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NOTES

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THE JOURNAL OF Organic Chemistry®

VOLUME 38, NUMBER 24

NOVEMBER 30, 1973

Chrysanthemylcarbenes. An Isobutenyl Substituent Effect and Conformational Control in Cyclopropylcarbene Rearrangements[1a]

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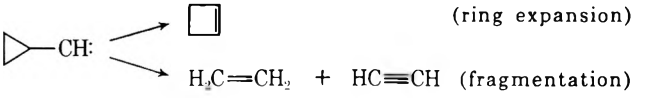
Received May 22, 1973

Thermal and photodecompositions of sodium and lithium salts of *cis*- and *trans*-chrysanthemyl-(2,2-dimethyl-3-isobutenylcyclopropyl-) aldehyde *p*-tosylhydrazones (*cis*- and *trans*-5) and *cis*- and *trans*-chrysanthemyl methyl ketone tosylhydrazones (*cis*- and *trans*-6) were carried out under various conditions. The products from *cis*- and *trans*-5 under aprotic conditions were 2,5-dimethyl-2,4-hexadiene (8), a fragmentation product, and 3,3-dimethyl-4-isobutenylcyclobutene (9), a ring-expansion product, in 62–68:38–32 ratio, respectively. Thermal decomposition of lithium salts of *cis*- and *trans*-6 under aprotic conditions afforded predominantly a ring-expanded product, 1,3,3-trimethyl-4-isobutenylcyclobutene (12) rather than the fragmentation product 8 with 70:30 and 92:8 ratios, respectively, indicating an exclusively selective C_1–C_3 bond migration. Under protic conditions, both *cis*- and *trans*-5 gave 2,5,5-trimethyl-1,3,6-heptatriene (10) and 2,5-dimethyl-3-vinyl-1,4-hexadiene (11). A notable isobutenyl substituent effect as well as a conformational effect of divalent carbon is advanced to rationalize the intramolecular cyclopropylcarbene rearrangements.

The nature and extent of carbene interactions with neighboring heteroatoms like oxygen or chemical bonds of unsaturated character involving phenyl, carbonyl, and cyclopropyl functions has recently become a fascinating problem, on which the reorganization of highly reactive intermediates is particularly focused.[2,3] Cyclopropylcarbene is well known to undergo a ring-expansion reaction to give cyclobutene accompanied with a fragmentation to acetylene and ethylene.[4]



However, the diversity of mechanistic pathways for this very reactive intermediate seems not to be well clarified compared with that for cyclopropylcarbinyl cation rearrangements.[5] In the previous papers[6] we have described carbonium ion promoted cyclopropane ring opening reactions of *cis*- and *trans*-chrysanthemyl (2,2-dimethyl-3-isobutenylcyclopropyl) systems, where a notable substituent effect of an isobutenyl group is realized in the facile and selective ring-opening reactions.[7] This paper deals with chemical behaviors of chrysanthemyl- and chrysanthemylmethylcarbenes generated *via* the Bamford–Stevens reaction[8] in order to obtain information on steric and electronic substituent effects on cyclopropylcarbene reactivity, and thus to effect synthetic application of such a highly reactive intermediate.[2]

(1) (a) Studies on Chrysanthemic Acid. XI. Part X of this series: T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *Chem. Lett.*, 503 (1972). (b) Toyoda Physical and Chemical Research Institute Postdoctoral Research Fellow, 1972 to present.

(2) For recent reviews on carbene chemistry, see (a) R. A. Moss, *Chem. Eng. (N. Y.)*, June 16, 60 (1969); June 30, 50 (1969); (b) G. L. Closs, "Topics in Stereochemistry," Vol. 3, Interscience, New York, N. Y., 1968, p 193; (c) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971.

(3) For oxacarbene–1-oxo-1,4-diradical rearrangement, see (a) A. M. Foster and W. C. Agosta, *J. Amer. Chem. Soc.*, **94**, 5777 (1972); (b) D. R. Morton, E. Lee-Ruff, R. M. Southam, and N. J. Turro, *ibid.*, **92**, 4349 (1970). For carbonylcarbene–oxirene rearrangement, see (c) S. A. Matlin and P. G. Sammes, *Chem. Commun.*, 11 (1972); (d) J. Ciabattoni, R. A. Campbell, C. A. Renner, and P. W. Concannon, *J. Amer. Chem. Soc.*, **92**, 3826 (1970). For arylcarbene rearrangement, see (e) W. D. Crow and M. N. Paddon-Row, *ibid.*, **94**, 4746 (1972), and references cited therein. For β-cyclopropylcarbene, see (f) P. K. Freeman, R. S. Raghavan, and D. G. Kuper, *ibid.*, **93**, 5288 (1971).

(4) For cyclopropylcarbenes, see (a) L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **82**, 1002 (1960); (b) H. M. Frey and I. D. R. Stevens, *Proc. Chem., Soc., London*, 144 (1964); (c) J. A. Smith, H. Shechter, J. Bayless, and L. Friedman, *J. Amer. Chem. Soc.*, **87**, 659 (1965); (d) J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Shechter, *ibid.*, **87**, 661 (1965); (e) K. B. Wiberg and J. M. Lavanish, *ibid.*, **88**, 365 (1966); (f) F. Cook, H. Shechter, J. Bayless, L. Friedman, and R. L. Flots, *ibid.*, **88**, 3870 (1966); (g) P. B. Shevlin and A. P. Wolf, *ibid.*, **88**, 4735 (1966); (h) A. Guarino and A. P. Wolf, *Tetrahedron Lett.*, 655 (1969); (i) C. L. Bird, H. M. Frey, and I. D. R. Stevens, *Chem. Commun.*, 707 (1967); (j) S. Nishida, I. Moritani, E. Tsuda, and T. Teraji, *ibid.*, 781 (1969); (k) R. R. Sauers, S. B. Schlosberg, and P. E. Pfeffer, *J. Org. Chem.*, **33**, 2175 (1968); (l) W. Kirmse and K. H. Pook, *Angew, Chem., Int. Ed. Engl.*, **6**, 594 (1966); (m) M. A. Battiste and M. E. Burns, *Tetrahedron Lett.*, 523 (1966); (n) J. W. Wilt, Jr., J. M. Kosturik, and R. C. Orlowski, *J. Org. Chem.*, **30**, 1052 (1965); (o) L. A. Paquette and G. H. Birnberg, *J. Amer. Chem., Soc.*, **94**, 164 (1972); (p) H. E. Zimmerman and L. R. Sousa, *ibid.*, **94**, 834 (1972); (q) P. K. Freeman and D. G. Kuper, *J. Org. Chem.*, **30**, 1047 (1965); (r) J. W. Wheeler, R. H. Chung, Y. N. Vaishnav, and C. C. Shroff, *ibid.*, **34**, 545 (1969).

(5) For cyclopropylcarbinyl cation rearrangements, see (a) R. Breslow in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963; (b) references in F. Majerski and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 665 (1971).

(6) T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *J. Org. Chem.*, **63**, 1968 (1971), and ref 1a.

(7) For ring openings in the Cope rearrangement, see (a) T. Sasaki, S. Eguchi, and M. Ohno, *J. Amer. Chem. Soc.*, **92**, 3192 (1970); (b) T. Sasaki, S. Eguchi, and M. Ohno, *J. Org. Chem.*, **37**, 466 (1972).

(8) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).

TABLE I

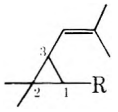
PRODUCT COMPOSITION OF THERMAL AND PHOTODECOMPOSITIONS OF TOSYLHYDRAZONES 5 AND 6 ALKALI SALTS

Tosylhydrazone	Alkali metal	Medium	Conditions, temp, °C (mm)	Product composition,[a] % 8	9	12	10	11
trans-5	Li	None	90–110 (2)	68	32			
cis-5	Li	None	90–110 (2)	73	27			
trans-5	Na	None	90–110 (2)	46	24		8	22
	Na	Celite	90–110 (2)	52	32		4	12
	Na	DEG[b]	80–120 (21)	8	4		19	69
cis-5	Na	None	90–110 (2)	54	29		4	13
	Na	Celite	90–110 (2)	55	26		4	15
	Na	DEG[b]	80–120 (21)	16	9		19	56
trans-5	Na	Ether	$h\nu$[c]	54	25		5	16
cis-5	Na	Ether	$h\nu$[c]	45	22		7	26
trans-6	Li	None	110–120 (2)	8		92		
cis-6	Li	None	105–120 (2)	30		70		
21[d]	Na	DEC[b]	180	Ethylene, 13–18 Cyclobutene, 82–87				

[a] Based on relative peak areas on glpc. [b] DEG, diethylene glycol; DEC, diethylcarbitol. [c] Irradiated with a 100-W high-pressure mercury lamp (quartz filter). [d] Taken from ref 4a.

Results

cis- and *trans*-chrysanthemylaldehydes (*cis*- and *trans*-**3**) and -chrysanthemyl methyl ketones (*cis*- and *trans*-**4**) were obtained by oxidation of chrysanthemol (*cis*- and *trans*-**2**) with the Sarett reagent, and by reaction of chrysanthemic acid (*cis*- and *trans*-**1**) with methyllithium, respectively. The corresponding *p*-tosylhydrazones (*cis*- and *trans*-**5** and -**6**) were prepared by the standard procedure.



1. R = COOH
2. R = CH_2OH
3. R = CHO
4. R = $COCH_3$
5. R = CH=NNHTs
6. R = $C(CH_3)$=NNHTs

Thermal decomposition of the lithium salt of *trans*-**5** under reduced pressure of nitrogen at 90–110° afforded an extremely volatile oil in a 60% yield, which was a 68:32 mixture of two hydrocarbons **8** and **9** (Scheme I). Compound **8** was identified as 2,5-dimethyl-2,4-hexadiene, a fragmentation product,[9] by spectral and glpc comparisons with an authentic specimen. Compound **9** was not thermostable enough to be isolated by preparative glpc at 80°. The structure was assigned as 3,3-dimethyl-4-isobutenylcyclobutene, a ring-expansion product, on the basis of spectral and glpc comparisons with a specimen synthesized by photocycloaddition of maleic anhydride to **8**, followed by alkaline hydrolysis and oxidative decarboxylation (Scheme II). Thermal decomposition of *cis*-**5** afforded also **8** and **9** in 73:27 ratio. The decomposition products of *cis*- and *trans*-**5** and -**6** under various conditions are summarized in Table I and Scheme I.

Thermal decompositions of *cis*- and *trans*-**5** in diethylene glycol with a high protonicity[10] resulted in the formation of 2,5,5-trimethyl-1,3,6-heptatriene (artemisia triene)[11] (**10**) and 2,5-dimethyl-3-vinyl-1,4-hexadiene (santorina triene)[12] (**11**) as the major products and **8** and **9** as the minor products (Scheme I and Table I). Both **10** and **11** might be produced *via* a cationic precursor, since the deamination of chrysanthemylamine gives similar ring-opened products.[6,13] Photolytic decompositions[14] of *cis*- and *trans*-**5** gave results similar to those of thermal ones, though the use of sodium methoxide as a base in the photolytic and thermal decompositions resulted in contamination with the products *via* cationic intermediate because of the very strong hygroscopicity of the sodium salt of **5**. It is notable that no appreciable difference in the product distributions was observed between the cis and trans isomers of **5** (Table I).

Thermal decomposition of the lithium salt of *trans*-**6** afforded a 8:92 mixture of two hydrocarbons in a 95% yield. The minor product was one of the fragmentation products **8** and the major one was assigned as as 1,3,3-trimethyl-4-isobutenylcyclobutene (**12**), a ring-expansion product, on the basis of analysis and spectral and glpc comparisons with a specimen prepared by photocycloaddition of methylmaleic anhydride to **8**, followed by hydrolysis and oxidative decarboxylation (Scheme II). Purification of the crude photoadducts on a silica gel column, followed by an alkaline hydrolysis, afforded a regio- and stereoisomerically pure dicarboxylic acid **19**, in which the location of a methyl group at C_1 was determined by the characteristic nmr signals at τ 7.27 (1 H, s, C_2 H), 6.42 (1 H, d, J = 10 Hz, C_4 H), and 4.80 (1 H, d, J = 10 Hz, C_4 CH=C).[15]

(9) Formation of acetylene was also confirmed, at least qualitatively, as another fragment of this cheletropic reaction.

(10) (a) J. H. Bayless, L. Friedman, F. B. Cook, and H. Shechter, *J. Amer. Chem. Soc.*, **90**, 531 (1968); (b) for solvent effect on the Bamford–Stevens reaction, see ref 2c, pp 30–32.

(11) L. Crombie, R. P. Houghton, and D. K. Woods, *Tetrahedron Lett.*, 4553 (1967); see also ref 6.

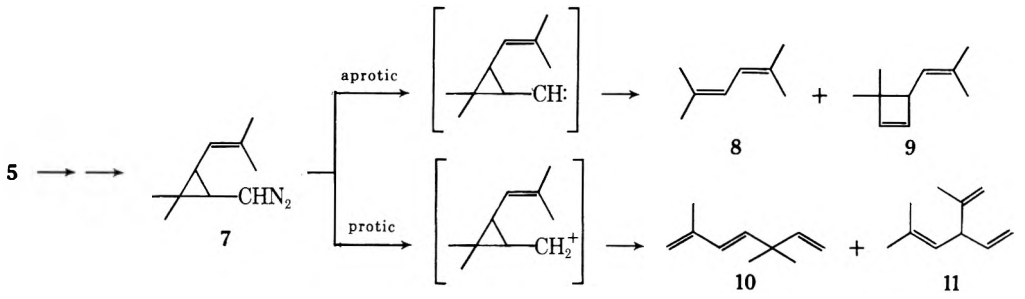
(12) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, 3775 (1964), and ref 1a.

(13) Reexamination of the deamination products in acetic acid revealed the formation of **11**, santorina acetate, **10**, and artemisia acetate in a 10:4:29:27 ratio; *cf.* also ref 1a and 6.

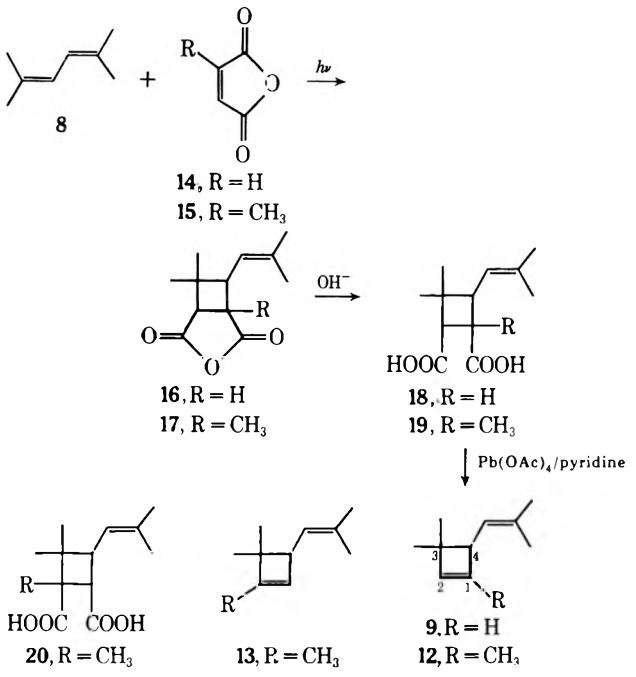
(14) For photolytic decompositions of dimethylcyclopropylidazomethane, see ref 4h.

(15) For vicinal coupling constants in cyclobutanes, see, for example, L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 287.

SCHEME I



SCHEME II



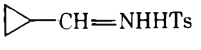
Thus corroborated, diacid **19** was decarboxylated by lead tetraacetate oxidation to give a single olefinic product which was completely identical (ir, nmr, and glpc) with a hydrocarbon **12** from the decomposition of *trans*-**6**.

Thermolysis of *cis*-**6** lithium salt afforded **12** and **8** in a 70:30 ratio, indicating 100% selectivity of the C_1–C_3 bond migration even in the cis isomer as in the trans isomer (Table I).

It is notable that no trace of *cis*- and *trans*-1-vinyl-2,2-dimethyl-3-isobutenylcyclopropanes[7b] as possible hydrogen migration products was produced in the decompositions of both *cis*- and *trans*-**6** lithium salts.

Discussion

In a sharp contrast to a number of cyclopropylcarbenes reported in the literature,[4] *cis*- and *trans*-chrysanthemylcarbenes *via* the Bamford–Stevens reactions of *cis*- and *trans*-**5** provide novel examples where the fragmentation process predominates substantially over the ring-expansion process; even when the parent cyclopropanecarboxaldehyde tosylhydrazone (**21**) is



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used as a carbene precursor, the major product is known to be cyclobutene[4a,c] (Table I). The presence of a C_3-isobutenyl substituent might lower the transition-state energy for the fragmentation reaction by virtue of formation of a conjugated diene, assuming that the carbene reaction proceeds *via* either a concerted process or stepwise ones (ion-pair or radical-pair)[16–18] (Chart I).

Unsymmetrically substituted cyclopropylketone tosylhydrazone is known to rearrange to cyclobutenes in two possible directions, but the migration of a less substituted (*i.e.*, less sterically hindered) bond of cyclopropane is prefered.[4i,j,m] The present results that both *cis*- and *trans*-**6** lead to the formation of only a single ring-expansion product **12** with migration of the isobutenyl-substituted bond (C_3–C_1 bond) could not be explainable only by the steric hindrance. A similar steric bulkiness is conceivable for C_2-methyl and C_3-isobutenyl substituents in the cis isomer,[19] from which the observed exclusively selective C_3–C_1 bond migration could never be expected. Hence, it could be concluded that the electronic effect of a C_3-isobutenyl substituent should play an important role at the transition state. Such a remarkable substituent effect is commonly observed in the ring-opening reactions of cyclopropane attached to an electron-deficient carbon such as carbonium ion.[1,20]

Finally, we wish to discuss the considerable difference of the product distributions between the aldehyde and ketone tosylhydrazones **5** and **6**. The diversity of cyclopropylcarbene reactions, such as fragmentation

(16) The concerted process seems to be most likely as shown recently by a successful prediction of forbiddeness–allowedness of the rearrangement from correlation diagrams of reacting cyclopropylcarbene (see ref 4p). However, the possibility of a stepwise process should also be considered in general.

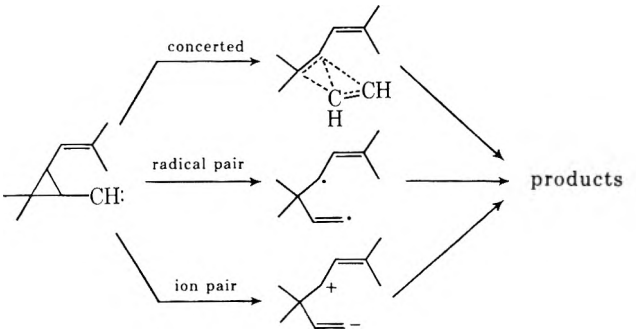
(17) For an ion-pair mechanism, *cf.* ref 4q.

(18) For a radical-pair mechanism, see M. Jones, Jr., J. D. Reich, and L. T. Scott, *J. Amer. Chem., Soc.*, **92**, 3118 (1970).

