz, *Tetrahedron Lett.*, 1953 (1975).
(19) After submission of this manuscript, a paper by Gergely, Akhavin, and Vogel [*Helv. Chim. Acta.*, **58**, 871 (1975)] was published which explained the hypsochromic uv shift in a limited series of similar compounds mainly in terms of hyperconjugation of the diene moiety with the σ skeleton of the bicyclic system. The compounds given in this paper are in agreement with our theory. The hypsochromic shift observed in 2,3-dimethylene-5,6-exo-epoxynorbornane and 2,3-dimethylene-5,6-exo-epoxy-7-oxanorbornane is predicted from the interactions of the CNDO/2 MO's of the ethylene oxide and ethane moieties with the MO's of **1** and **5**. Furthermore, the approach of Gergely et al. does not account for the absence of the hypsochromic shift in compounds **14**, **15**, **16**, **25**, and **31** nor for the bathochromic shift in **9**, **10**, and **13**.

Absolute Configuration of *cis*- and *trans*-2-(*o*-Bromophenyl)cyclohexylamine and Related Compounds[1a]

Todd G. Cochran,[1b] Allan Weber, and Alain C. Huitric*

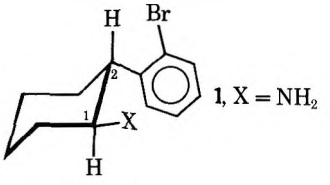
Department of Pharmaceutical Sciences, University of Washington, Seattle, Washington 98195

Arthur Camerman and Lyle H. Jensen

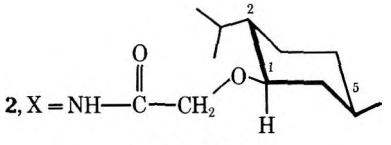
Department of Biological Structure, University of Washington, Seattle, Washington 98195

Received August 29, 1975

In connection with our investigation of the chiroptical properties of 2-arylcyclohexanols and 2-arylcyclohexylamines, we have observed significant differences in the CD spectra of chiral *cis*-2-(*o*-bromophenyl)cyclohexylamine when measured in methanol and in isooctane but no such differences were found with the trans isomer.[2] These observations made it important to obtain unequivocal proof of the absolute configuration of these compounds. This was accomplished by single-crystal x-ray diffraction analysis of **2**, the menthoxyacetamide of (+)-*trans*-2-(o-bromophenyl)cyclohexylamine (**1**), and by relating the absolute con-



(1*S*,2*R*)

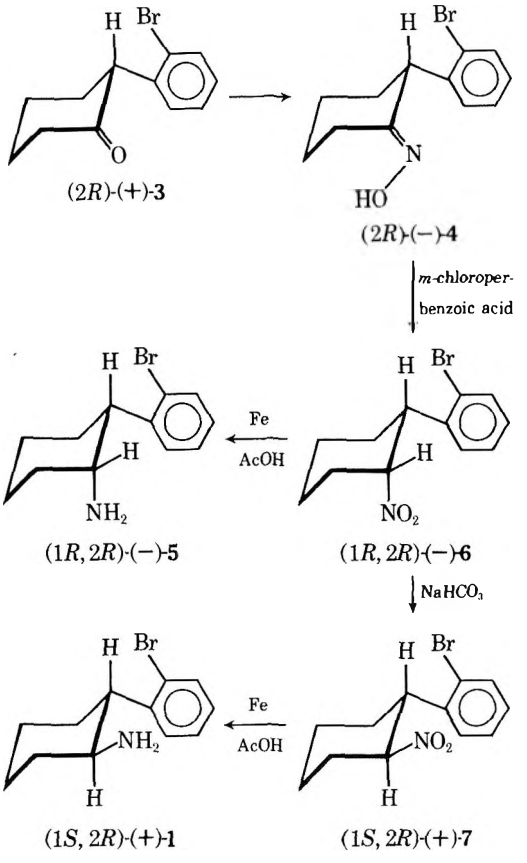


(1*R*, 2*S*,5*R*)

figuration of (−)-*cis*-2-(o-bromophenyl)cyclohexylamine (**5**) chemically to that of **1** by the method described in Scheme I.

The resolution of the amines via their menthoxyacetamides has been reported previously.[3] The crystalline menthoxyacetamide **2**, which yields the (+) amine **1** upon hydrolysis,[3] proved ideally suited for single-crystal x-ray diffraction analysis since it allowed the determination of the absolute configuration both from the anomalous dispersion of the bromine and from the known configuration of the (−)-menthol moiety.[4] The crystal structure analysis of **2** unequivocally shows that the absolute configuration of the (+) amine **1** is (1*S*,2*R*). Since (1*S*,2*R*)-(+)-**1** and the (−)-cis amine **5** are both obtained from (+)-2-(*o*-bromophenyl)cyclohexanone (**3**) by the reactions outlined in Scheme I, the absolute configuration of the (−)-*cis* amine **5** is established as (1*R*,2*R*) and that of the (+) ketone **3** as (*R*). This also establishes the absolute configurations of the nitro intermediates (1*R*,2*R*)-(−)-*cis*-**6** and (1*S*,2*R*)-(+)-*trans*-**7**, and it confirms the original assignment of the absolute configurations of (1*S*,2*S*)-(+)-*cis*-2-(*o*-bromophenyl)cyclohexanol, (1*S*,2*S*)-(+)-*cis*-2-(*o*-bromophenyl)cyclohexylamine,

Scheme I



(1*S*,2*S*)-(+)-*cis*-2-(o-bromophenyl)-1-azidocyclohexane, and (1*R*,2*S*)-(−)-*trans*-2-(*o*-bromophenyl)cyclohexanol, which were made on the basis of the CD spectrum of the common precursor (*S*)-(−)-2-(*o*-bromophenyl)cyclohexanone,[5] the enantiomer of **3**.

The menthoxyacetamide **2** crystallizes in the monoclinic space group $P2_1$ with two independent molecules in the asymmetric unit. Perspective drawings[6] of the two crystallographically independent molecules of **2** are shown in Figure 1. The two conformations adopted by this molecule in the crystalline state are similar but not identical. In both conformations, the cyclohexane rings of the amine and menthol moieties are in the chair form with all substituents equatorial. In addition, the N–C–C–O grouping of the menthoxyacetamide moiety is syn planar in both conformations (torsion angles of −10.5 and −3.9° in molecules A and B, respectively). The major conformational differences in the two crystallographically independent molecules appear in the rotational orientations of the aromatic and menthoxyacetamide groups with respect to the cyclohexylamine ring. Thus, in conformation B the aromatic ring is nearly perpendicular (94°) to the mean plane of the cyclohexane ring of the amine, while in conformation A the aromatic ring is tilted 26° from perpendicular (64° from the mean plane of the cyclohexane ring); see Figure 2. The *o*-bromo substituent is on the axial side of C2 in both conformations and in conformation A, where the rings are highly skewed, this substituent is directed away from the amide group on C1. The torsion angle about the C–N bond of the C2–C1–N–

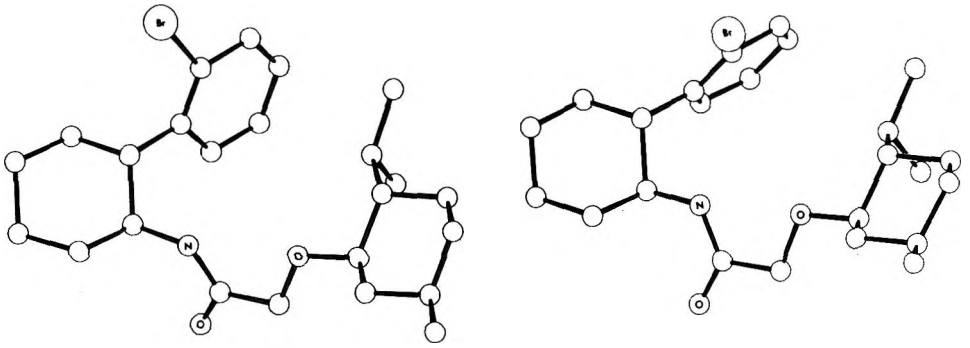


Figure 1. Perspective drawings of the two crystallographically independent molecules of 2 from the x-ray data.

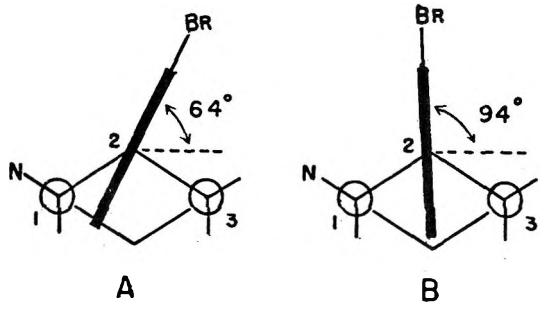


Figure 2. Conformations of the phenyl ring in the crystallographically independent molecules of 2 (projection down the phenyl–C_2 bond).

C=O grouping is 141° in conformation A and 169° in conformation B. This results in the menthoxyacetamide group being tilted further away from the aromatic ring in conformation B than in conformation A. All other differences in torsion angle are less than 10°.

The conformations adopted by molecules in solution are of significant importance to their chiroptical properties. While the conformational parameters observed for a molecule in the crystalline state are a complicated function of inter- and intramolecular forces, they do represent energy minima, and thus are conformations which are likely to be of importance in solution. It is therefore of interest that one of the major conformational differences in the two crystallographically independent molecules of 2 is the rotational orientation of the aromatic ring with respect to the cyclohexylamine ring. Solvent-induced changes in the relative populations of this type of rotamer are not unexpected and could account for the solvent inversion of the sign of the Cotton effect observed in the CD spectra of the cis amine 5.

Experimental Section

The amide 2, $C_{24}H_{36}NO_2Br$, $[\alpha]D$ −73° ($CHCl_3$),[3] crystallizes from *n*-hexane in space group $P2_1$ with the following crystal data: a = 13.748 ± 0.004 Å; b = 18.739 ± 0.004 Å; c = 9.876 ± 0.002 Å; β = 110.74 ± 0.02°; D_m = 1.27 g/cm^3 (flotation in CsCl solution); D_{calcd} = 1.26 g/cm^3 (Z = 4 molecules/unit cell). Systematic absences were observed for $0k0$ with $k = 2n + 1$. The alternate space group choice $P2_1/m$ was rejected by the known chiral asymmetry of the molecule. X-ray intensities were measured on a Picker FACS-1 four-circle diffractometer using the $\omega/2\theta$ scan technique and Nb-filtered Mo radiation (γ = 0.71069 Å). Intensities to 2θ = 50°, corresponding to an interplanar spacing of 0.83 Å, were recorded from a crystal which had been cut to cubic shape with edges approximately 0.33 mm. A total of 4592 independent reflections were measured, of which 3816 had intensities greater than twice the standard deviation of their measurement. No absorption corrections were applied, and structure amplitudes were obtained from the intensities in the usual manner. A sharpened, origin-removed three-dimensional Patterson synthesis enabled the positions of the two unique bromine atoms to be located and the coordinates of the 54 other nonhydrogen atoms comprising the two molecules in the asymmetric unit were determined from subsequent electron-density maps based on phases calculated from the bromine positions. The positional and anisotropic thermal parameters of all the atoms were refined using a full-matrix least-squares procedure with weights taken as $\sqrt{\omega} = 1/\sigma_F$[7] until a discrepancy factor, R, of 0.064 was achieved.[8] Up to this point, the normal bromine scattering curve, $f°_{Br}$, was used with no correction for anomalous scattering of the x rays by the bromine atoms. At this stage, the absolute configuration of the molecule was determined by applying the true bromine scattering curve including anomalous scattering effects, $f_{Br} = f°_{Br} + \Delta f'_{Br} + i\Delta f''_{Br}$. Structure factors were calculated[9] for molecules with atom coordinates x, y, z and for molecules with atom coordinates $-x, -y, -z$; that is, structure factors were calculated for both possible optical isomers. The conventional discrepancy factor R was 0.070 for one structure and 0.073 for its enantiomer. This difference is highly significant[10] and the absolute configuration for this molecule is unambiguously established as the one giving the lower R. An independent verification for this assignment of absolute configuration is that the absolute configuration of the (−)-menthol moiety of the structure producing the lower R is in agreement with the known absolute configuration of (−)-menthol.[4]

Although the positions of all 72 hydrogen atoms in the asymmetric unit could be either located in a difference Fourier map or calculated from the positions of the carbon atoms, they have not been included in the calculations since the additional significance does not compensate for the added cost of refinement for a structure of this size. (See paragraph at end of paper regarding supplementary material.)

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Specific rotations were measured at ambient temperature with a Rudolph polarimeter using a sodium lamp. Infrared spectra were obtained with a Beckman 1R-5A or 1R-20 spectrometer and ^{1}H NMR spectra on a Varian A-60 or T-60 spectrometer using tetramethylsilane as internal reference.

Chiral *cis*- and *trans*-2-(o-bromophenyl)cyclohexylamines and their (−)-menthoxyacetamides have been reported previously.[3]

(*S*)-(+)-2-(*o*-Bromophenyl)cyclohexanone Oxime. A solution of 0.45 g (1.78 mmol) of (*S*)-(−)-2-(o-bromophenyl)cyclohexanone[5] ($[\alpha]D$ −15°), 0.25 g (3.56 mmol) of hydroxylamine hydrochloride, and 0.245 g (1.78 mmol) of potassium carbonate in 50 ml of methanol was heated to reflux for 2 h, cooled, and added to 125 ml of ice water. Filtration and recrystallization from 95% ethanol gave 0.39 g of colorless, crystalline product, mp 160–161 °C, $[\alpha]D$ +39° (c 2, methanol).

(*R*)-(−)-2-(*o*-Bromophenyl)cyclohexanone Oxime (4). In the preparation of 4 from 3 ($[\alpha]D$ +15°) 85% ethanol was used as solvent instead of methanol and the recovered oxime had about 67% of the specific rotation of the (+) enantiomer described above, $[\alpha]D$ −26° (*c* 1, methanol), mp 160–161 °C.

(1*R*,2*R*)-(−)-*cis*-2-(*o*-Bromophenyl)nitrocyclohexane (6). This compound was obtained by a modified version of the known methods for peracid oxidation of oximes.[11] A mixture of 0.125 g (0.47 mmol) of 4 ($[\alpha]D$ −26°), 0.025 g (0.42 mmol) of urea, 0.075 g (0.068 mmol) of hydroquinone, and 0.5 g of dibasic sodium phosphate in 25 ml of acetonitrile was heated to reflux and a solution of 0.61 g of *m*-chloroperbenzoic acid (about 80% purity) in 25 ml of acetonitrile was added to the refluxing mixture over a period of 90 min. Refluxing was continued for 4 h. The solvent was removed under reduced pressure, water was added, and the aqueous mixture was extracted with dichloromethane. The dichloromethane solution was washed successively with 10% sodium bisulfite solution, saturated sodium bicarbonate solution, and water, and dried

over sodium sulfate. Removal of the solvent gave 0.165 g of dark oil which was chromatographed on deactivated silica gel (6% H_2O), using chloroform in hexane as eluting solvent (chloroform was increased from 5 to 20%), to yield 0.036 g (27%) of colorless solid: mp 69.5–70 °C (mp of racemic[3] is 82–83 °C); $[\alpha]D$ −71° (c 6, chloroform); NMR (CCl_4) δ 5.00 (m, 1, $W_{1/2}$ = 9.5 Hz, H-1), 3.37 (td, 1, $J_{2,3a} \sim 13$, $J_{2,1} \sim J_{2,3e} \sim 3.5$ Hz, H-2). The ir and NMR spectra are identical with those of racemic **6**.[3] In the absence of hydroquinone the yield of **6** was less than 15%. The above conditions, in the absence of hydroquinone, yielded about 90% of *cis*-2-phenylnitrocyclohexane from 2-phenylcyclohexanone oxime.

(1*S*,2*R*)-(+)-*trans*-2-(*o*-Bromophenyl)nitrocyclohexane (7). Isomerization of **6** by refluxing in methanol with a catalytic amount of sodium bicarbonate yielded **7**: mp 81–81.5 °C (mp of racemic[3] is 82–83 °C); $[\alpha]D$ +48° (c 5, chloroform); NMR (CCl_4) δ 4.80 (dt, 1, $J_{1,2} \sim J_{1,6a} \sim 11.2$, $J_{1,6e} \sim 4.2$ Hz, H-1), 3.70 (dt, 1, $J_{2,1} \sim J_{2,3a} \sim 11.2$, $J_{2,3a} \sim 4$ Hz, H-2). The ir and NMR spectra are identical with those of racemic **7**.[3]

(1*R*,2*R*)-(−)-*cis*-2-(*o*-Bromophenyl)cyclohexylamine (5). This compound was obtained by the reduction of **6** with iron in acetic acid as described for the racemic compound,[3] $[\alpha]D$ −76° (*c* 3, methanol) (69% optical purity compared to resolved amine[3]). The ir and NMR spectra are identical with those of racemic **5**.[3]

(1*S*,2*R*)-(+)-*trans*-2-(o-Bromophenyl)cyclohexylamine (1). This compound was obtained by the reduction of **7** with iron in acetic acid as described for the racemic compound,[3] $[\alpha]D$ +37° (*c* 2, methanol) (66% optical purity compared to resolved amine[3]). The ir and NMR spectra are identical with those of racemic **1**.[3]

The optical purity of **1** and **5** obtained by Scheme I, compared to **1** and **5** obtained by resolution via the menthoxyacetamides,[3] indicates that the oxime **4** and the nitro compounds **6** and **7** also have optical purities of about 67% and that the (+) oxime, $[\alpha]D$ +39°, is essentially optically pure.

Registry No.—**1**, 30808-90-3; **2**, 30808-84-5; **3**, 58342-33-9; **4**, 58298-49-0; **5**, 3080-92-5; **6**, 58342-34-0; **7**, 58342-35-1; (*S*)-(+)-2-(*o*-bromophenyl)cyclohexanone oxime, 58298-50-3; (*S*)-(−)-2-(*o*-bromophenyl)cyclohexanone, 31916-20-8; hydroxylamine hydrochloride, 5470-11-1.

Supplementary Material Available. A listing of the fractional atomic coordinates and thermal parameters for the (−)-methoxyacetamide of (1*S*,2*R*)-(+)-*trans*-2-(*o*-bromophenyl)cyclohexylamine (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) Supported in part by Grants NS-08329 and GM-13366 from the National Institutes of Health. Presented in part by A.C. at the American Crystallographic Association Summer Meeting, Ottawa, Canada, August 16–21, 1970. (b) NIH Predoctoral Fellow 1-FI-GM-41,752, 1968–1970.

(2) The CD spectra of the cis isomer give Cotton effects of opposite signs in the $1L_b$ region (270-nm region) when measured in methanol and in isooctane. This phenomenon will be discussed in a future publication treating the chiroptical properties of a series of 2-arylcyclohexanols and cyclohexylamines.

(3) T. G. Cochran and A. C. Huitric, *J. Org. Chem.*, **36**, 3046 (1971).

(4) (a) A. Fredga, *Acta Chem. Scand.*, **1**, 371 (1947); (b) W. Huckel, *J. Prakt. Chem.*, **157**, 225 (1941); V. Prelog. *Helv. Chim. Acta*, **36**, 308 (1953); (c) R. Parthasarathy, J. Ohrt, A. Horeau, J. P. Vigneron, and H. B. Kagan, *Tetrahedron*, **26**, 4705 (1970).

(5) T. G. Cochran, D. V. Wareham, and A. C. Huitric, *J. Pharm. Sci.*, **60**, 180 (1971).

(6) C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report ORNL-3794, 1965.

(7) The term σ_F is the standard deviation in the structure factor, based on counting statistics: G. H. Stout and L. H. Jensen, "X-Ray Structure Determination", Macmillan, New York, N.Y., 1968, p 456.

(8) Scattering factors for bromine were those of D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965), and those for oxygen, nitrogen, and carbon were from J. Berghuis, I. J. Haanappell, M. Potters, B. O. Loopstra, C. A. MacGillavry, and A. L. Veenendaal, *Acta Crystallogr.*, 8, 478 (1955).

(9) The anomalous dispersion corrections $\Delta f'$ and $\Delta f''$ were from "International Tables for X-Ray Crystallography", Vol. III, K. Lonsdale, C. H. MacGillavry, and G. A. Reich, Ed., Kynoch Press, Birmingham, England, 1962, p 216.

(10) The *R* factor ratio of 1.04 is significant at the 99.5% confidence level for the 505 parameters (positional and anisotropic thermal parameters for 56 atoms) and the 3816 observed reflections, as discussed by W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(11) (a) R. J. Sundberg and P. A. Bukowich, *J. Org. Chem.*, **33**, 4098 (1968); (b) W. D. Emmonds and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

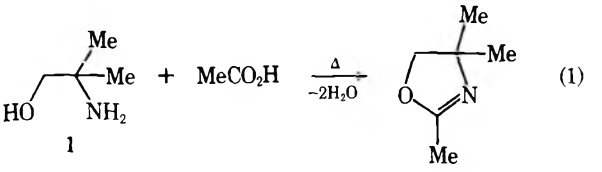
Reaction of Lactones and Thiolactones with 2-Amino-2-methyl-1-propanol. Synthesis of 2-Substituted 2-Oxazolines

Samuel P. McManus,*[1a] P. Judson Kelly,[1b] William J. Patterson,[1c] and Charles U. Pittman, Jr.[1d]

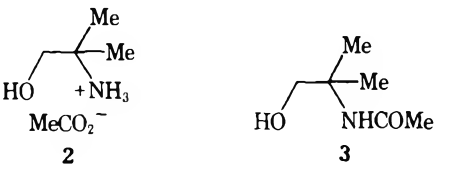
Departments of Chemistry, The University of Alabama in Huntsville, Huntsville, Alabama 35807, Oakwood College, Huntsville, Alabama 35805, University of Alabama, University, Alabama 35486, and Materials and Processes Laboratory, Marshall Space Flight Center, Huntsville, Alabama 35812

Received October 6, 1975

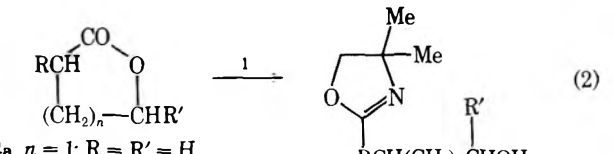
One of the simplest and least expensive preparative procedures for 2-oxazolines involves the reaction of an amino alcohol with a carboxylic acid[2,3] as exemplified in eq 1 with acetic acid and 2-amino-2-methyl-1-propanol (**1**). The reaction is assumed to proceed through successive steps involving the salt **2** and the amide **3**.



(1)



We describe a process similar to that shown in eq 1 which uses a lactone instead of the carboxylic acid. The product is a functionalized 2-oxazoline derivative. Thus, γ-butyrolactone (**4a**), δ-valerolactone (**4b**), and ε-caprolactone (**4c**), and the methylated derivatives of γ-butyrolactone **4d** and **4e** react with **1** to give the respective 2-substituted 4,4-dimethyl-2-oxazoline derivatives, **5a–e**. ε-Caprolactone reacted quantitatively, as determined by GC analysis, and gave a 60% yield of analytically pure product. Yields from the other lactones ranged from 11 to 65%.[4]



(2)

4a, $n = 1$; R = R′ = H
b, $n = 2$; R = R′ = H
c, $n = 3$; R = R′ = H
d, $n = 1$; R = Me; R′ = H
e, $n = 1$; R = H; R′ = Me

5a, $n = 1$; R = R′ = H
b, $n = 2$; R = R′ = H
c, $n = 3$; R = R′ = H
d, $n = 1$; R = Me; R′ = H
e, $n = 1$; R = H; R′ = Me

Steric factors in the lactone slowed the conversion rates measureably. The α- or γ-methyl-substituted lactones **4d** and **4e** reacted about half as fast as γ-butyrolactone. More severe steric factors made reaction progress very slow. Thus, 2,2-diphenylbutyrolactone was recovered unchanged after 8 days at reflux with the amino alcohol in xylene.

The reaction was extended to preparation of the ketooxazoline **5f** and the mercaptooxazoline **5g** by the utilization of α-angelicalactone (**4f**) and of γ-thiobutyrolactone (**4g**). The yields and the spectral and physical properties of all of the oxazolines are shown in Tables I and II.

Table I. Yields, Physical Constants, and Analytical Data for Oxazolines

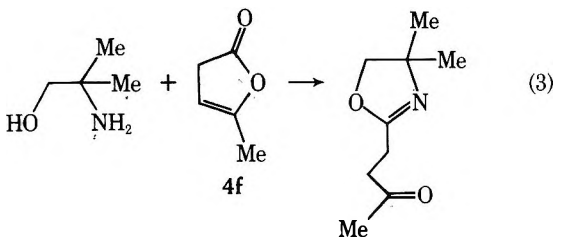
2 substituent	Conversion,[a] %	Yield,[b] %	Bp, °C (mmHg)	n^{25}D	Elemental anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
3-Hydroxy-1-propyl (5a)	65–80	65	77–78 (0.5)	1.4583	58.40	9.00	8.97	58.26	8.87	8.78
4-Hydroxy-1-butyl (5b)	75–92	25[c]	102–104 (0.5)	1.4620	63.13	10.01	*d*	63.10	9.95	*d*
5-Hydroxy-1-pentyl (5c)	100[e]	60	100–103 (1.5)	1.4630	64.83	10.34	*d*	64.90	10.36	*d*
4-Hydroxy-2-butyl (5d)	47–58	34	74–75 (0.19)	(158–159)[f]	45.00[f]	5.04	*d*	45.00	5.13	*d*
3-Hydroxy-1-butyl (5e)	45–57	11[c]	74–75 (0.25)	1.4530[g]	59.97	10.07	7.77	60.29	10.05	7.65
3-Oxo-1-butyl (5f)	100[e]	20	90–95 (3)	1.4580	63.88	8.93	8.28	63.74	9.09	8.42
3-Mercapto-1-propyl (5g)	50–62	46	74–77 (3)	1.4880	55.45	8.73	8.09	55.53	8.74	7.95

[a] Based on GC and ir analysis of the lactone remaining in the crude product mixture; conversion range is for amino alcohol:lactone ratios from 1:1 to 2:1 and a 48-h reaction period. [b] Yield of analytically pure distilled product. [c] Yield of purified product is low owing to competitive polymerization of the lactone. [d] Not determined. [e] Amino alcohol:lactone ratio was 1:1. [f] Picrate melting point and combustion analysis. [g] The purified liquid contained water as indicated by the combustion analysis and other analytical indicators. The combustion analyses compared best with a composition involving 2 mol of oxazoline to 1 mol of water; hence the calculated values are for $C_9H_{17}NO \cdot 1/2\ H_2O$. The picrate was an oil.

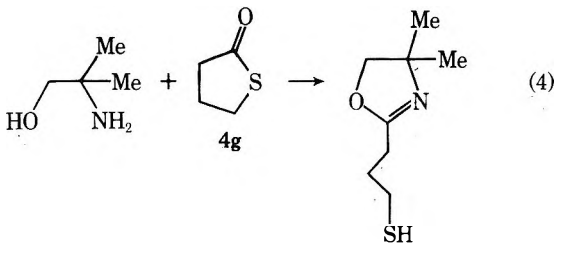
Table II. Ir and NMR Data on Oxazoline Products

Compd	$\nu_{C=N}$,[a] cm-1	ν_{O-H},[a] cm-1	Chemical shift, ppm[b] C-4 Me	C-5 H	OH	C-2 α-H	C-2 β-H	C-2 γ-H	C-2 δ-H	Other
5a	1667	3310	1.29 (6, s)	3.92 (2, s)	4.91 (1, s)	2.39 (2, t, 6.8)	1.88 (2, m)	3.64 (2, t, 6.1)		
5b	1663	3330	1.12 (6, s)	3.88 (2, s)	4.69 (1, s)	2.25 (2, t, 6.7)	1.44–1.89	1.89 (4, m)	3.56 (2, t, 6.1)	
5c	1660	3325	1.12 (6, s)	3.86 (2, s)	4.71 (1, s)	2.22 (2, t, 7.0)	1.30–1.90 (6, m)			3.53 (2, t, 5.8)[c]
5d	1658	3340	1.23 (6, s)	3.88 (2, s)	4.60 (1, s)	2.63 (1, m)	1.75 (2, m)	3.59 (2, t, 6.0)		1.16 (3, d, 7.0)[d]
5e	1665	3380	1.23 (6, s)	3.88 (2, s)	4.19 (1, s)	2.34 (2, t, 7.7)	1.75 (2, m)	3.77 (1, m)	1.15 (3, d, 6.5)	
5f	1670	(1718)[e]	1.17 (6, s)	3.93 (2, s)		2.72 (2, t, 7.8)	2.39 (2, t, 7.8)		2.09 (3, s)	
5g	1670	(2560)[f]	1.13 (6, s)	3.87 (2, s)		2.35 (2, t, 7.0)	1.93 (2, m)	2.57 (2, m)		

[a] Spectra taken as neat liquids; more detailed information is available, cf. W. J. Patterson, Ph.D. Dissertation, University of Alabama, 1974, and P. J. Kelly, M. S. Thesis, University of Alabama in Huntsville, 1976. [b] Values in parentheses indicate number of protons, multiplicity, and coupling constant in hertz; s = singlet, d = doublet, t = triplet, m = multiplet. [c] C-2 ε protons. [d] C-2 α-Me. [e] C=O stretching. [f] S–H stretching.



(3)



(4)

The recent work of Meyers and Mihelich[5] suggests the possible use of this procedure in the conversion of lactones to their alkylated forms and possibly in the preparation of asymmetric derivatives. For this purpose other amino alcohols may be of interest.[6]

Experimental Section

Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Melting points and boiling points are uncorrected. Ir spectra were recorded on a Beckman IR-10 spectrometer and NMR were recorded as 10–20% solutions in $CDCl_3$ at 90 MHz with a tetramethylsilane internal reference on a Bruker HFX-90 instrument.

All starting compounds and solvents were obtained from Aldrich Chemical Co. and were used without further purification.

The procedure below is typical. All reactions were monitored by infrared or by GC to determine the extent of reaction based on consumed lactone. Reactions were typically run for 48 h or until the volume of the aqueous layer in the Dean-Stark trap reached a maximum.

It was determined that the amino alcohol 1 was slowly distilling (bp 165 °C) as the reaction proceeded. This obviously could affect the percent conversion values (see Table I) when a 1:1 ratio of the amino alcohol:lactone is used. Actually, the effect was negligible with **4c** and **4f** owing to the high reactivity of the lactones. With the other lactones, even at an amino alcohol:lactone ratio of 2:1, the reactivities of the lactones were such that amino alcohol distillation affected percent conversion (Table I) as determined by the amount of lactone remaining (GC and quantitative ir measurements). This can be dealt with in two ways. In the case of γ-butyrolactone, with toluene as the solvent a successful reaction was achieved but at the expense of reaction time. On the other hand, the use of xylene allows a faster reaction (1–4 days for the range of lactones evaluated) and leads to no real losses since the amino alcohol, lactone, and xylene can be recycled by fractionation. Hence we prefer the latter method although one might want to explore the options for optimum conditions for an amino alcohol-lactone pair. We have not optimized conditions for any compounds reported here. A typical run for a 2:1 amino alcohol:lactone ratio is given below.

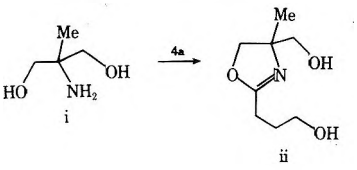
2-(3-Hydroxypropyl)-4,4-dimethyl-2-oxazoline (5a). To a 500-ml single-necked flask fitted with a magnetic stirrer, Dean-Stark trap, and condenser were added γ-butyrolactone (24.1 g, 0.29 mol), 2-amino-2-methyl-1-propanol (50.0 g, 0.56 mol), and xylene (100 ml). The mixture was stirred and refluxed gently, just allowing the xylene–water azeotrope to distill. The volume of the aqueous layer in the Dean-Stark trap with time was 5.5 ml at 5.75 h, 7.3 ml at 7.75 h, 12.3 ml at 15 h, 16.2 ml at 22 h, and 21 ml at 45 h. The reaction was stopped at 45 h. Analysis by GC indicated 80% conversion of the lactone. The xylene was removed on a rotary evaporator and the residue was distilled to yield 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline, bp 74–78 °C (0.5 mm), which still contained some lactone (GC). Distillation on an adiabatic spinning band column with a reflux ratio of 10/1 yielded 2-(3-hydroxypropyl)-4,4-dimethyl-2-oxazoline (65% yield based on conversion of lactone): bp 77–78 °C (0.5 mm); purity (GLC) 99.6%; ir (NaCl plates) 3310 (O–H), 2960, 2875, 1667 (C=N), 1460, 1363, 1164, 1065, 1038, 945, 819, and 775 cm^{-1}. Other analytical data are shown in Tables I and II.

Acknowledgment. S.P.M. acknowledges the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**1**, 124-68-5; **4a**, 96-48-0; **4b**, 542-28-9; **4c**, 502-44-3; **4d**, 1679-47-6; **4e**, 108-29-2; **4f**, 591-12-8; **4g**, 1003-10-7; **5a**, 51849-54-8; **5b**, 58241-39-7; **5c**, 58241-40-0; **5d**, 58241-41-1; **5e**, 51849-55-9; **5f**, 58241-42-2; **5g**, 58241-43-3.

References and Notes

(1) (a) The University of Alabama in Huntsville; (b) Oakwood College; (c) Marshall Space Flight Center; (d) University of Alabama.
(2) J. H. Billman and E. E. Parker, U.S. Patent 2 556 791 (1951); *Chem. Abstr.*, **46**, 525 (1952).
(3) For a review of oxazoline chemistry, see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).
(4) Polymerization of the lactone invalidates some of the conversion figures in Table I. Also, some amino alcohol was distilled with the water to give a low conversion; allowances were not made for this in the reaction stoichiometry in all cases; see the Experimental Section.
(5) A. I. Meyers and E. D. Mihelich, *J. Org. Chem.*, **40**, 1186 (1975).
(6) 2-Amino-2-methyl-1,3-propanediol (i) has been successfully employed in making diols such as (ii) by the same procedure employed here: S. P.



McManus and M. Ortiz, unpublished results; cf. M. Ortiz, M.S. Thesis, The University of Alabama in Huntsville, May 1973.

