/VOLUME 38 AUGUST 10, 1973 NUMBER 16 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D.C. 20036

BOOKS AND JOURNALS DIVISION

JOHN K CRUM *Director*

RUTH REYNARD *Assistant to the Director*

CHARLES R. BERTSCH *Head, Editorial Processing Department*

D. H. MICHAEL BOWEN *Head, Journals Department*

BACIL GUILEY *Head, Graphics and Production Department*

SELDON W. TERRANT *Head, Research and Development Department*

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 Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Head, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

Advertising Office: Centcom, Ltd., 142 East Ave., Norwalk, Conn. 06851.

The American Chemical Society and the Editors of *The Journal of Organic Chemistry* assume no responsibility for the statements and opinions advanced by contributors.

Business and Subscription Information

Send all new and renewal subscriptions *with payment* to Office of the Controller, 1155 16th Street, N.W., Washington, D. C. 20036. Subscriptions should be renewed promptly to avoid a break in your series. All correspondence and telephone calls regarding changes of address, claims for missing issues, subscription service, the status of records, and accounts should be directed to Manager, Membership and Subscription Services, American Chemical Society, P.O. Box 3337, Columbus, Ohio 43210. Telephone (614) 421-7230.

On changes of address, include both old and new addresses with ZIP code numbers, accompanied by mailing label from a recent issue. Allow four weeks for change to become effective.

Claims for missing numbers will not be allowed (1) if loss was due to failure of notice of change in address to be received before the date specified, (2) if received more than sixty days from date of issue plus time normally required for postal delivery of journal and claim, or (3) if the reason for the claim is "issue missing from files."

Subscription rates for 1973: $20.00 per volume to members of the ACS and $60.00 per volume to all others. Those interested in becoming members should write to the Admissions Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Add $5.00 per subscription for Canada and countries belonging to the Postal Union, and $6.00 for all other countries.

Single copies for current year: $3.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 16th St., N.W., Washington, D.C. 20036.

Subscriptions to this and the other ACS periodical publications are available on microfilm. Supplementary material not printed in this journal is now available in microfiche form on a current subscription basis. For information on microfilm or microfiche subscriptions, write Special Issues Sales Department at the address above.

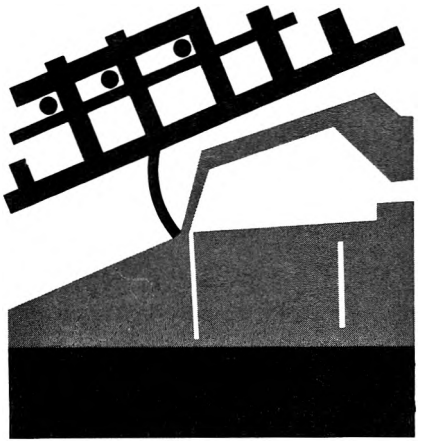
Notice to Authors last printed in the issue of June 1, 1973

JOCEAH 38(16) 2725-2920 (1973)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 16 AUGUST 10, 1973

Electrodeposition of Coatings



ADVANCES IN CHEMISTRY SERIES No. 119

A symposium sponsored by the Division of Organic Coatings and Plastics Chemistry of the American Chemical Society, with George E. F. Brewer, Chairman.

Seventeen papers report major new developments and research in the area of electrodeposition of organic coatings. This extensive collection discusses all aspects of this complex process including the advantage of better corrosion protection, lower cost, and virtual absence of pollution.

Principal topics covered:

- conversion and coatings; pretreating metals; surface changes; power supplies
- new polymers, copolymers, and pigments; preparation of resins; cathodic electrodeposition
- kinetics; dynamic simulation; throwing power
- bath maintenance; design of merchandise; influence of solvents

Each chapter offers material of permanent reference value for the industrial chemist working with automotive and appliance primers, as well as general-purpose one-coat systems.

243 pages with index Cloth (1973) $13.45.
Postpaid in U.S. and Canada, plus 40 cents elsewhere.

Other recommended books in the ADVANCES IN CHEMISTRY SERIES include:

No. 109 Chemical Reaction Engineering
Fixed and fluid bed reactors, polymerization kinetics and reactor design, optimization of reactor performance, catalysis in gas–solid surface reactions, two-phase slurry reactors, industrial process kinetics, and transient operation.
635 pages with index Cloth (1972) $16.50

No. 107 Industrial Color Technology
Summarizes present knowledge of colorant formulation and evaluation and its application to industrial processing. Basic colorimetry, instrumentation, color difference metrics, and color as an aspect of appearance; 32 color plates.
177 pages with index Cloth (1972) $11.50

No. 104 Pesticides Identification at the Residue Level
Is our environment really becoming more toxic, or are pesticides falsely condemned by instruments designed as quantitative rather than qualitative tools? Eleven papers discuss philosophical aspects of ultramicroanalysis, instrumental techniques, microchemical methods, and biological assay.
132 pages with index Cloth (1971) $8.50

No. 103 Origin and Refining of Petroleum
Twelve papers on petroleum origin, deposits, Athabasca tar sands; catalytic reforming, hydrocracking, alkylation, isomerization; ethylene, propylene, vinyl chloride in processing; homogeneous catalysis; future of oil in Canada.
230 pages with index Cloth (1971) $10.00

No. 102 Molecular Sieve Zeolites—II
Thirty-six papers from the Second International Conference on Molecular Sieve Zeolites covering sessions on sorption and catalysis.
459 pages with index Cloth (1971) $16.00

No. 99 Multicomponent Polymer Systems
Thirty-seven papers on systems from olefin, diene, vinyl halide, styrene, acrylic, urethane, and epoxy resins as well as from polyamides, polyesters, polyarylenes, and others. Theory, processing, and applications are included. Nine papers on polyblends, the rest on copolymers.
598 pages with index Cloth (1971) $16.50

No. 97 Refining Petroleum for Chemicals
Up-to-date status report on the advances made in an exciting new industry. Emphasis is on basic processing with specific discussions centering around the chemical reactions used, new developments in these reactions, products and economics, and new processing concept.
293 pages with index Cloth (1970) $11.50

No. 96 Engineering Plastics and Their Commercial Development
A "how-to-do-it" book with discussion and case histories on developing plastics in profitable commercial products. Topics include use research, process development, and patent and legal aspects including clear warnings on contributory infringement. Engineering properties of over 50 plastic products are included.
128 pages with index Cloth (1969) $7.50

No. 92 Epoxy Resins
Sixteen papers on formulation and performance of epoxy resins. Processes and reactions are discussed including condensation reactions, gelation, synthesis, electro-deposition, curing, and reactivity.
230 pages with index Cloth (1970) $10.50

No. 91 Addition and Condensation Polymerization Processes
Twenty-six chapters devoted to process improvements and the polymerization kinetics of common monomers. The last 22 papers deal with new and improved polymers designed for specific uses or properties.
767 pages with index Cloth (1969) $19.50

Order from: **Special Issues Sales**
American Chemical Society, 1155 Sixteenth St., N.W., Washington, D.C. 20036

NOTES

COMMUNICATIONS

■ Supplementary material for this paper is available separately, in photocopy or microfiche form. Ordering information is given in the paper.

* 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 38, NUMBER 16

AUGUST 10, 1973

Conformational Preferences in Acyclic Chloro Sulfides. A Semiquantitative Approach

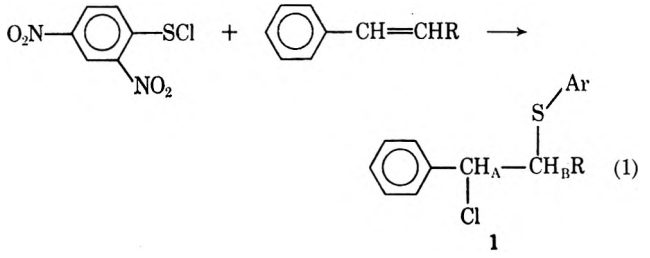
GARY M. UNDERWOOD, A. K. CHAN, T. GREEN, C. T. WATTS, AND CHARLES A. KINGSBURY*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received June 14, 1972

The erythro isomers in alkyl-substituted 1-chloro-1-phenyl-2-ethyl 2,4-dinitrophenyl sulfides increasingly favor the conformer having trans hydrogens as the size of R increases. The rates of solvolysis in 95% ethanol show evidence of anchimeric assistance by sulfur and give products of retained configuration. The rates are correlated with Taft's E_S values and corrected E_S values are taken. These E_S values are correlated with the nmr chemical shift of the 2′ hydrogen in the dinitrophenyl ring, and the E_S values are adjusted again. A linear free-energy correlation is made between the corrected E_S values and the equilibrium constant (gauche → trans conformers) $(J_{obsd} - J_G)/(J_T - J_{obsd})$. Unique values of the limiting coupling constants J_T and J_G cannot be obtained by this procedure. Reasons are given for choosing one solution of the correlation procedure, J_T = 13.5 Hz and J_G = 2.5 ± 1 Hz. The percentage of the trans conformer in several compounds is roughly calculated. The conformations of the solvolysis products (sulfide ethers and sulfide alcohols) are briefly discussed.

Previous work on acyclic conformational preferences has led to significant generalizations,[1,2] but, in general, one is still not able to predict conformation from a simple chemical formula. Each new type of group studied seems to introduce variables not previously suspected. The present work was intended to elucidate the effect of variation of the size of R on the conformational preferences of certain chloro sulfides of general structure **1**. A much larger variety of R groups was possible because of the facile synthesis indicated in eq 1.[3]



(1)

1

Part of our interest in these chloro sulfides stemmed from the possibility of an attractive interaction between these groups.[4] However, other work on alkyl-substituted chloro sulfides indicated that this interaction was weakly repulsive.[5] Since the conformation of each compound is the result of a balance between all attractive and all repulsive factors, which often are sensitive to exact internuclear distances, the study of the purturbation caused by moving from alkyl chloro sulfides to aryl chloro sulfides seemed attractive. In addition to the interaction between heteroatoms,[6] other factors, such as chlorine–alkyl and chlorine–hydrogen gauche interactions (presumably weakly attractive),[7] as well as the effects of restriction of motion of the SAr group, must be considered.[5]

Qualitative conformational preferences are determined from vicinal nmr coupling constants (J_{AB}). Large values for J_{AB} (10–13 Hz) indicate a preference for a conformer having trans hydrogens. Small values (1–3 Hz) show a preference for one of the conformers having gauche hydrogens. Intermediate values result from weighted means of the above values.[8] The nmr data for 12 pairs of diastereomers are listed in Table I. These data will be discussed in terms of the conformers shown in Chart I.

(1) D. H. R. Barton, *Experientia*, **23**, 316 (1950).

(2) (a) J. L. Mateos and D. J. Cram, *J. Amer. Chem. Soc.*, **81**, 2756 (1959); (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, pp 331–343.

(3) (a) N. Kharasch, *J. Chem. Educ.*, **33**, 585 (1956); (b) G. H. Schmid and V. Csizmadia, *Can. J. Chem.*, **44**, 1338 (1966); (c) G. H. Schmid, *ibid.*, **46**, 3757 (1968); (d) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **90**, 2075 (1968); (e) F. T. Bond, *ibid.*, **90**, 5326 (1968); (f) H. Kwart and R. K. Miller, *ibid.*, **78**, 5678 (1956); (g) S. J. Cristol, R. Arganbright, G. Brindell, and R. M. Heitz, *ibid.*, **79**, 6035 (1957); (h) C. Brown and D. R. Hogg, *J. Chem. Soc. B*, 1262 (1968); (i) T. L. Jacobs and R. Macomber, *J. Org. Chem.*, **33**, 2988 (1968); (j) G. Beverly, D. R. Hogg, and J. H. Smith, *Chem. Ind. (London)*, 1403 (1968).

(4) T. Bjorvatten and O. Hassel, *Acta Chem. Scand.*, **15**, 1429 (1961).

(5) G. M. Underwood and C. Kingsbury, *J. Org. Chem.*, **38**, 1553 (1973).

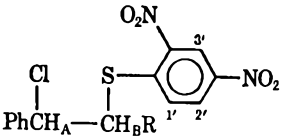
(6) (a) G. Hamer, W. F. Reynolds, and J. Wood, *Can. J. Chem.*, **49**, 1755 (1971); (b) G. Hueblein, R. Kuhmstadt, P. Kadura, and H. Dawcynski, *Tetrahedron*, **26**, 81, 91 (1970); (c) R. J. Abraham and K. Perry, *J. Chem. Soc. B*, 539 (1970); (d) R. J. Abraham and E. Gatti, *ibid.*, 961 (1969); (e) B. Hawkins, W. Bremser, S. Borcic, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4472 (1971); (f) R. A. Pethrick and E. Wyn-Jones, *Quart. Rev., Chem. Soc.*, **23**, 301 (1969); (g) R. D. Norris and G. Binsch, *J. Amer. Chem. Soc.*, **95**, 182 (1973).

(7) S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, New York, N. Y., 1954, p 15.

(8) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

TABLE I

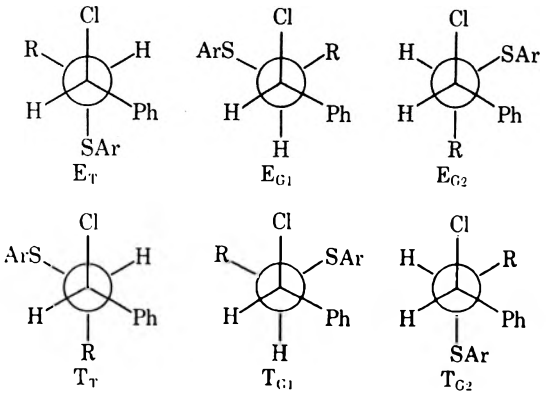
60-MHz CHEMICAL SHIFTS AND COUPLING CONSTANTS OF 2-12



Compd 2	R	Mp, °C	J, Hz: J_{AB} (CDCl3)[b,e]	J_{AB} (DMSO)[c]	J_{BR} (CDCl3)[e]	Chemical shifts (CDCl3)[b]: A[e]	B[e]	1'	2'	3'
	H	148	6.2, 8.5			5.12	3.74	7.55	8.31[a]	9.02
erythro-3	CH_3	92	7.1	7.1		5.03	3.99	7.52	8.20[a]	8.79[a]
threo-3		94	5.7	6.5		5.11	4.12	7.51	8.21	8.67
erythro-4	C_2H_5	144	8.7	8.7		4.96	3.82	7.55	8.12[a]	8.65[a]
threo-4		127	4.8	5.9		5.27	3.87	~7.4	8.21	8.91
erythro-5	*i*-C_3H_7	162	10.7	11.0	2.4	4.93	3.78	7.44	8.04[a]	8.42[a]
threo-5		138	6.1	7.6	6.2	5.32	3.77	~7.4	8.10	8.55
erythro-6	*t*-C_4H_9	134	4.7			5.46	3.88	7.86	8.21	8.69
threo-6		143	1.6			5.62	3.41	6.50	7.70	8.54
erythro-7	$CH(C_2H_5)_2$	161	11.0		2.8	5.12	3.74	7.55	8.01[a]	8.47
threo-7		116	7.0		~4	5.35	4.02	7.61	8.21	8.82
erythro-8	$CH_2C(CH_3)_3$	116	7.2		1.2, 8.7	4.90	3.81	7.65	8.19[a]	8.69[a]
threo-8		153	4.3		2.2, 8.3	5.21	3.94	~7.5	8.21	8.98
erythro-9	C_3H_5[f]	147	6.4		8.5	5.18	3.41	7.62	8.21[a]	8.78[a]
threo-9	C_3H_5	142	5.1		9.4	4.94	3.72	~7.4	8.19	8.92
erythro-10	C_4H_7[f]	105	7.0		8.4	5.05	3.95	7.74	8.19[a]	8.72
threo-10	C_4H_7	105	3.7		9.5	5.22	3.78	7.06	8.01	8.82
erythro[d]-10'	C_4H_7[f]	112	5.4		~8.4	4.76	4.24	~7.4	8.15	8.96
threo[d]-10'	C_4H_7	125	4.5		~9.2	5.00	3.84	7.98	8.26	8.82
erythro-11	C_5H_9[f]	148	9.5		~4.4	5.00	4.01	7.58	8.10[a]	8.55[a]
threo-11	C_5H_9	109	4.2	5.2	~7.5	5.35	3.75	~7.07	7.95	8.74
erythro-12	C_6H_{11}[f]	174	10.8		~2.9	4.99	3.72	7.42	8.03[a]	8.47[a]
threo-12	C_6H_{11}	139	5.4	6.8	~5.4	5.40	3.65	~7.3	8.04	8.77

[a] Determined at 100 MHz, 1.0% w/v in $CDCl_3$, corrected to 60 MHz. [b] *Ca.* 10% w/v solution, at 60 MHz. [c] 5.0% w/v solutions. [d] The chloride and sulfide groups in **10** are reversed in **10'**. [e] The coupling constants and chemical shifts were verified by computer simulation. Parameters were varied until the plot of the simulation was superimposible on the original spectrum. [f] Cycloalkyl groups.

CHART I



With increasing size of R (up to *tert*-butyl), the erythro isomers show a monotonic increase in J_{AB}, indicative of a growing preference for E_T (Chart I). This behavior is common to the majority of systems studied to date.[9,10a] The now familiar discontinuity occurs in moving from R = isopropyl (**5**) to R = *tert*-butyl (**6**).[10] This change gives rise to an apparent preference for a conformer having gauche hydrogens. However, the variation of dihedral angles from near 60° in order to achieve a more comfortable arrangement of groups in E_T would serve to reduce J_{AB}. The coupling constant may also be affected by the spreading of the C–C–*tert*-butyl bond angle.[10d] However, the lack of mutual shielding of the aromatic groups (*vide infra*) is consistent with a much smaller population of E_T in **6** than in **5**.

Compound **8** (R = neopentyl) shows an apparent preference for E_T of about the same magnitude as that in **3** (R = methyl), which was unexpected on the basis of relative sizes of R. However, as Chart II shows, the coupling constants of the methylene hydrogens are abnormally small. Again, bond angle spreading may be in effect, thus reducing the effect size of the neopentyl group.

The effect of size is strikingly evident in the erythro cycloalkyl compounds **9**–**12**. The cyclopropyl and cyclobutyl groups have apparent conformational preferences of about the same order as methyl. Where R = cyclohexyl, the preference for E_T is slightly larger than that of its closest analog, isopropyl. The compression of bond angles necessary for the closing of the small rings results in widening of the exocyclic bond angles,[11]

(9) One must be careful how the erythro diastereomer is defined. Strictly speaking, the above observation holds true where erythro configuration is defined on the basis of size [H. E. Zimmerman and W. Chang, *J. Amer. Chem. Soc.*, **81**, 3634 (1959)], and preferably where attractive interactions are absent.

(10) (a) C. Kingsbury and D. Best, *J. Org. Chem.*, **32**, 6 (1967); (b) H. Bodot, J. Fediere, G. Pouzard, and L. Pujol, *Bull. Soc. Chim. Fr.*, 3260 (1968); (c) L. M. Jackman, and D. Kelly, *J. Chem. Soc. B*, 110 (1970); (d) C. Altona and D. Faber, *Chem. Commun.*, 1210 (1971).

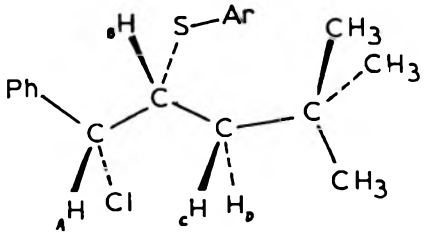
(11) H. C. Brown and M. Gerstein, *J. Amer. Chem. Soc.*, **72**, 2826 (1950).

TABLE II

RATES OF SOLVOLYSIS AND ACTIVATION PARAMETERS OF 2-12 IN 95% ETHANOL

Compd	R	$k_{obsd} \times 10^4$, sec^{-1} 50.0°	60.0°	70.0°	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
2	H	0.0278 ± 0.0001		0.47 ± 0.02		
erythro-3	CH_3	0.916 ± 0.014	2.27 ± 0.01	5.37 ± 0.06	18.9	−18.8
threo-3		0.036 ± 0.001	0.082 ± 0.0003	0.21 ± 0.01		
erythro-4	C_2H_5	2.61 ± 0.01	6.15 ± 0.15	14.1 ± 0.1	17.9	−19.6
threo-4		0.042 ± 0.001	0.11 ± 0.01	0.26 ± 0.01		
erythro-5	*i*-C_3H_7	5.30 ± 0.08				
threo-5		0.025 ± 0.007	0.062 ± 0.001	0.17 ± 0.01		
erythro-6	*t*-C_4H_9	124 ± 1			15.1	−20.6
threo-6		0.012 ± 0.01	0.028 ± 0.01	0.096 ± 0.001		
erythro-7	$CH(C_2H_5)_2$	3.67 ± 0.04				
threo-7				0.20 ± 0.01		
erythro-8	$CH_2C(CH_3)_3$	3.13 ± 0.01				
threo-8		0.034 ± 0.02	0.095 ± 0.002	0.23 ± 0.04		
erythro-9	C_3H_5	1.22 ± 0.01				
threo-9				0.17 ± 0.01		
erythro-10	C_4H_7	1.21 ± 0.01				
threo-10				0.31 ± 0.01		
erythro-11	C_5H_9	4.99 ± 0.05				
threo-11				0.55 ± 0.02		
erythro-12	C_6H_{11}	6.50 ± 0.05	16.7 ± 0.2	35.8 ± 0.3	18.3	−16.5
threo-12		0.045 ± 0.002	0.11 ± 0.01	0.33 ± 01		

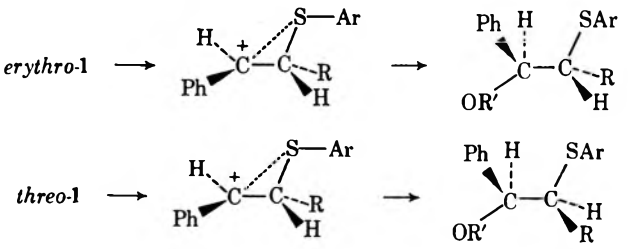
CHART II



a

J_{AB} = 7.2 Hz; J_{BC} = 1.2 Hz; J_{BD} = 8.7 Hz

CHART III



and leads to a reduction of the steric interaction with the neighboring phenyl or chloro group.

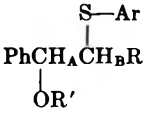
The regular increase in J_{AB} with increasing size of R prompted an attempt to establish a linear free energy correlation between the nmr data and the rates of solvolysis of these chlorides. As Table II shows, the rate of solvolysis of the erythro isomers increases as the size of R increases. It is quite reasonable that the same factors that affect conformation should also affect the rate of reaction. These solvolyses are subject to anchimeric assistance of ionization by neighboring sulfide.[12] Thus, the erythro isomers, which form the quite stable trans episulfonium ion (Chart III), are more reactive than the threo isomers, which form the less stable cis episulfonium ion. The trends of change of the nmr parameters of the solvolysis products as R is varied are consistent with products formed with retention of configuration (Table III). The size of R affects the rate of reaction by steric acceleration of anchimeric assistance.

A quantitative measure of the steric effect of an alkyl group on the rate of a standard reaction is avail-

(12) (a) K. Gunderman, *Angew. Chem., Int. Ed. Engl.*, **2**, 674 (1963); (b) A. G. Ogston, E. R. Holiday, J. Philpot, and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948); (c) P. D. Bartlett and C. G. Swain, *J. Amer. Chem. Soc.*, **71**, 1406 (1949); (d) R. C. Fuson, C. C. Price, and D. M. Burness, *J. Org. Chem.*, **11**, 475 (1946).

TABLE III

COUPLING CONSTANTS[a]



R	Ethers, R' = C_2H_5, Compd	J_{AB}, Hz	Alcohols,[b] R' = H, Compd	J_{AB}, Hz
CH_3	*erythro*-13	4.9	*erythro*-23	4.2
	threo-13	7.8	*threo*-23	7.2
C_2H_5	*erythro*-14	6.4	*erythro*-24	5.2
	threo-14	7.2	*threo*-24	6.4
i-C_3H_7	*erythro*-15	9.5	*erythro*-25	8.9
	threo-15	7.8	*threo*-25	6.7
t-C_4H_9	*erythro*-16	7.6	*erythro*-26	
	threo-16	6.8	*threo*-26	5.9
$CH(C_2H_5)_2$	*erythro*-17	9.5	*erythro*-27	8.9
	threo-17	8.4	*threo*-27	7.6
$CH_2C(CH_3)_3$	*erythro*-18	5.5	*erythro*-28	3.8
	threo-18	7.8	*threo*-28	6.5
Cyclopropyl	*erythro*-19	4.2	*erythro*-29	4.5
	threo-19	6.0	*threo*-29	
Cyclobutyl	*erythro*-20	5.7	*erythro*-30	
	threo-20	5.9	*threo*-30	5.2
Cyclopentyl	*erythro*-21	7.0	*erythro*-31	6.2
	threo-21	6.4	*threo*-31	5.2
Cyclohexyl	*erythro*-22	9.4	*erythro*-32	8.7
	threo-22	7.1	*threo*-32	5.9

[a] Spectra were determined from a mixture of about 85% ether and 15% alcohol in deuteriochloroform at ambient temperature. [b] Owing to the low concentration of alcohols, coupling constants are only considered accurate to ±0.3 Hz.

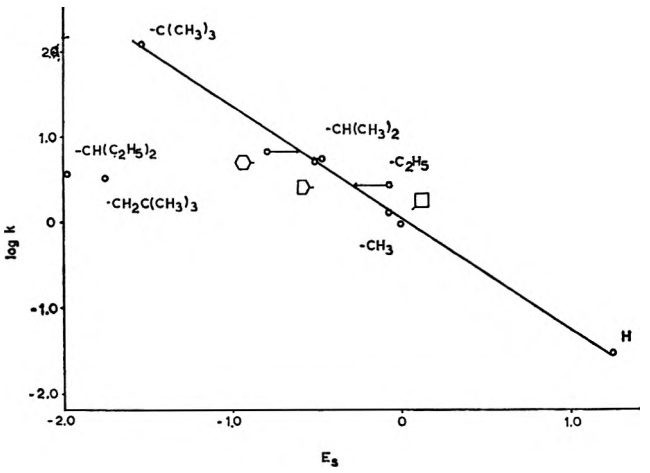
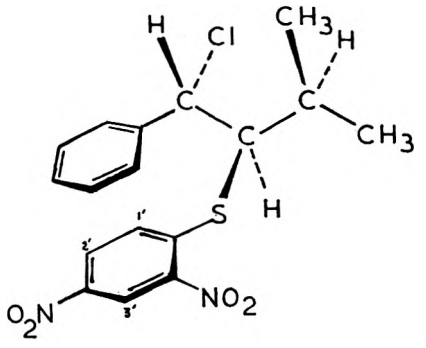


Figure 1.—Plot of the logarithm of solvolysis rate for compounds of general structure 1 (having the R groups indicated in the plot) *vs.* Taft's steric substituent constants (E_S).

able in the form of Taft's E_S values.[13] In general, the rates of solvolysis correlate adequately with E_S, although the points for certain compounds are far off the line (Figure 1). It seems quite likely that the reaction from which E_S values were defined, the hydrolysis of certain esters, was partly sensitive to the size of a substituent at its periphery. However, the degree of steric acceleration of anchimeric assistance of 2–12 is sensitive to the size of a substituent near its point of attachment to the ethanic skeleton. Thus, neopentyl, which has a huge E_S value, shows only a small conformational preference and a low reaction rate. For neopentyl, and other R groups which did not correlate with E_S, adjusted E_S values were taken (as shown by the arrows in Figure 1) essentially making all rates colinear. An E_S value for cyclopropyl was similarly determined (−0.05). Rather than the above treatment, an attempted correlation with cyclohexane conformational free energies[14] or with G values[15] would have been preferable, but data were not available for the full range of substituents.

Figure 1 shows that R = *tert*-butyl greatly accelerates the solvolysis rate, as expected from its great size. As indicated above, the probable conformation of *erythro*-**6** (R = *tert*-butyl) is different from that of other compounds having sizable groups, *e.g.*, **5** and **7**, which strongly prefer E_T. The transition state for the solvolysis resembles E_T, since the neighboring group, sulfide, is trans to the leaving group. Thus, in analogy to Curtin–Hammett considerations,[16] there is no requirement that a ground-state conformation favorable for neighboring-group assistance must be highly populated in order to observe rapid solvolysis. In fact, **5** and **7** solvolyze more slowly than **6**, though E_T is more highly populated. Numerous recent studies have correlated reactivity with ground-state conformation, and, in most cases, the data were carefully interpreted.[17] However, claims are made in certain papers that a favorable (or unfavorable) ground-state conformation is responsible for high (or low) reactivity. In our estimation, it is dubious whether ground-state conformation *per se* determines reactivity, in the absence of high barriers to conformational interconversion. Conformation and reactivity often parallel one another because both are related to the same basic factor, *i.e.*, the minimization of nonbonded interactions in the predominant ground-state conformation *and in the transition state.*

Since nothing *requires* ground-state conformation to be related in any way to solvolysis rate, a cross-check on the revised E_S values seemed advisable. This was possible through use of the chemical-shift data (Table I).[18] As the size of R increases, and E_T becomes increasingly important, an upfield shift of the aromatic hydrogens 1′–3′ is observed. This shift is most regular for 2′, which is not subject to variable steric interactions with other groups. As E_T becomes more highly populated, the preferred conformation of the dinitrophenyl groups becomes one in which this group is face to face (or, more likely, somewhat off center of face to face) with the other aromatic group (structure b).[19]



b

Thus 2′ suffers shielding owing to the ring current of the neighboring phenyl group. Models show that such shielding is also possible in E_{G1}, though less probable because the dinitrophenyl group is directed away from phenyl by R. The possibility of a intramolecular charge-transfer interaction[20] between the two rings in the face-to-face conformation was investigated by means of ^{13}C shifts. Additional electron density in the dinitrophenyl ring should result in an upfield shift. However, a downfield shift of 2.1 ppm was observed for $C_{1'}$, although upfield shifts of 1.1 ppm were noted for $C_{2'}$ and $C_{3'}$ in comparison to a compound in which

(13) (a) R. W. Taft, Jr. *J. Amer. Chem. Soc.*, **74**, 3120 (1952); (b) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 556.

(14) J. A. Hirsch, "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 199.

(15) J. E. Anderson and H. Pearson, *Chem. Commun.*, 871 (1971).

(16) D. Y. Curtin, *Rec. Chem. Progr. (Kresge-Hooker Sci. Lib.)*, **15**, 111 (1954).

(17) (a) D. R. Brook and A. J. Duke, *Chem. Commun.*, **62** (1970); (b) D. Koshland, Jr., *ibid.*, 854 (1971); (c) C. Spangler and R. Hennis, *ibid.*, **24** (1972); (d) G. A. Doorakian, H. H. Freedman, R. F. Bryan, and H. P. Weber, *J. Amer. Chem. Soc.*, **92**, 399 (1970); (e) J. S. Swenton and P. D. Bartlett, *ibid.*, **90**, 2056 (1968); (f) D. Craig, J. J. Shipman, and R. B. Fowler, *ibid.*, **83**, 2885 (1961); (g) J. F. Bunnett and C. Hauser, *ibid.*, **87**, 2214 (1965); (h) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 22.

(18) (a) G. Dana, J. Chuche, and M.-R. Monot, *Bull. Soc. Chim. Fr.* 3308 (1967); (b) S. L. Spassov, *Tetrahedron*, **25**, 3631 (1969).

(19) (a) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958); (b) J. S. Waugh and R. F. Fessenden, *J. Amer. Chem. Soc.*, **79**, 846 (1957); (c) H. O. House, R. Magin, and H. Thompson, *J. Org. Chem.*, **28**, 2403 (1963); (d) F. A. Bovey, F. Hood, E. Anderson, and L. Snyder, *J. Chem. Phys.*, **42**, 3900 (1965).

(20) (a) M. Oki and K. Mutai, *Tetrahedron*, **26**, 1181 (1970); (b) H. Craenen, J. Verhoeven, and T. deBoer, *ibid.*, **27**, 2561 (1971); *Tetrahedron Lett.*, **26**, 1167 (1970); (c) R. Carruthers, *Chem. Commun.*, 1206 (1967).

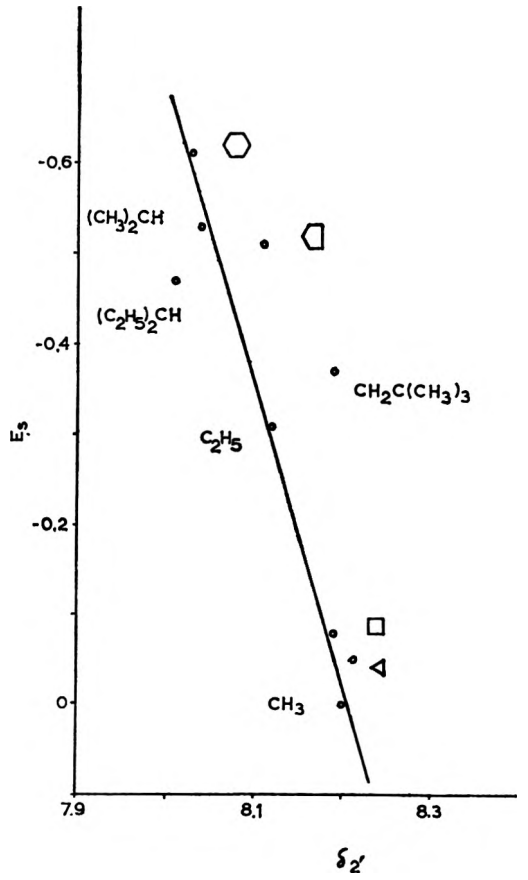


Figure 2.—Plot of corrected steric substituent constants (derived from Figure 1) *vs.* the chemical shift on the 2′ hydrogen of the dinitrophenyl ring in compounds of general structure 1 (having the various R groups indicated).

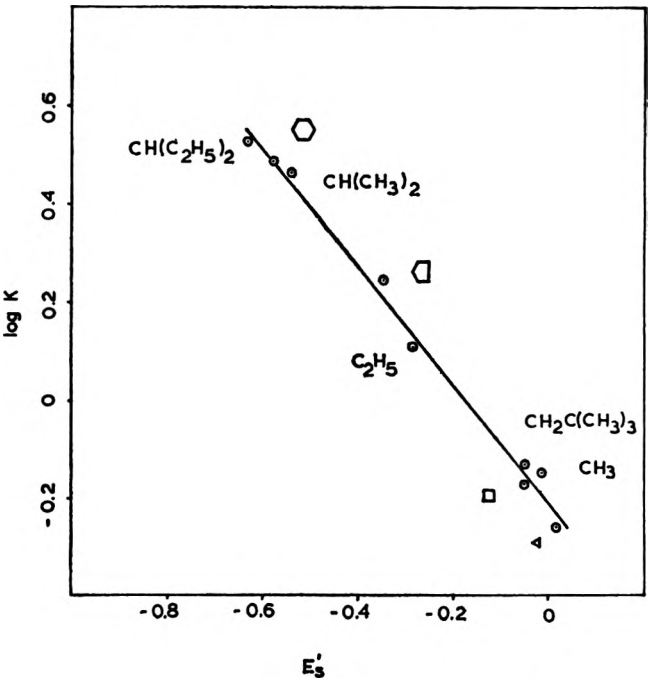


Figure 3.—Plot of the logarithm of the equilibrium constant for the conformational interconversion of trans and gauche conformers *vs.* steric substituent constants (derived from Figure 2).

isopropyl replaced phenyl. This variation does not permit the identification of a charge-transfer interaction, although it seems likely that one should occur.

Figure 2 shows a plot of revised E_S *vs.* the chemical shift of hydrogen 2′ (observed at high dilution). The plot is fortuitously linear, though some points are well off the line. From this plot, doubly corrected values for E_S are taken (major changes include diethylcarbinyl, −0.66; neopentyl, −0.05; cyclobutyl −0.05; and cyclopropyl, +0.02).

In setting up the above-mentioned linear free energy correlation, the usual expression for the equilibrium between the (sum of) gauche conformer(s) and the trans conformer is taken (eq 2)[21]

$$K = (J_{obsd} - J_G)/(J_T - J_{obsd}) \quad (2)$$

where J_T and J_G are the limiting values expected for a conformationally pure material (*i.e.*, 100% E_T and 100% E_{G1} and/or E_{G2}, respectively). This introduces an error, since the two conformers having gauche hydrogens will not have the same limiting coupling constant, J_G. The limiting value for E_{G1} should be smaller than that for E_{G2} because of the effect of the electronegative atom trans to hydrogen in E_{G1}. However, the population of E_{G1} should be comparatively small, particularly where R is large.

(21) K. A. McLauchlan, "Magnetic Resonance," Clarendon Press, London, 1972, p 70; see also F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 70, and ref 24.

For the comparison measurement

$$\Delta F^* = RT \ln (kT/hk_{rate})$$

or

$$\Delta F^* = -RT \ln k_{rate} + C \quad (3)$$

where k, T, and h have their usual significance, and where C is a constant. In comparison of the equilibrium with the data derived from rates, the linear relationship of eq 4 will be tested.

$$-RT \ln (J_{obsd} - J_G)/(J_T - J_{obsd}) = -rRT \ln k_{rate} + C'$$

or

$$\log (J_{obsd} - J_G)/(J_T - J_{obsd}) = r'E_S + C'' \quad (4)$$

Here it is convenient to use the doubly corrected E_S parameters in place of the rate constants, again redefining the constant C.

Computer-assisted analysis of eq 4 showed that a linear relationship did exist (Figure 3), but unique values for J_T and J_G could not be found by this technique. Of the various permitted solutions of eq 4 (*cf.* Appendix), that of $J_T = 13.5 \pm 1$ Hz and $J_G = 2.5 \pm 1$ Hz are considered probably closest to the true limiting values. Studies of the rigid molecule, 1-chloro-4-(1,1-dimethylpropyl)-2-cyclohexyl 2′,4′-dinitrophenyl sulfide showed a probable coupling constant of 2.1 Hz for the gauche (diequatorial) hydrogens analogous to A and B (*cf.* eq 1). However, the rigid system has the threo configuration, whereas the above analysis concerns only the erythro isomers. Also, the rigid system lacks the phenyl group. More important, deviations of the dihedral angles from the idealized value of 60° are probable, and these deviations may be quite different in the two cases. In conformer E_{G2}, a more comfortable fit of groups could be achieved by widening of the dihedral angle between vicinal hydrogens. In the cyclic molecule, the dihedral angle is probably less than

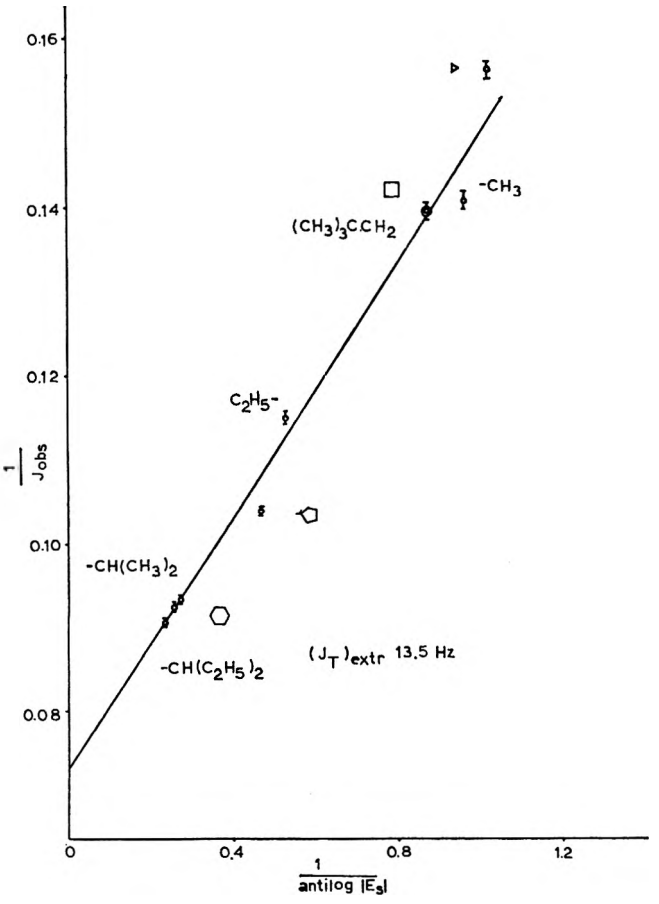


Figure 4.—Plot of the inverse of the observed nmr coupling constant *vs.* the inverse of the antilog of E_S (derived from Figure 2).

60°. Thus, there is no reason to expect exact correspondence of the limiting J values of the rigid system, and the acyclic molecules of interest, although these may be similar.

The limiting value for trans vicinal hydrogens of 13.5 Hz can be derived in a different way. A plot of $1/J_{obsd}$ *vs.* $1/a$ log E_S is fortuitously linear (Figure 4). The extrapolated value of J_{AB} is 13.5 Hz. Essentially, this treatment notes the monotonic increase in J_{AB} as the size of R increases up to *tert*-butyl, and determines the J_{AB} expected for an infinitely large R group, assuming that the linearity is maintained during the extrapolation.

Various attempts to determine the limiting coupling constants of conformers having trans or gauche hydrogens have appeared in the literature.[22] The rather common temperature-variation method now appears somewhat questionable.[23] Direct observation of the various conformers at very low temperature is in theory the best method, but it is impracticable for all but highly soluble compounds.[22c,24] A method of calculation of limiting J values from electrostatic and quadrupolar effects (resulting from solvent variation) upon observed coupling constants has been developed by Abraham, Cavelli, and Pachler.[23] This work suggests a serious drawback to our analysis, namely, that a group of compounds cannot be analyzed in terms of a single limiting value for J_T or for J_G. Each compound of a set may have its own limiting values.[6g] However, for **2**–**12**, only nonpolar groups are varied, and the limiting J values may all be rather similar (except[10b] for the *tert*-butyl compound **6**).[29] Unfortunately, the seriousness of this possible discrepancy is difficult to test.

In other cases, Bodot and coworkers have determined conformer populations by comparing nmr data with other experimental variables, *e.g.*, infrared spectra.[10b,24] Combinations of P–H and H–H nmr couplings have been used to estimate conformer preferences.[25] In still other cases, dipole moment data have been used in conjunction with infrared data to elucidate conformational preferences.[26] Various types of calculations have been used to determine conformational preferences, but their applicability to solution chemistry is open to question if polar groups are present.[27]

The limiting values for J_T and J_G of **2**–**12** may be compared to certain values from the literature. In very early work, Sheppard and Turner used 13 and 3 Hz as best values.[28] Gutowsky and coworkers favored J_T = 16 Hz, which was derived from temperature-variation measurements.[22] Whitesides and coworkers determined limiting values of *ca.* 14 and 4 Hz on certain *tert*-butyl-substituted ethanes.[29] Garbisch, Anet, and their respective coworkers determined values of *ca.* 13 and 3 Hz by direct observations on cyclohexane and its simple derivatives.[30] Altona and coworkers favored values of 9.2 and 0.9 Hz for the limiting coupling constants for the C-17 proton of a steroid and a side-chain proton[31] (a rather strained system[10b]). Eliel and coworkers determined values of *ca.* 12.5 Hz for trans diaxial protons, and 2.6–5.0 Hz for gauche (e–a) and 1.3 Hz for gauche (e–e) hydrogens in a 1,3-dioxane system, in which electronegativity effects play a large role.[32] Calculations by Fahey of limiting values in simple hydrocarbons showed J_T = 11.9 and J_G = 1.9 Hz.[33] Bodot and coworkers used values of *ca.* 10 and 2.8 Hz in calculations of conformer populations of certain chlorohydrins.[10b,33] From solvent effect studies, Abraham and coworkers calculated that J_G was 2.8 Hz in 1,1,2-trichloroethane. However, in various 1,2-dihaloethanes, J_G was of the order of 5.3 Hz when neither proton was trans to halogen but 2.5 Hz where one proton was so situated.[23] Cavanaugh used limiting

(22) (a) H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1958); (b) H. S. Gutowsky, G. Belford, and P. McMahon, *ibid.*, **36**, 3353 (1962); see however, V. Tabacik, *Tetrahedron Lett.*, 555 (1968); (c) R. A. Newmark and C. H. Sederholm, *J. Chem. Phys.*, **43**, 602 (1965); (d) R. A. Newmark and N. Miller, *J. Phys. Chem.*, **75**, 505 (1971); (e) See ref 6e, 10b, and 18.

(23) (a) R. J. Abraham, L. Cavelli, and K. Pachler, *Mol. Phys.*, **11**, 471 (1966); (b) R. J. Abraham and M. Cooper, *J. Chem. Soc. B*, 202 (1967); (c) see also ref 6c and 6d.

(24) J.-P. Aycard, H. Bodot, R. Garnier, R. Lauricella, and G. Pouzard, *Org. Magn. Resonance*, 7 (1970).

(25) W. G. Bentrude and K. C. Yee, *Chem. Commun.*, 169 (1972).

(26) G. Drefahl, G. Hueblein, and D. Voigt, *J. Prakt. Chem.*, **23**, 157 (1964); see also C. Altona, H. Buys, H. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2273 (1967).

(27) (a) L. Radom, W. Latham, W. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **95**, 693 (1973); (b) N. L. Allinger, J. Hirsch, M. Miller, I. Tyminski, and F. Van Catledge, *ibid.*, **90**, 1199 (1968).

(28) (a) N. Sheppard and J. Turner, *Proc. Roy. Soc., Ser. A*, **252**, 506 (1959); (b) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962); (c) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

(29) G. Whitesides, J. Sevenair, and R. Goetz, *ibid.*, **89**, 1135 (1967).

(30) (a) E. Garbisch, Jr., and M. Griffith, *ibid.*, **90**, 6543 (1968); (b) F. A. L. Anet, M. Ahmad, and L. Hall, *Proc. Chem. Soc.*, 145 (1965).

(31) (a) C. Altona and J. Hirschmann, *Tetrahedron*, **26**, 2173 (1970); (b) C. Altona and M. Sundaralingam, *ibid.*, **26**, 925 (1970).

(32) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **11**, 739 (1972).

(33) R. C. Fahey, G. Graham, and R. Piccioni, *J. Amer. Chem. Soc.*, **88**, 193 (1966).

values of 13.5 and 2.8 Hz in studies of phenylalanine.[34] In a rigid eight-membered ring, values of J_T = 10.6 and J_G = 2.2 or 5.6 Hz were reported.[35] In an exhaustive compilation of known values of coupling constants, Bothner-By concluded that J_T was commonly in the region of 10.5–12 Hz for rigid six-membered rings, although J_T could be as low as 8 Hz for certain monosaccharides.[36]

As a check on the limiting values derived in the present study, the populations of the three conformers of compound 2 may be calculated, where x is the population of E_T, y is that of E_{G1} and, z is that of E_{G2} (R = H). Here the more proper approach is used, namely, that the coupling constant of gauche hydrogens in E_{G2} is *ca.* 2 Hz less that of E_{G1}. Since R = H in this case, two equations can be listed. Using the relationship that x, y, and z add up to 1, all variables can be found.

$$\begin{aligned} J_{obsd} &= 6.2 = 13.5x + 0.5y + 2.5z \\ J_{obsd} &= 8.5 = 2.5x + 13.5y + 0.5z \end{aligned} \quad (5)$$

The solution is x = 0.43, y = 0.55, and z = 0.02. On the other hand, if E_{G1} and E_{G2} are assumed to have the same coupling constant, 2.5 Hz, x = 0.32, y = 0.55, and z = 0.12. In either case, the least stable conformer, E_{G2}, has the lowest population, and the most sterically unhindered conformer, E_{G1}, has the highest population.

From the limiting coupling constants defined above, the percentage of E_T can be roughly calculated to be 42% for **3**, 56% for **4**, 74% for **5**, 77% for **7**, 35% for **9**, 43% for **10**, 64% for **11**, and 75% for **12**. Using another solution of eq 4, J_T = 14.5 Hz and J_G = 1.5 Hz, the population of E_T would be 43% for **3** and 73% for **7**. Using limiting values of 12.5 and 3.5 Hz, the population of E_T would be 40% for **3** and 83% for **7**. Thus, the population of E_T is not strongly sensitive to the exact solution of eq 4. Holding J_T constant and permitting J_G to vary by ±1 Hz produces a maximum variation of ±10% in the compounds having a low population of E_T. Holding J_G constant and varying J_T by ±1 Hz, produces a maximum variation of ±7% (in the compounds rich in E_T). An allowance for the different coupling constants expected for E_{G1} and E_{G2} would vary the percentages of E_T quoted by a few per cent.

Threo Isomers.—The preferred conformation of the threo isomers results from a balance of a number of factors. An increase in the size of R results in an initial decrease in J_{AB} followed by an increase, *i.e.*, the series **2** → **3** → **4** → **5** shows a minimum in J_{AB} at **4** (R = ethyl); the series **9** → **10** → **11** → **12** has a minimum at **10** (R = cyclobutyl). When R is very small, a variety of conformations are populated. As R becomes somewhat larger, a preference for T_{G1} occurs in which R and phenyl are trans. As R becomes very large, models suggest that the motion of S–Ar becomes highly restricted in T_{G1} and conformer T_T becomes somewhat more important, resulting in an increase in J_{AB}. The latter conformer permits the S–Ar group somewhat more freedom, at the expense of placing R gauche to phenyl. In agreement with the larger population of T_T in **5** and **7**, hydrogens 1′, 2′, and 3′ of the dinitrophenyl ring are relatively unshielded, since the two aromatic rings are remote from one another in T_T. *threo*-**6**, however, strongly prefers T_{G1}. Models again show that the face-to-face conformation of the aromatic rings is preferred. The resonance of 1′ (6.5 ppm) lies upfield from phenyl, owing to extreme shielding, whereas in **2**–**5** this resonance lies downfield from phenyl.

The effect of moving to a more polar solvent (DMSO) is indicated in Table I. Little solvent effect is noted for the erythro isomers. The threo isomers show a uniform increase in J_{AB}. For **5** and **11**, an increase in J_{AB} in moving to DMSO as solvent was accompanied by a decrease in J_{BC}. This change of alternate coupling constants in opposite directions is thought to reflect a true conformation change, although solvent effects on J_T and J_G may also be important.[37] Reynolds and Wood have noted similar effects of DMSO.[38] Abraham and coworkers showed that solvents complex with the various conformers to different extents, causing a change in the conformer equilibrium to favor the complexed conformer.[23] No effect of DMSO was noted in compounds lacking the C_1 phenyl group. Similar effects (though smaller) were noted in moving from $CDCl_3$ to the dipolar, but poorly hydrogen bonding solvent, acetonitrile, We tentatively suggest that a polarization interaction occurs between the dipolar solvent and the aromatic group(s), coupled with a dipolar interaction between the complexed solvent and the polar groups of the substrate. However, further study is required to elucidate why such conformers as E_{G1} are not stabilized.

Solvolysis Products.—The solvolysis of the chloro sulfides in 95% aqueous ethanol cleanly gave product ethers and alcohols of retained configuration. The coupling constants of the products were easily determined from the product mixture. No attempt was made to separate and otherwise characterize the products. The data are listed in Table III. The coupling constants for the erythro isomers are generally considerably less than those for the threo isomers. This situation is frequently met where quite strong attractive interactions exist (*e.g.*, OH–OH hydrogen bonding).[18] Only with very bulky R groups does J_{AB} for the erythro isomer exceed that for the threo isomer. As Table III shows, the preference for E_T is quite small for the erythro ethers and still smaller for the alcohols. The preference for E_{G1} and/or E_{G2} in the case of the alcohols may be due to a OH–S hydrogen bond. However, sulfur is electron deficient in **3** → **5** owing to the inductive effect of the nitro groups. These compounds show little or no tendency to complex with $Eu(dpm)_3$ or $Eu(fod)_3$.[39] This electron withdrawal would also harm hydrogen bonding.

We originally considered the possibility of an attractive oxygen–sulfur gauche interaction which occurs independently of hydrogen bonding. However, a

(34) J. R. Cavanaugh, *J. Amer. Chem. Soc.*, **92**, 1488 (1970), and earlier papers.

(35) H. Gunther, *Angew. Chem., Int. Ed. Engl.*, **11**, 861 (1972).

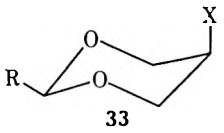
(36) A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 115 (1965); see also C. Kingsbury, R. Egan, and T. Perun, *J. Org. Chem.*, **36**, 2913 (1970).

(37) (a) H. Finegold, *J. Phys. Chem.*, **72**, 3244 (1968); (b) E. I. Snyder, *J. Amer. Chem. Soc.*, **85**, 2624 (1963).

(38) W. F. Reynolds and D. Wood, *Can. J. Chem.*, **47**, 1295 (1969).

(39) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) P. DeMarco, T. Elzey, R. Lewis, and E. Wenkert, *ibid.*, **92**, 5743 (1970); (c) W. DeW. Horrocks, Jr., J. Sipe III, and J. Luber, *ibid.*, **93**, 5259 (1971), and references cited therein.

recent review article by Eliel indicated that the axial thio ether function X in **33** was highly destabilized,



33

more so than *tert*-butyl. On the other hand, the analogous sulfoxide and sulfone groups X preferred the axial orientation.[32] Although the O–S interaction appeared unfavorable, the axial position was nearly equal in energy to the equatorial for several types of oxygen substituents.

The greater flexibility of the open-chain molecule, coupled with the fact that only one oxygen function is present, may permit gauche oxygen and sulfur groups in **13**, **14**, **18**, **19**, and **20** without the degree of repulsion between electron pairs found in **33** (X = SCH_3). In any case, the balance between all attractive and all repulsive interactions is such that these compounds will tolerate gauche OR′ and SAr groups to a considerably larger extent than gauche Cl and SAr groups (erythro isomers). According to Zefirov, electron–electron repulsions of groups having second-row atoms are substantially larger than repulsions of groups having first- and second-row atoms.[40]

Experimental Section

Compounds **2**–**12** were made by addition of 2,4-dinitrobenzenesulfenyl chloride (**34**) to the appropriate cis or trans alkene.[3,41] The alkenes were prepared by variations of the Wittig reaction.[42] The phosphonium salts, necessary for the Wittig reaction, were prepared by literature methods, and their properties were generally in accord with those reported in the literature.[42]

Preparation of Alkenes Using the Wittig Reaction (Method A.[43]—To the appropriate phosphonium salt and anhydrous potassium iodide, if used,[43] was added sufficient dry *N*,*N*-dimethylformamide (DMF) to make an approximate 1 *M* solution. The system was swept with dry nitrogen, the solution was cooled to 0–5°, and a 1 *M* solution of potassium *tert*-butoxide in dry DMF was added dropwise to the stirred mixture. An immediate red or red-orange color appeared. The addition was stopped after 1–3 ml of solution had been added. A 2 *M* solution of the appropriate aldehyde was then added dropwise until the red color disappeared. The solutions of base and aldehyde were alternately added in this manner until all aldehyde had been used, maintaining the temperature near 0°. The solution was allowed to warm to room temperature with stirring (approximately 1–2 hr), poured into water (approximately 1.1 times the volume of reaction mixture), and acidified to neutrality with dilute, aqueous HCl. The alkene was separated by extracting with petroleum ether (bp 30–60°), the combined extracts were washed with water and dried ($MgSO_4$), and the petroleum ether was removed by rotary evaporation at reduced pressure. The resulting oil was then vacuum distilled and used as the cis–trans mixture or the isomers were separated by distillation using a spinning band column or vapor phase chromatography, as indicated.

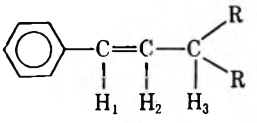
Preparation of Alkenes Using the Wittig Reaction (Method B).—The procedure used was similar to that of method A, with the exception that the base used was sodium methoxide. The base was added in small portions, in solid form (very low solubility in DMF), to the solution of phosphonium salt (and anhydrous potassium iodide, if used) until a red coloration was distinctly visible. The mixture was stirred for 2–5 min. The aldehyde solution was added dropwise, with stirring, until the red color disappeared. Alternate addition of base and aldehyde was repeated until aldehyde was exhausted. The work-up, purification, and separation of isomers were the same as in method A.

Preparation of Alkenes Using the Wittig Reaction (Method C).—To the appropriate phosphonium salt (and anhydrous potassium iodide, if used) was added enough dry DMF to make the resulting solution approximately 1 *M* in phosphonium salt. The system was swept with dry nitrogen, the solution was cooled to 0°, and a 1 *M* solution of potassium *tert*-butoxide in dry DMF was added dropwise, with stirring and cooling. When the addition was complete, a 3–5 *M* solution of aldehyde in DMF was added, dropwise, with stirring, to the reaction mixture. After stirring for an additional 2 hr, the mixture was permitted to warm to room temperature, and worked up as previously described.

Preparation of Alkenes Using the Wittig Reaction (Method D).—To the appropriate phosphonium salt (and anhydrous potassium iodide, if used) and aldehyde was added enough dry DMF to make the resulting solution approximately 1 *M* in each of the reactants. The solution was cooled to 0°, a dry nitrogen sweep was started, and a 1 *M* solution of potassium *tert*-butoxide in dry DMF was added dropwise, with stirring, maintaining the temperature near 0°. When the addition of base was complete, the mixture was stirred for 2 hr with no cooling, then worked up, and purified; the isomers were separated as discussed previously.

Addition of 2,4-Dinitrobenzenesulfenyl Chloride (34) to Alkenes. A.—A weighed amount of the appropriate alkene (usually 0.02 mol), glacial acetic acid or dry DMF (approximately 10 ml), and 2,4-DNBSC (10–50% excess) was heated on the steam bath, with swirling, for 5 min. During this time, the solid 2,4-DNBSC (**34**) dissolved. After 12–18 hr at room temperature, the solution was poured over 20 g of ice and allowed to remain until the ice had just melted. The solid obtained was separated by vacuum filtration, washed with water, and allowed to air dry. The resulting solid was recrystallized from dichloromethane–pentane or chloroform–pentane, as indicated for each compound.

B.—Alternatively, if the adduct did not crystallize upon pouring the solution over ice, the mixture was extracted with ether, washed with water, 5% sodium bicarbonate solution, and water, and dried ($MgSO_4$), and the ether was removed at reduced pressure. The resulting adduct, if it remained an oil, could be induced to crystallize by taking it up in ether–pentane. Recrystallization from appropriate solvents yielded pure adducts. In listings of parameters of the various alkenes the numbering system of structure c will be used.



c

Preparation of 1-Chloro-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (2).—To a solution of styrene (8.0 g, 0.075 mol) in dry acetic acid (20 ml) was added 2,4-dinitrobenzenesulfenyl chloride (**34**) (19.0 g, 0.081 mol), yielding, after recrystallization from chloroform–pentane, 21.8 g (83%) of yellow crystals, mp 148.0° (lit.[41] mp 143.0–143.5°).

Preparation of 1-Phenyl-1-propenes Using the Wittig Reaction.—To a solution of benzyltriphenylphosphonium bromide (108.5 g, 0.25 mol) in dry DMF (250 ml) was added potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (250 ml), and then acetaldehyde (12 g, 0.27 mol) in DMF (50 ml) was added according to Wittig method B. The crude oil that resulted, after work-up, was distilled using a spinning band column at reduced pressure, yielding 23 fractions of 1–1.5 ml each: fractions 2–12, bp 97–99° (82 mm); fractions 13–14, bp 100–106° (82 mm); fractions 15–23, bp 106–107° (82 mm). The fractions were analyzed by vapor phase chromatography using the QF-1 column. At a column temperature of 130° using a 60 ml/min helium flow, the retention times of the cis and trans alkenes were 6.0 and 7.25 min, respectively. Fractions 2–12 were found to be cis alkene of 99% purity, fractions 13–14 were a mixture of cis and trans alkenes, and fractions 15–23 were the trans isomer of 99% purity. The nmr spectra of these alkenes agreed with those obtained by Cabiddu, Maccioni, and Secci.[42]

(40) (a) N. S. Zefirov, V. Blagoveshchensky, I. Kazimirchik, and N. Surova, *Tetrahedron*, **27**, 3111 (1971). (b) In **13**–**20**, the nitro groups render sulfur electron deficient and reduce the size of the nonbonded pairs. Sulfur could then attract oxygen by the means noted by Pople[27a] [see also M. Robb, W. Haines, and I. Czizmadia, *J. Amer. Chem. Soc.*, **95**, 42 (1973)].

(41) (a) N. Kharasch and R. B. Longford, *Org. Syn.*, **44**, 47 (1944); (b) N. Kharasch and C. M. Buess, *J. Amer. Chem. Soc.*, **71**, 2724 (1949).

(42) S. Cabiddu, A. Maccioni, and M. Secci, *Ann. Chim. (Rome)*, **54**, 1153 (1964).

(43) L. D. Bergelson and M. M. Shemyakin, *Tetrahedron*, **19**, 149 (1963).

Preparation of *erythro*-1-Chloro-1-phenyl-2-propyl 2,4-Dinitrophenyl Sulfide (3).—To *trans*-1-phenylpropene (0.58 g, 0.0049 mol) in dry acetic acid (10 ml) was added 2,4-DNBSC (**34**) (1.20 g, 0.0051 mol), yielding, after recrystallization from $CHCl_3$–pentane, 1.52 g (89%) of yellow crystals, mp 91–91.5° (lit.[44] mp 91.5–92.0°).

Anal. Calcd for $C_{15}H_{13}ClN_2O_4S$: C, 51.07; H, 3.71. Found: C, 51.11; H, 3.78.

Preparation of *threo*-1-Chloro-1-phenyl-2-propyl 2,4-Dinitrophenyl Sulfide (3).—To *cis*-1-phenylpropene (0.58 g, 0.049 mol) in dry acetic acid (10 ml) was added 2,4-DNBSC (**34**) (1.21 g, 0.0051 mol). This yielded, after recrystallization from chloroform–pentane, 1.43 g (83%) of adduct, mp 93.5–94.5°.

Anal. Calcd for $C_{15}H_{13}ClN_2O_4S$: C, 51.07; H, 3.71. Found: C, 51.20; H, 3.59.

Preparation of 1-Phenyl-1-butenes.—The procedure of Wittig method A was followed using benzyltriphenylphosphonium bromide (108 g, 0.25 mol) and anhydrous potassium iodide (83 g) in DMF (250 ml), and alternately adding potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (300 ml) and propanal (16 g, 0.275 mol) in DMF (80 ml). The reaction yielded 27 g (82%) of a slightly yellow oil which was distilled, using a spinning band column, yielding 21 fractions of 0.5–1.5 ml each: fractions 1–3, bp 22–80° (20 mm); fractions 4–15, bp 80–83° (20 mm); fractions 16–17, bp 84–89° (20 mm); fractions 18–21, bp 89–91° (20 mm) [lit.[44] cis alkene bp 84.0–85.0° (23 mm); trans alkene, 91.0–92.0° (23 mm)]. The nmr of fractions 8 and 20 showed then to be *cis*- and *trans*-1-phenyl-1-butene, respectively.

cis-1-Phenyl-1-butene had nmr (CCl_4) δ 1.05 (t, 3, J_{CH_2,CH_3} = 7.5 Hz, CH_3), 2.00–2.60 (m, 2, CH_2), 5.57 (dt, 1, J_{1,CH_2} = 7.0 Hz, $J_{1,2}$ = 11.6 Hz, H_2), 6.33 (dt, 1, $J_{1,2}$ = 11.6 Hz, J_{1,CH_2} = 1.6 Hz, H_1), 7.05–7.30 (m, 5, aromatic protons).

trans-1-phenyl-1-butene had nmr (CCl_4) δ 1.09 (t, 3, J_{CH_2,CH_3} = 7.5 Hz, CH_3), 1.90–2.50 (m, 2, CH_2), 5.80–6.50 (m, 2, H_1 and H_2), 7.00–7.40 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-1-phenyl-2-butyl 2,4-Dinitrophenyl Sulfide (4).—To *trans*-1-phenyl-1-butene (1.53 g, 0.01 mol) in DMF (10 ml) was added **34** (2.65 g, 0.0108 mol). After recrystallization from dichloromethane–pentane, there resulted 3.21 g (88%) of pure adduct, mp 144.0–144.5° (lit.[45] mp 144.4–144.8°).

Anal. Calcd for $C_{16}H_{15}ClN_2O_4S$: C, 52.39; H, 4.12. Found: C, 52.24; H, 4.08.

Preparation of *threo*-4.—To *cis*-1-phenyl-1-butene (1.31 g, 0.01 mol) in DMF (10 ml) was added **34** (2.68 g, 0.0109 mol). Recrystallization from dichloromethane–pentane yielded 3.62 g (76%) of pure adduct: mp 127.0–127.5°; nmr δ 1.15 (t, 3, J_{CH_3,CH_2} = 7.2 Hz, CH_3), 1.60–2.50 (m, 2, CH_2), 3.87 (dt, 1, J_{2,CH_2} = 8.5, $J_{1,2}$ = 4.8 Hz, H_2), 5.27 (d, 1, $J_{1,2}$ = 4.8 Hz, H_1), 7.15–7.65 (m, 6, aromatic protons and $H_{1'}$), 8.21 (dd, 1, $J_{1',2'}$ = 8.9, $J_{2',3'}$ = 2.5 Hz, $H_{2'}$), 8.91 (d, 1, $J_{2',3'}$ = 2.5 Hz, $H_{3'}$).

Anal. Calcd for $C_{16}H_{15}ClN_2O_4S$: C, 52.39; H, 4.12. Found: C, 52.28; H, 4.26.

Preparation of 3-Methyl-1-phenyl-1-butenes. A.—The procedure of Wittig method C was followed using benzyltriphenylphosphonium bromide (108 g, 0.25 mol) and anhydrous potassium iodide (83.0 g, 0.5 mol) in DMF (270 ml). To this was added potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (360 ml), followed by a solution of 2-methylpropanal (19.8 g, 0.275 mol) in DMF (50 ml). The reaction yielded 39.3 g (89.5%) of a slightly yellow oil, which, the nmr spectrum indicated, consisted of a mixture of 89% cis alkene and 11% trans alkene. The mixture was used without further purification.

B.—The procedure of Wittig method D was followed using isobutyltriphenylphosphonium iodide (111.5 g, 0.25 mol), benzaldehyde (26.5 g, 0.25 mol) in DMF (300 ml), and potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (200 ml). The resulting oil was distilled, using a spinning band column, yielding 13 fractions (*ca.* 2 ml each): fractions 2–7, bp 76–77° (12 mm); fractions 8–9, bp 77–83° (12 mm); fractions 10–13, bp 84–85° (12 mm). These fractions were analyzed by vapor phase chromatography using the QF-1 column. At a column temperature of 155° and 60 ml/min helium flow, the retention times of the cis and trans alkenes were 3.25 and 4.75 min, respectively.

cis-3-Methyl-1-phenyl-1-butene had nmr (94 mg of alkene/744 mg of CCl_4) δ 1.02 (d, 6, J_{3,CH_3} = 6.5 Hz, CH_3), 2.50–3.30 (m, 1, H_3), 5.39 (dd, 1, $J_{1,2}$ = 11.6, $J_{2,3}$ = 9.95 Hz, H_2), 6.25 (d, 1, $J_{1,2}$ = 11.6 Hz, H_1), 7.18 (s, 5, aromatic protons).

trans-3-Methyl-1-phenyl-1-butene had nmr (139 mg of alkene/1.12 g of CCl_4) δ 1.06 (d, 6, J_{3,CH_3} = 6.3 Hz, CH_3), 2.15–2.85 (m, 1, H_3), 5.80–6.50 (m, 2, H_1 and H_2), 6.95–7.35 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-3-methyl-1-phenyl-2-butyl 2,4-Dinitrophenyl Sulfide (5).—To *trans*-3-methyl-1-phenyl-1-butene (2.86 g, 0.019 mol) in acetic acid (10 ml) was added **34** (4.71 g, 0.02 mol). The adduct, after recrystallization from chloroform–pentane, weighed 6.92 g (93%), mp 161–162°.

Anal. Calcd for $C_{17}H_{17}ClN_2O_4S$: C, 53.61; H, 4.50. Found: C, 53.68; H, 4.57.

Preparation of *threo*-5.—To the solution of a mixture of *cis*- and *trans*-3-methyl-1-phenyl-1-butene (89% cis, 11% trans alkene; 3.1 g, 0.0212 mol) in DMF (10 ml) was added **34** (5.3 g, 0.0225 mol). The mixture of diastereomers resulting from this reaction was separated by fractional recrystallization from chloroform–pentane, yielding 5.83 g (75%) of pure threo diastereomer, mp 137.5–138°.

Anal. Calcd for $C_{17}H_{17}ClN_2O_4S$: C, 53.61; H, 4.50; N, 7.36. Found: C, 53.62; H, 4.36; N, 7.39.

Preparation of *erythro*-1-Chloro-3,3-dimethyl-1-phenyl-2-butyl 2,4-Dinitrophenyl Sulfide (6).—To a solution of *trans*-3,3-dimethyl-1-phenyl-1-butene (1.0 g, 6.25 mmol) in acetic acid (10 ml) was added **34** (1.65 g, 7.0 mmol). The yield, after recrystallization from chloroform–pentane, was 1.67 g (68%), mp 134.0–134.5°.

Anal. Calcd for $C_{18}H_{19}ClN_2O_4S$: C, 54.75; H, 4.85. Found: C, 54.85; H, 4.85.

Preparation of *threo*-6.—To a solution of *cis*-3,3-dimethyl-1-phenyl-1-butene (1.0 g, 6.25 mmol) in acetic acid (10 ml) was added **34** (1.66 g, 7.0 mmol). There was obtained 1.96 g (79%) of yellow needles, mp 142.5–143.0° (chloroform–pentane).

Anal. Calcd for $C_{18}H_{19}ClN_2O_4S$: C, 54.75; H, 4.85; N, 7.09. Found: C, 54.76; H, 4.72; N, 7.22.

Preparation of 3-Ethyl-1-phenyl-1-pentenes.—The procedure of Wittig method A was followed using benzyltriphenylphosphonium bromide (108 g, 0.25 mol) in DMF (200 ml). To this solution was added, alternately, solutions of potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (325 ml) and 2-ethylbutanal (27.7 g, 0.252 mol) in DMF (50 ml). The reaction yielded 35.2 g (81%) of an oil with bp 64–69° (0.14 mm). This liquid was distilled, using a spinning band column, and yielded 17 fractions of 2–3 ml each: fractions 1–9, bp 87–89° (3.1 mm); fractions 10–11, bp 89.5–39° (3.1 mm); fractions 12–17, bp 90–93° (2.9–3.0 mm).

cis-3-Ethyl-1-phenyl-1-pentene (fractions 1–9) had nmr (neat liquid) δ 0.65–1.05 (m, 6, CH_3), 0.65–1.70 (m, 4, CH_2), 2.15–2.75 (m, 1, H_3), 5.32 (dd, 1, $J_{2,3}$ = 10.5, $J_{1,2}$ = 12.0 Hz, H_2), 6.50 (d, 1, $J_{1,2}$ = 12.0 Hz, H_1), 6.95–7.35 (m, 5, aromatic protons).

trans-3-Ethyl-1-phenyl-1-pentene (fractions 12–17) had nmr (neat liquid) δ 0.65–1.05 (m, 6, CH_3), 1.05–2.20 (m, 5, CH_2 and H_3), 5.87 (dd, 1, $J_{2,3}$ = 7.7, $J_{1,2}$ = 16.0 Hz, H_2), 6.30 (d, $J_{1,2}$ = 16.0 Hz, H_1), 7.00–7.40 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-3-ethyl-1-phenyl-2-pentyl 2,4-Dinitrophenyl Sulfide (7).—To a solution of *trans*-3-ethyl-1-phenyl-1-pentene (1.76 g, 0.01 mol) in DMF (10 ml) was added **34** (2.59 g, 0.015 mol), yielding 3.66 g (90%) of yellow crystals, mp 161.1–161.7°, after recrystallization from dichloromethane–pentane.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4S$: C, 55.81; H, 5.18. Found: C, 55.82; H, 5.05.

Preparation of *threo*-7.—To a solution of *cis*-3-ethyl-1-phenyl-1-pentene (1.74 g, 0.01 mol) in DMF (10 ml) was added **34** (2.60 g, 0.015 mol), yielding 3.41 g (83%) of recrystallized adduct, mp 115.5–116.0° (dichloromethane–pentane). Interpretation of the nmr spectrum was made difficult by the fact that the four methylene protons of the two ethyl groups and H_3 all had essentially the same chemical shift, causing extensive virtual coupling. The absorbance for H_2 was therefore very broad and an exact value for $J_{2,3}$ was impossible to obtain. Computer simulation of the spectrum showed that the best value for this coupling constant was *ca.* 4 ± 1 Hz.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4S$: C, 55.81; H, 5.18. Found: C, 55.82; H, 5.09.

Preparation of 4,4-Dimethyl-1-phenyl-1-pentenes.—The procedure of Wittig method D was followed, using a solution of 3,3-dimethylbutyltriphenylphosphonium bromide (171 g, 0.40 mol)

(44) T. DeWolfe, D. Hagman, and W. G. Young, *J. Amer. Chem. Soc.*, **79**, 4795 (1957).

(45) C. F. Hauser, T. Brooks, M. Miles, M. Raymond, and G. B. Butler, *J. Org. Chem.*, **28**, 372 (1963).

and benzaldehyde (45 g, 0.425 mol) in 600 ml of DMF and adding a solution of potassium *tert*-butoxide (75 g, 0.4 mol) in DMF (500 ml). The reaction yielded 81.3 g (80%) of a clear liquid, bp 52–58° (0.12 mm). The resulting oil was distilled, using a spinning band column, yielding 16 fractions: fractions 2–6, bp 90.5–92.5° (5 mm); fractions 6–8, bp 92.5–98° (5 mm); fractions 8–16, bp 98.0–99.5° (5 mm).

cis-4,4-Dimethyl-1-phenyl-1-pentene (fractions 2–6) had nmr δ 0.89 (s, 9, *tert*-butyl protons), 2.24 (dd, 2, J_{2,CH_2} = 7.4 Hz, J_{1,CH_2} = 1.8 Hz, CH_2), 5.77 (dt, 1, J_{2,CH_2} = 7.4 Hz, $J_{1,2}$ = 12.2 Hz, H_2), 6.53 (dt, 1, $J_{1,2}$ = 12.2 Hz, J_{1,CH_2} = 1.8 Hz, H_1), 7.05–7.40 (m, 5, aromatic protons).

trans-4,4-Dimethyl-1-phenyl-1-pentene (fractions 8–16) had nmr (neat liquid) δ 0.92 (s, 9, *tert*-butyl protons), 1.90–2.15 (m, 2, CH_2), 5.85–6.55 (m, 2, H_1 and H_2), 7.00–7.40 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-4,4-dimethyl-1-phenyl-2-pentyl 2,4-Dinitrophenyl Sulfide (8).—To a solution of *trans*-4,4-dimethyl-1-phenyl-1-pentene (1.77 g, 0.01 mol) in DMF (10 ml) was added **34** (2.58 g, 0.015 mol), yielding, after recrystallization from dichloromethane–pentane, 3.62 g (89%) of yellow needles, mp 115.5–116°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4S$: C, 55.81; H, 5.18. Found: C, 55.99; H, 5.22.

Preparation of *threo*-8.—To a solution of *cis*-4,4-dimethyl-1-phenyl-1-pentene (1.74 g, 0.01 mol) in acetic acid (10 ml) was added **34** (2.60 g, 0.015 mol), yielding 3.38 g (83%) of crude adduct, which, the nmr spectrum indicated, consisted of a mixture of Markovnikov and anti-Markovnikov addition products. The reaction was repeated in DMF with similar results. The mixture consisted of 54% *threo*-1-chloro-4,4-dimethyl-1-phenyl-2-pentyl 2,4-dinitrophenyl sulfide [Markovnikov addition product, with a doublet at δ 5.23 (J = 4.3 Hz) and a multiplet at δ 3.94] and 46% 2-chloro-4,4-dimethyl-1-phenyl-1-pentyl 2′,4′-dinitrophenyl sulfide [anti-Markovnikov addition product, with a doublet at δ 4.76 (J = 4.5 Hz) and a multiplet at δ 4.37]. The mixture was fractionally recrystallized from dichloromethane–petroleum ether, affording pure Markovnikov product, 1.37 g (33%), mp 152.8–153.1°.

Anal. Calcd for $C_{19}H_{21}ClN_2O_4S$: C, 55.81; H, 5.18. Found: C, 55.86; H, 5.15.

Preparation of 1-Cyclopropyl-2-phenylethylene.—The procedure of Wittig method A was followed, using a solution of benzyltriphenylphosphonium bromide (129 g, 0.30 mol) in DMF (300 ml), and adding, alternately, solutions of potassium *tert*-butoxide (57 g, 0.03 mol) in DMF (250 ml) and cyclopropanecarboxaldehyde (20.52 g,) The reaction yielded, upon distillation, 34.8 g of a clear, colorless oil, bp 54.0–64.5° (0.18–2.4 mm). The oil was spinning band distilled, yielding 22 fractions of 1–2 ml each: fractions 1–10, bp 60.5–61.5° (0.5 mm); fractions 11–12, bp 61.5–66.5° (0.5 mm); fractions 13–22, bp 67.0–69.0° (0.5 mm). The nmr spectra are in agreement with those reported by Schweizer, Thompson, and Ulrich.[46]

cis-1-Cyclopropyl-2-phenylethylene (fraction 9) had nmr (neat liquid) δ 0.15–0.80 (m, 4, $-CH_2-$ of ring), 1.48–2.14 (m, 1, H_3), 4.96 (dd, 1, $J_{2,3}$ = 9.6, $J_{1,2}$ = 11.6 Hz, H_2), 6.35 (d, 1, $J_{1,2}$ = 11.6 Hz, H_3), 7.0–7.5 (m, 5, aromatic protons).

trans-1-Cyclopropyl-2-phenylethylene (fraction 16) had nmr (neat liquid) δ 0.15–0.85 (m, 4, $-CH_2-$ of ring), 1.05–1.70 (m, 1, H_3), 5.62 (dd, 1, $J_{2,3}$ = 8.4, $J_{1,2}$ = 16.0 Hz, H_2), 6.35 (d, 1, $J_{1,2}$ = 16.0 Hz, H_1), 6.90–7.35 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-2-cyclopropyl-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (9).—To a solution of *trans*-1-cyclopropyl-2-phenylethylene (1.47 g, 0.01 mol) in DMF (10 ml) was added **34** (2.62 g, 0.011 mol). The solution was heated briefly (1–2 min) until **34** went into solution, and then allowed to stand at room temperature for 8 days before work up. From the reaction was obtained 3.19 g (82%) of yellow needles, mp 147.2–147.8° (dichloromethane–pentane).

Anal. Calcd for $C_{17}H_{15}ClN_2O_4S$: C, 53.90; H, 3.99. Found: C, 53.80; H, 3.93.

Preparation of *threo*-9.—To a solution of *cis*-1-cyclopropyl-2-phenylethylene (1.45 g, 0.01 mol) in DMF (10 ml) was added **34** (2.62 g, 0.011 mol). The mixture was allowed to stand, without heating, for 31 days at room temperature. From this reaction was obtained 2.66 g (70%) of yellow needles, mp 141.8–142.1° (dichloromethane–pentane).

(46) E. Schweizer, J. Thompson, and F. Ulrich, *J. Org. Chem.*, **33**, 3082 (1968).

Anal. Calcd for $C_{17}H_{15}ClN_2O_4S$: C, 53.90; H, 3.99. Found: C, 54.00; H, 3.98.

Preparation of 1-Cyclobutyl-2-phenylethylene.—The procedure was that of Wittig method A using a solution of benzyltriphenylphosphonium bromide (119 g, 0.275 mol) in DMF (300 ml) and alternately adding solutions of potassium *tert*-butoxide (56 g, 0.30 mol) in DMF (300 ml) and cyclobutanecarboxaldehyde (23.1 g, 0.275 mol). From the reaction was obtained 25.3 g (58%) of an oil with bp 115–120° (9–10 mm). This product was analyzed and the isomers were separated by vapor phase chromatography using the QF-1 column. From 26 injections of 20–30 μl each were collected 133 mg of cis alkene and 84 mg of trans alkene. At a column temperature of 185°, using a 60 ml/min helium flow, the retention times of the cis and trans alkenes were 3.15 and 4.20 min, respectively.

cis-1-Cyclobutyl-2-phenylethylene had nmr ($CDCl_3$) δ 1.70–2.50 (m, 6, $-CH_2-$ of ring), 3.05–3.80 (m, 1, H_3), 5.81 (dd, 1, $J_{2,3}$ = 8.8, $J_{1,2}$ = 11.6 Hz, H_2), 6.33 (dd, 1, $J_{1,2}$ = 11.6, $J_{1,3}$ = 0.7 Hz, H_1), 7.10–7.50 (m, 5, aromatic protons).

trans-1-Cyclobutyl-2-phenylethylene had nmr ($CDCl_3$) δ 1.50–2.50 (m, 6, $-CH_2-$ of ring), 2.75–3.45 (m, 1, H_3), 6.25–6.45 (m, 2, H_2 and H_3), 7.00–7.60 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-2-cyclobutyl-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (10).—To a solution of *trans*-1-cyclobutyl-2-phenylethylene (85 mg, 5.3 mmol) in DMF (2 ml) was added **34** (140 mg, 6.0 mmol), yielding 183 mg (88%) of yellow crystals, mp 104.5–105.0° (dichloromethane–petroleum ether).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36. Found: C, 54.95; H, 4.30.

Preparation of *threo*-10.—To a solution of *cis*-1-cyclobutyl-2-phenylethylene (133 mg, 8.4 mmol) in DMF (2 ml) was added **34** (215 mg, 9.2 mmol), yielding 259 mg (78%) of yellow crystals, mp 105.0–105.5° (ether–pentane).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36. Found: C, 55.03; H, 4.33.

Preparation, Rearrangement, and Separation of Isomeric Mixture of 2,4-DNBSC Adducts to *cis*- and *trans*-1-Cyclobutyl-2-phenylethylene.—To a solution of a mixture of *cis*- and *trans*-1-cyclobutyl-2-phenylethylene (3.16 g, 0.02 mol) in dry acetic acid (10 ml) was added **34** (5.15 g, 0.022 mol), yielding 6.97 g (89%) of a yellow-brown oil which could not be induced to crystallize. The nmr spectrum of the product oil indicated that the mixture consisted of threo and erythro adducts in the ratio of approximately 6:4, plus small amounts of impurities. The oil was placed on a 2 × 60 cm Florisil column and eluted with petroleum ether, 4:1 petroleum ether–benzene, 7:3 petroleum ether–benzene, 1:1 petroleum ether–benzene, 2:3 petroleum ether–benzene, 9:1 petroleum ether–ether, 4:1 petroleum ether–ether, 1:1 petroleum ether–ether, ether, dichloromethane, ethyl acetate, and acetone. From the 4:1 petroleum ether–benzene fractions, 2.34 g of a yellow oil was obtained. The oil solidified upon standing, and was recrystallized from ether–petroleum ether, yielding 2.15 g (27.4%) of yellow crystals, mp 105.0–105.5°. This was identified, by nmr and melting point as *threo*-1-chloro-2-cyclobutyl-1-phenyl-2-ethyl 2,4-dinitrophenyl sulfide (10).

From the 7:3 petroleum ether–benzene fractions was obtained 2.11 g of a yellow brown oil which solidified upon standing. When recrystallized from ether–petroleum ether, there was obtained 1.98 g (25.3%) of *erythro*-2-chloro-1-cyclobutyl-2-phenyl-1-ethyl 2,4-dinitrophenyl sulfide (anti-Markovnikov adduct **10′**) as light yellow needles: mp 111.5–112.0°; nmr δ 1.60–2.25 (m, 6, $-CH_2-$ of ring), 2.50–3.10 (m, 1, H_3), 4.24 (dd, 1, $J_{2,3}$ = 8.4, $J_{1,2}$ = 5.4 Hz. H_2), 4.67 (d, 1, $J_{1,2}$ = 5.4 Hz, H_1), 7.22–7.68 (m, 6, aromatic protons and $H_{1'}$), 8.15 (dd, 1, $J_{1',2'}$ = 8.8, $J_{2',3'}$ = 2.5 Hz, $H_{2'}$), 8.96 (d, 1, $J_{2,3'}$ = 2.5 Hz, H_3).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36. Found: C, 54.95; H, 4.24.

From the 9:1 petroleum ether–ether fractions there was obtained 1.56 g of yellow oil. This was induced to crystallize from ether–petroleum ether, yielding 1.48 g (18.8%) of brilliant yellow flakes, mp 124.7–125.0°, apparently the threo anti-Markovnikov isomer (**10′**) (see below): nmr δ 1.60–2.90 (m, 7, $-CH_2-$ of ring and H_3), 3.84 (dd, 1, $J_{2,3}$ = 9.2, $J_{1,2}$ = 4.5 Hz, H_2), 5.00 (d, 1, $J_{1,2}$ = 4.5 Hz, H_1), 7.15–7.50 (m, 5, aromatic protons), 7.98 (d, 1, $J_{1,2'}$ = 8.9 Hz, $H_{1'}$), 8.26 (dd, 1, $J_{1,2'}$ = 8.9, $J_{1,2'}$ = 2.5 Hz, $H_{2'}$), 8.82 (d, 1, $J_{1,2'}$ = 2.5 Hz, $H_{3'}$).

Anal. Calcd for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36. Found: C, 54.97; H, 4.30.

Although some yellow color was observed to remain on the column, elution by ether, dichloromethane, ethyl acetate, or acetone failed to remove the colored material completely. The yellow-brown oil material that was eluted by these solvents (total 0.97 g) failed to show, in the nmr spectra, peaks characteristic of the final desired product, *erthro*-**10**. The eluted material would not crystallize, had a foul odor, and was unidentifiable by nmr, showing only broad absorptions in the aliphatic and aromatic regions, 0.6–2.8 and 7.0–7.8 ppm, respectively.

Rearrangement of *threo*-1-Chloro-2-cyclobutyl-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (10) to *threo*-1-Chloro-1-cyclobutyl-2-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (10').—On a 1 × 15 cm Florisil column was placed the threo Markonikov adduct (0.620 g, 1.57 mmol). After 2 days, the column was eluted with 4:1 petroleum ether–benzene and yielded 0.407 g (65.8%) of yellow crystals indentified by nmr and melting point as the Markovnikov adduct as originally placed on the column. Continued elution by 9:1 petroleum ether–ether yielded 0.203 g (32.8%) of bright yellow flakes mp 123–124°. The nmr of this latter compound was identical with that of the compound obtained from the large column using the same eluents.

Preparation of 1-Cyclopentyl-2-phenylethylenes.—The procedure of Wittig method A was followed, using a solution of benzyltriphenylphosphonium bromide (108 g, 0.25 mol) and potassium iodide (83 g, 0.50 mol) in DMF (300 ml). To this solution was added, alternately, solutions of potassium *tert*-butoxide (50 g, 0.268 mol) in DMF (250 ml) and cyclopentanecarboxaldehyde (26.5 g, 0.25 mol) in DMF (25 ml). The product was vacuum distilled, yielding 30.2 g (75.2%) of a clear oil, bp 78–79° (0.25 mm). The oil was distilled, using the spinning band column, yielding 24 fractions of 1–2 ml each: fractions 3–11, bp 86–88° (0.9 mm); fractions 12–13, bp 90–94° (1.0–1.1 mm); fractions 14–24, bp 92–96° (0.9–1.1 mm).

cis-1-Cyclopentyl-2-phenylethylene (fractions 3–11) had nmr (neat liquid) δ 1.0–2.1 (m, 8, $-CH_2-$ of ring), 2.55–3.40 (m, 1, H_3), 5.53 (dd, 1, $J_{2,3} = 9.8$ $J_{1,2} = 11.6$ Hz, H_2), 6.37 (d, 1, $J_{1,2} = 11.6$ Hz, H_1), 6.80–7.40 (m, 5, aromatic protons).

trans-1-Cyclopentyl-2-phenylethylene (fractions 14–24) had nmr (neat liquid) δ 1.0–2.1 (m, 8, $-CH_2-$ of ring), 2.1–2.9 (m, 1, H_3), 5.85–6.60 (m, 2, H_1 and H_2), 7.05–7.45 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-2-cyclopentyl-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (11).—To a solution of *trans*-1-cyclopentyl-2-phenylethylene (1.71 g, 0.01 mol) in DMF (10 ml) was added **34** (2.61 g, 0.011 mol), affording 3.75 g (92%) of yellow crystals, mp 148.5–148.7° (dichloromethane–pentane).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4S$: C, 56.09; H, 4.71. Found: C, 55.95; H, 4.67.

Preparation of *threo*-11.—To a solution of *cis*-1-cyclopentyl-2-phenylethylene (1.72 g, 0.01 mol) in DMF (10 ml) was added **34** (2.60 g, 0.011 mol), producing 3.51 g (86%) of yellow needles, mp 109.0–109.5° (dichloromethane–pentane).

Anal. Calcd for $C_{19}H_{19}ClN_2O_4S$: C, 56.09; H, 4.71. Found: C, 55.97; H, 4.73.

Preparation of 1-Cyclohexyl-2-phenylethylene.—The procedure of Wittig method B was followed, using a solution of benzyltriphenylphosphonium bromide (108 g, 0.25 mol) and potassium iodide (83 g, 0.50 mol) in DMF (300 ml). To this was alternately added sodium methoxide (13.5 g, 0.25 mol) and a solution of cyclohexanecarboxaldehyde (28 g, 0.25 mol) in DMF (100 ml). The crude product oil from this reaction, weighing 26 g (56%), was distilled using a spinning band column, yielding 12 fractions of 1–3 ml each: fractions 3–5, bp 98–101° (2.55 mm); fraction 6, bp 101–103° (2.50–2.55 mm); fractions 7–11, bp 103–108° (2.45–2.50 mm).[46] These fractions were analyzed by vapor phase chromatography using the QF-1 column. At a column temperature of 200° using a helium flow of 75 ml/min, the cis and trans alkenes had retention times of 2.57 and 3.48 min, respectively.

cis-1-Cyclohexyl-2-phenylethylene had nmr ($CDCl_3$) δ 0.80–2.20 (m, 10, $-CH_2-$ of ring), 2.20–3.00 (m, 1, H_3), 5.43 (dd, 1, $J_{2,3} = 9.6$, $J_{1,2} = 11.6$ Hz, H_2), 6.28 (d, 1, $J_{1,2} = 11.6$ Hz, H_1), 6.85–7.40 (m, 5, aromatic protons).

trans-1-Cyclohexyl-2-phenylethylene had nmr (neat liquid) δ 0.80–2.35 (m, 11, $-CH_2-$ of ring and H_3), 5.83–6.50 (m, 2, H_1 and H_2), 6.95–7.45 (m, 5, aromatic protons).

Preparation of *erythro*-1-Chloro-2-cyclohexyl-1-phenyl-2-ethyl 2,4-Dinitrophenyl Sulfide (12).—To a solution of *trans*-1-cyclohexyl-2-phenylethylene (1.86 g, 0.01 mol) in acetic acid (10 ml) was added **34** (2.58 g, 0.011 mol), yielding 3.83 g (89%) of yellow needles, mp 173.5–174.0° (dichloromethane–pentane).

Anal. Calcd for $C_{20}H_{21}ClN_2O_4S$: C, 57.07; H, 5.03. Found: C, 56.97; H, 5.12.

Preparation of *threo*-12.—To a solution of *cis*-1-cyclohexyl-2-phenylethylene (1.86 g, 0.01 mol) in acetic acid (10 ml) was added **34** (2.58 g, 0.011 mol), yielding 3.76 g (87%) of yellow needles, mp 139.0–139.5° (dichloro methane–pentane).

Anal. Calcd for $C_{20}H_{21}ClN_2O_4S$: C, 57.07; H, 5.03. Found: C, 56.94; H, 5.13.

Solvolysis of 2,4-DNBSC Derivatives of the β-Substituted Styrenes.—The 2,4-DNBSC derivatives or the β-substituted styrenes were solvolyzed in aqueous ethanol (*ca.* 95%). Commercial absolute ethanol was distilled from magnesium ethoxide, taking the center cut, and diluted to desired density with dionized, triple-distilled water.

It was necessary to prepare the solvent twice. The first 5-l. quantity (solvent A) had density 0.80116 g/ml (28.4°, average of five determinations), and the second quantity of 9 l. (solvent B) had density 0.80096 g/ml (28.4°, average of six determinations). The ethanolysis rates of two compounds were determined in both solvents. It was found that the rates of B had to be multiplied by a factor of 1.0610 and 1.0609, respectively, to obtain the rate values received using solvent A. The lower of these two factors, 1.0609, was used for the rate correction of subsequent kinetics runs. Rates were determined conductiometrically, using a calibrated Wheatstone bridge, manufactured by the Clough-Brengle Co., Chicago, Ill.

Typically, the rates were determined as follows. Approximately 1–2 mg of powdered adduct was dissolved in 10 ml of solvent (at reaction temperature) and forced through a fritted glass disk filter (25–50 μ pore diameter) directly into the conductivity cell containing a further 50–75 ml of solvent and immersed in a thermostated bath at the desired temperature. After thorough shaking for *ca.* 1 min, the first point was obtained (used as zero time). Points were continuously taken until the resistance of the solution showed no change over an extended length of time (*ca.* 12 hr for erythro compounds and 24 hr for threo compounds). The value of the resistance at this time was used as the infinity point.

The first-order rate constants were determined by applying the integrated first-order rate equation

$$kt = 2.303 \log \left(\frac{\frac{1}{R_\infty} - \frac{1}{R_0}}{\frac{1}{R_\infty} - \frac{1}{R_T}} \right)$$

where t = time in seconds, R_0 = resistance at zero time, R = resistance at infinity point, and R_T = resistance at time t.

For each compound, two to seven rate determinations (each containing 30–100 data points) were made at each temperature. All calculations were accomplished by computer, using a linear least squares program containing a provision for correction of the infinity point by incremental variation. The infinity point value used was that which allowed the smallest standard deviation from the least squares line. The maximum observed correction of infinity point was 7.21%, with typical runs showing 0–1.5% correction. The linearity of each determination extended to only two or three half-lives.

The products consisted of mixtures of β-ethoxy and β-hydroxy sulfides, the relative amounts of which were determined by integration of the nmr spectra.

Two typical runs follow.

Solvolysis Products from *erythro*-3 (R = CH_3).—The mixture consisted of 86% ether and 14% alcohol: mp 73–78°; nmr ($CDCl_3$) δ 1.05–1.55 (m, 5.58, CH_3 of ether and alcohol and OCH_2CH_3), 3.25–4.00 (m, 2.72, H_2 of ether and alcohol and OCH_2CH_3), 4.54 (d, 0.86, $J_{1,2} = 4.9$ Hz, H_1 of ether), 5.03 (d, 0.14, $J_{1,2} = 4.2$ Hz, H_1 of alcohol), 7.16–7.50 (m, 5, aromatic protons), 7.76 (d, 0.86, $J_{1',2'} = 9.0$ Hz, $H_{1'}$ of ether), 7.23 (d, 0.14, $J_{1',2'} = 9.0$ Hz, $H_{1'}$, of alcohol), 8.25 (dd, 1, $J_{1',2'} = 9.0$, $J_{2',3'} = 2.5$ Hz, $H_{2'}$ of ether and alcohol), 8.88 (d, 1, $J_{2',3'} = 2.5$ Hz, $H_{3'}$ of ether and alcohol).

Solvolysis Products from *threo*-3 (R = CH_3).—The mixture consisted of 84% ether and 16% alcohol: mp 101–109°; nmr δ 0.95–1.70 (m, 5.52, CH_3 of ether and alcohol and OCH_2CH_3), 2.75 (5, broad, 0.16, OH), 3.20–4.10 (m, 3, H_2 of ether and alcohol, OCH_2CH_3 and OH), 4.35 (d, 0.94, $J_{1,2} = 7.8$ Hz, H_1 of ether), 4.85 (d, 0.16, $J_{1,2} = 7.2$ Hz, H_1 of alcohol), 7.25–7.65

(m, 5, aromatic protons), 7.81 (d, 0.16, $J_{1',2'}$ = 9.0 Hz, $H_{1'}$ of alcohol), 7.91 (d, 0.84, $J_{1',2'}$ = 9.0 Hz, $H_{1'}$ of ether, 8.33 (dd, 1, $J_{1',2'}$ = 8.0, $J_{2',3'}$ = 2.5 Hz, $H_{2'}$ of ether and alcohol), 8.97 (d, 1, $J_{3',3'}$ = 2.5 Hz, $H_{3'}$ of ether and alcohol).

Appendix

For a nonlinear multivariable function, eq 6, the

$$f(x_k) = 0, k = 1, 2, 3..k \quad (6)$$

optimized values may be obtained by a numerical search technique, *i.e.*, the method of steepest descent.[47] Beginning with a good approximation to the solution, P_0, which is sufficiently close to the true solution, and proceeds along the direction of negative gradients, a point P_1 can be obtained that is closer to the true solution (eq 7)

$$P_1 = P_0 - \lambda d_0 \quad (7)$$

where $d_0 = -(\partial f/\partial x)_k$ evaluated at the base point. λ is the parameter which will minimize the function and it can be determined by a one-dimensional Fibonacci search technique, or by setting $\partial f/\partial x = 0$. This process is repeated until no further improvement is obtained.

If eq 4 is recast as eq 8, then by applying the prin-

$$J_{obsd} = \frac{(J_G + J_T e^{rE_s+C})}{(1 + e^{rE_s+C})} \quad (8)$$

ciple of least squares, eq 9 is determined.

$$\delta = \sum_i r_i^2 = \sum_i \left[J_{obsd} - \left(\frac{J_G + J_T e^{rE_s+C}}{1 + e^{rE_s+C}} \right) \right]^2 \quad (9)$$

The problem now is to find the best values that will minimize the sum of the squares of the residuals, or the function δ. The method of the steepest descent gives the following results: $J_T = 13.46$, $J_G = 2.52$, $r = 2.78$, and $C = 0.236$.

Acknowledgments.—G. M. U. acknowledges support by the Texaco fellowship. We are also grateful for support of T. G. by project SEED. The XL-100 nmr instrument was purchased with partial support by NSF Grant GP-10293, which is gratefully acknowledged.

Registry No.—**2**, 21851-47-8; *erythro*-**3**, 35031-24-4; *threo*-**3**, 35031-22-2; *erythro*-**4**, 40128-17-4; *threo*-**4**, 40128-18-5; *erythro*-**5**, 40128-19-6; *threo*-**5**, 40128-20-9; *erythro*-**6**, 40128-21-0; *threo*-**6**, 40128-22-1; *erythro*-**7**, 40128-23-2; *threo*-**7**, 40128-24-3; *erythro*-**8**, 40128-25-4; *threo*-**8**, 40128-26-5; *erythro*-**9**, 40128-27-6; *threo*-**9**, 40128-28-7; *erythro*-**10**, 40128-29-8; *threo*-**10**, 40128-30-1; *erythro*-**10'**, 40128-31-2; *threo*-**10'**, 40128-32-3; *erythro*-**11**, 40128-33-4; *threo*-**11**, 40128-34-5; *erythro*-**12**, 40128-35-6; *threo*-**12**, 40128-36-7; *erythro*-**13**, 40128-37-8; *threo*-**13**, 40128-38-9; *erythro*-**14**, 40128-39-0; *threo*-**14**, 40128-40-3; *erythro*-**15**, 40128-41-4; *threo*-**15**, 40317-80-4; *erythro*-**16**, 40128-42-5; *threo*-**16**, 40128-43-6; *erythro*-**17**, 40128-44-7; *threo*-**17**, 40128-45-8; *erythro*-**18**, 40128-46-9; *threo*-**18**, 40128-47-0; *erythro*-**19**, 40128-48-1; *threo*-**19**, 40128-49-2; *erythro*-**20**, 40128-50-5; *threo*-**20**, 40128-51-6; *erythro*-**21**, 40128-52-7; *threo*-**21**, 40128-53-8; *erythro*-**22**, 40128-54-9; *threo*-**22**, 40128-55-0; *erythro*-**23**, 40128-56-1; *threo*-**23**, 40128-57-2; *erythro*-**24**, 40128-58-3; *threo*-**24**, 40128-59-4; *erythro*-**25**, 40128-60-7; *threo*-**25**, 40128-61-8; *erythro*-**26**, 40128-62-9; *threo*-**26**, 40128-63-0; *erythro*-**27**, 40132-46-5; *threo*-**27**, 40132-47-6; *erythro*-**28**, 40132-48-7; *threo*-**28**, 40132-49-8; *erythro*-**29**, 40132-50-1; *threo*-**29**, 40132-51-2; *erythro*-**30**, 40132-52-3; *threo*-**30**, 40132-53-4; *erythro*-**31**, 40132-54-5; *threo*-**31**, 40132-55-6; *erythro*-**32**, 40132-56-7; *threo*-**32**, 40132-57-8; **34**, 528-76-7; benzyltriphenylphosphonium bromide, 1449-46-3; potassium *tert*-butoxide, 865-47-4; acetaldehyde, 75-07-0; *trans*-1-phenylpropene, 873-66-5; *cis*-1-phenylpropene, 766-90-5; propanal, 123-38-6; *cis*-1-phenyl-1-butene, 1560-09-4; *trans*-1-phenyl-1-butene, 1005-64-7; 2-methylpropanal, 78-84-2; *cis*-3-methyl-1-phenyl-1-butene, 15325-56-1; *trans*-3-butene 15325-61-8; *trans*-3,3-dimethyl-1-phenyl-1-butene, 3846-66-0; *cis*-3,3-dimethyl-1-phenyl-1-butene, 3740-05-4; 2-ethylbutanal, 97-96-1; *cis*-3-ethyl-1-phenyl-1-pentene, 40132-61-4; *trans*-3-ethyl-1-phenyl-1-pentene, 40132-62-5; 3,3-dimethylbutyltriphenylphosphonium bromide, 40139-34-2; benzaldehyde, 100-52-7; *cis*-4,4-dimethyl-1-phenyl-1-pentene, 40132-63-6; *trans*-4,4-dimethyl-1-phenyl-1-pentene, 40132-64-7; cyclopropanecarboxaldehyde, 1489-69-6; *cis*-1-cyclopropyl-2-phenylethylene, 16958-34-2; *trans*-1-cyclopropyl-2-phenylethylene, 16948-35-3; cyclobutanecarboxaldehyde, 2987-17-9; *cis*-1-cyclobutyl-2-phenylethylene, 40132-65-8; *trans*-1-cyclobutyl-2-phenylethylene, 40132-66-9; cyclopentanecarboxaldehyde, 872-53-7; *cis*-1-cyclopentyl-2-phenylethylene, 40132-67-0; *trans*-1-cyclopentyl-2-phenylethylene, 40132-68-1; cyclohexanecarboxaldehyde, 2043-61-0; *cis*-1-cyclohexyl-2-phenylethylene, 40132-69-2; *trans*-1-cyclohexyl-2-phenylethylene, 18869-27-7.

(47) G. S. Beveridge and R. S. Schechter, "Optimization: Theory and Practice," McGraw-Hill, New York, N. Y., 1970.

Reaction of α,β-Ethylenic Sulfur Compounds with Organocopper Reagents

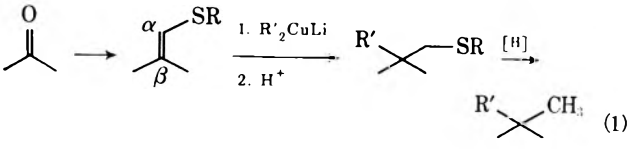
GARY H. POSNER* AND DANIEL J. BRUNELLE[1]

Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

Received February 26, 1973

The results of lithium dimethyl- and di-*n*-butylcuprate(I) reactions with alkenyl sulfides **1–3** and the corresponding sulfonium salts, with 2-alkylidene-1,3-dithianes **5–7** and the corresponding bis sulfonium salts, and with alkenyl sulfones **11–24** are reported. In the series styryl methyl sulfide (**3**), styryl methyl sulfone (**12**), and styryl *p*-chlorophenylsulfone (**17**) there is an increasing amount of organocopper addition to the olefinic carbon β to sulfur. 2-Alkylidene-1,3-dithianes **5–7**, in contrast to 2-methylene-1,3-dithiane, are inert to organolithium and organocopper reagents. Alkenyl *p*-chlorophenyl sulfones undergo organocopper addition β to sulfur, and the resulting alkyl aryl sulfones can be selectively hydrogenolyzed at the alkyl–sulfur bond using 6% sodium amalgam in ethanol to form alkanes in high yields; this sequence allows effective conversion of aldehyde carbonyls to tertiary alkyl carbon atoms in which each of the three alkyl groups may be different and permits transformation of certain ketone carbonyl groups to quaternary carbon atoms.

Organocopper reagents undergo addition to the β carbon of a variety of α,β-unsaturated compounds, such as α,β-ethylenic and acetylenic ketones and esters,[2] α,β-ethylenic epoxides,[3] allylic[4] and propargylic[5] acetates, and acetylenic and allenic phosphine oxides and sulfides.[6] Several of these addition reactions have been used as one of the key steps in syntheses of such natural products of nootkatone,[7] fulvoplumierin,[8] juvenile hormone,[9] and various prostaglandins.[10] The recent development of effective methods for converting carbonyl compounds to α,β-ethylenic sulfides,[11] 2-alkylidene-1,3-dithianes (ketene thioacetals),[12] and α,β-ethylenic sulfones[13] has made these readily available substrates for study with organocopper reagents. Determining which type of α,β-unsaturated sulfur compound undergoes most effective organocopper β addition to form a sulfur-stabilized carbanion would be of general interest, and would specifically permit conversion of an aldehyde or ketone carbonyl group to a tertiary or quaternary carbon atom (eq 1, sequence



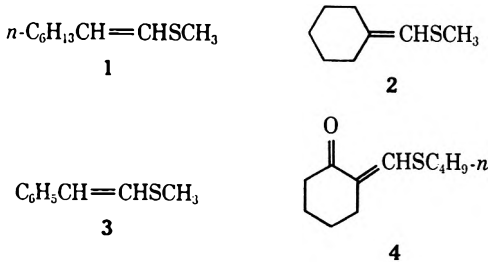
(1)

illustrated with vinyl *sulfides*).[14] Such a transformation would increase significantly the versatility of carbonyl groups in organic synthesis.

We report herein the results of organocopper interaction with alkenyl sulfides and sulfonium salts, with 2-alkylidene 1,3-dithianes and the corresponding bis sulfonium salts, and with various alkenyl sulfones.

Results and Discussion

Alkenyl Methyl Sulfides.—Alkenyl methyl sulfides **1–3** were prepared in high yields from the corresponding carbonyl compounds and lithium diethyl methylthiomethylphosphonate.[11] It was already known that alkenyl sulfide **4** undergoes reaction with lithium dimethyl-



cuprate(I) to place a methyl group specifically on the carbon β to the carbonyl group and not β to the sulfur atom.[15] The inability of sulfide sulfur to activate a double bond toward organocopper β addition was established when sulfides **2** and **3** were recovered in high yield even after prolonged exposure to lithium dimethylcuprate(I). Although cyclohexylidene sulfide **2** is inert also to lithium di-*n*-butylcuprate(I),[16] styryl sulfide **3** undergoes replacement of the methythio group by the *n*-butyl group to form 1-phenyl-1-hexene in 90% yield.[17] This substitution of the methylthio by the *n*-butyl group most likely occurs *via* an addition–elimination mechanism; the higher reactivity of styryl sulfide **3** compared to cyclohexylidene sulfide **2**, therefore, is probably due to the relative stability of the benzylic species generated by organocopper addition to the carbon atom β to the phenyl group.

An attempt was made to increase the electrophilicity of these alkenyl sulfides by converting them to the corresponding *S*-methyl sulfonium salts.[18] Treating alkenyl sulfide **1**, for example, with methyl fluoro-

(1) NSF Trainee, 1970–present.

(2) G. H. Posner, *Org. React.*, **19**, 1 (1972).

(3) (a) J. Staroscik and B. Rickborn, *J. Amer. Chem. Soc.*, **93**, 3046 (1971); (b) D. M. Wieland and C. R. Johnson, *ibid.*, **93**, 3047 (1971).

(4) R. J. Anderson, C. A. Henrick, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 735 (1970).

(5) P. Rona and P. Crabbé, *J. Amer. Chem. Soc.*, **91**, 3289 (1969).

(6) (a) A. M. Aguiar and J. S. R. Irelan, *J. Org. Chem.*, **34**, 4030 (1969); (b) J. Berlan, M. Capman, and W. Chodkiewicz, *C. R. Acad. Sci.*, **273**, 295 (1971).

(7) M. Pesaro, G. Bozzato, and P. Schudel, *Chem. Commun.*, 1152 (1968).

(8) G. Buchi and J. A. Carlson, *J. Amer. Chem. Soc.*, **91**, 6470 (1969).

(9) E. J. Corey, J. A. Katzenellenbogen, S. A. Roman, and N. W. Gilman, *Tetrahedron Lett.*, 1821 (1971).

(10) (a) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Amer. Chem. Soc.*, **94**, 925 (1972); (b) E. J. Corey and D. J. Beames, *ibid.*, **94**, 7210 (1972), and references cited therein.

(11) E. J. Corey and J. I. Shulman, *J. Org. Chem.*, **35**, 777 (1970).

(12) (a) F. A. Carey and A. S. Court, *J. Org. Chem.*, **37**, 1926 (1972). (b) P. F. Jones and M. F. Lappert, *Chem. Commun.*, 526 (1972).

(13) G. H. Posner and D. J. Brunelle, *J. Org. Chem.*, **37**, 3547 (1972).

(14) (a) For preliminary communications, see G. H. Posner and D. J. Brunelle, *Tetrahedron Lett.*, 293 (1972), and G. H. Posner and D. J. Brunelle, *ibid.*, 935 (1973). (b) For two recent related studies of geminal dialkylation of carbonyls, see B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, **95**, 2038 (1973), and E. J. Corey and J. I. Shulman, *ibid.*, **92**, 5522 (1970).

(15) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1027 (1971).

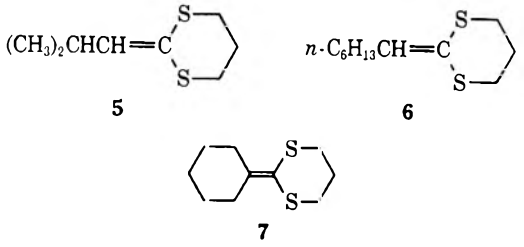
(16) Lithium di-n-alkylcuprates are more reactive than dimethylcuprate; see ref 2.

(17) The yield is based on 40% recovered starting material.

(18) For examples of vinyl sulfonium salts, see (a) J. Gosselck, L. Beress, H. Schenk, and G. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **4**, 1080 (1965); (b) G. Wittig and M. Schlosser, *Chem. Ber.*, **94**, 1373 (1961).

sulfonate ("magic methyl") produced dimethyl 1-octenylsulfonium fluorosulfonate as an oil showing an nmr singlet at δ 3.10 for the *S*-methyl groups. Reaction with lithium dimethylcuprate(I), however, did not produce an ylide *via* β addition of an anionic methyl group but rather gave parent alkenyl sulfide **1** in 97% yield upon aqueous work-up. Expecting that two sulfur atoms would stabilize an adjacent carbanion better than one sulfur atom, we directed attention next to olefins in which two sulfide sulfur atoms are attached to the same carbon atom of the double bond.

2-Alkylidene-1,3-dithianes.—2-Methylene-1,3-dithiane has been reported to undergo addition of organolithium compounds to give 2-substituted 2-lithio-1,3-dithianes,[19] and much speculation has appeared on the potential utility of this reaction as a general method for extension of the carbon chain in alkyllithium reagents.[12,20,21] We have prepared 2-alkylidenedithianes **5–7** in high yields from the corresponding carbonyl

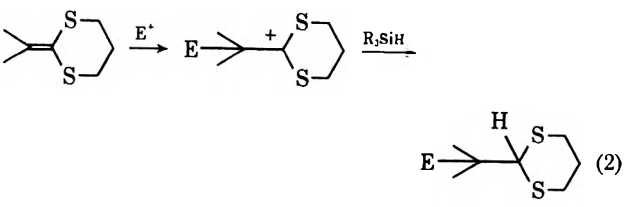


5 **6**

7

compounds and 2-lithio-2-trimethylsilyl-1,3-dithiane.[12] In sharp contrast to 2-methylene-1,3-dithiane, however, none of these 2-alkylidenedithianes **5–7** reacts with either methyllithium or lithium dimethylcuprate(I)! In fact, lack of deuterium incorporation upon D_2O quenching shows that methyllithium and lithium dimethylcuprate(I) do not even abstract an allylic proton from these alkylidenedithianes to produce stable 2-lithio-2-alkenyl-1,3-dithianes. The more reactive butyl metallic species, *n*-BuLi and $(n\text{-Bu})_2\text{CuLi}$, also fail to react with ketene thioacetals **5** and **7**, as shown by lack of deuterium incorporation on D_2O work-up. This substantially lower reactivity of 2-alkylidene- *vs.* 2-methylene-1,3-dithianes toward organolithium reagents is possibly due to unfavorable steric interactions between the organolithium reagent and the alkyl groups attached to the double bond of the alkylidenedithiane. These results firmly establish that 2-alkylidene-1,3-dithianes do not undergo addition of organolithium (or organocopper) reagents so easily as originally anticipated.[12,20,21]

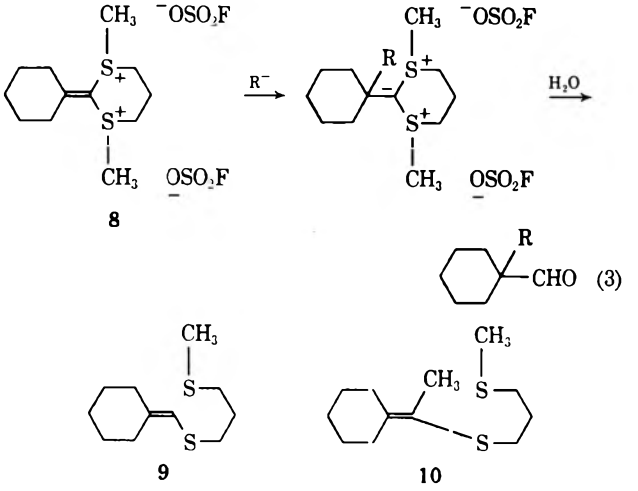
Because generation of a sulfur-stabilized carbanion failed to occur *via* anionic addition to these alkylidenedithianes, we next tried to take advantage of the known ability of sulfur to stabilize an adjacent carbonium ion.[20] Electrophilic addition of a proton (and bromonium, chloronium, and acylium ions) to several alkylidenedithianes followed by hydride attack has been reported[20] (eq 2). If electrophilic attack by an incipient alkyl carbonium ion could be achieved, followed by hydride attack, then the desired regio-



(2)

specific addition of R and H across the double bond of alkylidene dithianes would be accomplished. Treating 2-cyclohexylidene-1,3-dithiane (**7**) with excess methyl fluorosulfonate gave a white precipitate (nmr singlet at δ 3.2 for *S*-methyl groups, 6 H) which was immediately treated *in situ* with triethylsilane; aqueous work-up gave parent dithiane **7** as the major product, which indicated that methylation, to the extent to which it had occurred, had taken place on sulfur (possibly forming a bis sulfonium salt) rather than on alkenyl carbon, and therefore that pursuing this approach would not be fruitful.

This apparent generation of 2-alkylidene-1,3-dithiane bis sulfonium salts[22,23] suggested that *anionic* addition to the alkylidene double bond of these salts might lead to an ylide type structure which could undergo several subsequent reactions, for example, hydrolysis to an aldehyde (eq 3).[24] Although the bis sulfonium salt of



8

(3)

9 **10**

dithiane **5** reacted with lithium dimethylcuprate(I) to give 17 products, none of which was present in more than 20% yield by vpc analysis, 2-cyclohexylidene-1,3-dithiane bis sulfonium salt **8** reacted more cleanly. With methyllithium it gave parent 2-cyclohexylidene-1,3-dithiane (**7**) in 90% yield on aqueous work-up, and with lithium dimethylcuprate(I) it gave vinyl sulfide **9** in 55% yield and what appeared to be dimethylated vinyl sulfide **10** in 30% yield. Although the mechanism for formation of vinyl sulfides **9** and **10** is not

(19) (a) R. M. Carlson and P. M. Helquist, *Tetrahedron Lett.*, 173 (1969); (b) D. Seebach, *Synthesis*, 17 (1969).

(20) F. A. Carey and J. R. Neergaard, *J. Org. Chem.*, **36**, 2731 (1971).

(21) Conjugated ketene thioacetals have recently been shown to undergo Michael-type addition of alkyllithium reagents: D. Seebach, M. Kolb, and B.-T. Grobel, *Angew. Chem.*, **85**, 42 (1973).

(22) These salts were prepared from 2 equiv of magic methyl but could not be purified by chromatography or by distillation and therefore were used *in situ*.

(23) Bis sulfonium salts have been reported: (a) I. Stahl, M. Hetschko, and J. Gosselck, *Tetrahedron Lett.*, 4077 (1971); (b) C. P. Lillya, E. F. Miller, and P. Miller, *Int. J. Sulfur Chem.*, **1**, 89 (1971); (c) C. P. Lillya and P. Miller, *J. Amer. Chem. Soc.*, **88**, 1559 (1966); (d) J. Gosselck, G. Schmidt, L. Beress, and H. Schenk, *Tetrahedron Lett.*, 331 (1968).

(24) S-Alkylation of thioketals with $Et_3O^+BF_4^-$ and with methyl fluorosulfonate followed by hydrolysis produces carbonyl compounds: (a) T. Oishi, K. Kamemoto and Y. Ban, *Tetrahedron Lett.*, 1085 (1972); (b) M. Fetizon and M. Jarion, *Chem. Commun.*, 382 (1972).

clear,[25] isolation of vinyl sulfide **9** in 55% yield from one initial experiment prompted a thorough study of the effect of solvent, temperature, time, and organometallic reagent on the relative distribution of sulfides **9** and **10** (Table I); hydrolysis of vinyl sulfide **9** was expected

TABLE I

REACTION OF BIS SULFONIUM SALT 8 WITH 10 EQUIV OF METHYLMETALLIC REAGENTS

Organometallic	Solvent	Temp, °C	Time, hr	% yield[a] of products 9	10	7
CH_3Li	Et_2O	−78	3			81
		0	1			
CH_3Cu	Et_2O	−78	2			23
		25	6			
	Pyridine	0	2.5			
$(CH_3)_2CuLi$	Et_2O	0	1	55	30	15
$(CH_3)_2CuLi$	Et_2O	−78	2	50	32	9
		−20	2			
		0	2			
$(CH_3)_2CuLi$	1:1 Toluene:Et_2O	0	2	77	8	10
$(CH_3)_2CuLi$	THF[b]	0	3	65	30	5

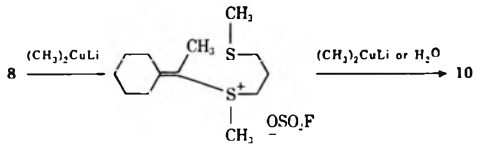
[a] Yield was determined by analytical vpc using an internal standard. [b] THF = tetrahydrofuran.

to give, and did indeed produce, cyclohexanecarboxaldehyde.[11]

Several conclusions can be drawn from the data in Table I: (1) neither methylcopper nor methyllithium is effective in converting sulfonium salt **8** into either sulfide **9** or **10**; (2) a toluene–ether solvent mixture or tetrahydrofuran as solvent increase the amount of vinyl sulfide **9** at the expense of dimethylated sulfide **10**. Most of the yields reported in Table I are average values of several experiments in which yield variation ranged from 5 to 15%, owing presumably to the heterogeneity of the reaction mixture and to the use of unpurified[22] sulfonium salt **8**.

Recent preparation of thioacetal bis sulfoxides[26] and bis sulfones[27] and their conversion to carbonyl compounds prompted us to investigate 2-alkylidene-1,3-dithiane bis sulfoxides and bis sulfones. Various attempts at oxidation of 2-cyclohexylidene-1,3-dithiane (**7**) with 1-chlorobenzotriazole[26a] failed to give pure bis sulfoxide; direct treatment of unpurified bis sulfoxide with lithium dimethylcuprate(I) gave unclear results. Oxidation of cyclohexylidenedithiane **7** with hydrogen peroxide in acetic acid[18b] did not produce any **7**-bis sulfone, nor did condensation of 2-lithio-1,3-dithiane bis sulfone with cyclohexanone, presumably owing to the stability of the disulfolane anion (pK_a = 13).[28] Consequently, attention was directed to alkenyl monosulfones, compounds which were known to undergo nucleophilic addition of alkoxides and thioalkoxides.[29]

(25) A possible mechanism for formation of dithiane **10** may be outlined as follows.

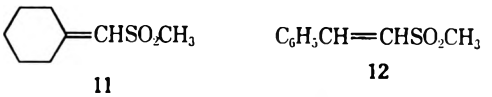


(26) (a) P. R. Heaton, J. M. Midgley, and W. B. Whalley, *Chem. Commun.*, 750 (1971); (b) H. Nieuwenhuyse and R. Low, *Tetrahedron Lett.*, 4141 (1971).

(27) S. J. Daum and R. L. Clarke, *Tetrahedron Lett.*, 165 (1967).

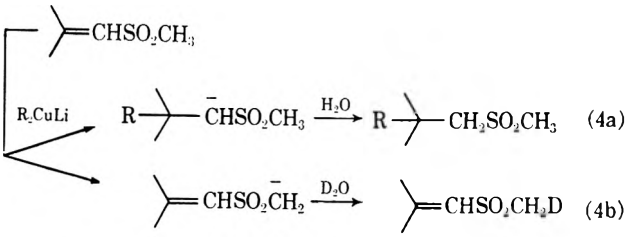
(28) E. J. Corey, H. Konig, and T. Lowry, *Tetrahedron Lett.*, 515 (1962).

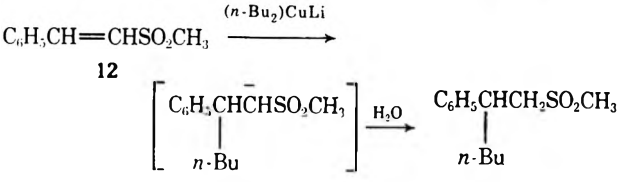
Alkenyl Methyl Sulfones.—Alkenyl methyl sulfones **11–13** were prepared in high yields from the corresponding carbonyl compounds and lithium diethyl methylsulfonomethylphosphonate.[13] It was anticipated that the sulfonyl group would facilitate organocopper β addition primarily by stabilizing the adjacent carbanion produced by such addition (eq 4a).[30] If alkenylsulfonomethyl carbanion formation were to occur before organocopper addition to the double bond, however, then such organometallic addition would be severely retarded by the negative charge already on the alkenyl sulfone (eq 4b). In experimental fact, cyclohexylidene



n-$C_6H_{13}CH{=}CHSO_2CH_3$

13





sulfone **11** is deuterated in the methyl group when exposed first to lithium dialkylcuprates(I) and then *in situ* to D_2O, and no addition to the double bond is observed. Likewise, methyllithium and lithium dimethylcuprate(I) do not add to styryl sulfone **12**, but lithium di-*n*-butylcuprate does; besides 35% of methyl-deuterated styryl sulfone **12**, β adduct **14** is formed in 50% yield. The occurrence of *n*-butyl addition β to sulfur in styryl sulfone **12** but not in styryl sulfide **3** is probably due to the larger stabilization of adjacent negative charge by the methylsulfonyl than by the methylthio group.

Lithium dimethyl- and di-*n*-butylcuprate(I) addition to alkenyl sulfone **13** also takes place specifically β to sulfur to give adducts **15** and **16** in 70–75% yields.

n-$C_6H_{13}CHCH_2SO_2CH_3$
|
R

15, R = CH_3
16, R = Bu-*n*

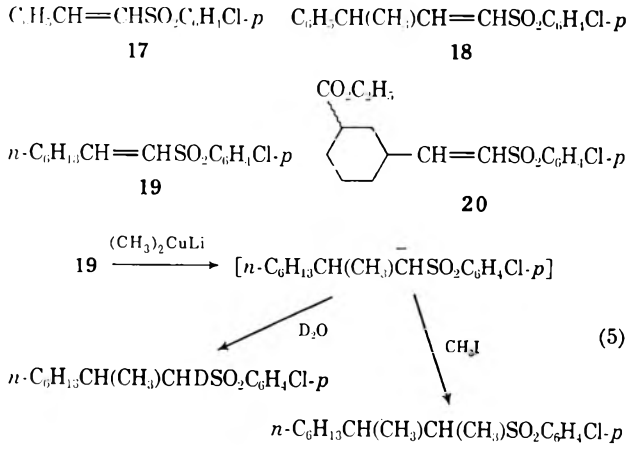
Isolation of 10–20% starting alkenyl sulfone **13** is due presumably to the intermediacy of a small amount of alkenylsulfonymethyl anion which is protonated upon aqueous work-up (eq 4b).

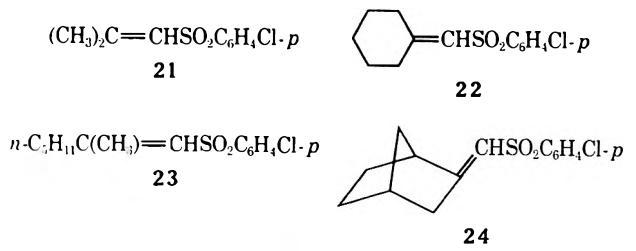
(29) M. F. Shostakovskii, E. N. Prilzhaeva, L. V. Tsymbal, V. A. Azovskaya, and N. G. Starova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2239 (1959); *Chem. Abstr.*, **54**, 10847e (1959).

(30) The pK_a of most aliphatic sulfones is about 23, roughly comparable to that of aliphatic esters: R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

In order to prevent the organocopper reagents from acting as bases which remove a proton from the methyl group adjacent to sulfonyl sulfur, and to increase the stabilizing effect of the sulfonyl group on adjacent carbanions, attention was turned to alkenyl *aryl* sulfones.

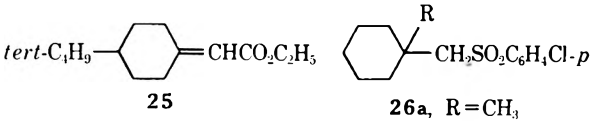
Alkenyl Aryl Sulfones.—Alkenyl *p*-chlorophenyl sulfones **17–20** were prepared in high yields from the corresponding aldehydes, even from 3-ethoxycarbonylcyclohexanecarboxaldehyde, and lithium diethyl *p*-chlorophenylsulfonomethylphosphonate.[13,31] The *p*-chlorophenyl group was selected primarily because the *p*-chloro substituent would help stabilize the carbanion formed *via* organocopper addition to the β carbon atom of the alkenyl aryl sulfones and because *p*-chlorothiophenol (from which the phosphonate is made) is commercially available at a reasonable price. *p*-Chlorophenyl styryl sulfone (**17**) reacts with lithium dimethyl- and di-*n*-butylcuprates(I) to place a methyl and an *n*-butyl group specifically on the carbon β to the sulfonyl group in 100 and 75% yields, respectively.[32] Alkenyl styryl sulfone **17** then culminates the series of styryl sulfur compounds (**3**, **12**, and **17**) and allows successful addition of methyl and *n*-alkyl groups to the β carbon of an α,β-ethylenic sulfur compound. Interestingly, attempts to introduce *sec*- and *tert*-alkyl groups using the new lithium *tert*-butoxy-*sec*- and *tert*-alkylcuprates(I)[33,34] failed completely; styryl sulfone **17** was recovered in good yield in all cases. Addition of lithium dialkylcuprates(I) to the β carbon of α,β-ethylenic *p*-chlorophenyl sulfones **18–20** also proceeded in excellent yields, as described previously.[14a] That such organocopper β addition to alkenyl aryl sulfone **19**, for example, produced a sulfonyl-stabilized anionic species was shown by quenching the reaction mixture with excess D_2O or excess methyl iodide and isolating α-deuterated or α-methylated sulfone in good yield (eq 5).





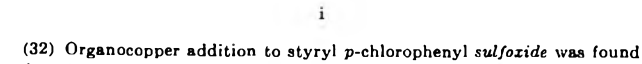
Preparation of α,β-ethylenic *p*-chlorophenyl sulfones from most ketones was difficult even under forcing conditions and use of special cosolvents (*e.g.*, hexamethylphosphoramide).[11] Although acetone and cyclohexanone were converted in good yields to the corresponding alkenyl *p*-chlorophenyl sulfones **21** and **22**, the yields of alkenyl sulfones **23** and **24** (from 2-heptanone and 2-norbornanone) dropped to 30–40%, and to 0% from 5-nonanone and benzophenone. These results, together with the good yield of alkenyl *methyl* sulfone from 2-heptanone,[14a] suggest a steric interference between the bulky diethyl *p*-chlorophenylsulfonomethylphosphonate anion and di-*n*-alkyl or other large ketones.[35] Attempts to condense lithium diethyl *p*-chlorophenyl*thio*methylphosphonate with most ketones also failed.[36] This difficulty in preparing alkenyl *p*-chlorophenyl sulfones from most ketones limits the generality of the scheme outlined in eq 1 for conversion of ketone carbonyls to quaternary carbon atoms.

Lithium dimethyl- and di-*n*-butylcuprate(I) addition to the double bond of alkenyl sulfone **21** proceeds in 72 and 89% yields, respectively, whereas methyl and *n*-butyl addition to cyclohexylidenemethyl sulfone **22** proceeds in 30 and 50% yields, respectively. Organocopper conjugate addition to α,β-ethylenic carbonyl compounds is known to be retarded by disubstitution on the β carbon, and, although lithium dimethylcuprate(I) adds to isopropylideneacetates in modest yields, cyclohexylideneacetate **25** is essentially inert to lithium dimethylcuprate(I).[2] It is not unexpected, therefore, that organocopper reagents add well to alkenyl sulfone **21** but poorly to cyclohexylidenemethyl sulfone **22**. Because six-membered rings are so prominent in many types of natural products and are so useful as synthetic intermediates, several variations of organometallic reagent, solvent, time, temperature, and work-up procedure were tried in order to optimize the yield of alkyl sulfones **26** (Table II).



The data in Table II indicate that the optimum conditions for methyl addition to sulfone **22** involve using lithium dimethylcuprate(I) in diethyl ether at room temperature for 72 hr and hydrogen sulfide work-up, which gives adduct **26** (R = CH_3) in 27% yield. Addition of the *n*-butyl group is best achieved in diethyl

(31) On occasion we have observed that column chromatography of some α,β-ethylenic sulfones causes isomerization to β,γ-ethylenic sulfones which are thermodynamically more stable [D. E. O'Connor and W. I. Lyness, *J. Amer. Chem. Soc.*, **86**, 3840 (1964)]; in fact, reaction of acetophenone with lithium diethyl *p*-chlorophenylsulfonomethylphosphonate forms allylic sulfone i in 20% yield.



(32) Organocopper addition to styryl *p*-chlorophenyl *sulfoxide* was found to be substantially slower than addition to the corresponding sulfone.

(33) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 1815 (1973).

(34) G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, **95**, 3076 (1973).

(35) Compare, for example, the sensitivity of the bisulfite carbonyl addition reaction to apparently slight changes in structure of carbonyl compounds. Some methyl but not di-*n*-alkyl ketones undergo bisulfite addition: L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd ed, Reinhold, New York, N. Y., 1956, p 202.

(36) Had *p*-chlorophenyl alkenyl *sulfides* been formed, these could have been oxidized to the corresponding sulfones (ref 18b).

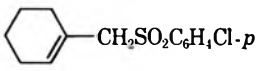
TABLE II

REACTION OF CYCLOHEXYLIDENEMETHYL SULFONE 22 WITH 10 EQUIV OF ORGANOMETALLIC REAGENTS[a]

Organometallic	Solvent	Time, hr	Temp, °C	% isolated yield of 26[b]
$(CH_3)_2CuLi$	Et_2O	5	0	11
$(CH_3)_2CuLi$	Pentane	5	0	10
$(CH_3)_2CuLi$	THF	5	0	0
$(CH_3)_2CuLi$	Toluene	5	0	10
$(CH_3)_2CuLi$	Toluene	24	25	18
$(CH_3)_2CuLi$	2:1 Pentane:Et_2O	12	25	20
$(CH_3)_2CuLi$	Et_2O	72	25	27[c]
CH_3Li	Et_2O	3	25	5
CH_3Li·TMED[d]	Et_2O	3	0	0[e]
$(n\text{-}Bu)_2CuLi$	Et_2O	12	25	0
$(n\text{-}Bu)_2CuLi$	Et_2O	16	10	0
$(n\text{-}Bu)_2CuLi$	Et_2O	5	0	38
$(n\text{-}Bu)_2CuLi$	Et_2O	2	−20	48
		5	0	
$(n\text{-}Bu)_2CuLi$	2:1 Et_2O:Pentane	5	0	30

[a] Typical work-up involved use of aqueous ammonium chloride. [b] Substantial amounts of starting material were recovered in all 5-hr reactions. [c] H_2S work-up. [d] TMED = tetramethylenediamine. [e] Cyclohexenylmethyl *p*-chlorophenyl sulfone was formed in 45% yield.

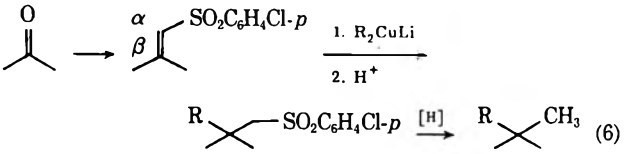
ether for 2 hr at −20° and then 5 hr at 0° followed by aqueous ammonium chloride work-up to give adduct **26** (R = C_4H_9-*n*) in 50% yield. Cyclohexylidenemethyl sulfone **22** is inert to methyllithium but reacts with the methyllithium–tetramethylethylenediamine complex to form β,γ-alkenyl sulfone **27** in 45% yield upon aqueous ammonium chloride work-up.[31]



27

In an attempt to increase the electrophilicity of cyclohexylidenemethyl sulfones, cyclohexylidenemethyl *p-fluoro*phenyl sulfone was prepared from lithium diethyl *p*-fluorophenylsulfonomethylphosphonate (*p*-fluorothiophenol is commercially available) and cyclohexanone.[13] It was hoped that the larger electron-withdrawing inductive effect of fluorine compared to that of chlorine (σ_I = 0.52 *vs.* 0.47)[37] might outweigh the larger electron-releasing resonance effect of fluorine compared to that of chlorine (σ_R = −0.44 *vs.* −0.24);[37] the relative importance of inductive and resonance effects in stabilization of *p*-halophenylsulfonylmethyl carbanions could not be evaluated beforehand because search of the literature failed to show any data for the relative acidities of *p*-halophenylsulfonic acids or of *p*-halophenyl methyl sulfones. Lithium dimethyl- and di-*n*-butylcuprate(I) add to cyclohexylidenemethyl *p-fluoro*phenyl sulfone in significantly lower yield than to *p-chloro*phenyl sulfone **22**. It would thus appear that *p*-chlorophenylsulfonylmethyl anions may be more stable than the corresponding *p*-fluorophenyl anions and that *p*-chlorophenyl methyl sulfones may be more acidic than *p*-fluorophenyl methyl sulfones. Attempts to prepare cyclohexylidenemethyl *m,p*-dichlorophenyl sulfone failed.

Hydrogenolysis of Alkyl Aryl Sulfones.—The successful β addition of lithium dimethyl- and di-*n*-butylcuprate(I) to the double bond of alkenyl *p*-chlorophenyl sulfones to form alkyl *p*-chlorophenyl sulfones now required selective *alkyl*–sulfur bond hydrogenolysis to permit overall conversion of an aldehyde or ketone carbonyl to a tertiary or quaternary carbon atom (eq 6). No general method had been reported for such



(6)

selective hydrogenolysis, and indeed treating alkyl aryl sulfones with lithium in methylamine causes cleavage of the *aryl*–sulfur bond.[38] An indirect route which seemed workable was lithium aluminum hydride reduction of alkyl aryl sulfones to the corresponding sulfides[39] followed by alkyl–sulfur bond hydrogenolysis,[38] but overall yields in these two steps are not high. An early report[40] that sodium amalgam in refluxing ethanol caused cleavage of methyl phenyl sulfone to benzenesulfinic acid suggested the possibility of using this method for selective hydrogenolysis of alkyl *p*-chlorophenyl sulfones. As summarized in Table III, 6% sodium amalgam in refluxing ethanol for about 12 hr does indeed cause *alkyl*–sulfur bond hydrogenolysis to form alkane and *p*-chlorobenzenesulfinic acid consistently in high yields.[14a]

The overall sequence (eq 6) described herein allows effective conversion of aldehyde carbonyls to tertiary alkyl carbon atoms in which each of the three alkyl groups may be different and permits transformation of certain ketone carbonyl groups to quaternary carbon units. The maximum efficiency of this sequence is exemplified by the conversion of heptanal to 2-methyloctane in 82% overall yield and benzaldehyde to isopropylbenzene in 89% overall yield.[14a]

Experimental Section

General.—Infrared spectra were obtained with Perkin-Elmer 337 and 457 infrared spectrophotometers as liquid films, KBr pellets, or in $CHCl_3$ or CCl_4 solution. Nmr spectra were obtained with a Varian A-60 or a Jeol MH-100 spectrometer in CCl_4 or $CDCl_3$ solution, with TMS internal standard. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Melting points, determined with a Mel-Temp melting point apparatus, and boiling points are uncorrected. Analytical vpc were performed on a Varian Aerograph series 1200 gas chromatograph, using a 7 ft × 0.125 in. 5% SE-30 on Chrom G column (column A), a 10 ft × 0.25 in. 10% FFAP on Chrom W column (column B), a 10 ft × 0.25 in. 10% Carbowax 20M on Chrom W column (column C), or an 18 ft × 0.125 in. 20% Reoplex on Anachrom AS column (column D). Preparative vpc was performed on a Varian Aerograph Model 90-P gas chromatograph, using a 20 ft × 0.375 in. 20% Carbowax on Chrom W column (column E), a 20 ft × 0.375 in. 20% QF-1 on Chrom W column (column F), or a 20 ft × 0.375 in. 20% SE-30 on Chrom W column (column G). Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Chemalytics, Inc., Tempe, Ariz.

All reactions involving organometallic compounds were performed in three-neck round-bottom flasks equipped with serum

(37) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 243.

(38) W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960).

(39) F. G. Bordwell and W. H. McKellin, *J. Amer. Chem. Soc.*, **73**, 2251 (1951).

(40) R. E. Dabby, J. Kenyon, and R. F. Mason, *J. Chem. Soc.*, 4881 (1952).

TABLE III

SODIUM AMALGAM REDUCTIONS OF ALKYL ARYL SULFONES IN REFLUXING ETHANOL

Alkyl aryl sulfone	Registry no.	Reflux time, hr	Hydrocarbon product	Registry no.	Vpc % yield[a] (column, temp in °C)	Bp, °C (mm)	n_D (temp, °C)
n-$C_6H_{13}CH(CH_3)CH_2SO_2Ar$[b]	40582-87-4	4	n-$C_6H_{13}CH(CH_3)_2$	3221-61-2	85 (D, 70)		1.4024 (20)[c]
n-$C_6H_{13}CH(n$-Bu$)CH_2SO_2Ar$	40582-88-5	12	n-$C_6H_{13}CH(n$-Bu$)CH_3$	1632-70-8	72 (B, 110)		1.4192 (20[d]
$C_6H_5CH(CH_3)CH_2SO_2Ar$	40582-89-6	5	$C_6H_5CH(CH_3)_2$	6031-02-3	99 (B, 110)		
$C_6H_5CH(n$-Bu$)CH_2SO_2Ar$	40582-90-9	15	$C_6H_5CH(n$-Bu$)CH_3$	5099-92-7	92 (B, 130)		1.4862 (28)[e]
26a		15	1,1-Dimethylcyclohexane		70 (D, 62)[f]		
26b		15	1-n-Butyl-1-methylcyclohexane		55 (B, 110)	188–189 (760)[g]	
n-$C_4H_9C(CH_3)_2CH_2SO_2Ar$	40582-91-0	15	n-$C_4H_9C(CH_3)_3$	590-73-8	70 (D, 20)	105 (760)[h]	
$C_6H_5CH(CH_3)CH(CH_3)CH_2SO_2Ar$	40582-92-1	18	$C_6H_5CH(CH_3)CH(CH_3)_2$	448:-30-5	100 (B, 130)	187 (760)[i]	1.4915 (20)[i]
$C_6H_5CH(CH_3)CH(n$-Bu$)CH_2SO_2Ar$	40582-93-2	15	$C_6H_5CH(CH_3)CH(n$-Bu$)CH_3$	40582-96-5	80 (B, 140)	244–245 (760)[j]	1.4862 (27.5)

[a] Yield based on added internal standard; see Experimental Section for details. [b] Ar = p-ClC_6H_4. [c] Lit. $n^{20}D$ 1.4032: F. C. Whitmore and H. A. Southgate, *J. Amer. Chem. Soc.*, **60**, 2571 (1938). [d] Lit. $n^{20}D$ 1.4198: D. H. Gibson and R. Pettit, *ibid.*, **87**, 2620 (1965). [e] Lit. $n^{20}D$ 1.4902: H. N. Stephens and F. L. Roduta, *ibid.*, **57**, 2380 (1935). [f] Yield based on 60% pure **26a**; product identified by comparison of nmr, vpc retention time, and mass spectra with those of an authentic sample. [g] Lit. bp 191.5°: S. I. Khromov, E. S. Balenkova, P. A. Akishin, and B. A. Kazanskii, *Dokl. Akad. Nauk SSSR*, **97**, 103 (1954); *Chem. Abstr.*, **49**, 8828a (1955). [h] Lit. bp 107°: C. R. Noller, *J. Amer. Chem. Soc.*, **51**, 598 (1929). [i] Lit. bp 188–189°, $n^{16}D$ 1.4972: M. Konowalloff and J. Egeroff, *Chem. Zentr.*, **1**, 776 (1899); A. Klages, *Ber.*, **36**, 3691 (1903). [j] *Anal.* Calcd for $C_{14}H_{22}$: C, 88.35; H, 11.65. Found: C, 88.06; H, 12.01.

stoppers and a nitrogen-filled balloon. Prior to the introduction of reactants, the apparatus was dried with a Bunsen burner flame while being purged with N_2. Freshly opened bottles of commercial anhydrous diethyl ether, pentane, or toluene were used without purification. Tetrahydrofuran (THF) was dried over $LiAlH_4$ and stored under N_2 prior to use. Methyllithium and n-butyllithium were obtained in *ca.* 2.0 and 1.8*M* ether and pentane solutions, respectively, from Alfa Inorganics, Inc., Bevery, Mass., and were titrated[41] prior to use.

Preparations of Starting Materials. Alkenyl Methyl Sulfides.—1-Octenyl methyl sulfide (**1**), cyclohexylidenemethyl methyl sulfide (**2**), and methyl styryl sulfide (**3**) were prepared from heptanal, cyclohexanone, and benzaldehyde, in yields of 89, 67, and 77%, according to the procedure of Corey and Shulman,[11] using lithium diethyl methylthiomethylphosphonate.

2-Alkylidene-1,3-dithianes.—2-(2-Methyl)propylidene-1,3-dithiane (**5**) and 2-cyclohexylidene-1,3-dithiane (**7**) were prepared in 78 and 72% yields according to the procedure of Carey and Court,[12] from isobutyraldehyde and cyclohexanone, using 2-lithio-2-trimethylsilyl-1,3-dithiane.

2-Heptylidene-1,3-dithiane (6).—Analogous to the procedure of Carey and Court,[12] dithiane **6** was prepared from 20.0 mmol of heptanal, 9.1 ml of 2.2 *M* n-BuLi, and 20.0 mmol of 2-trimethylsilyl-1,3-dithiane, giving, after distillation, 3.378 g (78%) of dithiane **6**: bp 92–95° (0.05 mm); nmr (CCl_4) δ 0.90 (distorted t, 3, CH_3), 1.3 [broad d, 8, $(CH_2)_4$], 2.2 (m, 4, CH_2 α to olefin and CH_2 β to S), 2.8 (distorted t, 4, CH_2's α to S), 6.85 (t, J = 7 Hz, 1, vinyl).

Anal. Calcd for $C_{11}H_{20}S_2$: C, 61.05; H, 9.32; S, 29.63. Found: C, 60.89; H, 9.21; S, 29.69.

Dimethyl 1-Octenyl Sulfonium Fluorosulfonate.—Methyl fluorosulfonate ("magic methyl," 0.200 g, 1.50 mmol) was added to a solution of 1.00 mmol of alkenyl sulfide **1** in 10 ml of anhydrous ether at 0° and under N_2, slowly forming a brown oil on the sides of the flask. The ether was evaporated to yield the crude product: nmr ($CDCl_3$) δ 0.89 (distorted t, 3, CH_3), 1.1–1.7 (m, 8, methylenes), 3.10 [s, 6, $S(CH_3)_2$], 6.3–7.2 (m, 2, vinyl protons). The vinyl sulfonium salt decomposed during purification attempts by column chromatography.

Dimethyl 2-Cyclohexylidene-1,3-dithiane Bis Sulfonium Fluorosulfonate (8).—Methyl fluorosulfonate (0.3422 g, 3.00 mmol) was added to 1.00 mmol (0.200 g) of dithiane **7** in 20 ml of anhydrous ether at 0° and under N_2, and the solution was stirred at 25° overnight. Sulfonium salt **8**, isolated by filtration, showed a singlet in the nmr ($CDCl_3$) at δ 3.2 which integrated for six protons; it is therefore probably a bis and not a monosulfonium salt. The organocopper solution, prepared as in the general procedure, was added *via* syringe to the unpurified sulfonium salt **8**.

Attempted Formation of Bis Sulfoxide of 2-Cyclohexylidene-1,3-dithiane (7).—To a stirred solution of 10.00 mmol (2.00 g) of dithiane **7** in 100 ml of CH_2Cl_2 at −78° and under N_2 was added a solution of 20.00 mmol of 1-chlorobenzotriazole[26a] in CH_2Cl_2, reacting at −78° for 4 hr, then allowing the temperature to rise to −50° and quenching with 3% NaOH when that temperature was reached. Work-up involved extraction into three 50-ml portions of ether, treatment with Norit, drying over $MgSO_4$, filtration and evaporation. Upon evaporation, a gummy residue formed. Column chromatography over 100 g of silica did not yield pure product. The procedure was repeated, reacting only at −78°, and using MeOH as solvent, but no pure bis sulfoxide was formed.

Attempted Formations of Bis Sulfone of 2-Cyclohexylidene-1,3-dithiane (7). A.—Analogous to the procedure of Wittig and Schlosser[18b] for oxidation of alkenyl sulfides, 0.7 ml of 30% H_2O_2 was added to a stirred slurry of 1.00 mmol (0.200 g) of dithiane **7** in 2.6 ml of glacial acetic acid at 0°. An additional 2.0 ml of HOAc was added, and the mixture was stirred overnight. Work-up by extraction into ether and washing with H_2O and 10% $NaHCO_3$ yielded only 0.029 g of oily residue, which was not identified.

B.—To a solution of 5.0 mmol (0.6012 g) of 1,3-dithiane in 10 ml of glacial acetic acid at 20° was added 3.5 ml of 30% H_2O_2. The solution was stirred for 5 min, and 10 ml of HOAc was added. The solution was stirred at 20° for 2 hr, then at 50° for 12 hr. After 12 hr, a thick precipitate had formed, which was separated by suction filtration to give 0.719 g of the bis sulfone of 1,3-dithiane (1,3-disulfolane,[28] 79%): mp 308.5–310° after recrystallization from 1:1 methanol–acetone; ir (KBr) 1340, 1145, and 1109 cm^{-1} (SO_2).

To 5.00 mmol (0.9212 g) of 1,3-disulfolane in a three-neck flask under N_2 was added 15 ml of dry THF, and the slurry was cooled to −78°; then 3.8 ml (5.0 mmol) of 1.32 *M* n-BuLi was added at that temperature. A Gilman test with Michler's ketone taken after 15 min was negative to alkyllithium.[42] The heterogeneous mixture was stirred at −78° for 1 hr; then 5.00 mmol (0.490 g) of cyclohexanone was added, the mixture was stirred at that temperature for an additional 1 hr and then allowed to warm to 0°, and stirring was continued for 1 hr. Acetic acid (3.0 ml) was added in 3 ml of THF, and the mixture was stirred at 0° for 30 min, then warmed to 25° for 90 min. The white precipitate (which had been present during the entire course of reaction) was removed by filtration, washed with 10 ml of ether and 10 ml of H_2O, and dried to yield 0.710 g of white solid identified by melting point (305–309°) as 1,3-disulfolane (77% recovery).

Alkenyl Methyl Sulfones.—Cyclohexylidenemethyl methyl sulfone (**11**), methyl *trans*-styryl sulfone (**12**), and methyl 1-octenyl sulfone (**13**) were prepared as previously described[13] from cyclohexanone, benzaldehyde, and heptanal, by condensation with lithium diethyl methylthiomethylphosphonate in yields of 97, 87, and 97%, respectively.

Alkenyl Aryl Sulfones.—p-Chlorophenyl *trans*-styryl sulfone (**17**), p-chlorophenyl 1-octenyl sulfone (**19**), and p-chlorophenyl cyclohexylidenemethyl sulfone (**22**) were prepared as previously described[13] from benzaldehyde, heptanal, and cyclohexanone by condensation with lithium diethyl (p-chlorophenyl)sulfonomethylphosphonate, in yields of 90, 80, and 72%, respectively.

(41) G. M. Whitesides, C. P. Casey, and J. Krieger, *J. Amer. Chem. Soc.*, **93**, 1379 (1971).

(42) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

p-Chlorophenyl 3-Phenyl-1-butenyl Sulfone (18).—From 22.00 mmol of diethyl (*p*-chlorophenyl)sulfonomethylphosphonate (28), 20.0 mmol of *n*-BuLi, and 20.0 mmol of 2-phenylpropionaldehyde (2.684 g, Aldrich), crude alkenyl sulfone 18 was formed and was recrystallized from ethanol to give 4.877 g (80%) of sulfone 18: mp 61.5–62.5°; nmr ($CDCl_3$) δ 1.37 (d, J = 7 Hz, 3, CH_3), 3.65 (p, J = 7 Hz, 1, benzylic CH), 6.28 (d of d, J = 15, 1 Hz, 1, vinyl proton α to SO_2), 7.0–8.0 (m, 10, aromatic and vinyl protons).

Anal. Calcd for $C_{16}H_{15}SO_2Cl$: C, 62.64; H, 4.93; S, 10.45; Cl, 11.56. Found: C, 62.98; H, 5.14; S, 10.48; Cl, 11.57.

p-Chlorophenyl 2-(3-Ethoxycarbonylcyclohexyl)ethenyl Sulfone (20).—Phosphonate 28 (20.00 mmol), 11.05 ml (20.0 mmol) of 1.81 *M* *n*-BuLi, and 20.00 mmol (3.690 g) of 3-ethoxycarbonylcyclohexanecarboxaldehyde (Aldrich) in 120 ml of dry THF were allowed to stir at −78° for 45 min, then warmed to 25° and stirred overnight.[13] Standard work-up yielded 7.174 g of yellow oil (theoretical 6.888 g), which was purified by column chromatography using 100 g of silica and benzene eluent to give 3.785 g (55%) of sulfone 20: nmr ($CDCl_3$) δ 1.0–2.1 (broad m with t superimposed, J = 7.5 Hz, 13, cyclohexyl protons and CH_3 of ester), 4.1 (J = 7.5 Hz, 2, CH_2 of ester), 6.34 (d, J = 16 Hz, 1, vinyl proton α to SO_2), 6.7–7.2 (m, 1, vinyl proton β to SO_2), 7.55 and 7.88 (pair of d, J = 9 Hz, 4 aromatic).

p-Chlorophenyl 2-Methyl-1-propenyl Sulfone (21).—Phosphonate 28 (20.00 mmol), 11.0 ml (20.0 mmol) of 1.81 *n*-BuLi, and 2.0 ml (~28 mmol) of acetone in 100 ml of dry THF were allowed to stir at −78° for 1 hr, then overnight at 25°.[13] Standard work-up yielded 5.129 g of crude sulfone 21, which was distilled to give 4.618 g of sulfone 21 (100%), which crystallized to a white solid: mp 39–39.5°; bp 125–130° (0.03 mm); nmr δ 1.90 (d, J = 1.3 Hz, 3, CH_3), 2.17 (d, J = 1.3 Hz, 3, CH_3), 6.25 (p, J = 1.3 Hz, 1, vinyl proton), 7.57 and 7.93 (pair of d's, J = 9 Hz, 4, aromatic protons).

Anal. Calcd for $C_{10}H_{11}SO_2Cl$: C, 52.06; H, 4.81; S, 13.90; Cl, 15.38. Found: C, 52.10; H, 4.76; S, 13.81; Cl, 15.32.

p-Chlorophenyl 2-Methyl-1-heptenyl Sulfone (23).—Phosphonate 28 (10.00 mmol), 7.5 ml (10.0 mmol) of 1.31 *M* *n*-BuLi, and 10.00 mmol of 2-heptanone in 50 ml of dry THF were stirred at −78° for 2 hr, then at 25° overnight.[13] Standard work-up yielded 3.448 g (theoretical 2.860 g) of crude sulfone 23, which was found to be 42% pure by nmr integration. Purification of the crude product by column chromatography over Alcoa F-20 alumina was attempted, but isomerization of the double bond was found to occur. The nmr spectrum showed about a 50:50 mixture of allylic and vinylic sulfones: δ 0.7–1.7 (m, aliphatic chain), 1.8–2.4 (s superimposed on m, CH_3 and CH_2 of vinyl sulfone), 3.85 (s, CH_2 α to SO_2 in allylic sulfone), 4.83 and 5.05 (broad s's, vinylidene protons of allylic sulfone), 6.22 (m, vinyl proton of vinyl sulfone), 7.0–7.8 (m, aromatic).

Attempts were made to increase the yield of vinyl sulfone 23 by several methods. (a) Repeating the reaction in anhydrous ether at 25° yielded neither starting materials nor desired product. (b) Reaction in cyclohexane at 25° yielded only a very small amount of vinyl sulfone 23; unreacted phosphonate was recovered. (c) The reaction was repeated forming the phosphonate anion at −20°, then cooling to −78°, and reacting as usual; only 8% formation of vinyl sulfone 23 was detected. (d) The reaction was repeated forming the phosphonate anion as −78°, then adding 1.0 equiv of tetramethylethylenediamine after 30 min at −78°. After an additional 30 min, 2-heptanone was added, and the reaction was completed as usual; standard work-up indicated only 17% formation of vinyl sulfone 23 and 70% recovered phosphonate.

p-Chlorophenyl 2-Norbornylidenemethyl Sulfone (24).—According to the standard procedure,[13] 20.00 mmol of phosphonate, 20.0 mmol of *n*-BuLi, and 20.00 mmol of 2-norbornanone were allowed to react at −78° for 2 hr, then at 25° overnight. Standard work-up yielded 7.110 g of yellow oil (theoretical 5.650 g). Column chromatography over 150 g of silica using hexane, 1:1 hexane–benzene, and benzene eluents yielded 3.148 g of yellow semisolid, which was recrystallized from ethanol to yield 2.023 g (36%) of white crystalline sulfone 24: mp 81.5–82.5°; nmr spectrum indicated approximately a 50:50 mixture of *E* and *Z* isomers, δ 1.1–2.2 (m, 7, norbornyl ring protons), 2.28–2.50 (m, 2, allylic methylene), 2.78 and 3.90 (two broad s's, total of 1, allylic bridgehead protons in *E* and *Z* isomers), 5.98 and 6.12 (s and t, J = 3 Hz, total of 1, vinyl proton in *E* and *Z* isomers), 7.3–7.8 (m, 4, aromatic).

Anal. Calcd for $C_{14}H_{15}SO_2Cl$: C, 59.46; H, 5.35; S, 11.34; Cl, 12.54. Found: C, 59.46; H, 5.02; S, 11.04; Cl, 12.55.

Attempted Formations of Vinyl Sulfones from 5-Nonanone and Benzophenone.—Reactions were carried out as previously described,[13] treating the anion of phosphonate 28 with 5-nonanone or benzophenone at −78° for 2 hr. Standard work-up of each reaction gave no desired vinyl sulfone and recovery of 99% starting materials.

Attempted Formation of *p*-Chlorophenyl Vinyl Sulfides from 2-Heptanone and 5-Nonanone.—According to the procedure previously described,[11] lithium diethyl(*p*-chlorophenyl)thiomethyl phosphonate was treated with 5-nonanone and 2-heptanone at −78° for 2 hr. Heating for 5 hr at 50°, followed by standard work-up, yielded only starting materials. No vinyl sulfide was detected by nmr.

Cyclohexylidenemethyl *p*-Fluorophenyl Sulfone.—Chloromethyl *p*-fluorophenyl sulfide (61.3 mmol), which had been prepared in 81% yield from *p*-fluorothiophenol analogous to Fancher's[43] procedure, was treated with triethyl phosphite (102 mmol) to form diethyl (*p*-fluorophenyl)thiomethylphosphonate (94% yield), which was oxidized according to the procedure previously described,[13] to form diethyl *p*-fluorophenylsulfonomethylphosphonate (71% yield, mp 85–85.5°).

Analogous to the standard procedure, 10.00 mmol of the phosphonate was treated with 10.0 mmol of *n*-BuLi at −78° for 2 hr, then 10.0 mmol of cyclohexanone was added, and the solution was stirred at −78° for 1 hr, then at 25° overnight. Standard work-up yielded 2.579 g of colorless oil (theoretical 2.544 g), which was purified by column chromatography over 100 g of silica using hexane, 3:1 hexane–benzene, and benzene eluents. The benzene fractions were combined and evaporated to yield 2.454 g of white solid which was recrystallized from ethanol to yield 1.3225 g of pure cyclohexylidenemethyl *p*-fluorophenyl sulfone (52%): mp 63.5–65.5°; nmr ($CDCl_3$) δ 1.6 (broad s, 6, cyclohexyl protons), 2.15 (broad m, 2, cyclohexyl protons γ to SO_2), 2.70 (broad m, 2, cyclohexyl protons γ to SO_2), 6.20 (s, 1, vinyl proton), 7.0–7.5 and 7.8–8.2 (m, 4, aromatic).

Anal. Calcd for $C_{13}H_{15}SO_2F$: C, 61.40; H, 5.94; S, 12.61; F, 7.47. Found: C, 61.25; H, 5.94; S, 12.84; F, 7.59.

Reactions of α,β-Ethylenic Sulfur Compounds with Organocopper Reagents. General Procedure for Organocopper Reactions.—To a three-neck flask, fitted with two serum stoppers and a T-joint to which a nitrogen-filled balloon was attached, was added 10.0 equiv of cuprous iodide, and a magnetic stirring bar. The flask was evacuated while being flamed, then purged with nitrogen from the balloon. This procedure was repeated three times, to exclude oxygen and water. Enough anhydrous diethyl ether was added *via* a dry syringe that upon addition of MeLi–ether solution (*n*-BuLi–pentane or hexane), a 0.25 *M* $Li(CH_3)_2Cu$ [$Li(n\text{-}Bu)_2Cu$] solution resulted. The CuI–ether mixture was stirred and cooled to 0° [−40° for $Li(n\text{-}Bu)_2Cu$], and 20 equiv of MeLi–ether solution was added (20 equiv of BuLi–pentane or hexane) *via* a dry syringe. The resulting 0.25 *M* $Li(CH_3)_2Cu$ [$Li(n\text{-}Bu_2Cu)$] solution was adjusted to the reaction temperature, and 1 equiv of substrate was added in *ca.* 10% ether solution. The reaction was stirred and maintained at the appropriate temperature for the specified time, then quenched by pouring into 50 ml of saturated NH_4Cl solution. The organic layer was extracted three times with equal portions of ether, dried over $MgSO_4$, filtered, and rotoevaporated to give the crude product.[44]

Cyclohexylidenemethyl Methyl Sulfide (2).—The reaction was carried out as in the general procedure, treating 1.0 mmol of sulfide 2 with 10 mmol of $Li(CH_3)_2Cu$. Vpc analysis (column C at 120°) indicated 100% starting material after 1 hr at 0°, 97% starting material after 2 hr at 0°, and 97% starting material after 40 hr at 25°. The nmr spectrum was identical with that of starting material.

Reaction of 1.00 mmol of sulfide 2 with 5 mmol of $Li(n\text{-}Bu)_2Cu$ was carried out as in the general procedure. Vpc analysis indicated 95% starting material after 1 hr at 0° and 94% starting material after 15 hr at 25°. The nmr spectrum was identical with that of starting material.

(43) German Patent 1,112,735 (1958) to L. W. Fancher (Stauffer Chemical Co.); *Chem. Abstr.*, **56**, 11499 (1962).

(44) New compounds were purified and subjected to microanalysis; some new liquid sulfone products could not be purified sufficiently for microanalysis and therefore were identified spectroscopically (nmr, ir, mass) and by hydrogenolysis to known compounds.

Methyl Styryl Sulfide (3).—Reaction was carried out as in the general procedure, with 10 mmol of $Li(CH_3)_2Cu$ reacting with 1.00 mmol of sulfide **3** at 25° for 15 hr. Starting material (93%) was recovered and identified by nmr.

In reaction of 1.00 mmol of sulfide **3** with 10 mmol of $Li(n\text{-}Bu)_2Cu$ at 25° for 15 hr, starting material was detected in 40% recovery by vpc analysis (column A at 120°), along with *trans*-1-phenyl-1-hexene, in 50% yield. The hydrocarbon product was separated from sulfide **3** by preparative vpc (column G at 190°), and identified by comparison to literature nmr and ir spectra for *trans*-1-phenyl-1-hexene.[46]

2-Cyclohexylidene-1,3-dithiane (7).—The reaction was carried out as in the general procedure, treating 1.00 mmol of dithiane **7** with 10 mmol of $Li(CH_3)_2Cu$ at 25° for 50 hr. Vpc analysis (column A at 200°) indicated no reaction.

In reaction of 1.00 mmol of dithiane **7** with 10 mmol of MeLi or *n*-BuLi at 25° for 22 hr, vpc analysis (column A at 200°) indicated no reaction; the nmr spectra were identical with those of starting material.

2-(2-Methyl)propylidene-1,3-dithiane (5).—The reactions were carried out as in the general procedure, treating 1.00 mmol of dithiane **5** with 10 mmol of $Li(CH_3)_2Cu$ or $Li(n\text{-}Bu)_2Cu$ for 50 hr at 25°. Vpc analysis (column A at 150°) and nmr indicated no reaction and complete recovery of starting material.

In reaction of 1.00 mmol of dithiane **5** with 10 mmol of MeLi at 25° for 24 hr, vpc analysis and nmr indicated no reaction and complete recovery of starting material.

2-Heptylidene-1,3-dithiane (6).—The reaction was carried out as in the general procedure, treating 1.00 mmol of dithiane **6** with 10 mmol of $Li(CH_3)_2Cu$ at −78° for 2 hr, then at 25° for 15 hr. The reaction was quenched with D_2O and worked up as usual. The nmr spectrum indicated no reaction and no deuteration, with 95% recovery of starting material.

In reaction of 1.00 mmol of dithiane **6** with 10 mmol of MeLi at 25° for 15 hr, with D_2O quench, no reaction or deuteration was observed in the nmr spectrum.

Dimethyl 1-Octenyl Sulfonium Fluorosulfonate.—The reaction was carried out by adding 10 mmol of a solution of $Li(CH_3)_2Cu$, formed as in the general procedure, to an ether suspension of 1.00 mmol of the sulfonium salt formed as above, and stirring at 25° for 2 hr. After the usual work-up, methyl 1-octenyl sulfide (**1**) was recovered (97%) and identified by nmr.

Dimethyl 2-Cyclohexylidene-1,3-dithiane Bis Sulfonium Fluorosulfonate (8).—(A) To 1.00 mmol of bis sulfonium salt **8**, formed as above, was added 2.0 mmol of triethylsilane, and the reaction was stirred for 12 hr. Work-up by washing with H_2O and $NaHCO_3$ yielded only 0.067 g of material, the nmr of which was identical with that of dithiane **7**. (B) To 1.00 mmol of bis sulfonium salt **8**, formed as above, was added 10 ml of H_2O, and the reaction mixture was stirred for 1 hr; addition of H_2O caused complete disappearance of the white precipitate. Work-up by washing with H_2O and $NaHCO_3$, drying, and evaporation yielded only 0.090 g of liquid, which could not be identified. (C) The organocopper reactions were carried out by forming an 0.5 *M* solution of 10 mmol of $Li(CH_3)_2Cu$ as in the general procedure, and adding it *via* a dry syringe to the suspension of 1.00 mmol of bis sulfonium salt **8**, with solvent and temperature adjusted to the conditions listed in Table I, and allowing reaction to proceed for the required time. Work-up as in the general procedure, followed by analytical vpc (column A, 200°), gave the results shown. In reactions with MeLi and MeCu, no products were seen by vpc other than starting materials. The products from reaction with $Li(CH_3)_2Cu$ were separated by preparative vpc (columns F and G at 240°), to yield cyclohexylidenemethyl (3-methylthio)propyl sulfide (**9**): nmr ($CDCl_3$) δ 1.5 (broad s, 6, cyclohexyl protons), 1.6–2.3 (m with s at 2.02 superimposed, 9, methyl superimposed on methylenes), 2.3–2.8 (m, 4, methylenes α to S), 5.40 (s, 1, vinyl proton); mass spectrum (70 eV) *m/e* (rel intensity) 216 (77), 201 (28), 123 (32), 121 (88), 95 (71), 89 [100, $(CH_2)_3SCH_3$], 73 (63); hydrolysis with NBS in 80% acetonitrile[46] yielded cyclohexanecarboxaldehyde, identified by comparison of ir and nmr spectra with those in the literature.[47]

Also isolated was 1-(cyclohexylidene)ethyl (3-methylthio)propyl sulfide (**10**): nmr ($CDCl_3$) δ 1.5 (broad s, cyclohexyl protons), 1.6–2.3 (m with 2 s's superimposed, methyl groups superimposed on methylenes), 2.4–2.8 (m, methylenes α to S); mass spectrum (70 eV) *m/e* (rel intensity) 230 (18), 216 (3), 141 (37), 121 [100, $S(CH_3)_2SCH_3$], 109 (18), 107 (22), 85 (27), 79 (18).

Dimethyl 2-(2-Methyl)propylidene-1,3-dithiane Bis Sulfonium Fluorosulfonate.—To 1.00 mmol of the bis sulfonium salt formed from dithiane **5** as above was added at −78° 10 mmol of $Li(CH_3)_2Cu$, formed as in the general procedure, and the reaction was stirred at −78° for 1 hr, at −20° for 1 hr, and at 0° for 2 hr. The reaction mixture was worked up as in the general procedure to give 0.264 g of yellow oil. Vpc analysis (column A, with temperature programming 160–240°) indicated 20 peaks, with the largest five representing 55% of the total; no product was present in more than 20%; only a small amount of starting material was evident in the nmr and vpc.

Cyclohexylidenemethyl Methyl Sulfone (11).—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **11** with 10 mmol of $Li(CH_3)_2Cu$ for 48 hr at 25°. Vpc analysis (column A at 135°) indicated no reaction.

In reaction of 1.00 mmol of sulfone **11** with 5 mmol of $Li(n\text{-}Bu)_2Cu$ at 0° for 17 hr, vpc analysis of an aliquot (column A at 135°) indicated a 98% recovery of starting material; the reaction was quenched with D_2O at that time, and worked up as usual. The nmr spectrum indicated partial deuteration of the sulfonyl methyl, from broadening of the singlet; a mass spectral study indicated only deuterated sulfone.

Methyl *trans*-Styryl Sulfone (12).—The reaction was carried out as in the general procedure, using 10 mmol of $Li(CH_3)_2Cu$, treating with 1.00 mmol of sulfone **12** at 25° for 36 hr; vpc analysis (column A, 150°) indicated 80% recovery of starting material in an aliquot removed at that time. The reaction was quenched in D_2O and worked up as usual. The nmr spectrum indicated starting material, with partial deuteration, evidenced by broadening of the sulfonyl methyl singlet.

In reaction of 1.00 mmol of sulfone **12** with 10 mmol of MeLi for 24 hr at 25°, starting material was recovered (90%), identified by nmr.

In reaction of 1.00 mmol of sulfone **12** with 5 mmol of $Li(n\text{-}Bu)_2Cu$ at 25° for 5 hr, a mixture of 35% starting sulfone **12** and 50% methyl 2-phenylhexyl sulfone was obtained. The product was isolated by column chromatography over silica gel, and identified by nmr ($CDCl_3$): δ 0.9–2.0 (m, 9, *n*-butyl group), 2.32 (s, 3, sulfonyl CH_3), 3.3 (m, 3, benzylic methine, sulfonyl methylene), 7.2–7.6 (m, 5, aromatic).

Methyl 1-Octenyl Sulfone (13).—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **13** with 10 mmol of $Li(CH_3)_2Cu$ at 25° for 9 hr, giving 70% of methyl 2-methyloctyl sulfone and 20% starting material, identified by nmr. The methylated product could not be separated from sulfone **13** by vpc, tlc, or column chromatography.

In reaction of 2.00 mmol of sulfone **13** with 20 mmol of $Li(n\text{-}Bu)_2Cu$ for 9 hr at 0°, 75% of methyl 2-butyloctyl sulfone was formed, and 11% starting material was recovered. The product was purified by column chromatography over silica gel, and identified by nmr ($CDCl_3$): δ 0.90 (pair of distorted t, 6, methyl groups), 1.3 (broad s, 17, methylenes and methine), 2.9 (s superimposed on d, 5, $CH_2SO_2CH_3$).

***p*-Chlorophenyl *trans*-Styryl Sulfone (17).**—The reaction was carried out as in the general procedure, using 10 mmol of $Li(CH_3)_2Cu$, treating with 1.00 mmol of sulfone **17** for 2 hr at 0°. The standard work-up yielded 0.296 g of solid *p*-chlorophenyl 2-phenylpropyl sulfone (100%): mp 101.5–102°; nmr ($CDCl_3$) δ 1.38 (m, 3, methyl), 3.34 (m, 3, methine and methylene), 6.9–7.7 (m, 9, aromatic).

Anal. Calcd for $C_{15}H_{15}SO_2Cl$: C, 61.11; H, 5.13; S, 10.88; Cl, 12.03. Found: C, 61.08; H, 5.21; S, 10.56; Cl, 12.04.

In reaction of 1.00 mmol of sulfone **17** with 5 equiv of $Li(n\text{-}Bu)_2Cu$ for 1 hr at 0°, *p*-chlorophenyl 2-phenylhexyl sulfone was formed (75%), identified by nmr ($CDCl_3$): δ 0.8–2.0 (m, 9, butyl group), 3.0–3.5 (m, 3, methylene and methine), 6.9–8.0 (m, 9, aromatic); mp 69–72°.

***p*-Chlorophenyl (3-Phenyl)-1-butenyl Sulfone (18).**—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **18** with 10 mmol of $Li(CH_3)_2Cu$ for 1 hr at 0°, to give *p*-chlorophenyl 2-methyl-3-phenylbutyl sulfone (97%). Recrystallization from ethanol (83%) gave mp 86.5–88.5°; nmr ($CDCl_3$) δ 1.04 (pair of overlapping d, 6, methyl groups), 2.0–3.2 (m, 4, methines and methylene), 7.0–7.8 (m, 9, aromatic).

(45) G. H. Posner, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1968; *Diss. Abstr.*, **29**, 1613B (1968).

(46) B. W. Erickson, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1970.

(47) (a) R. E. Klinck and J. B. Stothers, *Can. J. Chem.*, **44**, 45 (1966); (b) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965); (c) J. F. King and B. Vig, *Can. J. Chem.*, **40**, 1023 (1962).

Anal. Calcd for $C_{18}H_{19}SO_2Cl$: C, 63.24; H, 5.93; S, 9.93; Cl, 10.98. Found: C, 63.43; H, 5.93; S, 10.00; Cl, 11.20.

In reaction of 2.00 mmol of sulfone **18** with 20 mmol of Li(*n*-Bu)$_2$Cu at 0° for 5 hr, 0.692 g of *p*-chlorophenyl 2-butyl-3-phenylbutyl sulfone was formed (95%): nmr ($CDCl_3$) δ 0.8–2.2 (m, 13, methyl, butyl, and methine protons), 2.7–3.1 (m, 3, sulfonyl methylene and benzylic methine), 6.7–7.6 (m, 9, aromatic).

p-Chlorophenyl 1-Octenyl Sulfone (19).—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **19** with 5 mmol of Li$(CH_3)_2$Cu for 4 hr at 0° to form 0.294 g of *p*-chlorophenyl 2-methyloctylsulfone (97%): nmr ($CDCl_3$) δ 0.87 (distorted t, 3, CH_3), 1.0–1.4 (m, d superimposed on m, 13, β-methyl and methylenes), 1.7–2.1 (m, 1, β-methine), 2.9–3.1 (m, 2, sulfonyl methylene), 7.55 and 7.92 (pair of d, J = 9 Hz, 4, aromatic).

In reaction of 1.00 mmol of sulfone **19** with 5 mmol of Li(*n*-Bu)$_2$Cu at 0° for 2 hr, 0.321 g of *p*-chlorophenyl 2-butyloctyl sulfone was formed (93%): nmr ($CDCl_3$) δ 0.87 (m, 6, methyl), 1.1–1.6 (m, 16, methylenes), 1.8–2.1 (m, 1, β-methine), 2.9–3.1 (broad d, J = 5.5 Hz, 2, sulfonyl methylene), 7.56 and 7.93 (pair of d, J = 9 Hz, 4, aromatic).

In reaction of 1.00 mmol of sulfone **19** with 10 mmol of Li$(CH_3)_2$Cu for 3 hr at 0°, followed by quenching with 50 mmol of CH_3I and stirring for 12 hr at 25° before work-up, 0.621 g of *p*-chlorophenyl 1,2-dimethyloctyl sulfone was formed (90%): nmr ($CDCl_3$) δ 0.7–1.4 (m, 19, methylenes and methyls), 1.7–2.2 (m, 1, β-methine), 2.9–3.1 (m, 1, α-methine), 7.3–7.9 (m, 4, aromatic).

In reaction of 2.00 mmol of sulfone **19** with 10 mmol of Li$(CH_3)_2$Cu for 3 hr at 0°, followed by quenching with 1.0 ml of D_2O, and stirring at 25° for 1 hr before work-up, 0.551 g of *p*-chlorophenyl 2-methyloctyl sulfone was formed with 95% d_1 and 5% d_2, as characterized by nmr ($CDCl_3$): δ 0.84 (distorted t, 3, methyl), 1.0–2.4 (d superimposed on broad s, 13, β-methyl and methylenes), 1.8–2.2 (m, 1, β-methine), 2.8–3.1 (m, 1, sulfonyl methine), 7.42 and 7.76 (pair of d, J = 8 Hz, 4, aromatic).

p-Chlorophenyl 2-(3-Ethoxycarbonylcyclohexyl)ethenyl Sulfone (20).—The reaction was carried out as in the general procedure, treating 5.00 mmol of sulfone **20** with 25 mmol of Li$(CH_3)_2$Cu at 0° for 3 hr, to form 1.673 g of *p*-chlorophenyl 2-(3-ethoxycarbonylcyclohexyl)propyl sulfone (90%). The crude product was purified by column chromatography over F-1 alumina to give 1.020 g of the pure sulfone (55%): nmr ($CDCl_3$) δ 0.8–2.8 (m, 17, cyclohexyl and methyl), 2.9–3.2 (m, 2, sulfonyl methylene), 3.5–3.7 (m, 1, methine α to ester), 4.0–4.3 (split q, 2, OCH_2), 7.56 and 7.88 (pair of d, J = 8 Hz, 4, aromatic); ir ($CHCl_3$) 1730 (C=O), 1155 and 1090 cm^{-1} (SO_2).

In reaction of 2.00 mmol of sulfone **20** with 10 mmol of Li(*n*-Bu)$_2$Cu for 2 hr at 0°, 0.792 g of *p*-chlorophenyl 2-(3-ethoxycarbonylcyclohexyl)hexyl sulfone was formed (97%): nmr ($CDCl_3$) δ 0.8–2.8 (m, 23, cyclohexyl and *n*-butyl protons), 2.9–3.2 (m, 2, sulfonyl methylene), 3.5–3.7 (m, 1, methine α to ester), 4.0–4.3 (split q, 2, OCH_2), 7.55 and 7.90 (pair of d, J = 8 Hz, 4, aromatic).

p-Chlorophenyl 2-Methyl-1-propenyl Sulfone (21).—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **21** with 10 mmol of Li$(CH_3)_2$Cu for 5 hr at 0°, to give 0.225 g of colorless semisolid, which was shown to be *p*-chlorophenyl neopentyl sulfone (72%): nmr ($CDCl_3$) δ 1.20 (s, 9, *t*-Bu), 3.05 (s, 2, CH_2), 7.57 and 7.92 (pair of d's, J = 9 Hz, 4, aromatic); recrystallization from ethanol gave mp 142–145°; ir ($CHCl_3$) 1340 (CH_3 bend), 1155 and 1090 (SO_2), 1015, 910 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 246 (4.6), 177 (11), 159 (18), 111 (22), 71 (100).

In reaction of 4.00 mmol of sulfone **21** with 20 mmol of Li(*n*-Bu)$_2$Cu for 2 hr at 0°, 1.155 g of *p*-chlorophenyl 2,2-dimethylhexyl sulfone was formed (100%): nmr ($CDCl_3$) δ 0.88 (distorted t, 3, CH_3), 1.18 (s, 6, *gem*-dimethyl), 1.1–1.6 (m, 6, methylenes), 3.05 (s, 2, sulfonyl methylene), 7.57 and 7.92 (pair of d's, J = 9 Hz, 4, aromatic); ir ($CHCl_3$) 1340 (CH_3 bend), 1155 and 1090 (SO_2), 1015 cm^{-1}.

p-Chlorophenyl Cyclohexylidenemethyl Sulfone (22).—The reactions were carried out with 1.00 mmol of sulfone **22** reacting with 10 mmol of Li$(CH_3)_2$Cu in the appropriate solvent, reacting for the times and temperatures listed in Table II. The yields were determined by multiplying the mass balance and the nmr yield (nmr yields were determined by integration). In quenching a reaction of 1.00 mmol of sulfone **22** after 72-hr reaction with 10 mmol of Li$(CH_3)_2$Cu at 25° by bubbling H_2S through the reaction mixture, 0.1220 g of crude product was obtained, which was found to be 60% pure by nmr ($CDCl_3$), having a singlet for the sulfonyl methylene at δ 3.07. The product could not be separated from the starting materials by tlc or vpc.

Reactions of 1.00 mmol of sulfone **22** with 10 mmol of Li(*n*-Bu)$_2$Cu formed in the appropriate solvent were carried out as in the general procedure, at the times and temperatures shown in Table II. Yields were determined by multiplying mass balance and nmr (integration) yield. Treating 5.0 mmol of sulfone **22** with 50 mmol of Li(*n*-Bu)$_2$Cu in toluene for 2 hr at −20°, then 5 hr at 0°, 1.482 g of crude *p*-chlorophenyl (1-butylcyclohexyl)-methyl sulfone were obtained, which was 50% pure. Purification by preparative tlc over silica gel gave pure butylated sulfone: nmr ($CDCl_3$) δ 0.90 (distorted t, J = 5 Hz, 3, methyl), 1.1–1.8 (m, 16, methylenes), 3.04 (s, 2, sulfonyl methylene), 7.42 and 7.78 (pair of d, J = 9 Hz, 4, aromatic).