(19) The evidence rests on the nmr study concerning a diastereotopic phenomenon in the chrysanthemyl system. We examined nmr spectra of several chrysanthemyl derivatives such as **1** [R = CH_2CONH_2, $CH_2N(CH_3)_2$, CH_2NH_2, CH_2OH, CH_2OAc, $CH_2OCOC_6H_3(NO_2)_2$-2,4] and dihydrochrysanthemol, all of which have a methylene group attached to an asymmetric C_1 carbon. As an unequivocal difference between the cis and trans isomers, an A_2X pattern for the cis isomers and an ABX pattern for the trans isomers were observed. The difference must be associated with the anisotropy of a cyclopropane ring and unequal conformer populations due to the difference of nonbonded interactions between the methylene group and the substituents (hydrogen, methyl, and isobutenyl). The equivalency of methylene protons in the cis isomers contrary to the nonequivalency in the trans isomers suggests similar steric bulkiness of C_2-methyl and C_3-isobutenyl groups. *Cf.* also (a) J.-L. Pierre, R. Perraud, and P. Arraud, *Bull. Soc. Chim Fr.*, 1537 (1970); (b) J. Edmond, G. Popják, S.-M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971); (c) C. D. Poulter, *J. Amer. Chem. Soc.*, **94**, 5515 (1972).

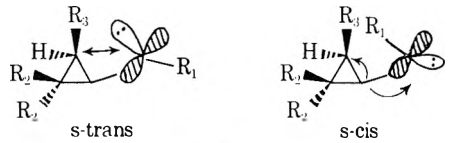
(20) (a) H. M. Walborsky and L. Plonker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961); (b) T. Shono, I. Nishiguchi, and R. Oda, *J. Org. Chem.*, **35**, 42 (1970); (c) for a recent theoretical study, see L. D. Kispert, C. Engleman, C. Dyas, and C. U. Pittman, Jr., *J. Amer. Chem. Soc.*, **93**, 6948 (1971).

CHART I



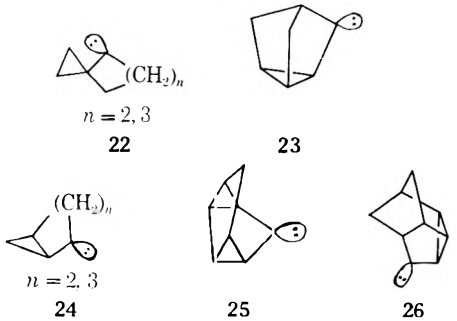
and ring expansion, has been explained by considering mainly strain factors as well as electronic effects,[4q,r] but no conformational effect. We advance here that not only the strain effect but also the conformational effect play a very significant role in determining the cyclopropylcarbene rearrangement reactivity. A maximum interaction of the carbene with the rearranging bond could be possible when the substituent R_1 takes an s-trans-like conformation against the cyclopropane ring, while in an s-cis-like conformation, the interaction is apparently unfavorable as illustrated in Chart II.[21]

CHART II



R_1 = H, CH_3; R_2 = CH_3; R_3 = $CH=C(CH_3)_2$

The known results of intramolecular rearrangement of geometrically constrained cyclopropylcarbene can be rationalized by considering the conformational effect. For example, spirocarbene (22) where an s-trans conformation is geometrically fixed is known to undergo the ring expansion exclusively.[41,22] On the contrary, cyclopropylcarbenes such as **23**,[23] **24**,[4q] **25**,[24] and **26**,[25]



where an s-cis conformation is inevitably fixed by the geometrical constraint, undergo predominantly the fragmentation reaction.

For the present crysanthemyl systems, an s-trans conformation is expected to be more favored for the carbenes from *cis*- and *trans*-**6** than for the carbenes from *cis*- and *trans*-**5**.[26] Therefore, the observed predominant ring expansion of chrysanthemylmethylcarbenes from **6** could be rationalized by the conformational effect. A somewhat larger fragmentation for the cis isomer (30%) than the trans one (8%) may result in a steric hindrance to the ring expansion of the former, *i.e.*, the steric crowdedness at the transition state for the ring expansion even with an s-trans-like conformation hinders to some extent the ring expansion, permitting the fragmentation *via* the s-trans conformation also.[27]

Thus, the substituent effect of an isobutenyl group at C_3 is concluded to play a remarkable role electronically as well as sterically in the cyclopropylcarbene reactivity. The conformational effect of the carbene against a cyclopropane ring is postulated as a primarily controlling factor to determine the cyclopropylcarbene rearrangement aptitude.

Experimental Section[28]

***cis*- and *trans*-2,2-Dimethyl-3-isobutenylcyclopropanecarboxaldehydes (*cis*- and *trans*-3).**—*trans*-Chrysanthemol (*trans*-**2**, 6.00 g, 38.9 mmol) was added to a pyridine–CrO_3 complex solution (the Sarett reagent)[29] prepared from pyridine (200 ml) and chromic anhydride (12 g, 120 mmol) at room temperature. After standing overnight, the mixture was poured onto cold water (500 ml) and extracted with three 200-ml portions of ether. The combined extracts were washed with three 100-ml portions of 10% hydrochloric acid, two 50-ml portions of saturated sodium carbonate aqueous solution, and finally with 100-ml of water. After being dried over anhydrous sodium sulfate, the extract was concentrated *in vacuo* and distilled to afford the aldehyde (*trans*-**3**) as a colorless oil (3.83 g, 65%), bp 57–58° (2.5 mm) [lit.[30] bp 43–44° (0.1 mm)].

The cis aldehyde (*cis*-**3**) was obtained similarly from *cis*-chrysanthemol (*cis*-**2**) as a colorless oil (58%), bp 58–60° (2.5 mm) [lit.[30] bp 63–64° (2.0 mm)].

***cis*- and *trans*-2,2-Dimethyl-3-isobutenylcyclopropyl Methyl Ketones (*cis*- and *trans*-4).**—To a stirred and refluxing solution of *trans*-chrysanthemic acid (*trans*-**1**, 6.0 g, 38.9 mmol) in dry ether (30 ml) was added an ethereal methyllithium solution prepared from methyl bromide (9.8 g, 103 mmol) and metallic lithium (1.3 g, 187 mmol) under nitrogen.[31] After standing overnight at room temperature, the mixture was poured onto ice water (*ca.* 200 ml) and the organic layer was separated, washed with saturated sodium chloride aqueous solution and water successively, and

(21) Zimmerman and Sousa reported recently on the correlation diagrams for cheletropic fragmentation and hydrogen migration of carbenes considering the nodal properties. They also predict the geometrical requirements at the transition states such as an s-cis-like conformation for the fragmentation and a somewhat twisted s-trans-like conformation for the hydrogen migration (alkyl migration); see ref 4p.

(22) K. B. Wiberg, G. J. Burzmaier, and P. Warner, *J. Amer. Chem. Soc.*, **93**, 246 (1971). In these cases the fragmentation is highly unfavorable also owing to the inordinate strain required to generate cyclobutyne and cyclopentyne.

(23) (a) S. J. Cristol and J. K. Harrington, *J. Org. Chem.*, **28**, 1413 (1963); (b) D. M. Lemal and A. J. Fry, *ibid.*, **29**, 1673 (1964).

(24) R. G. Bergman and V. J. Rajadhyaksha, *J. Amer. Chem. Soc.*, **92**, 2163 (1970).

(25) P. K. Freeman and D. M. Balls, *J. Org. Chem.*, **32**, 2354 (1967).

(26) (a) For a conformational study on cyclopropanecarboxaldehyde, see L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647 (1965); (b) for cyclopropyl methyl ketone, see L. S. Bartell, J. P. Guillory, and A. T. Parks, *J. Phys. Chem.*, **69**, 3043 (1965); (c) for chrysanthemylaldehyde and methyl ketone, see W. G. Dauben and G. W. Shaffer, *J. Org. Chem.*, **34**, 2301 (1969), and ref 7b, footnote 20.

(27) Geometrically this fragmentation process seems to be allowed from the correlation diagram by Zimmerman and Sousa (ref 4p), though energetically the fragmentation *via* this conformation might be less favorable than that *via* the s-cis one.

(28) All melting points were obtained on a hot-stage type micro melting point apparatus and are corrected. Nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer at 60 MHz with TMS as an internal standard, and ir spectra on a JASCO IR-S ir spectrophotometer. High-resolution mass spectra were obtained with a Hitachi RMS-4 mass spectrometer at 80 eV. Glpc analyses were performed on a Varian gas chromatograph Model 1400 and preparative glpc on a Varian Aerograph Model 700. Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer.

(29) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(30) *Cf.* footnote 9 in ref 7b.

(31) *Cf.* M. J. Jorgenson, *Org. React.*, **18**, 1 (1970).

dried (Na_2SO_4). Removal of solvent *in vacuo* and distillation gave the ketone *trans*-**4** as a colorless oil (3.5 g, 59%), bp 60–61° (4 mm) [lit.[30,32] bp 90–91° (15 mm)]. The cis ketone (*cis*-**4**) was obtained similarly as a colorless oil (52%): bp 60–62° (4 mm); $n^{21}D$ 1.4780; ir (neat) 1690, 1457, 1415, 1385, 1358, 1193, 970, 842, and 798 cm^{-1}; nmr (CCl_4) τ 4.50–4.90 (mound, 1 H, CH=C), 7.88 (s, 3 H, $COCH_3$), 8.08–8.40 [m, 8 H, C=C-(CH_3)$_2$ and C_1 H and C_1 H], 8.80 and 8.82 (each s, 6 H, C_2 *gem*-dimethyl).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.56; H, 10.82.

p-Tosylhydrazones (*cis*- and *trans*-**5**) of *cis*- and *trans*-**3**.—To a stirred solution of *p*-toluenesulfonylhydrazide (2.45 g, 13.1 mmol) in methanol (10 ml) was added *trans*-**3** (2.00 g, 13.1 mmol) at room temperature. After stirring was continued for 2 hr, the mixture was cooled to precipitate colorless crystals which were collected by filtration and recrystallized from methanol to give *p*-tosylhydrazone *trans*-**5** (3.44 g, 82%): mp 100–101°; ir (KBr) 3220 (NH), 1615 (C=N), 1600 (phenyl), and 860 cm^{-1} (CH=C); nmr (CCl_4) τ 1.96 (s, 1 H, NH, disappeared on deuteration), 2.10–2.90 (complex m, 4 H, phenyl protons), 3.03 and 3.55 (each d, J = 8.0 Hz, 0.6 H and 0.4 H, anti and syn CH=NNHTs), 5.20 (broad d, J = 7.5 Hz, 1 H, CH=C), 7.60 (s, 3 H, tosyl CH_3), 8.32 [s, 6 H, C=C(CH_3)$_2$], 8.55–9.10 (m, 2 H, C_1 H and C_3 H), 8.91 and 8.95 (s, 6 H, C_2 *gem*-dimethyl).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.73; H, 7.54; N, 8.74. Found: C, 63.73; H, 7.51; N, 8.76.

Similarly *cis*-**5** was prepared from *cis*-**3** and *p*-toluenesulfonylhydrazide. Since crystallization of the crude product was difficult, an analytical sample was obtained after purification on a silica gel column ($CHCl_3$) followed by preparative tlc (silica gel, $CHCl_3$) as a colorless oil: ir (neat) 3230 (NH), 1615 (C=N), 1600 (phenyl), 860 cm^{-1} (CH=C); nmr (CCl_4) τ 1.10 (broad s, 1 H, NH, disappeared on shaking with D_2O), 2.10–2.95 (m, 5 H, phenyl protons and CH=NNHTs), 5.12 (d, J 7.5 Hz, 1 H, CH=C), 7.61, (s, 3 H, tosyl CH_3), 8.38 [s, 6 H, C=C(CH_3)$_2$], 8.65–9.35 (m, overlapped with strong singlet signals at τ 8.88 and 8.99, 8 H, C_2 *gem*-dimethyl and C_1 H and C_3 H).

Anal. Calcd for $C_{17}H_{24}N_2O_2S$: C, 63.73; H, 7.54; N, 8.74. Found: C, 63.48; H, 7.5[illegible]; N, 8.41.

p-Tosylhydrazones (*cis*- and *trans*-**6**) of *cis*- and *trans*-**4**.—*trans*-**4** (2.32 g, 13.9 mmol) was treated similarly with *p*-toluenesulfonylhydrazide (2.60 g, 13.9 mmol) in methanol (15 ml) to afford the *trans*-tosylhydrazone (*trans*-**6**) as colorless crystals (3.22 g, 69%): mp 141–142.5°; ir (KBr) 3250 (NH), 1630 (C=N), 1600 (phenyl), and 860 cm^{-1} (CH=C); nmr (CCl_4) τ 2.55 (broad s, 1 H, NH), 2.13–2.87 (complex m, 4 H, phenyl protons), 5.18 (broad d, J = 8.0 Hz, 1 H, CH=C), 7.60 (s, 3 H, tosyl CH_3), 8.12 and 8.18 (each s, 1 H and 2 H, syn and anti TsNHN=CCH_3), 8.31 [s, 6 H, C=C(CH_3)$_2$], 8.45–9.45 (m, 8 H, C_1 H, C_3 H, and C_2 *gem*-dimethyl).

Anal. Calcd for $C_{18}H_{26}N_2O_2S$: C, 64.64; H, 7.84; N, 8.37. Found: C, 64.96; H, 7.77; N, 8.41.

Similar treatment of *cis*-**4** gave *cis*-**6** as colorless crystals (58%): mp 136–137°; ir (KBr) 3230 (NH), 1640 (C=N), 1600 (phenyl), and 845 cm^{-1} (CH=C); nmr ($CDCl_3$) τ 2.12–2.83 (m, 5 H, phenyl protons and NH, the integration decreased to *ca.* 4 H on shaking with D_2O), 5.23 (broad d, J = 8.0 Hz, 1 H, CH=C), 7.62 (s, 3 H, tosyl CH_3), 8.15 and 8.36 (each s, 1 H and 2 H, syn and anti TsNHN=CCH_3), 8.27 [s, 6 H, C=C(CH_3)$_2$], 8.84, 8.94, 9.19, and 9.28 (each s, 6 H, C_2 *gem*-dimethyl), and 8.0–9.0 (m, 2 H, C_1 H and C_3 H).

Anal. Calcd for $C_{18}H_{26}N_2O_2S$: C, 64.64; H, 7.84; N, 8.37. Found: C, 64.48; H, 7.73; N, 8.61.

Decompositions of Tosylhydrazones (*cis*- and *trans*-5 and -6) Alkali Salts. General Procedure.—Tosylhydrazone alkali salt prepared from the corresponding tosylhydrazone (*cis*- and *trans*-**5** or -**6**) and an appropriate base (1.1 equiv) was decomposed by heating at 90–120° under a reduced pressure of nitrogen in a reaction flask fitted with a distillation head connected directly to a trap followed by another trap of the same size. The distillate collected in the traps at −73° was analyzed on glpc by using a 6 ft × $^2/_{25}$ in. column packed with silicone SE-30 (3%) on Varaport 30 at 60–80°. For preparative glpc, a 6 ft × $^8/_{25}$ in. U-shaped column packed with silicone SE-30 (10%) on 60–80 mesh Chromosorb W was used. For other conditions, see Table I.

(1) To a solution of *cis*-**5** (or *trans*-**5**) (320 mg, 1.00 mmol) in dry THF (1 ml) was added *n*-butyllithium solution in *n*-hexane (0.70 ml of 10% w/v solution, 1.01 mmol) at 0° under nitrogen atmosphere. After standing for 0.5 hr at room temperature, the solvent was removed *in vacuo* to leave colorless solids which were heated at 90–110° to yield a volatile, oily product (51 mg, 43%) (60 mg, 51% from *trans*-**5**). The crude product was analyzed on glpc as a mixture of two hydrocarbons (Table I). The major product eluted first on preparative glpc was identified as 2,5-dimethyl-2,4-hexadiene (**8**) by comparisons of its ir and nmr spectra and glpc retention time with those of a commercially available authentic specimen. Isolation of the minor second product on glpc was unsuccessful because of its thermolability. However, analysis of ir and nmr spectral data of a mixture of this product and **8**, and glpc retention times in comparison with a specimen prepared from **8** and maleic anhydride as described below permitted the assignment of this second product as 3,3-dimethyl-4-isobutenylcyclobutene (**8**) (for physical data of **9**, see below).

(2) Tosylhydrazones *cis*- and *trans*-**6** were decomposed according to method 1 above to afford a mixture of two hydrocarbons (72 and 95% from *cis*- and *trans*-**6**, respectively) which were isolated on preparative glpc. The first component was identical with **8** by spectral and glpc comparisons. The second component, assigned as 1,3,3-trimethyl-4-isobutenylcyclobutene (**12**), had the following physical data: $n^{18}D$ 1.4691; ir (CCl_4) 1660, 1640, and 865 cm^{-1}; nmr (CCl_4) τ 4.35 (q, J = 1.5 Hz, 1 H, C_2 H), 5.00 [d, septuplet, J = 9.0 and 1.5 Hz, 1 H, CH=C(CH_3)$_2$], 7.06 (d, J = 9.0 Hz, 1 H, C_4 H), 8.25 (d, J = 1.5 Hz, 3 H, C_1 CH_3), 8.37 and 8.44 [each d, J = 1.5 Hz, each 3 H, C=C(CH_3)$_2$], 8.86 and 9.07 (each s, each 3 H, C_3 *gem*-dimethyl) (irradiation at the signal at τ 8.25 changed the quartet at τ 4.35 to a sharp singlet); mass spectrum m/e (rel intensity) 150 (10, M^+), 109 (100), 91 (36), 81 (54).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.14; H, 11.86.

(3) To a solution of *trans*-**5** (960 mg, 3.00 mmol) in methanol (7 ml) was added sodium methoxide (162 mg, 3.00 mmol) under nitrogen. The mixture was stirred for 0.5 hr and the solvent was removed *in vacuo* to afford colorless solids which were subjected to thermal decomposition as above under the conditions in Table I. An oily product (220 mg) collected at a trap at −73° was analyzed and purified on glpc. The first and second fractions were identified as **8** and **9**, respectively, by means of method 1. The third fraction was characterized as **2,5-dimethyl-3-vinyl-1,4-hexadiene (santorina triene)** (**11**) by comparison of its ir and nmr spectra with reported ones.[12] The fourth fraction was identified as **2,5,5-trimethyl-1,3,6-heptatriene (artemisia triene)** (**10**) by comparison of glpc retention time and ir and nmr spectra with those of a specimen prepared by an alternative method.[6]

(4) A suspension of *trans*-**5** sodium salt (90 mg, 0.26 mmol) in dry ether (30 ml) in a quartz tube was irradiated with stirring under nitrogen steam at room temperature from a 100-W high-pressure mercury lamp for 3 hr and the product was analyzed on glpc (Table I).