Trifluoromethylthiocopper.[1] A Reagent for the Introduction of the Trifluoromethylthio Group into Aromatic Nuclei

David C. Remy,* Kenneth E. Rittle, Cecilia A. Hunt, and Mark B. Freedman

Merck Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

Received December 29, 1975

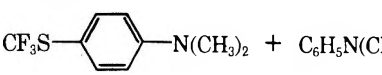
The trifluoromethylthio and trifluoromethylsulfonyl groups are important nuclear substituents in the preparation of potential new dyes,[2] medicinal agents,[3] and novel heterocyclic systems.[4] At present, there are two standard procedures for the introduction of a trifluoromethylthio group into an aromatic nucleus. The first method requires a photoinitiated chlorination of an aryl methyl sulfide side chain, followed by reaction with antimony trifluoride[5] (eq 1).

$$ArSCH_3 + Cl_2 \xrightarrow{h\nu} ArSCCl_2 \xrightarrow{SbF_3} ArSCF_3 \quad (1)$$

The second method uses trifluoromethanesulfenyl chloride in either one of two ways. In one procedure[6] (eq 2), reaction of an aryl Grignard reagent with trifluoromethanesulfenyl chloride gives the desired aryl trifluoromethyl sulfide, while in the other procedure[7] (eq 3), reaction of activated aromatic derivatives, such as anilines, with trifluoromethanesulfenyl chloride leads to para-substituted aryl trifluoromethyl sulfides. When higher temperatures and Lewis acid catalysts are used, less activated aryl derivatives undergo reaction, but mixtures of aryl trifluoromethyl sulfide isomers are obtained.

$$ArMgX + CF_3SCl \longrightarrow ArSCF_3 + (ArH + ArCl) \quad (2)$$

$$C_6H_5N(CH_3)_2 + CF_3SCl \longrightarrow$$



$$+ C_6H_5N(CH_3)_2 \cdot HCl \quad (3)$$

Table I. Preparation of Aryl Trifluoromethyl Sulfides

Example[a]	Starting material	Registry no.	Solvent; reaction temp, °C; time, h	Moles starting material/ moles $Hg(SCF_3)_2$/ moles Cu	Product[b]	Registry no.	% yield and (% purity, GLC) of isolated crude product	Product bp, °C (mm)	Product mp, °C, or $n^{25}D$
1	*p*-$IC_6H_4CO_2C_2H_5$	51934-41-9	DMF; 110–120; 3	1/2/0	None				
2	*p*-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/2/7.3[c]	*p*-$CF_3SC_6H_4CO_2C_2H_5$	587-19-9	90 (98.4)	81 (0.9)[d]	1.4845[d]
3	*p*-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/2/7.3[e]	*p*-$CF_3SC_6H_4CO_2C_2H_5$		88 (96.7)	106–110 (7)	
4	*p*-$IC_6H_4CO_2C_2H_5$		DMF; 110–120; 3	1/1/3.6[e]	*p*-$CF_3SC_6H_4CO_2C_2H_5$		98.5 (84)		
5	*m*-$IC_6H_4CO_2C_2H_5$	58313-23-8	DMF; 110–120; 2	1/2/7.3[e]	*m*-$CF_3SC_6H_4CO_2C_2H_5$[f]	58313-24-9	90 (92.5)		72–74[g]
6	*o*-$IC_6H_4CO_2C_2H_5$	1829-28-3	DMF; 110–120; 1	1/2/7.3[e]	*o*-$CF_3SC_6H_4CO_2C_2H_5$	58313-25-0	100 (97.9)	71 (0.7)	1.4879
7	*p*-$BrC_6H_4CO_2C_2H_5$	5798-75-4	Quinoline; 150–190; 10	1/2/7.3[e]	*p*-$CF_3SC_6H_4CO_2C_2H_5$		100 (88.6)		
8	*p*-$ClC_6H_4CO_2C_2H_5$	7335-27-5	Quinoline; 238; 4	1/2/7.3[e]	None				
9	*p*-$I_2C_6H_4$	624-38-4	DMF; 110–120; 2.5	1/4/14.5[e]	*p*-$(CF_3S)_2C_6H_4$	886-82-8	61.5 (96.9)	71–74 (15)	39–42[h]
10	*p*-$IC_6H_4NO_2$	636-98-6	DMF; 110–120; 2.5	1/2/7.3[e]	*p*-$CF_3SC_6H_4NO_2$	403-66-7	89 (82)	115–122 (20)[i]	
11	*p*-IC_6H_4Cl	637-87-6	DMF; 110–120; 2.5	1/4/14.5[e]	*p*-$CF_3SC_6H_4Cl$	407-16-9	78 (100)	173–175[j]	1.4900
12	*p*-$BrC_6H_4N(CH_3)_2$	586-77-6	HMPA[18]; 160–175; 12	1/3/10.9[e]	*p*-$CF_3SC_6H_4N(CH_3)_2$	2677-71-6	100 (89.2)	56–59 (0.10)[k]	1.5269[k]
13	3-IC_5H_4N	1120-90-7	DMF; 110–120; 3	1/3/10.9[e]	3-$CF_3SC_5H_4N$	58313-26-1	95 (83.5)	150–151	1.4676
14	*p*-$BrC_6H_4CH_3$	106-38-7	HMPA[18]; 160–180; 12	1/2/7.3[e]	*p*-$CF_3SC_6H_4CH_3$	351-60-0	79 (84.5)	67–85 (15)[l]	1.4657

[a] Example number corresponds to procedure number in Experimental Section. [b] All compounds exhibited ^1H and ^{19}F NMR spectra consistent with the assigned structure. [c] Trifluoromethylthiocopper was preformed. See Experimental Section. [d] Lit.[4a] bp 96–97 °C (5 mm), $n^{23}D$ 1.4812. [e] Trifluoromethylthiocopper was formed in situ during reaction. See Experimental Section. [f] Hydrolyzed by the procedure used to hydrolyze the ortho isomer; see Experimental Section, example 6. [g] Melting point of 3-(trifluoromethylthio)benzoic acid. Lit.[12] mp 75–76 °C. [h] Lit.[13] mp 42–43 °C. [i] Lit.[14] bp 115 °C (20 mm). [j] Lit.[15] bp 173–174 °C. [k] Lit.[7] bp 54 °C (0.15 mm). [l] Lit.[16] bp 80 °C (15 mm).

Alkyl trifluoromethyl sulfides have been prepared from the reaction of bis(trifluoromethylthio)mercury[8] or trifluoromethylthiosilver[9,10] with alkyl iodides. Also, trifluoromethylthiosilver has been used to prepare benzyl trifluoromethyl sulfides from benzyl iodides.[10] As an extension of this type of reaction, we wish to report that the reaction of trifluoromethylthiocopper with aryl bromides and iodides provides a convenient, one-step route to the synthesis of aryl trifluoromethyl sulfides. This procedure offers a number of advantages over existing processes, in that (1) the aromatic nucleus may contain electron-donating or electron-withdrawing groups, (2) Grignard sensitive groups may be present in the molecule, (3) pure ortho, meta, and para isomers are obtained from the reaction of trifluoromethylthiocopper with the respective ortho, meta, and para aromatic bromide or iodide derivative, (4) yields of products range from good (60%) to excellent (100%), and (5) selective halide displacements are possible since aromatic iodides react at a significantly lower temperature than do aromatic bromides while aryl chlorides do not react.

Ethyl *p*-(trifluoromethylthio)benzoate (**4**) is formed in 90% yield (98.4% pure by GLC) when ethyl *p*-iodobenzoate (**3**) is allowed to react with trifluoromethylthiocopper (**2**) formed by the reaction of copper with bis(trifluoromethylthio)mercury (**1**).[11] Bis(trifluoromethylthio)mercury, alone, does not

react with **3**. The copper reagent **2** does not need to be prepared prior to the condensation reaction. Indeed, a product of comparable yield and purity is obtained when **2** is formed in situ during reaction. Since the efficiency of preparing **2** from **1** is not known, excess copper and **1** (and, therefore, **2**) were

used in the general reaction conditions. Empirically, it has been found that a ratio of 2 mol of **1** per mole of aryl iodide or bromide gives good to excellent yields of products. These products are often of sufficient purity to be used directly in subsequent reactions, as, for example, oxidation to the trifluoromethylsulfonyl derivatives. Both **1** and **2** are known to form very stable complexes with a variety of compounds, including amines.[11] For this reason, a ratio of 3 mol of **1** per mole of substrate was used for amines as in examples 12 and 13, Table I.

The scope and utility of the reaction of aryl iodides and bromides with trifluoromethylthiocopper is illustrated in Table I. Examination of Table I shows that the aromatic nucleus may contain electron-withdrawing or electron-donating groups. Pure ortho-, meta-, and para-substituted aryl trifluoromethyl sulfides are obtained from ortho-, meta-, and para-substituted aryl iodides or bromides. The yield and purity of the crude, isolated products are often greater than 90%. Also, disubstitution of *p*-diiodobenzene occurs readily as does selective replacement of iodine in *p*-chloroiodobenzene.

Because of the operational ease and efficiency of the process, trifluoromethylthiocopper appears to be a desirable re-

agent for the introduction of the trifluoromethylthio group into aromatic nuclei.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. NMR spectra were determined on a Varian T-60 spectrometer with $CDCl_3$ as a solvent. Proton chemical shifts are relative to tetramethylsilane as an internal standard, while fluorine chemical shifts are relative to fluorotrichloromethane. Gas–liquid chromatographic analyses were carried out on a Hewlett-Packard Model 5700 A/3370B gas chromatograph using a column (6 ft × 2 mm) packed with 1% OV-17 on 100/120 Gas-Chrom Q.

Copper metal (electrolytic dust), purified, was purchased from Fisher Scientific Co. Bis(trifluoromethylthio)mercury was prepared by the method of Man, Coffman, and Muetterties.[11] The mercuric fluoride used in this preparation was purchased from Ozark-Mahoning Company, Tulsa, Okla. *Caution: The toxicity of bis(trifluoromethylthio)mercury has been reported.*[11] *All reactions involving this reagent should be carried out in a well-ventilated hood.*

Ethyl-*p*-(trifluoromethylthio)benzoate. Example 2. An intimate mixture of 21.87 g (0.0543 mol) of bis(trifluoromethylthio)-mercury and 12.53 g (0.197 mol) of copper dust was heated at 80–100 °C until development of a bright orange color. Heating was continued at 150 °C for 0.5 h. After cooling, 7.50 g (0.027 mol) of ethyl *p*-iodobenzoate and 30 ml of DMF were added to the copper-colored residue, and the mixture was stirred and heated at 110–120 °C for 3 h. The cooled dark reaction mixture was poured into 500 ml of water and 200 ml of benzene. After stirring vigorously, the mixture was filtered through Celite, and the filter cake was washed with hot benzene. The combined benzene phases were washed with water, dried ($MgSO_4$), and filtered. The benzene was removed on a rotary evaporator to give 6.10 g (90%) of ethyl *p*-(trifluoromethylthio)benzoate that was 98.4% pure by GLC.

General Procedure for the Preparation of Neutral Aryl Trifluoromethyl Sulfides. Ethyl o-(Trifluoromethylthio)benzoate. Example 6. A mixture of 15.0 g (0.0543 mol) of ethyl *o*-iodobenzoate, 43.78 g (0.1087 mol) of $Hg(SCF_3)_2$, 25.07 g (0.395 mol) of copper dust, and 60 ml of DMF was stirred and heated at 110–120 °C for 1 h. The reaction mixture was worked up as in example 2 to give a quantitative yield of ethyl *o*-(trifluoromethylthio)benzoate that was 97.9% pure by GLC. The slight yellow color of this crude product was removed by distillation, bp 70–71 °C (0.7 mm), $n^{25}D$ 1.4879.

A solution of 5.0 g of ethyl *o*-(trifluoromethylthio)benzoate, 30 ml of ethanol, and 20 ml of 10% sodium hydroxide was refluxed for 1.5 h. After cooling, the solution was acidified with 6 N hydrochloric acid. The product was collected by filtration, dried, and recrystallized from a mixture of 60% hexane–40% benzene to give *o*-(trifluoromethylthio)benzoic acid, mp 119–121 °C.

Anal. Calcd for $C_8H_5F_3O_2S$: C, 43.24; H, 2.27; F, 25.65. Found: C, 43.31; H, 2.30; F, 25.86.

General Procedure for the Preparation of Basic Aryl Trifluoromethyl Sulfides. 3-Trifluoromethylthiopyridine. Example 13. A mixture of 5.0 g (0.024 mol) of 3-iodopyridine,[17] 29.48 g (0.0732 mol) of bis(trifluoromethylthio)mercury, 16.96 g (0.267 mol) of copper dust, and 50 ml of DMF was stirred and heated at 110–120 °C for 3 h. After cooling in an ice bath, 100 ml of ether and 50 ml of 5 N sodium hydroxide were added and the mixture was stirred overnight at room temperature. The mixture was filtered through Celite, and the aqueous phase was separated and extracted with two 100-ml portions of ether. All of the ether phases were combined, washed with three 100-ml portions of water, dried ($MgSO_4$), and filtered, and the ether removed on a rotary evaporator. The yield of crude 3-trifluoromethylthiopyridine was 4.15 g (95%) that was 83.5% pure by GLC. The product was purified by distillation, bp 150–151 °C, $n^{25}D$ 1.4676. The ^1H NMR ($CDCl_3$) showed three multiplets centered at δ 7.42 (1 H), 8.08 (1 H), and 8.83 (2 H), while the fluorine spectrum showed a sharp singlet at δ 41.9.

Anal. Calcd for $C_6H_4F_3NS$: C, 40.22; H, 2.25; N, 7.82; F, 31.82; S, 17.89. Found: C, 39.79; H, 2.42; N, 7.79; F, 31.53; S, 17.80.

Acknowledgments. The authors are indebted to Mr. A. Augenblick for the GLC analyses, Mr. W. Riley McGaughran for the NMR spectra, and Mr. K. Streeter and Mr. Y. Lee for the microanalytical data.

Registry No. —1, 21259-75-6; 2, 3872-23-9; Cu, 7440-50-8; *o*-(trifluoromethylthio)benzoic acid, 37526-67-3.

References and Notes

(1) Cuprous, [(trifluoromethyl)thio]-; trifluoromethanethiol, copper(I) salt.
(2) L. M. Yagupol'skii and M. S. Marenets, *Zh. Obshch. Khim.*, **25**, 1771 (1955); *Chem. Abstr.*, **50**, 5635 (1956).
(3) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960).
(4) (a) L. M. Yagupol'skii and M. S. Marenets, *Zh. Obshch. Khim.*, **24**, 887 (1954); *Chem. Abstr.*, **49**, 8172 (1955); (b) D. M. Mulvey and H. Jones, *J. Heterocycl. Chem.*, **12**, 597 (1975).
(5) O. Scherer, *Angew. Chem.*, **52**, 457 (1939); French Patent 820 796 (1937).
(6) W. A. Sheppard, *J. Org. Chem.*, **29**, 895 (1964).
(7) S. Andreades, J. F. Harris, Jr., and W. A. Sheppard, *J. Org. Chem.*, **29**, 898 (1964).
(8) U.S. Patent 3 062 894 (1962); *Chem. Abstr.*, **58**, 8907 (1963); J. F. Harris, *J. Org. Chem.*, **32**, 2063 (1967).
(9) H. J. Emeleus and D. E. MacDuffie, *J. Chem. Soc.*, 2597 (1961).
(10) V. V. Orda, L. M. Yagupol'skii, V. F. Bystrov, and A. U. Stepanyants, *Zh. Obshch. Khim.*, **35**, 1628 (1965); *Chem. Abstr.*, **63**, 17861 (1965).
(11) E. H. Man, D. D. Coffman, and E. L. Muetterties, *J. Am. Chem. Soc.*, **81**, 3575 (1959).
(12) L. M. Yagupol'skii and B. E. Gruz, *Zh. Obshch. Khim.*, **31**, 1315 (1961); *Chem. Abstr.*, **55**, 24720 (1961).
(13) L. M. Yagupol'skii and V. V. Orda, *Zh. Obshch. Khim.*, **34**, 1979 (1964); *Chem. Abstr.*, **61**, 8217 (1964).
(14) French Patent 820 796 (1937).
(15) U.S. Patent 2 108 606 (1938).
(16) L. M. Yagupol'skii, M. S. Marenets, and N. V. Kondratenko, *Zh. Obshch. Khim.*, **35**, 377 (1965); *Chem. Abstr.*, **62**, 14551 (1965).
(17) Sapon Laboratories.
(18) Hexamethylphosphoramide. A recent report, *Science*, **190**, 422 (1975), discusses the carcinogenic potential of hexamethylphosphoramide. *Caution should be used in handling this chemical.*
(19) NOTE ADDED IN PROOF. After this manuscript had been prepared, an article by Yagupol'skii appeared [L. M. Yagupol'skii, N. V. Kondratenko, and V. P. Sambur, *Synthesis*, 721 (1975)] in which an alternate synthesis of trifluoromethylthiocopper was described.

Phenolic Oxidations with Sodium Bismuthate in Acetic Acid

Emil Kon

Chemistry Department, Touro College, New York, New York 10036

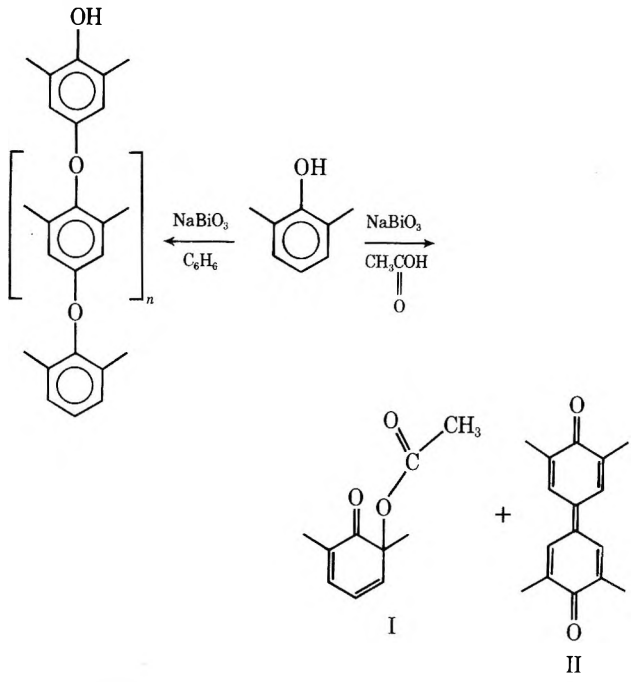
Edward McNelis*

Chemistry Department, New York University, New York, New York 10003

Received November 21, 1975

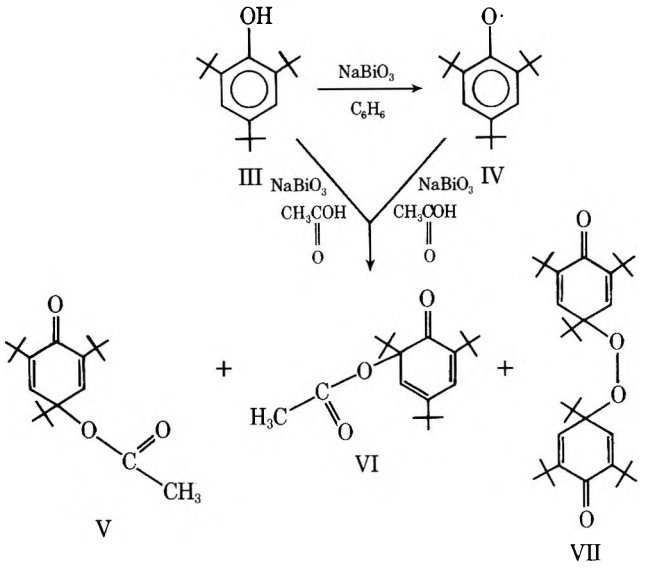
The oxidations of phenols in neutral aromatic solvents by sodium bismuthate has been shown to proceed by one-electron oxidation.[1] The principal products of such oxidations of 2,6-xylenol and related phenols were the corresponding polyphenylene oxides. When the reaction solvent was changed to acetic acid, no polymer was detected. The oxidation products for 2,6-xylenol were 2-acetoxy-2,6-dimethylcyclohexadien-3,5-one (I) and 3,3′,5,5′-tetramethyldiphenoquinone (II). A two-electron oxidation may be inferred from the acetoxy product. Adler, Holmberg, and Ryrfors have reported that the oxidation of mesitol (2,4,6-trimethylphenol) in aqueous acetic acid with sodium bismuthate produced acetoxylated cyclohexadienone products, which were similar to those formed by periodate, a two-electron oxidant.[2] Adderley and Hewgill noted that sodium bismuthate in acetic acid and lead tetraacetate in nonpolar solvents had the same effects on the oxidations of 2-bromo-5(6)-*tert*-butyl-4-methoxyphenols.[3] Additional results on this change of sodium bismuthate from a one-electron oxidant to a two-electron oxidant are given to further clarify this drastic product change.

The oxidation of 2,6-xylenol in benzene by sodium bismuthate affords the polyphenylene oxide in yields of 70 to 80%.[1] When the phenol was dissolved in a 6% (w/v) solution of acetic acid in benzene and oxidized with sodium bismuthate at reflux temperature, the yield of polymer de-



creased to 20% and the yield of diphenoquinone II was 37%. Usually, little or no II was recovered from bismuthate oxidations in benzene. When the acetic acid content of the solvent was increased to 12%, the yield of II was 15% and the yield of isolated I was 64%. No polymer was detected. Approximately similar values were obtained when the solvent was glacial acetic acid.

In order to ascertain if acidic bismuthate could oxidize a possible radical intermediate in two one-electron oxidation steps, the oxidations of 2,4,6-tri-*tert*-butylphenol (III) were carried out. The corresponding stable phenoxyl (IV) was the product of bismuthate oxidation in benzene. [1]When the solvent was changed to glacial acetic acid, the oxidation products were 2,4,6-tri-*tert*-butyl-4-acetoxycyclohexadien-2,5-one (V), 2,4,6-tri-*tert*-butyl-6-acetoxycyclohexadien-2,4-one (VI), and bis(1,3,5-tri-*tert*-butyl-2,5-cyclohexadien-4-one) 1-peroxide (VII) in yields of 62, 22, and 5%, respectively. The molar oxidant to phenol ratio was 3:1.



When this same ratio was used in the generation of the blue phenoxyl IV in benzene under a nitrogen atmosphere, addition of acetic acid brought about a color discharge. Addition of acetic acid to benzene solutions of phenoxyl IV without the bismuthate gave no such color discharge. The isolated products and yields from the color discharging experiment were V (54%), VI (19%), and VII (5%). The similar yield values support the possibility that the phenoxyl IV is an intermediate in the acidic oxidation. To test the notion that peroxide VII was not a precursor for V and VI by a reaction with acetic acid, VII was treated with acetic acid under the same conditions of the previous two experiments. The only product was 2,6-di-*tert*-butyl-1,4-benzoquinone (VIII) in 16% yield. Cyclohexadienones V and VI were not detected and the peroxide was recovered in 61% yield. The source of the oxygen for the peroxide was probably the decomposition of bismuthate during the reaction. This decomposition with oxygen evolution has been shown to be very vigorous at higher temperatures.[1]

In order to test if acidic bismuthate delivered a hydroxyl radical to the phenoxyl IV to give intermediates such as 2,4,6-tri-*tert*-butyl-4-hydroxycyclohexadien-2,5-one (IX) which might have reacted with acetic acid to give V, authentic IX was treated with acetic acid. Compound IX was recovered in 89% yield.

The acetic acid medium is not acidic enough to induce an aryoxyl disproportionation to the corresponding cationic species, a source for V and VI, and a neutral phenol as proposed in a general way by Waters.[4] Rather, there is an increase in oxidation potential of the oxidant. In this case, sodium bismuthate is converted to an unknown bismuth species which is able to remove an electron from the stable phenoxyl IV, whose intermediacy in an overall two-electron process is consistent with the observations.

Experimental Section

Materials and instruments were the same as those of the prior report.[1]

2,6-Xylenol Oxidation. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of 2,6-xylenol (4.1 g, 0.033 mol) in 100 ml of glacial acetic acid. The mixture was stirred for 3 days at room temperature. The mixture was filtered and the residual sodium bismuthate was washed with small quantities of acetic acid. The combined acetic acid solutions were diluted with water to a volume of 500 ml and extracted several times with ether. The extracts were neutralized with dilute $NaHCO_3$ solution and dried. The ether was stripped to a crude oil (2.65 g) which was subjected to dry column chromatography (silica gel–chloroform). The main isolated band weighed 1.7 g (38% yield). It melted at 35 °C and its infrared spectrum was identical with that of I.[5] The other bands were also compound I. The mass spectrum showed a base peak of *m/e* 36 and a parent ion of 5% *m/e* 180. The residual bismuthate was washed with ether, dried, and treated with concentrated HCl. A red solid weighing 0.63 g (15% yield) remained and was identified as II.[6]

2,4,6-Tri-*tert*-butylphenol Oxidation. The reaction conditions and ratios were as above for 2,6-xylenol. The filtrate was mixed with 150 ml of benzene and 150 ml of water. The benzene layer was washed with a $NaHCO_3$ solution. The dried benzene was removed to give an oil which was chromatographed on silica gel with petroleum ether and benzene as eluents. The first band was identified as V by an infrared spectrum[7] and weighed 6.59 g (62% yield), NMR ($CDCl_3$) δ 0.95 (s, 9 H), 1.21 (s, 18 H), 2.05 (s, 3 H), and 6.45 (s, 2 H). The base peak in the mass spectrum was *m/e* 220; no parent peak was observed. A second band weighed 2.30 g (22% yield) and melted at 97.5–99 °C after crystallization from methanol–water. It was identified as VI, NMR ($CDCl_3$) δ 0.98 (s, 9 H), 1.12 (s, 9 H), 1.21 (s, 9 H), 2.05 (s, 3 H), 5.8 (d, 1 H), and 6.85 (d, 1 H). The base peak in the mass spectrum was *m/e* 222; a parent peak at *m/e* 320 (1%) was observed. The dried recovered sodium bismuthate was dissolved in concentrated HCl. The residue weighed 0.45 g (5% yield) and was identified as peroxide VII, which after methanol crystallization melted at 142–144 °C.[8]

2,4,6-Tri-*tert*-butylphenoxyl Oxidation. Sodium bismuthate (66.0 g, 0.236 mol) was added to a solution of 2,4,6-tri-*tert*-butylphenol (8.73 g, 0.033 mol) in 100 ml of benzene. The mixture was held under a nitrogen atmosphere while being stirred for 20 h at room temperature. To this mixture was added 250 ml of glacial acetic acid while the nitrogen atmosphere was maintained. After 20 min the dark blue color faded completely to a pale green. The mixture was worked up in the same manner as above to give 5.75 g of V (54%), 2.02 g of VI (19%), and 0.470 g of VII (5.4%).

Stability of 2,4,6-Tri-*tert*-butylphenol in Acetic Acid. Sodium bismuthate (33.0 g, 0.118 mol) was added to a solution of III (8.73 g, 0.033 mol) in 50 ml of benzene. The mixture was stirred for 6 h at room temperature under nitrogen. The mixture was filtered rapidly. The dark blue filtrate was mixed with 100 ml of glacial acetic acid and kept under nitrogen for 2 weeks. The color persisted until the nitrogen supply was exhausted.

Stability of Hydroxycyclohexadienone IX in Acetic Acid. Compound IX was prepared from 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one[9] by the method of Müller and Ley.[10] In 5 ml of glacial acetic acid was dissolved 0.330 g of IX. The solution was kept at room temperature for 3 days. The solution was poured into 75 ml of water. The precipitate was filtered, dried, and weighed at 0.294 g (89%) and found to be identical with the starting material by an infrared spectrum and mixture melting point determination.

Registry No.—I, 7218-21-5; II, 4906-22-3; III, 732-26-3; IV, 2525-39-5; V, 20778-61-4; VI, 20778-58-9; VII, 1975-14-0; VIII, 719-22-2; IX, 4971-61-3; sodium bismuthate, 12125-43-8; 2,6-xylenol, 576-26-1; 2,4,6-tri-*tert*-butyl-4-nitrocyclohexadien-2,5-one, 1665-87-8.

References and Notes

(1) E. Kon and E. McNelis, *J. Org. Chem.*, **40**, 1515 (1975).
(2) E. Adler, K. Holmberg, and L.-O. Ryrfors, *Acta Chem. Scand., Ser. B*, **28**, 888 (1974).
(3) C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc. C*, 2710 (1968).
(4) W. A. Waters, *J. Chem. Soc. B*, 2026 (1971).
(5) J. Derkosch and W. Kaltenegger, *Monatshefte*, **90**, 874 (1959).
(6) E. McNelis, *J. Org. Chem.*, **31**, 1255 (1966).
(7) T. Matsuro and K. Ogura, *Tetrahedron*, **24**, 6157 (1968).
(8) E. Müller and K. Ley, *Chem. Ber.*, **87**, 922 (1954).
(9) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).
(10) E. Müller and K. Ley, *Chem. Ber.*, **88**, 602 (1955).

A Two-Step Synthesis of (*E*)-4-Chloro-2-methylcrotonaldehyde from Isoprene. An Unprecedented Oxidative Chlorination of a 1,3-Diene Monoepoxide by Cupric Chloride

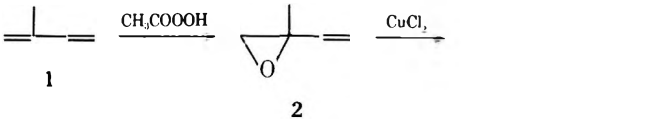
Giancarlo Eletti-Bianchi, Felice Centini, and Luciano Re*

Snamprogetti S.p.A., L.P.M., 00015 Monterotondo (Rome), Italy

Received June 30, 1975

A key intermediate in the Pommer industrial synthesis of vitamin A acetate from β-ionone is (*E*)-4-acetoxy-2-methylcrotonaldehyde (**4**).[1] However, the known syntheses of the latter derivative are multistep and/or low-yield procedures.[1-4]

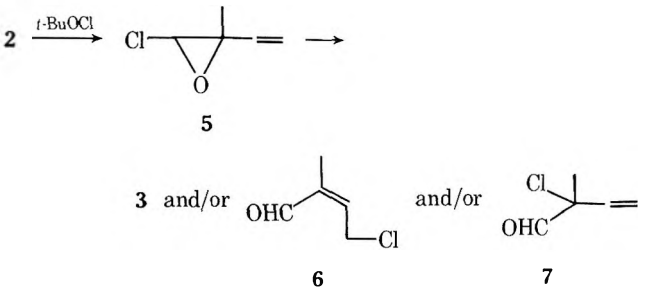
The scope of the present paper is to report a more efficient route to **4** involving epoxidation of isoprene (**1**) with peracetic acid to 3,4-epoxy-3-methyl-1-butene (**2**) followed by oxidative chlorination of the latter with cupric chloride to afford (*E*)-4-chloro-2-methylcrotonaldehyde (**3**), a known direct precursor of **4**.[2]



1 2 3 4

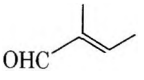
Although the peracetic acid epoxidation of **1** to **2** has been already described, the yield claimed is only 42%.[5] By using a modified procedure, i.e., carrying out the reaction at about 5 °C in chloroform solution in the presence of sodium bicarbonate (to neutralize the acetic acid formed which otherwise gave side reactions with **2**),[6] we could, however, increase the yield of **2** to 80% (VPC analysis of the reaction mixture). Furthermore, the resulting reaction mixture, containing also some residual **1** (87% conversion[7]), could be used, after filtration from the salts, directly for the reaction with cupric chloride.

In preliminary attempts to convert **2** to useful precursors of **4** we speculated that **2**, by free-radical reaction with *tert*-butyl hypochlorite, could give 4-chloro-3,4-epoxy-3-methyl-1-butene (**5**)[8] and that the latter, by rearrangement (possibly in situ),[9] could afford either **3** or its *Z* stereoisomer (**6**) or the constitutional isomer 2-chloro-2-methyl-3-butenal (**7**).



5 6 7

In fact, after gas-phase reaction[10] over alumina of an equimolar mixture of **2**[11] and *tert*-butyl hypochlorite (added dropwise, from the top, to a heated (125 °C) column charged with alumina pellets, using nitrogen as carrier gas and collecting the product at the bottom of the column in a liquid air cooled trap), VPC analysis of the reaction mixture revealed formation of a product (37% yield) with the same retention time as **3**. The same analysis revealed also formation of a product (37% yield) with retention time as for (*E*)-2-methylcrotonaldehyde (**8**). Structures **3** and **8** for

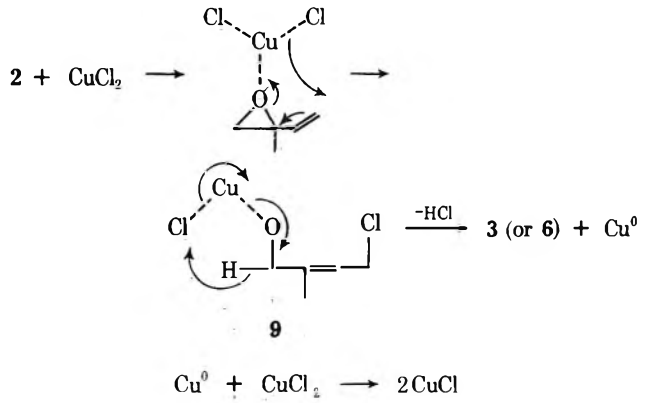


8

these two products were confirmed by the NMR and ir spectra and the boiling points of the compounds isolated, in low yields, by fractionation. Derivative **8**, the rearrangement product of **2**, was obtained in quantitative yields when the gas-phase reaction of **2** over alumina was carried out in the absence of the hypochlorite. On the other hand, when **8** was treated with the hypochlorite under the conditions used for **2**, no **3** was produced, supporting the intermediate formation of **5**, rather than **8**, in the reaction of **2** with the hypochlorite to give **3**.

Although it is known that by oxidative chlorination with cupric chloride **8** can be converted to **3** in moderate yields,[4] we thought that a more direct and possibly more efficient synthesis of **3** (or **6**) from **2** might be achieved by reaction of **2** itself with cupric chloride. To our knowledge, oxidative halogenation of an epoxide with a cupric halide has no precedent in the literature.[12] We speculated, however, that reaction of **2** with cupric chloride could afford **3** (or **6**), either via rearrangement in situ (cupric chloride acting as a Lewis acid catalyst) of **2** to **8** (or to its *Z* stereoisomer) or via cupric alcoholate **9**.

In fact, when the chloroform solution of **2** obtained from the peracetic acid epoxidation of **1** was treated, after addition of an equal volume of ethyl acetate,[13] with cupric chloride in the presence of lithium chloride,[14] VPC analysis of the organic extracts revealed formation of a major product (80% yield) with the same retention time as **3**. The retention time of the only by-product (20% yield) was as for **8**.



Structures 3 and 8 for these two products were confirmed by the NMR and ir spectra and the boiling points of the isolated pure compounds. However, for the acetoxylation[15] step the isolated crude 3 (78% pure, yield corrected for pure 3: 80%) was not distilled since the impurities consisted mainly of residual solvents and the distillation resulted in considerable decomposition of the product (57% yield). The acetoxylation afforded, after removal of low-boiling impurities from the isolated crude product, a 90% yield of 4, which did not require distillation, being already quite pure (95%).

When 2 was treated with cupric chloride in chloroform–ethyl acetate in the absence of lithium chloride the reaction was quite slower (2.5 h instead of 10–15 min), the amount of 8 formed was practically the same (23%), and the purity as well as the yield of the isolated crude 3 were somewhat lower (70% purity, 72% corrected yield). The yield of the distilled 3 was 50%.

By treatment of 8 with cupric chloride in the presence (or absence) of lithium chloride and in chloroform–ethyl acetate solution, using the same reaction conditions as for 2, the starting material was recovered practically unchanged.[16] Therefore, in the oxidative chlorination of 2 to 3 under these conditions the intermediacy of 8 can be excluded and the formation of the latter attributed only to a side reaction.

Finally, when the cuprous and lithium chlorides recovered together from the oxidative chlorination of 2 were submitted to air oxidation in aqueous hydrogen chloride (to regenerate the cupric chloride) and recycled several times, the yields of 3 (and 8) remained unchanged.

In conclusion, peracetic acid epoxidation of 1 followed by cupric chloride oxidative halogenation of the resulting solution and final acetoxylation of the crude 3 represents, on comparison with the previously known syntheses,[1-4] the most efficient route to 4.

Experimental Section

Materials. Isoprene obtained from Fluka (purum a) was purified by distillation over sodium; 82% peracetic acid was prepared according to Swern.[17]

General. Gas chromatography–mass spectrometry analysis was performed with a Varian MAT 111 instrument under the following conditions: 6 ft × 0.125 in. 3% OV-1 on Chromosorb W (80–100 mesh) column, at 40 °C for 3 min then 40 → 180 °C (20 °C/min) and with 24 ml/min of He; ionizing energy, 70 eV. Quantitative VPC analyses were performed with a Hewlett-Packard Model 7620-A gas chromatograph equipped with a thermal conductivity detector. The following columns were employed: (A) 10 ft × 0.125 in. 10% Carbowax 20M on silanized Chromosorb G (60–80 mesh); (B) 6 ft × 0.125 in. 4% SE-30 on silanized Chromosorb G (60–80 mesh). The 60-MHz NMR spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. The following designations were used: s, singlet; dt, doublet of triplets; dq, doublet of quartets; tq, triplet of quartets; qq, quartet of quartets. The ir spectra were taken with a Perkin-Elmer 457 spectrometer.