In reaction of 1.00 mmol of sulfone **22** with 10 mmol of MeLi for 3 hr at 25°, starting material was recovered (95%), identified by nmr.

In reaction of 1.00 mmol of sulfone **22** with 10 mmol of 1:1 MeLi–tetramethylenediamine for 3 hr at 25°, 0.244 g of liquid were obtained, which was identified by nmr as a mixture of 50% *p*-chlorophenyl 1-cyclohexenemethyl sulfone (**27**) and 35% starting sulfone **22** (CH_2SO_2 at δ 3.72, vinyl proton at δ 5.40).

p-Chlorophenyl 2-Methyl-1-heptenyl Sulfone (23).—The reaction was carried out as in the general procedure, treating 1.00 mmol of sulfone **23** with 10 mmol of Li$(CH_3)_2$Cu at 0° for 12 hr, then at 25° for 12 hr before work-up, to give 0.293 g of crude product. The nmr spectrum ($CDCl_3$) indicated that *p*-chlorophenyl 2,2-dimethylheptyl sulfone had been formed (50%), and starting material recovered (25%); methylated sulfone was evident from a large singlet at δ 1.17 (*gem*-dimethyl) and a smaller singlet at δ 3.06 (CH_2SO_2). The product could not be separated from the starting material by tlc or vpc.

p-Chlorophenyl 2-Norbornylidenemethyl Sulfone (24).—The reactions were carried out as in the general procedure, treating 1.00 mmol of sulfone **24** with 10 mmol of Li$(CH_3)_2$Cu for 24 hr at 25°, or with 10 mmol of Li(*n*-Bu)$_2$Cu for 5 hr at 0°, to give 0.080 and 0.154 g of crude products, respectively. The nmr spectra of the products showed that the desired reaction had not occurred from the absence of the expected singlet at δ ~3 for CH_2SO_2; starting material was not recovered from the reactions.

Cyclohexylidenemethyl p-Fluorophenyl Sulfone.—The reactions were carried out as in the general procedure, treating 1.00 mmol of the *p*-fluorophenyl sulfone with 10 mmol of Li$(CH_3)_2$Cu at 0° for 5 hr, or with 10 mmol of Li(*n*-Bu)$_2$Cu at 0° for 2 hr. The nmr spectra of the crude products showed 95 and 80% starting material recovery, respectively.

General Procedure for Sodium Amalgam Reductions of Alkyl Aryl Sulfones.—To 5.0 g of 6% sodium amalgam in a round-bottom flask were added 1.00 mmol of alkyl aryl sulfone in 20 ml of anhydrous ethanol, and the mixture was stirred and refluxed for 4–20 hr. At that time, the solution was washed with 30 ml of 3% NaOH and extracted with three 20-ml portions of pentane, and the combined pentane layers were washed twice with 20-ml portions of H_2O. After drying ($MgSO_4$), an aliquot was removed for vpc analysis to give yields listed in Table III, and the remainder of solution was evaporated to give crude products, which were identified by nmr, ir, and mass spectra. Boiling points and refractive indices were obtained after purification by bulb-to-bulb distillation or preparative vpc (column E).

Acknowledgment.—We thank the National Science Foundation for financial support (GP-33667) and Mr. K. Chang for technical assistance.

Registry No.—**1**, 40582-68-1; **6**, 40582-69-2; **7**, 37891-71-7; **8**, 40582-71-6; **9**, 40582-72-7; **10**, 40582-73-8; **12**, 15436-11-0; **13**, 35324-47-1; **17**, 16215-12-6; **18**, 40582-76-1; **19**, 35324-49-3; **20**, 40582-78-3; **21**, 40582-79-4; **22**, 35324-50-6; **23**, 40582-81-8; **24**, 40582-82-9; **26a**, 40582-85-2; **26b**, 40582-86-3; **27**, 40582-83-0; **28**, 40137-12-0; CH_3Li, 917-54-4; CH_3Cu, 1184-53-8; $(CH_3)_2CuLi$, 15681-48-8; CH_3Li–TMED, 39296-37-2; (*n*-Bu)$_2$CuLi, 24406-16-4; heptanal, 111-71-7; 2-trimethylsilyl-1,3-dithiane, 13411-42-2; dimethyl 1-octenyl sulfonium, fluorosulfonate, 40582-98-7; methyl fluorosulfonate, 421-20-5; 2-phenylpropionaldehyde, 3805-10-5; 3-ethoxycarbonylcyclohexanecarboxaldehyde, 40582-99-8; 2-heptanone, 110-43-0;

2-norbornanone, 497-38-1; cyclohexylidenemethyl *p*-fluorophenyl sulfone, 40583-00-4; chloromethyl *p*-fluorophenyl sulfide, 459-27-8; cyclohexanone, 108-94-1; methyl 2-butyloctyl sulfone, 40583-02-6; *p*-chlorophenyl 1,2-dimethyloctyl sulfone, 40583-03-7; *p*-chlorophenyl 2-(3-ethoxycarbonylcyclohexyl)propyl sulfone, 40583-04-8; *p*-chlorophenyl 2-(3-ethoxycarbonylcyclohexyl)hexyl sulfone, 40583-05-9; *p*-chlorophenyl neopentyl sulfone, 40583-06-0.

Asymmetric Additions of Organolithium Reagents to Allylic Alcohols

DONALD R. DIMMEL* AND SUCHIN HUANG

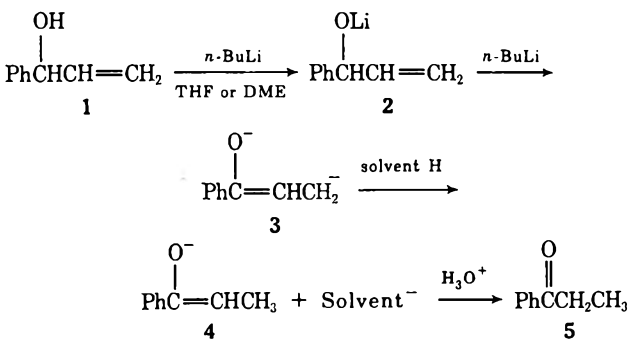
Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233

Received March 15, 1973

The reaction of α-vinylbenzyl alcohol (1) with *n*-butyllithium in hexane–TMEDA affords 1-phenyl-2-methyl-1-hexanol (6) and 5-benzyldecane (7) in an 3:1 ratio. The hydroxyl group in 1 induces the *n*-butyllithium to attack the double bond in a highly stereospecific manner, such that only one pair of enantiomers (**6a** and **6b**) are formed from 1 (*dl*). Addition to the double bond of 1 is also observed with *tert*-butyllithium except that in this case the addition is exclusively to the terminal end of olefin. The corresponding methyl ether of α-vinylbenzyl alcohol (12) does not react with *n*-butyllithium in an addition manner, but rather undergoes 1,2 and 1,4 Wittig rearrangements.

The reaction of 2 equiv of *n*-butyllithium in hexane–THF or hexane–DME (dimethoxyethane) with α-vinylbenzyl alcohol (1) gives a good yield of propiophenone (5).[1] The mechanism of this rearrangement has been established to be that shown in Scheme I.

SCHEME I



1 2 3 4 5

The dianion intermediate **3** never reaches a large concentration, because, soon after it forms, it abstracts a proton from the solvent. Organic dianions have proven to be useful synthetic intermediates;[2] consequently, we sought ways to increase the effective yield of this highly reactive species and possibly others like it.

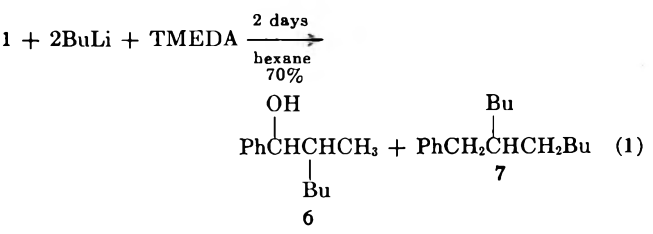
An ideal solvent for running these reactions would be pure hexane, since it has no acidic hydrogens; however, *n*-butyllithium loses much of its metalation powers in nonoxygenated solvents.[3] Thus, it was not surprising to find that α-vinylbenzyl alcohol was recovered "unchanged" when treated with excess *n*-butyllithium in pure hexane. Since tertiary amines are known[3,4] to enhance the reactivity of alkyllithium compounds, we repeated the later reaction in the presence of *N*,*N*,-*N*¹,*N*¹-tetramethylethylenediamine (TMEDA) and found that a completely different reaction had occurred—the butyllithium added to the double bond.

Although one would not normally expect an electron-rich organometallic reagent to add to nonconjugated olefins, there are several reported cases that this kind of reaction can occur.[5] Most of the reported organometallic additions to olefins have involved allylic alcohols. There appears to be a complex formed between lithium alkoxides and alkyllithium reagents which can subsequently deliver the RLi to an adjacent olefin in an intramolecular fashion. It is known that the solubility of lithium butoxide in *n*-heptane increases proportionately with increasing *n*-butyllithium concentration.[6] This suggests that a complex is formed between butoxide and lithium alkyl by the interaction of an oxygen unshared electron pair with a vacant hybridized orbital of lithium.[6,7]

The role that TMEDA plays is not clear. Some organolithium additions to allylic alcohols are known to occur in the absence of this reagent. It seems reasonable that the increased reactivity of organolithium reagents in the presence of TMEDA is due to complexation of the lithium atom with one or more amine sites.[8] Since the TMEDA does not interfere with addition of RLi to the allylic alkoxide, the alkoxide must either join with TMEDA to give a tetrahedral complex of the RLi or displace one of the amino groups of the bidentate ligand.

Results

The reaction of 2 equiv of *n*-butyllithium with 1 equiv of α-vinylbenzyl alcohol in hexane in the presence of 1–4 equiv of TMEDA for 2 days produced a 70% yield of three products: 1-phenyl-2-methyl-1-hexanol (6), 68%, 5-benzyldecane (7), 22%, and an unidentified



component, 10%. When only 0.5 equiv of TMEDA was used over a reaction period of 1 day, the yield

(1) D. R. Dimmel and S. B. Gharpure, *J. Amer. Chem. Soc.*, **93**, 3991 (1971).

(2) T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155 (1969).

(3) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

(4) R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972), and references cited therein.

(5) J. K. Crandall and A. C. Clark, *J. Org. Chem.*, **37**, 4236 (1972), and references cited therein.

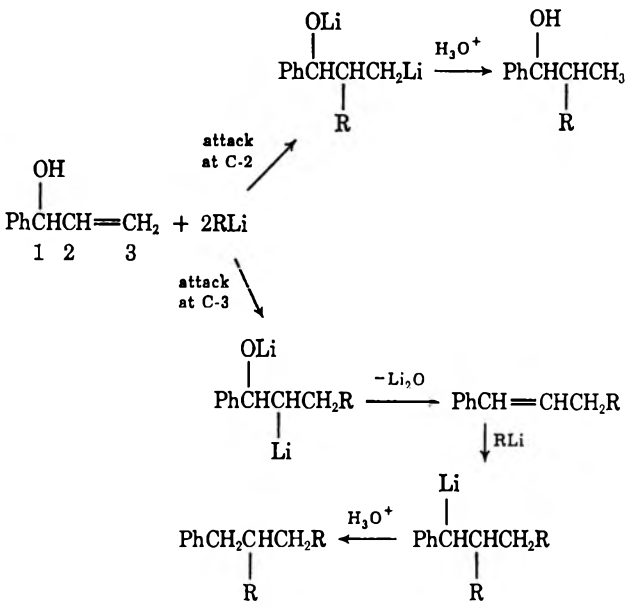
(6) C. W. Kamienski and D. H. Lewis, *ibid.*, **30**, 3498, 3502 (1965).

(7) T. L. Brown, J. A. Ladd, and G. N. Newman, *J. Organometal. Chem.*, **3**, 1 (1965).

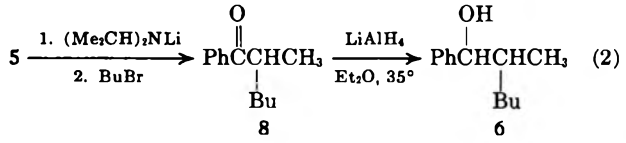
(8) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).

dropped to 36% but the product distribution remained the same. The products were characterized mainly by spectral means (see the Experimental Section). A probable mechanism which explains the formation of **6** and **7** is shown in Scheme II.

SCHEME II



To verify the structure of **6**, the synthesis shown in eq 2 was carried out. The two samples of **6** were not



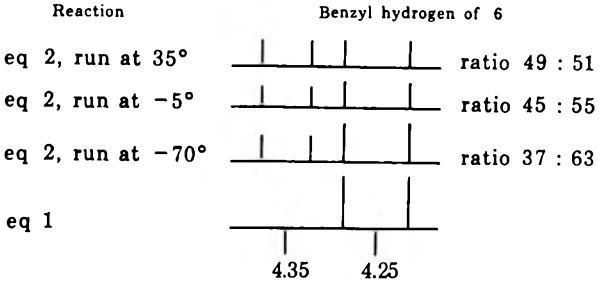
(2)

identical. For **6** prepared from **8** the benzyl proton in the 100-MHz nmr spectrum appeared as two separate, equally intense doublets, one at δ 4.25 (J = 6.5 cps) and the other at δ 4.35 (J = 5.5 cps). The sample of **6** derived from **1** showed only the δ 4.25 (J = 6.5 cps) doublet. The two benzyl proton doublets correspond to the two diastereomeric enantiomer pairs which **6**, with its two asymmetric carbons, could possess. The fact that **6** derived from *n*-butyllithium addition to **1** gives just the one doublet means that the addition is highly stereoselective (at least 98%).

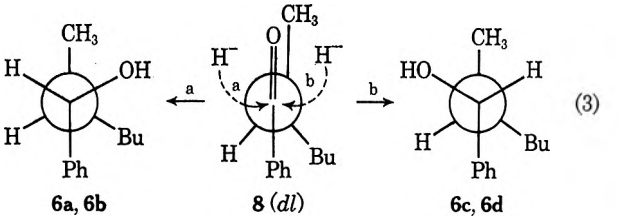
Since there is an asymmetric carbon next to the carbonyl of **8**, one might expect the hydride reduction of this ketone to give an imbalance of diastereomeric products. Under the conditions of refluxing ether, the hydride reduction of **8** gave nearly an equal mixture of diastereomers. However, reduction of **8** at lower temperatures[9] gave a greater percentage of the δ 4.25 doublet (Chart I). According to the rules set down for asymmetric reductions of ketones,[10] the δ 4.25 doublet would correspond to the major set of enantiomers **6a** and **6b** and the δ 4.35 doublet to the minor set of enantiomers **6c** and **6d**. Consequently, the principal

CHART I

THE APPEARANCE OF THE BENZYL PROTON REGION IN THE NMR SPECTRA OF 6 PREPARED IN SEVERAL WAYS

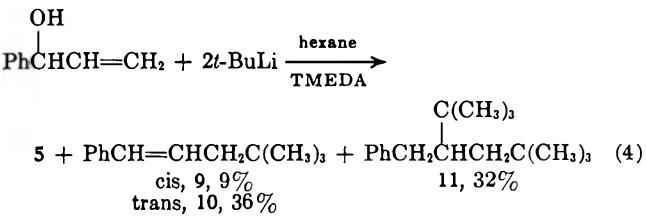


product of *n*-butyllithium addition to **1** is the enantiomer pair **6a, 6b**.



(3)

To test how general this reaction is, several other alkyllithium reagents were screened. Methyllithium in hexane–TMEDA and phenyllithium in THF seemingly had no effect on α-vinylbenzyl alcohol; no addition or dianion products were observed. In contrast, *tert*-butyllithium in hexane–TMEDA reacted rapidly with α-vinylbenzyl alcohol to give both dianion and addition products (eq 4). In the case of *tert*-butyl-



(4)

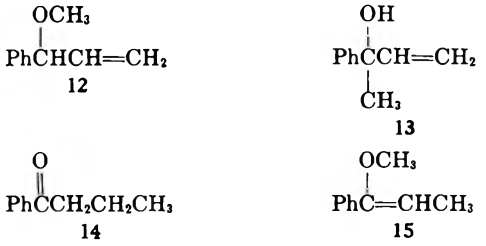
lithium all of the observed addition products, **9**–**11**, result from RLi attacking the terminal carbon of the double bond of **1**, *i.e.*, attack at C-3 (see Scheme II).

The importance of the hydroxyl group of **1** to direct attack at the allylic double bond is shown by the following results. Compound **1** was treated with base and methyl iodide to afford the methyl ether **12**. Reaction of **12** with 2 equiv of *n*-butyllithium in hexane–TMEDA gave, according to vpc analysis, the following mixture of volatile products: **5** (2%), **13** (46%), **14** (22%), and **15** (28%). If the reaction was done in THF as the solvent the same set of products resulted except that the ratios of volatile products were now different: **5** (35%), **13** (24%), **14** (27%), **15** (2%), and two unidentified components of 10 and 2% intensities. The reaction appears to be an example of a Wittig rearrangement, in which the 1,2 Wittig rearrangement product **13** predominates in hexane, while both 1,2 and 1,4[11] processes are occurring to about the same extent in THF. The ketone **5** more than likely arises from

(9) The ratio of diastereomers produced in an asymmetric reduction is known to increase with decreasing temperatures: Y. Gault and H. Felkin, *Bull. Soc. Chim. Fr.*, 1342 (1960).

(10) (a) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952); (b) G. J. Karabatsos, *ibid.*, **89**, 1367 (1967); (c) M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, 2199, 2205 (1968).

(11) For another example of 1,4 Wittig rearrangement see H. Felkin and A. Tambuté, *ibid.*, 821 (1969).

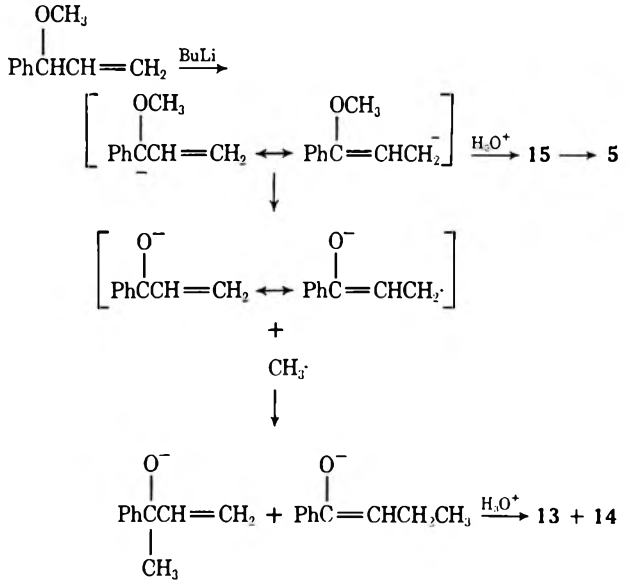


12 13

14 15

hydrolysis of the vinyl ether **15** during work-up. A possible mechanism is shown in Scheme III.[12]

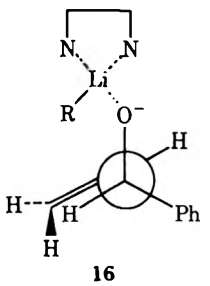
SCHEME III



Structural variations of the allylic alcohol can have a profound effect on the course of the reaction. For example, the tertiary alcohol **13** showed no observable addition or rearrangement products upon treatment with *n*-butyllithium in hexane–TMEDA.

Conclusions

Assuming a conformational preference where the phenyl group is in the least hindered environment and the alkoxide is perpendicular to the plane of the olefin group, the stereochemistry of the *n*-butyllithium addition to α-vinylbenzyl alcohol can be explained by the intermediacy of a structure like **16**.



16

Felkin and coworkers[13] have also observed some stereospecific additions of lithium alkyls to secondary allylic alcohols. In fact, they have added ethyllithium to α-vinylbenzyl alcohol (**1**) and got a compound similar to **6** (ethyl instead of butyl) in 30% yield and a 6:1 preference of diastereomers. Exactly why the butylation of **1** goes in better yield and is more stereoselective than the ethylation is not clear.

Except for cyclic alcohols, the principal attack of a RLi reagent on an allylic alcohol occurs at the olefinic carbon closest to the alcohol.[5,13] However, in the case of *tert*-butyllithium addition to **1**, the only addition products result from attack at the olefinic carbon furthest from the alcohol group. In direct contrast to this is the observation by Crandall[5] that *tert*-butyllithium exclusively adds to C-2 of allyl alcohol. It is obvious that steric factors play an important role in these additions. This is especially borne out by the fact that the tertiary alcohol **13** gives no addition products with *n*-butyllithium. The failure of this latter reaction may be a consequence of the intermediate species not preferentially existing in a conformation, such as **16**, that is essential for reaction.

Experimental Section

Boiling points are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A-60D spectrometer using tetramethylsilane as the reference. Infrared spectra were recorded on a Perkin-Elmer Model 137B Infracord. Mass spectra were taken on a Consolidated Electrodynamics Corp. 103C mass spectrometer. Analytical and preparative analyses of liquid products were performed on a 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on 80–100 mesh Chromosorb W, a 13 ft × 0.25 in. aluminum column packed with 20% diethylene glycol succinate (DEGS) on 80–100 mesh Chromosorb W, and a 8 ft × 0.25 in. aluminum column packed with 20% Reoplex 400 on 60–80 mesh Chromosorb W using an F & M Model 700 gas chromatograph equipped with a thermal conductivity detector. The thermal responses of the components in the vpc traces were not calibrated; thus, the relative areas on the traces, as reported, may not represent the relative molar proportions of the volatile components.

Dimethoxyethane and tetrahydrofuran were distilled from Na/K alloy before use. Commercial anhydrous reagent grade ethyl ether and hexane were used without further purification. Concentrated solutions of *n*- and *tert*-butyllithium in hexane were purchased from Alfa Inorganics, Inc.

***n*-Butylation of α-Vinylbenzyl Alcohol (1).**—To a stirred, cold (0°) solution of 5.0 g (37.3 mmol) of α-vinylbenzyl alcohol (**1**)[14] and 4.34 g (37.3 mmol) of TMEDA in about 60 ml of hexane was added, over a 15-min period, 36 ml (79 mmol) of a solution of *n*-butyllithium. The resulting solution was stirred at room temperature for 2 days under a nitrogen atmosphere and then added to 30 ml of ice–water. Ether was added and the organic layer was separated. The aqueous layer was extracted with ether several times. The combined ether extracts were successively washed with 10% HCl, 5% NaOH, and water, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator to leave 5.1 g of liquid products. The two major components were separated by preparative vpc (SE-30, 180°, He flow 75 ml/min).

1-Phenyl-2-methyl-1-hexanol (6) (69%) had retention time 26 min; ir (neat) 3600 cm^{-1} (OH); nmr (CCl_4) δ 0.6–1.6 [m, 13, $-CH(CH_3)C_4H_9$], 3.62 (s, 1, OH), 4.28 (d, 1, J = 6.5 Hz, PhCH), and 7.18 (s, 5, Ph); 100 MHz nmr (CCl_4) δ 4.25 (d, 1, J = 6.5 Hz, PhCH); mass spectrum (70 eV) m/e 192 (molecular ion), 174, 154, 107 (base peak), 105, 91, 79, and 77.

5-Benzyldecane (7) (25%) had retention time 39 min; ir, only aromatic and aliphatic hydrocarbon absorptions; nmr (CCl_4) δ 0.89–1.55 [m, 21, $-CH(C_4H_9)CH_2(C_4H_9)$], 2.52 (d, 2, J = 7 Hz, $PhCH_2$), and 7.18 (s, 5, Ph); mass spectrum (70 eV) m/e 232 (molecular ion), 92, 91 (base), 85, 77, 71, 57, 55, 43, and 41.

The same reaction when done with 4 equiv of TMEDA per 1 equiv of **1** afforded 5.1 g of liquid residue composed of 65% **6**, 22% **7**, and 13% of an unidentified product. When the re-

(12) Recent evidence suggests that the Wittig rearrangement involves radical anion intermediates: (a) P. T. Lansbury, V. A. Pattison, J. D. Siller, and J. B. Bieber, *J. Amer. Chem. Soc.*, **88**, 78 (1966); (b) H. Schäfer, U. Schöllkopf, and D. Walter, *Tetrahedron Lett.*, 2809 (1968).

(13) H. Felkin, G. Swierczewski, and A. Tambuté, *ibid.*, 707 (1969).

(14) R. Delaby and L. Lecomte, *Bull. Soc. Chim. Fr.*, **4**, 738 (1937).

action was done with 0.5 equiv of TMEDA for 1 day, 2.7 g of a mixture of 69% **6**, 21% **7**, and 10% of an unknown component was obtained.

2-Methylhexanophenone (8).—To a stirred solution of 55 ml (110 mmol) of a solution of *n*-butyllithium in 300 ml of DME, and cooled to −50°, 16.0 ml (110 mmol) of diisopropylamine was added dropwise.[15] The resulting solution was stirred at −50 to −20° for a few minutes and then 30 ml of a solution containing 12.7 g (95 mmol) of propiophenone in DME was added dropwise and with stirring over 30 min, during which time the temperature of the solution was kept between −20 and 0°. The resulting solution was rapidly warmed to 30° with stirring and then 40 g (300 mmol) of *n*-bromobutane was added rapidly (15 sec). The temperature of the resulting mixture rose to 50° and then began to fall. The mixture was stirred at reflux for 2 hr and at room temperature for 15 hr, and then poured into 300 ml of cold, saturated $NaHCO_3$ and extracted with ether. The ether extract was washed successively with 5% HCl and 5% $NaHCO_3$ and then dried over $MgSO_4$, concentrated, and vacuum distilled to give 14.2 g (78% yield) of a liquid: bp 113–115° (2 mm) [lit.[16] bp 107–110° (2 mm)]; analysis by vpc (Reoplex 400) showed a purity of 96%; ir (film) 1690 cm^{-1} (C=O); nmr (CCl_4) δ 0.82 (t, 3, J = 5.0 Hz, $-CH_2CH_3$), 1.15 (d, 3, J = 7 Hz, $-CHCH_3$), 1.57 [m, 6, $-(CH_2)_3-$], 3.49 (m, 1, −CH−), 7.3–8.0 (m, 5, Ph); 2,4-DNP mp 74–76° (lit.[16] mp 74.5–76.0°).

1-Phenyl-2-methyl-1-hexanol (6) from Reduction of 2-Methylhexanophenone (8).—Into a dry 250-ml round-bottom flask was placed 1 g (26 mmol) of $LiAlH_4$ and 150 ml of anhydrous ether. From the top of the condenser, 10 g (52 mmol) of 2-methylhexanophenone was added dropwise. The solution was refluxed with stirring for 7 hr and then cooled in an ice bath. Saturated Na_2SO_4 was added dropwise (no excess) until the gray solution turned white. The mixture was filtered and the filtrate was dried over $MgSO_4$. After the ether was removed on a rotary evaporator, the residue was vacuum distilled to give 7.2 g (70% yield) of 1-phenyl-2-methyl-1-hexanol, bp 126–129° (6.2 mm) [lit.[17] bp 130–132° (5 mm)], 98% pure by vpc (Reoplex 400) analysis. The vpc retention time was identical with that of **6** prepared from butylation of **1**. Spectral properties were also quite similar except for the nmr appearance of the benzyl protons, which in this case showed a triplet-like signal at δ 4.3 in the 60-MHz spectrum and two equally intense doublets in the 100-MHz spectrum, one at δ 4.25 (J = 6.5 Hz) and the other at 4.35 (J = 5.5 Hz).

Repeating the reaction as described above except for cooling the flask during the reaction in an ice–salt bath gave a 55:45 ratio of the δ 4.25 to 4.35 doublets. Repeating the reaction again in a Dry Ice bath (−68 to −72°) gave a product showing a 63:37 ratio of the δ 4.25 to 4.35 doublets.

***tert*-Butylation of α-Vinylbenzyl Alcohol (1).**—To a 250-ml three-neck round-bottom flask fitted with a dropping funnel, N_2 inlet, and drying tube was added 3.4 g (25 mmol) of compound **1**, about 70 ml of hexane, and 1.5 g (14 mmol) of TMEDA. To the cool solution, 45 ml (55 mmol) of a solution of *tert*-butyllithium was added dropwise. After stirring at room temperature for 36 hr and refluxing for 2 hr, the solution was cooled to room temperature and quenched with water. A work-up similar to the *n*-butylation of **1** afforded 2.3 g of a liquid.

Analysis by vpc (SE-30) showed several components. The major components were collected by preparative vpc. The properties of the four major components collected are reported in the following way—compound (no.) (per cent of the mixture, retention time on a SE-30 at 170°, He flow 150 ml/min), then ir; nmr; uv; mass spectral data.

Propiophenone (5) (23%, 7 min) was identical in retention time, nmr, ir, and mass spectral properties with an authentic sample.[18]

***cis*-β-Neopentylstyrene (9)** (9%, 9 min) had ir (CCl_4) 1370 and 1390 cm^{-1} (*t*-Bu); nmr (CCl_4) δ 0.91 (s, 9, CH_3), 2.21 (d, 2, J = 7 Hz, CH_2), 6.18–6.4 (m, 2, −CH=CH), 7.23 (s, 5, Ph); uv λ_{max} (EtOH) 240 nm (ϵ_{max} 17,200);[19] mass spectrum (70 eV) *m/e* 174 (molecular ion), 159, 118, 117, 115, 91, 77, 65, 63, 57 (base), 51, 43, 41, 39, 29, and 27.

***trans*-β-Neopentylstyrene (10)** (35%, 13 min) had ir (CCl_4) 1370 and 1390 (*t*-Bu) and 970 cm^{-1} (trans RCH=CHR); nmr (CCl_4) δ 0.94 (s, 9, $-CH_3$), 2.19 (d, 2, J = 6 Hz, CH_2), 6.3–6.7 (m, 2, −CH=CH−), 7.26 (s, 5, Ph); uv λ_{max} (EtOH) 248 nm (ϵ_{max} 30,000);[19] mass spectrum (70 eV) *m/e* 174 (molecular ion), 159, 118, 117, 115, 91, 77, 65, 63, 57 (base), 51, 43, 41, 39, 29, and 27.

3-Benzyl-2,2,5,5-tetramethylhexane (11) (23%, 28 min) had ir (CCl_4) 1370 and 1400 cm^{-1} (*t*-Bu), plus strong aliphatic and aromatic absorptions; nmr (CCl_4) δ 0.82 (s, 18, CH_3), 0.95–1.68 (m, 3, $-CHCH_2-$), 2.6–2.88 (m, 2, $PhCH_2$), and 7.20 (s, 5, Ph); mass spectrum (70 eV) *m/e* 232 (molecular ion), 176, 141, 140, 120, 119, 117, 105, 91 (base), 85, 77, 71, and 41.

Rearrangement of Methyl 1-Phenylallyl Ether (12).—The starting material, **12**, was prepared by methylation of α-vinylbenzyl alcohol (**1**),[1] bp 69–75° (3.5 mm) [lit.[20] bp 88–90° (10 mm)]. To a 150-ml three-neck round-bottom flask was added 5.0 g (34 mmol) of **12**, about 50 ml of hexane, and 2.2 g (20 mmol) of TMEDA. The mixture was placed in an ice bath and agitated by means of a magnetic stirrer. From a dropping funnel, 18 ml (36 mmol) of a solution of *n*-butyllithium was added over a period of a few minutes. The color of the solution changed from light yellow to dark red. After stirring for 42 hr, the reaction was cooled in an ice bath and quenched with 10 ml of water. The mixture was extracted with several portions of ether. The water layer was acidified with 10% HCl, then extracted with ether, and the ether layer was washed with 5% NaOH and water. The combined ether extracts were dried over Na_2SO_4, concentrated, and vacuum distilled to afford 2.4 g of crude product, bp 107–116° (10 mm). Analysis by vpc (Reoplex 400) showed several components, the major of which were collected by preparative vpc. The properties of the four components collected are reported in the following way—compound (no.) (per cent of the mixture, retention time on a Reoplex 400 at 160°, He flow 100 ml/min), then ir; nmr; mass spectral data.

1-Phenyl-1-methoxypropene (15) (28%, 4 min) had nmr (CCl_4) δ 1.75 (d, 3, J = 7 Hz, CCH_3), 3.50 (s, 3, OCH_3), 5.28 (q, 1, J = 7 Hz, =CH), 7.18–7.42 (m, 5, Ph); mass spectrum (70 eV) *m/e* 148 (molecular ion), 147 (base), 117, 105, 91, 77, 55, and 51. Literature[21] nmr reports δ 1.75 (d, 3, J = 7 Hz), 3.45 (s, 3), 5.22 (q, 1, J = 7 Hz), and 7.04–7.48 (m, 5) for **15** with cis related methyl and methoxy and δ 1.66 (d, 3, J = 7 Hz), 3.54 (s, 3), 4.67 (q, 1, J = 7 Hz), and 7.26 (s, 5) for **15** with trans related methyl and methoxy. Thus, it appears that the **15** derived from **12** is the cis isomer (methyl–methoxy).

Propiophenone (5) (2%, 7.5 min) was identical in retention time, ir, nmr, and mass spectral properties with an authentic sample.[18]

***n*-Butyrophenone (14)** (22%, 9.5 min) was identical in retention time, ir, nmr, and mass spectral properties with an authentic sample.[18]

2-Phenyl-3-buten-2-ol (13) (46%, 11 min) had ir (CCl_4) 3400 (OH), 1650, 995, and 925 cm^{-1} ($-CH=CH_2$); nmr (CCl_4) δ 1.50 (s, 3, $-CH_3$), 2.59 (s, 1, OH), 4.89–5.35 (m, 2, $-C=CH_2$), 6.07 (doublet of doublets, 1, J_{trans} = 17, J_{cis} = 10 Hz, −CH=C), 7.05–7.50 (m, 5, Ph); mass spectrum (70 eV) *m/e* 148 (molecular ion), 133, 121, 119, 105, 91, 77, 55, 51, and 43 (base peak); identical with a sample of **13** prepared by treating acetophenone with vinyllithium.

The reaction was repeated using THF as the solvent, and no TMEDA, to give the same set of products except that the ratios were different: **15** (2%), **5** (35%), **14** (27%), **13** (24%), and two unidentified peaks of longer retention times with intensities of 10 and 2%.

Acknowledgments.—We would like to thank the Marquette University Committee on Research for their

(15) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).

(16) G. L. Goerner, H. L. Muller, and J. L. Corbin, *ibid.*, **24**, 1561 (1959).

(17) T. I. Temnikova, A. K. Petryaeva, and S. S. Skorokhodov, *Zh. Obshch. Khim.*, **25**, 1575 (1955); *Chem. Abstr.*, **50**, 4891*g* (1956).

(18) Purchased from Aldrich Chemical Co., Milwaukee, Wis.

(19) It is well recognized that cis β-substituted styrenes absorb at lower wavelengths and exhibit smaller extinction coefficients than the corresponding trans isomers; for example, *cis*-β-methylstyrene shows λ_{max} 242 nm (ϵ 13,200) and *trans*-β-methylstyrene shows λ_{max} 249 nm (ϵ 16,000) as reported by C. G. Overberger, D. Tanner, and E. M. Pearce, *J. Amer. Chem. Soc.*, **80**, 4566 (1958).

(20) S. Mamedov and D. N. Khydyrov, *Zh. Obshch. Khim.*, **33**, 457 (1963); *Chem. Abstr.*, **59**, 488*g* (1965).

(21) R. C. Fahey and C. Schubert, *J. Amer. Chem. Soc.*, **87**, 5172 (1965).

financial support and Dr. E. A. Hill, University of Wisconsin—Milwaukee, for obtaining the 100-MHz nmr spectra for us.

Registry No.—1, 4393-06-0; 5, 93-55-0; 6, 40600-05-3; 7, 40600-06-4; 8, 17180-39-1; 9, 40132-63-6; 10, 40132-64-7; 11, 40587-41-5; 12, 22665-13-0; 13, 6051-52-1; 14, 495-40-9; 15, 4518-65-4.

Conversion of 1,3-Dihalopropanes to Propanes and/or Cyclopropanes on Treatment with Different Reducing Agents[1]

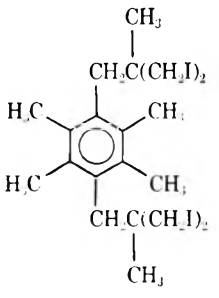
MELVIN S. NEWMAN,* G. S. COHEN,[2] ROBERT F. CUNICO,[3] AND L. W. DAUERNHEIM[4]

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

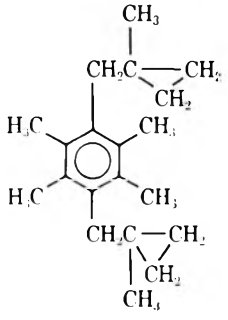
Received March 7, 1973

Treatment of 2-benzyl-2-methyl-1,3-diiodopropane (**3a**) with lithium aluminum hydride in ether or chromous sulfate in dimethylformamide yields mainly 1-benzyl-1-methylcyclopropane (**5**), whereas, when tri-*n*-butyltin hydride is used, solvent-dependent mixtures of **5** and neopentylbenzene (**6**) result. When 2-benzyl-2-methyl-1,3-dibromopropane (**3b**) is treated with $LiAlH_4$, solvent-dependent mixtures of **5** and **6** are formed. When 2-benzyl-1,3-dihalopropanes are treated with $LiAlH_4$, mixtures rich in isobutylbenzene, **8**, are obtained.

The cyclization of **1** to **2** on treatment with lithium aluminum hydride, W-2 Raney nickel, and sodium



1



2

in liquid ammonia has been reported.[5] A similar reduction of 1,3-diiodocyclobutane to bicyclobutane by $LiAlH_4$ has been observed.[6] Because of continuing interest in this type of reaction, further studies on the reduction of 1,3-dihalides with a variety of reducing agents have been made. As substrates 2-benzyl-2-methyl-1,3-dihalopropanes **3a–c** and 2-benzyl-1,3-dihalopropanes **4a–c** were chosen.

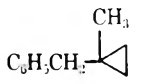
$C_6H_5CH_2C(CH_3)(CH_2X)_2$

3a, X = I
b, X = Br
c, X = Cl

$C_6H_5CH_2CH(CH_2X)_2$

4a, X = I
b, X = Br
c, X = Cl

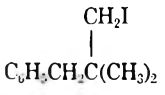
Reductions with Lithium Aluminum Hydride.—Reduction of **3a** with $LiAlH_4$[7] in refluxing ether, tetrahydrofuran (THF), and dioxane yielded mixtures of 1-benzyl-1-methylcyclopropane (**5**) (about 95%) and neopentylbenzene (**6**) (about 5%). When pure 2,2-dimethyl-3-phenylpropyl iodide (**7**) was reduced similarly only **6** was formed. Thus, **5** is formed directly from **3a**. Competitive reduction of **3a** and **7** showed that **3a** is reduced slightly faster[4] than **7**. These results indicate that two competitive processes are involved, one leading directly to the formation of **5** and the second to **7** which is then further reduced to **6**.



5

$C_6H_5CH_2C(CH_3)_3$

6



7

In contrast to the behavior of **3a**, reduction of the dibromide **3b** with $LiAlH_4$ in THF yielded mixtures of **5** and **6** in a ratio of about 5:95, respectively. In dioxane the ratio was about 30:70. Reduction of the dichloride **3c** proved too slow in ether or THF to be considered as a synthetic route to hydrocarbons. In refluxing dioxane reduction occurred slowly to yield about 18% of **5** and 62% of **6**.

In order to compare the behavior of less hindered 1,3-dihalides with that of **3a–c** the reduction of the corresponding halides **4a–c** was studied. In all cases, isobutylbenzene (**8**) was the main product. With the iodide **4a** small amounts of benzylcyclopropane (**9**) were produced but with **4b** only **8** was detected.

The above results are summarized in Table I.

Reductions with Other Reducing Agents.—The behavior of **3a** on treatment with a variety of reducing agents is summarized in Table I. The most discriminating reagent with regard to cyclopropane formation is chromous sulfate,[8] a reagent used earlier to effect dehalogenation of vicinal dihalides.[9] The reductions with Raney nickel and sodium in ammonia were not studied in detail because they did not seem to offer promising synthetic routes to **5** or **6**.

The reaction of **3a** with tri-*n*-butyltin hydride (TBTH)[10] was studied not only because cyclopropane formation seemed predominant but also because reduction of halides with TBTH undoubtedly involves free-radical chain processes[10] in contrast to $LiAlH_4$ reductions, which are assumed to proceed by hydride

(1) This work was supported in part by Grant 12445 from the National Science Foundation.

(2) Summer NSFURP Fellow, 1967.

(3) Postdoctoral Research Associate, The Ohio State University, 1966–1968.

(4) Taken in part from the Ph.D. thesis of L. W. Dauernheim, The Ohio State University, 1969. Details of the reduction experiments are given.

(5) M. S. Newman, J. R. LeBlanc, H. A. Karnes, and G. Axelrod, *J. Amer. Chem. Soc.*, **86**, 868 (1964).

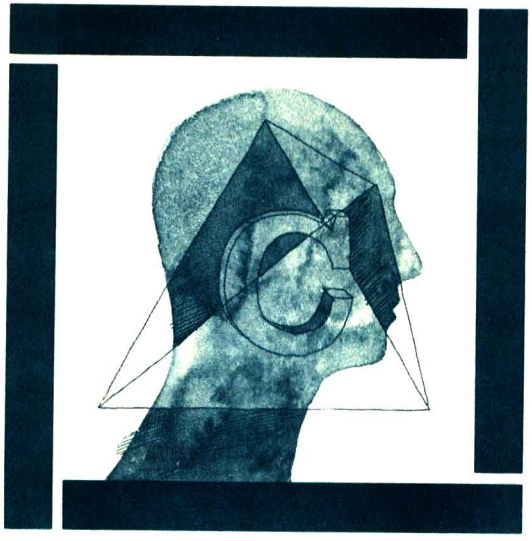
(6) W. von E. Doering and J. F. Cobuin, Jr., *Tetrahedron Lett.*, 991 (1965).

(7) Unless otherwise stated a ratio of 2 mol of $LiAlH_4$ to 1 mol of halide was used.

(8) J. K. Kochi and D. M. Singleton, *J. Org. Chem.*, **33**, 1027 (1968).

(9) W. C. Kray, Jr., and C. E. Castro, *J. Amer. Chem. Soc.*, **86**, 4603 (1964).

(10) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968).



Enter your personal one year subscription to THE JOURNAL OF ORGANIC CHEMISTRY. Subscribe to the leading journal devoted to general organic chemistry. Forty papers per biweekly issue give you the total picture. Complete the form and start benefiting from this informative publication right now.

THE JOURNAL OF ORGANIC CHEMISTRY

*ACS members	☐ U.S. $20.00	☐ **Canada, PUAS $25.00	☐ **Other Nations $26.00
Nonmembers	☐ U.S. $60.00	☐ **Canada, PUAS $65.00	☐ **Other Nations $66.00

☐ Payment enclosed *(payable to American Chemical Society)* ☐ Bill me ☐ Bill company

Name _____ Position _____

Your Employer _____

Address ☐ Home
☐ Business _____

City _____ State _____ Zip _____

Employer's Business ☐ Manufacturing ☐ Government ☐ Academic ☐ Other _____

If Manufacturer, Type of Products Produced _____

*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

3-8

THE PUBLICATIONS OF THE AMERICAN CHEMICAL SOCIETY

FIRST CLASS
PERMIT No. 1411-R
WASHINGTON, D.C.

BUSINESS REPLY MAIL
No Postage Stamp Necessary if Mailed in the United States

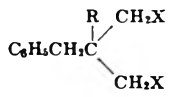
POSTAGE WILL BE PAID BY

AMERICAN CHEMICAL SOCIETY
1155 Sixteenth Street, N.W.
Washington, D.C. 20036

ATTN: J. MEDINA

TABLE I

REDUCTION OF 2-BENZYL-1,3-DIHALOPROPANES[a]



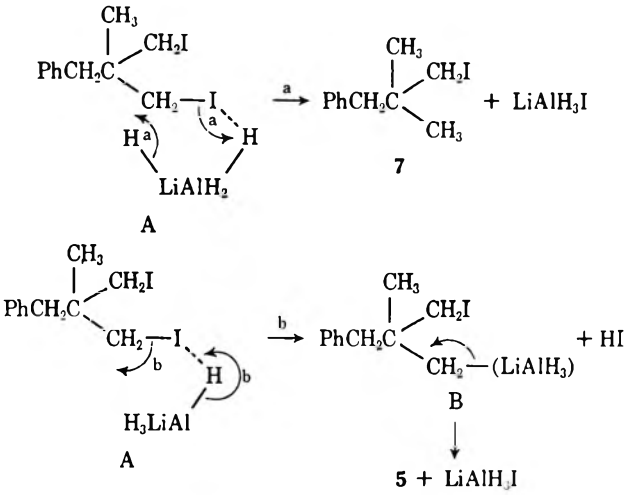
	Reducing agent, solvent	6	5
3a, R = CH_3; X = I	$LiAlH_4$, ether[b]	3	97
	W-2 Ni	67	33
	Na, NH_3	20	80
	$CrSO_4$, DMF	0	100
	$(C_4H_9)_3SnH$, benzene	6	94[c]
	$(C_4H_9)_3SnH$, ether	14	86[d]
	$(C_4H_9)_3SnH$, cyclohexane	56	44[e]
3b, R = CH_3; X = Br	$LiAlH_4$, THF	95	5
	$LiAlH_4$, dioxane[f]	68	30
3c, R = CH_3; X = Cl	$LiAlH_4$, ether[g]	UD[h]	UD[h]
	$LiAlH_4$, THF[i]	4	4[j]
	$LiAlH_4$, dioxane	62	18[k]
		8	9
4a, R = H; X = I	$LiAlH_4$, ether	70	30
	$LiAlH_4$, THF[l]	96	4
4b, R = H; X = Br	$LiAlH_4$, THF[l]	D[m]	UD[h]
4c, R = H; X = Cl	$LiAlH_4$, THF[n]	D[m]	UD[h]
X = OMs	$LiAlH_4$, THF (6)	D[m]	UD[h]

[a] In general 0.02 mol of $LiAlH_4$ was used for 0.01 mol of dihalide. [b] Refluxed for 20 hr. Similar results were obtained after 6 hr at reflux in THF and dioxane. [c] Hydrogen (60% based on cyclopropane formed) obtained. [d] Hydrogen, 80% as for *c*. [e] Hydrogen, 70% as for *c*. [f] 1:1 ratio of $LiAlH_4$ to halide, 24 hr at reflux. [g] 25 hr. [h] UD = undetected by glpc. [i] 82 hr. [j] In addition, 52% of 2-benzyl-2-methyl-1-chloropropane and 40% of **3c** were shown to be present by glpc. [k] In addition 20% of 2-benzyl-2-methyl-1-chloropropane was present. [l] At reflux, 5 hr. [m] Detected by glpc. [n] At reflux, 26 hr.

ion (or complexed hydride) intermediates.[11-13] Interestingly, the proportions of **5** and **6** formed from **3a** with TBTH proved sensitive to solvent. The reaction in benzene and in ether gives mainly **5**, whereas in cyclohexane the formation of **6** predominates (see Table I).

Mechanism ($LiAlH_4$).—Because of the difficulty of designing crucial experiments, little can be said with certainty about the mechanism of the $LiAlH_4$ reductions. We do not believe that the formation of **6** occurs by two SN2 displacements of halide ion, a type of reaction generally assumed to occur in reductions of halides and other functions because of the studies reported.[11,12] Rather, we suggest that the diiodide **3a** first interacts with $LiAlH_4$ by association of an iodine atom with hydrogen to form the complex A. Two paths are available for further reaction of A: in path a, an intramolecular rearrangement leads to **7** and $LiAlH_3I$ (reduction of **7** by a path similar to path a leads to the formation of **6**); in path b, a different intramolecular decomposition leads to formation of a molecule of hydrogen iodide (which reacts further with $LiAlH_4$ to form hydrogen[14,15] and $LiAlH_3I$) and a new intermediate, B, which rapidly cyclizes with loss of I^- to yield **5**. Alternately, an anion (formed by removal of the $LiAlH_3^+$ ion) cyclizes with expulsion of an iodide ion. These reactions are outlined in Scheme I.

SCHEME I

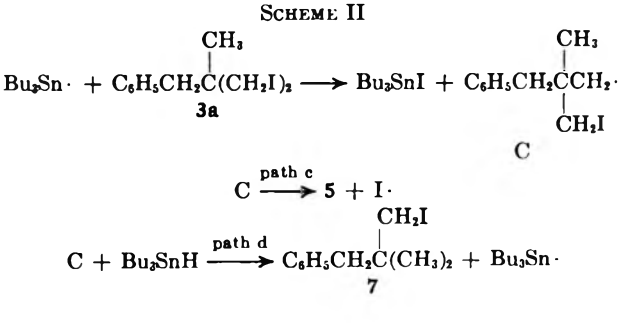


We prefer the above explanations largely because of the steric factors involved which should militate against SN2 type reactions. The initial interaction of **3a** with $LiAlH_4$ by hydrogen–iodine attraction would not be expected to be sterically hindered and subsequent reactions (paths a and b) are intramolecular and hence less slowed by steric factors than intermolecular reactions. In addition, the formations of **5**, **6**, and **7** are all accompanied by a release of strain.

The differences in behavior of the halides **3a**, **3b**, and **3c** can be interpreted in terms of the differences in size of the atoms, coordination tendencies, and strengths of bonds. However, we do not feel that the experimental results justify detailed comment. The preference of **3b** to yield **6** rather than **5** is rationalized by assuming that reaction by path a is preferred over reaction by path b. In the case of the reduction of the halides **4a**, **4b**, and **4c**, the incursion of SN2-type reactions[11,12] becomes more likely because of the decreased steric factors. Hence, the greater proportions of reduction to isobutylbenzene may be attributed to SN2 reduction rather than reaction by path a.

Mechanism (TBTH).—The formation of the cyclopropane **5** from **3a** seems best explained as shown in Scheme II. We prefer to view the formation of **5** from

SCHEME II



the radical C by expulsion of an iodine atom (path c) rather than to assume a reaction between C and another

(11) L. W. Trevoy and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 1675 (1949).

(12) E. L. Eliel, *ibid.*, **71**, 3970 (1949).

(13) However, it is noteworthy that a small amount of a mixture of *dl*- and *meso*-2,3-diphenylbutane was obtained on reduction of α-chloroethylbenzene with $LiAlH_4$.[12] Hence, a free-radical path might be involved to some extent.

(14) The gas formed was assumed to be hydrogen. In the reductions with TBTH, we thank Professor Sheldon Shore for the determination of hydrogen by gas density measurement.

(15) See R. J. Strunk, P. M. D. Giacomo, K. Aso, and H. G. Kuivila, *J. Amer. Chem. Soc.*, **92**, 2849 (1970), for an analogous reaction with vicinal dibromides.

radical to produce a 1,3-diradical which cyclizes[16] to **5**. The formation of cycloalkanes from diiodides has been noted and discussed.[17-19] In the cases studied unsaturated dihaloalkanes were involved, whereas in **3a** in *gem*-dialkyl effect is present[20] and may be responsible for the much higher yield of cyclopropane.

The fact that neopentylbenzene (**6**) is formed shows that the radical C can abstract a hydrogen atom from another species (probably TBTH or solvent) to yield the monoiodo compound **7** (path d). The latter is then converted to **5** by a conventional free radical path.[10] The sensitivity to solvent of the relative rates by paths c and d is remarkable and may indicate that TBTH in cyclohexane is a better donor of H· to C than it is in benzene or ether. This view seems preferable to an alternate one which would require C to collapse to **5** and I· less readily in cyclohexane than in benzene or ether.

Experimental Section

Gas-liquid phase chromatography (glpc) was carried out using a 5 ft × 0.125 in. stainless steel column of 5% SE-30 on 60–80 mesh Chromosorb W. An Aerograph Hi-Fi with glass-lined injection port and flame ionization detector was employed. Analyses of reduction mixtures were determined at an initial column temperature of 90°, followed by maximum programming of the oven temperature to 200° one minute after elution of **5** and **6**. Yield determinations were obtained from glc data by disk integration and corrected for detector response variations. Bromomesitylene, unreactive under the conditions employed for reduction and analyses, was used as an internal standard. Infrared data was obtained on a Perkin-Elmer Infracord. Nmr spectra were obtained with a Varian A-60 spectrometer in carbon tetrachloride or deuteriochloroform solutions containing tetramethylsilane as internal standard. All proton integration value were consistent with the structures assigned. All microanalyses were by the Galbraith Laboratories, Knoxville, Tenn.

2-Benzyl-2-methyl-1,3-propanediol Bismethanesulfonate.—To an ice-cooled solution of 132 g of 2-benzyl-2-methyl-1,3-propanediol, mp 68–70°, prepared in 86% yield essentially as described[21] by reduction of diethyl benzylmethylmalonate[22] with $LiAlH_4$ in THF, in 320 g of pyridine and 500 ml of benzene was added 450 g of methanesulfonyl chloride dropwise to maintain the temperature at 10° or below. After 6 hr the solution was held at room temperature for 42 hr and then poured into 1 l. of cold water. After a conventional work-up, including a Darco G-60 (charcoal) treatment of the crude yellow oil in absolute ethanol, there was obtained 218 g (86%) of colorless, needlelike crystals of the bismethanesulfonate, mp 48–50°. A recrystallized sample (ethanol) melted at 49–50°.

Anal. Calcd for $C_{13}H_{20}O_6S_2$: C, 47.1; H, 6.2. Found: C, 47.0; H, 6.2.

2-Benzyl-2-methyl-1,3-diiodopropane (3a[23]‡).—A mixture of 36.0 g of the above bismethanesulfonate, 170 g of potassium iodide, and 300 ml of freshly distilled 2-ethoxyethanol was stirred at reflux for 10.5 hr. After a conventional work-up, the crude diiodide was rapidly distilled at low pressure to yield a brown liquid. Two low-temperature crystallizations from 60-ml portions of absolute alcohol followed by vacuum drying at 0–10° for 20 hr yielded 29.0 g (68%) of **3a** as a light yellow, powdery solid, mp 22.0–22.5° (98% pure by glpc). A glass liner was needed at the injection part. This diiodide did not discolor further if kept sealed in a refrigerator.

Anal. Calcd for $C_{11}H_{14}I_2$: C, 33.0; H, 3.5. Found: C, 33.3; H, 3.7.

2-Benzyl-2-methyl-1,3-dibromopropane (3b‡).—A stirred mixture of 60.0 g of dimesylate, 102 g of dry lithium bromide, and 400 ml of freshly distilled 2-ethoxyethanol was held at reflux for 46 hr. After a conventional work-up, fractional distillation through a 170 × 19 mm Vigreux column afforded 46.0 g (87%) of colorless **3b**, bp 115–120° (0.7 mm). Crystallization from absolute ethanol at −78° followed by distillation yielded 37 g (70%) of colorless pure **3b**, bp 94–95° (0.1 mm), mp 29–30°.

Anal. Calcd for $C_{11}H_{14}Br_2$: C, 43.2; H, 4.6. Found: C, 43.5; H, 4.4.

2-Benzyl-2-methyl-1,3-dichloropropane (3c‡).—A stirred mixture of 80 g of bismethanesulfonate, 80 g of lithium chloride, and 500 ml of 2-ethoxyethanol was held at reflux for 52 hr and worked up as usual. On fractionation 47.0 g (90%) of **3c**, bp 100-104° at 0.25 mm, was obtained. Glpc analysis showed this to be 99% pure.

Anal. Calcd for $C_{11}H_{14}Cl_2$: C, 60.8; H, 6.5. Found: C, 60.6; H, 6.5.

2-Benzyl-1,3-propanediol Bismethanesulfonate.—Treatment of diethyl benzylmalonate with $LiAlH_4$ essentially as described above yielded colorless crystals of 2-benzyl-1,3-propanediol,[24] mp 66.5–69.0°, in 66% yield. Mesylation as described above afforded the bismethanesulfonate as colorless crystals, mp 84.0–86.5°, in 97% yield in the best run.

Anal. Calcd for $C_{12}H_{18}O_6S_2$: C, 44.8; H, 5.6. Found: C, 45.0; H, 5.4.

2-Benzyl-1,3-diiodopropane (4a).—A stirred mixture of 25.0 g of bismethanesulfonate, 70 g of potassium iodide, and 200 ml of 2-ethoxyethanol was held at reflux for 8 hr. After a conventional work-up there was obtained 29.5 g (91%) of brown liquid, **4a**, bp 140–150° (3 mm). Low-temperature crystallization and drying as described above for **3a** afforded 18.0 g of pale yellow solid, **4a**, mp 39.0–43.5°.

Anal. Calcd for $C_{10}H_{12}I_2$: C, 31.1; H, 3.1. Found: C, 31.1; H, 3.3.

2-Benzyl-2-methyl-1-iodopropane (7).[25]—A stirred mixture of 14.4 g (0.10 mol) of isobutyl 2-methylpropanoate, 6.0 g of a 50% sodium hydride dispersion in mineral oil (0.12 mol of NaH), and 12.7 g (0.10 mol) of benzyl chloride was heated at 100° under nitrogen for 2 hr. Dioxane (50 ml) was then added to the thick slurry, and the reaction mixture was refluxed for an additional 2 hr. After hydrolysis and work-up, distillation afforded 10.4 g (44%) of isobutyl 2,2-dimethyl-3-phenylpropanate, bp 135–137° (9 mm). Reduction with $LiAlH_4$ yielded 6.4 g (90%) of 2,2-dimethyl-3-phenyl-1-propanol,[25] bp 68° (0.2 mm). Mesylation of this alcohol followed by reaction with potassium iodide essentially as described above gave 64% of **7**, bp 68–70° (0.1 mm).

Anal. Calcd for $C_{11}H_{15}I$: I, 46.3. Found: I 46.6.

W-2-Raney Nickel Reduction of 3a.—A mixture of 10.4 g of W-2 Raney nickel,[26] 0.5 g of **3a**, and 40 ml of absolute ethanol was refluxed under nitrogen. Aliquots taken 0.5 hr later and subsequently all showed a 2:1 distribution of **6** to **5**. No **3a** or **7** was in evidence after 0.5 hr; the glpc-determined yield of products after 4 hr was 88%.

Sodium in Ammonia Reduction of 3a.—Sodium was introduced piecemeal into a rapidly stirred solution of 1.0 g of **3a** in 30 ml of liquid ammonia and 20 ml of dry tetrahydrofuran until the persistence of a dark blue color. After 10 min, the reaction mixture was quenched with ammonium chloride. Glpc analysis indicated a 20:80 ratio of **6** to **5**.

Chromous Sulfate Reduction of 3a.—A mixture of 1.0 g (2.5 mmol) of **3a**, 50 ml of a chromous sulfate–zinc sulfate solution 0.7 *N* in Cr(II),[27] and 60 ml of dimethylformamide was stirred under nitrogen for 92 hr at 25°. After work-up, glpc analysis showed only the presence of **5**.

Tri-*n*-butyltin Hydride Reduction of 3a.—The following procedure was used with all solvents employed. A dry, steamed-out, one-neck flask was equipped with stirring bar and addition

(16) K. V. Ingold and B. P. Roberts, "Free Radical Substitution Reactions," Wiley-Interscience, New York, N. Y., 1971, p 81 ff.

(17) W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967).

(18) J. F. Garst and J. T. Barbas, *J. Amer. Chem. Soc.*, **91**, 3385 (1969).

(19) R. F. Drury and L. Kaplan, *J. Amer. Chem. Soc.*, **94**, 3982 (1972).

(20) For a discussion of the *gem*-dialkyl effect see M. S. Newman and R. E. Dickson, *J. Amer. Chem. Soc.*, **92**, 6880 (1970), and references cited therein.

(21) G. Ferrari and C. Casagrande, *Farmaco, Ed. Sci.*, **18**, 780 (1963).

(22) D. F. DeTar and C. Weis, *J. Amer. Chem. Soc.*, **79**, 3045 (1957).

(23) All compounds marked with ‡ gave nmr and *m/e* consistent with the formulas proposed. We thank Mr. R. Weisenberger for the mass spectra.

(24) R. Mozingo and K. Folkers, *J. Amer. Chem. Soc.*, **70**, 227 (1948).

(25) The procedure used here is similar to that of P. Warrick, Jr., and W. Saunders, Jr., *J. Amer. Chem. Soc.*, **84**, 4095 (1962).

(26) E. C. Horning, Ed., "Organic Syntheses," Collect. Vol. 3, Wiley, New York, N. Y., 1955, p 181.

(27) C. E. Castro, *J. Amer. Chem. Soc.*, **83**, 3262 (1961).

funnel. After a solution of 0.50 g (1.3 mmol) of **3a** in 2 ml of the appropriate solvent was introduced to the flask, the addition funnel was charged with a solution of 0.75 g (2.6 mmol) of TBTH in 4 ml of the same solvent. Immediately after attaching the gas-measuring line (water displacement and dibutyl phthalate in a leveling buret were both used), the hydride solution was added at once to **3a**. Gas evolution began after a short (about 1 min) induction period; after correction to standard conditions, comparison was made with the amount of gas expected on the basis of the actual yield of **5** obtained (Table I). This evolved gas was shown to be hydrogen by gas-density measurements.[14] A control reaction in which the evolved gas was passed through a sodium hydroxide solution of known strength showed that no significant amount of acidic material was lost from the reaction.

Glpc analyses were performed by withdrawing aliquots and quenching with one-fourth their volume of methyl iodide. Bromomesitylene was then added as internal standard. Besides consuming excess hydride, methyl iodide inhibited the thermal (wall-catalyzed) cyclization of **3a** upon contact with the hot injection part of the gas chromatograph. Combined yields of **6** and **5** were typically in the 95–100% range by glpc, with **6**:**5** ratios as reported in Table I.

In a large-scale run, 21.9 g (75.3 mmol) of TBTH was added at once to 15.0 g (37.5 mmol) of **3a** in 120 ml of dry benzene. After gas evolution was complete, solvent was removed and distillation afforded 4.9 g (90%) of material, bp 80–84° (14 mm), which glpc analysis indicated to be a 5:95 mixture of **6** and **5**. 1-Benzyl-1-methylcyclopropane (**5**) had nmr ($CDCl_3$) δ 7.22 (s, PhH), 2.58 (s, $PhCH_2$), 0.80 (s, CH_3), and 0.38 (m, CH_2CH_2). A near-infrared spectrum of **3a** (Applied Physics Corp., Cary Model 14, 0.500 *M* **3a** in CCl_4) displayed an absorption maximum at 1.642 μ with a molar absorptivity (A) of 0.33 per cyclopropyl methylene group.[28]

Measurement of Hydrogen Evolution from $LiAlH_4$ Treatment of 3a.—A flask and Claisen head assembly was fitted with a septum seal, stirring bar, and gas line to a leveling buret containing di-*n*-butyl phthalate. After 2 ml of a $LiAlH_4$ in ether solution (2.5 mequiv $LiAlH_4$/ml), the hydride was diluted with 20 ml more ether, and after the system had stabilized, 1.20 g (3.00 mmol) of **3a** was introduced by syringe through the septum. Slow but steady gas evolution began immediately, leading to a total of 65.3 ml of gas (corrected to STP) over a 15-hr period (further standing led to a 5-ml *decrease* of volume over a 2-day period). Assuming that of **3a** is converted to products in a typical ratio of 3:97 (6:5), this represents a quantitative yield of gas based on the amount of **5** formed.

Registry No.—**3** (X = OMs), 40548-53-6; **3** (X = OH), 2109-99-1; **3a**, 40548-52-5; **3b**, 40548-55-8; **3c**, 40548-56-9; **4** (X = OMs), 40548-57-0; **4** (X = OH), 2612-30-8; **4a**, 40548-59-2; **4b**, 35694-75-8; **4c**, 40548-61-6; **5**, 30836-86-3; **6**, 1007-26-7; **7**, 40548-64-9; **8**, 538-93-2; **9**, 1667-00-1; $LiAlH_4$, 16853-85-3; TBTH, 688-73-3; methanesulfonyl chloride, 124-63-0; potassium iodide, 7681-11-0; lithium bromide, 7550-35-8; lithium chloride, 7447-41-8; isobutyl 2-methylpropanoate, 97-85-8; isobutyl 2,2-dimethyl-3-phenylpropanate, 40548-66-1; 2,2-dimethyl-3-phenyl-1-propanol, 13351-61-6.

(28) Compare λ_{max} = 1.638 μ and A = 0.324 for the known 1-benzylcyclopropane; P. G. Gassman and F. V. Zalar, *J. Org. Chem.*, **31**, 166 (1966).

Intermediates in the Reaction of Grignard Reagents with Nitromethane

STANLEY WAWZONEK* AND JAMES VERN KEMPF[1]

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

Received February 15, 1973

The reaction of *n*-butylmagnesium bromide with nitromethane formed *N*-*n*-butyl-*N*-methylhydroxylamine, *N*-*n*-pentyl-*N*-methylhydroxylamine, octane, and *n*-butyl alcohol. The same reaction in the presence of styrene gave a small amount of 2-butyl-5-phenylisoxazolidine. These results point to a complex between nitromethane and *n*-butylmagnesium bromide and to 2-butylnitrone as intermediates in the formation of the hydroxylamines isolated.

The actual mechanism for the formation of hydroxylamines from Grignard reagents and nitromethane is not known.[2] Semiquantitative studies of

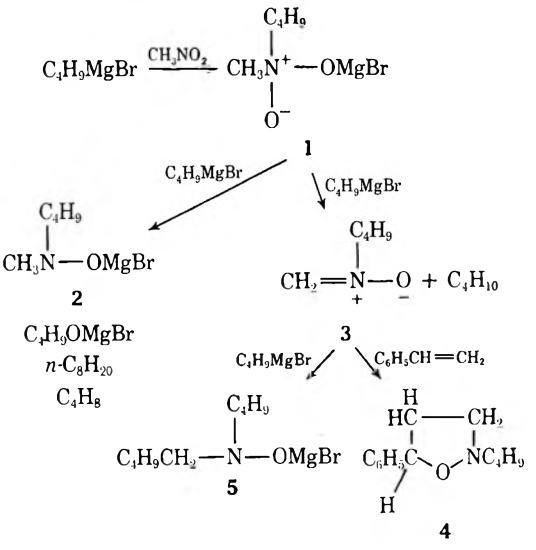
$$RMgX + CH_3NO_2 \longrightarrow \underset{\displaystyle R}{CH_3NOH} + \underset{\displaystyle R}{RCH_2NOH}$$

the reaction of ethylmagnesium bromide and *n*-butylmagnesium bromide with nitromethane carried out in the present work gave results which point to certain intermediates in this reaction.

The reaction with ethylmagnesium bromide was used to follow the influence of the concentration of the Grignard reagent upon the ratio of the hydroxylamines produced. The hydroxylamines were converted into the *O*-trimethylsilyl derivatives and analyzed by vpc. The results are shown in Figure 1.

The reaction using *n*-butylmagnesium bromide with nitromethane gave information about the gases evolved and the neutral products formed. The amounts of butane and butenes generated with the addition of successive amounts of Grignard reagent are shown in Figures 2 and 3. This reaction also produced *n*-octane and *n*-butyl alcohol.

These results point to the following steps in the formation of the hydroxylamines. The addition of 1 mol of *n*-butylmagnesium bromide to nitromethane forms mainly the complex **1** since very little butane



and butenes are formed at this point. A similar complex has been proposed for the reaction product be-

(1) Abstracted in part from the Ph.D. Thesis of J. V. K., 1973.

(2) S. Wawzonek and J. V. Kempf, *Org. Prep. Proced. Int.*, **4**, 135 (1972).

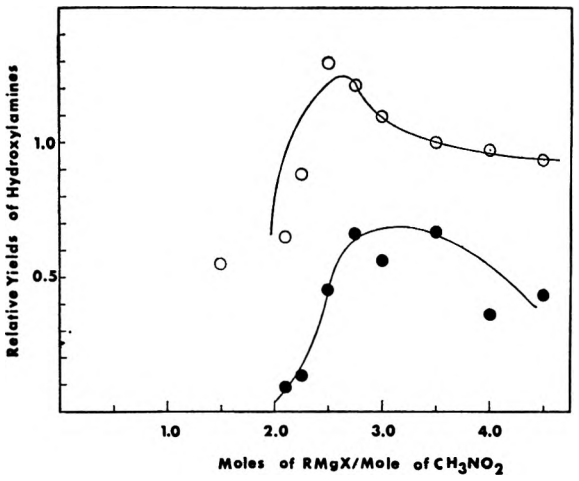


Figure 1.—Relative yields of ethylmethylhydroxylamine (○) and ethylpropylhydroxylamine (●) wth respect to benzene as an internal standard formed in the reaction of ethylmagnesium bromide with nitromethane.

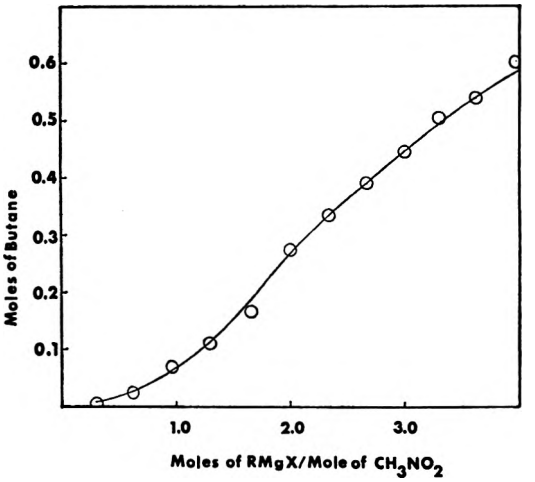


Figure 2.—Moles of butane formed in the successive addition of *n*-butylmagnesium bromide to nitromethane.

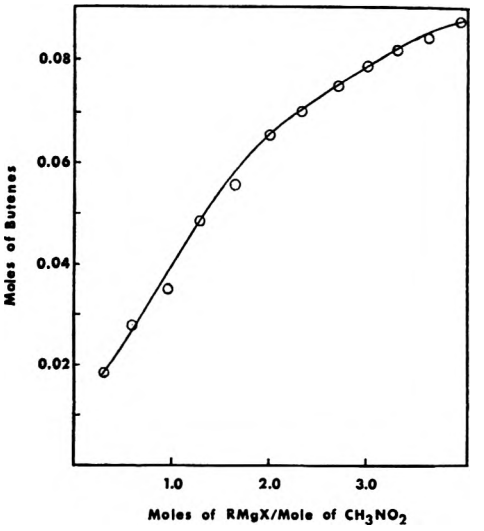


Figure 3.—Moles of butenes formed in the successive addition of *n*-butylmagnesium bromide to nitromethane.

tween molar amounts of ethylmagnesium bromide and nitroethane by Buckley.[3]

Complex **1** when treated with more *n*-butylmagnesium bromide reacts in two ways. Reduction to **2** occurs with the formation of *n*-octane, *n*-butyl alcohol, and butenes. The yield of *n*-octane corresponded to 15.6% based on the nitromethane used in a run involving 3 mol of Grignard reagent for 1 mol of nitromethane. This hydrocarbon could also be formed in the preparation of the Grignard reagent since the formation of the latter is reported to proceed in a yield of 94%.[4] Based on this yield at least 6.6% of the *n*-octane is formed by the reduction of complex **1**.

n-Butyl alcohol was isolated in an 8.8% yield, but vpc analysis directly on the ether extracted indicated a larger amount.

The reduction of complex **1** in this manner resembles that reported for dimethylaniline oxide by phenylmagnesium bromide; dimethylaniline, phenol, and biphenyl were reported as products.[5]

Reduction of **1** to **2** probably also occurs to a minor extent with the formation of butenes. This behavior would be similar to the reduction of ketones by Grignard reagents to alcohols. This type of reaction seems to be favored by excess Grignard reagents (Figure 3).

A more powerful reducing agent such as zinc and hydrochloric acid is reported to reduce the complex form ethylmagnesium bromide and nitroethane to diethylamine.[3]

The second reaction of complex **1** with excess Grignard reagent produces the nitrone **3** and butane. This reaction based on the results shown in Figure 1 proceeds at a slower rate than the reduction of **1**. A similar evolution of ethane was reported for the reaction of ethylmagnesium bromide and nitroethane.[3] Proof for the nitrone **3** was the formation of 2-butyl-5-phenylisoxazolidine (**4**) in the reaction of nitromethane (1 mol) with *n*-butylmagnesium bromide (2 mol) in the presence of excess styrene. The yield (<0.2%) of **4** was low since the conditions using refluxing ether and a 6.5-hr reaction time were less rigorous than those required to prepare a good yield of an authentic sample from *N*-butylnitrone and styrene; the latter required heating in toluene for 24 hr.

The last step involving the formation of a hydroxylamine (**5**) by the addition of a Grignard reagent to a nitrone is well documented in the literature.[2]

$$C_4H_9MgBr + CH_3NO_2 \longrightarrow CH_2{=}\overset{+}{N}(OMgX)O^- + C_4H_{10}$$

The formation of the aci derivative of nitromethane by the Grignard reagent occurs to a slight extent in this reaction; about 0.075 mol of butane was liberated during the addition of the first mole of Grignard reagent. This intermediate is responsible for the small amount of oxime formed in this reaction; addition of the Grignard reagent would form a complex **6** which

$$C_4H_9MgBr - CH_2{=}\overset{+}{N}OMgBr\,O^- \longrightarrow \underset{\mathbf{6}}{C_4H_9CH_2N(OMgBr)_2}$$

would hydrolyze to the oxime. Evidence for the presence of valeraldoxime was obtained in the present

(3) G. D. Buckley, *J. Chem. Soc.*, 1492 (1947).
(4) H. Gilman, E. H. Zoellner, and J. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).
(5) V. Belov and K. K. Savich, *J. Gen. Chem. USSR*, **17**, 262 (1947).

work by a nmr study of the products obtained by decomposing the Grignard product solely with water.

The conversion of nitromethane into the aci derivative becomes more important with increasing amounts of Grignard reagent since the yield of hydroxylamines drops with more than 3 mol of Grignard reagent (Figure 1) and the yield of butane (Figure 2) increases.

Experimental Section[6]

Preparation and Gas Chromatographic Analysis of *O*-Trimethylsilyl Derivatives of *N*-Ethyl-*N*-methylhydroxylamine and *N*-Ethyl-*N*-propylhydroxylamine.—Ethylmagnesium bromide (0.25 mol) in ether (150 ml) was added dropwise with stirring to nitromethane (5.4 ml, 0.1 mol) in ether (200 ml) at 0°. The reaction mixture was gently refluxed for 12 hr and then decomposed by addition of water. Hydrochloric acid was added to adjust the solution to a pH of 9–10, and the reaction mixture was subjected to steam distillation. The distillate was collected in dilute hydrochloric acid, a total of 2.5 l. being collected. The acidic steam distillate was reduced to a small volume *in vacuo*, made basic with concentrated aqueous sodium hydroxide, and extracted four times with 75-ml portions of ether. The ether solution was dried ($CaSO_4$) and filtered, and the ether was distilled from the mixture through a 20-in. zigzag column until only 15–20 ml of solution remained. The concentrated ether solution was transferred to a 50-ml glass-stoppered flask and treated with 6.0 ml of pyridine and 6.0 ml of trimethylchlorosilane at 0°. The mixture was brought to room temperature and allowed to stand for several hours. Then, 2.00 ml of benzene was added; the solution was thoroughly mixed and subjected to gas chromatographic analysis using a 6 ft by $^1/_8$ in. column of 10% W-98 silicon rubber on 100–200 mesh Chromsorb P with an injection port temperature of 250°, column temperature programmed to start at 50° and rise to 200° at 10°/min, detector temperature of 360° and gas flow of 50 ml/min at 50 psi. The retention times follow: benzene, 2.6 min; *N*-ethyl-*N*-methyl-*O*-trimethylsilylhydroxylamine, 4.4 min; *N*-ethyl-*N*-propyl-*O*-trimethylsilylhydroxylamine, 7.2 min. In the manner described above, ethylmagnesium bromide was added to nitromethane in mole ratios of 1.50, 2.10, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, and 4.50 and analyses were by gas chromatograph. The mixture of 3 mol of ethylmagnesium bromide with 1 mol of nitromethane using normal addition was also analyzed. The yields of hydroxylamines were less than those obtained by the inverse method. The use of a known quantity of benzene in the gas chromatography sample made it possible to calculate relative yields of the trimethylsilanated dialkylhydroxylamines with respect to nitromethane by comparing the area of their signals to that of benzene. The results are shown in Figure 1.

***N*-Ethyl-*N*-methyl-*O*-trimethylsilylhydroxylamine.**—In a 250-ml flask were placed 100 ml of ether, 10.0 ml of triethylamine, and 5.0 ml of *N*-ethyl-*N*-methylhydroxylamine. The solution was cooled in ice and 5.0 ml of trimethylchlorosilane was added. The flask was stoppered and cooled in ice with occasional shaking for 2 hr; it was then allowed to stand at room temperature for 2 hr. Water (70 ml) was added to the nearly solid reaction mixture. The ether layer was separated, washed with four 100-ml portions of water, and dried ($CaSO_4$). The ether upon removal under reduced pressure gave 1.5 ml of liquid. A sample of the desired product was isolated by preparative gas chromatography using a 10 ft by $^1/_8$ in. column of SE-30 on 100–120 mesh Chromosorb P with an injection port temperature of 175°, column temperature of 90°, detector temperature of 175°, and a gas flow of 170 ml/min at 30 psi. The retention time was 7.8 min; micro bp 117° (740 mm); n^{24}D, 1.3995; nmr ($DCCl_3$, $HCCl_3$ as internal standard) δ 2.67 (q, 2, J = 7 Hz, NCH_2), 2.67 (s, 3, NCH_3), 1.02 (t, 3, J = 7 Hz, CH_3CH_2); ir (neat) 3.36, 3.47, 6.96, 7.27, 8.05, 9.58, 9.78, 10.77, 11.46; 11.87; 1313, 13.35, 14.65 μ.

Anal. Calcd for $C_6H_{17}NOSi$: C, 48.92; H, 11.64; N, 9.51. Found: C, 48.66; H. 11.67; N, 9.33.

***N*-Ethyl-*N*-propyl-*O*-trimethylsilylhydroxylamine.**—*N*-Ethyl-*N*-propylhydroxylamine (10 ml) was converted into the *O*-trimethylsilyl ether (4.08 g) by the method described for the *N*-ethyl-*N*-methyl derivative: bp 65–65.5° (30 mm); n^{24}D 1.4128; retention time on column described for the ethylmethyl derivative 14.9 min; nmr ($DCCl_3$, $HCCl_3$ as internal standard) δ 2.67 (m, 4, $N(CH_2)_2$), 1.49 (sextet, 2, J = 7 Hz, $CH_3CH_2CH_2$), 1.02 (t, 3, J = 7 Hz, NCH_2CH_3), 0.90 (t, 3, J = 7 Hz, $CH_3CH_2CH_2$); ir (neat) 3.36, 3.45, 6.25, 7.25, 8.05, 10.53, 10.56, 10.91, 11.09, 11.45, 11.94, 13.35, 14.26, and 14.66 μ.

Anal. Calcd for $C_8H_{21}NOSi$: C, 54.79; H, 12,07; N, 7.99. Found: C, 54.71; H, 11.89; N, 7.86.

2-Butyl-5-phenylisoxazolidine. A.—*n*-Butylmagnesium bromide (2 mol) in ether (500 ml) was added with stirring to a solution of nitromethane (1 mol) and styrene (2 mol) in ether (630 ml) during a period of 2.5 hr. The resulting solution was refluxed with stirring for an additional 4 hr and then hydrolyzed by addition of 150 ml of water; the magnesium salts were filtered from the mixture. Extraction of the ether solution with 4 *N* hydrochloric acid followed by basification of the acid extract gave an oil which by nmr analysis did not contain aromatic material. The magnesium salts from the reaction were continuously extracted with benzene for 2.5 days. The benzene was removed at reduced pressure and the resultant oil taken up in 300 ml of ether. The ether solution was extracted with four 100-ml portions of 6 *N* hydrochloric acid. The acid solution was diluted with 200 ml of water and made basic with concentrated aqueous sodium hydroxide. The solution was then extracted with five 150-ml portions of benzene. The benzene solution was dried ($CaSO_4$) and the benzene upon removal *in vacuo* gave 11.4 g of oil. The oil was chromatographed on a 2.5 ft × 2.0 in. column of silica gel using hexane and hexane–ether as the developing solvent. The fraction, which by nmr analysis contained aromatic material, was rechromatographed on a 2.5 ft × 1 in. column of silica gel using 2.5% ether in hexane as the eluent. The fraction which contained aromatic material was purified by preparative thin layer chromatography using a silica gel plate and chloroform as the developing solvent. The material was removed from the silica gel with methylene chloride. Removal of the methylene chloride *in vacuo* at room temperature gave 0.40 g of 2-butyl-5-phenyloxazolidine: n^{25}D, 1.5178; nmr ($DCCl_3$) δ 7.28 (m, 5, C_6H_5), 4.99 (t, 1, J = 7 Hz, C_6H_5CH), 2.80 (poorly resolved t, 4, J = 7 Hz, $N(CH_2)_2$), 1.1–1.85 (m, 6, CH_2CH_2, CH_2CHPh), 0.92 (t, 3, J = 7 Hz, CH_3); ir (neat) 3.38, 6.68, 6.85, 7.30, 9.70, 13.21, and 14.37 μ.

B.—A solution of *N*-butylhydroxylamine (2.12 g), paraformaldehyde (1.07 g), and styrene (2.73 g) in toluene was refluxed for 24 hr. The water (0.6 ml) which formed immediately was removed using a Dean-Stark trap. One-half of the toluene was distilled from the reaction mixture, and the remainder of the solution was extracted with three 100-ml portions of 3 *N* hydrochloric acid. The acid solution was made basic with concentrated aqueous sodium hydroxide and extracted with four 100-ml portions of ether. The ether solution was dried ($CaSO_4$) and upon removal of the solvent gave 3.53 g of an oil. Fractionation of the material gave 2.60 g (25.0%) of a pale yellow oil distilling at 97–99° (0.92 mm): n^{25}D 1.5128; nmr ($DCCl_3$) δ 7.25 (m, 5, C_6H_5), 4.95 (t, 1, J = 7 Hz; C_6H_5CH), 2.77 (poorly resolved t, 4, J = 7 Hz, $N(CH_2)_2$), 1.1–1.85 (m, 6, CH_2CH_2, $CH_2CHC_6H_5$), 0.92 (t, 3, J = 7 Hz, CH_3).

Anal. Calcd for $C_{12}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.26; H, 9.48; N, 6.81.

A yellow solid was formed by treating 2-butyl-5-phenylisoxazolidine with chloroplatinic acid. Two recrystallizations from ethanol containing a drop of concentrated hydrochloric acid gave a solid which decomposed at 168–71° when the heating rate was 12°/min. The sample prepared from the product isolated from the Grignard reaction decomposed at 167–70°. A mixture of the two decomposed at 167–171°. The actual structure of this material is not known.

Anal. Calcd for $C_{12}H_{21}Cl_4NOPt$: C, 28.68; H, 3.89; N, 2.57. Found: C, 28.54; H, 3.80; N, 2.51.

Gaseous Products from the Reaction of *n*-Butylmagnesium Bromide with Nitromethane.—A 500-ml three-necked flask was equipped with a 50-ml buret containing 0.505 *M* *n*-butylmagnesium bromide, a stirrer, and a condenser. The condenser was fitted with a small cold finger cooled by a liquid nitrogen-

(6) Melting points are corrected and boiling points are not corrected. Ir data were recorded using a Perkin-Elmer Infracord double beam recording spectrometer and nmr data on a Varian A-60 spectrometer. Analytical gas chromatography was carried out using an F & M Model 5750 dual column gas chromatograph equipped with Disc chart integrator. Peak areas were measured either by counting the integrator trace or using a compensating polar planimeter. Preparative gas chromatography was carried out using an F & M Model 500 gas chromatograph with a Model 720 oven.

isopropyl alcohol slush. The entire system was purged with nitrogen which was saturated with ether. A solution of 2.442 g (0.040 mol) of nitromethane in 150 ml of ether was placed in the reaction vessel. The solution was refluxed with stirring, and aliquots of Grignard solution were added. After each addition, the solution was allowed to continue refluxing for about 20 min. The cold trap was then warmed to room temperature and the gases were collected in a gas-measuring buret containing water. After measurement, the gases were analyzed using a 11 ft by 1/4 in. column of 33% 2,4-dimethylsulfolane on 60–80 mesh Chromosorb P with an injection port temperature of 125°, column temperature of 50°, detector temperature of 270°, and a gas flow of 33 ml/min at 40 psi. Retention times follow: air, 1.7 min; butane, 3.55 min; 1-butene, 4.6 min; *cis*-2-butene, 5.2 min; and *trans*-2-butene, 5.8 min. A trace amount of unidentified material with a retention time of 2.5 min was also detected. The results are shown in Figures 2 and 3.

Neutral Products from the Reaction of *n*-Butylmagnesium Bromide with Nitromethane.—The ether used in this experiment was dried over sodium wire and distilled immediately before use. The *n*-butyl bromide was filtered through a 5 in. × 1 in. column of alumina to remove all traces of *n*-butyl alcohol. Its purity was assured by gas chromatographic analysis. All phases of the reaction were conducted under nitrogen which was purified by passage through two bottles of Fieser's solution, two bottles of concentrated sulfuric acid, solid sodium hydroxide, and solid calcium chloride.

A solution of *n*-butylmagnesium bromide was prepared from 19.4 g (0.80 mol) of magnesium and 80.5 ml (0.75 mol) of *n*-butyl bromide in 300 ml of ether. The Grignard flask was attached to a 1-l. three-necked flask equipped with mechanical stirrer, heating mantle, and reflux condenser. A solution of 13.5 g (0.25 mol) of nitromethane in 150 ml of ether was placed in the reaction vessel and the *n*-butylmagnesium bromide solution was added dropwise with stirring at a rate which maintained constant reflux. After addition was complete, the reaction mixture was refluxed with stirring for an additional 4 hr. The Grignard solution was decomposed by the dropwise addition of 125 ml of 6 *N* hydrochloric acid. After an additional 30 ml of concentrated hydrochloric acid was added to the solution, the ether was separated and the aqueous solution was extracted with three 100-ml portions of ether. The combined ether solutions were dried ($CaSO_4$) and distilled using a spinning band column. The fraction boiling from 80–118° weighed 6.78 g and by gas chromatographic analysis using a Carbowax column consisted of ether (0.60 g), *n*-octane (4.55 g), and *n*-butyl alcohol (1.63 g). Gas chromatographic analysis was carried out using a 6 ft by 1/8 in. column of 15% Carbowax 4000 on 100–120 mesh Chromosorb P with an injection port temperature of 165°, column temperature of 100°, detector temperature of 225°, and a gas flow of 30 ml/min at 40 psi. The retention times follow: ether, 0.3 min; *n*-octane, 0.5 min; and *n*-butyl alcohol, 2.3–2.5 min, depending on sample size.

Registry No.—4, 40548-43-4; nitromethane, 75-52-5; ethyl bromide, 74-96-4; trimethylchlorosilane, 75-77-4; *N*-ethyl-*N*-methyl-*O*-trimethylsilylhydroxylamine, 40548-44-5; *N*-ethyl-*N*-methylhydroxylamine, 13429-36-2; *N*-ethyl-*N*-propyl-*O*-trimethylsilylhydroxylamine, 40548-46-7; *N*-ethyl-*N*-propylhydroxylamine, 40548-47-8; *n*-butyl bromide, 109-65-9; *N*-butylhydroxylamine, 5080-24-0; chloroplatinic acid, 17083-70-4.

Palladium(II)-Catalyzed Exchange and Isomerization Reactions. IX. The Hydration of Enol Acetates in Wet Acetic Acid[1]

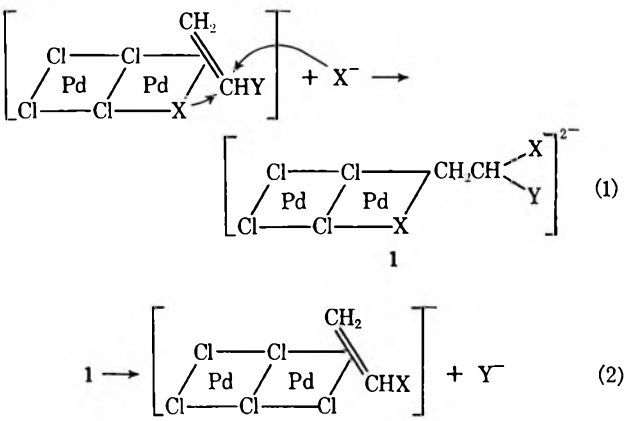
PATRICK M. HENRY[2]

Contribution No. 1603 from the Research Center, Hercules Incorporated, Wilmington, Delaware 19899

Received May 3, 1973

The rate expression for hydration of vinyl acetate to acetaldehyde was found to be rate = $k[Li_2Pd_2Cl_6][C_2H_3OAc][H_2O]^n/[LiCl]$ where n has a value of between 1 and 2. The rate expression is consistent with attack of external water on a dimeric palladium(II) vinyl acetate π complex to give a hydroxypalladation adduct which decomposes to acetaldehyde and $Li_2Pd_2Cl_6$. The decomposition of this adduct is not by simple acetate elimination to give vinyl alcohol since this mechanism would predict that 1-cyclopenten-1-yl acetate would not react. In fact this enol acetate is rapidly saponified. Formation of a palladium(II)-substituted acetaldehyde which then reacts with acetic acid solvent to give CH_3CHO seems to be the most likely mechanism. The determination of the rate expression is complicated by the fact that water is not only a reagent but affects the various equilibria present in the system. As with previous exchanges, substitution on vinyl carbon retards the rate of exchange. The nonintegral order in $[H_2O]$ is believed to be due to preferential solvation of the reactive metal ion species.

Previous papers of this series have considered exchange of vinyl[3] and allylic[4] ester with acetic acid, allylic esters with chloride,[5] and vinylic chlorides with radioactive chloride[6] and acetic acid.[7] A general feature of these exchanges is that they involve attack of acetate or chloride on a dimeric palladium(II) π complex to give a palladium(II) σ-bonded intermediate, **1**. For vinylic exchange the reaction scheme would be given by eq 1 (X and Y = Cl or OAc). Exchange is completed by elimination of Y to give back the olefin. When X is acetate, attack occurs only from outside the coordination sphere of the palladium(II);



(1)

1

(2)

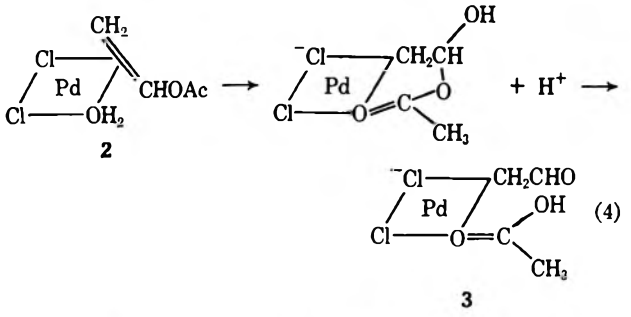
when X is chloride, attack can occur from either outside or inside the coordination sphere.

This paper will describe the palladium(II) chloride catalyzed reaction of vinyl acetate with a third and

(1) Paper VIII: P. M. Henry, *J. Org. Chem.*, **38**, 1140 (1973).
(2) Address correspondence to author at Department of Chemistry, University of Guelph, Guelph, Ontario, N1G 2W1, Canada.
(3) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3853 (1971).
(4) P. M. Henry, *ibid.*, **94**, 1527, 5200 (1972).
(5) P. M. Henry, *Inorg. Chem.*, **11**, 1876 (1972).
(6) P. M. Henry, *J. Org. Chem.*, **37**, 2443 (1972).
(7) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 7311 (1972).

unique reagent, water. Smidt and coworkers[8] reported that aqueous Pd(II) salts saponify vinyl acetate. A kinetic study of this reaction in wet acetic acid led to the conclusion that the reaction was proceeding *via* eq 4 and 5.[9] However, because the various

$$CH_2{=}CHOAc \xrightarrow[H_2O]{Pd(II)} CH_3CHO \qquad (3)$$



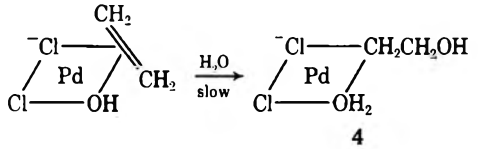
(4)

$$3 + H_2O + H^+ + C_2H_3OAc \longrightarrow 2 + CH_3CHO \qquad (5)$$

equilibria in the system were not determined, the detailed reaction path could not be defined.

Water is different from most nucleophiles because not only can it act as a reactant but it can also change the nature of the solvent. Thus the various equilibria operative in a system containing metal salts would be affected. This shift in equilibria complicates the determination of the rate equation.

As a reagent, water is of special interest because it could react in the same mode as acetate in previous exchanges studied, or it could react in the manner found for olefin oxidation in water. Thus the slow step of this reaction is the addition of coordinated hydroxyl to coordinated ethylene to give the hydroxypalladation intermediate (eq 6), which decomposes



(6)

to acetaldehyde in a subsequent fast step of the reaction.[10-12] The hydroxypalladation step in acetic acid

$$4 \longrightarrow CH_3CHO + Pd(0) + 2Cl^- + 2H_2O \qquad (7)$$

may proceed by such an insertion or may involve attack of water from outside the coordination sphere in a manner found for the acetate exchanges studied previously.

Results

All studies were carried out at 25°. In order to properly interpret the kinetic results it is necessary to determine how the addition of water affects the equilibria represented by eq 8 and 9. In dry acetic acid

$$Li_2Pd_2Cl_6 + 2LiCl \overset{K_1}{\rightleftharpoons} 2Li_2PdCl_4 \qquad (8)$$

$$2LiCl \overset{K_D}{\rightleftharpoons} Li_2Cl_2 \qquad (9)$$

the values of K_1 and K_D were previously found[13] to be 0.1 and 2.56 M^{-1}, respectively, at 25°.

The addition of water to Pd(II)–LiCl solutions with various ratios of total palladium(II), [Pd(II)], to total chloride, $[Cl]_t$, caused spectral changes. However, at constant $[Pd(II)]_t$ and $[Cl]_t$ the spectra at various water levels displayed three isosbestic points. This result would not be expected if Pd(II) species other than the two in eq 8 were being formed. In fact the addition of water caused the same spectral changes as the addition of LiCl. This result suggests that water is not directly involved in the spectral changes but is rather causing a shift in the equilibrium represented by eq 8 or, in other words, is changing the value of K_1. To confirm this, studies of the equilibrium were carried out at 1.0 and 10.0 M H_2O, using the nonlinear regression program employed previously in the study of the dry system.[13] At both water levels the data were consistent with eq 8 being the only equilibrium involving Pd(II). Values of K_1 were 0.48 and 5.6 M^{-1} at 1.0 and 10.0 M $[H_2O]$, respectively. Since the value of K_1 in dry acetic acid is 0.1 M^{-1}, the value of K_1 increases approximately linearly with water concentration. Values of K_1 at other water concentrations were calculated from this linear relationship.

When water was present in tenfold excess, kinetic plots, assuming a first-order dependence on [vinyl acetate], were linear for 4 half-lives. Furthermore, the initial vinyl acetate concentration was varied fivefold without an appreciable change in the first-order constant. Thus at $[Pd(II)_t]$ of 0.0224 M, $[Cl]_t$ of 0.1346 M, and $[H_2O]$ of 0.5 M, the first-order rate constant was found to be 2.8×10^{-5} sec^{-1} at an initial vinyl acetate concentration of 0.2 M and 2.66×10^{-5} sec^{-1} at an initial concentration of 1.0 M. In most runs the initial [vinyl acetate] was 0.2 M.

Lithium acetate was found to have no effect on the rate of hydration. Under one set of reaction conditions rates in the absence of acetate and at [LiAOc] = 0.1 M were within 5% of each other.

The order in dimer was determined using solutions of $Na_2Pd_2Cl_6$ which are saturated in NaCl. Since NaCl is sparingly soluble in acetic acid, the chloride is kept at a low but constant level and the Pd(II) should be entirely in the form of dimer. As shown in Figure 1 the reaction is first order in dimer at a water level of 0.5 M.

In Table I are listed the results of a series of runs at a water concentration of 0.5 M and constant $[Pd(II)]_t$ but varying $[Cl]_t$. The concentrations of the Pd(II) species were calculated using a value of K_1 of 0.3 M^{-1}. A problem arises at this point in treatment of data. The equilibria represented by eq 9 would be expected to be greatly affected by water but it is not easy to measure the magnitude of the effect. However, if K_D is assumed to be 2.6 M^{-1}, the value of the quotient in the last column of Table I was found to decrease systematically at the high $[Cl]_t$ at which dimerization becomes serious. However, if dimeriza-

(8) J. Smidt, R. Jira, J. Sedlmeier, R. Sieber, R. Rottinger, and H. Kojer, *Angew. Chem.*, **71**, 176 (1959).
(9) R. G. Schultz and P. R. Rony, *J. Catal.*, **16**, 133 (1970).
(10) I. I. Moiseev, M. N. Vargaftik, and Ya K. Sirkin, *Dokl. Akad. Nauk SSSR*, **163**, 140 (1963).
(11) R. Jira, J. Sedlmeier, and J. Smidt, *Justus Liebigs Ann. Chem.*, **693**, 99 (1966).
(12) P. M. Henry, *J. Amer. Chem. Soc.*, **86**, 3246 (1964).
(13) P. M. Henry and O. Marks, *Inorg. Chem.*, **10**, 373 (1971).

TABLE I
EFFECT OF [LiCl] ON THE RATE OF HYDRATION[a]

$[Cl]_t$, M	$[Li_2Pd_2Cl_6]$,[b] M	$[Li_2PdCl_4]$,[b] M	[LiCl], M	k_{obsd}, $sec^{-1} \times 10^5$	$k_{obsd}[LiCl]/[Li_2Pd_2Cl_6]$, $sec^{-1} \times 10^4$
0.0852	0.01075	0.00090	0.0170	9.8	1.55
0.105	0.01033	0.00174	0.0366	5.15	1.82
0.1346	0.0098	0.038	0.065	2.8	1.85
0.184	0.00911	0.0042	0.113	1.87	2.32
0.2334	0.00855	0.0053	0.161	1.1	2.07
0.2852	0.00805	0.0063	0.212	1.05	2.78
0.4852	0.0067	0.0090	0.409	0.4	2.44
0.8852	0.0051	0.0122	0.810	0.13	2.06

[a] $[Pd(II)]_t = 0.0224\ M$, [LiOAc] = 0.1 M, and [vinyl acetate] = 0.2 M in all runs. [b] Calculated using $K_1 = 0.3\ M^{-1}$ in eq 8.

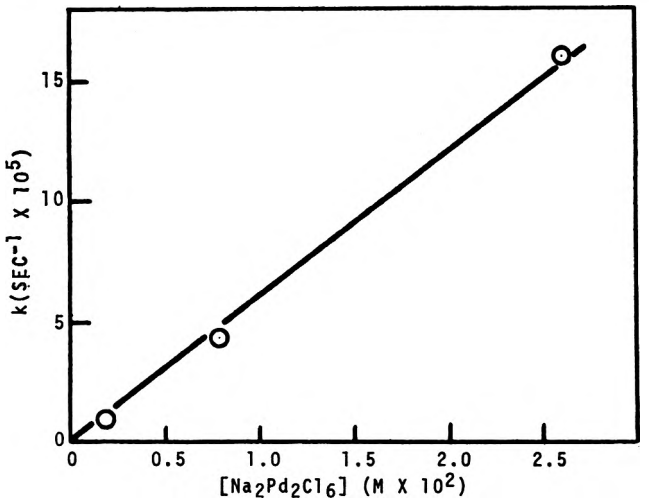


Figure 1.—Plot of k_{obsd} *vs.* $[Na_2Pd_2Cl_6]$ in saturated NaCl solutions; $[H_2O] = 0.5\ M$.

tion is assumed *not* to occur, then the values remain approximately constant. Thus dimerization of LiCl is ignored in the treatment of data in Table I.

The effect of water concentration on rate is shown in Table II. The increase in rate with H_2O is somewhat greater than expected for a first-order term in $[H_2O]$ but less than required for a $[H_2O]^2$ term. The complete rate expression is thus given by eq 10

$$\text{rate} = \frac{k[Li_2Pd_2Cl_6][C_2H_3OAc][H_2O]^n}{[LiCl]} \quad (10)$$

where

$$1 \leq n \leq 2 \quad (11)$$

The rates for three enol acetates under one set of reaction conditions are given in Table III.

Discussion

There seems little reason to doubt that the reaction proceeds *via* a hydroxypalladation analogous to that suggested previously[9] and there is considerable analogy for this type of reaction in the Hg(II)- and Tl(III)-catalyzed hydration of enol acetates.[14] However, the previous work was unable to define the kinetics because of lack of equilibrium data and the mechanism derived on the basis of kinetic data alone gave an erroneous view of the mode of hydroxypalladation.

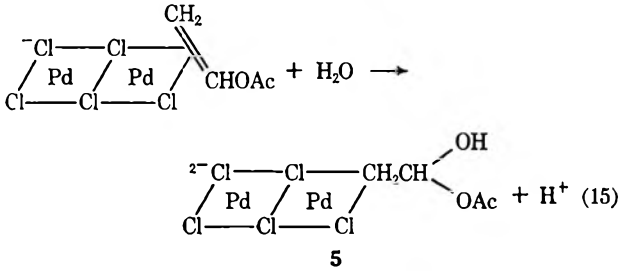
Since the reaction was found to be zero order in vinyl acetate,[15] complete formation of π complex according to eq 12 was assumed. Thus formation of π complex does not contribute a chloride inhibition term to the rate equation. The first-order inhibition term observed was attributed to replacement of chloride by water according to eq 13. The hydroxypalladation then occurs as shown in eq 4. The postulated mode of addition is analogous to the cis attack of hydroxyl which apparently takes place in the Wacker reaction.[17]

$$PdCl_4^{2-} + C_2H_3OAc \rightleftharpoons PdCl_3(C_2H_3OAc)^- + Cl^- \quad (12)$$

$$PdCl_3(C_2H_3OAc)^- + H_2O \rightleftharpoons PdCl_2(C_2H_3OAc)(H_2O) + Cl^- \quad (13)$$

The rate expression derived in the present study (eq 10) requires that the dimer be the reactive species. Furthermore, the interaction of the dimer with vinyl acetate to give π complex (eq 14) must be an equilibrium which is far to the left (*i. e.*, K_2 is small) since the reaction is first order in vinyl acetate concentration. The LiCl inhibition term in eq 10 must also result from the equilibrium. The lack of a second LiCl inhibition term indicates that water cannot be attacking from inside the coordination sphere of Pd(II). This suggests trans stereochemistry.[18] The most important result of this study, then, is the demonstration that hydroxypalladation can occur by more than one route. This result is in keeping with

$$Li_2Pd_2Cl_6 + C_2H_3OAc \overset{K_2}{\rightleftharpoons} LiPd_2Cl_5(C_2H_3OAc) + LiCl \quad (14)$$



5

(14) P. Abley, J. E. Byrd, and J. Halpern, *J. Amer. Chem. Soc.*, **94**, 1985 (1972).

(15) In the present work the reaction was found to be definitely first order in vinyl acetate, in direct disagreement with the studies of Schultz and Rony.[9] However, in the same paper they report studies of the formation of acetaldehyde in dry acetic acid for which the reaction is zero order in vinyl acetate under some reaction conditions.[16] Perhaps because the order was zero in dry acetic acid they assumed it to be zero in wet acetic acid. In any case they did not vary [vinyl acetate] which is the best way of determining order.

(16) P. M. Henry, *J. Org. Chem.*, in press.

(17) The kinetics do not absolutely require cis attack of Pd(II)–OH. See P. M. Henry, *Advan. Chem. Ser.*, **No. 70**, 136 (1968).

(18) A referee has suggested that the kinetics do not eliminate attack of water from an axial position. This is true, but other exchange studies indicate that attack or elimination using axial coordination positions is not important in Pd(II) chemistry.[19]

(19) P. M. Henry, *Accounts Chem. Res.*, **6**, 16 (1973).

TABLE II

EFFECT OF WATER CONCENTRATION ON THE RATE OF HYDRATION[a]

$[Cl]_t$, M	K_1[b]	$[H_2O]$, M	$[Li_2Pd_2Cl_6]$, M	[LiCl], M	k_{obsd}, $sec^{-1} \times 10^5$	$k_{obsd}[LiCl]/[Li_2Pd_2Cl_6]$, M
0.1346	0.3	0.5	0.0098	0.065	2.8	1.85
	0.48	1.0	0.0095	0.064	7.8	5.3
	1.34	2.5	0.00855	0.0625	20.3	14.8
	2.75	5.0	0.0077	0.0604	66.0	51.7
0.2334	0.3	0.5	0.00855	0.161	1.1	2.07
	2.75	5.0	0.0036	0.151	13.0	54.8

[a] $[Pd(II)]_t = 0.0224$ and [vinyl acetate] = 0.2 M in all runs. [b] This value of K_1 used in calculating $[Li_2Pd_2Cl_6]$ and [LiCl]; $[Li_2Pd_2Cl_4]$ can be calculated from $[Pd(II)]_t$ and $[Li_2Pd_2Cl_6]$.

TABLE III[a]

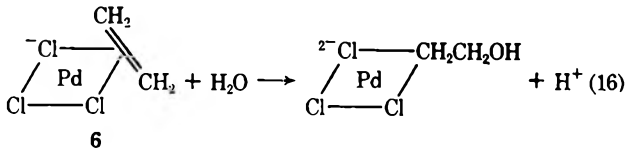
EFFECT OF ENOL ACETATE STRUCTURE ON RATE OF HYDRATION[a]

Registry no.	Enol acetate	k_{obsd}, $sec^{-1} \times 10^4$
108-05-4	CH_2=CHOAc	3.6
1528-10-5	*trans*-CH_3CH=CHOAc	0.023
933-06-2		0.021

[a] $[Na_2Pd_2Cl_6] = 0.0137$; $[H_2O] = 2.5$ M; reaction mixture saturated with NaCl.

other studies,[19] which indicate that the mode of addition of Pd(II) and nucleophiles across double bonds is not unique but depends very much on the nucleophile and the reaction conditions.

The reason that the mode of hydroxypalladation is different from that in water most likely results from the equilibria present in the two systems. In acetic acid the predominant Pd(II) species is the reactive dimer $Li_2Pd_2Cl_6$, while in water containing greater than 0.1 M Cl^-, Pd(II) exists solely as $PdCl_4^{2-}$.[20] Thus in water the dimer route is not available to the Pd(II). The question then arises as to why the monomeric π complex does not decompose by attack of H_2O from outside the coordination rather than by



(16)

6

internal attack of hydroxyl (eq 6). The answer may lie in the charge on the monomeric complex. In the study of allylic ester exchange[4] it was found that monomeric π complex was formed *via* eq 17 in

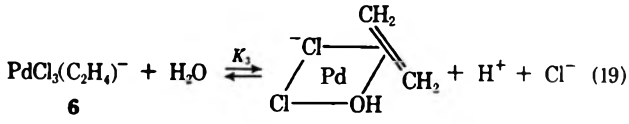
$$Li_2Pd_2Cl_6 + 2 \text{ allylic ester} \rightleftharpoons \underset{7}{2LiPdCl_3(\text{allylic ester})} \quad (17)$$

much larger quantities than reactive dimer π complex *via* eq 18. Yet the monomeric π complex was com-

$$Li_2Pd_2Cl_6 + \text{allylic ester} \rightleftharpoons \underset{8}{LiPd_2Cl_5(\text{allylic ester})} + LiCl \quad (18)$$

pletely unreactive. The reason postulated for lack of reactivity of **7** as compared with **8** was the higher negative charge of the Pd(II) containing the olefin in **7**. In the dimer the negative charge resides mainly on the Pd(II) not complexed to the olefin. This higher charge on the monomer π complex would cause the olefin to be less susceptible to nucleophilic attack. With negatively charged nucleophiles an additional factor would be the mutual repulsion of the negative charges.

Since attack of water from outside the coordination sphere is an unfavorable process, the monomeric π complex incorporates H_2O and releases a proton to give the more potent nucleophile hydroxyl, which attacks cis as shown in eq 6. The reason hydroxyl is formed



(19)

6

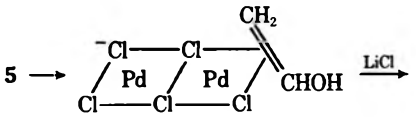
in the coordination sphere is that complexing greatly increases the acidity of water.[21] Thus complexed hydroxyl is much more readily than free hydroxyl. Another factor could be repulsion between the negative charges on the hydroxyl and the monomeric π complex **6** if attack were from outside the coordination sphere.

The final step in the reaction is the decomposition of **5** (eq 15) to product. Now formation of **5** must be rate-limiting step, for if eq 15 were an equilibrium

$$5 + LiCl \longrightarrow Li_2Pd_2Cl_6 + CH_3CHO + LiOAc \quad (20)$$

the reaction would have a dependence on LiOAc since proton is formed in this reaction. Acetate would shift the equilibrium to the right and increase the rate. Thus the kinetics tell us nothing about the decomposition reaction.

The most straightforward route would be simple elimination of OAc to give coordinated vinyl alcohol, which then rearranges to acetaldehyde. However,



$$Li_2Pd_2Cl_6 + CH_3CHO \quad (21)$$

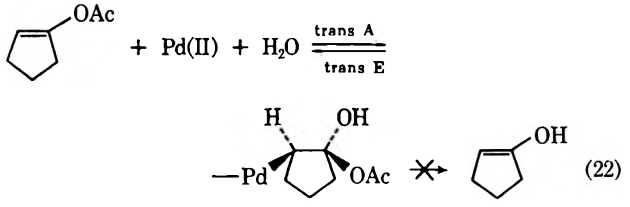
the results with 1-cyclopenten-1-yl acetate are not consistent with this type of decomposition. Because water attacks from outside the coordination sphere of Pd(II), the stereochemistry of hydroxypalladation would be expected to be trans. The stereochemistry of acetoxypalladation, and thus deacetoxypalladation, by the principle of microscopic reversibility, has been shown to be trans.[22] As shown by eq 15, cyclic enol

(20) A. Aguilo, *Advan. Organometal. Chem.*, **5**, 321 (1967).

(21) F. Basolo and R. G. Pearson in "Progress in Inorganic Chemistry," Vol. 4, F. A. Cotton, Ed., Interscience, New York, N. Y., 1962.

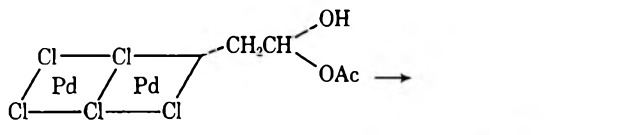
(22) P. M. Henry and G. A. Ward, *J. Amer. Chem. Soc.*, **93**, 1494 (1971).

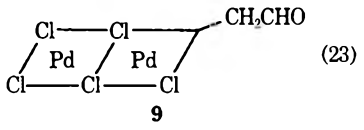
acetates should not undergo hydration by this scheme if both addition and elimination have the same stereochemistry (A = addition, E = elimination).



(22)

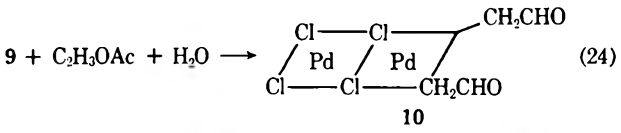
A mode of decomposition which avoids this objection and which is consistent with the mechanism found for Hg(II)-catalyzed hydration of enol acetates[23] is given by eq 23–25. Other possible modes of de-





(23)

9



(24)

10

$$10 + HOAc + Cl^- \longrightarrow 9 + CH_3CHO + OAc^- \quad (25)$$

composition are direct reaction of **9** with acid or disproportion of two of **9** to give **10** followed by reaction with acid. The important point is that decomposition need not occur in the case of hydration by the general route represented by eq 2, as was the case for the previous exchanges studied.[3-7]

The fact that the order in water is not an integral value but between 1 and 2 is probably explicable in terms of solvation of the dimeric π complex by water. There would be a greater portion of water in the region around the polar catalytic species than in the bulk of the solution, giving an apparent order in water of greater than one. In this regard it was reported[9] that at higher $[H_2O]$ (>25 M), the rate actually decreased with increasing $[H_2O]$. This range of water concentrations was not included in the present study but the decrease is understandable in terms of the effect of water on the equilibrium represented by eq 8. As K_1 is increased by increasing $[H_2O]$, the amount of reactive dimer is decreased. At a certain water level this effect must become more important than catalysis by water. Another factor may be decreasing solubility of the vinyl acetate.

Another effect water apparently has is on the equilibrium represented by eq 9. The kinetics (Table I) are consistent with a much smaller value of K_D at 0.5 M $[H_2O]$ than in anhydrous acetic acid. This result is not surprising, since increased solvent power would discourage dimerization.

The effect of structure on rate shown in Table III shows the expected trends with structure. The ratio of rates for vinyl acetate and *trans*-1-propen-1-yl acetate is about the same as that found for vinyl ester exchange[3] and indicates steric hindrance to addition of the elements of Pd(II) and acetate or water.

(23) J. E. Byrd and J. Halpern, *Chem. Commun.*, 1332 (1970).

Experimental Section

Materials.—Sources of chemicals and preparation of stock solutions have been described previously.

Kinetic Runs.—Reaction mixtures were prepared by mixing known amounts of $Li_2Pd_2Cl_6$, LiCl, LiOAc, and H_2O stock solutions of known composition and diluting to a fixed volume, usually 5 ml. The reaction mixtures were placed in a 25° bath for about 1 hr and the run was started by adding a given amount of enol acetate. Samples were analyzed by gas chromatography using a 6-ft 20% Carbowax 20M on ABS (70–80 mesh) column programmed from 80 to 200° at 7.5°/min. Helium flow rate was 60 ml/min.

Ultraviolet Spectra Study.—Procedure was essentially the same as that used previously[13] except that in the present study the solutions contained a known amount of water. At 1.0 and 10.0 M $[H_2O]$ the absorbancies of 16 solutions containing various amounts of Pd(II) and total chloride was measured at 245, 250, and 280 nm. At a given water level all the data were treated simultaneously in the nonlinear regression technique described earlier. The value of K_1 at 1.0 M $[H_2O]$ was found to be 0.48 M^{-1} with a standard deviation of absorbance of 0.028. At 10.0 M $[H_2O]$, K_1 was 5.6 M^{-1} with a standard deviation of 0.047. One problem in the treatment of data was that the program used a value for K_D of 2.6 M^{-1} while the actual value was probably much lower (see Results). However, this would have little effect on the calculated values of K_1, since most of the experimental points were at chloride concentrations at which the calculated amounts of dimerization would be small.

Acknowledgment.—The author is grateful to Mr. O. Marks, who wrote the computer program, and Mr. F. Kriss, who did most of the laboratory work.

Registry No.—LiCl, 7447-41-8; $Li_2Pd_2Cl_6$, 31183-05-8; Li_2PdCl_4, 15525-45-8; $Na_2Pd_2Cl_6$, 16010-02-9.

The Reactions of Vinyl Chloroformate and Oxime Chloroformates with Silver Salts

PETER BEAK* AND JAMES A. BARRON

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

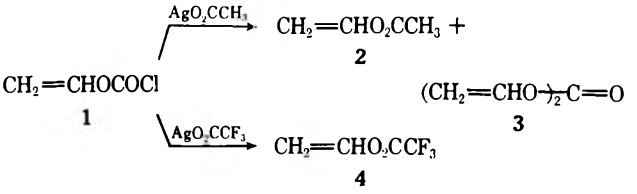
Received February 28, 1973

Vinyl chloroformate (1) reacts with silver acetate in chlorobenzene at 60° to give 17% vinyl acetate (2) and 65% divinyl carbonate (3). Under the same conditions 1 reacts with silver trifluoroacetate to give 77% vinyl trifluoroacetate (4). The latter reaction is shown on the basis of ^{18}O labeling to proceed with retention of the carbon–oxygen bond and is considered to involve a carbonate intermediate. In the presence of tetramethylurea, vinyl chloroformate reacts with silver hexafluoroantimonate in chlorobenzene to give *O*-(carboxyvinyl)tetramethyluronium hexafluoroantimonate (7) in 80% yield. The reaction of phenyl chloroformate with silver hexafluoroantimonate in chlorobenzene at 100° in the presence of tetramethylurea to give phenyl *N*,*N*-dimethyl carbamate is suggested to involve a uronium salt 9 similar to 7. The oxime chloroformates of benzophenone, fluorenone, and *syn*- and *anti*-4-methylbenzophenone react with silver tetrafluoroborate to give amides by the normal Beckmann rearrangement. Cationic intermediates with sp–sp²-hybridized carbon and nitrogen do not appear to be involved in these reactions.

The generation of species exhibiting carbonium ion reactivity from silver ion and primary and bridgehead bicyclo[2.2.1]chloroformates for which the corresponding chlorides are unreactive has been taken to indicate that the loss of carbon dioxide provides a substantial driving force for reaction, analogous perhaps to the loss of nitrogen from a diazonium ion.[1-4] As a probe into the structural limits on the formation of cationic intermediates by this process, we have investigated the reactions of vinyl and oxime chloroformates with silver salts. Our results show that possible high-energy cationic intermediates with a positive charge on a formally sp–sp² hybridized unsubstituted carbon[5,6] or nitrogen[7] are avoided and alternative pathways are followed.

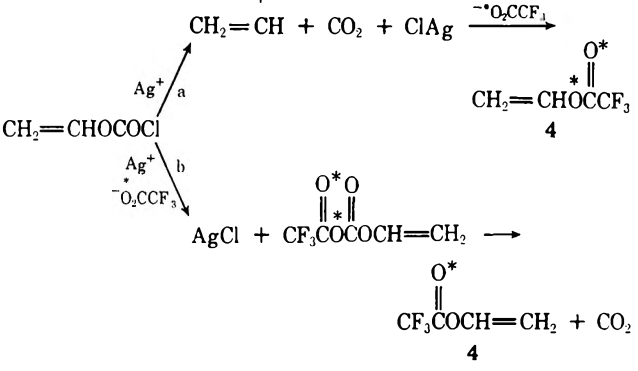
Results and Discussion

Vinyl Chloroformate.—The reaction of vinyl chloroformate (1) with silver acetate in chlorobenzene for 34 hr at 60° gives 17% vinyl acetate (2) and 65% divinyl carbonate[8] (3). When silver trifluoroacetate is used, 77% vinyl trifluoroacetate (4) is formed after 24 hr. The reactions give yields of 78 and 87% silver chloride, respectively.



While vinyl acetates 2 and 4 could be formed by cleavage of the oxygen–vinyl carbon bond (path a) and reaction of the resulting vinyl carbonium ion with acetate, an alternative process, formation of an intermediate carbonate by reaction of 1 with acetate (path b) followed by rearrangement to 4 without cleavage of the oxygen–vinyl carbon bond, can also be envisioned. These processes are outlined in Scheme I for reaction

SCHEME I



of 1 with ^{18}O-labeled silver trifluoroacetate. This scheme shows that the amount of ^{18}O in the trifluoroacetate 4 can be used to distinguish between these two possible processes.[9-11] If path a is followed, all of the oxygen-18 label in the silver trifluoroacetate will appear in 4; on the other hand, if path b is followed, 4 will

(1) P. Beak, R. J. Trancik, and D. Simpson, *J. Amer. Chem. Soc.*, **91**, 5073 (1969), and references cited therein.

(2) For an excellent review see D. N. Kevill, "The Chemistry of Acyl Halides," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1972, p 381.

(3) D. N. Kevill, W. A. Reis, and J. B. Kevill, *Tetrahedron Lett.*, 957 (1972) and references cited therein.

(4) For closely related reactions see G. A. Olah and P. Schilling, *Justus Liebigs Ann. Chem.*, **761**, 77 (1972), and references cited therein; W. E. Dupy, H. R. Hudson, and D. A. Karam, *Tetrahedron Lett.*, 3193 (1972).

(5) For recent reviews of vinyl carbonium ions see H. G. Richey and J. M. Richey, "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, (a) pp 900–922, (b) p 901; M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970); R. C. Fahey, *Top. Stereochem.*, **3**, 237 (1968); G. Modena and U. Tonellato, *Advan. Phys. Org. Chem.*, **9**, 185 (1971); C. A. Grob, *Chimia*, **28**, 87 (1971).

(6) For cases in which vinyl diazonium ions are considered to be precursors of vinyl cations, see M. S. Newman and A. E. Weinberg, *J. Amer. Chem. Soc.*, **73**, 4199 (1951); M. S. Newman and A. Kuther, *ibid.*, **73**, 4199 (1951); D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *ibid.*, **87**, 863 (1965); D. Y. Curtin, J. A. Kampmeier, and M. L. Farmer, *ibid.*, **87**, 874 (1965); W. M. Jones and F. W. Miller, *ibid.*, **89**, 1960 (1967); A. C. Day and M. C. Whiting, *J. Chem. Soc. B*, 991 (1967); M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **92**, 7564 (1970), and references cited therein.

(7) Although iminium ions are not usually considered intermediates in the Beckmann rearrangement, they have been postulated in special cases: P. T. Lansbury, "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, pp 405–419; R. M. Pinder, *J. Chem. Soc. C*, 1690 (1969), and references cited therein.

(8) The formation of **3** from reaction of **1** and triethylammonium or pyridium benzoate has been independently observed by Professor R. A. Olofson, private communication, Sept 1971. For an elegant use of the vinyloxycarbonyl function as a protecting group for amines in peptide synthesis, see R. A. Olofson and Y. S. Yamamoto, Abstracts of Papers, Division of Organic Chemistry, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, p 23.

(9) A critical assumption in Scheme I is that rearrangement of **5** to **4** proceeds with acyl oxygen cleavage, a pathway which has been established for other carbonates,[10] unless an alkyl group especially capable of stabilizing a carbonium ion is bonded to oxygen.[11]

(10) D. B. Denney and D. Z. Denney, *J. Amer. Chem. Soc.*, **84**, 2455 (1962); C. J. Michejda, D. S. Tarbell, and W. H. Saunders, Jr., *ibid.*, **84**, 4113 (1962).

(11) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964); R. C. L. Chow and D. S. Tarbell, *ibid.*, **32**, 2188 (1967); T. Kashiwazi and S. Oae, *Tetrahedron*, **26**, 3631 (1970); C. J. Michejda and D. Von Riesen, *J. Org. Chem.*, **37**, 3021 (1972).

be formed with only one half of the label originally in the silver trifluoroacetate. The results summarized in Table I show that, with silver trifluoroacetate-^{18}O

TABLE I

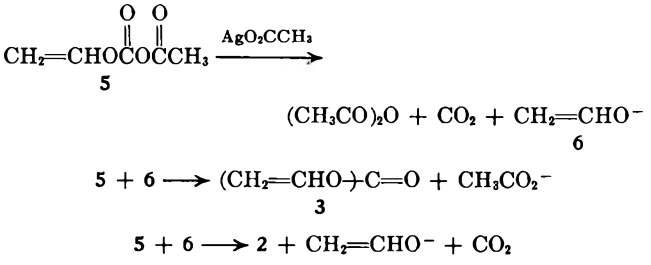
OXYGEN-18 LABELING OF VINYL TRIFLUOROACETATE (4) FROM THE REACTION OF VINYL CHLOROFORMATE (1) WITH OXYGEN-18 LABELED SILVER TRIFLUOROACETATE IN CHLOROBENZENE AT 60°

Compd	f (^{18}O)[a]	f (^{18}O) excess	Relative % enrichment
Unlabeled silver trifluoroacetate[b]	0.24 ± 0.01[c]	0	0
^{18}O-labeled silver trifluoroacetate[b]	5.87 ± 0.01	5.63 ± 0.05	100
Vinyl trifluoroacetate from the reaction of 1 with unlabeled silver trifluoroacetate	0.27 ± 0.01	0	0
Vinyl trifluoroacetate from the reaction of 1 with labeled silver trifluoroacetate	3.14 ± 0.03	2.87 ± 0.04	51.0 ± 0.8

[a] Calculated from f (^{18}O) = (b + 2c)/2, where a, b, and c are intensity values for I, I + 2, and I + 4 normalized so that $a + b + c = 100$. [b] Values for silver trifluoroacetate were determined after conversion to methyl trifluoroacetate. [c] Errors are standard deviations of the average of three scans from an isotope ratio mass spectrum.

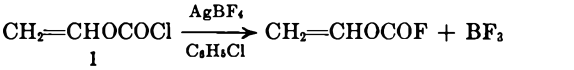
containing 5.63% isotopic excess, the vinyl trifluoroacetate produced contains 2.87% excess ^{18}O, thereby eliminating a as the path for formation of **4** and suggesting the carbonate, trifluoroacetic carbonic vinyl anhydride, as a reaction intermediate. If **4** and, by implication, **2** are produced according to path b *via* the corresponding carbonates, the conversion of these intermediates to ester can be considered to proceed either intra- or intermolecularly. Both processes have precedent,[10-13] although the latter, involving vinylate **6**, the enolate anion of acetaldehyde, as well as acetate in an ionic chain process analogous to that proposed by Tarbell,[12] is consistent with the formation of divinyl carbonate.

In an intermolecular scheme, attack of acetate on acetic vinyl carbonic anhydride (**5**) to give acetic anhydride, carbon dioxide, and **6**, probably in a series of steps, would be followed by reaction of **6** with **5** to give



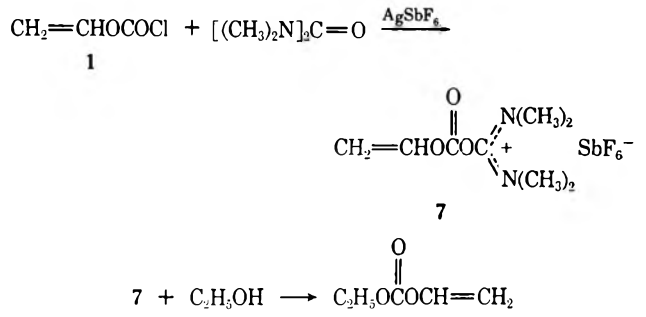
3 or **2**. However, a competing intramolecular rearrangement of **5** to **2** cannot be ruled out by the data. In view of the probable role of vinylate in these reactions, it is pertinent that the same reactants in acetic acid give acetaldehyde, identified as its 2,4-dinitrophenylhydrazone, the product expected from protonation of **6**. Control experiments did establish that the acetaldehyde is a primary reaction product and does not result solely from hydrolysis of vinyl acetate or vinyl chloroformate, which might be swept into the 2,4-dinitrophenylhydrazine solution.

The nucleophiles, acetate, vinylate, and trifluoroacetate, clearly play a critical role in the formation of **2**, **3**, and **4** from vinyl chloroformate. In an effort to eliminate the influence of such nucleophiles, reactions of **1** with silver tetrafluoroborate and silver hexafluoro-



antimonate were carried out. The product of the reaction of vinyl chloroformate and silver tetrafluoroborate in chlorobenzene at 60° is vinyl fluoroformate in 36% yield. The yield of the fluoroformate was determined indirectly by conversion to ethyl vinyl carbonate. This reaction is analogous to the conversion of phenyl chloroformate to phenyl fluoroformate previously reported.[1]

The reaction of vinyl chloroformate with silver hexafluoroantimonate in chlorobenzene at 40° is uneventful for *ca.* 10 min but then a violent exothermic reaction occurs.[14] No volatile products could be detected and *p*-chlorostyrene, a possible reaction product, was not stable under these conditions. In contrast, *p*-chlorostyrene was stable under these reaction conditions in the presence of 2 equiv of tetramethylurea. However, the product of the reaction of **1** and silver hexafluoroantimonate in the presence of tetramethylurea is *O*-(carboxyvinyl)tetramethyluronium hexafluoroantimonate (**7**) in 80% yield. The structure of



7 rests on ir, nmr, and analytical data as well as conversion to ethyl vinyl carbonate on reaction with ethanol. A similar species has been proposed as a reaction intermediate in the reaction of aryl chloroformates with dimethylformamide to give aryloxy immonium salts,[15] and related structures have been suggested as intermediates in the dehydration of carboxylic acids by carbodiimides[16] and in dicyclohexylcarbodiimide mediated sulfuration reactions.[17] The reaction of **7** with ethanol at the carbonyl carbon provides an analogy for the product-forming steps in the latter two cases.

The reaction of phenyl chloroformate with silver hexafluoroantimonate and tetramethylurea in chloro-

(12) E. J. Longosz and D. S. Tarbell, *J. Org. Chem.*, **26**, 2161 (1961); D. S. Tarbell, *Accounts Chem. Res.*, **2**, 296 (1969).

(13) R. Bochan, *J. Amer. Chem. Soc.*, **81**, 3341 (1959).

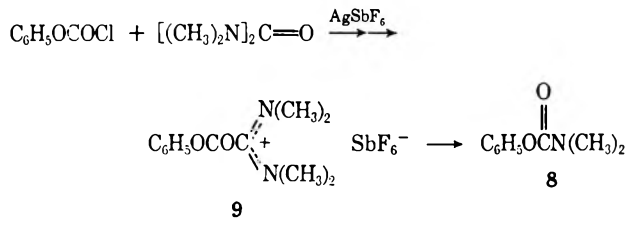
(14) A plausible rationalization for this observation is that small amounts of acid initially produced start a rapid polymerization of **1**.

(15) V. A. Pattison, J. G. Colson, and R. L. K. Carr, *J. Org. Chem.*, **33**, 1084 (1968).

(16) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(17) C. P. Hoiberg and R. O. Mumma, *J. Amer. Chem. Soc.*, **91**, 4273 (1971).

benzene at 100° gives an 82% yield of phenyl *N,N*-dimethylcarbamate (**8**).[1,15] In the absence of the urea, the same reaction gave only black, intractable precipitates. The similarity of the reactions of phenyl and vinyl chloroformate prompted a reinvestigation of the reaction of phenyl chloroformate in the presence of tetramethylurea to determine if carbamate formation might proceed *via* a uronium salt **9** similar to **7**. When this reaction is run at 80° for 20 hr, an 84.5% yield of the carbamate **8** is observed, along with 99% of silver chloride. Lowering the reaction temperature

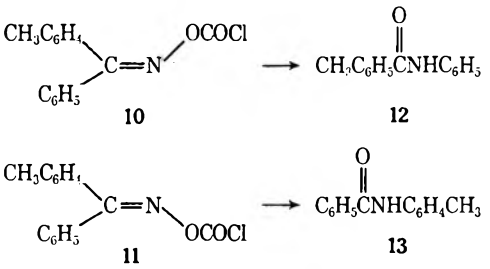


to 40° gives only 40% of **8** but 97% of silver chloride after 20 hr. The observed temperature dependence of the yield of **8** suggests that it may be formed *via* a thermally unstable intermediate. At ambient temperature phenyl chloroformate gives only 10% of **8** and an acetone-soluble oil in addition to silver chloride. The ir and nmr spectra of this material are very similar to those of **7**. Although a sample pure enough for elemental analysis could not be obtained, it seems likely that this material is *O*-(carboxyphenyl)tetramethyluronium hexafluoroantimonate (**9**) and that **9** is a reaction intermediate in the formation of **8**.

Comparison of the chloroformate–silver ion leaving group to other groups which have been reported to be effective in producing vinyl carbonium ions requires correlation of the present wholly unsubstituted vinyl system with substituted cases for the other functions. In the cases of the diazonium ions, however, the systems are β substituted, and, if those reactions are correctly formulated as involving primary vinyl carbonium ions, nitrogen appears to be a better leaving group than the combination of silver chloride and carbon dioxide offered in the present system.[6] A comparison with the sulfonates[5] is less indicative, however, since the cases which most clearly involve vinyl carbonium ions from sulfonates are α substituted by groups which would be expected to stabilize the transition state for carbonium ion formation.

Oxime Chloroformates.—Although iminium ions have been reported as reaction intermediates on reaction of oximes with polyphosphoric acid at 130–170°, for systems[7] with geometric requirements which discourage rearrangement concerted with nitrogen–oxygen bond cleavage, the silver ion induced Beckmann rearrangements of para-substituted *N*-chlorobenzophenone imines[18] and deamination of benzophenone hydrazones[19] have provided no evidence for such species. Both previous studies involved attempts to obviate internal assistance for ionization of the nitrogen–oxygen bond by loss of a very stable leaving group.[18,19] The reaction of oxime chloroformates with silver salts appears to provide another opportunity for formation of an iminium ion in an unhindered system.

Reaction of benzophenone oxime chloroformate with silver tetrafluoroborate in chlorobenzene at ambient temperature followed by exposure to aqueous acid gives the expected high yields of carbon dioxide and silver chloride as well as 75% benzanilide. A similar reaction of 9-fluoreneone oxime chloroformate and silver tetrafluoroborate requires heating to 55° to give yields of silver chloride and carbon dioxide of 88 and 84%, respectively, and, after hydrolysis, 87% phenanthridione. Since fluorenone oxime itself requires heating to 175–180° in polyphosphoric acid for Beckmann rearrangement,[20] this result suggests that some driving force is provided by silver chloride and carbon dioxide as leaving groups. Information about the intermediacy of iminium ions is provided by the stereoselectivity of the rearrangement,[7,18,19] Samples enriched in the syn and anti chloroformates of 4-methylbenzophenone oxime were prepared and treated with silver fluoroborate at ambient temperature. From the sample containing 15 ± 3% syn chloroformate **10** and 85 ± 3% anti chloroformate **11** are obtained 15 ± 3% *N*-phenyl-*p*-toluamide (**12**) and 85 ± 3% *N*-(*p*-tolyl)benzamide (**13**), while the sample which is 95 ± 3% **10** and 5 ± 3% **11** gives a product mixture of 88 ±



3% **12** and 12 ± 3% **13**. The apparent slight decrease in stereoselectivity in the latter case could be attributed to a small amount of isomerization of the chloroformate prior to reaction. Thus, the lack of stereospecificity expected for an iminium intermediate[7,18,19] is not observed and the reaction of oxime chloroformates, while perhaps a convenient procedure for the Beckmann rearrangement, is stereospecific and similar to that previously reported for other leaving groups.

Experimental Section[21]

Gas–Liquid Partition Chromatography (Glpc).—Glpc was performed on Aerograph Models A-90-P or A-90-P3. Product yields are reported in mole per cent based on starting chloroformate and were determined using internal standard with corrections for differences in detector responses between products and internal standards, unless otherwise noted, and planimetric measurement of peak areas. The glpc columns referred to are column A, 12 ft × 0.25 in. 15% XF-1150 on HMDS Chromosorb P; column B, 12 ft × 0.375 in. 20% XF-1150 on HMDS Chromosorb P; column C, 7 ft × 0.375 in. 16% SE-30 on Chromosorb P;

(18) R. N. Leoppky and M. Rotman, *J. Org. Chem.*, **32**, 4010 (1967).

(19) D. L. Fishel and B. L. Hawbecker, Abstracts of Papers, Division of Organic Chemistry, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, p 170.

(20) E. C. Horning, V. C. Stromberg, and H. A. Lloyd, *J. Amer. Chem. Soc.*, **74**, 5153 (1952).

(21) Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nmr spectra were obtained on Varian Models A-60A, A-56/60, HA-100, or T-60 spectrometers by Mr. Robert Thirft and his associates or by J. B. Chemical shifts are reported in δ (parts per million) relative to the internal standard tetramethylsilane unless otherwise noted. Ir spectra were obtained on Perkin-Elmer Models 137 or 521 spectrometers. Mass spectra were recorded by Mr. J. Wrona or Mr. P. Matejek on an Atlas CH-5 medium-resolution spectrometer. Elemental analyses were carried out by Mr. J. Nemeth and his associates.

column D, 8 ft × 0.25 in. 20% XF-1150 on AW-DMCS Chromosorb P; column E, 15 ft × 0.25 in. 20% XF-1150 on AW-DMCS Chromosorb P; column F, 6 ft × 0.25 in. 16% SE-30 on Chromosorb P; column G, 7 ft × 0.25 in. 30% UCON LB550x on firebrick; and column H, 2 ft × 0.25 in. 20% XF-1150 on AW-DMCS Chromosorb P. All solid supports were 60/80 mesh.

Materials.—Chlorobenzene (Fischer) and benzene (Baker and Adamson) were distilled from calcium hydride at atmospheric pressure under dry nitrogen. Glacial acetic acid (Du Pont) was refluxed with 1–2% acetic anhydride and distilled at atmospheric pressure under dry nitrogen. 1,1,3,3-Tetramethylurea (Aldrich) was distilled from calcium hydride under reduced pressure. Silver tetrafluoroborate and silver hexafluoroantimonate, obtained from the Ozark-Mahoning Co., were dried at room temperature over P_2O_5 at 0.3 mm for a minimum of 3 days and stored in amber bottles under dry nitrogen. Silver acetate (Fischer) was used as commercially obtained. Silver trifluoroacetate was prepared from trifluoroacetic acid and silver oxide according to the procedure of Janseen and Wilson.[22] Commercial vinyl acetate (Eastman) and vinyl trifluoroacetate (Pfaltz and Bauer) were distilled at atmospheric pressure. Vinyl chloroformate (1) was purchased from Penninsular ChemResearch and purified by distillation, bp 66–68° (lit.[23] bp 69°). The impurities 1,1- and 1,3-dichloroethane remained after distillation and amounted to 8–14% in different samples. These were present during reactions and all weights and yields have been corrected accordingly. All other commercial reagent grade materials were used as obtained unless otherwise noted.

Vinyl fluoroformate was prepared by halogen exchange of vinyl chloroformate and sodium floride in acetone and purified by preparative glpc (column D, 75°): ir (CCl_4) 3086, 1840 (C=O), 1678, 1650, 1357, 1300, 1248, 1218, 1134, 1041, 938, 889 cm^{-1}; nmr (CCl_4) δ 7.01 (q, 1, X of ABX), 5.12 and 4.81 (m, 2, AB of ABX split by fluorine, J_{AX} = 13.9, J_{BX} = 6.1, J_{AB} = 2.6 Hz); ^{19}F nmr (CCl_4) δ (relative to internal $CFCl_3$) −19.6 (d of d, J_{AF} = 2.0, J_{BF} = 4.8 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 90 (100, $M\cdot^+$), 47 (67), 46 (28).

Anal. Calcd for $C_3H_3FO_2$: C, 40.01; H, 3.36. Found: C, 39.82; H, 3.33.

Ethyl vinyl carbonate was prepared from vinyl chloroformate and absolute ethanol by preparative glpc (column F, 80°): ir (CCl_4) 3077, 2976, 2882, 1764 (C=O), 1653, 1368, 1299, 1258, 1163, 1095, 1007, 948, 878 cm^{-1}; nmr (CCl_4) δ 7.02 (q, 1, X of ABX), 4.70 (m, 2, AB of ABX, J_{AX} = 13.8, J_{BX} = 6.3, J_{AB} = 18 Hz), 4.18 (q, 2, J = 7.0 Hz), 1.32 (t, 3, J = 7.0 Hz).

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.85; H, 6.88.

***N*-(*p*-Toly)benzamide** was prepared from benzoyl chloride and *p*-toluidine, mp 157–159° (lit.[24] mp 158°).

***N*-Phenyl-*p*-toluimide** was prepared from *p*-toluic acid chloride and aniline, mp 146–148° (lit.[24] mp 145–146°).

4-Methylbenzophenone oxime was prepared from 4-methylbenzophenone, and the syn and anti isomers were separated by fractional crystallization from absolute ethanol. *syn*-4-Methylbenzophenone oxime crystallizes preferentially: mp 156.5–158° (lit.[24] mp 155–156°); nmr ($CDCl_3$) δ 7.40 (m, 9), 2.42 (s, 3). *anti*-4-Methylbenzophenone oxime is obtained from the concentrated mother liquor: mp 135–137° (lit.[24] mp 136–137.5°); nmr ($CDCl_3$) δ 7.28 (m, 9), 2.34 (s, 3).

Reaction of Vinyl Chloroformate with Silver Acetate in Chlorobenzene.—To a suspension of 2.57 g (15.4 mmol) of silver acetate in chlorobenzene was added 1.31 g (12.3 mmol) of vinyl chloroformate. After the reaction had been stirred at 60° for 34 hr, filtration and glpc analysis (column A, 80°) showed two peaks, which were collected by preparative glpc (column C, 150°) and isolated in pure form by further preparative glpc (column B, 110°). The compound of shortest retention time was identified as vinyl acetate (2) by comparison of its ir and nmr spectra to those of the commercially available authentic material. The yield of silver chloride, measured as the ammonium hydroxide soluble residue after filtration, was 1.38 g (78%).

The second compound gave spectra and analytical data consistent with the structure of divinyl carbonate[25] (3): ir ($CHCl_3$) 3125, 3030, 1786 (C=O), 1656, 1302, 1258, 1117, 945, 909, 885 cm^{-1}; nmr (CCl_4) δ 7.03 (q, 1, X of ABX), 4.73 (m, 2, AB of ABX, J_{AX} = 13.5, J_{BX} = 6.3, J_{AB} = 2.0 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 114 ($M\cdot^+$, 21.5), 71 (4.33), 69 (5.68), 44 (100), 43 (66.8).

Anal. Calcd for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.44; H, 5.39.

In a separate experiment 5.0 mmol of silver acetate and 4.8 mmol of vinyl chloroformate in chlorobenzene gave 17% vinyl acetate and 65% divinyl carbonate by glpc analysis (column A, 75°), using benzene as an internal standard. The divinyl carbonate yield is uncorrected for differences in thermal conductivity between the product and internal standard.

Reaction of Vinyl Chloroformate with Silver Trifluoroacetate in Chlorobenzene.—To a solution of 1.51 g (6.84 mmol) of silver trifluoroacetate in 10 ml of chlorobenzene heated to 60°, 0.73 g (6.85 mmol) of vinyl chloroformate was added. After 24 hr a slow nitrogen sweep was introduced and a clear, colorless liquid was collected in two Dry Ice cooled traps. The compound was isolated by preparative glpc (column A, 90°) and found to be identical with authentic vinyl trifluoroacetate by ir and nmr spectroscopy and mass spectrometry. The yield of silver chloride was 0.86 g (87%).

The yield of vinyl trifluoroacetate was determined in a separate experiment carried out under Dry Ice cooled condensers by glpc (column E, 65°, cyclohexane as internal standard) to be 77%.

Preparation of Silver Trifluoroacetate-^{18}O.—Trifluoroacetic acid (Aldrich), 0.70 g (6.1 mmol), and water, 3.6 g (200 mmol, 6.55 atom % excess ^{18}O), were heated at 55–60° for 48 hr followed by the addition of silver oxide, 1.5 g (16 mmol). After removal of excess water by distillation, extractive procedures with ether gave 0.70 g (52%) of silver trifluoroacetate-^{18}O. The amount of label shown in Table I was determined by conversion of the silver salt to methyl trifluoroacetate with methyl iodide and mass spectral comparison of the isotope ratios of the *m/e* 59 ($[CH_3OC{=}O]\cdot^+$) fragment for the labeled methyl ester and a sample prepared in a similar manner from unlabeled silver salt. The fragment peak was used for the analysis because methyl trifluoroacetate does not give a molecular ion.

Reaction of Vinyl Chloroformate with ^{18}O-Labeled Silver Trifluoroacetate in Chlorobenzene.—Reactions were carried out with 0.0555 g (0.52 mmol) of vinyl chloroformate and 0.112 g (0.51 mmol) of labeled and unlabeled silver trifluoroacetate in chlorobenzene at 60° for 24 hr, respectively. The vinyl trifluoroacetate was isolated directly from the reaction mixture by preparative glpc (column A, 90°) into a gas bulb for mass spectral analysis. The molecular ion peaks were used to provide the results summarized in Table I.

Reaction of Vinyl Chloroformate and Silver Acetate in Acetic Acid.—To silver acetate, 1.062 g (6.40 mmol), suspended in 41 ml of acetic acid and heated to 60°, 0.626 g (5.90 mmol) of vinyl chloroformate was added while a slow nitrogen sweep into a trap containing 2,4-dinitrophenylhydrazine solution was maintained. From the trap was obtained 1.01 g (77%) of the 2,4-dinitrophenylhydrazone derivative of acetaldehyde, authenticated by comparison of melting point and mixture melting point with those of an authentic sample.

In a control experiment carried out to establish that the 2,4-dinitrophenylhydrazone of acetaldehyde did not result from vinyl acetate, equimolar amounts of vinyl acetate and vinyl chloroformate were allowed to react with a slight excess of silver acetate in acetic acid at 60° and the reaction mixture was swept with nitrogen as before, but the 2,4-dinitrophenylhydrazone trap was replaced by a collection trap cooled in a Dry Ice–isopropyl alcohol slush. Analysis of the collected liquid by nmr showed it to be a mixture of acetaldehyde and vinyl acetate. A similar experiment without added vinyl acetate gave only acetaldehyde by nmr analysis.

Reaction of Vinyl Chloroformate with Silver Tetrafluoroborate in Chlorobenzene.—To silver tetrafluoroborate, 1.63 g (8.4 mmol), dissolved in 10 ml of chlorobenzene heated to 60°, 0.876 g (8.3 mmol) of vinyl chloroformate was added. After 4 hr at 60°, analyses by glpc (column D, 75°) revealed the one volatile product, which was isolated by preparative glpc (column D, 80°) and found by ir and nmr spectral criteria to be identical with those of a sample of vinyl fluoroformate. The yield of silver chloride was determined to be 1.19 g (100%).

(22) D. E. Janseen and C. V. Wilson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 547.

(23) L. Lee, *J. Org. Chem.*, **30**, 3943 (1965).

(24) R. F. Rekker and J. V. Veenland, *Rec. Trav. Chim. Pays-Bas*, **78**, 739 (1959).

(25) S. Murahashi, S. Nozabura, S. Fuji, and K. Kibukawa, *Bull. Chem. Soc. Jap.*, **38**, 1905 (1965).

The yield of vinyl fluoroformate was determined to be a minimum of 36% by conversion to ethyl vinyl carbonate in a separate experiment.

Reaction of Vinyl Chloroformate with Silver Hexafluoroantimonate in Chlorobenzene and Tetramethylurea.—Vinyl chloroformate, 0.223 g (2.09 mmol), silver hexafluoroantimonate, 0.754 g (2.18 mmol), and tetramethylurea, 0.5 g (4 mmol), were allowed to react in 7 ml of chlorobenzene at 42° for 4 hr. Filtration gave a solid which was washed with chlorobenzene and pentane and then leached with acetone. The residue was 0.270 g (90.5%) of silver chloride. Concentration of the acetone washings gave 0.710 g (80%) of *O*-(carboxyvinyl)tetramethyluronium hexafluoroantimonate (7) as a white solid recrystallized from acetone–benzene: mp 97–98.5°; ir (solid film) 2924, 1795 (C=O), 1709 (C=O), 1657, 1536, 1468, 1412, 1304, 1232, 1182, 1120, 1062, 991, 929, 886, 760, 741 cm^{-1}; nmr (acetone-d_6) δ 7.10 (q, 1, X of ABX), 5.10 (m, 2, AB of ABX), 3.42 (s, 12).

Anal. Calcd for $C_8H_{15}F_6N_2O_3Sb$: C, 22.72; H, 3.55; N, 6.62. Found: C, 22.81; H, 3.65; N, 6.64.

The uronium salt 7, 0.337 g (0.795 mmol), was allowed to react with excess absolute ethanol, 0.080 g (1.74 mmol), in 2.5 ml of acetone at 42° for 22 hr to give a 100 ± 5% yield of ethyl vinyl carbonate by glpc analysis on column D at 90° with 1,2-dichloroethane as internal standard.

Reaction of Phenyl Chloroformate with Silver Hexafluoroantimonate and Tetramethylurea in Chlorobenzene.—To a solution of 0.656 g (1.9 mmol) of silver hexafluoroantimonate and 0.403 g (3.5 mmol) of tetramethylurea in 6 ml of chlorobenzene stirred and heated to 80° was added 0.281 g (1.8 mmol) of phenyl chloroformate. After 20 hr at 80° the yield of 8 was determined directly by glpc analysis (column H, 175°) and uncorrected for thermal conductivity differences between the product and the internal standard, benzophenone (84.5%).

A similar reaction carried out at ambient temperature gave a precipitate which was washed repeatedly with chlorobenzene, then with pentane, and then leached with acetone. Concentration of the acetone solution gave a clear oil: ir (liquid film) 2933, 1808 (C=O), 1773 (C=O), 1706 (C=O), 1592, 1524, 1458, 1408, 1225, 1161, 1068, 969, 749, 763 cm^{-1} (shoulder); nmr (acetone-d_6) δ 7.45 (s, 5), 3.43 (s, 12), tentatively attributed to *O*-(carboxyphenyl)tetramethyluronium hexafluoroantimonate (9). The nmr spectrum also has a singlet at δ 3.0, which is attributed to an unidentified impurity.

Preparation of oxime chloroformates was carried out by reaction of the oxime at −10° with a five- to tenfold excess of phosgene in ether. Products were isolated from the organic phase after evaporation to dryness, addition of ether, and washing with a 5% solution of cold aqueous sodium bicarbonate.

Benzophenone oxime chloroformate is a white solid: mp 57–60° (lit.[26] mp 34–36°); ir ($CHCl_3$) 1790 (C=O), 1595 (C=N), 1110 cm^{-1} (COC). The material is sensitive to the atmosphere, and many attempts at further purification failed. The material was used as prepared and the structure was confirmed by the formation of a carbamate derivative.

Benzophenone imine *N*-benzylcarbamate was prepared from benzophenone oxime chloroformate and benzyl amine in benzene in 87% yield: mp 124–125° (lit.[26] mp 123–124°); ir ($CHCl_3$) 3480 (NH), 3070 (CH_2), 1740 (C=O), 1600 (C=N), 1110 (COC); nmr ($CDCl_3$) δ 7.35 (m, 15), 6.66 (broad s, 1), 4.35 (d, 2); mass spectrum (70 eV) *m/e* 180, 105, 90.

Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 76.36; H, 5.45; N, 8.48. Found: C, 76.38; H, 5.66; N, 8.54.

***syn*-4-Methylbenzophenone oxime chloroformate** (10) was prepared from *syn*-4-methylbenzophenone oxime in 90% yield: mp 79–82°; ir ($CHCl_3$) 3010 (CH_3), 1790 (C=O), 1601 (C=N), 1601 (C=N), 1100 (COC); nmr ($CDCl_3$) δ 7.52 (m, 9), 2.44, 2.38 (pair s, 3), ratio 18:1. The δ 2.38 singlet represents 5 ± 2% of the anti isomer.

***anti*-4-Methylbenzophenone oxime chloroformate** (11) was prepared from *anti*-4-methylbenzophenone oxime in 75% yield. The product was obtained as an unstable oil, nmr ($CDCl_3$) δ 7.30 (m, 9), 2.44, 2.38 (pair s, 3), ratio 15:85. The δ 2.44 singlet is 15 ± 3% of the syn isomer.

9-Fluorenone oxime chloroformate was prepared from 9-fluorenone oxime and phosgene in 95–100% yield as a yellow solid: mp 110–112°; ir ($CHCl_3$) 1795 (C=O), 1600 (C=N), 1100 (COC).

Reactions of oxime chloroformates with silver tetrafluoroborate were carried out in chlorobenzene for 4 hr, followed by heating to reflux with water for 20–30 min, filtration of precipitated silver chloride, and analysis of amide products in the organic layer by either glpc or direct isolation. Silver chloride was determined as the ammonium hydroxide soluble precipitate in the reaction mixture; carbon dioxide was determined as the acid-soluble precipitate from the barium hydroxide traps. The yields of both materials were consistently 90–100%.

Reaction of benzophenone oxime chloroformate with silver tetrafluoroborate in chlorobenzene gives 75 ± 5% benzanilide (glpc, column F). A preparative run gave a light brown solid, mp 157–160°. Chromatography on neutral alumina gave 66% benzanilide, mp 161–162°, mmp with authentic material 161–162°; the ir spectrum was identical with that of authentic benzanilide.

Reaction of 9-fluorenone oxime chloroformate with silver tetrafluoroborate in chlorobenzene was carried out at 55°. A pale brown solid was isolated from the organic layer in 87% yield. Recrystallization from methanol gave phenanthridinone: mp 290–292°, mmp 290–292°; the ir spectrum (Nujol mull), 1660 (C=O), 1600, 1460, 1370 cm^{-1}, was identical with that of authentic phenanthridinone.

Reaction of *syn*-4-methylbenzophenone oxime chloroformate (10) with silver tetrafluoroborate in chlorobenzene gave 90% of a brown solid: mp 130–136°; ir ($CHCl_3$) 3400, 2950, 1650, 1595, 1500, 1425, 1310, 1200 cm^{-1}; nmr ($CDCl_3$) δ 8.05 (broad s, 1), 7.50 (m, 9), 2.38, 2.32 (pair s, 3), ratio 6.8:1. Comparison of these spectra with those of mixtures of authentic samples indicates a 79 ± 3% yield of *N*-phenyl-*p*-toluamide (12) and an 11 ± 3% yield of *N*-(*p*-toly)benzamide (13).

Reaction of *anti*-4-methylbenzophenone oxime chloroformate (11) with silver tetrafluoroborate in chlorobenzene gave a pale brown solid: 96%; ir ($CHCl_3$) 3400, 3000, 1670, 1600, 1510, 1480, 1440, 1320 cm^{-1}; nmr ($CDCl_3$) δ 7.50 (m, 9), 2.38, 2.32 (pair s, 3), ratio 1:5.7. Comparison to known spectra indicates a 14 ± 3% yield of *N*-phenyl-*p*-toluamide (12) and an 82 ± 3% yield of *N*-(*p*-tolyl)benzamide (13).

Acknowledgment.—We are grateful to Professor Roy Olofson for providing an initial sample of vinyl chloroformate and to the National Institutes of Health and the National Science Foundation for support of this work. Purchase of the mass spectral equipment used in this studio was funded in part by the National Institutes of Health.

Registry No.—**1**, 5130-24-5; **3**, 7570-02-7; **7**, 40463-58-9; **9**, 40463-59-0; **10**, 40463-60-3; **11**, 40463-61-4; **12**, 6833-18-7; **13**, 582-78-5; vinyl fluoroformate, 40463-64-7; sodium fluoride, 7681-49-4; ethyl vinyl carbonate, 7570-06-1; *syn*-4-methylbenzophenone oxime, 2998-92-7; *anti*-4-methylbenzophenone oxime, 2998-91-6; 4-methylbenzophenone, 134-84-9; silver acetate, 563-63-3; silver trifluoroacetate, 2966-50-9; silver tetrafluoroborate, 14104-20-2; silver hexafluoroantimonate, 26042-64-8; phenyl chloroformate, 1885-14-9; benzophenone oxime chloroformate, 18304-44-4; benzophenone oxime, 574-66-3; benzophenone imine *N*-benzylcarbamate, 18304-48-8; 9-fluorenone oxime, 2157-52-0; 9-fluorenone oxime chloroformate, 40463-70-5.

(26) A. Jumar, P. Held, and W. Schulze, *Z. Chem.*, **7**, 344 (1967).

The Effect of Electronegative Substituents on the Reductive Dimerization of Schiff Bases. Formation of Vicinal Dianions

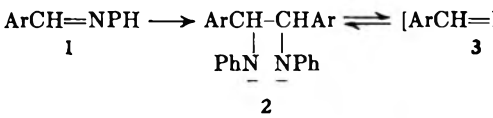
JAMES G. SMITH* AND ISAAC HO

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada

Received March 14, 1973

Reduction of *N*-(*p*-cyanobenzal)aniline by sodium metal in tetrahydrofuran produces initially the expected dimers which later dissociate as the radical anion is further reduced to a monomeric dianion. Alkylation and acylation of this dianion are described and similar observations are reported for *N*,*N*′-diphenylterephthalaldimine. The formation of the monomeric dianions is attributed to the stabilization of the radical anion which facilitates dissociation of the dimeric dianions initially formed and permits further reduction to occur. Analogies between these reductions and the electrochemical behavior of Schiff bases is noted.

When substituted *N*-benzalanilines, **1**, are dimerized by alkali metals in aprotic solvents,[1-4] an isomerization of the diastereomeric dimeric dianions,[3-4] **2**, is observed under certain reaction conditions. This isomerization has been traced[4] to an equilibrium between the dimeric dianion, **2**, and the radical anion **3**



which permits the original kinetic product to assume its more thermodynamically stable composition.

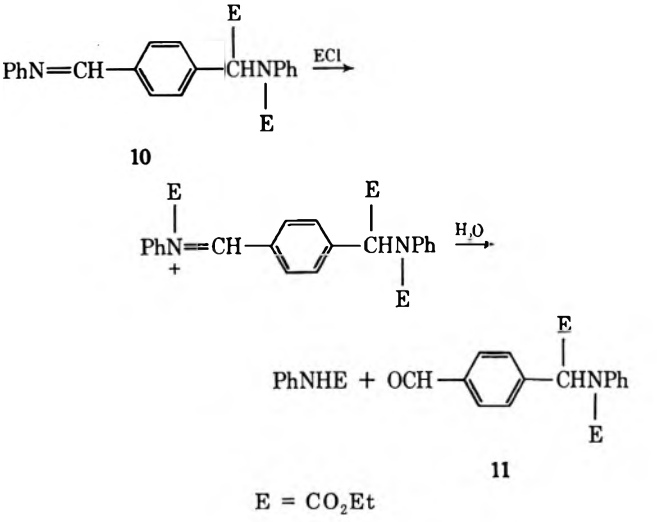
Substituents have a detectable effect on the isomerization but, with one exception, only electropositive substituents have been examined. The exception (**1**, Ar = *m*-ClC_6H_4) showed a marked increase in the rate of isomerization reflecting stabilization of the corresponding radical anion. Further studies of the *o*- and *p*-chloro analogs were frustrated by reductive dehalogenation of their radical anions.[5] However, the behavior of the *m*-chloro compound prompted an examination of other electronegative substituents with the consequences reported here.

The Schiff base *N*-(*p*-cyanobenzal)aniline (**4**, Y = CN) reacted rapidly with sodium in tetrahydrofuran (THF) and attained an equilibrium uptake of 2 g-atoms of sodium per 1 mol in 4 hr. Protonation of this reaction mixture produced the dimeric diamine **5** (Y = CN) and the monomeric amine **6** (Y = CN) but their relative proportions depended on the duration of the reaction, the amount of dimer decreasing as the reduction continued. This suggested that the ultimate product generated by the reduction was a monomeric dianion **7**.

The existence of **7** was established by alkylating the organometallic compound with methyl iodide and 1,3-diiodopropane and by acylating with ethyl chloroformate to form, respectively, **8**, **9**, and **10** (Y = CN), as outlined in Scheme I. In general, this chemical behavior resembled that of the well-known dianion derived from benzophenone anil by alkali metal reduction.[1,6]

A search for additional electronegative substituents showed that a *p*-carbomethoxy group was unsatisfactory,[7] but a second aldimine group provided analogous results. *N*,*N*′-Diphenylterephthalaldimine (**4**, Y = PhN=CH–) also was reduced to a dianion and products **8**, **9**, and **10** (Y = PhN=CH) were generated by alkylation and acylation. Isolation of **10** (Y = PhN=CH) was unsuccessful because of its easy hydrolysis and oxidation.

By taking advantage of the ready hydrolysis of these imines, the substituted benzaldehyde **11** was



isolated. Indeed, in one instance when excess chloroformate was used, hydrolysis occurred during normal aqueous work-up, reflecting the increased hydrolytic sensitivity of the probable intermediate iminium salt.[8]

Rather surprisingly, the isomeric bisaldimine, *N*,*N*′-dibenzal-*p*-phenylenediamine (**12**), was also reduced to a dianion by sodium. Protonation produced *N*,*N*′-dibenzylquinone diimine, but as yet resolution of the air-sensitive diastereomeric mixtures produced on alkylation has not been successful.

Qualitatively, the stabilization of radical anions by

(1) (a) W. Schlenk, J. Apprenrodt, A. Michael, and A. Thal, *Ber.*, **47**, 473 (1914); (b) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 281 (1928); M. Szwarc, *Accounts Chem. Res.*, **5**, 169 (1972), and V. Kalyanaraman and M. V. George, *J. Organometal. Chem.*, **47**, 225 (1973), present comprehensive reviews of the interaction of alkali metals with unsaturated compounds.

(2) J. J. Eisch, D. D. Kaska, and C. J. Peterson, *J. Org. Chem.*, **31**, 453 (1966).

(3) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2497 (1966).

(4) J. G. Smith and I. Ho, *J. Org. Chem.*, **37**, 653 (1972).

(5) J. G. Smith and I. Ho, *J. Org. Chem.*, **37**, 4260 (1972).

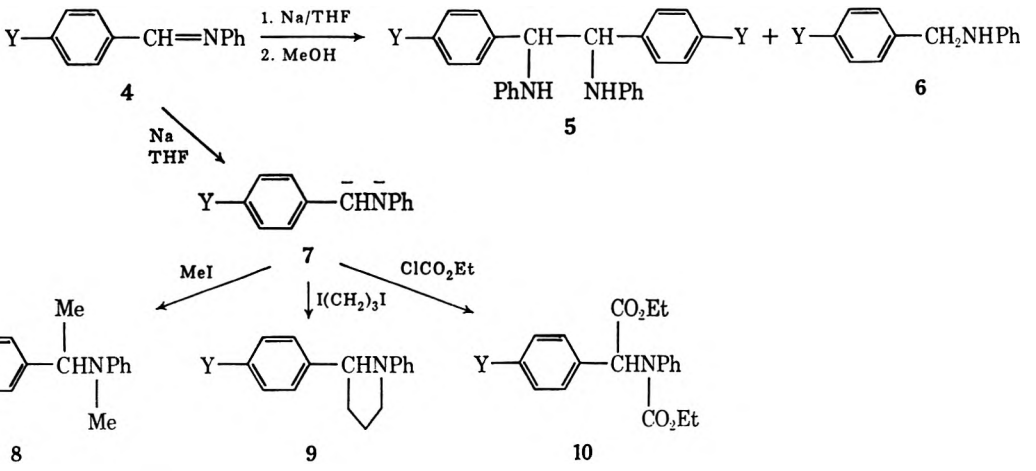
(6) (a) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2245 (1966); (b) J. G. Smith and R. A. Turle, *J. Org. Chem.*, **37**, 126 (1972).

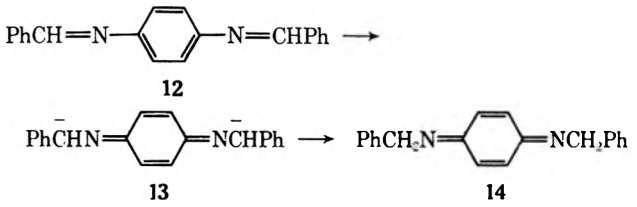
(7) No methyl groups could be detected in the crude reaction product, suggesting that extensive reduction and/or condensation reactions had occurred.

(8) (a) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, p 403. (b) The ethyl *N*-phenylcarbamate was also isolated.

SCHEME I

REACTIONS OF THE VICINAL DIANION





electronegative substituents has been noted[9] in the reduction of substituted benzenes with alkali metals. Quantitatively, electrochemical reductions illustrate this nicely. For example, the half-wave reduction potentials of substituted benzophenones[10] become less negative as the substituent group increases in electronegativity. Similar observations[11] have been made for a variety of Schiff bases and relationships between the half-wave reduction potential and Hammett σ constants were noted.

Undoubtedly, the substituent effects a decrease in the energy of the lowest unoccupied molecular orbital,[12] facilitating both the electron transfer as well as the delocalization of the charge density in the generated radical anion.[13]

The nitrile group is a particularly interesting substituent, causing a marked change in the half-wave reduction potential[11a] commensurate with its strong electronegative character. However, while exerting an activating influence it is not itself reduced.[14]

Frequently, second one-electron reductions are observed in these electrochemical reactions and in general the behavior of these second waves resembles that of the first. The second wave is attributed to a reduction of the initially formed radical anion to a dianion (provided aprotic anhydrous solvents are used) in the manner suggested for hydrocarbons.[15]

It is readily apparent that the alkali metal reductions closely parallel the electrochemical observations. Stabilization of the radical anion by the electronegative substituent permits facile dissociation of the dimeric dianions initially formed as well as further reduction to the monomeric dianion. Since protonation of the latter by the reaction medium is slow, further chemical transformations of this dianion can be effected.

Considering the extensive delocalization[16] of the anionic charge in the conjugated systems, it is perhaps surprising that the reactions are not more complex. Indeed, the behavior of **7** (Y = PhN=CH) and **13**, where the electronegative nature of nitrogen failed to direct the reaction to a quinonedimethide product in the case of the former or to a reaction at only one of the imine groups in the latter,[17] leads us to suggest a stepwise alkylation. The less delocalized "terminal" anionic center reacts first, forming an ambident, highly delocalized anion which reacts fastest at its most reactive site, the carbanionic end, *i.e.*, Scheme II.

Experimental Section

Melting points are uncorrected and were determined in open capillaries with a Mel-Temp apparatus. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer. Chemical shifts are in parts per million downfield from internal tetramethylsilane (δ scale). Silica gel (0.05–0.2 mm) purchased from E. Merck AG was used for column chromatography and Eastman Chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analyses were determined by M-H-W Laboratories, Garden City, Mich.

The purification of solvents, the reaction of the imines with alkali metals, and the handling of the organometallic compounds have been described[4] elsewhere.

p-**Cyanobenzaldehyde** was prepared in 49% yield by the chromium trioxide oxidation of *p*-tolunitrile, the procedure being

(9) J. J. Eisch, *J. Org. Chem.*, **28**, 707 (1963).

(10) P. Zuman, O. Oxner, R. F. Rekker, and W. Th. Nauta, *Collect. Czech. Chem. Commun.*, **33**, 3213 (1968).

(11) (a) L. V. Kononenko, V. D. Bezuglyi, and V. N. Dmitrieva, *J. Gen. Chem. USSR*, **38**, 2087 (1968); (b) V. N. Dmitrieva, N. A. Rozanel'skaya, L. V. Kononenko, B. I. Stepanov, and V. D. Bezuglyi, *ibid.*, **41**, 57 (1971), and references cited therein; (c) V. N. Dimitrieva, N. I. Mal'tseva, V. D. Bezuglyi, and B. M. Krasovitskii, *ibid.*, **37**, 347 (1967); (d) J. M. W. Scott and W. H. Jura, *Can. J. Chem.*, **45**, 2375 (1967); (e) P. Martinet, J. Simonet, and J. Tendil, *C. R. Acad. Sci., Ser. C*, **268**, 303 (1969).

(12) In this respect, approximate molecular orbital calculations by Scott and Jura[11d] are of interest.

(13) K. W. Bowers in "Radical Ions," E. T. Kaiser and L. Kevan, Ed., Interscience, New York, N. Y., 1968, p 211.

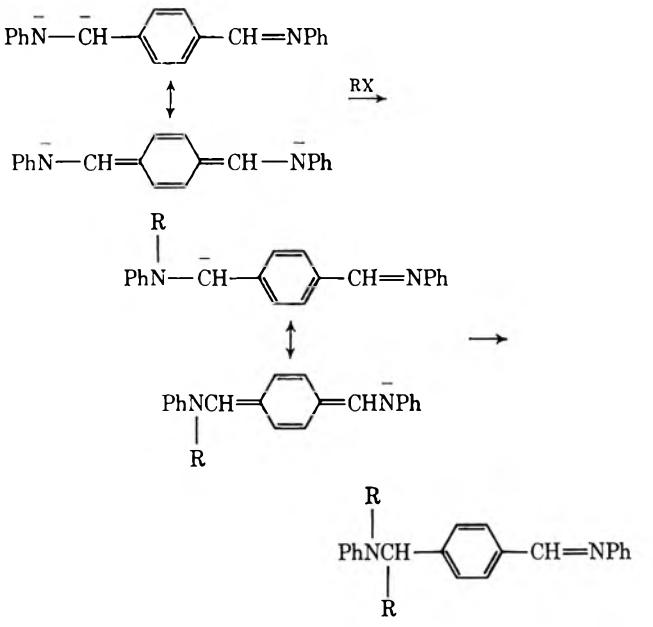
(14) J. P. Petrovich, M. M. Baizer, and M. R. Ort, *J. Electrochem. Soc.*, **116**, 743 (1969). (b) Provided conditions leading to protonation of the nitrile are avoided: P. Zuman and O. Manousek, *Collect. Czech. Acad. Sci.*, **34**, 1580 (1969).

(15) (a) H. A. Laitinen and S. Wawzonek, *J. Amer. Chem. Soc.*, **64**, 1765 (1942). (b) G. J. Hoytink in "Advances in Electrochemistry and Electrochemical Engineering," Vol. 7, P. Delahay and C. W. Tobias, Ed., Interscience, New York, N. Y., 1970, p 221.

(16) For the sake of brevity, we have represented the dianion by the structure most resembling the products, and the counterions have been omitted.

(17) Essentially the exact opposite was observed.

SCHEME II



the same as that used[18] for the preparation of *p*-nitrobenzaldehyde.

N-(*p*-**Cyanobenzal**)**aniline**.—Aniline (9.3 g, 0.1 mol) was added dropwise to a stirred solution of *p*-cyanobenzaldehyde at 80°. After 6 hr the solution was cooled, and the product, which precipitated, was recrystallized twice from ethanol to give 17.0 g (82% yield), mp 89–91°.

Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.55; H, 4.89; N, 13.59. Found: C, 81.35; H, 5.03; N, 13.42.

N,*N*′-**Diphenylterephthalaldimine** (**4**, **Y** = **PhN**=**CH**) was prepared by the same procedure in 82% yield,[19] mp 159–160°.

N,*N*′-**Dibenzal**-*p*-**phenylenediamine** (**12**) was prepared[20] in 91% yield, mp 138–140° (reported[20] mp 138°).

Reductive Dimerization of *N*-(*p*-**Cyanobenzal**)**aniline** (**4**, **Y** = **CN**).—The results of a time study in the case of **4** (Y = CN) are summarized in Table I. Individual products were isolated

TABLE I

PRODUCT COMPOSITION IN THE REDUCTION OF *N*-(*p*-CYANOBENZAL)ANILINE BY SODIUM IN THF

Time, hr	g-atoms of Na per mol of **4** (Y = CN)[a]	Product composition,[a] % **5** (Y = CN) Racemic	**5** (Y = CN) Meso	**6** (Y = CN)
0.5	0.20	69	31	Trace
1.0	0.73	62.5	18.8	18.8
2.0	1.36	34.2	9.8	56.0
4.0	1.95	7.7	Trace	92.3
8.0	2.05	~2.5	Trace	97.5
24.0	2.08	~2.5	Trace	97.5

[a] Analysis by nmr. Unreacted **4** (Y = CN) is omitted.

from separate experiments as described below. Attempts to effect a reductive metalation of **4** (Y = CN) with sodium in diethyl ether were not successful.

Isolation of *rac*-**1,2-Di**(*p*-**cyanophenyl**)-*N*,*N*′-**diphenylethylenediamine** (**5**, **Y** = **CN**).—The standard preparative run consisted of 2.06 g (0.01 mol) of *N*-(*p*-cyanobenzal)aniline, 100 ± 10 ml of THF, and 1.8 g (0.08 g-atom) of sodium in a Schlenk tube. After shaking for 2 hr, the solution (deep red) was drained from the excess metal into a nitrogen-filled flask, cooled to −60°, and treated with 2 ml of methanol.

After diluting with water, the crude reaction product (2.08 g) was isolated by ether extraction and chromatographed on 80 g of silica gel with benzene as eluent. The first fraction, 0.36 g (18% yield), was *N*-(*p*-cyanobenzyl)aniline, mp and mmp with an authentic sample 84–86°.

The second fraction, 1.16 g (80% yield), crystallized on standing. Recrystallization from ether provided an analytical sample of *rac*-**5** (Y = CN): mp 165–168°; ir (KBr) 3440 (NH), 2240 (CN), 1600, 1510, 1320, 850, 755, 695 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 4.51 (s, 2, benzylic H), 6.03–7.60 (m, 18, aromatic H).

Anal. Calcd for $C_{28}H_{22}N_4$: C, 81.14; H, 5.35; N, 13.52. Found: C, 80.91; H, 5.38; N, 13.33.

The meso isomer[21] has not yet been isolated but the nmr spectrum of the crude dimer showed a benzylic proton singlet at δ 5.03.

Isolation of *N*-(*p*-**Cyanobenzyl**)**aniline** (**6**, **Y** = **CN**).—A standard preparative run (6 hr reaction time) was treated as described above. The crude reaction product (2.01 g) was recrystallized three times from ethanol, 1.83 g (91% yield) of **6** (Y = CN): mp 86–87°; ir (Nujol) 3440 (NH), 2240 (CN), 1600, 1510, 810, 755, 690 cm^{-1} (aromatic CH); nmr ($CDCl_3$, D_2O washed), 4.45 (s, 2, CH_2), 6.5–7.4 (m, 5, C_6H_5N), 7.58 (q, 4, J = 9 Hz, $-C_6H_4CN$).

Anal. Calcd for $C_{14}H_{12}N_2$: C: 80.72; H, 5.81; N, 13.45. Found: C, 80.90; H, 5.92; N, 13.55.

Preparation of *p*-[1-(*N*-**Methylanilino**)**ethyl**]**benzonitrile** (**8**, **Y** = **CN**).—A standard preparative run (6 hr reaction time) was drained from excess sodium, cooled to −60°, and treated with 2.82 g (0.02 mol) of methyl iodide. After 2 hr of stirring at −60°, the reaction was warmed to room temperature overnight and diluted with water and the reaction product (2.10 g) was isolated by ether extraction. Chromatography on 80 g of silica gel with benzene as eluent provided one major fraction, 1.89 g (90% yield) of **8** (Y = CN) as a yellow oil: bp 158–159° (0.13 mm); ir (film) 2210 (CN), 1600, 1500, 830, 740, 680 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 1.56 (d, 3, J = 7 Hz, CH_3CH), 2.72 (s, 3, NCH_3), 5.23 (q, 1, J = 7 Hz, CH_3CH), 6.6–6.7 (m, 9, aromatic CH).

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.51; H, 6.70; N, 12.10.

Preparation of 2-(*p*-**Cyanophenyl**)-**1-phenylpyrrolidine** (**9**, **Y** = **CN**).—The above reaction was repeated using 2.96 g (0.01 mol) of 1,3-diiodopropane in place of the methyl iodide. Chromatography again provided 2.15 g (87% yield) of **9** (Y = CN) as a viscous yellow oil: bp 174–177° (0.08 mm); ir (film) 2220 (CN), 1600, 1510, 830, 740, 690 cm^{-1} (aromatic); nmr ($CDCl_3$) δ 1.8–2.6 (m, 4, $CH_2CH_2CH_2N$), 3.2–3.9 (m, 2, $CH_2CH_2CH_2N$), 4.75 (q, 1, J_A = 8 Hz, J_B = 2 Hz, $CHCH_AH_B$), 6.3–7.7 (m, 9, aromatic H).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.07; H, 6.62; N, 11.06.

Preparation of Ethyl α-(*N*-**Carbethoxyanilino**)-*p*-**cyanophenylacetate** (**10**, **Y** = **CN**).—The above reaction was repeated using 2.17 g (0.02 mol) of ethyl chloroformate instead of the alkyl iodide. The crude product, 2.48 g of a red oil, was chromatographed on 120 g of silica gel with benzene as eluent to give 0.81 g (33% yield) of ethyl α-anilino-*p*-cyanophenylacetate: bp 189–192° (0.08 mm); ir (film) 3400 (NH), 2210 (CN), 1730 (C=O), 1600, 1500, 740, 680 (aromatic CH), 1010 cm^{-1} ($-CO_2-$); nmr ($CDCl_3$, D_2O washed) δ 1.20 (t, 3, J = 7 Hz, CH_3CH_2), 4.22 (q, 2, J = 7 Hz, CH_3CH_2), 5.13 (s, 1, benzylic H), 6.5–7.3 (m, 5, C_6H_5N), 7.67 (s, 4, $-C_6H_4CN$).

Continuing the elution with chloroform gave the main fraction, a solid which after recrystallization from ethanol amounted to 1.28 g (52% yield) of **10** (Y = CN): mp 85–86°; ir (film) 2215 (CN), 1740 and 1700 (C=O), 1600, 1490, 760, 690 (aromatic CH), 1020 and 1040 cm^{-1} (CO_2); nmr ($CDCl_3$) δ 1.23 (q, 6, J = 7 Hz, CH_3CH_2), 4.27 (pentet, 4, J = 7 Hz, CH_3CH_2), 5.83 (s, 1, benzylic H), 7.1–7.7 (m, 9, aromatic H).

Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.07; H, 5.92; N, 7.92.

Preparation of *N*-(*p*-**Anilinomethylbenzal**)**aniline** (**6**, **Y** = **PhN**=**CH**).—The standard preparative run consisted of 1.42 g (0.005 mol) of **4** (Y = PhN=CH) and 1.8 g (0.08 g-atom) of sodium in 100 ± 10 ml of THF shaken for 24 hr in a Schlenk tube. The deep purple solution was drained from the excess alkali metal into a nitrogen-filled flask, cooled to −60°, and treated with 2 ml of methanol. The solution immediately became orange and, after warming to room temperature and diluting with water, the

(18) (a) S. V. Lieberman and R. Connor, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 441; (b) O. Schales and H. A. Graefe, *J. Amer. Chem. Soc.*, **74**, 4489 (1952).

(19) W. Steinkopf, R. Leitsmann, A. H. Müller, and H. Wilhelm, *Justus Liebigs Ann. Chem.*, **541**, 260 (1939), report mp 159°.

(20) A. Ladenburg, *Chem. Ber.*, **11**, 599 (1878).

(21) The stereochemical assignments are based on the assumptions described earlier.[4]

product was isolated by ether extraction. Recrystallization from ethanol gave 1.3 g (90% yield) of 6 (Y = Ph N=CH-): mp 94–96°; ir (KBr) 3400 (NH), 1635 (C=N), 1610, 1510, 830, 760, 700 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 4.1 (broad s, 1, NH), 4.38 (s, 2, benzylic H), 6.5–8.0 (m, 14, aromatic H), 8.45 (s, 1, CH=N).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.83; H, 6.33; N, 9.88. Found: C, 83.89; H, 6.29; N, 9.85.

Preparation of *N*-*p*-[1-(*N*-Methylanilino)ethyl]benzalaniline (8, Y = PhN=CH).—The above reaction was repeated using 1.42 g (0.01 mol) of methyl iodide in place of the methanol. After the solution was warmed to room temperature for 12 hr, the crude product was isolated by ether extraction and recrystallized from hexane, 1.42 g (90% yield) of 8 (Y = PhN=CH): mp 70–72°; ir (KBr) 1630 (C=N), 1590, 1500, 830, 730, 680 cm^{-1} (phenyl); nmr (C_6D_6) 1.22 (d, 3, J = 7 Hz, CH_3CH), 2.40 (s, 3, NCH_3), 4.88 (q, 1, J = 7 Hz, CH_3CH), 6.7–8.0 (m, 14, aromatic H), 8.27 (s, 1, CH=N).

Anal. Calcd for $C_{22}H_{22}N_2$: C, 84.05; H, 7.05; N, 8.92. Found: C, 84.19; H, 7.06; N, 9.04.

Preparation of *N*-*p*-[2-(1-Phenylpyrrolidinyl)]benzalaniline (9, Y = PhN=CH).—The above reaction was repeated using 1.48 g (0.005 mol) of 1,3-diiodopropane in place of the methyl iodide. Decolorization took place within 2 min at −60°. After 24 hr at room temperature, the product (oil, 1.50 g) was isolated and chromatographed on 60 g of silica gel with benzene as eluent. The major fraction, 1.2 g (80% yield), was recrystallized from ethanol to give an analytical sample of 9 (Y = PhN=CH): mp 132–135°; ir (KBr) 1630 (C=N), 1590, 1500, 770, 750, 700 cm^{-1} (aromatic CH); nmr ($CDCl_3$) δ 1.8–2.7 (m, 4, CH_2CH_2-CH_2N), 3.2–4.0 (m, 2, $CH_2CH_2CH_2N$), 4.82 (broad d, 1, J = 6 Hz, benzylic H), 6.3–8.0 (m, 15, aromatic H), 8.47 (s, 1, CH=N).