3,3-Dimethyl-4-isobutenylcyclobutene (9) from 8 and Maleic Anhydride.—A solution of **8** (9.00 g, 81.8 mmol), maleic anhydride (1.50 g, 15.2 mmol), and benzophenone (500 mg) in ether (100 ml) was irradiated under a slow nitrogen steam with a 100-W high-pressure mercury lamp using a cylindrical Pyrex jacket cooled by running water for 5 hr. The solvent was removed by evaporation and excess **8** was removed by distillation at 60–80° under reduced pressure (25 mm). An oily residue was chromatographed on a silica gel column with benzene as an eluent to afford crude 1:1 adduct **16** (2.10 g, *ca.* 66%) accompanied by an unidentified solid product (0.22 g). **16** exhibited ir (neat) absorptions at 1805 and 1780 (anhydride) and 1660 cm^{-1} (isobutenyl), and nmr (CCl_4) signals at τ 4.92 (d, J = 8.0 Hz, 1 H, CH=C) and 6.33–7.00 (m, 3 H, cyclobutane ring protons). A mixture of **16** (2.0 g) and 7% aqueous potassium hydroxide (20 ml) was stirred overnight at room temperature. The mixture was washed with ether (20 ml) and the aqueous layer was neutralized with 10% hydrochloric acid and extracted two times with 20-ml portions of ether. The combined extracts were dried (Na_2SO_4) and evaporated to give the dicarboxylic acid **18** as colorless solids (1.50 g, 68%) which were recrystallized from *n*-hexane–ether to afford an analytical sample as colorless crystals: mp 141–143°; ir (KBr) 1720, 1700 (COOH), and 850 cm^{-1} (CH=C); nmr ($CDCl_3$) τ −0.06 (broad s, 2 H, COOH), 4.66 (broad d, J = 10 Hz, 1 H, CH=C), 6.43 (t, J = 10 Hz, 1 H, C_1 H), 6.92 (d, J = 10

(32) R. H. Eastman and S. K. Freeman, *J. Amer. Chem. Soc.*, **77**, 6642 (1955).

Hz, 1 H, C_2 H), 6.92 (t, J = 10 Hz, C_4 H), 8.25 and 8.38 [each s, each 3 H, C=C(CH_3)$_2$], and 8.74 (s, 6 H, C_3 *gem*-dimethyl) (the triplet signal at τ 6.92 changed to a doublet on irradiation at the τ 4.66 signal); mass spectrum *m/e* (rel intensity) 226 (18, M^+), 126 (100), 111 (88), and 110 (56).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.84; H, 8.33.

A mixture of **18** (200 mg, 0.884 mmol) and lead tetraacetate (500 mg, 1.12 mmol) in dry pyridine (4 ml) was warmed at 80° for 1 min.[33] After evolution of carbon dioxide ceased, the mixture was quickly poured onto ice–water (50 ml) and extracted with petroleum ether (bp 39–44°, 30 ml). The extract was washed five times with 30-ml portions of water and dried (Na_2SO_4). After removal of solvent, the residual oil was purified by flask to flask distillation (bath temperature 40°, 2 mm, Dry Ice trap) to give the olefin **9** (20 mg, 16%) as an oil: ir (CCl_4) 1660, 1645, and 870 cm^{-1} (C=C); nmr (CCl_4) τ 4.02 and 4.16 (each d, J = 3.0 Hz, each 1 H, C_1 H and C_2 H), 4.99 [broad d, J = 9.5 Hz, 1 H, CH=C(CH_3)$_2$], 6.92 (d, J = 9.5 Hz, 1 H, C_4 H), 8.28 and 8.38 [each s, each 3 H, CH=C(CH_3)$_2$], 8.81 and 9.04 (each s, each 3 H, C_3 *gem*-dimethyl); mass spectrum *m/e* (rel intensity) 136 (100, M^+), 105 (45), 91 (50), and 79 (35).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.30; H, 11.69.

1,3,3-Trimethyl-4-isobutenylcyclobutene (12) from Methylmaleic Anhydride (15) and 8.—A solution of **8** (11.0 g, 99.8 mmol), **15** (2.20 g, 19.6 mmol), and benzophenone (650 mg) in ether (100 ml) was irradiated as above for 7 hr. Purification of the crude product on a silica gel column eluting with benzene afforded 1:1 adduct **17** as an oil (2.30 g) and unidentified solids (980 mg). The adduct **17** had ir (neat) absorptions at 1850, 1780 (anhydride), and 1660 (C=C) cm^{-1}, and nmr signals (CCl_4) at τ 4.81 and 5.13 [d, J = 9.5 Hz, CH=C(CH_3)$_2$], 6.89 and 7.23 (d, J = 9.5 Hz, C_4 H), and 7.33 and 7.23 (s, C_2 H). The appearance of the signals in pairs (each *ca.* 2:1 ratio) indicated that the adduct **17** is a mixture of two stereoisomers (syn and anti).

A mixture of **17** (550 mg, 2.47 mmol) and 3% aqueous KOH (15 ml) was stirred overnight at room temperature. The aqueous layer was washed with ether (20 ml), neutralized with 10% hydrochloric acid, and extracted twice with 20-ml portions of ether. The combined extracts were dried (Na_2SO_4) and evaporated to afford colorless solids (420 mg, 71%) which were recrystallized from *n*-hexane–ether to give the diacid **19** as crystals: mp 164–165°; ir (KBr) 1720 and 1670 cm^{-1} (COOH); nmr ($CDCl_3$) τ −0.94 (broad s, 2 H, COOH), 4.80 (broad d, J = 10 Hz, 1 H, CH=C), 6.42 (d, J = 10 Hz, 1 H, C_4 H), 7.27 (s, 1 H, C_2 H), 8.28 [s, 6 H, C=C(CH_3)$_2$], 8.53 (s, 3 H, C_1 CH_3), 8.78 and 8.87 (each s, each 3H, C_3 *gem*-dimethyl); mass spectrum *m/e* (rel intensity) 240 (18, M^+), 140 (60), 125 (72), and 110 (100).

Anal. $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.84; H, 8.33.

A mixture of **19** (90 mg, 0.38 mmol) and lead tetraacetate (250 mg, 0.57 mmol) in dry pyridine (3 ml) was warmed at 80° for 15 min. The mixture was poured onto 10% hydrochloric acid (20 ml) and extracted two times with 25-ml portions of ether. The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil which was purified by flask to flask distillation (bath temperature 80–100°, 25 mm) to afford the olefin **12** (10 mg, 18%).

Registry No.—*cis*-**1**, 15259-78-6; *trans*-**1**, 827-90-7; *cis*-**2**, 18383-59-0; *trans*-**2**, 18383-58-9; *cis*-**3**, 20104-06-7; *trans*-**3**, 20104-05-6; *cis*-**4**, 20104-10-3; *trans*-**4**, 20104-09-0; *cis*-**5**, 42077-36-1; *trans*-**5**, 42077-37-2; *cis*-**6**, 42077-38-3; *trans*-**6**, 42077-39-4; **8**, 764-13-6; **9**, 42077-40-7; **12**, 42077-41-8; **15**, 616-02-4; **16**, 42077-42-9; **17**, 42077-43-0; **18**, 42077-44-1; **19**, 42077-45-2; *p*-toluenesulfonylhydrazide, 1576-35-8; maleic anhydride, 108-31-6.

(33) *Cf.* R. Criegee, "Newer Methods of Preparative Organic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1963, p 368.

Molecular Design by Cycloaddition Reactions. VI.[1] Observation of the Enone-π-methane Moiety in Photochemical [1,3] and [3,3] Sigmatropic Rearrangements

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Photolyses (Pyrex, >290 nm) of several substituted tropone adducts are investigated. Mechanisms for [1,3] and [3,3] sigmatropic rearrangements of thus-produced bicyclo[3.2.2]nonadienone systems (enone-π-methane moiety) are discussed.

Recently much interest has arisen in the photochemical rearrangement of the enone-π-methane moiety.[2-7]

We have found that the incorporation of heteroatoms into the bicyclo[3.2.2]nonadienone system causes some changes in its photochemical behavior;[8] irradiation of tropone–4-phenyl-1,2,4-triazoline-3,5-dione adduct in methanol afforded two products by different [3,3] sigmatropic rearrangement followed by addition of methanol. Previously, we have also reported that irradiation of Diels–Alder adducts of tropolone and epoxy-bridged cyclic olefins in methanol led to diketones by successive [1,3] sigmatropic rearrangement[9] in contrast to previous reports[3,5,8] of the light-induced rearrangement of tropone adducts in nucleophilic solvents. Thus, the hydroxyl group at the bridgehead position (α to carbonyl group) has been shown to cause a marked variation in the photochemical behavior of this system, but the mechanism was not elucidated. From these facts it seems that substituents play an important role in the photochemistry of the bicyclo[3.2.*x*]dienone system.

With a hope of providing some additional data for understanding these substituent effects on the photochemical behavior, we have investigated the photochemistry of the cycloadducts of 1,4-epoxy-1,4-di-

(1) Part V of this series: T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Amer. Chem. Soc.*, **95**, 5632 (1973).

(2) O. L. Chapman and J. D. Lassila, *J. Amer. Chem. Soc.*, **90**, 2449 (1968).

(3) O. L. Chapman, M. Kane, J. D. Lassila, R. L. Loeschen, and H. E. Wright, *J. Amer. Chem. Soc.*, **91**, 6856 (1969).

(4) J. Ciabattoni, J. E. Crowley, and A. S. Kende, *J. Amer. Chem. Soc.*, **89**, 2778 (1967).

(5) (a) A. S. Kende, Z. Goldschmidt, and P. T. Izzo, *J. Amer. Chem. Soc.*, **91**, 6858 (1969); (b) A. S. Kende and Z. Goldschmidt, *Tetrahedron Lett.*, 783 (1970).

(6) T. Tezuka, R. Miyamoto, T. Mukai, C. Kabuto, and Y. Kitahara, *J. Amer. Chem. Soc.*, **94**, 9280 (1972).

(7) H. Hart and G. M. Love, *J. Amer. Chem. Soc.*, **93**, 6266 (1971).

(8) T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc. C*, 2142 (1971).

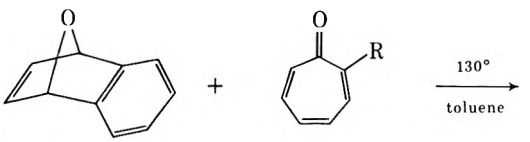
(9) T. Sasaki, K. Kanematsu, and K. Hayakawa, *J. Chem. Soc., Perkin Trans. 1*, 1951 (1972).

hydronaphthalene 1[10] with a series of 2-substituted tropones. In this connection, we have described the cycloaddition reactions of 1 with tropone as electron-poor components and explained them in terms of a Diels–Alder mechanism with inverse electron demands.[10]

Results and Discussion

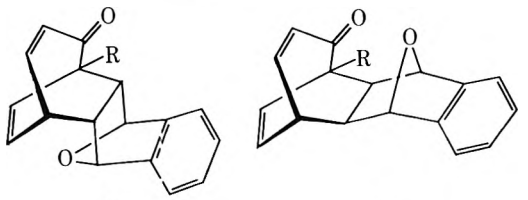
Cycloaddition Reactions.—The reactions were generally carried out in toluene at 130° in a sealed tube for 40 hr (Scheme I). The results are summarized in Table I.

SCHEME I

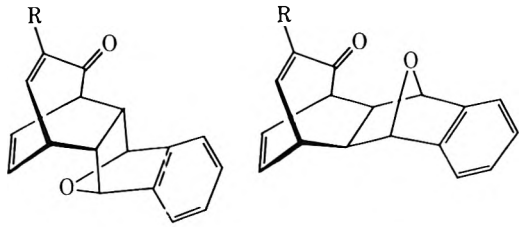


1 2

a, R = H d, R = OH
b, R = NH_2 e, R = $OCOCH_3$
c, R = $NHCOCH_3$ f, R = OCH_3



3 4



5 6

TABLE I

Starting material	Product (yields, %)[a]			
	Endo–exo (5)	Exo–exo (4)	Endo–exo (5)	Exo–exo (6)
2a	3a (100)[b]			
2b	3b (50.2)			
2c	3c (9.3)	4c (5.5)	5c (6.5)	
2d	3d (49)			
2e	3e (27.1)		5e (17.4)	
2f	3f (6.3)		5f (16.5)	6f (6.8)

[a] Isolated yields. [b] Reference 9.

Structural assignments were made on the basis of elemental analyses and spectroscopic data. The mass spectrum of each adduct showed a molecular ion peak and common characteristic fragment peak (*m/e* 118, C_8H_6O, isobenzofuran) of the retrocycloaddition reaction. The ir spectra showed a characteristic band of the α,β-unsaturated carbonyl group at 1650–1690 cm^{-1}. Unequivocal structural determinations were made on the basis of the nmr data as shown in Table II; while the absence of appreciable couplings between $H_{1,2}$, $H_{2,3}$, and $H_{10,11}$ in the nmr indicated **3b** to be an endo–exo adduct, the presence of the coupling between H_1 and H_2 (J = 6.0 Hz) and the absence of appreciable couplings between $H_{2,3}$ and $H_{10,11}$ indicated **4c** to be an exo–exo adduct. Likewise, the configurations of other adducts were determined by complete analyses of the nmr spectra. The formation of the endo–exo tropolone adduct (**3d**) is in contrast to the exclusive formation of the exo–exo adduct (**4d**) in chlorobenzene.[9] The yields of the cycloadducts and the regioselectivity of the cycloaddition reactions decrease with increase in bulkiness of the substituents.

Irradiation of the Adducts.—These adducts were irradiated with a high-pressure 100-W mercury lamp through a Pyrex filter under nitrogen at room temperature in methanol (Scheme II). The reaction mixtures were analyzed by vapor phase chromatography and the products were separated by column chromatography. The results are summarized in Table III.

Structural proofs were based on elemental analyses and spectroscopic data. Irradiation of the aminotropone adduct **3b** led to a complicated mixture consisting of more than nine components by tlc. Since the mixtures were very air sensitive, all attempts to isolate the products were unsuccessful. Such observation might be attributable to the intramolecular charge transfer[11,12] between amino and carbonyl groups.

Irradiation of **3a**,[9] **3c**, **3e**, and **4c** gave exclusively cyclopropane esters in good yields (Table III). In all cases the possible intermediates were cyclopropylketene derivatives (**7**) which were obviously formed by [3,3] sigmatropic rearrangement. Irradiation of **5c** gave a similar product **9** in a low yield. This low yield might be explained by sterically unfavored addition of methanol to the initially formed ketene **7** (R_2 = $NHCOCH_3$).

On irradiation of **3f**, the dihydro derivative **8g** was obtained in addition to the normal [3,3] product **8f**. The dihydro compound **8g** might be produced by a path independent of the general [3,3] sigmatropic rearrangement path because no transformation of **8f** to **8g** was observed under the same photochemical conditions (see Discussion).

The ir spectra of these products showed a characteristic absorption of ester carbonyl group at 1720–1750 cm^{-1} instead of the original carbonyl one at 1650–1690 cm^{-1}. Unequivocal structural determinations were made on the basis of the nmr data as shown in Table IV. From these results, it has been concluded that the configurations of these adducts could not affect the photochemistry.

On irradiation of **3d**, a quite different type of reaction occurred. In this case, the diketone **13** was obtained in a nearly quantitative yield and no other ester products could be observed. The nature of **13** as an isomer of **3d** was apparent from its mass spectrum (M^+ 266). The ir spectrum showed two carbonyl bands at 1740 and 1700 cm^{-1}. The nmr spectrum exhibited signals at δ 1.3–2.5 (m, 6 H), 2.65 (d, 1 H, J = 4.5 Hz), 3.50

(10) (a) G. R. Ziegler, *J. Amer. Chem. Soc.*, **91**, 446 (1969); (b) R. N. Warrener, *ibid.*, **93**, 2346 (1971); (c) T. Sasaki, K. Kanematsu, K. Hayakawa, and M. Uchide, *J. Chem. Soc., Perkin Trans. 1*, 2750 (1972).

(11) Although acetylaminotropone is photoisomerized to the valence isomer, aminotropone is photochemically inactive because of the intramolecular charge transfer: T. Mukai and M. Kimura, *Tetrahedron Lett.*, 717 (1970).

(12) (a) S. G. Cohen and M. N. Saddiqui, *J. Amer. Chem. Soc.*, **86**, 5047 (1964); (b) S. G. Cohen and J. I. Cohen, *J. Phys. Chem.*, **72**, 3782 (1968).

TABLE II

NMR SPECTRA OF DIELS–ALDER ADDUCTS

Compd	δ, ppm (J, Hz) C-1	C-2	C-3	C-10	C-11	C-12	C-14	C-15	C-16	C-17	ArH
3b	3.48 (t, $J_{1,16}$ = 7.5, $J_{1,15}$ = 9.8)	2.03 (d, $J_{2,11}$ = 8.0)	5.00 (s)	5.80 (s)	2.50 (d)	2.16 (s, NH_2)	5.67 (d, $J_{14,15}$ = 8.25)	7.0–7.3[a]	6.40 (t, $J_{16,17}$ = 9.0)	5.70 (d)	7.0–7.3 (m)
3c	3.45 (t, $J_{1,16}$ = 7.5, $J_{1,15}$ = 7.5)	2.40 (d, $J_{2,11}$ = 7.5)	5.10 (s)	5.65 (s)	2.62 (d)	6.90 (s, NH) 2.13 (s, CH_3)	5.80 (d, $J_{14,15}$ = 11.3)	7.0–7.3[a]	6.50 (t, $J_{16,17}$ = 9.0)	6.20 (d)	7.0–7.3 (m)
3e	3.50 (t, $J_{1,15}$ = 7.5, $J_{1,16}$ = 9.0)	2.44 (d, $J_{2,11}$ = 7.5)	5.02 (s)	5.49 (s)	2.65 (d)	2.30 (s)	5.74 (d, $J_{14,15}$ = 11.3)	6.9–7.3[a]	6.40 (t, $J_{16,17}$ = 9.25)	6.20 (d)	6.9–7.3 (m)
3f	3.50 (t, $J_{1,16}$ = 7.5)	2.32 (d, $J_{2,11}$ = 7.5)	4.98 (s)	5.53 (s)	2.45 (d)	3.58 (s, CH_3)	5.65 (d, $J_{14,15}$ = 9.75)	6.9–7.3[a]	6.40 (t, $J_{16,17}$ = 9.0)	6.12 (d)	6.9–7.3 (m)
3d	3.49 (t, $J_{1,16}$ = 9.25, $J_{1,16}$ = 9.25)	2.10 (d, $J_{2,11}$ = 7.5)	5.04 (s)	5.70 (s)	2.48 (d)	4.70 (br s, OH)	5.75 (d, $J_{14,15}$ = 10.5)	7.0–7.4[a]	6.40 (t, $J_{16,17}$ = 9.25)	6.00 (d)	7.0–7.4 (m)
4c	3.60 (m)	2.55 (dd, $J_{2,11}$ = 8.25, $J_{2,1}$ = 6.0)	4.96 (s)	5.00 (s)	3.58 (d)	1.90 (s, NH) 2.15 (CH_3)	6.15 (d, $J_{14,15}$ = 10.5)	6.9–7.3[a]	6.50 (t, $J_{16,17}$ = 7.0)	6.13 (d)	6.9–7.3 (m)
5c	3.61 (t, $J_{1,15}$ = 9.75, $J_{1,16}$ = 9.25)	2.30 (d, $J_{2,11}$ = 9.0)	5.06 (s)	5.16 (s)	2.60 (d)	3.93 (d, $J_{12,1}$ = 7.5)	1.91 (s, NH) 2.00 (s, CH_3)	8.19 (d)	6.60 (t, $J_{16,17}$ = 8.3)	6.10 (t)	7.0–7.3 (m)
5e	3.55 (t, $J_{1,15}$ = 9.0, $J_{1,16}$ = 9.0)	2.44 (d, $J_{2,11}$ = 8.25)	5.03 (s)	5.13 (s)	2.67 (d)	3.90 (d, $J_{12,17}$ = 9.0)	2.14 (s, CH_3)	6.80 (d)	6.54 (t, $J_{16,17}$ = 7.5)	6.20 (t)	7.0–7.3 (m)
5f	3.50 (m)	2.15 (d, $J_{2,11}$ = 9.0)	5.03 (s)	5.12 (s)	2.55 (d)	3.89 (d, $J_{12,17}$ = 8.25)	3.44 (s, CH_3)	6.10 (d)	6.60 (t, $J_{16,17}$ = 9.0)	6.13 (t)	7.0–7.3 (m)
6f	3.85 (q, $J_{1,2}$ = 4.5)	2.45 (m)	5.00 (s)	5.05 (s)	2.52 (m)	3.55 (t, $J_{12,11}$ = 4.5)	3.60 (s, CH_3)	5.90 (d, $J_{1,15}$ = 9.0)	6.60 (t, $J_{16,17}$ = 6.75, $J_{16,1}$ = 9.0)	6.12 (t, $J_{12,17}$ = 6.0)	7.0–7.3 (m)

[a] Overlapped with aromatic protons.