3,4-Epoxy-3-methyl-1-butene (2). To a solution of 20.4 g (0.30 mol) of 1 in 240 ml of chloroform was added 30.2 g (0.36 mol) of $NaHCO_3$ and a trace of radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol. To the stirred suspension was added dropwise over a 6-h period under ice-bath cooling and N_2 atmosphere 27.8 ml of 82% peracetic acid (corresponding to 0.30 mol of peracid). After an additional 24 h of stirring under the same conditions, the undissolved salts were removed by filtration. Gas chromatography–mass spectrometry analysis of the filtrate confirmed structure 2 for the reaction products on comparing its mass spectrum, *m/e* 84 (9), 83 (14), 69 (16), 55 (98), 53 (42), 43 (96), 41 (22), 39 (100), 29 (61), and 27 (41), to the one of authentic 2 (prepared as cited under ref 11). Quantitative VPC analysis (column A at 70 → 180 °C (30 °C/min) and with 60 ml/min of He, using *n*-octane as internal standard) of the filtrate revealed that 2 was formed in 80% yield and that 13% of the charged 1 was still present in the solution. This solution was used directly for the preparation of 3 by reaction with cupric chloride.

(*E*)-4-Chloro-2-methylcrotonaldehyde (3). To the chloroform solution obtained from the epoxidation of 1 and containing 20.2 g (0.24 mol) of 2 was added 240 ml of ethyl acetate followed by 81.6 g (0.48 mol) of $CuCl_2 \cdot 2H_2O$ and 10.0 g (0.24 mol) of LiCl. The mixture was refluxed (90 °C bath temperature) for about 15 min and then poured onto 240 g of ice. After filtration from the CuCl, the organic phase was separated and the aqueous layer extracted with 240 ml of hexane. The combined organic extracts were washed to neutrality with water and dried (Na_2SO_4). Quantitative VPC analysis (column B at 60 °C for 1 min then 60 → 200 °C (30 °C/min) and with 15 ml/min of He, using *n*-octane as internal standard) of the organic solution revealed formation of 3 and 8 in 80 and 20% yield, respectively. The greater part of the solvents and the aldehyde 8 were then distilled from the organic solution by concentration, first at 10–20 mm and room temperature and finally at 120 mm and 40 °C bath temperature (in both cases the distillation was monitored by VPC to prevent distillation of 3), leaving a residue, 29 g, of crude 3 (78% pure by VPC, the balance to 100% being mainly residual solvents; corresponding to an 80% corrected yield). Distillation of the crude product gave 16.2 g (57%) of 95% pure (VPC) 3: bp 39–42 °C (0.5 mm) [lit.[18] 41–43 °C (0.5 mm)]; NMR ($CDCl_3$) τ 0.57 (s, CHO), 3.43 (tq, J = 6.5 and 1.5 Hz, C=CH), 5.67 (dq, J = 6.5 and 1 Hz, CH_2Cl), 8.23 (dt, J = 1.5 and 1 Hz, CH_3); ir (film) 2710, 1685, 1645 cm^{-1}.

When the distillates obtained in the isolation of the crude 3 (see above) from a few runs were combined and concentrated first at atmospheric pressure and 85 °C bath temperature (until incipient distillation of 8, VPC monitoring) and then at 40 mm and 0 °C (to a 1:1 mixture of 8 and ethyl acetate, VPC monitoring), and the residue distilled at atmospheric pressure, some pure 8 could be obtained: bp 116–117 °C (lit.[19] 116.2 °C); NMR and ir spectra identical with the ones reported in literature for 8.[20,21]

When the oxidative chlorination with $CuCl_2 \cdot 2H_2O$ of the chloroform solution of 2 was repeated in the absence of LiCl, 3 and 8 were formed, after 2.5 h reflux, in 72 and 23% yields, respectively (quantitative VPC analysis of the organic extracts). The yields of the isolated, 70% pure, 3 amounted to 72% (corrected for pure 3) and the one of distilled, 95% pure, 3 to 50%.

Acetoxylation of 11.85 g of the 78% pure 3 (corresponding to 0.078 mol of 3) dissolved in 100 ml of anhydrous ethanol was carried out with 8.42 g (0.086 mol) of potassium acetate keeping the mixture at reflux for 3 h. From the cooled (0 °C) mixture the precipitated KCl was removed by filtration, the filtrate concentrated under vacuum, and the residue taken up in ether in order to dissolve the product from residual KCl. Evaporation of the solvent from the filtered solution gave, after removal of low-boiling impurities at 2–3 mm and room temperature, 10.5 g (90%, based on 0.078 mol of 3) of 4, which did not require distillation, being already quite pure (95% by VPC using column B at 80 → 180 °C (10 °C/min) with 15 ml/min of He and *n*-decane as internal standard). The NMR and ir spectra and the boiling point of the product obtained were identical with the ones reported in the literature for 4.[22]

Acknowledgments. The authors wish to express their thanks to Mr. B. Biancini for his technical assistance in this investigation. Thanks are due to Dr. A. Robertiello for the gas chromatography–mass spectrometry analysis and to Dr. L. Settembri for the NMR spectra.

Registry No.—1, 78-79-5; 2, 1838-94-4; 3, 26394-25-2; 8, 497-03-0; $CuCl_2$, 7447-39-4.

References and Notes

(1) W. Reif and H. Grassner, *Chem.-Ing.-Tech.*, **45**, 646 (1973).
(2) H. Mayer and O. Isler in "Carotenoids", O. Isler, Ed., Birkhäuser-Verlag, Basel, Switzerland, 1971, pp 394–397.
(3) Badische Anilin- & Soda-Fabrik A.-G., French Patent 1 587 943 (1970); *Chem. Abstr.*, **74**, 31556t (1971).
(4) H. K. Dietl, J. R. Normark, D. A. Payne, J. G. Thweatt, and D. A. Young, *Tetrahedron Lett.*, 1719 (1973).
(5) A. N. Pudovik and B. E. Ivanov, *Zh. Obshch. Khim.*, **26**, 2771 (1956).
(6) For epoxidations with peracetic acid in the presence of bases see M. Korach, D. R. Nielsen, and W. H. Rideout, *J. Am. Chem. Soc.*, **82**, 4328 (1960).
(7) Use of excess peracetic acid in order to complete the conversion of **1** resulted in lower yields of **2**.
(8) Ethylene and propylene oxides give the corresponding chloro epoxides by liquid-phase photochlorination with *tert*-butyl hypochlorite; see C. Walling and P. S. Fredricks, *J. Am. Chem. Soc.*, **84**, 3326 (1962).
(9) For related rearrangements of chloro epoxides see H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 313–314.
(10) Liquid-phase photochlorination of **2** with *tert*-butyl hypochlorite under various conditions was unsuccessful.
(11) For these experiments, because of difficulties in isolating the product from the solvent in the peracetic acid epoxidation of **1**, pure **2** was best prepared according to E. J. Reist, I. G. Junga, and B. R. Baker, *J. Org. Chem.*, **25**, 1673 (1960); the only modification being that the dehydrobromination was performed by treatment of the distilled isoprene bromohydrin (bp 60 °C, 10 mm) with solid sodium hydroxide at 90 °C and atmospheric pressure in a distillation flask equiped with a Vigreux fractionating column. Sodium sulfate drying of the distillate (bp 72–73 °C) afforded pure **2**.
(12) For a review on oxidative halogenations with cupric halides see W. G. Nigh in "Oxidation in Organic Chemistry", Vol. 5, Part B, W. S. Trahanovsky, Ed., Academic Press, New York, N.Y., 1973, pp 67–84.
(13) For the successful use of the chloroform–ethyl acetate solvent system in oxidative halogenations of carbonyl compounds with a cupric halide see literature cited under ref 12. The use of other solvents in the cupric chloride halogenation of **2**[11] gave less satisfactory results.
(14) Lithium chloride is a catalyst of oxidative halogenations of carbonyl compounds with cupric chloride; see literature cited under ref 12.
(15) For the acetoxylation of **3** to **4**, a procedure (see Experimental Section) different from the one cited under ref 2 gave more satisfactory results.
(16) The reaction conditions, especially with regard to solvents, used by the authors cited in ref 4 for the conversion of **8** to **3** with cupric chloride were quite different.
(17) D. Swern, "Organic Peroxides", Vol. 1, Wiley-Interscience, New York, N.Y. 1970, p 481.
(18) Badische Anilin- & Soda-Fabrik A.-G., German Patent 1 188 577 (1965); *Chem. Abstr.*, **62**, 13049c (1965).
(19) M. T. Rogers, *J. Am. Chem. Soc.*, **69**, 1243 (1947).
(20) A. W. Douglas and J. H. Goldstein, *J. Mol. Spectrosc.*, **16**, 1 (1965).
(21) S. Satsumabayashi, K. Nakajo, R. Soneda, and S. Motoki, *Bull. Chem. Soc. Jpn.*, **43**, 1586 (1970).
(22) G. Pattenden, J. E. Way, and B. C. L. Weedon, *J. Chem. Soc. C*, 235 (1970).

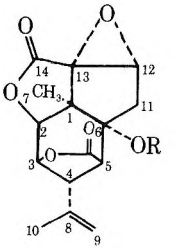
Hydroxyl Assisted Epoxide Opening in Picrotoxins

Haldean C. Dalzell, Raj K. Razdan,* and Reuben Sawdaye

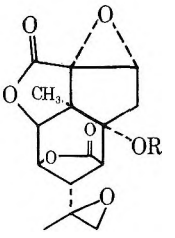
Sheehan Institute for Research, Inc., Cambridge, Massachusetts 02138

Received December 9, 1975

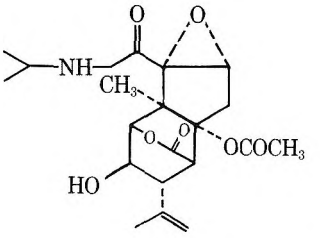
It is well documented that picrotoxinin (**1a**) is the potent analeptic component of picrotoxin.[1] In order to modify the analeptic properties of **1a**, we were interested in the introduction of a basic nitrogen moiety in the picrotoxinin molecule. Picrotoxinin possesses an epoxide ring which should theoretically be opened with amines or other nucleophiles, but is known to be very resistant to intermolecular nucleophilic attack. This unusual feature of the picrotoxinin structure is explained on the basis of shielding of the epoxide ring from rearward attack by the lactone groupings. However, the close proximity of the axial C-6 α-hydroxyl group to the C-4 α-isopropenyl group in **1** suggested to us that the 8,9-epoxide of picrotoxinin (i.e., **2a**) would be prone to nucleophilic attack due to participation by the C-6 hydroxyl group in oxirane ring opening. Indeed, this was found to be the case since epoxidation of **1a** with *m*-chloroperbenzoic acid in methylene chloride followed by aqueous work-up resulted in a mixture of the desired epoxide **2a** and the glycol **4d**. It is interesting to note that previous workers have reported similar problems in the synthesis of this epoxide.[2] In contrast, no difficulty was experienced in the epoxidation of picrotoxinin 6-acetate (**1b**) to give **2b** by the same procedure. Hence picrotoxinin epoxide (**2a**) appears to be much more reactive than **2b**. Because of this reactivity the epoxide **2a** was not isolated in pure form but was used, after a modified work-up procedure, directly in subsequent reactions with amines. On treatment of **2a** with pyrrolidine or diethylamine at room temperature, the corresponding amine derivatives **4a** and **4b** were obtained whereas chloroform reflux conditions were required to obtain **4c** from **2b** with diethylamine.



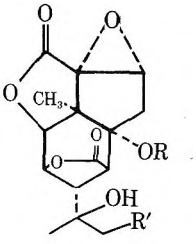
1a, R = H (picrotoxinin)
b, R = $COCH_3$



2a, R = H
b, R = $COCH_3$



3



4a, R = H; R′ =
b, R = H; R′ = $N(C_2H_5)_2$
c, R = $COCH_3$; R′ = $N(C_2H_5)_2$
d, R = H; R′ = OH
e, R = H; R′ = H (picrotin)

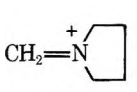
The ease of opening of the epoxide in **2a** with amines to yield compounds of type **4** can be ascribed to the neighboring 6-hydroxyl group participation in an "anionic" process. Only a few examples of such participation are known such as the neighboring hydroxy group participation in the alkaline hydrolysis of esters[3–5] and more recently the opening of epoxides by nucleophiles in steroids.[6] Neighboring group participation in "cationic" reactions, on the other hand, has been known for many years and is well understood.[3,7,8]

The structural assignment of these compounds (**4a–c**) seems secure on the basis of spectral data. The NMR spectra of **4a** and **4b** are compared in Table I with those of picrotoxinin (**1a**) and picrotin (**4e**). The NMR spectra of the latter two important compounds have apparently not been reported previously. Infrared spectra of the amines show that the lactone groupings are maintained in the picrotoxinin epoxide molecule during reaction with amines. The mass spectrum of **4a** showed principal ions at *m/e* 380 $(M + 1)^+$, 379 $(M^{\cdot+})$, 280, 128, and 84 (base). The base peak at *m/e* 84 and the peak at *m/e* 128 correspond to the ions i and ii, respectively, both of which confirm the presence and

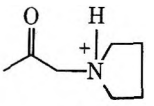
Table I. NMR Assignments of Picrotoxin Derivatives (δ, acetone-d_6)

Proton	Picrotoxinin (1a)	Picrotin (4e)	4a	4b
C_2	5.08, d $J_{2,3}$ = 4	4.88, d $J_{2,3}$ = 3.5	4.91, d $J_{2,3}$ = 3.5	4.90, d $J_{2,3}$ = 3.5
C_3	5.23, dd $J_{2,3}$ = 4; $J_{3,4}$ = 4	5.08, ddd $J_{2,3}$ = 3.5; $J_{3,4}$ = 4.0, $J_{3,5}$ = 1	5.11, dd $J_{2,3}$ = 3.5; $J_{3,4}$ = 5.0	5.12, dd $J_{2,3}$ = 3.5; $J_{3,4}$ = 4.5
C_4 C_5	3.6, b 3.0, d[a]	2.8–3.1, m	2.6–3.2, m[a]	2.8–3.1, m
C_7	1.21, s	1.22, s	1.23, s	1.23, s
C_9	4.98, bs	1.49, s	2.80, s	2.66
C_{10}	1.94, bs	1.46, s	1.46, s	1.43, s
C_{11}	α, 1.86, d[a] β, 2.88, dd $J_{11,11}$ = 15; $J_{11,12}$ = 3.5	α, 1.87, d J = 15 β, 2.82, dd; $J_{11,11}$ = 15; $J_{11,12}$ = 3.5	α, 1.98, d[a] J ~ 15 β, 2.82, dd[a] $J_{11,11}$ ~ 15; $J_{11,12}$ ~ 3.5	α, 2.02, d J ~ 15 β, 2.83, dd[a] $J_{11,11}$ ~ 15; $J_{11,12}$ ~ 3.5
C_{12}	3.60, d; $J_{11,12}$ = 3.5	3.58, d; $J_{11,12}$ = 3.5	3.58, d; $J_{11,12}$ = 3.5	3.60, d; $J_{11,12}$ = 3.5
OH	2.87, bs	5.52, 5.87, 2 bs	4.37, b	4.8, b
			1.6–1.9, m; 2.6–2.9, m	
				0.99, t 2.69, q J = 7.0

[a] Multiplet partially obscured.

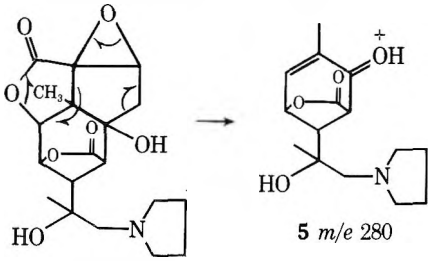


i



ii

establish the position of the pyrrolidine moiety in **4a**. The peak at *m/e* 280 is rationalized as arising from **5** as shown.



5 *m/e* 280

Similarly, the mass spectrum of **4b** showed principal ions at *m/e* 381 ($M^{\cdot+}$), 282, 130, and 86 (base) indicating a fragmentation pattern identical with that of **4a**, the increase in mass by 2 units being due to the substitution of pyrrolidine by diethylamine moiety.

A different course of reaction takes place on treatment of picrotoxinin acetate (**1b**) with isopropylamine at room temperature for 16 h, which results in an attack on the C-14 lactone with concomitant opening of the C-15 lactone to form the amide **3**, similar to the formation of hydroxy-α-picrotoxinic acid from 6-acetylpicrotin with dilute alkali.[9]

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. NMR spectra were measured on a Varian T-60 spectrometer and ir spectra were determined on a Perkin-Elmer Model 700 instrument.

8,9-Epoxypicrotoxinin 6-Acetate (2b). To a solution of 2.34 g (0.007 mol) of picrotoxinin 6-acetate[10] in 50 ml of methylene chloride was added a solution of 1.21 g (0.007 mol) of *m*-chloroperbenzoic acid (85%) in 50 ml of methylene chloride and the mixture was refluxed for 24 h. After cooling, a 10% aqueous solution of sodium sulfite was added and the organic layer was separated. The aqueous layer was twice extracted with methylene chloride and the combined extracts were washed with bicarbonate solution followed with water and dried. After evaporation of the solvent in vacuo, a white solid was obtained which was crystallized from chloroform–methanol mixture to give colorless needles: mp 175–177 °C; NMR ($CDCl_3$) δ 1.43 (6 H, s, C_1 CH_3, C_8 CH_3), 2.08 (3 H, s, acetate), 2.10 (1 H, d, $J_{11,11}$ = 15.5 Hz, C_{11} Hα), 2.54, 2.78 (2 H, AB, J = 4.4 Hz, C_9 H_2), 3.30 (1 H, dd, $J_{4,5}$ = 4.5, $J_{3,5}$ = 5.0 Hz, C_4 H), 3.57 (1 H, dd, $J_{11,11}$ = 15.5, $J_{11,12}$ = 3.5 Hz, C_{11} Hβ), 3.72 (1 H, d, $J_{4,5}$ = 4.5 Hz, C_5H), 3.79 (1 H, d, $J_{11,12}$ = 3.5 Hz, C_{12} H), 4.63 (1 H, d, $J_{2,3}$ = 3.5 Hz, C_2 H), 5.02 (1 H, dd, $J_{2,3}$ = 3.5, $J_{3,4}$ = 5.0 Hz, C_3 H); ir (KBr) 1790 (lactone), 1735 (acetate), 860, 830 cm^{-1} (epoxide). Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.25; H, 5.18. Found: C, 58.04; H, 5.32.

8,9-Epoxypicrotoxinin (2a). To a solution of 2.34 g (0.008 mol) of picrotoxinin in 50 ml of methylene chloride was added a solution of 1.38 g (0.008 mol) of *m*-chloroperbenzoic acid (85%) in 40 ml of methylene chloride and the mixture was refluxed for 27 h. After cooling, solid sodium sulfite was added to the mixture and stirred for 0.5 h. The solution was filtered and evaporated to leave a white solid: mp 100–105 °C; ir (KBr) 3450 (OH), 1800, 1770 (lactones), 860, 830 cm^{-1} (epoxide). Without further purification, this material was used in subsequent reactions with amines. When the epoxide **2a** was worked up as **2b** (aqueous work-up) a considerable amount of glycol **4d** was formed[2] (positive periodate test).

***N*-Isopropylpicrotoxininamide 6-Acetate (3).** A mixture of 0.33 g (0.001 mol) of picrotoxinin 6-acetate (**1b**) and 3 ml of isopropylamine was stirred at room temperature. After 16 h, the product was evaporated in vacuo and the residue was purified by preparative TLC (2-mm thick silica gel, Merck, ether) to yield a gum: NMR ($CDCl_3$) δ 1.13 [d, J = 6.5, Hz, $CH(CH_3)_2$], 1.37 (s, C_1 CH_3), 1.79 (bs, C_8 CH_3), 1.90 (s, acetate), 2.3–2.7 (bm, C_{11} H_2), 3.77 s, 3.95 d, J = 2 Hz, 3.7–4.3 m [C_5 H, C_{12} H, C_4 H, $CH(CH_3)_2$], 4.53 (bs, exchangeable, OH), 4.59 (d, J = 5.5 Hz, C_3 H), 5.00 (b=CH_2), 5.52 (s, C_2 H), 6.33 (d, J = 8 Hz, exchangeable, NH); ir ($CHCl_3$) 3430 (OH), 1760 (δ-lactone), 1740 (acetate), 1665 (amide), 1520, 1380, 1280, 1065, 1055 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.05; H, 6.92; N. 3.56. Found: C, 61.11; H, 6.79; N, 3.51.

8-Hydroxy-9-pyrrolidinopicrotoxinin (4a). To 0.462 g (0.0015 mol) of 8,9-epoxypicrotoxinin, an excess of pyrrolidine was added and the orange-colored solution was stirred at room temperature for 1 h. The pyrrolidine was removed in vacuo and 5 ml of 4 N hydrochloric acid was added. After filtration the solution was extracted with ether. The acid solution was neutralized with sodium bicarbonate and extracted with chloroform. The combined chloroform extracts were washed, dried, and evaporated to leave a solid. It was purified by preparative TLC (2-mm thick silica gel, Merck, 20% methanol–chloroform) followed by crystallization from chloroform–ether to yield colorless crystals: mp 149–151 °C; NMR (see Table I); mass spectrum *m/e* (rel intensity) 380 (0.21), 379 (0.18), 364 (0.95), 280 (6.86), 128 (3.63), 84 (100); ir (KBr) 3400 (OH), 1790 (five-membered lactone), 1140, 980 cm^{-1}. Anal Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.09, H, 6.65; N, 3.58.

8-Hydroxy-9-diethylaminopicrotoxinin (4b). To 0.616 g (0.002 mol) of 8,9-epoxypicrotoxinin, an excess of diethylamine was added and the orange solution was stirred at room temperature for 0.5 h. After evaporation in vacuo and similar work-up as in **4a**, a solid was obtained which was purified by preparative TLC (2-mm thick silica gel, Merck, 20% methanol–chloroform): mp 78–81 °C; NMR (see Table I); mass spectrum *m/e* (rel intensity) 382 (0.62), 381 (0.45), 366 (1.82), 282 (18.0), 130 (6.37), 86 (100), ir ($CHCl_3$) 3400 (OH), 1800 (γ-lactone), 1300, 1260, 1140, 1000 cm^{-1}.

8-Hydroxy-9-diethylaminopicrotoxinin 6-Acetate (4c). To a solution of 0.35 g (0.001 mol) of **2b** in 12 ml of chloroform containing a catalytic amount of *p*-toluenesulfonic acid was added 4 ml of diethylamine. After refluxing for 3 h, the solvent was removed and dilute hydrochloric acid was added. The mixture was extracted with ethyl acetate and the acid solution was evaporated in vacuo to leave a gummy solid: NMR ($CDCl_3$) δ 0.98 (t, J = 7.0 Hz, NCH_2CH_3), 1.33 (s, C_1 CH_3), 1.40 (s, C_8 CH_3), 2.10 (s, acetate), 2.09 (d, $J_{11,11}$ = 15 Hz, C_{11} Hα), 2.40 (s, C_9H_2), 2.65 (q, J = 7.0 Hz, NCH_2CH_3), 3.3 (m, C_4 H), 3.59 (dd, $J_{11,11}$ = 15, $J_{11,12}$ = 3.5 Hz, C_{11} Hβ), 3.73–3.87 (m, C_5 H, C_8 H), 4.93–5.13 (m, C_2 H, C_3H); ir (KBr) 3450 (OH), 1790 (γ-lactone), 1730 (acetate), 1260, 1160, 1000 cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_8$·HCl: C, 54.84; H, 6.59; N, 3.04, Cl, 7.71. Found: C, 55.27; H, 6.90; N, 3.17; Cl, 7.80.

Acknowledgment. This work was carried out with the support of Office of Naval Research Contract N0014-71-C-0422. We are grateful to Professor John C. Sheehan for helpful discussions.

Registry No.—**1a**, 17617-45-7; **1b**, 17617-62-8; **2a**, 58281-91-7; **2b**, 58281-92-8; **3**, 58281-93-9; **4a**, 58281-94-0; **4b**, 58281-95-1; **4c** HCl, 58281-96-2; **4e**, 21416-53-5; isopropylamine, 75-31-0; pyrrolidine, 123-75-1; diethylamine, 109-89-7.

References and Notes

(1) L. A. Porter, *Chem. Rev.*, **67**, 441 (1967).
(2) R. B. Johns, S. N. Slater, and R. J. Woods, *J. Chem. Soc.*, 4715 (1956).
(3) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45 (1964).
(4) S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962).
(5) H. B. Henbest and B. J. Lovell, *J. Chem. Soc.*, 1965 (1959).
(6) D. H. R. Barton and Y. Houminer, *J. Chem. Soc., Perkin Trans. 1*, 919 (1972); *J. Chem. Soc., Chem. Commun.*, 839 (1973); Y. Houmlner, *J. Chem. Soc., Perkin Trans. 1*, 1663 (1975), and references cited therein.
(7) L. Goodman, *Adv. Carbohydr. Chem.*, **22**, 109 (1967).
(8) W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, p 8.
(9) C. J. Coscia in "Cyclopentanoid Terpene Derivatives", W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N.Y., 1969, p 162.
(10) D. E. Hathway, *J. Chem. Soc.*, 4953 (1957).

Conformational Analysis of the 17(20) Bond of 20-Keto Steroids

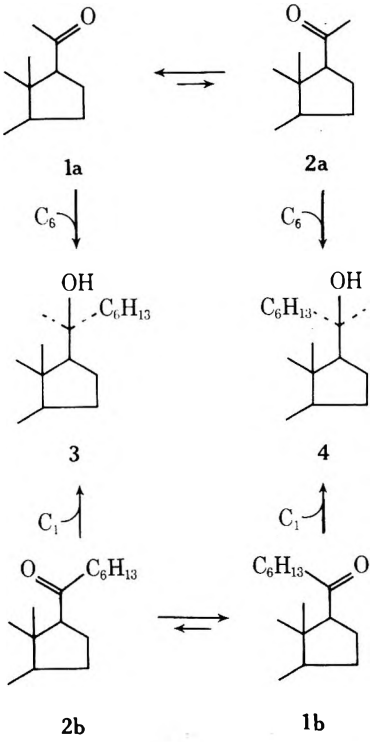
William R. Nes* and Thankamma E. Varkey

Department of Biological Sciences, Drexel University, Philadelphia, Pennsylvania 19104

Received September 12, 1975

From the reduction of pregnenolone (**1a** and **2a**) and other 20-keto steroids as well as from other data, it has been concluded[1] that rotation about the 17(20) bond can occur and that the preferred conformation at the time of reaction is dependent on certain structural factors. Lithium aluminum hydride reduction of pregnenolone, for instance, yields a 2:1 mixture of the 20-hydroxy epimers.[2,3] As predicted qualitatively by Cram's rule, the dominant epimer is the one derived by α-side attack of the reagent on conformer **1a** in which C-21 is cis oriented relative to C-13. Surprisingly, however, the Grignard reaction of the same ketone is reported[4–6] to be completely stereospecific, yielding only the product from conformer **1a**, which led us to a reinvestigation of this problem.

Since the angular methyl group on C-13 should direct attack of the large Grignard reagent to the α face of the steroid, the product composition from the reaction of pregnenolone acetate (**1a** and **2a**) should indicate what the conformational equilibrium is about the 17(20) bond in the ketonic starting material. The α-hydroxy product (**3**) must be derived from the cis conformer (**1a**) with the methyl group



toward C-13 and the β-hydroxy product (**4**) from the trans conformer (**2a**) with the methyl group away from C-13. We have found that both epimers are indeed formed which implies that an equilibrium does exist between both conformers as expected from the work on reductions. Our data also show that conformer **1a** is present in the greater amount at the moment of reaction, since the α epimer (**3**) was present in greater amount in the product mixture, and this is in agreement with deductions based on dipole moment measurements[7] and application of the axial halo ketone rule.[8]

While the cis conformer (**1a**) will yield the 20α epimer (**3** from **1a**) when the incoming group is C_6, the 20β epimer (**4** from **1b**) should be formed when the incoming group is C_1. Furthermore, examination of molecular models reveals that the trans conformer should be destabilized when the alkyl group is increased in size owing to interaction of C-22 with C-16, and the ratio of cis to trans conformer should increase, i.e., the ratio of **1b** to **2b** should be greater than that of **1a** to **2a**. These conclusions require that 20-keto-21-norcholesteryl acetate, which is tantamount to 21-isovalerylpregnenolone acetate, should exist with conformer **1b** being present in larger amount compared to conformer **2b** than is so for conformer **1a** compared to **2a** in the pregnenolone case. The observed facts from the respective Grignard reactions are in agreement, since we find that the 20β epimer is formed in much greater amount from 21-isovalerylpregnenolone than is the 20α epimer from pregnenolone. The ratio of 20β to 20α epimer in the former case is 10:1.0 while the inverse ratio in the latter case is only 1.7:1.0.

In the NMR spectra of the 20α- and 20β-hydroxycholesterols (**3** and **4**, respectively) the signals for C-18 are exactly the same. The downfield chemical shift compared to cholesterol is δ 0.19 which agrees with expectation[9] for a 1,3-diaxial relationship between the 20-hydroxy group and C-18. Such a relationship coincides with the conformations of each of the epimers which would result from Grignard reagent attack on the ketone conformers (**3** from **1a** or **2b** and **4** from **1b** or **2a**). The spectrum thus implies conformational preference leading to the structure of the 20-hydroxycholesterol being "frozen" in the conformation existing at the end of the reaction. The 20α-hydroxy epimer (**3**)

consequently bears the C_6 group on the right, while in the 20β-hydroxy epimer (4) the C_6 group must be on the left. Further weight to this conclusion is given by the fact that C-21 would be in a different environment in the two epimers, and the NMR signals for this carbon atom differ (by δ 0.15) in the two cases.

We conclude from these various facts that rotation about the 17(20) bond occurs when C-20 is in the trigonal state. However, when C-20 is tetrahedral and fully substituted, conformational preference is enhanced. It is interesting that in the presence of two substituents on C-20 with the same structure, the addition of restricted rotation could confer asymmetry. This has actually been observed[10] with 20-methyl-20-(2-hydroxyethoxy)pregn-5-ene-3β,17-diol. Despite the fact that C-20 bears two methyl groups, the substance exists as two separable isomers, and they have spectroscopic properties consistent with the ether group lying toward or away from C-13.

Experimental Section

The NMR spectra were performed in 2% solutions of deuterated chloroform at ambient temperature on a 220-MHz instrument through the services of Morgan-Schaffer of Montreal, Canada, who also supplied the mass spectral data. Melting points were determined on a Kofler hot stage. Gas–liquid chromatography was performed on a column of 1% of nitrile silicone gum (XE-60) on Chromosorb W in a 6-ft U-tube at 235 °C.

Grignard Reaction with Pregnenolone Acetate (3 and 4 from 1a and 2a). A benzene solution of pregnenolone acetate was added to 4-methylvalerylmagnesium bromide in ether. After the reaction had subsided the mixture was refluxed for 2 h. The product was acetylated (Ac_2O–pyridine, room temperature) and submitted to GLC analysis. Two substances were present with retention times relative to cholesteryl acetate of 2.07 and 1.95 in a ratio of 1.8:1.0 based on peak heights. The NMR spectrum also showed the presence of two substances, one with a C-21 signal at δ 1.28 and the other with the analogous signal at δ 1.13 in a ratio of about 1.6:1.0. The major component was 20α-hydroxycholesteryl acetate (3) and the minor one 20β-hydroxycholesteryl acetate (4) as shown by a comparison of the retention times and NMR values with those of authentic samples which are described in what follows.

The product mixture was crystallized from ethanol, and the precipitate was recrystallized several times, giving 5.1 g (from 14.6 g of pregnenolone acetate) of authentic 20α-hydroxycholesteryl acetate (3) with a retention time relative to cholesteryl acetate of 2.07. The melting point (153–155 °C), NMR spectrum [δ 0.87 (d, J = 6 Hz, 6 H, C-26 and C-27), 0.87 (s, 3 H, C-18), 1.03 (s, 3 H, C-19), and 1.28 (s, 3 H, C-21)], and mass spectrum [m/e 384 ($M^+ - CH_3COOH$, 61%), 366 (384 − H_2O, 88%), 351 (366 − CH_3, 63%), 299 (384 − C_6H_{13}, 100%), 281 (299 − H_2O, 86%), 256 (87%), 253 (46%), 241 (37%), 228 (61%), 213 (73%), and 211 (52%)] were in agreement with the corresponding values for the product (20α-hydroxycholesteryl acetate) reported earlier.[5,6] The free alcohol derived from hydrolysis (KOH in methanol, 10 min at reflux) of the 20α-hydroxycholesteryl acetate melted at 133–134 °C, δ 0.87 (d, J = 6 Hz, C-26 and C-27), 0.86 (s, C-18), 1.01 (s, C-19), and 1.28 (s, C-21) as previously reported.[5] Although the mother liquor from the first crystallization of the 20α-hydroxycholesteryl acetate was enriched in the β epimer, attempts to obtain the latter pure by concentration and recrystallizations of the succeeding crops of crystals failed. The best material was a mixture in which the β epimer had twice the concentration of the α epimer by GLC analysis.

Grignard Reaction with 20-Keto-21-norcholesteryl Acetate (3 and 4 from 1b and 2b). Authentic 20β-hydroxycholesteryl acetate (4) was prepared by the Grignard reaction of 20-keto-21-norcholesteryl acetate with methylmagnesium iodide. This reaction is reported[5] to give both epimers in a ratio of about 1:10 (α to β). The GLC analysis of our reaction product was in agreement with this. After acetylation, chromatography on alumina, and crystallization from methanol the β epimer (530 mg from 1.04 g of ketone) had a retention time relative to cholesteryl acetate of 1.95. Its melting point (110–111 °C), NMR spectrum [δ 0.88 (d, J = 6 Hz, 6 H, C-26 and C-27), 0.87 (s, 3 H, C-18), 1.03 (s, 3 H, C-19), and 1.13 (s, 3 H, C-21)], and mass spectrum [m/e 384 ($M^+ - CH_3COOH$, 33%), 366 (384 − H_2O, 89%), 351 (366 − CH_3, 77%), 299 (384 − C_6H_{13}, 40%), 281 (299 − H_2O, 100%), 256 (65%), 253 (50%), 241 (32%), 228 (84%), 213 (90%), and 211 (63%)] agreed with the literature.[5,6] The free alcohol melted at 115–117 °C as previously reported.[5] Since the melting point of the β epimer is much lower than that of the α epimer, it is not surprising that the β epimer was missed by earlier workers in the Grignard reaction with pregnenolone. It was easily isolated only when the α epimer was present in very small concentration.

Acknowledgment. This investigation was supported by National Institutes of Health Grant AM-12172.

Registry No.—**1a,** 1778-02-5; **1b,** 6570-97-4; **3,** 7484-20-0; **4,** 7429-99-4; 4-methylvaleryl bromide, 58298-91-2.

References and Notes

(1) S. Rakhit and C. R. Engel, *Can. J. Chem.*, **40,** 2163 (1962).
(2) W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950).
(3) J. K. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).
(4) V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 4675 (1956).
(5) A. Mijares, D. I. Cargill, J. A. Glasel, and S. Lieberman, *J. Org. Chem.*, **32,** 810 (1967).
(6) N. K. Chaudhuri, J. G. Williams, R. Nickolson, and M. Gut, *J. Org. Chem.*, **34,** 3759 (1969).
(7) N. L. Allinger and M. A. DaRooge, *J. Am. Chem. Soc.*, **81,** 2383 (1959).
(8) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81,** 2383 (1959).
(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 19–20.
(10) F. Kohen, R. A. Mallory, and I. Scheer, *Chem. Commun.*, 580 (1969).