Anal. Calcd for $C_{23}H_{22}N_2$: C, 84.65; H, 6.80; N, 8.59. Found: C, 84.47; H, 7.01; N, 8.57.

Preparation of *p*-(α,*N*-Dicarbethoxyanilinomethyl)benzaldehyde (11).—The above reaction was repeated using 1.09 g (0.01 mol) of ethyl chloroformate in place of alkyl iodide. Decolorization to a deep orange occurred in 20 min at −60°. After 24 hr at room temperature, the crude product was diluted with 200 ml of ether. The solution was filtered (NaCl) and solvent was evaporated, leaving a crude yellow oil which was hydrolyzed with 1.0 ml of HCl in 100 ml of ether for 12 hr. After diluting with more ether, washing with water, and drying, the solvent was evaporated. The residue was recrystallized from methanol to give 11, 1.25 g (70% yield): mp 72–74°, ir (Nujol) 1740 (aldehyde CO), 1700 and 1685 (ester CO), 1590, 1490, 780, 730, 700 (aromatic CH), 1200 cm^{-1} (CO_2); nmr ($CDCl_3$) δ 1.22 (q, 6, J = 7 Hz, CH_3CH_2), 4.25 (pentet, 4, J = 7 Hz, both CH_3-CH_2), 5.90 (s, 1, benzylic H), 7.17 (s, 5, C_6H_5N), 7.37 and 7.77 (AB q, 4, J = 8 Hz, $-C_6H_4-$), 10.05 (s, 1, CHO).

Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96, N, 3.94. Found: C, 67.63; H, 5.96; N, 3.82.

When the reaction was repeated with an excess (2.1 g, 0.02 mol) of ethyl chloroformate, hydrolysis occurred during an aqueous work-up. The crude product (an oil, 2.0 g) was distilled to give 1.2 g (60% yield), bp 99–102° (0.6 mm), which solidified, mp 46–47.5°, undepressed on admixture with ethyl *N*-phenylcarbamate. The pot residue from the distillation crystallized on digestion with a small amount of methanol. The solid, 0.5 g (25% yield), mp 72.5–74°, was identified as 11 by mixture melting point.

Preparation of *N*,*N*′-Dibenzylquinonediimine (14).—The reduction of 12 (0.005 mol) by sodium metal in THF followed the same procedure as the reduction of 4 (Y = PhN=CH). The dark brown solution of the organosodium compound was quenched with 2 ml of methanol at room temperature. The crude product was isolated by ether extraction of the water-diluted reaction mixture and recrystallized from hexane under nitrogen to give 1.21 g (85% yield) of 14: mp 95.5–97°; ir (KBr) 1520, 1470, 1450, 1400, 1290, 810, 735, 695 cm^{-1}; nmr (C_6D_5) δ 3.27 (s, 4, CH_2), 5.70 (s, 4, vinyl H), 6.47 (broad s, 10, aromatic H).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.87; H, 6.33; N, 9.78. Found: C, 83.65; H, 6.41; N, 9.73.

Acknowledgment.—This research was financially supported by the National Research Council of Canada.

Registry No.—4 (Y = CN), 22257-39-2; 4 (Y = PhN=CH), 14326-69-3; *rac*-5 (Y = CN), 40577-01-3; *meso*-5 (Y = PhN=CH), 40577-02-4; 6 (Y = CN), 37812-49-0; 6 (Y = PhN=CH), 40577-04-6; 8 (Y = CN), 40577-05-7; 8 (Y = PhN=CH), 40577-06-8; 9 (Y = CN), 40577-07-9; 9 (Y = PhN=CH), 40577-08-0; 10 (Y = CN), 40577-09-1; 11, 40577-10-4; 12, 797-20-6; 14, 40577-12-6; aniline, 62-53-3; *p*-cyanobenzaldehyde, 105-07-7; *N*-(*p*-formylbenzal)aniline 40577-14-8; ethyl α-anilino-*p*-cyanophenylacetate, 40577-15-9.

Kinetics of the Autoxidation of Diisopropylbenzenes and Derivatives

YOSHIRO OGATA* AND MICHIO HABA

Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Chikusa-ku, Nagoya, Japan

Received December 29, 1972

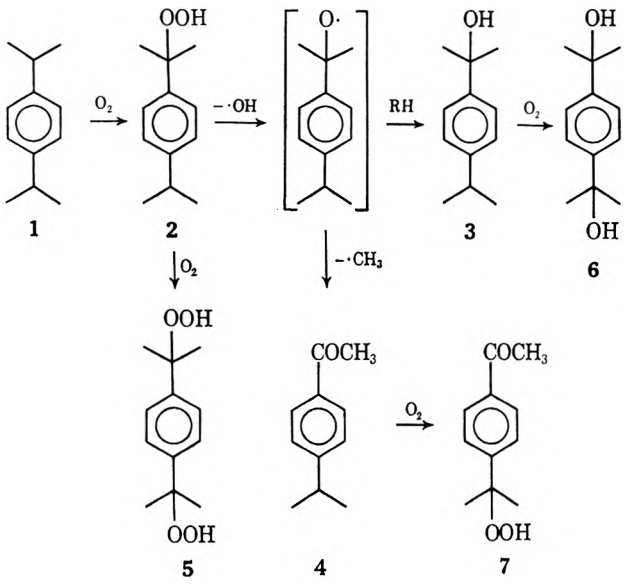
The oxidation of meta- and para-substituted isopropylbenzenes with molecular oxygen has been studied kinetically in chlorobenzene at 60°, using azobisisobutyronitrile as an initiator. The rate constants are in a range of 5.58×10^{-3} to 2.22×10^{-3} $(mol\ sec)^{-1/2}$ and decrease in the order *p*-diisopropylbenzene > *p*-isopropylcumyl hydroperoxide > *m*-diisopropylbenzene > isopropylbenzene > *m*-isopropylcumyl hydroperoxide > *m*-isopropylacetophenone > *m*-isopropylcumyl alcohol > *p*-isopropylacetophenone > *p*-isopropylcumyl alcohol. The observed relative rates fit Hammett's equation, giving a ρ value of −0.50 (r = 0.955). The plot and the observed relative rates give σ_p = −0.14 and σ_m = 0.06 for $-C(CH_3)_2OOH$, σ_p = 0.60 and σ_m = 0.47 for $-C(CH_3)_2$-OH. These substituent effects are discussed in terms of electronic theory.

The autoxidation of *m*- and *p*-diisopropylbenzenes (DIB) to give the corresponding dihydroperoxides has been studied to obtain information on the preparation of resorcinols (from *m*-DIB) and hydroquinones (from *p*-DIB) by acid-catalyzed decomposition of their hydroperoxides.[1-3] The maximum yields of dihydroperoxides in the autoxidation was *ca.* 10%, because dihydroperoxides, once formed, may pyrolyze, resulting in the formation of ketones and alcohols. The autoxidation of DIB may proceed according to Scheme I in analogy with other autoxidation of alkylbenzene.[4,5]

The meta isomer would analogously give the corresponding compounds: (1) diisopropylbenzene; (2) isopropylcumyl hydroperoxide; (3) isopropylcumyl alcohol; (4) isopropylacetophenone; (5) bis(2-hydroperoxy-2-propyl)benzene; (6) bis(2-hydroxy-2-propyl)benzene; (7) acetylcumyl hydroperoxide. Isopropylcumyl alcohols 3 and isopropylacetophenones 4 are formed by the decomposition of diisopropyl-

(1) Distillers Co. Ltd., British Patent 641,250 (1950).
(2) Distillers Co. Ltd., British Patent 646,102 (1950).
(3) Distillers Co. Ltd., British Patent 982,515 (1965).
(4) T. G. Traylor and G. A. Russell, *J. Amer. Chem. Soc.*, **87**, 3698 (1965).
(5) H. S. Blanchard, *J. Amer. Chem. Soc.*, **81**, 4548 (1959).

SCHEME I



cumyl hydroperoxides and they are further oxidized to 6 and 7, respectively.

The effect of substituent in isopropylbenzene on the rates of autoxidation have been reported by Russell[6] to give a ρ value of -0.43. However, as to the autoxidation of isopropylcumyl hydroperoxides, isopropylcumyl alcohols, and isopropylacetophenones, little kinetic information is available, and no substituent constants are reported for α-hydroxyisopropyl and α-hydroperoxyisopropyl groups. Emanuel,[7] *et al.*, studied the autoxidation of *m*- and *p*-DIB and *m*- and *p*-isopropylcumyl hydroperoxides at 100–120° to the corresponding mono- and dihydroperoxides. The formed hydroperoxide should considerably decompose under their reaction conditions; hence the accurate estimation of substituent effect seems to be difficult. These α-hydroxyisopropyl and α-hydroperoxyisopropyl groups are rather unstable under the ordinary oxidation conditions, but under carefully controlled conditions we could measure the rate with virtually no side reactions.

The rates of autoxidation of isopropylbenzene derivatives 2, 3, and 4 were measured by following the absorbed volume of oxygen at a definite temperature under atmospheric pressure. The mechanism and substituent effects will be discussed on the basis of the observed kinetics.

Results

Products.—The autoxidation of cumene derivatives may produce several products through hydroperoxides. The examination of the possibility of decomposition of hydroperoxide in chlorobenzene at 60° gave the following results. For the reaction of 1.80 *M* *p*-DIB initiated by 0.0786 *M* AIBN, 4.10×10^{-3} mol of molecular oxygen was consumed, giving 3.96×10^{-3} mol of hydroperoxide in a reaction at 60° for 3 hr; *i.e.*, the oxygen was consumed to give an almost theoretical yield of hydroperoxide. The formed hydroperoxides were reduced to alcohols with sodium hydrosulfide in aqueous methanol and analyzed by glpc. The only detectable product was monoalcohol, and no decomposition products were detected.

Kinetics.—The rates of autoxidation of cumene, tetralin[6] ring[8]- and α-substituted[9] toluenes, and acyclic ethers[10] have been reported to fit the following equation.

$$-\frac{d[O_2]}{dt} = \frac{k_p}{(2k_t)^{1/2}}[RH]v_i^{1/2} \quad (1)$$

Here, RH is a substrate, v_i is the radical-initiated rate, and k_p and k_t are the propagation and termination rate constants, respectively.

Equation 1 suggests the following mechanism with bimolecular termination by coupling of peroxy radicals.

initiator	$\xrightarrow{k_i}$	2X·	(2)
RH + X·	$\longrightarrow$	R· + HX	(3)
R· + O_2	$\xrightarrow{k_p}$	ROO·	(4)
RH + ROO·	$\longrightarrow$	ROOH + R·	(5)
2ROO·	$\xrightarrow{k_t}$	nonradical products	(6)

AIBN was reported to have a decomposition rate constant k_i of 1.15×10^{-5} sec^{-1} and an initiator efficiency (e) of 0.60 in chlorobenzene at 60°, the half-life of AIBN being 16.7 hr.[5] We can estimate that the concentration of the radical X· is constant for the reaction time of 2–4 hr under these conditions. The data in Table I show that rate eq 1 and the mechanism are applicable to AIBN-initiated autoxidation of diisopropylbenzenes in chlorobenzene.

TABLE I
EFFECTS OF AIBN AND *p*-DIB CONCENTRATIONS ON THE RATE OF THE AUTOXIDATION OF *p*-DIB IN CHLOROBENZENE AT 60°

Run	*p*-DIB, *M*	AIBN, *M*	$10^3 k_p/(2k_t)^{1/2}$, $(mol\ sec)^{-1/2}$
1	1.75	0.101	5.17[a]
2	1.75	0.0500	5.61[a]
3	1.75	0.0786	5.71[a]
4	1.21	0.0906	5.50[a]
5	2.63	0.0589	5.68[a]

[a] The value divided by two of the observed rate constant.

Structural Effect.—Table II lists the rate data calculated by eq 1 for some isopropylbenzene derivatives. It is apparent from Table II that *p*-diisopropylbenzene is the highest in reactivity and *p*-isopropylcumyl alcohol is the lowest among them.

Relations between rate constant and Hammett's σ constant are shown in Figure 1. The ρ value was calculated to be -0.50 ($r = 0.955$), *i.e.*, the electron-withdrawing group decreases the reactivity of isopropylbenzene.

Comparison of the Relative Rate Constants with Those from Competitive Oxidation.—The competitive oxidation was done for the confirmation of the relative rate constants, the results being shown in Table III. Table III confirms that CMe_2OH is electron withdrawing and CMe_2OOH is electron releasing. Also the order of effects of *m*- and *p*-CMe_2OH and *m*- and *p*-CMe_2OOH are the same as those observed by non-competitive methods; *i.e.*, *m*-isopropylcumyl alcohol

(6) G. A. Russell, *J. Amer. Chem. Soc.*, **78**, 1047 (1956).
(7) N. M. Emanuel in "Uspekhi Khimii Organicheskii Perekisnykh Soedinenie Autookisleniya," Vol. 3 (Proceedings of All-Union Conference, USSR), 1965, pp 137–142, 370–376; *Chem. Abstr.*, **72**, 21429g, 21431t (1970).
(8) B. R. Kennedy and K. U. Ingold, *Can. J. Chem.*, **44**, 2381 (1966).
(9) J. A. Howard and S. Korcek, *Can. J. Chem.*, **48**, 2165 (1970).
(10) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **48**, 873 (1970).

TABLE II

EFFECTS OF STRUCTURE ON THE RATES OF AUTOXIDATION OF ISOPROPYLBENZENE DERIVATIVES IN CHLOROBENZENE AT 60°

Registry no.	Substrate	M	AIBN, M	$10^3 k_p/(2k_t)^{1/2}$, (mol sec)$^{-1/2}$	σ^a
100-18-5	p-$Me_2CHC_6H_4CHMe_2$	1.75	0.0786	5.58[b]	−0.15
99-62-7	m-$Me_2CHC_6H_4CHMe_2$	1.75	0.0786	4.73[b]	−0.07
98-49-7	p-$Me_2CHC_6H_4C(OOH)Me_2$	1.57	0.0801	5.20	Unknown
80-24-0	m-$Me_2CHC_6H_4C(OOH)Me_2$	1.54	0.0801	4.09	Unknown
645-13-6	p-$Me_2CHC_6H_4COMe$	1.96	0.0786	2.52	0.50
40428-87-3	m-$Me_2CHC_6H_4COMe$	1.84	0.0786	2.81	0.38
3445-42-9	p-$Me_2CHC_6H_4C(OH)Me_2$	0.671	0.121	2.22	Unknown
14860-89-0	m-$Me_2CHC_6H_4C(OH)Me_2$	2.10	0.0707	2.58	Unknown
98-82-8	$Me_2CHC_6H_5$	2.39	0.0786	4.17	0

[a] H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953). [b] The value was obtained by dividing the observed rate constant by two.

TABLE III

RELATIVE RATE CONSTANTS[a] FROM COMPETITIVE AUTOXIDATION

Reaction time, hr	$k_{m\text{-ICA}}/k_{IB}$	$k_{m\text{-ICH}}/k_{IB}$	$k_{m\text{-ICA}}/k_{p\text{-ICA}}$	$k_{m\text{-ICH}}/k_{p\text{-ICH}}$
2	0.75	1.11	1.50	0.77
4	0.62	1.37	1.26	0.75
6	0.83	1.56	1.35	0.74
Relative rate from noncompetitive method	0.62	1.13	1.16	0.79

[a] k's are first-order rate constants of meta- or para-substituted isopropylbenzenes; ICA, isopropylcumyl alcohol; IB, isopropylbenzene; ICH, isopropylcumyl hydroperoxide.

> *p*-isopropylcumyl alcohol and *m*-isopropylcumyl hydroperoxide < *p*-isopropylcumyl hydroperoxide. A little difference of relative rates obtained by competitive and noncompetitive methods may be due to the difference in reaction conditions; *i.e.*, the AIBN concentration for the competitive method was over twofold higher than that for the noncompetitive method and the conversion was confined to 20–30%. The noncompetitive method is more reliable than the competitive one in view of their experimental error. Hence, the data of the noncompetitive method alone were listed in Table II.

Discussion

As a number of workers have pointed out, eq 1 suggests steps 2–6 for the autoxidation mechanism. In this work the initiation by decompositions of formed hydroperoxide is improbable because of the fairly good constancy of the observed rate constant derived from AIBN-initiated steps. In view of the negative ρ value of −0.50, electron-withdrawing groups decrease the rate of autoxidation as reported for another autoxidation.[6] Thus far the σ constants for α-hydroperoxyisopropyl and α-hydroxyisopropyl groups are unavailable in the literature; the plot in Figure 1 can give their values as listed in Table IV.

TABLE IV

HAMMETT σ VALUES OF α-HYDROPEROXYISOPROPYL AND α-HYDROXYISOPROPYL GROUPS

Group	σ_p	σ_m
$C(Me)_2OOH$	−0.14	0.06
$C(Me)_2OH$	0.60	0.47

It is of interest to note that only the *p*-α-hydroperoxyisopropyl group is electron releasing among them.

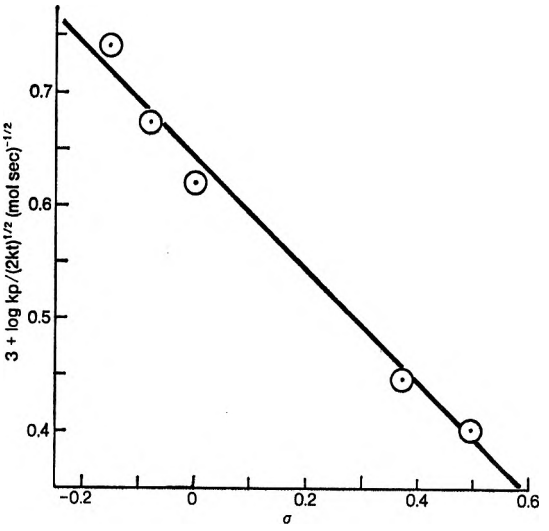
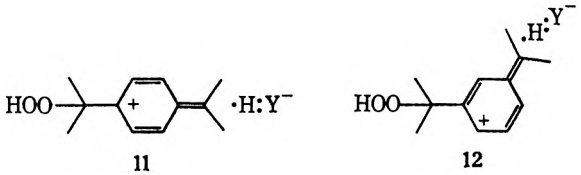


Figure 1.—Hammett plots for the rate of autoxidation of isopropylbenzenes in chlorobenzene at 60°.

It is accepted generally that the transition state for hydrogen abstraction has resonance forms.[6]

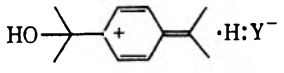
$$R{:}H + \cdot Y \longrightarrow \underset{\mathbf{8}}{[R{:}H\cdot Y} \leftrightarrow \underset{\mathbf{9}}{R^+\cdot H{:}Y^-} \leftrightarrow \underset{\mathbf{10}}{R\cdot H{:}Y]} \longrightarrow R\cdot + H{:}Y \quad (7)$$

An electron-releasing group stabilizes the resonance form **9**. Hence, *p*-isopropylcumyl hydroperoxide at the transition state for the hydrogen abstraction with Y· is more stabilized than the meta isomer in view of resonance forms **11** and **12**, since the $-CMe_2OOH$ group is electron releasing.



11 **12**

On the other hand, the *p*-α-hydroxyisopropyl group was found to be electron withdrawing and to decrease the rate more than the meta isomer.



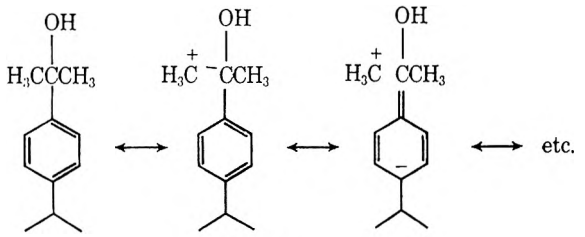
13

Polarization of $-C^{\delta+}-^{\delta-}OH$ makes the OH group electron withdrawing, but the polarization of $O^{\delta-}-$

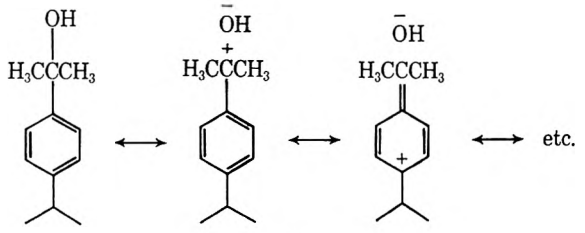
$H^{\delta+}$ seems to lower its effect. Thus, the overall inductive effect of OH is of poor electron withdrawing. In contrast to electron-releasing *m*-CMe_3 ($\sigma = -0.12$) and *p*-CMe_3 ($\sigma = -0.197$), the *m*- and *p*-hydroxycumyl (-CMe_2OH) groups are weakly electron withdrawing because of the electron-withdrawing nature of OH. The C–C hyperconjugation **14** should render *p*-CMe_2OH less electron withdrawing than *m*-CMe_2OH, but actually a reverse effect is observed (Table III).

The authors suppose that the hyperconjugation,[8] such as those reported for α-fluorinated toluenes[11,12] ($C{=}CCF \leftrightarrow C^+{-}C{=}CF^-$) may predominate to give a σ_p value higher than σ_m.

In contrast to the electron-withdrawing resonance forms **15** of Me_2COH the corresponding resonance form,



14



15

$Me_2C^+{-}OOH$, may contribute less to the hydroperoxycumyl group, in view of the electron-releasing nature of the neighboring oxygen atom. Further, the higher acidity[13] of $Me_2COO{-}H$ than $Me_2CO{-}H$, *i.e.*, the stronger polarization of $Me_2COO^{\delta-}{-}^{\delta+}H$, may suppress the resonance of $Me_2C^+{-}OOH$. The C–C hyperconjugation analogous to **15** makes *p*-CMe_2OOH group electron releasing as a whole ($\sigma = -0.14$).

The autoxidation for *p*-isopropylacetophenone is slower than that of the meta isomer because of the electron-withdrawing resonance effect of acetyl groups (Table II).

Emanuel[7] and collaborators, who studied the autoxidation of *m*- and *p*-diisopropylbenzenes and *m*- and *p*-isopropylcumyl hydroperoxides, observed the reactivity in the following order: *m*-diisopropylbenzene > *p*-diisopropylbenzene and *m*-isopropylcumyl hydroperoxide < *p*-isopropylcumyl hydroperoxide. This order differs from our observations. However, their experiments were conducted under conditions where the initiation rate was not kept constant and the formed hydroperoxides may easily decompose. Our order of *m*-diisopropylbenzene < *p*-diisopropylbenzene is convincing in view of the σ_m and σ_p values for isopropyl groups in the literature.[14]

(11) J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Amer. Chem. Soc.*, **72**, 408 (1950).
(12) W. A. Sheppard, *J. Amer. Chem. Soc.*, **84**, 3072 (1962).
(13) A. J. Evere and G. J. Minkoff, *Trans. Faraday Soc.*, **49**, 410 (1953).
(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

Experimental Section

Materials.—Commercial chlorobenzene (bp 132°) was shaken with concentrated sulfuric acid until no color was observed on addition of the acid and then, after being dried (Na_2SO_4), fractionally distilled. Analysis by glpc showed it to be 99.5% pure. Azobisisobutyronitrile (AIBN) was recrystallized several times from methanol, mp 104.0–105.7° dec. *m*- and *p*-diisopropylbenzenes (Mitsui Petrochemical Co., Ltd.) were purified similarly to chlorobenzene; the analysis by glpc showed that the meta isomer [bp 114–115° (50 mm)] was 98.0% pure and the para isomer [bp 119–120.5° (50 mm)] was 99.5% pure. *p*-Isopropylacetophenone[15] was prepared by the Friedel–Crafts acetylation of isopropylbenzene, and purified by distillation: bp 85–86° (2 mm); $n^{20}D$ 1.5292; λ_{max}^{MeOH} 252 mμ (ϵ 19,530). *m*-Isopropylacetophenone[16] was prepared by decomposition of *m*-isopropylcumyl hydroperoxide with cobalt acetate in acetic acid and purified similarly, bp 90–95° (3 mm). Glpc analysis showed that it was 99% pure. *m*- and *p*-isopropylcumyl hydroperoxides were prepared by autoxidation of *m*- and *p*-diisopropylbenzenes and purified as their sodium salts; *i.e.*, the sodium salts were neutralized with Dry Ice to isolate the free hydroperoxides. Iodometry showed that their purities were 100% for the meta isomer (liquid at room temperature) and 97.0% for the para isomer (mp 28–29°), respectively. *m*- and *p*-isopropylcumyl alcohols[17] were prepared by reduction of *m*- and *p*-isopropylcumyl hydroperoxides with 50% aqueous NaOH at 120°. They were recrystallized three times by cooling a saturated *n*-hexane solution with Dry Ice–methanol. Glpc analysis showed that *m*-isopropylcumyl alcohol was 97.5% pure (mp 35.6°) and the para isomer was 98.0% pure (mp 42.9°).

Kinetics.—The apparatus for kinetic study on autoxidation of diisopropylbenzenes was the same as shown in our previous paper.[18] The pressure in the system was controlled to keep the atmospheric pressure by an electrolysis attachment. A reaction vessel and a gas buret were filled with pure oxygen by repeating six times introduction of oxygen and evacuation. A chlorobenzene solution (15–20 ml) containing 0.05–0.1 *M* AIBN and 0.5–2.0 *M* isopropylbenzenes was introduced into the reaction vessel through a dropping funnel and magnetically stirred in a thermostat kept at 60°. The gas buret was kept at a constant temperature of 30°. The preliminary experiments confirmed that the rate of the autoxidation was not affected by diffusion rate, if vigorous stirring (over 100 rpm) was maintained.

Decomposition of Isopropylcumyl Hydroperoxide.—The induced decomposition of isopropylcumyl hydroperoxide might occur during the autoxidation owing to the reaction of chlorobenzene with AIBN. To test the possibility of induced decompositions, chlorobenzene was degassed by evacuation at the liquid N_2 temperature, and treated with the hydroperoxide at 60° for 5–40 hr. The content of hydroperoxide was estimated iodometrically at appropriate time intervals and listed in Table V. Table V shows that the induced decomposition of hydroperoxides may be neglected under these conditions, although the

TABLE V
A TEST FOR THE DECOMPOSITION OF *m*- AND *p*-ISOPROPYLCUMYL HYDROPEROXIDES IN CHLOROBENZENE AT 60°

Hydroperoxide	*M*	AIBN, *M*	Time, hr	Purity,[a] wt %
m-$HOOCMe_2C_6H_4CHMe_2$	1.63	0.121	0	27.8
			5	27.9
p-$HOOCMe_2C_6H_4CHMe_2$	1.57	0.0801	0	28.5
			5	28.9
m-$HOOCMe_2C_6H_4CHMe_2$	1.02	None	0	18.6
			20	18.5
			40	18.4

[a] Iodometric titration.

(15) B. N. Campbell and E. C. Spaeth, *J. Amer. Chem. Soc.*, **81**, 5611 (1959).
(16) Imperial Chemical Industry Ltd., British Patent 784,681 (1957).
(17) V. A. Belyaev and M. S. Nemtsov, *Zh. Obshch. Khim.*, **32**, 3131 (1962); *Chem. Abstr.*, **58**, 8868c (1963).
(18) T. Morimoto and Y. Ogata, *J. Chem. Soc. B*, 62 (1967).

very slow induced decomposition of cumene hydroperoxide was reported to occur with AIBN.[19]

Competitive Reactions.—Competitive autoxidations were carried out with an equimolar mixture of two substituted isopropylbenzenes (each *ca.* 1.2–0.6 *M*) in chlorobenzene at 60° in the presence of AIBN (0.26–0.09 *M*). Aliquots (each 1 ml) were taken out at appropriate intervals of time and reduced with 15% KSH in aqueous methanol. After completion of reduction, the solution was washed with water, extracted with two 4-ml portions of chloroform, and analyzed by means of glpc. The products were analyzed by a Yanagimoto gas chromatograph with a flame ionization detector, Model GCG-550F, employing a 1.0 m × 2.5 mm column packed with Apiezon Grease (5%) on Chamelite CS of 80–100 mesh using N_2 as a carrier gas at 160–220°. The internal standards for glpc were nitrobenzene for cumene and *m*-diisopropylbenzene for isopropylcumyl hydroperoxide and isopropylcumyl alcohol. The relative rate constants of competitive oxidation were calculated from the equation $k = k_m/k_p = \log[(b - y)/b]/\log[(a - x)/a]$. Here, a and b are initial concentrations of substrates and x and y are corresponding concentrations at time t.

(19) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **46**, 2655 (1968).

Acknowledgment.—The authors wish to thank Dr. M. Yamashita for his helpful advice in performing these experiments.

Spiro Hydrocarbons and Dibenzo[*c*,*p*]chrysene from 1-Tetralone

JOHN W. BURNHAM,[1a] ROBERT G. MELTON,[1b] AND EDMUND J. EISENBRAUN*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

GARY W. KEEN AND MYNARD C. HAMMING

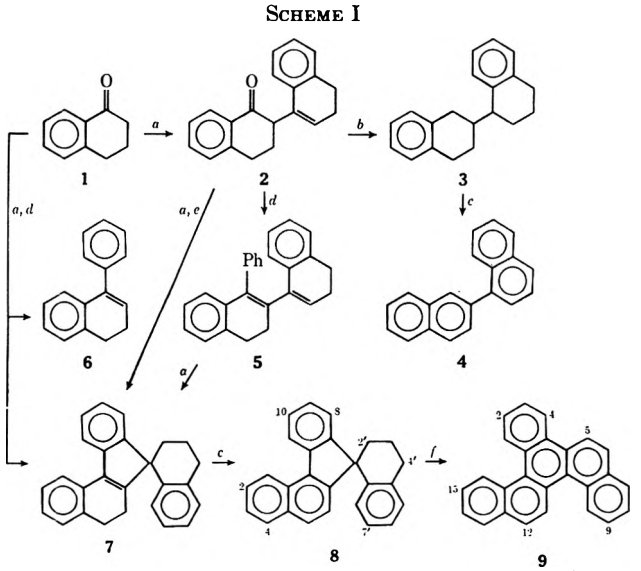
Research and Development Department, Continental Oil Company, Ponca City, Oklahoma 74601

Received December 29, 1972

1-Tetralone (1) and phenylmagnesium bromide yield 3,4-dihydro-1-phenylnaphthalene (6) and 1′,2′,3′,4′,5,6-hexahydrospiro[7*H*-benzo[*c*]fluorene-7,1′-naphthalene] (7). The latter is formed in a series of reactions involving the self-condensation of 1 to 2-(3,4-dihydro-1-naphthyl)-3,4-dihydro-1(2*H*)-naphthalenone (2), addition of Grignard reagent, acid-catalyzed dehydration to the diene 5, and its subsequent cyclization to 7. The latter was dehydrogenated with Pd/C to 1′,2′,3′,4′-tetrahydrospiro[7*H*-benzo[*c*]fluorene-7,1′-naphthalene] (8) and then 8 was converted to dibenzo[*c*,*p*]chrysene (9) by heating in the presence of Pd/C and sulfur.

1-Tetralone (1) serves as a useful starting material in the synthesis of 3,4-dihydro-1-phenylnaphthalene (6) or 1-phenylnaphthalene.[2] It is of interest that a low yield (2–3%) of 1′,2′,3′,4′5,6-hexahydrospiro[7*H*-benzo*c*]fluorene-7,1′-naphthalene] (7) is formed during the acid-catalyzed work-up. The latter is more conveniently prepared from either 2 or 5 as shown in Scheme I.

SCHEME I



[a] Amberlyst-15, toluene, Δ. [b] Pd/C, H_2, CH_3CO_2H. [c] Pd/C, Δ. [d] C_6H_5MgBr. H_3O^+. [e] C_6H_5Li. [f] Pd/C, S, Δ.

Although 2 and 5 may readily be detected by glc as products during the preparation of 6, their direct isolation, particularly that of 2, is difficult. Accordingly, to establish that 2 and 5 may be intermediates to 7, and to obtain a quantity of 7, we prepared 2[3–5] and 5 and then used these compounds for the synthesis of 7, 8, and 9 as shown in Scheme I. Also to substantiate the 2,1′ linkage of 2, we converted it *via* 3 to 1,2′-binaphthyl (4).[6]

The best preparation of 7 (55%) resulted from addition of phenyllithium to 2 (*cf.* steps *a* and *e* of Scheme I). The latter was completely consumed in this reaction. This preparation of 7 involves acid-catalyzed dehydration and cyclization.[5,7a] We also noted that the reaction of 2 with phenylmagnesium bromide, regardless of mode of addition, was incomplete, at least 30% of 2 being recovered. By cautious acidification[7b] of Grignard reaction products, the diene 5 may be isolated. It, in turn, is readily converted to 7 with Amberlyst-15.[5,7a]

Inverse addition (adding phenylmagnesium bro-

(1) (a) American Petroleum Institute Graduate Research Assistant, 1969–1973; Continental Oil Company Fellow, 1973; (b) American Petroleum Institute Graduate Research Assistant, 1968–1971.

(2) (a) R. Weiss, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 729. (b) The distillation residue obtained by the procedure of ref 2a weighed 7 g and yielded 3% of 7 (based on 0.4 mol of 1) after treatment with Amberlyst-15. *Cf.* Experimental Section for inverse addition of phenylmagnesium bromide and the phenyllithium procedure leading to 7.

(3) (a) E. J. Eisenbraun, J. M. Springer, C. W. Hinman, P. W. K. Flanagan, and M. C. Hamming, *Amer. Chem. Soc., Div. Petrol. Chem., Prepr. Gen. Papers*, **14** (3), A-49 (1969); (b) J. M. Springer, C. W. Hinman, E. J. Eisenbraun, P. W. K. Flanagan, and M. C. Hamming, *J. Org. Chem.*, **35**, 1260 (1970).

(4) (a) H. L. Retcofsky, L. Reggel, and R. A. Friedel, *Chem. Ind. (London)*, 617 (1969); (b) M. Orchin, L. Reggel, and R. A. Friedel, *J. Amer. Chem. Soc.*, **71**, 2743 (1949).

(5) We thank Rohm and Haas Co., Philadelphia Pa., for a sample of Amberlyst-15 sulfonic acid resin. Literature describing its use may be obtained from this source.

(6) Correspondence regarding samples of 4, 1-phenylnaphthalene, 6, and 8 should be addressed to A. J. Streiff, American Petroleum Institute, Carnegie-Mellon University, Pittsburgh, Pa. 15213.

(7) (a) Amberlyst-15[5] in boiling benzene or toluene was effective in causing dehydration and cyclization to 7. (b) Cold hydrochloric acid was used to decompose Grignard reaction products and to cause dehydration to 5. (c) A structure analogous to 7 was proposed earlier for a product obtained from the reaction of *o*-tolylmagnesium bromide and 1: M. Orchin, L. Reggel, and R. A. Friedel, *J. Amer. Chem. Soc.*, **73**, 1449 (1951).

mide to 1) gave 12% of 7 as final product. Presumably the higher concentration of ketone 1 in this mode of addition permits self-condensation to 2 as compared to addition of the phenyl group to 1.

To establish the structure[7c] of 7, it was dehydrogenated to the spiro hydrocarbon 8 by heating in the presence of Pd/C. The strongest argument for the structure of these spiro hydrocarbons is the anisotropy exhibited by the C-1, C-11, and C-8′ protons in the pmr spectra (100 MHz) of both hydrocarbons 7 and 8. Dreiding models of 7 and 8 indicate that the C-1 and C-11 protons should experience deshielding.[8a] For 7, this strong interaction results in a downfield triplet at δ 7.88 for both protons. For 8, the C-1 and C-11 protons give separated signals (pair of doublets) shifted to δ 8.79 and 8.37, respectively. Strong shielding is observed for the C-8′ proton of 7 and 8. These high-field shifts appear as doublets centered at δ 6.49 and 6.25, respectively. Dreiding models of 7 and 8 also show that the C-8′ proton is situated above the aromatic rings of the fluorene system and hence should be influenced by aromatic ring currents.[8b]

Aromatization of 8 to dibenzo[*c,p*]chrysene (9) was accomplished by heating it in the presence of Pd/C and sulfur.[8c] The structure of 9 is supported by its high-resolution mass spectrum, which shows a molecular ion peak (*m/e* 328), peaks resulting from loss of 1, 2, and 4 H atoms, and the formation of doubly charged ions *m/e* 164 $(M)^{2+}$, 163 $(M - 2\ H)^{2+}$, and 162 $(M - 4\ H)^{2+}$. The *m/e* 326 ion apparently loses CH and C_2H_2 to yield doubly charged ions *m/e* 156.5 and 150. These fragmentations are characteristic of condensed polynuclear aromatic hydrocarbons.[9a,b] The pmr spectrum of 9 shows a multiplet of six aromatic protons at δ 9.56–8.19. This corresponds to the bay protons at positions C-4 and C-5 and fjord protons at C-1, -10, -11, and -16. The remaining ten peninsular protons give rise to an upfield multiplet centered at δ 7.93. A similar spectrum was reported for dibenzo[*g,p*]chrysene.[9c]

Experimental Section[10]

Conversion of 1-Tetralone (1) to 2-(3,4-Dihydro-1-naphthyl)-3,4-dihydro-1(2*H*)-naphthalenone (2).—1-Tetralone (292 g, 2 mol), 30 g of Amberlyst-15,[6] and 750 ml of dry toluene were combined in a 2-l., one-neck flask equipped with a Dean–Stark trap. The mixture was heated at reflux for 4.5 hr with magnetic stirring until production of water (4 ml) ceased. The reaction mixture was cooled, filtered, and concentrated with a rotary evaporator. The concentrated oil was mixed with 100 ml of ether, and the yellow-white crystals of 2 (37 g) that formed after refrigeration for 2 days were filtered out. The mother liquor was distilled at 80° (0.1 mm) to give 193 g of recovered 1. A small forerun containing naphthalene was collected. Ether (150 ml) was added to the cooled viscous pot residue which then crystallized on seeding. An additional 45 g of 2 was obtained as brown crystals. The combined yield of crude 2 was 91% based on recovered 1. This mixture was washed with ether and recrystallized from acetone to give 2 as colorless crystals: mp 132.5–135° (lit.[4b] mp 132.5–134.2°); orange 2,4-dinitrophenylhydrazone mp 249–250° dec (lit.[4b] mp 247–248°); mass spectrum (70 eV) *m/e* (rel intensity) 274 (77), 146 (75), 129 (100), 43 (97), 29 (91); pmr ($CDCl_3$) δ 8.24 (m, 1, isolated ArH at C-8), 7.63–7.24 (m, 7, ArH), 5.88 (t, 1, vinylic), 3.89 (t, 1, C=CCH and adjacent to C=O), 3.21–2.02 (m, 8, $-CH_2-$); uv as previously recorded.[3b,4b]

Pd/C-Catalyzed Hydrogenation of 2 to 1,2,3,4,1′,2′,3′,4′-Octahydro-1,2′-binaphthyl (3).—A 100-g (0.36 mol) sample of 2 in 400 ml of acetic acid in the presence of 5 g of 10% Pd/C was hydrogenated at 50 psi and at 65° for 12 hr. The catalyst was filtered out with Dicalite. Water (1.5 l.) was added to the filtrate and the mixture was extracted with ether (2 × 500 ml). The extract was washed with water and 100 ml of 10% sodium hydroxide, dried ($MgSO_4$), filtered, and distilled to give 89 g (95%) of 3: bp 165° (0.1 mm) [lit.[11] bp 175–180° (0.2 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 262 (8), 132 (21), 131 (100), 130 (30), 129 (17), 115 (15), 91 (22); pmr (CCl_4) δ 7.32–6.72 (m, 8, ArH), 3.08–1.12 (envelope, 14, ArCH, $ArCH_2$, and $-CH_2-$); uv as previously recorded.[11]

Pd/C-Catalyzed Dehydrogenation of 3 to 1,2′-Binaphthyl (4).—A 89-g (0.34 mol) sample of 3 and 5 g of 10% Pd/C were heated together at 300° under nitrogen for 2.5 hr. The cooled mixture was dissolved in benzene and filtered through Dicalite to remove catalyst. An equal portion of petroleum ether[10f] was added and the solution was decolorized by elution through a 1 × 4 in. column of basic alumina. The solvents were removed by rotary evaporation to give 86 g of crystalline 4. Recrystallization from petroleum ether[10f] gave 80 g (93%) of 4 free of impurity by glc:[10a] mp 76–78° (lit.[11] mp 76.5–77.5°); mass spectrum (70 eV) *m/e* (rel intensity) 254 (100), 253 (72), 252 (53), 250 (13), 127 (10), 126 (27); pmr ($CDCl_3$) δ 8.05–7.18 (m, ArH).

Conversion of 1-Tetralone (1) to 3,4-Dihydro-1-phenylnaphthalene (6) and 1′,2′,3′,4′,5,6-Hexahydrospiro[7*H*-benzo[*c*]fluorene-7,1′-naphthalene] (7).—The preparation of 6 from 584 g (4 mol) of 1 and 4.8 mol of phenylmagnesium bromide was carried out as described[2a] except that commercial Grignard reagent[12] was substituted and Amberlyst-15[6] in boiling toluene was used for dehydration. Glc studies[10a] at 240° of this reaction mixture showed the presence of 1-phenyl-1,2,3,4-tetrahydronaphthalene–6–1-phenylnaphthalene in a ratio of 5:80:15. The hydrocarbon mixture was distilled at 95–99° (0.01 mm) through an 18-in. vacuum-jacketed Vigreux column to give 486 g (67%) of crude 6 and 32 g of distillation pot residue. Redistillation[10g] gave pure 6: bp 91° (0.01 mm) [lit.[13] bp 130.5–135.5° (0.3 mm)]; mass spectrum (70 eV) *m/e* (rel intensity) 206 (100), 205 (29), 202 (18), 191 (38), 128 (25), 91 (22); pmr (CCl_4) δ 7.36–6.97 (m, 9, ArH), 5.96 (t, 1, vinylic), 2.91–2.59 (m, 2, $ArCH_2-$), 2.44–2.03 (m, 2, allylic); uv max (95% ethanol) 205 mμ (log ε 4.39), 220 (4.36), 267 (3.91).

The identity of the glc peaks assigned to 1-phenyl-1,2,3,4-tetrahydronaphthalene and 1-phenylnaphthalene in the reaction product mixture was established by glc[10a] comparison at 225° with authentic materials. Samples of these hydrocarbons were obtained from 6 by catalytic hydrogenation and catalytic dehydrogenation in the presence of 10% Pd/C catalyst.

The pot residue (32 g) was recrystallized twice from benzene to give colorless crystals of 7: mp 189–190°; mass spectrum (70 eV) *m/e* (rel intensity) 334 (100), 305 (12), 303 (12), 289 (10), 229 (11), 215 (21); pmr ($CDCl_3$) δ 7.88 (t, 2, isolated ArH at C-1 and C-11), 7.42–6.72 (m, 9, ArH), 6.49 (d, 1, ArH at C-8′), 3.08–2.56 (m, 4, $ArCH_2$), 2.50–1.61 (m, 6, $ArCH_2CH_2-$ and $ArCH_2-CH_2CH_2-$); uv max (95% ethanol) 203 mμ (log ε 4.75), 238 (4.46), 266 (3.87), 294 (3.86).

(8) (a) K. D. Bartle and D. W. Jones, *Advan. Org. Chem.*, **8**, 317 (1972); (b) *cf.* ref 8a, p 353; (c) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 781.

(9) (a) M. C. Hamming and N. G. Foster, "Interpretation of Mass Spectra of Organic Compounds," Academic Press, New York, N. Y., 1972; (b) R. Engel, D. Halpern, and B.-A. Funk, *Org. Mass Spectrom.*, **7**, 177 (1973); (c) R. H. Martin, N. Defay, F. Geerts-Evrard, and S. Delavarene, *Tetrahedron*, **20**, 1073 (1964).

(10) (a) The glc studies used a Hewlett-Packard Model 5750 instrument with a 0.25 in. × 12 ft column of 80–100 mesh Chromosorb G (acid washed and DMCS treated) treated with 5% silicone rubber UC W-98. (b) A similar 0.25 in. × 5 ft column of 100–120 mesh Chromosorb W (AW and DMCS treated) coated with 5% UC W-98 was used for analysis of the C_{26} hydrocarbons. (c) Nmr spectra were obtained with a Varian XL100 spectrometer. (d) Mass spectra were obtained with CEC Model 21-103C and 21-110B spectrometers. (e) Ir and uv spectra were obtained with Beckman IR-5A and Cary 14 spectrometers, respectively. (f) The petroleum ether, bp 60–68°, was redistilled before use. (g) A Nester/Faust autoannular spinning band distillation system, Model NFA-200, was used.

(11) L. E. Harris, E. J. Eisenbraun, P. W. Flanagan, M. C. Hamming, and G. W. Keen, *J. Org. Chem.*, **37**, 336 (1972).

(12) Phenylmagnesium bromide was obtained from Arapahoe Chemicals, Boulder, Colo.

(13) M. S. Newman, H. V. Anderson, and K. H. Takemura, *J. Amer. Chem. Soc.*, **75**, 347 (1953).

Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.23; H, 6.79.

Inverse Addition of Phenylmagnesium Bromide to 1 to Form 6 and 7.—To a mechanically stirred solution of 44 g (0.3 mol) of 1 in 500 ml of dry ether at 10° was added 200 ml (0.6 mol) of 3 *M* phenylmagnesium bromide[12] over a 15-min period. Reflux was established after 5 min and the mixture was stirred for 1.5 hr. The reaction mixture was then added to 500 g of ice and 200 ml of concentrated hydrochloric acid. The ether extract was dried ($MgSO_4$) and concentrated to give 63 g of red-brown oil. The oil was dissolved in 350 ml of toluene and stirred at reflux for 1.5 hr with 3 g of Amberlyst-15.[5] Filtration and steam distillation gave 41 g of volatile hydrocarbon and 20 g of nonsteam-volatile material. The nonvolatiles were dissolved in petroleum ether[10f] and percolated through a 2 × 3 in. column of basic alumina; concentration of the effluent and crystallization from petroleum ether[10f] gave 6 g (12%) of **7**.

Inverse Addition of Phenylmagnesium Bromide to 2 to Form 1-Phenyl-3,3′,4,4′-tetrahydro-2,1′-binaphthyl (5).—To a stirred mixture of 27.4 g (0.1 mol) of **2** in 500 ml of dry ether was added 67 ml (0.2 mol) of a 3 *M* phenylmagnesium bromide[12] solution during 5 min. There was no apparent temperature change; the mixture was then heated at reflux for 24 hr. The reaction mixture was added to 500 g of ice and 50 ml of concentrated hydrochloric acid. Extraction with benzene (250 ml), drying ($MgSO_4$), and concentration gave 37 g of yellow oil. Petroleum ether[10f] (150 ml) was added and 10 g of **2** was recovered on cooling and filtering. The filtrate was percolated through two 2 × 3 in. columns of Merck basic alumina to give 16 g of concentrated oil. This oil crystallized from 25 ml of cold acetone after 3 days to give 8.5 g (40%) of **5**: mp 95–97°; mass spectrum (70 eV) *m/e* (rel intensity) 334 (100), 333 (12), 332 (11), 305 (11), 215 (10), 117 (11); pmr (CCl_4) δ 7.26–6.62 (m, 13, ArH), 5.54 (t, 1, vinylic), 3.04–2.76 (m, 2, $ArCH_2$ at C-4), 2.70–2.28 (m, 4, $ArCH_2CH_2$ and $ArCH_2$ at C-3 and C-4′, respectively), 2.10–1.81 (m, 2, $ArCH_2CH_2$ at C-3′); uv max (95% ethanol) 205 mμ (log ε 4.65), 267 (3.97).

Anal. Calcd for $C_{26}H_{22}$: C, 93.37; H, 6.63. Found: C, 93.18; H, 6.68.

Amberlyst-15-Catalyzed Cyclization of 5 to 7.—Three grams of **5** was cyclized over 30 min by heating in 150 ml of boiling toluene containing 2 g of Amberlyst-15.[5] The reaction mixture was cooled, filtered, and concentrated and the crude product was crystallized from 50 ml of petroleum ether[10f] to give 2.7 g (90%), mp 189–190°, found to be identical with **7** from other experiments.

Conversion of 2 to 7 Using Phenyllithium.—Phenyllithium (0.4 mol) was prepared as described[14] from 63 g of bromobenzene and 3 g of Li. To the stirred reagent was added, during 40 min at 25–30°, 27.4 g (0.1 mol) of **2** dissolved in 300 ml of dry benzene. The mixture was heated at reflux for 10 hr. During this period the temperature rose from the boiling point of ether to that of benzene. The reaction mixture was cooled and added to ice and 300 ml of 10% HCl. Extraction with ether gave 34 g of concentrated oil, ir (neat) 3460 cm^{-1} (OH). The oil was dehydrated and cyclized with 3 g of of Amberlyst-15[5] in 300 ml toluene heated at reflux temperature for 1 hr. Two milliliters of water was collected. The filtered and concentrated product was dissolved in 200 ml of toluene–petroleum ether (1:1) and the mixture was passed through a 1.5 × 3 in. column of basic Merck alumina. Removal of the solvent and crystallization from 75 ml of toluene gave 18 g (55%) of colorless **7**, mp 188–190°. This sample was found to be identical with other samples of **7**.

Pd/C Catalyzed Dehydrogenation of 7 to 1′,2′,3′,4′-Tetrahydrospiro[7*H*-benzo[*c*]fluorene-7,1′-naphthalene] (8).—A 18.3-g sample of **7** and 3 g of 10% Pd/C were heated together at 310° (bath temperature) for 20 min under a blanket of N_2. The cooled product mixture was dissolved in chloroform and filtered through Dicalite, the chloroform removed by rotary evaporation, and 50 ml of petroleum ether was added to the oil. Refrigeration and filtration gave 16.9 g (92%) of **8** as white plates: mp 157–159°; mass spectrum (70 eV) *m/e* (rel intensity) 332 (100), 304 (17), 303 (52), 302 (6), 300 (8), 151 (13); pmr ($CDCl_3$) δ 8.79 (d, 1, isolated ArH at C-1), 8.37 (d, 1, isolated ArH at C-11), 7.98–6.95 (m, 10, ArH), 6.76 (t, 1, isolated ArH at C-7′), 6.25 (d, 1, isolated ArH at C-8′), 3.24–3.01 (m, 2, $ArCH_2$), 2.41–1.95 (m, 4, $ArCH_2CH_2CH_2$); uv max (95% ethanol) 204 mμ (log ε 4.70), 237 (4.69), 252 (4.49 sh), 306 (3.97 sh), 317 (4.10), 326 (4.05), 342 (4.16).

Anal. Calcd for $C_{26}H_{20}$: C, 93.94; H, 6.06. Found: C, 93.79; H, 6.14.

The Pd/C and Sulfur Dehydrogenation of 8 to Dibenzo[*c,p*]chrysene (9).—A 2-g sample of **8** was heated under nitrogen at 325° in the presence of 0.75 g of 10% Pd/C and 0.75 g of sulfur for 10 min. The mixture was cooled, dissolved in benzene, and filtered through Dicalite to give a green solution. This solution was diluted with an equal volume of petroleum ether[10f] and passed through a 1.5 × 2.5 in. column of Merck acidic alumina. Concentration and trituration with petroleum ether[10f] gave 1.2 g of yellow **9**: mp 200–202° dec; mass spectrum (70 eV) *m/e* (rel intensity) 328 (100), 327 (33), 326 (40), 324 (15) [accurate mass values (±0.003 of theoretical) were obtained for the doubly charged ions 164 (7), 163 (14), and 162 (15)]; pmr ($CDCl_3$) δ 9.56–8.19 (m, 6, ArH), 8.19–7.66 (m, 10, ArH); uv max (95% ethanol) 213 mμ (log ε 4.64), 276 (4.84), 295 (4.71), 305 (4.79), 334 (4.09), 350 (3.87).

Anal. Calcd for $C_{26}H_{16}$: C, 95.09; H, 4.91. Found: C, 95.03; H, 4.91.

Acknowledgments.—We thank the American Petroleum Institute for support of this research and Dr. O. C. Dermer for reading the manuscript. We also thank Mr. N. F. Chamberlain, Esso Research and Engineering Company, for advice on pmr spectroscopic assignments.

Registry No.—**1**, 529-34-0; **2**, 23804-16-2; **2** 2,4-dinitrophenylhydrazone, 23796-79-4; **3**, 27426-98-8; **4**, 4325-74-0; **5**, 40548-39-8; **6**, 7469-40-1; **7**, 40548-41-2; **8**, 40548-42-3; **9**, 196-52-1.

(14) J. C. Evans and C. F. H. Allen, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 517.

Selective Reductions. XIX. The Rapid Reaction of Carboxylic Acids with Borane–Tetrahydrofuran. A Remarkably Convenient Procedure for the Selective Conversion of Carboxylic Acids to the Corresponding Alcohols in the Presence of Other Functional Groups

NUNG MIN YOON AND CHWANG SIEK PAK

Department of Chemistry, Sogang University, Seoul, Korea

HERBERT C. BROWN,* S. KRISHNAMURTHY,[1] AND THOMAS P. STOCKY[2]

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

Received March 7, 1973

Aliphatic and aromatic carboxylic acids are reduced rapidly and quantitatively to the corresponding alcohols by borane in tetrahydrofuran, either at 0° or 25°. Even sterically hindered acids, such as 1-adamantanecarboxylic acid, dicarboxylic acids, such as adipic acid, phenolic acids, and amino acids undergo facile and quantitative reduction with borane. Aliphatic carboxylic acids are reduced at faster rates than aromatic carboxylic acids. Unlike more conventional, very powerful reducing agents, such as lithium aluminum hydride, the mildness of the reagent, borane, permits the presence of other functional groups less susceptible to the reducing action of the reagent, groups such as ester, nitro, halogen, nitrile, keto, etc. The remarkable utility of this reagent for the selective reduction of carboxylic acids was confirmed by the selective conversion of adipic acid monoethyl ester to ethyl 6-hydroxyhexanoate and *p*-cyanobenzoic acid to *p*-cyanobenzyl alcohol in yields of 88 and 82%, respectively. This reaction provides a highly convenient synthetic procedure for the selective reduction of the carboxylic acid group where this is required in synthetic operations.

Reduction of carboxylic acids to the corresponding alcohols has been examined with a variety of complex metal hydrides and metal hydrides, such as lithium aluminum hydride, lithium trimethoxyaluminohydride (LTMA), lithium tri-*tert*-butoxyaluminohydride (LTBA), aluminum hydride, "mixed hydride," etc.[3] Lithium aluminum hydride has been widely applied for such reductions. However, lithium aluminum hydride and lithium trimethoxyaluminohydride are exceedingly powerful reducing agents capable of reducing practically all organic functional groups, whereas lithium tri-*tert*-butoxyaluminohydride is a mild reducing agent which does not reduce the carboxylic acid group. Consequently, this introduces a severe limitation in utilizing these reagents for the selective reduction of carboxylic acids to alcohols in the presence of other reducible functional groups in multifunctional molecules. Recently, the development of aluminum hydride as a reducing agent in our laboratories made it possible to overcome some of the limitations of lithium aluminum hydride, to achieve, for example, the selective reduction of the carboxylic acid group in the presence of nitro and halogen substituents. Unfortunately, aluminum hydride is highly reactive toward other functional groups, such as ester, nitrile, keto group, epoxide, etc., so that its utilization for selective reductions is not broadly applicable.

We recently reported an extensive investigation of the approximate rates and stoichiometry of the reaction of borane in tetrahydrofuran (THF) with organic compounds containing representative functional groups.[4] During the course of this investigation, it was observed that carboxylic acids, such as hexanoic acid and benzoic acid, are reduced by borane to the corresponding alcohols rapidly and quantitatively under remarkably mild conditions (eq 1).

$$\mathrm{RCOOH} \xrightarrow[0^\circ]{\mathrm{BH_3\text{-}THF}} \underset{>95\%}{\mathrm{RCH_2OH}} \qquad (1)$$

R = alkyl or aryl

The results of this investigation suggested that the unique reduction characteristics of borane should permit selective reduction of the carboxylic acid group to the corresponding primary alcohol in the presence of many other less reactive functional groups. Accordingly, we undertook a detailed study of the scope of the reduction and its applicability for multifunctional molecules. The results of this investigation are reported in the present paper.

Results and Discussion

Stoichiometry.—Simple carboxylic acids, such as hexanoic acid or benzoic acid, should require one borane unit or a total of three "active hydrides"[5] for the reduction to alcohol stage, one hydride for the reaction with the acidic hydrogen and two hydrides for the reduction. Similarly, dicarboxylic acids, such as adipic acid, should need a total of six "active hydrides" for complete reduction.

With acids containing hydroxy groups, such as salicylic acid, a total of four "active hydrides" (two for the acidic hydrogens present in the molecule and two for the reduction) would be required for the reduction.

Finally, amino acids, such as *p*-aminobenzoic acid,

(1) Postdoctoral Research Associate on Grant No. ARO-D-31-124-73-G1 supported by the U. S. Army Research Office (Durham).

(2) Graduate Research Assistant on Grant No. GM 10937 from the National Institutes of Health.

(3) (a) For a summary of the literature, see N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, pp 322–372; (b) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966); (c) H. C. Brown and P. M. Weissman, *ibid.*, **87**, 5614 (1965); (d) H. C. Brown and P. M. Weissman, *Israel J. Chem.*, **1**, 430 (1963); (e) H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1464 (1966); (f) N. M. Yoon and H. C. Brown, *ibid.*, **90**, 2927 (1968); (g) R. F. Nystrom, *ibid.*, **81**, 610 (1959); (h) E. E. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); (i) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966).

(4) (a) H. C. Brown, P. Heim, and N. M. Yoon, *ibid.*, **92**, 7161 (1970); (b) H. C. Brown and B. C. Subba Rao, *ibid.*, **82**, 681 (1960); (c) H. C. Brown and W. Korytnyk, *ibid.*, **82**, 3866 (1960).

(5) It is convenient to discuss the utilization of the reagents in terms of moles of hydride taken up per mole of acid. However, it should not be confused that free "hydride" ion is the active species. An "active hydride" refers to one B–H bond, 1 equiv of borane.

might require a maximum of eight "active hydrides," three for the reaction with "active hydrogens" present on nitrogen and oxygen, two for the reduction, and the remaining three (1 mol of borane) for the formation of an amine–borane complex.

General Procedure for Rate and Stoichiometry Studies. Effect of Structure of the Acid on the Reactivity.—In order to understand the influence of the structure of the carboxylic acid on the rate of this reaction, the reactivity of a series of acids of representative structural features was examined toward borane. The general procedure adopted was to add 4 mmol of acid to 3.66 mmol of borane solution in sufficient THF to give 20 ml of solution. This makes the reaction mixture 0.33 *M* in BH_3 and 0.2 *M* in substrate. The solutions were maintained at constant temperature (*ca.* 25°) and aliquots were removed at appropriate intervals of time and analyzed for "residual hydride" by hydrolysis. In the case of dicarboxylic acids and amino acids, the concentration of borane alone was increased to 0.5 *M*.

All of the acids examined react instantaneously and quantitatively to evolve hydrogen, forming triacyloxyboranes. Simple carboxylic acids, such as propionic acid and benzoic acids, are reduced rapidly and quantitatively in 1 hr. Introduction of alkyl substituents α to the carbonyl group (propionic acid *vs.* trimethylacetic acid) does not influence the rate of reduction, revealing insensitiveness of the reaction to steric effects. However, introduction of electron-withdrawing substituents, such as halogen, α to the carbonyl group, decreases the rate of reduction (trichloroacetic acid *vs.* propionic acid). The results are summarized in Table I.

TABLE I

RATES OF REACTION OF BORANE WITH REPRESENTATIVE CARBOXYLIC ACIDS IN TETRAHYDROFURAN AT 25°[a,b]

Registry no.	Acid	Reduction,[c] % 0.5 hr	1.0 hr	3.0 hr	6.0 hr	12.0 hr	24.0 hr	48.0 hr
79-09-4	Propionic	95	100	100				
65-85-0	Benzoic	99	99					
75-98-9	Trimethylacetic	95	100	100				
79-11-8	Chloroacetic	100	100	100				
76-03-9	Trichloroacetic			8	18	37	48	61
90-64-2	Mandelic		80	88	92	100	100	
69-72-7	Salicylic		87	100				
150-13-0	*p*-Aminobenzoic[d]		100	100				
124-04-9	Adipic[d]	93	96	98	100			

[a] Unless otherwise indicated, reaction mixtures were 0.33 *M* in BH_3 and 0.2 *M* in the compound. [b] In all of the acids, the hydrogen evolution from the acidic hydrogen is instantaneous and complete. Hydrogen evolution from the amino group in *p*-aminobenzoic acid is slow and incomplete (38%) [c] Reactions were monitored by the decrease in the hydride concentration. [d] Solutions were 0.5 *M* in BH_3 and 0.2 *M* in the acid.

Competition Experiments.—Extensive study of the reaction of typical organic functional groups with excess borane gave a rough indication of the relative ease of reduction by this reagent of representative functional groups.[4] It has been established that borane is essentially inert toward nitro (both aliphatic and aromatic), sulfone, sulfide, disulfide, tosylates, and halogen (both alkyl and aryl). However, functional groups, such as ketone, esters, and nitriles, are reduced fairly rapidly by this reagent. Consequently, before undertaking to test the feasibility of selective reduction of carboxylic acid groups in the presence of such functional groups, it appeared desirable to establish the reactivities of these groups relative to the carboxylic acid group by means of competitive experiments. Accordingly, equimolar amounts of a carboxylic acid and a compound containing the functional group were allowed to compete for a limited quantity of borane in THF. The borane was added slowly to the reaction mixture, maintained at −15°. After 12 hr the mixture was hydrolyzed and analyzed by glpc using an internal standard.

The ease of reduction of carboxylic acids by this reagent is remarkable. Thus, the acid group is reduced completely in the presence of an ester (*n*-octanoic acid *vs.* ethyl hexanoate) and a nitrile (benzoic acid *vs.* benzonitrile). Even in the presence of a ketone, the carboxylic acid group is preferentially reduced (*n*-hexanoic acid *vs.* *p*-chloroacetophenone).

Representative results are summarized in Table II.

Synthetic Utility.—In order to establish the synthetic utility, product studies for the reduction of representative carboxylic acids were carried out. The rate and stoichiometric studies previously discussed indicated that for complete reduction 1 mol of borane is required per 1 mol of the carboxylic acid group. We established that simple acids, such as hexanoic acid, undergo rapid and quantitative reduction using only the stoichiometric quantity of borane. With carboxylic acids containing functional groups, such as halogen, nitro, etc., which are essentially inert toward borane, we utilized a modest excess of borane, 1.33 mol of BH_3 per 1 mol of RCO_2H (33% excess). The borane in THF was added slowly to the acid in THF at 0°. After the addition was completed, the reaction mixture was allowed to warm up to room temperature in the course of 1 hr (procedure A). In extending this procedure to the hydroxy acids and amino acids, the amount of borane used was increased by $^1/_3$ equiv for each equiv of active hydrogen present in the molecule. With amino acids an additional mol of borane per mol of acid was utilized to overcome the difficulties resulting from the formation of less reactive amine–borane complexes.

With the carboxylic acids containing more reactive functional groups, such as ester, keto, nitrile, etc., the precise stoichiometric amount of borane was utilized (1 mol of borane per mol of carboxylic acid group). The borane in THF was added drop by drop slowly to the acid in THF maintained at −15°. After the addition was completed, the mixture was allowed to warm up to room temperature and allowed to remain there overnight for a total reaction time of 12 hr (procedure B).

Simple carboxylic acids, such as *n*-hexanoic acid and benzoic acid, were converted into *n*-hexyl alcohol and benzyl alcohol in yields of 99 and 89%, respectively.

Even a sterically hindered carboxylic acid, such as 1-adamantanecarboxylic acid, was converted without difficulty into 1-adamantanemethanol in a yield of 95% (eq 2).

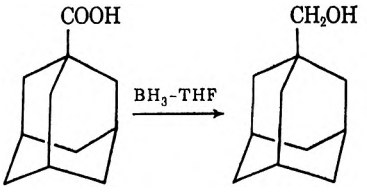
Dicarboxylic acids, such as adipic acid and phthalic acid, were converted into their corresponding diols in yields of 99 and 95%, respectively.

TABLE II

RELATIVE REACTIVITIES OF CARBOXYLIC ACIDS TO OTHER FUNCTIONAL GROUPS TOWARD BORANE IN TETRAHYDROFURAN[a]

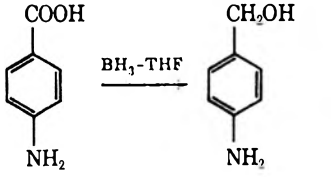
Expt	Registry no.	Compounds used	Mmol	Borane, mmol	Reaction products	Mol %
1	124-07-2	*n*-Octanoic acid	10.0		*n*-Octyl alcohol	50
				10.0	*n*-Octanoic acid[b]	0
	123-66-0	Ethyl hexanoate	10.0		*n*-Hexyl alcohol	<0.2
					Ethyl hexanoate	50
2		Benzoic acid	10.0		Benzyl alcohol	48
				10.0	Benzoic acid[b]	2
	100-47-0	Benzonitrile	10.0		Benzylamine[b]	<0.2
					Benzonitrile	49.8
3[c]	142-62-1	*n*-Hexanoic acid	15.0		*n*-Hexyl alcohol	40
				15.6	*n*-Hexanoic acid	10
	99-91-2	*p*-Chloroacetophenone	15.0		*p*-Chlorophenylethanol	7
					p-Chloroacetophenone	43

[a] Borane in THF was added to the THF solution of the compounds at −15°. [b] Not determined directly; estimated by difference. [c] Data taken from ref 4c.



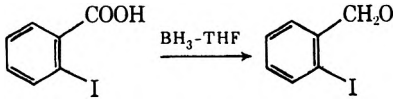
(2)

The presence of acidic or basic functional groups, such as the phenolic or amino group, did not interfere in the smooth reduction of the carboxylic acid group to the alcohol. Thus, salicylic acid was reduced to *o*-hydroxybenzyl alcohol in 92% yield. Similarly, *p*-aminobenzoic acid was converted to *p*-aminobenzyl alcohol in 80% yield (eq 3).



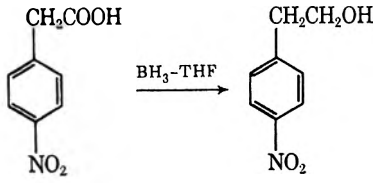
(3)

Carboxylic acids containing halogen substituents were quantitatively and cleanly converted into the corresponding halogen-substituted alcohols. For example, chloroacetic acid and 2-bromododecanoic acid were converted into 2-chloroethanol and 2-bromododecanol in essentially quantitative yield. Similarly, 11-bromoundecanoic acid was reduced to 11-bromoundecanol in a yield of 91%. Further, *o*-iodobenzoic acid and *o*-bromobenzoic acid were converted into *o*-iodobenzyl alcohol and *o*-bromobenzyl alcohol in yields of 92 and 93%, respectively (eq 4).



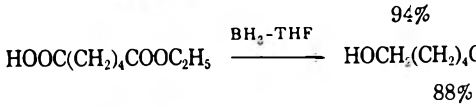
(4)

Finally, we examined *p*-nitrophenylacetic acid, adipic acid monoethyl ester, and *p*-cyanobenzoic acid to test the utility of this procedure for selective reductions. The products, 2-*p*-nitrophenylethanol, ethyl 6-hydroxyhexanoate, and *p*-cyanobenzyl alcohol, were all obtained in excellent yield, confirming the value of this procedure for selective reductions (eq 5–7). The results are summarized in Table III. Work-up procedures for the individual compounds are discussed in detail in the Experimental Section.



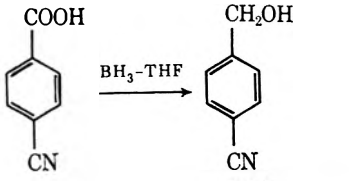
94%

(5)



88%

(6)



82%

(7)

Scope and Applicability.—Preliminary exploratory studies have established many unusual reducing characteristics of borane, quite different from those observed for aluminum hydride, lithium aluminum hydride, and its alkoxy derivatives. The reactivity of various functional groups toward borane decreases in the order carboxylic acids ≥ olefins > ketones > nitriles > epoxides > esters > acid chlorides. This is in marked contrast to the order of reactivity exhibited by these groups toward lithium aluminum hydride and its alkoxy derivatives (which are "basic"). This difference in behavior has been attributed to the Lewis acid character of borane.

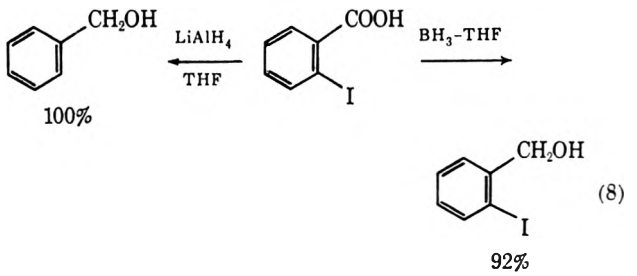
For achieving the conversion of the carboxylic acid group to the $-CH_2OH$ grouping, borane has three major advantages over the conventional reagents, such as lithium aluminum hydride, aluminum hydride, etc. First, the reaction is exceedingly rapid and quantitative, free of side products. Second, the stoichiometric quantity of borane is adequate to bring the reaction to completion in a reasonable time under mild conditions. Third, the unique reducing characteristics exhibited by borane enable the reaction to tolerate the presence of almost any other functional group, such as nitro, halogen (alkyl and aryl), nitrile, ester, epoxide, sulfone, sulfide, sulfoxide, tosylate, disulfide, etc. No other hydride reagent currently available exhibits such a unique selectivity.

In utilizing lithium aluminum hydride, the reduction of the carboxylic acids often requires conversion of the acid to other derivatives with more favorable properties, such as ester or acid chloride, to achieve smooth reduction. However, borane reduces even sterically hindered acids and polycarboxylic acids directly to the alcohol stage with exceptional ease in a single step.

p-Aminobenzoic acid has been reduced to *p*-aminobenzyl alcohol with lithium aluminum hydride in 20% yield,[6] whereas the use of borane has improved the yield to 80%. Indeed, borane has been the reagent of choice for such transformations involving amino acids to amino alcohols.[7]

Recently, borane has been successfully applied to the specific reduction of C-terminal carboxyl groups in model peptides and proteins without affecting the peptide linkage.[8] This opens up many major applications for borane in biological chemistry, such as specific modification of peptides and proteins. With some additional research in this area, it should be possible to develop this reaction as a general procedure for C-terminal determination in proteins.

Lithium aluminum hydride causes extensive hydrogenolysis of the carbon–halogen bonds in both aliphatic and aromatic substrates.[9] Thus the yield of 2-chloroethanol from chloroacetic acid utilizing lithium aluminum hydride has been reported to be 5%.[10] Use of aluminum hydride improved the yield to 69%.[3f] (Similarly, use of "mixed hydride" increased the yield of 3-bromopropanol from 3-bromopropionic acid to 50%.[3g]) In the present study, use of borane dramatically enhanced the yield of 2-chloroethanol to 100%. Similarly, iodo- and bromo-substituted benzoic acids on reduction with lithium aluminum hydride undergo extensive hydrogenolysis of the carbon–halogen bond. Particularly, it has been reported that *o*-iodobenzoic acid reacts with lithium aluminum hydride to yield only benzyl alcohol (dehalogenated product) and none of the desired product.[11] Use of borane in the present study yielded *o*-iodobenzyl alcohol in 92% yield and none of the dehalogenated product (eq 8).



(8)

The applicability of borane for such specific transformations is further evidenced by the successful selective reduction of the carboxyl function in the presence of ester or cyano group where both lithium aluminum hydride and aluminum hydride would fail. Indeed, since the original suggestion that it should be possible to reduce the carboxyl group selectively in the presence of an ester group,[4c] there have been a number of such applications of borane.[12]

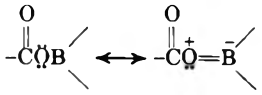
Finally, even carboxylic acids containing keto groups can be successfully reduced to the corresponding keto alcohols in reasonably good yield[13] (eq 9).

$$C_6H_5COCH_2CH_2COOH \xrightarrow[THF]{BH_3} \underset{60\%}{C_6H_5COCH_2CH_2CH_2OH} \quad (9)$$

Mechanism. Trialkoxylboroxine as Final Reduction Product.—Previous studies[4b,c] have established that the first step in these reactions involves formation of the triacyloxyborane[14] (eq 10). It is postulated that

$$3RCOOH + BH_3 \xrightarrow{\text{very fast}} (RCO)_3B + 3H_2 \quad (10)$$

the carbonyl group in triacyloxyborane must be "activated" as a consequence of resonance involving the boron atom and the lone pair on oxygen (eq 11).

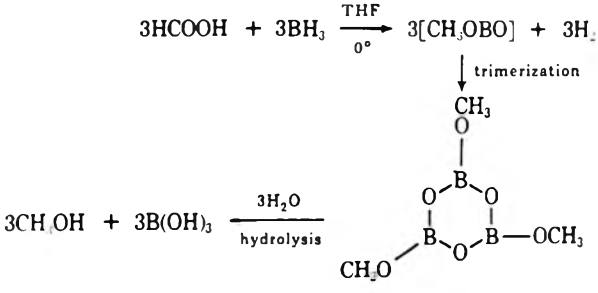


(11)

According to this interpretation, the carbonyl group in triacyloxyborane should resemble those in aldehydes and ketones, much more than those in derivatives such as esters, acid chlorides, etc.[15] Consequently, this moiety undergoes further reaction with borane.

The stoichiometry of the reaction suggests that the final product should be the trialkoxyboroxine. This substance should give the alcohol and boric acid on hydrolysis. Indeed, this proposal has now been confirmed. Reaction of 1 mol of formic acid with 1 mol of borane resulted in the formation of trimethoxyboroxine, isolated in 78% yield, and identified by its proton nmr (singlet at δ 3.59) (Scheme I).

SCHEME I



(6) A. P. Phillips and A. Maggiolo, *J. Org. Chem.*, **15**, 659 (1950).

(7) (a) M. Siddiqueullah, R. McGarth, L. C. Vining, F. Sala, and D. W. Westlake, *Can. J. Biochem.*, **45**, 1881 (1967); (b) A. V. Emes and L. C. Vining, *ibid.*, **48**, 613 (1970); (c) C. K. Wat, V. S. Malik, and L. C. Vining, *Can. J. Chem.*, **49**, 3653 (1971).

(8) (a) A. F. Rosenthal and M. Z. Atassi, *Biochim. Biophys. Acta*, **147**, 410 (1967); (b) M. Z. Atassi and A. F. Rosenthal, *Biochem. J.*, **111**, 593 (1969).

(9) (a) H. C. Brown and S. Krishnamurthy, *J. Org. Chem.*, **34**, 3918 (1969); (b) H. C. Brown and S. Krishnamurthy, manuscript in preparation.

(10) E. L. Eliel and J. T. Traxler, *J. Amer. Chem. Soc.*, **78**, 4049 (1956).

(11) G. J. Karabatsos and R. L. Shone, *J. Org. Chem.*, **33**, 619 (1968).

(12) (a) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965); (b) C. C. Schroff, W. S. Stewart, S. J. Uhm, and J. W. Wheeler, *ibid.*, **36**, 3356 (1971); (c) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, Part II, 541 (1966); (d) R. A. Firestone, E. E. Harris, and W. Reuter, *Tetrahedron*, **23**, 943 (1967); (e) S. Hagishita and K. Kuriyama, *ibid.*, **28**, 1435 (1972).

(13) B. C. Subba Rao and G. P. Thakar, *Current Science*, **32**, 404 (1963).

(14) Hydrogen evolution is instantaneous and quantitative even at −20°, indicating the remarkable ease with which triacyloxyboranes are formed. Recently, it has been reported that the triaryloxyboranes initially formed can undergo dismutation to acid anhydrides and oxybisdiacyloxyboranes and the resulting dismuted products undergo further reduction with borane–THF to the alcohol stage; see A. Pelter, M. G. Hutchings, T. E. Levitt, and K. Smith, *Chem. Commun.*, 347 (1970). However, the rates of reduction of carboxylic acids observed in the present study are far faster than the rates of dismutation for triacyloxyboranes in the majority of instances. This indicates that dismutation need not be an important factor in the presence of excess borane–THF.

(15) A detailed study of the unusual chemistry of triacyloxyboranes is underway with Mr. Thomas P. Stocky.

TABLE III

PRODUCTS OF REDUCTION OF CARBOXYLIC ACIDS WITH BORANE IN TETRAHYDROFURAN[a]

Compd	Procedure	Time, hr	Hydride/compd	Product	Yield,[b] %
Benzoic acid	A	1.0	4.0	Benzyl alcohol	89
1-Adamantanecarboxylic acid	A	1.0	4.0	1-Adamantanemethanol	95
Adipic acid	A	6.0	7.0	1,6-Hexanediol	100
Phthalic acid	A	6.0	7.0	Phthalyl alcohol	95
Salicylic acid	A	3.0	5.0	*o*-Hydroxybenzyl alcohol	92
p-Aminobenzoic acid	A	4.5	8.0	*p*-Aminobenzyl alcohol	80
Chloracetic acid	A	0.5	4.0	Chloroethanol	100[c]
2-Bromododecanoic acid	A	1.0	4.0	2-Bromododecanol	92
11-Bromoundecanoic acid	A	1.0	4.0	11-Bromoundecanol	91
o-Iodobenzoic acid	A	1.0	4.0	*o*-Iodobenzyl alcohol	92
o-Bromobenzoic acid	A	1.0	4.0	*o*-Bromobenzyl alcohol	93
p-Nitrophenylacetic acid	A	2.0	4.0	2-*p*-Nitrophenyl ethanol	94
Adipic acid monoethyl ester	B	16.0	3.0	Ethyl 6-hydroxyhexanoate	88
p-Cyanobenzoic acid	B	12.0	3.0	*p*-Cyanobenzyl alcohol	82

[a] Reactions were carried out on a 25-mmol scale. [b] Unless otherwise indicated, the reported yields are isolated yields. [c] Determined by glpc.

Conclusions

The facile reaction of borane with olefins led to the discovery of hydroboration reaction and the exploration of the remarkable chemistry of organoboranes.[16] The rapid and quantitative reduction of amides to amines by borane resulted in numerous applications of this procedure for such conversions in medicinal, pharmaceutical, and biological chemistry.[17] The subject of the present study, the selective reduction of carboxylic acids in the presence of almost any functional group, provides yet another major application for the reagent, borane–THF.

Experimental Section

Materials.—Tetrahydrofuran was dried with excess lithium aluminum hydride, distilled under nitrogen, and stored over 5-Å molecular sieves. Borane solution in THF was prepared from sodium borohydride and boron trifluoride etherate.[18,19] The borane–THF solution was standardized by hydrolyzing a known aliquot of the solution with glycerine–water–THF mixture and measuring the hydrogen evolved. For most experiments the concentration was approximately 2 *M* in BH_3.

Carboxylic acids used were the commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. In all of the cases, physical constants agreed satisfactorily with constants in the literature.

All glassware was dried thoroughly in a drying oven and cooled under a dry stream of nitrogen. All reduction experiments were carried out under a dry nitrogen atmosphere. Hypodermic syringes were used to transfer the solution.

Rates of Reduction of Carboxylic Acids.—Reduction of benzoic acid is representative. A 100-ml flask was dried in an oven and cooled down in a dry nitrogen atmosphere. The flask was equipped with a rubber syringe cap, a magnetic stirring bar, and a reflux condenser, connected to a gas buret. The flask was immersed in a water bath at room temperature (*ca.* 25°) and 6.6 ml (6.6 mmol) of 1.0 *M* borane solution in THF was introduced into the reaction flask, followed by 9.4 ml of THF. Then 4 mmol of benzoic acid in 4 ml of THF was introduced slowly. Now the reaction mixture was 0.33 *M* in BH_3 and 0.2 *M* in acid. Hydrogen evolution, 4 mmol, was almost instantaneous, which corresponds to 1 mmol of hydrogen evolution per mmol of the acid. The mixture was stirred well.

At the end of 30 min, a 5.0-ml aliquot of the reaction mixture was removed with a hypodermic syringe and injected into a hydrolyzing mixture in a 1:1 mixture of 2 *N* sulfuric acid and ethylene glycol. The hydrogen evolved was measured with a gas buret. This indicated that 2.99 mmol of hydride has reacted per mmol of the acid, indicating the completion of the reaction. An aliquot taken at the end of 1 hr showed no further hydride utilization.

The results for other acids are summarized in Table I.

Reduction of Hexanoic Acid with a Stoichiometric Quantity of Borane in THF.—A clean, dry 25-ml flask, equipped with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was cooled down with nitrogen. Then 5 ml (10 mmol) of a 2 *M* solution of hexanoic acid was injected into the reaction flask, followed by 1 ml of *n*-dodecane as the internal standard. The flask was immersed in an ice bath and cooled to 0°. Then 4.3 ml (10 mmol) of 2.33 *M* borane solution in THF was added slowly. There was evolved 260 ml (10.1 mmol) of hydrogen during the course of the addition. The ice bath was removed and replaced by a water bath (*ca.* 25°). At the end of 0.5 hr, 1 ml of the reaction mixture was hydrolyzed with water and analyzed by glpc on a 5% Carbowax 20M column, 6 ft × 0.125 in., indicating the presence of 97% *n*-hexyl alcohol. At the end of 1 hr a 99% yield of *n*-hexyl alcohol was realized. The reaction mixture was devoid of any residual hydride.

A similar study was made utilizing 3.3% of excess borane. *n*-Hexyl alcohol was formed in 100% yield in 30 min. Hydrolysis of the reaction mixture with water indicated the presence of 2.5 mmol of residual hydride.

Competitive Experiments. Reaction of *n*-Octanoic Acid and Ethyl Hexanoate with a Limited Quantity of Borane in THF.—The experimental set-up was the same as in the previous experiments. To the reaction flask was added 5 ml (10 mmol) of a 2 *M* solution of octanoic acid in THF, followed by 5 ml (10 mmol) of a 2 *M* solution of ethyl hexanoate in THF; 1 ml of *n*-dodecane was added to serve as an internal standard. The mixture was stirred well and a minute sample was withdrawn and analyzed by glpc. The mixture was cooled to −15° using an ice–salt bath. Then 4.3 ml (10 mmol) of a 2.33 *M* solution of BH_3 was added slowly, drop by drop, over a period of 20 min. There was evolved 9.9 mmol of hydrogen during the course of addition (hydrogen evolution was instantaneous even at −15°). The mixture was stirred for 12 hr, allowing it to warm up to room temperature slowly. The mixture was hydrolyzed with water. There was observed no hydrogen evolution, indicating the complete utilization of borane. The aqueous phase was saturated with anhydrous potassium carbonate. Gas chromatographic examination of the ethereal layer indicated the presence of 10 mmol of *n*-octyl alcohol, traces of *n*-hexyl alcohol, and 9.9 mmol of ethyl hexanoate (recovered as unreacted).

The results are summarized in Table II.

General Preparative Procedures for the Reduction of Carboxylic Acids to Alcohols.—A series of carboxylic acids of representative structural features was reduced on a 25-mmol scale and the products were isolated to establish the synthetic utility of the

(16) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972, pp 255–446.

(17) (a) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964); (b) *J. Org. Chem.*, **38**, 912 (1973), and references cited therein.

(18) G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963); H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **90**, 2915 (1968).

(19) One molar solution of borane in tetrahydrofuran is now commercially available from Aldrich Chemical Co., Milwaukee, Wisconsin.

reaction. (Depending upon the other substituents present, the time required may require an increase or decrease.)

A. Sterically Hindered Acids.—The following procedure for the reduction of 1-adamantane carboxylic acid is representative (procedure A). An oven-dried 100-ml flask with a side arm fitted with a silicone rubber stopple, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler was cooled down to room temperature under dry nitrogen. Then 4.57 g (25 mmol) of 1-adamantanecarboxylic acid dissolved in 10 ml of THF was placed into the reaction flask. The flask was immersed in an ice bath and cooled to 0°. To this 14.3 ml (33.3 mmol) of 2.33 *M* borane solution in THF was slowly added during a 15-min period. There was evolved 24.5 mmol of hydrogen. The ice bath was replaced by a 25° bath and the mixture was stirred well. At the end of 1 hr, analysis of a minute aliquot of the reaction mixture indicated the completion of the reaction. Excess hydride was carefully destroyed with 10 ml of a 1:1 mixture of THF and water (620 ml of H_2 was evolved, equivalent to 24.5 mmol of residual hydride). The aqueous phase was saturated with anhydrous potassium carbonate. The THF layer was separated and the aqueous layer was extracted with three 20-ml portions of ether. The combined organic phase was dried over magnesium sulfate. The solvents were removed by careful distillation to yield 3.926 g (95%) of 1-adamantanemethanol as a white solid, mp 114.5–115° (lit.[20] mp 115°).

B. Dicarboxylic Acids.—Reduction of adipic acid to 1,6-hexanediol is representative of the general procedure utilized. The experimental set-up was the same as in the previous experiments. A typical reaction setup was assembled and 3.65 g (25 mmol) of adipic acid was placed into the reaction flask, followed by 15 ml of THF. The resulting slurry was cooled to 0° in an ice bath. To this 27 ml (64.5 mmol) of 2.39 *M* borane solution in THF was added dropwise. There was evolved 50.9 mmol of hydrogen. The resulting mixture was stirred for 6 hr at 25°. The excess hydride was destroyed carefully with 15 ml of a 1:1 mixture of THF and water. The aqueous phase was saturated with 8–10 g of potassium carbonate (this is highly essential to drive the water-soluble diol from the aqueous to the THF phase). The THF layer was separated. The aqueous phase was extracted with two 15-ml THF portions and the combined THF extract was dried over magnesium sulfate. Solvent was removed on a rotary evaporator to yield 3.0 g (100%) of pure 1,6-hexanediol, mp 41–42° (lit.[21] mp 41–42°).

Similarly, phthalic acid was converted into the corresponding diol in a yield of 95%.

C. Phenolic Acids.—The following reduction of salicylic acid to *o*-hydroxybenzyl alcohol illustrates the practicality of utilizing borane-THF for such transformations. A typical reaction setup was assembled. To 3.45 g (25 mmol) of salicylic acid dissolved in 10 ml of THF at 0°, 18 ml (42 mmol) of 2.33 *M* borane solution in THF was added dropwise. There was evolved 49.8 mmol of hydrogen. The resulting clear mixture was stirred for 3 hr at 25°, at the end of which analysis of a small aliquot of the reaction mixture indicated the completion of the reaction. Excess hydride was destroyed with water, and the mixture was treated with 30 ml of 3 *N* sodium hydroxide and stirred well for 15 min to form the sodium salt of the phenol. The aqueous phase was separated, and the volatile solvents of the THF phase were removed on a rotary evaporator. The residue of the THF phase was combined with the aqueous phase. The basic aqueous phase was cooled to 0°, carefully neutralized with dilute acetic acid to a pH of 6.7, and extracted six times with 20-ml portions of ether. The ether extract was dried over magnesium sulfate. Stripping off ether yielded 2.84 g (92%) of *o*-hydroxybenzyl alcohol as white plates, mp 78–80°. The material was essentially pure except for a small amount of acetic acid present as the impurity. Recrystallization from boiling benzene yielded 1.97 g as white plates, mp 85–86°; concentration of the mother liquor yielded further crystals (second crop), 0.47 g, mp 82–84°. Yield after recrystallization was 79%.

A variety of work-up procedures, such as the use of methanol or mannitol for removing boric acid as borate ester, and the use of 5% sodium bicarbonate solution instead of the usual potassium carbonate, were examined. They were all less satisfactory (yields ranged from 50 to 66%).

D. Amino Acids.—The following general procedure illustrated for the reduction of *p*-aminobenzoic acid is suggested for the reduction of amino acids. *p*-Aminobenzoic acid (freshly recrystallized from hot water at 80°, mp 187–187.5°), 3.43 g (25 mmol) dissolved in 12.5 ml of THF, cooled to 0°, was treated with 31.9 ml (75 mmol) of 2.35 *M* borane solution in THF. The resulting mixture, which was colorless and homogeneous, was stirred at 25° for 4.5 hr. Then the mixture was cooled to 0° and 15 ml of 3 *N* sodium hydroxide was added to destroy excess hydride and to hydrolyze the amine–borane complex, which required 12 hr at 25°. The pH of the resulting solution was adjusted to 11.0 by adding a few pellets of sodium hydroxide. The aqueous phase was saturated with potassium carbonate, the THF phase was separated, and the aqueous phase was extracted with five 30-ml portions of ether. The combined organic extracts were dried over anhydrous sodium sulfate. Stripping off the solvents on a rotary evaporator gave 2.46 g (80%) of *p*-aminobenzyl alcohol as pale brownish crystals, mp 60–63° (lit.[6] mp 63–64°).

E. Selective Reduction of Acid in the Presence of Halogen Substituents.—The following procedure for the reduction of *o*-iodobenzoic acid is representative. The experimental setup was the same as in the previous experiments. *o*-Iodobenzoic acid, 6.2 g (25 mmol), was placed into the flask, and the flask was immersed in an ice bath and cooled to 0°. Then 14.5 ml (33.3 mmol) of borane–THF was slowly added over a period of 15 min and the solution was vigorously stirred for an additional period of 1 hr, by which time reaction was essentially complete, as indicated by the residual hydride analysis. Excess hydride (24.7 mmol) was carefully destroyed with 15 ml of a 1:1 mixture of THF and water and the aqueous phase was saturated with 5–6 g of potassium carbonate. The THF layer was separated and the aqueous phase was extracted four times with 25-ml portions of ether. The combined organic extracts were dried over magnesium sulfate. Glpc examination of the organic extract revealed the absence of any benzyl alcohol (dehalogenated product). Removal of the solvents gave 5.34 g (92%) of *o*-iodobenzyl alcohol as the white solid, mp 89–90° (lit.[22] mp 91°). A small portion was recrystallized from boiling petroleum ether (bp 30–60°) as needles: mp 90°; nmr ($CDCl_3$, TMS) δ 2.58 (s, 1, -OH), 4.72 (s, 2, $-CH_2-$), 7.0–8.0 (m, 4, aromatic).

F. Selective Reduction in the Presence of the Nitro Substituent.—Since both aliphatic and aromatic nitro groups are essentially inert toward borane, use of excess borane offers no disadvantages. Reduction of *p*-nitrophenylacetic acid to 2-*p*-nitrophenylethanol is representative. To a solution of *p*-nitrophenylacetic acid, 4.53 g (25 mmol) dissolved in 12.5 ml of THF, 14.2 ml (33.3 mmol) of borane in THF was slowly added, evolving 26 mmol of hydrogen. After vigorous stirring for 2 hr at room temperature, the excess hydride (23 mmol) was carefully destroyed with water. The mixture was worked up as in the previous experiments. The solvents were removed in a rotary evaporator to yield 2-*p*-nitrophenylethanol, 3.94 g (94%), as a pale yellow solid: mp 63–64° (lit.[23] mp 63–64°); nmr ($CDCl_3$, TMS) δ 2.7 (s, 1, -OH), 3.0 (t, 2, CCH_2C), 3.95 (t, 2, $-CH_2-$), 7.8 (q, 4, aromatic).

G. Selective Reduction in the Presence of the Ester Group.—Since the esters of aliphatic acids are reduced at a reasonable rate by borane in THF, only a stoichiometric quantity of borane should be employed (procedure B). The procedure described below for the reduction of adipic acid monoethyl ester illustrates the practicality of using BH_3–THF for such conversions. A typical reaction setup was assembled. Into the reaction flask was placed 4.36 g (25 mmol) of adipic acid monoethyl ester (recrystallized from petroleum ether, mp 28–29°), followed by 12.5 ml of THF. The flask was immersed in an ice–salt bath and cooled to −18°. Then 10.5 ml (25 mmol) of 2.39 *M* borane solution in THF was slowly added dropwise over a period of 19 min. There was evolved 25.3 mmol of hydrogen. The resulting clear reaction mixture was stirred well and the ice–salt bath was allowed to equilibrate slowly to room temperature during a 16-hr period. The reaction mixture was hydrolyzed with 15 ml of water at 0°. No hydrogen evolution was observed, indicating the complete utilization of the borane. The aqueous phase was treated with 6 g of potassium carbonate and the THF phase was separated. The aqueous phase was extracted three times with a total of 150 ml of ether. The combined ether extract was washed with 30 ml of a saturated solution of sodium chloride and dried over magnesium sulfate. Removal of the solvent on a rotary

(20) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

(21) W. A. Lazier, J. W. Hull, and W. J. Amend, *Org. Syn.*, **19**, 48 (1939).

(22) R. G. R. Bacon and W. S. Lindsay, *J. Chem. Soc.*, 1375 (1958).

(23) P. S. Pishchimuka, *J. Russ. Phys. Chem. Soc.*, **48**, 1 (1916).

evaporatory yielded 3.5 g (88%) of ethyl 6-hydroxyhexanoate as a colorless liquid, n^{20}D 1.4374. Distillation yielded 2.98 g (75%) of the material: bp 79° (0.7 mm); n^{20}D 1.4375 [lit.[24] bp 134° (15 mm)]; ir (neat) 3150–3750 (-OH), 1745 cm^{-1} (>C=O); nmr (CCl_4, TMS) δ 1.27 (t, 3, $-CH_3$), 1.0–2.0 [m, 6, $-(CH_2)_3-$], 2.28 [t, 2, $CH_2(C=O)O$], 3.53 (t, 2, $HOCH_2-$), 3.75 (s, 1, -OH), 4.17 (q, 2, $O=COCH_2-$).

H. Selective Reduction in the Presence of the Cyano Group.—Reduction of *p*-cyanobenzoic acid is representative. The experimental setup and the reaction conditions were the same as in the previous experiments (procedure B). *p*-Cyanobenzoic acid, 3.68 g (25 mmol), was suspended in 30 ml of THF (the acid has low solubility in THF) and to this at −15° 10.5 ml (25 mmol) of borane in THF was slowly added dropwise over a period of 20 min. The resulting mixture was stirred well and the ice–salt bath was allowed to equilibrate to room temperature (*ca.* 25°) slowly over a 12-hr period. Then the reaction mixture was worked up as described in the reduction of adipic acid monoethyl ester. Stripping off the solvent gave a pale yellowish, viscous oil. Distillation *in vacuo* gave 2.73 g (82%) of *p*-cyanobenzyl alcohol as a white solid: bp 108–109° (0.35 mm); mp 39–41° [lit.[25] bp 203° (53 mm), mp 41–42°]; nmr ($CDCl_3$, TMS) δ 3.6 (s, 1, -OH), 4.77 (s, 2, $-CH_2$), 7.6 (q, 4, aromatic).

(24) R. Robinson and L. H. Smith, *J. Chem. Soc.*, 371 (1937).

(25) J. N. Ashley, H. J. Barber, A. J. Ewins, G. Newbery, and A. D. H. Self, *ibid.*, 103 (1942).

Reduction of Formic Acid with Borane in THF. Isolation of Trimethoxyboroxine.—A typical reaction setup was assembled. Formic acid, 1.1412 g (24.8 mmol) dissolved in 5 ml of THF, was placed in the reaction flask. The flask was immersed in an ice bath and cooled to 0°. To this solution was added dropwise with stirring 10.4 ml (24.8 mmol) of borane in THF. There was evolved 23.6 mmol of hydrogen. The mixture was stirred vigorously for 1.5 hr at 25°. Analysis of a small aliquot of the reaction mixture indicated the absence of any residual hydride. Most of the THF was removed by distillation under nitrogen, yielding a colorless liquid, 1.58 g. Nmr examination of this material indicated a sharp singlet at δ 3.59 (from TMS) characteristic of trimethoxyboroxine (trimethoxyboroxine spectrum in Sadtler No. 9157 exhibits a sharp singlet at δ 3.59); methyl borate was found to exhibit a sharp singlet at δ 3.43 (Sadtler Spectrum No. 10916 for methyl borate exhibits a singlet at δ 3.43). The mixture had 27% of the THF by weight as determined by the integration of the protons of THF. Correcting for the amount of THF, the yield of the boroxine was 78%.

Registry No.—Borane, 13283-31-3; *o*-hydroxybenzyl alcohol, 90-01-7; *o*-iodobenzoic acid, 619-58-9; *o*-iodobenzyl alcohol, 5159-41-1; *p*-nitrophenylacetic acid, 104-03-0; *p*-nitrophenylethanol, 100-27-6; adipic acid monomethyl ester, 627-91-8; ethyl 6-hydroxyhexanoate, 5299-60-5; *p*-cyanobenzoic acid, 619-65-8; *p*-cyanobenzyl alcohol, 874-89-5; formic acid, 64-18-6; trimethoxyboroxine, 102-24-9.

Solvolyses of Axial and Equatorial Epimers of *trans*-2-Decalyl Tosylate and Their 6-Keto and 6-Keto $\Delta^{5(10)}$ Derivatives[1]

HIROSHI TANIDA,* SADAO YAMAMOTO, AND KEN'ICHI TAKEDA

Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received February 22, 1973

The tosylates of *trans*-2(a and e)-decalols (**1a**-OTs and **1e**-OTs), 6-keto-*trans*-2(a and e)-decalols (**2a**-OTs and **2e**-OTs), and 6-keto-$\Delta^{5(10)}$-*trans*-2(a and e)-decalols (**3a**-OTs and **3e**-OTs) were solvolyzed in trifluoroacetic, formic, and acetic acids and ethanol. Rates in all the solvents and products in acetic acid were investigated. Product patterns from the axial and equatorial 2 tosylates were similar to those reported for the counterparts in the 1 system. Axial to equatorial relative reactivities of the tosylates in the 1 and 2 systems vary insignificantly with solvents being in the range of 3.0 to 5.0 at 50°. Those in the 3 system change from 0.89 in acetic acid and 0.90 in formic acid to 1.29 in ethanol. The greatly reduced ratios for the 3 system in the acids are ascribed to the fact that, while the rates for the axial tosylate are normal, those for the equatorial tosylate are enhanced owing to participation of the 5(10) double bond. The acetates produced from **3e**-OTs show an unusually low inversion–retention ratio, which is compatible with such participation.

Since the *trans*-decalin system is incapable of undergoing chair inversion, it is one of the models most conveniently used for the study of the relationship between conformation and reactivity of cyclohexane derivatives.[2] The higher reactivity of the axial over the equatorial tosylate in conformationally fixed cyclohexane derivatives has been investigated by several workers.[3-9] In the study of solvolyses of *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates, Winstein and Holness suggested steric acceleration arising from the axial conformation in the initial ground state.[3] Baker and his associates[7,8b] proposed the importance of participation of the β-axial hydrogen in the transition state in solvents of low nucleophilicity and high ionizing power. As an extension of our previous work,[10] we carried out the determination of solvolysis rates and products of the axial and equatorial epimers of *trans*-2-decalyl tosylate (**1**-OTs), 6-keto-*trans*-2-decalyl tosylate (**2**-OTs), and 6-keto-$\Delta^{5(10)}$-*trans*-decalyl tosylate (**3**-OTs) in trifluoroacetic, formic, and acetic acids and ethanol. Effects of solvents and the 5,10 double bond upon the relative reactivity of the epimeric tosylates are reported.[11]

Results

Preparations.—The axial and equatorial epimers of 6-keto-$\Delta^{5(10)}$-*trans*-decalin-2-ol (**3e**-OH, **3a**-OH) were

(1) Presented in part at the 23rd Symposium on Organic Reaction Mechanisms, Kobe, Japan, Oct 1972.

(2) (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 8; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morison, "Conformational Analysis," Interscience, New York, N. Y., 1965, Chapter 2.

(3) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

(4) V. J. Shiner, Jr., and J. G. Jewett, *ibid.*, **87**, 1382, 1383 (1965).

(5) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southan, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).

(6) K. Okamoto, S. Saito, and H. Shingu, *Bull. Chem. Soc. Jap.*, **42**, 3288, 3298 (1969).

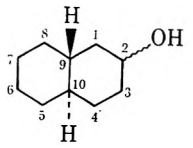
(7) R. Baker, J. Hudec, and K. L. Rabone, *Chem. Commun.*, 197 (1969).

(8) (a) R. Baker, J. Hudec, and K. L. Rabone, *J. Chem. Soc. B*, 1446 (1970); (b) R. Baker and K. L. Rabone, *ibid.*, 1598 (1970).

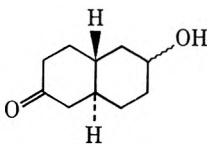
(9) I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, **81**, 3420 (1959).

(10) H. Tanida, S. Yamamoto, and K. Takeda, *J. Org. Chem.*, **38**, 2077 (1973).

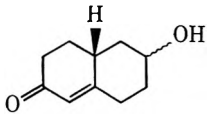
(11) All the compounds used in the present study are *dl* mixtures. For convenience, only one enantiomorph is shown in the figures and according to steroid convention, the hydrogen at C-9 is assigned the β orientation. The same convention was used in the previous work.[10]



1e-OH (equatorial OH)
1a-OH (axial OH)



2e-OH
2a-OH



3e-OH
3a-OH

synthesized from 6-methoxy-2-tetralol[12] by the procedure of Clarke and Martin.[13] The epimers of *trans*-decalin-2-ols (**1e**-OH, **1a**-OH) and 6-keto-*trans*-decalin-2-ols (**2e**-OH, **2a**-OH) were obtained from **3e**-OH and **3a**-OH by the methods described in the literatures.[13,14] Configurations at C_2 of these alcohols were determined by infrared and nmr spectra and vpc analyses.[14b] Each of the alcohols (**1**–**3**) used in the present study was shown by vpc to be over 99.0% pure. Treatment of the alcohols with *p*-toluenesulfonyl chloride in pyridine led to the tosylates (**1**-OTs–**3**-OTs), whose nmr spectral parameters and other physical constants are given in the Experimental Section.

Rates.—Acetolysis, formolysis, and trifluoroacetolysis were performed in buffered media (in the presence of 1.1 equiv of sodium salt of the respective acid), but ethanolysis was carried out without addition of base except in the case of **3**-OTs. Rates of formolysis, acetolysis, and ethanolysis were determined at several temperatures following the procedure described by Winstein and coworkers[10,15] using a potentiometer. Theoretical infinity values were obtained in all runs after about 10 half-lives at the reaction temperature. In each experiment the reaction was followed to 80% completion. The rates of trifluoroacetolysis were measured by a modification[10,16] of the spectrophotometric method advanced by Peterson and coworkers.[17] In trifluoroacetolysis the reaction was followed to 50% completion. The first-order rate constants were calculated by means of the least squares method with a FACOM 270-20 computer, the correlation coefficients of all the plots being 0.999 ± 0.001.

(12) W. Nagata, and T. Terasawa, *Chem. Pharm. Bull*, **9**, 267 (1961).
(13) R. L. Clarke and C. M. Martin, *J. Amer. Chem. Soc.*, **81**, 5716 (1959).
(14) (a) K. Takeda, and S. Yamamoto, *Chem. Pharm. Bull.*, **20**, 314 (1972); (b) *ibid.*, **20**, 1125 (1972).
(15) S. Winstein, C. Hanson, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).
(16) Since the obtained infinity titers did not correspond to the theoretical values, the rates of trifluoroacetolysis were determined from the plots against time of log c_{OT_s}, which were calculated according to the following equations,

$$A = c_{OT_s}\epsilon_{OT_s} + c_{PS}\epsilon_{PS} \quad (1)$$

$$c^{\circ}_{OT_s} = c_{OT_s} + c_{PS} \quad (2)$$

$$c_{OT_s} = \frac{A - c_{OT_s}\epsilon_{PS}}{\epsilon_{OT_s} - \epsilon_{PS}} \quad (3)$$

where A is the absorbance at 273.2 mμ of an actual sample, $c^{\circ}_{OT_s}$ is the initial concentration (moles/liter) of tosylate, c_{OT_s} and c_{PS} are the concentration of tosylate and *p*-toluenesulfonic acid, respectively, and ϵ_{OT_s} and ϵ_{PS} are the molar extinction coefficients at 273.2 mμ of tosylate and *p*-toluenesulfonic acid, respectively. See ref 10.
(17) P. E. Peterson, R. E. Kelly, Jr., R. Belloli, and K. A. Sipp, *J. Amer. Chem. Soc.*, **87**, 5169 (1965).

The rate constants and activation parameters thus obtained are listed in Table I.

Acetolysis Products—A detailed analysis of solvolysis products from axial and equatorial *trans*-2-decalyl tosylates and some related tosylates has been reported;[18] so the present work deals with the products from the four tosylates, **2e**-, **2a**-, **3e**-, and **3a**-OTs. The tosylates were solvolyzed in glacial acetic acid buffered with 1.1 equiv of sodium acetate at 100.0° for about 10 half-lives. Olefins (products of elimination) and acetates (products of substitution) were separated by elution chromatography. The acetate fractions were identified by comparison of retention times on vpc with those of authentic samples,[14] and their yields were determined by vpc with internal standards. The olefin fractions were shown to be composed of the Δ^1 olefin and Δ^2 olefin by nmr and mass spectra and vpc analyses. However, these two olefins could not be completely separated by vpc analyses using several kinds of columns. Very small amounts of unknown products were observed but not identified. The results are summarized in Table II.

Discussion

The axial tosylate shows a higher reactivity than the equatorial epimer in the solvolysis of conformationally fixed cyclohexyl derivatives, although evidence has been presented that the tosylates react by different transition states.[18,19] The relative rate of the axial (cis) to the equatorial (trans) 4-*tert*-butylcyclohexyl tosylate at 50° is 3.90, 3.24, and 3.58 in ethanol, acetic acid, and formic acid, respectively.[3] That of *trans*-2-decalyl tosylate epimers (1-OTs) has been reported as 2.86[8b] (or 3.1[9]) at 75° in acetic acid and 5.55[8b] at 25° in formic acid. The axial–equatorial rate ratios (k_{ax}/k_{eq}) determined in the present work are listed in Table III. It is seen that the ratios for **1**-OTs are relatively insensitive to change in solvent from trifluoroacetic acid of high ionizing power and low nucleophilicity to formic acid, acetic acid, and then ethanol of low ionizing power and high nucleophilicity. These data would qualify Baker's suggestion[8b] that the extent of hydrogen participation is reflected in such changes in rate ratio, a conclusion which he arrived at from data in only two solvents, acetic and formic acids. From Table I, the differences in activation enthalpies and entropies between the axial and equatorial tosylates of **1**-OTs are −1.6 kcal/mol and −2.2 eu in trifluoroacetolysis, −2.0 kcal/mol and −3.0 eu in formolysis, −0.2 kcal/mol and 1.5 eu in acetolysis, and −1.4 kcal/mol and −1.4 eu in ethanolysis, respectively. The higher rate of the axial over the equatorial tosylate is thus attributable to the favorable difference in activation enthalpy, despite the unfavorable difference in activation entropy (except the entropy difference in acetolysis).

It was recently demonstrated that acetolysis of the monocyclic, conformationally unfixed cyclohexyl tosylate to form the substitution products occurs almost entirely by an inversion mechanism without rearrange-

(18) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc. B*, 355 (1968).
(19) (a) V. J. Shiner, Jr., and J. G. Jewett, *J. Amer. Chem. Soc.*, **86**, 945 (1964); (b) *ibid.*, **87**, 1382, 1383 (1965).

TABLE I

RATES AND ACTIVATION PARAMETERS IN SOLVOLYSES[a,b]

Compd	Solvent	Temp, °C	k_1, sec^{-1} [c]	$\Delta H^{\pm}$, kcal/mol[d]	$\Delta S^{\pm}$, eu[d]
1e-OTs	CF_3COOH[e]	25.0	1.19×10^{-4}	21.2 ± 0.2	−5.5 ± 0.6
		50.0	2.04×10^{-3}		
	HCOOH[f]	25.0	$(1.52 \pm 0.02) \times 10^{-5}$	24.4 ± 0.2	1.1 ± 0.5
		50.0	$(4.08 \pm 0.04) \times 10^{-4}$		
	CH_3COOH[e]	25.0	3.80×10^{-8}	26.7 ± 0.1	−2.8 ± 0.2
		50.0	1.35×10^{-6}		
	C_2H_5OH[e]	25.0	2.43×10^{-8}	25.2 ± 0.3	−8.8 ± 0.8
		50.0	7.26×10^{-7}		
1a-OTs	CF_3COOH	0.0	$(2.37 \pm 0.08) \times 10^{-5}$	19.6 ± 0.3	−7.7 ± 0.9
		15.0	$(1.59 \pm 0.02) \times 10^{-4}$		
		25.0	$(5.40 \pm 0.17) \times 10^{-4}$		
		25.0[b]	5.32×10^{-4}		
		50.0[b]	7.49×10^{-3}		
	HCOOH[f]	25.0	$(8.44 \pm 0.08) \times 10^{-5}$	22.4 ± 0.4	−1.9 ± 1.3
		50.0	$(1.78 \pm 0.08) \times 10^{-3}$		
	CH_3COOH	25.0[b]	1.18×10^{-7}	26.5 ± 0.1	−1.3 ± 0.3
		50.0[b]	4.07×10^{-6}		
		67.4	$(3.55 \pm 0.10) \times 10^{-5}$		
		80.1	$(1.49 \pm 0.07) \times 10^{-4}$		
		95.0	$(7.23 \pm 0.31) \times 10^{-4}$		
	C_2H_5OH	25.0[b]	1.30×10^{-7}	23.8 ± 0.5	−10.2 ± 1.2
		50.0[b]	3.16×10^{-6}		
		76.6	$(5.64 \pm 0.24) \times 10^{-5}$		
		90.0	$(2.16 \pm 0.04) \times 10^{-4}$		
		105.0	$(7.98 \pm 0.25) \times 10^{-4}$		
2e-OTs	CF_3COOH[e]	25.0	1.52×10^{-6}	22.7 ± 0.1	−8.9 ± 0.2
		50.0	3.20×10^{-5}		
	HCOOH	25.0[b]	1.57×10^{-6}	24.2	−3.8
		50.0	$(4.03 \pm 0.05) \times 10^{-5}$		
		70.0	$(3.86 \pm 0.17) \times 10^{-5}$		
	CH_3COOH[e]	25.0	4.73×10^{-9}	28.1 ± 0.3	−2.3 ± 0.9
		50.0	2.01×10^{-7}		
	C_2H_5OH[e]	25.0	1.81×10^{-8}	24.1 ± 0.06	−13.2 ± 0.1
		50.0	4.56×10^{-7}		
2a-OTs	CF_3COOH	25.0[b]	4.23×10^{-6}	22.7 ± 0.2	−7.0 ± 0.6
		40.0	$(2.76 \pm 0.06) \times 10^{-5}$		
		50.0	$(9.04 \pm 0.23) \times 10^{-5}$		
		50.0[b]	8.90×10^{-5}		
		70.0	$(7.38 \pm 0.06) \times 10^{-4}$		
	HCOOH	25.0[b]	5.03×10^{-6}	23.9	−2.7
		50.0	$(1.23 \pm 0.05) \times 10^{-4}$		
		70.0	$(1.14 \pm 0.08) \times 10^{-3}$		
	CH_3COOH	25.0[b]	2.26×10^{-8}	26.4 ± 0.4	−5.0 ± 1.1
		50.0[b]	7.61×10^{-7}		
		81.7	$(3.27 \pm 0.09) \times 10^{-5}$		
		95.0	$(1.36 \pm 0.12) \times 10^{-4}$		
		110.2	$(5.71 \pm 0.43) \times 10^{-4}$		
	C_2H_5OH	25.0[b]	1.08×10^{-7}	22.6 ± 0.3	−14.4 ± 0.8
		50.0[b]	2.26×10^{-6}		
		79.6	$(4.73 \pm 0.49) \times 10^{-5}$		
		95.0	$(1.95 \pm 0.10) \times 10^{-4}$		
		105.1	$(4.46 \pm 0.32) \times 10^{-4}$		
3e-OTs	HCOOH	50.0	$(2.65 \pm 0.08) \times 10^{-5}$	23.3	−7.6
		70.0	$(2.33 \pm 0.12) \times 10^{-4}$		
	CH_3COOH	50.0[b]	4.00×10^{-7}	25.3 ± 0.1	−9.8 ± 0.2
		100.1	$(9.04 \pm 0.25) \times 10^{-5}$		
		115.2	$(3.57 \pm 0.28) \times 10^{-4}$		
		130.0	$(1.22 \pm 0.05) \times 10^{-3}$		
	C_2H_5OH[g]	50.0[b]	4.74×10^{-7}	23.8 ± 0.3	−14.1 ± 0.8
		90.0	$(3.11 \pm 0.14) \times 10^{-5}$		
		105.1	$(1.24 \pm 0.08) \times 10^{-4}$		
		120.0	$(4.15 \pm 0.14) \times 10^{-4}$		
3a-OTs	HCOOH	50.0	$(2.39 \pm 0.09) \times 10^{-5}$	24.0	−5.4
		70.0	$(2.25 \pm 0.09) \times 10^{-4}$		
	CH_3COOH	50.0[b]	3.55×10^{-7}	26.6 ± 0.01	−6.0 ± 0.03
		94.5	$(6.04 \pm 0.29) \times 10^{-5}$		
		110.1	$(2.77 \pm 0.15) \times 10^{-4}$		
		125.1	$(1.07 \pm 0.04) \times 10^{-3}$		

TABLE I
(*Continued*)

Compd	Solvent	Temp, °C	k_1, sec^{-1} [c]	$\Delta H^{\pm}$, kcal/mol[d]	$\Delta S^{\pm}$, kcal/mol[d]
3a-OTs	C_2H_5OH[e]	50.0[b]	6.10×10^{-7}	23.9 ± 0.1	−13.2 ± 0.3
		90.0	$(4.12 \pm 0.33) \times 10^{-5}$		
		105.0	$(1.61 \pm 0.07) \times 10^{-4}$		
		120.0	$(5.58 \pm 0.23) \times 10^{-4}$		

[a] The concentrations of tosylates were 50 m*M* for trifluoroacetolyses, 20 m*M* for formolyses, and 1.0 m*M* for acetolyses and ethanolyses. Temperature deviation was ±0.03°. [b] Rates at 25 and 50° were calculated from observed rates. [c] Error limits for rate constants are 95% confidence limits [degree of freedom, $\phi = n - 2$ ($n = 10$)]. [d] With standard deviations. [e] Reference 10 gives the rates at 50°, from which the rates at 25° are calculated using the reported activation parameters. [f] Cited from ref 8b. [g] In the presence of 2,6-lutidine (2.0 m*M*).

TABLE II
PRODUCTS AND YIELDS[a] FROM ACETOLYSES AT 100.0°

Compd	Olefin, %[b]	Acetate, % 2α (eq)	Acetate, % 2β (ax)
1e-OTs[c]	64.0	2.2	33.3
1a-OTs[c]	86.4	7.8	4.0
2e-OTs	55.2	1.1	31.9
2a-OTs	78.2	10.2	3.5
3e-OTs	55.1	6.4	17.9
3a-OTs	63.9	21.5	5.8

[a] Based on theory. [b] Composed of Δ^1 and Δ^2 olefins. [c] Cited from ref 18.

TABLE III
AXIAL–EQUATORIAL RATE RATIOS (k_{ax}/k_{eq}) AT 50.0°

Compd	CF_3COOH	HCOOH	CH_3COOH	C_2H_5OH
1-OTs	3.67	4.36[a]	3.01	4.35
2-OTs	2.78	3.05	3.82	4.96
3-OTs		0.902	0.888	1.29

[a] Calculated from the rate data in ref 8b, where the ratio at 25° has been reported as 5.55.

TABLE IV
ELIMINATION/SUBSTITUTION RATIOS AND INVERSION/RETENTION RATIOS IN PRODUCTS OF ACETOLYSIS AT 100.0°

Compd	Elimination/ Substitution	Inversion/ Retention
1a-OTs[a]	7.23	1.95
2a-OTs	5.71	2.92
3a-OTs	2.34	3.71
cis-4-*tert*-Butylcyclohexyl OTs[a]	6.45	8.9
Cholestanyl a-OTs[b]	10.0	3.53
Δ^6-Cholestanyl a-OTs[b]	23.0	2.56
1e-OTs[a]	1.82	15.1
2e-OTs	1.67	29.5
3e-OTs	2.19	2.80
trans-4-*tert*-Butylcyclohexyl OTs[a]	3.61	48
Cholestanyl e-OTs[b]	1.45	31.3
Δ^6-Cholestanyl e-OTs[b]	1.71	176

[a] Cited from ref 5. [b] Cited from ref 8b.

ment (the solvent-assisted k_s mechanism).[20] On the other hand, according to the detailed product analysis by Whiting, *et al.*,[18] the substitution products from acetolysis of 1e-OTs were the inverted acetate in 33.3% and the retained acetate in 2.2% yield, while those from 1a-OTs were the inverted acetate in 7.8% and the retained acetate in 4.0% yields (presented in Table II). Similar products distributions were observed in the acetolyses of 2e- and 2a-OTs. The ratios of elimination products (olefins) to substitution products (acetates) and the ratios of inverted acetates to retained acetates, observed from 1-, 2-, and 3-OTs and reported for some related conformationally fixed cyclohexyl tosylates, are listed in Table IV. There is accumulated evidence that the intermediates in the borderline solvolysis of secondary substrates are ion pairs, and not free carbonium ions.[21–23] Regarding the substitution stereochemistry in solvolysis, Sneen[21b] has recently proposed that inversion arises from the intimate ion pair, retention from the solvent-separated ion pair, and racemization from the dissociated ion. Good evidence for inversion may be the stereochemical studies with 2-octyl substrates[21a] and that for retention may be the kinetic and product studies on 2-adamantyl arenesulfonates in 70% aqueous ethanol with various arenesulfonate leaving groups.[23] By Sneen's argument, the large ratio of inversion to retention for 1e-OTs (15.1) relative to that for 1a-OTs (1.95) would mean a favorable reaction at the intimate ion-pair stage. Since it has been suggested that solvolysis of *trans*-4-*tert*-butylcyclohexyl tosylate[8b,18,19b] and 1e-OTs[8b,18] takes place largely *via* nonchair (twist–boat) conformers and to some extent *via* the main, equatorial chair conformer, the formation of an incipient cationic center from any of these conformers would bring about flattening of the ring about the reaction site and, as a consequence, solvent participation from the back side resulting in inversion would be facilitated with reduction of the compression among the C_2 axial hydrogen and neighboring hydrogens (in particular, among the C_2 hydrogens and the C_1 and C_3 hydrogens in the nonchair conformer) at the expense of emerging bond-angle and torsional strains. Such an effect favorable for inversion is not obtained by the transition-state formation in the reactions of *cis*-4-*tert*-butylcyclohexyl tosylate[3,19] and 1a-OTs,[18] which are considered to react *via* the axial chair conformer. In addition, solvent participation from the backside in this conformer would be disturbed by emerging compression among the solvent and the axial hydrogens at C_1 and C_3. The small inversion/retention ratio observed for 1a-OTs may indicate competing substitutions on an intimate ion pair and a solvent-separated ion pair, effects specially favorable for either one of the substitutions being either absent or in a compensating balance with other, unfavorable factors.

In contrast to the above cases, the axial tosylate in the 3 system solvolyzes more slowly than the equa-

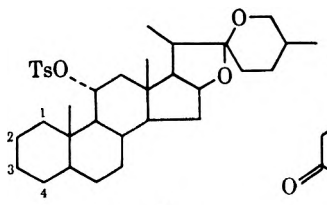
(20) (a) J. B. Lambert, G. J. Putz, and C. E. Mixan, *J. Amer. Chem. Soc.*, **94**, 5132 (1972); (b) J. E. Nordlander and T. J. McCrary, Jr., *ibid.*, **94**, 5133 (1972).

(21) (a) H. Weiner and R. A. Sneen, *ibid.*, **87**, 287, 292 (1965); (b) R. A. Sneen, *Accounts Chem. Res.*, **6**, 46 (1973), and references cited therein.

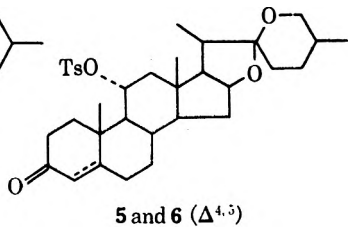
(22) V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, **91**, 4838 (1969); V. J. Shiner, Jr., and W. Dowd, *ibid.*, **91**, 6528 (1969); V. J. Shiner, Jr., R D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969); V. J. Shiner, Jr., and R D. Fisher, *ibid.*, **93**, 2553 (1971).

(23) J. M. Harris, J. F. Fagan, F. A. Waden, and D. C. Clark, *Tetrahedron Lett.*, 3023 (1972).

torial epimer in formic and acetic acids. This reverse reactivity can be considered in two ways: (a) the rate of the axial tosylate is normal, but that of the equatorial one is unusually enhanced; (b) the rate of the axial tosylate is unusually retarded, but that of the equatorial one is normal. In a previous paper we reported the rates of acetolysis of A-ring substituted 11α-*p*-toluenesulfonyloxy steroidal sapogenins[24] and the rates of solvolyses of 6-substituted *trans*-decalyl-2α-*p*-toluenesulfonates in various solvents, and we showed, by linear correlation using the modified Hammett–Taft equation, that inductive effects are dominant in governing the rates. For example, transformation of 11α-tosyloxy-25D,5α-spirostan (**4**) into its 3-one derivative (**5**) and 4-en-3-one derivative (**6**) slows down the



4



5 and **6** ($\Delta^{4,5}$)

rate by factors of 0.19 and 3.9 $\times$ 10^{-2}, respectively, while the same transformation in the present systems (from **1** to **2** and **3**) decreases the rate by factors of 0.19 and 8.7 $\times$ 10^{-2}, respectively. This situation is summarized in Table V. It is seen from this table

TABLE V

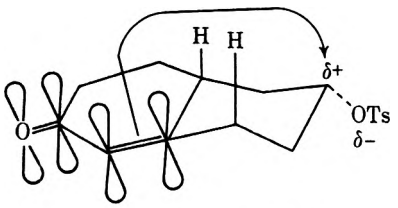
ACETOLYSIS RATES OF 2-DECALYL TOSYLATES (**1**, **2**, AND **3**) AT 65.0° [a] AND 11α-TOSYLOXY-25D,5α-SPIROSTAN DERIVATIVES (**4**, **5**, AND **6**) AT 65.4° [b]

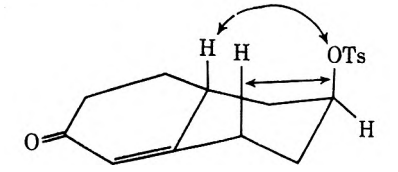
Compd	ax-OTs	eq-OTs	ax-OTs	eq-OTs
1	26.6	8.96	1	1
2	4.95	1.46	0.19	0.16
3	2.31	2.38	8.7×10^{-2}	0.27
4		379		1
5		71.7		0.19
6		14.8		3.9×10^{-2}

[a] Rates at 65.0° were calculated from the observed rates in Table I. [b] The data at 65.4° are cited from our paper (ref 24).

that the relative rate of **3a**-OTs (8.7×10^{-2}) is normal, but that of **3e**-OTs (0.27) is unusually large. Further, when the observed rate of the equatorial epimer (4.00×10^{-7} sec^{-1} in Table I) is compared with that estimated by extrapolation of the reported Hammett–Taft linearity, $k_1 = 9.0 \times 10^{-8}$ sec^{-1} (at 50° in acetic acid), a rate enhancement in **3e**-OTs is seen. We propose that participation of the $\Delta^{5(10)}$ unsaturation from the back side of the leaving equatorial tosyloxy group is the main factor contributing to this enhancement. A molecular model indicates that the 1,3-diaxial interactions existing between the tosyloxy group at C_2 and the hydrogens at C_4 and C_9 in the **1** and **2** systems should be reduced slightly with introduction of the $\Delta^{5(10)}$ unsaturation as a result of the slight outward movements of the hydrogens at C_4 and C_9. This decrease in the 1,3-diaxial interactions should result in a decreased solvolysis rate for **3a**-OTs. In ethanol, however, just as with systems **1** and **2**, the

(24) K. Takeda, H. Tanida, and K. Horiki, *J. Org. Chem.*, **31**, 734 (1966).





axial tosylate **3a**-OTs is observed to be more active than the equatorial tosylate (k_{ax}/k_{eq} = 1.29 in Table III). It therefore seems difficult to explain this solvent effect upon relative reactivity in terms of 1,3-diaxial interaction, though it can be explained in terms of a decrease or absence of participation in the ethanolysis of **3e**-OTs, it being well established that neighboring group participation is not favored in a solvent of such high nucleophilicity and low ionization powder as ethanol.[25]

The ratios of inversion to retention in products (Table IV) from all the present axial tosylates (**1a**–**3a**) are normal. They are comparable to one another and to those for the reference compounds. The ratios for the two equatorial tosylates, **1e**-OTs and **2e**-OTs, are similarly normal, but **3e**-OTs is exceptional in that it shows a very low inversion/retention ratio (2.80). The increased yield of the retained acetate from **3e**-OTs can be regarded as a result of stereochemical control exerted by the $\Delta^{5(10)}$ double bond.

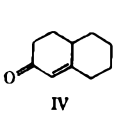
Experimental Section

Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Infrared spectra were measured on a Nippon Bunko DS201B spectrometer. Uv spectra were measured on a Hitachi EPS-032 and/or a Hitachi EPU-2A spectrometer. Vpc analyses were performed on a Hitachi gas chromatograph Model K53 equipped with a hydrogen frame ionization detector using the following columns: (A) 1 m $\times$ 3 mm stainless steel column packed with Carbowax 20M 5%, (B) 2 m $\times$ 3 mm Carbowax 20M 10%, and (C) 2 m $\times$ 3 mm DEGS 10%. Nitrogen was used as a carrier gas.

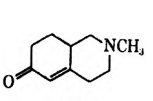
All the alcohols (1-OH–3-OH) used in the present study were synthesized from 6-methoxy-2-tetralol by methods described in a previous paper.[14] Each of the alcohols was shown by vpc analysis to be over 99.0% pure.

Preparation of *p*-Toluenesulfonates.—Tosylates (1-OTs–3-OTs) were prepared according to our previous paper,[10] in which

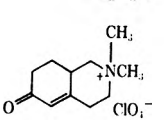
(25) In an ultraviolet study of the bicyclic ketones IV, V, and VI, which contain a quaternary nitrogen atom at a distance of about 3.1 Å from the α,β-unsaturated ketone group, E. M. Kosower and D. C. Remy, *Tetrahedron*, **5**, 281 (1959), observed that the absorption maximum for the $\pi-\pi^*$ transi-



IV



V



VI

tion shifts to a shorter wavelength with increasing positive charge on the nitrogen atom (from compound IV to V to VI), while that for the $n-\pi^*$ transition shifts to a longer wavelength. Although the mechanisms underlying the kinetic data and this ultraviolet data are, of course, different, it can be said that both the findings are based on long-range electrical effects operating from the $\Delta^{5(10)}$ double bond to the C_2 position.

nmr spectral parameters and other physical data are also given. Recrystallized from ether–*n*-hexane, *trans*-2β-decalyl *p*-toluenesulfonate (1a-OTs) has mp 107–108°; nmr ($CDCl_3$) δ 2.43, 7.55 (OTs), 4.80 (1 H, broad s, $W_{1/2}$ = 7 Hz, C_6 eq H); ir (KBr) 909, 1174, 1342 cm^{-1} (OTs); uv max (CH_3OH) 273.2 mμ (ε 445).

Anal. Calcd for $C_{17}H_{24}O_3S_1$: C, 66.20; H, 7.85; S, 10.39. Found: C, 65.95; H, 7.79; S, 10.58.

Recrystallized from ether, 6-keto-*trans*-2β-decalyl *p*-toluenesulfonate (2a-OTs) has mp 102–103°; nmr ($CDCl_3$) δ 2.45, 7.57 (OTs), 4.86 (1 H, broad s, $W_{1/2}$ = 7 Hz, C_6 eq H); ir (KBr) 900, 1166, 1355 (OTs), 1715 cm^{-1} (C=O); uv max (CH_3OH) 273.2 mμ (ε 456).

Anal. Calcd for $C_{17}H_{22}O_4S_1$: C, 63.33; H, 6.87; S, 9.94. Found: C, 63.07; H, 6.96; S, 9.84.

Recrystallized from acetone-*n*-hexane, 6-keto-$\Delta^{5(10)}$-*trans*-decalyl *p*-toluenesulfonate (3e-OTs) has mp 100–101.0°; nmr ($CDCl_3$) δ 2.46, 7.58 (OTs), 4.67 (1 H, broad s, $W_{1/2} \cong$ 23 Hz, C_2 ax H), 5.83 (1 H, broad s, C_5 H); ir (KBr) 1625, 1673 cm^{-1} (α,β-unsaturated ketone).

Anal. Calcd for $C_{17}H_{20}O_4S_1$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.45; H, 6.31; S. 9.90.

Recrystallized from acetone-*n*-pentane, 6-keto-$\Delta^{5(10)}$-*cis*-decalyl *p*-toluenesulfonate (3a-OTs) has mp 121–122°; nmr ($CDCl_3$) δ 2.46, 7.60 (OTs) 4.93 (1 H, broad s, $W_{1/2}$ = 8 Hz, C_2 eq H), 5.84 (1 H, t, J = 2 Hz, C_5H); ir (KBr) 1618, 1672 cm^{-1} (α,β-unsaturated ketone).

Anal. Calcd for $C_{17}H_{20}O_4S_1$: C, 63.73; H, 6.29; S, 10.01. Found: C, 63.79; H, 6.34; S, 9.86.

Kinetic Measurements.—The conditions and procedure for the solvolyses in trifluoroacetic acid, acetic acid, and ethanol were the same as previously reported.[10]

For formolysis, the tosylates were dissolved at a concentration of 20 mM in formic acid containing 22 mM sodium formate. The acid was purified by distillation with pure boric anhydride. Aliquots (1.0 ml) were distributed into tubes and sealed under nitrogen after freezing in Dry Ice–acetone. The tubes were placed in a constant-temperature bath and then successively withdrawn after appropriate intervals of time. The tubes were cooled and opened, and the contents were diluted with 10 ml of acetic acid. The solutions were titrated with 0.04 N perchloric acid in acetic acid using a Metrohm potentiograph E336A. Plots of log ($A_t - A_\infty$) *vs.* time, where A_∞ and A_t are titers at infinity and at given times, respectively, were uniformly linear. The slopes multiplied by −2.303 gave the pseudo-first-order rate constants.

Acetolysis Products.—The method employed was essentially the same as that described previously.[10] The olefin and acetate fractions were the separated by a small column of silica gel. The olefin fractions were collected, dried under reduced pressure, and weighed. The olefin fractions were shown to consist of the Δ^1 olefin and Δ^2 olefin by nmr and mass spectra and vpc analysis. The acetate fractions were collected and identified with authentic samples.[14] The yields of the acetates were determined by vpc with internal standards. Products and yields from the tosylates (1-OTs–3-OTs) are given in the Results and, in part, in the preceding paper.[10] The olefin fraction from 2a-OTs showed nmr ($CDCl_3$) δ 5.5–5.7 (2 H, m, olefinic protons); mass spectrum m/e 150 (M^+). That from 3e-OTs showed nmr ($CDCl_3$) δ 5.75 (1 H, broad s, C_6 H), 6.2–6.3 (2 H, m, olefinic protons); mass spectrum m/e 148 (M^+). That from 3a-OTs showed nmr ($CDCl_3$) δ 5.75 (1 H, broad s, C_5 H), 6.2–6.3 (2 H, m, olefinic protons); mass spectrum m/e 148 (M^+).

Registry No.—1a, 5746-69-0; 1a-OTs, 40429-90-1; 1e, 36667-73-9; 1e-OTs, 40429-92-3; 2a, 36667-84-2; 2a-OTs, 40429-94-5; 2e, 39089-10-6; 2e-OTs, 40429-96-7; 3a, 40429-97-8; 3a-OTs, 40429-98-9; 3e, 40429-99-0; 3e-OTs, 40550-47-8.

Formation of Endo Acetate in Acetolysis of a Fused *endo*-Norbornyl Brosylate *via* C-7 Participation[1,2]

ROBERT K. HOWE*

Research Department, Agricultural Division, Monsanto Company, St. Louis, Missouri 63166

S. WINSTEIN[3]

Department of Chemistry, University of California at Los Angeles, Los Angeles, California 90024

Received February 21, 1973

XII-OH, a new alcohol, was obtained in low yield by sodium amalgam reduction of the oxymercurials from endo,endo diene. Upon acetolysis, XII-OBs undergoes ~98% rearrangement *via* cation A to VI-OBs; no endo acetate XIII-OAc is formed. Acetolysis of the endo brosylate XIII-OBs results in 22.5% XIII-OAc, apparently *via* C-7 participation and cation C.

In continuance of studies in the bird-cage hydrocarbon system,[4] we reported[5] recently that acetolysis of exo brosylate VI-OBs produced 27% endo acetate VII-OAc *via* anchimerically unassisted solvolysis in competition with anchimerically assisted solvolysis. The endo brosylate VII-OBs produced 3% VII-OAc through 10% intimate ion pair return to and subsequent solvolysis of VI-OBs.[5] We now report the striking results of acetolysis of the related pair of brosylates XII-OBs and XIII-OBs, of which the most salient feature is formation of endo acetate XIII-OAc from endo brosylate XIII-OBs but not from exo brosylate XII-OBs.

Results and Discussion

XII-OH, a previously unknown alcohol,[4-6] and thus XIII-OH became accessible as a result of studies[7] of oxymercuration of endo,endo diene. Reaction of the diene[7,8] with mercuric acetate in acetic acid, treatment of the reaction mixture with aqueous sodium chloride, and reduction of the resultant solid mixture with sodium amalgam in water led to formation of *ca.* 62% bird-cage hydrocarbon, 5% residual unhydrolyzed acetates, 24% VI-OH, a trace of V-OH, and 9% XII-OH (Scheme I). Isolation of 98% pure XII-OH containing 2% V-OH was effected by chromatography of the crude product mixture on alumina. Final purification by gas chromatography, sublimation,

(1) Taken in part from the Ph.D. Thesis of Robert K. Howe, UCLA, Los Angeles, Calif., 1965.

(2) An extension of compound designations used previously[4] is employed herein for ease of cross reference between the papers of this series.

(3) Deceased November 23, 1969.

(4) L. deVries and S. Winstein, *J. Amer. Chem. Soc.*, **82**, 5363 (1960).

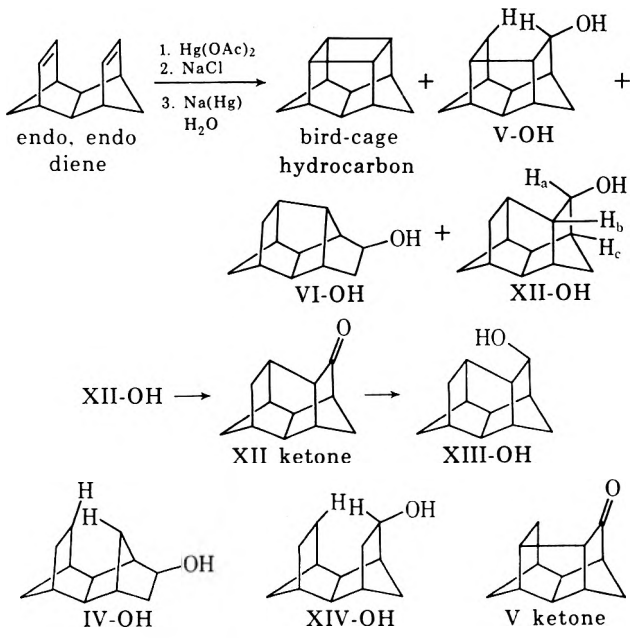
(5) Robert K. Howe, Peter Carter, and S. Winstein, *J. Org. Chem.*, **37**, 1473 (1972).

(6) The alcohol with mp 72–73°, originally thought[4] to possess the XII-OH structure, has been shown[5] to be the endo epimer of VI-OH.

(7) K. C. Pande and S. Winstein, *Tetrahedron Lett.*, 3393 (1964).

(8) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960).

SCHEME I



and crystallization gave XII-OH, mp 84.5–85.0°, that contained <0.05% of isomeric alcohols.

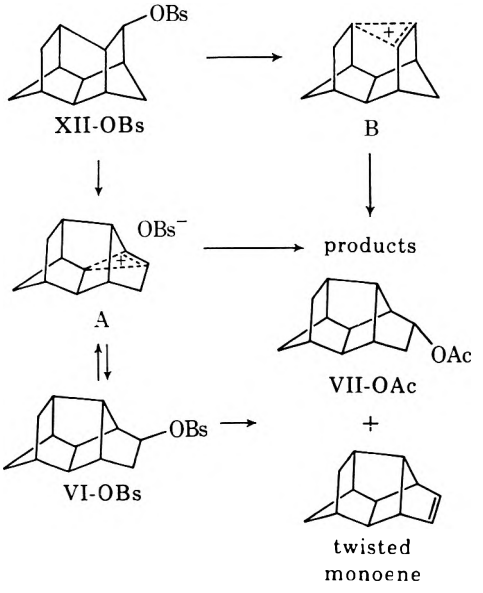
The structure of this new alcohol was deduced from the carbon and hydrogen analyses (consistent with $C_{12}H_{16}O$), from spectra of the alcohol and derived ketone, and from the XII-OBs acetolysis results. The ir spectrum of XII-OH distinguished this material from all the previously known C_{12} alcohols in our studies[4,5,8-15] and revealed no CH absorption above 3000 cm^{-1}. Thus, XII-OH has no sterically opposed hydrogens[11] such as exist in IV-OH, V-OH, and XIV-OH. In the nmr spectrum of XII-OH, the α proton H_a appears as a very slightly broadened singlet at τ 6.25 (CCl_4 solvent), consistent with the assigned structure since the H_a–C–C–H_b dihedral angle is *ca.* 80–85° and the H_a–C–C–H_c dihedral angle is *ca.* 70–75°, for which coupling constants of the order of 0–1 Hz are to be expected.[16] Similarly, half-cage V-OH exhibits a singlet (very slightly broadened) for the α proton.

XII ketone, derived from oxidation of XII-OH, has the carbonyl absorption at 1755 cm^{-1}, indicative of greater angle strain than in V ketone[13] (1746 cm^{-1}), VI ketone[5] (the ketone derived from VI-OH; 1746 cm^{-1}), and VIII ketone[5] (1744 cm^{-1}). XII ketone exhibits no ir absorption at 1410–1420 cm^{-1}, which demonstrates the lack of a methylene group adjacent to the carbonyl group.[17] Reduction of XII ketone with lithium aluminum hydride in ether proceeds with a high degree of steric approach control to yield 96.2% XIII-OH and 3.8% XII-OH. Pure XIII-OH, mp 177–177.5°, was obtained by fractional crystallization.

The most conclusive data for the structural assignment for XII-OH stems from the extensive rearrangement (*ca.* 98%) of XII-OBs to VI-OBs during acetolysis, a result reconcilable only with the structure proposed for XII-OH. The XII-OBs initial acetolysis rate constant, k_{XII}, drifts upward extremely rapidly; at 25°, $k_{XII} = 1.25 \times 10^{-6}$ sec^{-1}, and at 1% reaction (acid production) the integrated rate constant is 4.7×10^{-6} sec^{-1}. The initial acetolysis rate constant, k_{XII}, was determined fairly accurately by extrapolation to 0% reaction of a plot of integrated rate constant *vs.* per cent reaction. For this plot, titration points were taken as early as 0.102, 0.237, and 0.294% reaction. The acetolysis rate constant integrated from 76% reaction is quite steady at 4.03×10^{-5} sec^{-1}, in good agreement with the value 3.91×10^{-5} sec^{-1} reported[4] for VI-OBs. The XII-OBs rearrangement rate constant, $k_r = 8.01 \times 10^{-5}$ sec^{-1}, was determined by the method of Young, Winstein, and Goering.[18] The product mixture from solvolysis of 0.00663 *M* XII-OBs in acetic acid (0.020 *M* sodium acetate) at 50° was found to contain 64.8 ± 1.5% VI-OAc, 27.9 ± 1.5% VII-OAc, 6.5 ± 0.5% twisted monoene (the olefin[4,5] derived from VI-OBs), 0.4% bird-cage hydrocarbon, 0.34% V-OAc, and 0.07% XII-OAc. There was less than 0.03% XIII-OAc (none detected). This product composition is identical within experimental error with that obtained from VI-OBs,[5] except for the presence of *ca.* 1% of other products (bird-cage hydrocarbon, V-OAc, and XII-OAc). Thus, both the kinetic analysis and the product mixture reveal the extensive rearrangement of XII-OBs to VI-OBs in acetolysis.

This rearrangement most likely occurs *via* an intimate ion pair consisting of cation A and brosylate anion. The ratio $k_r/k_{XII} = 64$ is a minimum measure of the ratio of ion pair return to VI-OBs and acid production from A in XII-OBs acetolysis, since part of k_{XII} is due to solvolysis *via* cation B (Scheme II).

SCHEME II

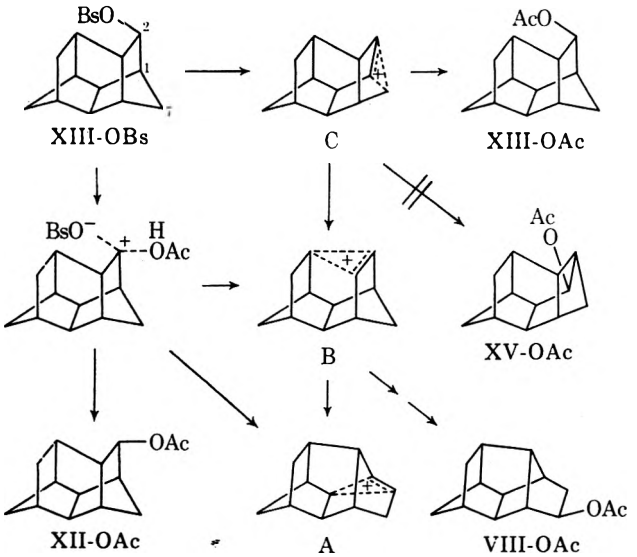


(9) S. Winstein and R. L. Hansen, *Tetrahedron Lett.*, 4 (1960).
(10) S. Winstein and R. L. Hansen, *J. Amer. Chem. Soc.*, **82**, 6206 (1960).
(11) D. Kivelson, S. Winstein, P. Bruck, and Robert L. Hansen, *J. Amer. Chem. Soc.*, **83**, 2938 (1961).
(12) Peter Carter, Robert Howe, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 914 (1965).
(13) R. Howe and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 915 (1965).
(14) S. Winstein, Peter Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5247 (1965).
(15) Peter Carter and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2171 (1972).
(16) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(17) S. A. Francis, *J. Chem. Phys.*, **19**, 942 (1951).
(18) W. G. Young, S. Winstein, and H. L. Goering, *J. Amer. Chem. Soc.*, **73**, 1958 (1951).

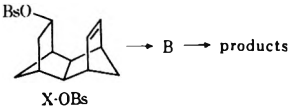
Since the intimate ion pair consisting of A and brosylate anion is the first intermediate formed in VI-OBs acetolysis, the ratio $k_r/k_{XII} = 64$ is also a minimum measure of ion pair return in VI-OBs acetolysis.[5] The VI-OBs formed in XII-OBs acetolysis undergoes solvolysis *via* competing anchimerically assisted and anchimerically unassisted routes; the latter route results in formation of the VII-OAc observed in both XII-OBs and VI-OBs acetolyses.[5] Formation of 1.7% of cation B from XII-OBs would account for the amounts of bird-cage hydrocarbon, V-OAc, and XII-OAc produced in XII-OBs acetolysis.[19] Significantly, there is less than 0.03% (none detected) of the classical solvolysis product XIII-OAc produced.

XIII-OBs acetolyzed with fairly steady first-order kinetics, $k = (1.03 \pm 0.02) \times 10^{-5}$ sec^{-1} at 50° and $k = (2.44 \pm 0.04) \times 10^{-4}$ sec^{-1} at 75°, and produced 99% of the theoretical amount of acid. The titrimetric rate ratio $(k_r + k_{XII})/k_{XIII}$ is *ca.* 200 at 25°. Although the extent of ion pair return in XIII-OBs acetolysis is not known, it appears that XIII-OBs ionizes more slowly than XII-OBs. The product mixture from acetolysis of XIII-OBs at 50° was found to consist of 6.6% V-OAc, 49.9% VI-OAc, 6.1% VII-OAc, 1.9% VIII-OAc, 6.5% XII-OAc *22.5% XIII-OAc*, 5.1% bird-cage hydrocarbon, and 1.4% twisted moncene. None of the other isomeric brosylates, including XII-OBs, yields any XIII-OAc. Anchimerically unassisted solvolysis of XIII-OBs would be expected to yield predominantly XII-OAc, and most of the 6.5% XII-OAc that is formed probably arises through this path. Even if a classical cation solvated on both sides were produced from XIII-OBs, more XII-OAc than XIII-OAc would be expected since the steric hindrance about the endo side of the carbonium ion is greater than that about the exo side.

SCHEME III



(19) Acetolysis of X-OBS results in 100% cation B initially, which then



forms 24% bird-cage hydrocarbon, 24% V-OAc, and 4.1% XII-OAc, among other products, after 100% acid production.[5]

(20) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1154 (1952).

Apparently, the formation of 22.5% XIII-OAc from XIII-OBs can be rationalized only with anchimerically assisted ionization to form the nonclassical cation C (Scheme III); this is formed in competition with anchimerically unassisted ionization to give the classical cation. No detectable amount of XV-OAc was observed. Possibly part of the large amount of strain in this acetate is felt in the transition leading to it and makes its formation unfavorable.

For neighboring group participation to be effective, a trans coplanar arrangement of the participating group and the leaving group is generally required. For example, this requirement is met and participation occurs in solvolysis of *exo*-norbornyl brosylate.[20] The trans coplanar requirement is not met in *endo*-norbornyl brosylate, and this brosylate solvolyzes without C-7 participation. The XIII system is so twisted by the bond that joins the ethano bridges that the C_2–OBs bond and the C_1–C_7 bond are nearly trans coplanar. This allows C-7 participation[21,22] to occur more readily than in the case of *endo*-norbornyl brosylate; there is at least 22.5% of cation C formed in XIII-OBs acetolysis.

The 5.1% bird-cage hydrocarbon, 6.6% half-cage V-OAc, and 1.9% VIII-OAc arise *via* cation B, which is formed from C and/or the XIII-OBs classical cation. The remainder of the product mixture arises *via* cation A. Since the cation A and the brosylate anion are generated from XIII-OBs with a geometry relatively unfavorable for ion-pair return, *ca.* 71% of the A cations produced undergo collapse with solvent to give VI-OAc and only *ca.* 29% undergo ion pair return to VI-OBs, which then forms the observed amounts of VII-OAc and twisted monoene.

Experimental Section

Melting points are corrected. Standard acetolysis procedures were employed.[23]

1,4,4a,5,8,8a-Hexahydro-*endo*,*endo*-1,4:5,8-dimethanonaphthalene (Endo,endo Diene).[24]—*Caution. Unpleasant physiological reactions (headache, depression) upon exposure to this diene have been experienced by two workers. Avoid inhalation of the vapors of and skin contact with this material.* To 50 g (0.137 mol) of technical grade isodrin and 93 g (1.26 mol) of *tert*-butyl alcohol in 400 ml of dry THF stirred under nitrogen in a 5-l. flask fitted with an efficient reflux condenser and stirrer was added 17.5 g (2.52 mol) of lithium wire cut into 0.5-in. lengths so as to allow the freshly cut pieces to fall directly into the flask. The mixture was stirred vigorously under nitrogen. An exothermic reaction ensued with considerable foaming, and the solvent began to boil violently. Ice-bath cooling was employed only as long as necessary to keep the reaction under control. The reaction was

(21) Solvolysis of 1-methoxy-2-*endo*-norbornyl brosylate provided the first example of C-7 participation and ring contraction (5–9%) in solvolysis of a norbornyl system: Y.-i Lin and A. Nickon, *J. Amer. Chem. Soc.*, **92**, 3496 (1970). Formation of the rearranged oxocarbonium ion in this system provides a measure of stabilization and driving force not present in the parent norbornyl system.

(22) Several examples of C-7 migration from C-1 to C-2 exist in vibrationally excited ("hot") carbonium ions generated from certain substituted *endo*-norbornyl diazonium ions: C. J. Collins, V. F. Raaen, B. M. Benjamin, and I. T. Glover, *J. Amer. Chem. Soc.*, **89**, 3940 (1967); P. Yates and R. J. Crawford, *ibid.*, **88**, 1561 (1966); W. Kirmse, G. Arend, and R. Siegfried, *Angew. Chem., Int. Ed. Engl.*, **9**, 165 (1970); W. Kirmse and G. Arend, *Chem. Ber.*, **105**, 2738, 2746 (1972).

(23) S. Winstein, C. Hansen, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948); S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(24) Since the diene is unstable in air (half-cage V ketone is formed in good yield within a few hours), no delays in the preparation should be allowed until after formation of the silver nitrate complex.

stirred until the spontaneous reflux subsided (0.75 to 1.5 hr) and then was held at reflux on a steam bath for 0.5 hr. The hot mixture was poured through a wire screen to remove residual pieces of lithium. Crushed ice and then 1 l. of water were added, and the mixture was extracted three times with pentane. The pentane extracts were combined, washed with water, dried (Na_2SO_4), and distilled. From two such runs a total of 36.7 g (85% yield) of crude diene, bp 62–80° (2 mm), was obtained.

A 22-g sample of crude diene was added to a solution of 67 g of silver nitrate in 54 ml of water with stirring under nitrogen. To the resultant solid cake was added 216 ml of absolute ethanol, and the mixture was stirred with a stirring rod. The mixture was then stirred under nitrogen overnight. The white precipitate was collected and washed with ethanol. Upon exposure to air, the 39.5 g of diene–silver nitrate complex, mp 207° dec, turned gray. It was stored under nitrogen in a tightly sealed bottle at −10° in a freezer.[25]

A mixture of 39.5 g of complex and 1 l. of concentrated ammonium hydroxide in a 3-l. flask fitted with a spiral condenser was heated on a steam bath. Periodically, the solid diene which steam distilled into the condenser was washed out with pentane, and additional ammonium hydroxide was added to the flask. This process was repeated until diene no longer formed in the condenser (2–3 hr or longer). The aqueous mixture was cooled and extracted with pentane. All the pentane washings and extracts were combined, washed with water, dried (Na_2SO_4), and concentrated. The residual white solid was sublimed at 80° (1 mm) to give 9.0 g (41% from the crude diene) of solid, mp 94–96° (lit.[7] mp 90–92), that was 99.3% endo,endo diene and 0.7% endo,endo monoene (gc analysis on a 25% SE-30 on Chromosorb W column[26]): ir (CCl_4) 3.21 (w), 3.30 (m), 3.41 (s), 3.52 (m), 6.39 (w), 6.90 (m), 7.49 (s), 7.88 (w), 8.00 (s), 8.11 (w), 8.20 (w), 8.85 (m), 9.12, (w), 9.71 (w), 10.13 (w), 10.35 (w), 10.99 (s), 11.31 (s), 11.45 (s), 14.00 (vs), 14.50 μ (w).

Decahydro-4,7-methano-2,5,8-methenoazulen-*exo*-3-ol (XII-OH).—To a solution of 9.0 g (0.0570 mol) of endo,endo diene in 200 ml of acetic acid was slowly added in small portions 18.1 g (0.0568 mol) of mercuric acetate. After a few minutes the pale yellow solution was filtered into 600 ml of aqueous NaCl solution. The white precipitate was collected after 1 day, washed with water and pentane, and shaken for 13 hr with 350 g of 3% sodium amalgam in 250 ml of water. The cloudy mixture was extracted with three 100-ml portions of ether. The ether extracts were combined, dried (Na_2SO_4), and concentrated to a colorless oil. Gc analysis indicated the oil to consist of 62% bird-cage hydrocarbon, 24% VI-OH, 9% XII-OH, a trace of V-OH, and 5% acetates. The oil was chromatographed on a 1.25 × 14 in. column of neutral, activity 2.5 alumina. Bird-cage hydrocarbon, 3.5 g, was eluted with pentane. Elution with 10% ether in pentane yielded 0.46 g of acetate mixture. Elution with 20% ether in pentane gave first 0.67 g of XII-OH, mp 81–83°, then 0.30 g of a 40:60 mixture of XII-OH and VI-OH, and finally 1.85 g of VI-OH. Two crystallizations of the VI-OH from pentane at 5° gave 1.1 g of VI-OH, mp 75.5–76.5° (lit.[1] mp 76.2–77.6°).

The XII-OH was crystallized five times from pentane to give 0.23 g of XII-OH, mp 85.5–86.5°, that contained *ca.* 2% of V-OH (gc assay).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.89; H, 9.22.

The XII-OH was further purified by gas chromatography on a UCON 50-HB 2000 column, sublimation, and crystallization from pentane at −20° to give XII-OH, mp 84.5–85.0°, that contained less than 0.05% of isomeric alcohols (gc assay).

XII-OBs.—A solution of 75 mg of pure XII-OH and 218 mg of brosyl chloride (100% excess) in 2 ml of pyridine was held at 0° for 26 hr. Ice water, 30 ml, was added, and the mixture was extracted with three 15-ml portions of ether. The combined ether extracts were washed with three 25-ml portions of 2 *N* HCl, three 25-ml portions of saturated $NaHCO_3$ solution, and 50 ml of water. The ether solution was dried (Na_2SO_4) and concentrated under vacuum at 20° to an oil. The oil was dissolved in 25 ml of pentane at 20°. The solution was concentrated with a stream of nitrogen; when crystallization began, the mixture was placed in a freezer. The resultant solid XII-OBs was recrystallized in the same way to give 75 mg of XII-OBs, mp 80–81.5°, which produced 98% of the theoretical amount of acid upon acetolysis.

Anal. Calcd for $C_{18}H_{19}SO_3Br$: C, 54.68; H, 4.84. Found: C, 54.88; H, 4.92.

Decahydro-4,7-methano-2,5,8-methenoazulen-3-one (XII Ketone).—Solutions of 150 mg of 98% pure XII-OH in 10 ml of ether and 2.0 g of CrO_3 in 10 ml of water were stirred together for 4 hr. Then 50 ml of pentane was added, and the organic layer was washed with water until it was colorless. The solvent was removed under vacuum, and the ketone was chromatographed on alumina and sublimed at 90° (0.5 mm) to give 90 mg of XII ketone, mp 146.5–148.5°, that was 99% pure (gc assay; *ca.* 1% V ketone was present): ir (CCl_4) 1755 ± 1 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.68; H, 8.28.

Decahydro-4,7-methano-2,5,8-methenoazulen-*endo*-3-ol (XIII-OH).—Reduction of 10 mg of 99% pure XII-OH with excess lithium aluminum hydride in ether gave an alcohol mixture that contained 96.2% XIII-OH, 3.8% XII-OH, and a trace of half-cage oxygen-inside alcohol (gc assays on NMPN and UCON columns). On a larger scale, 0.56 g of XII-OH that contained 1% V-OH and 4% VI-OH was oxidized, and the resultant crude XII ketone was reduced with excess lithium aluminum hydride. The crude alcohol mixture was crystallized twice from pentane at −10° and five times from aqueous ethanol to give 0.15 g of 100% pure (gc assay) XIII-OH, mp 177–177.5°, as fine needles.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.86, H, 9.35.

XIII-OBs.—From 70 mg of XIII-OH and 218 mg of brosyl chloride there was obtained (by the method employed for XII-OBs) 90 mg of XIII-OBs, mp 107.5–108.5°, which produced 99% of the theoretical amount of acid upon acetolysis.

Anal. Calcd for $C_{18}H_{19}SO_3Br$: C, 54.68; H, 4.84, Found: C, 54.87; H, 4.70.

XII-OBs Acetolysis Products.—A 25-ml solution (0.0066 *M* XII-OBs) was prepared from 65.5 mg of XII-OBs and acetic acid that contained 0.020 *M* sodium acetate. The solution was held at 50° for 4.16 hr (20 half-lives of VI-OBs), cooled, and diluted with 25 ml of pentane. The solution was extracted with 50 ml of water. The water layer was extracted with 15 ml of pentane. The pentane layers were combined, extracted with three 25-ml portions of saturated $NaHCO_3$ solution and 50 ml of water, dried (Na_2SO_4), and concentrated to 1 ml with use of a 0.375 × 14 in. column packed with glass helices. Gc analysis on a 0.25 in. × 4 m column of 5% DOW X2405 on Chromosorb W, 80–100 mesh, at 155° and 30 psi helium pressure, indicated the product mixture to consist of 65.2 ± 1.5% V-OAc plus VI-OAc plus XII-OAc (retention time 67 min), 27.9 ± 1.5% VII-OAc (retention time 57 min), 6.5 ± 0.5% twisted monoene (retention time 5.5 min), and 0.4% bird-cage hydrocarbon (retention time 5.1 min). The acetates were converted to alcohols with excess lithium aluminum hydride. Gc analysis on a UCON 50-HB 2000 column showed the alcohol fraction to consist of 99.56% VI-OH plus VII-OH, 0.07% XII-OH, and 0.37% V-OH. There was <0.03% XIII-OH (none detected).

XIII-OBs Acetolysis Products.—A 16-ml solution (0.00984 *M* XIII-OBs) was prepared from 62.2 mg of XIII-OBs and acetic acid that contained 0.02 *M* sodium acetate. The solution was held at 50° for 328.5 hr (17.5 half-lives). After work-up, the product mixture was analyzed on the DOW X2405 column and was found to consist of 5.1% bird-cage hydrocarbon, 1.4% twisted monoene, 8.0% VII-OAc plus VIII-OAc, and 85.5% V-OAc plus VI-OAc plus XII-OAc plus XIII-OAc.

The acetates were converted to alcohols with excess lithium aluminum hydroxide in ether. Gc analysis on a 0.125 in. × 5 ft column of 5% UCON 50-HB 2000 on Chromosorb W, 80–100 mesh, at 150° revealed the alcohol fraction to consist of 61.8% VI-OH plus VII-OH plus VIII-OH (unresolved, retention time 16.6 min), 24.1% XIII-OH (retention time 19.8 min), 7.0% XII-OH (retention time 21.1 min), and 7.1% V-OH (retention time 23.9 min).

The alcohol mixture was oxidized to a ketone mixture, which then was analyzed by gc on a 0.125 in. × 20 ft column of 2% UCON 50-HB 2000 on Chromosorb W, 80–100 mesh, at 150°. Less than 0.1% of any of the alcohols remained unoxidized. The ketone mixture consisted of 7.23% V ketone (retention time 35.5 min), 33.1% VIII ketone plus XII ketone (unresolved, retention time 37.7 min), and 59.7% VI ketone (retention time 42.1

(25) The silver nitrate complex has been stored at −10° for 6 months with no apparent decomposition or impairment of the purity of the diene.

(26) Traces of acid in the gc system, including acid-washed column supports, cause rearrangement of the diene to bird-cage hydrocarbon and twisted monoene and should be avoided.

min). Since the alcohol mixture consisted of 31.1% XII-OH plus XIII-OH, there must have been 2.0% VIII ketone in the ketone mixture and thus 2.0% VIII-OH in the alcohol mixture.

Combination of the data from the three gc analyses gave the composition of the XIII-OBs acetolysis product mixture: 6.6% V-OAc, 49.9% VI-OAc, 6.1% VII-OAc, 1.9% VIII-OAc, 6.5% XII-OAc, 22.5% XIII-OAc, 5.1% bird-cage hydrocarbon, and 1.4% twisted monoene.

Registry No.—VI-OH, 40577-16-0; XII-OH, 40577-17-1; XII-OBs, 40577-18-2; XII ketone, 40577-19-3; XIII-OH, 40577-20-6; XIII-OBs, 40577-21-7; endo,endo diene 1076-13-7; brosyl chloride, 98-58-8.

Isobutyraldehyde. The Kinetics of Acid- and Base-Catalyzed Equilibrations in Water[1]

LAWRENCE R. GREEN* AND JACK HINE

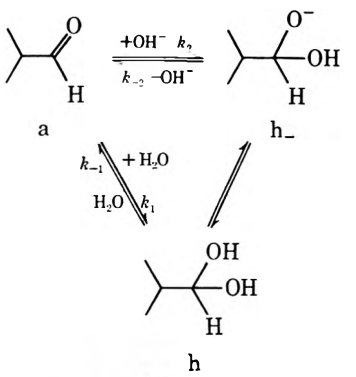
Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received January 4, 1973

The rates and equilibrium constants for the reversible acid- and base-catalyzed hydration of isobutyraldehyde in water have been determined by temperature jump and nmr spectrometry. The standard enthalpy and entropy changes for isobutyraldehyde hydration are −5.6 kcal/mol and −19.9 eu. The standard enthalpy and entropy for the reaction of isobutyraldehyde hydrate with hydroxide ion is 0.6 kcal/mol and −1.9 eu. The activation enthalpies for the hydrogen ion and hydroxide ion catalyzed hydration of isobutyraldehyde are 7.8 and 11.7 kcal/mol, respectively.

Among the many studies on the hydration of aldehydes and ketones[2] are reports concerning isobutyraldehyde.[3-7] A solution of isobutyraldehyde in water equilibrates rapidly to a mixture of hydrate (h), hydrate anion (h−) and isobutyraldehyde (a) (Scheme I).

SCHEME I



$$K_h = \frac{[h]}{[a]} \quad (1)$$

$$K_{h^-} = \frac{[h^-]}{[h][OH^-]} \quad (2)$$

$$K_{ao^-} = \frac{[h^-]}{[a][OH^-]} \quad (3)$$

In connection with various studies on isobutyraldehyde we needed reliable values of these rate and equilibrium constants over a wide range of temperatures. Recently Pocker and Dickerson reported on the rates of hydration of isobutyraldehyde.[6b] By extrapolation to a time immediately following the mixing of reactants, and assuming the extinction coefficient of the free aldehyde to be temperature independent, they were able to obtain values of K_h at several temperatures. A plot of log K_h *vs.* $1/T$ gave values of K_h at 25 and 35° in good agreement with the earlier values[4b] obtained by nmr experiments. However, the nmr data were not corrected for possible saturation effects, and the hydration above 25° is so fast as to make extrapolation to zero time much less reliable than at 0°. Furthermore, a precise relationship between ln K_h and reciprocal temperature, especially around 25–35°, is necessary for a study by temperature jump spectrometry. A rapid kinetic technique was necessary to study hydroxide ion catalysis under conditions where the hydroxide ion concentration was known accurately.

Experimental Section

Isobutyraldehyde (bp 63.5–64.0°) was freshly distilled before preparing solutions. No impurities were detected by glpc analysis. Oxidation of isobutyraldehyde to isobutyric acid was negligible under the conditions used. Doubly distilled dust-free degassed water (boiled) was used for the preparation of all solutions. Standard solutions of perchloric acid and sodium hydroxide were periodically checked by use of primary standard (potassium hydrogen phthalate) by titration to a phenolphthalein end point. Carbonate-free sodium hydroxide solutions were prepared by filtration of saturated sodium hydroxide solutions.

T-Jump and combined T-jump stopped-flow experiments were conducted on a Durrum-Gibbson stopped-flow spectrometer equipped with a D-150 modular control unit. A permanent record of the photomultiplier signal was obtained by photographing the image on a Tektronix 564 storage oscilloscope.

A standard solution of about 0.08 *M* isobutyraldehyde was placed in one of two storage reservoirs. Acid catalysis was studied by placing 0.02–0.18 *M* perchloric acid in the second reservoir. The ionic strength of the acid solution was adjusted to 0.2 by adding sodium chloride. Equal volumes of the two solutions were mixed by actuating the stopped-flow apparatus, and T-jump experiments were conducted on the resultant mixture (ionic strength 0.1). The effect of base on the rate of equilibration was studied by placing in the second reservoir solutions 0.02–0.1 *M* in sodium hydroxide with enough sodium chloride to give an ionic strength of 0.2. Since isobutyraldehyde and base react to form aldol condensation products, it was neces-

(1) This investigation was supported in part by Grants GP-14697 and GP-32461X from the National Science Foundation.

(2) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).

(3) L. C. Gruen and P. T. McTigue, *J. Chem. Soc.*, 5217, 5224 (1963).

(4) (a) J. Hine, J. G. Houston, and J. H. Jensen, *J. Org. Chem.*, **30**, 1184 (1965); (b) J. Hine and J. G. Houston, *ibid.*, **30**, 1328 (1965).

(5) (a) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89**, 749 (1967); (b) P. Greenzaid, Z. Rappoport, and D. Samuel, *Trans. Faraday Soc.*, **63**, 2131 (1967).

(6) (a) Y. Pocker and J. E. Meany, *J. Phys. Chem.*, **71**, 3113 (1967); **72**, 655 (1968); **73**, 1857 (1969); (b) Y. Pocker and D. G. Dickerson, *ibid.*, **73**, 4005 (1969).

(7) M. G. Champetier and P. Le Henaff, *C. R. Acad. Sci., Ser. C*, **265**, 175 (1967).

sary that the two substrates remain apart until immediately prior to discharge of the heating cell capacitor. The rate of aldolization is sufficiently slow that no appreciable fraction of the aldehyde is lost due to aldol condensation in the first several seconds if concentrations of aldehyde and base are small.[4] Experiments were conducted in such a manner that the T-jump occurred precisely 2 sec after the mixing of reactants. No correction was made for the amount of hydroxide ion used up in conversion of aldehyde hydrate to hydrate anion, since the concentration of hydroxide ion is in all cases several times that of the hydrate.

A heating pulse of 250 μsec and oscilloscope delay of 400 μsec proved to be sufficient to ensure that perturbations attributable to the heating pulse were absent. The rate of isobutyraldehyde equilibration was determined at the carbonyl absorption maximum (285 nm) spectrometrically.

All nmr experiments were made using a Varian Model A-60A spectrometer equipped with a temperature controller Model V6040. The probe temperature was determined by the methanol resonance technique.[8] The ratio of the area of the methyl doublet of the hydrate to that of the free aldehyde was determined by use of a polar planimeter, Keuffel and Esser Model 62-0015, and found to be highly reproducible. The average of three integrations was in all cases well within 0.5% of any individual integration. No appreciable variation in the relative areas could be detected for solutions 0.1–0.3 *M* in aldehyde.

All ultraviolet measurements were made using a Cary Model 16 spectrometer and 10-cm thermostated cells. Solutions and pipettes were precooled prior to measurements in a bath adjusted to the same temperature as that of the cell. Since isobutyraldehyde reacts in basic solution to yield aldol condensation products, it was necessary to determine the absorbance (at 285 nm) immediately after mixing the aldehyde and base solutions. Several solutions of varying concentrations of sodium hydroxide were adjusted so that the total volume was 45 ml and then immersed in a thermostated bath. Another solution of isobutyraldehyde in doubly distilled water was also brought to thermal equilibrium and 5-ml aliquots were added to each base solution just before the uv determination. The amount of time (approximately 50 sec) necessary to mix solutions and place them in the cell was taken into account and the actual absorbance reading was determined by extrapolation to the time of mixing. Although the extrapolation never gave a very large difference in absorbance value, it was felt to be a more accurate measure of the true value immediately after the equilibration of free aldehyde, hydrate, and hydrate anion. The absorbance of the aldehyde in the absence of base was determined similarly, using a sample containing doubly distilled water rather than sodium hydroxide.

Results

The nmr spectrum of an aqueous solution of isobutyraldehyde shows two methyl doublets, one of which is at a higher field than the other. The area ratios of the two doublets are dependent on the temperature. Contamination of the sample with a trace amount of isobutyric acid shows that the methyl doublet of isobutyric acid is easily discernible in the mixture of hydrate, aldehyde, and acid. The low-field methyl doublet was attributed to isobutyraldehyde, and the higher field methyl doublet was attributed to isobutyraldehyde hydrate. The equilibrium constant for hydration was calculated as the ratio of integrated areas of the two doublets.

The calculated equilibrium constants at a particular value of the oscillator field strength are found to correlate precisely (linear least-squares analysis) with the equation

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \qquad (4)$$

where ΔH° is the standard enthalpy change (assumed to vary negligibly over the temperature range studied), ΔS° is the standard entropy change, R is the gas constant (cal/deg mol), and T is the temperature (degrees Kelvin). The value of K_h calculated is found to depend greatly on the field strength at which the experiment is conducted. For example, at 286.55°K, the values of K_h calculated are 0.884 (0.005 mG), 0.896 (0.0075 mG), 0.911 (0.010 mG), and 1.120 (0.020 mG). The results of a number of experiments are summarized in Tables I and II. Values of K_h at 0 mG field strength are obtained as follows. Values of K_h at 0.02, 0.01, 0.0075, and 0.0050 mG are calculated for a particular temperature. The results of these calculations are then placed on a graph correlating K_h and field strength, and a smooth curve is drawn to enable extrapolation to zero field strength (Figure 1).

TABLE I

DEPENDENCE OF K_h ON TEMPERATURE AND FIELD STRENGTH

	K_h		
Temp, °K	0.0050 mG	0.0075 mG	0.0100 mG
320.42		0.334	0.353
317.52			0.412
316.55		0.356	0.348
303.49	0.580	0.528	
301.07	0.615	0.598	0.608
297.20	0.612	0.639	0.640
295.75	0.667	0.640	0.686
292.84	0.678	0.723	0.769
290.91	0.788	0.805	0.805
286.55	0.884	0.896	0.911
283.65	0.931	1.051	1.035
277.84	1.219	1.133	1.137
276.39	1.285	1.250	1.277
272.52	1.585	1.620	1.712

TABLE II

SLOPES AND INTERCEPTS OF EQUATION 4 AS A FUNCTION OF APPLIED OSCILLATOR FIELD STRENGTH

Field, mG	No. of expts	ΔH°, kcal/mol	ΔS°, eu
0.0200	22	−5.01	−17.2
0.0100	14	−5.36	−18.9
0.0075	13	−5.44	−19.2
0.0050	10	−5.59	−19.7
0.0000		−5.64	−19.9

The ultraviolet spectral results are in accord with these nmr results, as evidenced by the temperature dependence of the optical density at 285 nm. A dilute solution of isobutyraldehyde in water obeys the Beer–Lambert law. The apparent extinction coefficient is given by the equation

$$\epsilon_{app} = \frac{\epsilon_{C=O}}{1 + K_h} \qquad (5)$$

The equilibrium constant for the hydrate–hydrate anion equilibrium was determined by the equation

$$K_{h^-} = \frac{\Delta D(K_h + 1)}{DK_h[OH^-]_e} \qquad (6)$$

where D, ΔD, and $[OH^-]_e$ are defined as the optical density of a solution in the absence of base, the difference in optical density between that of such a solution and that of a solution of identical isobutyraldehyde concentration in the presence of base, and the equilibrium concentration of base, respectively. For example, at 34.0° a solution calculated to be 1.548 *M*

(8) A. L. Van Geet, *Anal. Chem.*, **40**, 2227 (1968); **42**, 679 (1970).

sodium hydroxide before the addition of isobutyraldehyde had an absorption of 0.7664, whereas a solution of identical isobutyraldehode concentation in water alone had an absorption of 1.1195.[9] From these data a value of 0.956 for K_{h-} may be calculated ($K_h = 0.337$). The average of six values determined at 34.0° is 0.93 with an average deviation of ± 0.09. A summary of results appears in Table III.

TABLE III
EFFECT OF TEMPERATURE ON THE ISOBUTYRALDEHYDE HYDRATE–HYDRATE ANION EQUILIBRIUM CONSTANT

Temp, °C	K_{h-}, N^{-1}	No. of expt
34.0	0.932 ± 0.09[a]	6
29.0	0.968 ± 0.05	5
28.8	1.170 ± 0.04	8
21.0	1.045 ± 0.09	8
15.0	1.031 ± 0.17	9

[a] Average deviation from the average.

The value of k_{obsd} was determined by a linear least-squares analysis of the integrated first-order equation

$$\ln \log \frac{P}{P_e} = -k_{obsd}t + \ln \log \frac{P_0}{P_e} \quad (7)$$

where P is the amplitude of the recorded photomultiplier signal and the subscripts 0 and e refer to the initial and equilibrium values. In general the data gave excellent linear correlations for time periods in excess of 3 half-lives. The temperature at which the reaction occurred was determined by the equation

$$\ln \left(\frac{a_T}{a_0 + \frac{1}{\epsilon_l} \log \frac{P_0}{P_e} - 1} \right) - \ln \{K_h(1 + K_{h-}[OH^-])\} = 0 \quad (8)$$

where a is the amount of aldehyde present and the subscripts T and 0 refer to the total amount of aldehyde and the initial amount of aldehyde present in the free form. The left side of eq 8 will at some temperature (from which are calculated the values of K_h and K_{h-}) satisfy the equality expressed by eq 8. That temperature is the temperature at which the reaction occurred.

Variations in the magnitude of the temperature jump were observed even though the ionic strength remained constant (0.1). These variations are attributable to the different ions present in the various solutions employed. A summary of results for the sodium hydroxide and perchloric acid catalyzed equilibrations of isobutyraldehyde appears in Tables IV and V.

Discussion

A number of investigators have reported on the common features a solution containing both the free carbonyl and its hydrate shows in its nmr spectrum.[2-5] The nmr spectrum at several different oscillator field strengths reveals the degree to which the applied field has affected the calculated equilibrium constant. This behavior is most reasonably attributable to the effects of selective saturation. Anderson has reported that saturation effects generally increase with decreasing half-width.[10] The experimental findings reveal

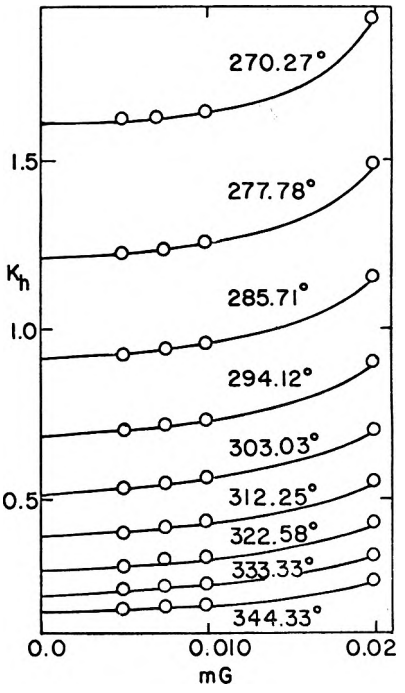


Figure 1.—Variations in apparent values of K_h as a function of R_f field at several temperatures.

that the half-width of the aldehyde band is less than that of the hydrate band. These results, coupled with the generality of Anderson, lead to the expectation that the methyl protons of the aldehyde are saturated to a greater degree than those of the hydrate, in accordance with the results of Table I.

The correlation of the logarithm of the equilibrium constant with $1/T$ tacitly assumes that $\Delta H°$, the standard enthalpy change, is nearly temperature independent. This is known to be true for the hydration of acetaldehyde, for which $\Delta C_p°$ is reported to be only -10 ± 5 cal/deg mol,[11] and appears to be true in the present case, where there is no obvious curvature in the plot of $\ln K_h$ *vs.* $1/T$. A summary of thermodynamic parameters and the results of other investigators appears in Table VI.

The results of this study are in excellent agreement with those of Pocker and Dickerson. Other results[3,4] appear to be in error by slightly overestimating the magnitude of both $\Delta H°$ and $\Delta S°$.

We observed no variation in the extinction coefficient other than that attributable to experimental difficulties over a wide range of temperatures. The calculated value, 22.13 ± 0.52, is within the experimental uncertainty of Pocker and Dickerson's value of 22.3 determined at 0° by extrapolation to a time where the initially added isobutyraldehyde was completely unhydrated. One may conclude that the extinction coefficient does not vary appreciably as a function of temperature. This result is reasonably strong evidence in support of the hypothesis that only the aldehyde and hydrate species are present in aqueous solution over the range of temperatures herein employed. If a significant fraction of enol is present, the equilibrium between the aldehyde and its enol is surprisingly temperature independent (over the temperature range 0–35°). Furthermore, no enol absorption signals were detectable in the nmr spectra.

(9) The absorptivity of all solutions has been corrected for the small but nonnegligible absorption of the sodium hydroxide solutions at 285 nm.

(10) W. A. Anderson, *Phys. Rev.*, **104**, 850 (1965).

(11) J. L. Kurz, *J. Amer. Chem. Soc.*, **89**, 3524 (1967).

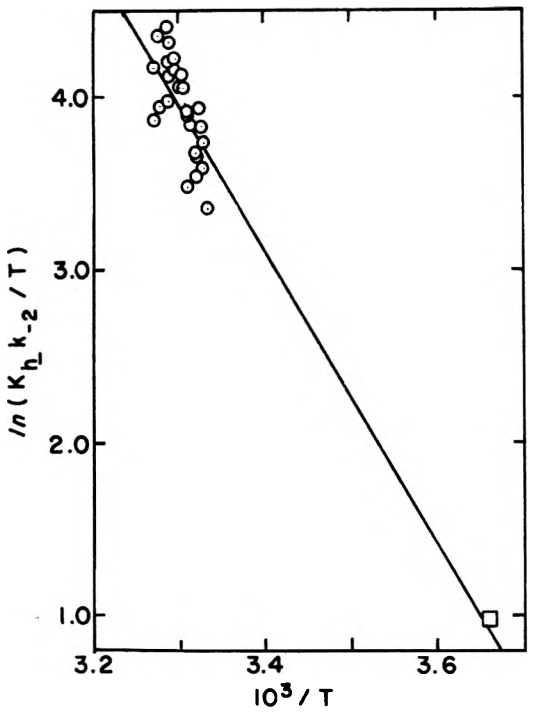


Figure 2.—Correlation (least squares) of ln $(K_h k_{-2}/T)$ *vs.* $1/T$ (standard deviation, 0.18).

The only previous report on the acidity of isobutyraldehyde hydrate gave a K_{h-} value of 1.68 at 25°.[4a] The results of the present study indicate that the true value is considerably smaller (K_{h-} 1.03 at 25°). Although the temperature dependence of this equilibrium is very slight, it does appear that the hydrate is less acidic at high temperatures than at low temperatures. On the basis of the five values at 15–34°, the calculated standard enthalpy change and entropy change for the reaction of the hydrate with hydroxide ion is −0.6 kcal/mol and −1.9 eu, respectively. The acidity constant of isobutyraldehyde hydrate at 25° is 1.03×10^{-14}, which may be compared with the values of acetaldehyde (2.7×10^{-14}) and formaldehyde (5.4×10^{-14}) hydrates determined by Bell and Onwood.[12]

The rate of appearance of isobutyraldehyde, following thermal equilibration of the reaction cell, is given by the equation

$$\frac{d[a]}{dt} = (k_{-1}[h] + k_{-2}K_{h-}[h][OH^-]) - (k_1[a] + k_2[a][OH^-]) \quad (9)$$

As shown in Scheme I, the rate constants k_1 and k_{-1} are specifically associated with the reaction of isobutyraldehyde and water, and the rate constants k_2 and k_{-2} are to be associated with the reaction of isobutyraldehyde and hydroxide ion. The assumption is that the equilibration of isobutyraldehyde hydrate with the hydrate anion (h $\rightleftharpoons$ h$_-$) is much faster than any of the other reactions.[13]

The pseudo-first-order rate constant k_{obsd} is given by the equation

$$k_{obsd} = (k_2[OH] + k_1)\left(1 + \frac{1}{K_h(1 + K_{h-}[OH^-])}\right) \quad (10)$$

(12) R. P. Bell and D. P. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1962).
(13) M. Eigen, *Discuss. Faraday Soc.*, **39**, 7 (1965).