SCHEME II

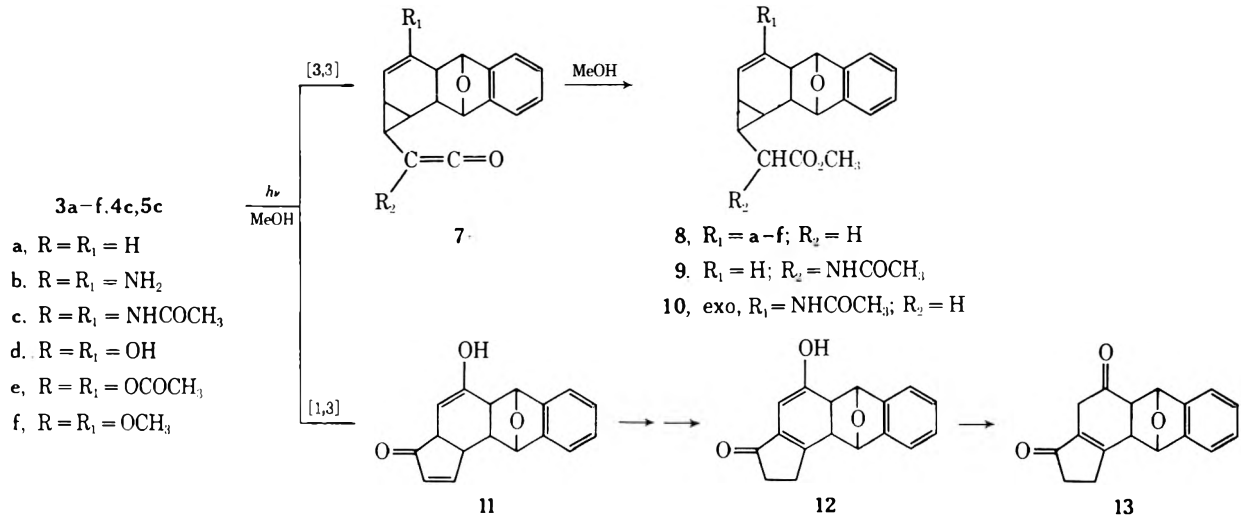


TABLE III

Starting material	Product (yield, %) [3,3] type	[1,3] type
3a	**8a** (100)	
3b	Decomposition	
3c	**8c** (100)	
3d		**13** (84)
3e	**8e** (100)	
3f	**8f** (45) + dihydro compound (**8g**) (19)	
4c	**10** (82)	
5c	**9** (28)	

(d, 1 H, J = 4.5 Hz), 5.33 (s, 1 H), 5.85 (s, 1 H), and 7.0–7.4 (m, 4 H). The formation of **13** could be explained in terms of the initial [1,3] acyl migration of **3d** to **11d** followed by successive [1,3] hydrogen shift to the conjugated diene **12d** and ultimate enol–keto tautomerization as shown in Scheme II.[9]

It is noteworthy that only the [1,3] sigmatropic rearrangement had occurred even in a nucleophilic solvent such as methanol. This is apparently due to the presence of the hydroxyl group at the bridgehead position (α to carbonyl group).

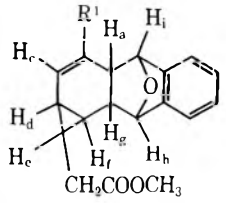
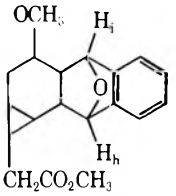
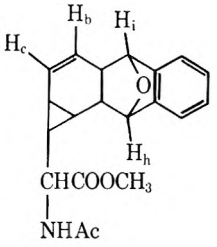
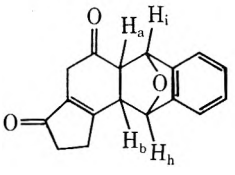
In further attempts to evaluate a role of the hydroxyl group in the photochemistry of the bicyclo[3.2.2]-nonadienone system, we have investigated the photochemical behavior of other α-hydroxy ketones such as **14**[13] and **15**.[14] These ketones were prepared from the Diels–Alder reaction of tropolone with benzyne[13] and *N*-phenylmaleimide,[14] respectively. Irradiation of **14**

(13) M. Kato, Y. Okamoto, and T. Miwa, *Tetrahedron*, **27**, 4013 (1971).

(14) Structural determination was based on elemental analysis and spectroscopic data (see Experimental Section).

TABLE IV

NMR SPECTRA OF PHOTOREARRANGED PRODUCTS

Structure	Compd	δ, ppm (J, Hz)					
		H_c	H_b,H_i	Ar–N	$COOCH_3$	R_1	Other protons
	8c	5.70 (d, J = 4.5)	5.15 (s)	7.0–7.5 (m)	3.59 (s)	$NHCOCH_3$ 2.15 (s)	0.7–2.8 (m, 8 H, NH, CH_2, H_a, H_d, H_e, H_f, and H_g)
	10	5.75 (d, J = 4.5)	5.25 (s)	6.9–7.4 (m)	3.62 (s)	$NHCOCH_3$ 2.08 (s)	2.0–3.0 (m, 5 H, NH, CH_2, H_a, and H_g), 1.2–1.9 (m, 3 H, H_d, H_e, and H_f)
	8e	5.55 (d, J = 6.0)	5.22 (s)	6.9–7.4 (m)	3.58 (s)	$OCOCH_3$ 2.18 (s)	1.2–2.5 (m, 7 H, CH_2, H_a, H_d, H_e, H_f, and H_g)
	8f	4.85 (d, J = 4.5)	5.20 (s) 5.30 (s)	7.0–7.4 (m)	3.60 (s)	OCH_3 3.60 (s)	1.0–2.3 (m, 7 H, CH_2, H_a, H_d, H_e, H_f, and H_g)
		H_h,H_i		$COOCH_3$	OCH_3		Other protons
	8g	5.25 (s) 5.60 (s)		3.40 (s)	3.33 (s)		1.0–3.3 (m, 10 H) 7.0–7.3 (m, 4 H)
		H_b,H_c	H_h,H_i	$COOCH_3$	$COCH_3$		Other protons
	9	5.95 (m)	4.98 (s), 5.19 (s)	3.70 (s)	1.90 (s)		1.1–2.0 (m, 4 H), 2.15 (d, 2 H), 4.05 (t, CH, J = 7.5, 9.0) 6.9–7.3 (m, 4 H)
		H_a	H_b	H_b,H_i			Other protons
	13	3.50 (d, J = 4.5)	2.65 (d)	5.33 (s), 5.85 (s)			1.3–2.5 (m, 6 H), 7.0–7.4 (m, 4 H)

in methanol was found to give a photoisomer **16** as only one isolable main product (17%) together with several minor products (see Scheme III). No ester products could be detected by nmr spectroscopy. The isomeric nature of **16** was confirmed by mass spectrum which displayed a molecular ion peak at *m/e* 198. The uv spectrum showed maxima at 215 nm (ε 68,000), 260 (157,000), 280 (80,000), 370 (7050), and 430 (382, sh), suggesting the presence of a naphthalene ring. The ir spectrum exhibited a band at 1670 cm^{-1}. Unequivocal structural assignments were made on the basis of its nmr spectrum: δ 2.75 (t, 2 H, J = 7.5 Hz), 3.25 (t, 2 H, J = 7.5 Hz), 2.5–3.0 (1 H, exchangeable by D_2O, OH), and 7.0–8.0 (m, 5 H, aromatic H).

Irradiation of **15** in methanol gave a diketone **17** in a quantitative yield (see Scheme III). The structural assignment was based on the spectral data: ir (KBr) 1790, 1740, 1710, and 1659 cm^{-1}; nmr ($CDCl_3$) δ 1.34–2.85 (m, 6 H, methylene), 3.68 (d, 1 H, J = 10.5 Hz), 3.75 (d, 1 H, J = 10.5 Hz), and 7.0–7.5 (m, 5 H, aromatic).

These results indicate that [1,3] sigmatropic rearrangement is more significant than [3,3] rearrangement on irradiation of the tropolone adduct even in a nucleophilic solvent. This is in a sharp contrast to Kende's conclusion for the tropone adduct.[5] Attempts to sensitize photolysis of **15** in methanol using benzophenone (absorbing over 90% of incident light) sharply retarded the appearance of **17** and led to a complex mixture (no ester products by nmr inspection).[15]

This strongly suggested that the [1,3] rearrangement of a tropolone adduct may arise from a singlet excited state similar to [1,3] and [3,3] rearrangements of tropone adducts.[5,6] Thus, the presence of a hydroxyl group at the bridgehead position (α to carbonyl carbon) is a major factor governing the photoisomerization of this system. This can be explained in terms of intramolecular hydrogen bonding between carbonyl oxygen and hydroxyl group.[16] Evidence for such hydrogen bonding in the excited state was obtained by the uv spectral comparison of **3a**[9] with **3d** in various solvents (Table V).

For a tropone adduct **3a**, the typical solvent dependence on n–π* transition (*i.e.*, hypsochromic shift with increasing solvent polarity)[17] was observed. In

(15) Use of benzophenone as a sensitizer in a solvent with readily abstractable hydrogen atoms can lead to photoreduction of the substrate due to hydrogen abstraction by excited benzophenone followed by hydrogen atom transfer to the substrate. Unless the concentration of substrate is high enough to quench the benzophenone triplet efficiently, this can be the predominant reaction. This may be the reason for the complex mixture which was observed.

(16) The reaction course of tropolone adduct could not be changed by replacement of the H bond with a weaker D bond, since irradiation of **15** in CH_3CN–D_2O (1:1), in which over 90% of the hydroxyl proton was exchanged by D_2O, gave exclusively the [1,3] product.

(17) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, New York, N. Y., 1965.

SCHEME III

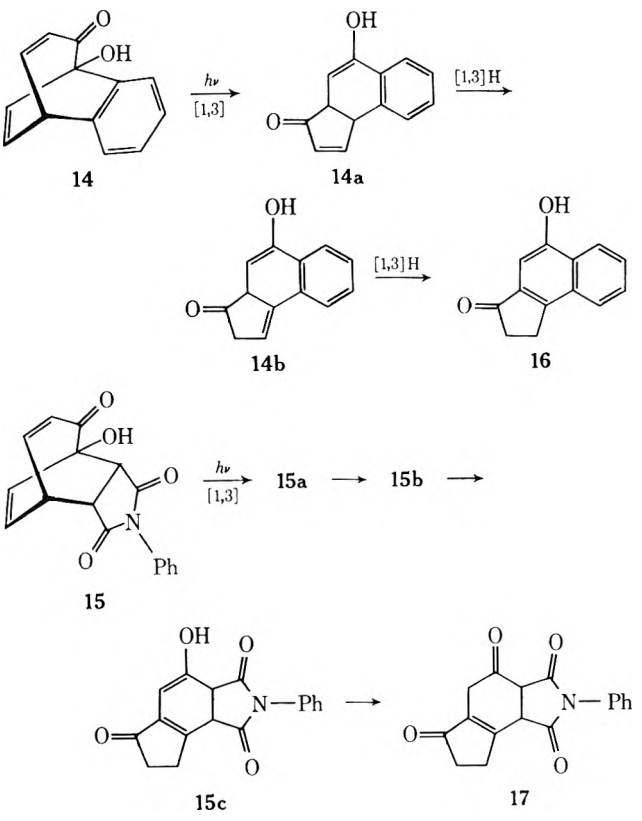


TABLE V

Solvent	Dielectric constant[a]	λ_{max}, nm (ε) 3a	3d
n-Hexane	1.87	355 (52)	335 (102)
Chloroform	4.9	350 (121)	335 (143)
Ethanol	25.7	350 (100)	335 (100)
Methanol	33.7	345 (108)	335 (114)
Acetonitrile	38.8	345 (106)	332 (124)

[a] International Critical Tables (at 20°).

contrast, the uv spectrum of the tropolone adduct **3d** was not affected by changing the solvents. These differences are probably attributed to the intramolecular hydrogen bonding of the ketone **3d**.

Further, the hydroxyl absorption of **3d** in 1 and 10% chloroform solutions by ir showed the same pattern suggesting the presence of intramolecular hydrogen bonding.

According to the Woodward–Hoffmann rule,[18] suprafacial [$_{\pi}2_s + {}_{\sigma}2_s$] [1,3] sigmatropic rearrangement is photochemically allowed, but a [3,3] shift is symmetry forbidden.

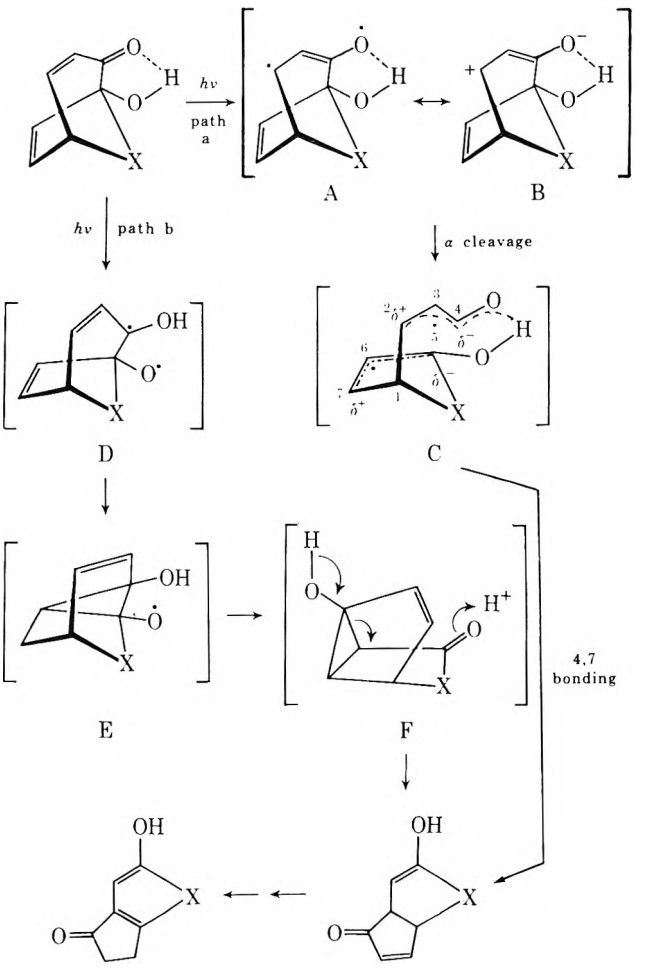
From these results, two mechanistic paths a and b may be postulated to account for the formation. Assuming the initial α cleavage of the tropolone adducts to give the diradical intermediate C, the above results can be depicted in Scheme IV; the α cleavage of ketones is well known to be favored by substitution α to the carbonyl.[19,20] Two allyl radical moieties (*i.e.*, C_2–C_3–C_4 and C_5–C_6–C_7) in C must be somewhat polarized by the intramolecularly hydrogen-bonded oxygens.

(18) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie-Academic Press, New York, N. Y., 1970.

(19) (a) P. J. Wagner and R. W. Spoerk, *J. Amer. Chem. Soc.*, **91**, 4437 (1969); (b) J. C. Dalton, D. M. Pond, D. S. Weuss, F. D. Lewis, and N. J. Turro, *ibid.*, **92**, 564 (1970).

(20) W. C. Agosta and A. B. Smith, III, *J. Amer. Chem. Soc.*, **93**, 5513 (1971).

SCHEME IV



Hence 2,5 and 4,7 bonding rather than 2,7 bonding would be electronically favored. Considering the stability of the resulting structures, it is apparent that 4,7 bonding is more favored than 2,5 bonding which would lead to a more strained structure (*i.e.*, bicyclo[2.2.1]heptene). In other cases[3,5,9] where there is no such hydrogen bonding, 2,7 bonding (*i.e.*, [3,3] rearrangement) is most favored because of the closer bond distance between C-2 and C-7. On the other hand path b might proceed by a complete hydrogen atom transfer to the carbonyl, followed by a "walk" process (*via* D → E) and then a prototropic shift.[21]

The formation of the photoreduction product **8g** from the ketone **3f** suggests the diradical mechanism depicted in Scheme V. The initially formed diradical intermediates G and H are somewhat stabilized by the methoxyl group and abstract hydrogen from the solvent leading to **8g**. Thus, path c could compete with path d *via* intramolecular ring closure by [3,3] rearrangement.

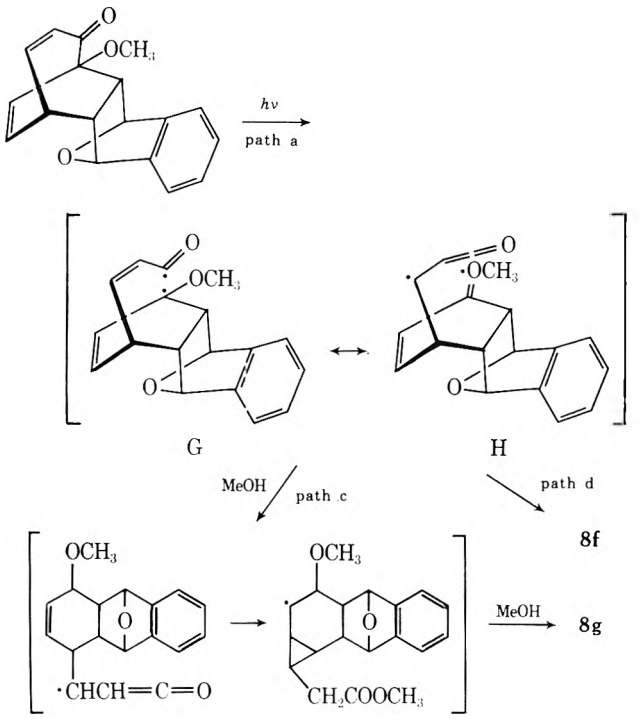
From these results, it is to be noted that intramolecular hydrogen bonding plays an important role in governing the photoisomerization of the bicyclo[3.2.2]nonadienone system, although further studies are necessary to settle the mechanism.

Experimental Section

Melting points are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Uv spectra were determined with a JASCO ORD-UV-5 recorder. Nmr

(21) We are indebted to a referee for pointing out this possibility to us.