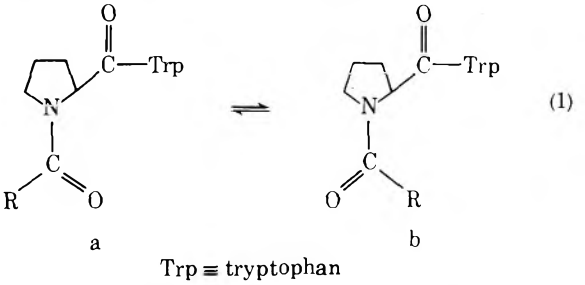
Attempted Synthesis of 2-Methylalanyl-L-prolyl-L-tryptophan. An Unexpected Result

J. T. Gerig* and R. S. McLeod

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

Received August 15, 1975

A program in our laboratory required the synthesis of tripeptides containing proline or 4-fluoroproline[1] as the central amino acid residue and an N-terminal group which biased the conformational equilibrium shown in eq 1



(1)

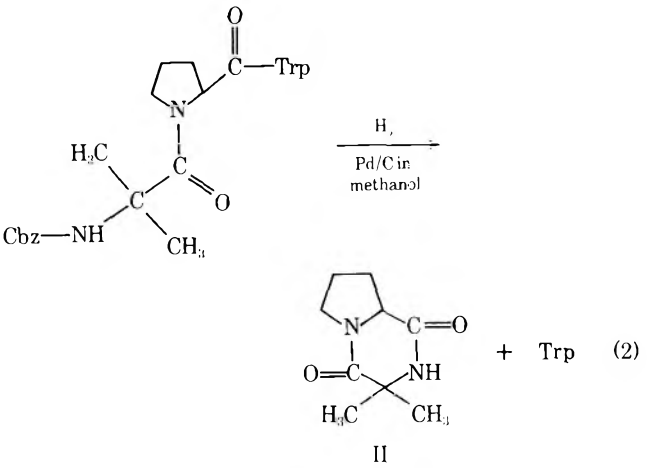
Trp ≡ tryptophan

strongly in favor of one conformer. A recent ^1H NMR study has demonstrated that pivaloylproline exists as essentially one rotational isomer.[2] This corresponds to R = $(CH_3)_3C$ in eq 1, and we reasoned that 2-methylalanine [R = $(CH_3)_2CNH_3^+$] as the N-terminal would provide a tripeptide which meets the above specification since the pivaloyl and 2-methylalanyl groups would be expected to be nearly isosteric. Our attempts to synthesize 2-methylalanyl-L-prolyl-L-tryptophan and 2-methylalanyl-4-fluoro-L-prolyl-L-tryptophan by conventional methods did not cleanly afford these tripeptides but culminated, instead, in the results described here.

Results

The protected tripeptide, carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan (I), was synthesized in ade-

quate yields by standard methods.[3] Attempts to remove the carbobenzyloxy (Cbz) group by hydrogenolysis at room temperature or 0 °C did not generate the expected tripeptide but rather a mixture of the diketopiperazine (II) and tryptophan (Trp). The reaction was followed by TLC and



II

appeared to be complete within several minutes. The disappearance of the protected tripeptide occurred simultaneously with the appearance of a spot (R_f 0.63) which could readily be identified as L-tryptophan by comparison to an authentic sample. A second product (R_f 0.72) was ninhydrin negative and stained only slightly with iodine. A third component (R_f 0.49), ninhydrin positive, was observed in low amounts. Attempts to isolate and identify this latter material were unsuccessful but comparison of the R_f to those of glycylprolyltryptophan (R_f 0.50) and alanylprolyltryptophan (R_f 0.51) suggested that this spot may have represented the desired tripeptide.

The ^{1}H NMR spectrum of the reaction product mixture in basic D_2O indicated, by signal positions and relative intensities, the presence of the three amino acids that were initially linked in the starting material. Several extractions of this sample with deuteriochloroform left an aqueous solution containing predominantly free tryptophan, as shown by the ^{1}H NMR spectrum. The combined organic extracts gave a ^{1}H NMR spectrum which exhibited resonances assignable to 2-methylalanine and proline and a resonance at ~7.5 ppm from Me_4Si assigned to amide protons. A mass spectrum of the extracted material showed a molecular ion at *m/e* 182; the molecular weight of 2-methylalanylprolyldiketopiperazine (II) is 182.2. Thus, although the anticipated tripeptide may initially form during hydrogenolysis, it must rapidly react to give free tryptophan and II.

Similar results were obtained in attempts to reduce carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan and carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan; TLC analysis of the reaction mixtures indicated that the same decomposition reaction had occurred as observed with the nonfluorinated protected tripeptide. However, carbobenzyloxyglycylprolyltryptophan and carbobenzyloxyalanylprolyltryptophan (R = NH_2CH_2 and NH_2CHCH_3 respectively, in eq 1) both reduced smoothly to the expected tripeptides under our conditions.

Carbobenzyloxy-2-methylalanylprolyltryptophan also was treated with a solution of hydrogen bromide in glacial acetic acid at room temperature. TLC of the residue obtained upon removal of the reaction medium showed a ninhydrin-positive spot at R_f 0.47 which might correspond to the hoped-for tripeptide. However, an unidentified broad band (R_f 0.3–0.4), intensely stained by iodine but ninhydrin negative, was also apparent.

Discussion

Previous synthetic studies have indicated that steric hindrance can be a major problem in the chemistry of 2-methylalanine and some atypical results have been described.[4,5] Many examples of peptide cleavages are known when peptides or their derivatives are subjected to conditions used to form cyclic peptides; these conditions include high temperatures and solvents such as pyridine, phenol, and *sec*-butyl alcohol. Cyclization of this type can be particularly prevalent when proline or sarcosine are present.[6,7] However, the reaction described here occurs under very mild conditions and is apparently without precedent.

It seems likely that the ability of *gem*-dimethyl groups to enhance the rate of cyclization reactions by "stereopopulation control"[8,9] plays a role in the reaction of the 2-methylalanylpeptides reported here. Consideration of space-filling models of 2-methylalanylprolyltryptophan suggests that in rotational isomer b the *gem*-dimethyl group could force a free amino group very close to the carbonyl carbon of the proline–tryptophan peptide bond, thus favoring the formation of a tetrahedral intermediate at this position. Expulsion of tryptophan from the intermediate would lead to the diketopiperazine observed. Conformer b is expected to be present in low, but not zero, concentration.[2]

We have abandoned attempts to obtain the title compound and its fluorinated analogues since it seems likely that, even if these materials could be prepared and purified, they would decompose according to eq 2 in aqueous solution.

Experimental Section[10]

2-Methylalanine (Baker), L-proline (Mann), L-tryptophan (Mann), carbobenzyloxy chloride (Aldrich), and dicyclohexylcarbodiimide (Aldrich) were used as obtained from commercial sources. The cis and trans isomers of 4-fluoroproline were prepared by the method of Gottlieb et al.[1] as previously described.[11] Preparation of carbobenzyloxy-2-methylalanine followed published procedures;[5] amino acid methyl ester hydrochlorides were prepared with methanolic HCl.[12]

Carbobenzyloxy-2-methylalanyl-L-proline Methyl Ester. To a solution of proline methyl ester hydrochloride (1.65 g, 0.010 mol) in 15 ml of dichloromethane was added triethylamine (1.4 ml), and the solution was mixed with a solution of carbobenzyloxy-2-methylalanine (2.60 g, 0.011 mol) in 15 ml of dichloromethane at 0 °C. Then dicyclohexylcarbodiimide (2.10 g, 0.010 mol) was added and the solution was stirred overnight at room temperature. Dicyclohexylurea was removed by filtration, and the filtrate was washed with 1 M HCl, water, and 1 M sodium bicarbonate, and finally dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo to yield 2.86 g (82%) of the protected dipeptide as an oily product. Additional dicyclohexylurea was removed by dissolving the oil in ethyl acetate and filtering. A ^{1}H NMR spectrum ($CDCl_3$) of the crude oil showed δ 1.5 (doublet, 6 H), 1.8 (broad band, 4 H), 3.6 [broad band, 5 H including a singlet at 3.6 ppm (~3 H)], 4.5 (broad peak, ~1 H), 5.1 (singlet, 2 H), 6.2 (broad singlet, 1 H), and 7.1 (singlet, ~5 H).

Carbobenzyloxy-2-methylalanyl-L-proline. Crude carbobenzyloxy-2-methylalanyl-L-proline methyl ester (1.02 g, 0.015 mol) was dissolved in 10 ml of methanol, and 1.0 ml of 4 M NaOH was added. The resultant solution was let stand for 16 h at room temperature. At the end of this time, the solution was diluted with 20 ml of water and extracted with ether. The ether layer was discarded. The aqueous layer was acidifed with concentrated HCl and extracted twice with ethyl acetate. The organic layer was washed with saturated NaCl solution and dried over anhydrous sodium sulfate, and the solvent was evaporated to yield 0.70 g (72%) of the oily carbobenzyloxy dipeptide. The ^{1}H NMR spectrum ($CDCl_3$) of the crude oil showed the disappearance of the singlet (3 H) at 3.6 ppm, but the rest of the spectrum was virtually the same as that of the corresponding carbobenzyloxy dipeptide methyl ester.

Carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan Methyl Ester. The preceding crude carbobenzyloxy dipeptide was coupled to tryptophan methyl ester hydrochloride by the same procedure described above for formation of the 2-methylalanyl-

prolyl peptide bond. The product was recrystallized from chloroform to obtain white crystals, mp 155–156 °C. The ^{1}H NMR spectrum in CD_3OD had resonances at δ 1.5 (doublet, 6 H), 1.8 (broad multiplet, 4 H), 3.6 (singlet, 3 H), 5.1 (singlet, 2 H), and 7.3 [multiplet, 10 H, including a singlet in the center (~5 H)]; other peaks were obscured by residual protons in the solvent.

Carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan was prepared from the above carbobenzyloxy tripeptide methyl ester in the same manner as was done at the dipeptide stage of the synthesis. The product was obtained in 82% yield and was recrystallized from methanol to afford white crystals, mp 158–159 °C. The mass spectrum exhibited a parent ion at *m/e* 520 and the ^{1}H NMR spectrum, in acetone-d_6, showed signals at δ 1.5 (broad singlet, 6 H), 1.8 (multiplet partially obscured by residual solvent peaks), 3.3 (singlet, 3 H), 3.5–4.7 (broad complex region, 6 H), 5.0 (singlet, 2 H), and 7.2 [complex multiplet, 10 H, including a singlet in the center (~5 H)]. The singlet at 3.3 ppm (3 H) represents a solvating molecule of methanol found in the crystalline material.

Anal. Calcd for $C_{28}H_{32}N_4O_6 \cdot CH_3OH$: C, 63.03; H, 6.57. Found: C, 62.94; H, 6.29.

Carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan and carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan were prepared by exactly the same methods as the unfluorinated carbobenzyloxy tripeptide described above. As in the unfluorinated case, the *cis*- and *trans*-4-fluoroprolyl peptide derivatives afforded carbobenzyloxy dipeptide methyl esters (85 and 78%, respectively) and carbobenzyloxy dipeptides (70 and 73%, respectively) which were oils, whereas the carbobenzyloxy tripeptide methyl esters (79% mp 109.5–111 °C, and 76%, mp 158–159 °C, respectively) and carbobenzyloxy tripeptides (80%, mp 190–191 °C, and 85%, mp 126–127 °C, respectively) were crystalline. Each step in these syntheses went smoothly, and ^{1}H NMR spectra were consistent with the expected products at each step. The ^{1}H NMR spectrum of the protected tripeptide containing *cis*-fluoroproline showed signals at δ 1.4 (unsymmetrical doublet, 6 H), 2.1–2.6 (broad band, 2 H), 5.6 (broad peak, 0.5 H), and 7.2 (broad, complex multiplet, 10 H). A number of peaks, some partially obscured by signals from residual protons of the solvent and spinning side bands, were observed between δ 3.0 and 5.0. The ^{1}H NMR spectrum (CD_3OD) of the corresponding trans isomer had δ 1.4 (doublet, 6 H), 1.8–2.5 (broad multiplet, 2 H), 2.7–4.9 (a number of resonances, many partially obscured by residual solvent signals and spinning side bands), 5.0 (singlet, 2 H), 6.0 (broad peak, 0.5 H), and 7.2 (broad complex multiplet, 10 H).

Carbobenzyloxyglycyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxyglycyl-L-proline (Sigma) by the same reactions described above, affording the carbobenzyloxy tripeptide methyl ester in 75% yield and carbobenzyloxy tripeptide in 79% yield. Both products were solids upon exhaustive evaporation of solvent, but could not be recrystallized, possibly because of traces of dicyclohexylurea present. The impure carbobenzyloxy tripeptide product had a ^{1}H NMR spectrum ($CDCl_3$) containing signals at δ 5.0 (singlet, 2 H), 6.0 (broad peak, 1 H), and 7.1 (complex multiplet, 10 H).

Carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan was synthesized from carbobenzyloxy-L-alanyl-L-proline (Sigma) by reactions similar to those used above. The saponification of the methyl ester resulted in a solid rather than an oily precipitate on addition of concentrated HCl. This solid was not readily extracted into ethyl acetate and was collected by vacuum filtration, washed with cold water, and dried (mp 171–173 °C). ^{1}H NMR (CD_3OD) of this unpurified solid had δ 1.2 (doublet, 3 H), 1.9 (broad band, 4 H), 5.0 (singlet, 2 H), and 7.3 (complex multiplet, 10 H). The solvent signals made accurate integration of other parts of the spectrum unreliable.

Hydrogenolyses of the carbobenzyloxy tripeptides were carried out by bubbling H_2 through a magnetically stirred solution of 0.4 mmol of the material in 14 ml of methanol; ~100 mg of 10% Pd/C was used as the catalyst.

The peptide syntheses and hydrogenolyses were monitored by TLC using Eastman Chromogram silica gel plates developed with a mixture of 1-butanol (63 ml), glacial acetic acid (23 ml), and water (14 ml). Plates were visualized with ninhydrin spray and iodine vapor.

^{1}H NMR spectra were recorded on a Varian Associates T-60 or HA-100 spectrometer using, as appropriate, deuterium oxide, acetone-d_6, deuteriochloroform, or deuterated methanol as solvents; chemical shifts are given relative to tetramethylsilane. Mass spectra were determined with an AEI MS-902 mass spectrometer. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Acknowledgments. We are indebted to the National Science Foundation (Grant 43984X) for support of this work. J. T. G. is a Research Career Development Awardee of the National Institutes of Health (Grant GM-70373).

Registry No.—I, 58281-74-6; Carbobenzyloxy-2-methylalanyl-L-proline methyl ester, 15030-91-8; proline methyl ester HCl, 2133-40-6; carbobenzyloxy-2-methylalanyl-L-proline, 58281-75-7; carbobenzyloxy-2-methylalanyl-L-prolyl-L-tryptophan methyl ester, 58281-76-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan, 58281-77-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan, 58281-78-0; *cis*-4-fluoroproline methyl ester HCl, 58281-79-1; *trans*-4-fluoroproline methyl ester HCl, 58281-80-4; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline methyl ester, 58281-81-5; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline methyl ester, 58281-82-6; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoroproline, 58281-83-7; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoroproline, 58281-84-8; carbobenzyloxy-2-methylalanyl-*cis*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-85-9; carbobenzyloxy-2-methylalanyl-*trans*-4-fluoro-L-prolyl-L-tryptophan methyl ester, 58281-86-0; carbobenzyloxyglycyl-L-proline, 1160-54-9; carbobenzyloxyglycyl-L-prolyl-L-tryptophan methyl ester, 58281-87-1; carbobenzyloxyglycyl-L-prolyl-L-tryptophan, 58281-88-2; carbobenzyloxy-L-alanyl-L-proline, 21027-01-0; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan methyl ester, 58281-89-3; carbobenzyloxy-L-alanyl-L-prolyl-L-tryptophan, 58281-90-6.

References and Notes

(1) A. A. Gottlieb, Y. Fujita, S. Udenfriend, and B. Witkop, *Biochemistry*, **4**, 2507 (1965).
(2) H. Nishihara, K. Nishihara, T. Uefuji, and N. Sakota, *Bull. Chem. Soc. Jpn.*, **48**, 553 (1975).
(3) M. Bodansky and M. A. Ondetti, "Peptide Synthesis", Interscience, New York, N.Y., 1966, p 119.
(4) M. T. Leplawy D. S. Jones, G. W. Kenner, and R. C. Sheppard, *Tetrahedron*, **11**, 39 (1960).
(5) D. S. Jones, G. W. Kenner, J. Preston, and R. C. Sheppard in "Peptides", L. Zervas, Ed., Pergamon Press, Elmsford, N.Y., 1966, p 313.
(6) M. Rothe, R. Theysohn, D. Mühlhausen, F. Eisenkeiss, and W. Schindler in "Chemistry and Biology of Peptides", J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, p 51.
(7) K. Titlestad in ref 6, p 59.
(8) S. Milstein and L. A. Cohen, *J. Am. Chem. Soc.*, **94**, 9158 (1972).
(9) T. C. Bruice and W. C. Bradbury, *J. Am. Chem. Soc.*, **87**, 4838, 4856, 4851 (1965).
(10) Details are available in the Ph.D. Thesis of R. S. M., University of California, Santa Barbara, Sept 1975.
(11) J. T. Gerig and R. S. McLeod, *J. Am. Chem. Soc.*, **95**, 5725 (1973).
(12) R. A. Boissonnas, St. Guttmann, R. L. Huguenin, P.-A. Jaquenoud, and E. Sandrin, *Helv. Chim. Acta*, **41**, 1867 (1958).

Diels–Alder Reactions of *trans,trans*-1,4-Diacetoxybutadiene. Observations Concerning Some Literature Reports

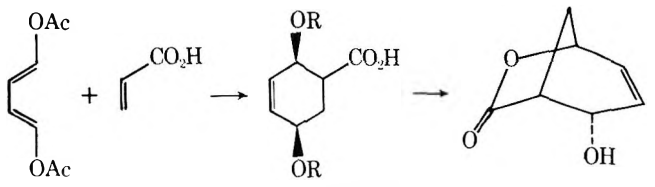
Gene W. Holbert and Bruce Ganem*

Department of Chemistry, Cornell University, Ithaca, New York 14853

Received December 5, 1975

Diels–Alder cycloadditions of *trans,trans*-1,4-diacetoxybutadiene (1) with electrophilic olefins provide one valuable source of highly oxygenated six-membered carbocycles[1] which we have had occasion to explore. In this note we disclose further details regarding the reactivity of 1 as a diene component. We also describe the outcome of experiments which bring important new results to bear on some previously described cycloadditions.

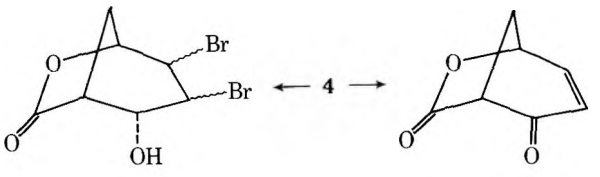
The condensation of 1 with acrylic acid and its esters has been the subject of some debate, focusing on the stereochemistry of the adduct 2.[2-4] Comprehensive NMR spectroscopic data have been gathered by Raphael,[5] Hill,[6] and Smissman[7] in support of the all-cis stereochemistry (shown in 2) predicted from an endo transition state. We have pre-



1 2, R = $COCH_3$ 3, R = H 4

pared this adduct (mp 141–143 °C) and now present *chemical* evidence consistent with the all-cis assignment.

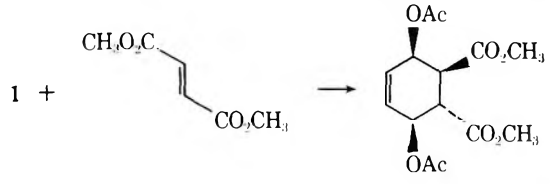
Saponification of **2** (10% NaOH, 0 °C, 2 h) proceeds *without elimination to afford the dihydroxy acid* **3**. When subjected to *p*-toluenesulfonic acid in chlorobenzene at reflux **3** is transformed into the bicyclic γ-lactone **4** in 85% yield after distillation. Consistent with its structure, **4** forms a customary dibromo derivative **5** and can as well be oxidized (Jones reagent) cleanly to the bicyclic enone **6**.



5 6

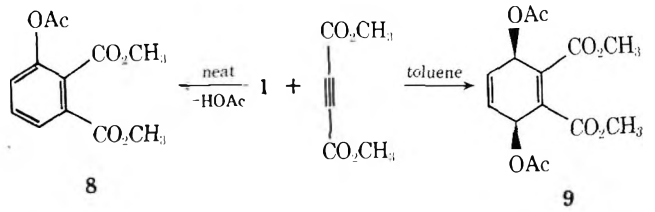
This lactonization thus provides chemical affirmation of the stereochemical assignment in **2**.

We have also investigated for the first time addition of **1** with more highly functionalized acrylate derivatives. Although **1** with fumaric acid affords only phthalic anhydride under a variety of conditions, the ene-tetraester **7** can be



7

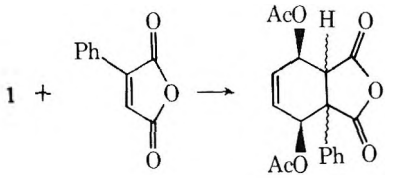
obtained in 76% yield (recrystallized) after boiling an equimolar mixture of **1** and dimethyl fumarate in xylene for 24 h. Surprisingly the crude reaction mixture gives no evidence of any *aromatic by-products. Hill has reported the* utility of **1** in constructing substituted aromatic rings by direct cycloaddition with acetylenic dienophiles and subsequent elimination of acetic acid.[8] In that work, a mixture of **1** and dimethyl acetylenedicarboxylate when heated at 110 °C (no solvent) furnished **8**. We have repeated this experiment in toluene at reflux (50 h) and found, in contrast, that a 70% (distilled) yield of the cyclohexadiene **9** may be ob-



8 9

tained consistently. Efforts to extend this useful 1,4-cyclohexadiene synthesis to propiolic acid and ethyl propiolate were far less successful. In both cases numerous products in addition to diene were formed. None of these was acetylsalicylic acid (ethyl ester) or *m*-acetoxybenzoic acid (ethyl ester), the expected aromatic derivatives.

As part of another project we required the previously unprepared adduct of **1** with phenylmaleic anhydride.[9] This



10

bicyclic anhydride **10** (mp 160–162 °C) could be isolated in 52% yield (xylene, reflux) as a mixture (ca. 10:1) of unassigned stereoisomers which were separable by high-pressure liquid chromatography. In other cycloadditions we have surveyed for purposes of natural product synthesis, no reaction could be engendered between **1** and ethyl cinnamate, ethyl *p*-nitrocinnamate, or cinnamoyl chloride.

Experimental Section

Melting points were determined in capillaries and are uncorrected. NMR spectra were recorded on a Varian A-60A spectrometer with tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer 137 spectrophotometer. Mass spectra were carried out using a computerized AEI MS-902 instrument. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

***all-cis*-2,5-Dihydroxycyclohex-3-enecarboxylic acid (3).** *all-cis*-2,5-Diacetoxycyclohex-3-enecarboxylic acid (**2**,[3] 1.00 g, 4.13 mmol) was stirred with 10% aqueous NaOH solution (10 ml) at 0 °C for 2 h. While cold, the solution was acidified to pH 3 (10% H_2SO_4) and washed with three 25-ml portions of ether. The aqueous layer was evaporated to dryness under vacuum (0.5 mmHg) and the residue stirred overnight with 50 ml of distilled THF. The supernatant was dried ($MgSO_4$), filtered through Celite, and concentrated to yield 0.524 g (80%) of **3**, mp 155–157 °C after trituration with cold ether: NMR δ (D_2O) 5.90 (d, 2 H, J = 2 Hz), 4.1–4.5 (m, 2 H), 2.78 (d of t, 1 H, J = 12, 4, 3 Hz), 1.28–2.33 (complex m, 2 H); ir (nujol) 3.15, 5.76, 5.99 μ.

Anal. Calcd for $C_7H_{10}O_4$: C, 53.2; H, 6.4. Found: C, 53.2; H, 6.4.

Preparation of 6-Oxo-7-oxabicyclo[3.2.1]oct-2-en-4-ol (4). A 50-ml round-bottom flask containing **3** (0.097 g, 0.615 mmol) and a trace (<1 mg) of *p*-toluenesulfonic acid was fitted with a Soxhlet extractor containing a thimble half-filled with CaH_2. The apparatus was flushed with N_2, then chlorobenzene (30 ml, deaerated for 15 min in a stream of N_2) added. The mixture was heated at reflux for 6 h. After removal of solvent at reduced pressure the residue was stirred with solid $NaHCO_3$ in $CHCl_3$ for 30 min and filtered, and the filtrate was concentrated. Kugelrohr distillation (140 °C, 0.2 mm) afforded 0.073 g (85%) of lactone **4** as a colorless solid: mp 79–84 °C; NMR δ ($CDCl_3$) 6.33 (d of d, 1 H, J = 9, 5 Hz), 5.91 (broad d, 1 H, J = 9 Hz), 4.83 (broad d, 1 H, J = 5 Hz), 4.68 (m, 1 H), 3.78 (s, 1 H, hydroxyl), 3.10 (t, 1 H, J = 5 Hz), 2.55 (d of t, 1 H, J = 12, 5 Hz), 2.11 (d, 1 H, J = 12 Hz); ir ($CHCl_3$) 5.63 μ; mass spectrum (CI, methane) m/e 141 (M + 1), 123 (base).

Anal. Calcd for $C_7H_8O_3$: C, 60.0; H, 5.8. Found: C, 60.0; H, 5.7.

Preparation of 4,6-Dioxo-7-oxabicyclo[3.2.1]oct-2-ene (6). Oxidation of 4. A solution of the lactone **4** (0.047 g, 0.336 mmol) in acetone (5 ml) was chilled to 0 °C. Standard Jones reagent was added dropwise until the red color of the reagent persisted. Excess oxidant was destroyed with isopropyl alcohol, then sufficient water added to dissolve the chromium salts. Three ether extractions afforded 0.023 g (50%) of the enone as a yellow oil: NMR δ ($CDCl_3$) 7.42 (d of d, 1 H, J = 10, 5 Hz), 6.01 (d, 1 H, J = 10 Hz), 5.17 (broad t, 1 H), 3.64 (m, 1 H), 2.89 (m, 2 H); ir (film) 5.60, 5.88 μ.

Cycloaddition of 1 with dimethyl fumarate. A solution of dimethyl fumarate (1.695 g, 11.76 mmol) and **1**[10] (2.000 g, 11.76 mmol) in deaerated xylene (50 ml) was heated at reflux for 24 h under N_2. Removal of the solvent at reduced pressure, then crystallization of the residue from 1:2 benzene–hexane afforded 2.812 g (76%) of **7** as fine, colorless needles: mp 129–131 °C; NMR δ ($CDCl_3$) 5.98 (m, 2 H), 5.62 (m, 2 H), 3.72 and 3.71 (overlapping singlets, 6 H), 3.18 (d of d, 2 H, J = 6, 1.5, 1.5 Hz), 2.10 (s, 3 H), 2.00 (s, 3 H); ir ($CHCl_3$) 5.75 μ.

Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.5; H, 5.8. Found: C, 53.6; H, 5.7.

Cycloaddition of 1 with Dimethyl Acetylenedicarboxylate. Dimethyl acetylenedicarboxylate (0.302 g, 2.14 mmol) and **1** (0.200 g, 1.18 mmol) were dissolved in deaerated toluene (15 ml) and the solution heated at reflux under N_2 for 48 h. Removal of the solvent at reduced pressure followed by Kugelrohr distillation (100–150 °C

at 0.1 mm) from a base-washed flask yielded 0.355 g (70%) of colorless oil which solidified on standing in the freezer (mp 56–61 °C): NMR δ ($CDCl_3$) 6.08 (s, 4 H), 3.85 (s, 6 H), 2.12 (s, 6 H); ir ($CHCl_3$) 5.75, 6.05 μ; mass spectrum (CI, methane) *m/e* 313 (M + 1), 222 (base). After one recrystallization from 2:1 cyclohexane–hexane the adduct **9** had mp 64–67° (recovery 56%).

Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.8; H, 5.2. Found: C, 54.1; H, 5.2.

Cycloaddition of 1 with Phenylmaleic Anhydride. Phenylmaleic anhydride (0.870 g, 5.0 mmol) and **1** (0.750 g, 5.0 mmol) in xylene (25 ml, deaerated) were heated at reflux under N_2 for 40 h. Removal of the solvent at reduced pressure followed by crystallization (1:2 benzene–hexane) gave 0.900 g (50%) of **10** as fine, pale yellow needles: mp 160–162 °C; NMR δ ($CDCl_3$) 7.46 (s, 5 H), 6.20 (d, 2 H, J = 2 Hz), 5.72 (d of d, 1 H, J = 8, 2 Hz), 5.64 (d, 1 H, J = 2 Hz), 4.19 (d, 1 H, J = 8 Hz), 2.20 (s, 3 H), 2.05 (s, 3 H); ir ($CHCl_3$ 5.36, 5.58, 5.71 μ; mass spectrum *m/e* 284 (M − 60), 43 (base).

Anal. Calcd for $C_{18}H_{16}O_7$: C, 62.8; H, 4.7. Found: C, 63.0; H, 4.6.

Analysis of this product by high-pressure liquid chromatography[11] (Porasil, eluting with CH_2Cl_2) indicated two isomers with the major (ca. 10:1) having a longer retention time.

Acknowledgment. We acknowledge the Research Corporation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

Registry No.—**1**, 15910-11-9; **2**, 58298-62-7; **3**, 58324-77-9; **4**, 58298-63-8; **6**, 58298-64-9; **7**, 58298-65-0; **9**, 58298-66-1; **10**, 58298-67-2; dimethyl fumarate, 624-49-7; dimethyl acetylenedicarboxylate, 762-42-5; phenylmaleic anhydride, 36122-35-7.

References and Note

(1) See, inter alia, A. S. Onishchenko, "Diene Synthesis", Israel Program for Scientific Translations, Jerusalem, 1964, p 225.
(2) The controversy is summarized in L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 184. See also ref 3 and 4.
(3) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).
(4) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *J. Am. Chem. Soc.*, **84**, 1040 (1962).
(5) R. McCrindle, K H. Overton, and R. A. Raphael, *Tetrahedron Lett.*, 1847 (1968).
(6) R. K. Hill and G. R. Newkome, *Tetrahedron Lett.*, 1851 (1968).
(7) E. E. Smissman and J. P. Li, *Tetrahedron Lett.*, 4601 (1968).
(8) (a) R. K. Hill and R. M. Carlson, *Tetrahedron Lett.*, 1157 (1964); (b) *J. Org. Chem.*, **30**, 2414 (1965).
(9) R. K. Hill, *J. Org. Chem.*, **26**, 4746 (1961).
(10) R. M. Carlson and R. K. Hill, *Org. Synth.*, **50**, 24 (1970).
(11) We are grateful to Mr. David P. Warren for carrying out this analysis.

Selective Removal of an Aromatic Methylenedioxy Group

Sidney Teitel* and Jay P. O'Brien

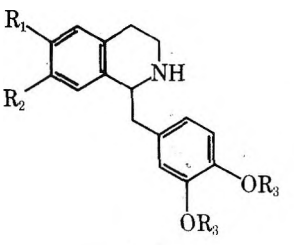
Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

Received December 2, 1975

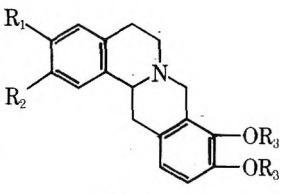
The preparation of tetrahydroisoquinolines devoid of substituents in one of the aromatic rings, such as **1e** and **2e**, by standard methods was recently described.[1] We now report the novel synthesis of related compounds based on the preferential O-demethylenation of dimethoxymethylenedioxy-substituted isoquinolines with boron trichloride[2] followed by elimination of the resulting catechol function via hydrogenolysis of the bistetrazoyl ether intermediate.[3]

To demonstrate the feasibility of removing a catechol function from a tetrahydroisoquinoline, the dimethoxycatechol **1b**[4] was treated with 2 equiv of 5-chloro-1-phenyl-1*H*-tetrazole in refluxing acetone containing anhydrous K_2CO_3 to furnish 70% of the bistetrazoyl ether **1c**. Hydrogenation of **1c** in acetic acid over Pd/C then provided 80% of the known[5] dimethoxy-substituted tetrahydroisoquinoline **1d**.

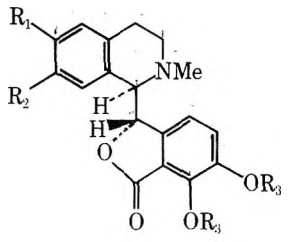
In applying this procedure to the selective removal of a methylenedioxy group from an isoquinoline, the dimethoxymethylenedioxy tetrahydroprotoberberine **2a**, obtained by borohydride reduction of the commercially available alkaloid berberine,[6] was O-demethylenated with 2 mol of boron trichloride in methylene chloride to provide 95% of the known[7] dimethoxycatechol **2b**. Etherification of **2b** with 5-chloro-1-phenyl-1*H*-tetrazole gave 95% of the bistetrazoyl ether **2c** which was then hydrogenolyzed to form 64% of the dimethoxy tetrahydroprotoberberine **2d** (58% overall from **2a**).



1b–e

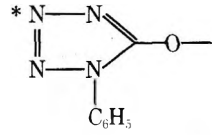


2a–e



3a–d

	R_1	R_2	R_3
a	$-OCH_2O-$		Me
b	OH	OH	Me
c	*	*	Me
d	H	H	Me
e	H	H	H



Finally, to test whether hydrogenolysis of an optically active substrate would cause racemization, the (+)-dimethoxydiphenolic phthalide **3b**, obtained in 81% yield by treating the alkaloid (−)-β-hydrastine (**3a**) with boron trichloride,[2] was converted into the (+)-bistetrazoyl ether **3c** (85% yield). Catalytic hydrogenation of **3c** in the presence of Pd/C then afforded 90% of the (−)-dimethoxyphthalide **3d** whose 1*R*,9*S* configuration was indicated by its NMR, ORD, and CD spectra.

Based on the above transformations, the novel elimination of a methylenedioxy group from a dimethoxymethylenedioxy isoquinoline has provided a facile route to a dimethoxy-substituted benzylisoquinoline, a tetrahydroprotoberberine, and a phthalideisoquinoline. The method appears to be applicable to secondary as well as tertiary amines and in the instant example did not affect the chiral centers of the substrate. Extension of this approach to other optically active isoquinolines is presently under investigation.

Experimental Section[8]

6,7-Bis(1-phenyl-1*H*-tetrazol-5-yloxy)-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1c HCl). A mixture of 5.3 g (15 mmol) of 6,7-dihydroxy-1-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline hydrochloride[5] (**1b** HCl), 6 g (30 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole, and 6.8 g (50 mmol) of anhydrous potassium carbonate in 300 ml of acetone was stirred and refluxed for 48 h, cooled, and filtered. The filtrate was evaporated, and the residue dissolved in ethanolic hydrogen chloride, evaporated, and crystallized from acetonitrile to give 6.6 g (70%) of **1c** HCl: mp 192–193 °C; NMR δ 2.8–3.8 (m, 6, 3 CH_2), 3.73 (s, 6, 2 OCH_3), 4.48 (m, 1, CH), 6.81 (m, 3, aromatic), 7.48, 7.51 (2 s, 10, aromatic), 7.80, 7.90 (2 s, 2, aromatic).

Anal. Calcd for $C_{32}H_{29}N_9O_4$·HCl: C, 59.68; H, 4.68; N, 19.70. Found: C, 59.24; H, 4.80; N, 19.28.

1-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (1d HCl). A solution of 4 g (6.6 mmol) of **1c** in 200 ml of acetic acid was hydrogenated at 50 psi in the presence of 2 g of 10% Pd/C at 40 °C in a Parr apparatus for 17 h and filtered. The filtrate was evaporated, the residue distributed between a mixture of 100 ml of 2 N hydrochloric acid and ethyl acetate, and the organic layer washed with 100 ml of water. The aqueous layers were combined, rendered alkaline with 10% sodium hydroxide, and extracted with ethyl acetate, and the organic phase was acidified with ethanolic hydrogen chloride, and evaporated. The residue was crystallized from a mixture of ethanol and ether to give 1.7 g (80%) of **1d** HCl, mp 228–230 °C, identical in mixture melting point, TLC, and NMR with authentic **1d** HCl.[4]

2,3-Bis(1-phenyl-1*H*-tetrazol-5-yloxy)-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine Hydrobromide (2c HBr). To a solution of 6.8 g (20 mmol) of (±)-canadine[6] (**2a**) in 200 ml of methylene chloride at room temperature was added 48 ml of a methylene chloride solution containing 4.8 g (40 mmol) of boron trichloride. After storage overnight, 50 ml of methanol was added over 15 min, the mixture evaporated, and the residue crystallized from methanol to give 5.8 g (80%) of 2,3-dihydroxy-9,10-dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine hydrochloride (**2b** HCl): mp 259–261 °C; NMR δ 2.6–3.7 (m, 8, 4 CH_2), 3.77, 3.79 (2 s, 6, 2 OCH_3), 4.2–4.8 (m, 1, CH), 6.08 (s, 1, aromatic), 6.15 (s, 1, aromatic), 7.01 (s, 2, aromatic), 8.91, 9.15 (b, 2, 2 OH).