TABLE IV
EXPERIMENTAL RESULTS OF BASE-CATALYZED EQUILIBRATION OF ISOBUTYRALDEHYDE

NaOH, *M*	*KV*	P_e[a]	Temp,[b] °K	k_{obsd}, sec^{-1}
0.05[c]	4.0	81.75	304.79	1460
	3.75	83.25	304.16	1167
	3.5	92.00	300.84	1174
	3.0	94.75	299.76	1348
0.045[d]	5.0	80.00	305.64	1276
	4.75	81.00	305.16	1256
	4.5	83.50	304.10	1365
	4.25	87.00	302.70	1091
	4.0	86.50	302.88	1172, 817
	3.75	88.75	302.02	1092, 893
	3.5	90.00	301.54	1050, 1124
	3.25	91.50	301.01	904
	3.0	92.38	300.72	980
0.040[d]	5.0	80.75	305.30	844
	4.5	84.75	303.58	1038
	4.25	86.50	302.88	1213
	4.0	87.50	302.51	907
	3.5	90.13	301.54	984
	3.25	92.50	300.66	1099
	3.0	93.25	300.38	852
0.035[d]	5.0	81.25	305.10	806
	4.75	83.75	304.03	961
	4.5	84.75	303.58	1087
	4.25	87.75	302.39	983
	4.0	87.00	302.70	845, 1017
	3.75	90.00	301.54	373
	3.5	91.00	301.19	548
	3.25	91.63	300.95	614
	2.5	95.00	299.76	459
0.030[d]	5.0	81.00	305.16	1220
	4.75	83.13	304.29	1094
	4.5	86.00	303.07	898
	4.25	87.00	302.70	950
	4.0	86.50	302.88	660
	3.75	88.50	302.14	441
	3.5	90.63	301.30	541
	3.25	92.25	300.72	426, 627
	3.0	93.00	300.49	407, 504
0.020[d]	5.0	83.50	304.10	713
	4.75	86.50	302.88	648
	4.5	85.00	303.51	613
	4.0	88.25	302.20	458
	3.0	93.25	300.38	351, 390
0.010[c]	3.5	91.25	301.07	166
	3.25	91.25	301.07	170
	3.0	92.00	300.84	234
	2.5	93.00	300.49	128

[a] Photomultiplier signal at equilibrium relative to the initial value (at $t = 0$) of 800 mV in per cent. [b] Temperature (°K) calculated. Initial temperature 298.15°K. [c] Isobutyraldehyde $0.5 \times 8.339 \times 10^{-2}$ *M*, μ 0.1. [d] Isobutyraldehyde $0.5 \times 8.278 \times 10^{-2}$ *M*, μ 0.1.

from which are obtained the catalytic constants for acid and base catalysis. The results of our study are found in Table VII along with those results obtained by other investigators.[4,6,14]

Pocker and Dickerson have reported that the acid-catalyzed hydration of isobutyraldehyde is characterized by a catalytic constant ($k_{h+} + k_{-h+}$) of 97.5 M^{-1} sec^{-1} at 0°. Their results, based on a series of successive approximations, were under the constraints of the best fitting to a linear polynomial in hydronium ion, hydroxide ion, water, acetate ion, and acetic acid, from which were derived the catalytic coefficients of

(14) J. Hine and F. A. Via, *J. Amer. Chem. Soc.*, **94**, 190 (1972).

TABLE V

EXPERIMENTAL RESULTS FOR ACID-CATALYZED EQUILIBRATION OF ISOBUTYRALDEHYDE

$HClO_4$, M	KV	P_e[a]	Temp,[b] °K	k_{obsd}, sec^{-1}	$HClO_4$, M,	KV	P_e[a]	Temp,[b] °K	k_{obsd}, sec^{-1}
0.090	5.0	75.00[c]	312.2	146	0.050	5.0	76.88[c]	310.9	86.5
	4.25	89.87[d]	311.0	134		4.25	81.50	307.7	73.6
	4.0	84.50[c]	305.9	121		4.0	83.50	306.6	71.8
		91.25[d]	309.0	130		3.5	87.50	304.2	71.8
	3.5	93.00	306.6	104		3.0	90.00	302.9	52.3
	3.25	93.75	305.6	98.4	0.040	4.25	87.50[e]	307.6	41.0
	3.0	94.63	304.4	99.6			91.88[d]	308.1	68.8
		91.25[c]	302.3	71.2		4.0	92.50	307.3	63.6
	2.5	93.25	301.2	81.7		3.5	90.63[e]	305.0	31.2
		96.38[d]	302.3	92.1			94.00[d]	305.3	51.7
0.0878	4.0	93.50	305.9	108		3.25	91.88[e]	304.0	28.6
	3.5	95.13	303.8	113			94.88[d]	304.2	53.5
	3.25	95.63	303.2	102		3.0	93.50[e]	302.7	30.3
	3.0	96.25	302.4	96.1			95.63[d]	303.2	36.8
	2.5	97.38	301.1	99.7		2.5	95.06[e]	301.5	23.7
0.080	4.25	92.25	307.7	126	0.025	4.25	79.00[c]	309.3	29.4
	3.5	94.25	305.0	99.8			90.63[d]	309.9	30.3
	3.25	95.44	303.5	102		4.0	81.50[c]	307.7	28.5
	2.5	97.44	301.0	82.0			91.50[d]	308.6	29.5
0.075	5.0	73.43[c]	313.4	83.2		3.5	85.00[c]	305.5	27.8
	4.25	89.15[e]	305.6	130			93.00[d]	306.6	24.1
	4.0	84.00[c]	306.3	90.3		3.25	86.50[c]	304.8	22.9
		90.13[e]	305.4	95.4			93.75[d]	305.6	23.4
	3.5	86.00[c]	305.0	83.1		3.0	89.00[c]	303.5	22.6
		92.13[e]	303.8	80.4			94.50[d]	304.6	20.8
	3.25	92.81	303.2	71.4		2.5	96.25	302.4	23.3
	3.0	90.50[c]	302.6	86.4	0.01	4.25	77.50[c]	310.4	12.2
		94.50[e]	302.0	76.8			90.00[d]	311.0	11.5
0.060	4.25	88.50	306.7	104		4.0	90.63	309.9	13.2
		91.75[d]	308.3	102		3.75	82.50[c]	307.2	11.8
	4.0	90.13[e]	305.4	88.1		3.5	85.75	305.2	11.3
		92.88[d]	306.8	99.2			91.50[d]	308.6	9.28
	3.5	92.13[e]	303.8	63.0		3.25	93.25	306.3	9.14
	3.25	92.75	303.3	55.6		3.0	89.75[c]	303.1	10.5
		95.13[d]	303.8	79.6			94.00[d]	305.3	8.32
	3.0	93.75[e]	302.5	56.3		2.5	95.94	302.8	7.96
		95.88[d]	302.9	89.6					
	2.5	95.69[e]	301.1	45.9					
		97.31[d]	301.2	51.0					

[a] Photomultiplier signal at equilibrium relative to the initial value (at $t = 0$) of 800 mV in per cent. [b] Temperature calculated. Initial temperature 298.15°K. [c] Isobutyraldehyde 0.030 M, μ 0.1. [d] Isobutyraldehyde 0.012 M, μ 0.1. [e] Isobutyraldehyde 0.020 M, μ 0.1.

TABLE VI

SUMMARY OF THERMODYNAMIC PARAMETERS

Reaction	ΔH[a]	ΔS[b]	$\epsilon_{C=O}$[c]	K_X 0°	K_X 25°	K_X 35°	Ref
X = h	−6.5	−26.9			0.61	0.428	5
	−7.3	−26	17.7		0.44		4
	−5.8	−20.4	22.3	1.58	0.66	0.43	8b
	−5.6	−19.9	22.1	1.43	0.600	0.440	This work
	−5.4				0.615		11
					0.43		7a
X = h_	−0.6	−1.9		1.13	1.03	1.00	This work
					1.68		5
X = ao^-	−6.2	−21.8		1.62	0.620	0.441	This work

[a] kcal/mol. [b] cal./mol deg. [c] l./mol cm.

TABLE VII

SUMMARY OF RATE CONSTANTS FOR THE ACID- AND BASE-CATALYZED HYDRATION OF ISOBUTYRALDEHYDE

Rate constant	K_X 0°	K_X 25°	K_X 35°	Ref
$(k_{H_2O} + k_{-H_2O})$[a]	0.000515			8d
			0.00769	31
$(k_{h+} + k_{-h+})$[b]	97.5			8d
	122	693	1340	This work
			1470	5b
k_{h+}	71.5	260	411	This work
k_{-h+}	50.0	433	933	This work
$(k_2 + K_{h-}k_{-2})$[b]	1770			8d
	1660	1590	37,000	This work
			32,000	31
k_2	987	5980	11,400	This work
$K_{h-}k_{-2}$	688	10,000	26,000	This work
k_{-2}	610	9690	26,000	This work

[a] Dimensions, sec^{-1}; water included in the rate constant. [b] Dimensions, M^{-1}, sec^{-1}.

each substrate. They have also reported on the base-catalyzed hydration of isobutyraldehyde, where it was found that a linear polynomial was best fit by use of the parameter k_{OH-} equal to 1.77×10^3 M^{-1} sec^{-1} at 0°. At the small concentration of hydroxide ion present, k_{OH-} is essentially identical with what we define as $(k_2 + K_{h-}k_{-2})$.

The results of Pocker and Dickerson and those of Hine and Houston have been used in determining the most reasonable slope and intercept associated with the equation correlating ln k/T with reciprocal temperature. Those values of K_hk_{-2} and $(k_{h+} + k_{-h+})$ determined at 0°, where the rate of reaction is considerably slower, should serve to estimate the true rate constant better than values that we would ob-

tain by extrapolation. The enthalpy and entropy of activation were calculated from the plot of ln $(K_h k_{-2}/T)$ *vs.* $1/T$ shown in Figure 2.[15]

The hydrogen ion and hydroxide ion catalyzed hydration of isobutyraldehyde is characterized by enthalpies of activation of 7.8 and 11.7 kcal/mol, respectively. Enthalpies of activation for dehydration of isobutyraldehyde hydrate are 13.4 kcal/mol for the acid catalysis and 17.3 kcal/mol for hydroxide ion catalysis. Calculated entropies of activation for hydration are 26 and 45 eu for hydrogen ion and hydroxide ion, respectively. Entropies of activation for the acid- and base-catalyzed dehydration of isobutyraldehyde hydrate are 46 and 65 eu, respectively.

The magnitudes of our rate constants are similar to those recently obtained by Ahrens and Maass for the acid-catalyzed hydration of 2-methylbutyraldehyde.[16] These authors apparently assumed that the extinction coefficient of their aldehyde was the same in water as in tetrahydrofuran. Because of the uncertainties arising from this approach,[2] it is probably not worthwhile to make a detailed comparison of data.

The hydration and dehydration of isobutyraldehyde has previously been reported to be subject to both general acid and general base catalysis.[4a,6,16b] In an attempt to measure the rate of carbinolamine formation through the use of dimethylamine and isobutyraldehyde, we observed on several occasions the marked acceleration of the overall rate of hydration, apparently attributable to the action of dimethylamine as a general base. Unfortunately, we have not been successful in our attempts to determine the rates of carbinolamine formation, which appears to proceed at a pace beyond the capabilities of our present instrumentation.

Registry No.—Isobutyraldehyde, 78-84-2.

(15) Values of k_{h+} were determined by the equation $k_{h+} = k_{obsd}[HClO_4]^{-1} \cdot K_h/(1 + K_h)$. A weighting factor of 7 was used and the value of k_{h+} taken from the work of Hine and Houston entered into the correlation. Values of k_{h+} and $K_h k_{-2}$ (*ca.* 728 M^{-1} sec^{-1} at 0°) taken from the work of Pocker and Dickerson were each weighted as one.

(16) M. Ahrens and G. Maass, *Angew. Chem., Int. Ed. Engl.*, **10**, 80 (1971)

Reaction of Sulfonium Ylides with Diene Esters

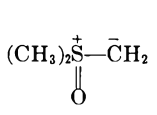
CYRIL S. F. TANG AND HENRY RAPOPORT*

Department of Chemistry, University of California, Berkeley, California 94720

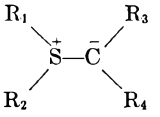
Received February 13, 1973

The reaction between diphenylsulfonium isopropylide and the diene esters, ethyl 1,3-cyclohexadienecarboxylate and methyl *trans*-2,4-hexadienoate, has been examined in dimethoxyethane, tetrahydrofuran, and tetrahydropyran. Both gave mixtures of isomeric cyclopropane products resulting from ylide addition across the α,β and γ,δ double bonds. The isomer distribution in the case of the cyclic diene ester was found to be solvent dependent, whereas the acyclic system showed preferential addition to the γ,δ double bond irrespective of solvent. The widely used method of preparing *n*-alkyldiphenylsulfonium salts by reaction between diphenyl sulfide, *n*-alkyl halide, and silver tetrafluoroborate was found to give mixtures of primary and secondary sulfonium salts. However, pure primary alkyldiphenylsulfonium salts can be prepared, although in low yield, by the reaction of diphenyl sulfide with *n*-alkyl trifluoromethanesulfonates.

Since the isolation of the first sulfur ylide[1] other more reactive and less stable sulfur ylides such as **1** and **2**



1



2a, $R_1 = R_2 = CH_3$; $R_3 = R_4 = H$
2b, $R_1 = CH_3$; $R_2 = C_6H_5$; $R_3 = R_4 = H$
2c, $R_1 = R_2 = C_6H_5$; R_3, R_4 = H or alkyl
1d, $R_1 = R_2 = C_6H_5$; $R_3 = R_4 = CH_3$

have been prepared.[2] These ylides have found much use in organic syntheses, especially for the formation of epoxides and cyclopropanes. Both dimethylsulfoxonium methylide (**1**) and sulfonium alkylides **2** add to aromatic and unconjugated aldehydes and ketones to give epoxides. However, the sulfoxonium ylide **1** adds to α,β-unsaturated ketones to give cyclopropanes, while the sulfonium ylides **2** add to the same unsaturated systems to give oxiranes exclusively.[2,3] Further studies showed that, under certain circumstances, **2** also will add to an olefin conjugated to an ester.[2c,3,4]

Much less is known about the action of sulfur ylides on substrates containing extended conjugation, *viz.*, an $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl. The ylide **1** in DMSO (dimethyl sulfoxide) has been shown to add to eucarvone to give the α,β-cyclopropyl ketone **3**, while **2a** in DMSO–THF (tetrahydrofuran) added exclusively at the carbonyl of eucarvone to give the oxirane **4**.[2b] Only two other examples of sulfur ylide addition to an $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl system have been reported. The dicyclopropylamide **5** was obtained when 2 mol of ylide **1** in DMSO or DMF (dimethylformamide) were allowed to react with sorbic acid anilide.[5] The other example is the addition of diphenylsulfonium isopropylide (**2d**) in DME (dimethoxyethane) to methyl 5-methyl-*trans*-2,4-hexadienoate to give methyl *trans*-chrysanthemate (**6**).[6]

We now wish to report our findings on the reaction of diphenylsulfonium isopropylide **2d** with a cyclic diene ester, ethyl 1,3-cyclohexadienecarboxylate (**7**), and an acyclic diene ester, methyl *trans*-2,4-hexadienoate (**10**, methyl *trans,trans*-sorbate).

(1) C. K. Ingold and J. A. Jessop, *J. Chem. Soc.*, 713 (1930).

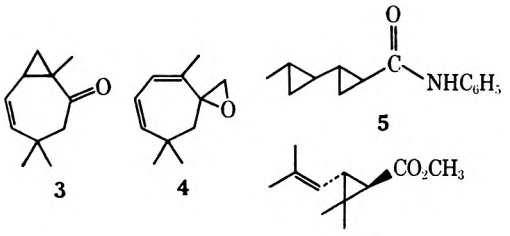
(2) (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962); (b) **84**, 3782 (1962). (c) V. Franzen and H. E. Driessen, *Chem. Ber.*, **96**, 1881 (1963). (d) A. W. Johnson, V. J. Hruby, and J. L. Williams, *J. Amer. Chem. Soc.*, **86**, 918 (1964).

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965), and references therein.

(4) E. J. Corey and M. Chaykovsky, *Tetrahedron Lett.*, 169 (1963).

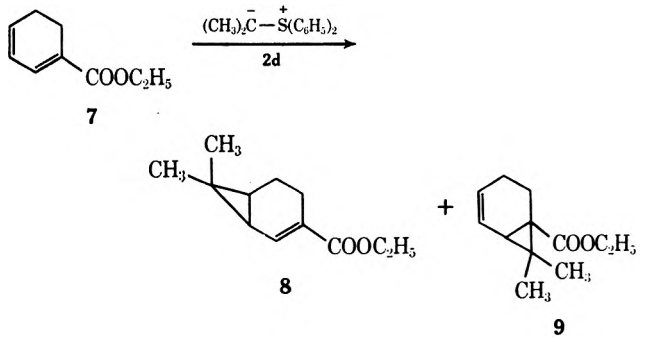
(5) H. Metzger and K. Seelert, *Angew. Chem.*, **75**, 919 (1963).

(6) E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, **89**, 3912 (1967).



3 4 5 6

When the cyclohexadiene ester **7** was allowed to react with **2d** in DME, a 70% yield of cyclopropane products was obtained consisting of **8** and **9** in a ratio of 4:1. Compounds **8** and **9** were identified by their uv, ir, and nmr spectra. The α,β-unsaturated ester moiety of **8** was evident from its ir (1690 cm^{-1}) and uv (250 nm) absorptions, whereas the unconjugated ester **9** exhibited ir



7 8 9

and uv maxima at 1720 cm^{-1} and 205–210 nm, respectively. In their nmr spectra, the β-vinylic proton of **8** appeared at δ 7.1, integrating for one proton, whereas the vinyl protons of **9** absorbed at δ 5.66, integrating for two protons.

When the reaction was carried out in THF the cyclopropane product consisted of **8** and **9** in a 1:2 ratio. The cause of this reversal of isomer distribution could be either the change in solvent or in base, or both. We had employed dichloromethyllithium[7] as the base for generation of ylide **2d** when the solvent was DME and *tert*-butyllithium when THF was the medium, since *tert*-butyllithium reacts with DME. Therefore, sulfonium ylide **2d** also was generated by means of dichloromethyllithium in THF and was allowed to react with **7** in THF. The cyclopropane products again showed 33% addition occurring at the γ,δ position and 66% at the α,β position. Using THP (tetrahydropyran) as solvent and *tert*-butyllithium as base, we observed a similar preferential attack at the α,β position, and these results are presented in Table I.

The extent of this dramatic dependence of isomer distribution on solvent then was examined with the acylic diene ester, **10**. When **10** was allowed to react with the ylide **2d** in DME, the γ,δ- and α,β-addition products **11** and **12**, respectively, were obtained in a ratio of 4:1. Reaction of **10** with **2d** in THF and THP, however, also showed preferential attack at the γ,δ position to give predominantly **11** (Table I) in contrast to the cyclic diene ester **7**, where the isomer distribution was reversed on changing the solvent.

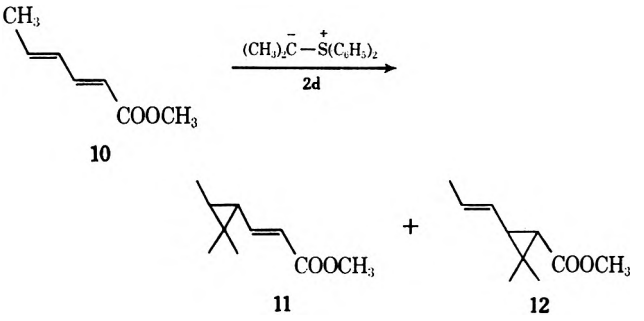
Barring solvation and steric effects, a carbanion should preferentially add to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl systems at the δ position, as in the case of Michael

(7) E. J. Corey, M. Jautelat, and W. Oppolzer, *Tetrahedron Lett.*, 2325 (1967).

TABLE I

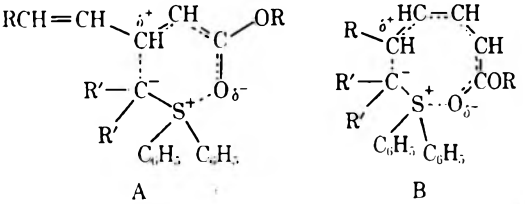
REACTION OF DIPHENYLSULFONIUM ISOPROPYLIDE (2d) WITH ETHYL 1,3-CYCLOHEXADIENECARBOXYLATE (7) AND METHYL *trans*-2,4-HEXADIENOATE (10) TO FORM CYCLOPROPANES

Substrate	Base	Solvent	Ratio of α,β to γ,δ addition 9:8	12:11
7	$CHCl_2Li$	DME	1:4	
7	*t*-BuLi	THF	2:1	
7	$CHCl_2Li$	THF	2:1	
7	*t*-BuLi	THP	3:1	
10	$CHCl_2Li$	DME		1:4
10	*t*-BuLi	THF		1:4
10	*t*-BuLi	THP		1:3.5



10 11 12

additions.[8] Although the reaction of sulfur ylides with both unconjugated and conjugated carbonyl systems proceeds by similar carbanion attack at a positive center of the substrate, the sulfonium ylide reaction is complicated by the fact that the carbanion is adjacent to a positive sulfur ion. Thus the degree of interaction between the sulfur cation of the ylide and the carbonyl oxygen should consequently affect the extent of addition across the α,β or γ,δ double bonds. In the extreme case, where the interaction between these two centers is maximum, a six-membered (A) or eight-membered (B)



A B

cyclic complex is formed. One would expect predominant addition across the α,β double bond, since the six-membered cyclic intermediate is favored. In general, depending upon the degree of $^{+}S\cdots O^{\delta-}$ interaction, the amount of γ,δ addition will decrease as this interaction increases.

This picture may be used to rationalize our experimental observations. Normally, γ,δ addition will be favored, as it is for all cases with the acyclic diene ester **10**. With the cyclohexadiene ester **7**, the rigidity imposed by the cyclic system allows a stronger polar interaction, and complexing of type A leads to predominant α,β addition in THF and THP. When DME is the solvent, this polar interaction between ylide and substrate is diminished by solvation of the sulfur cation, involving coordination with the two oxygen atoms of DME. This weakening of the ylide–substrate complexing results in a return to the predominance of the normal γ,δ addition in DME.

(8) (a) E. H. Farmer and A. T. Healey, *J. Chem. Soc.*, 1060 (1927); (b) E. H. Farmer and T. N. Mehta, *ibid.*, 1610 (1930); (c) J. Bloom and C. K. Ingold, *ibid.*, 2765 (1931).

It should be noted that the reaction between **2d** and methyl 5-methyl-*trans*-2,4-hexadienoate in DME has been reported[6] to give only α,β addition, yielding **6**. This difference with our results can be attributed to the presence of the 5-methyl group in **6** which sterically hinders carbanion approach at the δ position. Such steric hindrance was also observed in the case of Michael additions to methyl 5-methyl-*trans*-2,4-hexadienoate.[9]

In the course of our work with sulfonium ylide **2d** we investigated the preparation of *n*-alkyldiphenylsulfonium salts **13**. When R = CH_3, the salt **13a** can be

$$(C_6H_5)_2\overset{+}{S}-CH_2R\ X^-$$

13a, R = CH_3; X = Br^-, I^-, BF_4^-, $CF_3SO_3^-$
b, R = CH_2CH_3
c, R = $CH_2CH_2CH_3$

prepared unambiguously by treatment of diphenyl sulfide with triethyloxonium tetrafluoroborate[7] or by reaction between diphenyl sulfide, ethyl iodide, and silver tetrafluoroborate.[10] However, for longer chain *n*-alkylsulfonium salts, *e.g.*, **13b** and **13c**, we found that the use of diphenyl sulfide, *n*-alkyl halide, and silver tetrafluoroborate gave, distinctly, a mixture of primary and secondary diphenylsulfonium salts, contrary to previous reports.[10]

Initially, we carried out salt formation by addition of silver tetrafluoroborate to a solution of diphenyl sulfide and *n*-butyl bromide in methylene chloride. The crystals which were isolated showed, in the nmr, a mixture of primary and secondary sulfonium salts in the ratio of 3:2. The protons adjacent to the positive sulfur in the primary and secondary salts were seen at δ 4.26 and 4.88, respectively.[11a] In an attempt to obtain the pure primary sulfonium salt, we repeated the reported[10] procedure in which *n*-butyl bromide was added in large excess. Once again the nmr of the crystals isolated from this procedure[11b] displayed signals at δ 4.48 and 5.1 corresponding to the methylene and methine protons adjacent to positive sulfur in the primary and secondary sulfonium salts, respectively, in the ratio of 3:2. Similarly, *n*-propyl iodide by the previous[10] method gave a mixture of primary and secondary sulfonium salts in the ratio of 2:1, respectively.[11b]

In seeking a preparation of pure *n*-alkylsulfonium salts, we found that reaction between diphenyl sulfide and *n*-alkyl triflates (trifluoromethanesulfonates)[12] at temperatures between −35 and +45 in carbon tetrachloride gave unrearranged *n*-alkyldiphenylsulfonium triflates, although in poor yield. It was also observed that treatment of silver triflate with *n*-propyl iodide[13] resulted in greater than 40% isomerization to the isopropyl triflate. However, the unrearranged primary alkyl triflate could be obtained by treatment of the *n*-alkyl alcohol with trifluoromethanesulfonic acid anhydride.[12]

The dependence of isomer distribution upon solvent in the case of cyclic diene ester, **7**, provides a convenient and selective route into the carene system using the sulfonium ylides. Although the widely used method of preparing *n*-alkylsulfonium salts by means of silver tetrafluoroborate, *n*-alkyl halide, and diphenyl sulfide[2d,14] is not suitable for alkyl groups greater than ethyl, an unambiguous entree into this class of salts for alkyl groups higher than ethyl would be to alkylate diphenyl sulfide with the proper *n*-alkyl triflate. Alternatively, the alkylation of diphenylsulfonium methylide with alkyl halides might be a practical method for preparing such salts.

Experimental Section

Ethyl 1,3-cyclohexadienecarboxylate (**7**) was prepared as described.[15] Methyl *trans,trans*-sorbate was obtained by esterification of *trans-trans*-sorbic acid using the Stodola method.[16] Uv spectra were recorded on a Cary 14 spectrophotometer and are reported as $\lambda_{max}^{95\%\ EtOH}$ in nanometers; ir spectra were obtained on a Perkin-Elmer 236 spectrophotometer and are reported as $\nu_{max}^{CCl_4}$ in reciprocal centimeters. Nmr values are reported as δ values and were obtained on a Varian T-60 using CCl_4 as solvent and internal TMS (δ 0) unless otherwise stated. Mass spectra were obtained on a Varian M-66 spectrometer. Sample purity was determined by tlc and glpc using an Aerograph gas chromatograph, Model A-90-P. Analytical samples were collected at 160° from a 20-ft 10% SE-30 column. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley.

7,7-Dimethyl-3-ethoxycarbonyl-2-norcarene (8) and 7,7-Dimethyl-6-ethoxycarbonyl-2-norcarene (9).—To a mixture of 0.54 g (0.41 ml) of CH_2Cl_2 and 50 ml of DME was added 2 g (6.35 mmol) of isopropyldiphenylsulfonium tetrafluoroborate. The mixture was cooled to −78° and a dry nitrogen atmosphere was maintained throughout. A solution of 6.95 mmol of lithium diisopropylamide in DME, prepared at −78° by the addition of 6.95 mmol of *n*-butyllithium to 6.95 mmol of diisopropylamine in 10 ml of DME, was added leading to an immediate intense orange color, and the solution was allowed to stir for 1 hr at −78°. Ethyl 1,3-cyclohexadienecarboxylate (**7**, 6.35 mmol) was injected into the ylide solution at −78°, the mixture was stirred for 45 min, the temperature of the bath was allowed to rise to −57°, and the reaction mixture was stirred for 10 hr between −57 and −40°. The mixture was then allowed to rise to room temperature overnight with stirring, 50 ml of water was added, and the aqueous phase was extracted with *n*-pentane. The pentane extracts were washed, dried, filtered, and evaporated to give 2.2 g of crude product. Glpc of this crude showed four compounds, *viz.*, **7** (30% recovery), diphenyl sulfide, and cyclopropane products (70%) of which 80% was **8** and 20% was **9**. Separation was effected on columns (a) 10 ft × 0.25 in. 10% EGA, 150° (R_T of **7**, 1.95 min; **8**, 4.0 min; **9**, 2.54 min); (b) 10 ft × 0.25 in., 5% SE-30, 135° (R_T of **7**, 1.16 min; **8**, 3.36 min; **9**, 2.15 min).

Where the reactions were carried out in THF with *t*-BuLi as the base and in THF with $CHCl_2Li$ as base, the conditions were as described above. When THP was used as the solvent with *t*-BuLi as base, ylide generation was accomplished at a bath temperature of −50°. After addition of diene ester **7** the reaction mixture was stirred for 2.5 hr at −50° and then allowed to reach room temperature gradually over a period of 8 hr. Isolation was as described above.

7,7-Dimethyl-3-ethoxycarbonyl-2-norcarene (8): uv λ_{max} 250 nm; ir ν_{max} 1690, 1250 cm^{-1}; nmr δ 0.93 (s, CCH_3), 1.14 (s, CCH_3), 1.25 (t, CH_2CH_3), 1.6–2.5 (m, CH_2CH_2), 4.2 (q, CH_2CH_3), 7.1 (br d, C=CH); mass spectrum *m/e* 194 (M^+).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 74.4; H, 9.6.

7,7-Dimethyl-6-ethoxycarbonyl-2-norcarene (9): uv λ_{max} 205–210 nm; ir ν_{max} 1720, 1275 cm^{-1}; nmr δ 0.98 (s, CCH_3), 1.14 (s, CCH_3), 1.28 (t, CH_2CH_3), 1.78–2.4 (m, CH_2CH_2), 4.02 (q, CH_2CH_3), 5.66 (m, HC=CH); mass spectrum *m/e* 194 (M^+).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 74.3; H, 9.2.

(9) E. B. Reid and H. W. Sause, *J. Chem. Soc.*, 516 (1954).
(10) V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).
(11) Nmr spectra were taken in (a) CD_3OD, (b) DMSO-d_6.
(12) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957).
(13) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 173 (1956).
(14) E. J. Corey and W. Oppolzer, *J. Amer. Chem. Soc.*, **86**, 1899 (1964).
(15) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).
(16) F. H. Stodola, *J. Org. Chem.*, **29**, 2490 (1964).

Methyl β-(2,2,3-trimethylcyclopropyl)acrylate (11) and 1-methoxycarbonyl-2,2-dimethyl-3-(1-propenyl)cyclopropane (12) were prepared from methyl *trans,trans*-sorbate (**10**) according to the procedures described above. The isomers were separated by glpc using a 20 ft × 0.25 in. column of 10% SE-30 at 160° (R_T of **10**, 7.8 min; **11**, 16.4 min; **12**, 11.8 min.

Methyl β-(2,2,3-trimethylcyclopropyl)acrylate (11): uv λ_{max} 242 nm; ir ν_{max} 1725 cm^{-1}; nmr δ 1.2 (9 H's, $C<^{CH_3}_{CH_3}$ and CH_3CH), 3.65 (s, $COOCH_3$), 5.85 (d, J = 15 Hz, C=CH-$COOCH_3$), 6.4 (m, C=CHCH); mass spectrum m/e 168 (M^+).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.5. Found: C, 71.4; H, 9.7.

1-Methoxycarbonyl-2,2-dimethyl-3-(1-propenyl)cyclopropane (12): uv λ_{max} 200–210 nm; ir ν_{max} 1725 cm^{-1}; nmr δ 1.2 (6 H's, $C<^{CH_3}_{CH_3}$), 1.7 (d, J = 5 Hz, CH_3CH=C), 1.41 (d, J = 5 Hz, cyclopropane CH), 1.9 (m, cyclopropane CH), 3.65 (s, $COOCH_3$), 4.7 (CH_3CH=CH), 5.35 (m, CH_3CH=CH); mass spectrum m/e 168 (M^+).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.4; H, 9.5. Found: C, 71.6; H, 9.4.

***n*-Propyldiphenylsulfonium Triflate (13b) and *n*-Butyldiphenylsulfonium Triflate (13c).**—To a solution of 3 g (10.6 mmol) of trifluoromethanesulfonic anhydride[12] was added 10.6 mmol of the *n*-alkyl alcohol and 1.1 g (11 mmol) of triethylamine in 10 ml of CH_2Cl_2 at 0°. The mixture was stirred for 1 hr at 0°, the CH_2Cl_2 was evaporated, and the residue was chromatographed on silica eluting with *n*-pentane to give a 16% yield of the *n*-alkyl triflate.

***n*-Propyl triflate (13b)**: nmr δ 1.1 (t, CH_3CH_2), 1.83 (m, CH_3CH_2), 4.5 (t, $CH_2CH_2OSO_2CF_3$).

***n*-Butyl triflate (13c)**: nmr δ 1.0 (br d, CH_3CH_2), 1.65 (m, $CH_3CH_2CH_2CH_2$), 4.5 (t, $CH_2CH_2OSO_2CF_3$).

To a solution of 1.5 mmol of *n*-alkyl triflate was added a tenfold excess of diphenyl sulfide at −35°. With stirring, the mixture was allowed to rise to room temperature, remained at room temperature for 24 hr, and was heated to 45° for 0.5 hr. The oil that was formed was separated, washed with CCl_4, and dried *in vacuo* to give ~10% yields of sulfonium triflates **13b** and **13c**.

***n*-Propyldiphenylsulfonium triflate (13b)**: nmr (DMSO-d_6) δ 1.09 (t, CH_2CH_3), 1.85 (m, CH_2CH_3), 4.4 (t, $<S^+-CH_2CH_2$), 7.8 (m, Ar H's).

***n*-Butyldiphenylsulfonium triflate (13c)**: nmr (DMSO-d_6) δ 1.0 (br d, CH_2CH_3), 1.7 (m, $CH_2CH_2CH_2CH_3$), 4.4 (br t, $>S^+-CH_2CH_2$), 7.9 (Ar H's).

Registry No.—**2d**, 16601-43-7; **7**, 3725-40-4; **8**, 40464-16-2; **9**, 40464-17-3; **10**, 689-89-4; **11**, 40447-54-9; **12**, 40447-55-0; **13b** triflate, 40447-56-1; **13c** triflate, 40447-57-2; isopropyldiphenylsulfonium tetrafluoroborate, 40447-58-3; trifluoromethylsulfonic anhydride, 358-23-6.

Chemistry of the Sulfur–Nitrogen Bond. VI.[1] A Convenient One-Step Synthesis of Sulfenimines (*S*-Aryl Thiooximes)[2]

FRANKLIN A. DAVIS,* WILLIAM A. R. SLEGEIR, STEVEN EVANS,[3] ALAN SCHWARTZ,[3] DAVID L. GOFF,[3] AND ROBERT PALMER

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

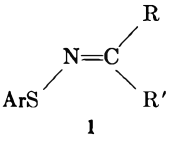
Received March 13, 1973

The scope and limitations of a convenient one-step synthesis of sulfenimines (*S*-aryl thiooximes) from aromatic disulfides, silver nitrate, ammonia, and aldehydes or ketones is described. The procedure fails with aliphatic disulfides and diaryl ketones. The structure, properties, and mechanism of formation of sulfenimines are discussed.

The carbon–nitrogen double bond in imines ($RN=CR_2$) has been extensively studied[4] and is an important intermediate in organic syntheses and biological transformations. The mechanism of syn–anti isomerization or stereomutation at the C–N double bond has been the subject of considerable interest.[2,5]

Compounds that contain the sulfur–nitrogen bond are important both from practical as well as theoretical points of view. They have found applications in synthesis, as pesticides, and as accelerators in the vulcanization of rubber. Knowledge of the various types of interactions possible between adjacent sulfur and nitrogen are essential to understanding lone-pair interactions, bond polarization effects, and p–d π bonding.[6]

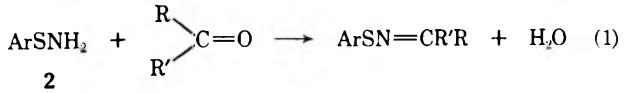
A study of sulfenimines (*S*-aryl thiooximes) **1**, which



1

contains both the imine and sulfur–nitrogen functional groups, is therefore of considerable interest. Although a few sulfenimines have been known for some time, their chemistry is relatively unexplored. Undoubtedly this is due to the lack of a convenient synthetic route to these compounds.

The method generally used for the preparation of sulfenimines is condensation of a sulfenamide, **2**, with



$$ArSNH_2 + \begin{matrix} R \\ R' \end{matrix}\!\!>\!C{=}O \longrightarrow ArSN{=}CR'R + H_2O \quad (1)$$

2

R′ = alkyl, aryl, H

an aldehyde or ketone (eq 1).[7–11] Quinoline sulfenimines have been prepared by oxidation of the cor-

(1) Part V: F. A. Davis, C. J. Horner, E. R. Fretz, and J. F. Stackhouse, *J. Org. Chem.*, **38**, 695 (1973).

(2) For a preliminary communication see F. A. Davis, W. A. R. Slegeir, and J. M. Kaminski, *Chem. Commun.*, 634 (1972).

(3) Undergraduate Research Participant.

(4) (a) P. Y. Sollenberger and R. B. Martin in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1968, Chapter 7; (b) S. Patai, Ed., "The Chemistry of the Carbon–Nitrogen Bond," Interscience Publishers, New York, N. Y., 1970; (c) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963).

(5) (a) J. H. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1970); (b) H. Kessler *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970); (c) M. Raban and E. Carlson, *J. Amer. Chem. Soc.*, **93**, 685 (1971); (d) W. B. Jennings and D. R. Boyd, *ibid.*, **94**, 7187 (1972).

(6) For a recent review see F. A. Davis, *Int. J. Sulfur Chem., B*, in press.

(7) T. Zincke and J. Baeumer, *Justus Liebigs Ann. Chem.*, **416**, 86 (1918).

(8) N. V. Khromov-Broisoc and M. B. Kolesova, *J. Gen. Chem. USSR*, **25**, 361 (1955).

(9) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 3072 (1957).

(10) J. J. D'Amico, *J. Org. Chem.*, **26**, 3436 (1961).

(11) D. Kaminsky, J. Shavel, Jr., and R. I. Meltzer, *Tetrahedron Lett.*, 859 (1967).

TABLE I

SULFENIMINES PREPARED FROM BIS(3-NITROPHENYL) DISULFIDE AND ALDEHYDES AND KETONES IN METHANOL

Entry	Sulfenimine[a]	Aldehyde or ketone	Yield, %	E/Z ratio[b]	Mp or bp, °C (mm)	Nmr[c]
1	3	Acetaldehyde	97	56:44	63	2.1 (q, 3, J = 5 Hz), 7.6 (m, 3), 8.4 (m, 2)
2	4	Isobutyraldehyde	60	97:3	160 (0.1)	1.2 (d, 5.8), 1.4 (d, 2), 2.7 (m, 1), 7.3–8.3 (m, 5)
3	5	Benzaldehyde	64		94–95	7.7 (m, 7), 8.6 (m, 2), 8.8 (s, 1, CH=)
4	6	4-Nitrobenzaldehyde	94		187	7.6–8.5 (m, 8), 8.9 (s, 1, CH=)
5	7	4-Methoxybenzaldehyde	87		114	4.0 (s, 3, OCH_3), 7.0–8.2 (m, 8), 8.7 (s, 1, CH=)[d]
6	8	Furfural	88		109	6.5–8.6 (m, 8)
7	9	Acetone	92		50–51	2.2 (d, 6), 7.8–8.6 (m, 3), 8.9 (m, 1)
8	10	2-Butanone	60	73:27	139 (0.7)	1.2 (t, 2.2, CH_3), 1.5 (t, 0.8, CH_3), 2.1 (s, 2.2, CH_3), 2.2 (s, 0.8), 2.4 (q, 2), 7.4–8.1 (m, 3), 8.5 (m, 1)
9	11	Methyl *tert*-butyl ketone	30		138 (0.45)	1.2 (s, 9), 2.1 (s, 3), 7.3–8.1 (m, 3), 8.4 (m, 1)
10	12	Acetophenone	60		58–60	2.5 (s, CH_3), 7.3–8.7 (m, 9)
11	13	Cyclohexanone	61		143–144	1.7(br s, 6), 2.4 (br s , 4), 7.2–8.0 (m, 3), 8.4 (m, 1)
12		Benzophenone	*e*			
13		Camphor	*e*			
14		Acetylacetone	Polymer			
15		Crotonaldehyde	Polymer			

[a] Satisfactory elemental analyses, ±0.3%, were obtained for all new compounds unless otherwise noted. [b] Measured from the nmr spectra. [c] Solvent $CDCl_3$ unless otherwise noted. [d] DMSO solvent. [e] No reaction.

responding sulfenamides[12] and by reaction of aromatic thiols with *N*-chloro-*p*-quinone imine.[13] Only a relatively few sulfenimines have been reported, since there is difficulty in preparing the necessary precursors.

In this paper we wish to report on the scope and limitations of a convenient one-step synthesis of sulfenimines. In addition, their structure and properties, as well as the probable mechanism of formation, will be discussed.

Synthesis.—Sulfenimines, **1**, are prepared in one step from aryl disulfides, silver nitrate, ammonia, and aldehydes or ketones (eq 2). One equivalent each of di-

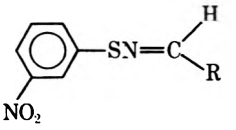
$$(ArS)_2 + AgNO_3 + \begin{matrix} R' \\ \diagdown \\ \quad C{=}O \\ \diagup \\ R \end{matrix} \xrightarrow{NH_3} \underset{\mathbf{1}}{ArSN{=}CR'R} + AgSR + NH_4NO_3 + H_2O \quad (2)$$

sulfide and silver nitrate are dissolved in methanol; ammonia is passed through the solution and an excess of the aldehyde or ketone is added. After stirring for 12 hr the precipitated silver mercaptide is removed by filtration to give the sulfenimine.

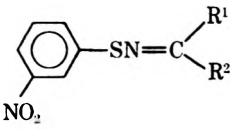
Occasional difficulty was encountered in separating the sulfenimine from imine polymers that were always formed. The imine polymers result from the reaction of ammonia with aldehydes and ketones to give unstable imines which polymerize.[14] In the majority of cases the sulfenimine was separated from these polymers by extraction into ether, washing with water, and distillation.

This synthetic procedure (eq 2) works well with aldehydes (compounds **3**–**8**), less well with ketones (compounds **9**–**13**), and fails with diaryl ketones. Sterically hindered ketones such as methyl *tert*-butyl ketone gave only 30% yield of the sulfenimine **11**, and camphor failed. These results are summarized in Table I.

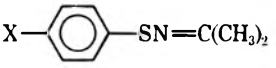
This procedure also works well with a variety of substituted aromatic disulfides. Sulfenimines **14**–**21** were



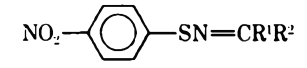
3, R = CH_3
4, R = $CH(CH_3)_2$
5, R = C_6H_5
6, R = 4-$NO_2C_6H_4$
7, R = 4 $CH_3OC_6H_4$
8, R = 2-C_4H_3O



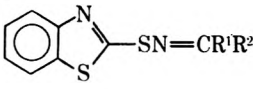
9. $R^1 = R^2 = CH_3$
10. $R^1 = CH_3$; $R^2 = C_2H_5$
11. $R^1 = CH_3$; $R^2 = C(CH_3)_3$
12. $R^1 = CH_3$; $R^2 = C_6H_5$
13. R^1, $R^2 = C_5H_{10}$



14, X = H
15, X = Cl
16, X = Br
17, X = NO_2



18, R^1, $R^2 = C_5H_{10}$
19. R^1 = H; R^2 = 4-$(CH_3)_2NC_6H_4$



20, $R^1 = R^2 = CH_3$
21. R^1 = H; $R^2 = C_6H_5$
22, R^1, $R^2 = C_5H_{10}$

prepared using this method (Table II). Not only is this procedure more convenient than those previously reported, but the yields, in many cases, are also higher (entries 4–6, Table II).

This synthetic procedure may also be used to prepare benzisothiazoles from the corresponding disulfide. For example, 2-acetyl-4-methylphenyl disulfide (**23**)[15] gave a greater than 30% yield of 3,5-dimethylbenzisothiazole (**24**).

All attempts to prepare *S*-alkyl thiooximines by this

(12) E. Gebauer-Felnegg and H. A. Beatty, *J. Amer. Chem. Soc.*, **49**, 1361 (1927).

(13) D. N. Kramer and R. M. Gamson, *J. Org. Chem.*, **24**, 1154 (1959).

(14) R. H. Hasek, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **26**, 1822 (1961).

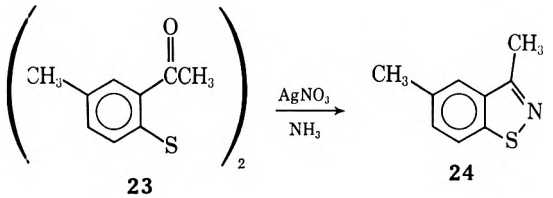
(15) D. Walker and J. Leib, *J. Org. Chem.*, **28**, 3077 (1963).

TABLE II

SULFENIMINE FROM AROMATIC DISULFIDE AND ALDEHYDES AND KETONES

Entry	Sulfenimine	Disulfide	Ketone or aldehyde	Yield, %	Mp or bp, °C (mm)	Nmr (CDCl₃)
1	14	Phenyldisulfide	Acetone	60	66 (0.5)	2.0 (d, 6), 7.0–7.5 (m, 5)
2	15	4-Chlorophenyl disulfide	Acetone	65	39–40	2.1 (d, 6), 7.4 (m, 4)
3	16	4-Bromophenyl disulfide	Acetone	60	48–49	2.1 (d, 6), 7.4–7.9 (m, 4)
4	17	Bis(4-nitrophenyl) disulfide	Acetone	94 (75)[a]		2.1 (d, 6), 7.5–8.3 (ab q, 4)
5	18	Bis(4-nitrophenyl) disulfide	Cyclohexanone	98 (90)[b]		1.8 (br s, 6), 2.5 (br s, 4), 8.0 (ab q, 4)
6	19	Bis(4-nitrophenyl) disulfide	4-*N*,*N*-Dimethylaminobenzaldehyde	55 (51)[a]		3.0 (s, 6, CH_3), 6.6 (d, 2, J = 9 Hz), 7.5 (d, 4, J = 9 Hz), 8.1 (d, 2, J = 9 Hz), 8.5 (s, 1, CH=)
7	20	2-Benzothiazolyl disulfide	Acetone	49 (89)[c]		2.3 (d, 6), 7.4–7.9 (m, 4)
8	21	2-Benzothiazolyl disulfide	Cyclohexanone	Polymer (72)[c]		1.7 (br s, 6), 2.4 (m, 4), 7.25 (m, 2), 7.8 (m, 2)
9	22	2-Benzothiazolyl disulfide	Benzaldehyde	60 (69)[c]		8.2–8.0 (m, 9), 8.6 (s, 1, CH=)
10	24	2-Acetyl-4-methyl phenyl disulfide		30	50–55 (0.7)	2.5 (s, 3, imine CH_3), 2.7 (s, 3), 7.0–8.0 (m, 3)
11		Ethyl disulfide	Acetone	*d*		
12		Benzyl disulfide	Acetone	*d*, *e*		

[a] Reference 8. [b] Reference 11. [c] Reference 10. [d] No reaction. [e] Less than 1% of the sulfenimine may have formed as indicated by nmr.

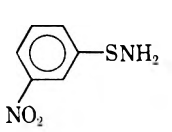


23 24

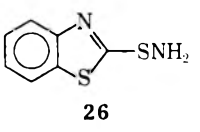
method failed. Starting material was recovered from both ethyl and benzyl disulfide (Table II, entries 11 and 12).

The crotonaldehyde and acetylacetone 3-nitrobenzenesulfenimines as well as the cyclohexanone 2-benzothiazolesulfenimines (**18**) could not be prepared using this method (eq 2). In these examples the sulfenimine could not be separated from the imine polymers.

An alternate procedure, which avoids the presence of excess ammonia, is to condense the sulfenamide **2** with aldehydes and ketones (eq 1).[7-10] The major difficulty of using this method involves the preparation of the required sulfenamides (**2**). Our recent report of the synthesis of sulfenamides from aryl disulfides, silver nitrate, and amines[16] is applicable to the synthesis of the required sulfenamides (**2**). Sulfenamides **25** and **26** were prepared using this method in 72 and 90% yields, respectively.



25

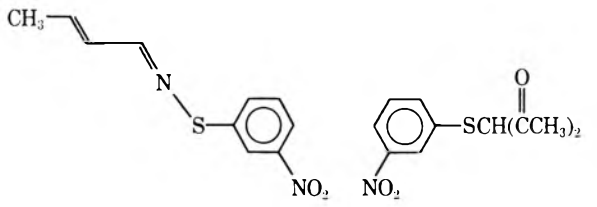


26

Using procedure 1, ammonium chloride as a catalyst, and 3-nitrobenzenesulfenamide (**25**), the crotonaldehyde sulfenimine **27** was prepared in good yield.

(16) M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, F. A. Davis, and S. J. Eitelman, *Chem. Commun.*, 1625 (1971).

Sulfenamide **25** with acetylacetone, however, gave **28**. Sulfenamides are well known to react with com-



27 28

pounds containing activated methylene groups to give the mono- and disulfenylated products[6,17] (Table III). D'Amico has reported similar products in the base-catalyzed reaction of **26** with acetylacetone.[10]

TABLE III

SULFENIMINES PREPARED FROM SULFENAMIDES IN ETHANOL

Entry	Sulfenamide	Ketone or aldehyde	Catalyst[a]	Products[b] (yield, %)
1	**25**	Acetone		**9** (13), **25** (87)
2		Acetone	NH_4NO_3	**9** (25)
3		Acetone	NH_4Cl	**9** (96)
4		Acetone	NaCl	**9** (17), **25** (83)
5		Acetone	$NaNO_3$	**9** (15), **25** (85)
6		Acetone	HCl[c]	**9** (95)
7		Acetone	KOH[d]	**25** (86)
8		Crotonaldehyde	NH_4Cl	**27** (60)
9		Acetylacetone	NH_4Cl	**28** (63)
10		Acetophenone	NH_4Cl	**12** (46), **25** (54)
11	**26**	Acetone	NH_4Cl	**20** (83)
12		Cyclohexanone	NH_4Cl	Polymer
13		Cyclohexanone	KOH[d]	**20** (80)

[a] 0.019 mol of catalyst added unless otherwise noted. [b] Determined by isolation and nmr. [c] 3 drops of 10% HCl added. [d] 0.0007 mol of potassium hydroxide added.

(17) T. Kumamoto, S. Kobayashi, and Y. Mukaiyama, *Bull. Chem. Soc. Jap.*, **45**, 866 (1972).

Similar yields of sulfenimines were obtained using either procedure 1 or 2 (compare entries 7 and 10, Table I, with entries 2 and 10, Table III). The exception was with 2-benzothiazolyl disulfide. Using procedure 1, 2-benzothiazolyl disulfide with acetone gave a 49% yield of **20** and with cyclohexanone polymer was isolated (entries 7 and 8, Table II). Sulfenamide **26** with ammonium chloride and acetone gave an 83% yield of **20**, but with cyclohexanone polymer was still the only product isolated (entries 11 and 12, Table III). A good yield of **21** was obtained using a basic catalyst as previously reported by D'Amico.[10]

Properties and Structure of Sulfenimines.—The majority of sulfenimines were considerably more resistant to hydrolysis than the corresponding imines. They could be stored at 10–20° almost indefinately with little decomposition. Aqueous acid gave the disulfide, ammonia, and the aldehyde or ketone.

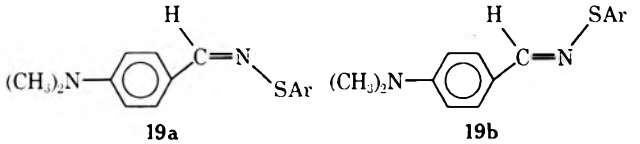
Satisfactory elemental analyses were not obtained for sulfenimines **4**, **10**, and **11** despite repeated crystallization and purification by preparative gas chromatography. On standing at room temperature for several days the odor of ammonia was detected. The mass spectra, however, were consistent with the proposed structures. Gas chromatographic analysis indicated the presence of bis(3-nitrophenyl) disulfide. All these sulfenimines contain bulky groups, which may contribute to their instability.

Structural proofs of **3**–**22**, **24**, and **27** were based on elemental analysis, infrared and nmr spectra and in some cases mass spectra. The infrared spectra of **3**–**22** and **27** showed weak to medium absorption at 1600–1620 cm^{-1}. We attribute this absorption to C=N stretching, since absorption in this area was absent in the corresponding disulfides. Benzisothiazole, **24**, showed weak absorption at 1610 cm^{-1} and absorption in the ultraviolet (ethanol) at λ_{max} 233 nm (ϵ 15,200) and 312 (3300).

The proton nmr spectra of **3**–**22**, **24**, and **27** were also in agreement with the proposed structures. The R and R′ groups in **1** are diastereotopic and occupy magnetically nonequivalent sites. If the barriers to syn–anti isomerization or stereomutation are sufficiently high a separate signal in the nmr will be observed for R and R′ at ambient temperatures when R = R′.

The barriers to stereomutation in diaryl and dialkyl ketone sulfenimines have been reported to be 18.5[18] and 20.1[2] kcal/mol. The two methyl groups in the nmr spectra of sulfenimines **9**, **14**–**17**, and **20**, therefore, appear as doublets separated by about 9 Hz.

Unsymmetrical sulfenimines like oximes are capable of forming geometric isomers. Two isomers, **19a**,



19a **19b**

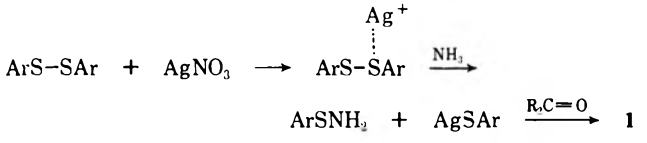
Ar = 4-nitrophenyl

and **19b**, were reported isolated in the preparation of **19**.[8] The unstable isomer, presumably **19a**, was converted on heating to the more stable isomer **19b**. Using procedure 2 for the synthesis of **19**, however, gave only one isomer, presumably **19b**.

The presence of two isomers was detected by nmr for several of the unsymmetrical sulfenimines. The methyl group in the nmr spectrum of sulfenimine **3** appears as two doublets almost equally populated. Assuming that the *E* isomer[19] is the more stable and therefore more abundant, then the *E*:*Z* ratio is 56:44. As one of the groups in the sulfenimine became large only one isomer was detected (Table I).

Mechanism of Formation.—The mechanism of formation of sulfenimines by procedure 2 most likely involves formation of the sulfenamide **2**. Silver ion complexes with one of the lone pairs of electrons in the disulfide bond followed by nucleophilic attack by ammonia on the activated disulfide bond. The resulting sulfenamide condenses with the aldehyde or ketone, giving the sulfenimine (Scheme I).

SCHEME I



Cooperative assistance to nucleophilic displacement by an electrophile at the disulfide bond has been discussed by Kice,[20] and silver ion is well known to form complexes with disulfides.[21] Thiosulfonate esters[22] and sulfenamides[16] have been prepared under similar conditions.

Additional evidence for the proposed scheme is the isolation of sulfenamide **25** in good yield when bis(3-nitrophenyl) disulfide is treated according to procedure 2 without adding the aldehyde or ketone. Sulfenamide **25** condenses separately with acetone in the presence of ammonium nitrate to give a high yield of sulfenimine **9** (Table III). Ammonium nitrate is a by-product in the sulfenimine synthesis (eq 2). The inability to prepare sulfenimines from ethyl and benzyl disulfides probably results from the known instability of alkyl sulfenamides.[6,16]

The condensation of sulfenamides with aldehydes and ketones is acid catalyzed. Ammonium salts and aqueous hydrochloric acid with sulfenamide **25** and acetone gave greater than 96% yield of the sulfenamide **9**. In the absence of these catalysts only 13–15% yield of the sulfenamide was isolated. Basic catalysts such as potassium hydroxide have been used in the preparation of 2-benzothiazole sulfenimines from **26**.[9,10] With sulfenamide **2** base catalyst failed to give any sulfenimine (entry 7, Table III).

Two additional mechanism must also be considered. Ammonia reacts with aldehydes and ketones to give unstable imines.[14] The sulfenamide **2** may condense with this unstable imine to give the sulfenimine. For example, *N*-benzylidenemethylamine reacts quantitatively with **25** to give **5**. A second possibility is that

(18) C. Brown, G. T. Grayson, and R. F. Hudson, *Tetrahedron Lett.*, 4925 (1970).

(19) J. E. Blackwood, C. L. Gladys, K. L. Leoning, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(20) J. L. Kice, *Accounts Chem. Res.*, **1**, 58 (1968).

(21) R. Cecil and J. R. McPhee, *Biochem. J.*, **66**, 538 (1957).

(22) M. D. Bentley, I. B. Douglass, and J. A. Lacadie, *J. Org. Chem.*, **37**, 333 (1972).

the unstable imine attacks the silver disulfide complex to give the sulfenimine. However, attempts to form a sulfenimine by addition of phenylethylketimine[23] to a silver nitrate disulfide solution failed.

Experimental Section

Disulfides were prepared and purified according to literature procedures. Melting points were obtained on a Fisher-Johns apparatus. Proton nmr spectra were measured on a Varian A-60A instrument. Infrared spectra were measured on a Perkin-Elmer 457 spectrometer. Mass spectra were obtained on a Hitachi RMU-6 instrument. Gas chromatographic analyses were performed on a Perkin-Elmer 900 gas chromatograph using a 3% OV-17 on 80/100 Chromosorb W (regular) column.

General Procedure for the Synthesis of Sulfenimines (Procedure 2).—In a 100-ml, three-necked flask equipped with mechanical stirrer and ammonia inlet was dissolved 4.5 g (0.027 mol) of silver nitrate in 300 ml of methanol. The solution was cooled in an ice bath, an equivalent amount of disulfide was added, and ammonia was passed through the solution for about 15 min. The aldehyde or ketone was added in excess (usually 5 equiv) and the reaction was allowed to stir overnight at room temperature. The precipitated silver mercaptide was removed by filtration; solvent was removed to give a residue which was redissolved in ether and filtered. The ether solution was washed (4 × 100 ml) with water and dried over $MgSO_4$. Removal of the solvent gave the sulfenimine. At this point it was occasionally necessary to distill off the imine polymer. The sulfenimine was either distilled or crystallized from ether–pentane or ethanol.

3,5-Dimethylbenzisothiazole (24).—In a 100-ml, three-necked flask equipped with magnetic stir bar and ammonia inlet was dissolved 0.24 g (0.0017 mol) of silver nitrate and 0.5 g (0.0017 mol) of 2-acetyl-4-methylphenyl disulfide[15] in 35 ml of methanol. The solution was warmed to about 50° for 5 min and allowed to cool to room temperature. Ammonia was passed through the solution for 4 min, and the reaction mixture was stirred overnight. The precipitated silver mercaptide was removed by filtration, solvent was removed under vacuum (water pump), and the resulting residue was dissolved in ether. The ether solution was washed with water (3 × 50 ml) and dried over $MgSO_4$. Removal of the ether solvent gave an oil which was distilled, bp 50–55° (0.7 mm), to give 0.08 g (30%) of a pale yellow oil which solidified on cooling below ambient temperature: ir (thin film) 1610 cm^{-1} (w, C=N); uv (absolute ethanol) λ_{max} 233 nm (ϵ 15,500) and 312 (3300); nmr see Table II.

Anal. Calcd for C_9H_9NS: C, 66.20; H, 5.52. Found: C, 66.37; H, 5.63.

3-Nitrobenzenesulfenamide (15).—Sulfenamide **25** was prepared as described above (procedure 2), omitting the addition of aldehyde or ketone, from 2.8 g (0.0162 mol) of silver nitrate and 5.0 g (0.0162 mol) of bis(3-nitrophenyl) disulfide in 250 ml of methanol. After the dried ether solvent was removed the resulting residue was crystallized from ethanol to give 2.0 g (72%) of orange-yellow needles: mp 60–61°; ir (KBr) 3280 and 3380 cm^{-1} (m, NH_2); nmr ($CDCl_3$) δ 2.8 (br s, 2, NH_2) and 7.3–8.3 (m, 4).

Anal. Calcd for $C_6H_6N_2O_2S$: C, 42.35; H, 3.53. Found: C, 42.45; H, 3.75.

(23) C. Mourear and G. Mignonac, *C. R. Acad. Sci.*, **156**, 1801 (1913).

2-Benzothiazolesulfenamide (26).—Sulfenamide **26** was prepared as described above from 5.0 g (0.015 mol) of 2-benzothiazalyl disulfide and 2.6 g (0.015 mol) of silver nitrate. Crystallization from chloroform gave 2.5 g (90%) of white crystals: mp 123° (lit.[9] mp 122–124°); ir (KBr) 3160 and 3320 cm^{-1} (s, NH_2); nmr ($CDCl_3$) δ 3.3 (br s, 2, NH_2), 7.3 (m, 2), and 7.8 (m, 2).

General Procedure for the Synthesis of Sulfenimines from Sulfenamides (Procedure 1).—In a 500-ml round-bottom flask equipped with magnetic stir bar was placed the appropriate sulfenamide (0.006 mol) and the appropriate catalyst in 250 ml of absolute ethanol. A 5 *M* excess of the aldehyde or ketone was added, and the reaction mixture was stirred overnight. The solvent was removed under vacuum to give a residue which was dissolved in ether. The ether solution was washed with water (3 × 50 ml), dried over $MgSO_4$, and removed to give the sulfenimine.

Crotonaldehyde-3-nitrobenzenesulfenimine (27).—Sulfenimine **27** was prepared as described above (procedure 1) from sulfenamide **25** and crotonaldehyde to give a clear yellow oil which was chromatographed on Florisil (elution with 20:80 ether–pentane). The resulting yellow solid was crystallized from pentane to give 0.67 g (50%) of yellow needles: mp 45–46°; ir (KBr) 1640 (w), 1525, and 1350 cm^{-1} (s, NO_2); nmr ($CDCl_3$) δ 2.0 (m, 3, CH_3), 6.3 (m, 2), and 7.2–8.4 (m, 5).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.50. Found: C, 53.77; H, 4.30.

3-(3-Nitrophenylthio)-2,4-pentandione (28).—Sulfenamide **25** and acetylacetone were allowed to react as described above (procedure 1). The residue remaining after the ether solvent was removed was sublimed at 120° (0.25 mm) and crystallized from ether–pentane to give 1.0 g (64%) of cream-colored needles: mp 72–73°; ir (KBr) 1700–1600 cm^{-1} (br, C=O); nmr ($CDCl_3$) δ 2.4 (s, 7, CH_3 and SCH) and 7.2–8.0 (m, 4).

Anal. Calcd for $C_{11}H_{11}NO_4S$: C, 52.17; H, 4.35. Found: C, 52.05; H, 4.28.

Reaction of 3-Nitrobenzenesulfenamide (25) and *N*-Benzylidenemethylamine.—In a 250-ml round-bottom flask equipped with stir bar was placed 1.0 g (0.006 mol) of sulfenamide **25** and 0.7 g (0.006 mol) of *N*-benzylidenemethylamine (Aldrich) in 100 ml of methanol. After stirring overnight the solvent was removed to give 1.5 g (100%) of a yellow solid identified as sulfenimine **5** by comparison of its infrared and nmr spectra with those of an authentic sample.

Registry No.—**3**, 40576-71-4; **4**, 40576-72-5; **5**, 40576-73-6; **6**, 40576-74-7; **7**, 40576-75-8; **8**, 40576-76-9; **9**, 38205-95-7; **10**, 40576-78-1; **11**, 40576-79-2; **12**, 40576-80-5; **13**, 40576-81-6; **14**, 38206-14-3; **15**, 38205-93-5; **16**, 38205-94-6; **17**, 38205-96-8; **18**, 14006-46-3; **19**, 40576-87-2; **20**, 40576-88-3; **21**, 40576-89-4; **22**, 40576-90-7; **23**, 40576-91-8; **24**, 40576-92-9; **25**, 40576-93-0; **26**, 2801-21-0; **27**, 40576-95-2; **28**, 40576-96-3; bis(3-nitrophenyl) disulfide, 537-91-7; acetaldehyde, 75-07-0; isobutyraldehyde, 78-84-2; benzaldehyde, 100-52-7; 4-nitrobenzaldehyde, 555-16-8; 4-methoxybenzaldehyde, 123-11-5; furfural, 98-01-1; acetone, 67-64-1; 2-butanone, 78-93-3; methyl *tert*-butyl ketone, 75-97-8; acetophenone, 98-86-2; cyclohexanone, 108-94-1; phenyl disulfide, 882-33-7; 4-chlorophenyl disulfide, 1142-19-4; 4-bromophenyl disulfide, 5335-84-2; bis(4-nitrophenyl) disulfide, 100-32-3; 2-benzothiazolyl disulfide, 120-78-5; 4-*N*,*N*-dimethylaminobenzaldehyde, 100-10-7; crotonaldehyde, 4170-30-3; acetylacetone, 123-54-6; *N*-benzylidenemethylamine, 622-29-7.

Heterohelicenes Containing Seven-Membered Rings. 5,6-Dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepines

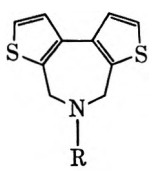
HANS WYNBERG*AND MAYO CABELL

Department of Organic Chemistry, The University, Zernikelaan, Groningen, The Netherlands

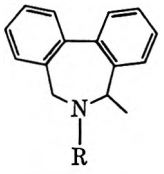
Received February 7, 1973

Two new heterohelicenes were prepared containing as central heterounit the 5,6-dihydro-4*H*-dithien-[2,3-*c*:3′,2′-*e*]azepine system. In a one-step reaction 3,3′-bithianaphthenyl-2,2′-dicarboxaldehyde was converted by treatment with benzylamine and sodium dithionite into the condensed azepine. The helical nature of the azepine is revealed by the nonequivalence of geminal protons.

In continuation of our study of the chemical and optical properties[1] of heterohelicenes we are pursuing several goals,[2] of which the following are pertinent to the work reported in this paper: (a) an efficient nonphotochemical helicene synthesis; (b) the use of heterocyclic systems other than thiophene. This article describes the synthesis of a novel ring system, the 5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine system (1).[3] The preparation of this class of compounds



1



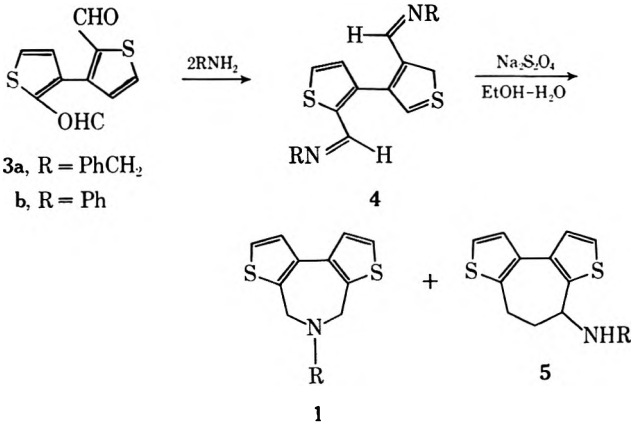
2

represents a preliminary stage in overcoming some of the synthetic obstacles in the preparation of helicenes. Thus, while maintaining an unambiguous helicene synthesis through the use of thiophene or thianaphthene, we found a useful nonphotochemical ring-closure step. The product, an azepine, provides us with an active site—the nitrogen atom—potentially valuable for resolution and for preparation of derivatives.[4]

An added novelty in the synthesis of this new helical ring system is the inclusion of a seven-membered ring. The presence of so large a ring in a helicene may be expected to lower the distortion in the aromatic portion of the molecule, whereas optical stability for the compounds is not unlikely. Even simple biphenyls having 2,2′ three-atom bridges and no 6,6′ substituents have in certain instances been resolved.[5]

Results

Our first attempts at the preparation of compounds 1 were patterned on the successful synthesis of 6,7-dihydro-5*H*-dibenz[c,*e*]azepines (2) by Hawthorne and coworkers.[6] This route involved the preparation and isolation of bis Schiff bases derived from biphenyl-2,2′-dicarboxaldehyde, followed by reductive cyclization to azepines 2 using sodium dithionite ($Na_2S_2O_4$). Although these authors report consistent and good yields for virtually all cases studied, the reaction sequence in our hands was of only limited value when 3,3′-bithienyl-2,2′-dicarboxaldehyde (3) was used as the starting dialdehyde. Thus attempts to convert bis Schiff bases **4** to the desired appropriate azepines (1) at elevated temperatures invariably gave mixture of **1** and the 7-aminobenzo[1,2-*b*:4,3-*b*′]dithiophenes **5**.



When aqueous sodium dithionite was added slowly to a refluxing solution of **4a** in ethanol only a 7% yield of **1a** was collected; the major product, to which we assigned the structure **5a**, was isolated in 74% yield. The two amines could be separated on the basis of their difference in basicity. Similar reduction of **4b** at elevated temperature afforded a mixture of **1b** and **5b** in an approximate ratio of 1:3; the products were both of low basicity and could not be separated.

After considerable experimentation it was discovered that high yields of azepine could be obtained when Schiff base formation was circumvented. Thus when the starting dialdehyde was treated *simultaneously* at room temperature with sodium dithionite and the appropriate amine in aqueous ethanol solution, no Schiff base color was observed and a high yield of the desired azepine crystallized from the reaction mixture within 1 hr; compound **5** was not detected. The white solid (1) slowly decomposed and was consequently purified periodically by sublimation. It must be noted that the formation of Schiff base **4b**, using the procedure of Hawthorne, required heating in

(1) J. H. Dopper D. Oudman, and H. Wynberg, *J. Amer. Chem. Soc.*, **95**, 3692 (1973).

(2) (a) M. B. Groen and H. Wynberg, *J. Amer. Chem. Soc.*, **93**, 2968 (1971); (b) H. Wynberg, *Accounts Chem. Res.*, **4**, 65 (1971).

(3) The potent *anti*-epinephrine properties of these compounds stimulated the initial investigations into their synthesis and properties: (a) W. Wenner, *J. Org. Chem.*, **16**, 1475 (1951); (b) W. Wenner, *ibid.*, **17**, 1451 (1952); (c) W. Wenner, U. S. Patent 2,619,484 (Nov 25, 1952); (d) R. A. Schmidt and W. Wenner, U. S. Patent 2,693,465 (Nov 2, 1954).

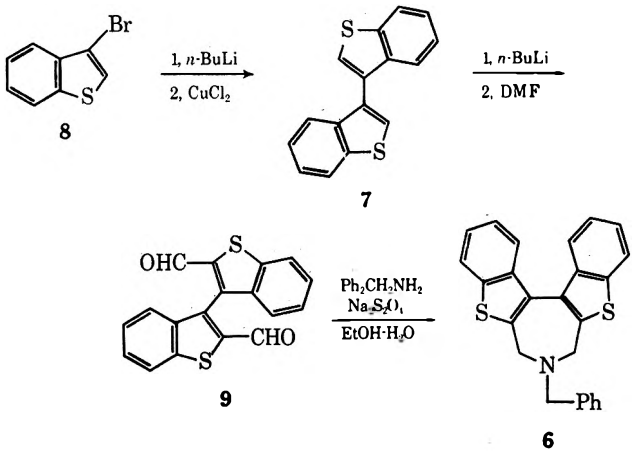
(4) For instance, a number of optically active dibenzazepines having auxiliary ortho substituents have been resolved by conversion to suitable diastereomeric salts; see (a) G. H. Beaven, D. M. Hall, M. S. Lesslie, and E. E. Turner, *J. Chem. Soc.*, 854 (1952); (b) S. R. Ahmed and D. M. Hall, *ibid.*, 3043 (1958); (c) D. M. Hall and M. Poole, *J. Chem. Soc. B*, 1034 (1966).

(5) (a) W. E. Truce and D. D. Emrick, *J. Amer. Chem. Soc.*, **78**, 6131 (1956); (b) D. C. Iffland and H. Siegel, *ibid.*, **80**, 1947 (1958); (c) D. C. Iffland and H. Siegel, *J. Org. Chem.*, **21**, 1056 (1956).

(6) J. O. Hawthorne, E. L. Mihelic, M. S. Morgan, and M. H. Wilt, *J. Org. Chem.*, **28**, 2831 (1963).

refluxing toluene for several hours, conditions considerably more drastic than needed for the preparation of the azepine **1b** directly from the dialdehyde.

We then turned our attention to the synthesis of the helical structure **6**. The starting material, 3,3′-bithianaphtenyl (**7**), had been prepared previously in 11% yield.[7] We were able to increase the yield to 72% by treating 3-bromobenzo[*b*]thiophene with *n*-butyllithium at −70°[8] and coupling at that temperature in the presence of copper(II) chloride.[9] Compound **7** was obtained as a white solid which slowly decomposes in air. Conversion of **7** to 3,3′-bithianaphthenyl-2,2′-dicarboxaldehyde (**9**) in 66% yield was



achieved *via* lithiathion with *n*-butyllithium and formylation with *N*,*N*-dimethylformamide.

Reaction of **9** at room temperature with a mixture of benzylamine and excess sodium dithionite produced **6** in 65% yield.[10] The white product soon began to turn yellow; it was sublimed whenever pure material was needed. The structure of the azepines **1** and **6** is assigned on the basis of analytical and spectral data. Convincing are the nmr spectra of the two amines, especially with respect to the signals due to the methylene protons. Thus, while **1** exhibits a singlet (4 H) at δ 4.23 due to the four equivalent methylene protons,[11] an AB quartet (J = 13 Hz) at δ 3.66 is clearly discernible for **6**, and is attributed to nonequivalent methylene protons. The nonequivalence of these latter geminal protons on the nmr time scale attests to the increasing optical stability of such compounds as additional ortho-condensed aromatic rings are introduced into the molecular framework. This effect has also been observed in the case of dibenzazepinium salts.[12]

(7) L. J. Pandya, D. S. Rao, and B. D. Tilak, *J. Sci. Ind. Res.*, **18B**, 516 (1959); *Chem. Abstr.*, **54**, 17391*d* (1959). Our melting point for this compound was in close agreement with that reported by these workers (see Experimental Section). The account of a synthesis of **7** of mp 370° by Schuetz and Ciporin is probably not correct: R. D. Schuetz and L. Ciporin, *J. Org. Chem.*, **23**, 206 (1958).

(8) It has been noted that mixtures of products are obtained when the 3-benzo[*b*]thienyllithium is prepared at higher temperatures, or in solvents other than diethyl ether: R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2733 (1968).

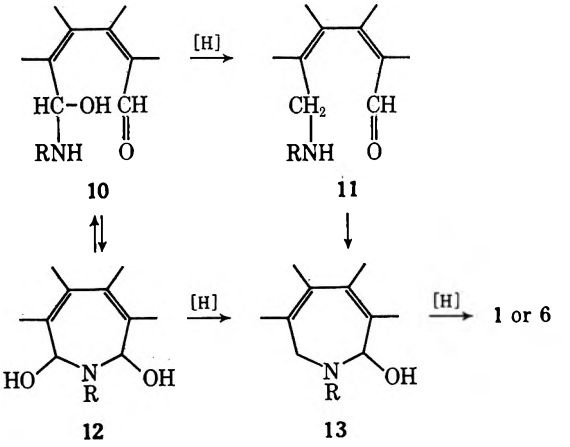
(9) This method is an adaptation of one used by S. Gronowitz and H. O. Karlsson, *Ark. Kemi*, **17**, 89 (1960).

(10) Azepine **6** could also be synthesized from the bis Schiff base **10**, by reduction with $Na_2S_2O_4$. Even when this reaction is carried out in refluxing aqueous ethanol, however, there is no detection of the amine **11**, which in light of previous results might have been an expected product.

(11) The nmr signal remained a singlet even at temperature as low as −40°.

Discussion

Under our conditions bis Schiff bases of **3** and **9** do not seem to serve as intermediates in the direct conversion of dialdehydes **3** and **9** to the appropriate dihydroazepines. This view is supported by the relative mildness of conditions permissible for the direct conversions (*vide supra*), as well as by the color sequence observed for the process (see Experimental Section). Although the nature of the multistep sequence in the direct conversions of **3** to **1** and **9** to **6** at room temperature remains a matter of conjecture, it seems reasonable to propose the following scheme. The dicarbonyl compound is in equilibrium with its carbinolamine adduct. The latter, a benzyl-type alcohol, may be reduced (to **11**), may cyclize (to **12**), and may, in a competing sequence, lose water to form a Schiff base. Both **11** and **12** may form azepine from the cyclic **13** *via* a second reductive step. The scheme



described above allows bis Schiff bases to serve as starting materials if their formation and subsequent hydrolysis to a carbinolamine is rapid.

We have not included the trans rotamer in this scheme. Obviously only the cis rotamer will yield cyclic product.

Experimental Section

All melting points are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60 instrument with tetramethylsilane (TMS) as internal standard. The infrared spectra were taken on Perkin-Elmer 125 and Unicam SP-200 instruments. A Zeiss PMQ II spectrophotometer was used for the ultraviolet spectra, while mass spectra were recorded with a AEI MS-9. Microanalyses were carried out in the analytical section of this department, under the direction of Mr. M. W. Hazenberg.

3,3′-Bithienyl-2,2′-dicarboxaldehyde (**3**) was prepared by the method of Wynberg and Sinnige[13] and purified by sublimation at 130° (0.04 mm).

***N*-Benzyl-5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine** (**1a**). **A.**—To a vigorously stirred[14] solution of **3** (0.165 g, 0.741 mmol) and 0.161 g (1.50 mmol) of benzylamine in 30 ml of absolute ethanol was added, all at once,[15] a solution of 0.950 g (5.50 mmol)

(12) (a) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, 1242 (1955); (b) ref 4b.

(13) H. Wynberg and H. J. M. Sinnige, *Recl. Trav. Chim. Pays-Bas*, **88**, 1244 (1969).

(14) Large quantities of dark material are often formed when stirring is inefficient.

(15) It was found that after *gradual* (1 min) addition of the reducing agent no reaction ensued, even upon heating to reflux temperature.

of sodium dithionite[16] in 30 ml of water. The resulting solution was stirred at room temperature in a nitrogen atmosphere. Within several minutes the solution became pink (temporarily) and after 10–15 min white needles began to separate. After 2 hr most of the ethanol was removed on a rotary evaporator. The remaining mixture was filtered and the white crystals were washed with water. Even when dried under vacuum the azepine was found to incorporate much water. The material was thus dissolved in ether and the resulting solution was dried over KOH pellets. Filtration, followed by solvent removal *in vacuo*, afforded 0.207 g (94%) of 1a. Sublimation at 120° (0.05 mm) gave the pure compound: mp 145–146°; uv max (cyclohexane) 230 mμ (ε 24,100), 282 sh (5540), 291 (6250), 302 sh (4360); nmr (CCl_4) δ 3.63 (s, 2 H), 4.23 (s, 4 H), 6.90–7.35 (AB q, 4 H, $J \approx$ 5 Hz), 7.21 (s, 5 H); mass spectrum (70 eV) *m/e* 297 (M^+ − benzyl).

Compound **1a** readily formed an insoluble hydrochloride salt when treated in ether solution with alcoholic HCl. The salt could not be obtained free of contamination by the free amine.

Picric acid and 1a reacted in ethanol to yield a yellow-orange picrate, which was recrystallized from ethanol, mp 144–145°.

Anal. Calcd for $C_{23}H_{18}N_4O_7S_2$: C, 52.46; H, 3.45; N, 10.64; S, 12.18. Found: C, 52.46; H, 3.58; N, 10.40; S, 12.09.

B.—A solution of 0.250 g (1.12 mmol) of 3 and 0.242 g (2.26 mmol) of benzylamine in 16 ml of absolute ethanol was refluxed for 2 hr. An aliquot of the resulting solution was stripped of solvent under vacuum, yielding an oily yellow solid. Trituration with a small amount of ethanol gave crude di Schiff base 4a as a pale yellow solid: mp 127–130°; ir (Nujol) 1620 cm^{-1}; nmr ($CDCl_3$) δ 4.71 (broad s, 4 H), 6.99–7.55 (AB q, 4 H, $J \approx$ 5 Hz), 7.33 (s, 10 H), 8.32 (broad s, 2 H).

Crude 4a in 16 ml of ethanol was stirred under reflux. Over a period of 1 min a solution of 1.18 g (6.77 mmol) of sodium dithionite in 8 ml of water was added. The resulting solution was refluxed for 45 min. The mixture was then cooled and most of the ethanol was removed under vacuum. The remaining mixture was extracted with 30 ml of ether in three portions. The combined extracts were washed several times with 30 ml of 5% HCl solution. The remaining ether solution was retained. The acid solution was washed with ether, then neutralized by the addition of ammonium hydroxide. An extraction with 25 ml of ether was carried out; the extracts were washed with water, dried over KOH, and filtered. Ether removal gave 0.024 g (7%) of 1a. The retained ether solution was likewise washed with water, dried over KOH, and filtered; solvent removal yielded a greenish solid. This was dissolved in 15 ml of ether. Dropwise addition of alcoholic HCl precipitated the hydrochloride salt of 5a. The solid was filtered, then dissolved in 10 ml of 5% HCl solution. After neutralization with aqueous ammonia, the mixture was extracted with 30 ml of ether in three portions. After being washed with water and dried over KOH, the combined extracts were filtered. Ether removal *in vacuo* gave 0.245 g (74%) of 5a as a white solid. This could be further purified by sublimation (140°, 0.05 mm): mp 113–114°; uv max (cyclohexane) 238 mμ (ε 20,700), 268 (13,000), 277 (11,900), 292 (13,500), 304 (18,000), 332 (7560); ir (KBr) 3410 cm^{-1}; nmr (CCl_4) δ 3.90 (broad s, 1 H), 4.43 (s, 2 H), 6.94 (s, 1 H), 7.07–7.64 (m, 9 H); mass spectrum (70 eV) *m/e* 295 (M^+), 204 (M^+ − benzyl).

Compound 5a formed a dark brown picrate derivative upon treatment with picric acid in ethanol, mp 155–156°.

Anal. Calcd for $C_{23}H_{18}N_4O_7S_2$: C, 52.67; H, 3.07; N, 10.68; S, 12.23. Found: C, 52.81; H, 3.20; N, 10.58; S, 12.21.

N-Phenyl-5,6-dihydro-4*H*-dithien[2,3-*c*:3′,2′-*e*]azepine (1b) was prepared in 86% yield at room temperature according to method A for the synthesis of 1a. The white needles were purified by sublimation (120°, 0.05 mm): mp 142–143°; uv max (cyclohexane) 233 mμ (ε 26,600), 246 sh (22,300), 283 (7730), 305 sh (3610); nmr (CCl_4) δ 4.90 (s, 4 H), 6.55–7.27 (m, 9 H); mass spectrum (70 eV) *m/e* 283 (M^+).

Azepine 1b failed to form a picrate. It readily gave a 2:1 complex with trinitrobenzene, however; recrystallization from benzene–ethanol gave maroon needles, mp 139–140°.

Anal. Calcd for $C_{38}H_{29}N_5O_7S_4$: C, 58.52; H, 3.75; N, 8.98; S, 16.44. Found: C, 58.38; H, 3.79; N, 8.80; S, 16.39.

3-Bromobenzo[*b*]thiophene (8) was prepared by the method of Szmuszkovicz and Modest.[17] The fraction of viscous yellow liquid distilling at 85–95° (1.5 mm) was collected.

3,3′-Bithianaphthenyl (7).—Into a three-necked flask under an atmosphere of dry nitrogen was placed 12.0 ml of 2.30 *M* *n*-butyllithium solution (27.5 mmol) in hexane, followed by 15 ml of dry ether. The resulting solution was stirred and cooled to −70°. Over a period of 10 min a solution of 5.32 g (25.0 mmol) of 8 in 9 ml of anhydrous ether was added dropwise to the cold solution. The mixture was stirred for an additional 30 min at −70°, giving a suspension of 3-thianaphthenyllithium. Then anhydrous copper(II) chloride (3.92 g, 29.1 mmol) was added and the resulting mixture was stirred vigorously at −70° for 3.5 hr. Afterwards the reaction mixture was allowed to warm up slowly. When the temperature reached 0° about 30 ml of 2 *M* HCl was added and the mixture was allowed to stand overnight. The copper salt was filtered off and washed with ether and dilute HCl solution. The resulting filtrate was separated and the ether layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. Solvent removal *in vacuo* afforded 2.40 g (72%) of 8 as a pink solid. The color could be removed by elution of the material with hexane on a column of silica gel. Recrystallization from petroleum ether (bp 40–60°) gave pure 7 as white plates: mp 82.7–83.0° (lit.[7] mp 85°); nmr ($CDCl_3$) δ 7.18–7.47 (m, 4 H), 7.54 (s, 2 H), 7.63–8.06 (m, 4 H); mass spectrum (70 eV) *m/e* 266 (M^+).

3,3′-Bithianaphthenyl-2,2′-dicarboxaldehyde (9).—To a stirred solution of 0.821 g (3.08 mmol) of 7 in 60 ml of dry ether, under a nitrogen atmosphere, was added 6.5 ml of a 2.30 *M* solution of *n*-butyllithium (14.9 mmol) in hexane. The mixture was refluxed for 90 min. A solution of *N*,*N*′-dimethylformamide (4.15 g, 56.7 mmol) in 6 ml of anhydrous ether was then added dropwise over a period of 5 min and the resulting mixture was refluxed for 30 min. It was then poured into a mixture of 17.8 ml of 2 *M* HCl and 60 g of ice. The ether was removed *in vacuo* and the remaining mixture was extracted with 100 ml of methylene chloride. The extracts were washed with water, dried ($MgSO_4$), and filtered. Solvent removal yielded a yellow oil, most of which soon solidified. Recrystallization from petroleum ether–methylene chloride afforded 0.655 g (66%) of 9. The analytical sample was obtained by two recrystallizations from benzene, followed by vacuum drying at 55°: mp 171–172°; uv max (EtOH) 232 mμ (ε 29,500), 250 sh (19,600), 303 (24,600), 345 sh (7280); ir (KBr) 1660 cm^{-1}; nmr ($CDCl_3$) δ 7.20–8.22 (m, 8 H), 9.88 (s, 2 H); mass spectrum (70 eV) *m/e* 322 (M^+), 293 (M^+ − CHO), 264 (M^+ − 2 CHO).

***N*-Benzyl-7,8-dihydro-6*H*-bis[1]benzothien[2,3-*c*:3′,2′-*e*]azepine** (6). A.—The desired compound was prepared in 65% yield at room temperature from 9, 2 equiv of benzylamine, and excess $Na_2S_2O_4$ in 40 ml of 1:1 ethanol–water according to method A for the synthesis of 1a. The white needles were purified by sublimation (160°, 0,01 mm): mp 175–176°; uv max (EtOH) 222 mμ (ε 51,200), 244 (37,800), 271 sh (9720), 289 (8020), 299 (9500), 308 (10,500); nmr ($CDCl_3$) δ 3.36–3.98 (AB q, 4 H, J = 13 Hz), 3.77 (s, 2 H), 7.08–7.61 (m, 9 H), 7.71–8.13 (m, 4 H); mass spectrum (70 eV) *m/e* 397 (M^+), 306 (M^+ − benzyl).

4 failed to form stable complexes with picric acid or trinitrobenzene.

B.—A solution of 0.0750 g (0.232 mmol) of 9 and 0.0498 g (0.464 mmol) of benzylamine in 5 ml of absolute ethanol was refluxed for 1 hr. An aliquot of the resulting solution was stripped of solvent, giving crude di Schiff base 10 as a pale yellow solid: mp 144–148°; ir (Nujol) 1625 cm^{-1}; nmr ($CDCl_3$) δ 4.69 (s, 4 H), 7.07–7.64 (m, 16 H), 7.80–8.05 (m, 2 H), 8.22–8.36 (m, 2 H); mass spectrum (70 eV) *m/e* 500 (M^+). Crude 10 in 5 ml of ethanol was stirred at reflux temperature. A solution of 0.340 g (1.95 mmol) of sodium hydrosulfite in 2 ml of water was added, and the mixture was refluxed for 2 hr. The mixture was diluted with 5 ml of water and most of the ethanol was removed *in vacuo*. The remaining mixture was extracted with 20 ml of ether. The combined extracts were washed with

(16) Available in 83% purity from Baker Chemical Co. Aqueous solutions should not be prepared until immediately before use, since the material undergoes facile hydrolysis.

(17) J. Szmuszkovicz and E. J. Modest, *J. Amer. Chem. Soc.*, **72**, 571 (1950). The purification problems noted by other authors were not encountered.

water, dried over KOH, and filtered. Solvent removal on the rotary evaporator gave an oily yellow solid. This was sublimed to give 64.8 mg (70%) of **6**.

Registry No.—**1a**, 40386-84-3; **1a** picrate, 40306-86-3; **1b**, 40306-87-4; **1b**-trinitrobenzene, 40306-88-5; **3**, 40306-89-6; **4a**, 40306-90-9; **5a**, 40306-91-0; **5a** picrate, 40531-26-8; **6**, 40306-92-1; **7**, 40306-93-2; **8**, 7342-82-7; **9**, 40306-95-4; **10**, 40306-96-5; benzylamine, 100-46-9; sodium dithionite, 7775-14-6; *n*-butyllithium, 109-72-8; copper(II) chloride, 7447-39-4; *N*,*N*'-dimethylformamide, 68-12-2.

Pteridines. XXXII. 2-Amino-3-cyano-5-chloromethylpyrazine 1-Oxide and Its Conversion to 6-Alkenyl-Substituted Pteridines[1,2]

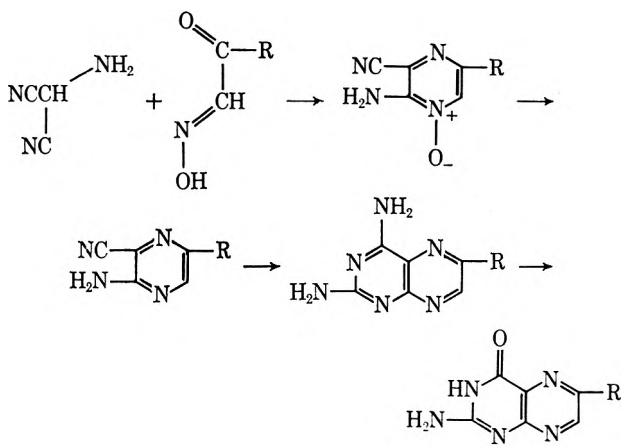
EDWARD C. TAYLOR* AND T. KOBAYASHI

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

Received February 22, 1973

2-Amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**), prepared by the condensation of β-chloropyruvaldoxime with aminomalononitrile tosylate, was deoxygenated with phosphorus trichloride to 2-amino-3-cyano-5-chloromethylpyrazine (**4**). Both **2** and **4** were converted by conventional procedures to triphenylphosphonium ylides (Wittig reagents) and, hence, by condensation with aldehydes to parallel series of 5-alkenylpyrazines (**9** and **10**). Cyclization of **10a–e** with guanidine gave 2,4-diamino-6-alkenylpteridines (**11a–e**), of interest as intermediates for the synthesis of biopterin and biopterin analogs. Some additional reactions of the above pyrazine intermediates are also described.

We have described in recent articles[1,3] a new, general, and versatile synthetic route to pteridines and pterins which involves, as its initial key step, the condensation of α-aminonitriles with α-oximino carbonyl compounds. For example, aminomalononitrile and α-ketoaldoximes give 2-amino-3-cyano-5-substituted pyrazine 1-oxides; deoxygenation and subsequent condensation with guanidine lead to 2,4-diamino-6-substituted pteridines, which upon acid or base hydrolysis yield pterins. One of the major advantages of this simple procedure over the classical Isay synthesis[4] is the unambiguous positioning of the side chain in the pyrazine ring.



Although this new procedure could, in principle, be adapted to the direct synthesis of pteridine natural products possessing multifunctional C-6 substituents (*i.e.*, biopterin, folic acid, methotrexate), complex, fragile, and difficultly accessible α-ketoaldoxime intermediates would be normally required. We describe in the present and subsequent papers a simple modification of this pteridine synthesis which permits deferral of the elaboration of the requisite C-6 side chains until *after* the initial construction of the pyrazine ring. The key intermediate, from which pteridines of both the biopterin and folic acid classes of natural products can be prepared, is 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**2**). This paper describes the preparation of **2** and its use for the preparation of pyrazines and pteridines suitable for final elaboration into the biopterin series.[5] A following paper will describe the elaboration of **2** to pteridines and pterins related to folic acid.

β-Chloropyruvaldoxime (**1**), readily prepared from diketene,[6] and less conveniently (and unreliably) by chlorination of α-oximinoacetone in chloroform solution,[7] was smoothly converted by reaction with aminomalononitrile tosylate in 2-propanol to **2**. Since **2** could be converted to 2-amino-3-cyano-5-methoxymethylpyrazine 1-oxide (**3**) upon refluxing in methanol solution, it appeared that the chloromethyl group of **2** might well be used for the introduction of diverse side chains at position 5 (pteridine position 6) by nucleophilic displacement reactions with suitable nucleophiles. Vindication of this prediction will be given in future papers in this series.

Treatment of **2** and **3** with phosphorus trichloride at room temperature in tetrahydrofuran solution resulted in smooth deoxygenation to give 2-amino-3-cyano-5-chloromethylpyrazine (**4**) and 2-amino-3-cyano-5-methoxymethylpyrazine (**5**), respectively. The ease with which these deoxygenations proceed contrasts with the vigorous conditions required for deoxygenation of 2-amino-3-cyano-6-chloromethylpyrazine 1-oxide[8] and may be a reflection of decreased steric hindrance at the *N*-oxide grouping. Deoxygenation

(1) Part XXXI: E. C. Taylor and R. F. Abdulla, *Tetrahedron Lett.*, 2093 (1973).

(2) This investigation was supported in part by grants to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service (Grants No. CA-2551 and 12876), and the Walter Reed Army Medical Research Institute (Contract No. DA-49-193-2777). This is contribution No. 1190 in the Army Research Program on Malaria.

(3) (a) E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Amer. Chem. Soc.*, in press; (b) E. C. Taylor, K. L. Perlman, Y.-H. Kim, I. P. Sword, and P. A. Jacobi, *ibid.*, in press.

(4) O. Isay, *Ber.*, **39**, 250 (1906).

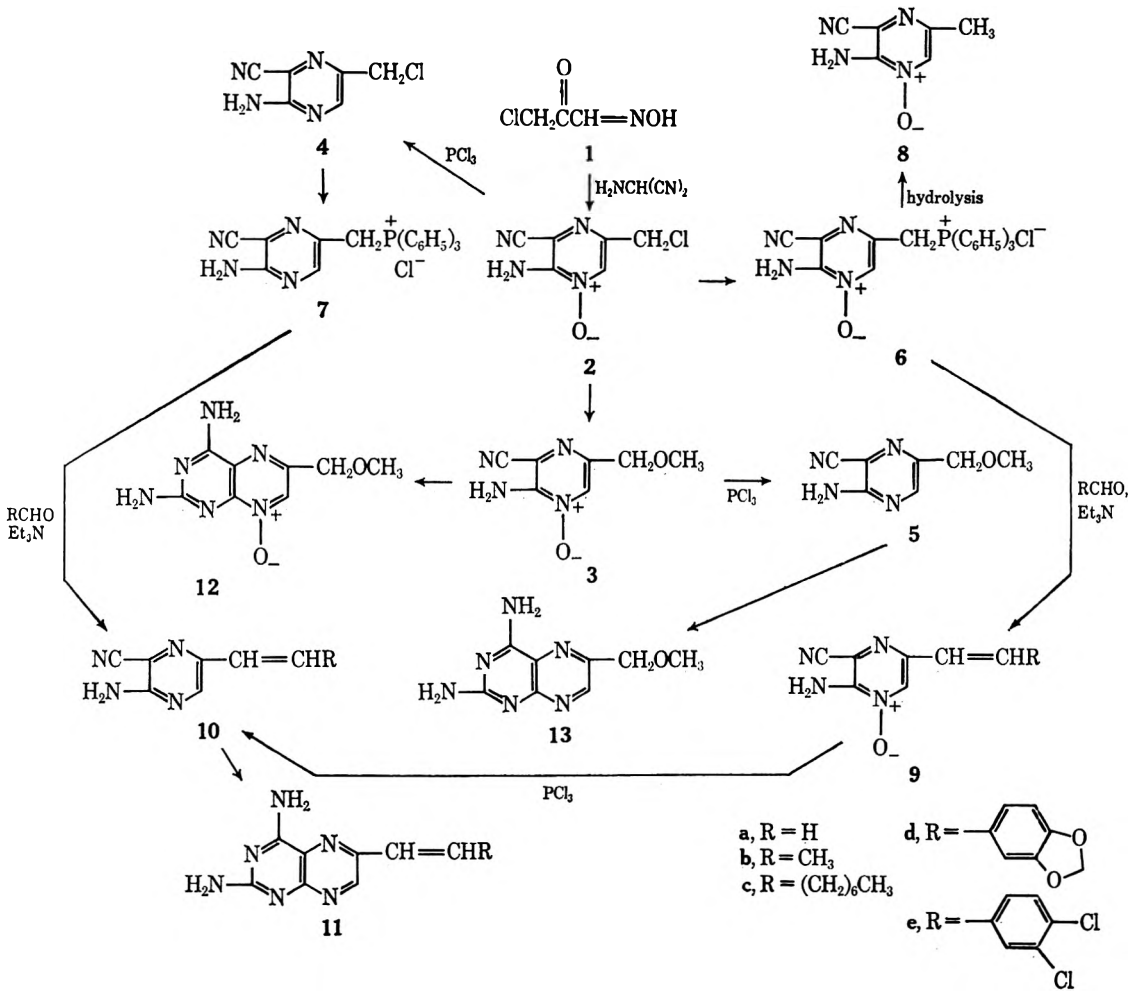
(5) A preliminary report of this work has appeared: E. C. Taylor in "The Chemistry and Biology of Pteridines," Fourth International Symposium, K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970.

(6) E. C. Taylor and R. C. Portnoy, *J. Org. Chem.*, **38**, 806 (1973).

(7) J. Armand, J.-P. Guette, and F. Valentini, *C. R. Acad. Sci., Ser. C*, 1388 (1966).

(8) E. C. Taylor and T. Kobayashi, manuscript in preparation.

SCHEME I



of **2** could also be effected with sodium hydrosulfite in boiling water, although the yield was poor. Under the same conditions, the isomeric 6-chloromethyl compound underwent both deoxygenation and reductive dehalogenation.

Both **2** and **4** were smoothly converted to the corresponding triphenylphosphonium chlorides (**6** and **7**) by treatment with triphenylphosphine in dimethylformamide. In both cases, the pyrazinylmethyltriphenylphosphonium chloride crystallized directly from the dimethylformamide solution and could be used in subsequent reactions without further purification. The structure of **6** was confirmed by hydrolysis with 30% aqueous ethanol containing a small amount of triethylamine to give 2-amino-3-cyano-5-methylpyrazine 1-oxide (**8**), identical in every respect with an authentic sample prepared as described previously[3b] by condensation of aminomalononitrile tosylate with oximinoacetone.

The phosphonium salts **6** and **7** were converted into trans olefins (the desired isomers since trans hydroxylation *via* epoxide formation and subsequent hydrolysis would yield the erythro glycol configuration found in the biopterin series of pteridine natural products) by reaction with aldehydes in a mixture of chloroform and triethylamine. Attempts to isolate the intermediate phosphoranes (Wittig reagents) were frustrated by the insolubility in water of the phosphonium salts **6** and **7** and by the apparent impurity of the products formed in methanol solution. Since trans olefins were desired, polar solvents such as methanol (in which both **6** and **7** were readily soluble) were avoided; attempts to use nonpolar solvents such as benzene and tetrahydrofuran were unsuccessful owing to insolubility. Mixtures of cis and trans isomers were occasionally obtained in the chloroform–triethylamine system. Thus, reaction of **6** with acetaldehyde gave a mixture of trans and cis isomers of 2-amino-3-cyano-5-(1-propenyl)pyrazine 1-oxide (**9b**) in a ratio of 77:23 (estimated by nmr). Fortuitously, however, the cis isomers in both the *N*-oxide series **9** and the deoxygenated series **10** were more soluble than the isomeric trans olefins, and recrystallization readily gave pure trans isomers. In this manner, the trans olefinic pyrazines **9** and **10** (Scheme I) were prepared from acetaldehyde, octylaldehyde, piperonal, and 3,4-dichlorobenzaldehyde. Treatment of **7** with paraformaldehyde in methanol solution containing triethylamine initially gave 2-methoxymethylamino-3-cyano-5-vinylpyrazine, but this latter intermediate could be hydrolyzed with aqueous acid to the desired 2-amino-3-cyano-5-vinylpyrazine (**10a**). In several cases (see Experimental Section), the olefinic pyrazine 1-oxides **9** were deoxygenated with phosphorus trichloride in tetrahydrofuran at room temperature to **10**.

Finally, annelation of the 2,4-diaminopyrimidine ring to give the pteridines **11**, **12**, and **13** was readily effected in the normal manner by condensation of the *o*-aminonitriles **3**, **5**, and **10** with guanidine in the presence

of sodium methoxide.[9] Since mild acid or base hydrolysis of these 2,4-diaminopteridines should give the corresponding pterins,[10] and trans hydroxylation of the trans olefins **11** must give erythro glycols, the above synthetic pathway should provide unequivocal and flexible procedures for the synthesis of biopterin and biopterin analogs. Furthermore, since annelation of the 2,4-diaminopyrimidine ring from **3** and **5** was effected without loss of the side chain methoxyl group, it would be expected that other side chains, introduced *via* nucleophilic displacement reactions on the chloromethylpyrazines **2** and **4**, would likewise proceed with retention of the side chain, thus offering a simple and unambiguous pathway to pterins related to folic acid. Both of these extensions of the above general pteridine synthesis are described in subsequent publications in this series.

Experimental Section

2-Amino-3-cyano-5-chloromethylpyrazine 1-Oxide (2).—A solution of 10.7 g of aminomalononitrile tosylate and 5.0 g of β-chloropyruvaldoxime[6] in 140 ml of 2-propanol was stirred at room temperature for 24 hr. The resulting dark red solution was evaporated to a small volume under reduced pressure, 100 ml of water added, and the solution extracted continuously overnight with methylene chloride. The extracts were dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure, and the residue was triturated with 50 ml of chloroform and filtered to give 4.7 g (62%) of **2**, mp 140–142° dec, as a bright yellow microcrystalline solid. The analytical sample, mp 143–144° dec, was obtained in the form of yellow prisms by recrystallization from methanol: nmr (DMSO-d_6) δ 4.68 (2, s, CH_2Cl), 8.10 (2, br s, NH_2), 8.71 (1, s, C_6H); ir 3440–3100 (NH_2), 2240 (CN) cm^{-1}.

Anal. Calcd for $C_6H_5ClN_4O$: C, 39.01; H, 2.71; N, 30.38, Cl, 19.25. Found: C, 39.19; H, 2.99; N, 30.37; Cl, 19.08.

2-Amino-3-cyano-5-methoxymethylpyrazine 1-Oxide (3).[11]—A solution of 552 mg of **2** in 10 ml of methanol was heated under reflux for 48 hr, concentrated to a small volume, and chilled. The yellow needles which separated were collected by filtration and washed with cold methanol: yield 412 mg (76%); mp 134–135° (recrystallization from methanol raised the melting point to 137–138°); nmr (DMSO-d_6) δ 3.28 (3, s, OCH_3), 4.32 (2, s, CH_2O–), 7.99 (2, br s, NH_2), 8.45 (1, s, C_6H); ir 3400–3150 (NH_2), 2230 (CN) cm^{-1}.

Anal. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.89; H, 4.56; N, 31.20.

2-Amino-3-cyano-5-chloromethylpyrazine (4).—To a solution of 13.0 g of **2** in 500 ml of tetrahydrofuran was added dropwise and with ice-bath cooling 27.0 g of phosphorus trichloride. The solution was stirred for 45 min at room temperature and then evaporated to a small volume under reduced pressure. Addition of ice water resulted in the separation of a solid which was collected by filtration and washed thoroughly with water to give 9.3 g (79%) of a yellow microcrystalline solid, mp 151–154°. The analytical sample, mp 156–157°, was obtained as pale yellow platelets by recrystallization from methanol: nmr (DMSO-d_6) δ 4.57 (2, s, CH_2Cl), 7.35 (2, br s, NH_2), 8.20 (1, s, C_6H); ir 3420–3220 (NH_2), 2230 (CN) cm^{-1}.

Anal. Calcd for $C_6H_5ClN_4$: C, 42.73; H, 2.97; N, 33.22; Cl, 21.07. Found: C, 42.59; H, 3.25; N, 33.22; Cl, 20.86.

2-Amino-3-cyano-5-methoxymethylpyrazine (5).—In the same manner as described above, 3.0 g of **3** in 180 ml of tetrahydrofuran was deoxygenated with 6.5 g of phosphorus trichloride: yield 1.6 g (59%); mp 137–140°. The analytical sample was prepared in the form of pale yellow platelets, mp 142–143°, by recrystallization from methanol: nmr (DMSO-d_6) δ 3.21 (3, s, OCH_3), 4.26 (2, s, CH_2O–), 7.18 (2, br s, NH_2), 8.20 (1, s, C_6H); ir 3400–3200 (NH_2), 2220 (CN) cm^{-1}.

Anal. Calcd for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 51.01; H, 4.73; N, 34.37.

(1-Oxy-2-amino-3-cyano-5-pyrazinyl)methyltriphenylphosphonium Chloride (6).—A solution of 5.0 g of **2** and 7.8 g of triphenylphosphine in 55 ml of dimethylformamide was stirred for 3 hr at 80–90°. The precipitate which had formed was collected by filtration and washed thoroughly with ether to give 10.8 g (90%) of pure **6**, mp 300° dec, as a pale yellow microcrystalline solid. The analytical sample was prepared in the form of pale yellow prisms by recrystallization from methanol, but without change in the melting point.

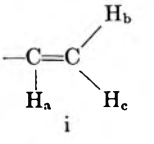
Anal. Calcd for $C_{24}H_{20}ClN_4OP$: Cl, 7.95. Found: Cl, 8.32.

(2-Amino-3-cyano-5-pyrazinyl)methyltriphenylphosphonium Chloride (7).—In the same manner as described above, 13.9 g of **4** and 28.0 g of triphenylphosphine in 80 ml of dimethylformamide gave 32.9 g (quantitative) of **7**, mp 313° dec, as a pale yellow microcrystalline solid. The analytical sample was prepared by recrystallization from methanol without change in the melting point.

Anal. Calcd for $C_{24}H_{20}ClN_4P$: Cl, 8.25. Found: Cl, 8.41.

2-Amino-3-cyano-5-methylpyrazine 1-Oxide (8).—A suspension of 1.0 g of **6** in 70 ml of 30% aqueous ethanol containing 0.25 g of triethylamine was heated under reflux for 3 hr and then evaporated to dryness. The residue was dissolved in chloroform–methanol (95:5) and passed through a short column of silica gel. The eluent was evaporated under reduced pressure to a small volume, benzene added, and the resulting mixture stirred for 30 min. Filtration then gave 0.26 g of **8** as a yellow powder. Recrystallization from methanol gave 0.25 g (75%) of fine yellow platelets, mp 187–188°. This compound was identical with an authentic sample of 2-amino-3-cyano-5-methylpyrazine 1-oxide prepared by the condensation of aminomalononitrile tosylate with oximinoacetone.[3b]

2-Methoxymethylamino-3-cyano-5-vinylpyrazine.—A mixture of 12.0 g of **7** and 8.5 g of paraformaldehyde in 600 ml of methanol containing 7.0 g of triethylamine was stirred at room temperature for 2 days and then heated under reflux for an additional day. The resulting clear solution was evaporated to dryness under reduced pressure and the residue dissolved in 100 ml of ethyl acetate. The resulting solution was washed well with water, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure to dryness. The residual solid was triturated for 30 min at room temperature with 50 ml of benzene and then filtered to give 3.0 g (57%), mp 159–160°, of a pale yellow microcrystalline solid. The analytical sample, mp 161–162°, was prepared by recrystallization from methanol: nmr ($DCCl_3$) δ 3.39 (3, s, OCH_3), 4.99 (2, d, OCH_2NH), 5.45 (1, q, H_c), 6.07 (1, q, H_b), 6.72 (1, q, H_a), 8.20 (1, s, C_6H) (partial structure i) (J_{ab} = 18.0, J_{ac} = 10.5 J_{bc} = 1.5 Hz); ir 3370 (NH), 2230 (CN), 1100 (C—O—C), 990, 900 (C=C) cm^{-1}.



i

Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.80; H, 5.50; N, 29.18.

2-Amino-3-cyano-5-vinylpyrazine (10a).—A mixture of 2.0 g of 2-methoxymethylamino-3-cyano-5-vinylpyrazine, 10 ml of 1 *N* hydrochloric acid, and 100 ml of methanol was heated under reflux for 5 hr and then evaporated to dryness under reduced pressure. The residue was dissolved in 50 ml of water and the resulting solution neutralized by the addition of solid sodium bicarbonate. Filtration then gave 1.3 g (85%) of **10a**, mp 171–172° dec. For analysis a small sample was recrystallized from methanol: mp 175–176° dec; nmr (DMSO-d_6) δ 5.20 (1, q, H_c) 5.84 (1, q, H_b), 6.58 (1, q, H_a), 7.20 (2, br s, NH_2), 8.30 (1, s, C_6H) (i) (J_{ab} = 17.5, J_{ac} = 12.0, J_{bc} = 1.5 Hz); ir 3420–3160 (NH_2), 2230 (CN), 985, 930 (C=C) cm^{-1}.

Anal. Calcd for $C_7H_6N_4$: C, 57.52; H, 4.14; N, 38.34. Found: C, 57.24; H, 4.29; N, 38.48.

2-Amino-3-cyano-5-(1-propenyl)pyrazine 1-Oxide (9b).—A suspension of 15.0 g of **6** in 1 l. of chloroform containing 11.0 g of triethylamine and 15.0 g of acetaldehyde was stirred at room temperature for 24 hr, washed with water, and then evaporated

(9) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Wiley-Interscience, New York, N. Y., 1970.

(10) See, for example, (a) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949); (b) E. C. Taylor and C. K. Cain, *ibid.*, **71**, 2538 (1949); (c) C. M. Baugh and E. Shaw, *J. Org. Chem.*, **29**, 3610 (1964).

(11) This compound was prepared by Robert C. Portnoy.

to dryness under reduced pressure. Trituration of the residual solid with 50 ml of benzene at room temperature for 30 min followed by filtration gave 5.3 g (90%) of crude **9b** as a mixture of trans and cis isomers (ratio of 77:23). Three recrystallizations from methanol gave the pure trans isomer as bright yellow needles: mp 214–215° dec; nmr (DMSO-d_6) δ 1.72 (3, d, CH_3), 6.10 (1, d, H_a), 6.52 (1, m, H_b), 7.64 (2, br s, NH_2), 8.40 (1, s, C_6H) (partial structure ii) (J_{ab} = 16.0 Hz); ir 3400–3100 (NH_2), 2230 (CN), 965 (C=C) cm^{-1}.

$$-CH_a{=}CH_bCH_3$$
ii

Anal. Calcd for $C_9H_9N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.42; H, 4.64; N, 31.80.

2-Amino-3-cyano-5-(1-propenyl)pyrazine (10b). Method A.—A suspension of 5.0 g of **7** in a mixture of 5.0 g of acetaldehyde, 2.2 g of triethylamine, and 300 ml of chloroform was stirred at room temperature for 24 hr. The resulting homogeneous solution was washed with a small amount of water and then evaporated to dryness. The residue was triturated with 20 ml of benzene for 30 min and then filtered to give 1.25 g (68%) of crude **10b** as a mixture of trans and cis isomers (ratio of 93:7). Recrystallization from methanol gave 0.96 g (52%) of the pure trans isomer of **10b** as bright yellow needles: mp 186–187° dec; nmr (DMSO-d_6) δ 1.69 (3, d, CH_3), 6.11 (1, d, H_a), 6.48 (1, m, H_b), 7.05 (2, br s, NH_2), 8.19 (1, s, C_6H) (ii) (J_{ab} = 16.0 Hz); ir 3420–3180 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_9H_8N_4$: C, 59.98; H, 5.03; N, 34.98. Found: C, 59.72; H, 5.12; N, 34.97.

Method B.—To a cooled solution of 5.0 g of crude **9b** (trans–cis 77:23) in 300 ml of tetrahydrofuran was added slowly and with stirring 11.0 g of phosphorus trichloride. After an additional 30 min of stirring at room temperature, the solution was evaporated to a small volume under reduced pressure and poured into ice water. The solid which precipitated was collected by filtration, triturated for 30 min at room temperature with 100 ml of water, and then filtered again to give 3.84 g (85%) of **10b** as a mixture of trans and cis isomers (ratio of 82:18). Recrystallization from methanol then gave 2.95 g of the trans isomer, mp 186–187° dec identical with the compound prepared above by method A.

2-Amino-3-cyano-5-(1-nonenyl)pyrazine (10c).—A suspension of 12.0 g of **7** in 650 ml of chloroform containing 7.5 g of octylaldehyde and 5.7 g of triethylamine was heated under reflux for 2 days. The resulting homogeneous solution was washed with a small amount of water and then evaporated to dryness under reduced pressure. Trituration of the oily residue with 20 ml of methanol resulted in separation of a yellow solid which was collected by filtration and recrystallized from methanol to give 3.6 g (53%) of bright yellow crystals of the pure trans isomer of **10c**: mp 123–124°; nmr (DMSO-d_6) δ 0.82 (3, t, $-CH_3$), ~2.2 (2, m, $=CHCH_2-$), 6.22 (1, d, H_a), 6.58 (1, sextet, H_b), 7.16 (2, br s, NH_2), 8.33 (1, s, C_6H) (partial structure iii) (J_{ab} = 16.0 Hz);

$$-CH_a{=}CH_bCH_2\cdots$$
iii

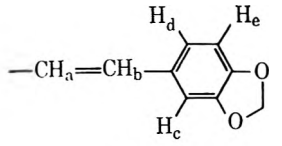
ir 3410–3170 (NH_2), 2940, 2860 (CH_2), 2230 (CN), 965 (C=C) cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.97; H, 8.50; N, 23.12.

2-Amino-3-cyano-5-(3,4-methylenedioxystyryl)pyrazine 1-Oxide (9d).—A suspension of 10.0 g of **6** in 650 ml of chloroform containing 9.0 g of piperonal and 4.4 g of triethylamine was stirred at room temperature for 24 hr and then heated under reflux for an additional 48 hr. The resulting precipitate was collected by filtration and washed with chloroform to give 5.3 g (84%) of **9d** as a deep yellow solid, mp 246° dec. This appeared to be the pure trans isomer by examination of its nmr spectrum (see below). The analytical sample was prepared by recrystallization from methanol without change in the melting point: nmr (DMSO-d_6) δ 5.71 (2, s, OCH_2O), 6.53 (1, d, H_a), 6.53 (1, d, H_e), 6.73 (1, d, H_d), 6.84 (1, s, H_c), 7.05 (1, d, H_b), 7.53 (2, br s, NH_2), 8.23 (1, s, C_6H) (partial structure iv) (J_{ab} = 16.0 Hz); ir 3400–3200 (NH_2), 2220 (CN) cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4O_3$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.81; H, 3.58; N, 19.68.

2-Amino-3-cyano-5-(3,4-methylenedioxystyryl)pyrazine (10d). Method A.—A suspension of 10.0 g of **7** in 650 ml of chloroform containing 7.5 g of piperonal and 5.0 g of triethylamine was stirred



iv

at room temperature for 24 hr and then heated under reflux for an additional 24 hr. The resulting precipitate was collected by filtration and washed with chloroform to give 5.0 g (82%) of the trans isomer of **10d** as a bright yellow solid, mp 225–226° dec. Recrystallization of a small sample from methanol gave the analytical sample: mp 228–229° dec; nmr (DMSO-d_6) δ 5.87 (2, s, $-OCH_2O$), 6.71 (1, d, H_e), 6.84 (1, d, H_a), 6.92 (1, q, H_d), 7.10 (2, s, NH_2), 7.16 (1, d, H_c), 7.24 (1, d, H_b), 8.23 (1, s, C_6H) (iv) (J_{ab} = 16.5 Hz); ir 3440–3100 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04. Found: C, 62.88; H, 3.99; N, 20.89.

Method B.—To a cooled solution of 5.0 g of **10d** in 300 ml of tetrahydrofuran was added slowly and with stirring 7.3 g of phosphorus trichloride. After 45 min of stirring at room temperature, the reaction mixture was evaporated to a small volume under reduced pressure and poured into ice water. The solid which was collected by filtration was washed well with water and recrystallized from tetrahydrofuran–methanol to give 3.9 g (83%) of the trans isomer of **10d** as a yellow solid, mp 227–228°. Recrystallization from methanol raised the melting point to 228–229° dec. This compound was identical in all respects with the product obtained as described above by method A.

2-Amino-3-cyano-5-(3,4-dichlorostyryl)pyrazine (10e).—A suspension of 10.0 g of **7** in 650 ml of chloroform containing 8.0 g of 3,4-dichlorobenzaldehyde and 4.7 g of triethylamine was stirred at room temperature for 24 hr. Filtration then gave 5.8 g (86%) of the trans isomer of **10e** as a yellow microcrystalline solid, mp 238–239° dec. The analytical sample, mp 239–240°, was prepared by recrystallization of a small sample from methanol: nmr (DMSO-d_6) δ 7.15 (2, s, CH=CH), 7.29 (2, br s, NH_2), 7.43 (2, s, H_{de}), 7.68 (1, s, H_c), 8.28 (1, s, C_6H); ir 3420–3220 (NH_2), 2220 (CN), 955 (C=C) cm^{-1}.

Anal. Calcd for $C_{13}H_8N_4Cl_2$: C, 53.64; H, 2.75; N, 19.24; Cl, 24.39. Found: C, 53.86; H, 2.94; N, 19.49; Cl, 24.32.

2,4-Diamino-6-methoxymethylpteridine 8-Oxide (12).—Guanidine hydrochloride (2.1 g) was added to a solution of 2.6 g of sodium methoxide in 95 ml of methanol and the precipitated sodium chloride removed by filtration. To the filtrate was added 2.5 g of **3**, the resulting mixture was heated under reflux for 6 hr, cooled, and filtered, and the collected solid was washed well with methanol to give 2.5 g (81%) of crude **12** as a dark green microcrystalline solid. Recrystallization (4×) from DMF (Norit) then gave 1.5 g (49%) of pure **12** as a bright yellow solid: mp 265° dec; nmr (CF_3CO_2H) δ 3.28 (3, s, OCH_3), 4.50 (2, s, $-CH_2O-$), 8.51 (1, s, C_7H).

Anal. Calcd for $C_8H_{10}N_6O_2$: C, 43.24; H, 4.54; N, 37.83. Found: C, 43.09; H, 4.54; N, 37.82.

The following compounds were prepared in the same manner from guanidine and the corresponding 2-amino-3-cyano-5-substituted pyrazines.

2,4-Diamino-6-vinylpteridine (11a): 63% yield; mp (from methanol) >300° dec; nmr (CF_3CO_2H) δ 5.51 (1, q, H_c), 6.14 (1, q, H_b), 6.65 (1, q, H_a), 8.53 (1, s, C_7H) (i) (J_{ab} = 17.5, J_{ac} = 10.0, J_{bc} = 1.0 Hz).

Anal. Calcd for $C_8H_8N_6$: C, 51.05; H, 4.28; N, 44.66. Found: C, 51.32; H, 4.20; N, 44.37.

2,4-Diamino-6-(1-propenyl)pteridine (11b): 88% yield; mp (from DMF) 312° dec; nmr (CF_3CO_2H) δ 1.62 (3, d, CH_3), 6.24 (1, d, H_a), 6.86 (1, m, H_b), 8.38 (1, s, C_7H) (ii) (J_{ab} = 16.0 Hz).

Anal. Calcd for $C_9H_{10}N_6$: C, 53.45; H, 4.98; N, 41.56. Found: C, 53.47; H, 5.13; N, 41.83.

2,4-Diamino-6-(1-nonenyl)pteridine (11c): 69% yield; mp (from methanol) 275–276° dec; nmr (CF_3CO_2H) δ 0.40 (3, t, CH_3), 1.95 (2, m, $=CHCH_2-$), 6.14 (1, d, H_a), 6.80 (1, sextet, H_b), 8.37 (1, s, C_7H) (iii) (J_{ab} = 16.0 Hz).

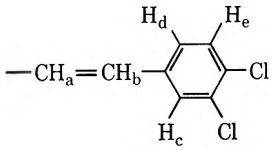
Anal. Calcd for $C_{15}H_{22}N_6$: C, 62.91; H, 7.74; N, 29.35. Found: C, 62.99; H, 7.92; N, 29.55.

2,4-Diamino-6-(3,4-methylenedioxystyryl)pteridine (11d): 93% yield; mp (after extraction with hot methanol) 336–337° dec; nmr (CF_3CO_2H) δ 5.43 (2, s, $-OCH_2O-$), 6.28 (1, d, H_e),

6.55 (1, d, H_a), 6.57 (1, d, H_d), 6.60 (1, s, H_e), 7.30 (1, d, H_b), 8.32 (1, s, C_7 H) (iv) (J_{ab} = 16.0 Hz).

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92; N, 27.26. Found: C, 58.16; H, 4.04; N, 27.33.

2,4-Diamino-6-(3,4-dichlorostyryl)pteridine (11e): 94% yield; mp (after extraction with hot methanol) 358–359° dec; nmr (CF_3CO_2H) δ 6.49 (1, d, H_a), 6.67 (2, s, H_{de}), 6.87 (1, s, H_c), 7.06 (1, d, H_b), 8.12 (1, s, C_7 H) (partial structure v) (J_{ab} = 15.5 Hz).



v

Anal. Calcd for $C_{14}H_{10}N_6Cl_2$: C, 50.45; H, 3.00; N, 25.22; Cl, 21.32. Found: C, 50.28; H, 3.05; N, 25.27; Cl, 21.56.

2,4-Diamino-6-methoxymethylpteridine (13): 85% yield: mp (from DMF) 255–256°; nmr (CF_3CO_2H) δ 3.26 (3, s, $-OCH_3$), 4.54 (2, s, $-CH_2O-$), 8.47 (1, s, C_7 H).

Anal. Calcd for $C_8H_{10}N_6O$: C, 46.59; H, 4.89; N, 40.76. Found: C, 46.43; H, 5.16; N, 41.01.

Registry No.—**2**, 40127-89-7; **3**, 40127-90-0; **4**, 40127-91-1; **5**, 40127-92-2; **6**, 40127-93-3; **7**, 40127-94-4; **8**, 19994-56-0; *cis*-**9b**, 40132-91-0; *trans*-**9b**, 40132-92-1; *trans*-**9d**, 40110-58-5; **10a**, 40110-10-9; *cis*-**10b**, 40132-93-2; *trans*-**10b**, 40132-94-3; *trans*-**10c**, 40132-95-4; *trans*-**10d**, 40110-59-6; *trans*-**10e**, 40110-60-9; **11a**, 40110-12-1; *trans*-**11b**, 40110-61-0; *trans*-**11c**, 40110-62-1; *trans*-**11d**, 40110-63-2; *trans*-**11e**, 40110-64-3; **12**, 40110-11-0; **13**, 40110-13-2; 2-methoxymethylamino-3-cyano-5-vinylpyrazine, 40110-14-3; aminomalononitrile tosylate, 5098-14-6; β-chloropyruvaldoxime, 14337-41-8; methanol, 67-56-1; phosphorus trichloride, 7719-12-2; triphenylphosphine, 603-35-0; paraformaldehyde, 30525-89-4; acetaldehyde, 75-07-0; octylaldehyde, 124-13-0; piperonal, 120-57-0; 3,4-dichlorobenzaldehyde, 6287-38-3; guanidine, 113-00-8.

The Cyanogen Azide Ring-Expansion Reaction

JOHN E. MCMURRY* AND ANTHONY P. COPPOLINO

Department of Chemistry, University of California, Santa Cruz, California 95064

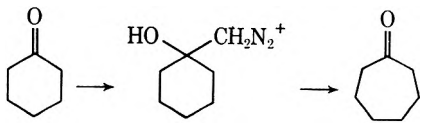
Received April 13, 1973

Reaction of alkylidenecycloalkanes with cyanogen azide, followed by hydrolysis, affords ring-expanded cyclic ketones. The reaction is applicable to a wide variety of ring sizes and to both saturated and α,β-unsaturated ketones. Application to several unsymmetrically substituted cyclic ketones indicates low migrational selectivity, paralleling the results of simple diazomethane ring expansion. An important finding is that α-substituted ring-expanded ketones can be obtained readily (ethylidenecyclohexane → 2-methylcycloheptanone, 80%). The method also should prove valuable in many instances since it is operationally simple and yields are good.

Several years ago, we reported briefly[1] on a new method of ring expansion whereby, if one treats a methylenecycloalkane with cyanogen azide, the homologous cycloalkanone is produced rapidly and in high yield. We have now completed an extensive study of the scope of the reaction, and we wish to report our findings.

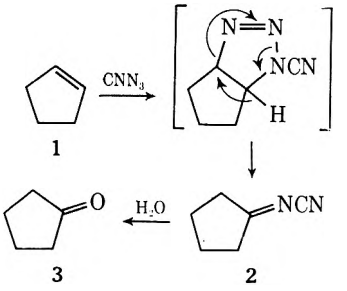
A great amount of effort has gone into developing methods of ring enlargement, and many ingenious solutions have been put forward.[2] We became interested in the subject in connection with our efforts in natural product synthesis and rapidly found that considerable room for improvements still exists.

Probably the most generally useful method of one-carbon ring expansion is by a pinacol-like rearrangement of a hydroxy diazonium ion.[2]



The required intermediate can be generated in several ways, but various difficulties usually interfere to some extent. For example, if one generates the intermediate directly from the ketone by reaction with diazomethane, the homologous cycloalkanone is produced and can itself undergo further reaction with diazomethane leading to overhomologated products.[3] On the other hand, if one attempts to avoid this difficulty by multistep Tiffeneau-type variations, low overall yields often result.

In 1964, Marsh and Hermes reported[4] that, when cyclopentene was treated with cyanogen azide, reaction occurred to yield cyclopentylidenecyanimide (2) and then, after hydrolysis, cyclopentanone. Presumably the reaction occurs by 1,3 dipolar addition followed by hydride migration and loss of nitrogen.



Marsh and Hermes also showed that, in unsymmetrical cases, the cyano-bearing nitrogen is always found on the more highly substituted carbon of the olefin, and it therefore occurred to us that, if one were to use an exocyclic olefin such as methylene cyclohexane, cycloaddition followed by alkyl migration might occur. The net effect would be a short and simple ring expansion which, since the required olefins are readily available from the corresponding ketones by Wittig reaction, should have considerable utility.

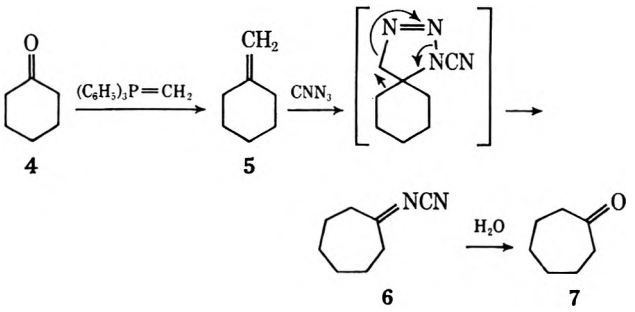
In fact, when we treated methylenecyclohexane with

(1) J. E. McMurry, *J. Amer. Chem. Soc.*, **91**, 3676 (1969).

(2) For a review of ring enlargements, see C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

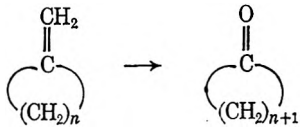
(3) See, for example, A. P. Giraitis and J. L. Bullock, *J. Amer. Chem. Soc.*, **59**, 951 (1937).

(4) F. D. Marsh and M. E. Hermes, *ibid.*, **86**, 4506 (1964).



1.3 equiv of CNN_3 in acetonitrile, and hydrolyzed the product with warm aqueous acid, cycloheptanone resulted in 80% yield. With the feasibility of the reaction thus established, we undertook a more detailed study. Some results are presented in Table I.

TABLE I
RING EXPANSION OF METHYLENECYCLOALKANES WITH CYANOGEN AZIDE



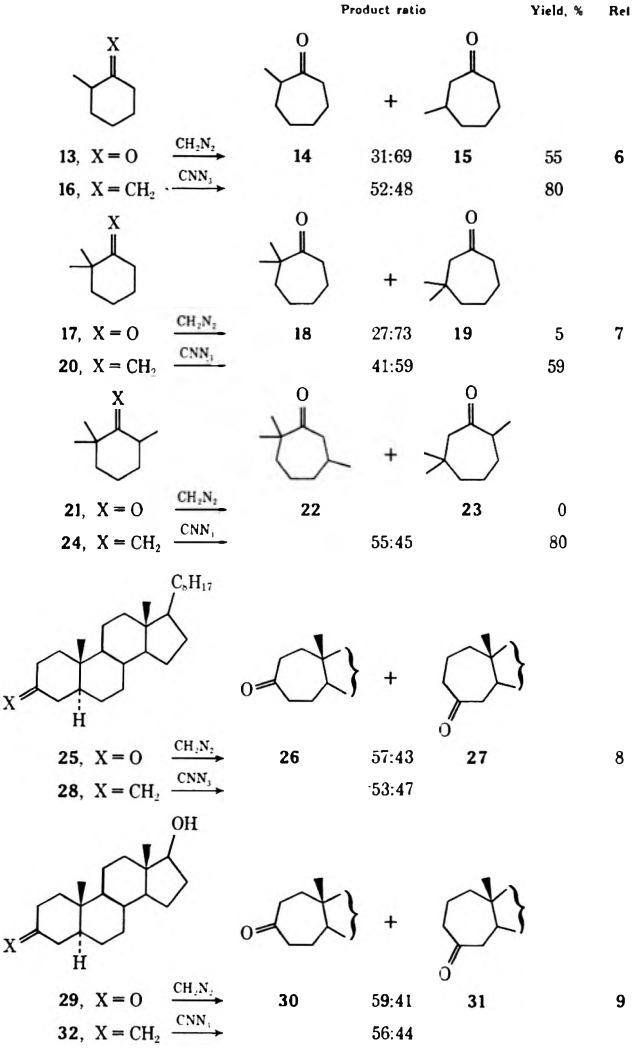
Compd	n	Yield, %
8	3	52
9	4	44
5	5	80
10	6	41
11	7	38
12	11	60

As can be seen, the reaction works on a variety of ring sizes and gives acceptable yields, although, since these examples are low molecular weight hydrocarbons, the volatility of the starting olefin causes some losses. It is particularly useful that methylenecyclododecane → cyclotridecanone works well in this reaction since ring expansion of these large ring ketones is ineffective by the usual diazomethane procedure.[5]

Unsymmetrical Cases.—In order for the reaction to be generally useful, however, it must also work well in the cases where unsymmetrically substituted rings are used, and some sort of migratory selectivity must exist. We therefore undertook a study of the cyanogen azide reaction with a number of ring-substituted methylenecycloalkanes. For comparison of the two methods it would be interesting to know also the migratory selectivity of the corresponding cycloalkanones in the diazomethane (or Tiffeneau) reaction. The literature[6,7] here is not trustworthy, however, since many results were obtained before glc became available, and we therefore repeated literature work with diazomethane. Our results are summarized in Table II.

From a synthetic point of view, the results in Table II are both discouraging and encouraging. They are discouraging because the hoped-for migrational selectivity was not observed; instead, primary, secondary, and tertiary ring bonds all seem to migrate with approximately equal facility. The situation with diazomethane, however, is little better. The results are also encouraging, however, in that all cases, even the strongly hindered 2,2,6-trisubstituted case (**24**), proceed in high yield. The diazomethane reaction by contrast is strongly sensitive to steric hindrance and gives no detectable reaction with 2,2,6-trimethylcyclohexanone, even with 100 equiv.

TABLE II
RING EXPANSION OF UNSYMMETRICALLY SUBSTITUTED CYCLOALKANONES



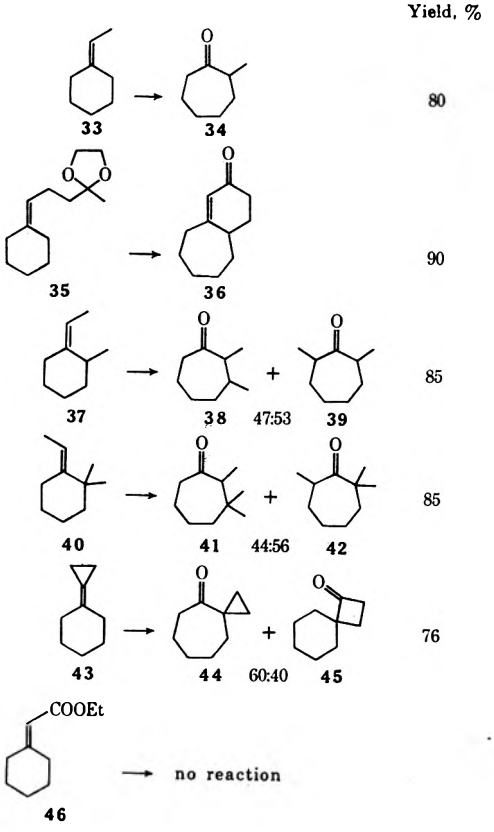
We also examined the ring enlargement of two typical 5α-3-keto steroids to see the effect of asymmetry at greater remove from the carbonyl group. There has been considerable confusion in the literature over the product distribution in the reaction of diazomethane with 5α-cholestanone (**25**)[8,9,10] and 17β-hydroxy-5α-androstan-3-one (**29**)[11,12] and several incorrect figures have been published.[9,10,12] Recent papers by Jones[11] and Levisalles,[8] however, have clarified the situation, and, as can be seen from the values given in Table II, little migrational selectivity is found in either case. Treatment of the corresponding exo methylene olefins with cyanogen azide, and determination of product composition by the ORD method of Levisalles,[8] showed that our

(5) E. Muller, M. Bauer, and W. Rundel, *Tetrahedron Lett.*, **No. 13**, 30 (1960).
(6) D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 181 (1939).
(7) M. Mousseron and G. Manon, *Bull. Soc. Chim. Fr.*, 392 (1949).
(8) J. Levisalles, G. Teutsch, and I. Tkatchenko, *ibid.*, 3194 (1969).
(9) N. A. Nelson and R. N. Schut, *J. Amer. Chem. Soc.*, **81**, 6486 (1959).
(10) G. D. Meakins and D. J. Morris, *J. Chem. Soc. C*, 394 (1967).
(11) J. B. Jones and J. M. Zander, *Can. J. Chem.* **47**, 3501 (1969).
(12) J. B. Jones and P. Price, *Can. J. Chem.*, **44**, 999 (1965).

method gave essentially identical results to the diazomethane method. Thus again no selectivity is observed.

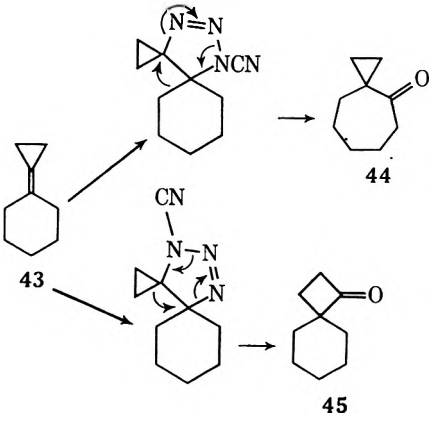
Ring Expansion of Alkylidenecycloalkanes.—One severe drawback to the diazoalkane ring expansion is that in a practical sense it is almost limited to the use of diazomethane. This is true for two reasons: (1) substituted diazoalkanes are not readily available; (2) yields are lower when substituted diazomethanes are used.[13] Thus a point of synthetic interest would be to study the reaction of cyanogen azide with alkylidenecycloalkanes with the expectation that 2-substituted homologous ketones would result. As noted previously, the required olefins are readily available by Wittig reaction. Some of our results are given in Table III.

TABLE III
RING EXPANSION OF ALKYLIDENECYCLOHEXANES WITH CYANOGEN AZIDE



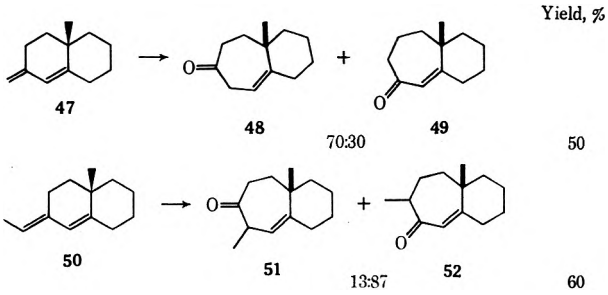
As can be seen from Table III, our hopes were borne out. All of the required olefins were readily made *via* Wittig reactions, and, with the exception of unsaturated ester **46**, all ring expansions went in high yield. Several of the cases require more specific comment. The ring expansion of unsaturated ketal **35** is potentially useful because the elements of a second ring are built into the molecule. In this specific case, ring expansion followed by cyclization occurred to give the bicyclic enone **36** in 90% overall yield. Compounds **37** and **40** were examined to see if any migrational selectivity might be present, but none was found.

Cyclopropylidenecyclohexane (**43**) proved to be one of the more interesting cases examined because it was the first tetracyclic olefin. Because of the near symmetry of the olefin, dipolar addition occurred in both possible orientations, and a mixture of products resulted. Even in this case, however, the reaction occurred in good yield, indicating again its steric insensitivity.



Ring Expansion of Enones.—The most difficult ring expansion to effect by classical methods is the ring expansion of an α,β-unsaturated ketone.[14] Although several methods[15-18] have been published, we have studied them in connection with a synthetic problem and have found them all to be ineffective or capricious. We were therefore hopeful that the cyanogen azide method would prove useful. In these cases, however, we are putting quite stringent requirements on the reaction. We are requiring first that cyanogen azide add only to the exocyclic double bond of the diene system, second that it add in only one of two possible orientations, and third that some migrational selectivity be obtained since the dienes will not be symmetrical. Our results are given in Table IV.

TABLE IV
RING EXPANSION OF DIENES WITH CYANOGEN AZIDE



The major result to be found in Table IV is that the cyanogen azide method of ring expansion is not particularly effective for α,β-unsaturated ketones. In all cases except one (**50** → **52**) bad mixtures of products are encountered and the yields are unacceptably low. From analogous ring expansions in the literature,[15,16] and from the results of a migratory aptitude study pub-

(13) See ref 2, pp 89–91.

(14) See, for example, E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964), and ref 15 therein.

(15) W. S. Johnson, M. Neeman, S. P. Birkelund, and N. A. Fedoruk, *ibid.*, **84**, 989 (1962).

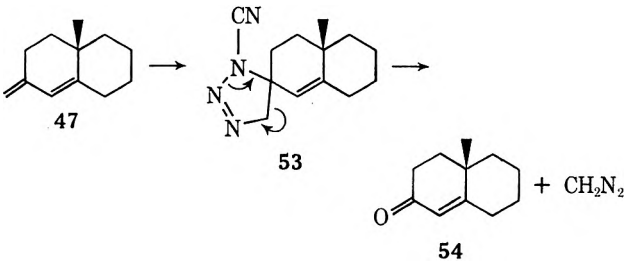
(16) E. Muller, H. Kessler, and B. Zeeh, *Fortschr. Chem. Forsch.*, **7**, 128 (1966).

(17) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964).

(18) G. Stork, M. Nussim, and B. August, *Tetrahedron, Suppl.*, **8**, 105 (1966).

lished by House,[19] we expected the ring vinyl group to migrate considerably better than the ring alkyl group. This was clearly not the case, however, and in fact the transformation **50** → **52** showed a strong preference for ring alkyl migration.

One other unexpected result which occurred during these studies on enones is that, when diene **47** was first treated with 1.3 equiv of CNN_3 in acetonitrile solution, the only product isolated after hydrolysis was starting enone **54**. This surprising occurrence can be readily explained by assuming a loss of diazomethane from the intermediate cyanotriazoline (**53**).



In this case, the carbon–carbon bond which breaks is allylic, and thus is weaker than in the corresponding saturated case, thereby accounting for the difference. We reasoned that, if the reaction medium were capable of stabilizing polar intermediates, the reaction might be induced to follow a more polar course and resemble more closely the diazomethane reaction which is presumed to go through a diazonium zwitterion.[20] We therefore repeated the experiment in 1 *M* $LiClO_4$ in 1:1 CH_3CN–CH_3OH and were gratified to find that ring expansion now occurred. All experiments on dienes were thereafter done in this polar medium.

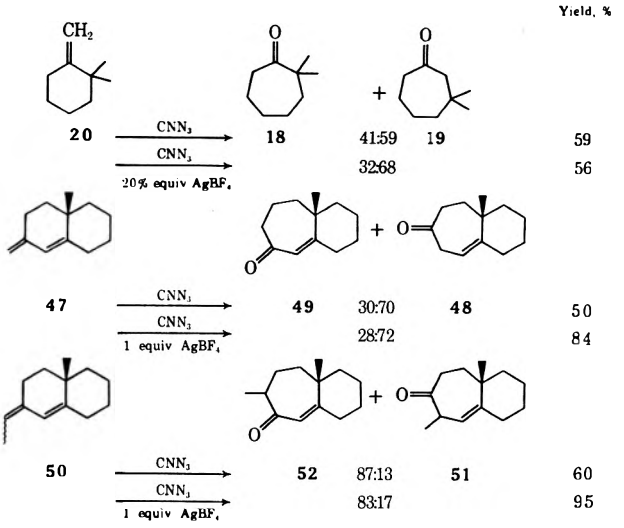
Effect of Ag^+.—In most of the cases discussed above, the cyanogen azide ring expansion occurs within 2 days at room temperature, but in some cases reaction is quite slow. We therefore considered ways in which the reaction rate might be increased. Unlike most reactions, we cannot merely raise the reaction temperature, since cyanogen azide thermally decomposes much above ambient.[21] It has been shown that the rate-determining step is dipolar addition of CNN_3 to the olefin and we must therefore catalyze that addition. Since it is known that silver ion strongly complexes olefins[22] and might therefore be expected to affect the rate of dipolar addition, we examined the effect of added Ag^+ on the reaction. Interestingly, however, the rates were not markedly affected. Instead there were minor changes in the product distribution, and there were considerable improvements in the yields for dienes **47** and **50**.[23] The results of Ag^+ on the reaction are shown in Table V.

The most striking feature of Table V is the yield improvement for enone ring expansion. This finding now allows us to ring expand all cases in good yield, although product mixtures still result.

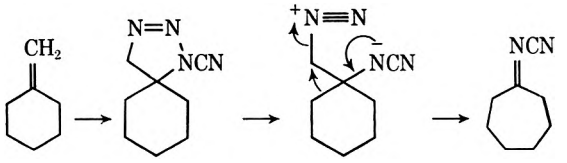
Mechanism.—Mechanistically, the cyanogen azide

TABLE V

EFFECT OF SILVER ION ON CYANOGEN AZIDE RING EXPANSION



ring expansion strongly resembles the diazomethane and Tiffeneau reactions, *i.e.*, a diazonium zwitterion intermediate is probably involved.[20]



The strongest piece of evidence pointing to this mechanism is the similarity in product distribution in unsymmetrical cases (Table II) with the results of the diazomethane reaction. In both reactions a very similar high-energy intermediate is evidently present.

The one uncertainty in this picture involves the timing of nitrogen loss and bond migration, but we feel that it is probably concerted for two reasons. In most carbonium ion rearrangements, the general rule is that the center best able to support a positive charge is the one which migrates.[24] One would therefore expect a migratory aptitude of tertiary > secondary > primary. This is clearly not found in these reactions, however; for example **20** gives 59% tertiary migration and 41% primary migration, an energetically insignificant difference. Secondly, in all of these reactions, bond migration and *N*-cyano imine formation account for the great majority of products. Direct displacement of nitrogen to form cyanoaziridines is relatively unfavorable, although this alternative reaction undoubtedly does occur[25] and the products do not survive our work-up conditions. If a carbonium ion intermediate were involved, one would expect much aziridine to be formed. If loss of nitrogen were concerted with rearrangement, however, little aziridine should be formed because of this difficulty of back-side displacement.

This argument assumes that rotation about the central C–C bond is slow, but this assumption is probably correct, since dipolar attraction between the two charge-bearing groups would tend to hold the system rigid and prevent rotation.

(19) H. O. House, E. J. Grubbs, and W. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960).

(20) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

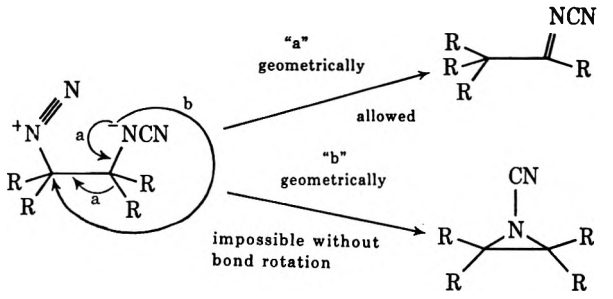
(21) A. G. Anastassiou, H. E. Simmons, and F. D. Marsh, *J. Amer. Chem. Soc.*, **87**, 2296 (1965).

(22) See F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Wiley-Interscience, New York, N. Y., 1968, pp 772–773.

(23) Th. J. DeBoer and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **73**, 589 (1954).

(24) For a review, see E. H. White in "The Chemistry of the Amino Group," S. Patai, Ed., Wiley, New York, N. Y., 1968, Chapter 8.

(25) M. E. Hermes and F. D. Marsh, *J. Org. Chem.*, **37**, 2969 (1972).



Marsh and Hermes have recently reported[25] similar conclusions about the rearrangement mechanism based on their studies with acyclic olefins.

Conclusions

In summary, we have shown that the cyanogen azide ring expansion competes favorably with other methods and in many cases is superior. The starting materials are readily available, the reactions generally go in good yields, and there are no by-products to hinder isolation.

Experimental Section

Melting points were taken on a Thomas-Hoover unimelt capillary apparatus, and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337, and nmr data were obtained using Varian A-56/60A or Jeolco Minimar 60 Mc spectrometers (TMS internal standard). Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6E spectrometer. Vpc analysis and semimicro collection were performed on a Varian Associates Model 90-P.

Caution! Cyanogen azide is a dangerous explosive which should only be generated and used in solution. The pure material is extremely shock sensitive. We recommend preparing only the necessary amount just prior to use at concentrations not greater than 4 M and at 0°.

General Preparation of Olefins.—All exocyclic olefins, with the exception of cyclopropylidene olefin **43**, were prepared by the modification of the Wittig reaction employing methylsulfinyl carbanion–dimethyl sulfoxide.[26] All olefins employed were >97% pure by vpc analysis on a 5 ft × 0.25 in. 20% SE-30 column.

General Preparation of 4 *M* Cyanogen Azide (27%) Solution.—Finely powdered sodium azide (6.50 g, 100 mmol) was added rapidly with magnetic stirring to a 0° solution of 10.59 g of cyanogen bromide (100 mmol) (use hood!) in 25 ml of acetonitrile in a 50-ml stoppered erlenmeyer flask. After 4 hr of stirring at ice-bath temperature, the reaction was complete and the clear supernatant was withdrawn by syringe.

General Ring Enlargement Reaction.—One to four equivalents of 2–4 *M* freshly prepared cyanogen azide solution was added to a 2 *M* solution of 1 equiv of olefin in an erlenmeyer flask containing, in most cases, 1 equiv of lithium perchlorate or, in special cases, silver fluoroborate. This mixture was capped with a rubber septum incorporating a syringe needle vent for nitrogen evolution and let stand at room temperature for 2 days to 2 weeks.

The reaction mixture was then treated with the same number of milliliters of 6 *N* aqueous hydrochloric acid as millimoles of olefin and warmed to 35–40° for 3 hr. The mixture was poured into water and extracted with ether, washed with brine, dried ($MgSO_4$), percolated through a mat of basic alumina (20 g/g) topped with Celite (to remove high-boiling, explosive complex impurities and to maintain clarity), and evaporated at the water pump to yield the expected ketone(s).

Ring Enlargement of Methylenecyclobutane.—To a solution of 0.500 g (1.33 mmol) of methylenecyclobutane (**8**) in 11 ml of methanol was added *via* syringe 11 ml of 2 *M* CNN_3 and the mixture was let stand for 65 hr followed by the usual hydrolysis and ether work-up to give cyclopentanone in 52% yield by vpc analysis with cyclohexanone internal standard and identified by comparison with authentic sample.

Ring Enlargement of Methylenecyclopentane.—To a solution of 1.310 g (15.96 mmol) of freshly distilled **9** in 11 ml of methanol was added *via* syringe 11 ml of 2 *M* CNN_3. The mixture was let stand for 42 hr followed by the usual hydrolysis and work-up to produce cyclohexanone in 44% yield on vpc analysis based on cycloheptanone internal standard and identified by comparison with an authentic sample.

Ring Enlargement of Methylenecyclohexane.—A solution of methylenecyclohexane (480 mg, 5.0 mmol) was treated with 1.3 equiv of CNN_3 in a 12 ml of 1:1 acetonitrile–methanol for 48 hr and the product was hydrolyzed to give cycloheptanone (2,4-DNP mp 147–148°, lit.[23] mp 148°) in 80% yield.

Ring Enlargement of Methylenecycloheptane.—A solution of 0.546 g (4.95 mmol) of freshly distilled **10** in 8 ml of methanol was treated *via* syringe with 8 ml of 2 *M* CNN_3 and the mixture was let stand for 41 hr. After hydrolysis and work-up in the usual fashion, cyclooctanone was realized in 41% yield based on vpc analysis with cyclohexanone internal standard and identified by comparison with an authentic sample.

Ring Enlargement of Methylenecyclooctane.—To a solution of freshly distilled **11** (5.10 mmol) in 11 ml of methanol was added *via* syringe 8 ml of 2 *M* CNN_3 and the mixture was let stand for 65 hr. The usual hydrolysis and work-up produces cyclononanone in 38% yield on vpc analysis using cycloheptanone internal standard and identified by comparison with an authentic sample.

Ring Enlargement of Methylenecyclododecane.—To a solution of 16.4 g (91 mmol) of pure **12** and 9.68 g (91 mmol) of lithium perchlorate in 90 ml of ethanol was added *via* syringe 91 ml of 4 *M* CNN_3. The mixture was let stand for 14 days and the usual hydrolysis and work-up procedure yielded 10.70 g (60%) of cyclotridecanone: bp 97–112° (0.4 mm); ir (neat) 1724 cm^{-1} (C=O); nmr (CCl_4) δ 1.26 (s, 16 H), 1.45–1.90 (m, 4 H), 2.22–2.53 (m, 4 H); semicarbazone mp 206.5–207° dec (lit.[27] mp 205–206° dec).

Ring Enlargement of 16 with CNN_3.—To a solution of 330 mg (3 mmol) of 2-methylmethylenecyclohexane (**16**) in 5 ml of methanol was added *via* syringe 4.5 ml of 1 *M* CNN_3 and this mixture was let stand for 48 hr. After the normal hydrolysis and work-up, a mixture of two isomeric ketones, **14** and **15**, was isolated in 80% overall yield in the ratio 52:48 as determined, separated, and collected on a 5 ft × 0.25 in. 15% FFAP (105°) 60 ml/min column. 2-Methylcycloheptanone (**14**), which represents the migration of the primary carbon center, was identified by spectral comparisons with an authentic sample. 3-Methylcycloheptanone (**15**), semicarbazone mp 179.5–180.5° (lit.[6] mp 179–181°), which represents the migration of the secondary center, was formed in 48% yield relative to **14**.

Ring Enlargement of 20 with CNN_3.—To a solution of 0.4315 g (3.474 mmol) of freshly distilled **20** in 5.5 ml of methanol was added *via* syringe 5.5 ml of 2 *M* CNN_3 and the reaction mixture was let stand for 90 hr. Hydrolysis and work-up in the usual fashion led to a mixture of isomeric ketones **18** and **19** formed in 59% overall yield in the ratio 41:59 *via* vpc analysis with cyclohexanone internal standard; separation and collection followed on a 5 ft × 0.25 in. 20% DEGS (120°) 60 ml/min column. 2,2-Dimethylcycloheptanone (**18**) [ir (neat) 1705 (C=O), 1122, 1060 cm^{-1}; nmr (CCl_4) δ 1.13 (s, 6 H), 1.45–1.85 (broad singlet, 6 H), 2.25–2.65 (m, 2 H); semicarbazone mp 173–174° (lit.[7] mp 174–175°)] corresponds to primary carbon center migration. 3,3-Dimethylcycloheptanone (**19**) [ir (neat) 1700 (C=O), 1292, 1249, 1208 cm^{-1}; nmr (CCl_4) δ 0.93 (s, 6 H), 2.10–2.40 (m, 2 H), 2.35 (s, 3 H); semicarbazone mp 191.5–192.5° (lit.[28] mp 184–185° and 2,4-DNP mp 120–120.5°)] resulted from tertiary carbon migration. When the reaction was repeated in the presence of 20% equiv of $AgBF_4$, a 58% yield of products was obtained consisting of 32% **18** and 68% **19**.

Ring Enlargement of 24 with CNN_3.—A solution of 0.3255 g (2.355 mmol) of freshly distilled **24** in 3.5 ml of methanol was treated with 3.5 ml of 2 *M* CNN_3 *via* syringe and let stand for 90 hr. After acid hydrolysis and work-up as usual, the expected isomeric ketones were obtained in 80% overall yield in 55:45 ratio of **22** to **23** as determined with cyclohexanone internal standard, separated, and collected on a 5 ft × 0.25 in. 20%

(26) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(27) N. J. Leonard and C. W. Schimelpheng, *J. Org. Chem.*, **23**, 1708 (1958).

DEGS (120°) 60 ml/min column. 2,2,6-Trimethylcycloheptanone (**22**) [ir (neat) 1699 (C=O), 1187, 1118, 1059 cm^{-1}; nmr (CCl_4) δ 0.93 (s, 3 H), 1.02 (s, 6 H), 1.25–1.85 (m, 6 H), 1.25–1.85 (m, 6 H), 1.86–2.76 (sextet, J = 10 Hz, 3 H), semicarbazone mp 177.5–178.5° (lit.[29] mp 194–195° and 2,4-DNP mp 136.5–137°)] resulted from secondary center migration. 2,6,6-Trimethylcycloheptanone (**23**) [ir (neat) 1701 (C=O), 1203, 1160, 970, 943 cm^{-1}; nmr (CCl_4) δ 0.93 (d, J = 2.5 Hz, 6 H), 1.07 (s, 3 H), 1.36–1.70 (m, 6 H), 2.31 (d, J = 4.5 Hz, 3 H); semicarbazone mp 182–184° (lit.[30] mp 185–187°)], also known as tetrahydroeucarvone, was formed by migrating the tertiary carbon center.

Ring Enlargement of 13 with Diazomethane.—To a stirred solution at 0° of 0.310 g (2.77 mmol) of 2-methylcyclohexanone in 40 ml of ether–85 ml of methanol containing 3.0 g of potassium hydroxide was added 2.28 g (10 equiv) of *N*-nitrosomethylurea. The mixture was stirred at 0° in an iced brine solution for 5 hr, treated with 25 ml of 10% aqueous hydrochloric acid, filtered from urea salts, and poured into water. The product mixture was extracted with ether, washed with water and brine, dried ($MgSO_4$), concentrated, and analyzed by vpc to give a good overall yield of two ring-enlarged products in a 30:70 ratio. 2-Methylcycloheptanone and 3-methylcycloheptanone were shown to be identical by vpc and mass spectral comparison with authentic samples. Vpc analysis was performed on a 5 ft × 0.25 in. 20% SE-30 (110°) 60 ml/min column.

Ring Enlargement of 17 with Diazomethane.—To 0.325 g (2.58 mmol) of 2,2-dimethylcyclohexanone in 25 ml of ether–60 ml of methanol containing 2.0 g of potassium hydroxide was added 2.66 g (10 equiv) of *N*-nitrosomethylurea. The resulting mixture was stirred for 5 hr at 0°. Then 5 ml of 10% aqueous hydrochloric acid was added, and the mixture was filtered from urea salts and extracted with ether. The ethereal extract was washed with water and brine, dried ($MgSO_4$), and concentrated. Vpc analysis indicated *ca.* 5% of ring-expanded products in 27:73 ratio with almost completely unreacted starting material. 2,2-Dimethylcycloheptanone and 3,3-dimethycycloheptanone were separated on a 5 ft × 0.25 in. 20% DEGS (120°) 60 ml/min column and found to be identical with authentic samples by comparison of mass-spectral fragmentations.

Ring Enlargement of 21 with Diazomethane.—To 0.1 g of 2,2,6-trimethylcyclohexanone in 40 ml of ether–140 ml of methanol containing 10.0 g of potassium hydroxide was added 7.31 g (100 equiv) of *N*-nitrosomethylurea. The mixture was stirred at 0° in a solid ice–Dry Ice bath which was allowed to come to room temperature in 5 hr and let stir for 25 hr total. The mixture was worked up as above and shown by vpc [on a 5 ft × 0.25 in. 20% DEGS (120°), 60 ml/min] to be 99% starting material.

Ring Expansion of 3-Methylene-5α-cholestane.—3-Methylenecholestane (800 mg, 2.1 mmol) was placed in a small flask with 5 ml of 1:1 ethyl acetate–methanol. Cyanogen azide (10 ml of a 1 *M* solution in ethyl acetate) was added and the reaction was stirred for 4 days. Hydrolysis followed by the usual work-up gave a semicrystalline mixture of ketone **26** and **27** contaminated with unreacted olefin. Chromatography on basic alumina gave 470 mg (55%) of the pure ketone mixture. The exact composition of the mixture was determined by the ORD method of Levisalles.[8] A solution of 19.2 mg of ketone mixture in CH_3OH gave θ 0.092; $[\alpha]$ 472°; $[\Phi]_{307}$ +1880°. This corresponds to a product distribution of 53% **26** and 47% **27**.

Ring Expansion of 3-Methylene-17β-hydroxyandrostane.[31]—A solution of **32** (60 mg, 0.20 mmol) in 5 ml of 1:1 ethyl acetate–methanol was treated with 1 ml of 2 *M* CNN_3 solution and the reaction was allowed to stand for 7 days. Hydrolysis followed by the usual work-up and preparative layer chromatography of the product gave 17 mg (26%) of the ketone mixture **30** and **31**. The composition of the mixture was determined by the ORD method of Levisalles.[8] The calculated value was $[\Phi]_{302}$ +1277°, which, from a knowledge of ORD values for the pure ketones,[32] allows one to determine the composition of the mixture as 56% **30** and 44% **31**.

Ring Enlargement of 33.—Ethylidenecyclohexane (**33**) was treated with 1.3 equiv of CNN_3 in 1:1 acetonitrile–methanol for 48 hr and the product was hydrolyzed. 2-Methylcycloheptanone (2,4-DNP mp 121–122°, lit.[1] mp 121–122°) was obtained in 80% yield.

Ring Enlargement of 35. A General Annelation Reaction.—A solution of 1.04 g (5.0 mmol) of **35** and 0.532 g (5.0 mmol) of lithium perchlorate in 2.5 ml of ethanol was treated with 8 ml of 4 *M* CNN_3 and the solution was let stand for 8 days. The reaction mixture was hydrolyzed and worked up to give 1.0 g of clear oil, which was shown to be free of ketal functionality by nmr spectra analysis of the crude product. This mixture of intermediate diketones and keto ketols was treated with 100 ml of 4% ethanolic potassium hydroxide. The sclution was heated for 4 hr at reflux and stirred for a further 14 hr at room temperature to effect the aldol condensation. The mixture was poured into water, extracted with ether, washed with water and brine, dried ($MgSO_4$), concentrated, and microdistilled [bath temperature 135° (0.7 mm)] to give 0.90 g of enone $\Delta^{1(11)}$-bicyclo[5.4.0]-undecen-10-one (**36**) as a mixture of α,β and β,γ isomers: ir (neat) 3040, 1710 (C=O), 1675 (unsaturated C=O), 1244, 1196, 883 cm^{-1}; nmr (CCl_4) δ 0.57–1.02 (m, 6 H), 1.05–1.35 (m, 2 H), 1.35–1.82 (m, 6 H), 1.82–2.78 (m, 2 H), 5.56–5.82 (s, 1 H); semicarbazone mp 212–214° (lit.[33] mp 212–214°).

Cyclopropylidenecyclohexane (43).—A solution of 1.925 g (5 mmol) of cyclopropyltriphenylphosphonium bromide in 18 ml of freshly distilled tetrahydrofuran under nitrogen was treated with 5.5 ml of 1.0 *M* *n*-butyllithium and refluxed for 1 hr, and 1.0 ml (*ca.* 10 mmol) of cyclohexanone was added. The reaction mixture was stirred for 24 hr at 45°, poured into water, and extracted with pentane. The pentane extracts were washed well with 100-ml portions of saturated sodium bisulfite and water, dried ($MgSO_4$), passed through 20 g of basic alumina, filtered, and evaporated to yield 0.47 g (77%) of **43**: ir (neat) 3065, 1258, 1234, 1072, 1001, 902, 861, 699 cm^{-1}; nmr (CCl_4) δ 0.87–1.04 (m, 4 H), 1.38–1.80 (m, 6 H), 1.97–2.50 (m, 4 H).

Ring Enlargement of Cyclopropylidenecyclohexane.—A solution of 0.427 g (3.5 mmol) of cyclopropylidenecyclohexane and 0.372 g (3.5 mmol) of lithium perchlorate in 15 ml of 14:1 ethanol–acetonitrile was treated with 4 ml of 4 *M* CNN_3 and the mixture was let stand for 7 days. Hydrolysis and work-up in the usual fashion followed by microdistillation [bath temperature 135° (19 mm)] gave 180 mg (37%) of material which by vpc analysis on a 5 ft × 0.25 in. 20% DEGS (135°) 60 ml/min column was shown to be 76% of a mixture of ring-expanded isomers **44** and **45** in a 60:40 ratio, and 24% of unidentified product. Spiro[2.6]nonan-4-one (**44**) [ir (neat) 3105, 3020, 1690 (unsaturated C=O), 1191, 1145, 1103, 907, 875, 828 cm^{-1}; nmr (CCl_4) δ 0.68 (quartet of doublets, J = 3, J' = 1 Hz, 2 H), 1.25 (quartet of doublets, J = 3, J' = 1 Hz, 2 H), 1.71 (s, 8 H), 2.40–2.77 (m, 2 H); 2,4-DNP mp 115–115.5° (as deep red crystals) (lit.[34] mp 110–111°)] represents the cyclohexyl ring migration product. Spiro[3.5]nonan-1-one (**45**) had ir (neat 1780 (C=O), 1150, 1115, 1055 cm^{-1}; nmr (CCl_4) δ 1.20–1.95 (m, 12 H), 2.86 (t, J = 8.5 Hz, 2 H); 2,4-DNP mp 134.5–135° (lit.[35] mp 134–135°). The ir and nmr spectra are in agreement with published results.[36]

Ring Enlargement of 37.—A solution of 0.632 g (5.09 mmol) of freshly distilled **37** and 0.532 g (5.0 mmol) of lithium perchlorate was treated with 10 ml of 4 *M* CNN_3 and the mixture was let stand for 7.7 days. Hydrolysis and work-up in the usual fashion gave an 85% total yield of two isomeric ketones **39** and **38** in a 53:47 ratio by vpc analysis, with **38** as a mixture of epimers at C_3. The ketones were separated and collected on a 5 ft × 0.25 in. 20% DEGS (135°) 60 ml/min column. 2,7-Dimethylcycloheptanone (**39**) [ir (neat 1707 (C=O), 1370, 1010, 960, 930 cm^{-1}; nmr (CCl_4) δ 0.95 and 1.07 (two doublets, J = J' = 1 Hz, 6 H total), 1.19–2.21 (m, 8 H), 2.20–2.95 (s, 2 H)] represents the migration of the primary carbon center and was unequivocally identified by mass spectral analysis of a

(28) E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5492 (1969).
(29) A. Eschenmoser, H. Schinz, R. Fisher, and J. Cologne, *Helv. Chim. Acta*, **34**, 2329 (1951).
(30) R. A. Barnes and W. J. Houlihan, *J. Org. Chem.*, **26**, 1609 (1961).
(31) This experiment was performed by Mr. Carl Hering.
(32) J. B. Jones and J. M. Zander, *Can. J. Chem.*, **46**, 1913 (1968).
(33) V. Prelog, P Barman, and M. Zimmerman, *Helv. Chim. Acta*, **32**, 1284 (1949).
(34) P. Leriverend and J. M. Conia, *Bull. Soc. Chim. Fr.*, 121 (1966).
(35) E. R. Buchman, D. H. Deutsch, and G. I. Fujimoto, *J. Amer. Chem. Soc.*, **75**, 6228 (1953).
(36) B. M. Trost, R. LaRochelle, and M. J. Bogdanowicz, *Tetrahedron Lett.*, 3449 (1970).

sample collected from a deuterium exchange vpc column[37] (8 ft × 0.25 in) [mass spectrum (80 eV) *m/e* (rel intensity) 143, 142, 141, 140 (M^+, 10, 100, 74, 81)]. 2,3-Dimethylcycloheptanone (**38**) [ir (neat) 1712 (C=O), 1317, 1158 cm^{-1}; nmr (CCl_4) δ 0.97 (s, 3 H), 1.06 (d, J = 3 Hz, 3 H), 1.22–1.97 (m, 6 H), 1.97–2.61 (m, 3 H)] results from migrating the secondary carbon center and is an epimeric mixture at C_3. It was positively identified *via* mass spectra data of a collection from the deuterium exchange column as being **38**-*2,7,7-d*$_3$ [mass spectrum (80 eV) *m/e* (rel intensity) 143, 142, 131, 140 (M^+, 100, 75, 50, 8)].

Ring Enlargement of 40.—A solution of 0.69 g (5.04 mmol) of freshly distilled **40** and 0.532 g of lithium perchlorate in 2.5 ml of ethanol was treated with 10 ml of 4 *M* CNN_3 and let stand for 7.7 days. The usual hydrolysis and work-up gave an 85% yield of the expected isomeric ketones **42** and **41** in a 56:44 ratio by vpc analysis. The ketones were separated and collected on a 5 ft × 0.25 in. 20% DEGS (135°) 60 ml/min column. 2,2,7-Trimethylcycloheptanone (**42**) [ir (neat) 1710 (C=O), 1370, 1017 cm^{-1}; nmr (CCl_4) δ 1.03 (s, 9 H), 1.31–2.01 (m, 8 H), 2.56–3.09 (m, 1 H)] resulted from primary carbon migration; and conclusive evidence was obtained from a mass spectral analysis of a deuterium exchange column collection of **42**-*7-d*$_1$ [mass spectrum (80 eV) *m/e* (rel intensity) 157, 156, 155, 154 (M^+, 0, 2, 20, 100)]. 2,3,3-Trimethylcycloheptanone (**41**) [ir (neat) 1705 (C=O), 1380, 1355 cm^{-1}; nmr (CCl_4) δ 0.85 (s, 3 H), 0.96 (d, J = 7 Hz, 3 H), 0.98 (s, 3 H), 1.62 (broad singlet, 6 H), 2.17–2.55 (m, 2 H), 2.43–2.96 (quartet, J = 7 Hz, 1 H)] was the result of tertiary carbon center migration and was unequivocally identified by deuterium-exchange vpc column collection followed by mass spectral analysis of **41**-*2,7,7-d*$_3$ [mass spectrum (80 eV) *m/e* (rel intensity) 157, 156, 155, 154 (M^+, 57, 100, 14, 10)].

Ring Enlargement of 47.—A solution of 0.486 g (3.0 mmol) of **47** in 3.0 ml of ethanol was treated with 1.2 ml (1.6 equiv) of 4 *M* CNN_3 to which was added 4.8 ml of acetonitrile and the mixture was let stand for 47 hr. Hydrolysis followed with 3.75 ml of 6 *N* aqueous hydrochloric acid for 30 min at room temperature and the usual ether work-up afforded 0.27 g of yellow oil (50%) of two ring-expanded products in the ratio 70:30 as determined by vpc analysis on a 5 ft × 0.25 in. 20% SE-30 (160°) 60 ml/min column. The ketones were separated and collected on a 5 ft × 0.25 in., 15% Carbowax 20M (160°) 60 ml/min column. 1,2,3,4,4a,5,6,8-Octahydro-4a-methyl-7*H*-benzocyclohepten-7-one (**48**) [ir (neat) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.99 (s, 3 H), 5.48 (m, 1 H)], in which vinyl migration had occurred, was formed in 70% yield. 1,2,3,4,7,8,9,9a-Octahyro-9a-methyl-6*H*-benzocyclohepten-6-one (**49**) [ir (neat) 1650 (unsaturated C=O), 1620 cm^{-1}; uv max (95% EtOH) 240 nm (ε 8000); nmr ($CDCl_3$) δ 1.22 (s, 3 H), 5.74 (s, 1 H)] was formed in 30% yield.

When the reaction was repeated with the addition of silver fluoroborate (0.585 g, 3.0 mmol), work-up gave 0.45 g (84%) of products in a ratio of 72% **48**, 28% **49**.

Ring Enlargement of 50 in the Presence of Ag^+.—A solution of 0.176 g (1 mmol) of freshly distilled **50** in 1.0 ml of ethanol was treated with 0.4 ml (1.6 equiv) of 4 *M* CNN_3 to which was added 1.6 ml of acetonitrile, and the mixture was let stand for 47 hr. Hydrolysis followed with 1.25 ml of 6 *N* aqueous hydrochloric acid for 30 min at room temperature and standard ether work-up gave a 60% yield of two ring-expanded products, **52** and **51** in the ratio 87:13 as determined, separated, and collected on a 5 ft × 0.25 in. 20% DEGS (165°) 60 ml/min column. 1,2,3,4-7,8,9,9a-Octahydro-7,9a-dimethyl-6*H*-benzocyclohepten-6-one (**52**) [ir (neat) 1675 (unsaturated C=O), 1645, 1620, 850 cm^{-1}; uv max (95% EtOH) 243 nm (ε 7500); nmr (CCl_4) δ 1.02 and 1.06 (two doublets, J = J' = 7 Hz, 3 H total), 1.19–1.21 (two singlets, 3 H total), 5.67 (s, 1 H)], the unexpected alkyl migration product, was formed in 87% yield as a mixture of epimers at the C_3 methyl group. 1,2,3,4,4a,5,6,8-Octahydro-4a,8-dimethyl-7*H*-benzocyclohepten-7-one (**51**) [ir (near) 1705 (C=O), 1660 cm^{-1}; nmr (CCl_4) δ 0.95 and 0.97 (two doublets, J = J' = 6 Hz, 3 H total), 1.07 (s, 3 H), 5.38–5.65 (m, 1 H)], the C_1 vinyl migration product, was formed in 13% yield.

When the reaction was repeated with the addition of $AgBF_4$ (0.195 g, 1.0 mmol), a near-quantitative yield of products was obtained consisting of 83% **52** and 17% **51**.

Acknowledgment.—This research was supported by PHS Research Grant CA11277 from the National Cancer Institute.

Registry No.—**5**, 1192-37-6; **8**, 1120-56-5; **9**, 1528-30-9; **10**, 2505-03-5; **11**, 3618-18-6; **12**, 32400-07-0; **13**, 583-60-8; **14**, 932-56-9; **15**, 933-17-5; **16**, 2808-75-5; **17**, 1193-47-1; **18**, 7228-52-6; **19**, 23438-70-2; **19** semicarbazone, 40514-60-1; **19** 2,4-DNP, 40514-61-2; **20**, 40514-62-3; **21**, 2408-37-9; **22**, 1686-41-5; **22** semicarbazone, 40514-64-5; **22** 2,4-DNP, 40568-89-6; **23**, 4436-59-3; **24**, 40514-66-7; **28**, 1173-33-7; **32**, 25845-84-5; **33**, 1003-64-1; **35**, 40514-68-9; **36**, 19198-29-9; **37**, 40514-70-3; **38**, 40514-71-4; **39**, 7272-19-7; **40**, 40514-73-6; **41**, 40514-74-7; **42**, 40514-75-8; **43**, 14114-06-8; **44**, 5743-85-1; **45**, 29800-45-1; **47**, 40514-76-9; **48**, 40514-77-0; **49**, 40514-78-1; **50**, 40514-79-2; **51**, 40514-80-5; **52**, 40514-81-6; cyanogen azide, 764-05-6; sodium azide, 26628-22-8; cyanogen bromide, 506-68-3; cyclononanone, 3350-30-9; cyclotridecanone, 832-10-0; *N*-nitrosomethylurea, 684-93-5; cyclopropyltriphenylphosphonium bromide, 14114-05-7.

(37) M. Senn, W. J. Richter, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **87**, 680 (1965).

Nitrosation of 9-Acylamidoxanthenes

TIMOTHY B. PATRICK* AND JAMES G. DOLAN

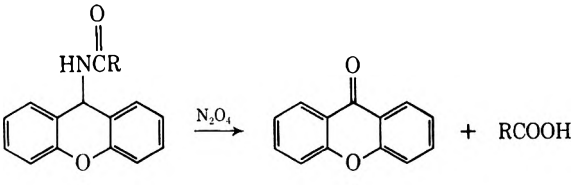
Department of Chemistry, Southern Illinois University, Edwardsville, Illinois 62025

Received February 28, 1973

The title compounds (1a–g) react with nitrosating agents at −60° to produce carboxylic acids and xanthone. The reaction is proposed as an alternate approach to carboxylic acid preparation when direct nitrosation of an amide fails. The reaction is shown not to proceed by the usual nitrosoamide decomposition mechanism from the fact that nitrosation of *N*-(9-xanthyl)benzamide-*carbonyl*-^{18}O produced xanthone containing no oxygen-18 and benzoic acid containing all of the oxygen-18. Mechanism studies were hampered owing to xanthone formation from several substrates. Plausible reaction intermediates were prepared and were found to produce xanthone on nitrosation. Thus attempts to trap intermediates were not successful.

Thermal nitrosoamide decomposition holds an important position in both synthetic and theoretical organic chemistry. Reaction yields are generally good and the products are easily isolated in pure condition. Alkyl nitrosoamides produce esters, acids, diazoalkanes, and olefins as major products. The actual products obtained in a particular reaction depend mainly on the structure of the alkyl group and the solvent polarity.[1]

In attempting to prepare 9-diazothioxanthene, we found that nitrosation of 9-acetylamidothioxanthene at −60° with dinitrogen tetroxide in tetrahydrofuran solution produced only acetic acid and thioxanthone. *N*-Nitroso-9-acetylamidothioxanthene was not observed. Also, we found that nitrosation of 9-acylamidoxanthenes (1) produced the corresponding carboxylic acid and xanthone (2) as the only products. Although nitrosation of N-unsubstituted amides is a useful method for converting carboxamides to carboxylic acid, the conversion of N-substituted amides into acids by nitrosation is not a generally useful reaction.[1,2] Thus we investigated the nitrosation of 9-acylamidoxanthenes for its synthetic utility. Also, we studied the reaction from a mechanistic point of view, since the facile conversion of **1** into a carboxylic acid and **2** without isolation or detection of a *N*-nitrosoamide indicated a deviation from the usual nitrosoamide decomposition mechanism.[1] These studies are the subject of this paper.

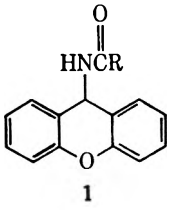


1 2

Nitrosation of the 9-acylamidoxanthenes[3] with nitrous acid, dinitrogen tetroxide, or nitrosyl chloride was successful only for the latter two reagents. Dinitrogen tetroxide was used extensively in the synthetic studies while both dinitrogen tetroxide and nitrosyl chloride were used in the mechanism studies. Reaction yields with nitrosyl chloride were comparable to the yields obtained using dinitrogen tetroxide, but a thorough comparison of the two reagents was not made. Product yields were best when the sodium salt of the 9-acylamidoxanthene was used. The results given in Table I show the yields of carboxylic acids and xanthone obtained from nitrosation of the 9-acylamidoxanthene *N*-sodium salt with dinitrogen tetroxide at −60° in tetrahydrofuran solution. We were unable to detect any *N*-nitroso compound by nmr spectroscopy at low temperatures.[4] We could observe that the carboxylic acid salt and xanthone were formed almost immediately after the addition of dinitrogen tetroxide. Nmr spectroscopy showed that the amount of carboxylic acid salt formed was equal to the amount of xanthone formed. We were able to isolate pure xanthone in good yield (75–99%), but the carboxylic acid was isolated in lower yields (40–62%) despite numerous attempts to improve the isolation procedure. We did not find any other products which would give a quantitative material balance.

TABLE I

NITROSATION OF 9-ACYLAMIDOXANTHENES (1)



1

Compd	R	Acid[a] (% yield)[b]	% xanthone
1a	$C_6H_4CH_3$	*p*-Toluic (55)	78
1b	OC_2H_5	Ethylbicarbonic (95)[c]	99
1c	C_6H_5	Benzoic (60)	75
1d	1-Naphthyl	1-Naphthoic (50)	78
1e	$CH_2C_6H_5$	Phenylacetic (42)	80
1f	$CH(C_4H_9)_2$	Di-*tert*-butylacetic (62)	99
1g	$C(C_6H_5)_3$	Triphenyacetic (40)	99

[a] Identified by comparison with authentic material. [b] Yields of isolated pure acid. [c] Identity and yield determined by nmr spectroscopy.

Direct nitrosation of carboxamides is generally a good method for preparing carboxylic acids. However, in the event that direct nitrosation fails, the nitrosation of 9-acylamidoxanthenes should be considered as a potentially useful alternate route.

The usual intermediate in nitrosoamide decomposition is a diazo ester formed by the combination of a carboxylate anion and a carbonium ion.[1a] In

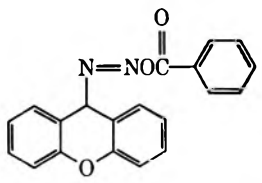
(1) (a) E. H. White and D. J. Woodcock, "Chemistry of the Amino Group," S. Patai, Ed., Wiley, New York, N. Y., 1968, Chapter 8; (b) T. J. Lobl, *J. Chem. Educ.*, **49**, 730 (1972).

(2) (a) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley-Interscience, New York, N. Y., 1970, p 752; (b) B. C. Challis and J. A. Challis, "The Chemistry of Amides," J. Zabicky, Ed., Wiley, New York, N. Y., 1970, Chapter 13.

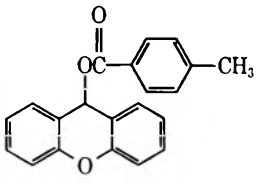
(3) R. F. Phillips and B. M. Pitt, *J. Amer. Chem. Soc.*, **65**, 1355 (1943).

(4) R. A. Moss, *Tetrahedron Lett.*, 611 (1961).

our case the expected diazo ester structure from **1c** would be that shown below (A). Diazo ester A could



A



3

decompose to the ester **3** and then oxidize to **2**. We found, however, that nitrosation of *N*-(9-xanthyl)-benzamide labeled with oxygen-18 in the carbonyl position produced xanthone and benzoic acid with all of the oxygen-18 being retained in the benzoic acid.