SCHEME V



spectra were taken with a JEOL C-60-XL spectrometer and with a Varian A-60 recording spectrometer, with tetramethylsilane as internal standard. Ir spectra were taken with a JASCO-IR-S spectrophotometer. Mass spectra were obtained with a Hitachi RMU-D double-focusing spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150°. Glpc analyses were performed with a NEVA gas chromatograph Model 1400 and preparative glpc with a Varian Aerograph Model 700 (silicon SE-30).

General Procedure for Cycloaddition Reactions.—A solution of 1:1 mixture of oxabenzonorbornadiene (1) and 2-substituted tropone in toluene was heated at 130° in a sealed tube for 40 hr. After removal of the solvent, the reaction mixture was analyzed by glpc and then purified by chromatography on a silica gel column.

A. With 2-Aminotropone (2b).—A solution of 595 mg of 1 and 500 mg of **2b** in 50 ml of toluene was heated. Work-up gave 550 mg of adduct **3b** as colorless crystals: mp 151–153° (benzene); ir (KBr) 3400, 1660 cm^{-1}; uv (ethanol) λ_{max} 225 nm (ϵ 6160), 263 (1620), 271 (1040), 340 (108); *m/e* 265 (parent), 118.

Anal. Calcd for $C_{17}H_{15}O_2N$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.66; H, 5.70; N, 5.21.

B. With 2-Acetylaminotropone (2c).—A solution of 1.2 g of 1 and 1.3 g of **2c** in 50 ml of toluene was heated. The reaction mixture was subjected to silica gel chromatography using chloroform. The first fraction gave 120 mg of adduct **5c** as colorless crystals: mp 177–179 (benzene–ethanol); ir (KBr) 3350, 1685, 1650, 1620, 1510 cm^{-1}; uv (ethanol) λ_{max} 264 nm (ϵ 3070), 271 (3200), 284 (3420), 345 (192); *m/e* 307 (parent), 118.

Anal. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.20; H, 5.66; N, 4.80.

The second fraction gave 100 mg of adduct **4c** as colorless crystalls: mp 220° dec (benzene–ethanol); ir (KBr) 3500, 1680, 1645, 1500 cm^{-1}; uv (ethanol) λ_{max} 240 nm (ϵ 4300), 265 (2580), 270 (1650), 330 (74) *m/e* 307 (parent), 118.

Anal. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.53; H, 5.74; N, 4.52.

The third fraction gave 170 mg of adduct **3c** as pale yellow crystals: mp 229° (benzene–ethanol); ir (KBr) 3400, 1690, 1655, 1520 cm^{-1}; uv (ethanol) λ_{max} 262 nm (ϵ 2080), 272 (1200), 340 (100); *m/e* 307 (parent), 118.

Anal. Calcd for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.88; N, 4.56. Found: C, 74.48; H, 5.78; N, 4.41.

C. With Tropolone (2d).—A solution of 520 mg of 1 and 400 mg of **2d** in 50 ml of toluene was heated. Work-up gave 450 mg of adduct **3d** as colorless crystals: mp 166–167.5° (ethanol); ir (KBr) 3400, 1650, 1630, 1100 cm^{-1}; uv (ethanol) λ_{max} 265 nm (ϵ 1690), 270 (980), 340 (84); *m/e* 266 (parent), 118.

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.46; H, 5.40.

D. With 2-Acetoxytropone (2e).—A solution of 590 mg of 1 and 620 mg of **2e** in 50 ml of toluene was heated. After evaporation of the solvent, the resulting residue was subjected to silica gel chromatography and fractional crystallization from ethanol to give 330 mg of adduct **3e** and 210 mg of adduct **5e**.

For the first, **3e**, the following was observed: mp 209–211° (ethanol); ir (KBr) 1740, 1660, 1240, 1060 cm^{-1}; uv (ethanol) λ_{max} 260 nm (ϵ 1620), 269 (1020), 340 (137); *m/e* 308 (parent), 118.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.96; H, 5.28.

For the second, **5e**, the following was observed: mp 189–191° (ethanol); ir (KBr) 1755, 1660, 1205 cm^{-1}; uv (ethanol) λ_{max} 265 nm (ϵ 2200), 270 (1440), 340 (59); *m/e* 308 (parent), 118.

Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.90; H, 5.34.

E. With 2-Methoxytropone (2f).—A solution of 480 mg of 1 and 550 mg of **2f** was heated. The reaction mixture was chromatographed on a silica gel column using benzene–acetone. The first fraction gave 65 mg of adduct **3f** as colorless crystals: mp 128–130° (ethanol); ir (KBr) 1655, 1105 cm^{-1}; *m/e* 280 (parent), 118.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.10; H, 5.79.

The second fraction gave 170 mg of adduct **5f** as colorless crystals: mp 185–188° (ethanol); ir (KBr) 1650, 1630, 1600, 1220, 1200, 1140, 1120 cm^{-1}; uv (ethanol) λ_{max} 265 nm (ϵ 3090), 267 (3220), 274 (3360), 280 (3190), 330 (174); *m/e* 280 (parent), 118.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.08; H, 5.79.

The third fraction gave 70 mg of adduct **6f**: mp 175–178° (ethanol); ir (KBr) 1650, 1620, 1610, 1120 cm^{-1}; *m/e* 280 (parent), 118.

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.00; H, 5.69.

General Procedure for Irradiations.—A solution of the adduct in dry methanol was irradiated by a high-pressure 100-W mercury lamp through a Pyrex filter under nitrogen at room temperature. The photolyses were monitered by tlc and glpc. The solvent was removed under reduced pressure, and the residue was analyzed by nmr and then purified by silica gel chromatography.

Photolysis of 3b.—A solution of 200 mg of **3b** in 50 ml of methanol was irradiated for 1 hr. Tlc analysis indicated the presence of more than nine components which decomposed to intractable materials during the purification.

Photolysis of 3c.—A solution of 100 mg of **3c** in 50 ml of methanol was irradiated for 75 min. Work-up gave 110 mg of ester (**8c**) as pale yellow crystals: mp 72–73° (benzene–hexane); ir (KBr) 3280, 1725, 1650, 1540 cm^{-1}; *m/e* 339 (parent), 118.

Anal. Calcd for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.91; H, 6.44; N, 3.92.

Photolysis of 4c.—A solution of 60 mg of **4c** in 40 ml of methanol was irradiated for 1 hr. Nmr analysis of the reaction mixture indicated the presence of unconverted **4c** (18%) and ester **10** (82%). After removal of solvent, the residue was subjected to silica gel chromatography using chloroform. The first fraction gave 50 mg of **10** as colorless crystals: mp 143–145° (benzene–hexane); ir (KBr) 3250, 1730, 1650, 1540 cm^{-1}; *m/e* 339 (parent), 118.

Anal. Calcd for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.88; H, 6.35; N, 4.01.

Photolysis of 5c.—A solution of 1.0 g of **5c** in 100 ml of methanol was irradiated for 11 hr. Work-up gave 310 mg of **9** as colorless crystals: mp 104–106° (benzene–hexane); ir (KBr) 3300, 1740, 1650, 1530 cm^{-1}; *m/e* 339 (parent), 118.

Anal. Calcd for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.53; H, 6.18; N, 4.00.

Photolysis of 3d. A solution of 250 mg of **3d** in 50 ml of methanol was irradiated for 1.5 hr. Work-up gave 210 mg of diketone **13** as colorless crystals: mp 193–195° (benzene–hexane); ir (KBr) 1740, 1700, 850, 760 cm^{-1}; *m/e* 266 (parent), 118.

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.45; H, 5.51.

Photolysis of 3e.—A solution of 70 mg of **3e** in 50 ml of methanol was irradiated for 0.5 hr. After evaporation of the solvent, the resulting residue was recrystallized from methanol to give 80 mg of **8e** as colorless crystals: mp 145.5–146°; ir (KBr) 1750, 1730, 1230, 1200 cm^{-1}; *m/e* 340 (parent), 118.

Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.41; H, 5.74.

Photolysis of 3f.—A solution of 75 mg of **3f** in 50 ml of methanol was irradiated for 0.5 hr. After evaporation of the solvent, the resulting residue was subjected to silica gel chromatography and then fractional crystallization from ether to give 50 mg of **8f** and 25 mg of **8g**.

For the first, **8f**, the following was observed: mp 97–98° (benzene–hexane); ir (KBr) 1730, 1660 1210, 1170 cm^{-1}; *m/e* 312 (parent), 118.

Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.03; H, 6.44.

For the second, **8g**, the following was observed: mp 212–214° (petroleum ether); ir (KBr) 1730, 1110 cm^{-1}; *m/e* 314 (parent), 118.

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.88; H, 6.99.

Reaction of 2d with *N*-Phenylmaleimide.—A solution of 500 mg of **2d** and 775 mg of *N*-phenylmaleimide in 30 ml of toluene was refluxed for 9 hr. Evaporation of the solvent under the reduced pressure gave a pale yellow residue which was recrystallized from ethanol to give 560 mg of colorless solid. Glpc and nmr analyses showed it to be a mixture of endo adduct **15** and exo adduct in the ratio 2:1. Because of its low solubility, the purification was very difficult and only major product **15** was isolated as colorless crystals by fractional crystallization from ethanol: mp 213–215°; ir (KBr) 3400, 1780, 1700, 1670, 1380 cm^{-1}; nmr ($CDCl_3$) δ 3.46 (d, 1 H, *J* = 7.5 Hz), 3.62 (d, 1 H, *J* = 7.5 Hz), 4.10 (m, 1 H), 4.90 (s, 1 H, exchangeable by D_2O), 6.0–6.3 (m, 3 H), 6.55 (t, 1 H, *J* = 9.0 Hz), 7.0–7.5 (m, 5 H); *m/e* 295 (parent).

Anal. Calcd for $C_{17}H_{13}O_4N$: C, 69.14; H, 4.44; N, 4.74. Found: C, 69.01; H, 4.63; N, 4.75.

Photolysis of 14.—A solution of 106 mg of **14** in 50 ml of methanol was irradiated for 2 hr under the same conditions as above. The reaction mixture was analyzed by nmr and then chromatographed on a silica gel column using chloroform. The first fraction gave 10 mg of unconverted **14**. The second fraction gave 15 mg of photoproduct **16**: mp 134–135° (ethanol); ir (KBr) 3300, 1665, 1585 cm^{-1}; *m/e* 198 (parent).

Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.54; H, 5.13.

Photolysis of 15.—A suspension of 150 mg of **15** in 50 ml of methanol was irradiated for 1 hr. After removal of the solvent, the resulting residue was chromatographed using chloroform. The first fraction gave 10 mg of unconverted **15** and the second fraction gave 90 mg of diketone **17** as colorless crystals: mp 199–201° (benzene–ethanol); ir (KBr) 1780, 1740, 1710, 1695, 1500 cm^{-1}; *m/e* 295 (parent).

Anal. Calcd for $C_{17}H_{13}O_4N$: C, 69.14; H, 4.44; N, 4.74. Found: C, 69.39; H, 4.57; N, 4.62.

Registry No.—**1**, 573-57-9; **2a**, 539-80-0; **2b**, 6264-93-3; **2c**, 6422-12-4; **2d**, 533-75-5; **2e**, 33739-54-7; **2f**, 2161-40-2; **3a**, 38276-32-3; **3b**, 42150-82-3; **3c**, 42150-83-4; **3d**, 42150-84-5; **3e**, 42150-85-6; **3f**, 42150-86-7; **4c**, 42150-87-8; **5c**, 42150-88-9; **5e**, 42150-89-0; **5f**, 42150-90-3; **6f**, 42150-91-4; **8c**, 42150-92-5; **8e**, 42150-93-6; **8f**, 42150-94-7; **8g**, 42150-95-8; **9c**, 42150-96-9; **13**, 38276-37-8; **14**, 33655-59-3; **15**, 42150-99-2; *exo*-**15**, 42151-00-8; **16**, 5824-32-8; **17**, 42151-02-0; *N*-phenylmaleimide, 941-69-5.

Halogenated Ketenes. XXIV. Cycloaddition of Alkylhaloketenes and Methylenecycloalkanes. Spiro Compounds[1]

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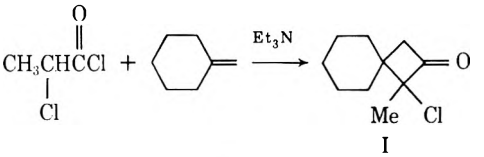
The cycloaddition of methylchloroketene with methylenecyclohexane, methylenecyclobutane, β-pinene, and 5-methylene-2-norbornene to yield the corresponding spiro[3.5] and spiro[3.3] ketones has been investigated. The cycloaddition of ethylchloroketene with methylenecyclobutane is also described. The spiro ketones are all readily reduced to the corresponding spiro alcohols. Some base-catalyzed rearrangement reactions are described including ring contractions to spiro[5.2] compounds.

A number of reports have appeared in recent years on the cycloaddition of ketenes and olefinic compounds. The majority of these reports have been concerned with the reactive cyclopentadiene and/or other activated olefins. Cycloadditions with methylenecycloalkanes has received little attention and in the scattered reports few details are given.[2-4]

We now report the cycloaddition of the reactive alkylhaloketenes and methylenecycloalkanes to yield [3.*n*] spiro ketones depending on the particular methylenecycloalkane employed. The spiro ketones and particularly the spiro alcohols undergo a base-catalyzed ring contraction reaction to yield other spiro compounds, thus providing an excellent general method for a wide variety of spiro compounds.

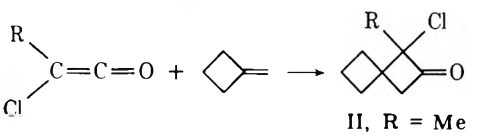
The *in situ* cycloaddition of methylchloroketene and methylenecyclohexane resulted in a 60% yield of the spiro[5.3]nonanone I. The optimum conditions



I

for effecting this cycloaddition are in refluxing hexane. A slow addition of acid halide to the amine and olefin in hexane are desirable to minimize the formation of the α-halovinyl ester.[5,6]

This *in situ* cycloaddition also occurs with methylenecyclobutane to yield the corresponding spiro[3.3]-heptanones in 30 and 35% yields, respectively (II and III). The yield is lower with this olefin because the



II, R = Me
III, R = Et

(1) Paper XXIII: W. T. Brady and G. A. Scherubel, *J. Amer. Chem. Soc.*, in press.

(2) P. R. Brook and J. G. Griffiths, *Chem. Commun.*, 1344 (1970).

(3) R. Maurin and M. Bertrand, *Bull. Soc. Chim. Fr.*, 998 (1970).

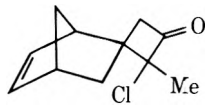
(4) J. R. Wiseman and H. F. Chan, *J. Amer. Chem. Soc.*, **92**, 4749 (1970).

(5) R. Giger, M. Rey, and A. S. Dreiding, *Helv. Chim. Acta*, **51**, 1466 (1968).

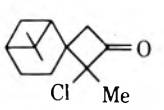
(6) W. T. Brady, F. H. Parry, III, R. Roe, Jr., E. F. Hoff, Jr., and L. Smith, *J. Org. Chem.*, **35**, 1515 (1970).

boiling point of the olefin dictates a lower reaction temperature. It was found desirable to isolate and distil these cycloadducts as soon after cycloaddition as possible because of side reactions which reduced the amount of cycloadducts isolated. The symmetrical nature of these three spiro compounds dictates only one isomer in each case.

The cycloadditions of methylchloroketene with 5-methylene-2-norbornene and β-pinene produce the following spiro[3.5] compounds in 65% yields (IV and V, respectively).



IV



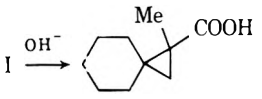
V

It is interesting to note that in the case of 5-methylene-2-norbornene two double bonds are available for cycloaddition with the ketene; yet cycloaddition occurs exclusively at the exo double bond, even though the strain is much greater in the internal double bond. This is a further indication that ketene olefin cycloadditions are in fact sterically controlled.[7]

Ethylchloroketene also undergoes cycloaddition with these two olefins; however, purification of the cycloadducts was difficult because of decomposition which occurs upon vacuum distillation.

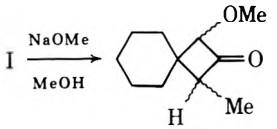
The *in situ* cycloaddition of dimethylketene with 5-methylene-2-norbornene in refluxing hexane was done in an effort to quantitatively compare this ketene with the alkylhaloketenes. The dimethylketene cycloadduct was produced as evidenced by ir and nmr spectra but in a yield of less than 10%. The cycloadduct was predominantly the spiro ketone resulting from cycloaddition with the exo double bond with some evidence of the other cycloadduct being present.

In an effort to effect a Favorskii-type ring contraction of I, this ketone was heated with aqueous base. Only a small amount of the ring-contracted acid was observed.[8,9]



VI

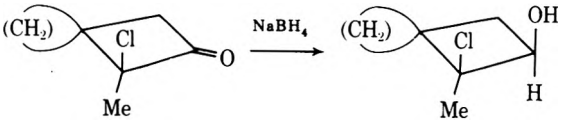
Treatment of I with NaOMe in methanol resulted in an allylic substitution through the enolate rather than ring contraction to produce the methoxy ketone VII. This is further evidence that only those halo-



VII

genated ketene–olefin cycloadducts will undergo the base-catalyzed ring contraction when the enol form is retarded, *i.e.*, cyclopentadiene adducts.[10]

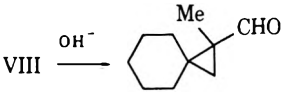
The sodium borohydride reduction of the five cycloadduct spiro ketones described above was effected in ethanol to give a quantitative or near-quantitative yield of the corresponding alcohols (VIII–XII). Of



VIII-XII

the two possible isomeric alcohols, only one was detected and this is believed to be the alcohol where the chloro and hydroxy substituents are cis. This is consistent with what Brook and Duke observed for the reduction of the cycloadducts of methylchloro- and chloroketene with cyclopentadiene.[6] The C–Cl dipole effect directs attack on the methyl side of the ketone, thus producing the alcohol shown.

1-Chloro-1-methylspiro[3.5]-2-nonanol (VIII) upon treatment with aqueous base underwent a ring contraction reaction in good yield to produce 1-methylspiro[2.5]octane-1-carboxaldehyde (XIII). Reduction



XIII

of the spiro ketone to the alcohol eliminates the undesirable enolization such that the allylic substitution reaction cannot occur and a smooth ring contraction takes place. The other spiro alcohols were also susceptible to this ring-contraction reaction. The spiro aldehydes produced are very sensitive to oxidation to the corresponding acids.

The following conclusions are drawn from this study.

(1) The cycloaddition of alkylhaloketenes with methylenecycloalkanes occurs in good yield under the appropriate conditions to yield spiro ketones. The halogenated ketenes appear to be much superior to alkylketenes in terms of yields of cycloadduct.

(2) These spiro ketones are not easily susceptible to base-catalyzed ring contraction reactions as are the cyclopentadiene adducts.

(3) Reduction of the spiro ketones to the corresponding alcohols and subsequent base-catalyzed ring contraction occurs smoothly to the spiro aldehydes, although these aldehydes are quite susceptible to oxidation.

(4) These cycloaddition and ring-contraction reactions represent an excellent general method for the preparation of various types of spiro compounds.