Neutralization of the above hydrochloride followed by acidification with hydriodic acid and crystallization from methanol afforded **2b** HI, mp 200–202 °C (lit.[7] mp 201–203 °C).

In a manner similar to the procedure for **1c** HCl, 3.3 g (10 mmol) of **2b** HCl, 4 g (20 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole and 4.5 g (33 mmol) of anhydrous potassium carbonate in 200 ml of acetone afforded 6.5 g (95%) of **2c** HBr: mp 205–207 °C (from acetonitrile); NMR δ 2.9–4.2 (m, 6, 3 CH_2), 3.80 (s, 6, 2 OCH_3), 4.2–5.2 (m, 3, CH_2 + CH), 7.04 (s, 2, aromatic), 7.50, 7.53 (2 s, 10, aromatic), 7.84, 8.02 (2 s, 2, aromatic).

Anal. Calcd for $C_{33}H_{29}N_9O_4$·HBr: C, 56.90; H, 4.34; N, 18.10. Found: C, 56.89; H, 4.33; N, 18.35.

9,10-Dimethoxy-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine Hydrochloride (2d HCl). By the procedure given for the preparation of **1d** HCl, 10 g (16 mmol) of **2c** in 200 ml of acetic acid was hydrogenated in the presence of 3 g of 10% Pd/C to give 3 g (64%) of **2d** HCl: mp 234–235 °C (from ethanol); NMR δ 2.7–3.9 (m, 6, 3 CH_2), 3.76, 3.78 (2 s, 6, 2 OCH_3), 4.45 (b, 3, $^+NCH_2C_6H_5$ + CH), 6.99 (s, 2, aromatic), 7.24 (s, 2, aromatic), 7.38 (b, 2, aromatic), 12.0 (b, 1, NH^+).

Anal. Calcd for $C_{19}H_{21}NO_2$·HCl: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.54; H, 6.69; N, 4.35.

(+)-1(*R*)-1-[3(*S*)-6,7-Dimethoxyphthalidyl]-2-methyl-6,7-bis(1-phenyl-1*H*-tetrazol-5-yloxy)-1,2,3,4-tetrahydroisoquinoline (3c). In a manner similar to the procedure for **1c** HCl, 11 g (30 mmol) of (+)-1-(*R*)-[6,7-dimethoxy-3-(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline hydrochloride[2] (**3b** HCl), 12 g (66 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole, and 9 g (66 mmol) of anhydrous potassium carbonate in 600 ml of acetone provided, after crystallization from ethyl acetate, 16.7 g (85%) of **3c**: mp 162–163 °C; $[\alpha]_D$ +9.0° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 2.20–3.36 (m, 4, CH_2CH_2), 2.60 (s, 3, NCH_3), 3.9, 4.03 (2 s, 3 each, 2 OCH_3), 4.08, 5.58 (AB, 2, J_{vic} = 4 Hz, CHCH), 6.86, 7.18 (AB, 2, J_{ortho} = 8.5 Hz, aromatic), 7.18 (s, 1, aromatic), 7.39, 7.43 (2 s, 10, aromatic), 7.56 (s, 1, aromatic); uv max 220 nm (ε 53 000), 235 (11 900) (infl), 278 (2700) (infl), 310 (4400); ORD (*c* 0.659, 50% MeOH in 0.1 N HCl) $[\phi]_{65C}$ +920°, $[\phi]_{589}$ +320°, $[\phi]_{250}$ +75 000° (pk), $[\phi]_{218}$ −300 000° (tr); CD (*c* 0.659, 50% MeOH in 0.1 N HCl) $[\theta]_{348}$ 0, $[\theta]_{318}$ −3200, $[\theta]_{290}$ 0, $[\theta]_{276}$ +11 500, $[\theta]_{232}$ +232 500, $[\theta]_{219}$ 0, $[\theta]_{205}$ −290 000, $[\theta]_{200}$ −185 000.

Anal. Calcd for $C_{34}H_{29}N_9O_6$: C, 61.91; H, 4.43; N, 19.11. Found: C, 62.03; H, 4.36; N, 19.23.

(−)-1-(*R*)-[3(*S*)-6,7-Dimethoxyphthalidyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline (3d). By the procedure given for the preparation of **1d** HCl, 7 g (10 mmol) of **3c** in 200 ml of acetic acid was hydrogenated in the presence of 3 g of 10% Pd/C to give, after crystallization from a mixture of ether and petroleum ether (bp 30–60 °C), 3.1 g (90%) of **3d**: mp 89–90 °C; $[\alpha]_D$ −27.4° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) δ 2.10–3.00 (m, 4, CH_2CH_2), 2.56 (s, 3, NCH_3), 4.00 (2 s, 3 each, 2 OCH_3), 4.10, 5.52 (AB, 2, J_{vic} = 4 Hz, CHCH), 6.28, 7.00 (AB, J_{ortho} = 8.5 Hz, aromatic), 6.90 (m, 1, aromatic), 7.12 (m, 3, aromatic); uv max 209 nm (ε 36 500), 263 (1130) (sh), 272 (1150), 310 (4150); ORD (*c* 0.679, MeOH) $[\phi]_{650}$ +220°, $[\phi]_{589}$ +275°, $[\phi]_{420}$ +510°, $[\phi]_{400}$ +520°, $[\phi]_{380}$ +470°, $[\phi]_{305}$ +5300°, $[\phi]_{294}$ +7400° (pk), $[\phi]_{283}$ +7100° (tr), $[\phi]_{231}$ +45 000° (pk), $[\phi]_{209}$ −137 500° (tr); CD (*c* 0.679, MeOH) $[\theta]_{365}$ 0, $[\theta]_{315}$ −6500, $[\theta]_{285}$ −1000, $[\theta]_{258}$ −4100, $[\theta]_{250}$ 0, $[\theta]_{236}$ +35 000, $[\theta]_{220}$ +118 750, $[\theta]_{207}$ 0, $[\theta]_{200}$ −81 250.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.55; H, 6.27; N, 4.03.

Acknowledgments. We wish to thank the following members of our Physical Chemistry Department (Director, Dr. R. P. W. Scott): Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the NMR spectra, and Dr. V. Toome for the uv, ORD, and CD spectra.

Registry No.—**1b** HCl, 19384-75-9; **1c**, 58298-39-8; **1c** HCl, 58298-40-1; **1d** HCl, 3972-77-8; **2a**, 29074-38-2; **2b** HCl, 58298-41-2; **2b** HI, 58298-42-3; **2c**, 58298-43-4; **2c** HBr, 58298-44-5; **2d** HCl, 58298-45-6; **3b** HCl, 58298-46-7; **3c**, 58298-47-8; **3d**, 58298-48-9; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

References and Notes

(1) S. Teitel and J. P. O'Brien, *Heterocycles*, **2**, 625 (1974).
(2) S. Teitel, J. P. O'Brien, and A. Brossi, *J. Org. Chem.*, **37**, 3368 (1972).
(3) C. F. Barfknecht, R. V. Smith, and V. D. Reif, *Can. J. Chem.*, **48**, 2138 (1970), removed the catechol function in certain dihydroxytoluenes via hydrogenolysis of the bistetrazoyl ethers. While this procedure has not been previously applied to isoquinolines, A. Mondon and P.-R. Seidel, *Chem. Ber.*, **104**, 2937 (1971), deoxygenated a diphenolic precursor of an erythrina-type alkaloid by esterification with diethyl phosphite followed by cleavage with lithium in liquid ammonia.
(4) E. Yamato, *Chem. Pharm. Bull.*, **18**, 2038 (1970).
(5) D. Tedeschi, U.S. Patent 3 272 707 to Smith, Kline and French (1966).
(6) I. Sallay and R. H. Ayers, *Tetrahedron*, **19**, 1397 (1963).
(7) T.-C. Sun, S.-H. Lu, and J.-Y. Chin, *Yao Hseuh Hsueh Pao*, **12**, 314 (1965); *Chem. Abstr.*, **63**, 7062 (1965).
(8) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. NMR spectra were obtained on a Varian HA-100 instrument in Me_2SO-d_6 unless otherwise noted. Uv spectra were measured in ethanol with a Cary recording spectrophotometer Model 14M and optical rotations with a Perkin-Elmer instrument. Rotatory dispersion curves were determined at 23 °C with a Durrum-Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Reported yields are of isolated products homogenous to TLC.

Proton Transfer from the Monoanion of 1,1-Cyclopropanedicarboxylic Acid

Carl D. Slater

Department of Chemistry, Memphis State University, Memphis, Tennessee 38152

Received May 9, 1975

Hydrogen bonding in the monoanions of dicarboxylic acids has received much study since Brown and McDaniel suggested that extraordinarily high K_1/K_2 ratios arise from it.[1] Eberson and Wadsö[2] concluded that it is responsible for ratios greater than about 10 000, and Dygert, Muzii, and Saroff[3] proposed that it might be important in compounds with ratios larger than 1200.

Proton transfer rates confirm this interpretation. Eyring and co-workers have studied two families of dicarboxylic acids, and found that the rate of proton removal by hydroxide ion from the monoanion is inversely related to the strength of the hydrogen bond.[4] With dialkyl substituted malonic acids, the hydrogen bond strength is seemingly closely related to the bulk of the substituent groups. The diisopropyl compound has the greatest K_1/K_2 ratio and the smallest k_f for proton removal. It was suggested that spreading the angle between the alkyl groups results in decreasing the angle between the carboxyl groups, and that "closing the jaws" produces a stronger hydrogen bond.[4b]

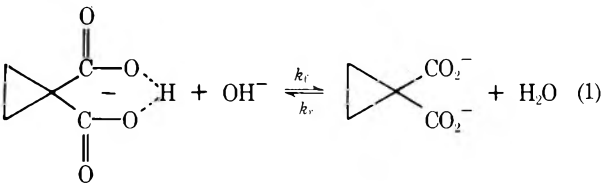
In this connection, a study of 1,1-cyclopropanedicarboxylic acid seemed of interest. X-ray crystallography has re-

Table I. Calculated Rate Constants, 25 °C, μ = 0.1 M (KNO_3)

pH	Total acid[a] × 10^4	Total indicator[b] × 10^6	$\tau \times 10^4$, s[c]	$k_f \times 10^{-8}$, l./mol s uncorr[d]	α[e]	$k_f \times 10^{-8}$, l./mol s corr[f]
8.14	2.610	5.439	2.65	1.07	1.10	2.17
8.33	5.150	8.000	1.91	1.11	1.06	2.20
8.37	5.150	12.23	2.06	1.11	1.47	2.57
8.37	5.150	17.29	2.02	1.13	2.08	3.18
8.39	5.150	10.299	2.09	1.14	1.17	2.33
8.44	2.610	5.439	3.72	1.31	0.54	1.90
8.52	5.208	4.786	2.62	1.14	0.38	1.53
8.62	5.208	2.393	2.73	1.31	0.14	1.47
8.66	2.604	4.786	3.89	1.72	0.24	2.02
8.69	2.604	8.000	3.83	1.80	0.37	2.25
8.80	2.083	2.393	4.48	1.93	0.08	2.01
8.84	2.604	2.393	4.08	1.89	0.07	1.96
8.84	1.572	2.393	4.46	2.25	0.07	2.31

[a] Total acid = $[A^{2-}] + [HA^-] + [H_2A]$. [b] Cresol red; p$K$ (μ = 0.1) = 8.20 (ref 4b). [c] Each relaxation time is an average of at least three runs. [d] Calculated from eq 4. [e] Correction factor defined in eq 2. [f] Calculated from eq 2.

vealed an angle of 118.3° between the carboxyl groups in this compound,[5] as contrasted to a corresponding angle of 110° in malonic acid.[6] This angle should be even less in the disubstituted malonic acids. The results of a temperature jump study of eq 1 are presented here.



$$+ H_2O \quad (1)$$

Experimental Section

1,1-Cyclopropanedicarboxylic acid was prepared by saponification of the commercially available (Aldrich) diethyl ester. Recrystallization from ethyl acetate–petroleum ether (bp 36–60 °C) gave white crystals, mp 140–140.5 °C (lit.[7] mp 136 °C). All other reagents were commercially available reagent grade materials that were used without further purification.

Solutions for measurement were prepared by mixing appropriate aliquots of 1.0 M potassium nitrate, ~1 × 10^{-2} M 1,1-cyclopropanedicarboxylic acid, and ~1 × 10^{-4} M indicator solution, and diluting with distilled, demineralized, freshly boiled water. The pH was adjusted by addition of a few drops of ~0.1 N sodium hydroxide. Stock solutions of cresol red were prepared in 95% ethanol. Final solutions thus contained ~0.5% (volume) ethanol, which was shown to have no effect on the heating time constant, and were 0.1 M in potassium nitrate. Final concentrations are shown in Table I. A portion of the solution for measurement was transferred to a tightly capped vial and thermostatted at 25 °C. The pH was recorded by means of a calibrated Orion 801 digital meter and a Sargent combination electrode. The remainder of the solution was thermostatted at 18 °C prior to the temperature jump experiment.

Temperature jump measurements were performed at 573 nm, the λ_{max} for cresol red, with a Durrum Instruments Model D-150 rapid kinetics spectrophotometer. Nominal jumps of 7 °C were effected. All analyses gave correlation coefficients of better than −0.99. Each relaxation time reported is the average of at least three measurements. The individual runs usually agreed to better than ±7%, and never exceeded ±15% deviation from the mean.

"Mixed" ionization constants were determined potentiometrically using a glass electrode and a calomel reference in solutions prepared so that μ = 0.1 M (potassium nitrate) at the midpoint of the titration.[8] Calculations were done as outlined by Albert and Serjeant.[9] Duplicate runs to establish pK_1^M using carbonate-free 0.1 N potassium hydroxide showed a scatter of ±0.02 pK units, while triplicate runs for pK_2^M using carbonate-free 1.0 N potassium hydroxide gave a scatter of ±0.01 pK units.

Results and Discussion

German, Jeffrey, and Vogel reported thermodynamic pK values of pK_1^T = 1.82 and pK_2^T = 7.43 for 1,1-cyclopropanedicarboxylic acid.[10] The corresponding values of the "mixed" pK's at μ = 0.1 M have now been found to be pK_1^M = 1.61 ± 0.02 and pK_2^M = 7.316 ± 0.01. The K_1/K_2 ratio ("mixed" constants) is therefore 509 000.

Rate constants for the forward reaction of eq 1 were evaluated using the coupled indicating equilibrium technique that has been detailed by Eigen and Kruse,[11] and elaborated by Eyring and co-workers.[4] The expression relating reaction time to rate constant is given in eq 2

$$\tau^{-1} = k_f([HA^-]/(1 + \alpha) + [OH^-] + K_w/K_2) \quad (2)$$

in which K_w is the ion product of water, K_2 is the second ionization constant of the acid, and α is the correction term $[HIn^-]/(K_w + [OH^-])$. The correction term allows for the perturbation of the coupled indicating equilibrium shown in eq 3

$$HIn^- + OH^- \rightleftharpoons In^{2-} + H_2O \quad (3)$$

and K_{In} refers to the equilibrium constant for this reaction. As has been noted,[4b,11] when α is small (<~0.5) the correction is small; but as α increases there is an apparent tendency for overcorrection. The uncorrected rate constants obtained from eq 4

$$\tau^{-1} = k_f([HA^-] + [OH^-] + K_w/K_2) \quad (4)$$

were shown to be satisfactory with two families of compounds.[4]

Table I contains the results of 13 runs made using a variety of concentrations. That the calculated rate constants belong to eq 1 can be inferred from the lack of indicator effects on the relaxation time. Entries 2–5 represent runs at constant total acid and pH with varying indicator concentrations. The relaxation times for these runs agree quite closely, however, suggesting that the indicator is not involved in the rate-determining step. The slight upward drift of the uncorrected rate constants as the pH is increased is thought to be insignificant, considering the wide variations of concentrations employed. The monoanion to hydroxide ion concentration ratio ranges from 32.7 at the lowest pH to 0.87 at the highest.

The best value of k_f can be obtained by use of eq 4. A plot for all points of $1/\tau$ vs. $[HA^-] + [OH^-]$ gives a straight line (correlation coefficient = 0.989) with least-squares slope of 8.0 × 10^7 l./mol s. In close agreement, a plot of $1/\tau$ vs. $[HA^-]/(1 + \alpha) + [OH^-]$ (eq 2), using the eight points for which $\alpha < 0.55$, gives a straight line (correlation coefficient = 0.987) with slope of 9.0 × 10^7 l./mol s. The inclusion of all points in this latter plot results in a correlation coefficient

of only 0.722, indicating once again the inadequacy of the correction term when it is large.

Both the K_1/K_2 ratio and the k_f value place 1,1-cyclopropanedicarboxylic acid in the same position within the series of substituted malonic acids previously studied. This finding reaffirms that the K_1/K_2 ratio and the k_f value are both reflections of the hydrogen bond strength in the monoanion, but suggests that the hydrogen bond strength is not necessarily related to the angle between the carboxyl groups.

Registry No.—1,1-Cyclopropanedicarboxylic acid, 598-10-7; monoanion of 1,1-cyclopropanedicarboxylic acid, 58325-50-1.

References and Notes

(1) D. H. McDaniel and H. C. Brown, *Science*, **118**, 370 (1953).
(2) L. Eberson and I. Wadsö, *Acta Chem. Scand.*, **17**, 1552 (1963).
(3) S. Dygert, G. Muzii, and H. Saroff, *J. Phys. Chem.*, **74**, 2016 (1970).
(4) (a) J. Haslam, E. Eyring, W. Epstein, G. Christiansen, and M. Miles, *J. Am. Chem. Soc.*, **87**, 1 (1965); (b) M. Miles, E. Eyring, W. Epstein, and R. Ostlund, *J. Phys. Chem.*, **69**, 467 (1965); (c) J. Haslam, E. Eyring, W. Epstein, R. Jensen, and C. Jaget, *ibid.*, 4247 (1965); (d) E. Eyring and J. Haslam, *ibid.*, **70**, 293 (1966); (e) R. Jensen, E. Eyring, and W. Walsh, *ibid.*, **70**, 2264 (1966); (f) M. Miles, E. Eyring, W. Epstein, and M. Anderson, *ibid.*, **70**, 3490 (1966); (g) J. Haslam and E. Eyring, *ibid.*, **71**, 4490 (1967).
(5) M. A. M. Meester, H. Schenk, and C. H. MacGillavry, *Acta Crystallogr., Sect. B*, **27**, 630 (1971).
(6) J. D. Goedkoop and C. H. MacGillavry, *Acta Crystallogr.*, **10**, 125 (1957).
(7) A. I. Vogel, *J. Chem. Soc.*, 1487 (1929).
(8) I thank Charles R. Wheatley for these determinations.
(9) A. Albert and E. P. Serjeant, "The Determination of Ionization Constants", 2d ed, Chapman and Hall, London, 1971, Chapter 3.
(10) W. German, G. Jeffrey, and A. Vogel, *J. Chem. Soc.*, 1624 (1935).
(11) M. Eigen and W. Kruse, *Z. Naturforsch., B*, **18**, 857 (1963).

Preparation of 9,10-Difluoroanthracene

Leon M. Stock* and Michael R. Wasielewski

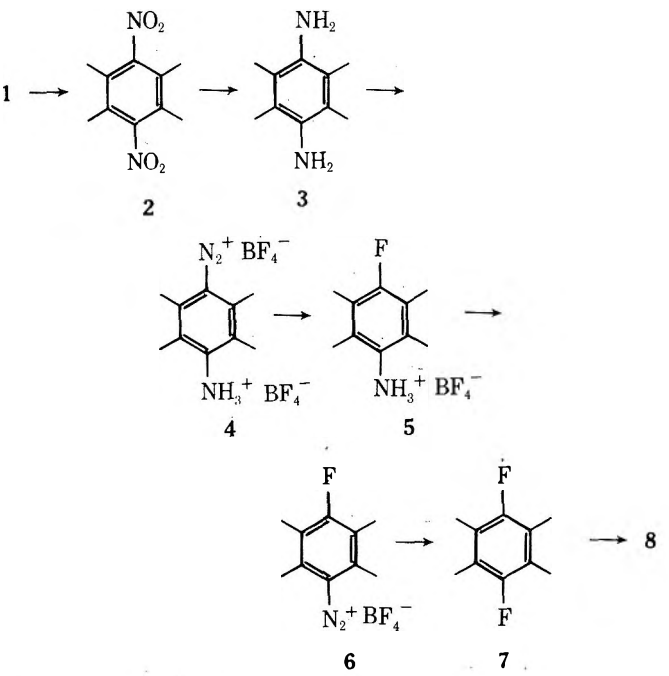
Department of Chemistry, University of Chicago, Chicago, Illinois 60637

Received December 9, 1975

Fluoroanthracene and 9,10-difluoroanthracene are valuable molecules for investigations in magnetic resonance and photochemistry.[1,2,3] These aryl fluorides are not readily prepared by the Schiemann reaction or its modifications.[4] Thus, the first successful preparation of 9-fluoroanthracene from 9-aminoanthracene used nitric oxide as the diazotization reagent.[5] However, 9-aminoanthracene is readily oxidized and widely variable amounts of the desired diazonium salt are obtained.[6] Dewar and Michl circumvented this problem by the use of 9-amino-1,2,3,4,5,6,7,8-octahydroanthracene as the starting material for conversion to 9-fluoro-1,2,3,4,5,6,7,8-octahydroanthracene and thence to 9-fluoroanthracene by dehydrogenation.[2] However, a new difficulty arises in the application of their procedure for the synthesis of 9,10-difluoroanthracene because charged substituents in the 10 position greatly enhance the rate of hydrolysis of 1,2,3,4,5,6,7,8-octahydroanthracene-9-diazonium tetrafluoroborate.[7] We wish to report a route, Chart I, for the synthesis of 9,10-difluoroanthracene in which these hydrolysis reactions are minimized. This known compound was previously obtained in less than 1% yield as a by-product in the reaction of fluorobenzyne with furan[8] and in 5% yield by the reaction of sulfur tetrafluoride with anthraquinone to yield 9,9,10,10-tetrafluoro-9,10-dihydroanthracene followed by iron gauze catalyzed defluorination.[9]

Octahydroanthracene (1) was converted to the diamine **3** in good yield using known procedures.[10] Not unexpectedly,

Chart I



the treatment of **3** in aqueous media with nitrous acid prepared from either sulfuric, hydrochloric, or fluoroboric acid led to small yields of octahydroanthraquinone as the only isolable product. This reaction was incomplete because the salts of **3** are insoluble in the aqueous media. The use of tetrahydrofuran as a cosolvent provided the quinone in excellent yield. As noted, the diazonium ions of duridines are unstable in water;[7] this problem is compounded in the diazonium derivatives of **3** with their activating ammonium and diazo groups. We were able to circumvent this difficulty through a reduction in the polar character of the medium using ethanol as a solvent and isoamyl nitrite as the diazotization agent in the presence of excess 48% fluoroboric acid. Under these conditions, **3** was cleanly and rapidly converted to **4** which precipitated. This salt is stable and may be stored for several weeks. Salt **4** was decomposed thermally in vacuo to give **5**, which is a useful intermediate for the preparation of many other fluoroanthracenes. Compound **5** was diazotized by the procedure used for **3**. The product, **6**, was precipitated by the addition of ether. Diazonium salt **6** is unstable and cannot be stored for more than 1 day without noticeable deterioration. Thermal decomposition of **6** in vacuo gave **7** in 90% yield. Dehydrogenation of **7** with dicyanodichloroquinone proceeded successfully to yield 57% of 9,10-difluoroanthracene.

Experimental Section

All melting points are corrected. Varian equipment was used to record the NMR spectra at 60 or 100 MHz with tetramethylsilane as an internal reference and fluorine NMR spectra at 56.4 or 94.1 MHz. Infrared and ultraviolet spectra were recorded with Beckman IR-10 and Cary 14 instruments, respectively. Octahydroanthracene (Columbia Organic Chemicals Co.) was used without further purification. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

9,10-Dinitro-1,2,3,4,5,6,7,8-octahydroanthracene (2). Chloroform (900 ml) and concentrated sulfuric acid (450 ml) were added to a flask fitted with a mechanical stirrer, thermometer, and addition funnel. The mixture was cooled to −20 °C and 100% nitric acid (27 ml) was added cautiously. A solution of octahydroanthracene (27.0 g, 0.145 mol) in chloroform (150 ml) was added dropwise to the stirred acid mixture over 30 min maintaining the temperature below −10 °C. The resulting dark red mixture was stirred for 15 min longer, poured onto ice, and extracted with chloroform (6 × 300 ml). The extracts were combined, washed to neutrality with saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was suspended in ethanol (500 ml) and

heated to reflux. After cooling the product was collected and washed repeatedly with cold ethanol. Air drying provided light tan crystals of **2** [29.2 g, 73%, mp 302–305 °C (lit.[10] mp 305 °C)]: NMR ($CDCl_3$) δ 1.73 (m, 8 H), 2.54 (m, 8 H); ir (KBr) 1540 (s, N–O), 1375 cm^{-1} (s, N–O).

9,10-Diamino-1,2,3,4,5,6,7,8-octahydroanthracene (3). A hot solution of stannous chloride dihydrate (143 g, 630 mmol) in concentrated hydrochloric acid (180 ml) was cautiously added to a refluxing solution of **2** (15.0 g, 54 mmol) in glacial acetic acid (635 ml). The mixture refluxed vigorously during the addition of the tin solution. The mixture was refluxed for 18 h. The tin salt was collected after the reaction mixture was cooled to ambient temperature. The crude solid was washed repeatedly with ether and air dried. The dry tin salt was taken up in 20% sodium hydroxide solution (400 ml). The liberated amine was extracted into methylene chloride (3 × 200 ml). The extracts were washed thoroughly with water and dried over magnesium sulfate. Removal of the solvent yielded golden crystals of **3** [9.3 g, 79%, mp 188–189 °C (lit.[10] 188–189 °C)]: NMR ($CDCl_3$) δ 1.82 (m, 8 H), 2.46 (m, 8 H), 3.13 (s, br, 4 H); ir (KBr) 3300, 3400 (m, N–H), 1640 cm^{-1} (s, N–H).

1,2,3,4,5,6,7,8-Octahydroanthracene-9-ammonium-10-diazonium Fluoroborate (4). A solution of **3** (10.8 g, 50 mmol) in ethanol (100 ml) and 48% fluoroboric acid (54.0 g) was cooled to −5 °C. The vigorously stirred purple solution was diazotized by the dropwise addition of isoamyl nitrite (14.0 g, 120 mmol) with the temperature kept below 0 °C. The mixture became greenish-yellow as a precipitate formed. Ten minutes after the addition was complete cold ether (250 ml) was added and the stirring maintained for 5 min longer. The bright yellow crystals were collected and washed thoroughly with cold ether. Air drying provided **4** (11.6 g, 58%, mp 160 °C dec); NMR ($CDCl_3$) δ 1.97 (m, 8 H), 2.58 (m, 8 H); ^{19}F NMR ($CDCl_3$) +148.2 ppm (s, br) relative to external $CFCl_3$; ir (KBr) 3360 (s, N–H), 2160 (s, $^+N{\equiv}N$), 1660 (s, N–H), 1570 (s, N–H), 1050 cm^{-1} (s, br, B–F).

9-Fluoro-1,2,3,4,5,6,7,8-octahydroanthracene-10-ammonium Fluoroborate (5). A mixture of **4** (11.7 g, 29 mmol) and sand (120 g) was decomposed in a sublimator at 1 Torr and 160 °C over 8 h to yield colorless crystals of **5** (6.9 g, 78%, mp 180–182 °C dec): NMR ($CDCl_3$) δ 1.81 (m, 8 H), 2.70 (m, 8 H), 6.42 (s, 3 H); ^{19}F NMR (Me_2SO) +120.4 (s), +146.2 ppm (s), relative to external $CFCl_3$; ir (KBr) 3230 (s, N–H), 1585 (s, N–H), 1510 (m, N–H), 1080 cm^{-1} (s, br, B–F).

The fluoro amine was liberated by the treatment of **5** with excess potassium hydroxide in ethanol. 9-Fluoro-10-amino-1,2,3,4,5,6,-7,8-octahydroanthracene (mp 107–109 °C) was obtained in quantitative yield: NMR ($CDCl_3$) δ 1.82 (m, 8 H), 2.58 (m, 8 H), 3.37 (s, br, 2 H); ^{19}F NMR ($CDCl_3$) +131.1 ppm (s), relative to external $CFCl_3$; ir (KBr) 3490, 3300 (s, N–H), 2960 (s, C–H), 1660 (s, N–H), 1070 cm^{-1} (s, C–F); mass spectrum *m/e* calcd for $C_{14}H_{18}NF$, 219.1422; found, 219.1429; *m/e* (rel intensity) 219 (100), 218 (13), 217 (12), 203 (6), 191 (24), 190 (7), 176 (10), 161 (7).

Anal. Calcd for $C_{14}H_{18}NF$: C, 76.68; H, 8.27; N, 6.38; F, 8.66. Found: C, 76.91; H, 8.34; N, 6.34; F, 8.59.

9-Fluoro-1,2,3,4,5,6,7,8-octahydroanthracene-10-diazonium Fluoroborate (6). A suspension of **5** (6.0 g, 19.5 mmol) in ether (55 ml) containing 48% fluoroboric acid (6.5 g) was cooled to −5 °C. The vigorously stirred mixture was diazotized by dropwise addition of isoamyl nitrite (6.5 g, 56 mmol) maintaining the temperature below 0 °C. Stirring and cooling were maintained for 30 min following the addition during which time the mixture became homogeneous. Cold ether (500 ml) was added and the mixture stirred vigorously for 5 min longer. The yellow precipitate was filtered, washed with cold ether, and quickly air dried to yield **6** (5.5 g, 89%, mp 100 °C dec): ir (KBr) 2240 (s, $^+N{\equiv}N$), 1060 cm^{-1} (s, br, B–F). Because it was unstable, this salt was promptly converted to **7**.

9,10-Difluoro-1,2,3,4,5,6,7,8-octahydroanthracene (7). A mixture of **6** (6.6 g, 21 mmol) and sand (66 g) was decomposed in a sublimator at 1 Torr and 100 °C for 12 h to give colorless crystals of **7** [4.16 g, 90%, mp 145–146 °C (sealed tube)]: NMR ($CDCl_3$) δ 1.73 (m, 8 H), 2.56 (m, 8 H); ^{19}F NMR ($CDCl_3$) +126.2 ppm (s), relative to external $CFCl_3$; ir (KBr) 1040 (s, C–F), 960, 835 cm^{-1} (s, C–H); mass spectrum *m/e* calcd for $C_{14}H_{16}F_2$, 222.1219; found, 222.1222; *m/e* (rel intensity) 222 (100), 221 (9), 220 (8), 194 (89), 193 (12), 181 (17), 180 (20), 179 (24), 178 (6), 177 (14), 167 (6), 165 (16), 164 (13), 151 (10), 146 (7), 133 (6).

Anal. Calcd for $C_{14}H_{16}F_2$: C, 75.65; H, 7.26; F, 17.10. Found: C, 75.81; H, 7.32; F, 17.00.

9,10-Difluoroanthracene (8). A solution of **7** (4.6 g, 19 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (18.4 g, 81 mmol) in toluene (184 ml) was refluxed under nitrogen for 8 h. The solution was cooled and filtered. The filtrate was concentrated prior to chromatography on neutral alumina (5 × 25 cm) with benzene. Removal of the solvent provided long yellow needles of **8** [2.58 g, 57%, mp 164–165 °C (lit.[8] 170–172 °C)]: NMR ($CDCl_3$) δ 7.51 (m, 4 H), 8.22 (m, 4 H); ^{19}F NMR ($CDCl_3$) +131.9 ppm (m), relative to external $CFCl_3$; ir (KBr) 1030 (s, , C–F), 1370, 745 cm^{-1} (s, C–H); mass spectrum *m/e* calcd for $C_{14}H_8F_2$, 214.0693; found, 214.0622; *m/e* (rel intensity) 214 (100), 107 (9), 94 (5). Recrystallization of the product from ethanol did not alter the melting point. Consequently, an analysis was obtained.

Anal. Calcd for $C_{14}H_8F_2$: C, 78.50; H, 3.76; F, 17.74. Found: C, 78.36; H, 3.82; F, 17.55.

Acknowledgment. We are indebted to the National Science Foundation, the Block Fund of the University of Chicago, and the Fannie and John Hertz Foundation for the support of this work.

Registry No.—**1**, 1079-71-6; **2**, 23585-27-5; **3**, 23585-28-6; **4**, 58325-07-8; **5**, 58325-09-0; **5** free amine, 58325-08-9; **6**, 58325-11-4; **7**, 58325-12-5; **8**, 1545-69-3.

References and Notes

(1) M. J. S. Dewar and J. Michl, *Tetrahedron*, **26**, 375 (1970).
(2) G. L. Anderson, R. C. Parish, and L. M. Stock, *J. Am. Chem. Soc.*, **93**, 6984 (1971).
(3) N. C. Yang, D. M. Shold, J. K. McVey, and B. Kim, *J. Chem. Phys.*, **62**, 4559 (1975).
(4) H. Suschitzky, *Adv. Fluorine Chem.*, **4**, 1 (1965).
(5) J. Rigaudy and J. Barcelo, *C. R. Acad. Sci.*, **258**, 4799 (1964).
(6) G. L. Anderson and L. M. Stock, *J. Org. Chem.*, **36**, 1140 (1971).
(7) S. Fattuta, *Ric. Sci., Parte 2: Sez. A*, **2**, 656 (1962).
(8) G. Wittig and H. Härle, *Justus Liebigs Ann. Chem.*, **623**, 17 (1959).
(9) A. L. Logothetis, *J. Org. Chem.*, **31**, 3686 (1966).
(10) B. Eistert, H. Fink, J. Riedinger, H. G. Hahn, and H. Dürr, *Chem. Ber.*, **102**, 3111 (1969).

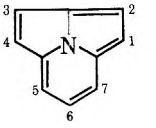
Synthesis of 1-Azacycl[3.2.2]azine

Michael DePompei and William W. Paudler*

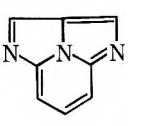
Department of Chemistry, The University of Alabama, University, Alabama 35486

Received December 23, 1975

Some time ago,[1] we expanded the chemistry of Boekelheide's[2] cycl[3.2.2]azine (**1**) to include the synthesis of 1,4-diazacycl[3.2.2]azine (**2**). This compound, in strong contrast



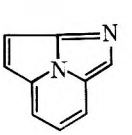
1



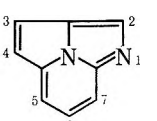
2

to the acid stability of **1**, is readily hydrolyzed to 5-aminoimidazo[1,2-*a*]pyridine-3-carboxaldehyde. In addition to this derivative, we recently described[3] the synthesis of 2-azacycl[3.2.2]azine (**3**) and established, among other chemical properties, that this ring system is stable to aqueous acid.

These hydrolytic results prompted us to prepare 1-azacycl[3.2.2]azine (**4**), a compound of "intermediate" structure between **1** and **2**.



3

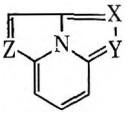


4

Results and Discussion

An application of the techniques developed for the synthesis of 2-azacycl[3.2.2]azine (**3**) to 5-methylimidazo[1,2-*a*]pyridine (**5**) afforded the desired compound as outlined in Scheme I.