This result shows that the normal mechanism for diazo ester production in diazo amide decompositions is not operative in this system. Other methods for forming a diazo ester are possible, however; so we cannot say that a diazo ester is not an intermediate. Ester formation is possible even though we did not detect any ester product. Nitrosation of 9-xanthyl *p*-toluate (**3**) produced toluic acid and xanthone, thus showing that 9-xanthyl esters do not survive the reaction conditions.

Attempts to trap free radical diazo,[5] carbenic,[6] free radical,[7] and ionic intermediates[8-10] were unsuccessful, as all attempts produced only xanthone. Nitrosation of some preformed possible intermediates also produced xanthone. Reactions which produced xanthone are summarized in Table II. The main

TABLE II

XANTHONE-PRODUCING REACTIONS

Substrate	Nitrosating agent	Trapping agent
1a	N_2O_4	$LiClO_4$, NaN_3
1b	N_2O_4	$(C_2H_5)_3SiH$, ethanedithiol, cyclohexene, vinyl acetate, methyl vinyl ketone
Xanthylium perchlorate	N_2O_4, NOCl	
Xanthylium perchlorate	N_2O_4	NaN_3
9-Chloroxanthene	NOCl, N_2O_4	
Xanthydrol	N_2O_4	

problem with these studies is that xanthone is formed easily and in high yield (>80%) from many different substrates and nitrosating agents regardless of the presence of a trapping agent. These reactions may proceed by different mechanisms and thus no firm mechanistic conclusions can be drawn. Further exemplifying this dilemma is the fact that the reaction of 9-chloroxanthene with silver nitrate solution also produced xanthone.

Thus our main mechanistic conclusion based on the oxygen-18 labeling results is that *N*-nitroso-9-acylamidoxanthenes decompose by a mechanism which deviates from the usual nitrosomide decomposition mechanism. At present we prefer a mechanism which involves separate carboxylate ions and the stable xanthylium cation.[8,11]

Experimental Section

All temperature readings are uncorrected. Nmr spectra were obtained on a Varian T-60 instrument. Mass spectral measurements were made on a Varian MAT-111 spectrometer at 70 eV.

Materials.—Pure xanthydrol (mp 122–124°) was obtained after several recrystallizations of commercial xanthydrol from ether–hexane. Urethane and benzamide were obtained from commercial sources. Phenylacetamide (mp 152–154°), *p*-toluamide (mp 158–159°), 1-naphthamide (mp 186–188°), and triphenylacetamide (mp 244–245°) were obtained from reaction of the corresponding acid chlorides with anhydrous ammonia in dry benzene. Di-*tert*-butylacetamide (mp 109–110°) was obtained by a reported procedure in 44% yield.[12]

9-Acylamidoxanthenes (1a–g) were prepared by the method of Phillips and Pitt.[3] A mixture of freshly recrystallized xanthydrol (0.015 mol) and an amide (0.007 mol) was heated at 80° in 125 ml of glacial acetic acid for 30 min. The mixture was then allowed to stand in a refrigerator overnight, during which the desired material crystallized. Pure material was obtained by recrystallization from 1:1 dioxane–water solution. The remaining filtrate was diluted with water (125 ml) and extracted with ether. Removal of the ether furnished any unreacted amide almost quantitatively. Yields of 1a–g ranged from 20 to 99% (1g, 20%). The nmr spectra ($CDCl_3$) of these compounds exhibited complex signals at τ 2.4–2.6 for the aromatic protons, the amide proton, and the carbinyl proton. Infrared spectra (KBr) showed absorptions at 3300–3460 (NH) and 1640–1690 cm^{-1} (C=O). Compounds **1b**, **1d**, **1f**, and **1g** are new compounds which gave satisfactory elemental analyses. Observed melting points follow: **1a**, 226–228° (224–225°[3]); **1b**, 164–166°; **1c**, 224–226° (222–223°[3]); **1d**, 244–245°; **1e**, 197–198° (194–195°[3]); **1f**, 89–92°; **1g**, 83–85°.

Nitrosation of 1a–g.—Into a 38 × 150 mm test tube equipped with a drying tube and magnetic stirring bar were placed 50 ml of tetrahydrofuran (distilled from lithium aluminum hydride) and 0.20 g (0.0083 mol) of sodium hydride which had been washed free of mineral oil with anhydrous ether. The 9-acylamidoxanthene (0.006 mol) was added and the mixture was stirred at room temperature overnight, during which the white suspension changed to a yellow solution. A rubber stopper fitted with glass inlet and outlet tubes equipped with calcium chloride drying tubes was inserted into the mouth of the test tube and the mixture was cooled to −60° in a Dry Ice–isopropyl alcohol bath. Dinitrogen tetroxide (0.05 mol) was bubbled into the mixture at −60°. After standing at −60° for 10–15 min, the mixture was poured into 15–20 ml of ice–water and made slightly acidic with dilute hydrochloric acid. The mixture was extracted thoroughly with ether. The dried ($MgSO_4$) ether solution was concentrated on a rotary evaporator to produce a mixture of acid and xanthone. The acid was separated by dissolving in sodium bicarbonate solution, acidification, and extraction into ether which after drying and evaporation furnished the pure acid (Table I). The products were identified by comparison with authentic material. Aqueous work-up did not change the outcome of the reaction and made the purification easier. A similar reaction of **1b** with dinitrogen tetroxide in an nmr tube at −20° failed to produce evidence for the presence of a *N*-nitroso function,[4] but showed that the reaction was essentially complete in 5–10 min and the yields were quantitative.

Preparation of 9-Xanthydryl *p*-Toluate (3).—To a mixture of 3.4 g (0.025 mol) of *p*-toluic acid was added 2 ml (0.028 mol) of thionyl chloride in 50 ml of benzene. The mixture was heated at reflux overnight (10 hr) and the benzene and excess thionyl chloride were removed on a rotary evaporator. The oily product was added to 5.0 g (0.025 mol) of freshly recrystallized xan-

(5) J. Hamer, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 1.

(6) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1971 Chapter 8.

(7) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, Chapter 21.

(8) D. Bethell and V. Gold, "Carbonium Ions an Introduction," Academic Press, New York, N. Y., 1967, Chapter 6.

(9) F. A. Carey and H. S. Tremper, *J. Amer. Chem. Soc.*, **90**, 2578 (1968); **91**, 2944 (1969).

(10) C. G. Swain, C. B. Scott, and K. H. Lohmann, *ibid.*, **75**, 136 (1953).

(11) Deviation from the usual nitrosoamide decomposition mechanism is known to occur when a highly reactive carbonium ion is involved [see E. H. White, H. P. Tiwari, and M. J. Todd, *ibid.*, **90**, 4734 (1968)]. Our studies suggest deviation from the usual mechanism when an especially stable carbonium ion is involved.

(12) M. S. Newman, A. Arkell, and T. Fukunaga, *ibid.*, **82**, 2498 (1960).

thydrol in dry benzene solution. The benzene was removed on a rotary evaporator to produce an oil which furnished 1.5 g (19%) of pure **3**, mp 84–85°, on addition of ethanol. The nmr spectrum ($CDCl_3$) showed absorptions at τ 2.1 (complex, aromatic and carbinyl protons, 13 H) and 7.5 (3 H, methyl). *Anal.* Calcd for $C_{21}H_{16}O_3$: C, 79.7; H, 5.1. Found: C, 79.7; H, 4.9.

Reaction of 3 with Dinitrogen Tetroxide.—A solution of 0.48 g (0.0015 mol) of **3** in 50 ml of dry tetrahydrofuran was treated at −60° with 3.0 g (0.032 mol) of dinitrogen tetroxide. After 15 min, the tetrahydrofuran was removed on a rotary evaporator. The remaining mixture was identified as xanthone and *p*-toluic acid by nmr. Separation by extraction with sodium bicarbonate solution followed by acidification furnished pure *p*-toluic acid and xanthone, each in 67% yield.

Preparation of *N*-(9-Xanthyl)benzamide-*carbonyl*-^{18}O.—Water (2.0 g, 0.10 mol) containing 3.15% oxygen-18 enrichment (Prochem) was added in a nitrogen atmosphere to 14.0 g (0.10 mol) of benzyl chloride. The mixture was stoppered and left standing for several days. Dry benzene was added and the mixture was dried by azeotropic distillation of any water present. Thionyl chloride (14.3 g, 0.12 mol) was added and the mixture was heated at reflux for several hours. Excess benzene and thionyl chloride were removed on a rotary evaporator and more dry benzene was then added. Dry ammonia was bubbled through the benzene solution. Benzamide (12.0 g, 99%) precipitated. Mass spectral analysis showed a 1.3 atom % oxygen-18 enrichment in the carbonyl oxygen. Reaction of 1.5 g (0.015 mol) of benzamide-^{18}O with xanthydrol according to the procedure given previously for the formation of 9-acylamidoxanthenes produced 2.2 g (61%) of *N*-(9-xanthyl)benzamide-*carbonyl*-^{18}O with an ^{18}O enrichment of 1.3% as determined by mass spectrometry.

Nitrosation of *N*-(9-Xanthyl)benzamide-^{18}O.—*N*-(9-Xanthyl)-benzamide-^{18}O (1.50 g, 0.0052 mol) and 0.20 g (0.0083 mol) of mineral oil free sodium hydride in dry tetrahydrofuran were stirred in a nitrogen atmosphere overnight. Dinitrogen tetroxide (4.0 g, 0.043 mol) was added at −60° during 15 min. The mixture was poured into water and worked up as described above to give xanthone in 100% yield and benzoic acid in 63% yield. Analysis by mass spectrometry showed that no oxygen-18 was present in the xanthone, but the benzoic acid contained a 1.3 atom % enrichment of the oxygen-18. The *m/e* 122 (parent) and 124 (P + 2) peaks were used in this analysis. Identical results were obtained in three separate runs.

Trapping Experiments Using *N*-(9-Xanthyl)urethane (1b).—Sodium hydride (0.20 g, 0.0083 mol) washed free of mineral oil was added to a solution of 1.2 g (0.0047 mol) of *N*-(9-xanthyl)-urethane (**1b**) in 50 ml of dry ether and the mixture was stirred overnight. Dinitrogen tetroxide (4.0 g, 0.042 mol) was added at −60° during 15 min. Methyl vinyl ketone (2.3 g, 0.033 mol) was then added and the mixture was allowed to warm to 0°. The mixture was extracted with ether and the organic phase was separated, dried ($MgSO_4$), and concentrated at 0° on a rotary evaporator. The product consisted of 93% xanthone and an unidentified red oil which appeared to be a mixture of polymeric methyl vinyl ketone or a product from the reaction of methyl vinyl ketone with dinitrogen tetroxide as determined by nmr and ir spectroscopy.

Spectral evidence was not found for any reaction between methyl vinyl ketone and a product derived from **1b**. Similar experiments using cyclohexene or vinyl acetate as trapping agents produced xanthone without evidence for any participation of the trapping agent in the decomposition reaction of **1b**. No observable change occurred when either chloroform or tetrahydrofuran were used as solvents. Ethanedithiol (excess) did not alter the course of the reaction.

Trapping Experiments Using *N*-(9-Xanthyl)-*p*-toluamide (1a).—Sodium hydride (0.20 g, 0.0083 mol) was added to a mixture of 1.20 g (0.0038 mol) of *N*-(9-xanthyl)-*p*-toluamide (**1a**) in 50 ml of dry tetrahydrofuran and the mixture was stirred overnight. Sodium azide (1.54 g, 0.024 mol) was added and the mixture was cooled to −60°. Dinitrogen tetroxide (2.0 g, 0.22 mol) was added at −60° and the mixture was allowed to warm to 0°. Tetrahydrofuran was removed at 0° on a rotary evaporator. Examination of the crude mixture by ir and nmr spectroscopy failed to show evidence for the presence for the presence of 9-azidoxanthene. Separation and purification of the components showed that the mixture consisted of **1a**, xanthone, and *p*-toluic acid in 20, 73, and 43% yields, respectively.

Using triethylsilane (0.018 g) instead of sodium azide resulted in the precipitation of a white, high-melting, nonflammable material assumed to be the product of a reaction between dinitrogen tetroxide and triethylsilane. The remaining reaction mixture was poured into water and extracted with ether. An 80% recovery of starting material was obtained.

Addition of lithium perchlorate (0.013 mol) did not affect the reaction, as xanthone and *p*-toluic acid were obtained in 70 and 50% pure yield, respectively.

Reaction of *N*-(9-Xanthyl)-*p*-toluamide (1a) with Nitrosyl Chloride.—The sodium salt of **1a** (0.0032 mol) was prepared as described above. Nitrosyl chloride (3.0 g, 0.46 mol) was added at −60° and the mixture was allowed to warm to 0°. Removal of the tetrahydrofuran on a rotary evaporator followed by the usual work-up gave a mixture of xanthone (80%) and *p*-toluic acid (80%).

Reactions of 9-Xanthyl Perchlorate.[13] **A. Dinitrogen Tetroxide.**—9-Xanthyl perchlorate (0.55 g, 0.0020 mol) and 0.25 g (0.0039 mol) of sodium hydride in 50 ml of dry tetrahydrofuran were treated at −60° with 5.4 g (0.060 mol) of dinitrogen tetroxide. After 15 min, the mixture was concentrated on a rotary evaporator. Xanthone was the only product observed (quantitative yield).

B. Nitrosyl Chloride.—The same procedure described in A above was used except that 3.0 g (0.046 mol) of nitrosyl chloride was used in place of dinitrogen tetroxide. Xanthone was the only product obtained.

C. Dinitrogen Tetroxide and Sodium Azide.—9-Xanthyl perchlorate (1.0 g, 0.0035 mol) and 0.25 g (0.0039 mol) of sodium azide in 50 ml of dry tetrahydrofuran were treated at −60° with 5.4 g (0.06 mol) of dinitrogen tetroxide. After 15 min the mixture was concentrated on a rotary evaporator, leaving a red oil which gave ir and nmr spectra identical with those of xanthone. Addition of 1 ml of hexane followed by cooling overnight at −5° produced 0.10 g (14%) of pure xanthone.

Reactions of 9-Chloroxanthene.[14] **A. Dinitrogen Tetroxide or Nitrosyl Chloride.**—9-Chloroxanthene (1.1 g, 0.0050 mol) in dry tetrahydrofuran was treated at −60° with 3.0 g (0.032 mol) of dinitrogen tetroxide or 3.0 g (0.046 mol) of nitrosyl chloride. The mixture was concentrated to produce xanthone quantitatively (crude). Pure xanthone was obtained in 80% yield.

B. Silver Nitrate.—9-Chloroxanthene (2.16 g, 0.010 mol) was added to 50 ml of 4% ethanolic silver nitrate solution. A white precipitate of silver chloride formed immediately. After filtration of the silver chloride, the mixture was concentrated to produce pure xanthone in 86% yield. Evidence for the presence of 9-xanthyl nitrate was not found.

Reaction of Xanthydrol with Dinitrogen Tetroxide.—The same procedure as that described above for the reaction of 9-chloroxanthene with dinitrogen tetroxide was followed. Pure xanthone was obtained in 90% yield.

Acknowledgment.—Financial support of this research by the Research Corporation and the Southern Illinois University Office of Research and Projects is gratefully acknowledged.

Registry No.—**1a**, 6319-64-8; **1b**, 6319-53-5; **1c**, 6319-60-4; **1d**, 40429-09-2; **1e**, 6319-63-7; **1f**, 40429-11-6; **1g**, 40429-12-7; **3**, 40429-13-8; N_2O_4, 10544-72-6; NOCl, 2696-92-6; *p*-toluic acid, 99-94-5; xanthydrol, 90-46-0; 9-xanthyl perchlorate, 40429-14-9; 9-chloroxanthene, 28447-91-8.

(13) K. A. Hofmann, R. Roth, K. Hobold, and A. Metzler, *Chem. Ber.*, **43**, 2624 (1910).

(14) F. G. Eny-Jones and A. M. Ward, *J. Chem. Soc.*, 535 (1930).

Conformational Requirements for the Existence of Bohlmann Bands in the Infrared Spectra of Indolo[2,3-a]quinolizidines. I. *cis*- and *trans*-2-*tert*-Butyl Derivatives

GORDON W. GRIBBLE*[1] AND RANDALL B. NELSON[2]

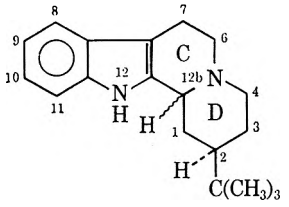
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received March 30, 1973

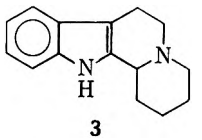
cis- and *trans*-2-*tert*-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**1** and **2**), respectively, are prepared from 3-acetylindole and 4-*tert*-butylpyridine by a sequence involving iodination–alkylation (64%), reductive cyclization (67%), and hydrogenation (94%). Whereas **1**, with a trans C/D ring fusion, shows two Bohlmann bands in the 2800–2700-cm^{-1} region of the infrared spectrum, epimer **2**, with a conformationally pure cis C/D ring fusion, is devoid of absorption in this region.

Quinolizidines having a trans ring fusion show characteristic absorption bands in the 2800–2700-cm^{-1} region of the infrared spectrum.[3,4] These absorptions, termed "Bohlmann bands," result from a specific interaction between the nitrogen lone pair and at least two axial hydrogens on carbons adjacent to the nitrogen atom. Quinolizidines having a cis ring fusion either show much weaker or show no Bohlmann bands, since with this stereochemistry only one α C–H bond can be trans diaxial with the nitrogen lone pair. The theoretical explanation for these low frequency C–H stretching vibrations remains unclear, although it is widely assumed that both specific charge delocalization (hyperconjugation) from the nitrogen lone pair to the axial α C–H bonds and vibrational coupling between two (or three) axial α C–H bonds accounts for the origin of Bohlmann bands.[3,4]

We undertook the present study to establish the conformational requirements for the existence of Bohlmann bands in the indolo[2,3-*a*]quinolizidine system, a structure which forms the basis for the *Corynanthe-Yohimbe* class of indole alkaloids. We were particularly interested in preparing and studying a simple derivative of this system which in one configuration would have a homogeneous cis C/D ring fusion. To this end and because it is clear that small alkyl groups are not sufficient to "lock"[5] a cis C/D ring fusion (*vide infra*), we chose to prepare and study *cis*- and *trans*-2-*tert*-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine,[6] **1** and **2**, respectively, and compare them with the known, unsubstituted indolo[2,3-*a*]-quinolizine **3**.



1(cis), 12bα-H
2(trans), 12bβ-H

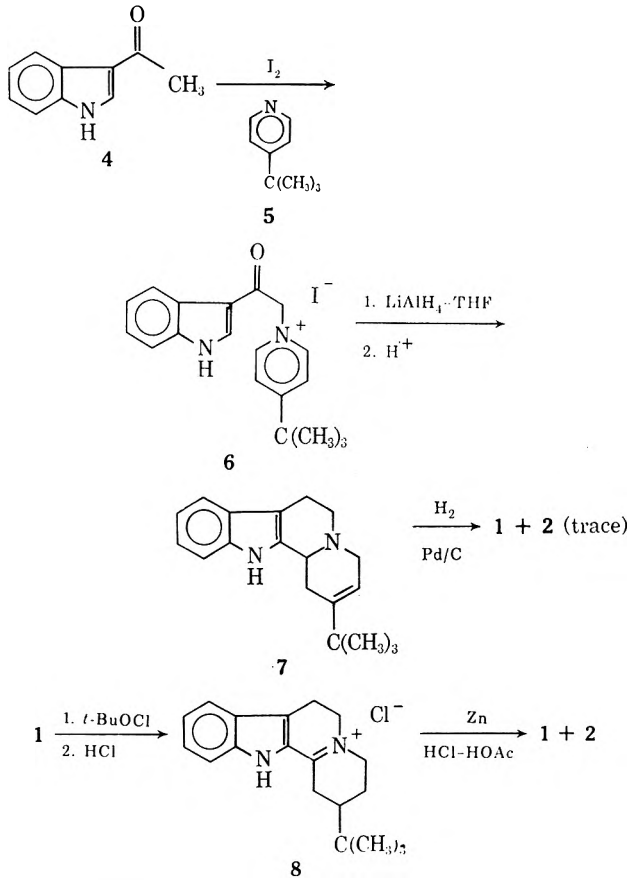


3

Results and Discussion

Synthesis.—Compounds **1** and **2** are prepared by the general method of Potts and Liljegren,[7] using 3-acetylindole (**4**) and 4-*tert*-butylpyridine (**5**), as summarized in Scheme I.

SCHEME I



(1) Recipient of a Public Health Service Research Career Development Award (1KO4-GM-23756) from the National Institute of General Medical Sciences, 1971–1976.

(2) NDEA Predoctoral Fellow, 1971–1973.

(3) J. Skolik, P. J. Krueger, and M. Wiewiorowski, *Tetrahedron*, **24**, 5439 (1968).

(4) For a review, see T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, **71**, 109 (1971).

(5) The term "lock" refers to the magnitude of the ground-state free energy difference between conformers and does not imply that there is a significant barrier to ring flipping and nitrogen inversion between conformers. Indeed, these processes are rapid at room temperature.

(6) Cis and trans refer to the relative orientation of the hydrogens at C-2 and C-12b, and should not be confused with the quinolizidine C/D ring fusion.

(7) K. T. Potts and D. R. Liljegren, *J. Org. Chem.*, **28**, 3066 (1963).

The iodination–alkylation reaction between **4** and **5** affords **6** in 64% yield. Treatment of **6** with lithium aluminum hydride in tetrahydrofuran followed by acid work-up gives **7** in 67% yield. The position of the double bond in **7** follows from previous work[7,8] and is supported by an intense peak at *m/e* 170 in the mass spectrum from the dihydro-β-carboline ion arising from a retro Diels–Alder reaction.[8] Hydrogenation of **7** in ethanol over palladium/charcoal gives essentially a single, crystalline compound in 94% yield. Small amounts (<5%) of an amorphous compound can be isolated from the hydrogenation reaction by a combination of column and thick-layer chromatography. This amorphous compound is present to the greatest extent (~5%) in hydrogenation reactions carried out in ethanol–ether (70:30). The crystalline and amorphous compounds are assigned structures **1** and **2**, respectively. Compound **2** is more conveniently obtained by treating **1** with *tert*-butyl hypochlorite followed by successive exposure to hydrogen chloride[9,10] and zinc[11] to give a mixture of **1** and **2** in nearly equal amounts, as judged by tlc.

The crystalline compound is assigned the cis configuration **1** and the amorphous compound is assigned the trans configuration **2** on the basis of their nmr and mass spectra. The amorphous material (**2**) exhibits an absorption at 4.44 ppm due to the C-12b proton, while the crystalline material (**1**) shows no saturated proton absorption below 3.3 ppm. This low-field chemical shift for the amorphous compound (**2**) is consistent with a cis C/D ring fusion and is well documented.[4,12-14] For example, this proton in 3-isoajmalicine, an alkaloid with a cis C/D ring fusion, appears at 4.45 ppm.[13]

The mass spectra of **1** and **2** are consistent with the assignments. The crystalline epimer (**1**), with a trans C/D ring fusion, shows an M − 1 ion (100%) more intense than the parent ion (87%). The amorphous epimer (**2**), with a cis C/D ring fusion, shows an M − 1 ion (94%) less intense than the parent ion (100%). We interpret this difference as being a consequence of the trans-diaxial orientation of the C-12b hydrogen and the nitrogen lone pair in **1**, which apparently

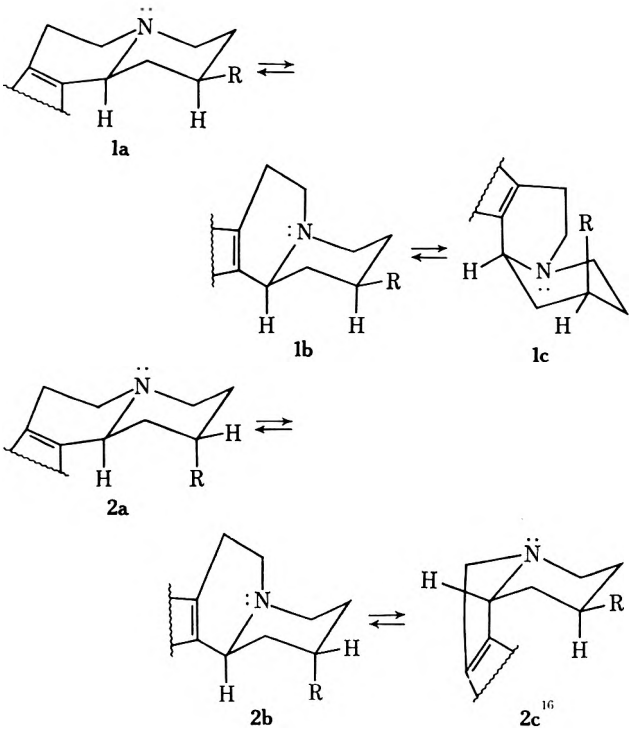
$$1 \xrightarrow{e^-} 8 \text{ cation} + H\cdot$$

provides a geometry for efficient loss of the C-12b hydrogen atom.[15]

Conformational and Infrared Spectral Analysis.— The 2-substituted indolo[2,3-*a*]quinolizidine system can exist in six conformations (two configurations), with equilibration by nitrogen inversion and *cis*-decalin ring inversion (Scheme II).

Regardless of the size of the R group in the cis configuration (**1**), conformer **1a** with all substituents equatorial on the D ring will dominate the equilibrium. Conformer **1b** with an ethyl-like axial substituent on nitrogen may contribute about 5% to the equilibrium.[17] The contribution from conformer **1c** with a cis-1,3-diaxial interaction between substituents will be negligible.

SCHEME II



It is clear from earlier work with compounds having the trans configuration **2** that the smaller alkyl groups and phenyl are incapable of shifting the equilibrium **2a** ⇄ **2b** ⇄ **2c** exclusively in favor of the cis-fused conformer **2c**. That is, the 2-methyl-,[18a] 2-phenyl-,[18a] and 3-ethylindolo[2,3-*a*]quinolizidine[18b] epimers corresponding to **2** exhibit infrared and nmr spectra consistent with a mixture of **2a** and **2c**.[19] Thus, alkyl substituents in **2** with *A* values of 1.7 (methyl) and 1.8 (ethyl) kcal/mol[20] cannot overcome the thermodynamic stability of the trans C/D quinolizidine ring fusion (*e.g.*, **2a**) which may be 2.6 kcal/mol more stable than the cis C/D ring fusion (*e.g.*, **2c**).[21] A phenyl substituent with an *A* value of 3.1 kcal/mol[20] can shift the equilibrium slightly in favor of **2c** (*i.e.*, ~70% of **2c** based on an *A*-value difference of 0.5 kcal/mol).

In contrast to methyl, ethyl, and phenyl, a *tert*-butyl substituent, with its overwhelming equatorial prefer-

(8) E. M. Fry and J. A. Beisler, *J. Org. Chem.*, **35**, 2809 (1970).
(9) L. J. Dolby and G. W. Gribble, *ibid.*, **32**, 1391 (1967).
(10) W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).
(11) W. F. Trager, J. D. Phillipson, and A. H. Beckett, *Tetrahedron*, **24**, 2681 (1968).
(12) W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.*, **83**, 4816 (1961).
(13) E. Wenkert, B. Wickberg, and C. L. Leicht, *ibid.*, **83**, 5037 (1961).
(14) M. Uskoković, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *ibid.*, **86**, 3364 (1964).
(15) The mass spectrum of a C-12b deuterium-substituted indolo[2,3-*a*]-quinolizidine supports **8** cation as being the main structure of the M − 1 ion: G. W. Gribble, *J. Org. Chem.*, **37**, 1833 (1972).
(16) For clarity, **2c** as illustrated is the enantiomer resulting from the ring inversion of **2b**.
(17) In ethylcyclohexane the axial conformer contributes about 5% based on an *A* value of 1.68 kcal/mol: W. F. Trager, C. M. Lee and A. H. Beckett, *Tetrahedron*, **23**, 365 (1967), and references cited therein.
(18) (a) J. Gootjes, A. M. De Roos, and W. Th. Nauta, *Recl. Trav. Chim. Pays-Bas*, **85**, 491 (1966); (b) E. Wenkert and B. Wickberg, *J. Amer. Chem. Soc.*, **84**, 4914 (1962).
(19) An alternative, less likely explanation for the observation[18] of Bohlmann bands in configuration **2** (R = Me, Ph) is that the cis-fused conformer **2c** (R = Me, Ph) gives rise to infrared absorption in the Bohlmann region. This explanation cannot be ruled out by the available data and was one of the reasons why we chose to study the unambiguous *tert*-butyl substituted derivative.
(20) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 44, 440.
(21) For quinolizidine itself, the trans fusion is 2.6 kcal/mol more stable than the cis fusion: H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, No. **59**, 6191 (1968).

ence (A value = 5.6 kcal/mol),[20] will force **2** to exist essentially only[5] as the cis-fused conformer **2c** (R = *t*-Bu).[22]

The solution infrared spectrum of **1** shows bands of medium intensity at 2811 and 2751 cm^{-1}. In contrast, the infrared spectrum of **2** is devoid of absorption in this region (Figure 1). The unsubstituted indolo[2,3-*a*]quinolizidine **3**,[15] which is also thought to exist mainly in conformation **1a** (R = H), shows Bohlmann bands at 2807 and 2757 cm^{-1}.

The bands at 2868, 2846, and 2856 cm^{-1} for **1**, **2**, and **3**, respectively, are assigned to the normal CH_2 symmetric vibrations and are, of course, common to both trans and cis C/D ring fusions.

From these results we conclude that (1) the infrared Bohlmann region of C/D trans-fused indolo[2,3-*a*]quinolizidines is best described as consisting of but two bands, at *ca.* 2810 and *ca.* 2755 cm^{-1}, the former being slightly more intense, and (2) a conformationally pure C/D cis-fused indolo[2,3-*a*]quinolizidine shows no absorption in the Bohlmann region.

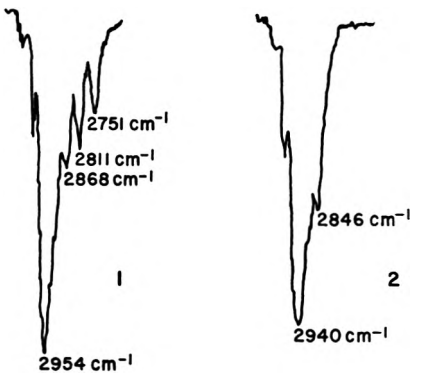


Figure 1.—Infrared spectra (C–H stretching region) of **1** and **2**.

Experimental Section

Melting points were determined with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Routine infrared spectra were obtained using Perkin-Elmer 21, 137, or 337 instruments. Nmr spectra were obtained from either a Varian Associates HA-60-IL or a Perkin-Elmer R-24 spectrometer. Mass spectral data were collected at Harvard University by Mr. J. W. Suggs. Adsorbents for column chromatography were activity III alumina (Merck) and silica gel (J. T. Baker). Adsorbents for thick layer chromatography and thin layer chromatography were silica gel (Merck) and silica gel G (Merck), respectively. The solvent system used was EtOAc–Et_3N (95:5) and chromatograms were developed by spraying with a solution of 3% $Ce(SO_4)_2$–10% H_2SO_4 followed by brief heat treatment at 110°. Organic solutions were dried with anhydrous granular K_2CO_3 and concentrated *in vacuo* with a Büchi rotary evaporator. Microanalyses were performed by Microtech, Skokie, Ill., and PCR Inc., Gainesville, Fla. Chloroform solutions of **1**, **2**, and **3** were examined on a Perkin-Elmer 21 instrument (path, 0.1 mm) at a concentration of 0.175 M.

4-*tert*-Butyl-1-[2-(3-indolyl)-2-oxoethyl]pyridinium Iodide (6).—A mixture of 4-*tert*-butylpyridine (**5**) (14.04 g, 0.104 mol) and 3-acetylindole (**4**) (5.40 g, 0.048 mol) was stirred magnetically and heated until solution was achieved. The solution was then treated with iodine (8.75 g, 0.0348 mol) and heated at 95–110° for 1.5 hr. The product began to precipitate after 0.5 hr and the reaction mixture thickened, preventing efficient stirring. After cooling, the dark solid mass was triturated with 95% EtOH, the slurry filtered, and the solid repeatedly treated with 95% EtOH until no red color remained in the filtrate. The pale tan solid was then dried at 100° for 10 min to give 9.93 g of **6** (64%). The analytical sample was recrystallized three times from aqueous EtOH (50%) to give pale white needles, mp 256–257°.

Anal. Calcd for $C_{19}H_{21}N_2OI$: C, 54.30; H, 5.04; N, 6.67; I, 30.19. Found: C, 54.58; H, 5.29; N, 6.78; I, 30.04.

Pertinent spectral data for **6** are as follows: ir (Nujol) 3175 (N–H), 1656 (C=O) cm^{-1}; uv max (95% EtOH) 214 mμ (log ε 4.46), 243 (4.20), 265 (4.13), 305 (4.11).

4-*tert*-Butyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine (7).—Compound **6** (30.0 g, 0.072 mol) was added over a period of 40 min to a stirred slurry of $LiAlH_4$ (13.5 g, 0.31 mol) and 1100 ml of anhydrous THF at −40° under nitrogen. A jade green color rapidly appeared as the reaction warmed to room temperature. The system was then refluxed with efficient stirring for 6 hr under N_2. After cooling to 0°, H_2O was added dropwise to destroy excess hydride. The slurry was stirred and enough 6 N NaOH was added to precipitate the aluminum salts (*ca.* 10 ml) to allow for efficient filtration of inorganic materials. The aqueous THF filtrate was treated with 600 ml of concentrated HCl and stirred for 0.5 hr. Making basic with concentrated NH_4OH, extraction of the base with CH_2Cl_2, drying, and removal of solvent provided 13.5 g (67%) of crude product, homogeneous by tlc (R_f 0.5). Recrystallization from Et_2O–pentane gave pure material, mp 154.5–155.5°.

Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.09; H, 8.63; N, 10.00.

Pertinent spectral data for **7** are as follows: ir ($CHCl_3$) 3463 (N–H), 2961, 2907, 2803, 2742 (C–H) cm^{-1}; uv max (95% EtOH) 233 mμ (log ε 4.23), 284 (3.84), 291 (3.77); mass spectrum (70 eV) *m/e* (rel intensity) 280 (49), 279 (36), 233 (35), 170 (100), 169 (89); nmr ($CDCl_3$) δ 7.22 (m, 4 H), 5.53 (t, 1 H, J = 2.1 Hz), 1.7–3.8 (m, 8 H), 1.07 (s, 9 H).

***cis*-2-*tert*-Butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (1).**—Compound **7** (1.0 g, 0.0036 mol) was dissolved in a mixture of absolute EtOH containing a trace of Et_2O and 0.5 g of 10% Pd/C. Hydrogenation at atmospheric pressure and 25° gave, after filtration, evaporation, and recrystallization of the crude product from Et_2O–hexane, 0.94 g (94%) of pure **1**, mp 157–158°. Hydrogenation of a solution of **7** in EtOH–Et_2O (7:3) gave a crude product (86% yield) shown by tlc to be a mixture of **1** and **2** (95:5).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.91; H, 9.35; N, 9.76.

Pertinent spectra data for **1** are as follows: ir ($CHCl_3$) 3502 (N–H), 3015, 2954, 2868, 2811, 2751 (C–H) cm^{-1}; uv max (95% EtOH) 227 mμ (log ε 4.22), 284 (3.62), 291 (3.55); mass spectrum (70 eV) *m/e* (rel intensity) 282 (87), 281 (100), 225 (61), 226 (14), 170 (5); nmr ($CDCl_3$) δ 6.9–7.8 (m, 4 H), 1.1–3.3 (m, 12 H), 0.92 (s, 9 H).

***trans*-2-*tert*-Butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (2).**—Compound **2** was obtained with difficulty by preparative layer chromatography of the crude hydrogenation mixture of **1**. A more convenient synthesis of **2** involved treating a CH_2Cl_2 solution of **1** (0.601 g, 0.00213 mol) at 0° with 5 ml of distilled Et_3N and adding dropwise under N_2 0.265 g (0.00213 mol) of *tert*-butyl hypochlorite over 5 min. After warming to room temperature, the mixture was stirred for 1 hr and then quenched by the addition of 100 ml of distilled H_2O. The organic layer was separated and then washed with 100 ml of distilled H_2O. Drying and removal of solvent *in vacuo* gave an oily amber mixture of chloroindolenines. This was treated immediately with 25 ml of 100% EtOH saturated previously with HCl(g) and added to a solution of 150 ml of glacial acetic acid and 25 ml of concentrated HCl. Zn dust (20 g) was added and the suspension (pale green) was refluxed overnight under a N_2 atmosphere with efficient stirring. The cooled reaction mixture was decanted from excess Zn and poured into 50 g of ice and 200 ml of concentrated NH_4OH. The residual Zn was washed with 25 ml of concentrated NH_4OH, and the washings were combined with the aqueous solution. Extraction with $CHCl_3$ followed by drying and evaporation gave 0.45 g (75%) of an amber oil composed of ~55% of **1** and ~45% of **2** as judged by tlc [R_f (blue-green, **1**) 0.68; R_f (blue-green, **2**) 0.37]. Preparative layer chromatography on silica gel with EtOAc (99%)–Et_3N (1%) separated the isomers. Two successive separations pro-

(22) A cyclohexane ring fused onto the D ring, as in the inside yohimbanes, can also be used to control the equilibrium: G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2769 (1967). In this system four configurations are possible and the analysis is somewhat more difficult than it is with monosubstituted indolo[2,3-*a*]quinolizidines.

vided 51 mg of pale amorphous material (2), completely homogeneous on tlc.

Anal. Calcd exact mass for $C_{19}H_{26}N_2$: 282.2096. Found: 282.2093.

Pertinent spectral data for **2** are as follows: ir ($CHCl_3$) 3484 (N–H), 3012, 2940, 2846 (C–H) cm^{-1}; uv max (EtOH) 229 mμ (log ε 4.21), 283 (3.77), 291 (3.72); mass spectrum (70 eV) *m/e* (rel intensity) 282 (100), 281 (94), 225 (89), 144 (63); nmr ($CDCl_3$) δ 8.06 (s, 1 H), 7.0–7.6 (m, 4 H), 4.44 (t, 1 H), 1.0–3.4 (m, 11 H) 0.9 (s, 9 H).

Acknowledgment.—We are grateful to the National Science Foundation (GP-13374), Eli Lilly, Merck Sharp and Dohme, and the National Institutes of Health (CA-14237) for their generous financial support of our research program, and to a referee for helpful comments.

Registry No.—**1**, 40587-68-6; **2**, 40587-69-7; **4**, 703-80-0; **5**, 3978-81-2; **6**, 40625-69-2; **7**, 40587-72-2.

Photochemical Conversion of 4-(o-Nitrobenzylidene)-4*H*-pyrans to 1-Hydroxy-3-oxospiro[indoline-2,4′-[4′*H*]pyran] Derivatives

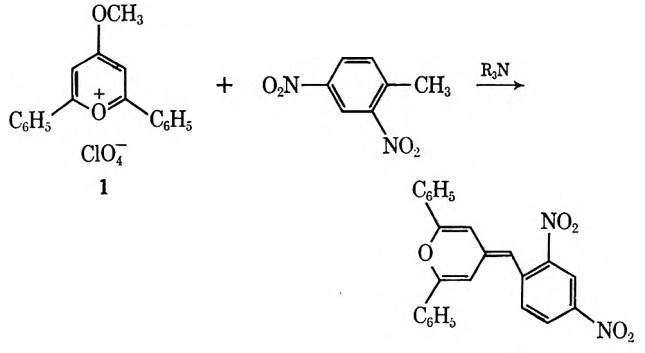
J. A. VAN ALLAN,* S. FARID, G. A. REYNOLDS, AND S. CHIE CHANG

Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Received February 7, 1973

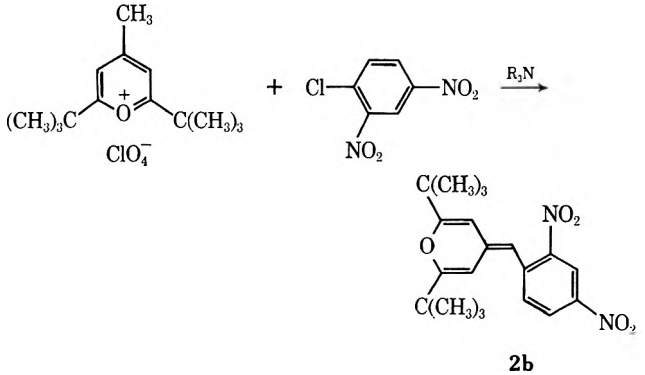
The conversion referred to in the title was investigated for three examples. The structures of the photoproducts were deduced from spectroscopic data and confirmed by chemical transformations.

A variety of compounds have been prepared by the reaction of pyrylium salts with nucleophiles,[1] and we have extended these to include the benzylidenepyran derivative **2a**, which was formed by the reaction of 4-methoxy-2,6-diphenylpyrylium perchlorate (**1**) with 2,4-dinitrotoluene in the presence of a tertiary amine.



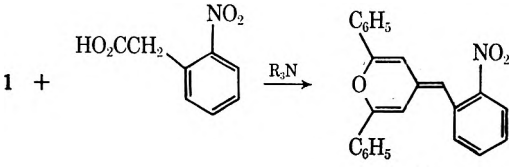
1 **2a**

In the course of handling **2a**, it was noticed that both the solid (KBr pressing) and a dilute solution rapidly faded when exposed to room light leading us to investigate this photoreaction. In order to facilitate the interpretation of nmr spectra of the photoproducts, we synthesized the di-*tert*-butyl analog (**2b**),



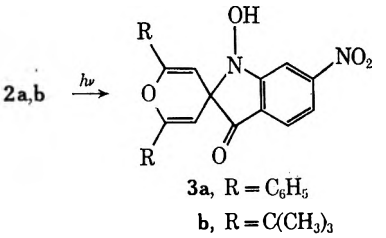
2b

and to simplify the mass spectra and chemical degradation as well as to test the scope of the reaction, we prepared the mononitro derivative **2c** and investigated the photolysis of these three compounds.

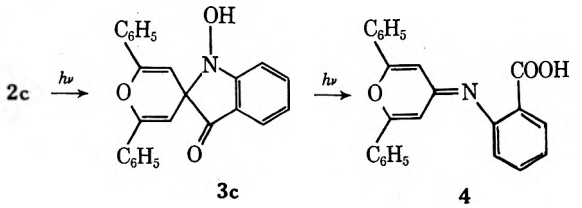


2c

The photolysis of **2a** and **2b** gave products that were isomeric with **2a** and **2b** in nearly quantitative yields. As shown below, structures **3a** and **3b** were assigned to these products. On the other hand, the photolysis of the mononitro compound **2c** yielded, besides the corresponding product (**3c**), another isomeric substance (**4**), which was found to be a photochemical rearrangement product of **3c**.



3a, R = C_6H_5
b, R = $C(CH_3)_3$



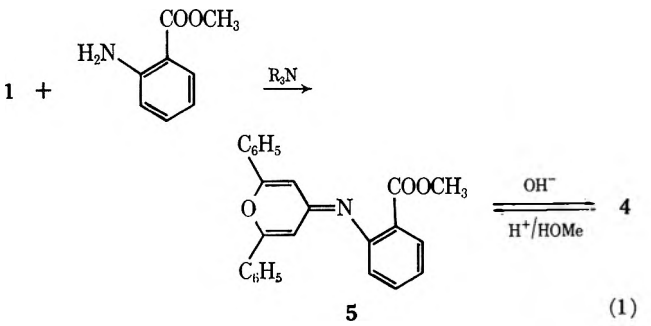
3c **4**

The structure of **4** was established through an independent synthesis shown in eq 1.

A number of chemical transformations were carried out on the photoproducts **3a–c** and are summarized in Scheme I. These and the spectroscopic data, discussed below, were used to elucidate the structure of the photoproducts **3a–c**.

Treatment of compounds **3a–c** with perchloric acid gave the benzisoxazole derivatives **6a–c**, which, in

(1) K. Dimroth, *Angew. Chem.*, **72**, 331 (1960).



5 (1)

turn, were hydrolyzed with aqueous pyridine to give **7a–c**. Compound **7a** with ammonia gave the pyridine derivative **8**.

The photoproducts **3a–c** were readily methylated with methyl iodide and potassium carbonate giving **9a–c**, which, in contrast to **3a–c**, did not undergo the facile rearrangement with acid to benzisoxazoles. Treatment of these methylated derivatives with 60% perchloric acid or trifluoroacetic acid led merely to ring opening to give **10a–c** as was shown by nmr. This reaction is reversible as **9a–c** were recovered on dilution with water. On the other hand, heating **9a–b** with 20% perchloric acid gave **11a–b**.

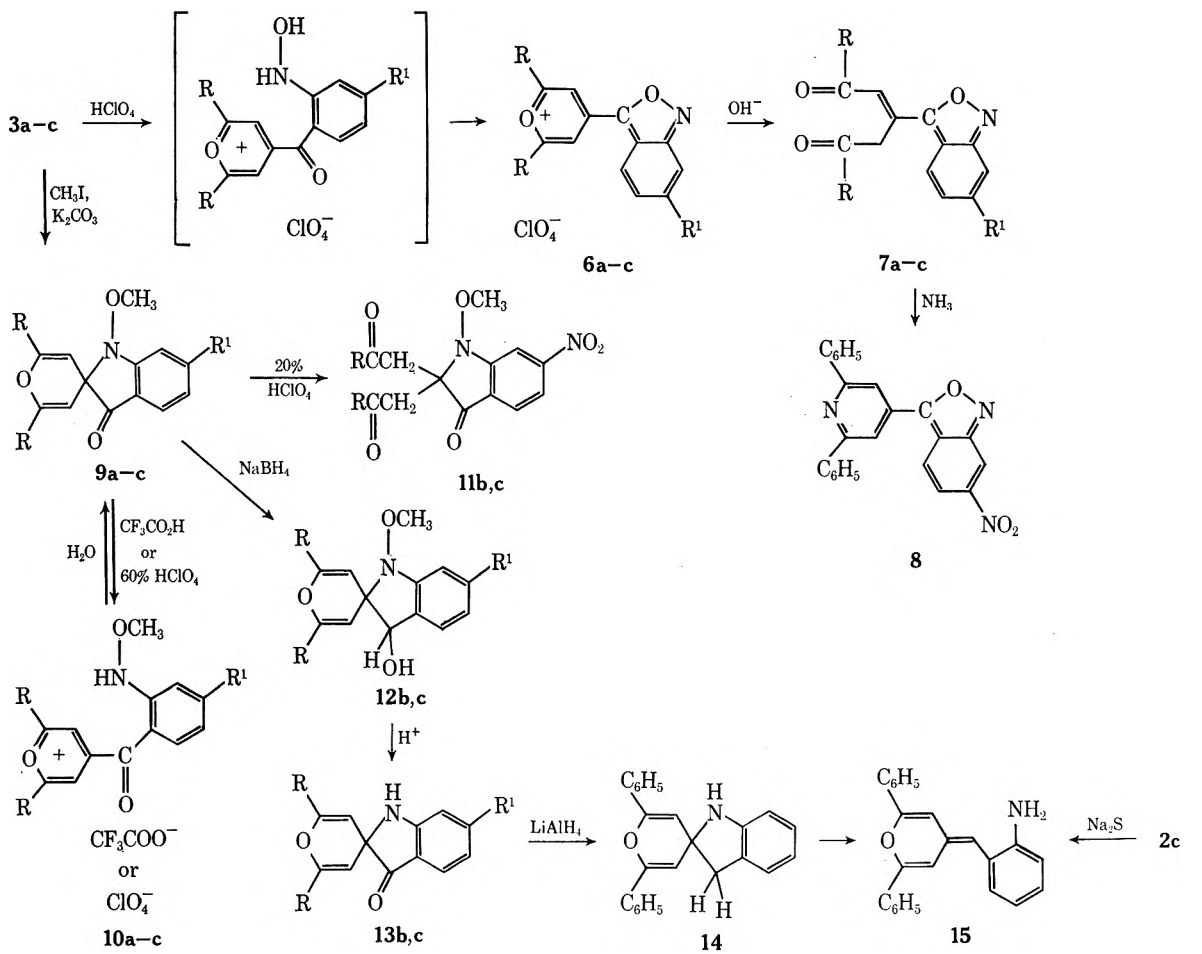
Compounds **9b** and **9c** were reduced with sodium borohydride to the carbinols **12b** and **12c**, which, on treatment with a trace of acid, eliminate methanol to give **13b** and **13c**. Interestingly, solutions of **12b** were very sensitive to aerial oxidation giving the starting ketone **9b**, and, in order to obtain pure **13b**, the reaction had to be carried out under oxygen-free conditions.

Compound **13c** was reduced with lithium aluminum hydride to give an unstable product **14** (identified by nmr), which quantitatively rearranged to the primary amine **15**. This last compound was prepared by an alternative method.

The ir spectrum of **3b** showed a broad hydroxyl band at *ca.* 3400 cm^{-1} and absorptions at 1718 and 1695 cm^{-1}, which we assign to the ketone and the pyran C=C double bond, respectively.

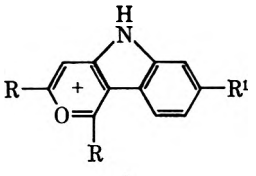
The photoproduct **3b** shows in the visible region a complex spectrum of overlapping bands [in benzene; broad maximum at 395–410 nm (ϵ 1950)]. Ethanol causes a shift to longer wavelength [λ_{max} 440 nm (ϵ 1850)]. Addition of a small amount of pyridine to the benzene solution led to a spectrum similar to that in ethanol. The spectrum of the methylated derivative **9b**, on the other hand, does not display such solvent dependency. Compound **9b** showed two poorly resolved maxima at 385 (ϵ 1890) and 415 nm (ϵ 1850) in either benzene or ethanol. The difference between the two compounds could be attributed to solvation of the hydroxyl compound *via* hydrogen bonding.

SCHEME I



a, R = C_6H_5; R^1 = NO_2
b, R = *t*-Bu; R^1 = NO_2
c, R = C_6H_5; R^1 = H

The photoproducts **3a–c**[2] and their methylated derivatives **9a–c**, as well as the acetylation product of **3a**, show in the mass spectrum an efficient cleavage of OH, OCH_3, or $OCOCH_3$, respectively, which is followed by decarbonylation to give an ion of the probable structure A. In a similar pattern the carbinols **12b**



A

R = C_6H_5 or *t*-Bu
R^1 = H or NO_2

and **12c** cleave OCH_3 and formaldehyde successively to give ion A. This ion is the base peak in the mass spectrum of **13b** and **13c**, which is formed by loss of HCO. The fact that the predominant cleavage of the carboxylic acid **4** is the loss of COOH gives support for the structure of the common ion A.

The two protons of the pyran moiety in the photoproducts **3a–c**, in their methylated derivatives **9a–c**, and in **13b**, **13c**, and **14** are equivalent.[3] The two *tert*-butyl groups in **3b**, **9b**, and **13b** are also equivalent. This equivalence is due to the rapid inversion at the ring nitrogen. The pyran protons in **12b** and **12c** and the *tert*-butyl groups in **12c** are not equivalent. This is due to the asymmetric >CH–OH group, which gives different environments to the substituents on the pyran ring. The measured long-range coupling constants of 2.4 and 2.3 Hz between the pyran protons in **12b** and **12c** are in the expected range.

Owing to internal asymmetry in **11b**, the geminal protons of each CH_2 group are not equivalent (δ 3.02 and 3.52, $|J|$ = 17.7 Hz), whereas both CH_2 groups and all methyl groups of the *tert*-butyl groups are identical. This nonequivalence of the methylene protons is intrinsic to the structure regardless of hindered rotation or preference of conformers. The two methylene protons, however, undergo different $Eu(dpm)_3$-induced shifts in the ratio of 1.2:1. This could be explained in terms of preference to one or more of the different rotamers which would result in uneven statistical distribution of these protons along the orbit they describe by rotation along the ring-carbon–CH_2 bond.

The $LiAlH_4$ reduction product of **13c** shows signals indicative of the spiro compound **14**: equivalent pyran protons (δ 5.82) and benzylic protons at 3.10. This compound, however, is not stable in $CDCl_3$ solution, even when the $CDCl_3$ was treated with $NaHCO_3$ and diluted with a few drops of pyridine-d_5. This spiro derivative underwent conversion into **15** within 1 hr at ~35°.

The photochemical cycloaddition of nitro compounds to olefinic bonds is well known, and reaction mechanisms for this type of reaction have been discussed.[4] From the reaction of nitrobenzene with cyclohexene, a thermally unstable five-membered cycloadduct was isolated.[4] Irradiation ($\lambda \geq 546$ nm) of **2a** or **2c** at −60° in dimethoxyethane or in toluene resulted in decoloration of the deep red solution to a pale yellow. Under these conditions the primary photoproduct appeared to be stable. After the solution had warmed to room temperature, the color changed to green and then rapidly to orange and **3a** or **3c** precipitated.[5] In chloroform or in methylene chloride the primary photoproduct had a much shorter lifetime, and the thermal reactions took place at −60°. This solvent dependency gives support to the nonpolar nature of this intermediate. In order to obtain evidence for an intermediate analogous to that reported for simple nitro compounds,[4] **3a** and **3c** were irradiated at −60° in the cavity of an nmr spectrometer in deuteriotoluene. The signals from the starting materials rapidly disappeared, and a completely washed out spectrum was obtained. This result must be due to the formation of some free radicals during the photolysis.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer 467 spectrophotometer, ultraviolet spectra with a Cary Model 15 spectrophotometer, nmr spectra with a Bruker 90-MHz spectrometer, and mass spectra with a Consolidated Electrodynamics Model 21-110B instrument. The nmr chemical shifts are reported on the δ scale downfield from internally added tetramethylsilane. The electronic spectra were determined in acetonitrile. The *m/e* with a relative intensity greater than 5% are listed.

2,6-Diphenyl-4-(2,4-dinitrobenzylidene)-4*H*-pyran (2a).—A mixture of 3.5 g of 1,[6] 2 g of 2,4-dinitrotoluene, 3 ml of diisopropylethylamine, and 20 ml of acetic anhydride was refluxed for 15 min, and chilled. The solid crystallized from acetonitrile yielding 4 g of **2a**: mp 209–210°; λ_{max} ($\epsilon \times 10^{-3}$) 250 (20.2), 315 (10.0), and 490 nm (11.6); mass spectrum *m/e* (rel %), 412 (33), 395 (36), 367 (12), 261 (100), and 105 (95).

Anal. Calcd for $C_{24}H_{16}N_2O_5$: C, 70.0; H, 3.9; N, 6.8. Found: C, 70.3; H, 4.1; N, 6.7.

2,6-Di-*tert*-butyl-4-(2,4-dinitrobenzylidene)-4*H*-pyran (2b).—A mixture of 9 g of 2,6-di-*tert*-butyl-4-methylpyrylium perchlorate,[7] 7 g of 2,4-dinitrochlorobenzene, 8.6 g of diisopropylethylamine, and 100 ml of ethyl alcohol was refluxed for 30 min and chilled; the solid crystallized from alcohol giving 7 g of **2b**: mp 125–126°; mass spectrum *m/e* 372 (41), 355 (63), 327 (13), 221 (100), and 209 (10).

Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.5; H, 6.5; N, 7.5. Found: C, 64.6; H, 6.4; N, 7.3.

2,6-Diphenyl-4-(2-nitrobenzylidene)-4*H*-pyran (2c).—A mixture of 7.4 g of *o*-nitrophenylacetic acid, 14 g of **1**, 12 ml of diisopropylethylamine, and 60 ml of alcohol was refluxed for 30 min and cooled, and 15 ml of 70% perchloric acid was added. After the mixture was chilled, the solid was collected and crystallized from a mixture of pyridine and methanol giving 3 g of **2c**: mp 102–103°; λ_{max} ($\epsilon \times 10^{-3}$) 248 (35.3), ~272 (21.7), 340 (24.5), 400 (12.2) with tail to 500 nm; mass spectrum *m/e* 367 (30), 350 (36), 322 (36), 261 (95), 220 (11), 215 (19), and 105 (100).

Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.7; H, 4.4; N, 3.8. Found: C, 79.0; H, 4.6; N, 3.5.

(2) The starting materials **2a–c** show in the mass spectrum, besides other ions, a pattern cleavage similar to that of their photolysis products (*i.e.*, successive loss of OH and CO). This could indicate that the electron impact leads to the same photolysis products.

(3) The signals of the pyran protons in the di-*tert*-butyl derivatives appear at δ 4.5 and those in the diphenyl derivatives at δ 5.3–5.8. The signals of the *tert*-butyl groups in the above compounds appear at δ 1.1–1.2.

(4) J. L. Charlton, C. C. Liao, and P. de Mayo, *J. Amer. Chem. Soc.*, **93**, 2463 (1971).

(5) We made use of the stability of this primary photoproduct to prepare **3c** in high purity without its partial photochemical conversion into **4**, which takes place if the irradiation is carried out at room temperature.

(6) J. A. Van Allan, G. A. Reynolds, and D. P. Maier, *J. Org. Chem.*, **33**, 4418 (1968).

(7) A. T. Balaban and C. D. Nenitzescu, *Justus Liebigs Ann. Chem.*, **625**, 74 (1959).

2',6'-Diphenyl-1-hydroxy-6-nitro-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (3a).—A solution of 1 g of **2a** in 800 ml of methylene chloride in a Pyrex flask was irradiated with a 75-W flood lamp for 1 hr. After the solvent had evaporated, the residue was crystallized from chlorobenzene yielding 0.9 g of **3a**: mp 211–212°; ir (KBr) 3343, (OH) 1714 (CO), 1680 (pyran), 1530, 1365 cm^{-1} (NO_2); λ_{max} ($\epsilon \times 10^{-3}$) 250 (49.0) and 380–450 nm (2.0); mass spectrum *m/e* 412 (27), 395 (100), 367 (32), 351 (14), 321 (41), and 320 (40).

Anal. Calcd for $C_{24}H_{16}N_2O_5$: C, 70.0; H, 3.9; N, 6.8. Found: C, 70.1; H, 4.2; N, 7.1.

2',6'-Di-*tert*-butyl-1-hydroxy-6-nitro-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (3b).—This compound was prepared by the method described for **3a**: yield 98%; mp 195–196° (from toluene); λ_{max} ($\epsilon \times 10^{-3}$) 249 (30.0) and 425 nm (2.0) very broad; mass spectrum *m/e* 372 (30), 355 (100), 327 (32), 313 (13), 289 (7), 287 (10), 271 (15), 225 (11), 209 (10), and 57 (77).

Ancl. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.5; H, 6.5; N, 7.5. Found: C, 64.3; H, 6.8; N, 7.2.

2',6'-Diphenyl-1-hydroxy-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (3c).—A solution of **2c** (1.0 g) in toluene (50 ml) was divided into five portions and each was irradiated for 40 min at −60° with a 200-W PEK super high pressure Hg arc through a Corning C.S. 3-70 filter (λ >490 nm). The deep red solution turned to pale yellow at the end of the irradiation. When the solution had warmed up to room temperature, its color changed to red and **3c** crystallized out: yield 0.72 g. Another 0.15 g of **3c** was obtained from the concentrated mother liquor: total yield 87%; mp 189–190°; ir (KBr) 3390 (OH), 1724 (CO), and 1695 (pyran); λ_{max} ($\epsilon \times 10^{-3}$) 238 (43.0) and 330–380 (2.0) very broad; mass spectrum *m/e* 367 (17), 350 (57), 322 (93), 246 (11), 218 (13), 217 (16), 105 (100), and 77 (57).

Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.7; H, 4.4; N, 3.8. Found: C, 78.3; H, 4.8; N, 3.7.

4-(2-Carboxyphenylimino)-2,6-diphenyl-4*H*-pyran (4). Method A.—This compound was prepared from **2c** as described under **3c** by using 1,2-dimethoxyethane as a solvent and irradiating at room temperature. During the irradiation compound **4** crystallized out: yield 75%, mp 203–205° (from dimethoxyethane). The same compound was obtained on starting with **3c** instead of **2c**.

Method B.—A mixture of 0.5 g of **4**-(2-carbomethoxyphenylimino)-2,6-diphenyl-4*H*-pyran (**5**) and 0.5 g of potassium hydroxide in 10 ml of methanol was refluxed for 30 min, and the solid was collected and crystallized from aqueous acetic acid giving 0.3 g of **4**, mp 260–262°, which showed spectral properties that were identical with those of **4** prepared by method A. The mass spectrum showed 367 (23), 322 (100), 246 (14), 218 (14), 217 (14), 105 (33), and 77 (42).

Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.7; H, 4.4; N, 3.8. Found: C, 78.4; H, 4.7; N, 3.8.

4-(2-Carbomethoxyphenylimino)-2,6-diphenyl-4*H*-pyran (5). Method A.—A mixture of 0.6 g of **4** (prepared by method A), 3 ml of concentrated sulfuric acid, and 30 ml of methanol was refluxed for 2 hr and concentrated. The residue was dissolved in water; 3 ml of 60% perchloric acid was added to the solution. The solid was collected and crystallized from ligroin (bp 63–75°) yielding 0.4 g of **5**, mp 149–150°.

Method B.—A mixture of 3 g of **1** and 10 ml of methyl anthranilate was refluxed for 10 min, cooled, diluted with methanol and ether until turbid, and then chilled giving 2.1 g of **5**: mp 150–151°; mass spectrum *m/e* 381 (78), 380 (8), 350 (6), 322 (100), 246 (16), 245 (8), 218 (15), 217 (16), 216 (11), 105 (73), 102 (6), and 77 (60).

Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.7; H, 5.0; N, 3.7. Found: C, 78.5; H, 5.1; N, 3.6.

4-(6-Nitro-2,1-benzisoxazol-3-yl)-2,6-diphenylpyrylium Perchlorate (6a).—To a solution of 0.5 g of **3a** in 10 ml of formic acid was added 0.5 ml of 70% perchloric acid, and the solid was collected and washed with ether: yield 0.5 g, mp 304° (explodes).

Anal. Calcd for $C_{24}H_{15}ClN_2O_8$: C, 58.1; H, 3.4; N, 5.7. Found: C, 58.0; H, 3.4; N, 5.6.

2,6-Di-*tert*-butyl-4-(6-nitro-2,1-benzisoxazol-3-yl)pyrylium Perchlorate (6b).—Compound **6b** was prepared from **3b** and perchloric acid in acetic acid: mp 244–245°; λ_{max} ($\epsilon \times 10^{-3}$) 244 nm (31.9).

Anal. Calcd for $C_{20}H_{23}ClN_2O_8$: C, 52.8; H, 5.1; N, 6.1. Found: C, 52.8; H, 5.1; N, 6.1.

4-(2,1-Benzisoxazol-3-yl)-2,6-diphenylpyrylium Perchlorate (6c).—Perchloric acid was added to a solution of **3c** in acetic acid giving **6c** in quantitative yield, mp 263–264°.

Anal. Calcd for $C_{24}H_{16}ClNO_6$: C, 64.2; H, 3.6; N, 3.1. Found: C, 63.9; H, 3.6; N, 3.1.

3-(2-Benzoyl-1-phenacylidenethyl)-6-nitro-2,1-benzisoxazole (7a).—A solution of 1 g of **6a** in 8 ml of boiling pyridine was diluted with 20 ml of methanol and chilled giving 0.6 g of **7a**: mp 164–165°; λ_{max} ($\epsilon \times 10^{-3}$) 278 (21.5) and 360 nm (13.0); mass spectrum *m/e* 412 (13), 383 (8), 307 (100), 291 (7), 290 (8), and 105 (off scale).

Anal. Calcd for $C_{24}H_{16}N_2O_5$: C, 69.7; H, 3.9; N, 6.8. Found: C, 70.0; H, 4.0; N, 7.0.

6-Nitro-3-(1,3-dipivaloylpropen-2-yl)-2,1-benzisoxazole (7b).—Compound **7b** was prepared from **6b** by the method described for **7a**: mp 94–95° (from methanol); λ_{max} ($\epsilon \times 10^{-3}$) 276 (16.7), 332 (9.55), and ~360 nm (8.7); mass spectrum *m/e* 372 (75), 352 (10), 315 (100), 288 (25), 287 (32), 273 (20), 271 (25), 260 (10), 259 (20), 245 (30), 231 (65), 204 (25), 203 (18), 85 (100), 57 (off scale), and 41 (100).

Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.5; H, 6.5; N, 7.5. Found: C, 64.7; H, 6.4; N, 7.2.

3-(2-Benzoyl-1-phenacylidenethyl)-2,1-benzisoxazole (7c).—The procedure described for the preparation of **7a** was used and water was added to precipitate the **7c**: yield 68%; mp 109–110° (from aqueous alcohol); mass spectrum *m/e* 367 (8), 339 (6), 338 (8), 262 (50), 246 (6), 245 (6), 234 (5), 105 (100), and 77 (67).

Anal. Calcd for $C_{24}H_{17}NO_3$: C, 78.5; H, 4.6; N, 3.8. Found: C, 78.2; H, 4.9; N, 4.0.

3-(2,6-Diphenyl-4-pyridyl)-6-nitro-2,1-benzisoxazole (8).—A solution of 0.5 g of **7a** and 0.5 g of ammonium carbonate in 20 ml of acetic acid was refluxed for 10 min and cooled. The solid was collected and crystallized from pyridine giving 0.3 g of **8**: mp 221–222°; mass spectrum *m/e* 393 (100), 347 (13), 346 (13), 319 (7), 318 (9), 290 (9), 244 (20), 230 (5), 216 (6), 127 (22), 77 (12).

Anal. Calcd for $C_{24}H_{15}N_3O_3$: C, 73.4; H, 3.8; N, 10.7. Found: C, 73.3; H, 3.6; N, 10.6.

2',6'-Diphenyl-1-methoxy-6-nitro-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (9a).—A mixture of 1 g of **3a**, 3 ml of methyl iodide, 1 g of potassium carbonate, and 10 ml of acetone was stirred in a stoppered flask for 3 hr and filtered; the filtrate was evaporated to dryness. The residue was crystallized from methyl alcohol giving 0.8 g of **9a**: mp 219–220°; λ_{max} ($\epsilon \times 10^{-3}$) 252 (47.0) and 370–420 nm (2.0); mass spectrum *m/e* 426 (27), 395 (100), 368 (10), 367 (15), 321 (28), 320 (15), 105 (75), 77 (30).

Anal. Calcd for $C_{25}H_{18}N_2O_5$: C, 70.5; H, 4.2; N, 6.4. Found: C, 70.4; H, 4.3; N, 6.5.

2',6'-Di-*tert*-butyl-1-methoxy-6-nitro-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (9b).—This compound was prepared from **3b** using the procedure described for the preparation of **9a**: yield 98%; mp 156–157° from methanol; ir no hydroxyl absorption, 1726 (CO), 1691 cm^{-1} (pyran); λ_{max} ($\epsilon \times 10^{-3}$) 249 (19.8) and 350–450 nm (1.1); mass spectrum *m/e* 386 (16), 355 (100), 328 (10), 327 (12), 313 (7), 289 (8), 271 (11), 255 (7), 225 (9), and 57 (65).

Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.0; H, 6.8; N, 7.3. Found: C, 65.3; H, 7.0; N, 7.4.

2',6'-Diphenyl-1-methoxy-3-oxospiro[indoline-2,4'-[4'*H*]pyran] (9c).—Compound **9c** was prepared from **3c** by the method described for **9a**: yield 82%; mp 119–120° from methanol; λ_{max} ($\epsilon \times 10^{-3}$) 238 (41.6) and 330–380 nm (1.8); mass spectrum *m/e* 381 (27), 350 (100), 322 (40), 217 (7), 216 (7), 105 (90), and 77 (37).

1-Methoxy-6-nitro-2,2-diphenacyl-3-indolinone (11a).—A mixture of 1 g of **9a**, 5 ml of 20% perchloric acid, and 25 ml of acetic acid was heated until a solution was obtained. The solution was cooled and diluted with water; the solid recrystallized from a mixture of methanol and pyridine giving 0.6 g of **11a**: mp 174–175°; λ_{max} ($\epsilon \times 10^{-3}$) 250 (48.0) and 300–420 nm (2.1); mass spectrum *m/e* 444 (12), 105 (100), and 77 (28).

Anal. Calcd for $C_{25}H_{20}N_2O_6$: C, 67.6; H, 4.5; N, 6.3. Found: C, 67.7; H, 4.7; N, 6.6.

1-Methoxy-6-nitro-2,2-bispivaloylmethyl-3-indolinone (11b).—The method described for **11a** was used with **9a** giving **11b**, yield 74%, mp 168–169° from methanol.

Anal. Calcd for $C_{11}H_{18}N_2O_6$: C, 62.4; H, 7.0; N, 6.9. Found: C, 62.1; H, 7.1; N, 6.8.

2',6'-Di-*tert*-butyl-3-hydroxy-1-methoxy-6-nitrospiro[indoline-2,4'-[4'*H*]pyran] (12b).—To a stirred solution of 1 g of **9b** in 75

ml of isopropyl alcohol was added 0.5 g of sodium borohydride, and the solution was stirred for 0.5 hr and diluted with water, and the solid crystallized from alcohol: mp 124–125° dec; λ_{max} ($\epsilon \times 10^{-3}$) 250 (22.8) and 360 nm (1.8); mass spectrum *m/e* 388 (15), 357 (100), 327 (23), 313 (13), 311 (14), 271 (10), 165 (8), and 57 (30).

Anal. Calcd for $C_{21}H_{28}N_2O_5$: C, 64.9; H, 7.3; N, 7.2. Found: C, 64.9; H, 7.0; N, 7.0.

2′,6′-Diphenyl-3-hydroxy-1-methoxyspiro[indoline-2,4′-[4′*H*]-pyran] (12c).—Compound **9c** was reduced with sodium borohydride as described for **12b** giving **12c**: mp 127–130°; mass spectrum *m/e* 383 (20), 252 (100), 322 (47), 246 (12), 233 (13), 218 (8), 217 (9), and 105 (36).

Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.3; H, 5.5; N, 3.7. Found: C, 77.9; H, 5.2; N, 3.5.

2′,6′-Di-*tert*-butyl-6-nitro-3-oxospiro[indoline-2,4′-[4′*H*]pyran] (13b).—A solution of 0.5 g of **12b** in 25 ml of degassed chloroform was acidified with 0.5 ml of acetic acid and concentrated under vacuum. The residue was recrystallized from alcohol giving 0.4 g of **13b**: mp 238–239°; λ_{max} ($\epsilon \times 10^{-3}$) 247 (21.6), 273 (15.2), and ~305 nm (11.1); mass spectrum *m/e* 356 (12), 327 (100), 315 (62), 313 (29), 282 (10), 281 (9), 271 (42), 267 (9), 266 (9), 225 (5), and 57 (13).

Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.4; H, 6.8; N, 7.9. Found: C, 67.1; H, 6.7; N, 7.9.

2′,6′-Diphenyl-3-oxospiro[indoline-2,4′-[4′*H*]pyran] (13c).—Compound **12c** was allowed to react as described for the preparation of **13b** giving **13c**: yield 65%; mp 208–209° from alcohol; mass spectrum *m/e* 351 (14.3), 324 (6), 323 (35), 322 (100), 246 (11), 218 (13), 217 (17), 216 (8), and 105 (20).

Anal. Calcd for $C_{24}H_{17}NO_2$: C, 82.0; H, 4.9; N, 4.0. Found: C, 81.8; H, 5.0; N, 4.0.

2,′6′-Diphenylspiro[indoline-2,4′-[4′*H*]pyran] (14).—A solution of 0.2 g of **13c** in 10 ml of ether was treated with 0.1 g of lithium aluminum hydride. After the mixture had been stirred for 15 min, an nmr spectrum was determined on a sample (for results see discussion of nmr spectrum).

4-(2-Aminobenzylidene)-2,6-diphenyl-4*H*-pyran (15). IS
Method A.—A solution of 0.5 g of **2c** in 50 ml of hot alcohol was treated with 2 g of sodium sulfide, refluxed overnight, and filtered; the hot filtrate was diluted with water and chilled. The solid was collected and crystallized from aqueous alcohol giving 0.3 g of **15**: mp 107–108°; mass spectrum *m/e* 337 (100), 336 (52), 232 (19), 230 (14), 168.5, 115 (7), 105 (26), and 77 (24).

Anal. Calcd for $C_{24}H_{19}NO$: C, 85.4; H, 5.6; N, 4.1. Found: C, 85.3; H, 5.5; N, 4.2.

Method B.—The ether solution of **14** was allowed to stand for 1 hr, and the nmr spectrum was identical with that of **15** prepared by method A.

Acknowledgment.—We wish to acknowledge the assistance of Mr. D. P. Maier for the mass spectral data and of Dr. T. H. Regan for the low-temperature nmr spectra.

Registry No.—**1**, 17539-77-4; **2a**, 40576-44-1; **2b**, 40576-45-2; **2c**, 40576-46-3; **3a**, 40576-47-4; **3b**, 40576-48-5; **3c**, 40576-49-6; **4**, 40576-50-9; **5**, 40576-51-0; **6a**, 40576-52-1; **6b**, 40576-53-2; **6c**, 40576-54-3; **7a**, 40576-55-4; **7b**, 40576-56-5; **7c**, 40576-57-6; **8**, 40576-58-7; **9a**, 40576-59-8; **9b**, 40576-60-1; **9c**, 40576-61-2; **11a**, 40576-62-3; **11b**, 40576-63-4; **12b**, 40576-64-5; **12c**, 40576-65-6; **13b**, 40576-66-7; **13c**, 40576-67-8; **14**, 40576-68-9; **15**, 40576-69-0; 2,6-di-*tert*-butyl-4-methylpyrylium perchlorate, 14604-52-5; *o*-nitrophenylacetic acid, 3740-52-1; 2,4-dinitrotoluene, 121-14-2; 2,4-dinitrochlorobenzene, 97-00-7.

Intermediates in Nucleophilic Aromatic Substitution. X.[1] Synthesis of *N*-Methyl-β-aminoethyl Nitroaryl Ethers *via* an Unusual Smiles Rearrangement

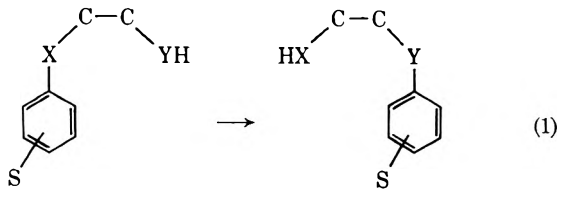
CLAUDE F. BERNASCONI,*[2] RITA H. DE ROSSI, AND CONSTANTIN L. GEHRIGER

University of California, Santa Cruz, California 95060

Received March 21, 1973

N-Methyl-β-aminoethyl nitroaryl ethers undergo a Smiles rearrangement into *N*-methyl-*N*-β-hydroxyethylnitroarylamines so readily that the aryl ethers cannot be prepared by obvious methods. However, when the aromatic system is sufficiently activated so that in the presence of base the aryl amine can be converted into a cyclic Meisenheimer complex, the Smiles rearrangement can be reversed and the ether obtained by rapidly acidifying the Meisenheimer complex. The aryl ether is the kinetically controlled product of the ring opening of the complex and can be trapped and isolated in the form of its ammonium salt.

Intramolecular rearrangements of the type shown in eq 1 are known as Smiles[3] rearrangements. The reaction is in fact an intramolecular activated (S = activating substituent) nucleophilic aromatic substitution. In most cases the displacement is by Y^- rather than by YH and thus the presence of a strong base is usually required. When YH is NH_2 or NHR a base may or may not be necessary for the reaction to proceed. The carbon chain joining X and Y may be saturated or be part of an aromatic system. The field has been reviewed recently.[4]



(1)

In this paper we are concerned with X = O, YH = NH_2 or NHR, and in particular with the inverse combination X = NH or NR, YH = OH. Most examples from the early literature[5] involve compounds where the C–C chain is part of an aromatic ring.[6]

More recently examples where the C–C chain is saturated have been reported by Kleb;[7] reaction 2 is representative. The rearrangement of **1** to **2** occurs so rapidly that **1** and a variety of similar β-aminoalkyl 4-nitrophenyl ethers could not be prepared from obvious starting materials. In fact the occurrence of reaction 2

(1) Part IX: C. F. Bernasconi and R. G. Bergstrom, *J. Amer. Chem. Soc.*, **95**, 3603 (1973).

(2) Alfred P. Sloan Fellow, 1971–1973.

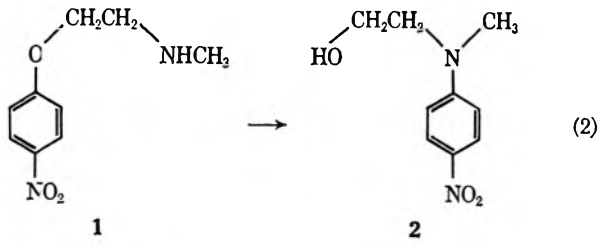
(3) (a) L. A. Warren and S. Smiles, *J. Chem. Soc.*, 956 (1930); (b) W. J. Evans and S. Smiles, *ibid.*, 181 (1935).

(4) (a) W. E. Truce, E. M. Kreider, and W. W. Brand, *Org. React.*, **18**, 99 (1970); (b) H. J. Shine, "Aromatic Rearrangements," Elsevier, New York, N. Y., 1967, p 307.

(5) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 275 (1951).

(6) K. C. Roberts and C. G. M. de Worms, *J. Chem. Soc.*, 737 (1934).

(7) K. G. Kleb, *Angew. Chem., Int. Ed. Engl.*, **7**, 291 (1968).



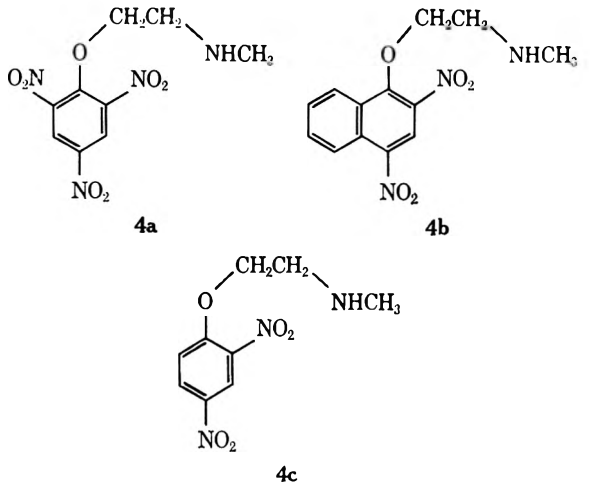
(2)

had to be inferred indirectly from a sequence where **1** was an intermediate.[7]

That reactions such as 2 are strongly favored thermodynamically in the direction indicated is in agreement with observations on a large number of *inter*molecular aromatic nucleophilic displacements of oxygen bases by amines.[8] We now report three examples in which, by judicious choice of conditions, the reaction can be forced into the reverse direction and the aryl ether can be isolated as the amine hydrochloride.

Results

***N*-Methyl-β-aminoethyl Picryl Ether (4a).**—Despite considerable effort, we were unable to synthesize *N*-methyl-β-aminoethyl picryl ether (**4a**), in an unreactive form such as the amine hydrochloride, by straightforward methods.[9] *N*-Methyl-*N*-β-hydroxyethyl picramide (**5a**) and/or other unidentified products formed instead.



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

On the other hand, the following procedure starting with *N*-methyl-*N*-β-hydroxyethyl picramide (**5a**) makes the picryl ether **4a** easily available. When base is added to a solution of **5a** either in a hydroxilic or a dipolar aprotic solvent, the cyclic Meisenheimer complex **7a** is formed immediately according to sequence 3. **7a** is very stable and can readily be isolated from ethanol, as was shown earlier by Hünig and Fleckenstein.[11] The spectra in Figure 1, taken in aqueous solution, of **5a** show the gradual conversion of **5a** into

(8) For recent reviews see (a) C. F. Bernasconi, *MTP Int. Rev. Sci., Org. Chem. Ser. 1*, **3**, 33 (1973); (b) F. Pietra, *Quart. Rev., Chem. Soc.*, **23**, 504 (1969); (c) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968; (d) T. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups," part I, H. Feuer, Ed., Interscience, New York, N. Y., 1969, p 487.

(9) These included the reaction of picryl chloride with *N*-methylethanolamine under protection of the amino group by the *tert*-butylcarbonyl group[10] in basic solution under a variety of conditions, the attempted nitration of *N*-methyl-β-aminoethyl phenyl ether, and some others.

(10) B. Iselin and R. Schwyzer, *Helv. Chim. Acta*, **44**, 169 (1961).

(11) S. Hünig and E. Fleckenstein, private communication (1970).

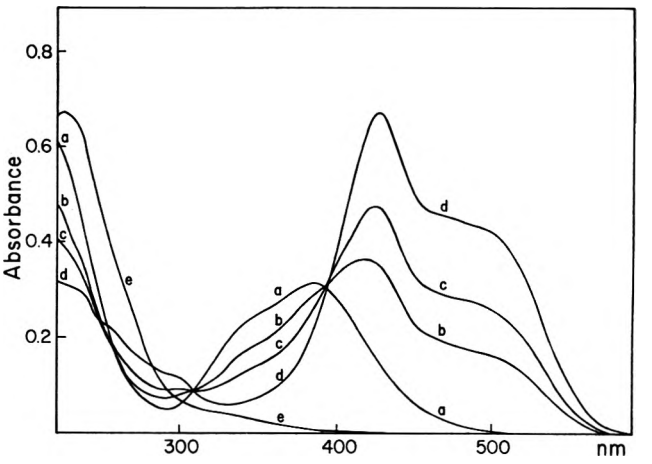
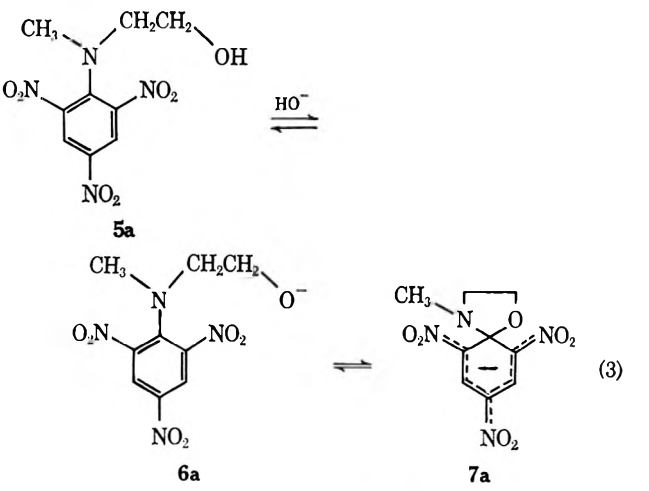


Figure 1.—Absorption spectra in the picryl system in aqueous solution at 25°: a–d, **5a** as a function of pH, $[\mathbf{5a}]_0 = 3 \times 10^{-5}$ *M*; a, pH 6.00; b, pH 9.40; c, pH 9.80; d, pH 12.00 (conversion to **7a** is complete at pH 12.00); e, after acidification of a solution of **7a**, spectrum of **8a** (3×10^{-5} *M*) in 1 *M* HCl.



5a **6a** **7a**

(3)

7a as the pH is increased. At pH ≥12 the conversion is virtually quantitative.

When a dilute aqueous solution (~10^{-4} *M*) of **7a** is added to a large enough volume of a 0.01 *M* HCl solution so that after neutralizing of all the base the pH is ≤3, the ether **4a** is formed quantitatively judging by uv spectroscopy; it is trapped as the corresponding ammonium ion. With minor modifications the procedure is conveniently carried out on a preparative scale in ethanolic solution from which the hydrochloride of **4a** is isolated in good yield.

Below pH 5 the ether solution is quite stable; above pH 5 it is gradually converted into the original starting material **5a**, the more rapidly the higher the pH.

***N*-Methyl-β-aminoethyl 2,4-Dinitronaphthalene Ether (4b).**—The reactions affording the picryl ether **4a** apply equally for the 2,4-dinitronaphthyl system. In fact *N*-methyl-*N*-β-hydroxyethyl 2,4-dinitronaphthyl amine (**5b**) is about as readily converted to the cyclic Meisenheimer complex **7b** as **5a** is converted to **7a**. In aqueous solution containing 2% DMSO (v/v) (added for solubility reasons) the conversion is complete at pH ≥12. Spectra of solutions of **5b** at various pH values are shown in Figure 2.

Acidification of **7b** with acid of the same concentration as for **7a** affords the ammonium salt of **4b** in quantitative yield (**8b**). As in the case of **4a** an increase in

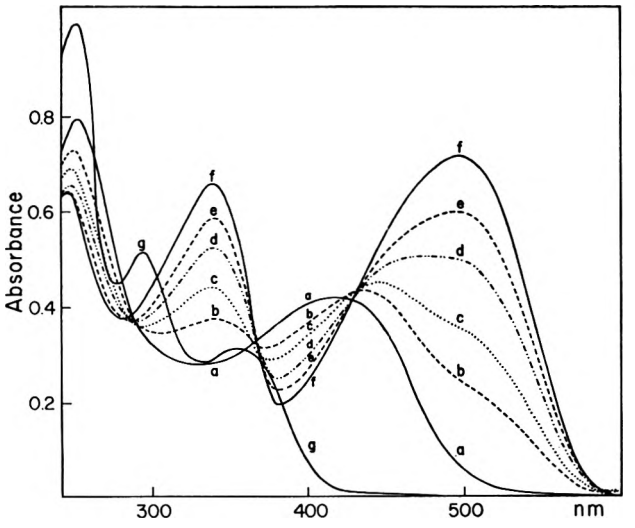
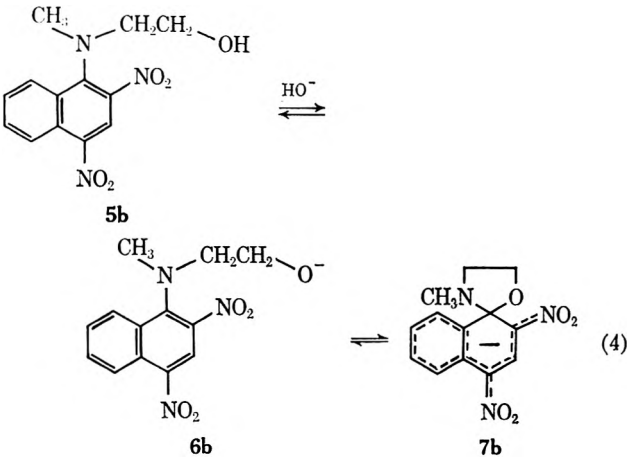
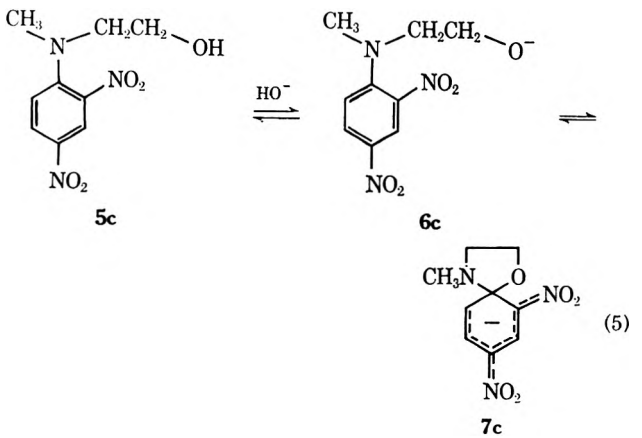


Figure 2.—Absorption spectra in the 2,4-dinitronaphthyl system in 2% DMSO–98% H_2O (v/v) at 25°: a–f, **5b** as a function of pH, $[\mathbf{5b}]_0 = 5.5 \times 10^{-5}$ *M*; a, 0.01 *M* HCl; b, pH 9.085; c, pH 9.375; d, pH 9.780; e, pH 10.115; f, 0.01 *M* NaOH (conversion to **7b** is complete in 0.01 *M* NaOH); g, after acidification of a solution of **7b**, spectrum of **8b** (5.5×10^{-5} *M*) in 0.01 *M* HCl.



pH above 5 leads to gradual conversion of **4b** to **5b**, which becomes more rapid as the pH is increased. Ethanol is again a convenient solvent for preparative work.

***N*-Methyl-β-aminoethyl 2,4-Dinitrophenyl Ether (4c).**—As has been shown recently,[12] conversion of **5c** to **7c** is insignificant in strongly alkaline aqueous solutions but extensive in aqueous solutions containing ≥80% (v/v). In 85% DMSO (v/v) and 0.01 *M* $(CH_3)_4$-NOH the conversion into **7c** is quantitative.



Attempts to transform **7c** quantitatively into **8c**, *i.e.*, the ammonium salt of **4c**, by acidifying the solution of **7c** in 90% DMSO (v/v) with aqueous acid were only successful when ≥1 *M* HCl was used. Significant amounts of **5c** were formed in more dilute acid. The yields of **4c** (**8c**), which tended to be variable when dilute HCl was employed, could be improved by adding the solution of **7c** dropwise to the acid under vigorous stirring; with such efficient mixing the product distribution was about 75% **4c** (**8c**) and 25% **5c** in 0.02 *M* HCl, end pH ~2.

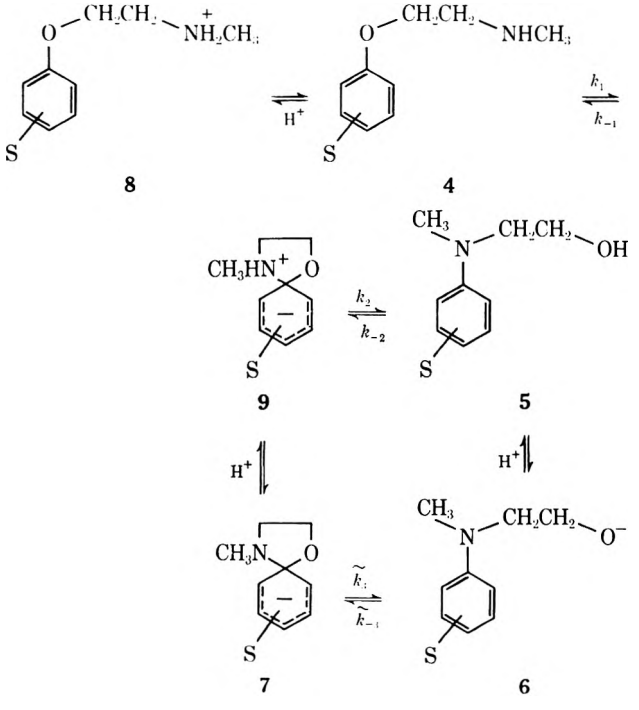
When the Meisenheimer complex was acidified with a ≥0.02 *M* HCl solution in 90% DMSO (v/v) instead of aqueous acid, **8c** was formed quantitatively, as determined spectrophotometrically.

From a preparative point of view the necessity to generate **7c** in the solution containing DMSO is a drawback since it is difficult to isolate the product. The possibility of generating **7c** in the dioxane–methanol–methoxide ion system[13] was explored. Acidifying the complex with 1.2 *M* HCl in 90% dioxane–10% water (v/v) yields about 20% of **8c**.

Discussion

Our approach to the synthesis of **4a**, **4b**, and **4c** and the experimental observations reported under Results are best discussed with reference to Scheme I, which includes the species believed to play a significant role in our reaction system.[14]

SCHEME I



The behavior of the picryl and the 2,4-dinitrona-

(12) C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, **38**, 500 (1973).

(13) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffith, *J. Org. Chem.*, **33**, 4141 (1968).

(14) The symbols for the rate coefficients are consistent with the ones used in representing the mechanism of nucleophilic aromatic substitution reactions by amines.[8a]

phthyl systems can be rationalized as follows. Upon acidifying an alkaline solution of **7a** (**7b**), there must be a rapid protonation of **7a** (**7b**) to form **9a** (**9b**). Following that, **9a** (**9b**) may decompose either toward **4a** (**4b**) and/or toward **5a** (**5b**). It is to be noted that step **9a** (**9b**) → **5a** (**5b**) is practically irreversible, whereas the reaction **4a** (**4b**) ⇌ **9a** (**9b**) is reversible. Formation of **4a** (**4b**) apparently occurs faster than the irreversible transformation into **5a** (**5b**). This is not unexpected, since frequently $k_{-1} \gg k_2$ in similar *intermolecular* substitutions involving secondary amines as nucleophiles.[8]

By keeping the pH low enough the kinetically favored product **4a** (**4b**) is converted into its unreactive from **8a** (**8b**) and formation of **5a** (**5b**) is prevented altogether.

If the conversion of **9a** (**9b**) to **4a** (**4b**) is carried out in a less acidic medium or if the pH of a solution containing **8a** (**8b**) is raised, the system is gradually drained off into the thermodynamically more stable form **5a** (**5b**), or, at high pH (~12), into **7a** (**7b**).

Similar considerations apply to the 2,4-dinitrophenyl system. However, the observation of increased yields of **8c** under vigorous stirring and/or when more concentrated acid was used indicates that under certain conditions the events are not only controlled by chemical rate processes but also by the rate at which the solutions becomes homogeneous (on the microscopic level) after mixing.

Thus in the early stages of the mixing process the pH of the microenvironment around **7** is still rather high and therefore little of **9**, which could decompose to **8** *via* **4**, is formed. On the other hand **5** may form *via* **6** as soon as the pH of the microenvironment has dropped low enough as to make the process **7** ⇌ **6** → **5** thermodynamically favorable, but not yet low enough to form significant amounts of **9**. Since we have indications that the pK_a's of **9** are around 6–7,[15] this situation must indeed arise: **5a** and **5b** become favored over their respective complexes **7a** and **7b** at pH <9.4 (see Figures 1 and 2), **5c** is always thermodynamically favored over **7c** in aqueous solution,[12] whereas in 90% DMSO **5c** is estimated to become favored when $[HO^-] < 10^{-5} M$.

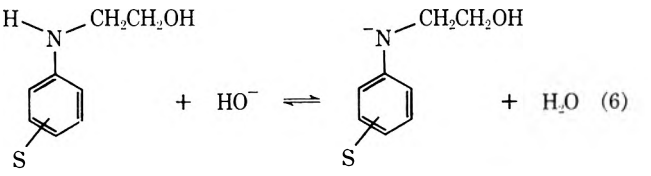
Whether there is sufficient time for a significant amount of **5** to form *via* **6** before the pH drops further (now favoring process **7** ⇌ **9** ⇌ **4** → **8**) depends on the magnitude of $\bar{k}_3$.

In the case of **7a** and **7b** $\bar{k}_3 < 10^{-2}$ sec^{-1} in aqueous solution;[15] this is much too low for the reaction **7a** (**7b**) ⇌ **6a** (**6b**) → **5a** (**5b**) to make any significant progress during the mixing process. For **7c** in 90% DMSO, $\bar{k}_3 < 9$ sec^{-1},[12] which apparently is also too low and explains why no **5c** is formed upon acidification of a basic solution of **7c** in 90% DMSO with an acid solution in 90% DMSO.

For **7c** in more highly aqueous DMSO $\bar{k}_3$ has been determined as follows: 923, 650, 332, 116, 53, and 9 sec^{-1} in 2, 20, 50, 65, 80, and 85% DMSO,[12] respectively. The magnitude of $\bar{k}_3$ in solutions with a not too high DMSO content, say 65% or less, is quite high and appears sufficient for the reaction **7c** ⇌ **6c** → **5c** to make some progress, even if the mixing time were in the 10-msec range. It is to be realized that when the aqueous acid and **7c** in basic 90% DMSO are added together, it not only takes time for the pH of the microenvironment to be lowered but also for part of the DMSO around **7c** to be replaced by water molecules. However, since a relatively small increase of the water content (*very* early stage of mixing process) has already a large accelerating effect on $\bar{k}_3$, $\bar{k}_3$ must apparently have reached a high enough value by the time the pH of the microenvironment has somewhat dropped to allow **5c** to accumulate on thermodynamic grounds. Better stirring as well as the use of a higher acid concentration allow the microenvironment of **7c** to reach a relatively low pH value at an earlier stage of the mixing process, thus cutting down the time during which formation of **5c** *via* **6c** competes with formation of **8c**. Both factors are expected to enhance the yield of **8c**, in agreement with experimental observation.

The method described here for synthesizing *N*-methyl-β-aminoethyl nitroaryl ethers is likely to be applicable to compounds with activating groups other than nitro. Based on the accumulated understanding of the relation between structure and thermodynamics as well as kinetic stabilities of Meisenheimer complexes,[16] one may in fact predict that the method is likely to work for all systems in which the Meisenheimer complex is as stable as or more stable than that of the 2,4-dinitrophenyl system.

On the other hand the method appears ill suited for systems lacking the *N*-methyl or some other *N*-alkyl group for two reasons. (1) In analogy to other systems, formation of the cyclic Meisenheimer complex is expected to compete unfavorably with proton loss according to eq 6 and possibly with nucleophilic



attack by HO^- at the 3 position of the aromatic ring. (2) Even if some cyclic Meisenheimer complex is formed, acidification would not yield significant amounts of the β-aminoethyl aryl ether because very likely $k_2 \gg k_{-1}$.[8a]

In fact, when a basic solution of *N*-β-hydroxyethyl picramide, which showed a spectrum somewhat similar to the one of **7a**, was acidified, the starting material was recovered almost quantitatively.

Experimental Section

***N*-Methyl-*N*-β-hydroxyethyl picramide (5a)** was prepared by adding 7.14 g (95 mmol) of freshly distilled *N*-methylethanolamine in 20 ml of ethanol to a solution of 11.8 g (47.5 mmol) of picryl chloride in 200 ml of ethanol. The dark red solution was refluxed for 15 min. After cooling, crystallization of the product started immediately, yielding 94% of the product, mp 144° after two recrystallizations from ethanol. *Anal.* Calcd for $C_9H_{10}N_4O_7$: C, 37.80; H, 3.52; N, 19.60. Found: C, 37.73; H, 3.64; N, 19.70. Uv max (H_2O) 384 nm[17] (ε 10,700).[17]

***N*-Methyl-*N*-β-hydroxyethyl 2,4-dinitronaphthylamine (5b)** was prepared after the same procedure as for **5a** by starting with

(15) C. F. Bernasconi, R. H. de Rossi, and C. L. Gehriger, unpublished results.

(16) For recent reviews see (a) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969); (b) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(17) From spectrum a in Figure 1. Possibly in equilibrium with traces of **8a** and/or **9a** and **7a**.

2,4-dinitrochloronaphthalene. Refluxing time was 2 hr. Purification was achieved by redissolving the filtered crystals in ethanol and precipitating by adding the solution to ice-cold water, yield 96%, mp 73–73.5°. *Anal.* Calcd for $C_{13}H_{13}N_3O_5$: C, 53.70; H, 4.45; N, 14.40. Found: C, 53.75; H, 4.38; N, 14.48. Uv max [2% DMSO–98% H_2O (v/v)] 420 nm[18] (ϵ 7620).[18]

N-Methyl-*N*-β-hydroxyethyl 2,4-dinitroaniline (5c) was available from a previous study.[12]

Meisenheimer complexes 7a and 7b were prepared by adding a solution of 4 mmol of KOH in 10 ml of ethanol to a solution of 2 mmol of 5a (5b) in 10 ml of ethanol. 7a was precipitated with cold ether, yield 93%. Recrystallization from ethanol[19] yielded a product decomposing at 298°. *Anal.*[20] Calcd for $C_9H_9N_4O_7K$: C, 33.33; H, 2.80; M, 17.28. Found: C, 32.87; H, 2.91; N, 17.14. Pmr (DMSO-d_6) δ 2.11 (s, 3, CH_3N), 3.24 (m, 2, CH_2N), 4.13 (m, 2, CH_2O), and 8.51 ppm (s, 2, ring); uv max (H_2O) 427 nm (ϵ 22,500). 7b after crystallization from the reaction solution was filtered and washed with ether *Anal.*[20] Calcd for $C_{13}H_{12}N_3O_5K$: C, 47.42; H, 3.65; N, 12.77. Found: C, 47.32; H, 4.56; N, 12.63. Pmr (DMSO-d_6) δ 1.90 (s, 3, CH_3N), 3.21 (m, 2, CH_2N), 4.25 (m, 2, CH_2O), 8.95 (s, 1, H_3),[21] 8.6 (m, 1, H_8),[21] and 7.3 ppm (broad m, 3, $H_{5,6,7}$);[21] uv max [2% DMSO–98% H_2O (v/v)] 497 nm (ϵ 13,000) and 338 (11,900); uv max (DMSO) 518 nm (ϵ 28,300) and 362 (17,000).

N-Methyl-β-aminoethyl picryl ether hydrochloride (8a) was prepared by rapidly adding 0.5 ml of concentrated HCl to a solution of 730 mg (2.25 mmol) of Meisenheimer complex 7a in 70 ml of ethanol. KCl precipitated and was filtered off, and the solution was concentrated for crystallization of the product, which was obtained in 76% yield, mp 140°. Recrystallization did not increase the melting point. *Anal.* Calcd for $C_9H_{11}N_4O_7Cl$: C, 33.48; H, 3.44; N, 17.35. Found: C, 33.41; H, 3.53; N, 17.20.

N-Methyl-β-aminoethyl 2,4-dinitronaphthyl ether hydrochloride (8b) was prepared by adding a solution of 300 mg (0.91 mmol) of Meisenheimer complex 7b in 30 ml of ethanol to 15 ml of ethanolic 0.5 *M* HCl; this latter solution was prepared from HCl gas and ethanol. After the precipitated KCl was filtered off the solution was added to 50 ml of ether, whereupon the product precipitated. For purification the filtered product was redissolved in acidic ethanol and precipitated with ether, yield 50%, mp 180–181°. *Anal.* Calcd for $C_{13}H_{14}N_3O_5Cl$: C, 47.71; H, 4.27; N, 12.84. Found: C, 47.50; H, 4.35; N, 12.71.

N-Methyl-β-aminoethyl 2,4-Dinitrophenyl Ether Hydrochloride (8c).—A 0.25-ml portion of a 14 *M* KOH solution in water was added to 834 mg (3.46 mmol) of *N*-methyl-*N*-β-hydroxyethyl 2,4-dinitroaniline (5c) in 2.5 ml of DMSO. The resulting emulsion was added to 10 ml of 1.2 *M* HCl in 90% DMSO. After addition of 4 ml of ethanol most of the KCl precipitated; it was filtered off and the solvent was evaporated at about 40° (0.3 mm). The residue was extracted with ether to remove DMSO and traces of 5c. The last traces of DMSO were removed by column chromatography with alumina oxide (Baker Analyzed Grade, activity grade I, acid). The ether hydrochloride 8c was eluted with 0.5 *M* HCl in ethanol. Precipitation with ether, redissolving in acidic ethanol, and reprecipitation with ether yielded a product with mp 182–183°. *Anal.* Calcd for $C_9H_{12}N_3O_5Cl \cdot H_2O$: C, 36.7; H, 4.75; N, 14.25. Found: C, 37.01; H, 4.45; N, 14.12.

Acknowledgments.—Partial support of this work by the National Science Foundation, financial assistance to R. H. de R. by the National University of Cordoba, Argentina, and a Monsanto Fellowship, administered by the Swiss Federal Institute of Technology, to C. L. G., are gratefully acknowledged. We also thank Professor J. F. Bunnett for critical discussions.

Registry No.—5a, 40711-00-0; 5b, 40711-01-1; 5c, 37580-86-2; 7a, 40704-76-5; 7b, 40704-77-6; 8a, 40711-03-3; 8b, 40711-04-4; 8c, 40711-05-5; *N*-methylethanolamine, 109-83-1; picryl chloride, 88-88-0; 2,4-dinitrochloronaphthalene, 2401-85-6.

(18) From spectrum a in Figure 2. Probably in equilibrium with traces of 8b as indicated by preliminary kinetic experiments.

(19) The crystallization was very slow. Use of trimethylbenzylammonium ion as gegenion gives better crystallization characteristics.[11]

(20) Meisenheimer complexes notoriously yield poor analyses.

(21) Assignments as for the spiro complex from 1-(2-hydroxyethoxy)-2,4-dinitronaphthalene.[22]

(22) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4141 (1968).

Photoreduction of 1,9-Methanodecal-2-ones. Comparison of Cis and Trans Isomers

GARY W. SHAFFER

Givaudan Corporation, Clifton, New Jersey 07014

Received March 8, 1973

Photoreduction of *cis*-1,9-methano-10-methyldecal-2-one (1c) occurs with retention of the stereochemistry at C9 to give *cis*-9,10-dimethyldecal-2-one (3c); however, photoreduction of the trans isomer 1t occurs with inversion of the stereochemistry at C9 to also give 3c as the major product. When the angular methyl group is absent, photoreduction of either isomer occurs with retention of the stereochemistry at C9. A conformational argument is offered as a possible explanation for this difference.

Irradiation (n–π*) of bicyclo[4.1.0]heptan-2-ones in 2-propanol usually affords cyclohexanones derived from reductive opening of the C1–C7 cyclopropyl bond.[1] Recently, it has been reported that this reaction course can be altered when the bicyclo[4.1.0]-heptan-2-one moiety is part of a decalone or steroidal ketone molecule. Photoreduction of either *cis*- or *trans*-4,5-methanocholestan-3-one gave predominantly *cis*-5-methylcholestan-3-one.[2] Likewise, photoreduction of *trans*-dihydromayurone gave *cis*-8,8,9,10-tetramethyldecal-2-one as one of several products, but no *trans*-8,8,9,10-tetramethyldecal-2-one was found.[3]

From inspection of molecular models, one would *a priori* predict that both *trans*-4,5-methanocholestan-3-one and *trans*-dihydromayurone should photoreduce with retention of the trans stereochemistry. The present study reports the results from photoreduction of a series of isomeric 1,9-methanodecal-2-ones which whould help to elucidate this problem.

The isomeric cyclopropyl ketones were prepared by Simmons–Smith cyclopropylation[4] of the corresponding $\Delta^{1,9}$-octal-2-ols, followed by Jones oxidation.[5] In each case the major alcohol obtained from lithium aluminum hydride reduction of the corresponding

(1) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969).

(2) W. G. Dauben, L. Schutte, and E. J. Deviny, *ibid.*, **37**, 2047 (1972).

(3) G. W. Shaffer, *ibid.*, **37**, 3282 (1972).

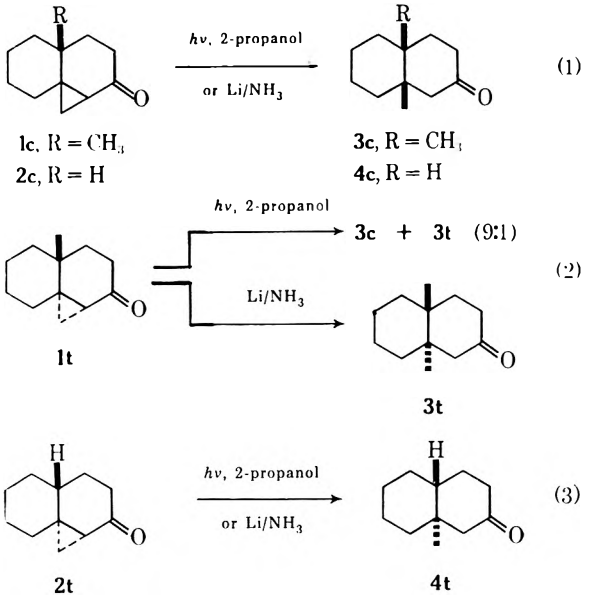
(4) W. G. Dauben, P. Lang, and G. H. Berezin, *ibid.*, **31**, 3869 (1966).

(5) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

enone was assigned the cis stereochemistry.[6] Separation of isomers was accomplished in low yield by chromatography of the cyclopropyl alcohols and/or ketones on alumina.

Photoreduction of *cis*- and *trans*-1,9-methano-10-methyldecal-2-one (**1c**, **1t**) parallels the behavior of the 4,5-methanocholestan-3-ones. Either isomer of **1** gives *cis*-9,10-dimethyldecal-2-one (**3c**) as the predominant product (eq 1 and 2). The small amount of **3t** formed from photoreduction of **1t** could not be isolated and identification was made only on the basis of a glc retention time comparison with **3t** prepared by lithium–ammonia reduction of **1t**. The lithium–ammonia reduction of **1t**, in direct contrast to photoreduction, gives **3t** in good yield (eq 2).

When the bridgehead methyl group is absent (**2c** and **2t**), photoreduction of either isomer parallels lithium–ammonia reduction and the stereochemistry of the cyclopropyl ring is retained in the product (eq 1 and 3).[7]



Irradiation at low temperature (−65°) also reveals a difference between the cis and trans isomers. When the C10 methyl group is present, the trans isomer is stable to prolonged irradiation at 300 nm in 2-propanol, whereas the cis isomer reacts. However, under the same irradiation conditions at 33°, there are no significant differences between **1c** and **1t** in either the quantum yields for disappearance of ketone or formation of product (Table I).

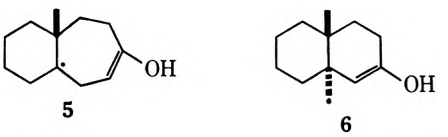
TABLE I

QUANTUM YIELDS FOR DISAPPEARANCE OF KETONE AND FORMATION OF PRODUCT IN 2-PROPANOL[a]

Ketone	Φ_{-k}	Φ (formation of product)
1c	0.50	0.23 (formation of **3c**)
1t	0.74	0.23 (formation of **3c**)
2c	0.45	0.08 (formation of **4c**)
2t	0.38	0.13 (formation of **4t**)

[a] 7–15% disappearance of ketone at 33° using RUL 3000-Å Rayonet lamps.

The results suggest a conformational control argument as one possible explanation. If the carbonyl group of **1t** should twist 25–30°, which is a maneuver easily accomplished with a Dreiding model, to relieve the 1,3-diaxial interaction of the angular methyl group and the axial hydrogen at C3, then the cyclopropyl ring would bisect the carbonyl p orbital. With this condition, the initial cyclopropyl rupture would occur to give tertiary radical **5** in preference to primary radical **6**.[8] This twisted conformation of **1t** would have



5 **6**

no effect on the result from lithium–ammonia reduction, since the anion intermediate involved[9] would prefer the primary position leading to **3t**.

Although a 1,3-diaxial interaction similar to that of **1t** exists for **1c** between the C3 hydrogen and the C5 methylene group, a corresponding 25–30° twist of the model carbonyl group is more difficult to accomplish. This nonflexibility of the carbonyl group of **1c**, as compared to **1t**, could allow the carbonyl p orbital to remain aligned for maximum overlap with the outside cyclopropyl bond. Thus, for *cis*-1,9-methano-10-methyldecal-2-ones, the outside cyclopropyl bond opens and the stereochemistry at C9 is retained. This would also be the case for C10 normethyl derivatives where the carbonyl group of the trans isomer would have a lesser tendency to twist owing to the absence of the 1,3-diaxial methyl–hydrogen interaction.

These generalizations are summarized in Chart I.

The failure to observe substantial amounts of cycloheptanone products from either *trans*-4,5-methanocholestan-3-one or **1t** is probably due to the greater hindrance toward hydrogen abstraction of tertiary as compared to primary radicals. When the primary radical is also in a hindered environment, such as exists during photoreduction of the dihydromayurones, then cycloheptanone products are observed.[3]

These experiments do not exclude the possibility that the angular methyl group affects the excited state rather than the ground state conformation.

Experimental Section

Preparative irradiations were carried out with a 450-W medium-pressure Hanovia mercury lamp in a quartz, water-cooled, immersion probe. The filter was a glass cylinder of Corex (>255 nm) insertable between the lamp and the probe. Solutions were outgassed with argon before and during the irradiations.

Infrared spectra were taken as neat samples on a Perkin-Elmer 457 and absorptions are reported as inverse centimeters, uv spectra were taken on a Beckman Acta III, nmr spectra were taken on a Varian A-60A as chloroform-d_1 solutions and are reported as δ units relative to TMS, and molecular weights were determined from mass spectra obtained with a Perkin-Elmer 270. Gas–liquid partition chromatography (glpc) was done on a 10% Carbowax 20M (12 ft × 1/8 in.) column. Melting points are uncorrected.

cis- and *trans*-1,9-Methano-10-methyldecal-2-one (**1c**, **1t**).—

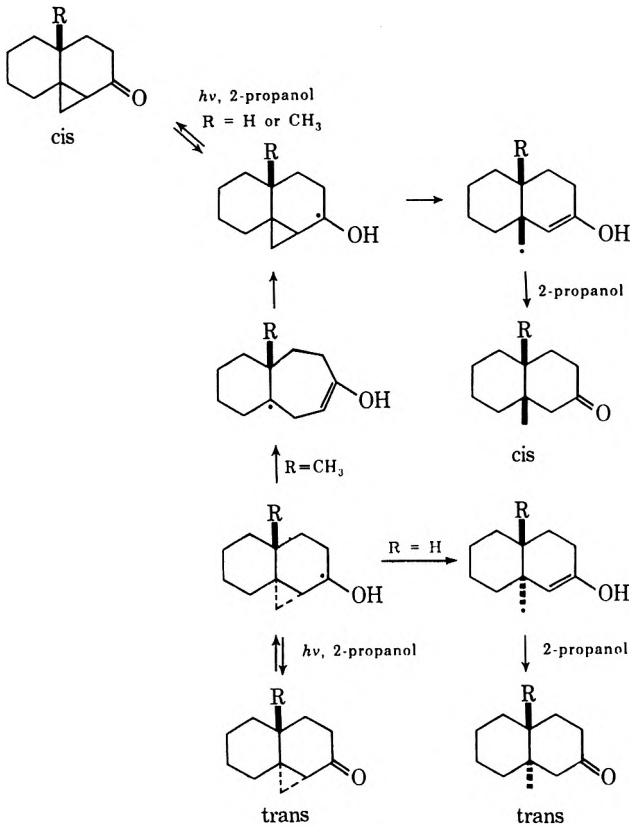
(6) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 30–32; H. B. Henbest and J. McEntree, *J. Chem. Soc.*, 4478 (1961).

(7) Identical results were obtained for *c*- and *t*-1,9-methano-*t*-6-isopropyl-*r*-(10*H*)-decal-2-one.

(8) W. G. Dauben, G. W. Shaffer, and E. J. Deviny, *J. Amer. Chem. Soc.*, **92**, 6273 (1970).

(9) W. G. Dauben and R. E. Wolf, *J. Org. Chem.*, **35**, 374 (1970).

CHART I



Lithium aluminum hydride reduction of 10-methyl-$\Delta^{1,9}$-octal-2-one gave 85% *cis*- and 15% *trans*-1-methyl-$\Delta^{1,9}$-octal-2-ol.[6] Nester–Faust spinning band distillation (10.0 g) afforded as the first fraction [1.28 g, bp 106–107° (3 mm)] a 1:1 mixture of the cis and trans isomers.

The alcohols (6.00 g, 0.036 mol, 85% cis, 15% trans) were allowed to react under Simmons–Smith conditions[4] to give 1,9-methano-10-methyldecal-2-ol: 85% cis, 15% trans; 3.79 g (58% yield); ir 3350 (s), 1465 (m), 1440 (m), 1040 (m), 962 (m), 925 (m); nmr 4.1–4.5 (1 H, m, α H), 1.00 (cis) (3 H, s, methyl H), 0.35–0.75 (2 H, m, cyclopropyl H), 0.0–0.21 (1 H, m, cyclopropyl H); mass spectrum M^+ (cis) 180, M^+ (trans) 180.

The cyclopropyldecalols were oxidized at 0° with excess Jones reagent[5] to give *cis*- and *trans*-1,9-methano-10-methyldecal-2-one (**1c**, **1t**): ir 1684 (s); nmr 2.03–2.42 (2 H, m, α H), 1.14 (cis), 1.09 (trans) (3 H, 2 s, methyl H), 0.5–1.0 (2 H, m, cyclopropyl H); mass spectrum M^+ (**1c**) 178, M^+ (**1t**) 178; the cis isomer eluted first on glc.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.57; H, 10.10.

Chromatography of the cyclopropyldecalols (4.40 g, 80% cis, 20% trans) on 300 g of alumina (neutral III, 2.5 cm i.d.) gave the pure cis isomer as the first fraction (1.52 g) eluted with benzene–ether (50:1). Oxidation gave pure **1c**.

The Simmons–Smith reaction was repeated on a mixture of 57% *cis*- and 43% *trans*-10-methyl-$\Delta^{1,9}$-octal-2-ol from the above distillation and chromatography on alumina (neutral III, benzene) gave as a later eluted fraction a mixture consisting of 85% *trans*- and 15% *cis*-1,9-methano-10-methyldecal-2-ol. Oxidation of this fraction and rechromatography on alumina (neutral II, benzene) gave a small fraction consisting of 92% **1t** and 8% **1c**.

***cis*- and *trans*-1,9-Methanodecal-2-one (2c, 2t).**—Lithium aluminum hydride reduction of $\Delta^{1,9}$-octal-2-one[10] gave a 3:1 mixture of *cis*- and *trans*-$\Delta^{1,9}$-octal-2-ol.[6]

The alcohols (16.7 g, 0.11 mol) were allowed to react under Simmons–Smith conditions[4] to give 1,9-methanodecal-2-ol: 69% cis, 31% trans; 14.1 g (77% yield); ir 3330 (s), 1440 (m), 1015 (s); nmr 4.1–4.5 (1 H, m, α H), 0.0–0.25 (1 H, m, cyclopropyl H); mass spectrum M^+ (cis) 166, M^+ (trans) 166.

The cyclopropyldecalols were oxidized at 0° with excess Jones reagent[5] to give *cis*- and *trans*-1,9-methanodecal-2-one (**2c**, **2t**): bp 80–82° (0.5 mm); ir 1670 (s), 1440 (m), 1241 (s), 925 (m), 878 (s); nmr 2.01–2.34 (2 H, m, α H), 0.66–1.12 (2 H, m, cyclopropyl H); mass spectrum M^+ 164. The epimeric ketones are inseparable on Carbowax glpc; therefore the isomer ratios were determined by glpc analysis of the precursor alcohols.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.32; H, 9.74.

The cyclopropyldecalols chromatographed twice on alumina (neutral II, ether) gave the pure trans (eluted first) and the pure cis isomer. Each isomer was separately oxidized to give pure **2c** and **2t**.

Photoreduction of *cis*- and *trans*-1,9-Methano-10-methyldecal-2-one (1c, 1t).—The photoreduction of 95% pure **1c** to *cis*-9,10-dimethyldecal-2-one (**3c**) has already been described.[3]

A solution of 0.476 g of a mixture of 53% **1c** and 47% **1t** in 150 ml of 2-propanol (0.018 *M*) was irradiated for 1.3 hr. The solvent was removed under reduced pressure, the residual oil (0.492 g) was oxidized with excess Jones reagent[5] and the resulting mixture (0.467 g) was chromatographed on 125 g of alumina (neutral III, 1.5 cm i.d.).

Benzene first eluted 0.155 g of 85% pure *cis*-9,10-dimethyldecal-2-one (**3c**) (28% yield), which was identified by comparison (nmr spectrum, glpc retention time) with **3c** obtained from lithium–ammonia reduction of **1c**. By glpc and nmr, this fraction contained a very small amount (*ca.* 1% yield) of *trans*-9,10-dimethyldecal-2-one (**3t**). This fraction also contained two other unidentified monomeric products in 4–5% combined yield.

Benzene later eluted 0.148 g (31%) of recovered starting material (1:1 mixture of **1c** and **1t** by nmr and glpc).

Repeating the above irradiation and separation on a mixture of 92% **1t** and 8% **1c** gave the following yields: 27% **3c**, 3% **3t** (identified by glpc retention time only), 41% starting material (94% **1t**, 6% **1c**), 7% of two unidentified monomeric products, and 22% of nonmonomeric material.

Photoreduction of *cis*- and *trans*-1,9-Methanodecal-2-one (2c, 2t).—A solution of 0.207 g of a 1:1 mixture of **2c** and **2t** in 150 ml of 2-propanol (0.008 *M*) was irradiated for 1 hr. The solvent was removed under reduced pressure, the residual oil (0.209 g) was oxidized with excess Jones reagent[5] and the resulting mixture (0.183 g) was chromatographed on 75 g of alumina (neutral III, 1.5 cm i.d.).

Hexane–benzene (4:1) eluted a mixture of *cis*- and *trans*-9-methyldecal-2-one (**4c**, **4t**): 0.059 g (28% yield); ir 1701 (s); nmr 0.97 (s, *cis*-methyl H, 55%), 0.79 (s, *trans*-methyl H, 45%); mass spectrum M^+ 166. This sample was identical (ir and nmr spectra, glpc retention time) with a sample of **4c** and **4t** obtained by lithium–ammonia reduction of a 1:1 mixture of **2c** and **2t**.

Hexane–benzene (1:1) eluted 0.060 g (29%) of unreacted starting material. The remaining 43% was nonmonomeric polar material and was not investigated.

***cis*- and *trans*-9,10-Dimethyldecal-2-one (3c, 3t).**—The preparation and properties of **3c** have already been described.[3] From lithium–ammonia reduction[11] of a mixture of **1c** and **1t** there was obtained a mixture of **3c** and **3t**: ir 1705 (s); nmr 1.22 (trans), 1.03 (cis), 0.95 (trans), 0.91 (cis) (4 s, methyl H); mass spectrum M^+ (cis) 180, M^+ (trans) 180. The two epimers were partially resolved on Carbowax glpc; **3c** eluted first.

***cis*- and *trans*-9-Methyldecal-2-one (4c, 4t).**—From lithium–ammonia reduction[11] of a mixture of **2c** and **2t** there was obtained a mixture of **4c** and **4t**: ir 1705; nmr 0.97 (s, *cis*-methyl H), 0.79 (s, *trans*-methyl H, reported[12] 0.79); mass spectrum M^+ 166.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.24; H, 10.75.

The two epimers are inseparable on Carbowax glpc. Lithium–ammonia reduction of two different mixtures of **2c** and **2t** (85% **2c**, 15% **2t**; 45% **2c**, 55% **2t**) showed that the **4c**:**4t** ratio could be determined by relative integrations of the two methyl nmr singlets.

Low Temperature Irradiations.—Quartz tubes containing solutions of the various ketones in 2-propanol were immersed in a

(10) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(11) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(12) J. A. Marshall and H. Roebke, *ibid.*, **34**, 4188 (1969).

methanol bath in a nonsilvered dewar flask which was cooled by circulation of methanol through an external Dry Ice–methanol mixture. The temperature range of the bath was −60 to −68°. The dewar flask was placed in the center of a Rayonet photochemical reactor and irradiated with 8-RUL 3000-Å lamps.

The following results were obtained: *cis*-dihydromayurone[3] in 22 hr gave 16% 7,11,11-trimethylbicyclo[5.4.0]-1-undecan-4-one and 4% *cis*-8,8,9,10-tetramethyldecal-2-one; *trans*-dihydromayurone[3] in 22 hr gave no detectable reaction by glpc; **1c** in 21 hr gave 12% **3c**; **1t** (91% pure) in 21 hr gave no detectable reaction by glpc; **2c** and **2t** (*ca.* 1:1 mixture) in 36 hr, after oxidation with Jones[6] reagent, gave 4% of **4c** and **4t** (1:1). In the case of **2**, the product was isolated and the presence of both **4c** and **4t** shown by the δ 0.97 (**4c**) and 0.79 (**4t**) methyl group nmr singlets. In all the other low temperature irradiations, the percentages were obtained by glpc analysis only.

Quantum Yield Determinations.—Quantum yields were determined according to the procedure of Wagner.[13] Separate solutions of **1c** (0.07 *M*), **1t** (0.07 *M*), **2c** (0.1 *M*), and **2t** (0.1 *M*) in 2-propanol containing octadecane as an internal standard were placed in 1.1-cm Pyrex tubes (each in triplicate), degassed, sealed, and irradiated in parallel at 33° on a merry-go-round using 8-RUL 3000-Å Rayonet lamps. At this concentration, the ketones absorbed >99% of the 300-nm radiation. The amount of ketone that disappeared was measured by glpc analysis (5% Carbowax 20M, 18 ft × ⅛ in.) by comparing the ketone/standard area ratios before and after irradiation. The quantum yields for disappearance (7–15%) of ketone follow: **1c**, 0.50; **1t** (92% pure, 8% **1c**), 0.74; **2c** 0.45; **2t**, 0.38.

The amount of product formed during the irradiation was measured by comparison of glpc peak height to a graph of peak height *vs.* known concentrations of the respective product, using constant volume injections. The quantum yields for product formation follow: **3c** from **1c**, 0.23; **3c** from **1t**, 0.23; **4c** from **2c**, 0.08; **4t** from **2t**, 0.13.

Two tubes containing 1.0 *M* acetone and 0.20 *M* *cis*-1,3-pentadiene in cyclohexane were irradiated in parallel with the above samples. The average yield (10%) of *trans*-1,3-pentadiene was measured by comparison of glpc (10% UCW 98, 18 ft × ⅛ in.) peak height to a graph of peak height *vs.* known concentrations of *trans*-1,3-pentadiene in the above solution of *cis*-1,3-pentadiene, acetone, and cyclohexane, using constant volume injections. The quantum yield for the cis to trans isomerization, after being corrected for back reaction, is 0.555.[14]

Acknowledgments.—The author would like to thank W. G. Dauben and A. R. Hochstetler for helpful discussions regarding this research, P. Shubiak for glpc analyses related to the quantum yield determinations, and J. Fischer for excellent technical assistance.

Registry No.—**1c**, 35340-22-8; **1t**, 40447-74-3; **2c**, 40447-75-4; **2t**, 40447-76-5; **3c**, 5523-99-9; **3t**, 40447-78-7; **4c**, 2530-17-8; **4t**, 1197-95-1; 10-methyl-$\Delta^{1,9}$-octal-2-one, 826-56-2; *cis*-10-methyl-$\Delta^{1,9}$-octal-2-ol, 31654-83-8; *trans*-10-methyl-$\Delta^{1,9}$-octal-2-ol, 40447-83-4; *cis*-1,9-methano-10-methyldecal-2-ol, 13903-60-1; *trans*-1,9-methano-10-methyldecal-2-ol, 40447-85-6; $\Delta^{1,9}$-octal-2-one, 1196-55-0; *cis*-$\Delta^{1,9}$-octal-2-ol, 30983-79-0; *trans*-$\Delta^{1,9}$-octal-2-ol, 2763-42-0; *cis*-1,9-methanodecal-2-ol, 40447-89-0; *trans*-1,9-methanodecal-2-ol, 40447-90-3.

(13) F. J. Wagner and R. W. Spoerke, *J. Amer. Chem. Soc.*, **91**, 4437 (1969).

(14) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

Mono- and Disubstituted Vinyltrialkylammonium Compounds. Synthesis and Stereochemistry

F. E. HERKES* AND H. E. SIMMONS

Contribution No. 2016 from the Central Research Department, E. I. du Pont de Nemours and Company, Experimental Station, Wilmington, Delaware 19898

Received March 15, 1973

Methyl propiolate reacts with trimethyl-, triethyl-, tri-*n*-butylammonium, and pyridinium halide salts in water–dioxane to yield *trans*-methoxycarbonylvinyltrialkylammonium salts. Similarly, dimethyl acetylenedicarboxylate adds trimethyl- and triethylammonium halide salts to produce the *cis*-bis(methoxycarbonyl)-vinyltrialkylammonium compounds. Other disubstituted vinyltrimethylammonium salts were prepared by dehydrobromination of 1,1,2-tribromoethyltrimethylammonium bromide and 2-carboxy-1,2-dibromoethyltrimethylammonium bromide to yield the respective (*E*)-dibromovinyltrimethylammonium and (*E*)-1-bromo-2-carboxyvinyltrimethylammonium bromides. The stereochemistry and chemical shift assignment of both the mono- and disubstituted vinylammonium salts were established using the additivity relationship developed by Matter and Tobey, $\delta_{C=CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$. The shielding parameters for the trialkylammonium substituent were determined to be $Z_{gem} = 1.00$, $Z_{cis} = 0.65$, and $Z_{trans} = 0.30$. A reinvestigation of the reaction of 1-bromovinyltrimethylammonium bromide with $NaOCH_3$ or KOC_2H_5 revealed that the isomeric *cis*-alkoxyvinyltrimethylammonium bromide is also formed in addition to the reported 1-alkoxyvinyltrimethylammonium bromide.

The synthesis of vinyltrimethylammonium compounds is well documented. In most cases they are prepared by addition of aqueous trimethylamine to acetylene or monosubstituted acetylenic derivatives.[1-3] Until 1969, there were few reports on the synthesis of vinyltrialkylammonium salts containing an alkyl group other than methyl. With ethoxyacetylene, Arens[2] found that aqueous solutions of triethyl- or tri-*n*-butylamine reacted sluggishly or not at all. In an improved modification of Reppe's[1] neurine synthesis, Fisher[4,5] succeeded in preparing a series of *N*-(2-formylvinyl)trialkylammonium salts by treating a mineral acid salt of a tertiary amine with propiolaldehyde. With few exceptions, these and other 2-monosubstituted vinyltrialkylammonium salts have been shown by nmr spectroscopy to possess a trans configuration.[4-7]

Other monosubstituted vinyltrimethylammonium salts have been synthesized either by dehydration[8] or

(1) W. Reppe, German Patent 860,058 (1949).

(2) J. F. Arens, J. G. Bouman, and D. H. Koerts, *Recl. Trav. Chim. Pays-Bas*, **74**, 1040 (1955).

(3) C. Gardner, V. Kerrigan, J. D. Rose, and D. C. L. Weeden, *J. Chem. Soc.*, 789 (1949).

(4) G. Fisher, *Chem. Ber.*, **102**, 2609 (1969).

(5) G. Fisher, *ibid.*, **103**, 3470 (1970).

(6) J.-M. Lehn and R. Sehr, *Chem. Commun.*, 847 (1966).

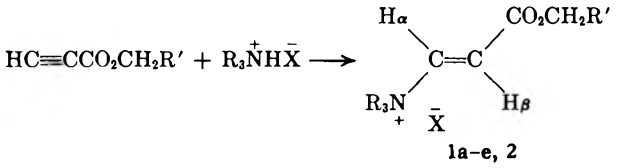
(7) M. Ohtsuru, K. Tori, J.-M. Lehn, and R. Sehr, *J. Amer. Chem. Soc.*, **91**, 1187 (1969).

(8) W. E. Truce and J. A. Simms, *J. Org. Chem.*, **22**, 762 (1957).

dehydrohalogenation[9-11] of 1,2-dihaloethyltrimethylammonium salts. In the latter case, the 1-halovinyltrimethylammonium salts are produced[12] instead of the 2-halo isomers.

Disubstituted vinyltrialkylammonium salts have not been reported. In the course of studying and preparing new monosubstituted vinyltrialkylammonium salts, we also succeeded in synthesizing several of the disubstituted derivatives. In this paper we report our observations on the synthesis and configurational assignments of new mono- and disubstituted vinyltrialkylammonium salts. We also formulate a set of nmr shielding parameters for the trialkylammonium substituent.

Monosubstituted Ammonium Salts.—When trimethyl-, triethyl-, or tri-*n*-butylammonium bromide was warmed (40°) in a 2:1 (v/v) water–dioxane solution containing an equivalent amount of methyl propiolate for 24 hr, the corresponding *trans*-methoxycarbonylvinyltrialkylammonium salts (**1a–e**) were isolated as



1a–e, 2

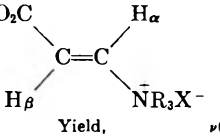
1a, R = CH_3; R′ = H; X = Cl
b, R = CH_3; R′ = H; X = Br
c, R = C_2H_5; R′ = H; X = Br
1d, R = *n*-C_4H_9; R′ = H; X = Br
e, R = CH_3; R′ = CH_2Cl; X = Br
2, R_3N = pyridine; R′ = H; X = Cl

crystalline compounds.[14] Similar results were obtained employing the hydrochloride salts or other acetylenic esters (Table I). The stereochemistry of the salts **1** was assigned as trans, since J = 13.8–14.0 Hz for all the alkoxycarbonyl derivatives studied (Table II). The chemical shift of H_α in **1c** and **1d** was shifted to lower field relative to **1b** by 0.25–0.30 ppm. H_β, however, remained invariant to any change in trialkyl substitution. Varying the halide counterion had no effect upon the chemical shifts of the vinyl protons because of minimal ion pairing in water.[16]

In contrast, a pronounced shielding effect was observed for H_α in *trans*-methoxycarbonylvinylpyridinium chloride (**2**), formed in 21% yield from pyridine hydrochloride and methyl propiolate under similar conditions. The absorption of H_α was δ 8.24 compared to the trimethyl analog (**1b**) which appeared at δ 7.50. The change in chemical shift of H_α in the series $CH_3O_2CCH_\beta{=}CH_\alpha NR_3^+X^-$ is qualitatively correlated with the polar inductive effect of the substituent R. The δ values decreased in the following order for R: C_5H_5N > CH_3 > C_2H_5 > *n*-C_4H_9. Pyridinium salts of structure **2** have been long postulated as transient intermediates in the reaction of pyridine with acetylenic esters producing indolizines.[17]

Because of the ambiguity in the literature regarding the structure of 1-bromovinyltrimethylammonium bromide (**3**) and the potential need for configurational assignments of the disubstituted vinyltrialkylammonium salts, a set of shielding increments for a trialkylammonium substituent on the ethylene moiety was determined. Several groups[18,19] using nmr spectroscopy have determined a series of shielding increments Z which, when used in conjunction with the equation $\delta_{C=CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$, aid in the determination of the stereochemistry of trisubstituted ethylenes. Comparative analysis (see Experimental Section) of the spectrum of neurine bromide and its derivatives with their calculated spectra using the shielding parameters of Matter[18] and Tobey[19] gave the following shielding increments—Z_{gem} = 1.00, Z_{cis} = 0.65, and Z_{trans} = 0.30—for a trialkylammonium substituent. The use of these shielding increments and those reported[18,19] gave calculated values of the chemical shifts for H_α and H_β in good agreement with those observed in this study and those previously reported[6,7] (Table II). The structure of **3** was reconfirmed by comparison of its observed (δ 6.50 and 6.07) *vs.* calculated (δ 6.45 and 5.98) olefinic chemical shifts. A similar analysis was performed for the 1-methoxy- (**4a**) and 1-ethoxyvinyltrimethylammonium bromide (**4b**) derivatives,[20] the latter prepared by two routes.[2,20] In the preparation[20] of **4**, a second isomeric vinyltrimethylammonium ether was observed. This isomer could be removed upon repeated recrystallization from methanol or acetonitrile. Nmr analysis of the product mixture resulting from **3** and $NaOCH_3$–CH_3OH at room temperature (Figure 1) indicated a 3:1 ratio of **4a** to *cis*-methoxyvinyltrimethylammonium bromide (**5a**). The spectrum of the mixture in DMSO-d_6 (or D_2O) showed an AB absorption pattern at δ 4.99 and 4.61 for the vinylic protons with J = 6.5 Hz and single peaks at δ 3.84 and 3.42 for the methoxyl and trimethylammonium

TABLE I
PHYSICAL PROPERTIES OF MONOSUBSTITUTED VINYLTRIALKYLAMMONIUM SALTS



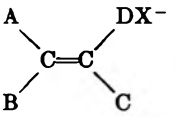
No.	R	R′	X	Yield, %[a]	Mp, °C	ν(C=C),[b] cm^{-1}	ν(C=O),[b] cm^{-1}
1a[c]	CH_3	H	Cl	35	179–180	166	1730
1b[c]	CH_3	H	Br	51	164–165	1661	1724
1c[c]	C_2H_5	H	Br	40	165–166	1664	1727
1d[c]	*n*-C_4H_9	H	Br	33	125–126	1653	1727
1e[c]	CH_3	CH_2Cl	Br	50	136	1661	1715
2[c]	R_3N = pyridine	H	Br	21	105–106	1642	1715

[a] Isolated yield. [b] Nujol mull. [c] Satisfactory analytical data (±0.4% for C, H, N) were provided for this compound: Ed.

(9) J. Bode, *Justus Liebigs Ann. Chem.*, **267**, 268 (1890).
(10) K. A. Hofmann and K. Hobald, *Chem. Ber.*, **44**, 1766 (1911).
(11) F. Klages and E. Sierup, *Justus Liebigs Ann. Chem.*, **547**, 65 (1941).
(12) In a recent report[13] the bromovinyltrimethylammonium bromide resulting from dehydrobromination was incorrectly assigned as the 2-bromo isomer.
(13) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, **91**, 468 (1969).
(14) After completing this study, we uncovered an observation made by Truce and Brady[15] on the reaction of trimethylammonium chloride and ethyl propiolate in methylene chloride to yield *trans*-ethoxycarbonylvinyltrimethylammonium chloride.
(15) W. E. Truce and W. T. Brady, *J. Org. Chem.*, **31**, 3543 (1966).
(16) A. G. Massey, E. W. Rundull, and D. Shaw, *Spectrochim. Acta*, **20**, 379 (1964); **21**, 263 (1965).
(17) R. M. Acheson in "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed. Academic Press, New York, N. Y., 1963, p 125.
(18) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691, 2023 (1969); C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).
(19) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).
(20) F. Klages and E. Drerup, *Justus Liebigs Ann. Chem.*, **547**, 65 (1941).

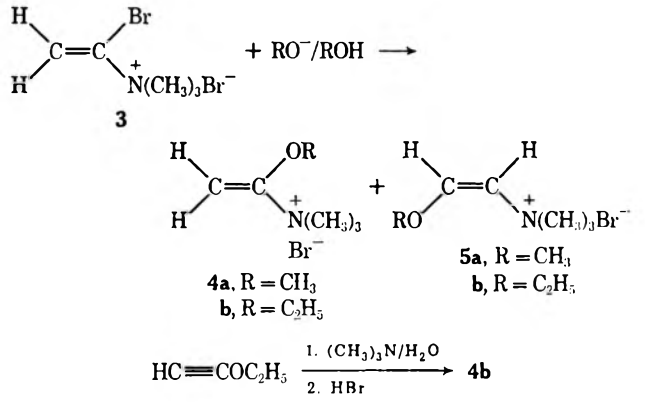
TABLE II

CALCULATED[a] *vs.* OBSERVED[b] NMR CHEMICAL SHIFTS OF MONOSUBSTITUTED VINYLTRIALKYLAMMONIUM SALTS



No.	A	B	C	D	X	δ_A, obsd	δ_A, calcd	δ_B, obsd	δ_B, calcd	δ_C, obsd	δ_C, calcd	δ_D, obsd
1a	H	CH_3O_2C	H	$N(CH_3)_3$	Cl	6.68	6.70	4.01		7.50	7.43	3.47
1b	H	CH_3O_2C	H	$N(CH_3)_3$	Br	6.63	6.70	3.86		7.47	7.43	3.37
1c	H	CH_3O_2C	H	$N(C_2H_5)_3$	Br	6.61	6.70			7.19	7.43	3.68, 1.31
1d	H	CH_3O_2C	H	$N(C_4H_9)_3$	Br	6.59	6.70			7.22	7.43	
1e	H	$ClCH_2CH_2O_2C$	H	$N(CH_3)_3$	Br	6.67	6.70			7.49	7.43	3.47
2	H	CH_3O_2C	H	NC_5H_5	Cl	6.92	6.70	3.77		8.24	7.43	*c*
3	H	H	Br	$N(CH_3)_3$	Br	6.50	6.45	6.07	6.01			3.54
4a	H	H	CH_3O	$N(CH_3)_3$	Br	4.99	4.69	4.61	4.49	3.84		3.42
4b	H	H	C_2H_5O	$N(CH_3)_3$	Br	4.95	4.69	4.58	4.49	1.37, 4.11		3.52
5a	CH_3O	H	H	$N(CH_3)_3$	Br	3.89		6.56	6.78	5.58	5.04	3.46
5b	C_2H_5O	H	H	$N(CH_3)_3$	Br	1.31, 4.18		6.54	6.78	5.61	5.04	3.52
9	H	HO_2C	H	$N(CH_3)_3$	Cl	6.58	6.90			7.40	7.66	3.42
16	H	HO_2C	H	$N(CH_3)_3$	Br	6.61	6.90			7.49	7.66	3.48
16a	H	HO_2C	H	$N(CH_3)_3$	BF_4	6.52	6.90			7.37	7.66	3.40
d	H	H	Br	$N(CH_3)_3$	BF_4	6.48	6.45	6.03	6.01			3.50
e	H	H	Cl	$N(CH_3)_3$	Br	6.48	6.45	6.03	6.01			3.50
e	H	H	C_6H_5	$N(CH_3)_3$	Br	6.96	7.28	6.75	6.64			

[a] U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691, 2023 (1969); C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966); S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969); for $^+NR_3$, Z_{gem} = 1.00, Z_{cis} = 0.65, Z_{trans} = 0.30. [b] Measured in D_2O relative to internal standard of 3-(trimethylsilyl)propanesulfonic acid sodium salt. [c] See Experimental Section. [d] Prepared from **3** and Ag_2O followed by acidification with 50% HBF_4. [e] Reference 7.



protons. A second AB pattern was observed downfield at δ 5.58 and 6.56 with J = 5.5 Hz. An additional set of peaks at δ 3.89 and 3.46 was also observed for the corresponding methoxyl and trimethylammonium protons. Similar results were obtained when KOH–C_2H_5OH was employed (Figure 2). Attempts to isolate **5a** and **5b** by fractional precipitation employing ethanol–ether or by recrystallization (acetonitrile) gave only **4** as the sole isolable salt. The cis stereochemistry of **5** was assigned on the basis of the vinyl proton coupling (5.5 Hz) and comparison of the observed *vs.* the calculated chemical shifts of the vinylic protons (Table II).

Both **4** and **5** are formed by a competitive substitution–elimination process inherent in many activated ethylenic systems employing alkoxide salts in hydroxylic solvents. Furthermore, isomer **4** can arise by one of two routes. The first involves an addition–elimination process whereby the alkoxide adds to the α carbon to give **6** followed by 60° rotation and rapid elimination of bromide ion, yielding **4**. The alternate and less

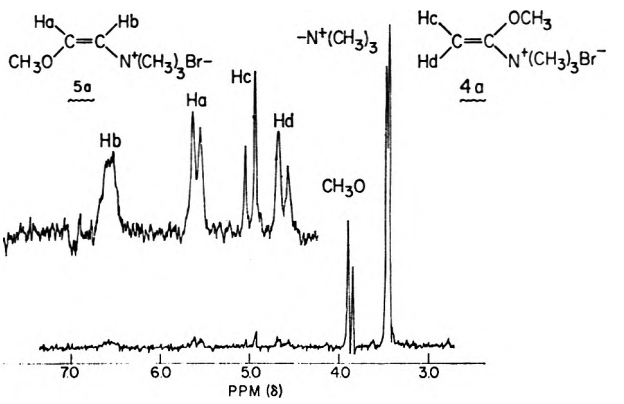


Figure 1.—^{1}H nmr spectrum of a mixture of **4a** and **5a** in DMSO-d_6 at 35°.

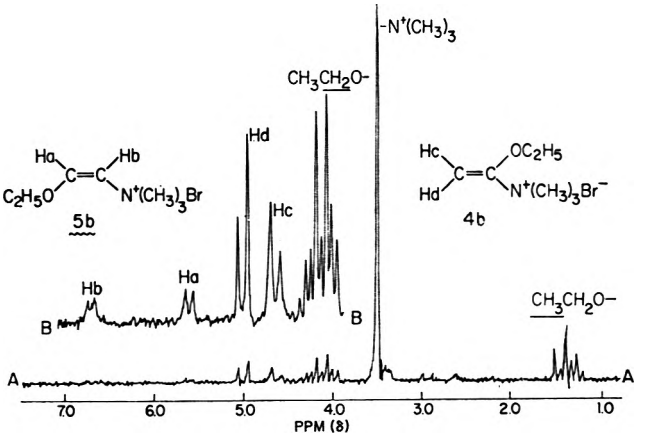
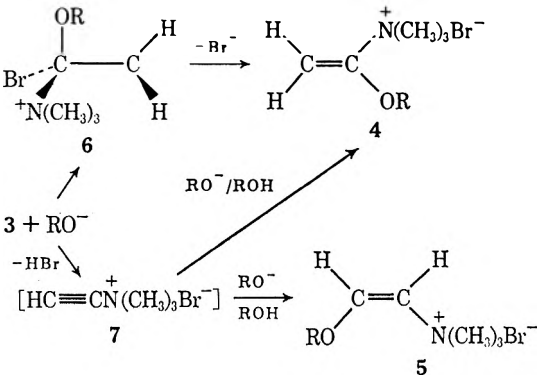
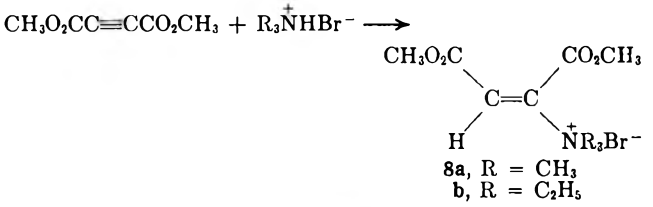


Figure 2.—^{1}H nmr spectrum of a mixture of **4b** and **5b** in DMSO-d_6 at 35°.

likely route to **4** would involve dehydrobromination of **3** producing **7**,[21] followed by trans addition (anti-Michael) of alkoxide and a proton. The formation of **5** involves the elimination of hydrogen bromide to produce an intermediate alkynyltrimethylammonium salt (**7**), which then adds alcohol in a trans stereospecific manner.[23,24]



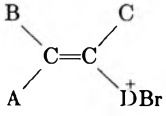
Disubstituted Salts.—When trimethyl- or triethylammonium bromide was treated with dimethyl acetylenedicarboxylate in a 2:1 (v/v) water–dioxane mixture, the corresponding dimethyl trialkylammonium maleates (**8a** and **8b**) were isolated in 60 and 56% yield,



respectively. The nmr spectrum of the trimethylammonium derivative **8a** showed only one set of methyl absorptions in addition to the singlet absorption at δ 7.11 for the vinyl proton (Table III). The triethyl

TABLE III

OBSERVED[a] *vs.* CALCULATED[b] NMR CHEMICAL SHIFTS FOR DISUBSTITUTED VINYLTRIALKYLAMMONIUM SALTS

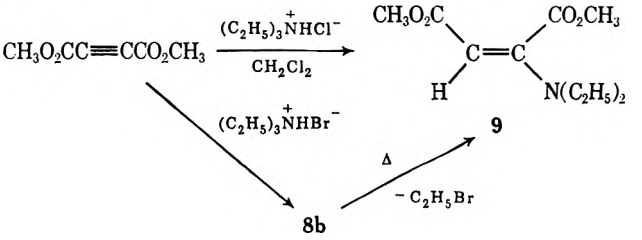


No.	A	B	C	D	Obsd δ_{vinyl}	Calcd δ_{vinyl}
8a	H	CH_3O_2C	CH_3O_2C	$N(CH_3)_3$	7.11	7.00
8b	H	CH_3O_2C	CH_3O_2C	$N(C_2H_5)_3$	7.00	7.00
13	Br	H	Br	$N(CH_3)_3$	8.12	7.08
14	C_2H_5O	H	Br	$N(CH_3)_3$	7.25	7.23
18	HO_2C	Br	H	$N(CH_3)_3$	7.91	7.77

[a] The chemical shifts were measured in D_2O solvent containing internal 3-(trimethylsilyl)propanesulfonic acid sodium salt at 40°. [b] The values were calculated from the equation $\delta_{C=CH} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$ using the values of Matter[18] and *Toby*[19] and $Z_{gem} = 1.00$, $Z_{cis} = 0.65$, and $Z_{trans} = 0.30$ for R_3N^+.

derivative **8b** showed an upfield shift for the vinylic proton (δ 7.00) similar to that observed in the methyl propiolate–triethylamine and tri-*n*-butylamine adducts.

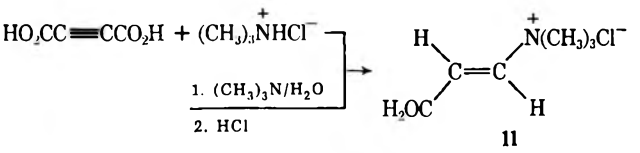
The cis stereochemistry of **8** was supported by comparison of the calculated *vs.* observed chemical shift of the olefinic proton (*i.e.*, δ 7.00 and 7.25 calculated for the cis and trans isomers, respectively) and the presumed similarity in mechanism for the formation of the salts obtained with trialkylammonium halides and methyl propiolate. The reaction of dimethyl acetylenedicarboxylate with triethylammonium chloride in methylene chloride has been reported[25] to yield dimethyl (diethylamino)maleate (**9**) as the sole product. It



appears in this case that the chloride salt of **8b** is formed initially and eliminates ethyl chloride producing **9**. When a *solution* of **8b** was refluxed in methylene chloride for 4 hr, the only product isolated was **9** in 93% yield.

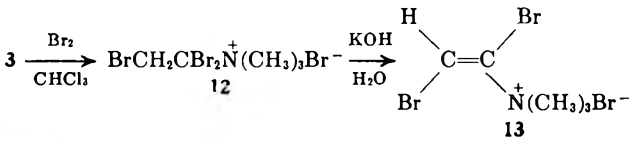
The nmr absorption for the ethylenic proton in **9** at δ 4.52 was in good agreement with that of δ 4.53 reported for dimethyl (dimethylamino)maleate (**10**).[26] The solubility of **8b** in methylene chloride may account for the facile elimination of ethyl chloride, since **10** was not formed when a suspension of insoluble **8a** was refluxed in methylene chloride for 24 hr.

When acetylenedicarboxylic acid reacted with trimethylammonium chloride under conditions similar to those described for the diester, decarboxylation occurred yielding only *trans*-carboxyvinyltrimethylammonium chloride (**11**). Salt **11** was also prepared[27] by the addi-



tion of aqueous trimethylamine to methyl propiolate followed by acidification with HCl.

Bromination and Dehydrobromination of Monosubstituted Salts.—Several additional disubstituted vinyltrimethylammonium salts (Table III) were prepared by bromination of the monosubstituted vinyl derivative in chloroform followed by dehydrobromination with base. Bromination of **3** in refluxing chloroform gave 62% yield of 1,1,2-tribromoethyltrimethylammonium bromide (**12**). Dehydrobromination of **12** with aqueous KOH produced (*E*)-1,2-dibromovinyltrimethylammonium bromide (**13**) as the only isolable product.



(21) The difficult isolation of ethynyltriethylammonium bromide and chloride from dibromoethylene and triethylamine in ether has recently been reported.[22]

(22) R. Tanaka and S. I. Miller, *J. Org. Chem.*, **36**, 3856 (1971).

(23) S. I. Miller, *J. Amer. Chem. Soc.*, **78**, 6091 (1956).

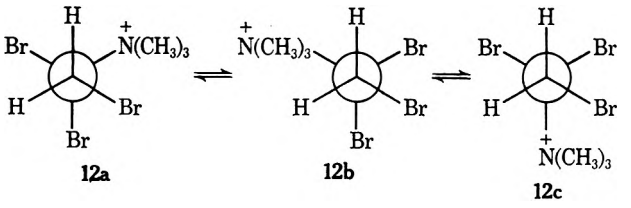
(24) W. E. Truce and J. A. Simms, *ibid.*, **78**, 2756 (1956).

(25) R. J. Alaimo and D. G. Farnum, *Can. J. Chem.*, **43**, 700 (1965).

(26) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).

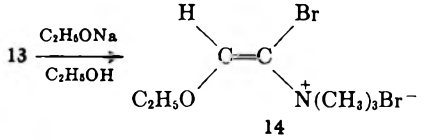
(27) Private communication from Professor J.-M. Lehn, Strasbourg. The procedure is similar to that described for ethoxyacetylene and aqueous trimethylamine.[2]

The chemical shift of the vinyl proton in **13** at δ 8.12 exhibited greater shielding than that predicted by the use of the nmr shielding parameters, possibly because of breakdown in the shielding mechanism when one of the substituents is forced out of coplanarity by steric crowding. Assuming trans addition of bromine to **3**, the resulting highly substituted ethane experiences large steric interactions in all three of its conformations. Trans elimination of HBr from **12a** or **12c** would yield



12a **12b** **12c**

(*E*)-**13**, whereas (*Z*)-**13** is expected from **12b**. The infrared spectrum of **13** showed a weak absorption at 1603 cm^{-1} indicative of an *E* configuration. Additional support for the *E* configuration of **13** came from its reaction with a stoichiometric amount of ethanolic KOH, which produced (*E*)-1-bromo-2-ethoxyvinyltrimethyl-

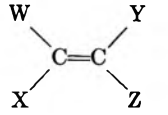


14

ammonium bromide (**14**). Analysis of the calculated chemical shifts for the six possible isomers (Table IV)

TABLE IV

CALCULATED CHEMICAL SHIFTS

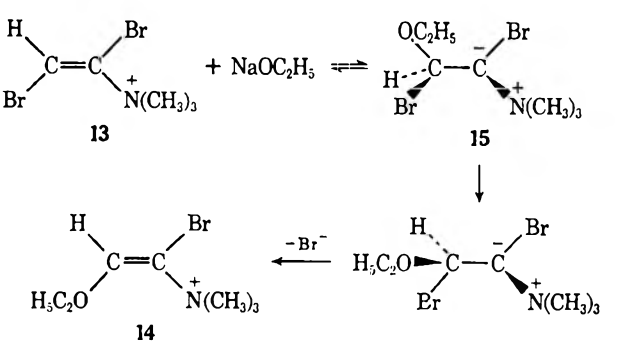


W	X	Y	Z	Calcd δ[a]	Obsd δ[b]
H	Br	C_2H_5O	$N(CH_3)_3$	5.56	
H	Br	$N(CH_3)_3$	C_2H_5O	5.76	
H	C_2H_5O	Br	$N(CH_3)_3$	7.23	7.25
H	C_2H_5O	$N(CH_3)_3$	Br	7.70	
Br	C_2H_5O	H	$N(CH_3)_3$	5.49	
Br	C_2H_5O	$N(CH_3)_3$	H	5.73	

[a] References 18 and 19 and, for R_3N, Z_{gem} = 1.00, Z_{cis} = 0.65, and Z_{trans} = 0.30. [b] In D_2O.

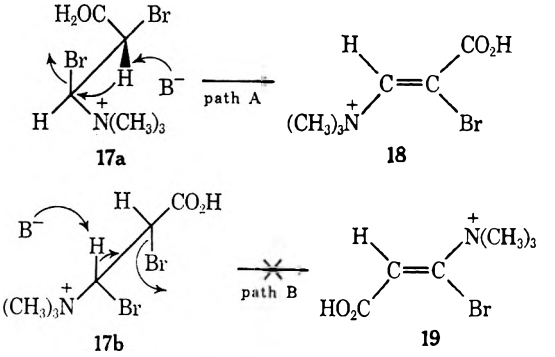
formed by either an addition–elimination or elimination–addition mechanism indicated the *E* configuration for **14**. The nmr spectrum of **14** exhibited a vinylic proton absorption at δ 7.25 compared to the calculated value of δ 7.23. The *E* configuration of **14** is consistent with an addition–elimination mechanism[28] involving addition of ethoxide ion to the 2-carbon atom producing a ylide-type intermediate (**15**). Clockwise rotation (minimal eclipsing) of **15** followed by fast C–Br bond breaking would yield **14** with retention of configuration. The *Z* isomer of **13** would be expected to undergo a facile elimination of HBr, producing an intermediate bromoethynyltrimethylammonium salt which would add C_2H_5OH to yield products whose calculated olefinic chemical shift would be δ <6.0 ppm (Table IV).

A second bromine-substituted vinyltrimethylammonium salt was prepared starting from *trans*-HO_2-



13 **15** **14**

$CCH{=}CHN(CH_3)_3^+Br^-$ (**16**). 2-Carboxy-1,2-dibromoethyltrimethylammonium bromide (**17**) was prepared in 82% yield from **16** and bromine in refluxing chloroform. The use of methanol[9] in place of chloroform yielded surprisingly only the methyl ester of **16** (**1a**). Elimination of HBr with methanolic KOH produced the *E* isomer of 1-bromo-2-carboxyvinyltrimethylammonium bromide (**18**). Decarboxylative debromination to *trans*-bromovinyltrimethylammonium bromide was not observed. Assuming a trans coplanar elimination of HBr by methoxide ion, path A would be favored leading to olefin because of the relative proton acidities of **17a** and **17b**.[29] If there was any contribution by an Elcb mechanism, rotamer **17a** would also be favored to yield olefin because of the enhanced stabilization by the carboxylate ion *vs.* that of an ylide intermediate in **17b**. The observed chemical shift of the vinyl proton in **18** at δ 8.06 was also in good agreement with the calculated value of δ 8.21 compared to that of δ 7.42 for isomer **19**.



17a **18**

17b **19**

Experimental Section

All melting points are uncorrected. Proton nmr spectra were recorded on a Varian Associates A-60 nmr spectrophotometer using D_2O as the solvent, unless noted otherwise. Chemical shifts are expressed in δ (parts per million downfield) from an internal standard of 3-(trimethylsilyl)propanesulfonic acid sodium salt. The infrared spectra were recorded on a Perkin-Elmer 137 infracord and the elemental analyses were performed by the Analytical Laboratories of the Central Research Department, Du Pont Company.

Materials.—Solutions of the trialkylammonium salts were prepared *in situ* by neutralization of an aqueous solution of the corresponding tertiary amine with either 6 *N* HCl or 50% aqueous HBr at 0°.

Dimethyl acetylenedicarboxylate, triethylamine, tri-*n*-butylamine, pyridine hydrochloride, and trimethylamine hydrochloride were obtained from Eastman Organic Chemicals. Methyl propiolate and 25% aqueous trimethylamine were purchased from Aldrich Chemical Co.

Determination of the Shielding Increments for the Trialkyl-

(28) G. Modina, *Accounts Chem. Res.*, **4**, 73 (1971).

(29) W. von E. Doering and K. C. Schreiber, *J. Amer. Chem. Soc.*, **77**, 514 (1955); W. von E. Doering and A. Kentaro, *ibid.*, **77**, 521 (1955); W. Schlenk and J. Holtz, *Chem. Ber.*, **50**, 274 (1917).

ammonium Group.—The shielding increments for the trialkylammonium group were obtained by first calculating the chemical shift of the vinyl protons in the parent structure using the shielding parameters of Matter[18] and Tobey[19] and subtracting these values from the observed chemical shift of the olefinic protons in the corresponding substituted vinyltrialkylammonium salt. Depending upon the configuration of the proton relative to the trialkylammonium group, a value for a cis, trans, or gem increment was obtained. Eighteen monosubstituted compounds were analyzed in this manner. The average value of these increments was $Z_{gem} = 1.00 \pm 0.22$, $Z_{trans} = 0.30 \pm 0.15$, and $Z_{cis} = 0.65 \pm 0.18$. These values compared favorably with the shielding increments obtained using only ethylene (δ 5.25) and vinyltrimethylammonium bromide.[30] The calculated values using the latter method were $Z_{gem} = 1.25$, $Z_{trans} = 0.29$, and $Z_{cis} = 0.51$.

trans-**Alkoxycarbonylvinyltrialkylammonium Salts (1a–e). General Method of Preparation.**—A solution of 38 mmol of the trialkylammonium halide salt in 20 ml of water containing 2 drops of the corresponding tertiary amine was treated in one portion at 25° with 46 mmol of the acetylenic ester dissolved in 10 ml of dioxane. An exothermic reaction occurred (ΔT 15–20°). The solution was heated at 35° for 15 hr followed by removal of solvents under vacuum (<40°). The residue was treated with acetonitrile (15 ml) and the product was filtered. Recrystallization from methanol–ether gave pure crystalline salts. The salts prepared by this method are summarized in Table I.

trans-**Methoxycarbonylvinylpyridinium Chloride (2).**—A mixture consisting of 4.3 g (38 mmol) of pyridine hydrochloride, 2 drops of pyridine, 3.3 g (37 mmol) of methyl propiolate, 20 ml of water, and 10 ml of dioxane was heated at 40–45° for 20 hr. The solvents were removed under vacuum to yield an orange semisolid. Acetonitrile (15 ml) was added and the product was filtered. Recrystallization from acetonitrile yielded 1.6 g (21%) of **2**: mp 105–106°; nmr (220 MHz, D_2O) δ 3.77 (s, OCH_3, 3 H), 6.92 (d, β-vinyl H, 1 H), and 8.24 (d, α-vinyl H, 1 H) with $J = 14.5$ Hz. The aromatic pyridinium protons had δ 8.60 (t, para H, 1H), 8.98 (d, ortho H, 2 H), and 8.11 (overlapping dd, meta H, 2 H).

1-Bromovinyltrimethylammonium Bromide (3) with Methanolic Sodium Methoxide.—Three grams (0.012 mol) of 1-bromovinyltrimethylammonium bromide in 150 ml of methanol was treated with a solution of sodium methoxide (0.66 g in 25 ml of methanol, 0.012 mol) at 25°. After 20 hr, the solution was neutral and a small amount of NaBr was observed. The solvent was removed to yield 3.6 g of a white solid (product and NaBr). After drying *in vacuo* over P_2O_5, the nmr spectrum was recorded in DMSO-d_6. The spectrum was consistent for two isomeric products. There were two closely spaced singlets for the $(CH_3)_3N^+$– group at δ 3.42 and 3.46, and a set of singlet absorptions at δ 3.84 and 3.89 for a CH_3O group. There were two sets of AB patterns for the vinyl protons, the first at δ 4.61 and 4.99 with $J = 6.4$ Hz, and the second at δ 5.58 and 6.56 with $J = 5.0$ Hz. The solid was extracted with ethanol and the solvent was removed *in vacuo*. Recrystallization from methanol–ether yielded 2.1 g (87%), mp 170–190°. The spectrum (DMSO-d_6) was similar to that recorded before recrystallization. The elemental analysis indicated two isomeric products.

Anal. Calcd for $C_5H_{14}NOBr$: C, 36.78; H, 7.22; N, 7.15. Found: C, 36.45; H, 6.71; N, 7.07.

The solid was stripped with boiling acetonitrile and an equal volume of ether was added to the filtrate. The precipitate was filtered and dried under vacuum over P_2O_5. The nmr (DMSO-d_6) spectrum indicated a single product attributed to **4a** with absorptions at δ 3.45 [s, $(CH_3)_3N^+$, 9 H], 3.85 (s, CH_3O, 3 H), and 4.60 and 4.98 (d, vinyl, 2 H) with $J = 6.5$ Hz.

1-Bromovinyltrimethylammonium Bromide (3) with Ethanolic Potassium Hydroxide.—A suspension of 15 g (0.061 mol) of 1-bromovinyltrimethylammonium bromide (**3**) in 350 ml of ethanol was treated dropwise with an ethanolic KOH solution (4.1 g of KOH in 50 ml, 0.061 mol) at 25°. The insoluble KBr was filtered, and an equal volume of ether was added to the filtrate. The product was filtered and purified by mixed solvent recrystallization employing methanol–ether to give 8.0 g (62%) of a mixture consisting of two isomeric products, 1-ethoxyvinyl- (**4b**) and *cis*-ethoxyvinyltrimethylammonium bromide (**5b**), ir (Nujol) 1672 cm^{-1} (C=C). The nmr spectrum of the original mixture before purification indicated the isomeric ratio to be *ca.* 3:1. Isomer **4b** (major) had δ 1.37 (t, CH_3, 3 H), 4.11 (q, CH_2, 2 H), 3.52 [s, $(CH_3)_3N^+$, 9 H], and an AB pattern at δ 4.99 and 4.61 (d, vinyl, 2 H) with $J = 6.5$ Hz. Isomer **5b** (minor) had δ 1.31 (t, CH_3, 3 H), 4.18 (q, CH_2, 2 H), 3.52 [s, $(CH_3)_3N^+$, 9 H], and an AB pattern at 5.61 and 6.54 (d, vinyl, 2 H) with $J = 5.0$ Hz.

Anal. Calcd for $C_7H_{16}NBrO$ (mixture): C, 40.02; H, 7.62; Br, 38.09. Found: C, 39.37; H, 7.31; Br, 37.69.

cis-**1,2-Bis(methoxycarbony)vinyltrimethylammonium Bromide (8a).**—Dimethyl acetylenedicarboxylate (5.4 g, 38.0 mmol) in 10 ml of dioxane was added in one portion at 25° to a solution consisting of 5.3 g (38.0 mmol) of trimethylammonium bromide and 3 drops of triethylamine in 25 ml of water. The temperature rose to 35° and the reaction mixture was subsequently heated at 35° for 15 hr. The solvents were removed *in vacuo* (<40°). The brown, tacky solid was stirred with acetonitrile (35 ml) and the mixture was filtered. Ether was added to the filtrate to produce additional product. Mixed solvent recrystallization using acetonitrile–ether gave 5.9 g (56%) of **8b**: mp 108°; ir (Nujol) 3448 (H_2O), 1730 (unsymmetrical doublet, C=O), and 1645 cm^{-1} (C=C); nmr δ 3.85, 3.99 (s, CH_3O_2C, 6 H), 1.35 (t, CH_3, 9 H), 3.73 (q, CH_2, 6 H), and 7.00 (s, vinyl, 1 H).

Anal. Calcd for $C_{12}H_{22}NO_4Br \cdot {}^1/_2H_2O$: C, 43.28; H, 6.96; N, 4.21. Found: C, 43.46; H, 7.39; N, 3.81.

Dimethyl (Diethylamino)maleate (9).—A solution of 1.5 g (4.5 mmol) of **8b** in 50 ml of dry methylene chloride was refluxed for 4 hr. The solvent was removed to yield 0.9 g (93%) of a light-yellow oil. Comparison of its ir and nmr spectra with those of an authentic sample prepared from dimethyl acetylenedicarboxylate and diethylamine in methanol indicated identical properties: ir (neat) 1754, 1701 (C=O), and 1587 cm^{-1} (C=C); nmr (CCl_4) δ 6.18, 6.46 (s, CH_3O, 6 H), 3.17 (q, CH_2, 4 H), 1.17 (t, CH_3, 6 H), and 4.52 (s, vinyl, 1 H).

trans-**Carboxyvinyltrimethylammonium Chloride (11) from Acetylenedicarboxylic Acid.**—A solution consisting of 4.3 g (38 mmol) of acetylenedicarboxylic acid, 3.7 g (37 mmol) of trimethylammonium chloride, 15 ml of dioxane, and 15 ml of water was heated at 45° for 20 hr. The solvents were removed under vacuum to yield an oil. Addition of acetonitrile to the oil yielded a tan solid (2.2 g, 36%). Mixed solvent recrystallization from methanol–ether gave *trans*-carboxyvinyltrimethylammonium chloride (**11**): mp 173–174° dec; ir (Nujol) 1706 (C=O) and 1667 cm^{-1} (C=C); nmr δ 3.42 [s, $(CH_3)_3N^+$, 9 H], 6.58 and 7.40 (d, vinyl, 2 H) with $J = 14.5$ Hz.

Anal. Calcd for $C_6H_{12}NO_2Cl$: C, 43.67; H, 7.24; N, 8.46. Found: C, 43.55; H, 7.34; N, 8.37.

1,1,2-Tribromoethyltrimethylammonium Bromide (12).—A mixture of 49 g (0.20 mol) of **3** and 60 g (0.40 mol) of bromine in 320 ml of chloroform was stirred vigorously at 50° for 18 hr. Chloroform and excess bromine were removed on a rotary evaporator to yield a red syrup. The viscous oil was stirred with 200 ml of acetonitrile and filtered (20.7 g). Ether (500 ml) was added to the filtrate to produce 27.8 g of additional product (62% crude product). The crude product was purified by mixed solvent recrystallization from trifluoroacetic acid–ether: mp 154–156°; nmr (CF_3CO_2H) δ 4.72 [s, $(CH_3)_3N^+$, 9 H], and 3.79 (s, CH_2, 2 H).

Anal. Calcd for $C_5H_{11}NBr_4$: C, 14.86; H, 2.74; N, 3.47. Found: C, 14.81; H, 2.65; N, 3.26.

(*E*)-**1,2-Dibromovinyltrimethylammonium Bromide (13).**—A 50-ml portion of a 1.24 *M* aqueous KOH solution was added dropwise at 25° to a suspension of 25 g (0.062 mol) of **12** in 600 ml of water. The homogeneous solution was evaporated to dryness with dry air over a 2-day period. The residual white crystals were recrystallized from ethanol to yield 13.7 g (70.6%) of **13**: mp 138–139°; ir (Nujol) 1603 cm^{-1} (very weak) (trans CBr=CBr); nmr δ 8.12 (s, vinyl 1 H), 3.58 [s, $(CH_3)_3N^+$, 9 H].

Anal. Calcd for $C_5H_{10}NBr_3$: C, 18.53; H, 3.08; N, 4.32. Found: C, 18.50; H, 3.17; N, 4.41.

(*E*)-**1-Bromo-2-ethoxyvinyltrimethylammonium Bromide (14).**—A suspension of 3 g (9.2 mmol) of **13** in 25 ml of ethanol was treated with 15 ml of a 0.6 *M* ethanolic KOH solution. After 0.5 hr, the KBr was filtered. Ether (25 ml) was added to the filtrate to produce 0.35 g of unreacted **13**. The second filtrate was treated with 100 ml of ether to precipitate a leaflike crystalline solid. The product was filtered and dried *in vacuo* over P_2O_5 to yield 1.3 g (50%) of **14**: mp 115° dec; ir (Nujol) 1661 cm^{-1} (C=C); nmr (DMSO-d_6) δ 1.42 (t, CH_3, 3 H), 3.50 [s, $(CH_3)_3N^+$, 9 H], 4.96 (q, CH_2, 2 H), and 7.25 (s, vinyl, 1 H).

(30) M. Ohtsuru and K. Tori, *Chem. Commun.*, 750 (1966).

Anal. Calcd for $C_7H_{15}NOBr_2$: C, 29.08; H, 5.18; N, 4.84. Found: C, 29.26; H, 5.33; N, 4.67.

trans-**Carboxyvinyltrimethylammonium Bromide (16).**—To a stirred mixture of 30 g (0.36 mol) of methyl propiolate in 80 ml of water was added with cooling 90 g of 25% aqueous trimethylamine solution at 25°. The dark mixture was stirred for an additional 3 hr, followed by removal of water and excess trimethylamine under vacuum (30–40° bath). The brown residue was dissolved in 200 ml of 48% aqueous HBr. The water and excess acid were removed on an evaporator. Recrystallization of the dark residue from methanol–ether yielded 44 g (59%) of **16**: mp 120° dec; ir (Nujol) 1724 (C=O) and 1661 cm^{-1} (C=C); uv max (CH_3OH) 208.5 nm (ϵ 2160); nmr (D_2O) δ 3.49 [s, $(CH_3)_3N$, 9 H], 6.61 and 7.49 (d, vinyl, 2 H) with J = 13.8 Hz.

Anal. Calcd for $C_6H_{12}O_2NBr$: C, 34.30; H, 5.72; N, 6.66. Found: C, 34.96; H, 6.09; N, 6.89.

Tetrafluoroborate Salt of 16a.—*trans*-Carboxyvinyltrimethylammonium tetrafluoroborate (**16a**) was prepared in an analogous fashion to that described for the bromide salt. Recrystallization from methanol–ether gave mp 135–136°; ir (Nujol) 1724 (C=O), 1661 (C=C), and 1053 cm^{-1} (BF_4^-); nmr δ 3.20 [s, $(CH_3)_3N^+$, 9 H], 6.41 and 7.22 (d, vinyl, 2 H) with J = 13.8 Hz.

Anal. Calcd for $C_6H_{12}NO_2BF_4$: C, 33.13; H, 5.76; N, 6.45; F, 35.25. Found: C, 33.63; H, 5.27; N, 6.55; F, 34.80.

Bromination of 16 in Methanol.—A solution consisting of 2.2 g (11.0 mmol) of **16** in 100 ml of methanol was treated dropwise with 8 g (50.0 mmol) of bromine in 40 ml of methanol at 35°. After the solution was stirred for 20 hr at 35–40°, the volatiles were removed under water aspirator vacuum. The residual red oil was redissolved in 100 ml of methanol, and an equal volume of ether was added. The precipitated yellow solid was again dissolved in methanol and treated with ether to yield 2.4 g (96%) of *trans*-methoxycarbonylvinyltrimethylammonium bromide (**1a**): mp 164–165°; ir (Nujol) 1658 (C=C) and 1715 cm^{-1} (C=O); nmr δ 3.37 [s, $(CH_3)_3N^+$, CH], 3.86 (s, OCH_3, 3 H), 6.63 and 7.47 (d, vinyl, 2 H) with J = 13.9 Hz.

Anal. Calcd for $C_7H_{14}NO_2Br$: C, 37.51; H, 6.25; N, 5.98; Br, 35.69. Found: C, 37.96; H, 6.40; N, 5.77; Br, 35.79.

2-Carboxy-1,2-dibromoethyltrimethylammonium Bromide (17).—A mixture of 44 g (0.21 mol) of **16** and 50 g (0.33 mol) of bromine in 250 ml of chloroform was stirred vigorously at 45° for 24 hr. The yellow solid was filtered, washed with 200 ml of acetonitrile, and purified by recrystallization from methanol to yield 62 g (82%) of **17**: mp 162–163°; nmr δ 3.58 [s, $(CH_3)_3N^+$, 9 H], 5.86 (d, β-CH, 1 H), and 6.57 (d, α-CH, 1 H) with J = 1.5 Hz.

Anal. Calcd for $C_6H_{12}NO_2Br_3$: C, 19.47; H, 3.26; N, 3.79; Br, 64.82. Found: C, 19.87; H, 3.37; N, 3.87; Br, 65.25.

Dehalogenation of 17 with Potassium Carbonate.—Five grams (0.014 mol) of **17** in 100 ml of water was treated with a potassium carbonate solution (0.94 g in 25 ml of water, 0.0068 mol) at 45–50°. Carbon dioxide was evolved during the addition. The solution was then heated at 60° for 2 hr. The water was removed under vacuum and the residual solid was extracted with ethanol. An equal volume of ether was added to the cooled extract to yield 2.2 g (55%) of (*Z*)-2-bromo-2-carboxyvinyltrimethylammonium bromide (**18**): mp 187° dec; ir (Nujol) 3401 (–OH), 1724 (C=O), and 1631 cm^{-1} (C=C); uv max (CH_3OH) 216 nm; nmr δ 8.06 (s, vinyl, 1 H), and 3.68 [s, $^+N(CH_3)_3$, 9 H].

Anal. Calcd for $C_6H_{11}O_2NBr_2$: C, 24.93; H, 3.81; N, 4.84. Found: C, 24.06; H, 3.58; N, 4.44.

Registry No.—**1a**, 40463-91-0; **1b**, 40463-92-1; **1c**, 40463-93-2; **1d**, 40463-94-3; **1e**, 40463-95-4; **2**, 40463-96-5; **3**, 14800-49-8; **4a**, 40463-98-7; **4b**, 14800-51-2; **5a**, 40464-00-4; **5b**, 40464-01-5; **8a**, 40550-39-8; **8b**, 40464-02-6; **9**, 996-85-0; **11**, 40464-04-8; **12**, 40464-05-9; **13**, 40464-06-0; **14**, 40464-07-1; **16**, 40464-08-2; **16a**, 40464-09-3; **17**, 40464-10-6; **18**, 40464-11-7; methyl propiolate, 922-67-8; 2-chloroethyl propiolate, 40464-12-8; trimethylammonium chloride, 593-81-7; trimethylammonium bromide, 2840-24-6; triethylammonium bromide, 636-70-4; tributylammonium bromide, 37026-85-0; pyridine hydrochloride, 628-13-7; dimethyl acetylenedicarboxylate, 762-42-5; acetylenedicarboxylic acid, 142-45-0; bromine, 7726-95-6; 1-bromovinyltrimethylammonium tetrafluoroborate, 40464-14-0; hydrogen tetrafluoroborate, 16872-11-0.

The Stereochemistry of 1-Alkyl-2-acyl-1,2-dihydroisoquinaldonitriles[1]

HARRY W. GIBSON[2]

Chemicals and Plastics Division, Union Carbide Corporation, Tarrytown, New York 10591

Received April 2, 1973

The pmr spectra and in particular the anisochronism (chemical shift differences) of diastereotopic groups (methyl or methylene) in a series of 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles (**3** and **4**) have been studied as a function of substituent, temperature, and solvent. On this basis, stereochemical analysis of these systems was accomplished. The amide group configuration is the same in all cases and has been established. The ring configuration is believed to be the one in which the 1-alkyl group is pseudoaxial. In the cases where the 1-alkyl group is isopropyl, only a single conformer about the ring–alkyl bond is observed and on the basis of chemical shift arguments has been assigned. In the cases where the 1-alkyl substituent is either isobutyl or benzyl, more than one such conformer may be present as indicated by spectral temperature dependence; the predominant conformer is tentatively assigned.

Though the preparation of 1-alkyl derivatives of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) (**1**) has been well documented,[3-9] only a few examples of these compounds (**3**) have been isolated and characterized.[5-7]

Several interesting stereochemical questions, therefore, remain unanswered for these systems. Among them are those concerning the ring conformation of the 1 substituent, the configuration of the amide moiety, and the conformation about the ring–alkyl bond. Additionally, in recent years there has been much interest in the anisochronism (chemical shift difference) of diastereotopic groups.[10]

In the interest of addressing these questions in the context of the relatively large anisochronisms[1] of the diastereotopic groups, a detailed study of these compounds was undertaken.

(1) A portion of this work was previously communicated: *Tetrahedron Lett.*, 5549 (1968), and Abstracts, 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, p O–008.

(2) Rochester Research Center, Xerox Corporation, 800 Phillips Road, Webster, N. Y. 14580

(3) F. D. Popp in "Advances in Heterocyclic Chemistry," Vol. 9, A. R. Katritsky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1968, p 1.

(4) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(5) F. D. Popp and J. M. Wefer, *J. Heterocycl. Chem.*, **4**, 183 (1967).

(6) J. Sam and A. J. Bej, *J. Pharm. Sci.*, **56**, 1441 (1967).

(7) J. L. Neumayer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Lett.*, 3107 (1967).

(8) B. C. Uff and J. R. Kershaw, *J. Chem. Soc. C*, 666 (1969).

(9) M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969).

(10) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

Results

The pertinent parts of the pmr spectra of series **3** and **4**[11] are recorded in Tables I–IV. Two signals were observed only for the diastereotopic groups indicated.

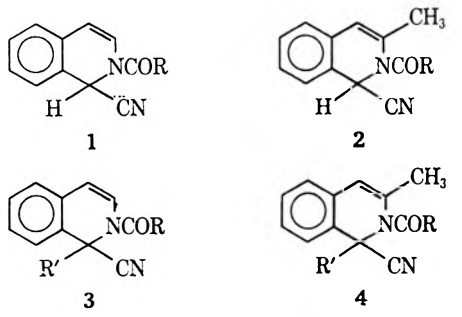
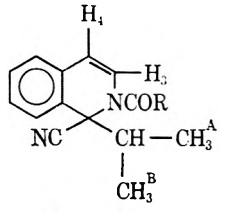


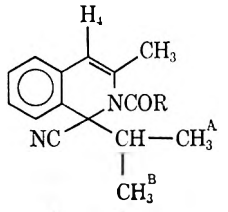
TABLE I
PMR SPECTRA OF
1-ISOPROPYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$



Compd	R	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{CH}	δ_{H_3}	δ_{H_4}
3p	OCH_2CH_3	0.83	1.16	0.33	2.75	7.08	5.82
3f	o-$C_6H_4CH_3$	0.87	1.18	0.31	2.94	6.30	5.67
3d	o-C_6H_4Cl	0.92	1.22	0.30	3.00	6.34	5.79
3g	p-$C_6H_4CH_3$	0.88	1.17	0.29	2.94	6.63	5.86
3a	CH_3	0.80	1.08	0.28	2.74	6.78	5.90
3e	p-C_6H_4Cl	0.88	1.16	0.28	2.92	6.57	5.92
3b[a]	C_6H_5	0.92	1.20	0.28	2.93	6.48	5.77
3b	C_6H_5	0.89	1.16	0.27	2.91	6.52	5.81
3c	$CH(CH_3)_2$	0.83	1.10	0.27	2.74	6.89	5.96

[a] 6,7-Dimethoxy derivative.