Experimental Section

Proton nmr spectra were recorded on Jeolco Minimar 60-MHz and Jeolco PS-100 nmr spectrometers employing tetramethylsilane as an internal standard and CCl_4 as the solvent. Vpc was performed on a F & M Scientific Model 700 gas chromatograph with a 10 ft × 0.25 in. column packed with 10% SE-30 on acid-washed Chromosorb W (80–100). Hexane and triethylamine were distilled from sodium and stored over Linde type 4-A Molecular Sieve.

General Procedure for *in Situ* Alkylhaloketene–Methylenecycloalkane Cycloadditions.—To a stirred, refluxing solution of 1 mol of methylenecycloalkane and 1.5 mol of triethylamine in hexane was slowly added 1 mol of α-chloropropionyl chloride. After the addition was complete, the reaction mixture was stirred for an additional 2 hr. The amine salt was removed by filtration

(7) W. T. Brady and R. Roe, Jr., *J. Amer. Chem. Soc.*, **93**, 1662 (1971).
(8) P. R. Brook and A. J. Duke, *Chem. Commun.*, 652 (1970).
(9) W. T. Brady and J. P. Hieble, *J. Amer. Chem. Soc.*, **94**, 4278 (1972).
(10) W. T. Brady and J. P. Hieble, *J. Org. Chem.*, **36**, 2033 (1971).

and the filtrate was concentrated on a rotatory evaporator and vacuum distilled to yield the cycloadduct spiro ketones.

1-Chloro-1-methylspiro[3.5]-2-nonanone (I).—This cycloadduct distilled at 67–70° (0.6 mm) (60%): ir 1785 cm^{-1} (C=O); nmr δ 1.5 (m, 13 H, singlet of methyl protons is meshed in this multiplet with cyclohexane methylene protons) and 2.78 (s, 2 H).

Anal. Calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.04. Found: C, 64.21; H, 7.91.

1-Chloro-1-methylspiro[3.3]-2-heptanone (II).—This cycloadduct distilled at 55° (0.8 mm) (30%): ir 1800 cm^{-1} (C=O); nmr δ 1.58 (s, 3 H), 2.0 (m, 4 H), 2.5 (m, 2 H), and 3.25 (s, 2 H).

Anal. Calcd for $C_8H_{11}ClO$: C, 60.56; H, 6.94. Found: C, 60.32; H, 6.88.

Cycloadduct of Methylchloroketene and β-Pinene (V).—This cycloadduct distilled at 95–98° (0.25 mm) (60%): ir 1785 cm^{-1} (C=O); nmr δ 0.98 (2 s, 3 H), 1.25 (s, 3 H), 1.6 (s, 3 H), 2.0 (m, 8 H), and 3.0 (s, 2 H).

Anal. Calcd for $C_{13}H_{19}ClO$: C, 68.87; H, 8.39. Found: C, 68.73; H, 8.42.

Cycloadduct of Methylchloroketene and 5-Methylene-2-norbornene (IV).—This cycloadduct distilled at 76–78° (0.5 mm) (70%): ir 1785 cm^{-1} (C=O); nmr δ 1.5 (m, 7 H), 3.0 (m, 4 H), and 6.45 (m, 2 H).

Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.17; H, 6.61. Found: C, 66.92; H, 6.53.

1-Chloro-1-ethylspiro[3.3]-2-heptanone (III).—Distillation occurred at 60° (0.6 mm) (35%): ir 1800 cm^{-1} (C=O); nmr δ 1.05 (t, 3 H), 1.85 (q, 2 H), 2.2 (m, 6 H), and 3.18 (s, 2 H).

Anal. Calcd for $C_9H_{13}ClO$: C, 62.60; H, 7.53. Found: C, 62.42; H, 7.51.

Rearrangement of I (VI).—A 2.5-g (2.7 mmol) portion of I was treated with 50 ml of 15% aqueous NaOH solution at 70° with stirring for 2 hr. After acidification with dilute HCl, the mixture was extracted with CCl_4 and dried over anhydrous $CaCl_2$. Vacuum distillation afforded a colorless oil at 90–100° (0.2 mm) (10%): nmr δ 0.43 (d, 1 H), 0.8 (d, 1 H), 1.25 (s, 3 H), 1.5 (m, 10 H), and 11 (s, 1 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.42; H, 9.52. Found: C, 71.59; H, 9.41.

Methoxy Substitution of I (VII).—A 5-g portion of I was treated with an excess of sodium methoxide in about 50 ml of methanol. An immediate precipitation of NaCl was observed. After removal of the salt by filtration and the solvent by evaporation, the substitution product was distilled at 60–62° (0.6 mm) to yield 3.4 g (70%): ir 1785 cm^{-1} (C=O); nmr δ 1.2 (d, 3 H), 1.5 (m, 10 H), 2.6 (m, 1 H), 3.4 (m, 3 H), and 4.05 (s 2, 1 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.52; H, 9.89. Found: C, 72.34; H, 9.73.

General Procedure for Reduction of Spiro Ketones.—To a stirred solution of 0.1 mol of the spiro ketone in 100 ml of absolute ethanol was slowly added at room temperature sodium borohydride until all the cycloadduct had been reduced. The course of the reduction was followed by vpc analysis. After the reduction was complete, the solvent was removed under reduced pressure and the residue was acidified and extracted with CCl_4. Upon distillation, a quantitative yield of the corresponding alcohol was obtained. Nmr and vpc analysis indicated that only one isomer was produced.

1-Chloro-1-methylspiro[3.5]-2-nonanol (VIII).—This spiro alcohol distilled at 62–63° (0.6 mm): ir 3500 cm^{-1} (OH); nmr δ 1.5 (m, 15 H; there is a singlet out of this multiplet at 1.6 which corresponds to the methyl protons), 3.4 (s, 1 H), and 4.0 (t, 1 H).

1-Chloro-1-methylspiro[3.3]-2-heptanol (IX).—Distillation occurred at 43–45° (0.6 mm): ir 3500 cm^{-1} (OH); nmr δ 1.45 (s, 3 H), 1.8 (m, 8 H), 3.4 (s, 1 H), and 3.65 (t, 1 H).

Anal. Calcd for $C_8H_{13}ClO$: C, 59.81; H, 8.09. Found: C, 59.72; H, 8.12.

Reduction of III (X).—This alcohol distilled at 85–87° (0.25 mm): ir 3500 cm^{-1} (OH); nmr δ 2.88 (s, 1 H of OH), other protons are in multiplet.

Reduction of IV (XI).—This spiro alcohol distilled at 70–72° (0.6 mm): ir 3500 cm^{-1} (OH); nmr δ 2.88 (s, 1 H), 3.75 (m, 2 H), and 6.45 (m, 2 H).

1 Chloro-1-ethylspiro[3.3]-2-heptanol (XII).—Distillation occurred at 51° (1.0 mm): ir 3500 cm^{-1} (OH); nmr δ 1.0 (t, 3 H), 2.0 (m, 10 H), 2.84 (s, 1 H), and 2.6 (t, 1 H).

1-Methylspiro[2.5]octane-1-carboxaldehyde (XIII).—A 5-g portion of the spiro alcohol VIII was treated with 50 ml of 15% aqueous NaOH solution at 70° with stirring for 2–3 hr. The ring-contracted product was extracted with CCl_4 and the extract was dried over anhydrous $CaCl_2$. Vacuum distillation afforded 2.8 g (70%) of the spiro aldehyde at 52–55° (0.5 mm): ir 1705 cm^{-1} (C=O); nmr δ 0.65 and 1.0 (2 d, 2 H), 1.25 (s, 3 H), 1.5 (m, 10 H), and 9.22 (s, 1 H).

This aldehyde was very susceptible to oxidation and did not give an acceptable elemental analyses for this reason. Consequently, the aldehyde was oxidized to the corresponding acid as described below.

1-Methylspiro[2.5]octane-1-carboxylic Acid (XIV).—A 0.5-g portion of XIII was suspended in 20 ml of dilute NaOH solution and treated dropwise at room temperature with a saturated aqueous potassium permanganate solution until the permanganate color persisted. After acidification of the basic reaction mixture, the acid was extracted with CCl_4. The extract was dried and the solvent was evaporated to yield an acid which was identical with VI.

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Registry No.—I, 42200-05-5; II, 42077-46-3; III, 42077-47-4; IV, 42077-48-5; V, 42077-49-6; VI, 42077-50-9; VII, 42077-51-0; VIII, 42077-52-1; IX, 42077-53-2; XI, 42077-54-3; XII, 42077-55-4; XIII, 42077-56-5; methylchloroketene, 7623-09-8; β-pinene, 127-91-3; 5-methylene-2-norbornene, 694-91-7.

Studies on the Stereochemistry of Polar 1,4 Addition of Bromine to Dienes. Structure Assignments for Dibromocyclohexenes and Dibromohexenes

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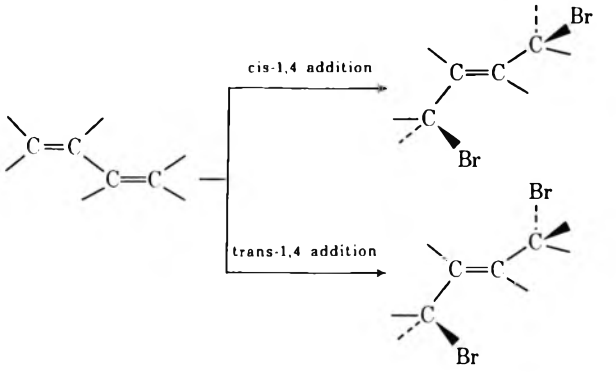
The compositions of dibromide mixtures obtained from the polar bromination of cyclopentadiene, 1,3-cyclohexadiene, and (*Z,Z*)-, (*E,Z*)-, and (*E,E*)-2,4-hexadiene under conditions of kinetic control have been determined. Compositions of equilibrated products were also determined. The stereochemistry of 1,4 addition is found to be primarily cis. The extent of 1,4 addition, which occurs cis, is highest with 1,3-cyclohexadiene and lowest with cyclopentadiene (96 and 52%, respectively, in carbon tetrachloride). The extent of cis 1,4 addition to the 2,4-hexadienes varies from 62 to 92% depending on diene and solvent. Structures of the 1,4-dibromides obtained from the 2,4-hexadienes, *rac*- and *meso*-2,5-dibromo-(*E*)-3-hexene, were proved by conversion *via* glycols to 2,3,4,5-diepoxyhexanes. The 1,2 addition to the 2,4-hexadienes was found to be nonstereospecific (91–69% trans addition), suggesting extensive charge dispersal in the intermediate vinylic bromonium ions of this system. Assignment of the structures of the three cyclohexadiene dibromides are established from their proton nmr spectra, physical properties, infrared spectra, and equilibrations. The proton nmr spectra of the three cyclopentadiene dibromides are shown to be completely consistent with previous structural assignments based on dipole moment measurements.

An important mechanistic problem which remains to be fully investigated is that of the stereochemistry of the 1,4 addition to 1,3-dienes. For example, the bromine molecule can add either cis or trans to the 1,4 carbon atoms of a diene, as illustrated by the following equations.

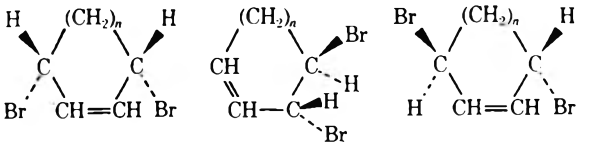


Previous studies on the polar bromination of certain acyclic conjugated dienes have shown that the 1,4-dibromide product consists predominantly of the trans isomer,[2-5] that the positive charge of the intermediate vinylic bromonium ion perturbs the neighboring vinyl group very little,[3,6,7] and that in many cases the kinetically controlled dibromide product (1,2 and 1,4 isomers) can be analyzed without rearrangement.[2-4,8]

In this paper we present results of further investigations into the mechanism of 1,4 addition of halogen to dienes. Reported here are quantitative studies of the polar addition of bromine to cyclopentadiene, 1,3-cyclohexadiene, and the three 2,4-hexadienes (*E,E*, *Z,Z*, and *E,Z*)[9] in solvents of widely different polarity. The bromination of these dienes has been reported previously[10] but the compositions of the kinetically controlled product mixtures were not determined, and in the cases of the dibromides from 1,3-cyclohexadiene and the 2,4-hexadienes the structures of the products were not established. In the case of the cyclohexadiene dibromides, nmr, infrared, and equilibration evidence are presented here which for the first time establish their structures. How the structures of the 2,4-hexadiene dibromides were established by chemical means is also described. Also discussed in detail are the previously unreported proton nmr spectra of the three cyclopentadiene dibromides; these data are useful in discussing the nmr spectra of the cyclohexadiene dibromides and confirm the previous structure assignments for these five-membered ring derivatives which were based on chemical[10a] and dipole moment results.[11]

Results

Products from the Bromination of the Dienes.—The structures of the probable products from the bromination of cyclopentadiene and 1,3-cyclohexadiene are shown below.



n = 1

cis-3,5-dibromocyclopentene (3) | *trans*-3,4-dibromocyclopentene (1) | *trans*-3,5-dibromocyclopentene (2)

n = 2

cis-3,6-dibromocyclohexene (6) | *trans*-3,4-dibromocyclohexene (4) | *trans*-3,6-dibromocyclohexene (5)

(1) (a) Bethany Nazarene College; (b) Pasadena College; (c) California Institute of Technology.

(2) V. L. Heasley, C. L. Frye, R. T. Gore, Jr., and P. S. Wilday, *J. Org. Chem.*, **33**, 2342 (1968).

(3) V. L. Heasley, G. E. Heasley, S. K. Taylor, and C. L. Frye, *ibid.*, **35**, 2967 (1970).

(4) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1959).

(5) K. Mislow, *J. Amer. Chem. Soc.*, **75**, 2512 (1953).

(6) V. L. Heasley and P. H. Chamberlain, *J. Org. Chem.*, **35**, 539 (1970).

(7) V. L. Heasley, G. E. Heasley, R. A. Loghry, and M. R. McConnell, *J. Org. Chem.*, **37**, 2228 (1972).

(8) V. L. Heasley and S. K. Taylor, *J. Org. Chem.*, **34**, 2779 (1969).

(9) For a discussion of alkene nomenclature see *J. Org. Chem.*, **35**, 2849 (1970).

(10) (a) Cyclopentadiene: W. G. Young, H. K. Hall, Jr., and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 4338 (1956). (b) Cyclohexadiene: E. H. Farmer and W. D. Scott, *J. Chem. Soc.*, 172 (1929). (c) 2,4-Hexadienes: A. V. Dombrovskii, *Zh. Obshch. Khim.*, **24**, 610 (1954).

(11) W. D. Kumler, A. C. Huitric, and H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 4345 (1956).

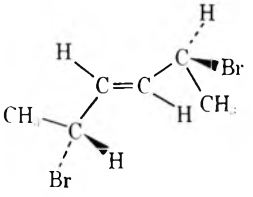
Structures of the probable dibromide products from the bromination of the isomeric 2,4-hexadienes are shown below.

1,2 Addition

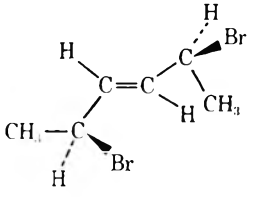
$CH_3CH{=}CHCH(Br){-}CH(Br)CH_3$, 4,5-dibromo-2-hexene

erythro, (*Z*), **7**; *threo*, (*Z*), **8**
erythro, (*E*), **9**; *threo*, (*E*), **10**

1,4 Addition



meso-2,5-dibromo-(*E*)-3-hexene (**11**)



dl-2,5-dibromo-(*E*)-3-hexene (**12**)

A stereospecific cis-1,4 addition of the bromine atoms to (*E*,*Z*)-2,4-hexadiene would yield the meso dibromide **11**, whereas trans-1,4 addition would give **12**, the racemic dibromide. Stereospecific cis-1,4 addition to (*Z*,*Z*)- and (*E*,*E*)-2,4-hexadiene should give **12**, and **11** would result from a stereospecific trans-1,4 addition.

The five dienes were brominated under carefully controlled conditions which should only result in polar addition[3,8] of halogen. The following dibromides were obtained: cyclopentadiene, **1**, **2**, and **3**; 1,3-cyclohexadiene, **4**, **5**, and **6**; (*Z*,*Z*)-2,4-hexadiene, **7**, **8**, **11**, and **12**; (*E*,*E*)- and (*E*,*Z*)-2,4-hexadiene,[12] **9**, **10**, **11**, and **12**. The kinetic yields of these dibromides are presented in Tables I (cyclic dienes) and II (acyclic dienes) as the percentages of cis-1,4 addition (per cent cis-1,4 addition = 100 × cis-1,4 addition/1,4 addition), the ratios of 1,4/1,2 addition, and the percentages of trans-1,2 addition (for the 2,4-hexadienes).

TABLE I

BROMINATION OF CYCLOHEXADIENE AND CYCLOPENTADIENE

Diene	Solvent	—Dibromides, %[a]— I	II	III	cis-1,4[b] addn, %	1,4/1,2 addn
C_5H_6	C_5H_{12}	48	24	28	54	1.1
C_5H_6	CCl_4	39	29	32	52	1.6
C_5H_6	CH_2Cl_2	26	21	53	72	2.8
C_5H_6	CH_3NO_2	31	29	40	58	2.2
C_6H_8	C_5H_{12}	25	13	62	83	3.0
C_6H_8	CCl_4	18	3	79	96	4.6
C_6H_8	CH_2Cl_2	19	2	79	98	4.3

[a] I, II, and III are **1**, **2**, and **3**, respectively, for cyclopentadiene and **4**, **5**, and **6**, respectively, for cyclohexadiene. [b] Computed as follows: 3/3 + 2 × 100 for cyclopentadiene, and 6/5 + 6 × 100 for cyclohexadiene.

Equilibrium Mixtures of the Dibromides.—Table III contains data on the mixtures of dibromides that are present at equilibrium. These data show that in general the mixtures of products formed under kinetic conditions (Tables I and II) show little resemblance to the thermodynamic mixtures. This is particularly evident in the case of the 1,3-cyclohexadiene dibromides, where the trans 3,6-dibromide is considerably more stable than the cis 3,6 isomer. For all dienes the percentages of cis 1,4 dibromide is higher under kinetic conditions than under thermodynamic conditions.

(12) In (*E*,*Z*)-2,4-hexadiene 1,2 addition of bromine occurs almost entirely at the cis bond. Small amounts (per cent of 1,2 addition) of **7** were formed (attack at the trans bond): pentane, 6.1; CCl_4, 1.3; CH_2Cl_2, 1.2; and CH_3NO_2, 1.2. A trace of **8** could have been formed but would not have been detected because it has the same retention time as **10**.