Table I. ^{1}H NMR Spectral Parameters of Some Cycl[3.2.2]azines[a]



1. X = Y = Z = CH
2. X = CH; Y = Z = N
3. Y = Z = CH; X = N
4. X = Y = CH; Z = N

Compd	Chemical shifts, τ						
	H_1	H_2	H_3	H_4	H_5	H_6	H_7
1	2.81	2.50	2.50	2.81	2.14	2.41	2.14
2		1.30	1.30		1.88	1.88	1.88
3	1.55		2.35	2.70	2.04	2.49	2.18
4		1.42	2.34	2.54	2.06	2.02	1.91
6		0.90	2.14		1.06	1.40	1.30[b]
8		1.05	1.82	2.00	multiplet centered at 1.36[c]		
10		1.46	2.30		2.04	1.90	2.00

	Coupling constants, Hz
1	$J_{56} = 8.0, J_{1,2} = 4.2$
2	$J_{56} = 8.0$
3	$J_{56} = 7.8, J_{62} = 7.0, J_{34} = 4.7, J_{1,4} = 1.0$
4	$J_{56} = J_{67} = 8.0, J_{34} = 4.8$
6	$J_{56} = 8.0, J_{67} = 8.0$
10	$J_{56} = 8.0, J_{67} = 8.0$

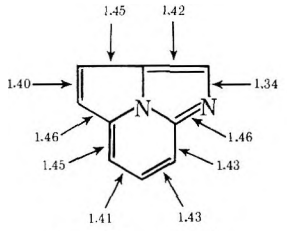
[a] Dilute solutions in $CDCl_3$. [b] TFAA solvent. [c] D_2O solvent.

The structures of compound **4** and its synthetic precursors (**6** and **7**) were established in the usual manner (synthetic sequence, elemental and mass spectral analyses).

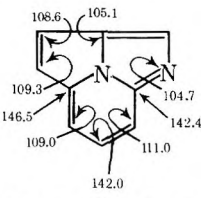
A comparison of the ^{1}H NMR spectrum of 1-azacycl[3.2.2]azine (**4**) with that of cycl[3.2.2]azine (**1**) demonstrates the anisotropic peri effect on N-1 upon the chemical shift of H-7 (0.23 ppm deshielding). This effect has been estimated to be about −0.15 to −0.20 ppm in quinolines, polyazaindenes, and related ring systems.[4]

The generally more deshielded chemical shifts of H-3 and H-4 simply reflect the "electron drift" into the imidazole portion of the 1-azacycl[3.2.2]azine (**4**) in comparison to the symmetrical cycl[3.2.2]azine (**1**). Another point of interest, implying more isolated double bond character for C_3–C_4, is the fact the J_{34} (4.8 Hz) is larger in compound **4** than in compound **1**. This coupling constant is consistent with an estimated bond order of 0.8.[6]

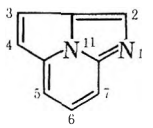
Geometry-optimized MINDO/2 calculations[5] gave the following ground-state parameters for compound **4**:



Bond lengths (Å)



Bond angles (deg)

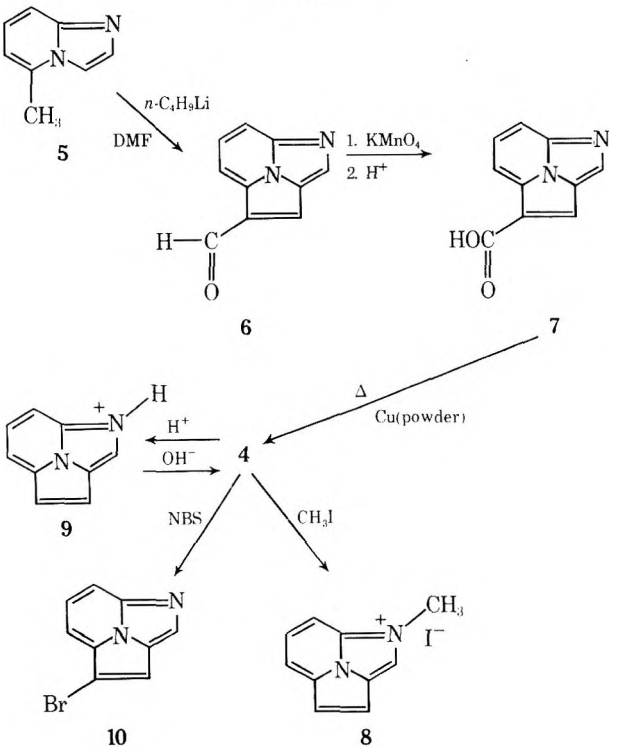


MINDO/2 total electron densities[7] (exclusive of $1s^2$)

N-1 = 5.16
C-2 = 3.88
C-3 = 3.96
C-4 = 4.13
C-5 = 4.01
C-6 = 3.98
C-7 = 4.05
N-11 = 4.91

The most significant observations of these calculations, as applied to this work, are that C_3–C_4 is the shortest carbon–carbon double bond and that C-2 is the most electropositive carbon atom in the ring system. The former observation is consistent with our comments regarding the nature of C_3–C_4 in the 2-azacycl[3.2.2]azine—as a rather "isolated" double bond.

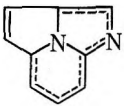
Scheme I



Thus, we suggest that the ground-state structure of 1-azacycl[3.2.2]azine is, perhaps, best represented by formulation **11**.

That the central nitrogen atom is not significantly involved in the delocalization is evident from the fact that its charge density is 4.91 (exclusive of the $1s^2$ electrons).

Bromination of compound **4** affords a monobromo deriva-

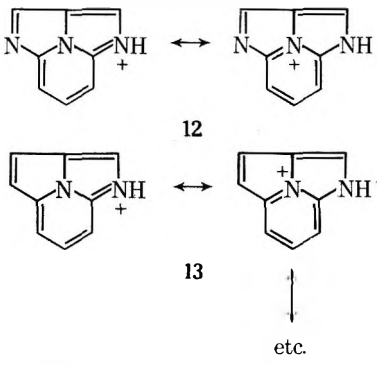


11

tive whose ^1H NMR spectrum (see Table I) clearly identifies it as the 4-bromo derivative (**10**). This is, of course, in agreement with the results of electrophilic substitution studies on cycl[3.2.2]azine and on its 2-aza derivative.[2]

Methylation of compound **4**, as expected, affords a *N*-methyl quaternary salt (**8**) (see Table I). The ^1H NMR spectrum of this compound is essentially superimposable upon that of the parent compound **4** in aqueous acid. The intriguing result is that the 1-azacyl[3.2.2]azine (**4**) is stable to aqueous acid, in contrast to the great acid lability of the 1,4-diaza analogue **2**.

If we consider the monoprotonated forms of compounds **2** and **4** (structures **12** and **13**), as being initially formed, the acid



12

13

etc.

lability of the HC=N– bond, an imine in **12**, as compared to the –CH=CH– bond in **13**, is understandable. Thus, the hydrolytic instability of the protonated diazacyl[3.2.2]azine (**12**) as compared to the monoazacycl[3.2.2]azine (**13**) is readily explained.

Experimental Section[8]

4-Formyl-1-azacycl[3.2.2]azine (6). To a stirred solution of 45 ml of 2 M BuLi (0.908 mol) in 20 ml of sodium-dried tetrahydrofuran (THF) was added tetramethylethylenediamine (TMEDA, 10.53 g, 0.0908 mol) under a N_2 atmosphere and at −15 °C. 5-Methylimidazo[1,2-*a*]pyridine (5.00 g, 0.0379 mol) in 30 ml of dried THF was then added to the solution. After 1 min, a solution of dry dimethylformamide (5.52 g, 0.0758 mol) in 30 ml of THF was added all at once. The resulting blue-green solution was stirred for an additional 30 min, after which time 100 ml of water was added to the reaction mixture. The mixture was extracted with $CHCl_3$ (3 × 150 ml), the combined extracts were dried over anhydrous Na_2CO_3 and filtered, and the solvent was evaporated in vacuo. The resulting brown solid was chromatographed over Al_2O_3 (grade III) and eluted with benzene. Evaporation of the solvent afforded a yellow solid which was recrystallized from chloroform to yield 0.580 g (9%), mp 210–212 °C. Anal. Calcd for $C_{10}H_6N_2O$: C, 70.59; H, 3.52; N, 16.47. Found: C, 70.35; H, 3.40; N, 16.22.

1-Azacycl[3.2.2]azine-4-carboxylic Acid (7). To a solution of 4-formyl-1-azacycl[3.2.2]azine (0.10 g, 0.588 mmol) in 10 ml of acetone was added 5 ml of water. Solid $KMnO_4$ (220 mg, 1.4 mmol) was added all at once, and the resulting solution was stirred for 1 h. The solution was treated with a small amount of solid $NaHSO_3$ and filtered through a Celite pad. The filtrate was evaporated in vacuo to approximately 5 ml and carefully acidified with 2 N HCl. The white precipitate was filtered and dried to yield 85 mg (75%) of 1-azacycl[3.2.2]azine-4-carboxylic acid, which decomposes at its melting point (318–320 °C).

1-Azacycl[3.2.2]azine (4). In a 10-ml distillation flask fitted with a short path condenser was placed a mixture of 1-azacycl[3.2.2]azine-4-carboxylic acid (0.350 g, 1.88 mmol) and Cu powder (400 mg). The flask and its contents were heated with a flame until a greenish liquid collected on the walls of the flask and condenser. The liquid was collected by dissolving it in $CHCl_3$. The $CHCl_3$ solution was placed on a short (5 cm) alumina column (grade III) and eluted with $CHCl_3$. Evaporation of the $CHCl_3$ eluent afforded 1-azacycl[3.2.2]azine (205 mg, 77%) as a low-melting solid. The picrate of compound **4** was obtained, mp 218–220 °C, and was analyzed. Anal. Calcd for $C_{15}H_9N_5O_7$: C, 48.52; H, 2.42; N, 18.87. Found: C, 48.42; H, 2.20; N, 18.35.

N_1-Methyl-1-azacycl[3.2.2]azinium Iodide (8). To a solution of 1-azacycl[3.2.2]azine (50 mg, 0.35 mmol) in 10 ml of reagent-grade acetone was added 0.5 ml of CH_3I. The resulting solution was allowed to stand at room temperature for 15 h. The crystalline precipitate was collected and washed with 5 ml of cold reagent-grade acetone to yield N_1-methyl-1-azacycl[3.2.2]azinium iodide (85 mg, 84%) as a brick-red solid, mp 142–144 °C. Anal. Calcd for $C_{10}H_9N_2I$: C, 42.24; H, 3.16; N, 9.86. Found: C, 42.05; H, 2.89; N, 9.50.

4-Bromo-1-azacycl[3.2.2]azine (10). To a solution of 1-azacycl[3.2.2]azine (100 mg, 0.70 mmol) in 10 ml of $CHCl_3$ was added *N*-bromosuccinimide (0.310 mg, 1.75 mmol). The resulting solution was stirred for 5 h at room temperature and filtered, and the filtrate was evaporated to dryness. The residue was placed on a short (5 cm) alumina column (grade III) and eluted with benzene. Evaporation of the benzene afforded a yellow solid which was sublimed to yield 95 mg (62.1%) of 4-bromo-1-azacycl[3.2.2]azine, mp 81–82 °C. Anal. Calcd for $C_9H_5N_2Br$: C, 48.87; H, 2.26; N, 12.67. Found: C, 48.51; H, 2.05; N, 12.48.

Registry No.—**1**, 209-81-4; **2**, 10558-77-7; **3**, 54384-90-6; **4**, 209-83-6; **4** picrate, 58374-91-7; **5**, 933-69-7; **6**, 58374-92-8; **7**, 58374-93-9; **8**, 58374-94-0; **10**, 58374-95-1.

References and Notes

(1) W. W. Paudler, R. A. Van Dahm, and Y. N. Park, *J. Heterocycl. Chem.*, **9**, 81 (1972).
(2) A. Galbraith, T. Small, R. A. Barnes, and V. Boekelheide, *J. Am. Chem. Soc.*, **83**, 452 (1961).
(3) O. Fuentes and W. W. Paudler, *J. Org. Chem.*, **40**, 1210 (1975).
(4) W. W. Paudler, "Nuclear Magnetic Resonance", Allyn and Bacon, Boston, Mass., 1975, p 107.
(5) N. C. Baird and M. J. S. Dewar, *J. Chem. Phys.*, **50**, 1262 (1969).
(6) W. B. Smith, W. H. Watson, and S. Chirangeevi, *J. Am. Chem. Soc.*, **89**, 1438 (1967).
(7) The electron densities given are exclusive of the $1s^2$ electrons.
(8) The ^1H NMR spectra were obtained with a Varian HA-100 spectrometer. Elemental analyses were done by Atlantic Microlab, Inc., Atlanta, Ga.

Reactions of Dichlorine Heptoxide with Olefins[1]

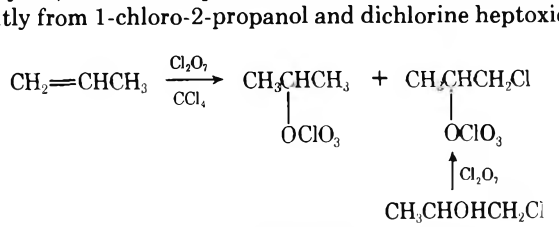
Kurt Baum

Flucrochem, Inc., Azusa, California 91702

Received December 15, 1975

Dichlorine heptoxide in carbon tetrachloride is a conveniently accessible perchlorylation reagent, and its reactions with alcohols,[2] amines,[3] ethers,[4] and alkyl iodides[5] have been described. As a continuation of this study of the utility of the reagent the present investigation deals with its reactions with olefins.

Propene was found to react with dichlorine heptoxide in carbon tetrachloride to give isopropyl perchlorate (32%) and 1-chloro-2-propyl perchlorate (17%). The yields of these impact sensitive materials were determined by NMR using a quantitative internal standard. Isopropyl perchlorate was identified by spectral comparison with an authentic sample.[2] A sample of 1-chloro-2-propyl perchlorate was isolated and analyzed, and the compound was also synthesized independently from 1-chloro-2-propanol and dichlorine heptoxide.



cis-2-Butene reacted with dichlorine heptoxide to give 3-chloro-2-butyl perchlorate (30%), 3-keto-2-butyl perchlorate (2%), and 2,3-butane diperchlorate (5%). When the reaction

was repeated with added lithium perchlorate in suspension, the yield of 3-keto-2-butyl perchlorate was increased to 20%, but the other products were unaffected. The 2,3-butane diperchlorate was identified spectrally by comparison with the compound prepared from 2-butene oxide and dichlorine heptoxide.[4] The other products were isolated by GLC and characterized. The isolation of 3-keto-2-butyl perchlorate is particularly noteworthy in that it is the first reported example of a carbonyl compound with a covalent perchlorate group.

$$\begin{matrix} CH_3 & CH_3 \\ | & | \\ HC{=}CH \end{matrix} \xrightarrow{Cl_2O_7} CH_3CH(OClO_3)CH(OClO_3)CH_3 +$$

$$CH_3CHClCH(OClO_3)CH_3 + CH_3\overset{O}{\overset{\|}{C}}CH(OClO_3)CH_3$$

trans-2-Butene gave the same product mixture that *cis*-2-butene did, with the exception of the stereochemistry of the 3-chloro-2-butyl perchlorate. This product from the two olefins was distinguishable by GLC, and in each case only one isomer was observed. Structural assignments were made by synthesizing 3-chloro-2-butyl perchlorate from dichlorine heptoxide and 3-chloro-2-butanol of known configuration. Lucas and Garner[6] showed that the addition of hydrochloric acid to the 2-butene oxides is stereospecifically a trans addition; *cis*-2-butene oxide gives *threo*-3-chloro-2-butanol and *trans*-2-butene oxide gives *erythro*-3-chloro-2-butanol. The reaction of dichlorine heptoxide with alcohols should not affect the carbon stereochemistry. It was found that the 3-chloro-2-butyl perchlorate thus prepared from *cis*-2-butene oxide was identical with that obtained from *cis*-2-butene and dichlorine heptoxide, and that from *trans*-2-butene oxide was identical with the *trans*-2-butene product. Thus, the formation of 3-chloro-2-butyl perchlorate from 2-butene and dichlorine heptoxide is a trans addition.

A completely substituted olefin, 2,3-dimethyl-2-butene, was also examined. A product insoluble in carbon tetrachloride was obtained that was identified as a mixture of 2,2-diperchloratopropane and 2,2-dimethyl-3,3-diperchloratobutane. The former was prepared previously from acetone and perchloric acid,[7] and the latter was characterized by the proximity of the NMR chemical shift of the methyl adjacent to the perchlorates to that of 2,2-diperchloratopropane. Treating the mixture in methylene chloride with sodium bicarbonate gave acetone and pinacolone.

$$(CH_3)_2C{=}C(CH_3)_2 \xrightarrow{Cl_2O_7} (CH_3)_2C(OClO_3)_2 + CH_3C(OClO_3)_2C(CH_3)_3$$

Both 2,2-diperchloratopropane and 2,2-dimethyl-3,3-diperchloratobutane were prepared, in yields of 70 and 52%, respectively, from the ketones and dichlorine heptoxide in carbon tetrachloride. This reaction is more convenient and provides higher yields than the anhydrous perchloric acid method[7] for preparing *gem*-diperchlorates.

$$R_2C{=}O + Cl_2O_7 \longrightarrow R_2C(OClO_3)_2$$

Electronegatively substituted olefins were unreactive with dichlorine heptoxide in carbon tetrachloride. Thus, 1,1-difluoroethylene and allyl chloride gave only trace amounts of 1,1-difluoroethyl perchlorate and 1-chloro-2-propyl perchlorate, respectively, the perchloric acid adducts, apparently resulting from the spurious introduction of water. The yields of these perchlorates were increased to 76 and 91%, respectively by introducing water into the reaction mixture. Under these conditions, propene gave a 65% yield of isopropyl perchlorate and a 10% yield of 1-chloro-2-propyl perchlorate. Ethylene was also unreactive with dichlorine heptoxide, but with water added, a 63% yield of ethyl perchlorate was obtained. The addition of water to the dichlorine heptoxide solution is an experimentally convenient source of small amounts of anhydrous perchloric acid for additions to olefins under mild conditions.

$$CH_2{=}CF_2 \xrightarrow[CCl_4]{Cl_2O_7,H_2O} CH_3CF_2OClO_3$$

$$CH_2{=}CHCH_2Cl \longrightarrow CH_3CH(OClO_3)CH_2Cl$$

$$CH_2{=}CHCH_3 \longrightarrow (CH_3)_2CHOClO_3 + CH_3CH(OClO_3)CH_2Cl$$

$$CH_2{=}CH_2 \longrightarrow CH_3CH_2OClO_3$$

A yellow gas soluble in carbon tetrachloride that causes NMR signal broadening, presumably chlorine dioxide, was generally observed in the olefin–dichlorine heptoxide reaction mixtures. This compound would be formed when dichlorine heptoxide functions as an oxidizing agent; oxidation products have been observed previously in dichlorine heptoxide reactions.[4,5] Chlorine dioxide has been reported[8] to react with olefins to give 2-chloro alcohols formed by trans additions, as well as epoxides and other oxidation products. This compound provides a possible route to the observed products from 2-butene, although other mechanisms are possible. The formation of the diperchlorate from the epoxide has been reported previously.[4] The oxidation reactions also provide water, leading to perchloric acid adducts. The products from 2,3-dimethyl-2-butene are also attributable to oxidation reactions. Pinacolone would be obtained by the pinacol rearrangement of the epoxide or glycol, and acetone would be formed by an oxidative cleavage similar to the well-known reactions of periodic acid.

Experimental Section

NMR spectra were recorded with a Varian T-60 spectrometer and ir spectra were recorded with a Perkin-Elmer 700 spectrometer. A Varian 920 chromatograph was used for GLC determinations.

Dichlorine heptoxide was utilized as a 0.3 M reagent in carbon tetrachloride, prepared by the previously described method[2]. *Caution:* alkyl perchlorates are sensitive explosives if not diluted with solvent, and previously noted precautions should be observed.[2]

Reaction of Propene with Dichlorine Heptoxide. Dichlorine heptoxide in carbon tetrachloride (2 ml, 0.6 mmol) was placed in a 25-ml flask with a magnetic stirrer and fitted with a stopcock syringe adapter. Air was partially removed by syringe and 3 ml (0.6 mmol) of propene was added. The mixture was stirred for 24 h. A yellow gas soluble in carbon tetrachloride, presumably ClO_2, was removed by a brief application of vacuum. NMR analysis of the carbon tetrachloride solution showed isopropyl perchlorate (32% yield) and 1-chloro-2-propyl perchlorate (17%). Isopropyl perchlorate was identified by comparison with an authentic sample.[2] An analytical sample of 1-chloro-2-propyl perchlorate was isolated by GLC (5 ft × 0.25 in. column of 12% QF-1 on Chromosorb W, 60 °C): NMR (CCl_4) δ 1.62 (d, 3 H, J = 6 Hz, CH_3), 3.67 (d, 2 H, J = 7 Hz, CH_2) and 5.17 (m, 1 H, CH); ir (CCl_4) 1005, 1230, and 1265 cm^{-1}.

Anal. Calcd for $C_3H_6Cl_2O_4$: C, 20.37; H, 3.42. Found: C, 20.08; H, 3.11.

1-Chloro-2-propyl Perchlorate. A 2:1 mixture of 1-chloro-2-propanol and 2-chloro-1-propanol was prepared from propylene oxide and hydrochloric acid by the reported method.[9] A sample of 1-chloro-2-propanol, the major component, was isolated by GLC (8 ft × 0.375 in. column of 12% QF-1 on Chromosorb W, 70 °C). The compound (0.012 ml) was stirred with 1 ml of 0.3 M dichlorine heptoxide in carbon tetrachloride for 16 h. The solution was washed with water and dried over sodium sulfate. The product was identical (NMR, ir, and GLC) with the product from propene.

Reaction of *cis*-2-Butene with Dichlorine Heptoxide. Dichlorine heptoxide (0.6 mmol) and *cis*-2-butene (0.6 mmol) were allowed to react for 4 h by the procedure used with propene. Analysis by NMR based on methyl signals showed 0.18 mmol (30%) of 3-chloro-2-butyl perchlorate and 0.012 mmol (2%) of 3-keto-2-butyl perchlorate. A similar reaction with 0.5 g of lithium perchlorate added gave the same yield of 3-chloro-2-butyl perchlorate but 0.12 mmol (20%) of 3-keto-2-butyl perchlorate.

Sufficient products for identification were obtained by adding 30 mmol of *cis*-2-butene to a mixture of 100 ml of 0.3 M dichlorine heptoxide in carbon tetrachloride and 10 g of lithium perchlorate at 0 °C. After 2 h of stirring at ambient temperature, the solution was washed with water, dried over sodium sulfate, and passed through a 2 × 32 cm slurry-packed column of silica gel. The product was eluted with carbon tetrachloride and the eluent was monitored by NMR. The 3-chloro-2-butyl perchlorate was contained in the first 100 ml of eluent. The next 50 ml contained no product, and the following 250 ml contained 3-keto-2-butyl perchlorate. The solutions of both compounds were concentrated to 25 ml by vacuum distillation with a Holzmann column, and analytical samples were isolated by GLC. The solution containing the 3-chloro-2-butyl perchlorate was distilled at ambient temperature into a −78 °C receiver at 20–0.1 mm. The residue, dissolved in carbon tetrachloride, was shown by NMR to contain 1.5 mmol (5%) of 2,3-butane diperchlorate.[4] 3-Chloro-2-butyl perchlorate was isolated from the distillate by GLC using a 5 ft × 0.25 in. column of 12% QF-1 on Chromosorb W, 100 ml/min helium, 70 °C, 15 min: NMR (CCl_4) δ 1.55 (d, 3 H, J = 6 Hz, $CHClCH_3$), 1.58 (d, 3 H, J = 6 Hz, $CHClO_4CH_3$), 4.25 (m, 1 H, CHCl), and 5.05 (m, 1 H, $CHClO_4$); ir (CCl_4) 1230 and 1265 cm^{-1}; the mass spectrum showed peaks at *m/e* 63, 65 (C_2H_4Cl), 91, 93 (C_4H_8Cl), 127, 129 ($C_2H_4ClO_4$), and 175, 177, 179 ($C_3H_5Cl_2O_4$).

A sample of 3-keto-2-butyl perchlorate was isolated from its carbon tetrachloride solution by GLC (5 ft × 0.25 in. column of 12% QF-1 on Chromosorb W, 100 ml/min He, 90 °C, 10 min retention time): NMR (CCl_4) δ 1.61 (d, 3 H, J = 7 Hz, CH_3CH), 2.30 (s, 3 H, CH_3CO), and 5.12 (q, 1 H, J = 7 Hz, $CHCH_3$); ir (CCl_4) 1720 (C=O), 1020, 1240, and 1270 cm^{-1} (ClO_4).

Anal. Calcd for $C_4H_7ClO_5$: C, 28.17; H, 4.13. Found: C, 28.32; H, 4.10.

Reaction of *trans*-2-Butene with Dichlorine Heptoxide. The reaction of *trans*-2-butene with dichlorine heptoxide proceeded in the same manner as that of *cis*-2-butene, and the product mixtures were indistinguishable with the exception of the stereochemistry of the 3-chloro-2-butyl perchlorate. Its GC retention time was 16 min, compared to 15 min for the product from *cis*-2-butene described above.

3-Chloro-2-butyl Perchlorates. Preparative GLC of commercial 2-butene oxide, a mixture of cis and trans isomers (0.375 in. × 12 ft column of 12% QF-1 on Chromosorb W, 100 ml/min He, 24 °C) gave *trans*-2-butene oxide, retention time 20 min, $n^{20}D$ 1.3741 (reported[10] $n^{20}D$ 1.3736), and *cis*-2-butene oxide, retention time 26 min, $n^{20}D$ 1.3821 (reported[10] $n^{20}D$ 1.3826). To 0.015 ml of *trans*-2-butene oxide and to 0.030 ml of cis-2-butene oxide, each in a GC collection tube, was added 0.15 ml of concentrated hydrochloric acid at 0 °C, and the mixtures were kept at ambient temperature for 1 h. Each product was extracted with 0.1 ml of methylene chloride after 0.15 ml of water was added. The crude chlorohydrins, 0.008 ml from *trans*-2-butene oxide and 0.02 ml from *cis*-2-butene oxide, were each added to 1 ml of 0.3 M dichlorine heptoxide in carbon tetrachloride. After 24 h, each reaction mixture was washed with 0.5 ml of water and dried over sodium sulfate. NMR showed only 3-chloro-2-butyl perchlorate. Mixed GLC showed that the product from *cis*-2-butene oxide was identical with that from cis-2-butene and dichlorine heptoxide, and the product from *trans*-2-butene oxide was identical with that from *trans*-2-butene and dichlorine heptoxide.

Reaction of 2,3-Dimethyl-2-butene with Dichlorine Heptoxide. 2,3-Dimethyl-2-butene (0.0708 g, 0.84 mmol) was added to 15 ml of 0.3 M dichlorine heptoxide at −10 °C. The mixture was kept at −10 °C for 18 h in order to allow the product to separate, although the reaction appeared to be substantially complete in 1 h. The liquid product, lighter than carbon tetrachloride, was separated. The NMR spectrum ($CDCl_3$) showed only prominent peaks assigned to 2,2-diperchloratopropane[7] and to 2,2-dimethyl-3,3-diperchloratobutane. Quantitative NMR using chloroform as a standard and CD_3NO_2 as solvent because of higher product solubility showed 0.195 mmol (11.6% based on 2 mol per mole olefin) of 2,2-diperchloratopropane and 0.195 mmol (23%) of 2,2-dimethyl-3,3-diperchloratobutane.

Reaction of Ketones with Dichlorine Heptoxide. Acetone (0.044 ml, 0.60 mmol) was added to 3 ml of 0.3 M dichlorine heptoxide in carbon tetrachloride at −5 °C. A separate liquid phase formed immediately, NMR ($CDCl_3$) δ 2.59 (s), identical with that reported for 2,2-diperchloratopropane.[7] The yield, 70%, was determined by quantitative NMR allowing a similar reaction mixture to stand for 18 h at −20 °C, removing the carbon tetrachloride by syringe, and dissolving the product in 1 ml of CD_3NO_2: δ 2.61.

By the same procedure, pinacolone gave 2,2-dimethyl-3,3-diperchloratobutane (52%): NMR ($CDCl_3$) δ 1.28 (s, 9 H), 2.48 (s, 3 H); NMR (CD_3NO_2) δ 1.33 (s, 9 H), 2.67 (s, 3 H).

Reactions of Olefins with Perchloric Acid. Water (0.0080 g, 0.44 mmol) was stirred with 2 ml of 0.3 M dichlorine heptoxide in carbon tetrachloride for 30 min in a 25-ml flask fitted with a syringe valve. The flask was evacuated partially and 0.6 mmol of 1,1-difluoroethylene was added by syringe. NMR analysis using chlorobenzene as a quantitative reference showed only 1,1-difluoroethyl perchlorate (0.46 mmol, 76%): ^1H NMR (CCl_4) δ 1.95 (t, J = 14 Hz); fluorine NMR ϕ 69.52 (q, J = 14 Hz); ir (CCl_4) 1390 (m), 1280 (vs), 1200 (s), 1150 (s), 1130 (s), 1030 (s), 970 (s), and 920 cm^{-1} (s).

By this procedure, propene gave isopropyl perchlorate (65%) and 1-chloro-2-propyl perchlorate (10%) in 24 h.

Allyl chloride gave 1-chloro-2-propyl perchlorate (91%) in 24 h by this procedure.

Ethylene gave ethyl perchlorate[2] (63%) in 24 h.

Registry No.—Cl_2O_7, 10294-48-1; propene, 115-07-1; 1-chloro-2-propyl perchlorate, 58426-27-0; 1-chloro-2-propanol, 127-00-4; *cis*-2-butene, 590-18-1; 3-chloro-2-butyl perchlorate, 58426-28-1; 3-keto-2-butyl perchlorate, 58426-29-2; *trans*-2-butene, 624-64-6; *trans*-2-butene oxide, 21490-63-1; *cis*-2-butene oxide, 1758-33-4; 2,3-dimethyl-2-butene, 563-79-1; acetone, 67-64-1; pinacolone, 75-97-8; 2,2-dimethyl-3,3-diperchloratobutene, 58426-30-5; 1,1-difluoroethylene, 75-38-7; 1,1-difluoroethyl perchlorate, 58426-31-6; allyl chloride, 107-05-1; ethylene, 74-85-1; 2,2-diperchloratopropane, 28078-46-8; ethyl perchlorate, 22750-93-2; isopropyl perchlorate, 52936-33-1.

References and Notes

(1) This work was supported by the Office of Naval Research.
(2) K. Baum and C. D. Beard, *J. Am. Chem. Soc.*, **96**, 3233 (1974).
(3) C. D. Beard and K. Baum, *J. Am. Chem. Soc.*, **96**, 3237 (1974).
(4) K. Baum and C. D. Beard, *J. Org. Chem.*, **40**, 81 (1975).
(5) K. Baum and C. D. Beard, *J. Org. Chem.*, **40**, 2536 (1975).
(6) H. J. Lucas and H. K. Garner, *J. Am. Chem. Soc.*, **70**, 990 (1948).
(7) K. Baum, *J. Am. Chem. Soc.*, **92**, 2927 (1970).
(8) B. O. Lindgrer, *Acta Chem. Scand.*, **19**, 7 (1965).
(9) C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).
(10) C. E. Wilson and H. J. Lucas, *J. Am. Chem. Soc.*, **58**, 2399 (1936).

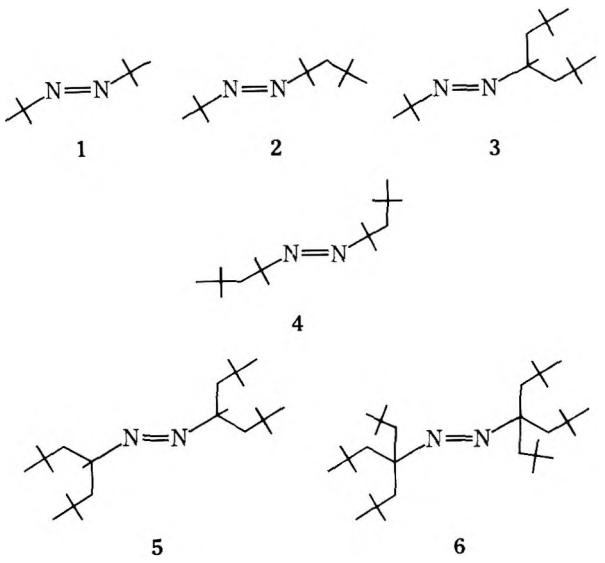
Steric Acceleration in Dialkyldiazene (Azoalkane) Decompositions. 2[1]

Summary: Rates of decomposition of several highly branched dialkyldiazenes have been determined; these data support a concerted mechanism of decomposition and show that tertiary alkyl radicals can be generated thermally at temperatures below 100 °C.

Sir: It has been shown that dialkyldiazenes are sensitive probes of radical stability and that structural changes can bring about pronounced rate enhancements.[1,2] Furthermore, these rate enhancements can be separated into electronic (resonance and inductive) and steric effects.[3] The latter were recognized as being important contributors in the work of Overberger and co-workers[4] and have more recently been examined by others.[5,6] In particular, we were intrigued by the idea that these steric effects could be enlarged to the point that alkyl radicals could be generated at relatively low temperatures, temperatures comparable with those used for azobisisobutyronitrile (AIBN) initiated reactions. These radical precursors might then be useful as polymer initiators without introducing "toxic dusting" problems.[7]

Rate constants for *tert*-butyl(2,4,4-trimethyl-2-pentyl)diazene (**2**), *tert*-butyl(2,2,4,6,6-pentamethyl-4-heptyl)diazene (**3**), and bis(2,2,4,6,6-pentamethyl-4-heptyl)diazene (**5**) chosen for this purpose are listed in Table I. Their activation parameters along with those for **1** and **4** reported earlier are shown in Table II. The previous study[6] was shown to be most consistent with a concerted decomposition mechanism because substitution of a methyl hydrogen in **1** with a *tert*-butyl group (**2**) gave a relative rate of decomposition intermediate to **1** and **4**, the latter having hydrogens replaced by *tert*-butyl groups on both sides. This effect would not be expected for a stepwise decomposition.[6] The same argument can be advanced here in comparing **1**, **3**, and **5**. The unsymmetrical analog (**3**) is once again intermediate in rate between the symmetrical analogs **1** and **5**.

It is interesting to note that there appears to be a dilution effect as the number of *tert*-butyl replacements is monotonically increased. Thus a replacement on one side (**2**) and two replacements (one on each side, **4**) lower $\Delta G^{\ddagger}_{100}$ by successive



increments of 2.7 kcal mol^{-1}. However, two replacements on the same side (**3**) does not have the same effect as one replacement on each side; $\Delta\Delta G^{\ddagger}_{100}$ of **1**–**3** = 4.5 kcal mol^{-1} while $\Delta\Delta G^{\ddagger}_{100}$ of **1**–**4** = 5.4 kcal mol^{-1} (i.e., $\Delta G^{\ddagger}_{100}$ of **3** $\neq$ that of **4**). It is, however, not unexpected to find a lack of additive energy since the steric requirements of these groups should be different. Even so, correction for this dilution still predicts that **6** would decompose approximately seven times faster than AIBN[8] and work is progressing toward a test of this prediction.