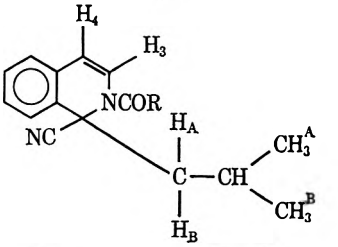
TABLE II
PMR SPECTRA OF 1-ISOPROPYL-2-ACYL-
3-METHYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$



Compd	R	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{CH}	$\delta_{3\text{-}CH_3}$	δ_{H_4}
4f	α-$C_{10}H_7$	0.91	1.38	0.46	2.60	1.41	6.04
4e	o-$C_6H_4CH_3$	0.87	1.29	0.42	2.58	1.56	6.08
4d	o-C_6H_4Cl	0.91	1.32	0.41	2.62	1.68	6.22
4c	$CH(CH_3)_2$	0.84	1.24	0.40	2.54	2.29	6.44
4h	OCH_2CH_3	0.82	1.22	0.40	2.55	2.28	6.22
4b	C_6H_5	0.87	1.26	0.39	2.58	1.68	6.14
4i	$OCH_2C_6H_5$	0.81	1.19	0.38	2.5	2.18	6.17
4a	CH_3	0.82	1.19	0.37	2.50	2.30	6.40

Examining first the data of Table I, one notes the relatively high anisochronisms of the isopropyl methyl groups of **3**, R′ = *i*-Pr.[12] However, the magnitude of the anisochronism does not appear to be greatly dependent upon the nature of the *N*-acyl group, R. The results for series **4** as shown in Table II exhibit a somewhat wider range of anisochronism and these, in contrast, are dependent upon the acyl group, R. In fact, the dependence appears to be steric in nature. This can be rationalized in terms of a steric buttressing effect by the 3-methyl substituent on the acyl group R, resulting in a greater steric interaction with the 1-isopropyl group, and thus differentially affecting the chemical shifts of the methyl groups. This effect can be seen clearly by comparison of corresponding pairs of series **3** and **4**, *e.g.*, **3e** with **4e** and **3d** with **4d**.

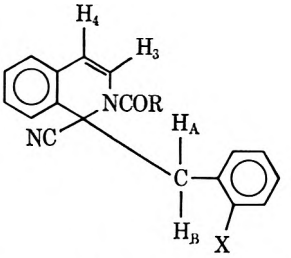
TABLE III
PMR SPECTRA OF
1-ISOBUTYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$



Compd	R	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
3h	CH_3	1.98	2.57	0.59	0.76	0.78	0.02	6.66	5.68
3j	o-$C_6H_4CH_3$	2.17	2.73	0.56	0.84	0.87	0.03	6.32	5.66
3i	C_6H_5	2.23	2.50	0.27	0.78	0.94	0.16	6.53	5.80
4g	α-$C_{10}H_7$				0.95	1.10	0.15	1.46[a]	6.04

[a] 3-CH_3 resonance.

TABLE IV
PMR SPECTRA OF
1-BENZYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$



Compd	R	X	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	δ_{H_3}	δ_{H_4}
3k	CH_3	H	3.28	3.74	0.45	6.40	5.47
3l	o-$C_6H_4CH_3$	H	3.56	3.92	0.36	6.16	5.45
3m	C_6H_5	H	3.51	3.73	0.22	6.35	5.54
3n[a]	C_6H_5	I	3.79	3.97	0.17	6.54	5.72
3o	C_6H_5	CH_3	3.63	3.63	0.00	6.43	5.68

[a] Through courtesy of J. L. Neumeyer, Northeastern University, Boston, Mass. [J. L. Neumeyer, H. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.*, **34**, 3786 (1969)].

The isobutyl derivatives listed in Table III possess pmr spectra containing ABX patterns attributed to the CH_2CH group. A unique inverse variation of $\Delta\delta_{AB}$ and $\Delta\delta_{CH_3}$ with the *N*-acyl group, R, occurs. For **3h** and **3j** large $\Delta\delta_{AB}$'s and small $\Delta\delta_{CH_3}$'s are displayed. On the other hand, **3i** reveals a relatively small $\Delta\delta_{AB}$ and large $\Delta\delta_{CH_3}$. A large $\Delta\delta_{CH_3}$ is also discernible for **4g**, but $\Delta\delta_{AB}$ could not be obtained directly. The anisochronisms ($\Delta\delta_{AB}$) for the benzyl derivatives **3k–o** (Table IV) are arrayed in a pattern analogous to that in the isobutyl compounds. These results do not appear to be sterically related to the *N*-acyl group R, however, since in both the isobutyl and benzyl deriva-

(11) H. W. Gibson, *J. Heterocycl. Chem.*, **7**, 1169 (1970).

(12) The largest reported isopropyl methyl anisochronisms to date are 0.73[13] and 0.75 ppm.[14] Generally much smaller values (0.1 ppm) are observed.

(13) M. Katjar and L. Radics, *Chem. Commun.*, 784 (1967).

(14) H. Kessler and B. Zeeh, *Tetrahedron*, **24**, 6825 (1968).

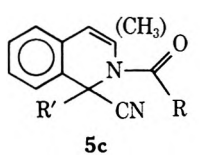
tives the acetyl compounds more closely resemble the toluyl than does the benzoyl; compare **3h**, **3j**, and **3i**, also **3k**, **3l**, and **3m**. Note also that in **3o** $\Delta\delta_{AB}$ is zero. It has been reported[14] that in 1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile the benzylic protons are equivalent at δ 3.68.

Discussion

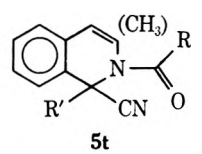
Nitrogen Inversion.—The umbrella-like inversion of nitrogen is generally a facile, low-energy (few kcal/mol) process even for amides.[15] Therefore, in these compounds two invertomers are present. While interconversion is rapid at the temperatures used in this study owing to the low energy of activation, the relative contributions of the invertomers will be dependent on the total energy content of each. For the sake of simplicity let us consider an average situation in which the three groups bonded to nitrogen are in a plane, as would be the case for equal energy invertomers, but let us bear in mind that the average conformation may be biased toward one invertomer.

Ring Inversion.—There is also a possibility of ring inversion in the title compounds. Ring inversion would result in transposition of pseudoaxial and pseudoequatorial groups at the 1 position (Figure 1). When the groups involved are of different conformational energy, this ring inversion would be manifested by a temperature-dependent equilibrium, and this in turn would normally result in changes in pmr spectra. In view of the lack of significant change in the pmr signals in these systems from low (−50°) to high (150°) temperatures (see below), it is concluded that a single ring form or two ring conformations of equal energy are present. The latter possibility is deemed highly unlikely for the following reason. It is known from dihydronaphthalene systems that interactions of equatorial groups at the 1 position with the peri (8) proton is severe and because of this the conformationally larger 1 substituent assumes the axial position.[16] From conformational energies (A values) determined in cyclohexyl systems, the effective bulk of alkyl groups such as those used in this study is known to be much greater than that of the cyano group.[17] In light of these facts the cyano group would be expected to occupy the more hindered pseudoequatorial position. The absence of a temperature effect is interpreted in terms of this being a very highly favored conformation. The possibility of coincidental isochronism of protons associated with two different ring conformers seems remote.

Amide Configuration.—Another factor which must be taken into account is the possibility of cis–trans amide configurational isomerism of the type shown in structures **5c** and **5t**. This type of isomerism is well



5c



5t

(15) P. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).

(16) M. J. Cooks, A. R. Katritsky, F. C. Pennington, and B. M. Semple, *J. Chem. Soc. B*, 523 (1969); D. C. Ayres and J. A. Harris, *Chem. Commun.*, 1135 (1969).

(17) E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 440–442.

RING CONFORMATIONS

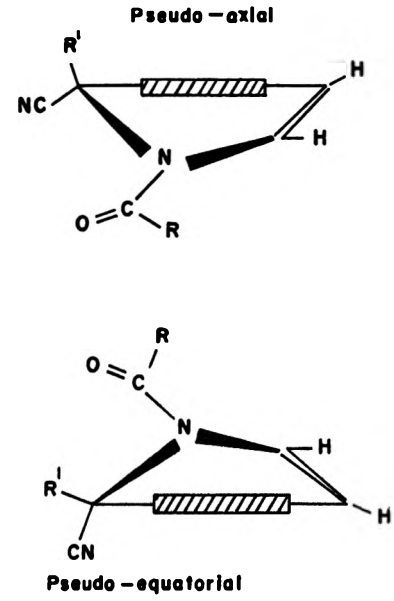


Figure 1.—Ring conformations of 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles.

known and has been extensively studied.[18–25] Generally, the activation energies are relatively large (15–20 kcal/mol), and hence at normal temperatures interconversion is slow enough that signals for both forms are observable in pmr spectra. In fact, in at least one case the isomeric forms have been isolated.[22]

The fact that no signal doubling for protons other than those in diastereotopic environments occurs in the compounds under examination at room temperature indicates the presence of a single isomer or that the activation energy is low enough to allow rapid interconversion of the two. (The possibility of isochronism of all other protons in the two isomers is very remote.) The spectra of compounds **3b**, **3i**, **3j**, and **3k** were obtained at a temperature of −50°; there was no evidence of a "freezing out" of two isomeric forms, *i.e.*, no signal doubling occurred. The spectrum of **3b** was determined in a variety of solvents (Table V) and

TABLE V

SOLVENT DEPENDENCE OF PMR SPECTRUM OF 1-ISOPROPYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (3b)

Solvent	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
$CDCl_3$	0.89	1.16	0.27	6.52	5.81
C_6H_6	0.78	1.11	0.33	6.17	5.37
$(CH_3)_2SO$	0.82	1.09	0.27	6.59	5.97
$C_6H_5NO_2$	0.90	1.22	0.32	6.59	5.86

(18) H. S. Gutowsky, J. Jonas, and T. H. Siddall, III, *J. Amer. Chem. Soc.*, **89**, 4300 (1967).

(19) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *ibid.*, **89**, 4910 (1967).

(20) Y. L. Chow, C. J. Colon, and J. N. S. Tarn, *Can. J. Chem.*, **46**, 2821 (1968).

(21) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *ibid.*, **46**, 2577 (1968).

(22) T. H. Siddall, III, W. E. Stewart, and A. L. Marston, *J. Phys. Chem.*, **72**, 2135 (1968).

(23) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).

(24) A. M. Monro and M. J. Sewell, *Tetrahedron Lett.*, 595 (1969).

(25) J. P. Chupp, J. F. Olin, and H. K. Landwehr, *J. Org. Chem.*, **34**, 1192 (1969).

again no signal doubling was discernible. These results suggest that only a single amide configuration is present in these compounds in the temperature range employed.

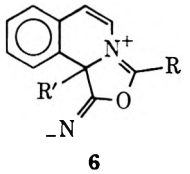
Aromatic solvent induced shifts (ASIS)[19] were employed to establish the configuration of the amide function. It is known that groups s-trans to the amide carbonyl oxygen experience a large upfield shift and groups s-cis to the carbonyl oxygen are subjected to a small downfield or upfield shift when the solvent is changed from carbon tetrachloride to benzene.[19] Owing to the limited solubility of these compounds in carbon tetrachloride, chloroform was used. Using materials soluble in both solvents, it was shown that the differences are slight; shifts in chloroform were 3 to 6 Hz downfield from those in carbon tetrachloride. The results of this solvent study are recorded in Table VI. On the basis of predicted ASIS effects, the protons of the R′ group (A and B) of isomer **5c** would undergo a large upfield (+) shift, while H_3 (or 3-CH_3) and H_4 would be slightly shifted upfield (+) or downfield (−). In contrast the protons of R′ in **5t** would be expected to exhibit a small shift in either direction, while H_3 (or 3-CH_3) and H_4 should undergo large upfield (+) shifts. In each case the data conclusively indicate configuration **5t**, in which the R group of the amide is cis to H_3 (or 3-CH_3) and the carbonyl function is cis to the R′ and cyano groups. This configuration is in accord with structure **6**, in which the interaction of the cyano and carbonyl moieties has been invoked to explain the lack of nitrile absorption in the infrared spectra of Reissert compounds (**6**, R′ = H).[4] Weak, barely detectable nitrile absorptions are found at 2245–2255 cm^{-1} (4–5 wt % solutions in $CHCl_3$) in all the compounds of series **3** and **4** except **4a**, which showed no such absorption. The nitrile absorbances were 1–5% of the carbonyl absorbances, which occurred at 1672–1694 cm^{-1}. Nitrile absorption intensities are known to be extremely variable, sometimes undetectable.[26] Therefore, the low nitrile absorption intensities in series **3** and **4** cannot be taken as proof of extensive contribution of form **6** to stabilization of amide configuration **5t**; at most it can be said that the results are consistent with this proposal.

TABLE VI

AROMATIC SOLVENT INDUCED SHIFTS OF PMR SPECTRA OF 1-ALKYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES

Compd	$\Delta\delta_{CDCl_3-C_6D_6}$, Hz[a] A[b]	B[b]	H_3	H_4
3c	+6.2	+0.8	+24.9	+18.8
3l	+2.6	−0.5	+23.9	+28.6
4c	+3.0	+9.0	+23.4[c]	+23.8
4d	+4.5	+2.5	+14.9[c]	+21.8

[a] + sign denotes upfield shift upon changing to C_6D_6; − sign, downfield shift. [b] A and B denote the diastereotopic groups of R′, *i.e.*, the CH_3 groups of R′ = i-C_3H_7 and the CH_2 protons of R′ = $CH_2C_6H_5$. [c] 3-CH_3 resonance.



6

The ASIS results are corroborated by the data of Table VII, relating the chemical shift of the acetyl methyl protons of compounds **3** and **4**, R = CH_3, to the alkyl substituent R′ and the presence of the 3-methyl group. In the **3** series variation of R′ from methyl (**3q**) to ethyl (**3r**) to isopropyl (**3a**) to isobutyl (**3h**) to benzyl (**3k**) alters δ_{CH_3} by only 0.07 ppm. Comparison of the 1-isopropyl compounds **3a** and **4a** reveals the effect of the 3-methyl group; the acetyl methyl protons undergo an upfield shift of 0.11 ppm. Additionally in compound **3c** the methyl protons of the *N*-isobutyryl group are diastereotopic with pmr signals at δ 1.22 and 1.28. In **4c** the corresponding resonances appear at δ 0.97 and 1.22.[27] Thus, addition of the 3-methyl function resulted in a slight (0.06 ppm) upfield shift in the downfield signal, but the upfield resonance underwent a large (0.25 ppm) upfield displacement. These data are consistent with the conclusion that the configuration of the amide group is that shown in **5t**; that is, the acyl R group is cis to the 3 position of the isoquinoline ring. Therefore, signals arising from protons in the R group are highly sensitive to the 3 substituent but relatively insensitive to the R′ group at the 1 position. In these terms the anisochronisms for the *N*-isobutyryl methyl signals are readily rationalized. If in accordance with other work[28] the carbonyl group prefers to eclipse one of the methyl groups, the other methyl group will be in close proximity to the 3 position. The two methyl groups will then be affected by different magnetic anisotropies. In **3c** the difference is small; in **4c** the carbonyl anisotropy is similar to that in **3c**, but, owing to the presence of the 3-methyl group, the isobutyryl methyl group in that region (the upfield signal) is subjected to a much different anisotropy and is shifted further upfield and a larger anisochronism results.

TABLE VII

THE EFFECT OF 1-ALKYL SUBSTITUENT ON THE CHEMICAL SHIFTS OF THE ACETYL METHYL PROTONS OF **3** AND **4** (R = CH_3) IN $CDCl_3$

Compd	R′	δ_{CH_3}
3q	CH_3	2.35
3r	CH_2CH_3	2.33
3a	$CH(CH_3)_2$	2.33
3h	$CH_2CH(CH_3)_2$	2.30
3k	$CH_2C_6H_5$	2.28
4a	$CH(CH_3)_2$	2.22

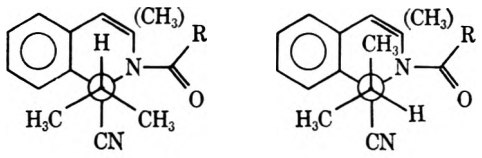
Conformation About the C_1–R′ Bond.—A further point of obvious consequence to the anisochronism of diastereotopic groups in R′ of **3** and **4** is the conformation about the C_1–R′ bond. Three noneclipsed conformations are possible for each compound. Conformations of the 1-isopropyl derivatives of **3** and **4** are shown in **7a**, **7b**, and **7c** as viewed along the methine–C_1 bond.

When the energy barrier due to eclipsing of groups in passing from one conformer to another is sufficiently low, all of the conformers will be represented in propor-

(26) L. J. Bellany, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, pp 265–267.

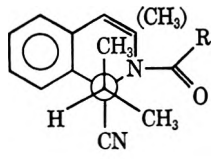
(27) This anisochronism (0.25 ppm) is very large; for structurally similar *N*-benzyl-*N*-(*o*-tolyl)-2-methylpropionamide the methyl anisochronism is 4 Hz (0.07 ppm).[19]

(28) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).



7a

7b



7c

tion to their free energy content. The presence of two or more rotamers of unequal energy is manifested as a temperature dependence of the relative populations. If the chemical shifts of the groups involved vary from conformer to conformer, as is usually the case, this temperature dependence is conveniently detected by pmr spectroscopy. In some cases, owing to preferential solvation the relative conformer populations are sensitive to changes in solvent and such changes can also be discerned by pmr.

The effect of temperature from −50 to 150° on the spectrum of 1-isopropyl-2-benzoyl-1,2-dihydroisoquinaldonitrile (**3b**) is listed in Table VIII. The solvent

TABLE VIII

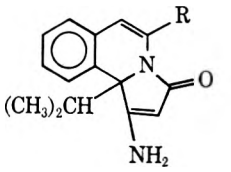
TEMPERATURE DEPENDENCE OF PMR SPECTRUM OF 1-ISOPROPYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (**3b**)

Temp, °C	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
−50[a]	0.96	1.23	0.27	6.59	5.89
−30[a]	0.96	1.23	0.27	6.58	5.88
40[a]	0.89	1.16	0.27	6.52	5.81
40[b]	0.90	1.22	0.32	6.59	5.86
95[b]	0.92	1.22	0.30	6.57	5.82
150[b]	0.93	1.20	0.27	6.57	5.82

[a] Solvent $CDCl_3$. [b] Solvent $C_6H_5NO_2$.

dependence of the spectrum of **3b** is listed in Table V. As can be seen, the spectrum in chloroform-*d* from −50 to 40° undergoes only minor chemical shift changes; the anisochronism ($\Delta\delta_{CH_3}$) is constant. In nitrobenzene solvent from 40 to 150° there is a slight change in $\Delta\delta_{CH_3}$ from 0.32 to 0.27 ppm, about a 10% decrease. This small change is believed to be related, not to changes in conformer ratio, but rather to the solvation of **3b** by the aromatic solvent, leading to a differential shielding dependent upon stereochemistry and electron density.[29] Thus, as the temperature is increased to 150° the solvation is effectively shorter lived and chemical shifts and anisochronisms closely resemble those in chloroform-*d* at room temperature. Nitrobenzene is not a highly electron-rich nucleus and thus its solvating power is less than that of benzene. The solvent dependence (Table V) seems to reflect only the same difference between aromatic and nonaromatic solvents with no gross changes taking place.

We believe that these data are indicative of the presence of a single stable rotamer as has been previously suggested for some 1-isopropyl-1,2,3,4-tetrahydroisoquinoline compounds.[13] In considering the isopropyl conformation several observations are important. The unfield methyl signal (CH_3^A) is not much affected by the presence or absence of the 3-methyl substituent (Tables I and II, *e.g.*, **3f** and **4e**, **3d** and **4d**, **3a** and **4a**) nor by formation of cyclic compounds **8a** and **8b** from compounds **3a** and **4a**.[30] This implies that



8a, R = H: δ_{CH_3} 0.83; δ_{CH} 2.2 (DMSO)
8b, R = CH_3; δ_{CH_3} 0.81, 0.84; δ_{CH} 2.3 (DMSO)

the high-field methyl group occupies a position removed from the 3 position and the amide region. Conversely, the low-field methyl (CH_3^B) and the methine proton are affected by the presence of the 3-methyl substituent (Tables I and II) and conversion to **8**; therefore, it is inferred that they lie in the vicinity of the 3 position and the amide function. Based on these inferences, **7a** and **7b** are the two possible conformers and the high-field methyl group CH_3^A is gauche to the nitrile and benzo groups. In **7a** the methine proton is expected to move upfield as the 3-methyl group is added while in **7b** the downfield methyl (CH_3^B) is expected to move upfield, both due to increased shielding by the double bond. Experimentally it is found that CH_3^B undergoes a downfield shift (~0.1 ppm, regardless of R) while the methine proton shifts upfield (~0.3 ppm), and this points to conformer **7a**.

As expected for **7a** the methine proton reveals the anisotropy of the R group. For alkyl R groups it is shielded relative to aryl R's; of the aryl R's phenyl is most like the alkyls, *i.e.*, it is less deshielding (Tables I and II). A similar effect can be seen in the H_3 signal (Table I); with ortho-substituted aryl R groups H_3 is shielded relative to other aryl R groups. In Tables I and II it can be seen that CH_3^B is slightly more deshielded with ortho-substituted aryl R groups than with other aryl or alkyl R groups. Molecular models indicate crowding of aryl R groups and the 3 substituent (H or CH_3) so that either (1) R rotates to become orthogonal to the NCO plane or (2) the N–COR bond is not quite coplanar in that the R group lies below the 3 position, or (3) a combination of 1 and 2 occurs. The chemical shifts of the methine proton and the CH_3^B are informative in this regard. In the series **3** the methine proton is relatively sensitive to changes in R in comparison to series **4**. The isopropyl CH_3^B is, however, changed by a nearly constant (0.11 ppm) amount for all R's in comparing series **3** and **4**; similarly changes of R in the two series result in about the same changes in CH_3^B, *e.g.* compare **3b–d** and **4b–d**. Also the chemical shift of the group at the 3 position is inversely related to that of the methine proton, while the shifts of the methine and CH_3^B are directly related. These results taken together suggest that the degree of orthogonality is dependent on R and is relatively constant for a given R whether it is in series **3** or **4**, but that introduction of the 3-methyl group causes a nearly constant change in the nonplanarity of the NCOR

(29) R. G. Wilson, D. E. A. Rivett, and D. H. Williams, *Chem. Ind. (London)*, 109 (1969).

(30) These and related compounds will be described in a forthcoming publication; see also Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, p 0–4.

grouping. This places the R group somewhat more below the 3-methyl group, away from the 3-methine proton, which is thereby less sensitive to R, and raises the carbonyl oxygen toward CH_3^B, placing it in a more highly deshielding area. The methine and the 3 substituent in both series reveal the dependence of the degree of orthogonality on R, *i.e.*, ortho substituents increase orthogonality, hence shielding. In this regard note the position of the 3-CH_3 group in **4f**.[31]

In an effort to ascertain the conformation in the benzyl and isobutyl series, an examination of the effect of substituents on the chemical shifts of various protons in the 1-alkyl substituent is informative. First, by inspection of Tables III and IV it can be seen that the upfield protons (H_A's) for the two systems are similarly affected by changes in R, *i.e.*, $\Delta\delta_H^A$ is relatively constant (*e.g.*, compare **3h–k** to **3i–l**). Likewise the downfield protons (H_B's) are similarly affected by R. The conclusion is that the conformation about the C_1–CH_2 bond is on the average the same for both series of compounds. Similarly, through comparison of the low-field methylene protons (H_B's) of the isobutyl and benzyl systems (Tables III and IV) with the methine protons of the isopropyl series (Tables I and II) as a function of R it can be seen that the chemical shifts vary similarly, *i.e.*, $\delta_{H_A} - \delta_{CH}$ is relatively constant. This implies that the H_B's occupy the same position conformationally as does the methine proton. The H_A signals of the isobutyl and benzyl series do not seem to vary in the same manner as either CH_3^A or CH_3^B of the isopropyl series, however. Thus, the conformational relationship of isobutyl and benzyl series to the isopropyl series is tenuous.

The diastereotopic methylene groups in the isobutyl and benzyl series show very similar anisochronism changes with temperature (Tables IX and X). However, the isopropyl group of the isobutyl compounds is fairly mobile and shows relatively large anisochronism changes; changes in conformer populations about this bond due to changes in R or temperature could affect the diastereotopic methylene protons' magnetic anisotropy. Therefore, the parallelism of the behavior of the methylene groups of the two series does not necessarily arise directly from the same variable.

TABLE IX

TEMPERATURE DEPENDENCE OF THE PMR SPECTRUM OF 1-ISOBUTYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (**3i**)

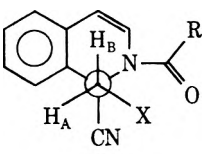
Temp, °C	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	$\delta^A_{CH_3}$	$\delta^B_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
−54 (CD_3COCD_3)	2.20	2.41	0.21	0.71	0.97	0.26	6.90	6.03
40 ($CDCl_3$)	2.23	2.50	0.27	0.78	0.90	0.12	6.53	5.80

TABLE X

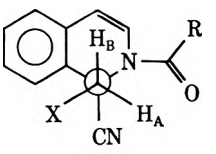
TEMPERATURE DEPENDENCE OF THE PMR SPECTRUM OF 1-BENZYL-2-ACETYL-1,2-DIHYDROISOQUINALDONITRILE (**3k**)

Temp, °C	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	δ_{H_3}	δ_{H_4}
−30 (CD_3COCD_3)	3.37	3.88	0.51	6.87	5.62
40 (CD_3COCD_3)	3.40	3.86	0.46	6.73	5.69
40 ($CDCl_3$)	3.28	3.74	0.46	6.40	5.47

Nonetheless, the following rationale is offered. Based on the similarity of H_B to the methine proton of the isopropyl series, either **9a** or **9b** is the predominant conformer in these two series at 40°. Of these two conformers **9b** seems less strained in molecular models. Thus, **9b** is probably the major conformer in these two series. This is supported by the presence of the aromatic methyl signal of **3o** at a relatively high field, δ 1.83. Molecular models indicate that the ortho substituents would prefer to be away from the carbonyl group and lie over the benzo ring of the isoquinoline. The behavior of H_A with changes in R is then understandable in terms of nonplanarity and orthogonality of the NCOR group. Changing R from methyl to phenyl (**3h** to **3i**, **3k** to **3m**) apparently results in decreased planarity, raising the carbonyl oxygen relative to H_A, increasing the deshielding of H_A, while the phenyl rotates relatively freely resulting in only slight shielding of H_3. Changing to *o*-tolyl (**3j** or **3l**) then causes increased orthogonality (shielding of H_3 and deshielding of H_B) which to some extent alleviates the need for noncoplanarity so that H_A is not changed much from phenyl.



9a



9b

The behavior of **3m–o** (Table IV) is interesting. If one plots δ_{H_B} as a function of the Hammett substituent constant *for para substitution*, a straight line (slope 0.77 ± 0.07, correlation coefficient 0.996) results; a similar plot for δ_{H_A} is nonlinear. The variation of H_A and H_B in **3m–o** may then be due to changing conformation about the CH_2–aryl bond, which has been reported for other benzylic systems and ascribed to either hyperconjugation of the benzylic hydrogens or paramagnetic shielding.[32]

In summary, through consideration of the pmr spectra and in particular the anisochronisms of the diastereotopic groups as functions of substituent, temperature, and solvent, the following stereochemical questions were addressed: ring conformation *via* ring inversion, amide configuration, and conformation about the ring–alkyl bond.

Experimental Section

All compounds used in this study were of analytical purity.[11] Nmr solvents were obtained from Merck Sharpe and Dohme. Nmr spectra were recorded on a Varian A-60 instrument equipped with Model A-6040 temperature controller. Chemical shifts relative to internal tetramethylsilane are believed accurate to ±0.5 Hz. Temperatures were calibrated by use of ethylene glycol and methanol spectra. Temperature was ambient (~40°) unless otherwise indicated. Infrared spectra were determined using a Beckman IR-4 instrument and 0.1-mm matched sodium chloride cells.

Acknowledgments.—The author thanks Dr. John Fager and Mrs. Elizabeth Hezel for spectral determinations. The encouragement of Drs. Fred Stone, Dale McKenzie, and James McKeon is gratefully acknowledged. Drs. John Pochan, Frank Saeva, and Wolfgang Gunther are acknowledged for critically evaluating the manuscript.

(31) See paragraph at end of paper regarding supplementary material.

(32) R. R. Fraser, Gurudata, R. N. Renaud, C. Reyes-Zamora, and R. B. Swingle, *Can. J. Chem.*, **47**, 2767 (1969).

Registry No.—**3a**, 21203-36-1; **3b**, 6457-26-7; **3b** 6,7-dimethoxy derivative, 21286-81-7; **3c**, 30202-19-8; **3d**, 30202-20-1; **3e**, 30202-21-2; **3f**, 21203-35-0; **3g**, 30202-23-4; **3h**, 21400-79-3; **3i**, 21203-37-2; **3j**, 21202-98-2; **3k**, 30201-84-4; **3l**, 30201-86-6; **3m**, 16576-35-5; **3n**, 21876-56-2; **3o**, 16576-36-6; **3p**, 30201-97-9; **3q**, 30201-89-9; **3r**, 30201-87-7; **4a**, 30297-18-8; **4b**, 30297-19-9; **4c**, 30201-91-3; **4d**, 30201-92-4; **4e**, 30201-93-5; **4f**, 30201-94-6; **4g**, 40463-54-5; **4h**, 40463-55-6; **4i**, 40550-46-7.

Supplementary Material Available.—Photographs of Stuart-Briegleb models of **3b** and **4b** showing the conformational effects discussed here will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20026. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2851.

A Stereospecific Synthesis of C-6(7) Methoxypenicillin and -cephalosporin Derivatives

TIMOTHY JEN,* JAMES FRAZEE, AND JOHN R. E. HOOVER

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101

Received February 28, 1973

A method for introducing the C-6(7) methoxy group on penicillins and cephalosporins *via* a route using presumably both carbanion and carbonium ion intermediates is described. Treatment of esters of C-6(7) benzylideneaminopenicillin and -cephalosporin with NaH and $MeSSO_2Me$ gave the corresponding C-6(7) methylthio derivatives. Hydrolytic removal of the benzylidene group of the above derivatives followed by treatment with $HgCl_2$ in methanol afforded benzyl 6-amino-6-methoxypenicillanate and *tert*-butyl 7-amino-7-methoxydeacetoxycephalosporanate. These compounds were converted to the appropriate penicillin and cephalosporin analogs by acylation and removal of the ester groups. Assignment of α configuration to the methoxy group is discussed.

A recent report that certain naturally occurring 7-methoxycephalosporins (cephamycins) have enhanced activity against gram-negative organisms[1,2] prompted us to investigate the synthesis of C-6(7) methoxypenicillin and -cephalosporin derivatives. Of the methods reported to date for synthesizing C-6(7)-disubstituted penicillins and cephalosporins,[2a] the C-6(7) methyl derivatives were made using appropriately protected carbanions[3,4] while the C-6(7) methoxy derivatives were synthesized by routes using carbonium ion[2] and acylimine[5] intermediates. We now report a facile synthesis of C-6(7) methoxy derivatives by a route using a combination of presumed carbanion and carbonium ion intermediates.

The Schiff base **1a**, prepared from equimolar amounts of benzaldehyde and **2a**,[6] on treatment with 1 equiv of NaH in anhydrous DMF followed by addition of 1 equiv of $MeSSO_2Me$[7] gave **1b** in 60% yield. Addition of 6 *N* HCl to **1b** in acetone precipitated **2b** HCl; the crystalline free base was generated by adding the salt to 5% $NaHCO_3$ solution. Treatment of **2b** in a mixture of anhydrous CH_3OH–DMF and pyridine with $HgCl_2$ gave the crystalline 7-methoxy derivative **2c** in 80% yield. Acylation of **2c** with 2-thienylacetyl chloride (TAC) and pyridine in CH_2Cl_2 gave **3a**. Trifluoroacetic acid (TFA) containing 10% anisole converted **3a** to **3c** in 67% yield. Alternatively, **3a** was prepared by first acylating (TAC–pyridine) **2b** and then treating the resulting **3b** with $AgNO_3$ in anhydrous MeOH. The 7-methylthiocephalosporin **3d** was obtained by treating **3b** with TFA containing anisole.

6-Methoxypenicillin G (**6b**) was prepared in a similar sequence of reactions. Thus, **4a**, prepared from **5a**[8] and benzaldehyde, reacted with NaH and $MeSSO_2Me$ to afford the methylthio derivative **4b** which was hydrolyzed by *p*-toluenesulfonic acid (*p*-TSA) hydrate to **5b** *p*-TSA. The salt was converted to the crystalline free base **5b** with 5% $NaHCO_3$ solution. Treatment of **5b** in anhydrous methanol–pyridine with $HgCl_2$ gave the crystalline methoxy derivative **5c**[9] which was converted *via* **6a** to the potassium salt of 6-methoxypenicillin G (**6b**) in a manner similar to that described previously (Chart I).[2]

We have assigned the α configuration to the CH_3S group in **2b** and **4b** based on the expected stereochemical course of the reaction by analogy to that for the synthesis of C-6(7) methyl β-lactam antibiotics.[3,4] Nmr studies using lanthanide shift reagents[10] and optical rotation data (Table I) also support the assignment. The α configuration of the methoxy group in **6a** was assigned on the grounds that the nmr and optical rotation data[11] of **6a** (Table II) are in agreement with those reported for 6α-methoxypenicillin G benzyl ester.[2] Since similar stereochemical course for introduction of the methoxy group in the cephalosporin and penicillin series is expected, we therefore assume the methoxy group in **2c** to have the α configuration.

The formation of **2c** and **5c** is stereospecific; epimers

(1) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

(2) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).

(2a) NOTE ADDED IN PROOF.—Since we submitted this paper, several publications which described related synthetic methods have appeared in the literature: W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.* **38**, 943 (1973); J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, **95**, 2401 (1973); G. A. Koppel and R. E. Koehler, *ibid.*, **95**, 2404 (1973).

(3) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

(4) R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(5) W. A. Spitzer and T. Goodson, *Tetrahedron Lett.*, 273 (1973).

(6) Method of J. Stedman, *J. Med. Chem.*, **9**, 444 (1966).

(7) M. D. Bentley, I. B. Douglass, and J. A. Lacadie, *J. Org. Chem.*, **37**, 333 (1972).

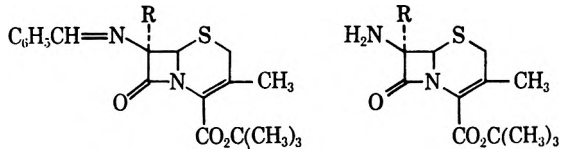
(8) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **84**, 2983 (1962).

(9) Reported in ref 2 as an "isolable intermediate" without melting point.

(10) Nmr studies on lanthanide-induced shift of the C-6 proton in **2a** and **2b** and in a mixture containing the epimer of **2a** suggest that the configuration of the amino group in **2a** and **2b** is identical.

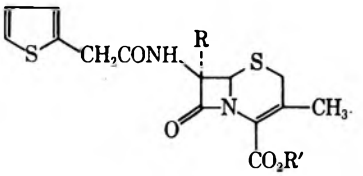
(11) The nmr spectrum of **6a** displayed a *singlet* (6 H) for the *gem*-dimethyl protons while that of the epimer **6c**[2] showed a *pair* of singlets (3 H each) for the corresponding protons. The high specific rotations of **6a** and **6d** in contrast to that of **6c** and **6e** are consistent with the assignment.

CHART I

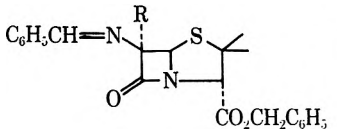


1a, R = H
b, R = CH_3S

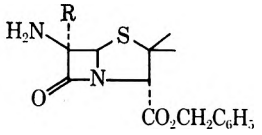
2a, R = H
b, R = CH_3S
c, R = CH_3O



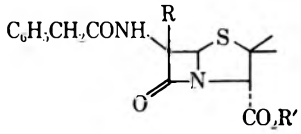
3a, R = CH_3O; R′ = $(CH_3)_3C$
b, R = CH_3S; R′ = $(CH_3)_3C$
c, R = CH_3O; R′ = H
d, R = CH_3S; R′ = H



4a, R = H
b, R = CH_3S



5a, R = H
b, R = CH_3S
c, R = CH_3O



6a, R = α-CH_3O; R′ = $C_6H_5CH_2$
b, R = α-CH_3O; R′ = K
c, R = β-CH_3O; R′ = $C_6H_5CH_2$
d, R = α-H; R′ = $C_6H_5CH_2$
e, R = β-H; R′ = $C_6H_5CH_2$

TABLE I

SPECTRAL DATA OF CEPHALOSPORINS

	Nmr,[a] δ (TMS)				
Compd	C-2 (d of d)	3-CH_3	C-6	SCH_2-(OCH_3)	$[\alpha]^{25}D$ (c 1, $CHCl_3$), degree
1b	3.26	2.05	5.07	2.30	
2a	3.32	2.07	4.96 (d)		+108.1
2b	2.29	2.12	4.75	2.35	+132.7
2c	3.21 (s)	2.13	5.81	3.51	+104.9
3a	3.21	2.11	5.03	3.52	
3b	3.24 (s)	2.15	4.90	2.28	
3c[b]	3.28	1.98	5.01	3.35	

[a] All spectra were taken in $CDCl_3$ except for 3c. [b] Spectrum taken in DMSO-d_6.

TABLE II

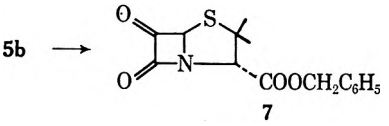
SPECTRAL DATA OF PENICILLINS

	Nmr,[a] δ (TMS)				$[\alpha]^{27}D$ (MeOH), degree
Compd	2-CH_3	H_3	H_5	$SCH_3(OCH_3)$	
4b	1.38, 1.50	4.40	5.49	2.24	
5b	1.40, 1.55	4.45	5.39	2.25	
5c	1.40, 1.53	4.44	5.36	3.43	
6a	1.34	4.41	5.60	3.39	+275.9 (c 1)
6a[b]	1.30	4.41	5.60	3.41	+226 (c 1.08)
6c[b]	1.38, 1.56	4.46	5.68	3.38	+86 (c 1)
6d[c]					+213 (c 1.09)
6e[b]					+160.9 (c 0.99)

[a] All spectra were taken in $CDCl_3$. [b] Spectral data reported in ref 2. [c] H. T. Clarke, J. R. Johnson, and R. Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p 94.

were not detected from the crude products by nmr and tlc analyses. The methoxylation reaction presumably involved removal of the methylthio group by mercuric salt to form a carbonium ion which should be attacked by methanol from the less-hindered α face.[12]

In a further extension of this preparative approach **5b** was converted to benzyl 6-oxopenicillanate **7**[13] by treat-



7

ment with $HgCl_2$ in DMF–H_2O (without pyridine). This α-keto-β-lactam is a potentially useful intermediate for transformation into novel β-lactam antibiotics.

Compounds **3c**, **3d**, and **6b** exhibited poor antibacterial activity against several gram-positive and gram-negative bacteria.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were performed by the Analytical Department of Smith Kline & French Laboratories. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer (neat or Nujol). Mass spectra were obtained on a Hitachi Perkin-Elmer RMN-6E spectrometer. Nmr spectra were obtained on a Varian T-60 instrument (Me_4Si). Optical rotations were recorded on a Perkin-Elmer 141 polarimeter.

tert-**Butyl 7β-Benzylideneamino-7α-methylthiodeacetoxycephalosporanate (1b).**—A solution of **2a**[6] (54 g, 0.2 mol) in MeOH (500 ml) was treated with benzaldehyde (23 g, 0.22 mol). After chilling the mixture, the crystalline product was filtered, washed with a small amount of cold MeOH, and dried to give 65 g (91%) of **1a**,[14] mp 117–120°.

To a stirred solution of **1a** (2.16 g, 6 mmol) in anhydrous DMF (60 ml, distilled over CaH *in vacuo*) at −15° under N_2 was added NaH (6.3 mmol, free from mineral oil). After 40 min methyl methanethiosulfonate (0.755 g, 6 mmol) was added and stirring was continued for 10 min. The mixture was then diluted with Et_2O (150 ml), washed thoroughly with H_2O and once with 5% $NaHCO_3$, and dried ($CaSO_4$). Evaporation of the solvent and recrystallization of the residue from Me_2CO–hexane gave 1.45 g (60%) of **1b**: mp 161–162°; nmr ($CDCl_3$) δ 1.57 (s, 9 H), 2.05 (s, 3 H), 2.30 (s, 3 H), 3.03 (d, 1 H, J = 18 Hz), 3.48 (d, 1 H, J = 18 Hz), 5.07 (s, 1 H); ir λ_{max} 5.74, 5.87, 6.22 μ. *Anal.* Calcd for $C_{20}H_{24}N_2O_3S_2$: C, 59.38; H, 5.98; N, 6.92. Found: C, 59.06; H, 6.10; N, 7.18.

tert-**Butyl 7β-Amino-7α-methylthiodeacetoxycephalosporanate (2b).**—A solution of **1b** (13.9 g, 34.4 mmol) in Me_2CO (150 ml) was treated with 6 *N* HCl (36 mmol). When crystallization occurred, the mixture was diluted with Et_2O (200 ml), chilled, and filtered to give 11 g (91%) of **2b** HCl, mp 130–135°. *Anal.* Calcd for $C_{13}H_{20}N_2O_3S_2 \cdot HCl$: C, 44.25; H, 5.99; N, 7.94. Found: C, 44.08; H, 6.43; N, 7.89.

The above HCl salt was converted quantitatively to the free base **2b** by shaking with 5% $NaHCO_3$ and extraction into CH_2Cl_2. Free base: mp 169–171°; ir λ_{max} 3.00, 5.70, 5.86 μ. *Anal.* Calcd for $C_{13}H_{20}N_2O_3S_2$: C, 49.34; H, 6.37; N, 8.85. Found: C, 49.58; H, 6.66; N, 8.61.

tert-**Butyl 7β-Amino-7α-methoxydeacetoxycephalosporanate (2c).**—To a stirred solution of **2b** (1 g, 3.16 mmol) in a mixture of

(12) This is consistent with a similar mechanism proposed by Christensen *et al.*;[3] the amino group should stabilize the carbonium ion more than the azido group. However, our data do not exclude the possibility of an alternative pathway involving an imino intermediate, although, starting with a free amino group, these sequences seem less likely to proceed *via* an imino intermediate than those[5] using the acylated amines as starting material.

(13) This compound was recently synthesized by Y. S. Lo and J. C. Sheehan, *J. Amer. Chem. Soc.*, **94**, 8253 (1972), *via* an independent route.

(14) This intermediate is named in ref 3 without describing its method of synthesis or properties.

anhydrous DMF (30 ml), MeOH (30 ml, distilled over Mg) and pyridine (0.55 g, 7 mmol) at −15° was added $HgCl_2$ (1 g, 3.7 mmol). Precipitation occurred immediately. The mixture was warmed to −10° during 10 min and filtered through Supercel. The residue was washed with MeOH. The filtrate was diluted with Et_2O (600 ml) and the DMF was removed by repeated washing with H_2O. Evaporation of the solvent gave a semisolid residue which on trituration with Et_2O–petroleum ether gave 0.77 g (80%) of **2c**: mp 98–100°; ir λ_{max} 5.61, 5.80 μ. *Anal.* Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33. Found: C, 52.30; H, 6.50; N, 9.12.

tert-**Butyl 7α-Methoxy-7β-(2-thienylacetamido)deacetoxycephalosporanate (3a). Method A.**—To a solution of 2-thienylacetyl chloride (0.32 g, 2 mmol) in CH_2Cl_2 (25 ml) at 0° was added **2c** (0.6 g, 2 mmol) immediately followed by a solution of pyridine (0.174 g, 2.2 mmol) in CH_2Cl_2 (2 ml). After stirring for 15 min the mixture was diluted with Et_2O and washed with dilute HCl (pH ~2) and then H_2O. The solution was dried ($MgSO_4$) and treated with activated carbon. After filtration, the solvent was evaporated and the residue washed with petroleum ether to give 0.52 g (61%) of **3a**: mp 158–160°; ir λ_{max} 5.66, 5.80, 5.88 μ. *Anal.* Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.70; N, 6.60. Found: C, 53.35; H, 5.84; N, 6.43.

Method B.—A solution of **3b** (0.22 g, 0.5 mmol) in a mixture of MeOH (3 ml) and DMF (3 ml) at 0° was treated with a solution of $AgNO_3$ (150 mg) in MeOH (1 ml) and DMF (1 ml). After 30 min the mixture was filtered and the filtrate diluted with Et_2O (100 ml) and EtOAc (25 ml). The organic solution was washed thoroughly with H_2O, dried ($CaSO_4$), and evaporated to dryness to give 0.1 g of a crystalline material having mp 161–163° after recrystallization from Me_2CO–hexane. This material had nmr, mass spectral, and tlc properties identical with those of **3a** prepared by method A.

tert-**Butyl 7α-Methylthio-7β-(2-thienylacetamido)deacetoxycephalosporanate (3b).**—A solution of **2b** (0.5 g, 1.84 mmol) in CH_2Cl_2 (20 ml) was treated with 2-thienylacetyl chloride (0.253 g, 1.84 mmol) and pyridine (0.14 ml) in the same manner as described for the preparation of **3a**. Recrystallization of the crude product from Me_2CO–hexane gave 0.55 g (70%) of **3b**: mp 143–144°; ir λ_{max} 5.72, 5.88, 5.95 μ. *Anal.* Calcd for $C_{19}H_{24}N_2O_4S_3$: C, 51.79; H, 5.49; N, 6.36. Found: C, 51.55; H, 5.53; N, 6.25.

7α-Methoxy-7β-(2-thienylacetamido)deacetoxycephalosporanic Acid (3c).—**3a** (0.55 g) in a mixture of trifluoroacetic acid (10 ml) and anisole (1 ml) was kept at 0° for 1 hr. The trifluoroacetic acid was evaporated *in vacuo* without external heating and the residue was washed with petroleum ether. This material was dissolved in MeOH and treated with activated carbon. After removal of the charcoal by filtration, the solvent was evaporated and the residue was triturated with petroleum ether and filtered to give 0.32 g (67%) of **3c** as an amorphous solid: ir λ_{max} 3.0, 5.60, 5.80, 5.95 μ; mass spectrum (as TMS derivative)[15] *m/e* 512 (M^+ for di-TMS derivative), 497 (M − 15), 415 (M − 97), 230; tlc on silica gel plate (MeOH–EtOAc 1:1) showed only one spot. *Anal.* Calcd for $C_{15}H_{16}N_2O_5S_2$: C, 48.90; H, 4.38; N, 7.60. Found: C, 49.04; H, 4.69; N, 6.34.

7α-Methylthio-7β-(2-thienylacetamido)deacetoxycephalosporanic Acid (3d).—**3b** was treated with TFA–anisole in the same manner as described for the preparation of **3c**. The crude product was recrystallized from Me_2CO–Et_2O to give **3d**: mp 107–110°; ir λ_{max} 5.64, 5.83, 5.90 μ. *Anal.* Calcd for $C_{15}H_{16}N_2O_4S_3$: C, 46.86; H, 4.19; N, 7.29 Found: C, 46.63; H, 4.38; N, 7.00.

Benzyl 6β-Benzylideneamino-6α-methylthiopenicillanate (4b).—A solution of **5a** in MeOH was treated with equimolar amount of benzaldehyde in the same manner as described for the preparation of **1a** to give **4a** as a gum. The last trace of MeOH was removed by azeotroping with C_6H_6 and heating under high vacuum.

A solution of **4a** (6.32 g, 16 mmol) in anhydrous DMF (150 ml) was treated with NaH (16 mmol) and $MeSSO_2Me$ (16 mmol) in the same manner as described for the preparation of **1b**. An oily crude product was obtained. This material was dissolved in CH_2Cl_2 and passed through a Florisil column. The residue obtained from evaporation of CH_2Cl_2 crystallized from hexane to give 2.85 g (41%) of **4b**: mp 78–81°; ir λ_{max} 5.64, 5.70 (sh), 6.15 μ. *Anal.* Calcd for $C_{23}H_{24}N_2O_3S_2$: C, 62.70; H, 5.49; N, 6.36. Found: C, 62.63; H, 5.66; N, 6.17.

Benzyl 6β-Amino-6α-methylthiopenicillanate (5b).—A solution of **4b** (0.9 g, 2.04 mmol) in a mixture of Et_2O (15 ml) and Me_2CO (1 ml) was treated with a solution of *p*-toluenesulfonic acid hydrate (0.43 g, 2.24 mmol) in a mixture of Et_2O (5 ml) and THF (2 ml). On cooling, the salt of **5b** (0.97 g, 90%) crystallized (mp 135°). Recrystallization from Me_2CO–Et_2O gave the analytical sample, mp 137° dec. *Anal.* Calcd for $C_{16}H_{20}N_2O_3S_2 \cdot C_7H_8O_3S$: C, 52.65; H, 5.38; N, 5.34. Found: C, 52.38; H, 5.47; N, 5.18.

Treatment of the above salt with 5% $NaHCO_3$, extraction into CH_2Cl_2, and, after evaporation, crystallization of the residue from Me_2CO–hexane gave the free base **5b** in 92% yield: mp 44–48°; ir λ_{max} 2.90, 5.60, 5.70 μ.

Benzyl 6β-Amino-6α-methoxypenicillanate (5c).—A solution of **5b** (0.26 g, 0.73 mmol) in anhydrous DMF (3 ml), MeOH (7 ml), and pyridine (0.15 ml) was treated with $HgCl_2$ (0.21 g) in the same manner as described for the preparation of **3a**. The oily residue thus obtained (167 mg, one major spot by tlc analysis: silica gel; Et_2O–hexane 7:3) was taken up in hexane and chilled. On prolonged standing, **5c** crystallized: mp 40–42°; for nmr, see Table II. *Anal.* Calcd for $C_{16}H_{20}N_2O_4S$: C, 57.13; H, 5.99; N, 8.33. Found: C, 56.91; H, 6.11; N, 8.06.

6α-Methoxy-6β-phenylacetamidopenicillanic Acid (6α-Methoxypenicillin G, 6b).—A solution of **5c** (0.22 g, 0.655 mmol) in CH_2Cl_2 (10 ml) at 0° was treated with equimolar amounts of phenylacetyl chloride and pyridine (0.6 ml). After 15 min EtOAC was added and the mixture washed with H_2O, 0.1 *N* HCl, and 5% $NaHCO_3$. After drying and evaporation of the solvent, the residue was triturated with petroleum ether. The residual oil in Et_2O was passed through a Florisil column to give 0.125 g of **6a** as an oil: tlc (silica gel, Et_2O) showed one major spot; for nmr and $[\alpha]_D$, see Table II.

The benzyl ester was hydrogenolyzed to the free acid by a procedure essentially the same as described by Christensen, *et al.*[2] A solution of the above product in EtOAc was hydrogenated over 10% Pd/C (0.15 g) at 50 psi for 3 hr. The catalyst was removed by filtration and the filtrate evaporated to dryness. The residue was dissolved in Et_2O and treated with potassium 2-ethylhexanoate in 2-PrOH. The precipitated potassium salt **6b** (50 mg, amorphous solid) was filtered, washed with Et_2O, and dried: ir λ_{max} 2.9, 5.6, 5.95, 6.13 μ; mass spectrum (as TMS derivative[15]) *m/e* 436 (M^+ of mono-TMS derivative); tlc (silica gel, MeOH–$CHCl_3$–AcOH 20:79:1) showed one major component, R_f ~0.7.

Benzyl 6-Oxopenicillanate (7).—A stirred solution of **5b** (70 mg, 0.2 mmol) in a mixture of DMF (3 ml) and H_2O (1 ml) at −20° was treated with $HgCl_2$ (60 mg). After 15 min, the mixture was stirred for 30 min at 0° and then diluted with Et_2O (25 ml). The precipitate was removed by filtration and the filtrate washed with H_2O, dried, and evaporated to give **7** as a yellow oil (45 mg): nmr ($CDCl_3$) δ 1.45 (s, 3 H), 1.52 (s, 3 H), 4.78 (s, 1 H), 5.22 (s, 2 H), 5.77 (s, 1 H), 7.38 (s, 5 H); ir λ_{max} 5.44, 5.60, 5.72 μ. The spectral data are in agreement with those reported.[13]

Registry No.—**1a**, 36954-81-1; **1b**, 37786-92-8; **2a**, 33610-06-9; **2b**, 40514-89-4; **2b** HCl, 40514-90-7; **2c**, 40514-91-8; **3a**, 40514-92-9; **3b**, 40514-93-0 **3c**, 40514-94-1; **3d**, 40514-95-2; **4b**, 40514-96-3; **5a**, 3956-31-8; **5b**, 40514-98-5; **5b** *p*-toluenesulfonate, 40514-99-6; **5c**, 35353-32-3; **6b**, 40515-01-3; **7**, 39126-59-5; methyl methanethiosulfonate, 2949-92-0; 2-thienylacetyl chloride, 39098-97-0; benzaldehyde, 100-52-7; *p*-toluenesulfonic acid, 104-15-4; phenylacetyl chloride, 103-80-0.

(15) Obtained by treatment with *N,O*-bis(trimethylsilyl)trifluoroacetamide.

Photoaddition Reaction of Biacetyl

HONG-SON RYANG,* KENSUKE SHIMA, AND HIROSHI SAKURAI

The Institute of Scientific and Industrial Research, Osaka University, Suita, Osaka, Japan

Received January 22, 1973

The photochemical reaction of biacetyl with various olefins has been investigated. Irradiations of biacetyl with indene, furan, and ethyl vinyl ether give oxetanes with higher orientational selectivity than that of monoketones. In the case of methyl-substituted olefins, it is found that novel products, 2-acetoethyl allyl ethers, accompany the oxetanes and are formed in good yield. The ratios of these products vary with the olefins used. The presence of biradical intermediates formed by addition of excited biacetyl to olefins is established by deuterium-labeling experiments. The quenching of biacetyl phosphorescence by an olefin indicates that the n-π^* triplet state of biacetyl is involved in these reactions. The absence of adduct in the case of electron-deficient olefins indicates that the excited biacetyl is electrophilic in its reaction with olefins. The mechanism of these reactions is best described as an electrophilic attack of the n-π^* triplet state of biacetyl to the olefins to give a biradical intermediate which undergoes competitive cyclization and disproportionation. The difference in the reactivity of biacetyl toward photoaddition relative to monoketones and *o*-quinones is discussed.

In recent years, the photochemical behavior of α-diketones has attracted a great deal of attention. The results reported in the literature[1-14] have produced considerable knowledge about the photochemical behavior of alkyl α-diketones.

It is well known that *o*-quinones undergo photoaddition to olefins to produce oxetanes and dioxenes.[15] Their formation is reasonably explained on the basis of a biradical intermediate. An interesting result, reported by Staab and Ipaktschi, was that irradiation of benzocyclobutanedione in the presence of olefins resulted in the formation of the spirolactonecyclopropane derivatives *via* carbene intermediates.[16] However, no report exists which describes photoaddition of acyclic alkyl α-diketones to olefins.

Biacetyl and other alkyl α-diketones exhibit phosphorescence in solution at room temperature, in spite of the general lack of phosphorescence from monoketones, and abstract hydrogen atoms with a rate constant which is very small relative to monoketones.[12d] Rubin and coworkers have demonstrated that photoreduction of *o*-quinones such as 9,10-phenanthrenequinone gives 1,2 and 1,4 adducts, whereas camphorquinone gives only 1,2 adducts.[17] Furthermore, Gream and coworkers have shown that the photoreactions of nonenolizable cyclic α-diketones with alcohols, amines, and olefins are not necessarily analogous to those of *o*-quinones.[8] These observations suggested to us that the photochemical behavior of acyclic alkyl α-diketones toward olefins might be different from that of monoketones and *o*-quinones. Hence, we investigated the photoaddition of biacetyl to various olefins and tried to compare our results with those of other compounds.[18]

Results

All photochemical reactions described herein were carried out with a 350-W high-pressure mercury lamp in Pyrex glass under nitrogen filtered through an *n*-hexane solution of naphthalene (λ >320 nm) at room temperature. Major products were 1:1 adducts in each case. The various adducts were isolated by distillation and preparative vapor phase chromatography, and their structures were determined by ir, nmr, and mass spectra and elemental analysis as detailed in the Experimental Section. The ratios of the products were determined by vpc.

The reactions of biacetyl with indene, furan, and ethyl vinyl ether gave oxetanes as main products. In the case of indene, two oxetanes, **1** and **2** (1:2), in which the C_2 position of indene was attached to the carbonyl oxygen of biacetyl, were obtained. The stereochemistry of **1** and **2** was assigned on the basis of the nmr spectra. Oxetane **3** and **4** were obtained from furan and ethyl vinyl ether, respectively.[19]

These results suggest that the addition of biacetyl proceeds with higher orientational selectivity than that of monoketones.[20] In no instance was there a detectable amount of dioxenes, and observation which contrasts with the results for 9,10-phenanthrenequinone.[15]

(1) (a) W. H. Urry and D. J. Trecker, *J. Amer. Chem. Soc.*, **84**, 118 (1962); (b) W. H. Urry, D. J. Trecker, and D. A. Winey, *Tetrahedron Lett.*, 609 (1962).

(2) P. W. Jolly and P. de Mayo, *Can. J. Chem.*, **42**, 170 (1964).

(3) W. G. Bentrude and K. R. Darnall, *Chem. Commun.*, 810(1968).

(4) R. Bishop and N. K. Hamer, *J. Chem. Soc. C*, 1193 (1970); 1197 (1970).

(5) T. L. Burkoth and E. F. Ullman, *Tetrahedron Lett.*, 145 (1969).

(6) B. Äkermark and N.-G. Johasson, *ibid.*, 371 (1969).

(7) S. P. Pappas, J. E. Alexander, and R. D. Zehr, Jr., *J. Amer. Chem. Soc.*, **92**, 6927 (1970).

(8) (a) G. E. Gream, J. C. Paice, and C. C. R. Ramsay, *Aust. J. Chem.*, **20**, 1671 (1967); (b) G. E. Gream, J. C. Paice, and B. S. J. Uszynski, *Chem. Commun.*, 895 (1970); (c) G. E. Gream, M. Mular, and J. C. Paice, *Tetrahedron Lett.*, 3479 (1970).

(9) W. M. Horspool and G. D. Khandelwal, *Chem. Commun.*, 257 (1970).

(10) (a) J. Lemaire, *J. Phys. Chem.*, **71**, 2653 (1967); (b) J. Lemaire, M. Niclause, X. Deglise, J. C. Andre, and G. Penson, and M. Bouchy, *C. R. Acad. Sci., Ser. C*, **267**, 33 (1968).

(11) R. G. Zepp and P. J. Wagner, *J. Amer. Chem. Soc.*, **92**, 7466 (1970).

(12) (a) N. J. Turro and R. Engel, *Mol. Photochem.*, **1**, 143 (1969); (b) *ibid.*, **1**, 235 (1969); (c) *J. Amer. Chem. Soc.*, **91**, 7113 (1969); (d) N. J. Turro and T.-J. Lee, *ibid.*, **91**, 5651 (1969); (e) *ibid.*, **92**, 7467 (1970).

(13) (a) H. L. J. Backstrom and K. Sandros, *Acta Chem. Scand.*, **12**, 823 (1958); (b) K. Sandros and H. L. J. Backstrom, *ibid.*, **16**, 958 (1962); (c) K. Sandros, *ibid.*, **18**, 2355 (1964).

(14) E. J. Baum and R. O. C. Norman, *J. Chem. Soc. B*, 227 (1968).

(15) G. P. Fundt and G. O. Schenck in "1,4-Cycloadditions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 345.

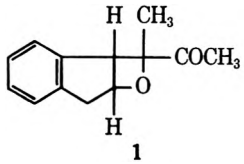
(16) H. A. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).

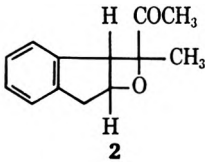
(17) (a) M. B. Rubin and P. Zwitkowits, *Tetrahedron Lett.*, 2453 (1965); (b) M. B. Rubin and R. G. Labarge, *J. Org. Chem.*, **31**, 3283 (1966); (c) M. R. Rubin and R. A. Reith, *Chem. Commun.*, 431 (1966); (d) M. B. Rubin, *Fortschr. Chem. Forsch.*, **13**, 251 (1969); (e) M. B. Rubin and Z. Hershitik, *Chem. Commun.*, 1267 (1970).

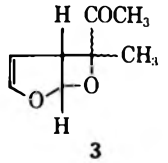
(18) For preliminary accounts of a portion of this work, see (a) H.-S. Ryang, K. Shima, and H. Sakurai, *Tetrahedron Lett.*, 1091 (1970); (b) *J. Amer. Chem. Soc.*, **93**, 5270 (1971).

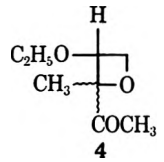
(19) Unfortunately, the configurations of **3** and **4** were not determined from present data.

(20) For example, The photoreaction of acetone with ethyl vinyl ether gave both 3-ethoxyoxetane (70%) and 2-ethoxyoxetane (30%), see (a) S. H. Schroeter and C. M. Orlando, Jr., *J. Org. Chem.*, **34**, 1181 (1969); (b) N. J. Turro and P. A. Wriede, *ibid.*, **34**, 3562 (1969).

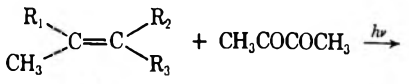

1

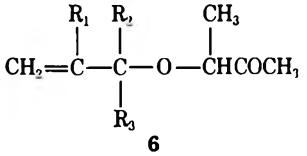

2

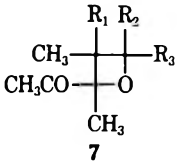

3

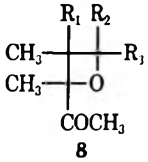

4

Photoaddition reactions of biacetyl were also carried out with methyl-substituted olefins, *i.e.*, 2-ethoxypropene (**5a**), α-methylstyrene (**5b**), isobutene (**5c**), 2-methyl-2-butene (**5d**), and 2,3-dimethyl-2-butene (**5e**). A new type of product, 1-acetoethyl allyl ethers **6**, accompanied the oxetane isomers **7** and **8** (Table I).


5


6


7


8

a, $R_1 = OC_2H_5$; $R_2 = R_3 = H$
b, $R_1 = C_6H_5$; $R_2 = R_3 = H$
c, $R_1 = CH_3$; $R_2 = R_3 = H$
d, $R_1 = R_2 = CH_3$; $R_3 = H$
e, $R_1 = R_2 = R_3 = CH_3$

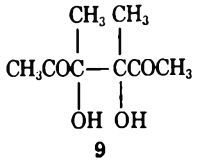
TABLE I

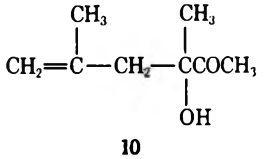
PRODUCT YIELD FOR DISPROPORTIONATION AND CYCLIZATION OF BIACETYL–METHYL-SUBSTITUTED OLEFIN PHOTOREACTION[a]

Olefin	Product yield, % 6	7	8	Ratio of (7 + 8)/6
5a	27	36	21	2.1
5b	27	41	7	1.8
5c	16	10		0.62
5d	54	21[b]		0.41
5e	70			0

[a] Irradiated at room temperature. Product distribution determined by vpc. [b] An isomer of oxetanes alone has been observed.

The ratios of these products vary with the olefins used. Two oxetanes were produced from **5a** and **5b**, whereas only one of the four possible oxetane isomers was isolated from **5d**. Irradiation with **5c** gave, in addition to an allylic ether and an oxetane, the corresponding pinacol **9** and an unsaturated alcohol **10**


9

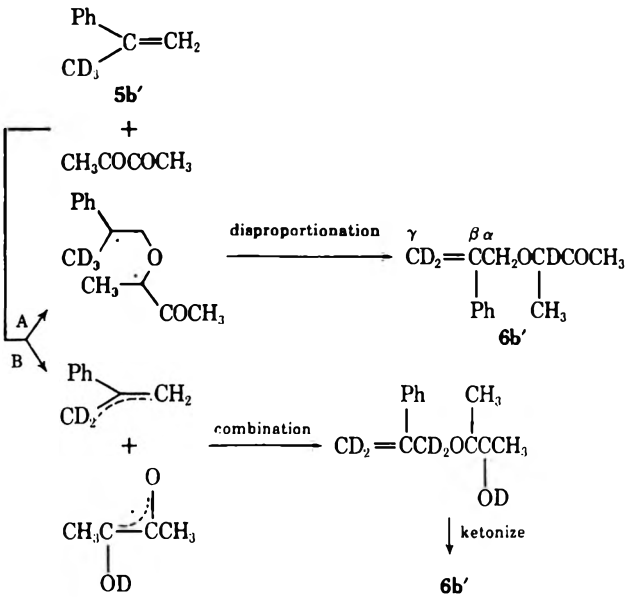

10

arising from initial hydrogen abstraction from **5c** by excited biacetyl and subsequent combination of the two radicals. No oxetane was isolated in the case of **5e**.[21]

The formation of **6** is of interest in comparison with the results from monoketones and *o*-quinones. Photostability studies[22] and constant product ratios during the irradiations[23] have shown that the adducts are the primary photochemical products.

It is generally recognized that α-diketones undergo primary photochemical addition to olefins in competition with hydrogen abstraction, α cleavage, and enol formation. This suggested to us that **6** is formed through either (A) an attack of the excited carbonyl oxygen of biacetyl on olefin to form a biradical intermediate followed by intramolecular hydrogen transfer or (B) initial hydrogen abstraction from olefin by the excited carbonyl of biacetyl followed by combination of the two radicals formed.[24]

In order to determine the mechanism for the formation of **6**, the photoreaction of biacetyl with α-*methyl-d*$_3$-styrene (**5b′**) was investigated. **5b′** was prepared by the Wittig reaction of trideuteriomethyl phenyl ketone with methyltriphenylphosphonium bromide.[25] Irradiation and isolation of the products were carried out as for **5b**. No deuterium was introduced into the position C_α of the allyl moiety in **6b′**.[26]



This result demonstrates that **6** is produced through path A, since path B would introduce deuterium equally into positions C_α and C_γ.

It is suggested that a two-step addition *via* the biradical intermediate is involved in this reaction, but

(21) Several small peaks detected by vpc do not exclude the possibility of the presence of small amounts of oxetane.

(22) Adducts **6b**, **7b**, and **8b** were individually irradiated under the reaction conditions. Each adduct was recovered unchanged.

(23) The yields of **6b**, **7b**, and **8b** were proportional to the irradiation time with the same ratio as in Table I.

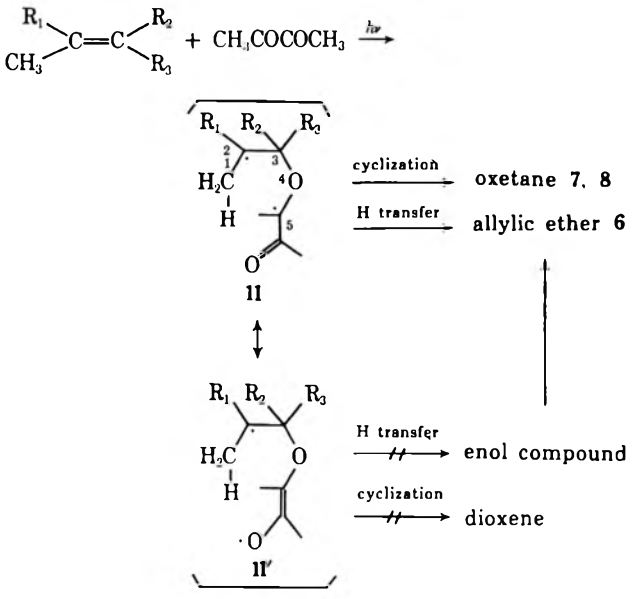
(24) A similar mechanism is discussed for the photoreaction of 2-cyclohexenone with isobutene and that of chromone with 2,3-dimethyl-2-butene, but exact mechanism for these reactions have not been determined, see (a) E. J. Corey, J. D. Bass, R. Lemahiew, and R. M. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (b) J. W. Hanifin and E. Cohen, *ibid.*, **91**, 4494 (1969).

(25) H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **86**, 677 (1967).

(26) Deuterium contents were determined by nmr. The oxetanes and the recovered olefin were deuterated the same per cent as the starting olefin (D = 87%), and no scrambling occurred in them.

there may be some question as to whether the hydrogen transfer proceeds *via* the carbon radical or the oxygen radical. It may be argued that the hydrogen transfer proceeds *via* a six-membered transition state involving the carbon radical, because hydrogen transfer to oxygen must involve an eight-membered transition state, where the probability of an encounter between the two active centers is lower than that in a six-membered transition state. Furthermore, the 1,4 cycloadduct is not obtained in this reaction. However, Padwa and coworkers have reported that irradiation of 2-phenylcyclobutyl phenyl ketone gave 1,5-diphenyl-4-penten-1-one, whose formation has been explained in terms of mechanism involving internal hydrogen abstraction followed by rearrangement of the enol to a carbonyl group.[27]

In order to clarify this point, a mixture of biacetyl and **5b** in deuteriomethanol was irradiated.[28] The nmr and mass spectra of the product showed no deuterium incorporation at any position. This observation can be reasonably interpreted in terms of hydrogen transfer *via* a six-membered transition state involving the carbon radical, since the deuterium atom should be introduced into the methine position if hydrogen transfer to oxygen occurred.



Irradiation of biacetyl in the presence of electron-deficient olefins such as acrylonitrile or *trans*-1,2-dichloroethylene were also carried out in a similar way, but adduct formation was not observed. These results suggest that excited biacetyl is electrophilic in its reaction with olefins.

In order to identify the excited state of biacetyl which is involved in these reactions, the emission of biacetyl (0.05 *M*) in the presence of **5e** (1.0 *M*) was examined in degassed benzene at room temperature and compared with the results in the absence of **5e**. The phosphorescence of biacetyl was completely quenched but the fluorescence was unaffected, which indicates that the reactions proceed by way of the n–π^* triplet of biacetyl.

(27) A. Padwa, E. Alexander, and M. Niemcyzk, *J. Amer. Chem. Soc.*, **91**, 456 (1969).

(28) A solution of biacetyl (0.03 *M*), **5b** (0.03 *M*), and MeOD (10 ml) in a Pyrex test tube was irradiated under the same conditions as in benzene. Deuterium incorporation of the isolated product was examined by nmr and mass.

Discussion

The most reasonable explanation for the above results is as follows. Electrophilic attack of the carbonyl oxygen of excited biacetyl (n–π^* triplet) on olefin leads to a biradical intermediate, which either cyclizes to form oxetane or disproportionates intramolecularly to give **6**. It is generally recognized that the free energy for cyclization is mainly governed by a strain factor and by the probability of the two active centers meeting each other.[29] It seems reasonable to think that the ratios of cyclization to disproportionation shown in Table I are governed by the difference in the activation energies between the two processes.

The results in Table I provide an interesting information on the behavior of the 1,4-biradical intermediates generated by biacetyl–olefin photoaddition (**11**). The decrease in amount of cyclization in going from **5c** to **5d** to **5e** suggests that R_2 and R_3 substituents affect this process considerably; *i.e.*, the decrease in cyclization for **5d** and **5e** is due to an increase of steric repulsion between the substituents at C_3 and C_5 positions in the transition state leading to oxetane formation. Lewis and Hilliard have shown that 1,3-diaxial interactions decrease cyclobutane formation which occurs *via* 1,4-biradical intermediate formed by γ-hydrogen abstraction in methyl-substituted butyrophenones.[30] The presence of a 1,3-diaxial interaction can be also considered as an important factor which governs ring closure *via* the biradical **11**. The more stereoselective oxetane formation for **5b** compared with **5a** may due to a 1,4 repulsive interaction which exists in **11** between the phenyl and acetyl groups. However, the ratios of cyclization to disproportionation for **5a** and **5b** markedly increase in comparison with that for **5c**. This result suggests that disproportionation rather than cyclization is influenced by R_1 substituents. The increase of these ratios for **5a** and **5b** may be due to the decrease in disproportionation for **5a** and **5b**. Probably, 1,4 steric repulsion by the large phenyl or ethoxy group decreases the probability of that conformation which leads to disproportionation in **11**.

In conclusion, the stereoselectivity of cyclization and the ratio of cyclization to disproportionation for biacetyl–olefin photoaddition are reasonably explained by considering steric interactions in 1,4-biradical intermediates. This indicates that the behavior of 1,4-biradical intermediates formed by biacetyl–olefin photoaddition is greatly influenced by substituents.

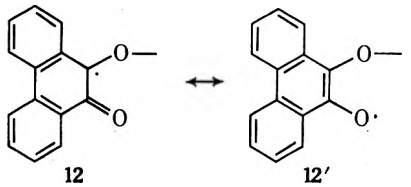
Our results unambiguously demonstrate that the photochemical behavior of biacetyl to olefins is different from that of monoketones and *o*-quinones such as 9,10-phenanthrenequinone, mainly in the following points: (1) the addition reactions give oxetanes with higher orientational and stereoselectivity than those of monoketones; (2) 1,4 cycloadduct is not formed in appreciable amount, which contrasts with the results for *o*-quinones; (3) in the case of monoketones or *o*-

(29) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.

(30) F. D. Lewis and T. A. Hilliard, *J. Amer. Chem. Soc.*, **94**, 3852 (1972).

quinones, an adduct such as **6** has not been obtained in spite of the extensive studies of photoaddition of such carbonyl compounds to olefins.

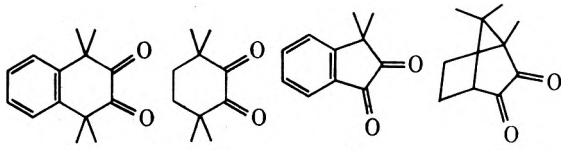
More detailed experimental studies will be required to clarify the difference of the reactivity between these classes of compounds. However, previous mechanistic investigations and our own results prompt us to offer the following explanation on the mechanism of the photoaddition. The difference between biacetyl and *o*-quinones can be attributed to the difference in the contribution of the two resonance-stabilized radicals to the biradical intermediates. For *o*-quinones such as phenanthrenequinone, there exist two resonance semiquinone radicals **12** and **12′**; **12′** is more stabilized



12 **12′**

($4n + 2$ electrons) than **12**. Hence, the contribution of **12′** is greater than that of **12**, whereas, in biacetyl which has no such resonance, the contribution of **11** is larger than that of **11′** because of the larger electronegativity of oxygen atom. Thus, the reactivity at the oxygen atom in the biradical derived from biacetyl is decreased in comparison with that of *o*-quinones.

In addition, the steric difference between biacetyl and *o*-quinones may be an important factor. Gream and coworkers have shown that photoadditions of nonenolizable six-membered cyclic α-diketones (**13** and **14**) with cyclohexene, stilbene, or 2,3-dimethylbuta-1,3-diene gave dioxenes and keto oxetanes, while no dioxene was obtained for 3,3-dimethyl-1,2-dioxoindan (**15**).[8c] Dolling and coworkers have reported that irradiation of camphorquinone (**16**) in the presence

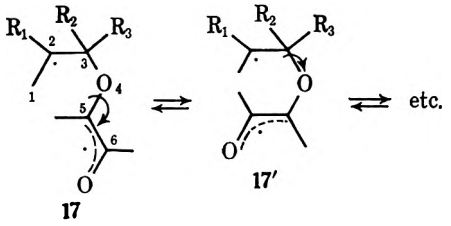


13 **14** **15** **16**

of buta-1,3-diene gave the keto oxetanes as main products.[31] These facts suggest that 1,4 cycloadditions are strongly affected by the bond angle between the two carbonyl groups of *o*-quinones. In biacetyl, in contrast to *o*-quinones, the carbonyl groups are trans in the ground and probably the first excited triplet states. An attack of biacetyl in the trans conformation on olefin gives a biradical intermediate, where the bond between carbon atoms 5 and 6 must have double bond character because of conjugation with the adjacent carbonyl group. Hence, in any conformation of the biradical intermediate (**17**), the two carbon–oxygen bonds are most likely to be trans.[32] Such a situation is sterically unfavorable for reaction at the oxygen atom. The above interpretation would be in accord with the observed results and is supported by studies of the photoreduction of *o*-quinones[17,32b] and alkyl α-diketones.[1-3]

(31) W. L. Dilling, R. D. Kroening, and J. C. Little, *ibid.*, **92**, 928 (1970).

(32) Esr study has indicated that the monoprotonated semidione radical of biacetyl is trans; see (a) R. J. Pritchett, *Mol. Phys.*, **12**, 481 (1967); (b) B. M. Monroe and S. A. Weiner, *J. Amer. Chem. Soc.*, **91**, 450 (1969).



17 **17′**

Subsequently, we would like to consider the difference between biacetyl and monoketones. It is well known that free radicals undergoes competitive reactions.[33] In fact, several examples of competing reactions from a 1,4-biradical intermediates, whose nature is governed by the electronic and steric factors, have been reported, *i.e.*, 1,4-dithiane and thietane formation from photoaddition of thiobenzophenone to styrene,[34] and elimination, cyclization, and hydrogen reversal in type II photolysis of the ketones bearing γ hydrogen.[35] In addition, Liao and de Mayo in analogy with our results have reported that irradiation of adamantanethione and α-methylstyrene gave thietane and 2-adamantyl 2′-phenylallyl sulfide, and provided a reasonable explanation in terms of a mechanism involving competitive cyclization with hydrogen abstraction of an intermediate thiatetramethylene.[36]

While competitive cyclization and disproportionation in the reaction of biacetyl with olefins can be explained on the basis of steric repulsion in the biradical intermediate, monoketone–olefin photoaddition such as photoaddition of benzophenone to methyl-substituted olefins[37] gave no disproportionation products. Since all previous work shows that monoketones regardless of type predominantly form oxetanes, it is suggested that the difference in the behavior of biacetyl and monoketones toward photoaddition should be attributed to factors other than steric ones. More detailed mechanistic studies will clarify this point.

Further work on the nature of the 1,4-biradical intermediate during photoaddition as well as on the scope and application to other systems is currently underway and will be the subject of future reports.

Experimental Section

Nmr spectra were determined on a Hitachi Perkin-Elmer R-20 spectrometer or on a Jeol JNM JS-100 spectrometer in CCl_4 using tetramethylsilane as an internal standard. Infrared spectrometer were obtained on a Hitachi EPI-S2 infrared spectrophotometer. Mass spectra were performed on a Hitachi Perkin-Elmer RMU-60 mass spectrometer. Gas chromatographic analyses were run on a Shimadzu gas chromatograph (GC-3AF). Emission spectra were obtained with a Shimadzu MPF-2A spectrophotometer.

Organic Substrates.—The following substrates were prepared by the reported procedures: 2-ethoxypropene (**5a**),[38] 2-methyl-2-butene (**5d**),[39] and 2,3-dimethyl-2-butene (**5e**).[40] The remaining substrates were obtained from commercial sources.

(33) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966.

(34) A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *J. Amer. Chem. Soc.*, **91**, 5038 (1969).

(35) F. D. Lewis, *ibid.*, **92**, 5602 (1970), and references cited therein.

(36) C. C. Liao and P. de Mayo, *Chem. Commun.*, 1525 (1971).

(37) (a) D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964); (b) N. C. Yang, M. Nussim, M. J. Jorgensen, and S. Murov, *ibid.*, 3657 (1964).

(38) M. A. Dolliver, T. L. Gersham, G. B. Kistiakowsky, E. A. Smith, and W. E. Vaugham, *J. Amer. Chem. Soc.*, **60**, 440 (1938).

(39) F. C. Whitmore, C. S. Rowland, S. N. Wrenn, and G. W. Kilmer, *ibid.*, **64**, 2970 (1942).

(40) I. Shurman and C. E. Boord, *ibid.*, **55**, 4930 (1933).

General Irradiation Procedure.—A mixture of 0.1 *M* of biacetyl and 0.1 *M* of an olefin in benzene (180 ml) was prepared in a Pyrex doughnut-type vessel. The solution was flushed with nitrogen for several minutes before being irradiated. Irradiation was run with a 350-W high-pressure mercury lamp in a quartz immersion well with water-cooled jacket at room temperature except for the case of isobutene (0°) using a filter solution with a path length of about 1 cm containing 12.8 g of naphthalene made up to 1 l. with distilled *n*-hexane which cut out wavelengths shorter than 320 nm and assured excitation of the first excited singlet state of biacetyl alone.

Biacetyl–Indene Photoadducts.—A solution of biacetyl and indene in benzene was irradiated for 48 hr. The volatile material was removed under reduced pressure and a fraction boiling at 100–120° (4 mm) (2.8 g) was collected; residues, 1.5 g. Vpc analysis using 3-m PEG 6000 column at 200° indicated two major peaks with the relative ratio of peak heights 1:2. A separation of these products was accomplished by preparative vpc on a 3-m PEG 6000 column (180°). The first component was identified as **1**: bp 120° (4 mm); *m/e* 202; ir 1720 (C=O) and 990 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.52 (3 H, s), 1.71 (3 H, s), 3.18 (2 H, d, J = 3.0 Hz), 3.90 (1 H, d, J = 5.5 Hz), 5.40 (1 H, q, J = 3.0 and 5.5 Hz), and 7.17 (4 H, m).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6,98. Found: C, 77.13; H, 6.87.

The second component was identified as **2**: bp 120° (4 mm); *m/e* 202; ir 1720 (C=O) and 990 cm^{-1} (oxetane ring); nmr (CCl_4) δ 0.86 (3 H, s), 2.31 (3 H, s), 3.13 (2 H, d, J = 3.0 Hz), 4.15 (1 H, d, J = 5.5 Hz), 5.25 (1 H, q, J = 3.0 and 5.5 Hz), and 7.20 (4 H, m).

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.49; H, 7.11.

Biacetyl–Furan Photoadduct.—After irradiation of a mixture of biacetyl and furan for 48 hr, the volatile material was removed under reduced pressure and a fraction boiling at 94° (24 mm) (2.5 g) was collected; residues, 1.0 g. Vpc analysis (PEG 6000 or UCON LB 550x, 3-m, 140°) of the distillate showed one major peak. Redistillation gave pure **3**: *m/e* 154; ir 1730 (C=O), 1625 (C=C), and 970 cm^{-1} (oxetane ring); nmr δ (CCl_4) 1.33 (3 H, s), 2.28 (3 H, s), 3.85 (1 H, m, J = 4.0 and 3.0 Hz), 5.11 (1 H, t, J = 3.0 Hz), and 6.11 (1 H, d, J = 4.0 Hz).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.12; H, 6.78.

Biacetyl–Ethyl Vinyl Ether Photoadducts.—After 48-hr irradiation of a mixture of biacetyl and ethyl vinyl ether, the volatile material was removed under reduced pressure and two fractions boiling at 70° (20 mm) (3.7 g) and 100–110° (3 mm) (0.5 g) were collected; residues, 1.0 g. Vpc analysis (PEG 6000 or UCON LB 500×, 3-m, 130°) of the first distillate showed one major component. Redistillation of the first fraction gave pure **4**: *m/e* 158; ir 1725 (C=O) and 960 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.23 (3 H, t, J = 7.0 Hz), 1.38 (3 H, s), 2.28 (3 H, s), 3.43 (2 H, q, J = 7.0 Hz), and 4.10–4.90 (3 H, m, ring protons).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.54; H, 8.98.

Vpc analysis (UCON LB 550×, 1-m, 100°) of the second fraction showed many peaks which seemed to be decomposed materials. The mass spectrum and elemental analysis indicated that this fraction mainly consisted 2:1 adducts of biacetyl and ethyl vinyl ether, but the structure has not been determined yet because of its complex nmr spectrum.

Biacetyl–2-Ethoxypropene (5a) Photoadducts.—A mixture of biacetyl and **5a** was irradiated for 72 hr. After the removal of the unreacted materials, the fraction boiling at 80–98° (23 mm) (8.4 g) was collected; residues, 1.4 g. Vpc analysis using 3-m PEG-6000 column at 140° indicated three major peaks with the relative ratio of peak heights 1.7:1.0:1.3. The products were isolated by preparative vpc on 3-m PEG-6000 column at 150°. The first component was identified as **7a**: bp 87° (23 mm); *m/e* 172; ir 1730 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.18 (3 H, t, J = 7.0 Hz), 1.31 (3 H, s), 1.40 (3, H, s), 2.15 (3 H, s), 3.38 (2 H, q, J = 7.0 Hz), 3.97 (1 H, d, J = 6.0 Hz), and 4.32 (1 H, d, J = 6.0 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.87; H, 9.38.

The second component was identified as **8a**: bp 87° (23 mm); *m/e* 172; ir 173 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.07 (3 H, t, J = 7.0 Hz), 1.32 (3 H, s), 1.45 (3 H, s), 2.32 (3 H, s), 4.20 (1 H, d, J = 6.0 Hz), 3.30 (2 H, q, J = 7.0 Hz), and 4.48 (1 H, d, J = 6.0 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.54; H, 9.62.

The third component was identified as **6a**: bp 90° (23 mm); *m/e* 172; ir 1730 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) δ 1.24 (3 H, d, J = 7.0 Hz), 1.28 (3 H, t, J = 7.0 Hz), 2.12 (3 H, s), 3.74 (1 H, q, J = 7.0 Hz), 3.74 (2 H, q, J = 7.0 Hz), 3.83 (2 H, m), 3.94 (1 H, d, J = 1.5 Hz), and 4.09 (1 H, d, J = 1.5 Hz).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.49; H, 9.67.

Biacetyl–α-Methylstyrene (5b) Photoadducts.—A solution of biacetyl and **5b** was irradiated for 48 hr. After the removal of the unreacted material under reduced pressure, a fraction boiling at 110–120° (6 mm) (1.4 g) was collected; residues, 0.5 g. Vpc analysis using 3-m PEG-6000 column at 180° indicated three major peaks with the relative ratio of peak heights 5.8:1.0:3.8. These three photoproducts were isolated by preparative vpc on a 3-m PEG-6000 column at 180°. The first component was identified as **7b**: bp 85° (3 mm); *m/e* 204; ir 1725 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.11 (3 H, s), 1.45 (3 H, s), 2.22 (3 H, s), 4.10 (1 H, d, J = 5.5 Hz), 4.96 (1 H, d, J = 5.5 Hz), and 7.12 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.54; H, 7.96.

The second component was identified as **8b**: bp 85° (3 mm); *m/e* 204; ir 1725 (C=O) and 970 cm^{-1} (oxetane ring); nmr (CCl_4) δ 1.53 (3 H, s), 1.61 (3 H, s), 1.87 (3 H, s), 4.40 (1 H, d, J = 6.0 Hz), 5.10 (1 H, d, J = 6.0 Hz), and 7.12 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.58; H, 8.13.

The third component was identified as **6b**: bp 90° (3 mm); *m/e* 204; ir 1730 (C=O), 1640 (C=C), and 1120 cm^{-1} (ether); nmr (CCl_4) δ 1.22 (3 H, d, J = 7.0 Hz), 2.00 (3 H, s), 3.74 (1 H, q, J = 7.0 Hz), 4.30 (2 H, m), 5.24 (1 H, d, J = 1.5 Hz), 5.42 (1 H, d, J = 1.5 Hz), and 7.22 (5 H, m).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.64; H, 7.86.

Biacetyl–Isobutene (5c) Photoadducts.—A solution of biacetyl and **5c** was irradiated 102 hr at 0° and distilled to obtain 2.4 g of photoproduct mixture, bp 60–90° (16 mm), and 0.7 g of residue. Dissolution of the distillate in hexane, cooling, and separation by suction filtration gave the pinacol **9** (0.4 g), recrystallized from hexane–ether: mp 95–96° (lit. mp 95–96°); nmr (CCl_4) δ 1.16 (3 H, s), 2.24 (3 H, s), and 4.46 (1 H, s). These were in accord with reported values.[2]

The filtrate was analysed by vpc (6-m PEG-6000 or UCON LB 550 ×, 110°). Three major peaks with the relative peak heights 1:1.6:4.1 were detected. The first and the second components [bp 55–60 (22 mm)] were separated as a mixture from the third component [bp 80° (22 mm)] by preparative vpc (3-m, UCON LB 550×, 110°), owing to the close retention time between the first and second components. Elemental analysis and mass spectra by a directly coupled gas chromatograph–mass spectrometer (Hitachi RMS-4) of a mixture of the first and the second component indicated that these components were 1:1 adduct of biacetyl and **5c** (*m/e* 142 for each component). Ir spectrum showed a carbonyl peak at 1720, vinyl peak at 1620, ether peak at 1110, and oxetane ring at 970 cm^{-1}. Nmr spectrum (100 MHz) of the mixture in CCl_4 showed that the first component was 3,3,4-trimethyl-4-acetyloxetane, having δ at 1.16 (3 H, s), 1.24 (3 H, s), 1.39 (3 H, s), 2.25 (3 H, s), and 4.13 (2 H, AB quartet, J = 5.5 Hz), and the second component was an allylic ether **6c**, having δ 1.31 (3 H, d, J = 7.0 Hz), 1.81 (3 H, m), 2.17 (3 H, s), 3.71 (1 H, q, J = 7.0 Hz), 4.87 (1 H, m), and 4.95 (1 H, m).

Anal (of the mixture). Calcd for $C_5H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.89; H, 9.99.

The third component was identified as **10**: *m/e* 142; ir 3450 (OH), 1720 (C=O), and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 1.30 (3 H, s), 1.72 (3 H, m), 2.17 (3 H, s), 2.38 (2 H, s), 3.40 (1 H, broad), 4.64 (1 H, m), and 4.78 (1 H, m).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.39; H, 9.72.

Biacetyl–2-Methyl-2-butene (5d) Photoadducts.—A mixture of biacetyl and **5d** was irradiated for 50 hr. After the removal of unreacted materials, the fraction boiling at 60–80° (25 mm) (5.3 g) was collected; residues, 1.5 g. The products were analyzed and separated by vpc using 3-m PEG 6000 at 130°. The relative ratio of peak heights of the two major peaks was 2.4:1.0. The first component was identified as **6d**: bp 65°

(20 mm); *m/e* 156; ir 1720 (C=O), 1650 (C=C), and 1110 cm^{-1} (ether); nmr (CCl_4) δ 1.22 (3 H, d, J = 7.0 Hz), 1.28 (3 H, d, J = 7.0 Hz), 1.72 (3 H, m), 2.11 (3 H, s), 3.70 (1 H, q, J = 7.0 Hz), 3.93 (1 H, q, J = 7.0 Hz), and 4.87 (2 H, m).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.29; H, 10.58.

The second component was identified as 2,3,3,4-tetramethyl-4-acetyloxetane: bp 70° (20 mm); *m/e* 156; ir 1720 (C=O) and 990 cm^{-1} (oxetane ring); nmr (CCl_4) δ 0.95 (3 H, s), 1.10 (3 H, s), 1.18 (3 H, d, J = 7.0 Hz), 1.33 (3 H, s), 2.15 (3 H, s), and 4.40 (1 H, q, J = 7.0 Hz).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.47; H, 10.13.

Biacetyl–2,3-Dimethyl-2-butene (5e) Photoadducts.—A mixture of biacetyl and **5e** was irradiated for 48 hr. After the removal of unreacted materials, the fraction boiling at 73–84° (13 mm) (8.1 g) was collected; residues, 0.6 g. Vpc analysis (3-m PEG 6000 or UCON LB 550 X, 140°) indicated that the photoproduct mixture contained one major component **6e** and several minor components (**6e**:others = 5.0:1.0). The ir spectrum of the fraction mixture indicated that the minor components mainly consisted of alcohol compounds. Separation by preparative vpc (3-m PEG 6000, 140°) gave pure **6e**: bp 74° (13 mm); *m/e* 170; ir 1728 (C=O), 1650 (C=C), and 1110 cm^{-1} (ether); nmr (CCl_4) δ 1.16 (3 H, d, J = 7.0 Hz), 1.23 (3 H, s), 1.28 (3 H, s), 1.73 (3 H, m), 2.08 (3 H, s), 3.61 (1 H, q, J = 7.0 Hz), and 4.86 (2 H, m).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66. Found: C, 70.39; H, 10.57.

Irradiation of Biacetyl to α-methyl-d_3-Styrene (5b').—**5b'** (D = 87%) was prepared by the Wittig reaction of methyltriphenylphosphonium bromide and trideuteriomethyl phenyl ketone.[26] A mixture of 2.6 g (0.03 M) of biacetyl and 3.6 g (0.03 M) of **5b'** in 180 ml of benzene was irradiated for 60 hr. After the recovery of **5b'** (1.6 g), a boiling fraction at 110–120° (6 mm) (0.7 g) was collected; residues, 0.4 g. Vpc analysis and isolation of the products done by the same conditions as for **5b**. The ratio of **6b**:**7b**:**8b** = 2.0:5.8:1.0. The % D of starting and recovered **5b'** and the photoproducts were determined by nmr. No deuterium was introduced into position C_α of the allyl moiety of **6b'** (% D of C_γ and methine protons, 87%).

Biacetyl–Isobutene Photoaddition at Room Temperature.—A mixture of biacetyl (0.01 M) and isobutene (0.01 M) in benzene was irradiated at room temperature in a Pyrex test tube for 6 hr. The reaction mixture was analyzed as described above. It was shown that the ratio of **6c**:oxetane was 1.62:1.0.

Registry No.—**1**, 26995-37-9; **2**, 26995-38-0; **3**, 26959-33-1; **4**, 26959-34-2; **5a**, 926-66-9; **5b**, 98-83-9; **5b'**, 16914-16-2; **5c**, 115-11-7; **5d**, 513-35-9; **5e**, 563-79-1; **6a**, 40519-21-9; **6b**, 40519-22-0; **6c**, 40519-23-1; **6d**, 26959-35-3; **6e**, 40519-25-3; **7a**, 40519-26-4; **7b**, 40519-27-5; **8a**, 40580-22-1; **8b**, 40519-28-6; **10**, 40519-29-7; biacetyl, 431-03-8; indene, 95-13-6; furan, 110-00-9; ethyl vinyl ether, 109-92-2; 3,3,4-trimethyl-4-acetyloxetane, 40519-30-0; 2,3,3,4-tetramethyl-4-acetyloxetane, 26959-36-4; methylphenylphosphonium bromide, 1779-49-3; trideuteriomethyl phenyl ketone, 17537-31-4.

A Simple, High Yield Synthesis of Arginine Vasopressin

DAVID A. JONES, JR.,* RICHARD A. MIKULEC, AND ROBERT H. MAZUR

Department of Chemical Research, Searle Laboratories, Division of G. D. Searle & Company, Skokie, Illinois 60076

Received February 27, 1973

Biologically fully active arginine vasopressin has been synthesized *via* the stepwise active ester and fragment condensation methods. The synthesis was begun with proline at the carboxyl terminus utilizing the trityl group for sulfhydryl protection of cysteine and the Boc group for amino nitrogen protection. Synthesis of Boc-Cys(Trt)-Tyr-Phe-Gln-Asn-Cys(Trt)-Pro was followed by cyclization of the cysteine moiety in 70% yield with I_2 in 80% acetic acid. The remaining dipeptide unit, Arg-Gly-NH_2, was attached to proline by means of the hydroxysuccinimide ester of the cyclized heptapeptide. The guanidyl group was protected as a picrate. The Boc group was then removed from protected vasopressin with 90% TFA to give, after final purification, vasopressin in an overall yield of 11%.

Many syntheses of the antidiuretic hormone arginine vasopressin, (**18**) have been published over the past 18 years. Most of these syntheses[1-5] have involved the fragment condensation method, the exception being the guanylation of a protected ornithine nonapeptide[6] and a solid phase synthesis.[7]

In all of these methods, however, the benzyl group has been utilized for the protection of the sulfhydryl group of cysteine. Treatment of a fully protected nonpeptide with sodium in liquid ammonia and subsequent oxidation to form the disulfide bridge has afforded the desired hormone in varying degrees of yield and purity. The main disadvantage of such an approach has been the rather low yield of pure material obtained in the final cyclization step.

In an effort to minimize side reactions during the cyclization to form the disulfide bridge and in order to obtain intermediates for biological testing, we have used a different approach in synthesizing this hormone. We achieved sulfhydryl protection by means of the easily removed trityl group, masking of the α-amino nitrogen with the *tert*-butoxycarbonyl (Boc)[8] group and blocking of the guanidyl group of arginine by protonation. The complete synthesis is outlined in Chart I and was achieved with an overall yield of 11% [based on Boc-Cys(Trt)-OCP] of biologically fully active hormone.

All coupling reactions were performed in DMF *via* active esters and all intermediates, other than **15**, have been characterized. Initially, 90% trifluoroacetic acid (TFA) was used to remove the Boc group. Although trityl groups apparently were removed from sulfur atoms to some extent during the procedure,[9] subsequent removal of the solvent *in vacuo* at 40° reversed the equilibrium and retritylated the peptide. Addition of ether to the resulting oily residue afforded a solid TFA

(1) V. du Vigneaud, D. T. Gish, and P. G. Katsoyannis, *J. Amer. Chem. Soc.*, **76**, 4751 (1954).

(2) P. G. Katsoyannis, D. T. Gish, and V. du Vigneaud, *ibid.*, **79**, 4516 (1957).

(3) V. du Vigneaud, D. T. Gish, P. G. Katsoyannis, and G. P. Hess, *ibid.*, **80**, 3355 (1958).

(4) R. O. Studer and V. du Vigneaud, *ibid.*, **82**, 1499 (1960).

(5) R. O. Studer, *Helv. Chim. Acta*, **46**, 421 (1963).

(6) M. Bodanszky, M. A. Ondetti, C. A. Birkhimer, and P. L. Thomas, *J. Amer. Chem. Soc.*, **86**, 4452 (1964).

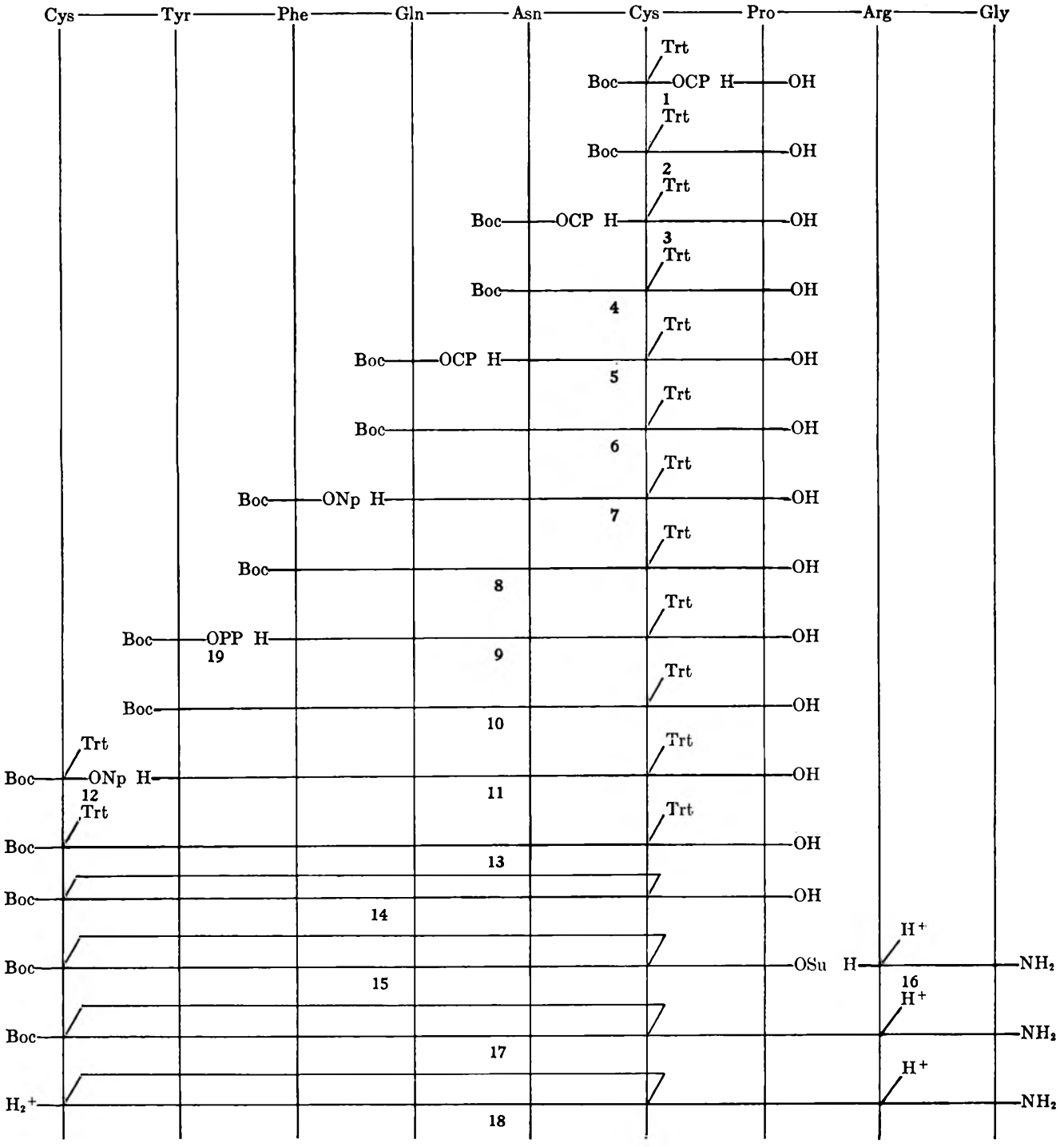
(7) J. Meienhofer, A. Trzeciak, R. T. Havran, and R. Walter, *ibid.*, **93**, 7199 (1970).

(8) Abbreviations according to IUPAC-IUB recommendations: *Biochem. J.*, **126**, 773 (1972). In addition, OCP = 2,4,5-trichlorophenoxy and OPP = pentachlorophenoxy. All amino acids have the L configuration.

(9) I. Photaki, J. Taylor-Papadimitriou, C. Sakarellos, P. Mazarakis, and L. Zervas, *J. Chem. Soc. C*, 2683 (1970).

CHART I

SYNTHESIS OF ARGININE VASOPRESSIN



salt which was <2% detritylated (based on recovered triphenylcarbinol). This method of deblocking was successfully used up to the preparation of **7**, at which step an approximately 1:1 mixture of **7** and <Glu-Asn-Cys(Trt)-Pro was obtained. We then turned to a tenfold excess of 2 *M* HCl in a 1:2 dioxane–acetic acid system as a means of deprotection and this afforded **7** in 90% yield with almost no pyroglutaminyl tetrapeptide being formed. The method of work-up was exactly as described for the Boc removal with TFA. Except for the final step in preparing **18** from **17**, the HCl method was used throughout the synthesis with excellent results.

One interesting observation should be briefly mentioned at this point. During the coupling of Boc-Asn-OCP with **3**, the usual excess of active ester (10–15%) was found to be insufficient to react completely with the dipeptide. It was apparent from thin layer chromatography data that the active ester was itself decomposing during the coupling reaction. This decomposition is currently being studied by us in order to determine the products formed by Boc-Asn-OCP under normal coupling conditions. Preliminary results have indicated that there is more than one decomposition product and the amounts of these products are de-

pendent on whether *N*-methylmorpholine is present in a DMF solution of the active ester.

Cyclization of protected heptapeptide **13** was accomplished by the addition of a 5×10^{-3} *M* solution of **13** in 80% acetic acid to an excess of I_2 (5×10^{-3} *M* in 80% acetic acid) in a manner similar to those previously described.[10,11]

To avoid removal of the Boc group during work-up, 1 *N* NaOH (equivalent to the HI formed) was added. The solvent was removed *in vacuo* and ether was added to give a solid which, after countercurrent distribution, gave a 70% yield of pure **14**.

Formation of the protected vasopressin **17** was accomplished by the *in situ* preparation of the *N*-hydroxysuccinimide active ester and coupling to H-Arg-Gly-NH_2·picrate (prepared *in situ* from the dipicrate[12]). Although crude **17** can be used satisfactorily in the final step, a small amount was purified by countercurrent distribution and characterized as a monopicrate. It was most interesting that the picrate salt remained intact during countercurrent distribution in the system *n*-BuOH–HOAc–H_2O (4:1:5) without formation of the expected acetate.

Crude **17** was deprotected in 90% TFA and then precipitated with ether. Purification of the vasopressin **18** and removal of picric acid were accomplished by means of gradient elution with 0.1 *N* to glacial acetic acid from an IRC-50 ion-exchange column. Fractions containing vasopressin were then collected; the solvent was removed *in vacuo* at 45° and the product lyophilized. Drying *in vacuo* at about 105° for 16 hr over magnesium perchlorate afforded the pure hormone as a diacetate·$^1/_2$ hydrate, homogeneous by thin layer chromatography. After standing in air for several days, subsequent elemental analysis showed the compound to be a diacetate·$3^1/_2$ hydrate. Bioassay[13] on the ethanol–saline loaded rat indicated an activity of 454 IU/mg.

Several advantages of this synthetic method are evident: (1) oxidation of a protected intermediate gives a high yield of easily purified disulfide; (2) the overall yield obtained is excellent; (3) it should be easy to scale-up this synthesis to allow preparation of gram quantities of the hormone or analogs; (4) the use of a cyclic disulfide as an intermediate does not pose any particular problems as **14** is stable to TFA, coupling conditions, countercurrent distribution, and ion-exchange chromatography.

We are currently optimizing yields at all stages of the reaction sequence, investigating the use of more stable sulfhydryl-protecting groups, and continuing to study the cyclization reaction under various conditions.

Experimental Section

Thin layer chromatograms (tlc) were run on silica gel G with 1-butanol–HOAc–H_2O (7:1:2) (R_{fA}), $CHCl_3$–MeOH–HOAc–H_2O (64:30:2:4) (R_{fB}), $CHCl_3$–MeOH (95:5) (R_{fC}), $CHCl_3$–MeOH (98:2) (R_{fD}), and $CHCl_3$–MeOH (90:10) (R_{fE}). Spots were revealed with *tert*-butyl hypochlorite followed by KI (1%)–starch (1%).[14] Purifications by means of countercurrent distribution (CCD) were performed in $CHCl_3$–CCl_4–MeOH–H_2O (26:27:37:10) (system 1) or 1-butanol–HOAc–H_2O (4:1:5) (system 2). Melting points[15] were obtained on a Mel-Temp capillary melting point apparatus and were uncorrected, and optical rotations were obtained with a Perkin-Elmer Model 141 polarimeter.

Boc-Cys(Trt)-OCP (1).—A solution of 28.1 g (60.6 mmol) of Boc-Cys(Trt)-OH[16] and 13.7 g (69.7 mmol) of 2,4,5-trichlorophenol in 110 ml of EtOAc was cooled to 4° in an ice bath. To the stirred solution was added 13.2 g (66.7 mmol) of dicyclohexylcarbodiimide (DCCD) in 30 ml of EtOAc; the reaction mixture was stirred in ice for 1.5 hr and then allowed to warm to room temperature over a 2.5-hr period. The precipitate of dicyclohexylurea (DCU) was removed by filtration, treated with boiling acetone, and filtered again. The combined filtrates were stripped *in vacuo* to leave a solid which was purified by crystallization from *i*-PrOH–EtOAc: yield 29.2 g (75%) of white compound; mp 166–167°; $[\alpha]^{24}D$ +24° (*c* 1, DMF); R_{fC} 0.78.

Anal. Calcd for $C_{33}H_{30}Cl_3NO_4S$: C, 61.64; H, 4.70; S, 4.99; Cl, 16.54. Found: C, 61.84; H, 4.64; S, 5.17; Cl, 16.24.

Boc-Cys(Trt)-ONp[17] (12).—A solution of 28.5 g (61.5 mmol) of Boc-Cys(Trt)-OH and 11.1 g (80.0 mmol) of *p*-nitrophenol in 225 ml of EtOAc was cooled to 20° and treated dropwise, with stirring, over a 15-min period with a solution of 14.0 g (68.0 mmol) of DCCD in EtOAc. The reaction mixture was stirred 1 hr at 20° and then at room temperature for 2 hr. The DCU was filtered and the filtrate was washed successively with 3 × 100 ml of 1 *M* K_2CO_3 and 3 × 100 ml of water and then dried (Na_2SO_4). Evaporation of the dried solvent *in vacuo* gave a solid which was dissolved in a minimum quantity of warm benzene and filtered into 1 l. of stirred Skellysolve B, yield 25.9 g (72.0%) of tan crystals, mp 160.5–164°. An analytical sample, recrystallized from xylene, had mp 164–167°, R_{fD} 0.64, $[\alpha]^{28}D$ +37° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{33}H_{32}N_2O_6S$: C, 67.79; H, 5.52; N, 4.79; S, 5.48. Found: C, 67.91; H, 5.40; N, 4.66; S, 5.27.

Boc-Cys(Trt)-Pro (2).—A 2.53-g (22.0 mmol) sample of (L)-Pro was dissolved in 75 ml of DMF with 3.64 ml of 6.04 *N* HCl in dioxane, and then 12.9 g of 1 was added. The reaction was initiated by the addition of 5.0 ml (45 mmol) of *N*-methylmorpholine and the reaction mixture stirred for 24 hr at room temperature, after which it was cooled. Unreacted proline was removed by filtration and the filtrate added to 800 ml of rapidly stirred, cold 1 *N* HCl. The resulting white precipitate was filtered, washed with cold water, and air-dried. Purification was effected by dissolving the crude protected dipeptide in 50 ml of EtOAc and adding the solution to 600 ml of cold, rapidly stirred Skellysolve B. After drying *in vacuo* at 40° for 1.5 hr, 10.8 g (91.4%) of 2 was obtained as a $1^1/_2$ hydrate: R_{fB} 0.89, R_{fC} 0.18; $[\alpha]^{29}D$ +31° (*c* 1, DMF), +26° (*c* 1, MeOH).

Anal. Calcd for $C_{32}H_{36}N_2O_6S \cdot 1^1/_2H_2O$: C, 65.39; H, 6.69; N, 4.77; S, 5.46. Found: C, 65.45; H, 6.23; N, 4.74; S, 5.20.

H-Cys(Trt)-Pro·HCl (3).—A 2.80-g (5.00 mmol) sample of 2 was dissolved in 17 ml of HOAc and then treated at room temperature for 5 min with 8.2 ml of 6.2 *N* HCl in dioxane. The solvents were removed *in vacuo* at 45°, and anhydrous ether was added to the residual oil to give a white precipitate. After filtering, washing several times with ether, and drying *in vacuo* at 75° for 1.5 hr, 2.21 g (89.0%) of **3** was obtained, R_{fA} 0.31, $[\alpha]^{27}D$ +46° (*c* 1, MeOH).

Anal. Calcd for $C_{27}H_{28}N_2O_3S \cdot HCl \cdot H_2O$: C, 62.96; H, 6.07; N, 5.44; S, 6.22; Cl, 6.88. Found: C. 62.98; H, 5.81; N, 5.66; S, 6.41; Cl, 6.48.

Boc-Asn-Cys(Trt)-Pro (4).—A solution of 19.8 mmol of **3**, 23.8 mmol (20% excess) of Boc-Asn-OCP,[18] and 4.5 ml (40 mmol) of *N*-methylmorpholine in 90 ml of DMF was stirred overnight at room temperature. A routine tlc of the reaction mixture showed some **3** still remaining and no active ester, which has R_{fE} 0.58. An additional 0.82 g (2.0 mmol) of Boc-Asn-

(10) B. Kamber, H. Brückner, B. Riniker, P. Sieber, and W. Rittel, *Helv. Chim. Acta*, **53**, 556 (1970).

(11) R. Geiger and W. König, German Patent 1917939 (1970).

(12) D. T. Gish and V. du Vigneaud, *J. Amer. Chem. Soc.*, **79**, 3579 (1957). Other salts of this dipeptide are extremely hygroscopic and difficult to store and manipulate.

(13) L. M. Hofmann, *Arch. Int. Pharmacodyn. Ther.*, **169**, 189 (1967).

(14) R. H. Mazur, B. W. Ellis, and P. S. Cammarata, *J. Biol. Chem.*, **237**, 1619 (1962).

(15) In many instances, the melting points of various peptide intermediates were undefined and therefore are not reported.

(16) H. Zahn and K. Hammerström, *Chem. Ber.*, **102**, 1048 (1969).

(17) E. Schnabel, H. Klostermeyer, and H. Berndt, *Justus Liebigs Ann. Chem.*, **749**, 90 (1971).

(18) W. Broadbent, J. S. Morley, and B. E. Stone, *J. Chem. Soc. C*, 2632 (1967).

OCP was added and the reaction mixture again stirred at room temperature overnight. At the end of this time, tlc showed no **3** present and some Boc-Asn-OCP, which was decomposed with 1 ml (9 mmol) of $(CH_3)_2NCH_2CH_2NH_2$ at room temperature for 1 hr. After cooling to 4°, the reaction mixture was added to 1250 ml of cold 1 *N* HCl with rapid stirring. The resulting white precipitate was filtered, washed with water, and air-dried. Dissolving the crude protected tripeptide in 90 ml of EtOAc, boiling, and cooling afforded a 78% yield of pure **4**: R_{fA} 0.78, R_{fE} 0.19; $[\alpha]^{27}D$ −4.2° (*c* 1, DMF); mp 199–200° dec.

Anal. Calcd for $C_{36}H_{42}N_4O_7S \cdot {}^1/_2H_2O$: C, 63.23; H, 6.48; N, 8.19; S, 4.69. Found: C, 63.49; H, 6.42; N, 8.48; S, 4.74.

H-Asn-Cys(Trt)-Pro·HCl (5).—It was prepared in 98% yield in the same manner as previously described for **3**, R_{fA} 0.45, $[\alpha]^{27}D$ +32° (*c* 1, MeOH).

Anal. Calcd for $C_{31}H_{34}N_4O_5S \cdot HCl \cdot H_2O$: C, 59.18; H, 5.93; N, 8.90; S, 5.10; Cl, 5.64. Found: C, 59.12; H, 5.89; N, 8.64; S, 5.34; Cl. 5.44.

Boc-Gln-Asn-Cys(Trt)-Pro (6).—It was prepared as described previously for **4** using a 10% excess of Boc-Gln-OCP.[18] Crude product was triturated with Skellysolve B and dried *in vacuo* to a glassy foam, R_{fA} 0.77, with faint impurities at R_{fA} 0.27 and R_{fA} 0.83. An analytically pure sample was obtained by stirring the impure product for 2 hr at room temperature in 1% HCl, filtering, drying, again triturating and washing with Skellysolve B and drying *in vacuo*, $[\alpha]^{28}D$ −13° (*c* 1, HOAc).

Anal. Calcd for $C_{41}H_{50}N_6O_9S$: C, 61.33; H, 6.28; N, 10.45; S, 3.99. Found: C, 61.21; H, 6.35; N, 10.26; S, 4.24.

H-Gln-Asn-Cys(Trt)-Pro·HCl (7).—Crude **6** was deprotected as previously described for **3** to give a 92% yield of tetrapeptide salt (based on two steps from **5**): R_{fA} 0.35; $[\alpha]^{28}D$ +9° (c 1, DMF), +7° (*c* 1, MeOH).

Anal. Calcd for $C_{36}H_{42}N_6O_7S \cdot HCl \cdot 3H_2O$: C, 54.50; H, 6.22; N, 10.59; S, 4.04; Cl, 4.47. Found: C, 54.40; H, 5.81; N, 10.31; S, 3.98; Cl, 4.55.

Attempted Preparation of H-Gln-Asn-Cys(Trt)-Pro·CF_3CO_2H.—A 402-mg (0.500 mmol) sample of **6** was stirred at room temperature for 5.5 hr with 1.5 ml of a 1:1 TFA–HOAc solution and then added to cold ether. The white precipitate was filtered and dried to give 358 mg of a compound which showed two spots at R_{fA} 0.25 and R_{fA} 0.42. The reaction was repeated on a larger scale using anhydrous TFA at room temperature for 5 min with the same results. Since it was suspected that one of the two products might be <Glu-Asn-Cys(Trt)-Pro resulting from the cyclization of glutamine, the following procedure was adopted.

A 1.51-g sample of the mixed products was dissolved with 0.91 g of Boc-Phe-ONp and 0.42 ml of *N*-methylmorpholine in 10 ml of DMF and the reaction followed by tlc. Over a period of 6 hr, the material at R_{fA} 0.25 gradually disappeared while the material having an R_{fA} of 0.42 remained unchanged. After 24 hr at room temperature, there was no change in the tlc other than what had taken place during the first 6 hr of reaction time. After work-up in the usual manner, the crude material (1.95 g) was purified *via* CCD (system 1). After 400 transfers, two products were obtained: 360 mg of a compound having K = 3.9 and R_{fA} 0.42, and the second (500 mg) having K = 0.9, R_{fA} 0.78. The compound having the higher R_f value and lower partition coefficient was identified by nmr and analysis as Boc-Phe-Gln-Asn-Cys(Trt)-Pro (**8**), $[\alpha]^{26}D$ +0.5° (*c* 1, DMF).

Anal. Calcd for $C_{50}H_{59}N_7O_{10}S \cdot 2H_2O$: C, 60.90; H, 6.44; N, 9.94; S, 3.25. Found: C, 60.56; H, 6.14; N, 9.78; S, 3.41.

The compound with the R_f value of 0.42 and K = 3.9 was tentatively identified by nmr and elemental analysis as <Glu-Asn-Cys(Trt)-Pro.

Anal. Calcd for $C_{36}H_{39}N_5O_7S \cdot H_2O$: C, 61.43; H, 5.87; N, 9.95; S, 4.56. Found: C, 61.62; H, 6.31; N, 9.97; S, 4.42.

Comparison of the ir and nmr spectra and tlc's of this material with those of authentic <Glu-Asn-Cys(Trt)-Pro (see following experiment) satisfactorily proved its structure.

<Glu-Asn-Cys(Trt)-Pro.—It was prepared in 75% yield in the usual manner from <Glu-OPP,[19] **5**, and *N*-methylmorpholine in DMF. The crude product was treated with Darco G-60 in a MeOH–EtOAc solution and added to a tenfold excess of ether. The resulting white powder was filtered, washed with ether, and dried *in vacuo* at 65°. Tlc showed one spot, R_{fA} 0.45 and R_{fB} 0.64; mp decomposes gradually from 160–200°, $[\alpha]^{28}D$ −5.2° (*c* 1, DMF).

Anal. Calcd for $C_{36}H_{39}N_5O_7S \cdot H_2O$: C, 61.43; H, 5.87; N, 9.95; S, 4.56. Found: C, 61.17; H, 5.92; N, 9.49; S, 4.59.

The compound had identical ir and nmr with those of the by-product isolated by CCD after the coupling of impure H-Gln-Asn-Cys(Trt)-Pro·CF_3CO_2H with Boc-Phe-ONp.

Boc-Phe-Gln-Asn-Cys(Trt)-Pro (8).—It was synthesized from 9.45 g (11.9 mmol) of **7**, 5.06 g (13.1 mmol) of Boc-Phe-ONp,[20] and 2.8 ml (25.2 mmol) of *N*-methylmorpholine in 50 ml of DMF as described for **2**. To remove <Glu-Asn-Cys(Trt)-Pro as a by-product, the crude material was purified *via* CCD (system 1). After 400 transfers, 9.30 g (80% yield) of pure pentapeptide (as a $1^1/_2$ hydrate) was collected from tubes 135–200 (K = 0.7). Tlc showed one spot, R_{fA} 0.78, $[\alpha]^{28}D$ −2.5° (*c* 1, DMF).

Anal. Calcd for $C_{50}H_{59}N_7O_{10}S \cdot 1^1/_2H_2O$: C, 61.46; H, 6.40; N, 10.04; S, 3.28. Found: C, 61.22; H, 6.13; N, 9.91; S, 3.20.

H-Phe-Gln-Asn-Cys(Trt)-Pro·HCl (9).—The protected pentapeptide **8** (1.65 g) was dissolved in 6 ml of HOAc and stirred with 3 ml of 6 *N* HCl in dioxane solution for 4 min. After removing the solvents *in vacuo* at 40°, adding ether to solidify the product, washing, and drying, a quantitative yield of the hydrochloride salt was obtained. Tlc showed one spot, R_{fA} 0.33, $[\alpha]^{26}D$ +3.0° (*c* 1, DMF).

Anal. Calcd for $C_{45}H_{51}N_7O_8S \cdot HCl \cdot 2H_2O$: C, 58.59; H, 6.12; N, 10.63; S, 3.48; Cl, 3.84. Found: C, 58.55; H, 6.17; N, 10.49; S, 3.72; Cl, 3.74.

Boc-Tyr-OPP (19).—To 10.1 g (35.8 mmol) of Boc-Tyr-OH[21] and 14.3 g (53.7 mmol) of pentachlorophenol in 50 ml of cold EtOAc was added a cooled solution of 8.12 g (39.4 mmol) of DCCD in 15 ml of EtOAc, and the reaction mixture was stirred in an ice bath for 1.5 hr. At that time an additional 50 ml of EtOAc was added to enhance stirring of the thick reaction mixture. After stirring overnight at room temperature, the precipitated DCU was removed by filtration and washed with acetone; the filtrate was dried over anhydrous $MgSO_4$ and stripped to a tan solid. Purification by crystallization from EtOAc–Skellysolve B afforded 10.4 g (54.7%), mp 167.5–168.5°, R_{fC} 0.53, $[\alpha]^{28}D$ −42° (*c* 1, MeOH).

Anal. Calcd for $C_{20}H_{18}Cl_5NO_5$: C, 45.35; H, 3.43; N, 2.64; Cl, 33.47. Found: C, 45.53; H, 3.42; N, 2.60; Cl, 33.70.

Boc-Tyr-Phe-Gln-Asn-Cys(Trt)-Pro (10).—It was synthesized as previously described for **2** from 8.67 g (9.22 mmol) of **9**, 5.36 g (10.1 mmol) of **19**, and 2.2 ml (19.8 mmol) of *N*-methylmorpholine in 60 ml of DMF. The crude product was boiled in 15 parts of EtOAc, the solution cooled, and ether added. After filtering, washing with ether, and drying, 9.45 g (89%) of pure hexapeptide was obtained. Tlc showed one spot, R_{fA} 0.72; $[\alpha]^{28}D$ −9.0° (*c* 1, DMF), −26.5° (*c* 1, MeOH).

Anal. Calcd for $C_{59}H_{68}N_8O_{12}S \cdot 2.5H_2O$: C, 61.17; H, 6.35; N, 9.67; S, 2.77. Found: C, 61.08; H, 6.07; N, 9.60; S, 3.08.

H-Tyr-Phe-Gln-Asn-Cys(Trt)-Pro·HCl (11).—Deprotection of 9.33 g (8.06 mmol) of **10** in 27 ml HOAc and 13.5 ml of 6.04 *M* HCl in dioxane as described for **3**, afforded a quantitative yield of the desired hydrochloride salt. Tlc showed one spot, R_{fA} 0.45, $[\alpha]^{28}D$ −9.0° (*c* 1, DMF).

Anal. Calcd for $C_{54}H_{60}N_8O_{10}S \cdot HCl \cdot 3H_2O$: C, 58.76; H, 6.12; N, 10.15; S, 2.90; Cl, 3.21. Found: C, 58.87; H, 5.91; N, 10.10; S, 2.82; Cl, 3.53.

Boc-Cys(Trt)-Tyr-Phe-Gln-Asn-Cys(Trt)-Pro (13).—It was synthesized in the usual manner from 3.40 g (3.16 mmol) of **11**, 2.07 g (3.54 mmol) of **12**, and 0.70 ml (6.30 mmol) of *N*-methylmorpholine in 25 ml of DMF. The crude product was dissolved in five parts of boiling EtOAc which, upon cooling, gave an oil. The oil solidified after trituration with cold EtOAc, and the product was filtered and dried, wt 3.76 g. An additional 0.63 g was obtained upon dilution of the filtrate with Skellysolve B. Tlc data on both crops showed identical results, R_{fA} 0.90, with a faint impurity at R_{fA} 0.40; both crops showed one spot at R_{fB} 0.87. Overall yield was 93% (as a dihydrate), $[\alpha]^{26}D$ −15° (*c* 1, MeOH).

Anal. Calcd for $C_{81}H_{87}N_9O_{13}S_2 \cdot 2H_2O$: C, 65.08; H, 6.14; N, 8.43; S, 4.29. Found: C, 65.35; H, 6.45; N, 8.35; S, 4.40.

(19) G. Flouret, *J. Med. Chem.*, **13**, 843 (1970).

(20) E. Sandrin and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1637 (1963).

(21) E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).

Boc-Cys-Tyr-Phe-Gln-Asn-Cys-Pro (14).—To 475 ml of 4.8 $\times 10^{-3}$ *M* I_2 (2.28 mmol) in 80% aqueous HOAc was added at room temperature over a 75-min period a solution of 3.15 g (2.13 mmol) of 13 in 425 ml of 80% aqueous HOAc. After stirring at room temperature for an additional 30 min, the excess I_2 was reduced with 1 *N* Na_2SO_3 and 5.1 ml of 1 *N* NaOH was added to neutralize HI. The reaction mixture was stripped to an oil which solidified upon trituration with cold ether. The solid was washed several times with ether and purified *via* CCD (system 2). After 480 transfers, the contents of tubes 170–206 (K = 7.9) were collected, the solvents were evaporated, and the resulting solid was dried *in vacuo* at 75° for 3 hr, wt 1.81 g. Tlc indicated some starting material still present, R_{fA} 0.76 with the desired product R_{fA} 0.47. Therefore, the compound was treated again with 120 ml of I_2 solution and worked up as previously described after stirring for 45 min at room temperature after the addition was completed. Another CCD purification (240 transfers) afforded 1.44 g (69.5%) of 14, R_{fA} 0.47, $[\alpha]^{26}D$ −74° (*c* 1, DMF). Recovered triphenylcarbinol from the ether washings of both cyclization reactions amounted to 985 mg or 88.7% of theory after recrystallization from MeOH.

Anal. Calcd for $C_{43}H_{57}N_9O_{13}S_2 \cdot 3H_2O$: C, 50.32; H, 6.19; N, 12.28; S, 6.25. Found: C, 50.09; H, 5.68; N, 12.64; S, 6.24.

Subsequently, it has been found in the synthesis of analogs that using a 15–20% excess of I_2 will give complete cyclization the first time.

H-Arg-Gly-NH_2·dipicrate (16).—A solution of 24.5 g (60.0 mmol) of Z-Arg(NO_2)-Gly-NH_2[22] in 250 ml of 90% acetic acid containing 2.5 g of Pd (black) was hydrogenated at 25 psi and room temperature for 6.5 hr. Removal of the catalyst and evaporation of the filtrate *in vacuo* left 36.1 g of a viscous oil containing the crude dipeptide and ammonium acetate. The residue was taken up in 125 ml of water and treated with 39.8 g of picric acid in 250 ml of warm ethanol. The resulting precipitate was recrystallized from 1 l. of 8:1 water–ethanol to give 17.9 g (44% yield) of the dipicrate, mp 210.0–210.5° dec, $[\alpha]^{27}D$ +15.3° (*c* 1, 50% aqueous acetone) [lit.[12] mp 209–210°, $[\alpha]^{24}D$ +15.9° (*c* 1, 50% aqueous acetone)].

Boc-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2·picrate (17).—A 1.54-g (1.53 mmol) sample of 14 and 196 mg (1.70 mmol) of *N*-hydroxysuccinimide were dissolved in 6 ml of DMF and treated for 2.5 hr at room temperature with 350 mg (1.70 mmol) of DCCD, after which was added 1.17 g (1.70 mmol) of 16 and 0.20 ml (1.8 mmol) of *N*-methylmorpholine. After stirring overnight at room temperature, the reaction mixture was cooled to 0° and the DCU removed by filtration (recovered 327 mg or 85.7% of theory). The filtrate was concentrated at 40° (oil pump) and the gummy solid triturated at −70° with ether. The resulting yellow solid was washed with ether several times and dried *in vacuo* (70°, 4 hr) to give 3.18 g of crude 17. The sample was divided into two equal portions and 1.59 g purified *via* CCD (system 2). After 240 transfers, the contents of tubes 176–190 (K = 3.4) were collected and solvents evaporated. The product was precipitated with ether in the cold. The filtered nonapeptide was dried *in vacuo* at 55°, yield 576 mg. Tlc showed product, R_{fA} 0.29, picric acid, R_{fA} 0.62, and some impurity still remaining at the origin. A repeat purification on 410 mg for 240 transfers afforded 229 mg of pure 17, $[\alpha]^{27}D$ −79° (*c* 0.5, MeOH), after isolation and drying *in vacuo* (3 hr, 75°) as described above, R_{fA} 0.29, homogeneous.

Anal. Calcd for $C_{51}H_{73}N_{15}O_{14}S_2 \cdot C_6H_3N_3O_7$: C, 48.43; H, 5.42; N, 17.84; S, 4.54. Found: C, 48.53; H, 5.65; N, 17.62; S, 4.54.

Arg^8-vasopressin (18).—To the remaining 1.59 g of crude 17 was added 25 ml of 90% aqueous TFA and the resulting solution stirred at room temperature for 2 hr. Cooling to 0° and the addition of 125 ml of cold ether gave a yellow solid, which weighed 1.17 g after drying *in vacuo* at room temperature. Purification of the crude vasopressin was performed by ion exchange on IRC-50 (100:1 weight ratio) using a gradient elution of 0.1 *N* to glacial acetic acid. Flow rate was 2 ml/min and 15-ml fractions were collected. The purified product was found in tubes 95–160, which were collected and the solvents evaporated. The resulting oily residue was lyophilized and then dried *in vacuo* over magnesium perchlorate for 16 hr at 105°: wt 414 mg or 44.5% yield (as diacetate hemihydrate) in two steps from 14: R_{fA} 0.1; $[\alpha]^{28}D$ −26° (c 0.5, 1 *N* HOAc).

Anal. Calcd for $C_{46}H_{65}N_{15}O_{12}S_2 \cdot 2CH_3CO_2H \cdot {}^1/_2H_2O$: C, 49.47; H, 6.15; N, 17.32; S, 5.28. Found: C, 49.25; H, 5.97; N, 17.17; S, 5.63.

Amino acid analysis[23] showed ½ Cys 1.65, Phe 1.01, Tyr 0.89, Glu 1.02, Asp 1.07, Pro 0.98, Arg 0.99, Gly 1.05, NH_3 2.95.

An eight-point bioassay was performed in the saline–alcohol loaded rat.[13] Results showed our arginine vasopressin to have an activity of 454 IU/mg as a free base (95% confidence limits being 340–534 IU/mg). Natural arginine vasopressin has a potency of *ca.* 450 IU/mg as free base.

Acknowledgment.—We wish to thank Mr. R. Nicholson for his assistance in chromatography, Mr. E. Zielinski for microanalyses, Mr. W. Selby for catalytic hydrogenation, and Dr. L. M. Hofmann of the Department of Biological Research for bioassays.

Registry No.—1, 40472-52-4; 2, 40472-53-5; 3, 40472-54-6; 4, 40472-55-7; 5, 40472-56-8; 6, 40472-57-9; 7, 40550-36-5; 8, 40472-58-0; 9, 40472-59-1; 10, 40472-60-4; 11, 40550-37-6; 12, 33642-47-6; 13, 40472-62-6; 14, 40472-63-7; 16, 40472-64-8; 17, 40472-65-9; 18, 113-79-1; 19, 40472-66-0; Boc-Cys(Trt)-OH, 21947-98-8; 2,4,5-trichlorophenol, 95-95-4; *p*-nitrophenol, 100-02-7; (L)-Pro, 147-85-3; Boc-Asn-OCP, 7536-57-4; Boc-Gln-OCP, 16947-96-9; Boc-Phe-ONp, 7535-56-0; <Glu-Asn-Cys(Trt)-Pro, 40472-71-7; <Glu-OPP, 28990-85-4; Boc-Tyr-OH, 3978-80-1; pentachlorophenol, 87-86-5; Z-Arg(NO_2)-Gly-NH_2, 4801-44-9; *N*-hydroxysuccinimide, 6066-82-6.

(22) M. E. Cox, H. G. Garo, J. Hollowood, J. M. Hugo, P. M. Scopes, and G. T. Young, *J. Chem. Soc.*, 6806 (1965).

(23) Worthington Biochemical Corp., Freehold, N. J.

Studies in Sesquiterpene Synthesis.[1] The Marasmic Acid Skeleton

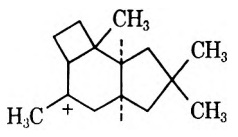
STEPHEN R. WILSON*[2] AND RICHARD B. TURNER[3]

Department of Chemistry, Rice University, Houston, Texas 77001

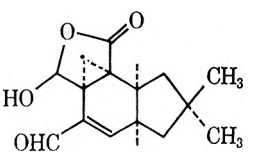
Received February 27, 1973

A route to the marasmic acid skeleton which uses as a key reaction Diels–Alder additions to β-(4,4-dimethyl-1-cyclopentenyl)acrylic acid and its derivatives is described.

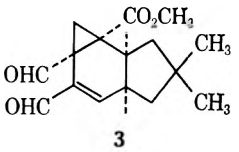
A growing number[4] of fungal metabolites have been isolated from the Basidiomycetes (true mushrooms). These compounds may be thought to arise by a new mode of cyclization of a humulene-type precursor to give ion **1**.



1



2



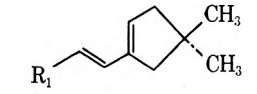
3

In a general survey[5] of the Basidiomycetes for antibacterial activity, a crystalline compound was found which possessed marked activity against *Staphylococcus aureus*. This substance, isolated from *Marasmius conigenus*, was partially characterized at that time and called marasmic acid. However, because its antibacterial activity decreased markedly in the presence of blood and because it was highly toxic, marasmic acid was not further investigated.

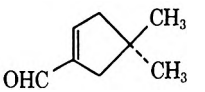
In 1965 de Mayo and others[6] reported the reisolation and characterization of marasmic acid. Its true structure (**2**) and stereochemistry were determined. A final point of the stereochemistry of marasmic acid was reported recently by Sim[7] in an X-ray analysis of a marasmic acid derivative.

Although synthetic efforts toward some Basidiomycete sesquiterpenes, notably the illudins,[8] have been successful, and a synthesis of illudol[9] has appeared, only a synthesis of methyl isomarasmate[10] (**3**) has been reported. This isomer differs from the marasmic acid series in the crucial cis relationship of the cyclopropane ring to the hydrogen at the ring fusion. We wish to report efforts in our laboratory directed toward a stereoselective synthesis of the crucial ring system.

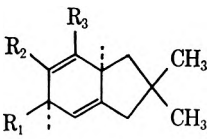
Our route to the marasmic acid system involves as a key reaction the Diels–Alder addition of a suitable dienophile to dienes **4a–e**. The required hydrindan ring system (**6**) is formed, the three functionalized carbons are incorporated, and a reactive group for the introduction of the three-membered ring is generated in one operation. For simplicity at the early stages of the investigation the system selected was $R_1 = R_2 = R_3 = COOCH_3$. Thus the dienophile is dimethyl acetylenedicarboxylate and the diene required is *trans*-β-(4,4-dimethyl-1-cyclopentenyl)acrylic ester (**4a**). Since diene **4a** could be transformed into other diene derivatives by hydrolysis, reduction, etc., compound **4a** was the initial target of synthesis.



4a, $R_1 = COOCH_3$
b, $R_1 = COOH$
c, $R_1 = CH_2OH$
d, $R_1 = CH_2OCOPh$
e, $R_1 = CH_2O$-3,5-dinitrobenzoate



5



6

The required diene was made by Wittig reaction of **5** with $Ph_3PCHCOOCH_3$[11] to form **4a** in 87% distilled yield.[12] The several routes to **5** are outlined in Scheme I. Compound **4a** was hydrolyzed to the acid **4b** and reduced with diisobutylaluminum hydride[13] to alcohol **4c**. When compound **4b** was treated with diazomethane, **4a** was regenerated. When alcohol **4c** was treated with PhCOCl or 3,5-dinitrobenzoyl chloride in pyridine, derivatives **4d** and **4e**, respectively, were obtained. Thus, with a variety of dienes available, the task of constructing the bicyclic ring system was undertaken.

When compound **4a** was refluxed in benzene solution containing excess dimethyl acetylenedicarboxylate for 3 days under nitrogen, or heated neat with the acetylene overnight at 100°, a Diels–Alder reaction occurred to give adduct **7**. In addition, variable amounts of compounds **8** and **9** were formed. (The stereochemistry of **7** must be as indicated because of the mechanism of the Diels–Alder reaction.) A slight excess of diene **4a**

(1) The financial support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

(2) NDEA Predoctoral Fellow, 1969–1972. Address correspondence to Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, Calif. 91109.

(3) Deceased, December 22, 1971.

(4) (a) M. Anchel, *et al.*, *Phytochemistry*, **9**, 2339 (1970); (b) M. Anchel and T. C. McMorris, *J. Amer. Chem. Soc.*, **87**, 1594 (1965); (c) S. Matsumoto, *et al.*, *Tetrahedron Lett.*, 3913 (1969); (d) T. C. McMorris, *et al.*, *J. Amer. Chem. Soc.*, **89**, 4562 (1967); (e) T. C. McMorris, *et al.*, *J. Org. Chem.*, **34**, 240 (1969); (f) S. Takahashi, *et al.*, *Tetrahedron Lett.*, 1637 (1970); (g) H. Matsumoto, *et al.*, *ibid.*, 3125 (1971); (h) G. Magnusson, *et al.*, *ibid.*, 1105 (1972); (j) M. S. R. Nair and M. Anchel, *ibid.*, 2753 (1972).

(5) W. J. Robbins, *et al.*, *Proc. Nat. Acad. Sci. U. S.*, **35**, 343 (1949).

(6) P. de Mayo, *et al.*, *J. Amer. Chem. Soc.*, **88**, 2838 (1966), and references cited therein.

(7) G. A. Sim and P. D. Cradwick, *Chem. Commun.*, 431 (1971).

(8) T. Matsumoto, *et al.*, *Tetrahedron Lett.*, 2049 (1971).

(9) T. Matsumoto, *et al.*, *ibid.*, 3521 (1971).

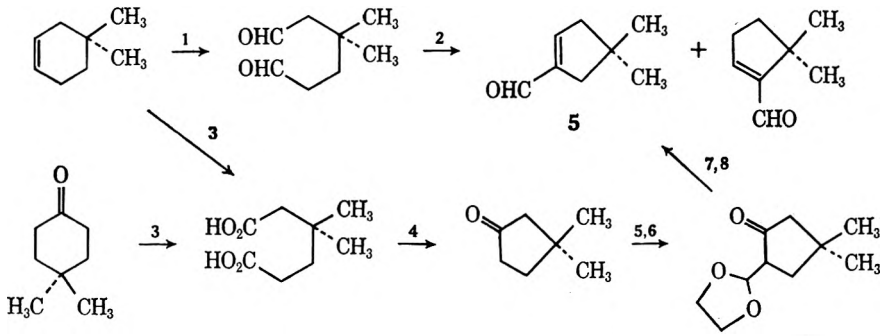
(10) P. de Mayo, *et al.*, *ibid.*, 349 (1970).

(11) P. Zeller, *et al.*, *Helv. Chim. Acta*, **40**, 1247 (1957).

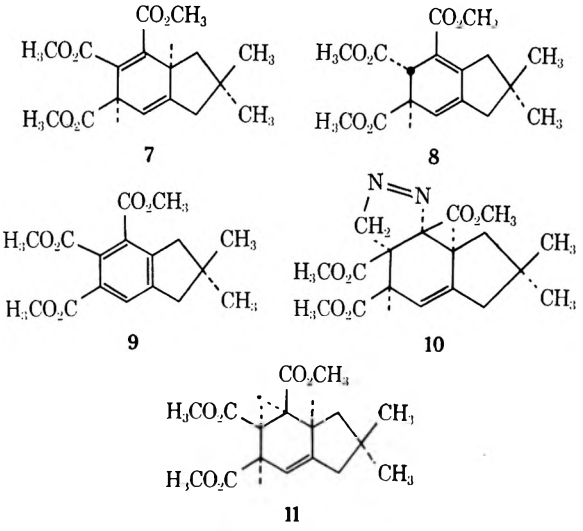
(12) All compounds possessed spectral data consistent with the assigned structures (see Experimental Section).

(13) H. C. Brown, *et al.*, *J. Amer. Chem. Soc.*, **88**, 1458 (1966).

SCHEME I[a]



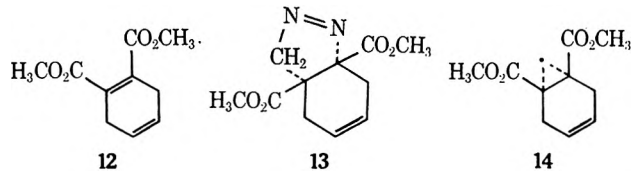
[a] 1, IO_4^{2-}, OsO_4; 2, piperidine-acetic acid; 3, $KMNO_4$; 4, potassium fluoride; 5, HCO_2Et, NaH; 6, ethylene glycol, H^+; 7, $NaBH_4$; 8, H_3O^+. *Cf.* ref 18.



and dimethyl acetylenedicarboxylate was sealed in a glass tube under vacuum, and heated at 60° for 2 weeks. Practically pure (>95%) **7** was obtained in this way and could be used in the next step without further purification.

With compound **7** in hand, the construction of the three-membered ring by diazomethane addition[14] and subsequent photolysis was envisioned. Since marasmic acid requires the cyclopropane to be cis to the adjacent proton and thus on the bottom side of the molecule as it is drawn, and since the decomposition of the Δ^1-pyrazoline is stereospecific, the addition of diazomethane to **7** must occur on the bottom side. The conformation of **7** is such that exo addition is expected and probably the least hindered approach of the 1,3 dipole would result in compound **10**. Decomposition of **10** would give the marasmic acid skeleton **11**.

At this point, we decided to turn to the model system **12**. When compound **12** was allowed to contact ethereal diazomethane at room temperature for 2 weeks, addition occurred exclusively to the conjugated double bond, giving adduct **13**. Thick layer chromatography (silica gel) of **13** gave pure material, mp 74–75°. The nmr showed a diagnostic methylene AB quartet centered at δ 4.75 (J_{AB} = 18 Hz) and the uv spectrum showed a fairly sharp absorption, λ_{max} 318 nm (ϵ 184), characteristic[15] of the azo group. When **13** was injected into the vpc (injection port temperature 240°), or was irradiated in dilute ether solution through quartz, a single compound **14**[16] was formed in nearly quantitative yield.



Encouraged by the success of the model system, we allowed compound **7** to contact ethereal diazomethane solution at room temperature. After 9 days the ether and excess diazomethane were evaporated to yield **10** in 70% yield.[17] No evidence of more than one pyrazoline could be found. Photolysis of **10** in dilute ether solution in a quartz vessel gave excellent yield of marasmic acid skeleton **11**. The synthesis of **11** represents the first stereospecific synthesis of the marasmic acid skeleton.

To proceed further toward the ultimate goal of the natural product, some method for distinguishing the functional groups is necessary. The Diels–Alder adducts of the other dienes **4b–e** with other dienophiles have been investigated and will be the subject of a subsequent report.

Experimental Section

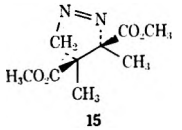
Infrared spectra were recorded on Beckman IR-8, IR-8a, and IR-18a spectrophotometers. Ultraviolet spectra were taken in 95% ethanol solution on a Bausch and Lomb Spectronic 505 spectrometer. Pmr spectra at 60 MHz were taken in dilute CCl_4 solution with internal TMS standard and 500-Hz sweep unless otherwise specified. Mass spectra were obtained on a Consolidated Electrodynamic Corp. 21-110 high-resolution spectrometer. Melting and boiling points were uncorrected. Microanalyses were obtained from Elek Microanalytical Lab-

(14) For a review see R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963).

(15) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p 39.

(16) Subsequent to its preparation in this laboratory, E. Vogel, *et al.*, *Tetrahedron Lett.*, 1941 (1970), reported the identical synthesis of **14**.

(17) The stereochemistry of compound **10** was deduced by a study of the lanthanide shifted nmr spectra of compound **10**, compound **13**, and reference compound **15**. See S. R. Wilson and R. B. Turner, *Chem. Commun.*, in press, and ref 18.



(18) S. R. Wilson, Ph.D. Thesis, Rice University, Houston, Tex., 1972. (See Scheme I.)

oratory, Harbor City, Calif. Thin layer chromatography employed Brinkman precoated silica gel F-254 plates.

Preparation of Compound (4a).—A benzene solution (50 ml) of 3.03 g of 4,4-dimethyl-1-cyclopentenyl-1-carboxaldehyde (5)[18] and 10.6 g of $Ph_3PCHCOOCH_3$ (prepared by the method of Zeller[11]) was refluxed overnight under nitrogen. The benzene was evaporated on a Rotavap and 50 ml of petroleum ether (bp 30–60°) was added. Stirring for about 10 min caused precipitation and crystallization of the Ph_3PO. The supernatant was filtered through a short column (30 g) of activity I Al_2O_3 and distilled to yield 3.92 g (87%) of diene **35**: bp 74–76° (0.5 mm); ir (neat) 1727, 1639 cm^{-1}; nmr δ 1.13 (6 H, s), 2.20 (4 H, s), 3.65 (3 H, s), 5.73 (1 H, d, J = 16 Hz), 6.17 (1 H, m), 7.49 (1 H, d, J = 16 Hz); uv λ_{max} 270 nm (ϵ 25,200); m/e 180 (P). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 9.07.

Preparation of Compound 4b.—Diene **4a** (3.18 g) was refluxed with 0.71 g of NaOH in 75 ml of water under nitrogen for 2 hr. The reaction mixture was then cooled to room temperature, acidified to pH 2 with concentrated HCl, and extracted with ether. Evaporation of the ether gave 2.26 g (95%) of acid **4b**, mp 119–125°. Recrystallization from ether gave the analytical sample: mp 126–128°; ir ($CHCl_3$) 2500–3400 (broad), 1680 cm^{-1}; nmr δ 1.13 (6 H, s), 2.32 (4 H, s), 5.72 (1 H, d, J = 15 Hz), 6.12 (1 H, m), 7.68 (1 H, d, J = 15 Hz), 10.90 (1 H, s); m/e 166 (P). *Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.93; H, 8.48.

Preparation of Compound 4c.—To a solution of 8.25 g of distilled diene **4a** in 30 ml of dry benzene at room temperature was added 137 ml of a 0.67 M diisobutylaluminum hydride (DIBAL-H, Texas Alkyls). The mixture was stirred for 2 hr and then 15 ml of 10% H_2SO_4 was added and the reaction mixture was extracted with ether. The organic layer was washed with water, twice with saturated $NaHCO_3$, and once with brine and dried over $CaSO_4$. Evaporation gave an oil which distilled at bp 69–75° (0.2 mm) to give 5.94 g (86% yield): ir (neat) 3125 cm^{-1}; nmr δ 1.08 (6 H, s), 2.18 (4 H, s), 3.2 (1 H, broad), 4.03 (2 H, d, J = 5 Hz), 5.3 (1 H, d, J = 14 Hz), 5.45 (1 H, m), 6.2 (1 H, d, J = 14 Hz); uv λ_{max} 233 nm (ϵ 3600); m/e 152 (P). This compound was somewhat sensitive and was analyzed as the 3,5-dinitrobenzoate (see compound **4e**).

Preparation of Compound 4d.—A solution of 392 mg of compound **4c** and 370 mg of PhCOCl (10% excess) in 5 ml of dry pyridine was stirred at room temperature overnight. The dark reaction mixture was poured into 150 ml of 1 N HCl and extracted twice with ether. The ether was washed with water, saturated $NaHCO_3$, and brine, and subsequently dried over $MgSO_4$ and evaporated to yield an oil. Thin layer chromatography (petroleum ether) gave 300 mg of **4d** (45% yield). For analysis the ester was evaporatively distilled (bath temperature 140°) at 0.1 mm: ir (neat) 1712 cm^{-1}; nmr δ 1.15 (6 H, s), 2.25 (4 H, s), 4.81 (2 H, d, J = 5 Hz), 5.2–5.8 (2 H, m), 6.51 (1 H, d, J = 16 Hz), 7.4 (3 H, m), 7.9 (2 H, m); m/e 256 (P). *Anal.* Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.22; H, 7.62.

Preparation of Compound 4e.—To a solution of 5.13 g of distilled compound **4c** in 50 ml of dry pyridine stirred and cooled was added 8.7 g (20% excess) of 3,5-dinitrobenzoyl chloride. The mixture was stirred overnight at room temperature. The reaction mixture was then poured into 1 l. of 1 N HCl and extracted three times with 50-ml portions of chloroform. The chloroform was washed with water, saturated $NaHCO_3$, and brine and dried. Evaporation gave 11.52 g (99%) of a solid, crystalline mass, mp 70–80°. Recrystallization from ether–petroleum ether gave 9.8 g of crystals: mp 79–84°; ir ($CHCl_3$) 3090, 1725, 1540, 1340 cm^{-1}; nmr δ 1.14 (6 H, s), 2.30 (4 H, s), 5.02 (2 H, d, J = 5 Hz), 5.5–6.0 (2 H, m), 6.68 (1 H, d, J = 16.5 Hz), 10.2 (3 H, s); m/e 346 (P). *Anal.* Calcd for $C_{17}H_{18}O_6N_2$: C, 58.96; H, 5.24. Found: C, 58.43; H, 5.42.

Preparation of Compound 7.—A mixture of 1.02 g of dimethyl acetylenedicarboxylate and diene **4a** (1.18 g) was placed in a glass tube, frozen and thawed several times under vacuum, and then sealed. The tube was heated in an oil bath maintained at about 60° for 2 weeks. At the end of this time the tube was opened and its contents were transferred to a 50-ml flask. Heating under vacuum for 2 additional hr at about 75° removed any excess acetylene dicarboxylate. The nmr showed almost pure **7** (2.01 g) with no trace of **8** or **9**. Also no trace of the long-wave absorptions of either **8** or **9** was seen in the uv. Tlc showed a single spot at R_f 0.29 (9:1 benzene–ethyl acetate). Attempted crystallization at −78° in petroleum ether gave crystals which melted below 0°: ir (neat) 1735, 1630 cm^{-1}; nmr δ 1.07 (3 H, s), 1.13 (3 H, s), 1.4–1.8 (2 H, ABX m), 2.17 (2 H, m), 3.2 (1 H, m), 3.68 (6, H, s), 3.74 (3 H, s), 3.80 (1 H, s), 5.30 (1 H, m); mass spectrum m/e 173 (19), 145 (19), 129 (23), 128 (23), 105 (17), 59 (95); uv λ_{sh} 264 nm (ϵ 1700). *Anal.* Calcd for $C_{17}H_{22}O_6$: mol wt, 322.14. Found: mol wt, 322.10 ± 0.04.

Preparation of Compounds 8 and 9.—Diene **4a** (1.8 g), dimethyl acetylenedicarboxylate (1.42 g), and a few crystals of pyrogallol were heated at 100° for 3 days under a nitrogen stream. A mixture of about 40% **9** and 60% **8** resulted. A 370-mg portion of this mixture was separated by tlc. Developing with 9:1 benzene–ethyl acetate showed bands at R_f 0.32 and 0.35. Collection of the first band gave after recrystallization 17 mg of **9**: mp 90–93°; ir ($CHCl_3$) 1725 cm^{-1}; nmr δ 1.15 (6 H, s), 2.78 (2 H, s), 2.98 (2 H, s), 3.87 (6 H, s), 3.92 (3 H, s), 7.82 (1 H, s); uv λ_{max} 294 nm (ϵ 1800); m/e 320 (P). Collection of the second band gave 40 mg of compound **8**: mp 71–72° from ether–petroleum ether; ir ($CHCl_3$) 1740, 1736, 1720 cm^{-1}; nmr δ 1.02 (3 H, s), 1.14 (3 H, s), 2.30 (4 H, broad s), 3.22 (2 H, broad s), 3.68 (6 H, s), 3.73 (3 H, s), 6.84 (1 H, m); uv λ_{max} 301 nm (ϵ 10,900); m/e 322 (P). *Anal.* Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.43; H, 6.85.

Preparation of Compound 10.—A solution of 2.01 g of freshly prepared compound **7** was allowed to contact a tenfold excess of diazomethane in ether (about 1 M) for 11 days at room temperature. The ether–diazomethane was evaporated and replenished twice in this period. On the 11th day, the ether and excess diazomethane were evaporated and 25 ml of ether was added. On cooling 1.72 g of crude crystals were obtained, mp 108–116°. Recrystallization from a small volume of ether gave 1.35 g of crystals, mp 130–131°, N_2 evolution, in a yield of 60%. Preparative tlc (8:2 benzene–ethyl acetate) of the mother liquor gave an additional 372 mg of pyrazoline **10** (15%, R_f 0.39) and 330 mg of compound **9** (20%, R_f 0.54): ir ($CHCl_3$) 1740, 1562 cm^{-1}; nmr δ 1.02 (3 H, s), 1.08 (3 H, s), 1.3–1.9 (2 H, ABX), 2.2 (2 H, m), 3.15 (1 H, d, J = 11 Hz), 3.58 (3 H, s), 3.74 (3 H, s), 3.82 (3 H, s), 4.98 (2 H, AB q, J = 19 Hz, $\delta_A - \delta_B$ = 30 Hz), 5.81 (1 H, m); uv λ_{max} 220 nm (ϵ 5400); λ_{max} 324 nm (ϵ 135). *Anal.* Calcd for $C_{18}H_{24}O_6N_2$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.10; H, 6.53; N, 7.46.

Preparation of Compound 11.—A solution of 471 mg of pyrazoline **10** in 50 ml of dry ether was degassed at −78° under vacuum for 30 min and then irradiated with a high-pressure mercury arc (450 W Hanovia lamp) for 2 hr at 0–5°. Evaporation of the ether gave 466 mg of an oil whose nmr showed nearly pure cyclopropane (**11**). Crystallization from petroleum ether gave five crops of needles, mp 49–52°, 76% yield. Four recrystallizations from petroleum ether gave the analytical sample: mp 55–56°; ir (neat) 1740 cm^{-1}; nmr δ 1.02 (3 H, s), 1.05 (3 H, s), 1.1–1.9 (4 H, m), 2.17 (3 H, m), 2.75 (1 H, m), 3.68 (3 H, s), 3.69 (3 H, s), 3.72 (3 H, s), 5.95 (1 H, m). *Anal.* Calcd for $C_{18}H_{24}O_6$; mol wt, 336.157; C, 64.27; H, 7.19. Found: mol wt, 336.158; C, 63.90; H, 7.12.

Preparation of Compound 12.—A 1-l. Parr pressure reactor was cooled in Dry Ice–acetone to about −20° and about 50–75 ml of butadiene was condensed. Dimethyl acetylenedicarboxylate (82 g, 0.58 mol), 200 ml of benzene, and 2 g of pyrogallol were added. The bomb was sealed and the reaction mixture was stirred at room temperature for 6 days. Excess butadiene was vented and the benzene was evaporated. The residual oil distilled at 80–85° (0.2 mm) to give 59 g of compound **12** (52% yield): ir (near) 1724, 1645 cm^{-1}; nmr δ 3.1 (4 H, s), 3.83 (6 H, s), 5.92 (2 H, s); m/e 196 (P).

Preparation of Compound 13.—Compound **12** (1.92 g) was dissolved in about 50 ml of ether, and 150 ml of diazomethane solution (containing about 1 g of diazomethane) was added. The flask was sealed with a cork and kept at room temperature for 5 days. Then the ether and excess of diazomethane was evaporated on a steam bath and 150 ml more diazomethane solution was added. After another 5 days at room temperature the excess diazomethane and ether were evaporated to yield 2.11 g of an oil which was by nmr 85% pyrazoline **13**. Thin layer chromatography developing with 9:1 benzene–ethyl acetate gave 450 mg of crystalline **13**, mp 65–72°. Recrystallization from ether gave a sample: mp 74–75°; ir ($CHCl_3$) 1748, 1555 (weak, and 1580 cm^{-1} (weak); nmr δ 2.2–3.1 (4 H, m), 3.60 (3 H, s), 3.67 (3 H, s), 4.75 (2 H, AB qt J = 18 Hz, $\delta_A - \delta_B$ = 44 Hz), 5.78 (2 H, m).

Preparation of Compound 14.—Compound **13** was injected into the vpc (injection port 240°; 6 ft × 0.375 in. Carbowax 20 M at 220°). This showed one peak which was collected and identified as **14**. Alternatively, compound **13** could be irradiated through Pyrex as a dilute ether soluton to give the cyclopropane in quantitative yield.

Registry No.—**4a**, 40447-60-7; **4b**, 40447-61-8; **4c**, 40447-62-9; **4d**, 40447-63-0; **4e**, 40447-64-1; **5**, 38312-94-6; **7**, 40447-66-3; **8**, 40447-67-4; **9**, 40447-68-5; **10**, 40447-69-6; **11**, 40447-70-9; **12**, 14309-54-7; **13**, 40447-72-1; 3,5-dinitrobenzoyl chloride, 99-33-2; dimethyl acetylenedicarboxylate.

Models for the Pyridine Nucleotide Coenzymes. Synthesis and Properties of Bridged Dinicotinamide Derivatives[1-3]

DONALD C. DITTMER* AND BRUCE B. BLIDNER

Department of Chemistry, Syracuse University, Syracuse, New York 13210

Received March 30, 1973

A number of dinicotinamide derivatives which are bridged between the 3 and the 5 positions have been prepared from dinicotinoyl chloride and α,ω-diamines. A special high-dilution technique involving introduction of reagents into the reaction flask by means of syringe pumps was employed which was superior to the use of constant-rate addition funnels. Models for coenzyme–substrate complexes in which a carbonyl group or alcohol group in the bridge is in close proximity to the 4 position of a dihydropyridine or of a pyridinium salt, respectively, have been prepared. Certain of the bridged derivatives show enhanced reactivity toward silver nitrate and protons which may be a function of the strain introduced into the pyridine ring. No evidence was obtained either for intramolecular hydrogen transfer from the dihydropyridine to the proximate carbonyl group, or for the transfer of hydride ion from the alcohol group to the pyridinium ring. Spectroscopic data, however, indicated addition of alkoxide ion in the bridge to the charged pyridine ring.

Proximity and orientation effects are presumed to be important factors in accounting for the catalytic power of enzymes.[4] The enzyme positions coenzyme and substrate in close proximity so that collisions between the reactants are more frequent. The enzyme also orients them so that the probability of a collision leading to a reaction is increased. Other factors such as acid–base catalysis, introduction of strain in the reactants, the formation of unstable, covalent intermediates, and the polarity of the microscopic environment also are believed to be important in enzyme catalysis.

The dehydrogenase enzymes catalyze the transfer of hydrogen to and from substrates *via* the pyridine nucleotide coenzymes. Relatively few successful model reactions for these hydrogen transfers have been accomplished in the absence of an enzyme.[5] For the model reduction of ketones or aldehydes by 1-substituted 1,4-dihydronicotinamides (models for the coenzyme), only the reduction of halo ketones,[6] the zinc ion catalyzed reduction of 1,10-phenanthroline-2-carboxaldehyde,[7a] and the reduction of pyridoxal phosphate and analogs by dihydropyridines[7b] appear to proceed in good yield in the absence of enzyme. The hydrogen transfer in the enzymic and nonenzymic reactions occurs *via* the 4 position of the pyridine ring[8] and is a direct transfer between coenzyme (or its model) and substrate,[9] although an indirect mechanism *via* tryptophane may operate in certain enzymic reactions.[10]

Introduction of a carbonyl group or an alcohol group close to the reactive 4 position of models for the pyridine nucleotide coenzymes would be a test of proximity effects. While a number of model systems for hydrogen transfer involving pyridine derivatives have been investigated,[5-7] at the time our work began no model system had been reported in which a carbonyl or alcohol moiety had been fixed in close proximity to the 4 position of the pyridine ring. Recently, the bridged dinicotinamide derivative **1** was prepared (6.6% yield in the cyclization step) and was converted to the bridged alcohol derivative **2**. A deoxy analog, **3**, and its 1-benzyl salt also were reported (6.9% yield in the cyclization step). No evidence for intramolecular hydrogen transfer in **2** was obtained,[11a] but an intramolecular hydrogen transfer to a carbonyl group in *N*-(2,6-dichlorobenzyl)-3-(*o*-formylbenzoyl)-1,4-dihydropyridine has been induced photochemically.[11b] A thermally induced intramolecular hydrogen transfer from a 1,2-dihydropyridine to the vinyl group of an acrylic ester has been proposed to account for transformations of the alkaloid, catharanthine.[11c]

We wish to describe in this paper a better procedure

(1) For complete details, see B. B. Blidner, Ph.D. Thesis, Syracuse University, 1972.

(2) This investigation was supported in part by Public Health Service Research Grant No. AM07770 from the National Institute of Arthritis and Metabolic Diseases.

(3) Reported at Northeast Regional Meeting, American Chemical Society, Buffalo, N. Y., Oct 1971, Abstract No. 80.

(4) Included in orientation effects are "freezing" or "stereopopulation control" and "orbital steering:" D. E. Koshland, Jr., and K. E. Neet, *Ann. Rev. Biochem.*, **37**, 370 (1968); D. R. Storm and D. E. Koshland, Jr., *Proc. Nat. Acad. Sci., U. S.*, **66**, 445 (1970); M. I. Page and W. P. Jencks, *ibid.*, **68**, 1678 (1971); S. Milstien and L. A. Cohen, *J. Amer. Chem. Soc.*, **94**, 9158 (1972); R. T. Borchardt and L. A. Cohen, *ibid.*, **94**, 9166, 9175 (1972).

(5) Model systems have been reviewed by T. C. Bruice and S. J. Benkovic, "Biorganic Mechanisms," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 9.

(6) D. C. Dittmer, L. J. Steffa, J. R. Potoski, and R. A. Fouty, *Tetrahedron Lett.*, 827 (1961); D. C. Dittmer and R. A. Fouty, *J. Amer. Chem. Soc.*, **86**, 91 (1964); T. P. Goldstein, Abstracts of Papers, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, C-196; A. Lombardo, Ph.D. Thesis, Syracuse University, 1967; C. S. Greene, Ph.D. Thesis, Syracuse University, 1971; J. J. Steffens and D. M. Chipman, *J. Amer. Chem. Soc.*, **93**, 6694 (1971).

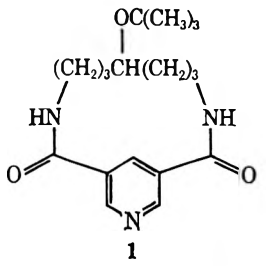
(7) (a) D. J. Creighton and D. S. Sigman, *J. Amer. Chem. Soc.*, **93**, 6314 (1971); (b) S. Shinkai and T. C. Bruice, *ibid.*, **94**, 8258 (1972).

(8) M. E. Pullman, A. San Pietro, and S. P. Colowick, *J. Biol. Chem.*, **206**, 129 (1954); G. W. Rafter and S. P. Colowick, *ibid.*, **208**, 773 (1954); F. A. Loewus, B. Vennesland, and D. L. Harris, *J. Amer. Chem. Soc.*, **77**, 3391 (1955); R. F. Hutton and F. H. Westheimer, *Tetrahedron*, **3**, 73 (1958); H. E. Dubb, M. Saunders, and J. H. Wang, *J. Amer. Chem. Soc.*, **80**, 1767 (1958).

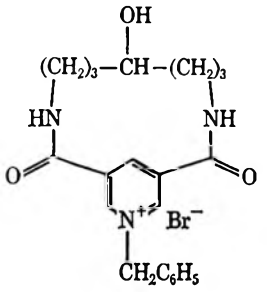
(9) F. H. Westheimer, H. F. Fisher, E. E. Conn, and B. Vennesland, *J. Amer. Chem. Soc.*, **73**, 2403 (1951); H. F. Fisher, E. E. Conn, B. Vennesland, and F. H. Westheimer, *J. Biol. Chem.*, **202**, 687 (1953).

(10) K. A. Schellenberg, *ibid.*, **240**, 1165 (1965); **242**, 1815 (1967). D. Palm, *Biochem. Biophys. Res. Commun.*, **22**, 151 (1966).

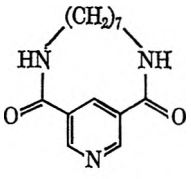
(11) (a) L. E. Overman, *J. Org. Chem.*, **37**, 4214 (1972); (b) J. D. Sammes and D. A. Widdowson, *J. Chem. Soc., Chem. Commun.*, 1023 (1972); (c) A. I. Scott and P. C. Cherry, *J. Amer. Chem. Soc.*, **91**, 5872 (1969).



1



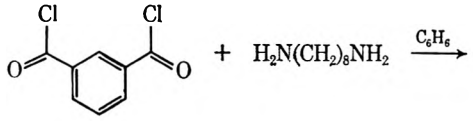
2

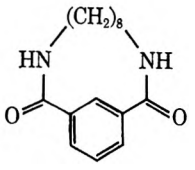


3

for the synthesis of meta bridged dinicotinamides. This new technique, which involves syringe pumps, is applied to the preparation of a number of new bridged dinicotinamides which are models for proximity effects in reactions catalyzed by the dehydrogenase enzymes. For example, we have prepared **3** and the ethylene ketal analog of **1** in 23 and 20% yields, respectively.

Syntheses of Bridged Dinicotinamide Derivatives.— Isophthaloyl chloride and 1,4-diaminobutane or 1,6-diaminohexane are reported to give cyclic diamides in 7 and 19% yield, respectively.[12] However, when we attempted to prepare a cyclic diamide from isophthaloyl chloride and 1,8-diaminooctane by the reported procedure, only a 1.5% yield of product **4** was

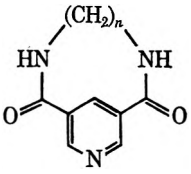




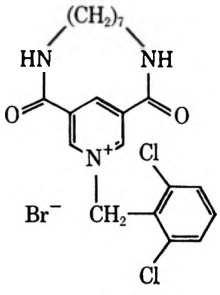
4

obtained. This procedure involved addition of reagents *via* constant-rate addition funnels to a large volume of benzene.[13]

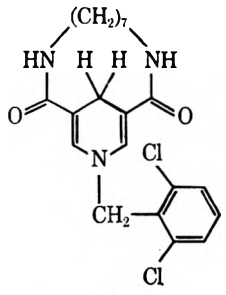
In an attempt to improve the yield of **4**, an alternate high-dilution procedure was tried in which the acid chloride and diamine were introduced separately and very slowly into the benzene solvent *via* a syringe pump.[14] This technique resulted in an increase in the yield of **4** from 1.5 to 38%. By this method, 1,8-diaminooctane, 1,7-diaminoheptane, 1,6-diaminohexane, and 1,5-diaminopentane were condensed with the acid chloride of pyridine-3,5-dicarboxylic acid (dinicotinoyl chloride) to yield bridged dinicotinamides **5a–d** (**5c** and **5d** appear to form stable hydrates). A zero yield of **5d** was reported when addition funnels were used.[11a] Compound **5b** was quaternized with 2,6-dichlorobenzyl bromide to yield **6** which was reduced with sodium dithionite to the dihydropyridine derivative **7**.



5a, $n = 8$ (41%) **5c**, $n = 6$ (9.8%)
b, $n = 7$ (23%) **d**, $n = 5$ (4.3%)



6



7

Scheme I shows the general synthesis of three diamino ketals and the construction of the 3,3- and 4,4-bridged dinicotinamide ketals **11a**, and **11b**. Removal of the ketal function from **11a** and **11b** yields bridged carbonyl derivatives **12a** and **12b**. Reduction of the carbonyl group with sodium borohydride gives the bridged alcohols **13a** and **13b**. Quaternization of **12a** and **12b** and **13a** and **13b** with 2,6-dichlorobenzyl bromide or with methyl iodide occurs readily to give salts **14a–c** and **15a** and **15b**. Reduction of **14a–c** with sodium dithionite yields the bridged dihydrodinicotinamides **16a–c**. CPK models indicate that the 4 position of the pyridine ring can lie in close proximity to the ketone or alcohol group of the bridge. The nmr spectra of several of the bridged dinicotinamides, most especially with **11a** which has a well-resolved spectrum, show different chemical shifts for the two amide protons ($\Delta\delta$ for **11a**, 0.74 ppm). The models show that different configurations such as an "in" or "out" for these amide protons are readily attainable within the macrocyclic ring. The different chemical shifts probably reflect either a particularly stable configuration in which the amide protons are nonequivalent chemically or two distinct but equally probable stable configurations for them.

Properties of Bridged Dihydrodinicotinamides.— Table I compares the uv absorption maxima, fluorescence emission, and approximate reactivity to ethanolic silver nitrate and to dilute acid of **7**, **16a**, **16b**, and **18**. Compounds **7** and **16a** which show a perturbed uv and fluorescence spectrum appear to be somewhat more

(12) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

(13) Constant-rate addition funnels from Ace Glass Co. were used. We obtained a 68% yield of cyclic product from adipyl chloride and 1,6-diaminohexane compared with Stetter's yield of 76% with specially constructed and slightly different funnels: H. Stetter and J. Marx, *Justus Liebigs Ann. Chem.*, **607**, 59 (1957).

(14) The use of syringe pumps was suggested by Dr. Owen Webster. A Sage syringe pump Model 352 was used. The plungers of two 50-ml syringes containing solutions of diamine and diacid chloride in benzene were driven at a constant rate by motor, which delivered the reagents to the reaction flask *via* thin, flexible, Teflon tubing. The rates of delivery could be varied widely, thus ensuring any dilution factor desired.

SCHEME I

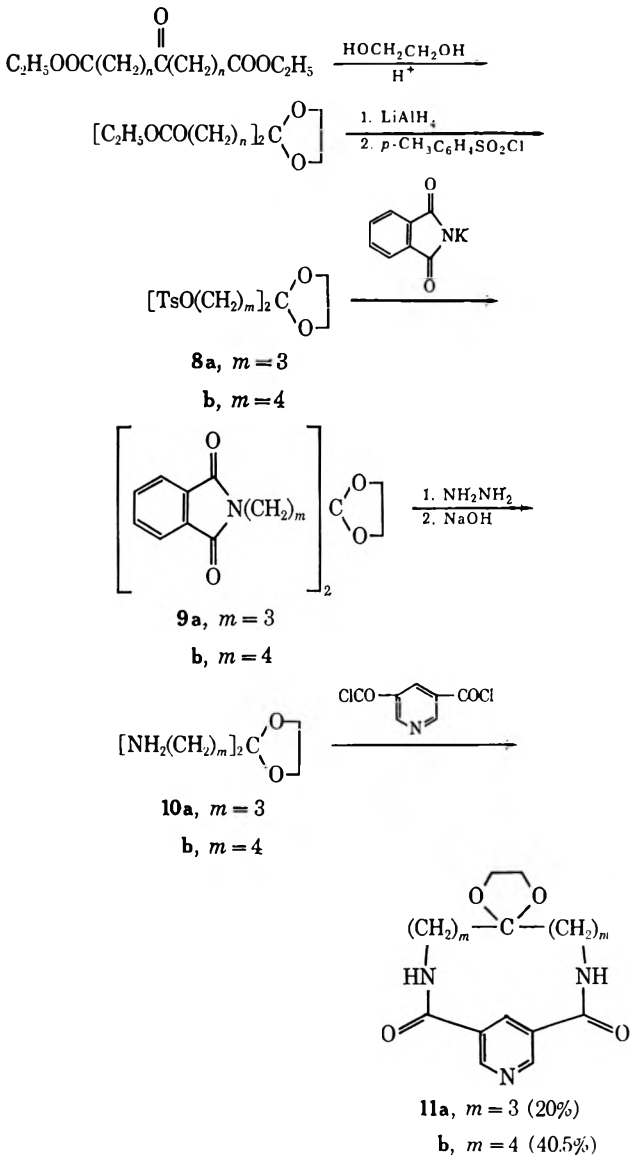


TABLE I

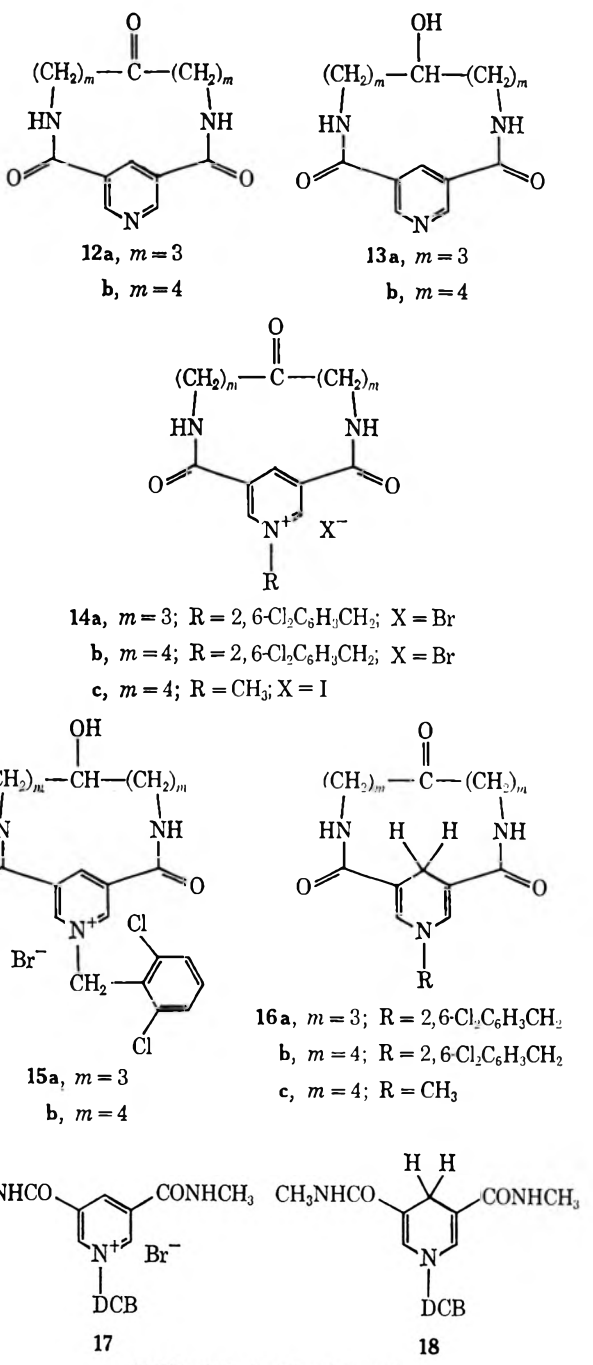
SOME PROPERTIES OF BRIDGED 1,4-DIHYDROPYRIDINES

Property	7	16a	16b	18
Uv max (ethanol), nm	338	338	381	391
Fluorescence emission, nm	478 (weak)[a]	451 (weak)[a]	447	445
$AgNO_3$,[b] hr	0.5	0.5	3	24
H_3O^+ [c]	80	125	21	1

[a] About 10% of the emission observed for 16b and 18. [b] Approximate time to form silver mirror. [c] Relative rate (27°, 87% ethanol).

reactive towards silver ion[15] and protons.[16,17] Strain introduced by the smaller bridges in these compounds is a likely source of the spectroscopic and chemical differences. Distortion of the dihydropyridine ring from planarity[18] with concomitant destabilization of the conjugated system could effect the increased rate of addition of silver ion or protons to the bis enamine system. Strain in the bicyclic system also may be reduced by reaction with the Lewis acids.

The reactivity of 1,4-dihydropyridines to aqueous acid has been investigated previously.[16a] The reaction is characterized by loss of absorption at ~360 and appearance of new absorption at 290–300 nm. The products are tetrahydropyridines and dimers derived from them. Addition of dilute acid to **7**, **16a**, **16b**, and **18** causes new absorption to appear at 289 nm. The presence of two electron-withdrawing amide groups in these compounds causes them to react



DCB, 2,6-dichlorobenzyl

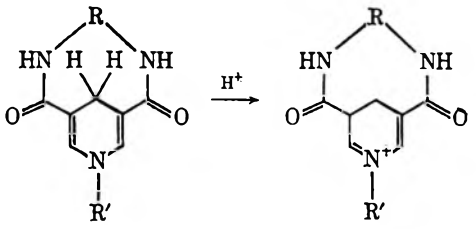
(15) The reduction of silver ions by dihydropyridines is well known: P. Karrer, G. Schwarzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 811 (1936).

(16) (a) A. G. Anderson, Jr., and G. Berkelhammer, *J. Amer. Chem. Soc.*, **80**, 992 (1958). (b) O. M. Grishin and A. A. Yasnikov, *Ukr. Khim. Zh.*, **28**, 707 (1962); *Chem. Abstr.*, **58**, 11183 (1963).

(17) The chemistry of dihydropyridines has been reviewed nicely by Bruice and Benkovic[5] and by U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).

(18) X-Ray analysis indicates that two 1,4-dihydropyridines are planar in the crystalline state: I. L. Karle, *Acta Crystallogr.*, **14**, 497 (1961); H. Koyama, *Z. Kristallogr., Kristallgeometrie, Kristallphys., Kristallchem.*, **118**, 51 (1963).

more slowly with protons than do the monosubstituted derivatives.[16a]

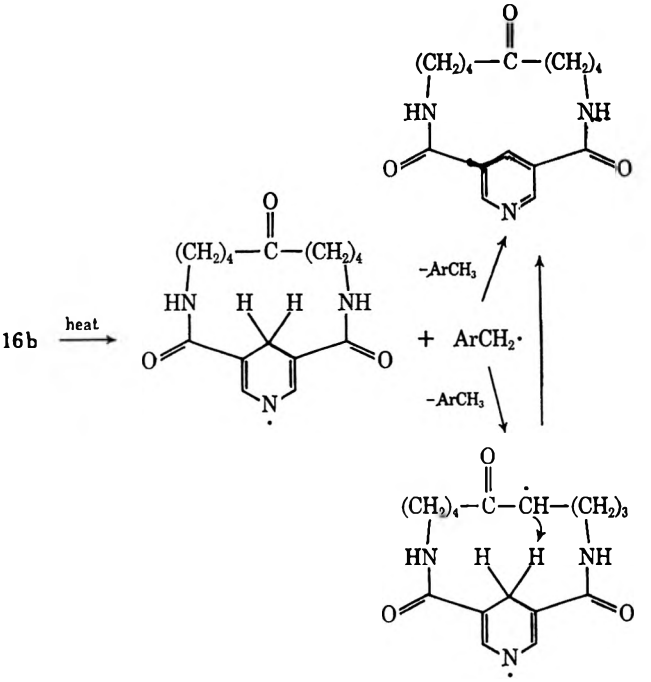


Zinc ions catalyze the reduction of 1,10-phenanthroline-2-carboxaldehyde by 1-*n*-propyl-1,4-dihydronicotinamide,[7a] but no change was observed in the uv spectrum of bridged ketone **16b** when it was treated with a solution of zinc chloride (2×10^{-2} *M*) in acetonitrile. The concentration of zinc ions may have been too low for catalysis to be observed, or the zinc ions may have preferentially coordinated with the acetonitrile solvent or other sites in the dihydrodinicotinamide.[19]

Photoexcitation of the carbonyl group of the bridged ketones should facilitate intramolecular hydrogen transfer. Cyclodecanone on photolysis undergoes intramolecular transfer of hydrogen to the carbonyl oxygen followed by cyclization to 9-hydroxydecalin.[20] Several remote hydrogen transfers in various systems have been reported.[11b,c,21] However, all attempts at photolysis of bridged ketones **16a** or **16b** resulted in destruction of the dihydropyridine ring, a not unexpected result.[22]

The possibility of a thermally initiated intramolecular hydrogen transfer in **16a** and **16b** was investigated. Thermolysis of **16b** was done on a Kofler hot stage melting point apparatus. The sample was heated slowly under silicone oil (to protect against oxygen); at 230° the sample melted with frothing and at 235° the melt solidified, only to melt again at 320–324°. The melting point and ir spectrum of this new substance identified it as the bridged pyridine derivative **12b**, mp 323–325°. Cleavage of the 2,6-dichlorobenzyl group to form, presumably, 2,6-dichlorotoluene (which would be soluble in the silicone oil) had occurred. A similar cleavage was observed with **16a**. The 1-methyl compound, **16c**, was stable at its melting point (231–234°). Previously, loss of toluene from 1-benzyl-1,4-dihydronicotinamide was observed at 125° *in vacuo*.[23] The themolysis very likely proceeds by cleavage of a benzyl radical which abstracts a hydrogen atom from the dihydropyridine radical. It is possible that the benzyl radical takes a hydrogen atom from the bridge instead of from the relatively less accessible 4 position of the pyridine ring (Scheme II). This could be ascertained by deuterium labeling.