TABLE II

BROMINATION OF THE 2,4-HEXADIENES

Diene	Solvent	—Dibromides, %[b]— I	II	III	IV	trans-1,2,[c] %	cis-1,4 addn,[d] %	1,4/1,2 addn
(*Z*,*Z*)	C_5H_{12}	4	44	14	38	92	73	1.1
(*Z*,*Z*)	CCl_4	7	27	7	59	79	89	1.9
(*Z*,*Z*)	CH_2Cl_2	4	15	6	75	79	93	4.3
(*Z*,*Z*)	CH_3NO_2	5	39	17	39	89	70	1.3
(*E*,*Z*)[a]	C_5H_{12}	5	39	38	15	89	72	1.2
(*E*,*Z*)[a]	CCl_4	7	24	54	15	77	78	2.2
(*E*,*Z*)[a]	CH_2Cl_2	4	22	58	16	85	78	2.8
(*E*,*Z*)[a]	CH_3NO_2	9	32	39	20	78	66	1.4
(*E*,*E*)	C_5H_{12}	37	5	17	41	88	71	1.4
(*E*,*E*)	CCl_4	23	6	15	56	79	79	2.4
(*E*,*E*)	CH_2Cl_2	23	4	15	58	85	79	2.7
(*E*,*E*)	CH_3NO_2	24	10	25	41	71	62	1.9

[a] See footnote 12. [b] I = **7** from (*Z*,*Z*)-; **9** from (*E*,*Z*)- and (*E*,*E*)-; II = **8** from (*Z*,*Z*)-; **10** from (*E*,*Z*)- and (*E*,*E*)-; III = **11**; IV = **12**. [c] Computed as follows: (*Z*,*Z*)-, 8/8 + 7 × 100; (*E*,*E*)-, 9/9 + 10 × 100; (*E*,*Z*)-, 10/10 × 9 × 100. [d] Computed as follows: (*E*,*Z*)-, 11/11 + 12 × 100; (*Z*,*Z*)- and (*E*,*E*)-, 12/11 + 12 × 100.

TABLE III

EQUILIBRIUM MIXTURES OF THE DIBROMIDES[a]

Dibromide system	Solvent	Temp, °C	—Dibromides, %— I	II	III	IV	cis 1,4, %	1,4/1,2
$C_5H_6Br_2$	CCl_4	25	26	45	29		39	2.8
$C_5H_6Br_2$	CCl_4	78	22	47	31		40	3.5
$C_5H_6Br_2$	C_5H_{12}	25	29	43	28		39	2.4
$C_6H_8Br_2$	CCl_4	25	25	59	16		24	3.0
$C_6H_8Br_2$	CCl_4	78	26	57	17		23	2.9
$C_6H_{10}Br_2$	CCl_4	80	20	16	33	31	52[b]	1.8
$C_6H_{10}Br_2$	CH_3NO_2	25	12	9	40	39	51[b]	3.8

[a] Percentages and ratios were computed as described in Tables I and II. [b] Value refers to percentage of **11**.

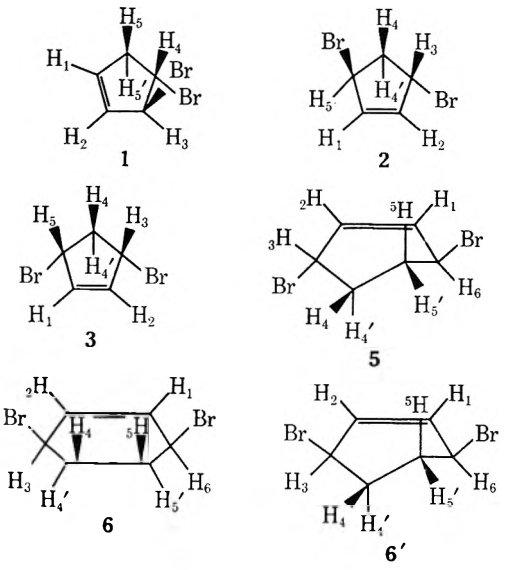
Structural Assignments for Cyclic Dibromides.—The correct assignment of the structure of the cyclic dibromides under study here is very crucial to discussion below of the mechanisms of the polar bromine addition reaction. Thus, we felt compelled to treat this aspect of the problem in considerable detail, especially since no previous assignment existed for the three dibromides isolated from bromination of 1,3-cyclohexadiene. The structural assignments of the cyclopentadiene dibromides have been previously made based primarily on dipole moment measurements.[10a,11] We now describe 60-MHz proton nmr results which completely confirm these earlier assignments.

The trans 3,4 isomer (**1**) exhibits five types of protons at 60 MHz in the ratio of 1:1:1:1:2 and would be expected to give rise to a ABCDEF spin system.[13]

The methylene protons are expected to be at highest field.[14] Thus, the sets of signals centered about 2.72 and 3.31 ppm from TMS are assigned to these protons. These nuclei grossly exhibit a four-line AB spin system

(13) J. W. Emsley, J. Feeney, and L. H. Satcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, Elmsford, N. Y., 1965, Chapter 8.

(14) See, for example, (a) D. D. Elleman and S. L. Manatt, *J. Chem. Phys.*, **36**, 2346 (1962); (b) D. D. Elleman, S. L. Manatt, and C. D. Pearce, *ibid.*, **42**, 650 (1965); (c) M. A. Cooper, D. D. Elleman, C. D. Pearce, and S. L. Manatt, *ibid.*, **53**, 2343 (1970).



pattern with a geminal coupling ($J_{55'}$) of -20.3 Hz.[15] Both members of the AB pattern possess much fine structure due to many other smaller couplings, but that at 3.31 ppm shows a well-resolved 5.4-Hz splitting which is characteristic of the vicinal coupling between two protons on the same side of a five-member ring.[16] This identifies these latter signals as due to proton H_5 so that $H_{5'}$ on the same side as the vicinal bromine is deshielded by 0.61 ppm. Then proton H_4 can be assigned to the signals at 4.72 ppm which also exhibit a well-resolved 5.4-Hz splitting. Indeed methine proton H_3 is expected to be less shielded than proton H_4 because of its adjacency to the vinyl group;[14b,c] so it is assigned to the signals centered at 5.22 ppm. The vinyl protons, as expected, give rise to a complex region centered at 6.05 ppm.[14a,c]

The trans 3,5 isomer (2) shows, as expected, only three kinds of protons in the intensity ratio of 1:1:1 and the signals are characteristic of a AA'BB'CC' spin system,[13] whose nature is such that no spacing in any region would give any of the spin–spin couplings directly. However, for our purposes of structure assignment, it is enough to ascertain that there are three types of protons in the ratio of 1:1:1 and that the three chemical shifts correspond to those in molecules possessing similar chemical types, *i.e.*, comparisons with the proton chemical shifts for the 3,4-dibromo isomer 1. Thus for 2 the methylene group is assigned to the triplet at 2.96 ppm. The triplet spacing of 5.5 Hz represents the sum of the couplings $J_{4'5}$ and J_{45} for the AA'BB' system[17] of the 3,5,4,4' protons. Since $J_{4'5}$ is probably very small[14b] (1 Hz or less), the observed splitting gives a reasonable approximation of J_{45}. The signals at 5.12 ppm are assigned to the H_3 and H_5 protons. Again a 5.5-Hz splitting is evident along with a 1.1-Hz splitting which arises from coupling of the methine protons with the vinyl protons. This 1.1-Hz splitting is the result of a positive vicinal coupling of one methine to the adjacent vinyl proton and a negative long-range coupling, $J_{HC=CCH'}$, to the distant vinyl proton.[14a] The vinyl protons' signal occurs as a deceptively simple doublet (1.1-Hz splitting) at 6.12 ppm.

The spectrum of the cis 3,5 isomer (3) consists of four types of protons in the ratio of 1:1:2:2 and should be of the AA'BB'CD symmetry type.[13] Indeed, two types of methylene protons are evident at 2.62 and 3.09 ppm. A geminal coupling of -17.4 Hz is evident for $J_{44'}$.[15] Proton $H_{4'}$ is identified from the observed splitting patterns as having a chemical shift of 2.62 ppm. This proton's signals exhibit a resolvable 2.2-Hz triplet splitting, which should be an accurate measure of $J_{34'}$, in the A_2BC system of protons 3,5,4,4'.[14a] Thus, $J_{34'}$ is rather larger than expected for a trans J_{HCCH} coupling in a cyclopentene ring.[14b,16] Perhaps the bromine atoms perturb the $H_{4'}$ proton so that the angle between the C–C–H_3 and C–C–H_4 planes is reduced away from 90°, where the vicinal coupling would be zero.[18] The assignment of proton H_4 to the signals centered at 3.09 ppm follows from its geminal coupling with the $H_{4'}$ proton and its 6.6-Hz triplet splitting, which is a good measure of J_{34} in the A_2BC spin system of the 3,5,4,4' protons. The assignment of the H_3 and H_5 protons to the doublet (6.6-Hz splitting) of doublets (2.2-Hz splitting) of doublets (1.5-Hz splittings) at 5.01 ppm then follows. The first two splittings arise as discussed above and the last one arises from couplings with the vinyl protons. Finally, the vinyl protons are assigned to the deceptively simple doublet at 6.12 ppm.

In summary, the nmr spectral symmetries, integrated intensities, chemical shifts, and observed splitting patterns for the isomers 1, 2, and 3 allow unequivocal assignment of their structure. It should be pointed out that a complete analysis of their nmr spectra to obtain exact proton–proton coupling constants would require a great amount of effort, as their nmr spectra are really quite complex. What we have done here is to skim off and use available splitting and chemical-shift information from the observed spectra. As discussed above, the observed splittings are expected to be reasonable approximations to the coupling we have identified. Thus, the nmr results discussed here are in complete agreement with the earlier assignments based on dipole moments and chemistry[10a,11] and other nmr results in related systems.[14,16]

Three dibromide isomers from the bromination of 1,3-cyclohexadiene were isolated many years ago by Farmer and Scott.[10b] The straightforward manner by which the isomeric five-membered ring dibromides were assigned, as described above, gave us hope that with these data as examples the assignments in the six-membered series could be accomplished. In our work in the later series, as before,[10b] two solid isomers, mp 108 and 68°, were isolated along with a very labile liquid dibromide which rearranges to mixtures of the two solid isomers. As described below, the three dibromides had different infrared spectra such that it was possible to devise a quantitative ir analysis procedure to measure the ratio of 4 to 6 and 5 to 6 from the brominations. However, the infrared spectra were not much help in establishment of the structures of the three dibromides.

(15) The sign of this geminal coupling is based on analogy to other systems; see, for example, ref 14b and 14c.

(16) See A. K. Bothner-By, *Advan. Magn. Resonance*, **1**, 195 (1965).

(17) For discussion of the spectra of AA'BB' spin system see (a) D. M. Grant, R. C. Hirst, and H. S. Gutowsky, *J. Chem. Phys.*, **38**, 470 (1963); (b) B. Disehler and G. Englert, *Z. Naturforsch. A*, **16**, 1180 (1961); (c) R. C. Hirst and D. M. Grant, *J. Chem. Phys.*, **40**, 1909 (1964).

(18) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

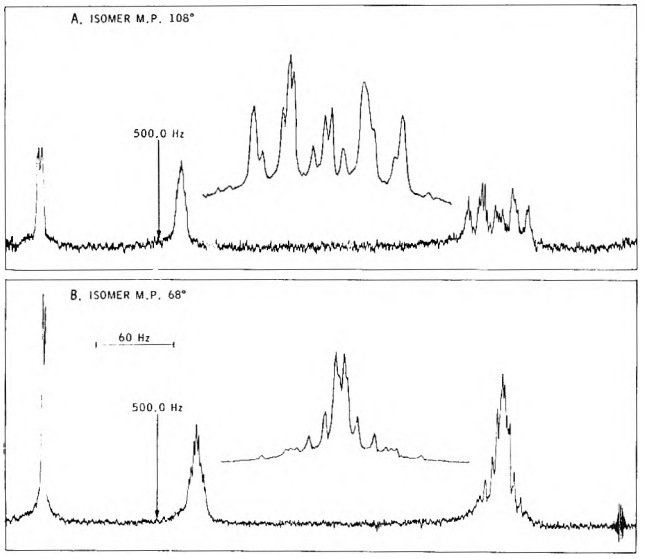


Figure 1.—Proton 100-MHz spectra of 3,6-dibromocyclohexene isomers in CCl_4. Point in spectra 500.0 Hz downfield from tetramethylsilane indicated. Inserts show methylene protons regions when methine protons irradiated.

In the case of a trans 3,4 isomer (**4**) we expected to observe a proton nmr spectrum somewhat analogous to that of **1** in the five-membered series and exhibiting two types of vinyl protons, two types of methine protons, and possibly four types of methylene protons or at least a complex methylene region. For the trans 3,6 and cis 3,6 isomers we expected to observe one type of vinyl proton, one type of methine proton, and two types of methylene protons. The symmetry of these proton nmr spectra were expected to be characteristic of very complex AA'BB'CC'DD' systems. If these spectra could be completely analyzed to provide vicinal proton–proton coupling constant data, then it would be possible to assign the cis and trans structures. The information which would be pivotal in deciding the issue would be the coupling parameters between the sets of chemical shift equivalent, magnetically nonequivalent methylene protons on the 4 and 5 carbon atoms. These protons form, within the eight-spin systems, two distinct types of AA'BB' spin systems. For the trans 3,6 isomer we would expect to extract a set of vicinal coupling parameters between the methylene protons which exhibit one vicinal coupling of a magnitude about 12–13 Hz which is characteristic of two C–C–H planes with a dihedral angle close to 180°. The two other vicinal couplings should be characteristic of dihedral angles close to 60°, which would give rise to vicinal coupling in the range of 3–5 Hz.[14c,18] Molecular models of a trans 3,6 isomer strongly suggest that a reasonably rigid conformation is favored. For the cis 3,6 isomer, models suggest the possibility of a rapid interconversion between two conformations having one bromine nearly axial and one equatorial or possibly a semirigid conformation with both bromines nearly equatorial. In either case, on an nmr time scale, one would expect to find a set of vicinal coupling constants, none of which are characteristic of a dihedral angle close to 180°. Instead, vicinal couplings for the methylene protons characteristic of the averages for two conformations like that in **6** [*i.e.*, $J^{obsd} = {}^1/_2(J^{trans}_{4'5'} + J^{gauche}_{45})$, $J^{obsd}_{45'} = J^{gauche}_{4'5'}$, and $J^{obsd}_{4'5} = J^{gauche}_{4'5}$][19] or of one rigid one similar to **6'** would be expected. A confirmation like **6'** would possess two vicinal couplings characteristic of a 0° dihedral angle and one characteristic for 60°.[20] Thus, extraction of the vicinal coupling information and subsequent assignment would seem to depend on the iterative analyses of two complex eight-spin systems. Analyses of such eight-spin systems are very formidable tasks and very costly in computer time. It seemed to us that it might be possible to greatly simplify the problem for the two 3,6 isomers if the methine protons could be decoupled in double-resonance experiments from the methylene protons. This would reduce the problem to analyses of two AA'BB' systems, which are much more tractable. It was expected that the vinyl protons would have only very small long-range couplings to the methylene protons. In addition, the nature of these two AA'BB' spin systems could be expected to be significantly different not only from the standpoint of the coupling parameters which would be obtained but from another more subtle standpoint. Thus, the trans 3,6 isomer would give rise to an AA'BB' system characteristic of a reasonably large M value, whereas we would expect the cis 3,6 isomer to possess a spectrum characteristic of small (about 1–2 Hz) or zero M.[21]

The labile liquid dibromide was never obtained in a reaonably pure state at a time convenient to record its nmr spectrum. Spectra were taken of mixtures of the three bromides and numerous extra signals not assignable to the two solid dibromides were evident. Unfortunately, it turned out that the signals from the various protons of the liquid isomer were masked by those of the other two isomers, even at 220 MHz. However, we felt that, if the configuration of the two solid dibromides turned out to be assignable to the trans 3,6 and cis 3,6 isomers, and from the fact that the liquid dibromide isomerized to the other two isomers, it would be quite reasonable to assign the liquid isomer the trans 3,4 structure. In addition, its boiling point was essentially identical with that of the 1,4 isomer, its melting point is much lower than those of either of the other isomers, thus suggesting a lower molecular symmetry, and the infrared spectrum is consistent and similar to those of the other isomers. The firm assignment of the structures of the two solid isomers then becomes crucial.

The 100-MHz nmr spectra of the two crystalline dibromides are shown in Figure 1. Indeed, both exhibit one type of vinyl proton, one type of methine proton, and a complex methylene region in the intensity ratio of 1:1:2. Both the vinyl and methine signal are characteristic of deceptively simple spectra which could be part of AA'BB'CC'DD' spin systems. To carry out fully the analyses of the spectra as they stand would be tedious and time-consuming tasks. We proceeded to carry out double-resonance experiments on each molecule where the methine protons were irradiated with a large modulation (about 40 Hz). The inserts in Figure 1 show that indeed the methylene proton regions in both cases were reduced to sym-

(19) See, for example, R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969).

(20) The spectrum and vicinal coupling parameters for 1,2-dihydronaphthalene appear to be close to this situation; see ref 14c.

(21) $M = J_{AA'} - J_{BB'}$; see ref 17.

metrical patterns characteristic of AA'BB' spin systems. These two experiments then establish unequivocally that we are dealing with molecules with a symmetry correct for the 3,6-dibromocyclohexene isomers. Iterative analyses on the AA'BB' spectrum with the largest chemical shift and dibromide, mp 108°, with the computer program NMRENIT[22] yielded vicinal coupling constants of 12.79, 2.64, and 4.27 Hz.[23] The large vicinal coupling is characteristic of a trans vicinal coupling and the two small ones of vicinal gauche ones.[16,18,19] Thus, based on these parameters, we assign the trans structure to the isomer with mp 108°. The iterative analysis of the AA'BB' spectrum for the isomer with mp 68° is still in progress.[23] This particular spectrum has proved difficult to assign in detail because of its small chemical shift between the protons (see Figure 1) and the fact that its parameter M is apparently zero. Thus far, two assignments have been found which correspond closely to the experimental spectrum. The two assignments yield vicinal couplings of 10.2 ± 0.5 and 2.2 ± 0.5 and 7.5 ± 0.5 and 3.2 ± 0.5 Hz, respectively.[23] The first pair would fit conformation **6'** and the second pair a fast interconversion of two conformations such as **6**. Significantly, in both of these assignments M is zero and no vicinal couplings as large as that observed in the case of the isomer with mp 108°, and consistent with vicinal $J_{180°}$,[19] are found. Thus, we assign the cis 3,6 configuration to the isomer with mp 68°.

The assignments and chemical shifts for five of the cylic dibromide isomers discussed above are summarized in Table IV.

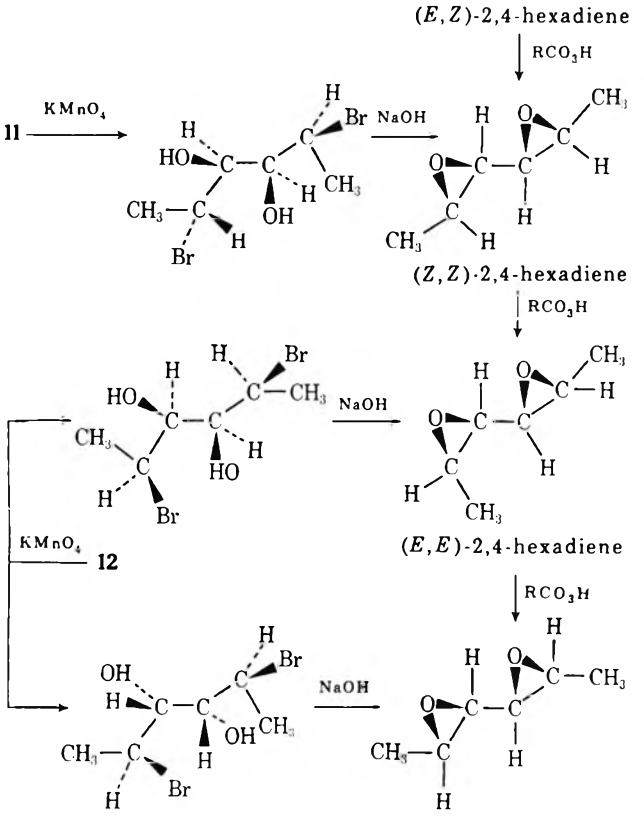
Table IV
Summary of Chemical Shift Assignments for Dibromides in CCl_4[a]

Compd	Methylene	Methine	Vinyl
trans-3,4-Dibromocyclopentene (1)	2.72, 3.31	4.72, 5.22	6.05
trans-3,5-Dibromocyclopentene (2)	2.96	5.12	6.12
cis-3,5-Dibromocyclopentene (3)	2.62, 3.09	5.01	6.12
trans-3,6-Dibromocyclohexene (5)	2.154, 2.454	4.826	5.942
cis-3,6-Dibromocyclohexene (6)	2.144, 2.304	4.700	5.906

[a] In parts per million downfield from tetramethylsilane.