Comparison of steric acceleration in diazenes with those of perester decompositions is also informative. Table III shows the much greater sensitivity of diazenes toward steric changes, a result recognized earlier and reconfirmed here.[9-11] Table III also contains a comparison of solvolytic rate data with diazene thermolyses. These results are in complete agreement with Rüchardt's conclusion that steric requirements in solvolysis and diazene thermolyses are linearly related.[5]

Acknowledgment. The authors wish to thank the Petroleum Research Fund, administered by the American Chemical Society, and the Army Research Office for support of this

Table I. Rate Constants for 2, 3 and 5

Compd	Temp, °C	$k \times 10^4$, sec^{-1}	Compd	Temp, °C	$k \times 10^4$, sec^{-1}	Compd	Temp, °C	$k \times 10^4$, sec^{-1}
2	155.0	1.61	3	140.0	1.93	5	100.1	3.03
	160.0	2.52		145.4	3.29		105.1	5.03
	165.7	4.75		150.1	5.29		109.2	7.62
	170.0	7.25		155.1	8.20		115.0	15.1
	175.0	11.9		160.0	12.9		120.1	24.8
	180.0	19.8		164.8	21.8		125.0	39.0

Table II. Activation Parameters for 1, 2, 3, 4 and 5

Compd	Rel rate, 100 °C	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, 100 °C
1	1	42.2 ± 0.3[a]	16.1 ± 0.6[a]	36.2
2	35	38.1 ± 0.6	12.3 ± 1.3	33.5
3	402	33.8 ± 0.6	5.7 ± 1.4	31.7
4	1320	31.7 ± 0.6[b,c]	2.4 ± 1.4[b,c]	30.8
5	57000	30.0 ± 0.5	5.2 ± 1.2	28.1

[a] J. C. Martin and J. W. Timberlake, *J. Am. Chem. Soc.*, 92, 978 (1970). [b] Reference 3. [c] J. W. Timberlake and M. L. Hodges, *J. Am. Chem.*, 95, 634 (1973).

Table III. Comparison of Diazenes, *tert*-Butyl Peresters, and Alkyl Chlorides

R	RN=NR, rel rate, 100 °C	$RCO_3C(CH_3)_3$, rel rate, 25 °C	RCl,[a] rel rate, 25 °C (80% ethanol)
$(CH_3)_3C-$	1	1[b]	1
$(CH_3)_3CCH_2C(CH_3)_2-$	35	4.1[b]	21
$CH_3C(CH_2C(CH_3)_3)_2-$	57000	5.7[c]	580

[a] E. N. Peters and H. C. Brown, *J. Am. Chem. Soc.*, **97**, 2892 (1975). [b] Reference 11. [c] Professor T. T. Tidwell, private communication.

project. The authors are grateful to Professors T. Tidwell and C. Rüchardt for unpublished results and useful discussions.

References and Notes

(1) J. W. Timberlake and M. L. Hodges, *Tetrahedron Lett.*, 4147 (1970).
(2) J. W. Timberlake, A. W. Garner, and M. L. Hodges, *Tetrahedron Lett.*, 309 (1973).
(3) B. K. Bandlish, A. W. Garner, M. L. Hodges, and J. W. Timberlake, *J. Am. Chem. Soc.*, **97**, 5856 (1975).
(4) C. G. Overberger, W. F. Hale, M. B. Berenbaum, and A. B. Finestone, *J. Am. Chem. Soc.*, **76**, 6185 (1954).
(5) W. Duismann and C. Rüchardt, *Tetrahedron Lett.*, 4517 (1974).
(6) A. W. Garner, J. W. Timberlake, P. S. Engel, and R. A. Melaugh, *J. Am. Chem. Soc.*, **97**, 7377 (1975).
(7) R. E. MacLeay and C. S. Sheppard, Canadian Patent 924299 (1973). For example, AIBN cannot be used for products by the food and drug packaging industries or as a blowing agent in the plastic foam market because of the high level of toxic residue left in the finished product.
(8) $\Delta G^{\ddagger}_6 \simeq \Delta G^{\ddagger}_1 - 2[2(\Delta G^{\ddagger}_1 - \Delta G^{\dagger}_4) - (\Delta G^{\ddagger}_1 - \Delta G^{\ddagger}_5)] = 25.4$ kcal mol^{-1}.
(9) C Rüchardt, *Int. Congr. Pure Appl. Chem., 23rd, 1971*, **4**, 223 (1971).
(10) G. J. Abruscato and T. T. Tidwell, *J. Am. Chem. Soc.*, **94**, 672 (1972).
(11) J. A. Ernst, C. Thankachan, and T. T. Tidwell, *J. Org. Chem.*, **39**, 3614 (1974).

J. W. Timberlake,* A. W. Garner
Department of Chemistry, University of New Orleans
New Orleans, Louisiana 70122
Received January 29, 1976

Iron Chloride–Sodium Hydride System as New Reducing Reagents of Carbonyl Compounds

Summary: Iron(II or III) chloride and sodium hydride in tetrahydrofuran provide an effective reagent system for the reduction of ketones and aldehydes to the corresponding alcohols under mild conditions.

Sir: Recently much attention has been paid toward reducing reagents consisting of a mixture of metal compounds. For example, an addition of metal salts to metal hydrides is known to modify the reducing ability.[1] Further, the reagents consisting of $TiCl_3$–$LiAlH_4$[2] or *n*-BuLi–WCl_6[3] have been demonstrated to be effective for the reductive coupling of carbonyl compounds to olefins and the reduction of epoxides to olefins. We have also described the deoxygenation of epoxides to olefins with $FeCl_3$–*n*-BuLi system using the strong affinity of iron to oxygen atom.[4] We now report the iron chloride–sodium hydride systems as effective reagents for the reduction of ketones and aldehydes to the corresponding alcohols under mild reaction conditions.

Sodium hydride is known as a strong base to abstract a proton from a carbonyl compound giving an enolate anion, but has, in general, little reducing ability for carbonyl compounds. A few exceptions reported so far are reductions of nonenolizable ketones under such drastic conditions as refluxing with sodium hydride in xylene[5] or as heating in an aprotic solvent.[6] Reductions of usual carbonyl compounds, however, were observed when they were added at room temperature to the yellow suspension generated by addition of iron(III) chloride to sodium hydride in tetrahydrofuran (THF). Table I reveals that the reagent is effective for aromatic aldehydes and ketones as well as aliphatic carbonyl compounds. The molar ratio of the hydride to the chloride seriously affected the yields of alcohols. The best result was obtained with the ratio of sodium hydride to iron(III) chloride being 3:1 and, above or below this ratio, diminished yields of alcohols were observed. It is important to note that the reducing procedure is specific, since no alcohol formation was observed when sodium hydride was added to a solution of a carbonyl compound and iron(III) chloride.

Table I. Reduction of Carbonyl Compounds

$$RCOR' \xrightarrow{FeCl_x\text{–}NaH} RCHR' \quad (OH)$$

R	R′	$FeCl_3$–NaH[a] Time, h	$FeCl_3$–NaH[a] Yield of alcohol,[c] %	$FeCl_2$–NaH[b] Time, h	$FeCl_2$–NaH[b] Yield of alcohol,[c] %
Ph	Me	30	82	45	72
Ph	Ph	43	81	45	0
n-C_6H_{13}	Me	42	75	48	88
$-(CH_2)_5-$		24	75	30	77
Ph	H	24	85	48	48
n-C_7H_{15}	H	24	79	24	77

[a] Typically, a solution of iron(III) chloride (14 mg equiv) in THF (20 ml) was added to a suspension of sodium hydride (42 mg equiv) in THF (5 ml), and the mixture was stirred for 4 h at room temperature under an atmosphere of argon. Then a solution of a carbonyl compound (2 mmol) in THF (2 ml) was added and stirring was continued at room temperature. [b] Iron(II) chloride (20 mg equiv) and sodium hydride (40 mg equiv) were mixed in THF (15 ml) at 0–5 °C; then a solution of carbonyl compound (2 mmol) in THF (2 ml) was added with continuous stirring at the same temperature. [c] Yields were determined by GLC.

The reducing system was prepared as follows. To a stirred solution of sodium hydride in THF, was added dropwise a solution of iron(III) chloride in THF. Evolution of molecular hydrogen was observed and a yellow suspension was obtained after one third the amount of hydrogen based on the hydride used was evolved. The stability of the reducing reagent depends on the solvent used. Ether cannot be used as a solvent, since fast decomposition of the reducing reagent prevents the reduction. Even in the case of using THF as the solvent, further evolution of hydrogen was observed when carbonyl compounds were added to the suspension. Thus, to obtain satisfactory results, an excess of the reducing reagent to carbonyl compounds was necessary. The reaction mixture became dark as the reduction proceeded. Although the reducing species is not exactly identified at present, it is considered to be some kind of iron hydride,[7] because no formation of coupling product, i.e., glycol derivatives,[8] which were obtained by the reduction of carbonyl compounds with lower valent metal compound,[9] were observed in the reduction.

It is interesting to note that the use of iron(II) chloride in place of iron(III) chloride in the reduction gave different results.[10] As shown in Table I, the reduction of enolizable aliphatic carbonyl compounds with iron(II) chloride[11]–sodium hydride system in THF gave also the corresponding

alcohols in good yields, but the reaction manner and the reactivity are different from those of the reduction with iron(III) chloride–sodium hydride system. For example, the reduction was smoothly carried out at 0–5 °C with the iron(II) chloride–sodium hydride system consisting of 2:1 ratio of the hydride and the chloride, since the reducing species decompose easily with the evolution of hydrogen at room temperature to lower the yields of alcohols. Moreover, in the case of nonenolizable aromatic carbonyl compounds, a clear-cut difference was observed between the reactivities of the reducing reagents prepared from trivalent and divalent iron chloride. With iron(II) chloride–sodium hydride system, benzophenone was not reduced and benzaldehyde gave the reductive coupling product, 1,2-diphenylethylene glycol, in a 22% yield, along with benzyl alcohol in a 48% yield. This suggests that one of the reduction routes may proceed via anion radical intermediates, similar to that of the reduction of carbonyl compounds with the $FeCl_3$–*n*-BuLi system.[9]

In any case, complex species are considered to act as reducing reagent in the above reaction system, but it is of interest to note that the reducing ability of sodium hydride is modified by using with iron chloride.

References and Notes

(1) M. N. Rerick, "Reduction", R. L. Augstine, Ed., Marcel Dekker, New York, N.Y., 1968, p 1.
(2) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974).
(3) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, and T. C. Flood, *J. Am. Chem. Soc.*, **94**, 6538 (1972).
(4) T. Fujisawa, K. Sugimoto, and H. Ohta, *Chem. Lett.*, 883 (1974).
(5) F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 2647 (1946).
(6) (a) P. Caubere and J. Moreau, *Bull. Soc. Chim. Fr.*, 3270 (1971); (b) 3276 (1971).
(7) A species of iron hydride was suggested to be generated from iron(III) chloride with lithium aluminum hydride: Y. Takegami, T. Ueno, and T. Fujii, *Bull. Chem. Soc. Jpn.*, **38**, 1279 (1965).
(8) In general, reductions of carbonyl compounds with metal hydrides give the corresponding alcohols; for example, see N. G. Gaylord, "Reduction with Complex Metal Hydrides", Wiley-Interscience, New York, N.Y., 1956. One exception is the reduction of fluorenone with sodium hydride that gives reductively coupled glycol as a main product; see ref 6a.
(9) The $FeCl_3$–*n*-BuLi system in THF reduced benzaldehyde to give benzyl alcohol (17%), 1,2-diphenylethylene glycol (46%), and stilbene (3%), which suggests that the reaction proceeds via anion radicals formed by lower valent iron; cf. ref 4.
(10) Iron(III) chloride has been suggested to be reduced to iron(II) chloride with lithium aluminum hydride: G. W. Schaeffer, J. S. Roscoe, and A. C. Stewart, *J. Am. Chem. Soc.*, **78**, 729 (1956).
(11) Anhydrous iron(II) chloride was prepared by the reaction of iron(III) chloride with chlorobenzene: P. Kovacic and N. O. Brace, "Inorganic Syntheses", Vol. VI, McGraw-Hill, New York, N.Y., 1960, p 172.

Tamotsu Fujisawa,* Kikuo Sugimoto, Hiromichi Ohta

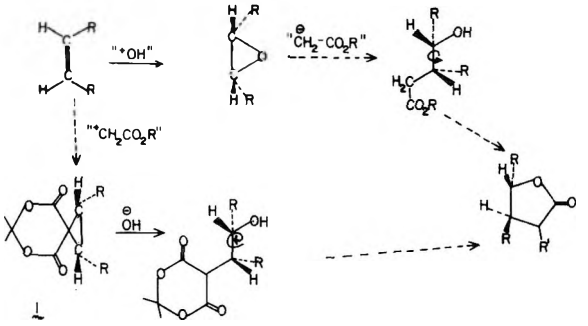
Sagami Chemical Research Center, Nishi-Ohnuma
Sagamihara Kanagawa, 229 Japan

Received January 5, 1976

The Cyclopropane Route to Trans-Fused γ-Lactones

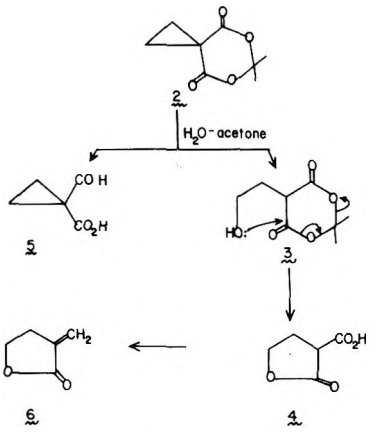
Summary: Suitably activated cyclopropanes can be converted to γ-lactones with inversion of configuration by solvolysis in aqueous acetone.

Sir: The usual route from olefins to trans γ-lactones involves epoxidation followed by nucleophilic attack by an equivalent of acetic acid carbanion.[1,2] Our findings concerning the remarkable electrophilic properties of spiroactivated cyclopropanes[3-5] suggested the feasibility of a conceptually different approach, wherein systems of the type **1** would be opened by hydroxide or an equivalent thereof. Clearly, the success of such a scheme depends, critically, on a stereospecific inversion result during the ring opening. A further requirement is that the ring opening be faster than hydrolytic cleavage of the activating acylal linkage. Below we report the results of testing this new approach in simple model systems. These results show that the two conditions cited above can be met and suggest that activated cyclopropanes may be of utility in the synthesis of the trans-fused γ-lactonic compounds present in a variety of biologically important natural products.[6-8]



When the parent cyclopropane acylal **2**[4] was heated with 2:1 acetone–water under reflux for 40 h, there was obtained upon evaporation of the solvents, a 9:1 mixture (NMR analysis) of 3-carboxybutyrolactone (**4**) and cyclopropane-1,1-dicarboxylic acid (**5**). Thus, with water as the nucleophile, ring cleavage is faster than acylal cleavage to a synthetically usable extent. Presumably, the spiroacylal functions as an active ester in the cyclization of **3**, the initially formed 1,5 adduct, to produce the observed **4**. Compound **3** itself was not detected under these conditions.

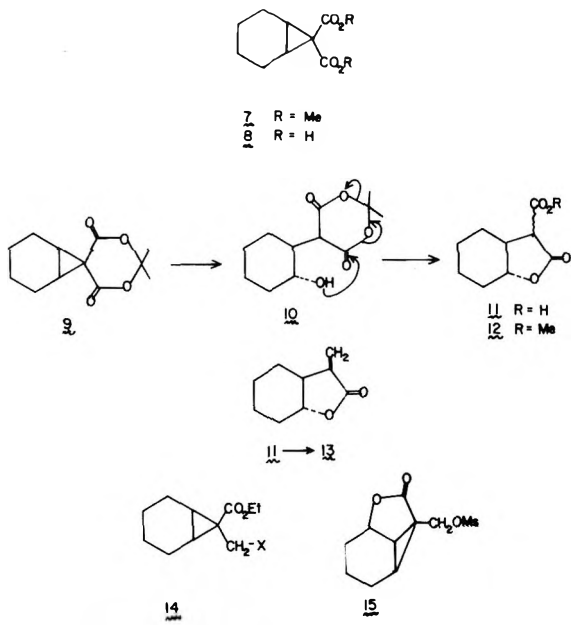
Without purification, the total reaction mixture was subjected to α-methylenation: (i) formalin–diethylamine; (ii) sodium acetate–acetic acid.[9] The well-known α-methylenebutyrolactone (**6**)[8] was obtained in 40% yield from **2**.



An insight into the stereochemical course of the process was gained by studying the solvolysis of spiroacylal **9**. The starting material for its preparation was the known 7,7-dicarbomethoxynorcarane (**7**).[10] This was converted to diacid[11] **8**. Reaction of **8** with isopropenyl acetate–sulfuric acid at 0 °C[4] gave **9**,[12] mp 87–88 °C, in 51% yield. Heating compound **9** with 2:1 acetone–water under reflux for 7 h gave, in one step, the α-carboxylactone **11**[1] characterized as its methyl ester **12**,[13] mp 81–83 °C.

The yield from **9** → **12** (purified by silica gel chromatography) is 65%. That **11** and **12** are, in fact, trans fused was shown by conversion of the former by the Mannich procedure[9] to the α-methylenelactone **13**, identical with an authentic sample provided by Professor Grieco.

The stereochemical course of the ring opening has thus been shown to involve inversion of configuration by solvent (water). It will be noted that Hudrlik[14] observed retention of configuration in the rearrangement of cyclopropylcarbinyl systems of the type **14**. This was explained by postulating intra-



molecular capture of the electron-deficient homoallylic carbon by the proximate ester oxygen.

Ziegler[15] was the first to demonstrate inversion of configuration in the course of acetolysis of the cyclopropylcarbinyl system, **15**. While this result is potentially of considerable interest in the control of stereochemistry of oxygen functionality adjacent to α-methylenelactones,[16] we believe that the transformation of **9** → **11** represents the first instance of using activated cyclopropanes for the de novo synthesis of a γ-lactone in the trans series.

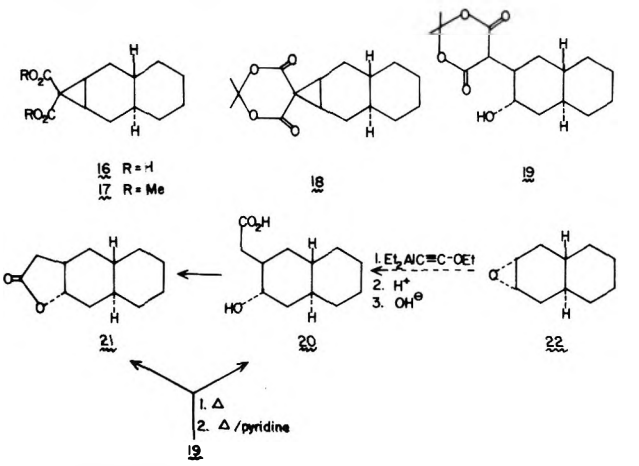
Parenthetically it will be noted that the cyclization of **10** → **11** is apparently[17] uncatalyzed and is occurring under conditions which must be regarded as quite mild for the closure of a trans-fused γ-lactone.[2] Again this is suggestive of particularly strong acylating powers of the cyclic acylal linkage.

A finer understanding of the stereochemical pathway of the solvolytic opening of spiroactivated cyclopropanes was possible in the context of the conformationally defined *trans*-decalin system, **18**. *trans*-Δ^2-Octalin was converted to the cyclopropane derivative **16**[12] (76%) by the action of dimethyl diazomalonate under the influence of copper bronze (3 equiv of diazo compound to 1 equiv of olefin, 150 °C). This was hydrolyzed to give diacid **17**, mp 195–197 °C,[12a] in 83% yield, which was converted to **18**,[12] mp 145–148 °C, in 82% yield via isopropenyl acetate.[4]

Compound **18** was heated in 1:1 acetone–water for 24 h under reflux. NMR analysis indicated the presence of two or more acidic components. Accordingly, the total reaction mixture was heated in pyridine[2] under reflux for 0.5 h thereby achieving decarboxylation. At this stage, an acidic product, identified as **20**, mp 117–120 °C (lit.[2] mp 116–117 °C), was isolated in 60% yield. A neutral product, mp 52–53 °C, shown to be Johnson's boat lactone **21** (lit.[2] 49.6 °C) was isolated in 30% yield. Although an authentic sample of **21** by the original method of synthesis[2] was not available, the lactone so produced was identical with the same compound obtained from the opening of the epoxide, **22**,[2] with diethyl ethoxyethynylalane.[18] Furthermore, **21** was also obtained by the cyclization of **20** by the method of Johnson (tosyl acid–xylene, reflux 30 min).

It is seen that a minimum of 90% of the solvolysis of **18** can be accounted for in terms of stereospecific opening of the activated cyclopropane to give trans-diaxial substitution. This is followed primarily by decarboxylation of the diacid produced by hydrolysis of the resultant acylal, **19**. To a small (but remarkable) extent, the acylal undergoes lactonization prior to the decarboxylation step with pyridine.

Application of this stereoelectronically specific conversion of fused spiroactivated cyclopropanes to trans-fused γ-lactones will be studied.



Acknowledgments. This research was supported by PHS Grant CA-12107-12. The authors wish to express their appreciation to the Andrew Mellon Foundation for a Fellowship to R.K.S. NMR services were maintained on instrumentation supported by RR-00292-06. Support from the Hoffmann-La Roche Company is gratefully acknowledged.

References and Notes

(1) M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).
(2) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dryer, and W. R. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(3) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, **97**, 3239 (1975).
(4) R. K. Singh and S. Danishefsky, *J. Org. Chem.*, **40**, 2969 (1975).
(5) S. Danihsefsky and R. K. Singh, *J. Org. Chem.*, **40**, 3807 (1975).
(6) K. Nakanishi, T. Goto, S. Ito, S. Nortori, and S. Nozoe, "Natural Products Chemistry", Vol. 1, Academic Press, New York, N.Y., 1974, Chapter 3, p 39.
(7) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(8) For a review of this area of synthesis, see (a) P. A. Grieco, *Synthesis*, 67 (1976); (b) R. B. Gamill, C. A. Wilson, and T. A. Bryson, *Synth. Commun.*, **5**, 245 (1975)
(9) J. Martin, P. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970).
(10) B. W. Peace and D. S. Wulfman, *Synthesis*, 137 (1973).
(11) H. Musso, *Chem. Ber.*, **101**, 3710 (1968).
(12) The structure of this compound is in accord with (a) its ir, NMR, and mass spectra; (b) its C and H combustion within 0.3% of theory.
(13) E. S. Behare and R. B. Miller, *Chem. Commun.*, 402 (1970).
(14) P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, *J. Am. Chem. Soc.*, **95**, 6848 (1973).
(15) F. E. Ziegler, A. F. Marino, O. A. C. Petroff, and W. L. Studt, *Tetrahedron Lett.*, 2035 (1974).
(16) For another application, see R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 529 (1975).
(17) Since malonic acids are almost certainly generated in this reaction these may function as acid catalysts.
(18) S. Danishefsky, T. Kitahara, M. Tsai, and J. Dynak, *J. Org. Chem.*, following paper.

Rajendra K. Singh, Samuel Danishefsky*
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received January 6, 1976

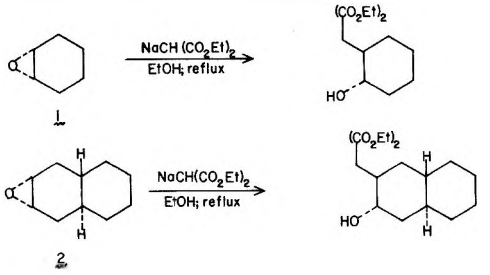
Functionalized Alanes for the Conversion of Epoxides to Trans-Fused γ-Lactones

Summary: Aluminum derivatives of *tert*-butylacetate and ethoxyacetylene have been shown to be useful for the opening of oxidocycloalkanes.

Sir: In view of the large number of biologically active natural products containing trans-fused γ-lactones,[1,2] a general method of reaching such systems via oxidocycloalkanes could be useful. The traditional route involves the opening of an

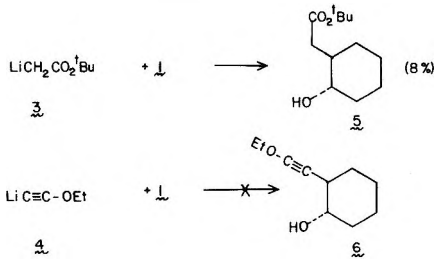
epoxide with an equivalent of carbanionic acetate and lactonization after suitable unravelling.

The usual nucleophile employed in such epoxide openings is malonic ester enolate.[3,4] Such ring openings [cf. cyclohexane oxides (1)] proceed with inversion of configuration, eventually furnishing the trans relationship of OH and CH_2CO_2R required for generation of a trans-fused γ-lactone. Johnson's elegant demonstration of trans-diaxial opening of the conformationally definable 2,3-oxido-*trans*-decalin[4] (2) provides further stereochemical insight into this reaction. However, a major weakness of the malonic ester enolate method of epoxide openings is the rather harsh conditions required even with unencumbered substrates such as 1 and 2. Thus, it is not surprising that this method has not been successfully employed with more complicated epoxides.



Other carbanionic acetate equivalents have been employed in epoxide openings. Dilithio trimethylsilylacetate reacts with simple epoxides but appears to fail to open compound 1.[5] Dilithio thiophenylacetate does open compound 1 but in rather modest yield.[6] Dilithio acetate itself may have potential with more hindered epoxides, though the yield of opening of compound 1, even under relatively forcing conditions, is somewhat discouraging.[7,8]

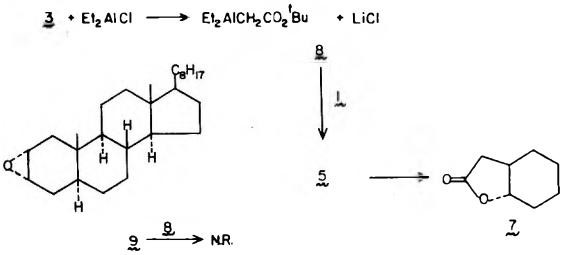
The first phase of our study involved the attempted reaction of lithium *tert*-butylacetate (Rathke's salt 3)[9] and lithium ethoxyacetylide (4) with compound 1. In our hands, the reaction of 3 + 1 afforded compound 5 in a maximum of 8% yield (toluene, room temperature, 12 h). The use of the more polar solvent, dimethoxyethane (DME), furnished only a 5% yield. The results of the reaction of 1 and 4 were even more discouraging in that no detectable amounts of 6 were noted.[10]



In view of the impressive success recorded by the Fried school in the opening of hindered epoxides with dialkylalkynylalanes,[11,12] it was of interest to study the application of this technology to the problem at hand. Treatment of 2.5 equiv of 3 with 2.5 equiv of diethylaluminum chloride in toluene (3 ml/mmol of lithium salt) at −40 °C led to the instantaneous deposition of lithium chloride. Reaction of this system, maintained at −30–40 °C for 6 h, with 1 gave a 34% yield of 5.[13] The stereochemistry of 5 was demonstrated by its transformation to the known[3] 7 in 85% yield upon reaction with tosyl acid/benzene under reflux for 15 h.

Since there is no reaction between 1 and 3 under these conditions, and, in view of the method of formation,[11] it seems reasonable to conclude that the active specie is, in fact, diethylcarbo-*tert*-butoxymethylalane (8). The yield of 5 was raised to 68% by allowing the reaction mixture containing 1 and 8 to warm to ambience where it was maintained for 6 h.

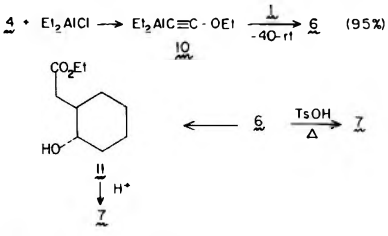
Although the chemistry of this interesting aluminum enolate[14] remains to be explored, this reagent does not constitute a satisfactory general acetic acid equivalent for opening hindered epoxides. For instance, attempted reaction of 8 with 2,3-oxido-α-cholestane (9) fails, leading to 86% recovered epoxy steroid. Attempts to increase reactivity by heating led to apparently rapid decomposition of the organometallic system.



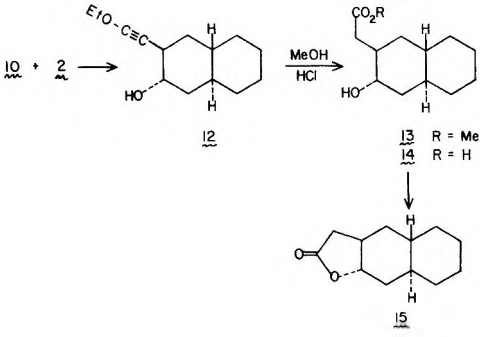
Treatment of lithium ethoxyacetylide (2.5 equiv, generated from the reaction of 2.5 equiv of *n*-butyllithium in hexane with 2.5 equiv of ethoxyacetylene) with 2.5 equiv of diethylchloroalane in toluene at −40 °C (2 ml/mmol of lithium salt) again led to the deposition of lithium chloride. Treatment of **10**, so produced, with **1**, from −40 to −30 °C for 6 h, followed by quenching with aqueous sodium bicarbonate at that temperature, gave, after chromatography on silica gel, a 66% yield of *trans*-2-ethoxyethynylcyclohexanol[13] (**6**) and 5% *trans*-2-carbethoxymethylcyclohexanol (**11**).[13a,15] The yield of the process was substantially improved (80% **6** and 10% **11**) by allowing the temperature of the reaction of **10** and **1** to warm from −40 °C to ambience, where it was maintained for 6 h. If analytically pure **6** is not needed, the crude yield of essentially pure compound is 95%.

The stereochemistry of **6** was demonstrated by its conversion (88%) to **7** upon reaction with tosyl acid toluene under reflux. The mechanism of this transformation has not been determined. There may be enough water present to effect the conversion of **6** → **11** and the latter may be the active acylating specie. Alternatively, cyclization of **6** may give a cyclic ketene acetal which is cleaved by aventitious water. Finally, **6** may suffer protonation followed by de-ethylation to give a ketene. The latter could well cyclize to give the observed **7**.

Alternatively, treatment of **6** with ethanolic HCl afforded a quantitative yield of **11**. The latter was converted in 90% yield to **7** by the action of tosyl acid–benzene under reflux.

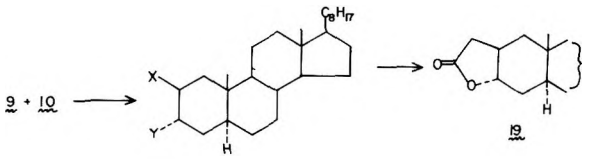


A clear trans-diaxial pathway was demonstrated in the reaction of **10** with **2**. There was produced an 80% yield of ethoxyethynylcarbinol **12** after 15 h (−40 °C to room temperature). Compound **12** was converted to *methyl* ester **13**[16] upon reaction with methanolic HCl. The latter was saponified



with methanolic KOH to give the known acid,[4] **14**, mp 114–116 °C which was converted to the known[4] boat lactone system **15**, mp 49–51 °C (lit.[4] 49.6 °C). No evidence for the formation of stereoisomers of **13** could be detected.

Reaction of **10** with 2,3-oxido-α-cholestane (**9**) under these conditions gave a 63% yield of **16**,[13] mp 92–93 °C, $[\alpha]D$ ($CHCl_3$) +4.7°. The epoxide was recovered to the extent of 15%. The diaxial nature of **16** was confirmed through the NMR spectrum[17] of its derived acetate, **17**,[13a] mp 112–114 °C. Treatment of **17** with methanolic HCl gave the methyl ester **18**,[13,16] mp 163–164 °C, $[\alpha]D$ ($CHCl_3$) +32.0°, in 85% yield. The latter was converted to the pentacyclic steroidal lactone **19**,[13a] mp 165–167 °C, $[\alpha]D$ ($CHCl_3$) +31.7°, in 73% yield by the forcing conditions of Johnson[4] (tosyl acid–xylene, reflux).



16 X = C≡C-OEt; Y = OH
17 X = C≡C-OEt; Y = OAc
18 X = CH_2CO_2Me; Y = OH

It is thus seen that this method of cleavage occurs in a stereoelectronically specific trans-diaxial fashion. The efficacy and stereoelectronic specificity of the method are not seriously disrupted by a 1,3-diaxial interaction with an angular methyl group. Other applications of these aluminum bound synthetic equivalents of acetic acid carbanion are currently under investigation.

Acknowledgments. This research was supported by PHS Grant CA-12107-12. NMR services were maintained on instrumentation supported by RR-00292-06. Support from the Hoffmann-La Roche Company is gratefully acknowledged.

Supplementary Material Available. Experimental procedures for these reactions (6 pages). Ordering information is given on any current masthead page.

References and Notes

(1) K. Nakanishi, T. Goto, S. Ito, S. Natori, and S. Nozoe, "Natural Products", Vol. 1, Academic Press, New York, N.Y.–Tokyo, 1974, Chapter 3.
(2) S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971).
(3) M. S. Newman and C. A. Vander Werf, *J. Am. Chem. Soc.*, **67**, 233 (1945).
(4) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dryer, and W. R. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).
(5) P. A. Grieco and C. L. Wang, *J. Chem. Soc., Chem. Commun.*, 714 (1975).
(6) K. Iwai, M. Kawai, H. Kosugi, and H. Uda, *Chem. Lett.*, 385 (1974).
(7) P. L. Creger, *J. Org. Chem.*, **37**, 1907 (1972).
(8) T. Fujita, S. Watanabe, and K. Suga, *Aust. J. Chem.*, **27**, 2205 (1974).
(9) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1972).
(10) For the successful reaction of lithium ethoxyacetylide with simple terminal epoxides, see J. Link, P. Vermeer, J. G. Kooiman, J. Meijer, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **93**, 92 (1974).
(11) (a) J. Fried, C. H. Lin, and S. H. Ford, *Tetrahedron Lett.*, 1379 (1969); (b) J. Fried and J. C. Sih, *ibid.*, 3899 (1973).
(12) The first preparation of an alane derivative of ethoxyacetylene was achieved in the laboratories of Professor Fried. The reagent was used in a successful opening of cyclopentane oxide. This successful reaction was described by J. Fried, M. Mehra, C. Lin, W. Kao, and P. Dalven in the *Ann. N.Y. Acad. Sci.*, **180**, 38 (1971). The resultant *trans*-ethoxyethynyl functions was converted to CH_2CHO by partial reduction of the triple bond followed by hydrolysis of the resultant enol ether. We thank Professor Fried for apprising us of his experimental procedures.
(13) The structure and homogeneity of this compound was established by (a) its ir, NMR, and mass spectra; (b) C and H combustion analysis was within 0.4% of theory.
(14) For the generation of aluminum enolates by the $Ni(acac)_2$-catalyzed conjugate addition of trimethyl aluminum to enones, see E. A. Jeffrey, A. Meisters, and T. Mole, *J. Organometal. Chem.*, **74**, 365 (1974).
(15) Compound **11** is an artifact produced on chromatography of the labile ethynyl ether **6**.
(16) We have found that treatment of the *trans*-2-hydroxyethynyl ethers **12** and **16** with ostensibly anhydrous HCl–methanol gives cleanly the methyl esters. We are, at present, unable to define the mechanism of this transformation. It may involve the presence of adventitious water, leading to a mixing of methyl and ethyl esters followed by transesterification of the latter in favor of the former. Alternatively, it may be the consequence of protonation followed by demethylation giving rise to a ketone intermediate. The latter is then captured by the solvent, methanol, to give the observed methyl ester. In any case, it is a useful method for transforming ethoxyethynyl ethers, arising from the commercially available ethoxyacetylene, into methyl esters which tend to be more easily crystalline and more readily amenable to NMR analysis.
(17) The resonance of the methine proton at C_3 in compound **16** is obscured by overlap with the methylene protons of the ethoxy group. However, in the derived acetate **17** the resonance ($CDCl_3$) is seen as a multiplet centered at δ 5 ppm with a line width at half-height of 5 Hz, clearly indicative of an equatorial proton. The β stereochemistry of the X group in compounds **16–18** follows from inversion of the α stereochemistry of the epoxide.

S. Danishefsky,* T. Kitahara, M. Tsai, J. Dynak
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260
Received January 9, 1976

Carbon-13 Magnetic Resonance. Downfield Shifts Induced by $M(CH_3)_3$ (M = Si, Ge, Sn, Pb) at the γ Position and Antiperiplanar to the Carbon-13 Center

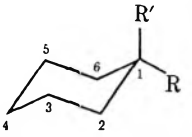
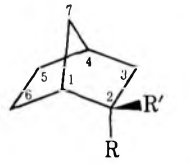
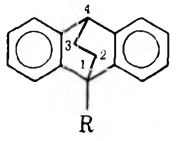
Summary: Carbon-13 NMR spectra of certain cycloalkyl derivatives of group 4B have been obtained, and the chemical shifts of γ carbons are discussed in terms of geometrical array and possible electronic interactions.