SCHEME II



The lack of transfer of hydrogen from the 4 position of the dihydrodinicotinamide to a carbonyl group in the bridge may reflect (1) the decreased reducing power of the dihydropyridine caused by the presence of two electron-withdrawing carboxamide groups and (2) the number of conformations of the bridge which are poor for intramolecular hydrogen transfer. Thus, in addition to the proximity effect, other forms of catalysis may be required to effect hydrogen transfer in the compounds discussed here.

Properties of Bridged Pyridinium Salts.—Although a number of reactions involving reduction of functional groups by dihydropyridine models for coenzymes are known, examples of nonenzymic oxidation of an alcohol by a pyridinium salt are rare. Oxidation of 9-fluorenol to fluorenone (8%) by 1-methyl-3,4,5-tricyanopyridinium perchlorate has been reported, the reaction apparently involving transfer of hydrogen to the pyridinium ring.[24] The oxidation of benzyl alcohol to benzaldehyde by 1-methyl-3-carbamoylpyridinium iodide also has been reported.[25] It was not clear in these two oxidations whether control reactions were run to check the possibility of autoxidation of the alcohol.

Bridged compound **2** on treatment with various bases was reported to undergo no observable intramolecular hydrogen transfer.[11a] Aqueous hydroxide apparently added to the 2 position of the charged pyridine ring and other bases in hexamethylphosphoramide caused alkoxyl exchange (aluminum isopropoxide) and destruction or modification of the pyridine ring [lithium bis(trimethylsilyl)amide, sodium hydride, potassium *tert*-butoxide].[11a]

Treatment of the nonbridged pyridinium salt **17**, bridged alcohols **15a** and **15b**, and methylene bridged salt **6** with aqueous sodium carbonate resulted in the appearance of two new absorptions in the uv spectrum

(19) Zinc ions actually decreased the rate of reduction of hexachloroacetone by 1-benzyl-1,4-dihydronicotinamide. A complex of zinc ion with the carboxamide group of the dihydronicotinamide was inferred from spectroscopic changes. The complexing of zinc ions in this way would decrease the reducing power of the dihydropyridine by increasing the electron-withdrawing character of the carboxamide group: A. Lombardo, Ph.D. Thesis, Syracuse University, 1967.

(20) M. Barnard and N. C. Yang, *Proc. Chem. Soc.* (*London*), 302 (1958).

(21) R. Breslow and M. A. Winnick, *J. Amer. Chem. Soc.*, **91**, 3083 (1969); R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); R. Breslow and P. Kalicky, *ibid.*, **93**, 3540 (1971); R. Breslow, *et al.*, *ibid.*, **94**, 3276 (1972).

(22) G. Stein, *J. Chim. Phys. Physicochem. Biol.*, **52**, 634 (1955); G. Stein and G. Stiassy, *Nature*, **176**, 734 (1955); U. Eisner, J. R. Williams, B. W. Matthews, and H. Ziffer, *Tetrahedron*, **26**, 899 (1970); D. Abelson, E. Parthe, K. W. Lee, and A. Boyle, *Biochem. J.*, **96**, 840 (1965). *Cf.* ref 11b.

(23) E. A. Ford, Ph.D. Thesis, Syracuse University, 1967, p 89.

(24) K. Wallenfels and W. Hanstein, *Angew. Chem., Int. Ed. Engl.*, **4**, 869 (1965).

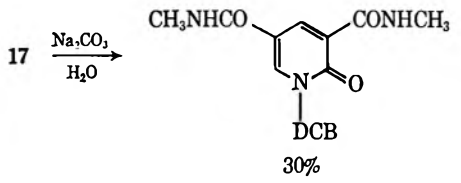
(25) B. Kadis, Abstracts of Papers, 135th National Meeting of the American Chemical Society, Boston, Mass., April 1959, 24-O.

TABLE II

NEW UV ABSORPTION MAXIMA OBSERVED ON TREATMENT OF PYRIDINIUM SALTS WITH BASES[a]

Base	Compound 6	15a	15b	17
Sodium carbonate-H_2O	345 (fast)	345 (fast)	345 (fast)	270, 340 (fast)
Potassium *tert*-butoxide-THF	380 (5 hr)	375 (20 min)	378 (fast)	348 (fast)
Sodium hydride-THF	No change	375 (3 hr)	340[b]	No change
Potassium 2,6-di-*tert*-butylphenoxide	No change	No change	383 (fast)	350 (fast)

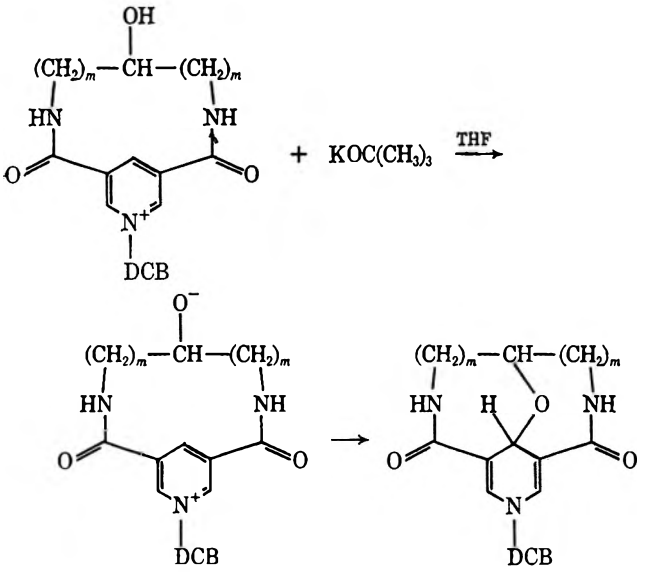
[a] Absorption maxima are reported in nanometers. Approximate times for the maximum development of the new absorption are given. [b] This weak absorption develops within 15 min and then slowly decreases in intensity.



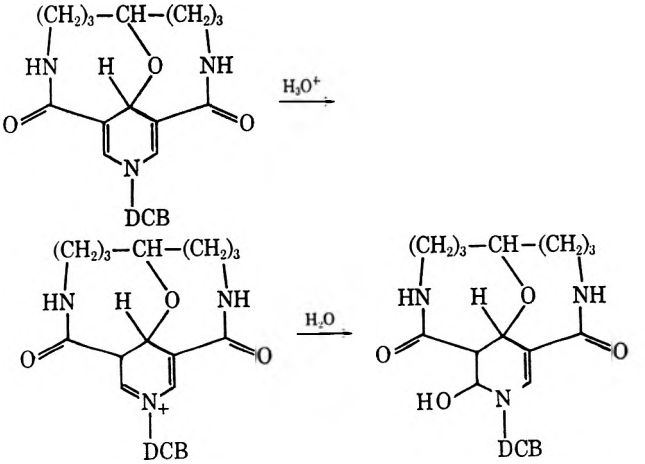
at 252–255 and at 340–345 nm. Addition of acid causes these spectra to revert to those of the pyridinium salts. These spectral data indicate addition of hydroxyl ion to the 2 position of the pyridinium salts by analogy with the spectra of similar dihydropyridine derivatives[26] and are in agreement with the data obtained on treatment of **2** with hydroxide ion.[11a] One of the products obtained from the nonbridged salt **17** was identified as the 2-pyridone (probably formed *via* oxidation of the hydroxide adduct) on the basis of its elemental analysis and its spectral data. Another, unidentified, product also was obtained.

Addition of potassium *tert*-butoxide to a saturated solution of **17** in dry THF resulted in the immediate formation of new absorption at 348 nm. Under the same conditions the methylene bridged salt **6** reacted slowly and after 5 hr only a small new absorption at 380 nm was observed. In marked contrast, bridged alcohol **15a**, which has the same number of atoms in the bridge as **6**, gave rapidly, on identical treatment with potassium *tert*-butoxide, a new absorption at 375 nm. Formation of bridged ketone **16a** was unlikely since the ketone absorbs at 330 nm in THF (it is stable to potassium *tert*-butoxide). The rapid attack of *tert*-butoxide on nonbridged **17** and the slow attack on bridged methylene salt **6** indicates that the site of attack is hindered in **6**. The 2 position in **6** does not seem to be more hindered than the 2 position of **17**; so perhaps the variation in rate reflects hindrance to attack at the 4 position. The rapid formation of new absorption from **15a** suggests alkoxyl transfer between *tert*-butoxide anion and bridged alcohol, followed by formation of a tricyclic ether resulting from attack of the proximate alkoxide on the 4 position. The aluminum salt of **2** investigated previously does not show interaction of the alkoxide with the pyridinium ring[11a] probably because of strong complexing of the oxygen anion with aluminum cation and because of stabilization of the ion by the more polar solvent, hexamethylphosphoramide. Bridged alcohol **15b** also reacts rapidly with potassium *tert*-butoxide to give new absorption at 378 nm.

Sodium hydride in THF produced no observable change with unbridged salt **17** or with bridged heptamethylene salt **6**, but, with bridged alcohol **15a**, new absorption at 375 nm was observed, again suggesting



intramolecular alkoxide addition to the ring. Addition of a few drops of concentrated hydrochloric acid to this solution destroyed the sodium hydride and led to disappearance (slow) of the absorption at 375 and to the appearance of a new band at 292 nm. This behavior is typical of that of 1,4-dihydropyridines toward aqueous acid[16] and indicates addition of a proton to the double bond of a 1,4-dihydropyridine system rather than cleavage of the tricyclic ether to yield the pyridinium salt.[27]



The feasibility of interaction of an alkoxide group in the bridge (*e.g.*, in **15a**) with the 4 position of the pyridinium ring is demonstrated by changes in the uv spectra of **6**, **15a**, and **17** in the presence of bases (Table II). The apparent failure of the bridged al-

(26) K. Wallenfels, H. Schüly, and D. Hofmann, *Justus Liebigs Ann. Chem.*, **621**, 106 (1959); K. Wallenfels and M. Gellrich *Chem. Ber.*, **92**, 1406 (1959); A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958); D. C. Dittmer and J. M. Kolyer, *ibid.*, **28**, 2288 (1963).

(27) Addition of sodium 2,6-di-*tert*-butylphenoxide in THF to **17** and to **15b** resulted in appearance of new absorption at 350 and at 382 nm, respectively. No evidence for any reaction with **6** or with **15a** was observed indicating, perhaps, that addition to these latter compounds with the smallest bridges was hindered.

koxides to transfer hydride ion to the charged pyridine ring may be ascribed to (1) the easy attack of negative oxygen itself on the electron deficient ring, (2) the number of conformations of the bridge which are poorly disposed for intramolecular hydride transfer, and (3) the decreased reducing power of the alkoxide caused by stabilization of the negative oxygen by solvent or by metal ions.

Experimental Section[28]

Isophthaloyl chloride[12] was prepared from isophthalic acid by treatment with thionyl chloride and a catalytic amount of dimethylformamide.[29] Dinicotinoyl chloride[30] (pyridine-3,5-dicarbonyl chloride) was prepared in a similar manner (88% yield).

General Procedure for the Synthesis of Macrobicyclic Diamides.—The freshly distilled diamine (0.02000 mol) was diluted to 24 ml with dry, reagent grade benzene (Baker and Adamson) (stored over sodium) in a 25-ml volumetric flask which had been dried for 24 hr at 120° and stored in a desiccator over sodium hydroxide. Recrystallized and freshly sublimed diacid chloride (0.01000 mol) was diluted to 24 ml with dry, reagent grade benzene in another dry 25-ml volumetric flask. These two solutions were allowed to stand for 2 hr at room temperature to equilibrate thermally and were then diluted to the 25-ml mark.

These solutions were introduced into two "delivery" 50-ml hypodermic syringes (Becton, Dickinson and Co., Yale, Luer-Lok), the ground glass plungers of which had been lubricated with silicone oil (Dow-Corning 550 fluid). A 2-ft Teflon "needle" (18 gauge) with Kel-F hub (Hamilton) was locked onto the "delivery" syringe and the air was pushed out of the barrel. The two syringes were then placed in a Sage syringe pump (Model 352) and the driving motor was started. When the air was forced out of both Teflon needles, the motor was stopped and the ends of the needles were dried and passed through airtight (tightly fitting and greased) holes in individual neoprene rubber stoppers into 1600 ml of dry, reagent grade benzene in a 2000-ml, five-necked, round-bottomed flask equipped with a nitrogen inlet, a calcium sulfate and sodium hydroxide drying tube which served as the nitrogen outlet, a cone-drive stirrer, and two neoprene rubber stoppers. A stream of nitrogen was passed through the flask during all operations. When the Teflon needles were placed below the surface of the benzene in the flask, the nitrogen flow was stopped, stirring was begun, and the syringe pump was set to deliver the solutions at a rate of 0.2 ml/hr (total time of delivery ~5 days) or at any convenient rate.

3,12-Diazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (4).—Benzene solutions (49 ml) of 1,8-diaminooctane (0.4591 *M*) and isophthaloyl chloride (0.2296 *M*) were introduced *via* syringe pump into 1200 ml of dry benzene at a rate of ~1 ml/hr. After 45 hr, when addition was complete, the Teflon needles were removed, and the mixture was stirred for an additional hour. The benzene solution was filtered to remove amine hydrochloride mixed with product, and the benzene was removed on a rotary evaporator. A small amount of product (0.035 g), mp 297°, was obtained by treatment of the material from evaporation of the benzene with hot ethanol, concentration of the ethanol solution to 7 ml, and chilling. All of the remaining solid obtained, including the amine hydrochloride mixture, was wetted with THF, placed in Soxhlet thimble, and continuously extracted with dry THF for ~2 days. The THF was removed on a rotary evaporator at room temperature. The yellow solid obtained was dissolved in hot ethanol (70 ml) and treated with activated charcoal. The charcoal was removed by filtration, and the filtrate was concentrated by heating until slightly turbid. It was allowed to stand for 1 hr at room temperature and 4 hr in a freezer. The white solid which had formed was collected by filtration, washed with ether, and dried for 0.5 hr in a vacuum oven. This product was combined with the small amount obtained earlier (total yield: 1.165 g, 0.00425 mol, 38%): mp 293–296°; ir (KBr) 3275 (NH), 1660 (sh), 1640 (amide C=O) cm^{-1}; pmr (100 MHz, DMSO-d_6) δ 8.00, 7.66 (m, 6, NH, C_6H_4), 3.28 (m, 4, CH_2N), 1.50 (m, 12, CH_2).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.07; H, 8.03; N, 10.22; mol wt, 274. Found: C, 70.17; H, 8.25; N, 10.06; mol wt, 295.

Octamethylene-Bridged Dinicotinamide: 3,12,16-Triazabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (5a).—A solution (25 ml) of freshly sublimed 1,8-diaminooctane (3.48795 g, 0.023485 mol) in dry, reagent grade benzene was placed in a 50-ml delivery syringe. Likewise, a solution (25 ml) of 3,5-pyridinedicarbonyl chloride (2.38323 g, 0.011743 mol) in benzene was placed in the other 50-ml syringe of the syringe pump. These solutions were added to dry benzene (1600 ml) at a rate of 0.2 ml/hr. After completion of addition of the reagents to the reaction flask, the white solid which had formed was removed by filtration and dried in a vacuum oven for 3 hr at 50°. The benzene was removed by a rotary evaporator to yield a white solid. The two solids were combined and extracted with THF in a Soxhlet extractor for 48 hr. The tetrahydrofuran was removed by a rotary evaporator to yield a white solid which was recrystallized from 95% ethanol to give the 3,5-octamethylene-bridged pyridine (5a) (1.335 g, 0.00476 mol, 41%): mp 341–343° dec; ir (KBr) 3300 (m, NH), 3100 (w, aromatic), 2925 (m), 2850 (m), 1670 (m, amide C=O), 1640 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.00, 8.85, 8.65, 8.25 (5, NH, pyridine H), 3.30 (m, 4, NCH_2), 1.45 (m, 12).

Anal. Calcd for $C_{15}H_{21}N_3O_2$: C, 65.45; H, 7.64; N, 15.27. Found: C, 65.72; H, 7.79; N, 15.32.

Heptamethylene-Bridged Dinicotinamide: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dione (5b).—Freshly sublimed 1,7-diaminoheptane (3.05869 g, 0.023485 mol) and 3,5-pyridinedicarbonyl chloride (2.38323 g, 0.011743 mol) were allowed to react as described for 5a to yield the 3,5-heptamethylene-bridged pyridine (5b) (0.706 g, 0.00271 mol, 23%): mp 342–343° dec; ir (KBr) 3250 (m, NH), 3050 (w aromatic), 2900 (m), 2850 (sh), 1640 cm^{-1} (s, amide C=O); pmr (DMSO-d_6) δ 8.92, 8.20 (br complex m, 5, NH, pyridine H), 3.16 (br m, 4, CH_2N), 1.38 (br m, 10).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.38; H, 7.28; N, 16.09. Found: C, 64.59; H, 7.41; N, 16.03.

Hexamethylene-Bridged Dinicotinamide: 3,10,14-Triazabicyclo[10.3.1]hexadeca-1(16),12,14-triene-2,12-dione (5c).—Freshly sublimed 1,6-diaminohexane (2.36309 g, 0.0203347 mol) and 3,5-pyridinedicarbonyl chloride (2.28764 g, 0.0101674 mol) were allowed to react as described above. Extraction with THF failed to separate the product from the benzene-insoluble material. The material insoluble in THF was removed from the Soxhlet extractor, dried for 1 hr in a vacuum oven at 50°, and treated with 50 ml of hot 95% ethanol. The insoluble material was removed by filtration. The treatment with ethanol was repeated on the ethanol-insoluble material. The insoluble solid was collected by filtration to yield 3,5-hexamethylene-bridged pyridine (5c) (0.246 g, 0.001 mol, 9.8%): mp 298–300°; ir (KBr) 3400 (sh), 3260 (m, NH), 3050 (w, aromatic), 2900 (m), 2940 (sh), 1635 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.23, 8.98, 8.78 (5, NH, pyridine H), 3.40 (br s, 4, CH_2N), 1.50 (br m, 8).

Anal. Calcd for $C_{13}H_{17}N_3O_2 \cdot {}^1/_3H_2O$: C, 61.67; H, 6.98, N, 16.60. Found (after 24 hr at 120° under vacuum): C, 61.73; H, 7.10; N, 16.71.

Pentamethylene-Bridged Dinicotinamide: 3,9,13-Triazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-2,10-dione (5d).—Freshly distilled 1,5-diaminopentane (2.40427 g, 0.0235298 mol) and 3,5-pyridinedicarbonyl chloride (2.40031 g, 0.011765 mol) were allowed to react as described above. Again, extraction with THF failed to separate the product from the benzene-insoluble material. The material insoluble in THF was removed from the Soxhlet extractor, dried for 1 hr in a vacuum oven at 50°, and treated with 50 ml of hot 95% ethanol. The insoluble

(28) Melting points were taken on either a Fisher-Johns or Mel-Temp melting point apparatus and are uncorrected. Ir spectra were obtained on either a Perkin-Elmer Model 521 spectrophotometer or a Perkin-Elmer Model 137 spectrophotometer: w, weak; m, medium; s, strong; sh, shoulder; d, doublet. Uv spectra were taken on a Perkin-Elmer uv-visible spectrophometer, Model 202. Proton nuclear magnetic resonance (pmr) spectra were recorded on a Varian Model A-60 or on a 100-MHz Japan Electronic Optics Laboratory Model JNM-4H-100 nmr spectrophotometer: s, singlet; d, doublet; m, multiplet; br, broad. Mass spectra were obtained on a Hitachi Perkin-Elmer mass spectrometer, Model RMU-6D. Fluorescence spectra were obtained on an Aminco-Bowman spectrophotofluorimeter. Nitrogen refers to Burco high purity nitrogen, oxygen content between 4 and 15 ppm. A drying tower containing Drierite and sodium hydroxide was used to remove the last traces of water from the nitrogen.

(29) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y. 1967, p 286.

(30) H. Meyer and H. Tropsch, *Monatsh. Chem.*, **35**, 782 (1914).

material was collected by filtration, and the treatment with ethanol was repeated. The insoluble 3,5-pentamethylene-bridged pyridine (**5d**) was again collected (0.123 g, 0.00053 mol, 4.3%): mp 236–238°; ir (KBr) 3400 (sh), 3230 (m, amide NH), 3030 (w, aromatic), 2900 (m, 2830 (sh), 1635 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.12, 8.84, 8.64 (5, NH, pyridine H), 3.35 (m, 4, NCH_2), 1.60 (br m, 6).

Anal. Calcd for $C_{12}H_{15}N_3O_2 \cdot 0.7H_2O$: C, 58.77; H, 6.78; N, 17.17. Found (after 24 hr at 100° under vacuum): C, 58.94; H, 7.09; N, 17.27.

1-Dichlorobenzylheptamethylene-Bridged Pyridinium Bromide: 15-(2,6-Dichlorobenzyl)-2,12-dioxo-3,11-diaza-15-azoniabicyclo-[11.3.1]heptadeca-1(17),13,15-triene Bromide (6).—Heptamethylene-bridged pyridine (**5b**, 0.260 g, 0.001 mol) was dissolved in a solution of α-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dimethyl sulfoxide (10 ml) (dried over 3A molecular sieves) and the reaction mixture was stirred and heated in an oil bath at 70° for 2 hr. A white precipitate was obtained by the addition of ether (100 ml). The solid was collected by filtration and recrystallized from ethanol to yield **6** (0.403 g, 0.00076 mol, 76%): mp 288–290°; ir (KBr) 1670 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.48, 9.29, 8.88, 8.62 (m, 5, NH, pyridine H), 7.73 (s, 3, Ar H), 6.33 (s, 2, Ar CH_2), 3.00 (m, NCH_2), 1.55 (m, 12).

Anal. Calcd for $C_{21}H_{24}BrCl_2N_3O_2$: C, 50.32; H, 4.83. Found: C, 50.39; H, 5.17.

1-Dichlorobenzylheptamethylene-Bridged 1,4-Dihydrodinicotinamide: 15-(2,6-Dichlorobenzyl)-3,11,15-triazabicyclo[11.3.1]-heptadeca-13,16-diene-2,12-dione (7).—Pyridinium bromide **6** (0.258 g, 0.0005 mol) was added to a solution of sodium hydrosulfite (0.350 g, 0.002 mol) and sodium carbonate (0.224 g, 0.002 mol) in distilled water (25 ml) at 70°. A stream of nitrogen was passed over the solution during all operations. The rapidly stirred reaction mixture immediately turned orange and within 10 min a yellow solution had formed. A yellow solid precipitated 15 min later. Heating and stirring continued for 1 hr, the mixture was allowed to cool to room temperature, and the yellow solid was collected by filtration and recrystallized from ethanol-water to yield **7** (0.130 g, 0.000296 mol, 60%): mp 230–231° dec; uv max (95% ethanol) 344 nm (ϵ 5100); fluorescence (max) (95% ethanol) excitation, 343 nm, and emission, 478 nm; ir (KBr) 3300 (br m, amide NH), 3020 (w), 2900 (m), 2830 (sh), 1640 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 7.90 (s, 2, vinyl H), 7.5–7.1 (5, NH, Ar H), 5.00 (s, 2, Ar CH_2), 3.35 (m, unintegrated, water contamination, CH_2N), 3.00 (s, unintegrated, 4-CH_2), 1.35 (m, 10).

Anal. Calcd for $C_{21}H_{25}Cl_2N_3O_2 \cdot {}^1/_3H_2O$: C, 58.89; H, 6.05. Found: C, 58.88; H, 5.93.

Ethylene Ketal of 1,7-Heptanediol-4-one Bis-*p*-toluenesulfonate (8a).—*p*-Toluenesulfonyl chloride (152 g, 0.80 mol) was added to a cold (−10°) solution of the ethylene ketal of 1,7-heptanediol-4-one[31] (38 g, 0.20 mol) in pyridine (400 ml, dried over potassium hydroxide). A precipitate appeared and after 1 hr the reaction mixture was poured into ice–water (3000 ml) which was rapidly stirred. A pink oil formed which solidified after 1 hr. This solid was collected by filtration, washed thoroughly with cold water, and dried overnight in a vacuum oven at room temperature to yield **8a** (94.5 g, 0.19 mol, 96%): mp 78–80°; pmr ($CDCl_3$) δ 7.56 (q, 8 H, C_6H_4), 4.00 (m, 4 H, SO_3CH_2), 3.82 (s, 4 H, OCH_2CH_2O), 2.43 (s, 6 H, CH_3), 1.56 (m, 8 H).

This compound could be stored at −20° without noticeable decomposition for periods of 1 week.

Ethylene Ketal of 1,9-Nonanediol-5-one Bis-*p*-toluenesulfonate (8b).—The ethylene ketal of 1,9-nonanediol-5-one[31] (43.6 g, 0.20 mol) was treated with *p*-toluenesulfonyl chloride (152 g, 0.80 mol) as described for the preparation of **8a**. The oily, impure product was dissolved in ether which was extracted with water. The ether was dried over 3A molecular sieves and removed on a rotary evaporator to yield **8b** (97 g, 0.185 mol, 92%): mp 79–80°; pmr ($CDCl_3$) δ 7.50 (q, 8, C_6H_4), 3.93 (m, 4, SO_3CH_2), 3.78 (s, 4, OCH_2CH_2O), 2.73 (s, 6, CH_3), 1.43 (m, 12).

Anal. Calcd for $C_{25}H_{34}O_8S_2$: C, 57.03; H, 6.46. Found: C, 56.96; H, 6.49.

Ethylene Ketal of 1,7-Bisphthalimidoheptan-4-one (9a).—Bis-*p*-toluenesulfonate **8a** (90 g, 0.18 mol) was dissolved in dimethylformamide (400 ml) and potassium phthalimide (140.7 g, 0.76 mol) was added to the rapidly stirred reaction mixture which was heated at 100° for 1 hr and then cooled to room temperature. The reaction mixture was transferred to an extraction funnel, treated with water (500 ml), and extracted with chloroform. The chloroform was washed with water, dried over 3A molecular sieves, and removed on a rotary evaporator to yield an oily, brown residue. The residue was treated with 95% ethanol (200 ml) and chilled to −20°. Recrystallization from 95% ethanol afforded white, crystalline **9a** (53.9 g, 0.12 mol, 66%): mp 135–136.5°; ir (KBr) 1725 cm^{-1} (vs, C=O); pmr (DMSO-d_6) δ 7.81 (s, 8, C_6H_4), 3.83 (s, 4, OCH_2CH_2O), 3.50 (br, 4, NCH_2), 1.57 (br, 8).

Anal. Calcd for $C_{25}H_{24}N_2O_6$: C, 66.96; H, 5.36; N, 6.25. Found: C, 66.82; H, 5.45; N, 5.96.

Ethylene Ketal of 1,9-Bisphthalimidononan-5-one (9b).—Bis-*p*-toluenesulfonate **8b** (94.7 g, 0.18 mol) was treated with potassium phthalimide (140.7 g, 0.76 mol) as described for the preparation of **9a**. Recrystallization from 95% ethanol gave **9b** (32 g, 0.067 mol, 37%): mp 149–150°; ir (KBr) 1700 cm^{-1} (vs, C=O); pmr ($CDCl_3$) δ 7.83 (s, 8, C_6H_4), 3.90 (s, 4, OCH_2-CH_2O), 3.56 (t, 4, J = 6.5 Hz, NCH_2).

Anal. Calcd for $C_{27}H_{28}N_2O_6$: C, 68.07; H, 5.88. Found: C, 68.20; H, 5.89.

Ethylene Ketal of 1,7-Diaminoheptan-4-one (10a).—Hydrazine (95%, 6.84 g, 0.206 mol) was added to a suspension of **9a** (44.8 g, 0.10 mol) in 95% ethanol (600 ml). After the reaction mixture had been refluxed for 5 min, a solution was formed; after an additional 10 min, a white precipitate appeared. The reaction mixture was heated for 6 hr. Addition of water (100 ml) to the hot mixture caused the precipitate to dissolve and the hot solution was treated with sodium hydroxide (8.1 g, 0.202 mol) and cooled to room temperature. Long white needles of sodium phthaloyl hydrazide slowly formed. The mixture was chilled to −20° for 2 hr and the phenyl hydrazide salt was removed by filtration and discarded. The filtrate was concentrated to 500 ml on a rotary evaporator and THF (300 ml) was added to precipitate the remainder of the salt, which was removed by filtration. The solvent was removed on a rotary evaporator and the residue distilled to yield **10a** (16.35 g, 0.087 mol, 87%): bp 105–108° (0.03–0.05 mm); ir (neat) 3325 (m, NH_2), 3250 (sh, NH_2), 1600 cm^{-1} (NH_2, m); pmr (neat) δ 3.90 (s, 4, OCH_2CH_2O), (2.56, t, 4, J = 5.5 Hz, CH_2NH_2), 1.51 (br, 8, $H_2NCH_2CH_2$), 1.32 (s, 4, NH_2).

Anal. Calcd for $C_9H_{20}N_2O_2$: C, 57.44; H, 10.64. Found: C, 57.23; H, 10.83.

Ethylene Ketal of 1,9-Diaminononan-5-one (10b).—Bis phthalimido derivative **9b** (32 g, 0.067 mol) was treated with hydrazine (4.6 g, 0.135 mol) as described for the preparation of **10a**. Distillation gave **10b** (12.7 g, 0.06 mol, 90%): bp 128–134° (0.02–0.04 mm); ir (neat) 3300 (m, NH_2), 3200 (m, NH_2), 1600 cm^{-1} (m, NH_2); pmr (neat) δ 3.87 (s, 4, OCH_2CH_2O), 2.58 (t, 4, J = 6 Hz, CH_2NH_2), 1.40 (m, 12), 1.22 (s, 4, NH_2).

Anal. Calcd for $C_{11}H_{24}N_2O_2$: C, 61.11; H, 11.11. Found: C, 61.40; H, 11.30.

3,3-Bridged Dinicotinamide Ketal: Spiro[3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dione-2′,7(1′,3′)-dioxolane] (11a).—Diamine **10a** (3.86322 g, 0.020519 mol) and 3,5-pyridinedicarbonyl chloride (2.09318 g, 0.010259 mol) were allowed to react as described in the preparation of **5a**. Isolation of the product was attempted by a Soxhlet extraction with THF; however, the solid material became gummy upon exposure to the atmosphere. It was dissolved in boiling 95% ethanol (50 ml) and the product was allowed to crystallize without removal of impurities. After several days, transparent, cubic crystals separated. This solid was collected by filtration and recrystallized from 95% ethanol (35 ml) to yield **11a** (0.642 g, 0.00202 mol, 20%): mp 266–267°; ir (KBr) 3450 (m, d, NH), 3225 (m, d, NH), 1640 cm^{-1} (vs, d, C=O); pmr (100 MHz, DMSO-d_6-D_2O) δ 8.92 (d of d, J = 2.5, 12 Hz, 2, pyridine α H), 8.30 (br s, 1, pyridine γ H), 3.77 (s, 4, OCH_2CH_2O), 3.20 (m, 4, CH_2N), 1.90 (m, 4, CH_2CO), 1.45 (m, 4, CH_2). In the absence of water, the amide protons appear as broadened multiplets at δ 8.16 and at 8.80, near and under the absorptions of the pyridine ring protons.

Anal. Calcd for $C_{16}H_{21}N_3O_4 \cdot {}^1/_3H_2O$: C, 59.07; H, 6.67; N, 12.92; O, 21.33. Found (after 24 hr at 120° under vacuum): C, 59.05, H, 6.54; N, 13.6; O, 21.25.

4,4-Bridged Dinicotinamide Ketal: Spiro[3,12,16-triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,14-dione-2′,8(1′,3′-dioxolane] (11b).—Diamine **10b** (4.43398 g, 0.0204965 mol)

(31) H. Stetter and H. Rauhut, *Chem. Ber.*, **91**, 2543 (1958).

and 3,5-pyridinedicarbonyl chloride (2.09087 g, (0.0102482 mol) were allowed to react as described for the preparation of **5a**. The same isolation and purification techniques used for **11a** were applied to yield **11b** (1.434 g, 0.00415 mol, 40.5%): mp 347–351° dec; ir (KBr) 3400 (sh, NH), 3275 (m, NH), 1660 (sh), 1640 cm^{-1} (s, C=O); pmr (100 MHz, DMSO-d_6) δ 8.81 (s, 2, pyridine α H), 8.17 (s, 1, pyridine γ H), 7.97 (br m, 2, NH), 3.86 (s, 4, OCH_2CH_2O), 3.35 (br m, CH_2N), 1.60 (m, 12).

Anal. Calcd for $C_{18}H_{25}N_3O_4$: C, 62.25; H, 7.20; N, 12.10. Found: C, 62.42; H, 7.01; N, 12.01.

3,3-Bridged Ketone Dinicotinamide: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,7,12-trione (12a).—Ketal **11a** (0.720 g, 0.0023 mol) was added to a solution of 48% hydrogen bromide (1 ml) in water (9 ml) and 95% ethanol (10 ml), warmed to 50°. The solid dissolved and the reaction mixture was stirred and heated for 1 hr. The ethanol was removed on a rotary evaporator and the aqueous solution was treated with a saturated solution of sodium carbonate. A white solid was collected by filtration, washed thoroughly with water, and dried to yield **12a** (0.578 g, 0.0021 mol, 91%): mp 313–316°; ir (KBr) 3400 (m, NH), 3150 (m, NH), 1700 (m, C=O), 1640 cm^{-1} (s, d, amide C=O); pmr (100 MHz, DMSO-d_6) δ 8.95–8.40, 7.95–7.6 (m, 5, NH, pyridine H), 3.20 (br m, NCH_2), 2.60 (m, unintegrated, DMSO interference, CH_2CO), 1.70 (br m, 4).

Anal. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.18; N, 15.27. Found: C, 61.07; H, 6.13; N, 15.18.

4,4-Bridged Dinicotinamide Ketone: 3,13,17-Triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,8,14-trione (12b).—Ketal **11b** (1.110 g, 0.0032 mol) was hydrolyzed according to the procedure given for **11a** to yield **12b** (recrystallized from ethanol) (0.708 g, 0.00234 mol, 73%): mp 323–325°; ir (KBr) 3250 (m, NH), 1700 (m, C=O), 1635 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 8.88 (s, 2, pyridine α H), 8.57–8.25 (m, 3, NH, pyridine γ H), 3.36 (m, not integrated, interference with H_2O, CH_2N), 1.65 (br m, 12).

Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.56, H, 7.12; N, 13.56.

3,3-Bridged Dinicotinamide Alcohol: 3,11,15-Triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene-2,12-dion-7-ol (13a).—Sodium borohydride (0.054 g, 0.00137 mol) was added to a suspension of **12a** (0.375 g, 0.00136 mol) in absolute ethanol (30 ml) and the mixture was stirred and heated at 60° for 2 hr after which water (5 drops) was added to the suspension. The mixture was allowed to come to room temperature and stirred overnight. The white insoluble material was collected by filtration and recrystallized from ethanol to yield **13a** (0.290 g, 0.00105 mol, 77%): mp 313–316°; ir (KBr) 3310 (s, OH), 3200 (m, NH), 3025 (m), 1660 (s, C=O), 1640 cm^{-1} (s, C=O); pmr (100 MHz, DMSO-d_6) δ 8.85 (d, 3, pyridine α H, NH), 8.10 (s, 2, pyridine γ H, NH), 4.42 (d, 1, COH), 3.50 and 2.95 (m, CHOH, CH_2N, water interference), 1.50 (br m, 8).

Anal. Calcd for $C_{14}H_{19}N_3O_3 \cdot {}^1/_3H_2O$: C, 59.36; H, 6.95. Found (after 24 hr at 120° under vacuum): C, 59.16; H, 7.02.

4,4-Bridged Dinicotinamide Alcohol: 3,13,17-Triazabicyclo[13.3.1]nonadeca-1(19),15,17-triene-2,14-dion-8-ol (13b).—Reduction of **12b** (1.100 g, 0.00345 mol) by sodium borohydride (0.76 g, 0.002 mol) as described for **12a** gave **13b** (0.950 g, 0.0031 mol, 90%): mp 352–354°; ir (KBr) 3250 (s, NH, OH), 1650 (sh), 1630 cm^{-1} (vs, C=O); pmr (100 MHz, DMSO-d_6) δ 8.83 (s, 2, pyridine α H), 8.40 (br s, 2, NH), 8.14 (s, 1, pyridine γ H), 4.37 (br s, 1, COH), 3.52 and 3.25 (m, water interference, CHOH, CH_2N), 1.57 (m, 12).

Anal. Calcd for $C_{16}H_{23}N_3O_3$: C, 62.95; H, 7.54; N, 13.77. Found: C, 63.18; H, 7.54; N, 13.62.

1-(2,6-Dichlorobenzyl)-3,3-Bridged Dinicotinamide Ketone Bromide: 15-(2,6-Dichlorobenzyl)-2,7,12-trioxo-3,11-diaza-15-azoniabicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (14a).—Bridged dinicotinamide ketone **12a** (0.275 g, 0.001 mol) was dissolved in dimethyl sulfoxide (10 ml) (dried over 3A molecular sieves) containing α-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol). The reaction mixture was stirred and heated in an oil bath at 60° for 90 min. A white precipitate, obtained by the addition of diethyl ether (100 ml), was collected by filtration and recrystallized from 20% aqueous ethanol to yield **14a** (0.452 g, 0.00087 mol, 87%): mp 257–259°; ir (KBr) 3150 (m, NH), 1700 (m, C=O), 1660 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.23, 9.11, and 8.39 (m, 5, NH, pyridine H), 7.67 (s, 3, Ar H), 6.29 (s, 2, Ar CH_2), 3.20 (m, 4, CH_2N), 2.73 (m, 4, CH_2CO), 1.77 (m, 4).

Anal. Calcd for $C_{21}H_{22}BrCl_2N_3O_3$: C, 48.93; H, 4.27; N, 8.16. Found: C, 48.93; H, 4.55; N, 8.16.

1-Dichlorobenzyl-4,4-Bridged Dinicotinamide Ketone Bromide: 17-(2,6-Dichlorobenzyl)-2,8,14-trioxo-3,13-diaza-17-azoniabicyclo[13.3.1]nonadeca-1(19),15,17-triene Bromide (14b). Bridged dinicotinamide ketone **12b** (0.303 g, 0.001 mol) was quaternized with α-bromo-2,6-dichlorotoluene (0.048 g, 0.002 mol) as described for **12a** to give salt **14b** (0.410 g, 0.00076 mol, 76%): mp 221–224°; ir (KBr) 3180 (m, NH), 1670 cm^{-1} (br, C=O and amide C=O); pmr (100 MHz, DMSO-d_6) δ 9.25, 9.10, and 9.00 (5, NH, pyridine H), 7.80 (s, 3, Ar H), 6.35 (s, 2, Ar CH_2), 3.40 (m, interference with H_2O, CH_2N), 1.70 (br m, 12).

Anal. Calcd for $C_{23}H_{26}BrCl_2N_3O_3$: C, 50.83; H, 4.79; N, 7.73. Found: C, 50.53; H, 4.84; N, 7.67.

1-Methyl-4,4-Bridged Dinicotinamide Ketone Iodide: 17-Methyl-2,8,14-trioxo-3,13-diaza-17-azoniabicyclo[13.3.1]nonadeca-1(19),15,17-triene Iodide (14c).—Bridged dinicotinamide **12b** (0.830 g, 0.00275 mol) was dissolved in dry dimethyl sulfoxide (10 ml) containing methyl iodide (2.8 g, 0.05 mol). The solution was refluxed gently for 5 hr and the solvent was removed on a rotary evaporator. The yellow solid was recrystallized from ethanol to yield **14c** (1.160 g, 0.0026 mol, 95%): mp 262–266°; ir (KBr) 3200 (m, NH), 1670 cm^{-1} (s, amide C=O and C=O); pmr (DMSO-d_6) δ 9.60 (s, 2, pyridine α H), 8.94 (d, 3, NH and pyridine γ H), 4.51 (s, 3, CH_3), 3.43 (m, 4, CH_2N), 1.70 (m, 12).

Anal. Calcd for $C_{17}H_{24}N_3O_3I$: C, 45.84; H, 5.39; N, 9.44. Found: C, 45.96; H, 5.48; N, 9.40.

1-Dichlorobenzyl-3,3-Bridged Dinicotinamide Alcohol Bromide: 15-(2,6-Dichlorobenzyl)-2,12-dioxo-7-ol-3,11-diaza-15-azoniabicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (15a).—Bridged alcohol **13a** (0.320 g, 0.00115 mol) was treated with α-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dry dimethyl sulfoxide (10 ml) as described for the preparation of **14a** to yield **15a** (0.541 g, 0.000965 mol, 84%): mp 254–255°; ir (KBr) 3400 (m, OH), 3150 (m, NH), 1655 cm^{-1} (s, C=O); pmr (100 MHz, DMSO-d_6) δ 9.50 (m, 1, NH), 9.25 (d, 2, pyridine α H), 8.88 (m, 1, pyridine γ H), 8.55 (s, 1, NH), 7.67 (s, 3, Ar H), 6.30 (s, 2, Ar CH_2), 4.46 (s, 1, COH), 3.15 (m, 5, CHOH, CH_2N), 1.60 (m, 8).

Anal. Calcd for $C_{21}H_{24}BrCl_2N_3O_3 \cdot {}^1/_3H_2O$: C, 48.18; H, 4.72; N, 8.02. Found (after 24 hr at 100° in vacuum); C, 48.11; H, 4.88; N, 7.72.

1-Dichlorobenzyl-4,4-Bridged Dinicotinamide Alcohol Bromide: 17-(2,6-Dichlorobenzyl)-2,14-dioxo-8-ol-3,13-diaza-15-azoniabicyclo[13.3.1]nondeca-1(19),15,17-triene Bromide (15b).—The bridged dinicotinamide **13b** (0.350 g, 0.00115 mol) was treated with α-bromo-2,6-dichlorotoluene (0.480 g, 0.002 mol) in dimethyl sulfoxide (10 ml) as described for the preparation of **14a** to give **15b** (0.480 g, 0.00088 mol, 77%): mp 224–226°; ir (KBr) 3300 (m, OH), 3160 (m, NH), 1660 cm^{-1} (vs, C=O); pmr (100 MHz, DMSO-d_6) δ 9.20 (m, 5, NH and pyridine H), 7.70 (s, 3, Ar H), 6.35 (s, 2, Ar CH_2), 4.05 (s, 1, OH), 3.35 (m, interference with H_2O, CHOH, CH_2N), 1.57 (m, 12).

Anal. Calcd for $C_{23}H_{28}Cl_2BrN_3O_3$: C, 50.64; H, 5.14; N, 7.71. Found: C, 50.65; H, 5.39; N, 7.75.

1-Dichlorobenzyl-3,3-Bridged 1,4-Dihydrodinicotinamide Ketone: 15-(2,6-Dichlorobenzyl)-3,11,15-triazabicyclo[11.3.1]heptadeca-13,16-diene-2,7,12-trione (16a).—Pyridinium bromide **14a** (0.743 g, 0.00144 mol) was added to a solution of sodium hydrosulfite (1.30 g, 0.0063 mol) (Mallinckrodt, 90%) and sodium carbonate (0.742 g, 0.007 mol) in distilled water (25 ml). The reaction mixture was heated and stirred at 90° under nitrogen. It immediately became orange and after 5 min the pyridinium salt had dissolved. A yellow solid precipitated 10 min later. Heating and stirring was continued for 4 hr after which the reaction mixture was cooled to room temperature and the yellow solid collected by filtration and recrystallized from ethanol–water to yield **16a** (0.389 g, 0.0009 mol, 62%): mp 265–268°; uv max (95% ethanol) 338 nm (ϵ 6700); fluorescence excitation (max), 340 nm, and emission (max). 451 nm; ir (KBr) 1700 (sh, C=O), 1650 cm^{-1} (s, amide C=O); pmr (100 MHz, DMSO-d_6) δ 7.52 (m, 4, Ar H, NH), 7.00 (m, 3, pyridine α H, NH), 4.95 (s, 2, Ar CH_2), 3.05 (m, 6, pyridine γ CH_2, CH_2N), 1.65 (m, 8).

Anal. Calcd for $C_{21}H_{23}Cl_2N_3O_3 \cdot {}^2/_3H_2O$: C, 56.26; H, 5.47; N, 9.38. Found (after 24 hr at 80° under vacuum): C, 56.01; H, 5.74; N, 9.54.

1-Dichlorobenzyl-4,4-Bridged 1,4-Dihydrodinicotinamide Ketone: 17-(2,6-Dichlorobenzyl)-3,13,17-triazabicyclo[13.3.1]-nonadeca-15,18-diene-2,8,14-trione (16b).—Bridged pyridinium salt **14b** (0.250 g, 0.00046 mol) was reduced by sodium hydrosulfite (0.300 g, 0.0015 mol) in aqueous sodium carbonate (0.160 g, 0.0015 mol, 25 ml) as described for **16a** except that the temperature was 70°. After 1 hr, the yellow solid was collected by filtration and recrystallized from ethanol–water to yield **16b** (0.160 g, 0.00035 mol, 75%): mp 215–217°; uv max (95% ethanol) 381 nm (ε 6450); fluorescence excitation (max) (ethanol), 375 nm, and emission (max), 447 nm; ir (KBr) 1690 (s, C=O) 1650 cm^{-1} (w, amide C=O); pmr (100 MHz, DMSO-d_6) δ 7.52 and 6.86 (7, Ar H, pyridine α H, NH), 4.85 (s, 2, Ar CH_2), 3.33 and 3.25 (interference with H_2O, pyridine γ CH_2, CH_2N), 1.55 (m, 12).

Anal. Calcd for $C_{23}H_{27}Cl_2N_3O_3 \cdot {}^1/_3H_2O$: C, 58.71; H, 5.94; N, 8.94; O, 11.33. Found (after 24 hr at 80° under vacuum): C, 58.86; H, 5.85; N, 8.98; O, 10.66.

1-Methyl-4,4-Bridged 1,4-Dihydrodinicotinamide Ketone: 17-Methyl-3,13,17-triazabicyclo[13.3.1]nonadeca-15,18-diene-2,-8,14-trione (16c).—The methyl-substituted salt **14c** (0.444 g, 0.0001 mol) was reduced by sodium hydrosulfite (0.6 g, 0.003 mol) in aqueous sodium carbonate (0.318 g, 0.003 mol, 25 ml) as described for **16a** except that the temperature was 60°. After 90 min, the yellow solid was collected by filtration and recrystallized from ethanol–water to yield **16c** (0.233 g, 0.0007 mol, 70%): mp 231–234°; uv max (95% ethanol) 388 nm (ε 7700); fluorescence excitation (max) (ethanol), 389 nm, and emission (max), 445 nm; ir (KBr) 1695 (s, C=O), 1650 cm^{-1} (m, amide C=O); pmr (100 MHz, DMSO-d_6) δ 7.24 (m, 2, NH), 7.01 (s, 2, pyridine α H), 3.45, (s, unintegrated, interference with pyridine α H, CH_3), 3.36 (s, unintegrated, interference with CH_3, pyridine α H), 3.20 (m, 4, CH_2N), 1.61 (m, 12).

Anal. Calcd for $C_{17}H_{25}N_3O_3$: C, 63.95; H, 7.84; N, 13.17. Found: C, 63.83; H, 7.91; N, 12.88.

1-(2,6-Dichlorobenzyl)-3,5-(*N,N'*-dimethyldicarbamoyl)-1,4-dihydropyridine (18).—Quaternization of 3,5-(*N,N'*-dimethyldicarbamoyl)pyridine[32] (5.4 g, 0.032 mol) with α-bromo-2,6-dichlorotoluene following the procedure described for the bridged dinicotinamide salts gave 1-(2-6-dichlorobenzyl)-3,5-(*N,N'*-dimethyldicarbamoyl)pyridinium bromide (**17**, 8.5 g, 0.020 mol, 62%): mp 248–250° dec; uv max (95% ethanol) 220 nm (ε 78,300); uv max (water) 200 nm (ε 78,000); ir (KBr) 1670 (vs, C=O), 1650 (vs, C=O), 1550 cm^{-1} (s, amide); pmr (DMSO-d_6) δ 9.66 (m, 1, pyridine γ H), 9.48 (m, 2, pyridine α H), 9.36 (m, 2, NH), 7.72 (s, 3, Ar H), 6.36 (s, 2, Ar CH_2), 2.90 (t, 6, NCH_3).

Anal. Calcd for $C_{16}H_{16}BrCl_2N_3O_2$: C, 44.34; H, 3.70. Found: C, 44.35; H, 3.88.

The pyridinium bromide **17** (7.5 g, 0.0173 mol) was reduced by sodium hydrosulfite as described for the bridged dihydronicotinamides and the crude product was recrystallized by dissolving the solid in hot 95% ethanol (100 ml) and adding hot distilled water (100 ml). This solution was cooled 3 hr at 0° and the precipitate collected by filtration to yield long yellow needles of **18** (4.1 g, 0.0114 mol, 61%): mp 205–207° (loses water of hydration at 105–108°); uv max (95% ethanol) 391 nm (ε 6070); fluorescence excitation (max) (ethanol), 378 nm, and emission (max), 445 nm; ir (KBr) 3380 (m), 1690 (s, C=O), 1580 (s), 1540 cm^{-1} (s, amide); pmr (DMSO-d_6) δ 7.58, 7.20, and 6.94 (m, 7, pyridine α H, NH, Ar H), 4.73 (s, 2, Ar CH_2), 3.13 (s, 2, pyridine γ CH_2), 2.68 (d, interference with DMSO, NCH_3).

Anal. Calcd for $C_{16}H_{17}Cl_2N_3O_2 \cdot {}^1/_4H_2O$: C, 53.56; H, 4.88; N, 11.71. Found (50° under vacuum, 24 hr): C, 53.67; H, 4.72; N, 11.82.

Chemical Properties of Bridged 1,4-Dihydrodinicotinamides. 1. Silver Nitrate.—Treatment of the dihydropyridines in ethanol (0.005 *M*) with an equal volume of aqueous silver nitrate (0.002 *M*) resulted in formation of a silver mirror.[33] The times for formation of the mirror are recorded in Table I.

2. Malachite Green.—Dihydropyridine derivatives **7**, **16a**, **16b**, and **18** (1.15×10^{-5} *M*) caused decoloration of Malachite Green (1.15×10^{-7} *M*) in ethanol solutions at 27°.[34] The kinetic behavior was complex but half-lives of 597, 666, 1044, and 918 sec, respectively, were noted.

3. Aqueous Hydrochloric Acid.—Ethanolic solutions (2×10^{-4} *M*, 25 ml) of **7**, **16a**, **16b**, and **18** were treated with aqueous hydrochloric acid (2.4 *N*, 1 ml). The absorption of aliquots were monitored at 27° at the uv maximum for each dihydropyridine and the relative pseudo-first-order rate constant given in Table I were obtained. The respective rate constants for **7**, **16a**, **16b**, and **18** are 1.25×10^{-4}, 1.96×10^{-4}, 3.22×10^{-5}, and 1.57×10^{-6} sec^{-1}.

4. Attempted Photoreduction.—Irradiation of **18** or bridged ketone **16b** (2×10^{-4} *M*) in 95% ethanol by a low pressure mercury immersion lamp (Hanovia, maximum output at 253.7 nm) for 30 min destroyed the 1,4-dihydropyridine chromophore. External irradiation of an ethanol solution of **18** in a Pyrex test tube in a Rayonet photochemical reactor of maximum output at 300 or 350 nm for 30 min gave the same result. Irradiation of **16b** (2×10^{-4} *M*) in ethanol for 30 min resulted in complete destruction of dihydropyridine chromophore at 381 nm, but **16a** was stable and only slowly underwent loss of its chromophore at 338 nm when irradiated at 300 nm. A large scale photolysis of **16a** (0.0441 g) in ethanol at 300 nm resulted in loss of the chromophore at 338 nm in 7 hr. Examination of the yellow solid obtained after removal of solvent revealed no evidence for formation of a pyridinium salt (nmr) and indicated loss of the vinyl protons at the 2 and the 6 positions of the starting material.

Chemical Properties of Bridged Dinicotinamide Salts. 1. Sodium Carbonate.—Solutions 2×10^{-4} *M* in salts **6**, **15a**, **15b**, and **17** were separately prepared and the uv spectrum of each was recorded. Sodium carbonate (0.106 g, 0.001 mol) was then added and the uv spectrum was recorded again. The solution was acidified by the addition of concentrated hydrochloric acid and the spectrum recorded. In all cases, addition of sodium carbonate caused new absorption to appear at 340–345 and at 252–255 nm. Addition of acid caused these absorptions to disappear and the spectrum reverted to that observed originally for the salts.

Compound **17** (1.300 g, 0.003 mol) was dissolved in distilled water (40 ml) heated at 65° and sodium carbonate (1.06 g, 0.01 mol) was added to this solution. The solution immediately turned yellow and became turbid. A yellow oil separated within 5 min. This oil was solidified by allowing the reaction mixture to stir for 1 hr in an oil bath and was collected by filtration and dried overnight at 50° in a vacuum oven.

Thin layer chromotography (Eastman prepared aluminum oxide sheet, elution by chloroform) indicated the presence of at least two components, one at R_f 0.9–0.7 which showed a purple fluorescence and the other at R_f 0.6–0.3 which showed a blue-white fluorescence.

The entire sample was dissolved in chloroform (10 ml) and chromatographed on a column of aluminum oxide (Woelm activity grade I, 200 ml, wet-packed with chloroform). The sample was eluted with chloroform and the separation of components was monitored by following the fluorescent bands which appeared when the column was irradiated with long-wavelength uv light. After the first band was collected, the second band was rapidly eluted with 10% ethanol in chloroform.

The first fraction yielded a white solid (0.287 g): mp 256–257°; uv max (95% ethanol) 333 nm (ε 8080), 253 (14,200);[35] ir (KBr) 3300 (m, NH), 3050 (w, Ar H), 1675 (vs, C=O), 1620 (m), 1530 cm^{-1} (s, amide); nmr (DMSO-d_6) δ 9.28 (m, 1, NH), 8.84 (d, 1, J = 2.5 Hz, 4-pyridine H), 8.55 (m, 1, NH), 8.03 (d, 1, J = 2.5 Hz, 6-pyridine H), 7.53 (s, 3, Ar H), 5.49 (s, 2, Ar CH_2), 2.85 (d, 3, J = 6.5 Hz, CH_3), 2.74 (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{16}H_{15}Cl_2N_3O_3$: C, 52.17; H, 4.08; N, 11.41; O, 13.04. Found: C, 51.92; H, 4.21; N, 11.27; O, 13.10.

The second fraction yielded a yellow oil which was triturated with diethyl ether to yield a yellow solid (0.634 g) (this compound sintered when heated and could not be purified by recrystallization: uv max (95% ethanol) 375 nm; nmr (DMSO-d_6) δ 7.51, 7.22, 6.92, 4.67, 3.33, 3.11, 2.66.

A structure consistent with the elemental analysis could not be determined.

Anal. Found: C, 52.72; H, 5.07; N, 11.92; O, 12.81.

(32) M. Samejima, *Yakugaku Zasshi*, **80**, 1713 (1960); *Chem. Abstr.*, **55**, 10439 (1961).

(33) The reactions were done in sealed tubes at room temperature.

(34) D. Mauzerall and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2261 (1955).

(35) The uv max for the 2-pyridone of 1-methylnicotinamide is at 330 nm: M. E. Pullman and S. P. Colowick, *J. Biol. Chem.*, **206**, 121 (1954).

2. **Potassium *tert*-Butoxide, Sodium Hydride, Sodium 2,6-Di-*tert*-Butylphenoxide in THF.**—Saturated solutions of the pyridinium salts **6**, **15a**, **15b**, and **17** were prepared by stirring 50 mg of each of the salts in THF (100 ml, freshly distilled from lithium aluminum hydride) for 24 hr. The uv spectra of the three solutions were recorded. The bases (50 mg) were added to 25-ml aliquots of the solutions of the pyridinium salts and the ultraviolet spectra recorded. Table II summarizes the observations.

Acknowledgment.—We wish to thank Professor Jack Vriesenga for assistance in obtaining the 100-MHz nmr spectra. Also, we wish to acknowledge the National Science Foundation for aid in the purchase of the 100-MHz nmr spectrometer and Bristol Laboratories for a gift of 60-MHz nmr spectrometer.

Registry No.—**4**, 40430-00-0; **5a**, 40430-01-1; **5b**, 36612-08-5; **5c**, 40513-85-7; **5d**, 40430-03-3; **6**, 40513-86-8; **7**, 40513-87-9; **8a**, 40430-04-4; **8b**, 40430-05-5; **9a**, 36844-27-6; **9b**, 40430-06-6; **10a**, 36844-26-5; **10b**, 40430-08-8; **11a**, 40513-89-1; **11b**, 40429-16-1; **12a**, 40429-17-2; **12b**, 40429-18-3; **13a**, 36612-07-4; **13b**, 40429-20-7; **14a**, 40429-21-8; **14b**, 40429-22-9; **14c**, 40429-23-0; **15a**, 40429-24-1; **15b**, 40429-25-2; **16a**, 40429-26-3; **16b**, 40429-27-4; **16c**, 40429-28-5; **17**, 40429-29-6; **18**, 40429-30-9; 1,8-diaminooctane, 373-44-4; isophthaloyl chloride, 99-63-8; 3,5-pyridinedicarbonyl chloride, 15074-61-0; 1,7-diaminoheptane, 646-19-5; 1,6-diaminohexane, 124-09-4; 1,5-diaminopentane, 462-94-2; α-bromo-2,6-dichlorotoluene, 20443-98-5; *p*-toluenesulfonyl chloride, 98-59-9; 1,7-heptanediol-4-one ethylene ketal, 5694-96-2; 1,9-nonanediol-5-one ethylene ketal, 5694-92-8; potassium phthalimide, 1074-82-4; 1-(2,6-dichlorobenzyl)-3,5-(*N*,*N*′-dimethyldicarbamoyl)-2(1*H*)-pyridone, 40429-36-5; 3,5-(*N*,*N*′-dimethyldicarbamoyl)pyridine, 40429-35-4.

Model Studies of the Synthesis of Echitamine and Related Indole Alkaloids.[1] II

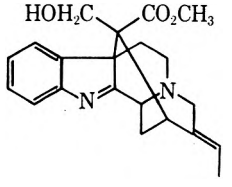
LLOYD J. DOLBY* AND STEPHEN J. NELSON

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

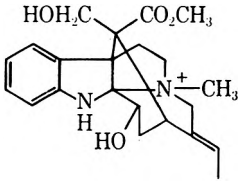
Received February 16, 1973

Attempts to synthesize the pentacyclic skeleton of akuammiline are described. The key step in this synthetic approach is the formation of the C-6 to C-7 bond by a nucleophilic substitution reaction. This transformation would complete the akuammiline skeleton from the tetrahydrocarbazole intermediate **16** which bears four of the required five rings. However, all attempts to generate the crucial C-6 to C-7 bond met with failure. The synthesis of several novel tetracyclic tetrahydrocarbazole derivatives is presented along with a sequence leading unexpectedly to indolo[2,3-*c*]norcar-3-en-2-one (**12**) and indolo[2,3-*b*]cyclohepta-2,4-dienone (**13**).

Echitamine and its probable biogenetic precursor deacetylakuammiline are examples of a group of indole alkaloids bearing a C-16–C-7 bond. A number of these alkaloids are now known[2,3] but no representative of this group has been obtained by chemical synthesis.



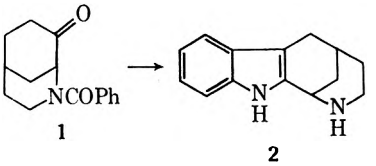
deacetylakuammiline



echitamine

In investigating routes to the pentacyclic framework of these molecules we sought to take advantage of the nucleophilic character of the indole nucleus in forming the final ring from a tetracyclic intermediate possessing the C-7–C-16 bond. Thus, elimination of *p*-toluenesulfonic acid from the tosylate shown in Scheme I would lead to the skeleton of deacetylakuammiline. A similar approach has been successfully employed in the synthesis of minovine,[4] and a previous report from these laboratories[5] describes results of a model system which proved encouraging.

The tetracyclic intermediate required for this scheme was obtained by two independent routes. In one route 2-azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (**2**) arose from a Fischer indole synthesis with 2-

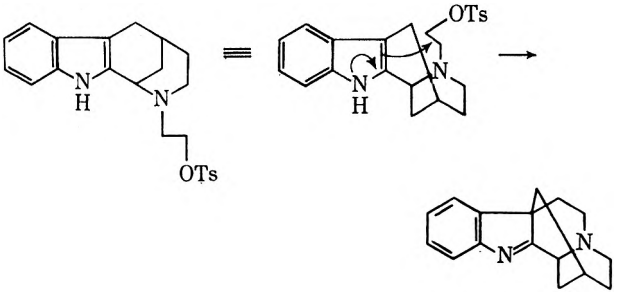


1 **2**

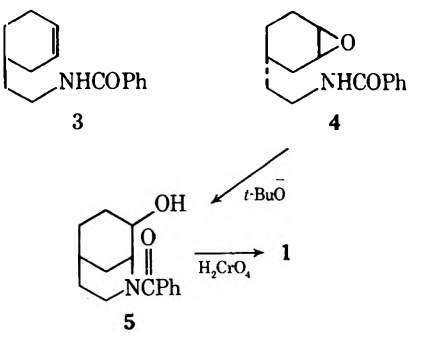
benzoyl-2-azabicyclo[3.3.1]nonan-8-one (**1**) followed by alkaline hydrolysis of the benzoyl moiety.

The ketone utilized in the Fischer indole synthesis was prepared following the route outlined in Scheme II.

SCHEME I



SCHEME II



3 **4** **5**

(1) The authors gratefully acknowledge financial support from the National Institutes of Health (Grant GM18196) and a Public Health Service Career Program Award (1-K3-NB-28,105) from the National Institute of Neurological Disease and Blindness.

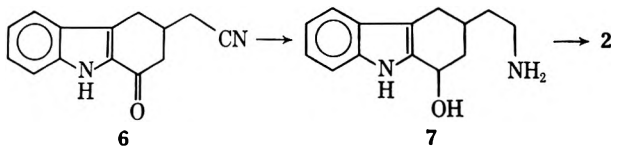
(2) J. E. Saxton, "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 501.

(3) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(4) F. E. Ziegler and F. B. Spitzner, *J. Amer. Chem. Soc.*, **92**, 3493 (1970).

(5) L. J. Dolby and Z. Esfandiary, *J. Org. Chem.*, **37**, 43 (1972).

SCHEME III



Oxidation of *N*-benzoyl-2-(Δ^3-cyclohexenyl)ethylamine (**3**) with *m*-chloroperbenzoic acid gave rise to an amorphous solid from which the trans epoxide **4** was obtained by fractional crystallization. On treatment with potassium *tert*-butoxide the amido epoxide **4** underwent cyclization to give 2-aza-2-benzoylbicyclo-[3.3.1]nonan-8-ol (**5**) in high yield. For preparative purposes the crude epoxide mixture was treated in a similar fashion to give **5** in 40–45% yields. Oxidation of **5** to the ketone **1** proved unexpectedly troublesome; a variety of methods gave rise to intractable mixtures. Ultimately, the ketone **5** was obtained in moderate yields with chromic acid in aqueous acetic acid.

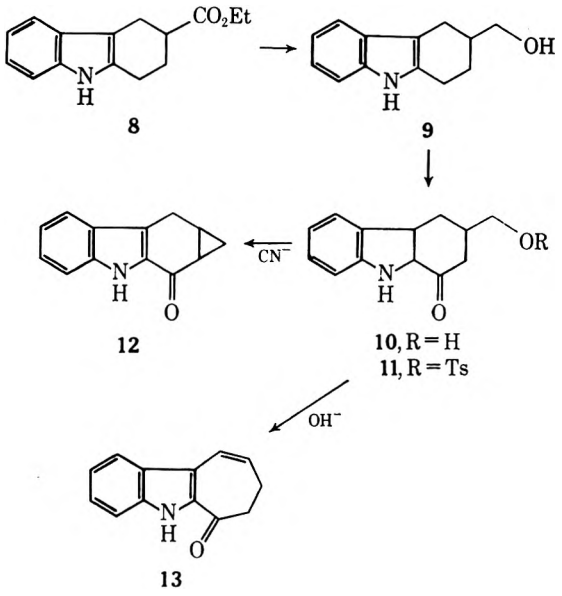
Brief treatment of the crude phenylhydrazone of **1** with hot dilute sulfuric acid gave rise to a dark product which was subjected directly to alkaline hydrolysis. The crystalline tetracyclic amine **2** was obtained from the hydrolysis mixture in 2–5% yields. The ultraviolet spectrum of **2** shows characteristic indole absorption. The pmr, ir, and mass spectra were likewise consistent with the expected structure. Ultimate confirmation of the structure was obtained, however, by an independent synthesis.

The great facility with which 2-hydroxyalkylindoles enter into elimination–addition reactions[6] suggested that the tetracyclic amine **2** could be obtained from 3-(2-aminoethyl)-1-hydroxy-1,2,3,4-tetrahydrocarbazole (**7**) (Scheme III). This proved to be the case. Reduction of 3-cyanomethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (**6**) with lithium aluminum hydride under carefully controlled conditions followed by pyrolysis of the crude reduction product in refluxing *o*-dichlorobenzene gave the tetracyclic amine **2** in yields of 40%. Material obtained by this route was identical with that obtained from the Fischer indole synthesis.

The preparation of the keto nitrile **6** was accompanied by an interesting rearrangement leading to indole[2,3-*b*]cyclohepta-2,4-dienone (**13**) (Scheme IV). Reduction of 3-carboethoxy-1,2,3,4-tetrahydrocarbazole (**8**) with lithium aluminum hydride gave the carbinol **9**. Oxidation of **9** with periodic acid[7] in methanol provided 3-hydroxymethyl-1-oxo-1,2,4,3-tetrahydrocarbazole (**10**), which was converted to the corresponding *p*-toluenesulfonate ester **11**.

On treatment with sodium cyanide in either ethanol or dimethyl sulfoxide, **11** gave rise not to the expected keto nitrile **6** but to indolo[2,3-*c*]norcar-3-en-2-one (**12**). The structure of **12** follows from elemental analysis and one-proton multiplets in the pmr spectrum centered at 0.8 and 1.4 ppm assigned to the methylene protons of the cyclopropane ring. In an effort to duplicate this reaction with sodium hydroxide in ethanol

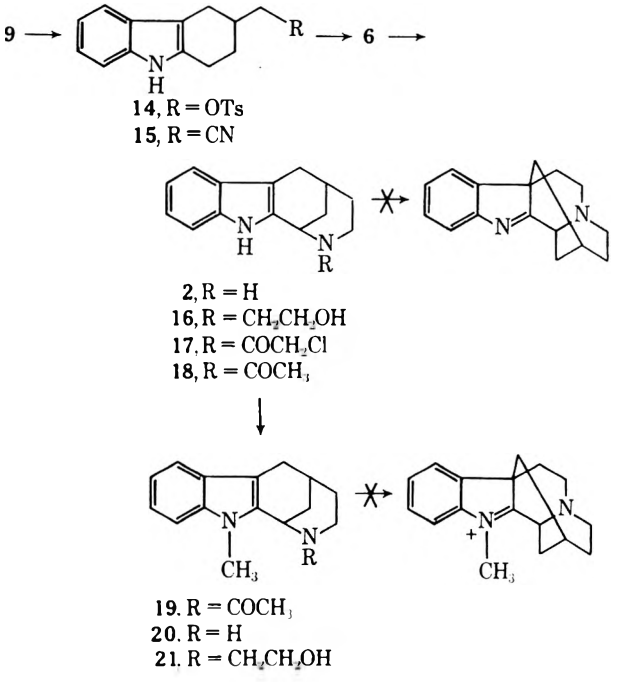
SCHEME IV



an excellent yield of the cycloheptadienone **13** was realized. The norcarenone **12** could be detected in the reaction mixture by tlc and is undoubtedly the precursor of **13**. Although unexpected, these results are not without precedent. Julia and coworkers have prepared benzosuberones in an analogous fashion from 3-hydroxymethyl-α-tetralones.[8]

To circumvent this difficulty, methylol **9** was converted to the corresponding *p*-toluenesulfonate ester **14**, which reacted smoothly with sodium cyanide in ethanol to give 3-cyanomethyl-1,2,3,4-tetrahydrocarbazole (**15**) (Scheme V). Periodic acid oxidation of

SCHEME V



15 in methanol then gave rise to the desired keto nitrile **6**. With a convenient source of the tetracyclic amine **2** at hand the amino alcohol **16** was readily obtained by treatment of **2** with ethylene oxide

(6) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 94–108; for pertinent examples see G. Büchi, R. E. Manning, and S. A. Monti, *J. Amer. Chem. Soc.*, **88**, 2532 (1966); R. J. Sundberg, *J. Org. Chem.*, **33**, 487 (1968); L. J. Dolby and P. D. Lord, *ibid.*, **34**, 2988 (1969).

(7) L. J. Dolby and D. L. Booth, *J. Amer. Chem. Soc.*, **88**, 1049 (1966).

(8) S. Julia, M. Julia, and C. Huynh, *C. R. Acad. Sci.*, **246**, 3464 (1958).

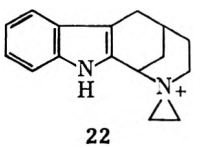
in tetrahydrofuran containing a small amount of methanol.

Treatment of the ethanolamine **16** with *p*-toluenesulfonyl chloride in pyridine resulted in the formation of a polymeric material which displayed typical indole absorption in its ultraviolet spectrum. Similar results were obtained with methanesulfonyl chloride–triethylamine in dimethylformamide or 1,2-dimethoxyethane. In no case was there obtained material having the characteristic indolenine absorption maxima near 260 nm.[4]

The chloroacetamide **17** was prepared in the expectation that generation of the indolic anion would result in the desired cyclization. Reaction of **17** with sodium hydride in tetrahydrofuran resulted in the formation of an amorphous material which retained the indole nucleus and the amide carbonyl by ultraviolet and infrared spectroscopy. The material was insoluble in hot 10% acetic acid and had no distinct melting point.

It was expected that methylation of the indole nitrogen would minimize polymer formation and the desired ring closure would be favored. The acetamide **18** was prepared from **2** by the action of acetic anhydride in pyridine. Reaction of **18** with sodium hydride followed by methyl iodide gave rise to the methylated acetamide **19**, which was directly subjected to hydrazinolysis, giving the methylated tetracyclic amine **20**. Treatment of **20** with ethylene oxide gave rise to the methylated ethanolamine **21**, which was treated with methanesulfonyl chloride or *p*-toluenesulfonyl chloride as described for the demethyl compound. Inasmuch as the product expected from the desired cyclization is an indoleninium salt, the reaction mixtures were treated with sodium borohydride to reduce the immonium moiety and facilitate the isolation of products. If water was added to the reaction mixture before the sodium borohydride a good recovery of starting material resulted. If the order of reagent addition was reversed a complex mixture of products was obtained from which three major components were obtained by preparative tlc. All of the products showed typical indole absorption in their ultraviolet spectra and were not further characterized. No absorption assignable to the expected indoline could be detected in either the reaction mixture or any of the products.

The failure of the cyclization reactions can be rationalized by postulating the aziridinium ion **22** as an



22

intermediate which fails to cyclize under the conditions employed.

Experimental Section[9]

N-Benzoyl-2-(Δ³-cyclohexenyl)ethylamine (**3**).—A mixture of 2-(Δ³-cyclohexenyl)ethylamine[10] (85 g, 0.67 mol) in 1 *N* sodium hydroxide (500 ml) was treated with benzoyl chloride (127 g, 0.910 mol) over 1 hr at 0°. Additional 1 *N* sodium hydroxide was added as required to maintain a pH above 10. After the addition of the benzoyl chloride the mixture was vigorously stirred for 1 hr. The precipitate was collected and taken up in ether. The organic solution was washed with sodium bicarbonate solution and brine and dried. The ether was removed under reduced pressure and the residue was recrystallized from benzene–hexane to give the benzamide **3** (143 g, 92%): mp 84–85°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3350 and 1650 cm^{-1}; pmr ($CDCl_3$) δ 0.80–2.91 (m, 9), 3.20–3.72 (m, 2), 5.66 (b s, 2), and 7.10–8.20 (m, 5).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.44; H, 8.41; N, 5.94.

N-Benzoyl-3-(2-aminoethyl)-7-oxabicyclo[4.1.0]heptane (**4**).—To a solution of the cyclohexenylbenzamide **3** (95.5 g, 0.420 mol) in chloroform (1 l.) was added 80% *m*-chloroperbenzoic acid (100 g, 0.46 equiv) in portions with cooling to maintain the temperature below 30°. After the addition was complete the mixture was stirred at room temperature for 16 hr. Potassium carbonate (100 g) in water (600 ml) was added and the phases were separated. The aqueous phase was extracted with chloroform and the combined chloroform solutions were washed with bisulfite solution and brine and dried. Removal of the chloroform under reduced pressure left the epoxide mixture **10** as an oil (104 g, 98%) which solidified on standing. Repeated crystallization from ethyl acetate–hexanes provided the trans isomer **4**: mp 113–115°; $\tilde{\nu}_{max}^{CHCl_3}$ 3500, 1660, and 1215 cm^{-1}; pmr ($CDCl_3$) δ 0.65–2.25 (m, 9), 3.08 (b s, 2), 3.38 (q, 2), 7.02 (b s, 1), 7.30 (u d, 3), and 7.72 (u d, 2).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.11; H, 7.69; N, 5.67.

2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-ol (**5**).—A solution of the crude epoxide mixture **4** (25 g, 0.10 mol) in tetrahydrofuran (60 ml) was added dropwise over 10 min to a solution of potassium (7 g, 0.2 mol) in *tert*-butyl alcohol (200 ml). The solution was refluxed for 12 hr and water (10 ml) was added. The mixture was concentrated under reduced pressure and the dark residue was triturated with methanol (20 ml) to separate the nonanol **5** (10 g, 40%) as a colorless powder. When the pure trans isomer was treated in an identical fashion an 87% yield was realized. Crystallization from ethanol provided an analytical sample: mp 197–198°; ir $\tilde{\nu}_{max}^{Nujol}$ 3365 and 1605 cm^{-1}; pmr δ 1.50–3.20 (m, 9), 3.60–5.05 (m, 5), and 7.25–8.20 (p, 5).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.41; H, 7.88; N, 5.65.

2-Aza-2-benzoylbicyclo[3.3.1]nonan-8-one (**1**).—A solution of potassium dichromate (720 mg, 2.94 mmol) in 9 *N* sulfuric acid (5 ml) was added dropwise to a solution of the nonanol **5** (1.80 g, 7.35 mmol) in acetic acid (10 ml) over 30 min. The mixture was then stirred for 30 min at room temperature and diluted with water (50 ml). The mixture was extracted with ethyl acetate and the extracts were washed with dilute sodium hydroxide, water, and brine and dried. Removal of the solvent left an oily mixture which was triturated with ether to separate starting material (525 mg, 29%). The ether solution was filtered through alumina (Woelm neutral, activity I, 5 g) eluting with additional ether. Removal of the solvent under reduced pressure gave the ketone **1** (520 mg, 29%) as an oil, homogeneous by tlc: ir $\tilde{\nu}_{max}^{CHCl_3}$ 1730 and 1635 cm^{-1}; pmr ($CDCl_3$) δ 1.10–2.80 (m, 9), 3.15–3.50 (b m, 2), 4.45 (b s, 1), and 7.10–7.80 (m, 5). The semicarbazone crystallized from acetone to give an analytical sample, mp 196–198°.

Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 64.04; H, 6.81; N, 18.66.

2-Azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (**2**).—A mixture of the ketone **1** (4.5 g, 18.5 mmol) and phenylhydrazine (2.2 g, 20

(9) All melting points were determined in a Drechsel stirring oil melting point apparatus and are uncorrected. All boiling points are also uncorrected. All boiling points are also uncorrected. Infrared spectra were measured with either Beckman IR-5A or IR-7 infrared spectrophotometers. Proton magnetic resonance spectra were determined at either 60 or 100 MHz with Varian Models A-60 and HA-100 pmr spectrometers. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the pmr spectra the following notations are used: b, broad; u, unsymmetrical; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; and m, multiplet. Ultraviolet spectra were determined on a Cary Model 15 recording spectrophotometer. The mass spectra were obtained with a Consolidated Electrodynamics Corp. Model 21-110 double focus mass spectrometer equipped with a direct inlet system. Thin layer chromatographic analyses were carried out on Baker-flex silica gel 1B precoated plates obtained from J. T. Baker, Chemical Co., Phillipsburg, N. J. A 3% ceric sulfate–10% sulfuric acid solution or a 5% phosphomolybdic acid was used to visualize the spots.

(10) L. A. Spurlock and R. J. Schultz, *J. Amer. Chem. Soc.*, **92**, 6302 (1970).

mmol) was refluxed in ethanol (30 ml) for 5 hr. The ethanol was removed under reduced pressure and the residue was dissolved in 6 *N* sulfuric acid (20 ml). The mixture was warmed on the steam bath for 10 min. The resultant precipitate was collected, washed with water, and dried. The dark powder was taken up in ethyl acetate and filtered through alumina (Woelm neutral, activity I, 60 g) eluting with ethyl acetate. The eluents were concentrated under reduced pressure to leave a light brown powder (1.62 g). Tlc indicated the presence of a minimum of six compounds. A portion of this crude material (0.49 g) was heated at 160° in ethylene glycol (7 ml) containing sodium hydroxide (850 mg) for 2 hr. The dark mixture was diluted with water (20 ml) and extracted with ethyl acetate. The extracts were washed with water and brine and dried. The solvent was removed under reduced pressure and the residue was sublimed (165°, 0.05 mm) to give crude tetracyclic amine **2** (26 mg, 2.2% based on starting ketone) as a yellow powder. Repeated crystallization from ethyl acetate gave an analytical sample: mp 223–225°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3470 and 1455 cm^{-1}; nmr ($CDCl_3$) δ 1.50–3.45 (m, 10), 4.45 (b s, 1), and 7.30–7.88 (m, 5); uv λ_{max}^{ETOH} 291 nm (ϵ 6200), 283 (7200), 276 (6900), and 226 (33,000); *m/e* 212 (M^+), 169 (100).

Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.17; H, 7.67; N, 13.38.

3-Carbethoxy-1,2,3,4-tetrahydrocarbazole (8).—Freshly distilled phenylhydrazine (43.0 g, 0.40 mol) was added dropwise to a refluxing solution of 4-carbethoxycyclohexanone[11] (68.0 g, 0.40 mol) in glacial acetic acid (600 ml) over 35 min. The mixture was refluxed for 1 hr and cooled in an ice bath with stirring. Water (300 ml) was added to complete precipitation and the product was collected and washed well with water. The product was dried in a vacuum oven overnight, giving **8** as a pale yellow powder (80.3 g, 80%). Crystallization from methanol gave an analytical sample: mp 95–97°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3510 and 1720 cm^{-1}; pmr ($CDCl_3$) δ 1.25 (t, 3), 1.90–3.20 (m, 7), 4.18 (q, 2), and 6.9–7.8 (m, 5); uv λ_{max}^{ETOH} 289 nm (ϵ 5940), 282 (7180), 274 (6720), and 226 (33,700).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04; N, 5.76. Found: C, 74.7; H, 6.97; N, 5.67.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole (9).—A solution of the ester **8** (80.0 g, 0.316 mol) in tetrahydrofuran (200 ml) was added to a slurry of lithium aluminum hydride (18.0 g, 0.475 mol) in ether (600 ml) over 1 hr at room temperature. The mixture was stirred for 2 hr and excess lithium aluminum hydride was decomposed with water (50 ml). Hydrochloric acid (400 ml, 6 *N*) was added and the phases were separated. The aqueous phase was extracted with ether and the combined organic solutions were washed with water and brine. Drying and removing the solvent under reduced pressure left the carbinol **9** as a yellow oil (64 g, 100%) which on standing set to a hard glass: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3450 and 1540 cm^{-1}; nmr ($CDCl_3$) δ 1.20–3.00 (m, 7), 3.56 (d, 2), and 6.90–7.80 (m, 5). The acetate crystallized from methanol as needles, mp 97–99°.

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.72; H, 6.96; N, 5.65.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole *p*-Toluenesulfonate (14).—A cooled solution of *p*-toluenesulfonyl chloride (72.5 g, 0.38 mol) in pyridine (150 ml) was added to a cooled solution of the carbinol **9** (64 g, 0.32 mol) in pyridine (150 ml). The solution was allowed to stand in the cold for 16 hr. The mixture was poured into water (600 ml) and after 30 min the precipitate was collected and dissolved in ethyl acetate. The organic solution was washed with 3 *N* sulfuric acid, water, and brine. Drying and removing the solvent under reduced pressure gave the crude tosylate **14** (86.5 g, 77%) as a tan powder. The analytical sample crystallized from acetone: mp 138–140° dec; ir $\tilde{\nu}_{max}^{CHCl_3}$ 4250, 1360, and 1175 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 1.52–2.81 (m, 7), 2.30 (s, 3), 3.92 (b d, 2 H), 6.71–7.80 (m, 9); uv λ_{max}^{EtOH} 290 nm (ϵ 5100), 283 (6000), 283 (6000), and 226 (39,500)

Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.50; H, 5.96; N, 3.94. Found: C, 67.26; H, 5.91; N, 3.81.

3-Cyanomethyl-1,2,3,4-tetrahydrocarbazole (15).—A solution of the tosylate **14** (85.0 g, 0.240 mol) and sodium cyanide (20.0 g, 0.408 mol) in ethanol (500 ml) was refluxed for 14 hr. The mixture was concentrated to 200 ml under reduced pressure and water (600 ml) was added. The dark mixture was extracted with ether and the extracts were washed with water and brine and dried. The solution was concentrated under reduced pressure to give a dark heavy oil which was filtered through alumina (100 g, Alcoa F-20) eluting with benzene. Concentration of the eluent gave the nitrile **15** as a pale yellow oil (44 g, 88%) which solidified on standing to a waxy solid. Crystallization from ether–hexane gave the analytical sample: mp 99–101°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3425 and 2260 cm^{-1}; pmr ($CDCl_3$) δ 1.25–3.10 (m, 9) and 6.80–7.62 (m, 5).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.29; H, 6.78; N, 13.55.

3-Hydroxymethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (10).—To a cooled solution of the carbinol **9** (10 g, 50 mmol) in methanol (50 ml) was added a solution of periodic acid (22.6 g, 100 mmol) in water (50 ml) over 45 min while the temperature was maintained below 5°. The mixture was stirred for 1 hr at 0° and the resultant precipitate was collected. The precipitate was taken up in ethyl acetate and the organic solution was washed with bisulfite solution and brine and dried. Evaporation of the solvent left a dark solid which was filtered through Florisil, eluting first with ether to remove a small amount of dark oil. Elution with ethyl acetate and evaporation of the eluent gave the keto alcohol **10** as a yellow powder (6.6 g, 62%). An analytical sample crystallized from ethyl acetate showed mp 173–175°; ir $\tilde{\nu}_{max}^{Nujol}$ 3300 and 1650 cm^{-1}; pmr (CD_3COOD) δ 2.40–2.90 (m, 4), 3.10 (b d, 1), 3.72 (b s, 2), 6.80–7.62 (m, 5); uv λ_{max}^{EtOH} 304 nm (ϵ 2200) and 237 (1400).

Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.72; H, 6.05; N, 6.45.

3-Hydroxymethyl-1-oxo-1,2,3,4-tetrahydrocarbazole *p*-Toluenesulfonate (11).—A cooled solution of *p*-toluenesulfonyl chloride (7.0 g, 36 mmol) in pyridine (15 ml) was added to a cooled solution of the alcohol **10** (6.58 g, 30.6 mmol). The mixture was allowed to stand in the cold overnight and was then poured into water (300 ml). After 15 min the mixture was acidified with concentrated hydrochloric acid and the precipitate was filtered. The precipitate was washed with water and cold methanol and dried to give the tosylate **11** as a yellow powder (9.67 g, 90%). The analytical sample crystallized from butyl acetate as plates: mp 188–190° dec; ir $\tilde{\nu}_{max}^{Nujol}$ 3290, 1645, 1350, and 1175 cm^{-1}; pmr ($CDCl_3$) δ 2.84 (s, 3) 2.90–3.70 (m, 5), 4.52 (d, 2 H), and 7.40–8.27 (m, 9).

Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 64.71; H, 5.24; N, 3.53. Found: C, 65.02; H, 5.18; N, 3.79.

3-Cyanomethyl-1-oxo-1,2,3,4-tetrahydrocarbazole (6).—A solution of 3-cyanomethyl-1,2,3,4-tetrahydrocarbazole (**15**) (2.00 g, 9.50 mmol) in methanol (30 ml) was added dropwise over 30 min to a solution of periodic acid (6.00 g, 26.6 mmol) in methanol (50 ml) at 10–20°. After the addition was complete the mixture was stirred at room temperature for 2 hr and then at 0° for 30 min. The mixture was poured into water (100 ml) and after stirring to coagulate the precipitate the aqueous solution was decanted. The precipitate was taken up in ethyl acetate, washed with sodium thiosulfate solution and brine, and dried. Concentration of the solution under reduced pressure gave the nitrile **6** as a tan powder (1.38 g, 65%). Crystallization from ethyl acetate gave an analytical sample: mp 218–219°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3350, 2250, and 1645 cm^{-1}; pmr ($CDCl_3$–DMSO-d_6) δ 2.44–2.90 (b d, 7), 6.98–7.83 (m, 5); uv λ_{max}^{EtOH} 308 nm (ϵ 2000) and 236 (1500).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.70; H, 5.27; N, 12.65.

Indolo[2,3-*c*]-2-oxobicyclo[4.1.0]-3-heptene (12).—A solution of the tosylate **11** (0191 g, 2.5 mmol) and sodium cyanide (1.0 g, 20 mmol) in 90% ethanol (50 ml) was refluxed for 2.5 hr. Water (30 ml) was added and the mixture was concentrated under reduced pressure to remove the ethanol. The aqueous mixture was extracted with ethyl acetate and the extract was washed with water and brine and dried. Evaporation under reduced pressure left the norcaranone **12** as a yellow solid (0.45 g, 93%). Crystallization from ethyl acetate gave an analytical sample: mp 156–157°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3460, 3300, and 1640 cm^{-1}; pmr ($CDCl_3$) δ 0.81 (q, 1 H), 1.25–1.60 (m, 1), 2.10 (m, 2), 3.42 (m, 2), and 7.02–7.70 (m, 5); uv λ_{max}^{EtOH} 307 nm (ϵ 1900) and 235 (1500); *m/e* 197 (M^+), 168 (100).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.65; H, 5.69; N, 7.16.

Indolo[2,3-*b*]cyclohepta-2,4-dienone (13).—A solution of the tosylate **11** (1.0 g, 2.7 mmol) and sodium hydroxide (0.32 g, 8.0 mmol) in ethanol (20 ml) was refluxed for 3.5 hr. After 1 hr tlc indicated the presence of the norcaranone **24**. The mixture was concentrated under reduced pressure and the residue was diluted with water and extracted with ethyl acetate. The extract was washed with water and brine and dried. Removal of the solvent

(11) R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, **30**, 4145 (1965).

under reduced pressure left the cyloheptadienone **13** (505 mg, 95%) as a yellow powder. Sublimation (130°, 0.05 mm) and crystallization from benzene–hexanes gave the analytical sample as long yellow needles: mp 145–146°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3460, 1640, and 1330 cm^{-1}; pmr ($CDCl_3$) δ 2.40 (q, 2), 2.75 (m, 2), 6.20 (m, 2), and 6.80–7.75 (m, 5); uv λ_{max}^{EtOH} 360 nm (ϵ 6400), 322 (13,300), 247 (25,300), and 232 (24,400).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 79.49; H, 5.68; N, 6.91.

Indoloazabicyclononene 2 from 6.—A warm solution of the nitrile **6** (6.1 g, 27 mmol) in dry tetrahydrofuran (200 ml) was added rapidly to a refluxing slurry of lithium aluminum hydride (5.0 g, 0.13 mol) in glyme (200 ml). After the addition was complete the mixture was refluxed for 20 min and cooled. Excess hydride was decomposed with water (5 ml); 4 *N* sodium hydroxide (5 ml) was added followed by additional water (15 ml). The salts were filtered and washed with tetrahydrofuran. Evaporation of the filtrate under reduced pressure left a colorless foam (5.8 g, 95% weight recovery). The foam was refluxed in *o*-dichlorobenzene (450 ml) for 1.5 hr. The solvent was evaporated under reduced pressure and the residue was taken up in 15% acetic acid and extracted with ether. The acidic solution was made alkaline with 50% sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and brine and dried. Evaporation of the solvent under reduced pressure followed by sublimation of the residue (165°, 0.05 mm) gave **2** (2.5 g, 44%) as a pale yellow powder. Crystallization from ethyl acetate gave small, colorless blocks, mp 220–222° dec. Admixture with material obtained from the Fischer indole synthesis gave mp 220–222° dec. The infrared spectrum of material obtained from this synthesis was identical with the infrared spectrum of material obtained previously.

2-Aza-2-(2-hydroxyethyl)indolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (16).—A solution of the tetracyclic amine **2** (2.53 g, 12 mmol) and ethylene oxide (2.5 g, 56 mmol) in 10% methanolic tetrahydrofuran (50 ml) was heated in a stainless steel bomb on the steam bath for 5 hr. The solvent was removed under reduced pressure and the residue was triturated with a small amount of ethyl acetate to give the ethanolamine **16** (2.47 g, 81%). Crystallization from ethyl acetate gave an analytical sample: mp 194–196°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3390 and 1450 cm^{-1}; pmr ($CDCl_3$) δ 1.80–4.00 (m, 10), 4.05–4.40 (m, 4), 4.55 (b, s, 1), 7.25–7.98 (m, 4), and 8.50 (b s, 1); *m/e* 256 (M^+), 225, 194, and 169 (100).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 75.26; H, 7.66; N, 10.76.

Reaction of Ethanolamine 16 with Methanesulfonyl Chloride.—A solution of the ethanolamine **16** (258 mg, 1.01 mmol) in dry dimethylformamide (5 ml) was cooled to −20°. Triethylamine (152 mg, 1.51 mmol) was added followed by dropwise addition of methanesulfonyl chloride (127 mg, 1.11 mmol) over 3 min. The mixture was stirred at −20° for 2 hr and allowed to stand at room temperature for 44 hr. Water (30 ml) was added and the mixture was extracted with chloroform. The organic solution was washed with water and brine and dried. Concentration under reduced pressure gave a brown gum (153 mg). The gum was taken up in methylene chloride (3 ml). Addition of a small amount of ether precipitated an amorphous white powder (148 mg, 58% weight recovery). The material was insoluble in hot 3 *N* hydrochloric acid. The uv spectrum showed absorption at λ_{max}^{EtOH} 291, 283, 276, and 227 nm. Tlc indicated that there was no starting material and showed a single spot at the origin with 6:3:1 ethyl acetate–methanol–triethylamine as eluent.

2-Aza-2-chloroacetylindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (17).—A solution of chloroacetyl chloride (520 mg, 4.65 mmol) in dry methylene chloride (10 ml) was added to a cold mixture of the tetracyclic amine **2** (677 mg, 3.19 mmol), potassium carbonate (880 mg, 6.31 mmol), methylene chloride (30 ml), and water (15 ml) over 15 min. The mixture was allowed to warm to room temperature and stirred for 3 hr. The phases were separated and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with bicarbonate solution, water, and brine. Drying and removal of the solvent left the crude chloroacetamide (923 mg, 97%) as a yellow oil. Crystallization from ethanol gave an analytical sample: mp 170–171°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3500, 1640, and 1455 cm^{-1}; pmr ($CDCl_3$) δ 1.15–3.45 (m, 9), 3.92 (s, 2), 5.75 (b s, 1), 6.90–7.52 (m, 4), and 8.92 (b s, 1).

Anal. Calcd for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.38; H, 6.00; N, 9.59.

Reaction of the Chloroacetamide 17 with Sodium Hydride.—The mineral oil of a 57% dispersion of sodium hydride (24.2 mg, 0.578 mmol) was removed by washing with dry 1,2-dimethoxyethane. A solution of the chloroacetamide **17** (111 mg, 0.385 mmol) in dry 1,2-dimethoxyethane (5 ml) was added to a slurry of the washed sodium hydride in dry 1,2-dimethoxyethane (8 ml) over 10 min. The mixture was stirred at room temperature for 2.5 hr. Water (1 ml) was added and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with chloroform and the extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown, amorphous powder (76.5 mg). The material was taken up in boiling chloroform and cooled to give a white, amorphous powder (25 mg). The material was insoluble in hot acetic acid or 2 *N* hydrochloric acid. The ultraviolet spectrum showed typical indole absorption (λ_{max}^{EtOH} 291, 285, 272, and 225 nm). The infrared spectrum showed amide carbonyl at 1645 cm^{-1}. The compound slowly charred at 315–330°. Concentration of the mother liquors under reduced pressure left a brown residue which had similar solubility and spectral properties.

2-Acetyl-1-azaindolo[2,3-*g*]bicyclo[3.3.1]non-7-ene (18).—To a cooled solution of the tetracyclic amine **2** (2.5 g, 12 mmol) in pyridine (20 ml) was added acetic anhydride (5.4 g, 53 mmol) over 2 min. The mixture was allowed to warm to room temperature and stirred for 4 hr. The mixture was poured into water (100 ml) and after 15 min was extracted with ethyl acetate. The extracts were washed with bicarbonate solution, water, and brine. Drying and removal of the solvent under reduced pressure left a brown solid which was filtered through alumina (Woelm neutral, activity I, 10 g) eluting with chloroform. Concentration of the eluent left the amide **18** (2.6 g, 87%) as a colorless solid. An analytical sample crystallized from ethyl acetate: mp 208–209°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3500 and 1625 cm^{-1}; pmr ($CDCl_3$) δ 1.50–3.78 (m, 9), 2.01 (s, 3), 5.70 (b s, 1), and 6.90–7.60 (m, 5).

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.05; H, 7.06; N, 10.76.

2-Azaindolo[2,3-*g*]-1′-methylbicyclo[3.3.1]non-7-ene (20).—The mineral oil of a 57% sodium hydride dispersion (0.80 g, 20 mmol) was removed by washing with dry tetrahydrofuran. The sodium hydride was slurried in tetrahydrofuran (20 ml) and a solution of the acetamide **18** (2.04 g, 8.05 mmol) in tetrahydrofuran (10 ml) was added. The mixture was brought to reflux for 15 min and then cooled in an ice bath. Methyl iodide (1.3 g, 9.2 mmol) was added and the mixture was stirred at room temperature for 5 hr. Water (20 ml) was added and the mixture was concentrated under reduced pressure to remove the tetrahydrofuran. The aqueous concentrate was extracted with chloroform and the organic phase was washed with water and brine and dried. Removal of the solvent under reduced pressure left a yellow oil (2.05 g) which was refluxed in hydrazine (50 ml) for 28 hr. Removal of the hydrazine under reduced pressure left a dark oil which was filtered through Florisil. Benzene eluted a dark oil (330 mg) which was discarded. Ethyl acetate eluted the methylated tetracyclic amine **20** (955 mg, 53%) obtained as a colorless solid. Sublimation (95°, 0.05 mm) and crystallization from benzene–hexanes gave an analytical sample: mp 105–107°; ir $\tilde{\nu}_{max}^{CHCl_3}$ 3300 and 1400 cm^{-1}; pmr ($CDCl_3$) δ 1.05–3.02 (m, 9), 3.55 (s, 3), 4.18 (b s, 1), and 6.92–7.65 (m, 4).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.50; H, 8.11; N, 12.09.

2-Aza-2-(2-hydroxyethyl)indolo[2,3-*g*]-1′-methylbicyclo[3.3.1]-non-7-ene (21).—A solution of the methylated tetracyclic amine **20** (430 mg, 1.59 mmol) and ethylene oxide (500 mg, 11.4 mmol) in 5% methanolic tetrahydrofuran was heated in a sealed tube for 8 hr on the steam bath. The solvent was removed under reduced pressure and the residue was filtered through alumina (Woelm neutral, activity I, 5 g) eluting with chloroform. Concentration of the eluents under reduced pressure gave the ethanolamine **21** (474 mg, 92%) as a yellow oil: ir $\tilde{\nu}_{max}^{CHCl_3}$ 3440 (b) and 1480 cm^{-1}; pmr ($CDCl_3$) δ 1.02–3.25 (m, 9), 3.51 (s, 3), 3.52–3.80 (m, 4), 3.90 (b s, 1), and 6.90–7.65 (m, 4). A picrate salt was prepared by the addition of a saturated solution of picric acid in ethanol to an ethanolic solution of the amine. Recrystallization from acetonitrile gave an analytical sample, mp 200–201°.

Anal. Calcd for $C_{23}H_{25}N_5O_8$: C, 55.31; H, 5.05; N, 14.02. Found: C, 55.18; H, 4.96; N, 13.65.

Reaction of the Methylated Ethanolamine 21 with *p*-Toluenesulfonyl Chloride.—To an ice-cold solution of the ethanolamine **21** (174 mg, 0.654 mmol) in dry pyridine (4 ml) was added freshly sublimed *p*-toluenesulfonyl chloride (150 mg, 0.785 mmol) in dry pyridine (1 ml). The mixture was allowed to warm to room temperature and was stirred under nitrogen for 49 hr. Water

(1 ml) was added and after 15 min sodium borohydride (100 mg) was added. The mixture was stirred for 30 min and then diluted with water (20 ml). The mixture was extracted with ethyl acetate and the extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown oil (160 mg, 92%) which was identical with the starting material by tlc and pmr spectroscopy.

Reaction of the Methylated Ethanolamine 21 with Methanesulfonyl Chloride.—A solution of the ethanolamine 21 (300 mg, 1.07 mmol) in dry 1,2-dimethoxyethane (5 ml) was cooled to −10° in an ice–salt bath. Freshly distilled triethylamine (360 mg, 3.60 mmol) was added followed by methanesulfonyl chloride (160 mg, 1.40 mmol) over 5 min. The mixture was allowed to warm to room temperature and was stirred for 3.5 hr under nitrogen. Excess sodium borohydride was added and the mixture was stirred at room temperature for 3 hr. Water (30 ml) was added and the mixture was extracted with chloroform. The extracts were washed with water and brine and dried. Removal of the solvent under reduced pressure left a brown gum (330 mg). Tlc indicated the material to be a mixture of at least three components. The mixture was separated by preparative tlc (Merck silica gel PF-254, ethyl acetate as eluent) to give three compounds of R_f 0.05, 0.5, and 0.8. The ultraviolet spectrum of all the components showed typical indole absorption (λ_{max}^{EtOH} 290, 283, 273, and 226 nm).

Registry No.—**1**, 40525-24-4; **1** semicarbazone, 40496-45-5; **2**, 40496-46-6; **3**, 40496-47-7; **4**, 40488-34-4; **5**, 40496-48-8; **6**, 40496-49-9; **8**, 26088-68-6; **9**, 26072-19-5; **9** acetate, 40496-52-4; **10**, 40496-53-5; **11**, 40496-54-6; **12**, 40496-55-7; **13**, 40496-56-8; **14**, 40496-57-9; **15**, 40496-58-0; **16**, 40496-59-1; **17**, 40496-60-4; **18**, 40496-61-5; **20**, 40496-62-6; **21**, 40496-63-7; **21** picrate, 40496-64-8; 2-(Δ^3-cyclohexenyl)ethylamine, 40496-65-9; benzoyl chloride, 98-88-4; *m*-chloroperbenzoic acid, 937-14-4; phenylhydrazine, 100-63-0; 4-carbethoxycyclohexanone, 17159-79-4; *p*-toluenesulfonyl chloride, 98-59-9; sodium cyanide, 917-61-3; sodium hydroxide, 1310-73-2; methanesulfonyl chloride, 124-63-0; chloroacetyl chloride, 79-04-9; sodium hydride, 7646-69-7; ethylene oxide, 75-21-8.

Studies on the Oxidation of "Reversed Nucleosides" in Oxygen. I. Synthesis of Eritadenine and Its Derivatives[1]

MITSUTAKA KAWAZU,* TAKESHI KANNO, SHIRO YAMAMURA, TOMISHIGE MIZOGUCHI, AND SEIICHI SAITO

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda Shi, Saitama, Japan

Received September 11, 1972

Reaction of methyl-5-*O*-tosyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (I) or 5-*O*-tosyl-1,2-*O*-isopropylidene-3-*O*-alkyl-β-D-arabofuranoses (IV) with the sodium salt of adenine in DMF afforded the corresponding "reversed nucleosides" in good yields. After removal of the protective groups of the sugar moiety by treatment with hydrochloric acid, the demasked reversed nucleosides were oxidized by air or oxygen in a dilute alkali solution at room temperature to give eritadenine and its α-*O*-alkyl derivatives. The yields of the acids were generally good. To confirm the structures and evaluate the biological activities, syntheses of their esters were also performed.

Several synthetic routes to eritadenine, one of the significant hypocholesterolemic components of *Lentinus edodes* Sing, have been reported employing D-erythrono lactone as the starting material.[2]

Although various synthetic pathways might be conceivable, a large-scale synthesis of eritadenine using this lactone appears to be somewhat uneconomical[3] because of the rather poor yield of the lactone in the preparations described in the literature.[4] The necessity for a large amount of eritadenine and its derivatives for biological studies required development of a more simplified method of preparation.

Since the low yield of the lactone by the literature method appears to be due to the complicated purification process during which a part of the lactone might have decomposed, it was conceivable that the derived product might be more easily separated from the oxidation mixture after prior condensation of the sugar moiety with a fairly insoluble material such as a purine, thus preventing decomposition. From this point of view, adoption of the procedure for the synthesis of a reversed nucleoside by Leonard[5] proved to be extremely useful.

Reaction of methyl-5-*O*-tosyl-2,3,-*O*-isopropylidene-β-D-ribofuranoside (I)[6] with the sodium salt of adenine in DMF gave the corresponding 9-substituted reversed nucleoside II in excellent yield. The attachment of the substituent was based on the characteristic uv absorption band at λ_{max} (H_2O) 258 nm at pH 2, 260 nm at pH 7, and 262 nm at pH 11. None of the other position isomers could be detected in the reaction mixture. Hydrolysis of II with dilute hydrochloric acid to remove the protective groups at 60–80° afforded the pure demasked reversed nucleoside III in 86.5% yield.

In a test reaction the air oxidation of III in dilute sodium hydroxide solution at room temperature proceeded as expected. Tlc of the reaction mixture showed a spot the R_f value of which was identical with that of an authentic sample of eritadenine. Hence III in 0.5% NaOH solution was stirred in an atmosphere of oxygen at room temperature. After 17 hr, the spot of III had completely disappeared and a single spot was observed at R_f 0.35 on tlc (silica gel GF 254;

(1) Preliminary communication: M. Kawazu, T. Kanno, N. Takamura, T. Mizoguchi, S. Saito, and K. Okumura, *Chem. Commun.*, 1045 (1970).

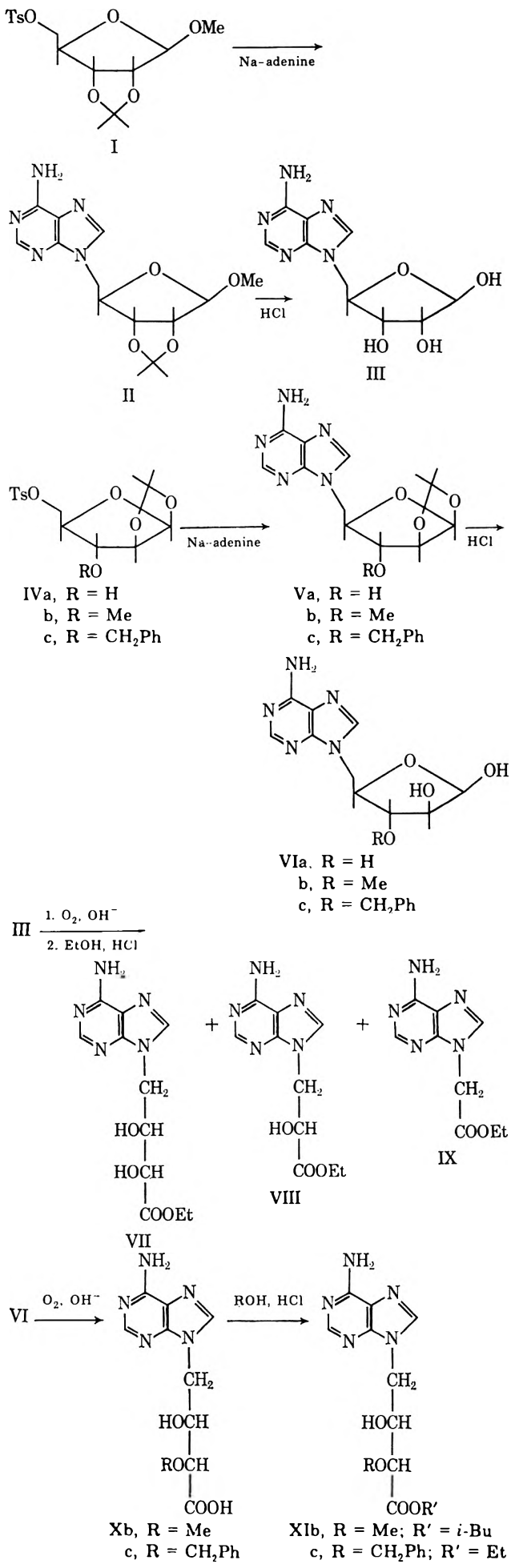
(2) (a) I. Chibata, K. Okumura, S. Takeyama, and K. Kotera, *Experientia*, **25**, 1237 (1969); (b) T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Tetrahedron Lett.*, 4729 (1969); (c) T. Kamiya, Y. Saito, M. Hashimoto, and H. Seki, *Chem. Ind. (London)*, 652 (1970).

(3) The situation has changed to some degree now, since a simple method for the preparation of the D-erythronolactone from D-glucose was explored in our laboratory and the method described in *J. Org. Chem.*, **36**, 1573 (1971), was also useful for a large-scale synthesis of eritadenine.

(4) E. Hardegger, K. Kreis, and H. El. Khadem, *Helv. Chim. Acta*, **34**, 2343 (1951).

(5) N. J. Leonard, F. C. Sciavolino, and V. Nair, *J. Org. Chem.*, **33**, 3169 (1968).

(6) N. J. Leonard and K. L. Carraway, *J. Heterocycl. Chem.*, **3**, 485 (1966).



n-butyl alcohol–acetic acid–water 4:1:5). The product was easily isolated as colorless plates by evaporating the water *in vacuo* and adding a volume of ethanol, and was identified as sodium eritadeninate by comparison of its spectral data with those of an authentic sample.

Although tlc showed a single spot, further treatment of the mother liquid gave no additionally pure eritadenine; hence the reaction had resulted in formation of a mixture. In order to separate the products, the evaporation residue was desalted by treatment with an ion exchange resin, and subsequently esterified with ethanol and HCl. Three esters could be separated chromatographically and were identified as ethyl 6-aminopurin-9*H*-9-yl acetate (IX), ethyl β-(6-aminopurin-9*H*-9-yl)-α-hydroxypropionate (VIII), and ethyl eritadeninate (VII), on the basis of analytical and spectral data. The total yield of eritadenine was thus over 80%.

In order to investigate the scope and limitations of this reaction, further work on the synthesis of some adenine reversed nucleosides and the oxidation by oxygen was carried out using D-arabinose.

Reaction of 1,2-*O*-isopropylidene-5-*O*-tosyl-β-D-arabofuranose (IVa), 1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-tosyl-β-D-arabofuranose (IVb),[7] and 1,2-*O*-isopropylidene-3-*O*-benzyl-5-*O*-tosyl-β-D-arabofuranose (IVc)[8] with the sodium salt of adenine in DMF led to the formation of the corresponding reversed nucleosides Va, Vb, and Vc, respectively. The yields were generally good except for the unprotected compound Va. A fairly large amount of adenine was recovered in this case. Dealkylation of the protected reversed nucleosides to give VIa, VIb, and VIc was carried out satisfactorily by treatment with dilute hydrochloric acid.

Oxygen oxidation of VIa under conditions similar to those for III afforded eritadenine in a 78% yield. Oxidation of VIb gave an acid Xb, in whose nmr spectrum the methyl protons of the methoxy group appeared as a singlet at δ 3.43 in D_2O. Esterification of Xb with isobutyl alcohol and hydrogen chloride yielded ester XIb, whose structure was confirmed analytically and spectrophotometrically. On the other hand, oxidation of VIc gave a mixture of eritadenine and Xc. Thus the yield of Xc was under 50%. This result indicated that the benzyl group had been partially removed, presumably by oxidation. The esterification of Xc with ethanol and hydrogen chloride gave XIc in 89% yield. Reduction of XIc in 5% hydrochloric acid in the presence of Pd on charcoal at room temperature afforded ethyl eritadeninate in good yield. Hence the method described here, which involves the synthesis of reversed nucleosides and their oxidation by oxygen, provides a simple synthesis of eritadenine and its derivatives.

Experimental Section

Melting points were taken on a Yamato capillary melting point apparatus Model Mp-1 and are uncorrected. Ir spectra were recorded using a Hitachi IR-E spectrophotometer as Nujol

(7) E. L. Hirst, T. K. N. Jones, and E. Williams, *J. Chem. Soc.*, 1062 (1947).

(8) Synthesized by the procedure similar to that of the *O*-methyl derivative.

suspension unless otherwise indicated. Nmr spectra were determined on a Model JEOL ME-60 spectrometer with tetramethylsilane as an internal standard.

General Procedure for the Reaction of the Sodium Salt of Adenine with 5-*O*-*p*-Toluenesulfonyl Sugar Derivatives.—The sodium salt of adenine was prepared by stirring a suspension of an equimolar amount of the adenine and sodium hydride (in oil suspension) in DMF (3–4 ml/mmol of the adenine) at room temperature for 1 hr and warming at 50–60° for 1 hr. After the mixture had been cooled, a solution of the 5-*O*-*p*-toluenesulfonyl sugar derivatives (0.9–1.0 molar equiv) in DMF (4–10 ml/mmol of the sugar derivatives) was added dropwise to this suspension. The suspension was stirred and warmed at 100° for 10 hr. The resulting clear solution was evaporated under vacuum at 50–90°. The residue was treated in an appropriate manner for the respective reaction.

Methyl 5-(6-Aminopurin-9*H*-9-yl)-2,3-*O*-isopropylidene-5-deoxy-β-D-ribofuranoside (II).—A solution of the sodium salt of adenine (2.48 g, 18.4 mmol) and I (5.5 g, 15.3 mmol) in DMF (100 ml) was treated in the manner described in the general procedure. The residual solid was extracted with hot chloroform and the chloroform extracts filtered were combined, washed with H_2O, and dried (Na_2SO_4). Evaporation of the chloroform afforded 4.7 g (95%) of crude I, mp 239–243°. Recrystallization from MeOH gave an analytical sample of II as colorless prisms: mp 248–249°; $[\alpha]^{25}D$ −8.4° (*c* 0.5, MeOH); ir 3220, 3090 cm^{-1} (NH_2); nmr (DMSO-d_6) δ 8.15 (s, 2 H, C_2H, C_8H of purine), 7.20 (broad s, 2 H, $-NH_2$), 4.92 (s, 1 H, C_1 H), 4.8–4.0 (m, 5 H), 3.20 (s, 3 H, –OMe), 1.26, 1.12 (s, 3 H, 3 H, CMe_2).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.34; H, 5.97; N, 21.50.

5-(6-Aminopurin-9*H*-9-yl)-1,2-*O*-isopropylidene-5-deoxy-β-D-arabofuranose (Va).—A solution of the sodium salt of adenine (2.16 g, 16 mmol) and IVa (5 g, 14.5 mmol) in DMF (200 ml) was treated in the same manner as described in the general procedure. The residual solid was washed with benzene (10 ml) and then cold water (20 ml). The insoluble solid (mp 232–237°) was recrystallized from H_2O to give an analytical sample of Va, 2.35 g (53%), as colorless needles: mp 240–241°; $[\alpha]^{18}D$ 135° (*c* 0.5, H_2O); ir 3400 (OH), 3240, 3090 cm^{-1} (NH_2); nmr (DMSO-d_6) δ 8.10 (s, 2 H), 7.16 (broad s, 2 H, $-NH_2$), 5.83 (d, 1 H, J = 4.0 Hz, C_1 H), 5.60 (broad, 1 H, –OH), 4.45–4.0 (m, 5 H), 1.45 (s, 3 H), 1.20 (s, 3 H).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.61; H, 5.60; N, 22.50.

5-(6-Aminopurin-9*H*-9-yl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-deoxy-β-D-arabofuranose (Vb).—A solution of the sodium salt of adenine (4.1 g, 29 mmol) and IVb in DMF (300 ml) was treated in the manner described in the general procedure. The residual solid was triturated in cold water (50 ml), and insoluble crystals were filtered to give 6.0 g (64%) of crude solid of Vb. Recrystallization from MeOH afforded an analytical sample of Vb, 5.5 g, as colorless prisms: mp 205–206°; $[\alpha]^{25}D$ 92.5° (*c* 1.0, MeOH); nmr (DMSO-d_6) δ 8.15, 8.04, (s, 1 H, 1 H, C_2 H, C_8 H of purine), 7.22 (broad s, 2 H, $-NH_2$), 5.83 (d, 1 H, J = 4.5 Hz, C_1 H), 4.65 (d, 1 H, J = 4.5 Hz, C_2 H), 4.35 (broad s, 3 H), 3.81 (s, 1 H, C_3 H), 3.02 (s, 3 H, –OMe), 1.43, 1.23 (s, 3 H, 3 H, $>CMe_2$).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.41; H, 6.04; N, 21.93.

5-(6-Aminopurin-9*H*-9-yl)-1,2-*O*-isopropylidene-3-*O*-benzyl-5-deoxy-β-D-arabofuranose (Vc).—A solution of the sodium salt of adenine (2.85 g, 2.11 mmol) and IVc (9.76 g, 19.2 mmol) in DMF (300 ml) was treated in the manner described in the general procedure. Water (20 ml) was added to the resulting residue and the insoluble crystals were collected by filtration to give 6.0 g of crude Vc. Recrystallization from MeOH afforded an analytical sample of Vc, 5.5 g (73%), as colorless prisms: mp 198–199°; $[\alpha]^{23}D$ 66.7° (*c* 0.3, MeOH); nmr (DMSO-d_6) δ 7.22 (s, 7 H, $C_6H_5CH_2$–, $-NH_2$), 5.90 (d, 1 H, J = 4 Hz, C_1 H), 4.72 (d, 1 H, J = 4 Hz, C_2 H), 4.6–4.2 (m, 5 H), 4.02 (s, 1 H, C_3 H), 1.47, 1.28 (s, 3 H, 3 H, $>CMe_2$).

Anal. Calcd for $C_{20}H_{23}N_5O_4$: C, 60.44; H, 5.83; N, 17.62. Found: C, 60.64; H, 5.77; N, 17.50.

General Procedure for the Hydrolysis of II, Va, Vb, and Vc.—A solution of the 5-(6-aminopurin-9-yl)-5-deoxy sugar derivative in water (20 ml/1 g of sugar derivative) and 6 *N* hydrochloric acid (0.55 ml/1 g of sugar derivative) was stirred and warmed at 70–80° for 3 hr. After the reaction mixture had been cooled, the solution was passed through a column of Amberlite IR-45 (OH form, 3 g/1 ml of 6 *N* hydrochloric acid). The eluate and washings were evaporated to dryness *in vacuo*. The resulting solid was treated in an appropriate manner for the respective reaction.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-D-ribofuranose (III).—A solution of II (21 g, 65.4 mmol) and 6 *N* hydrochloric acid (12 ml) in H_2O (400 ml) was treated in the manner described in the general procedure. The resulting solid was recrystallized from water to afford an analytical sample of III as colorless prisms: yield 15.12 g (86.5%); mp 168–169° dec; $[\alpha]^{25}D$ 32.3° (c 1.0, H_2O); ir 3300 (OH), 3220, 3110 cm^{-1} (NH); uv max (H_2O) 261.5 nm (pH 7 and 12), 260.5 (pH 2); nmr (DMSO-d_6) δ 8.20, 8.12 (s, 1 H, 1 H, C_2 H, C_8 H of purine), 7.25 (broad s, 2 H, NH_2), 6.51 (d, 1 H, J = 5 Hz, –OH), 5.05 (m, 3 H), 4.5–3.5 (m, 5 H).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_4H_2O$: 44.20; H, 5.00; N, 25.77. Found: C, 44.42; H, 4.87; N, 25.60.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-D-arabofuranose (VIa).—A solution of Va (1.7 g, 5.53 mmol) and 6 *N* hydrochloric acid (1 ml) in H_2O (30 ml) was treated in the manner described in the general procedure. The resulting solid was recrystallized from H_2O to give an analytical sample of VIa as colorless leaflets: yield 1.347 g (91.5%); mp 159–160° dec; $[\alpha]^{18}D$ 36° (c 0.5, H_2O); ir 3380 (OH), 3220, 3100 cm^{-1} (NH); nmr (DMSO-d_6) δ 7.15 (broad s, 2 H, NH_2), 6.23 (d, 1 H, J = 6 Hz, –OH), 5.35 (m, 2 H), 5.05 (m, 1 H), 5.75 (m, 3 H), 6.30 (m, 3 H).

Anal. Calcd for $C_{10}H_{13}N_5O_4 \cdot {}^1/_2H_2O$: C, 43.48; H, 5.11; N, 25.45. Found: C, 43.68; H, 5.32; N, 25.87.

5-(6-Aminopurin-9*H*-9-yl)-3-*O*-methyl-5-deoxy-D-arabofuranose (VIb).—A solution of Vb (5.3 g, 16.5 mmol) and 6 *N* hydrochloric acid (2.7 ml) in H_2O (110 ml) was treated in the manner described in the general procedure. The resulting solid was recrystallized from H_2O to give an analytical sample of VIb as colorless prisms: yield 4.25 g (92%); mp 196–197° dec; $[\alpha]^{20}D$ 24.8° (c 1.0, H_2O); ir 3425 (OH), 3220, 3100 cm^{-1} (NH); uv max (H_2O) 261 nm (pH 7 and 12), 260 (pH 2); nmr (DMSO-d_6) δ 7.30 (broad s, 2 H, $-NH_2$), 6.25 (d, 1 H, J = 5 Hz, –OH), 5.38 (d, 1 H, J = 4.5 Hz, –OH), 5.00 (s, 1 H), 4.5–3.5 (m, 6 H), 3.20 (s, 3 H, –OMe).

Anal. Calcd for $C_{11}H_{15}N_5O_4$: C, 46.97; H, 5.38; N, 24.90. Found: C, 46.89; H, 5.42; N, 24.65.

5-(6-Aminopurin-9*H*-9-yl)-3-*O*-benzyl-5-deoxy-D-arabofuranose (VIc).—A solution of Vc (5 g, 12.6 mmol) and 6 N hydrochloric acid (2.5 ml) in H_2O (100 ml) was treated in the manner described in the general procedure. The resulting solid was recrystallized from H_2O to give an analytical sample of VIc as colorless prisms: yield 4.2 g (93%); mp 177–179° dec; $[\alpha]^{20}D$ 46.7° (c 0.3, MeOH); ir 3100 cm^{-1} (NH); nmr (DMSO-d_6) δ 7.25 (s, 5 H, $C_6H_5CH_2$–), 7.12 (broad s, 2 H, $-NH_2$), 6.30 (broad, 1 H, D_2O-exchangeable –OH), 5.40 (broad, 1 H, D_2O-exchangeable –OH), 5.40 (broad 1 H, D_2O-exchangeable –OH), 5.05 (broad s, 1 H), 4.8–3.85 (m, 6 H), 3.76 (broad, 1 H).

Anal. Calcd for $C_{17}H_{19}N_5O_4 \cdot {}^1/_5H_2O$: C, 56.56; H, 5.42; N, 19.40. Found: C, 56.75; H, 5.30; N, 19.40.

Air Oxidation of 5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-D-ribofuranonse (III).—5-(6-Aminopurin-9 *H*-9-yl)-5-deoxy-D-ribofuranose (III) (15 g, 56.2 mmol) was dissolved in H_2O (3 l.) and NaOH (7.95 g, 169 mmol). This solution was stirred at room temperature in an oxygen atmosphere for 17 hr, and evaporated to 200 ml *in vacuo* at 50–60°. To the solution was added 400 ml of EtOH. The mixture was kept refrigerated overnight and the colorless leaflets which separated were collected by filtration. An additional crop of crystals was further obtained by adding EtOH to the mother liquid. This procedure was repeated three times to give 11.85 g (77%) of the sodium salt of eritadenine of which the physical data were completely identical with those of an authentic sample. The mother liquid was evaporated *in vacuo*; to remove EtOH the residual liquid was passed through a column of Amberlite IR-120 (H form, 250 ml) and the column was washed with H_2O, then eluted with 2.8% NH_4OH, and the eluate (2 l.) was evaporated to dryness completely *in vacuo*. The resulting solid was esterified with saturated EtOH and HCl. After the evaporation of EtOH, further EtOH was added and evaporated. This treatment was repeated more than twice. The residue was dissolved in EtOH (100 ml) and treated with dry Amberlite IR-45 (OH form, 10 g) to neutralize the solution. The mixture was stirred at room temperature overnight. After removal of Amberlite IR-45 by filtration, the filtrate was chromatographed with 80 g of silica gel. Elution with 5% EtOH–$CHCl_3$ gave 399 mg (3.2% from III) of ethyl 2-(6-aminopurin-9*H*-9-yl)acetate (IX) as a white, crystalline solid. Two recrystallizations from EtOH afforded an analytical sample of IX as

colorless prisms: mp 225–227°; ir 3200, 3060 (-NH), 1725 cm^{-1} (-CO); uv max (EtOH) 261 nm (pH 7 and 12), 259.5 (pH 2); nmr (DMSO-d_6) δ 7.35 (broad s, 2 H, $-NH_2$), 5.12 (s, 2 H, $-CH_2CO$), 4.20 (q, 2 H, J = 7.5 Hz, $-CH_2CH_3$), 1.22 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 49.02; H, 4.95; N, 31.60.

Elution with 5–10% EtOH–$CHCl_3$ gave 5.25 g (3.7% from III) of ethyl 3-(6-aminopurin-9*H*-9-yl)-2(*R*)-hydroxypropionate (VIII) as a white, crystalline solid. Three recrystallizations from EtOH afforded an analytical sample of VIII as colorless granulars: mp 175–178°; $[\alpha]^{21}D$ 8.3° (c 0.6, EtOH); ir 3200, 3080 (-NH), 1720 cm^{-1} (-CO); uv max (EtOH) 261 nm (pH 7), 262 (pH 12), 260 (pH 2); nmr (DMSO-d_6) δ 7.30 (broad s, 2 H, $-NH_2$), 6.12 (d, 1 H, J = 5 Hz, -OH), 4.70–4.20 (m, 3 H), 4.11 (g, 2 H, J = 7.5 Hz), 1.15 (t, 3 H, J = 7.5 Hz).

Anal. Calcd for $C_{10}H_{13}N_5O_3$: C, 47.80; H, 5.22; N, 27.88. Found: C, 47.79; H, 5.14; N, 27.58.

The last part of elution with 10–20% EtOH–$CHCl_3$ gave 620 mg (3.9% from III) of the ethyl ester of eritadenine VII as a colorless solid. Recrystallization from EtOH gave pure VII as colorless prisms, of which the physical data were identical with those of an authentic sample.

Oxidation of 5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-D-arabofuranose (VIa).—VIa (500 mg, 1.88 mmol) was dissolved in a dilute NaOH solution (226 mg, 5.64 mmol; H_2O, 100 ml). The solution was stirred at room temperature under an atmosphere of oxygen for 15 hr. The solution was evaporated to 20 ml at 50–60° *in vacuo*. The resulting solution was passed through a column of Amberlite IR-120 (H form, 10 ml), the column was washed with H_2O, then eluted with 2.8% NH_4OH, and the eluate (200 ml) was evaporated *in vacuo* at 50–60°. The resulting solid was dissolved in H_2O. The solution was treated with charcoal and filtered. The filtrate was evaporated to dryness *in vacuo* to give crude solid (440 mg). Recrystallization from H_2O gave 355 mg (78%) of eritadenine, of which physical data were completely identical with those of an authentic sample.

Air Oxidation of 5-(6-Aminopurin-9*H*-9-yl)-3-*O*-methyl-5-deoxy-D-arabofuranose (VIb).—VIb (100 mg, 0.358 mmol) was dissolved in a dilute KOH solution (40 mg, 0.714 mmol; H_2O, 15 ml). The solution was stirred at room temperature under an oxygen atmosphere for 20 hr. The solution was evaporated, and EtOH was added. The mixture was allowed to stand overnight at room temperature. The crystals which separated and were revealed as the potassium salt of 4-(6-aminopurin-9*H*-9-yl)-3(*R*)-hydroxy-2(*R*)-methoxybutyric acid (Xb) were collected by filtration to give 85 mg (78%): mp 225° dec; ir 3200 (-NH), 1680 cm^{-1} (-CO); nmr (D_2O) δ 8.02 (s, 2 H, C_2 H, C_8 H of purine), 4.25 (broad s, 4 H), 3.43 (s, 3 H, -OMe).

Oxidation of 5-(6-Aminopurin-9*H*-9-yl)-3-*O*-benzyl-D-arabofuranose (VIc).—VIc (1.76 g, 4.92 mmol) was dissolved in a dilute NaOH solution (590 mg, 14.8 mmol; H_2O, 350 ml). The solution was stirred at 10–15° for 20 hr under an oxygen atmosphere. The solution was evaporated at 20 ml and acidified to pH 3.0 with 100% formic acid. The crude product precipitated was collected by filtration. The crude product was dissolved in MeOH and the solution was treated with charcoal and filtered. The filtrate was evaporated and the residue was recrystallized from MeOH to give an analytical sample of 4-(6-aminopurin-9*H*-9-yl)-2(*R*)-benzyloxy-3(*R*)-hydroxybutyric acid (Xc) as colorless prisms: yield 830 mg (49%); mp 181–182°; $[\alpha]^{20}D$ 46.7° (c 0.3, DMSO); ir 3360, 3280 (-NH), 1675 cm^{-1} (-CO); uv max (MeOH) 261 nm (pH 7 and 12), 260 (pH 2); nmr (DMSO-d_6) δ 7.29 (s, 5 H, $C_6H_5CH_2-$) 7.18 (broad s, 2 H, $-NH_2$), 5.25 (broad m, 2 H), 4.9–3.8 (m, 5 H).

Anal. Calcd for $C_{16}H_{17}N_5O_4 \cdot {}^1/_4H_2O$: C, 55.24; H, 5.07; N, 20.14. Found: C, 55.10; H, 4.77; N, 20.10.

Isobutyl 4-(6-Aminopurin-9*H*-9-yl)-3(*R*)-hydroxy-2(*R*)-methoxybutyrate (XIb).—A suspension of the sodium salt of 4-(6-aminopurin-9*H*-9-yl)-3(*R*)-hydroxy-2(*R*)-methoxybutyric acid (Xb) (2 g, 7.27 mmol) in isobutyl alcohol (200 ml) was saturated with *dry* hydrogen chloride. The solution was evaporated *in vacuo*. H_2O (50 ml) was added to this residue and the solution was basified with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried (Na_2SO_4), and evaporated. The resulting solid was recrystallized from benzene to give an analytical sample of XIb as colorless needles: yield 837 mg (80%); mp 170–172°; $[\alpha]^{20}D$ 35° (c 0.3, MeOH); ir 3230, 3090 (-NH), 1742 cm^{-1} (-CO-); uv max (MeOH) 261 nm (pH 7 and 12), 260 (pH 2); nmr (DMSO-d_6) δ 7.30 (broad s, 2 H, $-NH_2$), 5.84 (broad s, 1 H, -OH), 4.7–3.8 (m, 4 H), 4.10 (d, 2 H, J = 6 Hz, $OCH_2CH<$), 3.55 (s, 3 H, -OMe), 2.15 (m, 1 H, $-OCH_2CH<$), 1.08 (d, 6 H, J = 7 Hz).

Anal. Calcd for $C_{14}H_{21}N_5O_4$: C, 52.00; H, 6.55; N, 21.66. Found: 52.26; H, 6.63; N, 21.36.

Ethyl 4-(6-Aminopurin-9*H*-9-yl)-3(*R*)-hydroxy-2(*R*)-benzyloxybutyrate (XIc).—Xc (730 mg, 2.12 mmol) was dissolved into a saturated EtOH–HCl solution. The mixture was gently refluxed for 3 hr and stirred at room temperature for 14 hr. The solution was evaporated *in vacuo*. The residue was dissolved in a sodium bicarbonate solution. The solution was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried, and evaporated to give 650 mg (89%) of crystals. Recrystallization from acetone–ether afforded an analytical sample of XIc as colorless prisms: mp 137°; $[\alpha]^{20}D$ 41.3° (c 0.42, MeOH); ir 3400 (-OH), 3200, 3100 (-NH), 1715 cm^{-1} (-CO-); nmr (CDCl_3) δ 7.34 (s, 5 H, $C_6H_5CH_2-$), 6.39 (broad s, 2 H, $-NH_2$), 4.9–3.8 (m, 8 H), 1.30 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{18}H_{21}N_5O_4$: C, 58.21; H, 5.70; N, 18.86. Found: C, 57.99; H, 5.58; N, 19.09.

Registry No.—I, 4137-56-8; II, 40429-49-0; III, 40429-50-3; IVa, 40429-51-4; IVb, 40429-52-5; IVc, 40429-53-6; Va, 40429-54-7; Vb, 40429-55-8; Vc, 40429-56-9; VIa, 40429-57-0; VIb, 40429-58-1; VIc, 40429-59-2; VIII, 40429-60-5; IX, 25477-96-7; Xb K salt, 40513-90-4; Xb Na salt, 40429-62-7; Xc- 40429-63-8; XIb, 40429-64-9; Xc, 40428-85-1; eritadenine, 25486-40-2; adenine Na salt, 40428-86-2.

Studies on the Oxidation of "Reversed Nucleosides" in Oxygen. II. Synthesis of Homoeritadenine and *threo*-Eritadenine[1]

NORIO TAKAMURA, NAOMASA TAGA, TAKESHI KANNO, AND MITSUTAKA KAWAZU*

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan

Received September 11, 1972

Condensation of 6-*O*-tosyl-1,2-*O*-isopropylidene-3,5-*O*-benzylidene-D-glucofuranose (I) and 1,6-*O*-ditosyl-2,3-*O*-isopropylidene-D-fructofuranose (V) with the sodium salt of adenine in DMF afforded the corresponding reversed nucleosides (II and VI) in good yields. After removal of the protective groups on the respective compounds by hydrolysis, oxidation of the demasked compounds (III and VII) by oxygen in a dilute alkali solution gave the identical acid which was revealed as 5-(6-aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric acid (IV). Reaction of 5-*O*-tosyl-1,2-isopropylidene-D-xylofuranose (XIV) or 5-*O*-tosyl-3-acetoxy-1,2-isopropylidene-D-xylofuranose (XV) with the sodium salt of adenine gave corresponding reversed nucleosides (XVIa and XVIb) in rather poor yield. D-*threo*-Eritadenine was obtained in good yield by the similar oxidation of 5-(6-aminopurin-9*H*-9-yl)-D-xylofuranose (XVII). The syntheses of some esters of these acids were also performed.

The success of the synthesis of eritadenine by oxidation of 5-(adenine-9-yl)pentoses in oxygen prompted us to proceed to further work on some reversed nucleosides of the hexose series. From the chemical as well as the pharmacological point of view, synthesis of homoeritadenine was of interest (Scheme I).

The reaction of 6-*O*-tosyl-1,2-*O*-isopropylidene-3,5-*O*-benzylidene-D-glucofuranose[2] and 6-*O*-tosyl-1,2,3,5-*O*-dibenzylidene-D-glucofuranose (I)[3] with the sodium salt of adenine in DMF afforded in good yield the corresponding reversed nucleosides (IIa and IIb), whose uv characteristics (λ_{max} 262 nm at pH 7 and 12, 259 nm at pH 2) proved them to be 6-aminopurin-9*H*-9-yl derivatives. None of the other position isomers could be isolated from the reaction mixture.

Hydrolysis to remove the protective groups of IIa or IIb with dilute hydrochloric acid was satisfactorily carried out by the usual methods. Although III was shown assumingly to be a furanose type, no evidence for this structure could be obtained because the nmr spectra of III, both in DMSO-d_6 and in D_2O, were equivocal. III was oxidized under conditions similar to those of the pentose derivatives.[4] Tlc of the reaction mixture showed several spots, including a trace spot of R_f 0.35 which was identical with that of eritadenine [developer: *n*-C_4H_9OH–HOAc–H_2O (4:1:5)]. Attempts to increase the amount of this minor product under a variety of oxidation conditions were unsuccessful; hence its structure remains unknown.

The major product was isolated as colorless plates by adding EtOH to the concentrated reaction mixture. Treatment of this product with HCOOH afforded the free acid, which was established as homoeritadenine (IV) on the basis of the spectral data and the analysis.

An attempt to synthesize eritadenine by air oxidation of the fructose derivative VI was also unsuccessful. Although it was conceivable that the reaction of 1,6-di-*O*-tosyl-2,3-*O*-isopropylidene-D-fructofuranoside (V)[5] with adenine would result in a mixture of 1-(adenin-9*H*-9-yl)fructose and 6-(adenin-9*H*-9-yl)fructose, eritadenine might be obtained if the latter compound was formed preferentially and the oxidative cleavage would occur between the inside carbon and the ketone. The main product, however, was also homoeritadenine. Thus the adduct was shown to be the 6-(adenine-9*H*-9-yl)fructose derivative VI. Synthesis of VI and oxidation of VII were carried out in the usual manner, as shown in the Experimental Section. Since each signal in the nmr of VIIb was dual whereas VIIb gave a single spot on tlc and the analysis agreed completely with the theoretical value, it appeared that VIIb might be a mixture of the α and β anomers. In the hope that evidence concerning the structure might be obtained, VIIb was treated with dilute NaOH solution to give VIIa. Unfortunately, the conformation of the sugar moiety of VIIa could not be established in detail because the nmr signals overlapped. Since no epimerization had been observed in the synthesis of eritadenine *via* 5-(6-aminopurin-9*H*-9-yl)-D-ribofuranose,[4] it appeared probable that the configuration of the three hydroxy groups of (IV) was 2(*S*), 3(*R*), and 4(*R*). Homoeritadenine possessing three hydroxy groups of *R* configuration was thus synthesized for comparison with IV physicochemically and pharmacologically.

The reaction of 5-*O*-tosyl-2,3-*O*-isopropylidene-D-ribonolactone[6] (VIII) with the sodium salt of adenine using rather milder conditions than those of the glucosides led to the formation of IX in good yield. Hydrolysis of IX with dilute hydrochloric acid afforded X accompanied by a slight amount of the lactone XI. Since neither IV nor X exhibited good nmr spectra, the synthesis of some lipid-soluble esters of these was attempted in the hope that clear-cut spectra might be obtained. Esterification of X by the usual methods, however, failed to yield the desired esters.

Humphlett[7] was successful in synthesizing higher alkyl esters unobtainable by the usual methods, such as treatment with a carbinol and hydrogen chloride, by heating D-arabino-1,4-lactone with a higher alcohol in the presence of sulfuric acid.

On the other hand, little is known about the preparation of ribonic acid esters. The difference in the ease of esterification between ribonic acid and arabinonic acid is similar to our case. Treatment of X, which

(1) Preliminary communication: M. Kawazu, T. Kanno, N. Takamura, T. Mizoguchi, S. Saito, and K. Okumura, *Chem. Commun.*, 1047 (1970).

(2) E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2025 (1960).

(3) H. B. Wood, Jr., H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **79**, 3862 (1957).

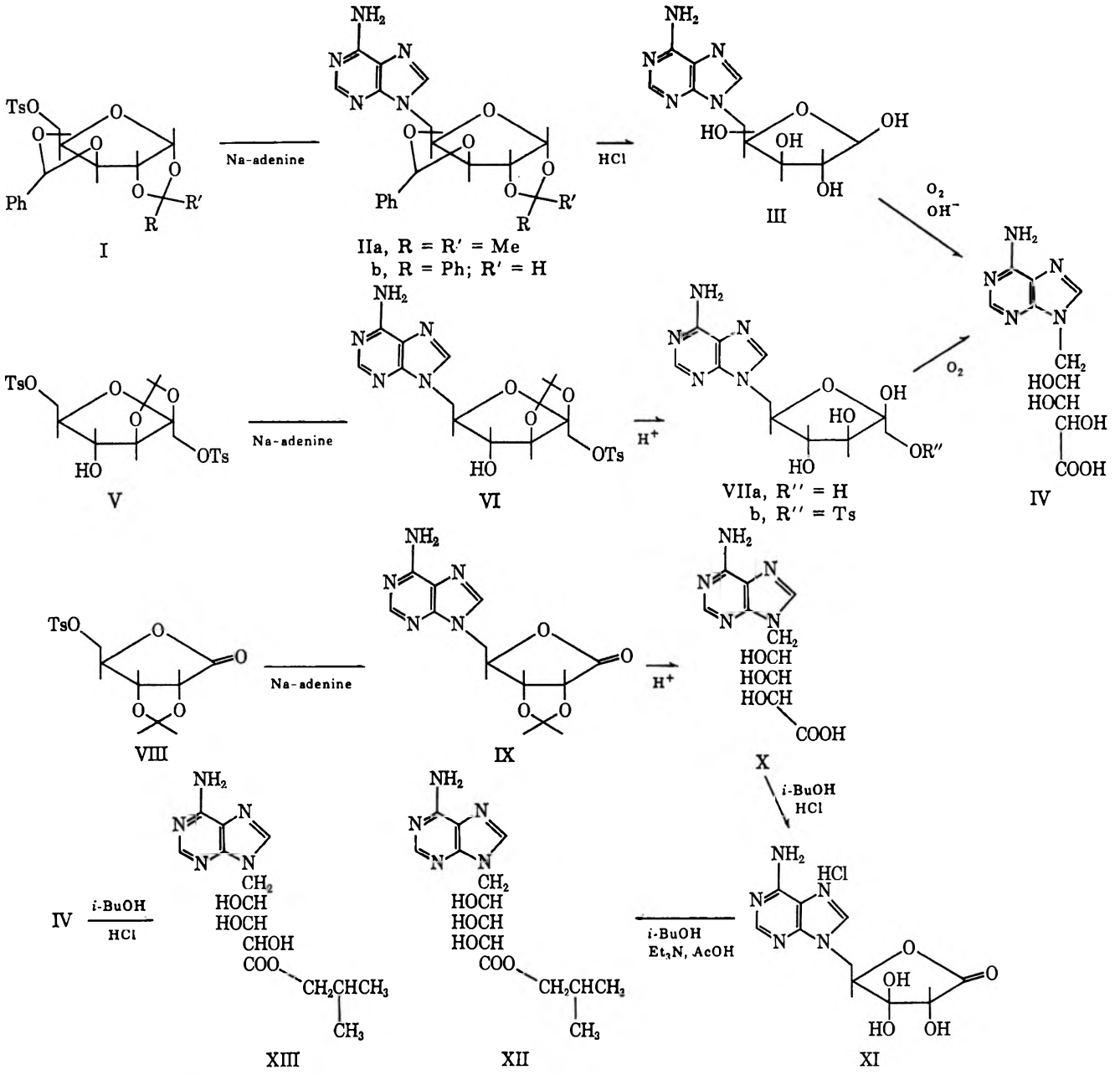
(4) Refer to part I of this series: M. Kawazu, T. Kanno, S. Yamamura, T. Mizoguchi, and S. Saito, *J. Org. Chem.*, **38**, 2887 (1973).

(5) W. T. T. Morgan and T. Reichstein, *Helv. Chim. Acta*, **21**, 1023 (1938).

(6) L. Hough, J. K. N. Jones, and D. L. Michell, *Can. J. Chem.*, **36**, 720 (1958).

(7) W. J. Humphlett, *Carbohyd. Res.*, **4(2)**, 157 (1967).

SCHEME I



should be 5-(6-aminopurin-9*H*-9-yl)-D-ribonic acid, with isobutyl alcohol and hydrogen chloride led to the formation of the lactone XI only, whereas isobutyl 5-(6-aminopurin-9*H*-9-yl)-D-arabinonate (XIII) was obtained from IV under similar conditions. Isobutyl 5-(6-aminopurin-9*H*-9-yl)-D-ribonate (XII) could be synthesized only when XI in isobutyl alcohol was warmed in the presence of triethylamine and acetic acid.

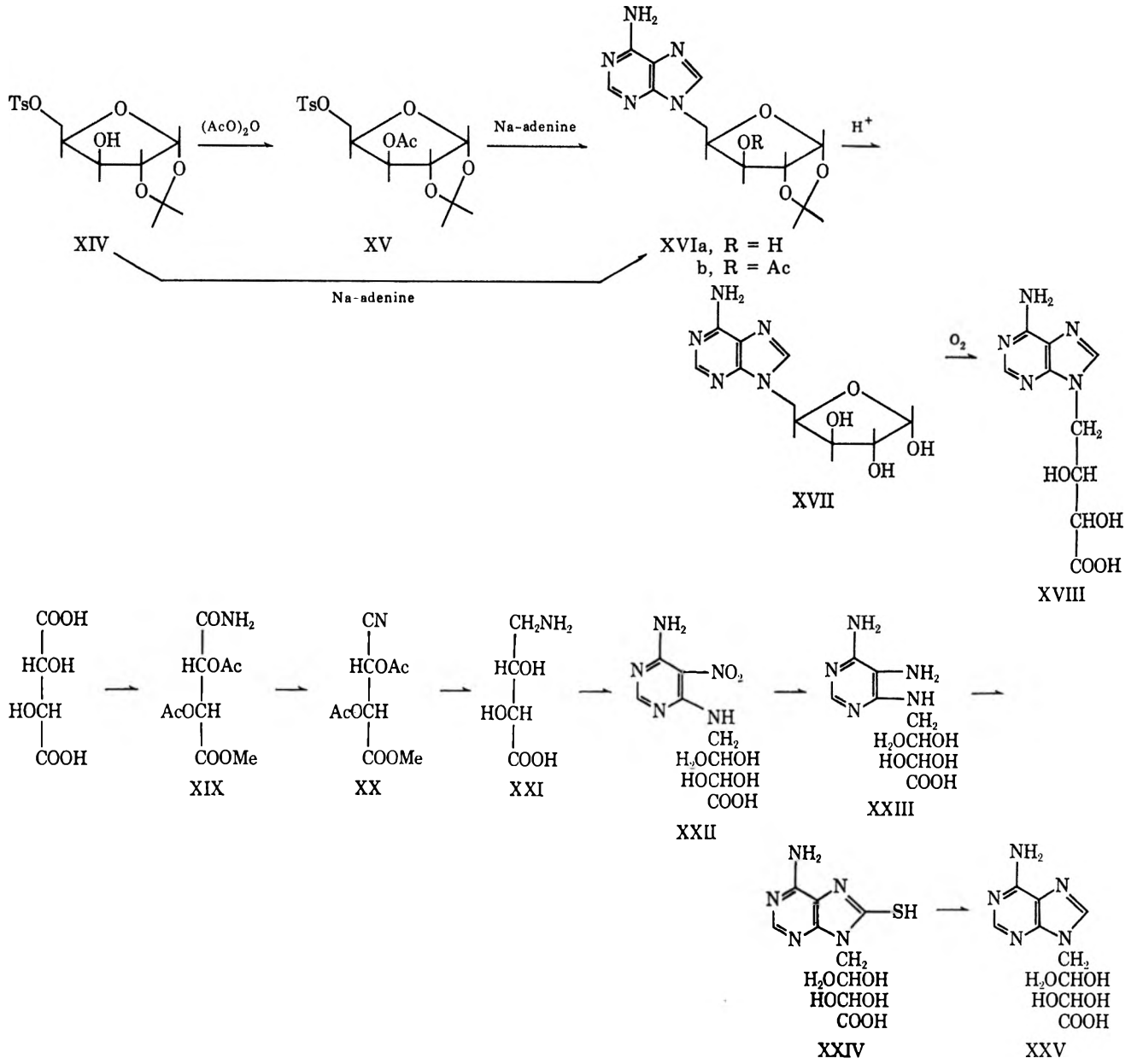
Unfortunately, neither of the esters afforded nmr spectra unequivocal enough to permit comparison of the absolute configuration of XIII with that of XII. However, the behavior of IV and X during esterification appeared to explain the structural relationship between these compounds.

An attempted extension of our method involving the preparation of a reversed nucleoside and its oxidation by oxygen to a synthesis of *threo*-eritadenine was disappointing, since condensation of 5-*O*-tosyl-1,2-*O*-isopropylidene-D-xylofuranose (XIV)[8] with the sodium salt of adenine gave an extremely poor yield of XVIa (Scheme II). Since the yield of the condensation product was excellent when the free hydroxyl group of the sugar had been masked in the case of the arabinose series,[4] it appeared that the yield of the product might be improved if 5-*O*-tosyl-3-acetoxy-1,2-*O*-isopropylidene-D-xylofuranose (XV) was used. The yield of XVIb, however, was only 30%, probably owing not only to the steric hindrance of the 3-acetoxy group but also to decomposition of the sugar. After removal of the protecting groups, XVIa or XVII were directly oxidized without purification because of its hygroscopic properties. The structure of D-*threo*-eritadenine obtained by this oxidation was conclusively confirmed by comparison with L-*threo*-eritadenine synthesized from L-tartaric acid *via* the 4-amino-4-deoxy-L-threonic acid as shown in Scheme II.[9] Prepa-

(8) B. Helterich and M. Burgdorf, *Tetrahedron*, **3**, 274 (1958).

(9) A short communication on the synthesis of this compound by similar methods has been reported: M. Hashimoto, Y. Sato, H. Seki, and T. Kamiya, *Tetrahedron Lett.*, 1359 (1970).

SCHEME II



rations of these compounds are given in the Experimental Section.

Experimental Section

Ir and nmr spectra were also recorded by the instruments described in the Experimental Section of this series part I. Melting points are uncorrected. Optical rotations were measured with a Yanagimoto polarimeter Model OR-20. All analytical samples were dried over P_2O_5 or KOH at 50–70° *in vacuo* overnight.

1,2:3,5-Di-*O*-benzylidene-6-*O*-*p*-tolylsulfonyl-D-glucofuranose (I, R = Ph; R′ = H).—To a solution of 1,2:3,5-di-*O*-benzylidene-D-glucofuranose (6.0 g, 16.8 mmol, mp 161–162°) in pyridine (20 ml) was added *p*-toluenesulfonyl chloride (3.52 g, 18.5 mmol) in $CHCl_3$ (22 ml) under ice cooling. The mixture was stirred for 17 hr at room temperature and evaporated *in vacuo* to give a syrup, which was dissolved in $CHCl_3$ (50 ml) and benzene (200 ml), washed with 1.2 *N* HCl, H_2O, saturated $NaHCO_3$, and H_2O, then dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give a colorless solid (7.70 g, 90%).

Recrystallization from benzene–isopropyl ether afforded colorless needles (5.88 g, 68%): mp 162°; $[\alpha]^{20}D$ +29.8° (*c* 1.03, $CHCl_3$); nmr ($CDCl_3$) τ 2.05–2.95 (m, 4 H, $-SO_2C_6H_4CH_3$), 2.60 (s, 5 H, $>CHC_6H_5$), 2.63 (s, 5 H, $>CHC_6H_5$), 3.84 (d, 1 H), 3.97 (s, 1 H), $>CHC_6H_5$), 4.25 (s, 1 H, $>CHC_6H_5$), 5.23 (d, 1 H), 5.36 (d, 1 H), 5.60 (s, 3 H), 5.90 (broad d, 1 H), 7.60 (s, 3 H, $-C_6H_4CH_3$).

Anal. Calcd for $C_{27}H_{26}O_8S$: C, 63.52; H, 5.13; S, 6.28. Found: C, 63.76; H, 5.23; S, 6.14.

6-(6-Aminopurin-9*H*-9-yl)-1,2:3,5-di-*O*-benzylidene-6-deoxy-D-glucofuranose (IIb).—Adenine (1.64 g, 12.1 mmol) and NaH (0.46 g, 64% in mineral oil, 12.1 mmol) in DMF (50 ml) and I (5.62 g, 11.0 mmol) in DMF (30 ml) were allowed to react and treated in the manner of the general procedure described in the Experimental Section of part I of this series. The residue was washed with ether and $CHCl_3$. Recrystallization from EtOH gave IIb as colorless prisms (3.12 g, 60%): mp 228°; $[\alpha]^{20}D$ 64.1° (*c* 1.17, DMSO); nmr (DMSO-d_6) τ 1.82 (s, 1 H), 1.86 (s, 1 H, C_2 H, C_8 H of purine), 2.61 (s, 5 H, $>CHC_6H_5$), 2.77 (s, 5 H, $>CHC_6H_5$), 2.94 (s, 2 H, $-NH_2$), 3.80 (d, 1 H), 3.85 (s, 1 H, $>CHC_6H_5$), 3.88 (s, 1 H, $>CHC_6H_5$), 4.80–5.55 (m, 5 H), 5.65 (broad d, 1 H).

Anal. Calcd for $C_{25}H_{23}O_5N_5$: C, 63.41; H, 4.90; N, 14.79. Found: C, 63.46; H, 4.95; N, 14.50.

6-(6-Aminopurin-9*H*-9-yl)-3,5-*O*-benzylidene-6-deoxy-1,2-*O*-isopropylidene-D-glucofuranose (IIa).—Adenine (9.65 g, 71.5 mmol), NaH (2.68 g, 64% in mineral oil, 71.5 mmol) in DMF (210 ml), and I (R = R′ = Me) (30.1 g, 65.0 mmol) in DMF (160 ml) were allowed to react and treated in a manner similar to that of IIb. The residual gummy solid was washed with

ether and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over Na_2SO_4, and evaporated *in vacuo* to give a pale yellow solid. Recrystallization from EtOH afforded colorless needles (19.2 g, 69%): mp 230°; $[\alpha]^{20}D$ +72.2° (*c* 1.10, DMSO); nmr (DMSO-d_6) τ 1.87 (s, 1 H), 1.90 (s, 1 H, C_2 H, C_8 H of purine), 2.78 (s, 5 H, C_6H_5–), 2.97 (s, 2 H, $-NH_2$), 3.94 (s, 1 H, CHC_6H_5), 4.05 (d, 1 H), 4.80–5.70 (m, 5 H), 5.88 (broad d, 1 H), 8.60 (s, 3 H, $-CH_3$), 8.75 (s, 3 H, $-CH_3$).

Anal. Calcd for $C_{21}H_{23}O_5N_5$: C, 59.28; H, 5.45; N, 16.46. Found: C, 59.24; H, 5.47; N, 16.30.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-D-glucose (III).—A solution of IIb (2.7 g, 5.71 mmol) and concentrated HCl (1.5 ml) in H_2O (40 ml) was warmed at 70° for 3 hr. It was then cooled, washed with ether, and passed through a column of an ion-exchange resin (Amberlite IR-45, OH^- form, 50 ml). The column was eluted with H_2O (300 ml). The eluate was concentrated *in vacuo* to *ca.* 20 ml, to which was added EtOH to crystallize out III (1.12 g, 66%). The recrystallizations from H_2O–EtOH afforded colorless prisms,[10] mp 230° dec, $[\alpha]^{20}D$ +60.0° (*c* 0.69, DMSO). III was also obtained from IIa in 83% yield by treatment similar to that described.

Anal. Calcd for $C_{11}H_{15}O_6N_5 \cdot {}^1/_4H_2O$: C, 43.78; H, 5.18; N, 23.21. Found: C, 43.99; H, 5.24; N, 23.06.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-2,3-*O*-isopropylidene-1-*O*-*p*-tolylsulfonyl-D-fructofuranose (VI).—A mixture of adenine (2.44 g, 18.0 mmol) and NaH (0.68 g, 64% in mineral oil, 18.0 mmol) in DMF (60 ml) was stirred at room temperature for 30 min and at 50° for 1 hr. To the suspension was added V (10.57 g, 20.0 mmol) in DMF (60 ml), and the solution was stirred at 100° for 5 hr. The dark brown mixture was evaporated *in vacuo* to give a semisolid, which was washed with ether and dissolved in $CHCl_3$. The $CHCl_3$ solution was filtered to remove insoluble material and the filtrate was washed with H_2O and dried over Na_2SO_4. Filtration and evaporation gave a solid (6.36 g, 72%). Twice, recrystallizations from AcOEt–isopropyl ether afforded colorless, silky crystals: mp 129–132°; $[\alpha]^{20}D$ +61.0° (*c* 0.22, $CHCl_3$); nmr ($CDCl_3$) τ 3.61 (s, 2 H, $-NH_2$), 7.62 (s, 3 H, $-SO_2-$, $C_6H_4CH_3$), 8.52 (s, 3 H, $-CH_3$), 8.66 (s, 3 H, $-CH_3$).

Anal. Calcd for $C_{21}H_{25}O_7N_5S$: C, 51.30; H, 5.13; N, 14.25; S, 6.53. Found: C, 50.77; H, 5.07; N, 14.22; S, 6.54.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-1-*O*-*p*-tolylsulfonyl-D-fructose (VIIb).—A mixture of VI (1.9 g, 3.87 mmol) and concentrated HCl (1 ml) in H_2O (30 ml) was warmed at 70° for 3.5 hr. It was then cooled and adjusted to pH 7 with $NaHCO_3$ to crystallize out VIIb, which was triturated with a small amount of MeOH to give pure VIIb (1.05 g, 60%), mp 155–158° dec. Twice, recrystallizations from EtOH–H_2O afforded colorless prisms, mp 161–163° dec, $[\alpha]^{26}D$ +36.0° (*c* 1.12, DMSO).

Anal. Calcd for $C_{18}H_{21}O_7N_5S \cdot {}^1/_2H_2O$: C, 46.94; H, 15.26; S, 6.96. Found: C, 46.92; H, 4.82; N, 15.33; S, 6.81.

6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-D-fructose (VIIa).—A mixture of VIIb (1.10 g, 2.44 mmol) and 1 *N* NaOH (6 ml) in H_2O (60 ml) was stirred for 15 min at room temperature. The clear solution was passed through a column (Amberlite IR-120, H^+ form, 20 ml). The column was washed with H_2O and then eluted with dilute NH_4OH (120 ml). The eluate was evaporated to dryness *in vacuo* to give a solid (0.50 g, 69%). Recrystallization from EtOH gave a colorless, crystal powder: mp 179° dec; $[\alpha]^{26}D$ +48.7° (*c* 0.83, DMSO); nmr (D_2O) τ 1.75 (s, 1 H), 1.78 (s, 1 H, C_2 H, C_8 H of purine), 4.50–6.70 (m).

Anal. Calcd for $C_{11}H_{15}O_5N_5 \cdot {}^1/_2C_2H_5OH$: C, 45.00; H, 5.66; N, 21.85. Found: C, 44.82; H, 5.62; N, 21.47.

5-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric Acid (IV). A. From 6-(6-Aminopurin-9-yl)-6-deoxy-D-glucose (III).—III (2.0 g, 6.75 mmol) was dissolved in warm H_2O (180 ml), and the clear solution was cooled. To the solution was added 1 *N* NaOH (20 ml, 20 mmol) and this was stirred for 48 hr at room temperature under O_2 atmosphere and concentrated *in vacuo* to *ca.* 40 ml. To the residue was added EtOH to crystallize out the Na salt of IV as colorless crystals (1.59 g, 78%), mp 230° dec. The Na salt (1.0 g) was dissolved in H_2O. The solution was acidified with formic acid to pH 3–4 to give IV (0.78 g, 84%) as a colorless, crystal powder: mp 224° dec; $[\alpha]^{26}D$ +26.5° (*c* 1.21, 1 *N* NaOH); ir (Nujol) 3340 (–OH), 3210, 3050 (–NH), 1695 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.29; H, 4.78; N, 24.33.

(10) This sample was not hygroscopic, but it became so after being dried at 50–60°.

B. From 6-(6-Aminopurin-9*H*-9-yl)-6-deoxy-1-*O*-*p*-tolylsulfonyl-D-fructose (VIIb).—A clear solution of VIIb (0.68 g, 1.5 mmol) and 1 *N* NaOH (6 ml) in H_2O (62 ml) was stirred for 47 hr at room temperature under an O_2 atmosphere. The reaction mixture was filtered, concentrated to *ca.* 20 ml, and adjusted to pH 3 with formic acid to give a colorless, crystal powder (0.18 g, 42%), mp 216–219° dec. After recrystallization from 1 *N* NaOH–formic acid, this product showed mp 221–223° dec. The ir of these crystals was identical with that of an authentic sample of IV.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,4-lactone (IX).—A mixture of adenine (3.38 g, 25 mmol) and NaOH (0.94 g, 64% in mineral oil, 25 mmol) in DMF (100 ml) was stirred at room temperature for 30 min and at 50° for 1 hr. To the suspension was added VIII (8.55 g, 25 mmol) in DMF (80 ml), and the solution was stirred at 50° for 6 hr. The reaction mixture was evaporated to dryness to give a semisolid, which was washed with ether, $CHCl_3$, and H_2O to give a colorless solid (4.29 g, 56%), mp 187–190°. Recrystallization from acetone afforded colorless, small needles: mp 192°; $[\alpha]^{26}D$ +31.7° (*c* 0.98, DMSO); ir (Nujol) 3320, 3110 (–NH), 1774 cm^{-1} (–CO); nmr (DMSO-d_6) τ 1.58 (s, 1 H), 1.66 (s, 1 H, C_2 H, C_8 H of purine), 2.45 (s, 2 H, $-NH_2$), 4.4–5.4 (m, 5 H), 8.48 (s, 3 H, $-CH_3$), 8.50 (s, 3 H, $-CH_3$).

Anal. Calcd for $C_{13}H_{15}O_4N_5$: C, 51.14; H, 4.95; N, 22.94. Found: C, 50.79; H, 4.88; N, 22.77.

5-(6-Aminopurin-9*H*-9-yl)-2(*R*),3(*R*),4(*R*)-trihydroxyvaleric Acid (X).—A mixture of IX (1.50 g, 4.91 mmol) and concentrated HCl (1.2 ml) in H_2O was warmed at 70° for 2.5 hr. This was cooled, adjusted to pH 8.5 with solid $NaHCO_3$, and heated on a steam bath for 5 min. The clear solution was cooled and acidified to pH 3 with formic acid to give colorless crystals (1.31 g, 94%), mp 218° dec. The crystals were reprecipitated from 1 *N* NaOH–formic acid to afford pure X: mp 225° dec; $[\alpha]^{26}D$ +40.6° (*c* 1.04, 1 *N* NaOH); ir (Nujol) 1695 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{13}O_5N_5 \cdot {}^1/_4H_2O$: C, 41.74; H, 4.74; N, 24.34. Found: C, 41.64; H, 4.84; N, 24.07.

5-(6-Aminopurin-9*H*-9-yl)-D-ribono-1,4-lactone Hydrochloride (XI).—Through the suspension of X (0.80 g, 2.83 mmol) in isobutyl alcohol (50 ml), HCl gas was bubbled for 15 min under ice cooling. The mixture was stirred at 100–110° for 3 hr and cooled to afford colorless crystals (0.72 g, 85%), mp 253° dec. Recrystallization from H_2O–DMSO–acetone afforded small, colorless needles: mp 255° dec; $[\alpha]^{26}D$ +61.0° (*c* 1.29, H_2O); ir (Nujol) 1769 cm^{-1} (–CO).

Anal. Calcd for $C_{10}H_{11}O_4N_5 \cdot HCl$: C, 39.81; H, 4.01; N, 23.22; Cl, 11.75. Found: C, 40.15; H, 4.15; N, 23.02; Cl, 11.12.

5-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*),4(*R*)-trihydroxyvaleric Acid Isobutyl Ester (XIII).—Through the suspension of IV (3.9 g, 13.8 mmol) in isobutyl alcohol (250 ml), HCl gas was bubbled for 15 min under ice cooling. The mixture was kept at 100 110° for 45 hr and evaporated *in vacuo* to give a pale brown solid, which was washed with ether and dissolved in isobutyl alcohol (500 ml). To the solution was added Amberlite IR-45 (22 g, OH^- form), and this was stirred for 20 hr at room temperature. Amberlite IR-45 was filtered off, and the filtrate was concentrated to 20 ml, to which was added, ether to precipitate XIII (2.52 g, 54%), mp 164° dec. Recrystallization from isobutyl alcohol afforded a colorless, crystal powder: mp 166° dec; $[\alpha]^{26}D$ +19.3° (*c* 0.70, DMSO); ir (Nujol) 1720 cm^{-1} (–CO).

Anal. Calcd for $C_{14}H_{21}O_5N_5$: C, 49.55; H, 6.24; N, 20.64. Found: C, 48.99; H, 5.93; N, 20.94.

5-(6-Aminopurin-9*H*-9-yl)-2(*R*),3(*R*),4(*R*)-trihydroxyvaleric Acid Isobutyl Ester (XII).—The solution of XI (0.72 g, 2.39 mmol) in H_2O was adjusted to pH 8 with $NaHCO_3$ to afford 5-(6-aminopurin-9*H*-9-yl)-D-ribono-1,4-lactone (0.41 g, 55%), mp 232° dec, ir (Nujol) 1768 cm^{-1} (–CO). A suspension of this lactone (0.33 g, 1.25 mmol), Et_3N (0.31 ml), and AcOH (0.10 ml) in isobutyl alcohol (70 ml) was stirred at room temperature for 18 hr and then at 85° for 24 hr. The reaction mixture was filtered and evaporated to dryness *in vacuo* to give a colorless solid, which was washed with ether, 0.32 g (76%), mp 227° dec. Recrystallization from isobutyl alcohol and a small amount of H_2O afforded colorless crystals of XII: mp 231° dec (slightly changed at 180°); $[\alpha]^{26}D$ +12.4° (*c* 0.65, DMSO); ir (Nujol) 1735 cm^{-1} (–CO).

Anal. Calcd for $C_{14}H_{21}O_5N_5 \cdot {}^1/_4H_2O$: C, 48.89; H, 6.30; N, 20.37. Found: C, 49.00; H, 6.33; N, 20.18.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-1,2-*O*-isopropylidene-D-xylo-

furanose (XVIa).—The sodium salt of adenine prepared from adenine (3.78 g), sodium hydride (1.05 g, 64% oil dispersion), and 1,2-*O*-isopropylidene-5-*O*-tosyl-D-xylofuranose (XIV) (9.53 g) in DMF (120 ml) was heated at 100–120° for 20 hr. After removal of the solvent *in vacuo*, the residue was extracted with hot chloroform repeatedly. The combined extracts were evaporated and the residue was triturated with *n*-hexane. The resulting solid was recrystallized from chloroform. XVIa was obtained as colorless needles (2.41 g): mp 208–210°; $[\alpha]^{25}D$ +20.6° (*c* 1.8, MeOH); uv max (MeOH) 262 nm (pH 7 and 12); nmr (DMSO-d_6) τ 1.90 (s, 1 H), 1.95 (s, 1 H, C_2 H, C_8 H of purine), 2.78 (broad s, 2 H, $-NH_2$), 4.27–4.25 (m, 2 H), 5.55–5.67 (m, 4 H), 6.03 (s, 1 H), 8.75 (s, 3 H), 8.85 (s, 3 H, $>CMe_2$).

Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.48; H, 5.73; N, 22.47.

5-(6-Aminopurin-9*H*-9-yl)-5-deoxy-1,2-*O*-isopropylidene-3-acetoxy-D-xylofuranose (XVIb).—The sodium salt of adenine (1.65 g) and 1,2-*O*-isopropylidene-3-*O*-acetyl-5-*O*-tosyl-D-xylofuranose (XV) (4.14 g) in DMF (50 ml) were heated at 100° for 10 hr. The solvent was removed under reduced pressure, and the residue was triturated with ether, taken up with chloroform, filtered, and evaporated. The residue was recrystallized from ethyl acetate. XVIb was obtained as colorless prisms (0.9 g): mp 201–202°; ir (Nujol) 1734, 1650, 1600 cm^{-1}; nmr ($CDCl_3$) τ 1.70 (s, 1 H), 2.10 (s, 1 H), 3.80 (broad s, 2 H, $-NH_3$), 4.04 (d, 1 H), 5.28–5.72 (m, 4 H), 7.92 (s, 3 H, $-COCH_3$), 8.56 (s, 3 H), 8.72 (s, 3 H, $>CMe_2$). *Anal.* Calcd for $C_{15}H_{19}N_5O_5$: C, 51.57; H, 5.48; N, 20.05. Found: C, 51.30; H, 5.52; N, 19.81.

4-(6-Aminopurin-9*H*-9-yl)-2(*S*),3(*R*)-dihydroxybutylic Acid (XVIII).—A solution of XVIa (1.5 g) in 1% HCl (50 ml) was warmed at 60° for 2.5 hr. After cooling, the solution was passed through a column of Amberlite IR-45. The eluates were spin evaporated *in vacuo* to dryness. The residue was taken up with $CHCl_3$, dried, and evaporated to give XVII as a powder (744 mg), nmr (DMSO-d_6) τ 1.85 (s, 1 H), 1.91 (s, 1 H, C_2 H, C_8 H of purine), 2.80 (broad s, 2 H, $-NH_2$), 4.10–6.20 (m, 8 H). A suspension of XVII (700 mg) in dilute NaOH solution (312 mg, 140 ml) was shaken with oxygen at room temperature for 30 hr. The resulting clear solution was passed through a column of Amberlite IR-120 to absorb the product. The column was eluted with dilute NH_4OH solution. The eluate was condensed under reduced pressure at 50–60°. The condensed solution (about 3 ml) was acidified with HCOOH, then the precipitates were collected and washed. XVIII was obtained as a colorless powder (320 mg): mp 300° dec; $[\alpha]^{25}D$ +66.4° (*c* 1.1, 1 *N* NaOH); ir 3500–3200 (broad, OH), 3200, 3080 (NH), 1660 cm^{-1} (COOH); λ_{max} (H_2O) 261 nm, 259 (H^+), 263 (OH^-).

Anal. Calcd for $C_9H_{11}N_5O_4$: C, 42.69; H, 4.38; N, 27.67. Found: C, 42.53; H, 4.52; N, 27.34.

Methyl 3-Aminocarbonyl-2,3-diacetoxypropionate (XIX).—This amido ester was synthesized from L-tartaric acid using a method similar to that of Yokoo, *et al.*,[11] as a colorless, crystalline powder: mp 147–148°; ir (Nujol) 3340 (NH), 1770, 1745 (–CO), 1680 cm^{-1} (–CONH).

Anal. Calcd for $C_9H_{13}O_7N$: C, 43.73; H, 5.30; N, 5.67. Found: C, 44.11; H, 5.41; N, 5.72.

Methyl 3-Cyano-2,3-diacetoxypropionate (XX).—The amido ester XIX (10 g) was refluxed with $POCl_3$ (45 ml) for 30 min. The excess $POCl_3$ was removed by distillation *in vacuo*. The residue was poured into ice–water saturated with Na_2CO_3 and extracted with ether and $CHCl_3$. The extracts were dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was recrystallized from benzene–petroleum ether to give colorless needles: mp 74–74.5°; 7 g (73%); ir (Nujol) 2210 (CN), 1768, 1755 cm^{-1} (CO).

Anal. Calcd for $C_9H_{11}O_6N$: C, 47.16; H, 4.48; N, 6.11. Found: C, 47.33; H, 4.83; N, 6.11.

4-Amino-2(*R*),3(*S*)-dihydroxybutyric acid (XXI).—The nitrile XX (6.5 g) in MeOH (100 ml) was reduced at 80° for 6 hr in an autoclave in the presence of Raney Co (3 g) at an initial pressure of hydrogen of 85 atm. The reaction mixture was filtered, and the filtrate was spin evaporated *in vacuo*. The residue, dissolved in 6 *N* HCl (40 ml), was refluxed for 2.5 hr, and the HCl solution was distilled off. The remaining water was azeotropically removed by benzene. To the residue dissolved in MeOH (40 ml) was added pyridine (2 ml) to give a crude precipitate of XXI. Recrystallization of the crude XXI from H_2O afforded colorless crystals: 2.7 g (71%); mp 222–224° dec (lit.[9] mp 221–222° dec); $[\alpha]^{25}D$ +43° (*c* 0.7, H_2O).

4-(4-Amino-5-nitropyrimidin-6′-yl)amino-2(*R*),3(*S*)-dihydroxybutyric Acid (XXII).—XXI (620 mg), 4-amino-6-chloro-5-nitropyrimidine (715 mg), KOH (258 mg), K_2CO_3 (475 mg), H_2O (10 ml), and acetone (5 ml) were mixed and refluxed for 1 hr. After cooling, the crystals which separated were collected and dried, mp 233–235° dec. A 952-mg quantity of the potassium salt of XXII was obtained: λ_{max} (H_2O) 347 nm; ir (Nujol) 1645 cm^{-1} (COOH); free acid mp 218–220° dec.

4-(4,5-Diaminopyrimidin-6-yl)amino-2(*R*),3(*S*)-dihydroxybutyric Acid (XXIII).—XXII (1.07 g) dissolved in H_2O (40 ml) was reduced in the presence of Raney Ni (2 ml) at an initial hydrogen pressure of 25 psi. The catalyst was filtered off, and the filtrate was adjusted to pH 4 with HCOOH. The crystals separated were collected and washed: mp >300°; 680 mg (84.3%); λ_{max} (H_2O) 286 nm, 279 (H^+), 289 (OH^-); ir (Nujol) 3350 (NH) 1640 cm^{-1} (COOH).

4-(6-Amino-8-mercaptopurin-9*H*-9-yl)-4-deoxy-L-threonic Acid (XXIV).—XXIII (670 mg) dissolved in DMF (180 ml), pyridine (10 ml), and CS_2 (5 ml) was refluxed for 2 hr, and spin evaporated *in vacuo*. The residue was triturated with H_2O to give XXIV: mp >300°; 475 mg (60.6%); λ_{max} (H_2O) 305 nm, 306 (H^+), 301 (OH^-).

4-(6-Aminopurin-9*H*-9-yl)-4-deoxy-L-threonic Acid (XXV).—XXIV (866 mg) dissolved in 3% NH_4OH (30 ml) was refluxed for 3.5 hr in the presence of Raney Ni (5 ml). The mixture was filtered. The filtrate was spin evaporated *in vacuo* and adjusted to pH 3 with 6 *N* HCl to give colorless crystals of XXV, mp 300° dec (lit.[8] mp 297° dec), $[\alpha]^{28}D$ −67° (*c* 1.0, 1 *N* NaOH). The uv and ir spectra of this compound were identical with those of an authentic sample of XVIII.

Acknowledgment.—The authors are indebted to Mr. M. Yamazaki, director of this laboratory, for his generous support and encouragement; we are also grateful to Dr. S. Saito and Dr. M. Mizoguchi for advice and useful suggestions. Thanks are due to the staff of the analytical section presided over by Dr. K. Kotera for elemental and spectral analyses.

Registry No.—I (R = R′ = Me), 7595-86-0; I (R = Ph; R = H), 40518-91-0; IIa, 29789-10-4; IIb, 40518-93-2; III, 29789-11-5; IV, 29973-43-1; V, 32087-60-8; VI, 40518-97-6; VIIa, 40518-98-7; VIIb, 40518-99-8; VIII, 40519-00-4; IX, 29789-12-6; X, 29789-14-8; XI, 40519-03-7; XII, 40519-04-8; XIII, 40519-05-9; XIV, 20513-95-5; XV, 33156-03-5; XVIa, 40519-08-2; XVIb, 40519-09-3; XVII, 40519-10-6; XVIII, 28617-16-5; XIX, 40519-12-8; XX, 40519-13-9; XXI, 40519-14-0; XXII, 33171-94-7; XXII potassium salt, 40429-84-3; XXIII, 40429-85-4; XXIV, 40429-86-5; XXV, 28617-17-6; 1,2:3,5-di-*O*-benzylidene-D-glucofuranose, 22164-08-5; *p*-toluenesulfonnyl-chloride, 98-59-9; adenine, 73-24-5.

(11) A. Yokoo and S. Akutagawa, *Bull. Chem. Soc. Jap.*, **35**, 644 (1962).

Introduction of a 2′,3′ Double Bond into Purine Ribonucleosides by Selective Elimination Reactions

TADASHI SASAKI,* KATSUMARO MINAMOTO, AND SHIGEHARU TANIZAWA

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

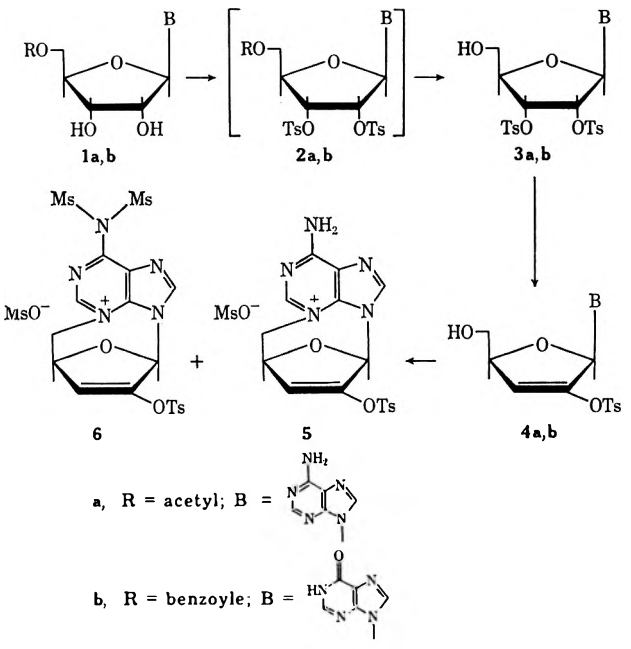
Received March 27, 1973

To investigate the direction of base-induced elimination reactions on 2′,3′-di-*O*-tosyl derivatives of purine ribonucleosides, 2,′3′-di-*O*-tosyladenosine (**3a**) and 2′,3′-di-*O*-tosylinosine (**3b**) were synthesized from 5′-acetyladenosine (**1a**) and 5′-benzoylinosine (**1b**) through ditosylation and 5′ deprotection. Sodium methoxide catalyzed elimination reactions on **3a–b** only gave the corresponding 2′,3′-didehydro purine nucleosides (**4a–b**) with a tosyl group at C_2'. Mesylation of **4a** gave 3′-deoxy-2′-*O*-tosyl-2,′3′-didehydro-3,5′-cycloadenosine mesylate (**5**) and its N^6-dimesylated derivative (**6**).

In previous papers,[1,2] the results of some base-catalyzed elimination reactions with the 2′,3′-di-*O*-mesyl derivatives of 3-benzyluridine and 1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil, as well as with the 2′-*O*-tosyl- (or -mesyl-) 3′-*O*-mesyl (or -tosyl) derivative of the latter compound have been described. In these reactions, 2′ hydrogen was always vulnerable to attack by basic catalysts, giving rise to 2′-uridinenes with a leaving group at C_2'.

The study has now been extended to similar elimination reactions with derivatives of some purine ribonucleosides in order to establish the generality of the selective 2′-hydrogen abstraction in the trans-elimination reactions of 2′,3′-di-*O*-mesyl (or -tosyl) derivatives of ribonucleosides. In this study, the 2′,3′-di-*O*-tosyl derivatives of adenosine and inosine were chosen as substrates for elimination reactions as shown in Scheme I.

SCHEME I



Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl

5′-*O*-Acetyladenosine[3] was treated with excess tosyl chloride to give 5′-*O*-acetyl-2′,3′-di-*O*-tosyladenosine (**2a**), which was directly converted to 2′,3′-di-*O*-tosyladenosine (**3a**). The ditosylation procedure presented some troubles, presumably for steric reasons, and always resulted in mixtures containing minor products as indicated by tlc, one of which seemed to be 2′-*O*-monotosylated derivative.[4] Deacetylation of **2a** with ammonia in methanol was also accompanied by some side reactions. In the present case, these side products were neglected and the synthetic procedure for **3a** was standardized as described in the Experimental Section.

5′-*O*-Benzoylinosine (**1b**) was obtained from 5′-*O*-benzoyl-2′,3′-*O*-isopropylideneinosine[5] by hydrolysis with 10% acetic acid. The formation of **1b** in a rather too low yield (60%) was due to depurination, which was confirmed by the separation and characterization of some hypoxanthine in a separate experiment. Compound **1b** was similarly converted to 2′,3′-di-*O*-tosylinosine (**3b**). Compounds **3a–b** were now allowed to react with sodium methoxide at 100° to give 9-(3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)-adenine (**4a**) and 9-(3′-deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)hypoxanthine (**4b**) in 55 and 37% yield, respectively, regenerating some starting material. Under the particular reaction conditions described in the Experimental Section, no other products were detected by tlc.[6] It must be noted that the reaction did not occur at ambient temperature, in contrast with the reported similar elimination reaction of 3′-*O*-tosyl-2′-deoxyadenosine.[7]

Structure assignments of **4a** and **4b** are essentially based on their nmr spectra, which exhibited similar resonance patterns for $H_{1'}$, $H_{3'}$, and $H_{4'}$. The appearance of a doublet of doublets for $H_{3'}$, a triplet for $H_{1'}$, and an octet for $H_{4'}$ in this order upfield are characteristic of this type of furanose-ene protons.[1,2] Reasons for the assignments of these signals were detailed previously.[1] Although in the case of **4b** the signal of $H_{4'}$ is not well resolved (see Experimental Section), the structure assigned is justified by the presence of a triplet for $H_{1'}$ and a doublet of doublets for $H_{3'}$ at 6.10 and 6.62 ppm, respectively.[8] Thus, selectivity in the

(1) T. Sasaki, K. Minamoto, and H. Suzuki, *J. Org. Chem.*, **38**, 598 (1973).

(2) T. Sasaki, K. Minamoto, and K. Hattori, *J. Org. Chem.*, in press.

(3) D. M. Brown, L. J. Haynes, and A. R. Todd, *J. Chem. Soc.*, 3299 (1950).

(4) A. Todd and T. L. V. Ulbricht, *J. Chem. Soc.*, 3276 (1960).

(5) M. Ikehara, H. Uno, and F. Ishikawa, *Chem. Pharm. Bull.*, **12**, 267 (1964).

(6) The results described here are the best of several experiments. Heating the reaction mixtures until the complete disappearance of the starting materials caused a couple of side-products to form. Reactions of **3a–b** with sodium benzoate in DMF were also examined, when trivial amounts of **4a–b** were obtained with intractable by-products.

(7) J. R. McCarthy, Jr., M. J. Robins, L. B. Townsent, and R. K. Robins, *J. Amer. Chem. Soc.*, **88**, 1549 (1966).