Sir: The γ effect (the usually *upfield* shift of a resonance for a carbon-13 nucleus gauche to another carbon or heteroatom at the γ position) is generally ascribed to steric compression which polarizes the C–H bonds causing shielding of the carbon nucleus.[1] When heteroatoms are incorporated, it was recognized[2-4] some years ago that significant upfield γ shifts may occur when such heteroatoms are anti to the carbon nucleus. More recently, Eliel and co-workers[5] established that a carbon nucleus anti to a second row heteroatom (N, O, F) in the γ positions generally resonates at higher field than when anti to methyl or methylene. The nature of this shielding mechanism is not established, but Eliel[5] favored interaction of free electron pairs (on N, O, F) with the C_α–C_β bond, resulting in a type of "conjugative" transfer of electron density to the C_γ region. On the other hand, Heumann and Kolshorn,[6] from their studies of 2-substituted bicyclo[3.3.1]nonan-9-ones, suggested that "electronically induced" anti γ effects were associated with back-lobe overlap, as originally outlined by Grutzner and Roberts.[2] Our studies of the ^{13}C spectra of geometrically well-defined cycloalkyl derivatives of group 4B elements have provided values for the γ effects of $M(CH_3)_3$ (M = Si, Ge, Sn, Pb) in gauche and antiperiplanar arrays. These data are particularly pertinent to the mechanism of the anti γ effect, but also make available a further assignment criterion for the spectra of the group 4B derived systems.

The chemical shift data for cyclohexyl[7] and certain norbornyltin compounds[8] are assembled in Table I, together with relevant information on the bicyclo[2.2.2]octyltin system.[9] The values in parentheses are the substituent chemical shifts and the γ effects are italicized. For the tin compounds, the γ effects are substantially downfield in anti arrangements (where steric compression cannot be important) and largest at C_6 in the *exo*-2-norbornyl compound (+3.9 ppm). Where steric compression is operative, e.g., in the axial conformer[7] of cyclohexyl trimethylstannane, the γ effect is upfield, perhaps as expected. The γ effect of $Sn(CH_3)_3$ attached to a bridgehead position (in the bicyclo[2.2.2]octyl system) is still significantly downfield (+2.4 ppm), in contrast to the observation[5] that the normally upfield anti γ effect of fluorine becomes downfield in such a situation.[10]

The equatorial cyclohexyl derivatives[11] of group 4B exhibit anti γ effects that are significantly downfield, i.e., from +0.8 ppm for $C(CH_3)_4$ to +3.06 ppm for $Pb(CH_3)_3$. It is instructive

Table I. Carbon-13 Chemical Shifts[a] of Some Group 4B Substituted Cycloalkyl Systems

Substituents	Carbon Number 1	2	3	4	5	6	7	Other
								
R^1 = H; R = H	27.0	27.0	27.0	27.0	27.0	27.0		
R^1 = H; R = $C(CH_3)_3$	48.9	28.2	27.8	27.2	27.8	28.2		32.7, 27.7
	(+21.9)	(+1.2)	(*+0.8*)	(+0.2)	(*+0.8*)	(+1.2)		
R^1 = H; R = $Si(CH_3)_3$[b]	26.39	27.49	28.25	27.14	28.25	27.49		−3.56
	(−0.61)	(+0.49)	(*+1.25*)	(+0.14)	(*+1.25*)	(+0.49)		
R^1 = H; R = $Ge(CH_3)_3$[c]	27.90	28.74	28.31	27.06	28.31	28.74		−4.50
	(+0.9)	(+1.74)	(*+1.31*)	(+0.06)	(*+1.31*)	(+1.74)		
R^1 = H; R = $Sn(CH_3)_3$	24.75	30.87	28.98	26.93	28.98	30.87		−11.92
	(−2.25)	(+3.87)	(*+1.98*)	(−0.07)	(+1.98)	(+3.87)		
R^1 = $Sn(CH_3)_3$; R = H	nl	nl	25.89	nl	25.89	nl		−9.18
			(*−1.11*)		(*−1.11*)			
R^1 = H; R = $Pb(CH_3)_3$	35.04	33.66	30.06	26.75	30.06	33.66		−5.31
	(+8.04)	(+6.66)	(*+3.06*)	(−0.25)	(*+3.06*)	(+6.66)		
R^1 $Pb(CH_3)_3$; R = H	38.72	32.19	25.88	26.75	25.88	32.19		−3.18
	(+11.72)	(+5.19)	(*−1.12*)	(−0.25)	(*−1.12*)	(+5.19)		
								
R^1 = H; R = H	36.8	30.1	30.1	36.8	30.1	30.1	38.7	
R^1 = $Sn(CH_3)_3$; R = H	40.3	27.6	37.6	34.9	29.5	34.0	38.6	−10.8
	(+3.5)	(−2.5)	(+7.5)	(*−1.9*)	(−0.6)	(*+3.9*)	(*−0.1*)	
R^1 = H, R = $Sn(CH_3)_3$	40.9	28.7	33.8	36.9	30.3	30.1	40.9	−10.2
	(+4.1)	(−1.4)	(−3.8)	(*+2.0*)	(+0.8)	*0*	(*+2.2*)	
								
R = H[d]	44.1	26.7	26.7	44.1				
R = $Sn(CH_3)_3$	43.0	30.7	29.1	44.8	*e*			
	(−1.1)	(+4.0)	(*+2.4*)	(+0.7)				

[a] For 10% solutions in $CDCl_3$ referenced to internal TMS. nl means not located. γ effects are italicized. [b] The assignments for $C_{2,6}$ and $C_{3,5}$ could be reversed, but this reversal does not alter any arguments. The listed values provide a more reasonable periodic response in the $C_{3,5}$ chemical shifts. [c] Confirmed by examination of the (2,6) deuterated analogue. [d] Arbitrary numbering system. [e] Reference 9.

to consider how this trend is accommodated by the possible mechanisms of the anti γ effect given the present understanding of the periodic properties of the elements in their compounds. The hyperconjugative mechanism suggested by Eliel[5] for atoms bearing free electron pairs could be applied to the lower members (i.e., Si downward) and would result in deshielding at C_γ, as observed. This would necessitate interaction of a vacant orbital, of π or pseudo-π symmetry on the central atom, and could conceivably be nd or C–M σ* in nature.[12] The degree of hyperconjugative interaction would then be reciprocal function of the energy difference between this π orbital and the C–C bonding level, to a rough approximation. As the interaction between a vacant "π level" on Si and adjacent π systems is not large,[13] it is difficult to envisage significant interaction with a σ level. Even if it were, we would expect a greater effect for Si, as the evidence[13-15] is that π bonding is more efficient for this element, presumably owing to better energy and radial matching of the interacting orbitals.[16]

We are left to consider the original "back-lobe overlap" idea,[2] which is also favored by a planar "zig-zag" or "W" array. Larger downfield γ effects then are related to a number of factors, including electronegativity, regulating the nature of the C–M σ bond. This explanation is consistent with the much enhanced γ effect (+3.9 ppm) at C_6 in the *exo*-2-norbornyltin compounds apparently because the C_2–C_1–C_6 angle is smaller, promoting the back-lobe interaction. It is of importance to note that vicinal $^{117,119}Sn$–^{13}C coupling is maximized[8] for a dihedral angle of 180°, and back-lobe transmission is a strong possibility. Furthermore, the vicinal coupling to C_6 in *exo*-2-norbornyltrimethylstannane appears to be the largest measured for a $RSn(CH_3)_3$ system.[8] Eliel noted[5] that anti γ effects did not extend to third row elements (e.g., chlorine), whereas such (deshielding) effects become more pronounced as group 4B is descended. It is possible that different blends of factors are involved in the two situations, and further experimental and theoretical efforts are required. In the meantime, it is essential to note that, for some substituents, γ effects of possibly variable sign but comparable magnitude may be encountered, depending on geometrical factors.

Acknowledgments. This work was supported in part by the Australian Research Grants Committee.

References and Notes

(1) For leading discussion see (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, and (b) G. C. Levy and G. L. Nelson, "^{13}C Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.

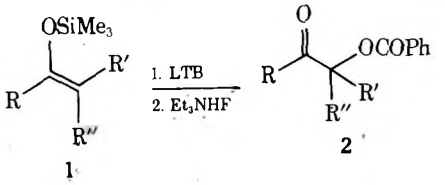
(2) J. B. Grutzner, M. Jantelat, J. B. Dence, R. A. Smith, and J. D. Roberts, *J. Am. Chem. Soc.*, **92**, 7107 (1970).
(3) H. J. Reich, M. Jantelat, M. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Am. Chem. Soc.*, **91**, 7445 (1969).
(4) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. H. Reich, *J. Am. Chem. Soc.*, **92**, 1338 (1970).
(5) E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.*, **97**, 322 (1975).
(6) A. Heumann and H. Holshorn, *Tetrahedron*, **31**, 1571 (1975).
(7) The cyclohexyl derivatives of tin and lead have been reported in another connection: W. Kitching, D. Doddrell, and J. B. Grutzner, *J. Organometal. Chem.*, in press. Cyclohexyltrimethylgermane [from cyclohexyl Grignard and $(CH_3)_3GeBr$] had bp 46° (4 mm) and C, 53.88; H, 10.10 (Calcd for $C_9H_{20}Ge$: C, 54.0; H, 10). Cyclohexyltrimethylsilane was prepared in the reported fashion [C. Eaborn, R. A. Jackson, and R. Pearce, *J. Chem. Soc., Perkin Trans. 1*, 475 (1975)].
(8) D. Doddrell, I. Burfitt, W. Kitching, M. Bullpitt, C. Lee, R. J. Mynott, J. L. Considine, H. G. Kuivila, and R. H. Sarina, *J. Am. Chem. Soc.*, **96**, 1640 (1974).
(9) W. Adcock, B. D. Gupta, W. Kitching, D. Doddrell, and M. Geckle, *J. Am. Chem. Soc.*, **96**, 7360 (1974); W. Adcock, B. D. Gupta, W. Kitching, and D. Doddrell, *J. Organometal. Chem.*, accepted for publication.
(10) We have noted also a positive (+0.94 ppm) anti γ effect of fluorine in the maleic anhydride adduct of 9-fluoroanthracene [W. Kitching, W. Adcock, T. C. Khor, and D. Doddrell, *J. Org. Chem.*, unpublished work].
(11) The data for the equatorial tin and lead compounds were obtained by direct observation of these conformers at low temperatures,[7] while the data for the silicon and germanium derivatives pertains to ambient (+35°) conditions. The populations of axial forms for these derivatives would be very small, with introduction of little error.
(12) See C. G. Pitt, *J. Organometal. Chem.*, **61**, 49 (1973).
(13) A π-bond order of 0.18 for an aryl silicon system has been calculated [M. D. Curtis and A. L. Allred, *J. Am. Chem. Soc.*, **87**, 2554 (1965)]. See also P. Bischof, M. J. S. Dewar, D. W. Goodman, and T. B. Jones, *J. Organometal. Chem.*, **82**, 88 (1974).
(14) C. J. Attridge, *Organometal. Chem. Rev., Sect. A*, **5**, 323 (1970).
(15) W. Adcock, S. Q. A. Rizvi, and W. Kitching, *J. Am. Chem. Soc.*, **94**, 3657 (1972); **92**, 6140 (1970).
(16) In relation to the mechanism (of the anti γ effect) favored by Eliel and coworkers,[5] CNDO/2 calculations suggest that the donation of the free-electrons on a heteroatom, in a σ-bonded framework, is preferentially to the β and not the γ position, the latter being positively charged [J. A. Pople and M. Gordon, *J. Am. Chem. Soc.*, **89**, 4253 (1967)]. Some experimental results appear to support these calculations [S. A. Holmes and T. D. Thomas, *ibid.*, **97**, 2337 (1975)]. Unfortunately, many factors determine the C_β chemical shift, and the electronic component is therefore difficult to assess.
(17) Doubts have been expressed by others [J. B. Lambert and S. I. Featherman, *Chem Rev.*, **75**, 625 (1975)] regarding the general validity of the suggested mechanism (as in ref 5) of the anti γ effect.
(18) To whom correspondence should be directed.

William Kitching,*[18] Mark Marriott
Department of Chemistry, University of Queensland Brisbane, Australia
William Adcock
School of Physical Sciences, Flinders University Adelaide, Australia
David Doddrell
School of Science, Griffith University Nathan, Australia
Received November 21, 1975

Lead Tetrabenzoate Oxidation of Trimethylsilyl Enol Ethers

Summary: A high yield, regiospecific procedure for the preparation of α-benzoyloxy carbonyl compounds is reported.

Sir: We wish to report that the reaction of trimethylsilyl enol ethers, **1**, with lead tetrabenzoate (LTB), followed by treatment with triethylammonium fluoride, affords α-benzoyloxy carbonyl compounds, **2**, in excellent yield (eq 1). Previous interest in the introduction of an acyloxy group adjacent to the carbonyl moiety has centered mainly upon the use of lead tetraacetate (LTA).[1] Enolizable ketones react with LTA in refluxing benzene to produce α-acetoxy ketones in moderate yield,[2] but the reaction is limited by the concurrent production of diacetates[2a] and rearrangement products.[3] The latter problem is a major deterrent in the use of LTA for the formation of α-acetoxy aldehydes[4] and no high yield method for the synthesis of these useful intermediates has as yet been reported.[5] Boron trifluoride has been employed to catalyze the LTA reaction with ketones,[6] and, in one instance, an enolate has been successfully trapped by LTA.[7] Other approaches have used the reactions of enamines with LTA[8] and thallium triacetate,[9] but both methods are of limited preparative value. The reaction of mercuric acetate with ketones also affords the corresponding acetoxy derivative, but the method lacks regiospecificity.[10] Electrochemical procedures for the introduction of acetoxy groups have also been investigated.[11] Recently, we have shown that **1** reacts with LTA to afford excellent yields of α-acetoxy ketones,[12,13] but this method when applied to the trimethylsilyl enol ethers of aldehydes results in the production of glycolic acid as well as acetic acid derivatives.[14]

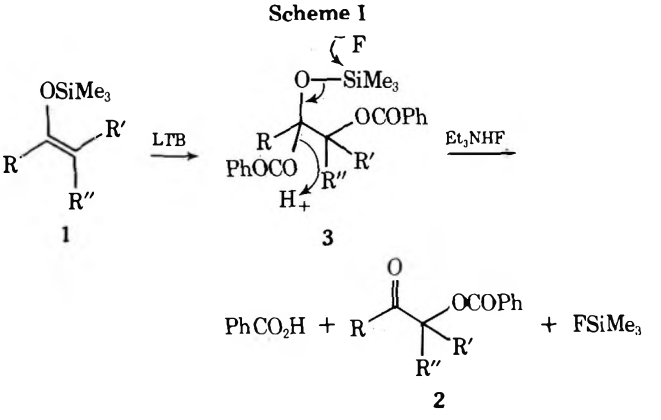


1 2 (1)

Representative examples of the LTB method are shown in Table I. The individual entries serve to point out the advantages of the procedure. All of the yields shown in Table I are quite acceptable, and the yields obtained for the production of **2a–d** are comparable with those obtained via LTA treatment of **1a–d** to afford the corresponding α-acetoxy ketones.[12] The successful preparation of **2f, 2g,** and **2h** indicates the generality of the method as applied to the synthesis of α-benzoyloxy aldehydes. NMR analyses of crude reaction mixtures evidenced that no rearrangement products (α-benzoyloxy ketones) were present.[15] The mildness of the procedure is exemplified by the isolation of **2l** and **2h.** Heating of **2h** resulted in the loss of benzoic acid and formation of cinnamaldehyde. Pyrolysis of **2** is currently being studied as an entry into regiospecifically generated α,β-unsaturated carbonyl systems. That the method provides a regiospecific synthesis of **2** from ketones, via **1**, is noted by the production of **2j**,[16] **2k**,[17] **2l**, and **2m.** The selectivity of LTB for the enol double bond in **1m** to form **2m** is in line with the reactivity of this linkage toward ozone[13d] and the Simmons–Smith reagent[18] in the presence of other unsaturation in **1.** Further, no evidence was obtained for the formation of cyclization products from **1m**, a reaction noted in the reaction of 1,5-pentadiene with LTA.[19]

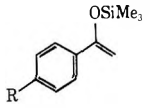
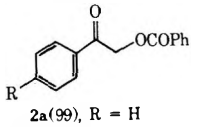
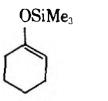
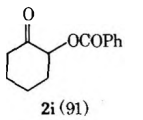
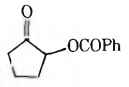
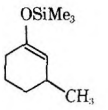
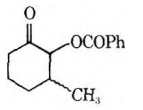
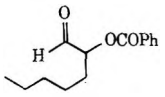
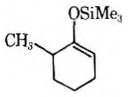
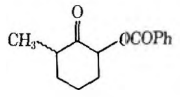
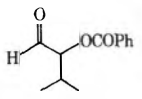
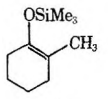
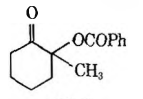
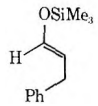
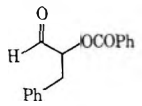
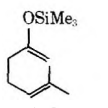
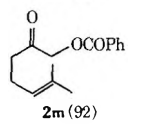
The general mechanism for the formation of **2** from **1** appears to be analogous to that observed in the treatment of **1** with LTA, in which the initial step of the reaction is the production of a diacetate.[12] In the present case, **1** reacts with LTB to form the dibenzoate **3**.[20] Subsequent attack by fluoride ion[21] frees the α-benzoyloxy compound, **2** (Scheme I).

Scheme I



1 3 2

Table I. Oxidation of Trimethylsilyl Enol Ethers, 1, With Lead Tetrabenzoate

1[a,b]	Isolated 2[a,b] (% yield)	1[a,b]	Isolated 2[a,b] (% yield)
 1a,[c] R = H 1b,[c] R = Cl 1c,[c] R = OCH_3 1d,[c] R = F	 2a(99), R = H 2b(96), R = Cl 2c(90), R = OCH_3 2d(97), R = F	 1i[c]	 2i(91)
 1e[c]	 2e(77)	 1j[e]	 2j[f] (83)
 1f[c,d]	 2f(90)	 1k[c]	 2k[g] (92)
 1g[c,d]	 2g(97)	 1l[c]	 2l (80)
 1h[c,d]	 2h(87)	 1m[c]	 2m (92)

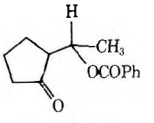
[a] All compounds have ir, NMR, and mass spectral properties consistent with the proposed structures. [b] All new compounds show C and H analyses within ±0.3% of theoretical. [c] Prepared by the method of H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, 34, 2324 (1969). [d] Mixture of *E* and *Z* isomers. [e] Prepared by the method of R. K. Beckman, Jr., *J. Am. Chem. Soc.*, 96, 6179 (1974). [f] Mixture containing 75% 1:1 mixture of *cis*-2j and *trans*-2j and 25% unidentified isomer; see ref 16. [g] Isolated as a 2:1 mixture of *trans*-2k and *cis*-2k; see ref 17.

The following is a typical experimental procedure. A solution of 2 mmol of LTB[22] in 30 ml of dry methylene chloride was cooled to 0 °C (ice bath) and treated with 2 mmol of **1i** (addition time ~30 sec). After 0.5 hr of stirring at room temperature, the resulting slurry was filtered to remove lead dibenzoate, and the solution thus obtained was treated with 6 mmol of triethylammonium fluoride.[21] The resulting solution was stirred at room temperature for 8 hr and then washed sequentially with 20 ml of 50% aqueous sodium carbonate solution, 20 ml of 1.5 N hydrochloric acid, and 20 ml of saturated sodium bicarbonate solution. After drying over anhydrous magnesium sulfate and filtration, solvent was removed in vacuo and the residue crystallized from ether to afford a 91% yield of **2i**, mp 86–87 °C (lit.[23] mp 85–86 °C).

Acknowledgments. The authors gratefully acknowledge the Research Council of the University of Idaho (G.M.R and J.M.G) and the NSF Undergraduate Research Participation Program (G.M.M).

References and Notes

(1) R. Criegee in "Oxidations in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press, New York, N.Y., 1965, p 277.
(2) (a) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955); (b) J. W. Ellis *J. Org. Chem.*, **34**, 1154 (1969).
(3) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 500 (1966).
(4) J.-J. Riehl and A. Fougerousse, *Bull. Soc. Chim. Fr.*, 4083 (1968).
(5) See A. Hassner, R. H. Reuss, and H. W. Pinnick, *J. Org. Chem.*, **40**, 3427 (1975), for a recent synthesis of α-acetoxy aldehydes.
(6) (a) H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc., 4472 (1961)*; (b) J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *ibid.*, 6 (1965); (c) H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc. C*, 756 (1967); (d) D. M. Piatak and E. Caspi, *Chem. Commun.*, 501 (1966); (e) G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970).
(7) J. W. Ellis, *Chem. Commun.*, 406 (1970).
(8) F. Corbani, B. Rindone, and C. Scolastico, *Tetrahedron Lett.*, 2597 (1972).
(9) M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, **33**, 3359 (1968).
(10) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).
(11) (a) A. J. Fry and J. J. O'Dea, *J. Org. Chem.*, **40**, 3625 (1975); (b) T. Shono, M. Okawa, and I. Nishiguchi, *J. Am. Chem. Soc.*, **97**, 6144 (1975).
(12) G. M. Rubottom, J. M. Gruber, and K. Kincaid, *Synth. Commun.*, **6**, 59 (1976).
(13) For recent examples of methods devised for the introduction of hydroxy groups adjacent to the carbonyl function, see (a) G. M. Rubottom, M. A. Vazquez, and D. R. Pelegrina, *Tetrahedron Lett.*, 4319 (1974); (b) G. M. Rubottom and R. Marrero, *J. Org. Chem.*, **40**, 3783 (1975); (c) A. G. Brooke and D. M. MacRae, *J. Organometal. Chem*, **77**, C19 (1974); (d) R. D. Clark and C. H. Heathcock, *Tetrahedron Lett.*, 2027 (1974); (e) H. H. Wasserman and B. H. Lipshutz, *ibid.*, 1713 (1975), and ref 7 cited therein; (f) E. Vedejs, *J. Am. Chem. Soc.*, **96**, 5944 (1974).
(14) G. M. Rubottom, unpublished results. This was also observed in the reaction of LTA with cyclopentadiene: F. V. Brutcher, Jr., and F. J. Vara, *J. Am. Chem. Soc.*, 78, 5695 (1956).
(15) Oxidation of the trimethylsilyl enol ether of phenylacetaldehyde with LTB afforded **2a**.
(16) NMR analysis of the distilled reaction product indicated the presence of a 1:1 mixture of *cis*-**2j** [δ 1.05 (d, 3, *J* = 7 Hz, CH_3), 5.45 (d, 1, *J* = 5 Hz, CHOCOPh)] and *trans*-**2j** [δ 1.18 (d, 3, *J* = 7 Hz, CH_3), 5.08 (d, 1, *J* = 11 Hz, CHOCOPh)] which accounted for 75% of the product. The presence of a third isomer was indicated by a methyl doublet at δ 1.08 coupled to a proton at ~5.4–5.5 (decoupling experiment). A tentative structure for this isomer is i which might arise from a small amount of rearrangement during oxidation.[3]



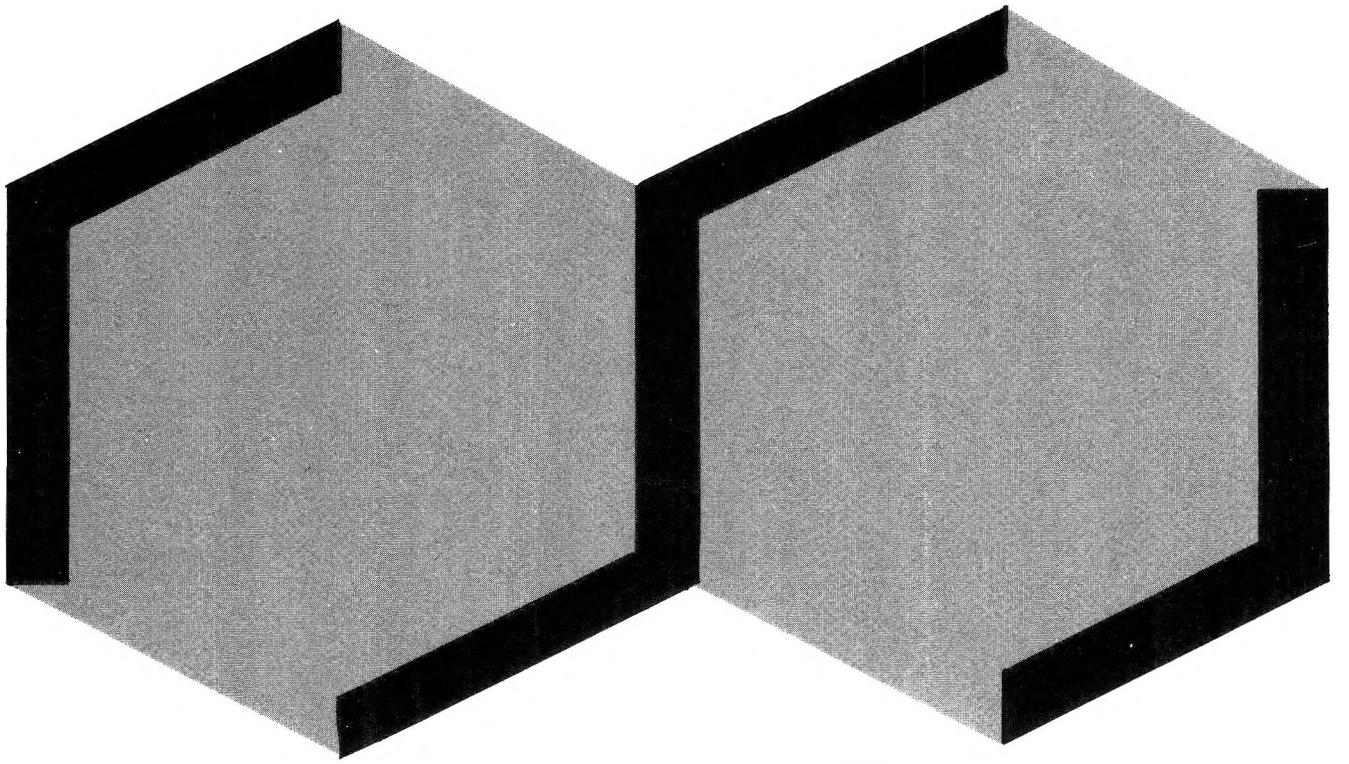
i

(17) *cis*-**2k**: mp 148.5–150 °C; ir (Nujol) 1710, 1725 (sh) cm^{-1}; NMR ($CDCl_3$/TMS) δ 1.08 (d, 3, *J* = 6 Hz, CH_3), 5.30 (m, 1, width at half-height ~20 Hz, CHOCOPh); mass spectrum (15eV) *m/e* (rel intensity) 232 (M^+, 51), 127 (18), 110 (9), 105 (100). *trans*-**2k**: mp 58.5–59.5 °C; ir (Nujol) 1719 cm^{-1}; NMR ($CDCl_3$/TMS) δ 1.17 (d, 3, *J* = 7 Hz, CH_3), 5.37 (m, 1, width at half-height ~14 Hz, CHOCOPh); mass spectrum (15eV) *m/e* (rel intensity) 232 (M^+, 35), 127 (23), 110 (8), 106 (10), 105 (100).
(18) C. Girard and J. M. Conia, *Tetrahedron Lett.*, 3327 (1974).
(19) I. Tabushi and R. Oda, *Tetrahedron Lett.*, 2487 (1966).
(20) NMR analysis of the reaction mixture obtained from the treatment of **1b** with LTB, prior to fluoride treatment, showed the presence of dibenzoate **3b**: NMR ($CDCl_3$/TMS) δ 0.19 [s, 9, $Si(CH_3)_3$], 4.89 (AB d of d, *J* = 12 Hz, 2, CH_2OCOPh), 7.2–8.2 (m, 14, Ar H).
(21) S. Hunig and G. Wehner, *Synthesis*, 180 (1975).
(22) C. D. Hurd and P. R. Austin, *J. Am. Chem. Soc.*, **53**, 1543 (1931).
(23) R. L. Augustine, *J. Org. Chem.*, **28**, 581 (1963).

George M. Rubottom,* John M. Gruber, Gary M. Mong
Department of Chemistry
University of Idaho, Moscow, Idaho 83843

Received February 9, 1976

The leading American journal devoted to general organic chemistry:



The Journal of Organic Chemistry

he career wise way to keep up with current thinking
the field. You get the *total picture* presented through
ɔrty some papers per biweekly issue. Areas of
mphasis include:

- Organic reactions
- Natural products
- Studies of mechanism
- Theoretical organic chemistry
- Various aspects of spectroscopy related to organic chemistry

u get all of this, in the 1100 articles and NOTES
ɔrief, concise accounts of studies of smaller scope)
ɲd over 4000 pages a year from your big informative
ssues of THE JOURNAL.

ɔu owe it to your career to find out for yourself why
ɲe Journal of Organic Chemistry is the leader in its
ɜld.

nd your order today.

. . . *another ACS service*

The Journal of Organic Chemistry
American Chemical Society **1976**
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

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

	U.S.	*Canada***	*Latin America***	*Other Nations***
ACS Member One-Year Rate*	☐ $26.00	☐ $34.25	☐ $33.25	☐ $34.25
Nonmember	☐ $104.00	☐ $112.25	☐ $111.25	☐ $112.25

Bill me ☐ Bill company ☐ Payment enclosed ☐

Air freight rates available on request.

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

Journal subscriptions start January '76

*NOTE: Subscriptions at ACS member rates are for personal use only. **Payment must be made in U.S. currency, by international money order, UNESCO coupons, U.S. bank draft, or order through your book dealer.

Peptide Reagents

It is in the Aldrich tradition to offer a wide variety of intermediates and reagents to the synthetic chemist. For peptide synthesis,[1] we offer one or two reagents for each peptide coupling method described in the literature. Since each method has its advantages and disadvantages, a variety of reagents is necessary.

We offer **isobutyl** and **ethyl chloroformates** for the classic "mixed anhydride" method.[2] Generally, **isobutyl chloroformate** is preferred for the synthesis of peptides of moderate to high molecular weights, and **ethyl chloroformate** for the synthesis of dipeptides.[3] The carbodiimide method[2] is another versatile and convenient method. The very popular **DCC** (*N,N'*-dicyclohexylcarbodiimide) is a highly reactive coupling agent and can be used in solid-phase peptide synthesis (SPPS). The related reagents, **1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate** (morpho-CDI) and **1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride,** are water-soluble diimides which permit simplified purification of the peptide products because the corresponding ureas are water-soluble. Racemization in the **DCC** method can be minimized or completely suppressed by using an additive,[1] such as ***N*-hydroxysuccinimide,*** ***N*-hydroxyphthalimide, *N*-hydroxypiperidine** or **1-hydroxybenzotriazole.** The last-named compound is exceptionally good at suppressing racemization, prohibiting *N*-acylurea formation and improving yields of high-purity peptides.[4] These additives can, of course, be used in SPPS.[1]

The use of **DCC-pentachlorophenol** (DCC-PCP) and **DCC-pentafluorophenol** (DCC-PFP) complexes in the preparation of acylpeptide-PCP and -PFP active esters,[5] as well as other uses[6] of **DCC**, has been described.

Another versatile reagent, **EEDQ** (*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline), has many more advantages: it gives volatile and easily-removable by-products, there is *practically no racemization, and it is useful with O-unprotected* hydroxy amino acids. **EEDQ** and its more reactive analog, **IIDQ** (2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline),[7] another Aldrich first, can also be used for SPPS. **Woodward's Reagents K** and **L** offer similar advantages: they afford water-soluble by-products, yields are high and they are useful with *O*-unprotected hydroxy amino acids.

An oxidation-reduction condensation method[8] employs **Aldrithiol-2** (2,2'-dipyridyl disulfide) and **triphenylphosphine** as coupling reagents. This system can be used in a variety of solvents at a wide range of temperature, affords high yields with little racemization,[8] and can be used in SPPS.[9]

Other reagents include trimethylacetyl chloride,[10] triphenylphosphine with CCl_4 or CBr_4,[11] triphenyl phosphite and imidazole,[12] 1,1'-carbonyldiimidazole,[2] α,α-dichloromethyl methyl ether,[1] chloroacetonitrile,*[1] *p*-nitrophenyl trifluoroacetate,*[13] 2-hydroxypyridine*[14] and 2-mercaptopyridine.*[15]

Listed below are six of the many peptide reagents we offer. Please send for a free list and/or consult our current Catalog-Handbook for packaging and pricing information on the reagents and blocked amino acids.

*Active ester reagents

References:

1) For a summary of some reviews, symposia and books on this subject see J.M. Stewart, *Ann. Rep. Med. Chem.*, **7**, 293 (1972). See also: Y.S. Klausner and M. Bodansky, *Synthesis,* 453 (1972); Y.S. Klausner and M. Bodansky, *ibid.*, 549 (1974); M. Bodansky and Y.S. Klausner, *Chem. Polypeptides,* 21 (1973).
2) Review: N.F. Albertson, *Org. React.*, **12**, 157 (1962).
3) T. Wieland and H. Bernhard, *Ann. Chem.*, **572**, 190 (1951).
4) W. König and R. Geiger, *Chem. Ber.*, **103**, 788 (1970).
5) a) J. Kovacs, L. Kisfaludy, and M.Q. Ceprini, *J. Amer. Chem. Soc.*, **89**, 183 (1967).
   b) J. Kovacs, L. Kisfaludy, M.Q. Ceprini, and R.H. Johnson, *Tetrahedron,* **25**, 2555 (1969).
6) F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
7) Y. Kiso and H. Yajima, *Chem. Commun.*, 942 (1972).
8) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).
9) T. Mukaiyama, R. Matsueda, and H. Marayama, *Bull. Chem. Soc. Japan,* **43**, 1271 (1973).
10) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, John Wiley and Sons, Inc., New York, N.Y., 1967, p. 1229.
11) S. Yamada and Y. Takeuchi, *Tetrahedron Lett.*, 3595 (1971).
12) Y.V. Mitin and O.V. Glinskaya, *ibid.*, 5267 (1969).
13) S. Sakakibara and N. Inukai, *Bull. Chem. Soc. Japan,* **37**, 1231 (1964).
14) A.S. Dutta and J.S. Morley, *J. Chem. Soc. C,* 2896 (1971).
15) K. Lloyd and G.T. Young, *ibid.*, 2890 (1971).

14,304-9	**Aldrithiol-2**	**5g $10.85; 25g $36.05**
C10,640-2	**1-Cyclohexyl-3-(2-morpholino-ethyl)carbodiimide metho-*p*-toluenesulfonate** (morpho-CDI)	**25g $23.00**
D8,000-2	***N,N'*-Dicyclohexylcarbodiimide**	**25g $3.00; 100g $10.00; 1kg $45.00; 10kg $320.00**
15,207-2	**EEDQ**	**25g $7.20; 100g $18.95**
E4526-0	***N*-Ethyl-5-phenylisoxazolium-3-sulfonate** (Woodward's Reagent K)	**5g $19.80; 30g $79.20**
17,824-1	**IIDQ**	**25g $7.20; 100g $18.95**

Aldrich Chemical Company, Inc.

Craftsmen in Chemistry

Corporate Offices:
Aldrich Chemical Co., Inc.
940 W. Saint Paul Ave.
Milwaukee, Wisconsin 53233
U. S. A.

Great Britain:
Aldrich Chemical Co., Ltd.
The Old Brickyard, New Road
Gillingham, Dorset SP8 4JL
England

Belgium/
Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

West Germany/
Continental Europe:
EGA-Chemie KG
7924 Steinheim am Albuch
West Germany