(8) If an alternative structure, in which the tosyl group is linked to $C_{3'}$, were concerned, the signals of $H_{1'}$ and $H_{2'}$ should appear as the same doublet of doublets with a relative intensity of 1:1:1:1, and equal splittings of 1.7 Hz.[1]

trans-elimination reactions was also proved in the series of purine ribonucleosides.

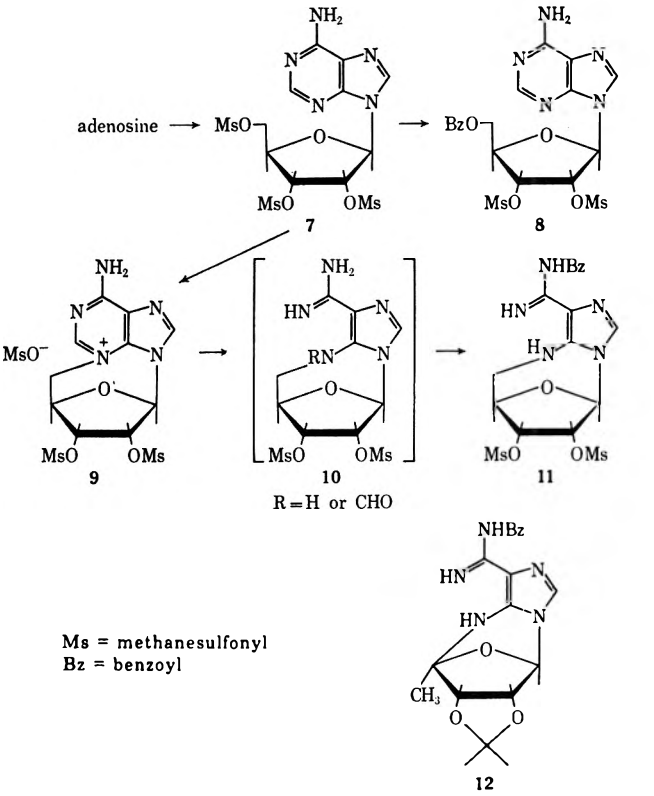
This effect could be due to the electron-deficient nature of $C_{2'}$ (and hence the high acidity of $H_{2'}$) stemming from the electron-withdrawing force of the base moiety in nucleosides. The generally observed, selective or quasiselective alkylation or acylation of 2′-OH might also be interpreted in the same sense.[9] The particularly high selectivity in the elimination reactions, irrespective of possible steric influences by the size of the basic portion or substituent at $C_{5'}$,[1,2] would be connected with the fact that 2′ hydrogen concerned can be directly influenced by the electron-deficient $C_{2'}$, while in alkylation or acylation of 2′-OH the effect of $C_{2'}$ might be reduced to some extent by the participation of the electron-rich oxygen atom.

Treatment of **4a** with mesyl chloride easily gave 3′-deoxy-2′-*O*-tosyl-2′,3′-didehydro-3,5′-cycloadenosine mesylate (**5**), the first 3,5′-cyclopurine ribonucleoside with a double bond in the sugar moiety. The quaternized structure (**5**) was clear on the basis of its ultraviolet absorption at 274 nm in contrast with that of **4a** at 258 nm. On treatment of **4a** with excess mesyl chloride at ambient temperature, N^6-dimesyl-3′-deoxy-2′-*O*-tosyl-2′,3′-didehydro-3,5′-cycloadenosine mesylate (**6**) was obtained with a small amount of **5**. The structure of **6** is based on its analysis and ultraviolet (219 and 269 nm) and nuclear magnetic resonance spectrum.[10] Interestingly, the nmr spectrum of **6** retained the characteristic furanose-ene proton resonances, *i.e.*, a triplet for $H_{1'}$ at 6.34 ppm and a doublet of doublets for $H_{3'}$ at 6.82 ppm with the same coupling constants as in the case of **4a**. This seems to explain the extremely facile cyclization at N^3, by which no substantial steric strain is generated to cause a conformational modification in the unsaturated sugar skeleton.

Although didehydro nucleosides **4a–b** were formed selectively from **3a–b**, their use as versatile synthetic intermediates seemed questionable, since the synthetic routes leading to the didehydro nucleosides **4a** and **4b** involved six steps starting from adenosine or inosine and their overall yields based upon **1a–b** were only 20–30%. Repeated attempts to separate **4a–b** or their analogs from the reaction mixtures obtained by the action of sodium benzoate or sodium methoxide on crude or semipurified **2a** and **2b** were unsuccessful.

At this stage, a path *via* 2′,3′,5′-tri-*O*-mesyl purine nucleosides was considered to be more economical, since Mizuno, *et al.*,[11] had succeeded in phosphorylating the 5′ position of N^6-acetyl-3,5-cycloadenosine and hence 5′-*O*-benzoyl-2′,3′-di-*O*-mesyl purine nucleosides seemed to be more easily accessible *via* an analogous route. Hence, a series of preliminary synthetic work (without N^6-acetylation) was carried out as shown in Scheme II. 2′,3′,5-Tri-*O*-mesyladenosine (**7**) obtained

SCHEME II



by the standard method was allowed to react with sodium benzoate in DMF at a rather high temperature, with the expectation that elimination might take place concomitantly. However, this reaction yielded only a limited amount of a water-insoluble product mixture, from which 5′-*O*-benzoyl-2′,3′-di-*O*-mesyladenosine (**8**) was isolated as the major product in 13.5% yield.

The location of the introduced benzoyl group as in structure **8** was evident from the nmr spectrum, in which the resonances of the tosyl-deshielded protons, $H_{2'}$ and $H_{3'}$, appeared at δ 6.22 ($J_{1',2'} = J_{2',3'} = 5.0$ Hz) and 5.97 ($J_{2',3'} = 5.0$, $J_{3',4'} = 4.2$ Hz), respectively, and are distinctly separated from the resonance envelope of $H_{4'}$ and $H_{5'}$ at δ 4.43–4.82 (see Experimental Section). It was thus concluded that most of the starting material **7** was lost in the form of water-soluble products after quaternization at N^3.

To clear up this point, **7** was converted to 2′,3′-di-*O*-mesyl-3,5′-cycloadenosine mesylate (**9**), which was treated with equimolar sodium benzoate under mild conditions to remove only the mesylate anion. The obtained water-soluble product (**10**, R = H or CHO)[12] was benzoylated to give N^5,5′-anhydro(5′-deoxy-2′,3′-di-*O*-mesyl-β-D-ribofuranosyl)-4-(*N*-benzoylcarboxamidino)-5′-aminoimidazole (**11**) as pale yellow crystals. Its structure was easily deduced from its characteristic

(9) See, for example, (a) N. C. Young and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961) (synthesis of 2′,5,-di-*O*-trityluridine). Although concomitant formations of 3′-O-substituted isomers of nucleoside derivatives have been known,[9b-e] their yields are usually lower than those of 2′ isomers. (b) J. Zemlicka, *Collect. Czech. Chem. Commun.*, **29**, 1734 (1964) (tritylation). (c) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967) (tritylation). (d) L. F. Christensen and A. D. Broom, *J. Org. Chem.*, **37**, 3398 (1972) (benzylation). (e) M. Ikehara and H. Tada, "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 188 (tosylation).

(10) Another structure with a mesyl group on N^1 and a second on N^6 might also be considered. At the present stage, however, we like to propose structure **6** based on its nmr spectrum, in which the signals of two mesyl groups appeared at 3.84 ppm as a sharp six-proton singlet. While no appropriate literature analog is available for direct uv spectral comparison, the absorption at 269 nm does not conflict with structure **6**, considering that a 5-nm hypsochromic shift was caused by blocking the amino group in **5** with the mesyl groups.

(11) Y. Mizuno and T. Sasaki, *J. Amer. Chem. Soc.*, **88**, 863 (1966).

(12) It is not clear when the formyl group was lost. We only suggest the possibility of its hydrolytic cleavage during the work-up of the reaction mixture from **9** and sodium benzoate, since the reaction mixture should have contained benzoic acid released from sodium benzoate, and further the experiment was not carried out under absolutely anhydrous conditions. A similar facile cleavage of a corresponding *N*-formyl group has been described.[13]

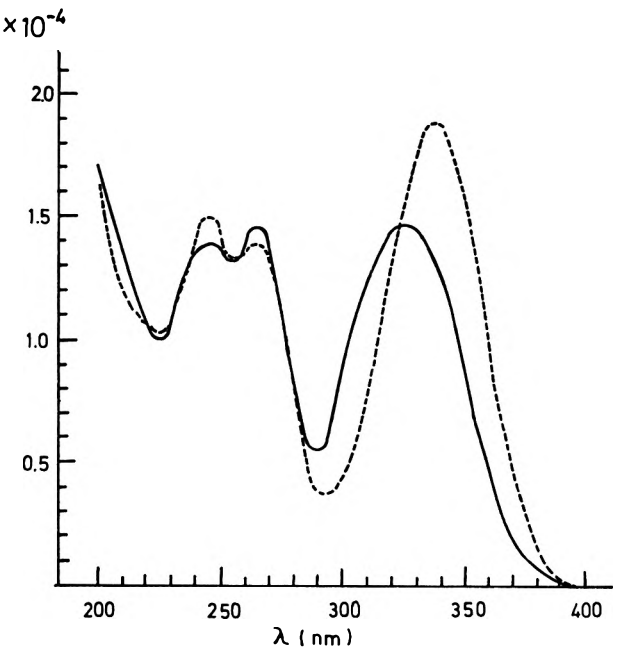


Figure 1.—Ultraviolet spectra of N^5,5′-anhydro-(5′-deoxy-2′,3′-di-*O*-mesyl-β-D-ribofuranosyl)-4-(*N*-benzoylcarboxamidino)-5′-aminoimidazole (**11**) (——) and N^6,4-anhydro(5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)-4-benzoylcarboxamidino-5-aminoimidazole (**12**) (- - - -) in ethanol.

uv absorption comparable with that of N^5,4-anhydro-(5′-deoxy-2′,3′-*O*-isopropylidene-α-L-lyxosyl)-4-benzoylcarboxamidino-5-aminoimidazole (**12**)[13] (Figure 1). The bathochromic shift (10 nm) of the longest wavelength absorption of **12** as compared with that of **11** seems to reflect the extension of the π conjugation of the base up to the ether oxygen of the furanose ring. A similar decomposition of a N^3-quaternized N^6-dimethyladenosine analog by barium hydroxide solution has previously been reported.[14] Thus, this series of experiments with **7** failed to give a didehydro nucleoside. It appears, however, that the tri-*O*-mesylate route, needs to be more thoroughly investigated.

Experimental Section

All the melting points are uncorrected. The electronic spectra were measured on a Jasco Model ORD/UV-5 spectrophotometer. The nmr spectra were recorded with a JNM C-60 HL spectrometer, TMS being used as an internal standard. In the case of the hydroxyl and/or NH-containing compounds, measurements after D_2O exchanges were also carried out. Wakogel B-5 silica gel, supplied by the Wako Pure Chemical Industries, Ltd., was used for thin layer chromatography. Elemental microanalyses were performed with a Perkin-Elmer 240 elemental analyzer in this laboratory.

5′-*O*-Benzoylinosine (1b).—5′-*O*-Benzoyl-2′,3′-*O*-isopropylideneinosine (1.5 g, 3.64 mmol) was heated in 10% acetic acid (100 ml) at 90° for 4 hr. The mixture was evaporated to a semisolid residue, which was dissolved in ethanol and again evaporated. This procedure was repeated to remove the residual acetic acid. The solid was dissolved in hot water and a small amount of insoluble material was removed by filtration. Concentration of the filtrate gave crystals, which were repeatedly crystallized from water to give colorless needles (0.85 g, 60%): mp 147–149°; λ_{max}^{EtOH} 230 nm (ε 18,400), 248 (12,100, inflection), and 260 (6700, inflection).

Anal. Calcd for $C_{17}H_{16}N_4O_6 \cdot H_2O$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.42; H, 4.78; N, 14.46.

2′,3′-Di-*O*-tosyladenosine (3a).—5′-*O*-Acetyladenosine (**1a**) (1.39 g, 4.5 mmol) was dissolved in anhydrous pyridine (6 ml) and treated with tosyl chloride (2.22 g, 11.6 mmol) at 0° overnight. The reaction mixture was added with ethanol (2 ml), left at room temperature for 30 min, and poured into ice–water (100 ml) under vigorous stirring. The collected precipitate was dissolved in chloroform and the chloroform solution was washed with 5% sodium bicarbonate and water in this order and dried with sodium sulfate. Evaporation of the solvent gave 2.54 g of a foam, which was dissolved in a mixture of methanol (75 ml) and concentrated ammonia (25 ml). After stirring at room temperature for 5 hr, the mixture was evaporated at below 40° to a semisolid residue, which was triturated with a small amount of ethanol to give crystals that were filtered and repeatedly crystallized from ethanol to colorless needles (1.36 g, 53%), mp 207–209°, λ_{max}^{EtOH} 226 nm (ε 23,000) and 260 (12,500).

Anal. Calcd for $C_{24}H_{25}N_5O_9S_2$: C, 50.09; H, 4.38; N, 12.17. Found: C, 50.28; H, 4.42; N, 11.88.

2′,3′-Di-*O*-tosylinosine (3b).—5′-*O*-Benzoylinosine (**1b**) (2.89 g, 7.4 mmol) was repeatedly coevaporated with ethanol to remove the water of crystallization and dried under high vacuum for 24 hr. This material was treated with tosyl chloride (3.53 g, 18.5 mmol) in anhydrous pyridine (9 ml) at room temperature overnight. An aliquot of the mixture was examined by tlc to show the presence of some starting material. Therefore, additional tosyl chloride (0.5 g) was added to the reaction mixture and the total was kept at 40–45° for a further 4 hr, added with ethanol (1 ml) after cooling, and poured into stirred ice–water (150 ml). The separating solid was filtered by suction, dissolved in chloroform while wet, and washed with dilute sodium bicarbonate solution and water. The chloroform solution was dried with sodium sulfate and evaporated *in vacuo* to give a foam, which was taken into a mixture of methanol (180 ml) and concentrated ammonia (60 ml) and stirred at room temperature for 5 hr. The reaction mixture was evaporated *in vacuo* at below 40° to a syrup, which was digested with ether, and the ether washing was decanted off. Recrystallization of the residue from methanol gave 2.0 g (65%) of colorless needles: mp 249–252°; λ_{max}^{EtOH} 226 nm (ε 26,100), 250 (9700, inflection), and 268 (6600, inflection); nmr ($CDCl_3$–DMSO-d_6) δ 2.33 (3 H, s, methyl), 2.48 (3 H, s, methyl), 3.64 (2 H, d, $H_{5'}$), 4.10 (1 H, br s, OH, D_2O exchangeable), 4.34 (1 H, br s, $H_{4'}$), 5.17 (1 H, d, $J_{2',3'}$ = 5.4 Hz, $H_{3'}$), 5.40 (1 H, dd, $J_{1',2'}$ = 7.4, $J_{2',3'}$ = 5.4 Hz, $H_{2'}$), 6.10 (1 H, d, $J_{1',2'}$ = 7.4 Hz, $H_{1'}$), 6.95–7.95 (8 H, m, aromatic protons of the tosyl groups), 7.71 (1, H, s, H_2 or H_8), 8.04 (1 H, s, H_8 or H_2), and 12.31 (1 H, br s, NH, D_2O exchangeable).

Anal. Calcd for $C_{24}H_{24}N_4O_9S_2$: C, 49.99; H, 4.20; N, 9.72. Found: C, 49.75; H, 4.30; N, 9.94.

9-(3′-Deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)adenine (4a).—2′,3′-Di-*O*-tosyladenosine (**3a**) (1.1 g, 1.91 mmol) and sodium methoxide (0.49 g, 9.6 mmol) were combined in *N*,*N*-dimethylformamide (DMF) (15 ml) and the mixture was heated at 100° for 80 min under stirring. The mixture was evaporated *in vacuo* at a bath temperature of 55° to a paste, which was dissolved in methanol (10 ml) and neutralized with acetic acid. The methanol was removed by evaporation and the residue was extracted with chloroform (4 × 50 ml) under the presence of water (20 ml). The chloroform solution was dried with sodium sulfate and evaporated to a solid residue, which was repeatedly crystallized from methanol to afford colorless needles (**4a**): mp 209–210°; yield 0.42 g (55%); λ_{max}^{EtOH} 228 nm (ε 14,500) and 258 (14,300); nmr (DMSO-d_6) δ 2.41 (3 H, s, methyl of the tosyl), 5.25 (1 H, br s, OH, D_2O exchangeable), 3.61 (2 H, br s, $H_{5'}$), 4.90 (1 H, octet, $J_{1',4'}$ = 1.6, $J_{3',4'}$ = 3.1, $J_{4',5'}$ = 3.1 Hz, $H_{4'}$), 6.17 (1 H, t, $J_{1',4'}$ = 1.6, $J_{1',3'}$ = 1.6 Hz, $H_{1'}$), 6.63 (1 H, dd, $J_{1',3'}$ = 1.6, $J_{3',4'}$ = 3.1 Hz, $H_{3'}$), 7.25 (2 H, br s, NH_2, lost on D_2O addition), 7.33 (2 H, d, J = 8.3 Hz, tosyl protons ortho to the methyl group), 7.66 (2 H, d, J = 8.3 Hz, tosyl protons meta to the methyl), 8.02 (1 H, s, H_2 or H_8), and 8.04 (1 H, s, H_8 or H_2).

Anal. Calcd for $C_{17}H_{17}N_5O_5S$: C, 50.62; H, 4.25; N, 17.36. Found: C, 50.44; H, 4.30; N, 17.13.

9-(3′-Deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)hypoxanthine (4b).—A mixture of 2′,3′-di-*O*-tosylinosine (**3b**) (1.125 g, 1.94 mmol) and sodium methoxide (0.65 g, 11.8 mmol) in DMF (12 ml) was heated at 100° for 1 hr. After almost all the solvent was evaporated *in vacuo*, the residue was dissolved in methanol (10 ml) and neutralized with acetic acid and the mix-

(13) T. Sasaki, K. Minamoto, and K. Hattori, *J. Amer. Chem. Soc.*, **95**, 1350 (1973).

(14) B. R. Baker and J. P. Joseph, *J. Amer. Chem. Soc.*, **77**, 15 (1955).

ture was again evaporated *in vacuo* at below 40°. The brown-colored residue was taken up in chloroform (150 ml), and the solution was washed with a small amount of water and dried over sodium sulfate. Evaporation of the solvent gave a paste, which gave 0.15 g of a colorless wool (4b) from acetone. The filtrate was concentrated and submitted to preparative thin layer chromatography with the use of a silica gel plate and a solvent mixture, ethanol–benzene (2:8 v/v), to give a second crop of crude **4b** (0.16 g). The combined product was recrystallized from acetone to give 0.29 g (37%) of colorless wool (**4b**): mp 148–149°; λ_{max}^{EtOH} 230 nm (ϵ 14,600), 248 (10,500), inflection), 263 (5600, inflection), and 271 (4400, inflection); nmr ($CDCl_3$ + DMSO-d_6) δ 2.08 (3 H, $\frac{1}{2}CH_3COCH_3$), 2.38 (3 H, methyl of the tosyl), 3.73 (2 H, d, $J_{4',5'}$ = 2.8 Hz, 2 $H_{5'}$), 4.30 (1 H, br s, OH, lost on D_2O addition), 4.95 (1 H, br m, $H_{4'}$), 6.10 (1 H, t, $J_{1',3'}$ = 1.7, $J_{1',4'}$ = 1.7 Hz, $H_{1'}$), 6.62 (1 H, dd, $J_{3',4'}$ = 3.2, $J_{1',3'}$ = 1.7 Hz, $H_{3'}$), 7.27 (2 H, d, J = 8.6 Hz, tosyl protons ortho to the methyl), 7.62 (2 H, d, J = 8.6 Hz, tosyl protons meta to the methyl), 7.85 (1 H, s, H_2 or H_8), 7.99 (1 H, s, H_8 or H_2), and 12.28 (1 H, br s, NH, D_2O exchangeable).

Anal. Calcd for $C_{17}H_{16}N_4O_6S \cdot \frac{1}{2}CH_3COCH_3$: C, 51.27; H, 4.42; N, 12.93. Found: C, 51.48; H, 4.49; N, 12.88.

The analysis values did not significantly change on drying the sample at 60–65° under high vacuum for 24 hr.

From the faster moving band of the tlc plate, *ca.* 0.1 g of the starting material was recovered.

3′-Deoxy-2′-*O*-tosyl-2′,3′-didehydro-3,5′-cycloadenosine Mesylate (5).—9-(3′-Deoxy-2′-*O*-tosyl-β-D-*glycero*-pent-2′-enofuranosyl)adenine (**4a**) (0.1 g, 0.25 mmol) was dissolved in anhydrous pyridine (1.5 ml) and added with mesyl chloride (0.02 ml, 0.26 mmol) at 0° with stirring. After standing at 0° overnight, the mixture was poured into ice–water (15 ml) to give a pasty precipitate, which was separated from the water, dissolved in chloroform, and dried over sodium sulfate. Evaporation of the solvent gave a brown paste, an aliquot of which was examined by tlc with the use of a silica gel plate and a mixed solvent, ethanol–benzene (2:8), to show the complete conversion of **4a** to a mixture (approximately in 2:1 ratio) of a faster moving substance (5′-*O*-mesylated derivative of **4a**) and an immobile substance (**5**). The total mixture was refluxed in acetone to give a crystalline precipitate (**5**), which was filtered. The filtrate was concentrated and again heated in acetone to give another crop of **5**. The total product was recrystallized from a mixture of acetone and methanol to give 80 mg (67%) of colorless prisms of **5**: mp 175–177°; λ_{max}^{EtOH} 216 nm (ϵ 18,800) and 274 (12,600).

Anal. Calcd for $C_{18}H_{19}N_5O_7S_2 \cdot \frac{1}{2}H_2O$: C, 44.08; H, 4.11; N, 14.28. Found: C, 44.23; H, 4.05; N, 14.14.

N^6-Dimesyl-3′-deoxy-2′-*O*-tosyl-2′,3′-didehydro-3,5′-cycloadenosine Mesylate (6).—**4a** (0.17 g, 0.42 mmol) was dissolved in anhydrous pyridine (1 ml) and added with mesyl chloride (0.05 ml, 0.64 mmol) and the mixture was left at room temperature overnight. The red-colored mixture was poured into ice–water (30 ml) to give a precipitate, which was filtered, dried by pressing on a porous plate, and dissolved in hot acetone. Sparingly soluble crystals (20 mg) were filtered and infrared spectroscopically identified with compound **5** after recrystallization from a mixture of acetone and methanol. The acetone solution separated from **5** was concentrated to a gum, which solidified on scratching with a spatula in the presence of a small amount of methanol. Repeated recrystallization of the solid from a mixture of methanol and acetone gave 80 mg of colorless needles (**6**): mp 156° λ_{max}^{EtOH} 219 nm (ϵ 14,100) and 269 (10,800); nmr (DMSO-d_6) δ 2.38 (3 H, s, methyl in the tosyl group), 3.07 (3 H, s, mesylate anion), 3.84 (6 H, s, two mesyl on N^6), 4.46 (2 H, d, J = 4.0 Hz, 2 $H_{5'}$), 5.23 (1 H, m, $H_{4'}$), 6.34 (1 H, t, $J_{1',3'}$ = $J_{1',4'}$ = 1.6 Hz, $H_{1'}$), 6.82 (1 H, dd, $J_{1',3'}$ = 1.6, $J_{3',4'}$ = 3.1 Hz, $H_{3'}$), 7.28 (2 H, J = 8.4 Hz, tosyl protons), 7.55 (2 H, J = 8.4 Hz, tosyl protons), 8.47 (1 H, s, H_2 or H_8), and 8.78 (1 H, s, H_8 or H_2).

Anal. Calcd for $C_{20}H_{23}N_5O_{11}S_4$: C, 37.68; H, 3.64; N, 10.99. Found: C, 37.64; H, 3.60; N, 10.95.

Tlc on the filtrate of **6** exhibited the presence of two faster moving substances (presumably unquaternized isomers corresponding to compound **5** and **6**), which were discarded.

2′,3′,5′-Tri-*O*-mesyladenosine (7) **and 2′,3′-Di-*O*-mesyl-3,5′-cycloadenosine Mesylate** (9).—To an ice-cold stirred solution of adenosine (1 g, 3.78 mmol) in anhydrous pyridine (20 ml) was gradually added mesyl chloride (0.94 ml, 12 mmol). After standing at 0° overnight, the mixture was added with ethanol (3 ml), left at room temperature for 20 min, and concentrated to a gum at below 40°. The gum was taken into methanol (10 ml) and precipitated into ice–water (100 ml). The separated precipitate was dissolved in ethyl acetate (50 ml), dried over sodium sulfate, and evaporated *in vacuo* to an essentially pure foam (**7**) (1.2 g, 64%) at below 40°. A portion of the product was further purified by tlc with the use of silica gel and ethanol–benzene (2:8) for elemental analysis.

Anal. Calcd for $C_{13}H_{19}N_5O_{10}S_3$: C, 31.14; H, 3.82; N, 13.97. Found: C, 30.94; H, 3.98; N, 14.08.

7 (0.4 g) was refluxed in acetone (10 ml) for several hours to yield a solid precipitate, which was filtered and washed with acetone (0.2 g). The filtrate was again heated to reflux for 3 hr and left at room temperature for 1 week to give an additional precipitate (0.15 g), which was filtered, combined with the product obtained above, and recrystallized from methanol to afford 0.32 g (80%) of colorless powder: mp 185–195° dec; λ_{max}^{EtOH} 274 nm (ϵ 12,500).

Anal. Calcd for $C_{13}H_{19}N_5O_{10}S_3$: C, 31.14; H, 3.82; N, 13.97. Found: C, 30.87; H, 4.05; N, 13.78.

Reaction of Sodium Benzoate with 2′,3′,5′-Tri-*O*-mesyladenosine (7). **Separation of 5′-*O*-Benzoyl-2′,3′-di-*O*-mesyladenosine** (8).—**7** (0.5 g, 1 mmol) and sodium benzoate (0.3 g, 2.1 mmol) were combined in DMF (10 ml) and the mixture was stirred at 120° for 1 hr and then at 130° for 40 min. After cooling, the mixture was evaporated *in vacuo* to a gum, which was digested with ice–water (40 ml). The insoluble part was filtered, dried by pressing on a porous plate, and checked by tlc using silica gel and ethanol–benzene (2:8) to show one main and two minor spots. Preparative thin layer chromatography with the use of the same solvent system gave crystals of mp 158–162° from the major band, which were recrystallized from acetone to give 80 mg (13.5%) of colorless needles: mp 162–164°; λ_{max}^{EtOH} 228 nm (ϵ 14,400) and 255 (14,200); nmr (DMSO-d_6) δ 2.08 (6 H, s, acetone of crystallization), 3.30 (3 H, s, mesyl), 3.40 (3 H, s, mesyl), 4.43–4.82 (3 H, br m, $H_{4'}$ and 2 $H_{5'}$), 5.97 (1 H, dd, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 4.2 Hz, $H_{3'}$), 6.22 (1 H, t, $J_{1',2'}$ = 5.0, $J_{2',3'}$ = 5.0 Hz, $H_{2'}$), 6.37 (1 H, d, $J_{1',2'}$ = 5.0 Hz, $H_{1'}$), 7.36 (2 H, br s, NH_2, D_2O exchangeable), 7.46–7.65 (3 H, m, phenyl protons), 7.93 (2 H, q, phenyl protons), 7.99 (1 H, s, H_2), and 8.31 (1 H, s, H_8).

N^5,5′-Anhydro(5′-deoxy-2′,3′-di-*O*-mesyl-β-D-ribofuranosyl)-4-(*N*-benzoylcarboxamidino)-5′-aminoimidazole (11).—Compound **9** (0.5 g, 1 mmol) and sodium benzoate (158 mg, 1.1 mmol) were combined in DMF (7 ml) and the mixture was stirred at 95–100° for 20 min. The benzoate salt was smoothly consumed and a clear solution resulted. The mixture was evaporated to a paste, which was repeatedly triturated with ether, and the ether washings were discarded. The residue was extracted with hot acetone (2 × 50 ml) and the acetone solution was filtered with charcoal. Evaporation of the solvent gave a glass (**10**), which was quite soluble in water, acetone, or methanol and resisted crystallization. This basic compound stuck strongly to silicic acid, thus rendering purification by tlc (silica gel) impossible even with the use of a polar solvent system, ethanol–benzene (5:5). Hence, the glass was repeatedly evaporated with dry acetone to a foam and treated with benzoyl chloride (0.14 ml, 1.2 mmol) in pyridine (1.5 ml) under the presence of triethylamine (0.15 ml). After 1 hr of stirring at room temperature, the mixture was evaporated *in vacuo* at below 40° to a paste, which was taken into methanol (5 ml) and dropped into stirred ice–water (50 ml). The precipitate was filtered, dried on a porous plate, and submitted to preparative thin layer chromatography with the use of ethanol–benzene (2:8). Elution of the main band with acetone gave a yellow paste, which was crystallized from a mixture of acetone and methanol to give 0.2 g of pale yellow needles: mp 139–142°; λ_{max}^{EtOH} 244 nm (ϵ 13,900), 264 (14,500) and 325 (14,800).

Anal. Calcd for $C_{18}H_{21}N_5O_8S_2 \cdot \frac{1}{2}H_2O$: C, 42.92; H, 4.36; N, 13.78. Fouud: C, 42.99; H, 4.42; N, 13.50.

Registry No.—**1a**, 2140-25-2; **1b**, 40601-48-7; **3a**, 40601-49-8; **3b**, 40601-50-1; **4a**, 40601-51-2; **4b**, 40601-52-3; **5**, 40601-53-4; **6**, 40601-54-5; **7**, 40620-79-9; **8**, 40601-55-6; **9**, 40620-80-2; **10** (R = H), 40620-81-3; **10** (R = CHO), 40620-82-4; **11**, 40620-83-5; **12**, 40620-84-6; tosyl chloride, 98-59-9; adenosine, 58-61-7; mesyl chloride, 124-63-0; sodium benzoate, 532-32-1; 5′-*O*-benzoyl-2′,3′-*O*-isopropylidineinosine, 40582-67-0.

Photocyclization of *keto*-D-Fructose Pentaacetate and *keto*-L-Sorbose Pentaacetate[1]

ROY L. WHISTLER* AND LANDIS W. DONER

Department of Biochemistry, Purdue University, Lafayette, Indiana 47907

Received January 4, 1973

Ultraviolet irradiation of both 1,3,4,5,6-penta-*o*-acetyl-*keto*-D-fructose (1) and 1,3,4,5,6-penta-*o*-acetyl-*keto*-L-sorbose (2) (epimeric at the γ carbon) has been found to produce crystalline 1(*S*),4(*S*)-diacetoxymethyl-2(*S*),-3(*S*),4-triacetoxycyclobutan-1-ol (3), the former giving a yield of 11.6% and the latter a yield of 26.2%. Reaction is envisioned from 1,4 biradicals in the triplet state, but no other diastereoisomers resulted. The cyclic photoproduct was converted to its hexaacetate and was also deacetylated to a hexose isomer, $C_{16}H_{12}O_6$. The deacetylated material was converted to a tetra-*p*-toluenesulfonylate, in which all but the tertiary hydroxyl functions were derivatized. This derivative was reduced by lithium aluminum hydride to 1(*S*),4(*S*)-dimethyl-3(*S*)-cyclobutanetriol. A minor photoproduct was produced in a 0.9% yield from 1. It presumably resulted from δ-hydrogen abstraction and formation of a 1,5-biradical intermediate, which underwent ring closure to *meso*-(1,2,3/4,5)-2-acetoxymethyl-1,3,4,5-tetraacetoxycyclopentan-2-ol (4).

Examination of the extensive literature[2,3] on alkanone photochemistry reveals that those possessing γ hydrogen atoms react almost exclusively to give smaller ketones and olefins, and cyclobutanols. It is evident that a useful route to cyclic polyols might be through the photoexcitation of appropriate ketoses, provided cyclization is maximized and the fragmentation route minimized. It is gratifying, therefore, to find that photoexcitation of acetylated open-chain ketoses leads to acceptable yields of polyhydroxycyclobutane. In addition, the reaction provides interesting information on the stereochemistry of the ring closure in these compounds.

Irradiation of 1,3,4,5,6-penta-*O*-acetyl-*keto*-D-fructose (1) in benzene requires 60 hr for complete conversion to photoproducts, but, in a mixture of *tert*-butyl alcohol with only sufficient benzene present to allow solubility, the reaction is complete in 18 hr with formation of 11.6% of cyclic product. Polar solvents are known to increase the rate of formation of photoproducts from alkanones.[4] Irradiation of 1,3,4,5,6-penta-*O*-acetyl-*keto*-L-sorbose (2) in benzene causes complete disappearance of starting material in 18 hr with formation of 26.2% of cyclic product. *tert*-Butyl alcohol cannot be used with 2 because of insolubility of the ketose derivative.

It appears that only one and the same polyhydroxy cyclobutane derivative 3 is produced from either 1 or 2. Three diastereomeric cyclobutanols could possibly arise from ring closure of the 1,4 biradical generated from irradiation of 1 or 2. These three are shown in Figure 1 and would be expected to have very similar R_f values on silica gel and be eluted from the column together. Crystallization of the column eluate resulted in the formation of a sharp-melting compound, however, and repeated crystallizations of the mother liquor yielded only additional amounts of 3. This suggests that both 1 and 2 are converted to the same most thermodynamically stable polyhydroxycyclobutane derivative. The other diastereomeric cyclobutane derivatives must have much higher instability factors, since none of these were produced.

The elemental analysis, nmr, and mass spectra of the photoproduct 3 show it to be isomeric with the starting ketoses 1 and 2. This is consistent with hydrogen abstraction followed by closure of a biradical intermediate. Acetylation of the free hydroxyl group attached to C-1 results in derivative 5, which possesses a twofold axis of symmetry, and the nmr spectrum indicates that the substituents on the ring become magnetically equivalent in pairs. The acetate of structure C (Figure 1) has no such axis of symmetry. Proof that the common photoproduct of ketoses 1 and 2 has the structure represented by 3 can be obtained from closer examination of the nmr spectra of the product and its acetylated derivative, 5. In rigid ring systems, the presence of an hydroxyl function cis to an α proton (nearly eclipsed) results in an upfield shift of the α proton of 0.56 ppm in the acenaphthene system[5] and 0.88–1.17 ppm in bicyclo[2.2.1]-heptane[6,7] and bicyclo[2.2.2]octane systems.[8] Such an arrangement exists in structure B (Figure 1) and protons C and D would be expected to differ significantly in chemical shift. However, a difference of only 0.18 ppm is observed for 3. Also the proton bonded to C-2 is observed to undergo a downfield shift of 0.12 ppm following acetylation of 3 to produce 5. Such a small α shift suggests a trans relationship between the C-1 hydroxyl function in 3 and the proton bonded to C-2. An α-cis proton (as in B, Figure 1) would be expected to shift downfield to a greater extent owing to the anisotropic effect of the carbonyl oxygen atom of the acetyl group. The small shift (0.12 ppm) observed is in agreement with the magnitude of α shifts of trans protons observed upon acetylation of an α-hydroxyl group in the rigid bicyclo[2.2.2]-octane[8] system and is further support for the structural assignments as 3. The reaction scheme leading to the cyclobutanol 3 from both ketones 1 and 2 is given in Figure 2.

Cyclobutanol has been shown from spectroscopic[9] and thermodynamic measurements[10] to be puckered and scale models show that there are two types of positions in cyclobutane, somewhat analogous to the axial–equatorial positions in cyclohexane. A group in the equatorial position is of lower enthalpy than

(1) This work was supported in part by a grant from the U. S. Department of Agriculture, 12-14-100-9984 (71). Journal Paper No. 5003 of the Purdue Agricultural Experiment Station, Lafayette, Ind. 47907.

(2) P. J. Wagner and G. S. Hammond, *Advan. Photochem.*, **5**, 21 (1968).

(3) J. C. Dalton and N. J. Turro, *Ann. Rev. Phys. Chem.*, **21**, 499 (1970).

(4) P. J. Wagner, *J. Amer. Chem. Soc.*, **89**, 5898 (1967).

(5) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance to Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969.

(6) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963).

(7) J. C. Davis and T. Van Auken, *J. Amer. Chem. Soc.*, **87**, 3900 (1965).

(8) K. Tori, Y. Takano, and K. Kitahonoki, *Ber.*, **97**, 2798 (1964).

(9) J. D. Dunitz and V. Schomaker, *J. Chem. Phys.*, **20**, 1703 (1952).

(10) G. W. Rathjens, Jr., N. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **75**, 5634 (1953).

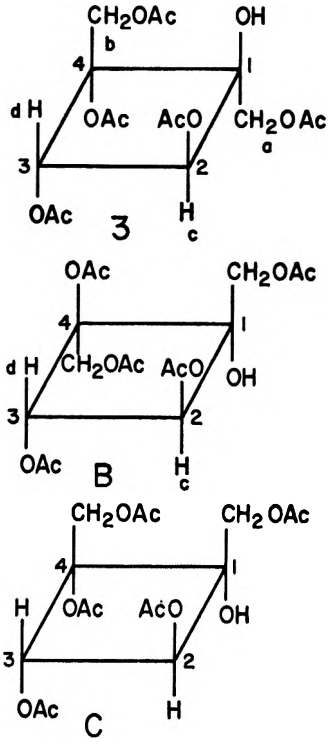


Figure 1.—Structures of the three cyclobutanol isomers that may result from ring closure of the 1,4 biradical generated upon irradiation of 1 and 2.

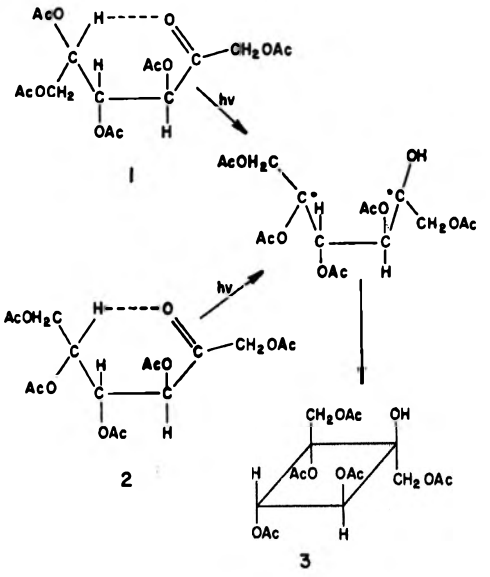


Figure 2.—Reaction sequence leading to the formation of 3 from 1 and 2.

one in the axial position and a 1,2-trans diequatorial relationship of substituents would be favored over an axial relationship.[11,12] If it is safe to assume that the acetoxymethyl substituents in the photoproduct **3** should be diequatorially oriented, this requires that the acetoxy groups on C-2 and C-3 also be diequatorial, while the acetoxy groups on carbon atoms C-2 and C-3 in B (Figure 1) would be axially oriented. Figure 3 shows the two isomeric cyclobutanols in the conformation expected to be the most stable for each, and

(11) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. B. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 200.

(12) N. L. Allinger and L. A. Tushaus, *J. Amer. Chem. Soc.*, **87**, 1945 (1965).

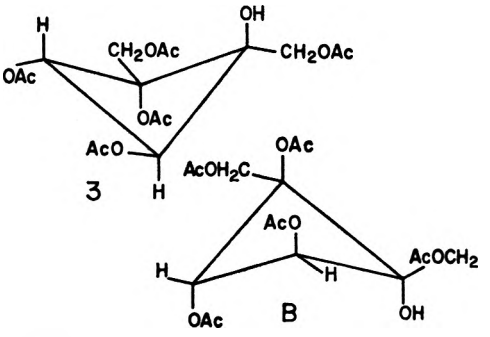


Figure 3.—Conformational representations of the isomeric cyclobutanols 3 and B.

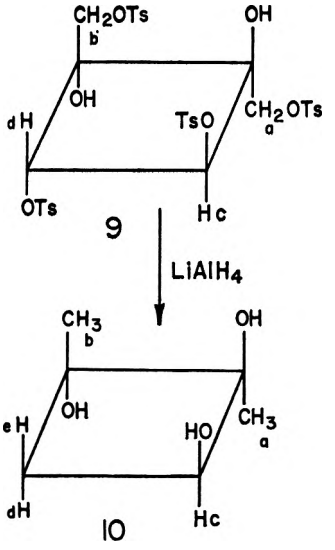


Figure 4.—Reduction of 9 to 10 by lithium aluminum hydride.

it appears that **3** would be more stable than B. Likewise, the 1,4-biradical conformation that led to **3** would be in a conformation more stable than that which might have led to B.

The nmr spectrum of the lithium aluminum hydride reduction product of the *p*-tolysulfonyl-oxylated product **9** further supports structure **3**. That the structure of this product is 1(*S*),4(*S*)-dimethyl-2(*S*)-cyclobutanetriol (**10**) is strongly supported by the observation that the ring methylene protons d and e (Figure 4) in this compound are magnetically very similar and their resonance occurs over a very narrow range (δ 1.50–1.61). If the reduction product were derived from the tetra-*p*-toluenesulfonate ester with the configuration of structure B (Figure 1), the two methylene protons would have very different chemical shifts. One would be shielded by two vicinal cis hydroxyl groups and its resonance would occur at a much higher field than the other, which would be trans to both hydroxyl groups.

A minor photoproduct is produced from **1** in a 0.9% yield. If such a product was formed from ketose **2**, it was not observed. The elemental analysis, nmr, and mass spectra of the product indicated it to be isomeric with **1**. The product's optical inactivity suggests that it may have formed by ring closure of a 1,5-biradical product[13] after δ-hydrogen abstraction by the photoexcited carbonyl group in **1**. The diastereomeric cyclopentanols from such a 1,5 biradical are

(13) L. M. Stephenson and J. L. Parlett, *J. Org. Chem.*, **36**, 1093 (1971).

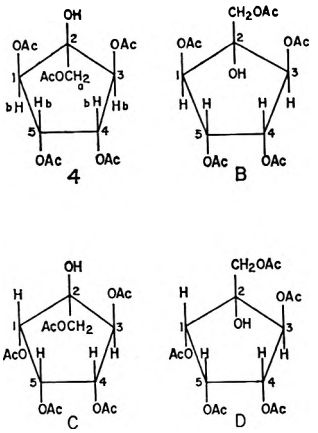


Figure 5.—Structures of the four cyclopentanol isomers that may result from ring closure of the 1,4 biradical generated upon irradiation of 1.

shown in Figure 5. All would be expected to have very similar R_f values on silica gel and be eluted from the column together. Crystallization of the column eluate resulted in the formation of a sharply melting compound, however, and repeated crystallizations of the mother liquor yielded only more of the same compound. Only 4 and B (Figure 5) would be optically inactive and that 4 is the photoproduct (Figure 6) is supported by the similar chemical shifts of the protons designated b (Figure 5). If the hydroxyl function in the cyclopentanol were cis to the α protons (as in B, Figure 5), they should be significantly upfield from the equivalent β protons. However, the four protons are present as a multiplet spread over only 0.3 ppm. Also, the α protons undergo but a small shift upon acetylation of the vicinal hydroxyl group (4, 7), suggesting the trans relationship of the hydroxyl group with the α protons as in 4.

The 1,4 biradicals produced by irradiation of the ketoses 1 and 2 apparently also decay by fragmenting to smaller molecules. The Norrish II product, 1,3-diacetoxyacetone, is found to be produced in significant amounts.

As benzene was present in the solvent for the irradiations of both ketoses 1 and 2, it might have been possible that this solvent behaved as a photosensitizer, and product formation was not a result of direct irradiation of the ketones. Irradiations in *p*-dioxane, however, led to rapid conversion of ketoses 1 and 2 to photoproducts, establishing that benzene is not essential. Quenching experiments using *cis*-piperylene establish that the photoproducts from both 1 and 2 arise from the triplet state, as no products are formed when irradiations are conducted with low concentrations of this triplet quencher present.

Experimental Section

Analytical Methods.—Purity of products and the courses of reactions were monitored by thin layer chromatography (tlc) on 5 × 13 cm plates coated with silica gel G.[14] Irrigants employed were A, chloroform–acetone (15:1); B, chloroform–methanol (4:1); C, chloroform–acetone (10:1); and D, chloroform–methanol (7:1). Compounds were located by spraying the dried plates with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Column chromatography was carried out on silica gel[15] with E, chloroform–acetone (15:1); F, chloroform–acetone (12:1); and G, chloroform–methanol (8:1) as eluents. All solvent ratios are based on volumes. Melting points were measured on a Fisher-Johns apparatus and are corrected. Optical rotations were determined with a Perkin-Elmer 141 polarimeter at 25°. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer and the samples were examined as Nujol mulls. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian Associates A-60 instrument in deuteriochloroform, using tetramethylsilane (TMS) as the internal standard, or in deuterium oxide, using sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as the internal standard. Evaporations were carried out under diminished pressure with bath temperatures below 40°.

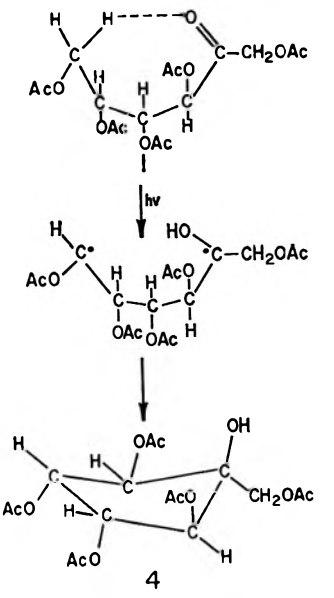


Figure 6.—Reaction sequence leading to the formation of 4 from 1.

Irradiation Procedures.—Irradiations with unfiltered ultraviolet light were conducted using an Hanovia 450-W mercury lamp (679A36) inserted into a water-cooled quartz immersion well. Solutions were flushed with nitrogen prior to irradiation. Triplet quenching experiments were carried out by irradiating benzene solutions of 1,3,4,5,6-penta-*O*-acetyl-*keto*-D-fructose and 1,3,4,5,6-penta-*O*-acetyl-*keto*-L-sorbose to which *cis*-piperylene had been added in concentrations of 0.067, 0.335, and 1.0 *M*. The *cis*-piperylene was obtained from Chemical Samples Co. and distilled immediately prior to use.

1,3,4,5,6-Penta-*O*-acetyl-*keto*-D-fructose (1).—Finely powdered D-fructose (100 g) was added to a stirred solution of freshly fused zinc chloride (15 g) in acetic anhydride (1 l.) that had been stirred for 1 hr at 0°. Stirring was continued for 12 hr at 0° and 12 hr at 25°, at which time the reaction was complete as revealed by tlc in solvent A. The solution was then poured into 3 l. of ice and water and the mixture was stirred for 24 hr at 0° to hydrolyze the acetic anhydride. A saturated aqueous solution of sodium bicarbonate was then gradually added to neutralize the acetic acid liberated. The solution was then extracted with two 500-ml portions of chloroform and the combined chloroform extracts were washed once with water. The chloroform solution was then dried over anhydrous sodium sulfate and evaporated under reduced pressure to a syrup, which was crystallized from ether (300 ml). The crystals formed overnight at −5° were filtered, as a second crop was found to contain a large amount of an isomer of 1, 1,2,3,4,5-penta-*O*-acetyl-β-D-fructopyranose. Recrystallization of the first crop of crystals from ether yielded pure 1: yield 96 g (44%); mp 69–70° (lit.[16,17] mp 69–70°).

1,3,4,5,6-Penta-*O*-acetyl-*keto*-L-sorbose (2).—2 was prepared by essentially the same procedure as was 1, except that finely powdered L-sorbose (100 g) was added to the zinc chloride–

(14) Brinkman Instruments, Inc., Westbury, N. Y.

(15) J. T. Baker Chemical Co., Phillipsburg, N. J.

(16) C. S. Hudson and D. H. Brauns, *J. Amer. Chem. Soc.*, **37**, 2736 (1915).

(17) F. B. Cramer and E. Pascu, *J. Amer. Chem. Soc.*, **59**, 1148 (1937).

acetic anhydride solution. Recrystallization from 600 ml of ether–chloroform (2:1, v/v) at 25° yielded pure **2**: yield 135 g (62%); mp 96–97° (lit.[18] mp 96–97°).

Irradiation Products of 1,3,4,5,6-Penta-*O*-acetyl-*keto*-D-fructose (1).—A solution of **1** (100 g) in 1800 ml of *tert*-butyl alcohol–benzene (20:1, v/v) was irradiated for 18 hr, at which time tlc in solvent A (two developments) showed no **1** remaining. Two major products were evident (both with R_f values less than **1**), as were five minor products. The *tert*-butyl alcohol and benzene were removed by concentrating under diminished pressure and a syrup was obtained. This syrup was taken up in 400 ml of ether–hexane (10:1, v/v) under reflux. The solution was stored overnight at −5°, whereupon 13.2 g of a crystalline mixture corresponding on tlc to the two major products was obtained by filtration. This mixture was dissolved in 10 ml of chloroform, applied to a silica gel column (600 g of silica gel), and eluted with solvent E. The column fractions containing the faster moving component were combined and concentrated to a syrup, which was crystallized from 80 ml of ether–chloroform (3:1, v/v) at 0° to give 1(*S*),4(*S*)-diacetoxymethyl-2(*S*),3(*S*)-4-triacetoxycyclobutan-1-ol (**3**): yield 11.6 g (11.6%); mp 114–115°; $[\alpha]^{25}D$ +72° (*c* 1, $CHCl_3$); ir (Nujol) 3420 (m), 1750 cm^{-1} (m); nmr ($CDCl_3$) δ 2–2.12 (15, acetyl), 3.96 (s, 1, hydroxyl, collapses D_2O), 4.19, 4.50 (q, J = 12 Hz, 2, a), 4.69, 5.01 (q, J = 12 Hz, 2, b), 5.16–5.34 (q, J_{cd} = 7 Hz, 2, c, d).

Anal. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.38; H, 5.63.

Further crystallization of the mother liquor yielded only more **3**. The column fraction containing the slower moving component was contaminated with a small amount of **3**, so this was applied to a silica gel column and eluted with solvent F. After an additional small amount of **3** was collected from the column, the lower R_f component came off pure and this fraction was concentrated to a syrup. This syrup was crystallized from 12 ml of chloroform–ether (3:1, v/v) to give *meso*-(1,2,3/4,5)-2-acetoxymethyl-1,3,4,5-tetraacetoxycyclopentan-2-ol (**4**): yield 0.9 g (0.9%); mp 172–173°; $[\alpha]^{25}D$ 0° (c 2, $CHCl_3$); ir (Nujol) 3335 (m), 1730 cm^{-1} (m); nmr ($CDCl_3$) δ 2.0–2.13 (15, acetyl), 3.0 (s, 1, hydroxyl, collapses D_2O), 4.02 (s, 2, a), 5.22–5.52 (m, 4, b).

Anal. Calcd for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.02; H, 5.48.

Further crystallization of the mother liquor yielded only more **4**.

An alternative method for the separation of **3** and **4** reduces the work-up time by several days. The 13.2-g mixture obtained by crystallization of the crude photoreaction mixture from ether–hexane (10:1, v/v) was taken up in 50 ml of ether–chloroform (10:1, v/v). **4** crystallized overnight from this solvent while **3** remained in solution. Filtration afforded pure **4** (0.8 g) while crystallization of the filtrate from 80 ml of ether–chloroform (3:1, v/v) afforded pure **3** (10.7 g). Yields are slightly lower by this procedure.

Irradiation Products of 1,3,4,5,6-Penta-*O*-acetyl-*keto*-L-sorbose (2).—A solution of **2** (50 g) in 1800 ml of benzene was irradiated for 18 hr, at which time tlc in solvent A showed no **2** remaining and the two major products were of similar R_f as the major products (**3** and **4**) produced from **1**. The benzene was removed by concentration under diminished pressure and the syrup obtained was taken up in 160 ml of ether–hexane (10:1, v/v). After storing overnight at −5°, the mixture was filtered and 13.7 g of a mixture corresponding to **3** and a minor product of slightly higher R_f was obtained. This mixture was taken up in acetone (80 ml) and stored overnight at −5°. A flocculent precipitate which was not characterized had formed (360 mg) and this was removed by filtration. The acetone was removed from the filtrate by concentration under diminished pressure and the syrup obtained was taken up in 80 ml of ether–chloroform (3:1, v/v). Storage overnight at −5° yielded 13.1 g (26.2%) of **3**. Only more **3** was obtainable from the mother liquor. The nmr and ir spectra were identical with those of the major photoproduct **3** of **1**, as were the melting point, optical rotation, and elemental analysis. The tlc spot of R_f similar to that of the photoproduct obtained by irradiation of **1**, suggesting a cyclopentanol analogous to **4**, was not obtainable in sufficient purity for subsequent characterization.

1(*S*),4(*S*)-Diacetoxymethyl-1,2(*S*),3(*S*),4-tetraacetoxycyclobutane (5).—To a solution of **3** (1.0 g) in acetic anhydride (15 ml) was added sodium acetate (2.5 g). The solution was refluxed with stirring for 2 hr, at which time no **3** remained as indicated by tlc in solvent A and one product had appeared. The mixture was poured into 25 ml of ice and water and this mixture was stirred for 1 hr to hydrolyze the acetic anhydride. A saturated aqueous solution of sodium bicarbonate was then gradually added until the acetic acid was neutralized. The mixture was transferred to a separatory funnel and extracted with three 25-ml portions of chloroform. The combined chloroform extracts were washed once with water and dried over anhydrous sodium sulfate. This mixture was then filtered and the chloroform solution was concentrated under diminished pressure to a syrup. This syrup was taken up in 8 ml of hexane–ether (1:1, v/v) and put for overnight crystallization at −5°. Pure **5** was obtained: yield 0.78 g (71%); mp 90–91°; $[\alpha]^{25}D$ +2.7° (*c* 1, $CHCl_3$); nmr ($CDCl_3$) δ 2.03–2.11 (18, acetyl), 4.68–4.97 (q, J = 12 Hz, 4, a, b), 5.28 (s, 2, c, d).

Anal. Calcd. for $C_{18}H_{24}O_{12}$: C, 50.00; H, 5.58. Found: C, 50.26; H, 5.57.

1(*S*),4(*S*)-Dihydroxymethyl-2(*S*),3(*S*)-cyclobutanetetrol (6).—To a solution of **3** (10 g) in methanol (50 ml) was added 50 ml of a 0.1 *M* solution of sodium methoxide in methanol. This solution was heated with stirring to 60°, at which time only the deacetylated product was present as indicated by tlc in solvent B. The solution was then neutralized with Amberlite IR-120 (H^+) resin and filtered. The filtrate was concentrated to a syrup which spontaneously crystallized. Recrystallization from 40 ml of methanol–water (19:1, v/v) yielded pure **6**: yield 4.48 g (97%); mp 133–134°; $[\alpha]^{25}D$ +23.8° (*c* 1, H_2O); nmr (D_2O) δ 3.67 (m, 4, a, b), 3.97 (s, 2, c, d).

Anal. Calcd for $C_6H_{12}O_6$: C, 40.00; H, 6.72. Found: C, 40.06; H, 6.81.

***meso*-(1,2,3/4,5)-2-Acetoxymethyl-1,2,3,4,5-pentaacetoxycyclopentane (7).**—To a solution of **4** (1.0 g) in acetic anhydride (25 ml) was added sodium acetate (2.5 g). The solution was refluxed with stirring for 3 hr, at which time no **4** remained as indicated by tlc in solvent A and one product of high R_f had appeared. The mixture was poured into 25 ml of ice and water and this mixture was stirred for 1 hr to hydrolyze the acetic anhydride. A saturated aqueous solution of sodium bicarbonate was then gradually added until the acetic acid was neutralized. This mixture was transferred to a separatory funnel and extracted with three 25-ml portions of chloroform. The combined chloroform extracts were washed once with water and dried over anhydrous sodium sulfate. This mixture was then filtered and the chloroform solution was concentrated under diminished pressure to a syrup. This syrup was taken up in 10 ml of hexane–ether (1:1, v/v) and stored at −5° overnight for crystallization. Pure **7** was obtained: yield 0.65 g (59%); mp 94–95°; $[\alpha]^{25}D$ 0° (*c* 2, $CHCl_3$); nmr ($CDCl_3$) δ 2.09 (s, 18, acetyl), 4.70 (s, 2, a), 6.36–6.58 (m, 4, b).

Anal. Calcd for $C_{18}H_{24}O_{12}$: C, 50.00; H, 5.58. Found: C, 50.15; H, 5.54.

***meso*-(1,2,3/4,5)-2-Hydroxymethylcyclopentanepentol (8).**—To a solution of **4** (1.0 g) in methanol (10 ml) was added 10 ml of a solution of 0.1 *M* sodium methoxide in methanol. This solution was heated with stirring to 60° for 12 hr. at which time only the deacetylated product was present as indicated by tlc in solvent B. The solution was then neutralized with Amberlite IR-120 (H^+) resin and filtered. The filtrate was concentrated to a syrup, which was crystallized from 8 ml of methanol–water (15:1, v/v). Pure **8** was obtained: yield 0.41 g (89%); mp 133–134°; $[\alpha]^{25}D$ 0° (*c* 2, H_2O); nmr (D_2O) δ 3.54 (s, 2, a), 3.78–4.12 (m, 4, b).

Anal. Calcd for $C_6H_{12}O_6$: C, 40.00; H, 6.72. Found: C, 39.74; H, 6.66.

1(*S*),4(*S*)-Di-*p*-tolylsulfonyloxymethyl-2(*S*),3(*S*)-di-*p*-tolylsulfonyloxycyclobutane-1,4-diol (9).—To a solution of **6** (3.0 g, 1 equiv) in pyridine (100 ml) was added *p*-toluenesulfonyl chloride (14.6 g, 10 equiv). This mixture was stirred at 25° for 24 hr, at which time tlc in solvent C indicated that no **6** remained and one major high R_f product was present. With the aid of toluene this solution was concentrated under diminished pressure to a syrup. Then water (25 ml) was added and the mixture was stirred for 1 hr to decompose excess *p*-toluenesulfonyl chloride. A saturated aqueous solution of sodium bicarbonate (10 ml) was then gradually added to neutralize the hydrochloric acid liberated. The residue formed by removal of the water by concentration under diminished pressure was transferred to a separatory funnel with water and chloroform. After extraction

(18) H. H. Schlubach and J. Vorwerk, *Ber.*, **66**, 1251 (1933).

with two 100-ml portions of chloroform, the combined extracts were washed once with water. The chloroform solution was dried over anhydrous sodium sulfate, decolorized with charcoal, and filtered. The filtrate was concentrated to a syrup, which was crystallized from 75 ml of ethanol–chloroform (25:1, v/v) by storage at −5° overnight. Recrystallization from this solvent yielded pure 9: yield 10.9 g (82%); mp 168–169°; nmr ($CDCl_3$) δ 2.43 (s, 12, CH_3 of tosyl), 3.12 (s, 2, hydroxyls, collapses D_2O), 4.13 (s, 4, a, b), 4.60 (s, 2, c, d), 7.24–7.85 (m, 16, aromatic of tosyl).

Anal. Calcd for $C_{34}H_{36}O_{14}S_4$: C, 51.24; H, 4.55; S, 16.09. Found: C, 51.20; H, 4.33; S, 16.00.

1(*S*),4(*S*)-Dimethyl-2(*S*)-cyclobutanetriol (10).—To a suspension of 9 (5.0 g, 1 equiv) in 150 ml of ether–benzene (2:1, v/v) was added with stirring lithium aluminum hydride (3.8 g, 16 equiv). The mixture was refluxed with stirring for 4 days with an oil bath temperature of 60°. The reaction mixture was shown to contain no 9 but the presence of a major component of lower R_f by tlc in solvent D. Ethyl acetate (50 ml) was then gradually stirred into the cooled reaction mixture to decompose excess lithium aluminum hydride. Then 100 ml of ether–water (10:1, v/v) was added to complete this decomposition. The mixture was then filtered through Celite and the alkaline filtrate was neutralized with Amberlite IR-45 (H^+) resin. The exchange resin was removed by filtration, and the filtrate was concentrated under diminished pressure to a syrup (300 mg). Crystallization of this syrup failed, so it was applied to a silica gel column and eluted with solvent G. A fraction consisting mainly of the major reduction product was obtained (120 mg) and this was further purified by repeated silica gel column chromatography, again using solvent G as eluent. This product was not crystalline: yield 80 mg (11%); nmr ($CDCl_3$) δ 1.13, 1.14 (s, 6, a,b), 1.61–1.5 (m, 2, d,e), 3.60 (s, 3, hydroxyls), 3.76 (m, 1, c).

Acknowledgment.—The authors would like to acknowledge Dr. John B. Grutzner and Dr. Harry Morrison of the Chemistry Department for helpful discussions.

Registry No.—1, 6341-07-7; 2, 35304-04-2; 3, 40627-21-2; 4, 40627-22-3; 5, 40695-92-9; 6, 40627-23-4; 7, 40627-24-5; 8, 40627-25-6; 9, 40627-26-7; 10, 40627-27-8; D-fructose, 57-48-7; L-sorbose, 87-79-6; *p*-toluenesulfonyl chloride, 98-59-9.

A Direct Low Temperature ^1H and ^{19}F Nuclear Magnetic Resonance Study of Boron Trifluoride Complexes with 4-Cholesten-3-one, 1(5β)-Androstene-3,17-dione, 5β-Androstane-3,17-dione, and Obacunone

RONALD E. SCHUSTER AND RAYMOND D. BENNETT*

Fruit and Vegetable Chemistry Laboratory, Western Region, Agricultural Research Service, U. S. Department of Agriculture, Pasadena, California 91106

Received March 12, 1973

A direct low temperature proton and fluorine-19 nmr study of boron trifluoride complexes with steroids **1**–**3** and a limonoid **4** is reported. In these systems ligand exchange is slow enough below −50° for observation of separate pmr signals for bulk ligand and molecules bound to the boron trifluoride. For ligands **1**, **2**, and **4**, the ^1H and ^{19}F nmr data indicate that complexing first occurs solely at the A-ring carbonyl group. In the remaining system **3** and for high BF_3/base ratios of **4**, complexing also occurs at a second site in the base, the carbonyl group in the D ring.

Complexes of boron trihalides with organic bases have been studied using several calorimetric and spectroscopic techniques to ascertain the chemical and structural features of the components which influence these interactions.[1-8] Nmr investigations of boron trihalide complexes include ligands such as trimethylamine, ethers, *N*,*N*-dimethylformamide, ureas and thioureas, and water (^{19}F and proton resonance). Recent publications have demonstrated the usefulness of the direct low temperature nmr method as a supplemental aid for these investigations.[8-12] The success of this low temperature method is based on the ability to slow ligand exchange, thereby allowing the observation of separate pmr signals for the ligand molecules bound to the boron trihalide and the bulk (uncomplexed) ligand. The information obtainable by this means includes chemical shifts induced in the ligand by complex formation, the stoichiometry of the complex, the ligand interaction site or sites, and competition between sites. Previous investigations of this type have been confined largely to ligands of relatively low molecular weight and complexity. To determine whether this low temperature technique could also be applied to larger and more complex ligands, we have now studied complexes of boron trifluoride with three steroids and a limonoid.

Experimental Section

The 2-nitropropane (2NP) used was the highest commercial grade available and was distilled before use. 4-Cholesten-3-one (**1**) and 1(5β)-androstene-3,17-dione (**2**) were generously supplied by Dr. Erich Heftmann, Western Regional Research Laboratory, Albany, Calif. 5β-Androstane-3,17-dione (**3**) was purchased from Mann Laboratories.[13] The purity of these three steroids was verified by their nmr spectra. Obacunone (**4**) was isolated from grapefruit seed meal by methods previously described.[14] Boron trifluoride (J. T. Baker) was purified by fractionation through a −110° petroleum ether (bp 30–60°)–liquid nitrogen cold trap, and its purity verified by ^{19}F nmr in anhydrous CH_2Cl_2. Van Ness Associates No. 105–7PP special purpose nmr sample tubes were employed for all measurements. These are

(1) J. M. Miller and M. Onyszchuk, *Can. J. Chem.*, **42**, 1518 (1954).
(2) E. Gore and S. S. Danyluk, *J. Phys. Chem.*, **69**, 89 (1965).
(3) M. Okada, K. Suyama, and Y. Yamashita, *Tetrahedron Lett.*, 2329 (1965).
(4) P. N. Gates, E. J. McLauchlan, and E. F. Mooney, *Spectrochim. Acta*, **21**, 1445 (1965).
(5) S. J. Kuhn and J. S. McIntyre, *Can. J. Chem.*, **43**, 375 (1964).
(6) N. N. Greenwood and B. H. Robinson, *J. Chem. Soc. A*, 511 (1966).
(7) R. J. Gillespie and J. S. Hartman, *Can. J. Chem.*, **45**, 859 (1966).
(8) A. Fratiello and R. E. Schuster, *Inorg. Chem.*, **8**, 480 (1969), and references cited therein.
(9) A. Fratiello, T. P. Onak, and R. E. Schuster, *J. Amer. Chem. Soc.*, **90**, 1194 (1968).
(10) A. Fratiello and R. E. Schuster, *Inorg. Chem.*, **7**, 1581 (1968).
(11) A. Fratiello and R. E. Schuster, *Org. Magn. Resonance*, **1**, 139 (1969).
(12) A. Fratiello, R. E. Schuster, and M. Geisel, *Inorg. Chem.*, **11**, 11 (1972).
(13) Reference to a company or product name does not imply endorsement by the U. S. Department of Agriculture to the exclusion of others that may be suitable.
(14) D. L. Dreyer, *J. Org. Chem.*, **30**, 749 (1965).

thin-walled, high resolution tubes, which can be sealed readily under high vacuum.

Stock solutions of each base were prepared and a portion of the solution was syringed into the nmr tube, placed on the vacuum line, and degassed several times before a measured amount of purified BF_3 was condensed into the tube at liquid nitrogen temperature. After the tube was sealed off under vacuum, its contents were thawed and mixed in a Dry Ice–acetone bath. It then was stored in liquid nitrogen until the spectrum could be recorded. Each sample contained a few per cent by volume of tetramethylsilane (TMS) and hexafluorobenzene (C_6F_6) for use as internal nmr chemical shift standards for the ^1H and ^{19}F nuclei, respectively.

The chemical shift and area measurements were made using a JEOL PS-100 spectrometer (operating at 94 MHz for the ^{19}F measurements) equipped with a variable temperature device permitting measurements down to −170°. The samples were cooled until separate pmr signals for bulk and complexed ligand molecules were observed. The pmr areas were determined by integration of suitable peaks in the spectrum. ^{19}F nmr data were obtained in the same manner and the signal or signals recorded at the temperature of maximum resolution.

Results

Pmr chemical shift and integration data for ligands 1–4 are presented in Table I, and representative pmr

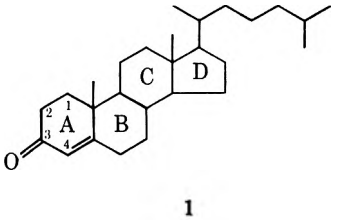
TABLE I

PROTON CHEMICAL SHIFT AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES OF 4-CHOLESTEN-3-ONE, 1(5β)-ANDROSTENE-3,17-DIONE, 5β-ANDROSTANE-3,17-DIONE, AND OBACUNONE

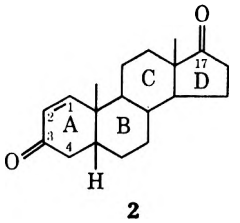
Base	Mole ratio of base/BF_3/solvent[a]	t, °C	Δν(C-B),[b] Hz H-1	H-2	H-4	H-15	Coordination no.
1	3.80:1.00:456	−50		60	80		1.0
2	3.40:1.00:408	−52	42	32			1.0
3	3.83:1.00:445	−57	Overlapping, unidentifiable				
4	4.31:1.00:517	−59	55	24		12	1.0

[a] The solvent in all cases was $CDCl_3$, and the accuracy of the mole ratios was within 1–2%. [b] The Δν(C-B) values refer to the separation in hertz between the complexed and bulk ligand protons indicated.

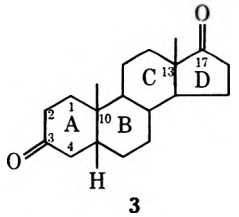
spectra of 4 complexed with BF_3, recorded at three temperatures, are shown in Figure 1. Table I lists the



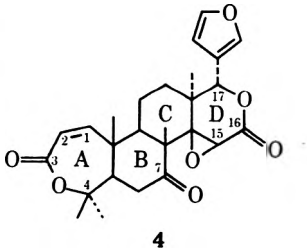
1



2



3



4

mole ratios of the systems studied and the temperatures at which the spectra were recorded. The high solvent to base ratio, 120:1 in all cases, was used to avoid intermolecular interactions between coordinated and bulk ligand molecules. Thus the chemical shift separations (for those protons able to be studied)

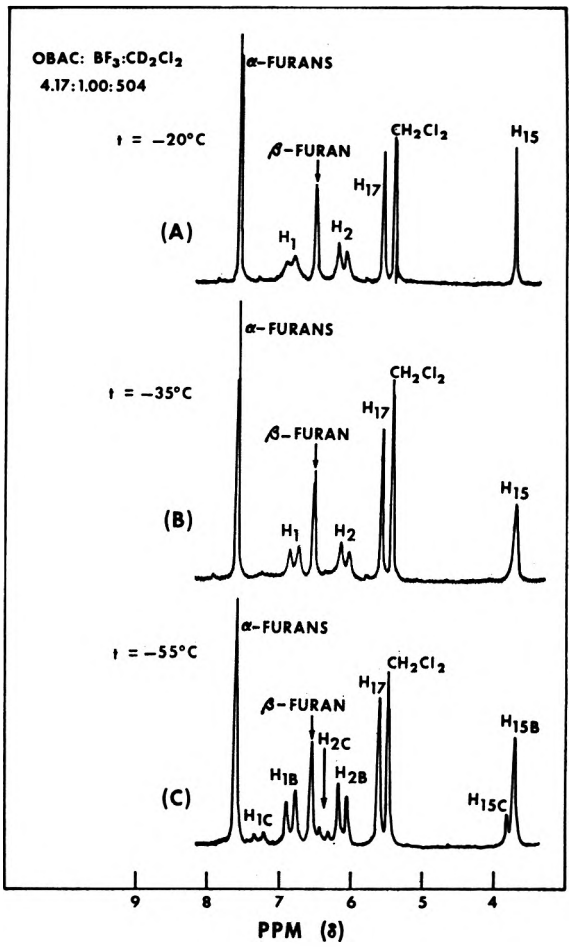


Figure 1.—The variable temperature pmr spectrum of an obacunone–BF_3 mixture in $CDCl_3$, recorded at 100 MHz. The signals arising from bulk (B) and coordinated (C) ligand molecules are labeled in the diagram and each proton is identified. Concentrations are in mole ratios.

between complexed and bulk ligand molecules, represented by the quantity Δν(C-B) in Table I, are an accurate measure of the effect of complex formation on individual protons. Since the resonance signals of complexed ligand molecules appear downfield from those of corresponding bulk molecules, the quantities under the heading Δν(C-B) in Table I are always positive. The last column of Table I lists the stoichiometry of the BF_3 complex with each base, as calculated from proton integrations. In every case data for chemical shift and area measurements represent two or more measurements with each sample and are precise to about 5% (Δν shifts) and 10% (areas), respectively.

It can be seen from Table I that it was not possible to obtain coordination data for all ligands by pmr, nor was it possible to measure Δν(C-B) values for all the protons in a particular ligand. These problems arise from spectral characteristics of the individual compounds and from the small complex to bulk chemical shift difference for protons far removed from the interaction site, and not from the inability to slow ligand exchange. Thus chemical shift differences under the heading Δν(C-B) are given only for those protons whose bulk and coordinated signals could be identified clearly.

The ^{19}F nmr chemical shifts listed in Table II were measured with respect to internal C_6F_6, and referred to $CFCl_3$, the usual standard for ^{19}F studies, by the

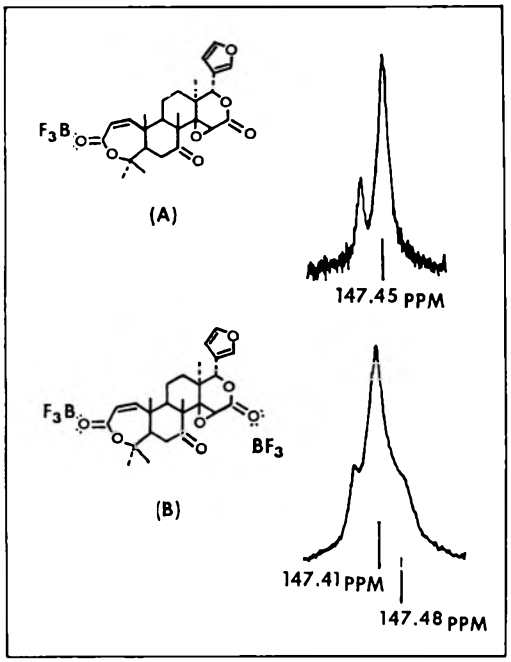


Figure 2.—The fluorine-19 nmr spectra for two obacunone/BF_3 ratios in (a) $CDCl_3$ and (b) 2-nitropropane (2NP), recorded at 94 MHz. The species present, mole ratios, and chemical shifts (δ) are labeled in the diagram.

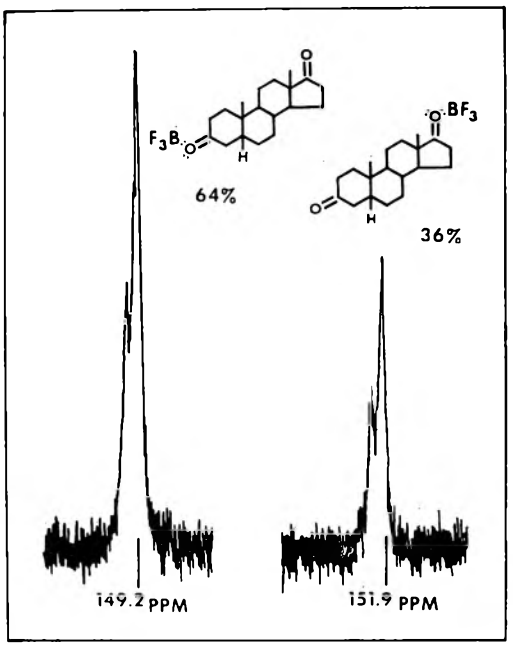


Figure 3.—The fluorine-19 nmr spectrum of a 1(5β)-androstane-3,17-dione–BF_3 mixture in $CDCl_3$, recorded at 94 MHz. The relative area of each signal and the chemical shifts (δ) are labeled in the diagram.

TABLE II

FLUORINE-19 CHEMICAL SHIFTS AND COORDINATION DATA FOR BORON TRIFLUORIDE COMPLEXES OF 4-CHOLESTEN-3-ONE, 1(5β)-ANDROSTENE-3,17-DIONE, 5β-ANDROSTANE-3,17-DIONE, AND OBACUNONE

Base	Mole ratio of base/BF_3/solvent[a]	t, °C	^{19}F chemical shifts,[b] δ, base–BF_3 complex
1	3.80:1.00:456	−46	149.6
2	3.40:1.00:408	−40	149.3
3	3.83:1.00:445	−57	149.2 (64%), 151.9 (36%)
4	4.31:1.00:517	−51	149.8
	1.02:1.00:132 (2NP)	−55	147.45
	0.68:1.00:81.5 (2NP)	−55	147.41, 147.48

[a] The solvent was $CDCl_3$, except where otherwise indicated. [b] Chemical shifts are in parts per million upfield from $CFCl_3$.

relationship, $\delta(C_6F_6) - \delta(CFCl_3) = +162.3$ ppm.[15] These chemical shifts were all upfield from $CFCl_3$ and were measured with a precision of at least 0.1 ppm. Typical ^{19}F nmr spectra are shown in Figures 2 and 3. Each BF_3–base complex signal appears as two signals due to the presence of both $^{10}BF_3$ and $^{11}BF_3$. Figure 2B illustrates the ^{19}F signals observed for the 0.68:1.00 obacunone–BF_3 system. Figure 3 shows the two ^{19}F signals, along with the relative area of each and the chemical shifts observed when two different sites in **3** are complexed by BF_3. In Table III pmr chemical shifts for two obacunone/BF_3 ratios, along with the temperature dependence of selected protons for the 0.68:1.00 obacunone–BF_3 system are listed.

Discussion

Since ^{19}F chemical shift differences are usually greater than ^1H values, separate ^{19}F signals can generally be observed at a higher temperature than bound and bulk ^1H ligand resonances. For instance, using the relationship $\tau = 10/2\pi\Delta\nu$ to approximate these rates, a lifetime of about 0.03 sec would be necessary to observe separate ^1H ligand signals, whereas for base **3** in Table II only 0.006 sec would be necessary to observe separate ^{19}F signals. These exchange rates are similar to those reported for other boron trihalide complexes with oxygen-containing bases, but are much faster than those involving nitrogen-containing bases such as pyridine, where ligand exchange is slowed enough to observe separate signals at about 0°.[8,11,12] The exchange rate may reflect the strength of these complexes.

TABLE III

PROTON CHEMICAL SHIFT DATA FOR OBACUNONE AS A FUNCTION OF TEMPERATURE

Mole ratio of obacunone/BF_3/2NP	t, °C	Chemical shift,[a] δ H-1	H-2	H-15	H-17
1.02:1.00:132	−57	7.34	6.19	3.80	5.52
0.68:1.00:81.5	−57	7.33	6.19	4.06	5.82
	−63	7.33	6.18	4.14	5.83
	−73	7.33	6.17	3.96	5.55
	−78	7.32	6.16	3.84	5.54
	−85	7.32	6.17	3.84	5.54

[a] Chemical shifts are in parts per million from internal TMS.

The ^1H and ^{19}F nmr data for **1**, in Tables I and II, provide a useful reference for the remaining three systems. As expected, the 1:1 adduct is formed with complexing occurring at the only possible interaction site, the A-ring carbonyl group. This is substantiated by the relatively large $\Delta\nu$(C-B) values for the 2 and 4 protons, the integration data, and the observation of only one ^{19}F nmr signal, occurring at +149.6 ppm. The coordination data for **2**, **3**, and **4**, however, show several interesting features. Compounds **2** and **3** have two possible interaction sites, the A- and D-ring carbonyl groups. However, **2** contains an α,β-unsaturated keto group in the A ring, whereas **3** is a com-

(15) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, 1st ed, Pergamon Press, New York, N. Y., 1966, Table 11.26.

pletely saturated diketone. The data of Tables I and II indicate that complexing in **2** occurs solely in the A ring. This is shown by the large $\Delta\nu$(C-B) values for H-1 and H-2, the coordination number of 1.0, and the single ^{19}F nmr signal at +149.3 ppm, which closely agree with those observed for the BF_3 complex of **1**. In contrast, complexing of **3** occurs at both carbonyl groups. At −56° the ^{19}F nmr spectrum of a BF_3 mixture with **3** consists of two well-defined and widely separated signals, one at +149.2 ppm amounting to 64% of the total ^{19}F area and the other at +151.9 ppm. The signal at +149.2 ppm can be attributed to that fraction of BF_3 complexed in the A ring, since the shift closely parallels those observed for **1** and **2**, and the signal at +151.9 ppm arises from that complexed in the D ring. This reasoning is confirmed by ^{19}F nmr data of BF_3 complexes with cyclohexanone and cyclopentanone, which have ^{19}F resonances at +149.0 and +151.8 ppm, respectively.[16]

In the pmr spectrum of **3** the signals of the protons on carbons α to the two carbonyl groups cannot be individually identified because of strong coupling and overlap. However, the signal of the 13-methyl group adjacent to the 17-carbonyl provides an indication of complexing at this site. In the presence of BF_3 this resonance is split into bulk and coordinated signals, with a separation of 22 Hz. The corresponding signal in complexed **2**, on the other hand, is not split. These findings support the conclusion drawn from the ^{19}F spectra that complexing occurs at both carbonyl sites in **3**.

Thus in **2** the D-ring carbonyl group cannot effectively compete for BF_3 in the presence of the conjugated A-ring carbonyl group. When the A ring is saturated, as in **3**, the D-ring carbonyl group then can compete for BF_3 to the extent indicated. These observations are in agreement with proton basicity data which indicate that α,β-unsaturated ketones are more basic than the corresponding saturated ketones.[17] Unfortunately, since the interaction sites, the A- and D-ring carbonyl groups, are so far apart, it cannot be demonstrated conclusively whether these interactions occur in different molecules, at two sites in the same molecule, or both.

The value of this low temperature nmr method in yielding information about coordination sites is well illustrated by the data for obacunone (**4**), a compound which has seven possible interaction sites. The pmr coordination and chemical shift data of Table I indicate that with high base/BF_3 ratios complexing occurs solely in the A ring, as evidenced by the large $\Delta\nu$(C-B) values for the 1 and 2 protons, 42 and 32 Hz, respectively. Integration of bulk and complex signals of H-1, H-2, and H-15 uniformly yields a coordination number of unity within experimental error. This demonstrates that complexing is at only one site. This is confirmed by the ^{19}F nmr spectrum, which shows only one signal at +149.8 ppm.

Since **4** contains many possible interaction sites, it was of interest to identify the second most basic site. Since the complex precipitated from $CDCl_3$ and CD_2Cl_2 solutions with base/BF_3 ratios approaching unity, use of a more polar solvent, 2-nitropropane, was necessary to keep it in solution. Unfortunately, the large solvent peaks in the proton spectrum then prevented observation of the H-15 and H-17 complex signals; so we were unable to determine $\Delta\nu$(C-B) values for these two protons. Instead we have used the change in chemical shift of the H-15 and H-17 resonances with temperature as a measure of the effect of complexing on these protons. Above the temperature at which exchange becomes slow on the nmr time scale, separate bulk and complex signals do not appear, but rather a single broadened resonance, which is an average of the two, is observed. The maximum downfield position of this average signal is thus less than, but proportionate to, the $\Delta\nu$(C-B) value and can be used similarly to the latter in comparing complexing effects.

Table III lists ^1H chemical shift data for two obacunone/BF_3 ratios in 2-nitropropane. The first entry gives the chemical shifts of the 1, 2, 15, and 17 protons of obacunone in a 1:1 complex at −55°. The second entry illustrates the temperature dependence of these protons when excess BF_3 is present. It is apparent that the 1- and 2-proton signals, at this concentration, are not temperature dependent, further demonstrating that the A-ring carbonyl group is completely complexed. However, as the temperature is decreased, the 15- and 17-proton signals first shift to lower field, *i.e.*, the broadened average signals are observed. At lower temperatures these then split, and the bulk signals move back upfield to about the same position as in the 1:1 complex. This indicates that the second mole of BF_3 is coordinating at a site close to the 15 and 17 protons. The ^{19}F spectrum for this sample shows two signals with very similar chemical shifts, as illustrated by Figure 2B. If the second site complexed was the 7-ketone, the downfield shift of H-15 with decreasing temperature should be considerably larger than that for H-17, but the two values are approximately the same. The small chemical shift difference for the two ^{19}F signals also tends to rule out the epoxide as one of the sites complexed. Thus, the ^1H and ^{19}F nmr results both suggest that the first site complexed is the carbonyl group of the A ring, and the second site is the carbonyl group of the D ring.

Since the $\Delta\nu$(C-B) values in Table I are all positive, the complexed ligand signals always appearing at lower applied magnetic field than the bulk signals, the protons of the former must experience a decreased electronic shielding. These positive $\Delta\nu$(C-B) values may reflect changes in electron density and field effects at that particular site in the ligand upon complex formation. For example, listed in Table I are $\Delta\nu$(C-B) values for the conjugated 1 and 2 protons of **2** and **4**. The values of 42 and 32 Hz for **2** and 55 and 24 Hz for **4** are consistent with other spectroscopic[18] and chemical[19] data which indicate that polarization of α,β-unsaturated carbonyl compounds causes a reduction in the electron density at the β-carbon atom, and hence decreases the effective shielding at the β proton. Thus the $\Delta\nu$(C-B) values give some indication concerning the magnitude of such changes occurring on complex formation. Of particular interest, and not readily explained, is the appearance of a complex signal for the 15 proton of **4**.

(16) A. Fratiello, private communication.

(17) A. M. Smoczkiewicz and R. I. Zalewski, *Steroids*, **12**, 391 (1968).

(18) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1963, Chapter 5.

(19) C. Djerassi, "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963.

Since complexing occurs solely at the carbonyl group of the A ring, at those concentrations given in Table I, the effect observed, $\Delta\nu$(C-B) equal to 12 Hz, must be transmitted through at least seven carbon atoms. This long-range effect is quite unexpected, since in aliphatic noncyclic bases previously studied the $\Delta\nu$-(C-B) values attenuate rapidly with distance. For example, in di-*n*-butyl ether,[20] the $\Delta\nu$(C-B) value for the methylene protons adjacent to the coordinated oxygen atom is approximately 80 Hz, whereas the terminal methyl group pmr signal is displaced only 6 Hz. Thus the 15 proton of **4** must be strongly affected by changes in the A ring.

These results demonstrate the advantages of this direct low temperature nmr method for investigating a variety of Lewis acid–base interactions involving structurally complex ligand molecules. The combination of ^{1}H and ^{19}F nmr provides a reliable method for determining the interaction site or sites in the ligand. For polyfunctional compounds the relative basicities of different sites thus can be determined. If BF_3 coordinates at each of two possible sites, they probably differ in basicity by less than 1 pK_{BH^+} unit.[8] This method could be of particular value in the steroid field, where quantitative data on basicities of functional groups are scarce.[17] Such knowledge could be used in explaining and predicting the course of acid-catalyzed reactions, although of course factors other than basicity also must be considered. For example, ketalization of **3** with methanol in the presence of *p*-toluenesulfonic acid gave largely the 3-ketal,[21] which is in accord with our finding of predominant binding of BF_3 at the 3-carbonyl. The observation of exclusive complexing at the conjugated carbonyl group of **2** and **4** also is consistent with numerous selective acid-catalyzed reactions of steroids of this type.[19] The fact that BF_3 itself frequently is used as a catalyst for steroid reactions adds to the value of the method reported here.

Acknowledgment.—We thank Dr. Anthony Fratiello for helpful discussions during the course of this work.

Registry No.—1-BF_3, 40715-58-0; 2-BF_3, 40715-59-1; 3-$2BF_3$, 40715-60-4; 4-BF_3, 40758-67-6; 4-$2BF_3$, 40758-68-7.

(20) A. Fratiello and R. E. Schuster, *J. Org. Chem.*, **37**, 2237 (1972).

(21) W. Nagata, *et al.*, *Chem. Pharm. Bull.*, **14**, 174 (1966).

Notes

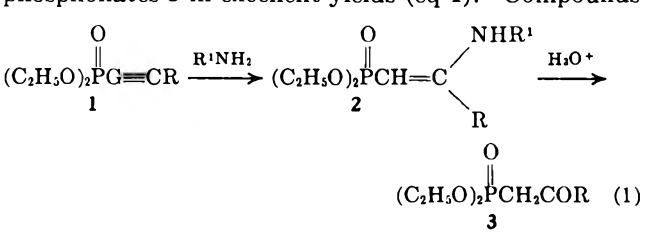
Organophosphorus Enamines. VIII. A Convenient Preparation of Diethyl β-Ketophosphonates[1]

MOHINDER S. CHATTHA AND ADAM M. AGUIAR*

Department of Chemistry, Rutgers University, Newark, New Jersey 07102

Received February 27, 1973

Recently we described the nucleophilic addition of aliphatic amines to the carbon–carbon triple bond in diethyl 1-alkynylphosphonates **1**,[2] giving enamine phosphonates **2** in fair to good yields.[3] Now we wish to report that an acid hydrolysis of **2** produces β-ketophosphonates **3** in excellent yields (eq 1). Compounds



(1)

R = alkyl, phenyl; R^1 = alkyl

3 prepared in this manner are listed in Table I along with their boiling points and yields.

TABLE I

Compd	R	Bp, °C (mm)	Yield,[a] %
a	*n*-C_5H_{11}	130 (0.15)	94
b	*n*-C_6H_{13}	125 (0.10)	89
c	*n*-C_7H_{15}	139 (0.1)	83
d	$(CH_3)_2CHCH_2CH_2$	137 (0.15)	91
e	*c*-C_5H_9	110 (0.10)	76
f	*c*-C_6H_{11}	151 (0.50)	81
g	C_6H_5	135 (0.10)	90
h	$C_6H_5CH_2CH_2$	162 (0.12)	91
i	$C_6H_5CH_2CH_2CH_2$	155 (0.08)	92

[a] This is the yield of the distilled material based upon the starting 1-alkynylphosphonates **1**.

The ir spectra of compounds **3a–i** display strong absorption at τ 5.85–5.90 (C=O). In the nmr spectra of **3a–i**, the *P*-methylene protons exhibit a doublet (J_{PH} = 22.5 Hz) in the region of δ 3.08–3.18. The methylenes from the *O*-ethyl groups display two quartets (J_{HH} = 7.5, J_{PH} = 9 Hz) at δ 4.12–4.20, which overlap to give a near quintet pattern. All other proton resonances were also found to be in agreement with the assigned structures. The structures were further supported by the elemental analyses of these phosphonates **3**.

The hydration of the triple bond in diethyl 1-alkynylphosphonates **1** to produce diethyl β-ketophosphonates **3** has also been reported;[4] our alternate method described here affords, under very mild conditions, a straightforward and high-yield synthesis of this very useful class of phosphonates.

(1) The work was initiated at Tulane University, New Orleans, La.
(2) M. S. Chattha and A. M. Aguiar, *J. Org. Chem.*, **36**, 2719 (1971).
(3) M. S. Chattha and A. M. Aguiar, *J. Org. Chem.*, in press.
(4) G. Sturtz and C. Charrier, *C. R. Acad. Sci.*, **261**, 1019 (1965).

Experimental Section

The nmr spectra were determined on a Varian A-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Diethyl 1-alkynylphosphonates were prepared by our method described earlier[3] and were redistilled before use.

Preparation of Diethyl β-Ketophosphonates 3a–i.—The diethyl 1-alkynylphosphonate 1 (0.025 mol) was refluxed for 3–5 days with a 10–12 molar excess of *n*-butylamine.[4] The excess amine was evaporated at aspirator pressure. The resulting adduct was dissolved in ether (100 ml), and 100 ml of 1% aqueous solution of oxalic acid was added. The two-layer reaction mixture was stirred for 7–8 hr at room temperature and then transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted twice with 25-ml portions of ether. The combined ether extracts were washed with dilute sodium bicarbonate solution, dried ($MgSO_4$), and filtered and ether was distilled off. The resulting oil was short path distilled under reduced pressure.

Acknowledgment.—We wish to acknowledge the National Institutes of Health for support of this work under Grant GM-16828 and the National Science Foundation under Grant GP-10739 We also wish to thank Hoffmann-La Roche, Inc., Nutley, N. J., for their unrestricted grant which helped us to complete this work.

Registry No.—**1a**, 3450-64-4; **1b**, 3450-66-6; **1c**, 40601-31-8; **1d**, 40601-32-9; **1e**, 30238-21-2; **1f**, 30238-20-1; **1g**, 3450-67-7; **1h**, 30238-19-8; **1i**, 40601-37-4; **3a**, 3450-65-5; **3b**, 3452-99-1; **3c**, 40601-40-9; **3d**, 40601-41-0; **3e**, 40601-42-1; **3f**, 40601-43-2; **3g**, 3453-00-7; **3h**, 40601-45-4; **3i**, 40601-46-5.

Dianions of β-Keto Phosphonates. A Two-Step Synthesis of (±)-*ar*-Turmerone

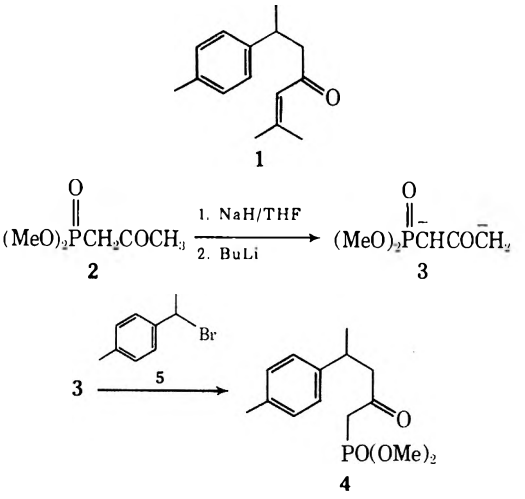
PAUL A. GRIECO* AND ROBERT S. FINKELHOR

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received March 12, 1973

The monocyclic aromatic sesquiterpene (±)-*ar*-turmerone (**1**) is the chief component of the essential oil from the rhizomes of *Curcuma Longa* Linn.[1] Although the structure of **1** has been confirmed by a number of syntheses,[2] we would like to describe a two-step synthesis of turmerone employing the recently reported method of specifically alkylating a β-keto phosphonate ester at the γ carbon atom.[3]

The alkylation of dianion **3** [prepared by treatment of dimethyl 2-oxopropylphosphonate (**2**) with sodium hydride in anhydrous tetrahydrofuran followed by subsequent metalation with *n*-butyllithium] with *p*-(1-bromoethyl)toluene (**5**) affords the γ-alkylated β-keto phosphonate **4** in 50% isolated yield after purification. The synthesis of β-keto phosphonates (*e.g.*, **4**) *via* the dianion procedure complements the existing methods: Michaelis–Arbusov[4] reaction of trimethyl phosphite with an α-halo ketone and the reaction of dimethyl



α-lithiomethanephosphonate with an ester.[5] We believe that the present method offers some obvious advantages over the existing methods.

Finally, treatment of β-keto phosphonate **4** with sodium hydride in anhydrous dimethoxyethane followed by addition of an excess of acetone affords after 14 hr at 55° a 52% isolated yield of (±)-*ar*-turmerone after purification. The synthetic material exhibits nmr, ir, and mass spectral data in agreement with the previously published data.[2c] The synthesis of **1**, despite its low overall yield, represents the shortest and most convenient route in comparison with previously reported syntheses.

Experimental Section[6]

Preparation of β-Keto Phosphonate 4.—To a suspension of 204 mg (4.8 mmol) of sodium hydride (57%, washed with hexane to remove mineral oil) in 10 ml of freshly distilled tetrahydrofuran under an atmosphere of nitrogen was added dropwise 663 mg (4.0 mmol) of dimethyl 2-oxopropylphosphonate (**2**)[7] in 1.5 ml of dry THF. The resulting slurry was stirred at room temperature for 2 hr to allow for complete formation of the sodio derivative of **2**. The reaction mixture was then cooled to 0° and 2.6 ml (4.2 mmol) of *n*-butyllithium (1.56 *M* in hexane) was added dropwise. Stirring was continued for 30 min, followed by addition of 855 mg (4.3 mmol) of *p*-(1-bromoethyl)toluene in 1.5 ml of THF. After addition was complete, the reaction mixture was warmed to room temperature and stirring was continued for 1 hr. The reaction mixture was quenched at 0° by the addition of 4 ml of 5% hydrochloric acid and the product was isolated by extraction with chloroform. After purification by passing through a column of silica gel (hexane–benzene–ethanol, 6:2:3) there was obtained 575 mg of phosphonate **4** (50% yield): ν_{max} ($CHCl_3$) 1710 cm^{-1}; nmr (CCl_4) δ 7.02 (s, 4 H), 3.67 (d, J = 11 Hz, 3 H), 3.60 (d, J = 11 Hz, 3 H), 2.92 (d, J = 22 Hz, 2 H), 2.26 (s, 3 H), 1.10 (d, 3 H); *m/e* 284.

(±)-*ar*-Turmerone.—To a suspension of 72 mg (1.7 mmol) of sodium hydride (57% dispersion; washed with hexane prior to use) in 5 ml of freshly distilled dimethoxyethane (DME) was added 436 mg (1.5 mmol) of phosphonate **4** in 0.5 ml of DME. After anion formation was complete (1.5 hr), the reaction mixture was cooled to 0° while 0.35 ml (4.8 mmol) of dry acetone was added dropwise. After addition was complete, the reaction mixture was heated to 55° and maintained at that temperature for 14 hr.

The reaction mixture was quenched by pouring it into 50 ml of a 50% aqueous sodium chloride solution. The product was ex-

(1) H. Rupe and A. Gassmann, *Helv. Chim. Acta*, **19**, 569 (1936).

(2) (a) J. Colonge and J. Chambion, *C. R. Acad. Sci.*, **222**, 557 (1946); (b) R. P. Gandhi, O. P. Vig, and S. M. Mukherji, *Tetrahedron*, **7**, 236 (1959); (c) R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972).

(3) P. A. Grieco and C. S. Pogonowski, *J. Amer. Chem. Soc.*, **95**, 3071 (1973).

(4) B. A. Arbusov, *Pure Appl. Chem.*, **9**, 307 (1964).

(5) E. J. Corey and G. T. Kwiatkowski, *J. Amer. Chem. Soc.*, **88**, 5654 (1966).

(6) Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Precoated plc silica gel F-254 Merck plates were used for preparative tlc. The following spectrometers were used: nmr, Varian A-60D; ir, Perkin-Elmer Model 247; mass spectrum, LKB-9.

(7) F. A. Cotton and R. A. Schunn, *J. Amer. Chem. Soc.*, **85**, 2394 (1963).

tracted with an ether–hexane mixture (3:1) and the combined extracts were dried over anhydrous magnesium sulfate. Preparative thin layer chromatography on silica gel afforded 165 mg (52%) of pure (±)-*ar*-turmerone (1): ν_{max} ($CHCl_3$) 1685 (C=O), 1620 (C=CH–), 1515 ($-C_6H_4-$), 819 cm^{-1} (p-C_6H_4–); nmr (CCl_4) δ 7.00 (s, 4 H, p-$CH_3C_6H_4$–), 5.90 [m, 1 H, $-CH=C(CH_3)_2$], 3.20 [m, 1 H, $C_7H_7CH(CH_3)$–], 2.50 (m, 2 H, $-CH_2CO$–), 2.25 (s, 3 H, p-$CH_3C_6H_5$–), 2.08 [s, 3 H, $-COCH=C(CH_3)_2$, methyl cis to carbonyl], 1.81 [s, 3 H, $-COCH=C(CH_3)_2$, methyl trans to carbonyl], 1.20 [d, 3 H, $C_7H_7CH(CH_3)$–]; *m/e* 216. The analytical sample was obtained as a colorless oil by preparative tlc followed by molecular distillation, bp (bath) 90° (0.07 mm).

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.42; H, 9.32.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—1, 38142-58-4; 2, 4202-14-6; 4, 40601-28-3; 5, 40601-29-4.

An Improved Synthesis of 2-Methoxypropene[1]

MELVIN S. NEWMAN* AND MICHAEL C. VANDER ZWAN

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received March 13, 1973

The advantages of the use of 2-methoxypropene[2] (1), 1-methoxycyclohexene (2), and 4-methoxy-5,6-dihydro-2*H*-pyran (3), over dihydropyran (4), for the protection of alcohol functions have been discussed.[3] The reaction of 1 with allylic alcohols to form allyl vinyl ethers which rearrange on heating to γ,δ-unsaturated ketones has been described.[4] Because we were interested in another use for 1, we sought to improve the tedious methods for preparation described.[5]

The improved method described herein involves adding acetone dimethyl ketal to a solution of succinic anhydride and benzoic acid[6] in pyridine and diethylene glycol dimethyl ether (diglyme) at 110–120°. The desired 1 distills as formed in excellent yield. An 8-mol run can be completed in 2–2.5 hr. When acetic anhydride[4] is used in place of succinic anhydride, methyl acetate codistills with 1 and an aqueous alkaline hydrolysis of the mixture is necessary to obtain pure 1.

The method using succinic anhydride is mainly valuable when a low-boiling vinyl ether is desired. In the case of the formation of α-methoxystyrene from acetophenone dimethyl ketal the method using succinic anhydride requires an aqueous work-up and hence has no advantage over that using acetic anhydride, but the example is given to indicate the generality of the method.

(1) This work was supported by Grant 12554 of the National Science Foundation.

(2) A. F. Kluge, K. G. Untch, and John H. Fried, *J. Amer. Chem. Soc.*, **94**, 7827 (1972).

(3) C. B. Reese, R. Saffhill, and J. E. Sulston, *J. Amer. Chem. Soc.*, **89**, 3366 (1967).

(4) G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 2091 (1967); R. Marbet and G. Saucy, *ibid.*, **50**, 2095 (1967).

(5) L. Claisen, *Chem. Ber.*, **31**, 1019 (1898); G. Saucy and R. Marbet, *Helv. Chim. Acta*, **50**, 1158 (1967).

(6) The reaction takes place much more slowly if benzoic acid is omitted.

Experimental Section

2-Methoxypropene (1).—To a stirred solution at 110–120° of 820 g (8.2 mol) of succinic anhydride and 24 g (0.2 mol) of benzoic acid in 640 g (8 mol) of pyridine and 600 ml of diglyme in a 3-l. three-necked round-bottomed flask fitted with a pressure-equalizing addition funnel, thermometer, and an efficient fractionating column[7] was added 832 g (8 mol) of acetone dimethyl ketal over 1.5 hr. Shortly after the ketal addition was commenced 1 distilled. After about 2 hr 547 g (95%) of 1 was obtained as a colorless liquid, bp 37°. This product, nmr (CCl_4, TMS δ 0.0) 3.80 (s, 2, $=CH_2$), 3.48 (s, 3, CH_3O–), 1.75 (s, 3, CH_3C), had a strong ir band (20% in CCl_4) at 6.08 μ (1640 cm^{-1}) for an olefin and no bands at 3.00 (3350 cm^{-1}, methanol), or near 5.8 μ (1750 cm^{-1}, acetone).

That the amount of pyridine used can be greatly decreased was shown by a similar experiment in which 208 g (2.0 mol) of acetone dimethyl ketal was added during 20 min to a solution at 110–120° of 220 g (2.2 mol) of succinic anhydride and 12 g (0.1 mol) of benzoic acid in 250 ml of diglyme and 16 g (0.2 mol) of pyridine. The yield of pure 1 obtained in 70 min was 130 g (90%).

α-Methoxystyrene (2).—To a solution at 110–120° of 33 g of succinic anhydride and 1.2 g of benzoic acid in 30 ml of pyridine and 35 ml of diglyme was added 46 g of acetophenone dimethyl ketal during 15 min. After a further 15 min the mixture was cooled and added to 200 ml of 2 *N* potassium hydroxide. The neutral product was extracted with ether and worked up in a conventional way to yield 36.0 g (97%) of 2, bp 114° (50 mm).[8]

Registry No.—1, 116-11-0; 2, 4747-13-1; acetone dimethyl ketal, 77-76-9; acetophenone dimethyl ketal, 4316-35-2.

(7) We used a 1.75 × 60 cm column packed with stainless steel heligrad packing. However, a 1.75 × 30 cm column packed with 0.25-in. glass helices worked almost as well.

(8) S. Winstein and L. L. Ingraham, *J. Amer. Chem. Soc.*, **77**, 1738 (1955), gave bp 85–89° (20 mm).

Improved Synthesis of Deuterated Olefins from the Wittig Reaction

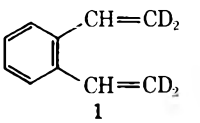
GERALD W. BUCHANAN* AND ALBERT E. GUSTAFSON

Department of Chemistry, Carleton University, Ottawa, Canada K1S 5B6

Received March 13, 1973

The utility of the Wittig reaction[1] for the synthesis of deuterated alkenes has been plagued by the occurrence of extensive deuterium scrambling and exchange with the reaction medium. Atkinson and coworkers[2] found that *n*-propyl- or *n*-butyllithium should be used as a base rather than the anion of dimethyl sulfoxide[3] in order to minimize deuterium exchange *via* enolization of the carbonyl compound. However, work-up procedures are tedious and yields are characteristically low.

In the course of some spectroscopic studies, we required a sample of *o*-divinylbenzene-d_4 (1). Survey of the literature revealed a synthesis[4] from Ph_3PCD_3Br



1

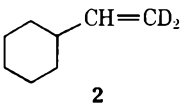
(1) G. Wittig and U. Schollkopf, *Chem. Ber.*, **87**, 1318 (1954).

(2) J. G. Atkinson, M. H. Fisher, D. Horley, A. T. Morse, R. S. Stuart, and E. Synnes, *Can. J. Chem.*, **43**, 1614 (1965).

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(4) M. Pomerantz and G. W. Gruber, *J. Amer. Chem. Soc.*, **93**, 6615 (1971).

and *o*-phthalaldehyde employing *tert*-butyllithium as base. ^{1}H nmr analysis indicated 93% incorporation of four deuteriums, but the yield of **1** was only 1.5%. We wish to report a 20-fold increase in the yield of **1** with no apparent scrambling of deuterium *via* a simple modification of the decomposition procedure of the intermediate betaine. The method is shown to be generally applicable to other vinyl compounds, exemplified by vinylcyclohexane-d_2 (**2**).



2

Rather than employing a thermal decomposition of the betaine by refluxing for several hours,[4] we find that addition of excess D_2O gives a 30% yield of **1** and a 70% yield of **2**. ^{1}H and ^{13}C nmr analysis[5] indicates 97 ± 3% **1**-d_4 and 97 ± 3% **2**-d_2 deuterated *solely* at the exo methylene carbons.

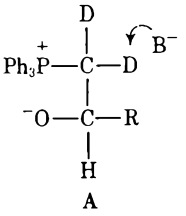
Notably, if *n*-butyllithium is used as base followed by D_2O work-up, measurable exchange occurs at the exocyclic carbons in all compounds studied. Mass spectral determination indicated that d_2 material was the main impurity in the preparation of **1** and d_1 material in the case of **2**. The absence of exchange when *tert*-butyllithium is employed as base may be explained on steric grounds. Owing to the inductive effects of the methyl groups, the *tert*-butyl carbanion is expected to be a stronger base, thermodynamically, than *n*-butyllithium. The *n*-butyl carbanion, however, can approach an acidic proton with less steric restriction and thus may be the stonger base kinetically, causing exchange at the intermediate betaine stage of the reaction.

The need for an appreciable "deuterium pool" in the work-up is clear from H_2O quenching experiments in which 10–40% exchange occurs, regardless of the base employed, to give mainly **1**-d_2 and **2**-d_1, respectively. Results of several exchange experiments are presented in Table I.

TABLE I
DEUTERIUM INCORPORATIONS FROM WITTIG REACTIONS (±3%)

Salt	Base	Quenching agent	% **1**-d_4	% **2**-d_2
Ph_3PCD_3Br	*n*-BuLi	D_2O	91	84
Ph_3PCD_3Br	*t*-BuLi	D_2O	97	97
Ph_3PCD_3Br	*n*-BuLi	H_2O	81	63
Ph_3PCD_3Br	*t*-BuLi	H_2O	93	68

It is interesting that the amount of exchange decreases with increasing steric hindrance in the substrate, a finding in accord with the steric approach control argument presented above. Although the precise mechanism of isotopic exchange is difficult to elucidate, the lack of observable scrambling at the methine olefinic carbon indicates the absence of exchange in the parent aldehyde. It is proposed that scrambling of label occurs in the betaine intermediate A.



A

(5) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Scridhar, and R. Weglein, *J. Amer. Chem. Soc.*, **94**, 8581 (1972).

Experimental Section

Spectra.—^{1}H nmr spectra were recorded on Varian T-60 and XL-100-12 nmr spectrometers at 60 and 100 MHz, respectively. ^{13}C spectra were recorded at 25.2 MHz on the XL-100-12 under conditions of complete proton noise decoupling. Mass spectra were recorded using a Varian Anaspec EM-600.

Materials.—Methyl-d_3-triphenylphosphonium bromide was prepared from triphenylphosphine and methyl bromide-d_3 (99.5%, obtained from Stohler Isotope Chemicals, Montreal) according to the method of Trippett.[6]

A typical procedure for preparation of **2** follows. Methyl-d_3-triphenylphosphonium bromide (5.4 g, 0.015 mol) in 60 ml of dry diethyl ether were placed in a 250-ml three-necked flask under nitrogen and the suspension was stirred for 20 min. To this was added 7.1 ml of a 2.1 *M* solution of *tert*-butyllithium in pentane *via* a hypodermic syringe. The resulting orange-yellow solution was stirred for 4 hr at room temperature, then cooled to 10° *via* an ice–water bath, and 1.68 g (0.015 mol) of cyclohexanecarbonaldehyde in 20 ml of ether was added over 1 min. The resulting heavy white suspension was stirred for 10 min and then quenched by the addition of 30 ml of D_2O. The reaction mixture was extracted with three 30-ml portions of ether and dried over anhydrous magnesium sulfate. Removal of the solvent by distillation at atmospheric pressure yielded an oil containing residual triphenylphosphine oxide and vinylcyclohexane. Addition of 15 ml of petroleum ether (bp 30–60°) caused precipitation of the oxide, which was removed by filtration. Final purification of the olefin was accomplished by column chromatography (neutral alumina, activity grade I) using ether as eluent. A 71% yield of vinylcyclohexane-d_2 was obtained.

Acknowledgment.—We thank the National Research Council of Canada for financial support.

Registry No.—**2**, 40600-04-2; methyl-d_3-triphenylphosphonium bromide, 1787-44-6; cyclohexanecarbonaldehyde, 2043-61-0.

(6) S. Trippett, "Advances in Organic Chemistry," Vol. 1, Interscience, New York, N. Y., 1960, pp 83–102.

Orientation in Base-Promoted β Eliminations from Chlorocyclodecane. The Role of Base Association

RICHARD A. BARTSCH* AND THEODORE A. SHELLY

Department of Chemistry, Washington State University, Pullman, Washington 99163

Received March 13, 1973

A striking control of orientation by choice of base in eliminations from chlorocyclodecane (**1**) has been reported by Traynham, Stone, and Couvillion.[1] Reaction of **1** with *t*-BuOK in DMSO produced 97% *cis*-cyclodecene. With lithium dicyclohexylamide [LiN(Cy)$_2$] in ethyl ether–hexane, 96% *trans*-cyclodecene was obtained. Although these authors offered no explanation for this interesting dichotomy, Buehler and Pearson[2] have proposed that, in DMSO, *t*-BuOK

(1) J. G. Traynham, D. B. Stone, and J. L. Couvillion, *J. Org. Chem.*, **32**, 510 (1967).

(2) C. A. Buehler and D. E. Pearson, "Survey of Organic Synthesis," Wiley-Interscience, New York, N. Y., 1970, p 77.

TABLE I

OLEFINIC PRODUCTS FROM REACTION OF CHLOROCYCLODECANE WITH VARIOUS BASE-SOLVENT SYSTEMS

Expt	Base–solvent	Conditions	% of total cyclodecenes: *trans*-Cyclodecene	% of total cyclodecenes: *cis*-Cyclodecene
1[a]	*t*-BuOK–DMSO	5 min, room temp	18 ± 1[b]	82 ± 1
2[a]	*t*-BuOK–DMSO	15 min, room temp	6 ± 1	94 ± 1
3[a]	*t*-BuOK–DMSO	2 hr, room temp	4 ± 1	96 ± 1
4[c]	$LiN(Cy)_2$–ether–hexane	24 hr, reflux	87 ± 2	13 ± 2
5[d]	$LiN(Cy)_2$–ether–hexane[e]	3 hr, reflux	69 ± 1	31 ± 1
6[d]	$LiN(Cy)_2$–ether–hexane[e]	24 hr, reflux	68 ± 3	32 ± 3
7[f]	*t*-BuOK–*t*-BuOH	24 hr, 50°	56 ± 2	44 ± 2
8[f]	*t*-BuOK–*t*-BuOH[g]	2 hr, 50°	62 ± 1	38 ± 1

[a] [1] = 0.6 *M*, [*t*-BuOK] = 0.9 *M*. [b] Standard deviation from repetitive analysis of extracted product mixture. [c] [1] = 0.3 *M*, $[LiN(C_6H_{11})_2]$ = saturated solution. [d] [1] = 0.3 *M*, $[LiN(C_6H_{11})_2]$ = 0.3 *M*. [e] Tetramethyl-12-crown-4 (0.3 *M*) present. [f] [1] = 0.6 *M*, [*t*-BuOK] = 0.6 *M*. [g] Dicyclohexyl-18-crown-6 (0.6 *M*) present.

is well dissociated, which favors anti elimination and the formation of *cis*-cyclodecene. However, in ether–hexane, association of the cation and anion of $LiN(Cy)_2$ promotes syn elimination and the production of *trans*-cyclodecene.[3,5] Because of our interest in the effect of base association upon orientation and stereochemistry in base-promoted β-elimination reactions,[7-9] an examination of this hypothesis was undertaken.

The relative proportions of isomeric cyclodecenes which are formed in reactions of **1** with three base–solvent systems are reported in Table I. For expt 3 and 4, procedures of Traynham, Stone, and Couvillion[1] were employed on a reduced scale. Under these conditions, reactions of **1** with *t*-BuOK–DMSO and $LiN(Cy)_2$–ether–hexane produce predominantly *cis*-cyclodecene and *trans*-cyclodecene, respectively.

However, the relative amounts of *cis*- and *trans*-cyclodecene which result from reaction of **1** with *t*-BuOK–DMSO vary with reaction time (compare expt 1–3). This suggests isomerization of initially formed *trans*-cyclodecene to the thermodynamically more stable cis isomer[10] by *t*-BuOK–DMSO.[11] Exposure of a cyclodecene mixture rich in the trans isomer (68% *trans*- and 32% *cis*-cyclodecene) to the reaction conditions of expt 3 resulted in isomerization to a mixture which contained 96% *cis*-cyclodecene.[12] Therefore, the high proportions of *cis*-cyclodecene which have been observed in reactions of **1** with *t*-BuOK–DMSO result from product isomerization, not from a special effect of a dissociated base.

A relatively minor influence of base association upon orientation in eliminations from **1** was demonstrated by use of crown ethers (macrocyclic polyethers).[13] Crown ethers strongly complex alkali metal cations[13] and markedly reduce the extent of base association in solvents of low polarity.[7,8,14] Reactions of **1** with $LiN(Cy)_2$–ether–hexane and tetramethyl-12-crown-4[15,16] (expt 5 and 6) and *t*-BuOK–*t*-BuOH and dicyclohexyl-18-crown-6[13] (expt 8) produced a somewhat greater proportion of *cis*-cyclodecene than in the absence of the crown ethers (expt 4 and 7, respectively). These increases probably result from a change in elimination stereochemistry for *cis*-cyclodecene formation from mostly syn with the associated bases to predominantly anti in the presence of the crown ethers.[14]

Experimental Section

Chlorocyclodecane[1,17] and tetramethyl-12-crown-4[15] were prepared by literature methods. Commercial *t*-BuOK (MSA, sublimed), DMSO (Baker, reagent), anhydrous ethyl ether (Mallenkrodt, reagent), hexane (Baker, reagent), and methyllithium in ether (Foote) were used directly. Dicyclohexylamine (Eastman) was purified by distillation. Solutions of *t*-BuOK–*t*-BuOH were prepared as before.[18]

Procedure.—Reactant concentrations, temperatures, and times are given in Table I. Reactions of **1** with *t*-BuOK–DMSO and *t*-BuOK–*t*-BuOH were conducted by adding **1** to 5 ml of the appropriate base–solvent solution. After the desired reaction period, the reaction mixture was poured into 25 ml of water and extracted with pentane (2 × 10 ml) and the volume of the pentane solution was reduced to 2 ml. The resulting liquid was analyzed by gas–liquid chromatography on a Varian Aerograph Model 1700 flame ionization gas chromatograph using 30 ft × 0.125 in. columns of 20% UCON 50HB100 on Chromosorb P operated at 150° Reactions of **1** with $LiN(Cy)_2$ in ether–hexane were performed by adding 0.50 g (3 mmol) of **1** in 5 ml of hexane to a mixture formed by addition of 1.76 ml (3 mmol) of methyllithium in ether to 0.50 g (3 mmol) of dicyclohexylamine in 5 ml of ether. Work-up and analysis were as given above.

Isomerization Studies.—A cyclodecene mixture (68 ± 3% trans and 32 ± 3% cis) was added to a solution of 2.5 ml of 0.9 *M* *t*-BuOK–DMSO. After 2 hr at room temperature, work-up, and analysis in the usual fashion, the cyclodecene mixture was found to be predominately *cis*-cyclodecene (4 ± 1% trans and 96 ± 1% cis).

Registry No.—Chlorocyclodecane, 7541-62-0; *trans*-cyclodecene, 2198-20-1; *cis*-cyclodecene, 935-31-9.

(3) In eliminations from cyclodecyl bromide induced by *t*-BuOK–*t*-BuOH and *t*-BuOK–benzene, *cis*-cyclodecene is formed by anti elimination and *trans*-cyclodecene by syn elimination. For reactions with *t*-BuOK–DMF and EtOK–EtOH, both cyclodecenes arise by anti elimination.[4]

(4) J. Závada, J. Krupička, and J. Sicher, *Collect. Czech. Chem. Commun.*, **33**, 1393 (1967).

(5) For discussions of the favoring of syn elimination relative to anti elimination by base association, see ref 4, 6, and 7.

(6) J. Závada and J. Svoboda, *Tetrahedron Lett.*, 23 (1972).

(7) R. A. Bartsch and K. E. Wiegers, *Tetrahedron Lett.*, 3819 (1972).

(8) R. A. Bartsch, G. M. Pruss, R. L. Buswell, and B. A. Bushaw, *Tetrahedron Lett.*, 2621 (1972).

(9) R. A. Bartsch, *J. Org. Chem.*, **38**, 846 (1973).

(10) N. L. Allinger, *J. Amer. Chem. Soc.*, **79**, 3443 (1957).

(11) The propensity of *t*-BuOK–DMSO for olefin isomerization is well known. See A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **84**, 3164 (1962), and papers cited therein.

(12) Equilibration of cyclodecenes with lithium 2-aminoethylamide in ethylenediamine yields 96% *cis*- and 4% *trans*-cyclodecene.[4]

(13) C. J. Pederson, *J. Amer. Chem. Soc.*, **89**, 7017 (1967); **92**, 391 (1970).

(14) M. Svoboda, J. Hapala, and J. Závada, *Tetrahedron Lett.*, 265 (1972).

(15) J. L. Down, J. Lewis, B. Moore, and G. Wilkinson, *J. Chem. Soc.*, 3767 (1959).

(16) Addition of tetramethyl-12-crown-4 caused the heterogeneous mixture of $LiN(Cy)_2$ ether–hexane to become homogeneous.

(17) We thank Cities Service Co., Cranbury, N. J., for a generous sample of cyclodecane.

(18) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **91**, 1376 (1969).

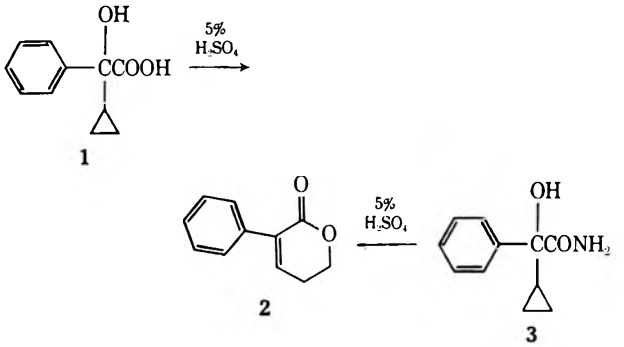
Boron Trifluoride Catalyzed Rearrangement of Cyclopropylphenylglycolamide

JOSEPH G. CANNON,* ROBERT V. SMITH, KEEVIN FRANZEN,[1a] AND JAMES MUSICH[1b]

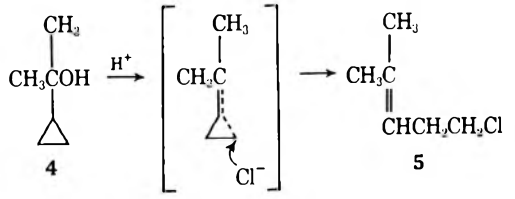
Division of Medicinal Chemistry and Natural Products, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242

Received March 20, 1973

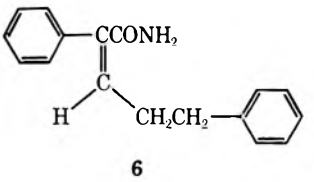
A prior communication[2] described acid-catalyzed rearrangement of cyclopropylphenylglycolic acid (**1**) to form 3-phenyl-5,6-dihydro-2-pyrone (**2**). Treatment of cyclopropylphenylglycolamide (**3**) under the



same experimental conditions utilized for **1** (5% aqueous sulfuric acid) afforded an equivalent yield of the dihydropyrone **2**. However, treatment of **3** with boron trifluoride etherate in anhydrous benzene provided, in addition to some polymeric material, a sizable amount of a nitrogen-containing solid whose infrared spectrum suggested the presence of amide carbonyl and whose mass spectrum revealed a parent ion of mass 251, corresponding to a formula of $C_{17}H_{17}NO$. These data suggested that the product contained an additional benzene ring, and that there was solvent participation in the BF_3-mediated rearrangement. Bruylants and Dewael[3] described formation of **5** by treatment of cyclopropyldimethylcarbinol (**4**) with HCl; the validity of this work was confirmed by Favorskaya and Fridman.[4] On the basis of a nonclassical carbonium ion structure proposed for some cyclopropylmethyl cations,[5,6] the Bruylants–Dewael reaction leading to **5** can be described as indicated.

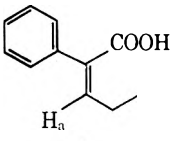


In the present work, it was speculated that a similar ion derived from **3** reacted with the benzene solvent to form **6**.

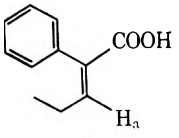


Nmr data were consistent with this structure. Ozonolysis of **6** permitted isolation of hydrocinnamic acid, which is likewise consistent with the proposed structure. Only a minute amount of the other ozonolysis product, phenylglyoxylamide, could be isolated from this reaction; a significant amount of nitrogen-containing polymeric material apparently was formed during the work-up of the reaction. Claisen[7,8] described the ease of polymerization of phenylglyoxylamide under acidic conditions similar to those employed in the work-up of the ozonolysis reaction.

The mass spectrum of **6** showed prominent ions at *m/e* (rel intensity) 251 (100, M^+), 160 (20, $M^- - CH_2C_6H_5$), 118 (96, phenylketene), and 91 (87, tropylium), which provide further evidence for its structure. A uv spectrum of **6** (ethanol) revealed λ 249 nm (ε 14,800), 283 sh (1260), and 291 (670). These data are consistent with those for compounds containing a styryl chromophore;[9] moreover, they seem to indicate the configuration about the double bond in **6**. Nilsson[10] reported significantly different uv spectra for **7** and **8**.



λ 249 nm (ε 11,000)
291 (370) (ethanol)
H_a = λ 6.25 (carbon tetrachloride)



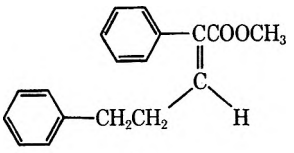
λ 235 nm sh (ε 5500) (ethanol)
H_a = 7.17 (beneath phenyl H's)
(carbon tetrachloride)

Since the primary amides of **7** and **8** would be expected to display similar uv chracteristics, the parallel agreement of the uv data for **6** and **7** suggests that **6** is (*Z*)-2,5-diphenyl-2-pentenoamide. This assignment is corroborated by comparison of the chemical shifts of the olefinic proton of **6** (δ 6.05) with those of the olefinic protons in **7** and **8**.[11] The remainder of the nmr spectrum of **6** is consistent with the proposed structure, which seems firmly established.

Catalytic hydrogenation of **6** permitted isolation of the saturated amide **9**. In studies aimed at unequivocal synthesis of **6**, phenylglyoxylamide was treated with a Wittig reagent derived from triphenyl-3-

(1) (a) National Science Foundation Undergraduate Research Participant, summer, 1971; (b) summer, 1970.
(2) L. L. Darko and J. G. Cannon, *J. Org. Chem.*, **32**, 2352 (1967).
(3) P. Bruylants and A. Dewael, *Bull. Sci. Acad. Roy. Belg.*, **14**, 140 (1928).
(4) T. A. Favorskaya and S. A. Fridman, *J. Gen. Chem. USSR*, **15**, 421 (1945).
(5) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).
(6) M. Vogel and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 2262 (1966).
(7) L. Claisen, *Ber.*, **10**, 1665 (1877).
(8) L. Claisen, *Ber.*, **12**, 632 (1879).
(9) C. G. Overberger and D. Tanner, *J. Amer. Chem. Soc.*, **77**, 369 (1955).
(10) K. Nilsson, *Acta Chem. Scand.*, **19**, 612 (1965).
(11) K. Nilsson and S. Sternhell, *Acta Chem. Scand.*, **19**, 2441 (1965).

phenylpropylphosphonium bromide; no identifiable product could be isolated. However, a reaction between this Wittig reagent and methyl phenylglyoxylate permitted isolation of methyl 2,5-diphenyl-2-pentenoate (**10**). Repeated attempts to effect amonolysis on **10** failed; either starting material was recovered or (under drastic conditions) the reaction mixture turned into an intractable tar. Attempts to effect acid- or base-catalyzed hydrolysis of **6** or **10** resulted in formation of complex mixtures. The olefinic proton of **10** appears to be buried beneath the aromatic protons. In light of the olefinic assignments in **7** and **8**, **10** is concluded to be *E* isomer, possessing a configuration opposite that of **6**.



10

A reasonable explanation for the rearrangement of **3** to the dihydropyrone **2** with aqueous sulfuric acid as contrasted with the behavior of **3** in the presence of boron trifluoride etherate and benzene is that, in aqueous environment, **3** first hydrolyzes to the acid **1**, which then rearranges to the dihydropyrone **2**. In boron trifluoride–benzene, no hydrolysis can occur and the amide moiety does not, under the reaction conditions, participate intramolecularly. The prior finding[2] that treatment of cyclopropylphenylglycolic acid (**1**) with boron trifluoride in benzene induces formation of the dihydropyrone **2** suggests that the differences in reaction products described herein cannot be related to the difference(s) in catalysts employed.

Experimental Section

Melting points were determined in open capillaries on a Thomas-Hoover Uni-melt apparatus and are corrected. Ir spectra were recorded in a Beckman IR-5-A instrument and nmr spectra were obtained on a Varian Associates T-60 instrument. Uv spectra were recorded on a Beckman DK-2 instrument. Elemental analyses were performed by the Microanalytical Service, College of Pharmacy, University of Iowa. Mass spectral data were supplied by Sadtler Research Laboratories, Inc., Philadelphia, Pa.

(*Z*)-2,5-Diphenyl-2-pentenoamide (6).—Cyclopropylphenylglycolamide (**3**)[2] (1.60 g, 0.0083 mol) was warmed in 150 ml of anhydrous, thiophene-free benzene until solution was achieved; then 10 ml of boron trifluoride etherate was added. The mixture was refluxed for 1 hr, allowed to stand at room temperature for 48 hr, then refluxed for 4 hr. The reaction mixture was cooled and decanted from gummy material which coated the sides of the reaction vessel. The benzene solution was washed several times with water and dried (Na_2SO_4), and volatiles were removed under reduced pressure to leave an off-white solid which was recrystallized from aqueous ethanol to afford 1.16 g (56%) of well-formed needles: mp 136–138°; ir ($CHCl_3$) 1670 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 2.7–3.0 (m, 4 H), 5.15 (unresolved m, 1 H), 5.9–6.2 (m, 2 H), 7.2–7.5 (m, 10 H); *m/e* 251.1323 (M^+).

2,5-Diphenylpentanoamide (9).—Compound **6** (0.83 g, 0.0033 mol) in 50 ml of ethanol was hydrogenated in the presence of 0.1 g of 10% Pd/C in a Parr shaker apparatus at room temperature and an initial pressure of 47 psig. When 1 equiv of H_2 was absorbed, the catalyst was removed by filtration. The water-white filtrate was evaporated under reduced pressure to afford a colorless oil which crystallized on standing and was recrystallized from 50% ethanol to afford 0.43 g (51%) of platelets: mp 90–92°; ir ($CHCl_3$) 1670 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 1.70 center (unresolved m, 4 H), 2.6 center (unresolved m, 2 H), 3.40 (t, 1 H), 7.2–7.5 (m, 10 H).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.75; H, 7.51; N, 5.54. Found: C, 80.60; H, 7.75; N, 5.21.

Methyl (*E*)-2,5-Diphenyl-2-pentenoate (10).—Sodium amide was prepared from 100 ml of liquid NH_3 and 1.15 g (0.05 g-atom) of Na according to a procedure of Bestmann,[12] and a Wittig procedure of Bestmann and Hartung[13] was employed. Triphenyl-3-phenylpropylphosphonium bromide[12] (18.0 g, 0.04 mol) was added to the suspension of sodium amide in liquid NH_3 in one portion. The NH_3 was permitted to evaporate under N_2 and 200 ml of Na-dried benzene was added. The reaction mixture assumed a deep red-brown color and it was refluxed for 8 hr. The mixture was cooled and 6.56 g (0.04 mol) of methyl phenylglyoxylate (Aldrich Chemical Co.) in 30 ml of Na-dried benzene was added dropwise with stirring. The resulting tan reaction mixture was stirred for 1 hr, then it was filtered, and volatiles were removed from the filtrate under reduced pressure (steam bath) to leave a brown oil. This was distilled, collecting the fraction with bp 140–160° (1.3 mm), which was redistilled, bp 145–152° (0.7 mm), to yield 2.60 g (25%) of a straw-colored liquid: ir ($CHCl_3$) 1690 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 2.3–2.9 (m, 4 H), 3.75 (s, 3 H), 7.0–7.4 (unresolved m, 11 H).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77. Found: C, 81.56; H, 6.87.

Ozonolysis of (*Z*)-2,5-Diphenyl-2-pentenoamide (6).—Compound **6** (0.32 g, 0.00127 mol) in 200 ml of Na_2SO_4-dried methanol, maintained at −60°, was treated with excess ozone. Methanol was removed from the reaction mixture under reduced pressure from a water bath (45–50°). The residual transparent oil was treated with 35 ml of 90% formic acid and 17 ml of 30% hydrogen peroxide, and this mixture was gently warmed on a steam bath until spontaneous reflux began. When the mixture ceased to boil spontaneously, it was refluxed vigorously for 1 hr and cooled, and excess $NaHCO_3$ was added. The resulting mixture was extracted repeatedly with ether (extract A); then the aqueous phase was acidified with sulfuric acid and excess KI was added. Na_2SO_3 was then added until the iodine color was discharged, and the resulting mixture was extracted several times with ether. Ether was removed from the pooled extracts to afford an oil which partly solidified on standing and was recrystallized from water to afford a low-melting (30–34°) solid whose ir spectrum ($CHCl_3$) was superimposable upon a similar spectrum of an authentic sample (mp 40–42° from water) of hydrocinnamic acid. Tlc of the ozonolysis product in several solvent systems gave R_f values identical with those of the authentic sample of hydrocinnamic acid. Work-up of extract A provided a small amount of hydrocinnamaldehyde (identified by comparison of its ir spectrum with that of an authentic sample) and, in addition to polymeric material, a very small amount of off-white crystals, mp 88–91°, was isolated (lit.[7] mp for phenylglyoxylamide 91°).

Registry No.—**3**, 13019-40-4; **6**, 40600-00-8; **9**, 40600-01-9; **10**, 40600-02-0; benzene, 71-43-2; boron trifluoride etherate, 109-63-7; triphenyl-3-phenylpropylphosphonium bromide, 7484-37-9; methyl phenylglyoxylate, 15206-55-0.

(12) H.-J. Bestmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 583 (1965).
(13) H.-J. Bestmann and H. Hartung, *Chem. Ber.*, **99**, 1198 (1966).

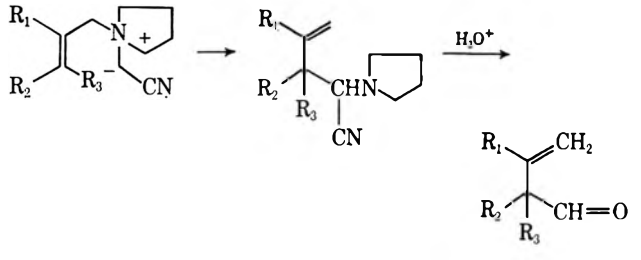
See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

The Synthesis of β,γ-Unsaturated Aldehydes by the [2,3]-Sigmatropic Rearrangement of Allylic Ammonium Ylides

Summary: The [2,3]-sigmatropic rearrangement of ylides derived from allylic *N*-cyanomethylpyrrolidinium salts followed by hydrolysis of the products affords β,γ-unsaturated aldehydes in >90% overall yields.

Sir: The utility of the [2,3]-sigmatropic rearrangements of allylic sulfonium ylides for the preparation of β,γ-unsaturated carbonyl compounds has been demonstrated in several elegant procedures.[1] We have found that analogous sequences based on tetraalkylammonium ylides[2] offer significant advantages in terms of flexibility and high overall yields. A generalized procedure is indicated in Scheme I. The ylide precursors are

Scheme I

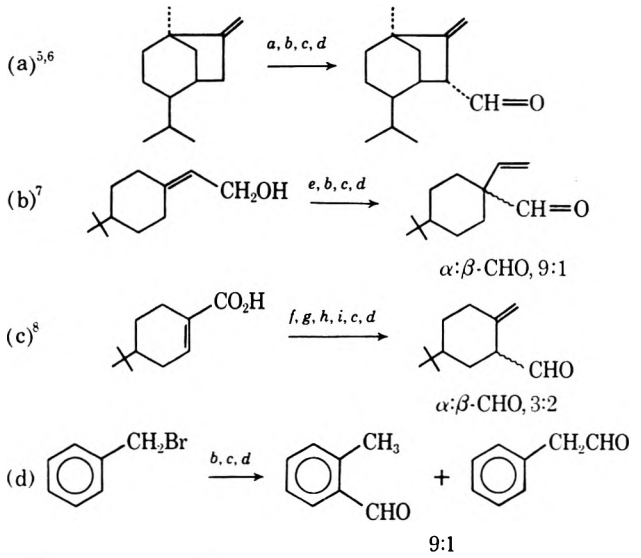


readily constructed either by alkylation of *N*-cyanomethylpyrrolidine (NCMP)[3] with allylic halides or from *N*-allylpyrrolidines and chloroacetonitrile. The alkylations are conveniently carried out in dimethyl sulfoxide (DMSO) and the ammonium salts are not normally isolated, but either tetrahydrofuran (THF) or liquid ammonia is added followed by potassium *tert*-butoxide. Ylide formation and concomitant rearrangement proceed slowly at −78° but rapidly at −33° in the latter solvent; somewhat higher temperatures are required in THF because of solubility problems.

The choice of a pyrrolidine derivative is optional, but was made so as to increase the nucleophilicity of the amine and to facilitate the removal of cyanide ion from the product.[4] The function of the nitrile group is to localize carbanion formation and, subsequently, to act as a leaving group to generate a carbonyl function in the final product. The properties of the nitrile group in such a role are probably difficult to duplicate.

The general utility of the procedure is indicated (Scheme II) by the array of substrates whose structural

Scheme II



[a−i] Reagents: *a*, *N*-bromosuccinimide; *b*, NCMP–DMSO; *c*, KO-*t*-Bu–THF; *d*, aqueous oxalic acid–THF; *e*, PBr_3, pyridine, and ether; *f*, oxalyl chloride and pyridine; *g*, pyrrolidine; *h*, AlH_3; *i*, $ClCH_2CN$.

and functional diversity illustrate the flexibility of this approach. Isolated yields of aldehydes were consistently between 90 and 95% from allylic halides. Formation of α,β-unsaturated aldehydes (where this was possible) accounted for ~15% of the products and occurred, apparently, through equilibration of the intermediate imminium salts with their conjugate dieneamines, since the β,γ-unsaturated aldehydes themselves were stable to the hydrolytic conditions. Stereoselectivity was total in the bicyclooctene example a,[5,6] but diminished as the alternative stereochemical pathways became more equivocal. Undoubtedly this trend could be opposed by the introduction of bulkier substituents, especially onto the cyanomethyl moiety. Marginal improvements in stereoselectivity were obtained in example b,[7] at lower temperatures (85–90%). Example c,[8] which indicated the preferential

(1) (a) J. E. Baldwin and J. A. Walker, *Chem. Commun.*, 354 (1972); (b) E. Hunt and B. Lythgoe, *ibid.*, 757 (1972); (c) E. J. Corey and S. W. Walinsky, *J. Amer. Chem. Soc.*, **94**, 8932 (1972); (d) G. Andrews and D. A. Evans, *Tetrahedron Lett.*, 5121 (1972).

(2) (a) G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *J. Amer. Chem. Soc.*, **93**, 2342 (1971); (b) R. W. Jemison and W. D. Ollis, *Chem. Commun.*, 294 (1969).

(3) A. Lespagnol, E. Cuingnet, and M. Debaert, *Bull. Soc. Chim. Fr.*, 383 (1960).

(4) P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, **92**, 4261 (1970); *cf.* ref 13.

(5) Correct analytical figures were obtained for all new compounds; spectra were consistent with structural assignments. Isomer ratios were determined by glpc and by nmr spectroscopy.

(6) The preparation of the methylene bicyclooctane will be reported elsewhere. Bromination gave a 3.5:1 mixture of secondary and primary bromides which, however, gave only the primary ammonium salt. The preparation of the aldehyde, semicarbazone mp 177–179°, serves as a useful model for the elaboration of prehelminthosporal and similar compounds; *cf.* F. Dorn and D. Arigoni, *Chem. Commun.*, 1342 (1972), and P. de Mayo, R. E. Williams, and Y. E. Spencer, *Can. J. Chem.*, **43**, 1357 (1965).

(7) The alcohol was prepared by AlH_3 reduction of ethyl 4-*tert*-butylcyclohexylideneacetate [H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966)]. Dr. D. A. Evans (*cf.* ref 1d) generously provided spectra and samples for direct comparison with the vinylcarbinols derived from our aldehyde products.

(8) 4-*tert*-Butyl-1-cyclohexenecarboxylic acid [L. Munday, *J. Chem. Soc.*, 1413 (1964)] was prepared by a modification of the method of F. Camps, J. Coll, and J. Pascual, *J. Org. Chem.*, **32**, 2563 (1967). The mixture of aldehydes was characterized by base-catalyzed isomerization to the α,β-unsaturated isomer, semicarbazone mp 204–207°.

formation of axial product, suggested a stereoelectronic requirement for the rearrangement.[9,10] Only in example d was a product arising from a [1,2] shift detected.[11]

We envisage extension of the above methodology by utilization of the metalated *N*-cyanoalkyl function as an acyl carbanion equivalent[12] and work is in progress; *e.g.*, example d simply carried out in DMSO-d_6 afforded α-[^{2}H]tolualdehyde [deuterium enrichment >95%; ν_{max} 2050, 1675 cm^{-1} (-C^{2}H=O)].[13]

Preparation of Pyrrolidinium Salts.—(a) Allylic bromide (10^{-3} mol) was added dropwise to a stirred solution of *N*-cyanomethylpyrrolidine (1.07×10^{-3} mol) in DMSO (3 ml) at ambient temperature under an atmosphere of nitrogen. Completion of salt formation (from 1.0 hr at 20° to 18 hr at 45°) was monitored by nmr spectroscopy. (b) Allylic amine (10^{-3} mol) in DMSO (3 ml) was treated with chloracetonitrile (1.01×10^{-3} mol) under a nitrogen atmosphere and the mixture stirred at 45° for 18 hr.

Ylide Formation and Rearrangement.—A solution of the salt (10^{-3} mol) in DMSO (3 ml) was diluted with dry THF (15 ml) cooled to −10° and treated with solid KO-*t*-Bu (1.25×10^{-3} mol). The reaction mixture was stirred for 3 hr, diluted with hexane (40 ml), washed with brine and water, and dried (Na_2SO_4). Removal of solvent gave rearranged amine.

Hydrolysis of α-Pyrrolidinonitriles.—The nitrile (10^{-3} mol) in THF (8 ml) was treated with a warm solution of oxalic acid (30% w:v, 8 ml); the two-phase mixture was heated under reflux for 0.25 hr, cooled, and extracted with hexane (40 ml). The hexane solution was washed with brine and water, dried (Na_2SO_4), and reduced to dryness to afford a mixture of aldehydes.

Acknowledgment.—J. V. T. gratefully acknowledges the award of an Australian Commonwealth Postgraduate Scholarship.

(9) The Claisen rearrangement of 4-*tert*-butyl-1-cyclohexenylmethyl vinyl ether affords only the axial product: Professor R. E. Ireland, personal communication. Presumably, the transition state for the Claisen rearrangement, with its higher activation energy, is structured more like product; *cf.* R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **27**, 1118 (1962).

(10) S. Mageswaran, W. D. Ollis, I. O. Sutherland, and Y. Thebtaranonth, *Chem. Commun.*, 1494 (1971).

(11) S. H. Pine, *Org. React.*, **18**, 403 (1970).

(12) (a) D. Seebach, *Angew. Chem, Int. Ed. Engl.*, **8**, 639 (1969); (b) G. Stork and L. Maldonado, *J. Amer. Chem. Soc.*, **93**, 5286 (1971).

(13) D. J. Bennett, G. W. Kirby, and V. A. Moss, *Chem. Commun.*, 218 (1967).

DEPARTMENT OF ORGANIC CHEMISTRY
UNIVERSITY OF ADELAIDE
ADELAIDE, SOUTH AUSTRALIA 5000
AUSTRALIA

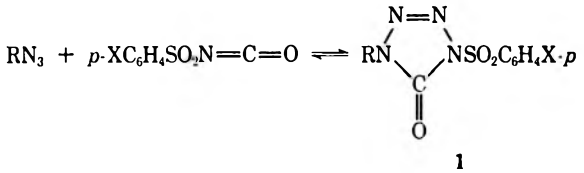
LEWIS N. MANDER*
JOHN V. TURNER

RECEIVED JUNE 8, 1973

1,3-Dipolar Cycloadditions of Alkyl Azides with Sulfonyl Isothiocyanates. A Synthetic Method for 1,2,3,4-Thiatriazolines

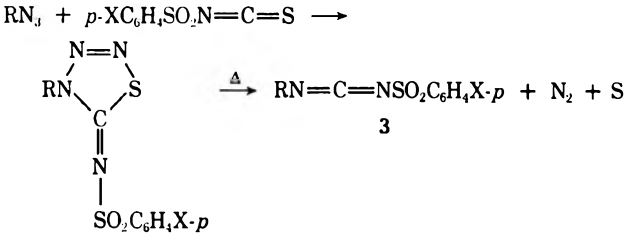
Summary: 4-Alkyl-5-sulfonylimino-Δ^2-1,2,3,4-thiatriazolines (2) are readily prepared from alkyl azides and sulfonyl isothiocyanates. Upon thermolysis, they give rise to a novel type of external stabilized 1,3 dipole (6) which undergoes cycloaddition with enamines and ynamines.

Sir: We recently reported[1] that alkyl azides and aryl azides reacted with sulfonyl isocyanates to give 1-alkyl- (or aryl-) 4-sulfonyl-Δ^2-tetrazolin-5-ones (**1**).



1

These compounds underwent cycloreversion on thermolysis. Extension of this study to isothiocyanates has led to the observation of a different behavior which we report briefly at this time. *n*-Butyl azide or benzyl azide reacted readily with equimolar amounts of sulfonyl isothiocyanates[2] at room temperature to yield 1:1 adducts in 50–75% yield which were characterized as 4-alkyl-5-sulfonylimino-1,2,3,4-thiatriazolines (**2**).

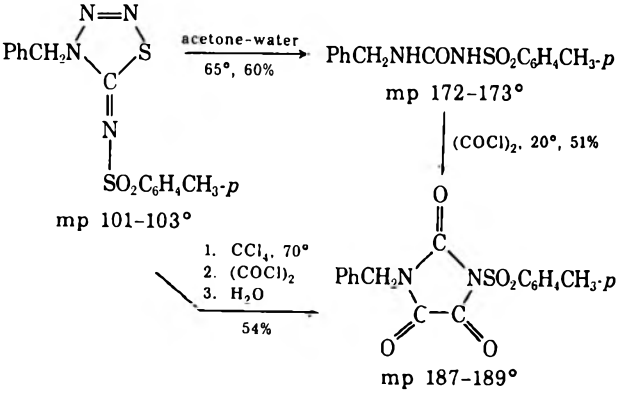


2

R = *n*-Bu, $PhCH_2$; X = H, CH_3, Cl

The structures **2** are consistent with analysis, nmr, ir (C=N at 1510–1535 cm^{-1}),[3] mass spectra (M·$^+$, M·$^+$ − N_2, M·$^+$ − N_2 − S), and degradation experiments. Thus, thermal decomposition of **2** at a moderate temperature (45–80°) furnished the carbodiimides **3** which exhibited a characteristic ir absorption band[4] at 2160 cm^{-1}. The latter were also trapped by typical reagents[5] as illustrated in Scheme I. That

SCHEME I



the isolated products **2** could not be formulated as the C=N adducts (*i.e.*, **5**) is clear from this chemical evidence. Indeed, the isomeric compounds **5**, prepared in 50–80% yield by sulfonation of 1-benzyl- (or butyl-)

(1) J.-M. Vandensavel, G. Smets, and G. L'abbé, *J. Org. Chem.*, **38**, 675 (1973).

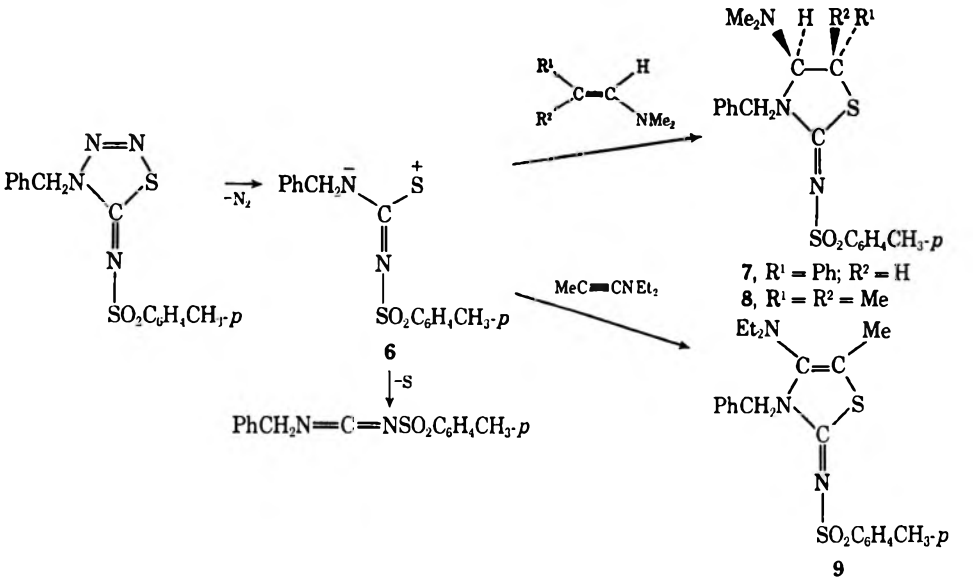
(2) K. Hartke, *Arch. Pharm. (Weinheim)*, **299**, 174 (1966).

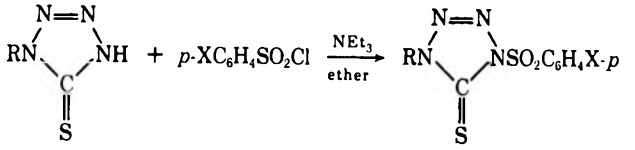
(3) J. Goerdeler and U. Krone, *Chem. Ber.*, **102**, 2273 (1969).

(4) R. Neidlein and E. Heukelbach, *Arch. Pharm. (Weinheim)*, **299**, 944 (1966); H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Tetrahedron*, **22**, 1565 (1966).

(5) H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953); F. Kurzer and K. D. Zadeh, *ibid.*, **67**, 107 (1967).

SCHEME II





4 5

R = *n*-Bu or $PhCH_2$; X = H, CH_3 or Cl

Δ^2-tetrazoline-5-thiones (**4**),[6] showed different physical and spectroscopic characteristics and a much higher thermal stability.

It is reasonable to assume that an external stabilized 1,3 dipole (*e.g.*, **6**) is the intermediate in the thermal conversion of **2** to **3**. This has been confirmed by carrying out the decomposition of 4-benzyl-5-tosylimino-Δ^2-1,2,3,4-thiatriazoline in the presence of electron-rich dipolarophiles.[7] Thus, thiazolidine **7** (mp 161–162°) was obtained in 73% yield when **2** (R = $PhCH_2$, X = CH_3) was decomposed in the presence of an equimolar amount of *β-trans-N,N*-dimethylaminostyrene in CCl_4 at 60°. The structure of **7** was deduced from microanalysis, ir (1530 cm^{-1}),[3] nmr [ring protons at τ 5.55 and 5.68 (J = 2.5 Hz), two nonequivalent benzyl protons at τ 4.72 and 5.81 (J = 14.5 Hz)], and mass spectra ($M\cdot^+$ at *m/e* 465, $M\cdot^+ - HNMe_2$ at *m/e* 420, and $\overline{PhCHC(NMe_2)HS}\cdot^+$ at *m/e* 179). Similarly, when **2** (R = $PhCH_2$, X = CH_3) was heated with an equimolar amount of *N,N*-dimethylaminoisobutene in benzene for 3 hr, a 1:1 adduct (mp 132–133°) was obtained in 55% yield, corresponding to structure **8** on the basis of ir (1530 cm^{-1}), nmr [ring proton at τ 6.12, ring methyls at τ 8.66 and 8.77, two nonequivalent benzyl protons at τ 4.55 and 6.08 (J = 14.5 Hz)], and mass spectra ($M\cdot^+$ at *m/e* 4.17, $M\cdot^+ - NMe_2$, $\overline{Me_2CC(NMe_2)HS}\cdot^+$ at *m/e* 131). The stereochemistry of **7** was deduced from the C-4–C-5 hydrogen coupling constant (J = 2.5 Hz), whereas the indicated regiochemistry rests upon the observed chemical shift values of the *C*-N and *C*-S absorptions in the ^{13}C nmr spectra of **7** and **8**. (See Scheme II.)

(6) E. Lieber and J. Ramachandran, *Can. J. Chem.*, **37**, 101 (1959).

(7) Preliminary experiments indicate that electron-poor olefins are not suitable dipolarophiles for **6**.

Ynamines also proved to be suitable dipolarophiles for **6**. For instance, when **2** (R = $PhCH_2$, X = CH_3) was heated with 1 equiv of *N,N*-diethylaminopropyne in benzene for 4 hr, thiazoline **9** (mp, 118–119°) was obtained (50–60% by nmr, 21% isolated). The adduct exhibited ir (C=N at 1500 cm^{-1}), nmr [benzyl protons at τ 4.90 (s), ring methyl at τ 7.85], and mass spectra ($M\cdot^+$ at 429, $M\cdot^+ - PhCH_2$ at *m/e* 338, $M\cdot^+ -$ Tos at *m/e* 274) consistent with the structure.

Acknowledgment. The authors are indebted to the IWONL for postdoctoral (E. V. L.) and doctoral (J. M. V.) fellowships and to the Centrum voor Hoogpolymeren (IWONL-Agfa-Gevaert) for financial support.

DEPARTMENT OF CHEMISTRY
LABORATORY OF MACROMOLECULAR AND ORGANIC CHEMISTRY
UNIVERSITY OF LOUVAIN
B-3030 HEVERLEE, BELGIUM

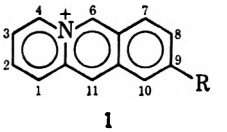
EMIEL VAN LOOCK
JEAN-MARIE VANDENSAVEL
GERRIT L'ABBÉ*
GEORGE SMETS

RECEIVED APRIL 9, 1973

Correlation between Proton Magnetic Resonance Chemical Shift and Rate of Polar Cycloaddition

Summary: A significant correlation has been found between the chemical shifts of the proton at position 6 of 9-substituted acridizinium perchlorates and the log of the ratio of rate constants (k/k^0) for the cycloaddition of 9-substituted acridizinium salts with styrene; the chemical shift data likewise give a significant correlation with Hammett substituent constants.

Sir: It was shown earlier that the rate of cycloaddition of the 9-substituted acridizinium cation (**1**) with



1

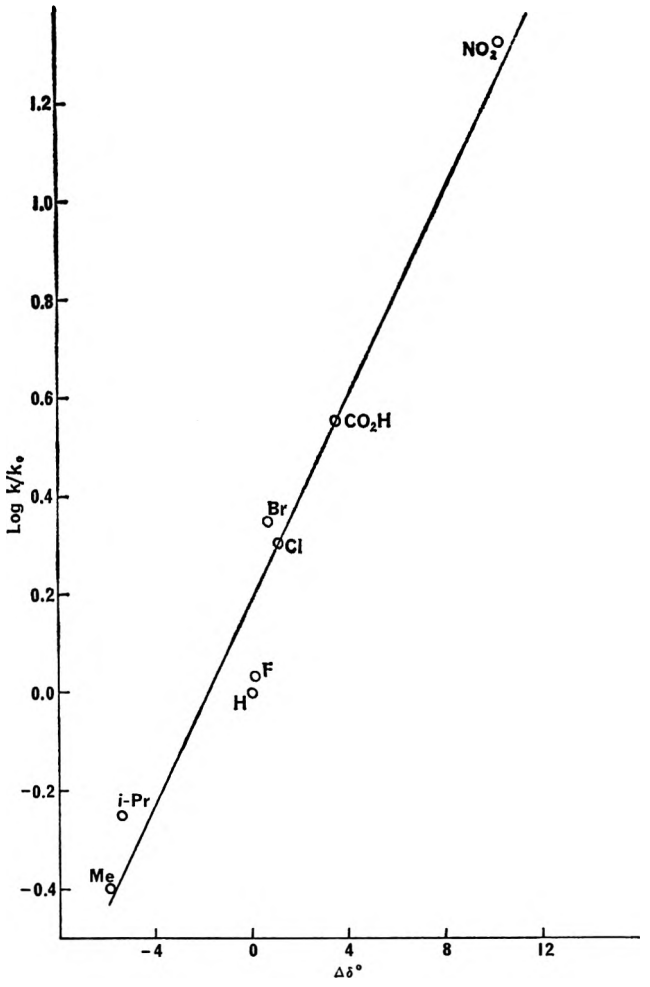


Figure 1.—Least-squares plot of log k/k^0 *vs.* $\Delta\delta^0$.

styrene[1] or acrylonitrile[2] was related to the electron deficiency at position 6. Like the pmr spectrum of other aromatic quaternary cations[3] that of the acridizinium ion shows the protons flanking the quaternary nitrogen to be strongly deshielded. Of these two strongly deshielded protons, that at position 6 gives resonance (isolated singlet) at the lower field, the chemical shift (10.6–11.0 ppm) varying with the nature of the 9 substituent.

Proton magnetic resonance spectra of the acridizinium perchlorates (1) were obtained at 39 ± 1° using a Varian A-60 spectrometer operating at 60 MHz. Chemical shifts of the proton at position 6 were measured from an internal benzene (Spectrograde) standard. Shifts were obtained at four concentrations in the range of 2.0–3.5 mol % in freshly distilled dimethyl sulfoxide. Each sample was scanned a minimum of five times at a rate of 1 Hz/sec. The standard deviation in δ varied from 0.08 to 0.26 Hz; the estimated average uncertainty is ±0.2 Hz. Dilution plots were made and extrapolated to infinite dilution to give δ^0. The data are recorded in Table I.

A least-squares plot of log k/k^0 for the addition of

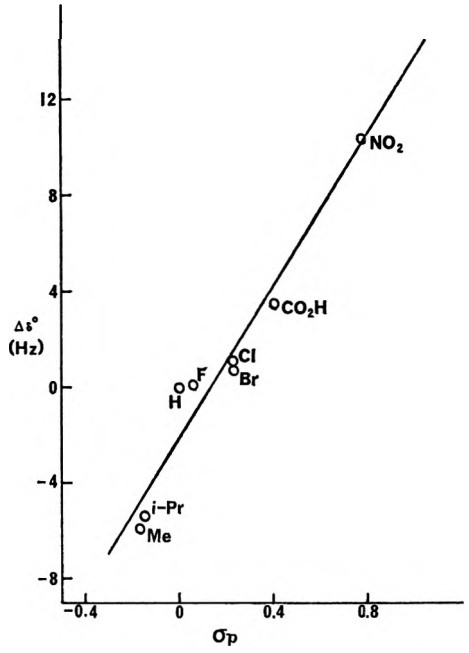


Figure 2.—Least-squares plot of $\Delta\delta^0$ *vs.* Hammett σ_p.

TABLE I
COMPARISON OF CHEMICAL SHIFT DATA WITH σ_p AND WITH THE RATE OF ADDITION OF STYRENE TO 9-SUBSTITUTED ACRIDIZINIUM PERCHLORATES

R	δ^0 (Hz)	$\Delta\delta^0$ (Hz)	σ_p	$k \times 10^3$ min^{-1} [a]
CH_3	187.5	−5.9	−0.170[b]	2.0 ± 0.1
i-Pr	188.0	−5.4	−0.151[b]	2.8 ± 0.1
H	193.4	0.0	0.000	5.0 ± 0.2
F	193.5	0.1	0.062[b]	5.4 ± 0.2
Cl	194.5	1.1	0.227[b]	10.1 ± 0.5
Br	194.1	0.7	0.232[b]	11.2 ± 0.8
CO_2H	196.9	3.5	0.406[c]	18.1 ± 0.7
NO_2	203.7	10.3	0.778[b]	105 ± 5

[a] Reference 1. [b] D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958). [c] H. Van Bekkum, P. E. Verkade, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **78**, 815 (1959).

styrene to 9-substituted acridizinium derivatives *vs.* $\Delta\delta^0$ (change in chemical shift from R = H) is shown in Figure 1. The correlation factor of 0.98 is quite satisfactory.

As follows from the earlier observation that log k/k^0 gave a significant linear free-energy plot with the Hammett σ_p, a plot (Figure 2) of $\Delta\sigma^0$ *vs.* σ_p gave a significant correlation of 0.97 (for all values or for primary values only).[4] This correlation of proton chemical shifts with Hammett substituent constants can be interpreted as arising from the polarization of the C–H bond at position 6 which must in turn arise from the density of π electrons at that position.[5-7] The slope[8] of the line (Figure 2) is 15.8 ± 1.3 Hz/sigma.

While there has been an increasing number of attempts to relate the pmr of aromatic ring hydrogens to

(1) I. J. Westerman and C. K. Bradsher, *J. Org. Chem.*, **36**, 969 (1971).
(2) C. K. Bradsher, C. R. Miles, N. A. Porter, and I. J. Westerman, *Tetrahedron Lett.*, 4969 (1972).
(3) *E.g.*, (a) H. Diekmann, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964); (b) I. C. Smith and W. G. Schneider, *Can. J. Chem.*, **39**, 1158 (1961); (c) W. W. Paudler and T. J. Kress, *J. Heterocycl. Chem.*, **5**, 561 (1968).
(4) An equally "significant" correlation (0.98) may be obtained by the use of σ^+.
(5) T. K. Wu and B. P. Dailey, *J. Chem. Phys.*, **41**, 2796 (1964).
(6) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).
(7) M. T. Tribble and J. G. Traynham, "Advances in Free Energy Relationships," N. B. Chapman and J. Shorter, Ed., Plenum Press, London, 1972, Chapter 4.
(8) The fairly common use of the symbol ρ to designate this slope may confuse the casual reader since it is not the dimensionless ρ of the Hammett relationship.

electron density at the carbon to which they are attached,[7,9] no one previously appears to have related the rate of cycloaddition of such systems to the pmr of a proton at a carbon atom which would be involved in the creation of a new σ bond. This is surprising in that Hobgood and Goldstein[10] nearly a decade ago demonstrated an "approximately linear" relationship between the chemical shift of the proton at the 4-trans position of substituted butadienes and the log of the rate constant for cycloaddition with maleic anhydride.

We feel that this correlation of chemical shift and cycloaddition rates will prove to be particularly important in the study of steric *vs.* electronic effects in polar cycloaddition.

(9) *E.g.*, T. Schaefer and W. G. Schneider, *Can. J. Chem.*, **41**, 966 (1963); P. J. Frank and H. S. Gutowsky, *Arch. Sci.*, **11**, 215 (1958); A. Veillard, *J. Chim. Phys.*, **59**, 1056 (1962); A. Veillard and B. Pullman, *C. R. Acad. Sci.*, **253**, 2418 (1961); K. T. Potts and J. Bhattacharyya, *J. Org. Chem.*, **37**, 4410 (1972).

(10) R. T. Hobgood, Jr., and J. H. Goldstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

GROSS CHEMICAL LABORATORY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA 27706

T. G. WALLIS
N. A. PORTER
C. K. BRADSHER*

RECEIVED MAY 30, 1973

Two-Step Synthesis of a Triketone of the *endo*-Tetracyclo[5.5.1.0^{2,6}.0^{10,13}]tridecane[1] Series. X-Ray Crystallographic Proof of Its Structure and Stereochemistry

Summary: A compound (**6**), obtained by reaction of glyoxal with dimethyl 3-ketoglutarate in aqueous solution at room temperature and subsequent treatment of an intermediate β-keto ester (**5**) with acid, is shown by X-ray crystallography to be *endo*-tetracyclo[5.5.1.0^{2,6}.0^{10,13}]tridecane-4,8,12-trione.

Sir: Reaction of glyoxal (**1**) with dimethyl 3-ketoglutarate (**2**) in aqueous solution at room temperature and pH 5.0 has been found[2] to give the ester **3**,[3] which yields *cis*-bicyclo[3.3.0]octane-3,7-dione (**4**)[3,4] on treatment with acid. Compound **4** was accompanied[2] by another ketone $C_{13}H_{14}O_3$ (mp 148–151°)[5] having spectroscopic properties very similar to those of **4**; it is undoubtedly derived from a β-keto ester analogous to **3** which, however, was not isolated. We now wish to report the isolation of this intermediate, and the elucidation of structure and stereochemistry of the C_{13} compound by X-ray crystallography.

Formation of a compound $C_{13}H_{14}O_3$ through reaction of **1** with **2**, followed by treatment with acid, could be rationalized by assuming that **3** forms initially and subsequently reacts with one molecule each of **1** and **2** in an aldol reaction analogous to the one taking place in its own formation; for the resulting β-keto ester, structure **5** appears logical.[6] Assuming the usual cis stereochemistry at the junction of two cyclopentane rings,[7] formula **5** represents two stereoisomers with ring D in syn or anti relationship to rings A and B. Treatment of **5** with acid would then give **6**, $C_{13}H_{14}O_3$, which could again be the syn or anti isomer.

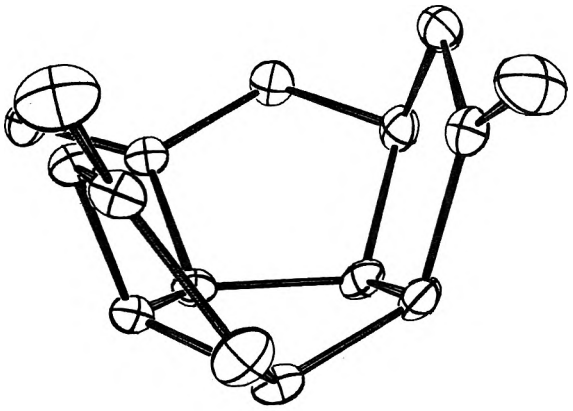


Figure 1.

An ester **5**, mp 173–176°, having the expected composition[8] and spectroscopic properties, was obtained in 10% yield when **1** and **2** were allowed to react in the required molecular ratio 2:3 for 1 week in aqueous solution at room temperature and pH 3 instead of the pH 5 used in the earlier work;[2] trituration of the resulting precipitate with methanol and recrystallization from the same solvent gave pure **5**. Treatment of **5** with hot 25% HCl[2] yielded **6**.

An X-ray crystallographic investigation has now shown that structure **6** is indeed correct and that the compound has the all-cis stereochemistry (**6a**). The crystals were monoclinic, $P2_1/n$, a = 6.299 (1) Å, b = 15.511 (1) Å, c = 10.943 (1) Å, β = 105.78 (1)°, Z = 4. A total of 1933 independent X-ray intensities (328, unobserved) were measured by means of an Enraf-Nonius CAD-4 diffractometer. The structure was solved by direct methods using our own semiautomatic program. With anisotropic thermal parameters for the C and O atoms and isotropic parameters for the hydrogen atoms, the structure has been refined by full-matrix least-squares to an R factor of 0.036. Estimated standard deviations of C–C and C–O bond lengths are typically 0.003 Å. An ORTEP drawing[9] of **6** (Figure 1) shows its conformation and demonstrates that the molecule is chiral, lacking the mirror plane which the conventional structural formula would indicate. The observed conformation is very reasonable if intramolecular interactions are taken into consideration. Since the crystals are centrosymmetrical,

(1) Dr. K. L. Loening, Director of Nomenclature, Chemical Abstracts Service, has advised us that compound **6** can be correctly designated either as octahydro-1*H*-dicyclopenta[*a*,*cd*]pentalene-1,4,6(2*H*,4a*H*)-trione or as tetracyclo[5.5.1.0^{2,6}.0^{10,13}]tridecane-4,8,12-trione. We wish to thank Dr. Loening for his helpful interest.

(2) J. M. Edwards and U. Weiss, *Tetrahedron Lett.*, 4885 (1968).

(3) G. Vossen, Dissertation, Bonn, 1910; P. Yates, E. S. Hand, and G. R. French, *J. Amer. Chem. Soc.*, **82**, 6347 (1960).

(4) H. W. Wanzlick, *Chem. Ber.*, **86**, 269 (1953).

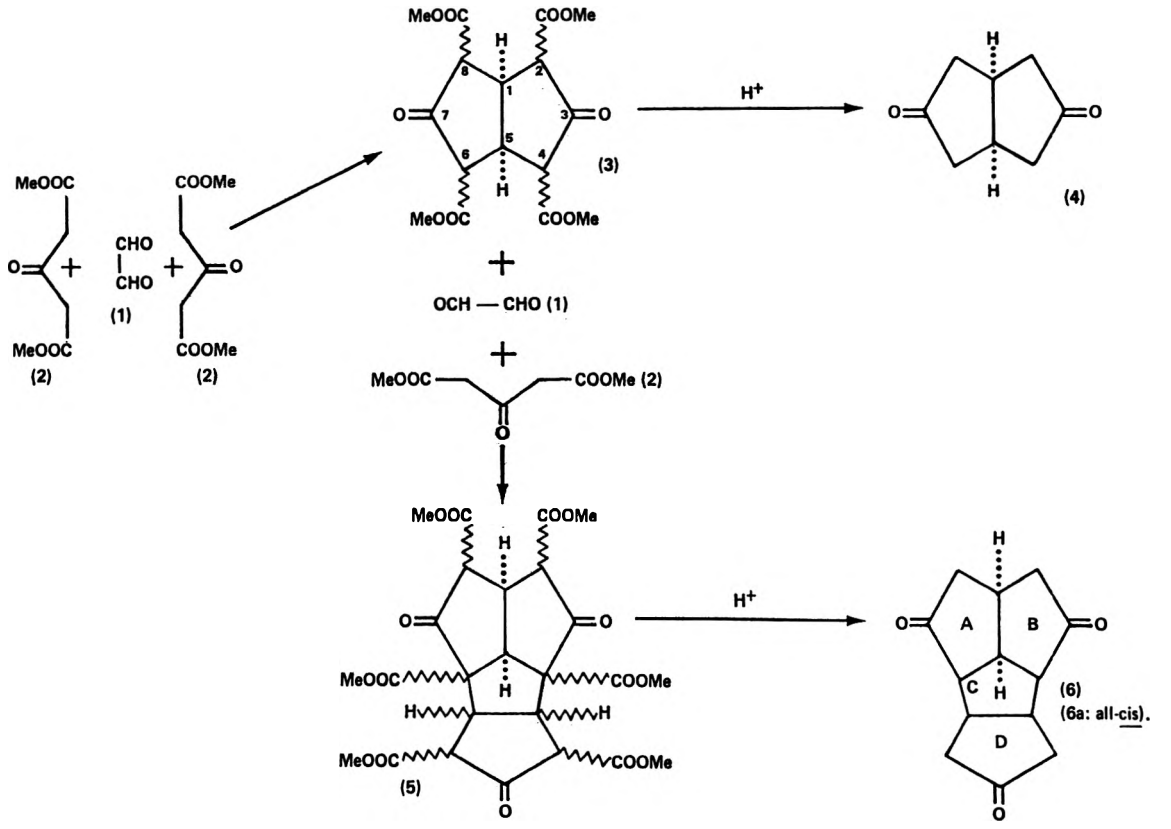
(5) It has been observed recently that recrystallization from methanol raises the melting point to 160°. The sample used for X-ray crystallography has this melting point.

(6) Reaction of **3** with **1** and **2** could also take place at positions 2 and 4, or 2 and 6. However, the resulting β-keto esters isomeric with **5** could undergo decarboxylation to a C_{13} compound only with violation of Bredt's rule and are thus quite unlikely. This point was brought to our attention by a referee on our earlier paper.[2]

(7) *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 273–274.

(8) Satisfactory analytical and mass spectrometric data were obtained for **5**.

(9) C. K. Johnson, ORTEP Report ORNL-3794 (2nd revision), 1970, Oak Ridge National Laboratory, Oak Ridge, Tenn.



both enantiomers are present. The X-ray crystallographic results will be published in detail in *Acta Crystallographica*.

The reaction which yields **5** and **6** provides a surprisingly simple entry into the *endo*-tetracyclo-[5.5.1.$0^{2,6}$.$0^{11,13}$]tridecane series; the low yields (probably capable of being much improved) are hardly surprising in view of the numerous possibilities for interaction of such reactive bifunctional compounds as **1** and **2** and are offset by ready availability of the starting materials and ease of manipulation. After completion of our work, the first representative of this ring system, a trienic hydrocarbon, was described by Srinivasan,[10] who prepared it from cycloheptatriene by a three-step sequence of photochemical and pyrolytic reactions.

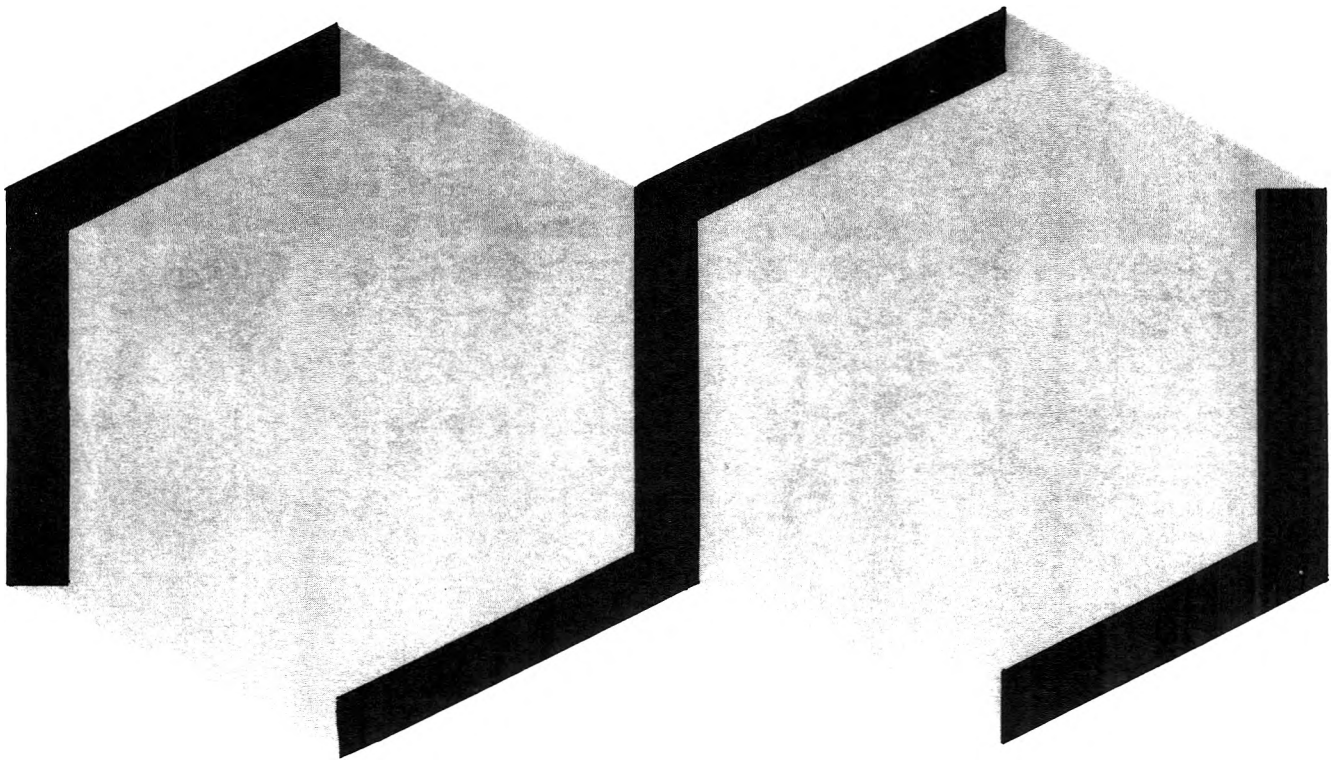
(10) R. Srinivasan, *J. Amer. Chem. Soc.* **94**, 8117 (1972).

LABORATORY OF CHEMICAL PHYSICS
NATIONAL INSTITUTE OF ARTHRITIS, METABOLIC, AND DIGESTIVE DISEASES
BETHESDA, MARYLAND 20014
J. M. EDWARDS
I. H. QURESHI
U. WEISS*

LABORATORY OF CHEMISTRY
NATIONAL HEART AND LUNG INSTITUTE
BETHESDA, MARYLAND 20014
T. AKIYAMA
J. V. SILVERTON

RECEIVED MAY 18, 1973

The leading American journal devoted to general organic chemistry:



The Journal of Organic Chemistry

The career wise way to keep up with current thinking in the field. You get the *total picture* presented through forty some papers per biweekly issue. Areas of emphasis include:

- Organic reactions
- Natural products
- Studies of mechanism
- Theoretical organic chemistry
- Various aspects of spectroscopy related to organic chemistry

You get all of this, in the 1100 articles and NOTES (brief, concise accounts of studies of smaller scope) and over 4000 pages a year from your big informative issues of THE JOURNAL.

You owe it to your career to find out for yourself why The Journal of Organic Chemistry is the leader in its field.

Send your order today.

. . . *another ACS service*

The Journal of Organic Chemistry
American Chemical Society
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 Personal-Use One-Year Rate	☐ $20.00	☐ $25.00	☐ $25.00	☐ $26.00
Nonmember	☐ $60.00	☐ $65.00	☐ $65.00	☐ $66.00

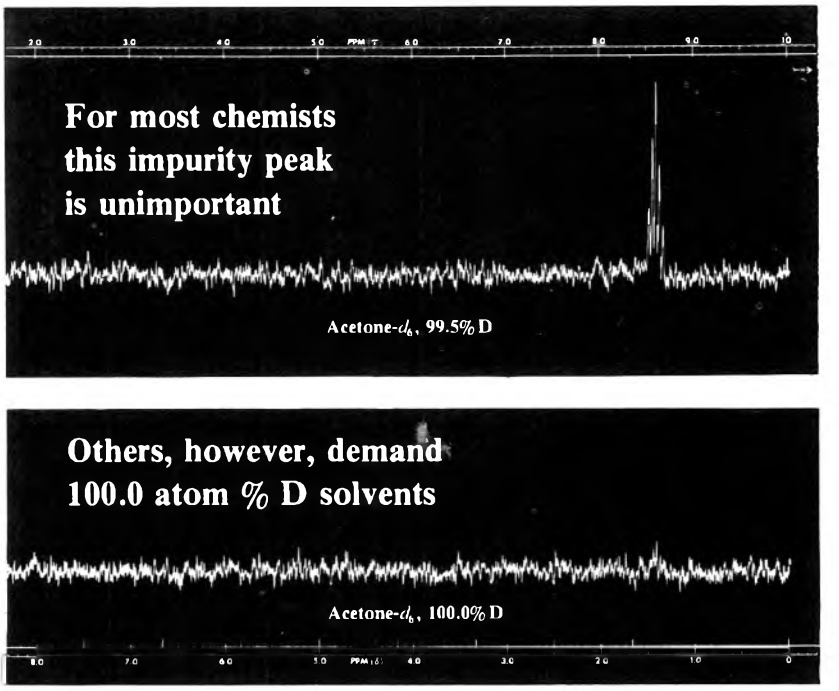
Bill me ☐ Bill company ☐ Payment enclosed ☐

Name _____

Street _____ Home ☐ Business ☐

City _____ State _____ Zip _____

G-73



All chemists want the lowest prices on Deuterated Solvents. Aldrich satisfies everyone.

Purity specifications of deuterated solvents for nmr spectroscopy are usually given in percentage of deuterium contained in the solvents, but one rarely finds information about the chemical purity of deuterated solvents. We pay particular attention to both aspects of quality control. Our deuterium purity is always given as atom per cent deuterium as determined by nmr dilution experiments. Thus, our 99.5% benzene-d_6 contains less than 5 protons per thousand deuterons and no other detectable impurity by gas chromatography.

We also offer 100.0 atom % deuterated solvents. These solvents eliminate the problem of partially masked nmr spectra due to solvent absorptions. They are also the solvents of choice for Fourier Transform nmr which allows scanning of very dilute solutions. In addition to the strict requirements of 100.0 atom % D, these materials undergo the same high quality controls expected of our conventional deuterated solvents and nmr standards. We routinely examine the entire nmr spectrum for proton-containing impurities and rigorously dry hygroscopic solvents. We also carefully monitor the purity of our tetramethylsilane to exclude contamination by tetrahydrofuran or diethyl ether which are scavengers for fluorinated lanthanide shift reagents.

Regular High Purity

15,179-3	Acetone-d_6, 99.5%	10 g	$ 9.50
		25 g	23.25
15,181-5	Benzene-d_6, 99.5%	10 g	12.25
		25 g	28.50
15,182-3	Chloroform-d, 99.8%	50 g	6.50
		100 g	12.50
15,188-2	Deuterium oxide, 99.7%	100 g	13.50
15,187-4	Methyl sulfoxide-d_6, 99.5%	10 g	9.50
		25 g	23.25
15,232-3	Pyridine-d_5, 99%	5 g	17.10
		10 g	30.00

Gold Label 100.0 atom % D

17,586-2	Acetone-d_6	5 g	$ 36.00
		25 g	130.00
17,587-0	Benzene-d_6	5 g	38.00
		25 g	135.00
15,185-8	Chloroform-d	10 g	18.00
		50 g	47.00
15,189-0	Deuterium oxide	10 g	15.00
		50 g	43.00
15,691-4	Methyl sulfoxide-d_6	5 g	35.00
		25 g	125.00
17,797-0	Pyridine-d_5	1 g	15.00
		5 g	68.00

T2400-7 Tetramethylsilane, 99.9+%, nmr grade ..... 25 g $11.70
100 g 31.20

Write for lower prices on larger units. Consult *The Aldrich Handbook of Organic Chemicals* for a complete listing of our deuterated products.

Aldrich Chemical Company, Inc.

Craftsmen in Chemistry

ALDRICH®

Home Office:
Aldrich Chemical Co., Inc.
940 W. St. Paul Ave.
Milwaukee, Wisconsin 53233

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd., Wembley Middx.,
HAO 1PY, England

In Continental Europe:
Aldrich-Europe
B-2340 Beerse,
Belgium

In Germany:
Ega-Chemie KG
7924 Steinheim am Albuch
Germany

CIRCLE 802 ON READER SERVICE CARD