Establishment of the Structures of Acyclic Dibromides 11 and 12.—Dibromides **11** and **12** were separated from each other and the 1,2-dibromides by fractional recrystallization. The proton nmr spectra of **11** and **12** were consistent with their expected compliment of protons. However, to obtain any configurational information from these spectra would have required fitting two complex ten-spin systems, which would be a formidable task, and detailed nmr studies of some model compounds. Thus, a chemical approach to assignment of their structures was sought. A feasible approach to this goal seemed to be through conversion to the diepoxides as indicated in Scheme I. The diepoxides

Scheme I



which were obtained from the dibromides were identified by comparison with the diepoxides produced by direct treatment of the 2,4-hexadienes with peroxy acids. The meso dibromide (**11**) yielded a single cis,trans diepoxide which was identical with one[24] of the diepoxides obtained by treatment of (*E,Z*)-2,4-hexadiene with peroxy acid. The racemic dibromide **12** formed two diepoxides. One of these diepoxides was identical with one of the diepoxides from peroxy acid reaction with (*Z,Z*)-2,4-hexadiene, and the other was identical with one of the diepoxides resulting from peroxy acid reaction with (*E,E*)-2,4-hexadiene. Using these procedures we were able to establish the structures of diastereomers **11** and **12**. The assumptions that we made in pursuing this line of structure proof are that (1) glycol formation with permanganate is a cis addition;[25] (2) formation of an epoxide from a bromohydrin occurs with inversion of configuration;[26] and (3) epoxidation of the diene is a stereospecific cis addition.[27]

Methods for Analysis of the 4,5-Dibromo-2-hexenes.—The amounts of 4,5-dibromo-2-hexenes (1,2-dibromides) which were formed in the brominations of the 2,4-hexadienes were obtained by direct vpc analysis of the bromination products, and by analysis of the

(22) M. T. Bowers, T. I. Chapman, and S. L. Manatt, *J. Chem. Phys.*, **50**, 5412 (1969); this program was adapted for use on a Hewlett-Packard 2116B with 16k of memory, 7900A Disc Drive, and 7970B Digital Tape Unit.

(23) S. L. Manatt, S. P. Sander, P. A. Kroon and V. Heasley, details to be published subsequently; for the mp 108° isomer the average observed minus calculated line position for 24 lines was 0.03 Hz.

(24) When the 2,4-hexadienes react with peroxy acid, two diastereomeric diepoxides are expected from each diene, assuming cis addition to each double bond. See ref 27.

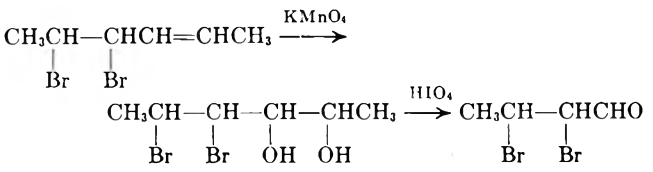
(25) K. Wiberg and K. Saegebarth, *J. Amer. Chem. Soc.*, **79**, 2822 (1957).

(26) S. Winstein and H. Lucas, *J. Amer. Chem. Soc.*, **61**, 1576 (1939).

(27) For example, see J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, p 619.

crotonaldehyde dibromides which were formed from the 1,2-dibromides as indicated in Scheme II.

SCHEME II

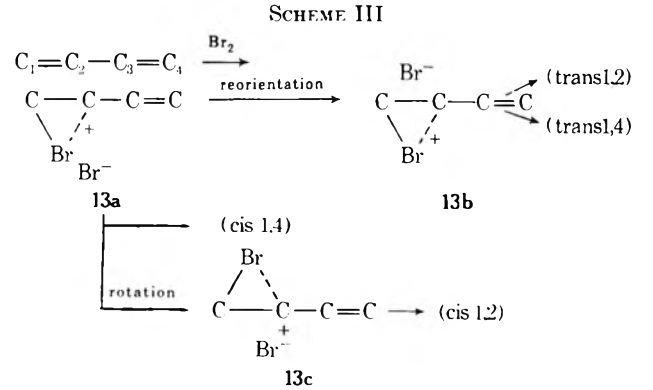


Crude 2,4-hexadiene bromination mixtures were converted to glycol mixtures, which were subjected to reaction with periodic acid. The crotonaldehyde dibromides (diastereomers) were analyzed by vpc. Authentic crotonaldehyde dibromides were obtained by brominating commercial crotonaldehyde (mainly *E*). The principle diastereomer from the bromination of crotonaldehyde was assumed to be the erythro dibromide on the basis that trans addition would predominate. The crotonaldehyde dibromides formed from the 1,2-dibromides (*via* Scheme II) were shown to be identical with the authentic crotonaldehyde dibromides by vpc and ir. Good agreement was observed between analyses obtained *via* crotonaldehyde dibromides and direct vpc analyses of 2,4-hexadiene bromination mixtures. A check on this method of analysis was made by subjecting a (*Z*)-1,3-pentadiene bromination product to the reactions of Scheme II. Only a single crotonaldehyde dibromide isomer (threo) was obtained, which is in accord with our previous finding that bromine addition to the 3,4 bond in the 1,3-pentadienes is stereospecific.[3]

Discussion

The mechanism which we are suggesting to account for the different dibromide products in the polar bromination of conjugated dienes is shown in Scheme III. In this mechanism a bromine molecule attacks a

SCHEME III

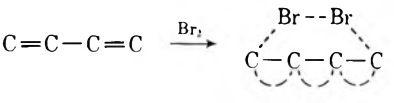


particular double bond of the diene, yielding a bromonium ion–bromide ion[28] pair, **13a**. Both the 1,2 adduct and the 1,4 adduct then arise from the same intermediate. Cis 1,4 addition results when the anion of this pair effects essentially an SN2′ attack on carbon atom 4. It is possible that some reorientation of the ion pair (perhaps solvent separation) would be necessary before this attack could occur. Trans 1,4 addition could result if a *reorientation* of the initial ion pair occurred to give **13b**. This same reorientation of the ion pair would normally be required for 1,2 addition, unless bridging in the brominium ion were so weak that the rate of *rotation* about the C_1–C_2 bond competed with the rate of reorientation, and 1,2 addition occurred *via* **13c** (possible with acyclic dienes only). However, SN2′ attack (1,4 addition) by anion in **13c** would still result in cis 1,4 product.

The fact that 1,4 addition is predominantly a cis addition for all of the cases in Tables I and II would seem to be due to the fact that collapse of ion pair **13a** is apparently a facile process, which may result from the fact that the anion in **13a** is generated in close proximity to carbon atom 4. We observe that where the ratio of 1,4 to 1,2 addition is particularly large [cyclohexadiene and (*Z*,*Z*)-2,4-hexadiene in CCl_4 and CH_2Cl_2; all dienes in CH_2Cl_2] the stereospecificity of 1,4 addition is also high. On the other hand, where 1,4 addition occurs to a lesser extent (that is, 1,2 addition is relatively more rapid) then the amount of 1,4 addition which is trans increases. This is reasonable if we assumed that trans 1,4 addition is occurring *via* the same intermediate as trans 1,2 addition, namely **13b**.

The substantially lesser amount of cis 1,4 addition with cyclopentadiene can also be explained by this mechanism. Studies with models indicate that considerable steric interaction would be expected when ion pair **13a** from cyclopentadiene collapses to cis 1,4 product, particularly if the anion should be the tribromide ion. This steric interaction would be substantially less with the other dienes. The unusually high percentage of cis 1,4 addition observed with cyclohexadiene (96 and 98% in CCl_4 and CH_2Cl_2, respectively) may be due to the fact that the geometry is most favorable in this case, so that collapse of ion pair **13a** *via* cis SN2′ attack by anion can occur with a minimum of steric interaction between bromines and with a minimum of reorientation within the ion pair.

Other mechanisms for 1,4 addition could be considered. A "Diels–Alder"-type addition to the cisoid form of the diene was formerly proposed, but the possibility of this mechanism has been eliminated for acyclic dienes by the finding that the remaining double bond in the 1,4 adduct is always trans.[2-5] A concerted Diels–Alder-type mechanism, where fission of the Br–Br bond is synchronous with formation of bonds to the 1,4 carbon atoms, is still a possibility for cyclic dienes and could also occur with acyclic dienes provided that addition occurred to the transoid form of the diene. Such a mechanism is indicated as follows.



The data in Tables I and II provide evidence against such a concerted 1,4 addition mechanism or at least against the consideration of this as being the sole mechanism responsible for 1,4 addition. The most obvious fact revealed by our data is that the 1,4 addition is in all cases predominantly a cis

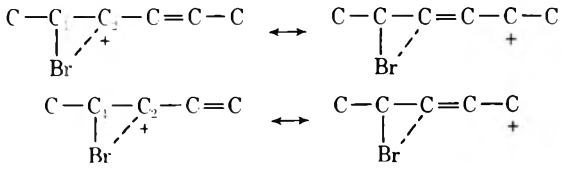
(28) We show the anion to be the bromide ion; however, from various kinetic studies,[29] it seems likely that our reaction conditions (addition of neat bromine) would lead to a mechanism in which more than one bromine molecule would be involved in the rate-determining step. Therefore, it is possible that the tribromide ion is the chief anionic species.

(29) For example, see J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1483 (1969).

process—*i.e.*, both bromine atoms are added to the same side of the molecule—but the degree of stereospecificity varies widely, meaning that either two mechanisms of 1,4 addition compete or the single mechanism which is occurring allows for both cis and trans 1,4 addition. If we look at the effect of structure of the diene, it is seen that 1,4 addition is most stereospecific (in the cis sense) with cyclohexadiene and least with cyclopentadiene. Examination of molecular models indicates that alignment of a bromine molecule for a concerted Diels–Alder-type addition should be nearly perfect for cyclopentadiene but that the alignment would not be as good for cyclohexadiene and would be still poorer for the 2,4-hexadienes. Since in comparable solvents, cyclopentadiene gives the lowest amount of cis 1,4 addition of any of the dienes, we feel that it is unlikely that a concerted mechanism contributes significantly. Further evidence against the concerted mechanism is that the amount of cis 1,4 addition (compared to trans 1,4 addition) tends for each diene to be low in the most nonpolar solvent, pentane. A concerted mechanism with little development of charged species ought to be favored (over competing ionic processes) in a nonpolar solvent.

An observation of considerable interest in this study has to do with the stereospecificity of 1,2 addition to the 2,4-hexadienes. Table II shows that the percentage of trans 1,2 addition varies between 91 and 69% depending upon diene and solvent. This result came as a considerable surprise, since in our studies on the 1,3-pentadienes[3] we found that addition to the 3,4 bond was stereospecific and we concluded on this basis that the intermediate in diene bromination (**13a**) should be viewed as a tightly bridged bromonium ion with little delocalization of charge into the vinyl group. The percentage of trans 1,2 addition which we observe here with the 2,4-hexadienes is very comparable to that observed by others[30] for the bromination of the 1-phenylpropenes in several solvents. The above workers did not observe significant difference in the degree of stereospecificity between the cis and trans olefin, an observation with which we concur in the present study (Table II).

The fact that 1,2 addition to the 2,4-hexadienes is not stereospecific is probably related to the slightly greater stabilization of intermediate **13a** in the hexadiene system over the same intermediate in the pentadiene system. As shown in the structures below, the con-



tributing resonance structure involving delocalization of charge is a secondary carbonium ion when derived from a hexadiene but a primary carbonium ion when derived from a pentadiene. Our interpretation is that delocalization of charge away from carbon 2 (in the accompanying structures) weakens interaction between bromine and carbon 2 so that the rate of rotation about the 1,2 bond (**13a** → **13c**) becomes competitive with the rate of reorientation of the ion pair (**13a** → **13b**). We assume, as have previous workers,[30] that direct collapse of the initially formed ion pair, **13a**, to the cis 1,2 adduct does not occur because excessive steric interaction between the attached bromine and the bromide ion would occur.

A further interesting comparison can be made between the stereospecificity of 1,4 addition and that of 1,2 addition. With two exceptions—(*Z*,*Z*)-2,4-hexadiene in CH_2Cl_2 and CCl_4—the data in Table II show that the stereospecificity for trans 1,2 addition is higher than that for cis 1,4 addition. This observation is consistent with the mechanism proposed in Scheme III, and suggests that intermediate **13b** plays an important role in the reaction (along with **13a**) since involvement of **13b** would lead to a stereospecific 1,2 addition but would diminish the ratio of cis to trans 1,4 addition. On the other hand, intermediate **13c** does not seem to play a significant role, since the stereospecificity of 1,2 addition is higher than that of 1,4 addition; the opposite observation would be expected if the contribution of **13c** were substantial.

Conclusion

This paper provides conclusive data on the structures of products obtained from several important conjugated diene systems, thus opening the way for a variety of bromination studies. The 2,4-hexadienes have been identified as a system having particular appeal for studying the factors effecting 1,2 and 1,4 addition, since each of these processes may be evaluated simultaneously *via* stereochemical results. The fact that 1,4 addition to a variety of dienes was found to be nonstereospecific but largely cis points to the lack of intrinsic stereochemical control in the S$_N$2′ displacement process, which we assume is operative here, and at the same time provides insight into the specific nature of the ion pair intermediates involved in these additions.

Experimental Section

General.—Melting points are uncorrected. Nuclear magnetic resonance spectra were obtained with Varian A-56/60, A-60, and HA-100 instruments. The 100-MHz spectrometer was based on three Hewlett-Packard 5100 Frequency Synthesizers. The frequency sweep was generated by a Barry Research LSC-7A Digital Programmer which drove one of the synthesizers. The decoupling modulation was supplied by a Hewlett-Packard 200 AB Oscillator. An Allison Labs Bond Rejection Filter Model 210R set at the decoupling audio modulation was inserted between the V-4311 unit and the V-4354 unit. In the decoupling experiments 4–16 spectra were accumulated in a Hewlett-Packard 5480 Averager which was triggered by the LSC-7A Digital Programmer. Unless otherwise stated, infrared spectra were obtained on a Beckman IR-10 spectrophotometer. Cyclohexadiene, (*E*,*Z*)-2,4-hexadiene (99%), and (*E*,*E*)-2,4-hexadiene (99%) were obtained from Aldrich Chemical Co. (*Z*,*Z*)-2,4-hexadiene (98%) was from Chemical Samples Co. Purities were confirmed by vpc. Cyclopentadiene was prepared from its dimer just prior to use.

Bromination Procedure.—Reactions were done in the dark at −15°. The diene concentrations were 0.02 mol fraction with respect to solvent.[31]

(30) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469 (1969); R. C. Fahey and H. J. Schneider, *ibid.*, **90**, 4429 (1968).

(31) In our previous studies on butadiene,[8] isoprene,[3] and the piperylenes,[3] we concluded that only a polar bromination mechanism occurred under these conditions. The known radical inhibitors, oxygen (all three dienes) and 2,6-di-*tert*-butyl-4-methylphenol (2,4-hexadiene and cyclopentadiene), were found to have no effect on product compositions in the present study.

Bromine was added neat from a small capillary dropper to well-stirred solutions. Reactions were carried to 20–25% of completion. Yields of dibromide products were found to be between 90 and 100% based on direct isolation of products (cyclohexadiene, 2,4-hexadienes) or use of vpc internal standards (cyclopentadiene).

Analysis of Cyclopentadiene and Hexadiene Dibromides.—Vpc analyses of the dibromides from cyclopentadiene and the 2,4-hexadienes were done on a Hewlett-Packard 7620A hydrogen flame chromatograph. Analysis conditions are (2,4-hexadiene dibromides): 6 ft × 0.25 in. SS, 2.5% SE-30 on 60–80 mesh Chromosorb W (AW-DMCS), 40°, 125 ml/min (N_2). Retention times under these conditions for **7**, **8**, **9**, **10**, **11**, and **12** are 17.0, 19.6, 17.8, 19.7, 23.2, and 25.8 min, respectively. Analysis conditions for the cyclopentadiene dibromides follow: 6 ft × 0.125 in. SS, 2.5% SE-30 on 80–100 mesh Chromosorb W (AW-DMCS), 55°, 55 ml/min (N_2). Retention times under these conditions for **1**, **2**, and **3** are 4.4, 5.4, and 8.0 min, respectively.

Reaction mixtures were analyzed directly without work-up.[32] Direct on-column injection of samples was generally employed. In the case of the cyclopentadiene dibromides the area/weight ratios for each dibromide were found to be identical. Because of their very similar structures, **11** and **12** would be expected to have similar area/weight ratios. Owing to the limited amounts of the 1,2-dibromides (also they were contaminated with some **11** and **12**) the area/weight ratios of the 1,2-dibromides with respect to **11** and **12** were not determined.

The cyclopentadiene dibromide mixtures were also analyzed by nmr and found to give results consistent with those obtained by vpc.

Analyses of the Cyclohexadiene Dibromides.—Attempts to analyze **4**, **5**, and **6** by vpc were unsuccessful since extensive rearrangement of the isomers occurred under all conditions. [Numerous liquid phases, column lengths (copper and steel) and temperatures were examined.]

The dibromide mixtures were analyzed by quantitative ir analysis using the following noninterfering absorption bands: **4** (590 cm^{-1}), **5** (1080 cm^{-1}), and **6** (980 cm^{-1}). Standard curves were prepared by plotting the ratio of **4**:**6** (and **5**:**6**) against a ratio of their respective absorbancies (at the wavenumbers mentioned above). **5** and **6** were obtained without traces of the other isomers. **4** contained traces of **5** and **6**. Solvent was removed from the bromination mixtures *in vacuo* without heat. It was established that no rearrangement occurred or dibromides were lost during this operation. The analyses were carried out using a Perkin-Elmer 337 grating spectrophotometer, KBr cells (0.05 mm), and CCl_4 as the solvent. At least two brominations were run for each set of reaction conditions. Most of the duplicate runs gave results which were within 1–2% of each other; none showed more than 4% difference.

***meso*- and *dl*-2,5-Dibromo-(*E*)-3-hexene (11 and 12).**—**11** was prepared in the following manner. The solvent was removed *in vacuo* from the product of bromination of (*E*,*Z*)-2,4-hexadiene. The residue was dissolved in pentane and fractionally recrystallized twice at Dry Ice temperatures to give **11** (98% pure by vpc): mp 35–37°; ir (CCl_4) trans CH=CH, 960 cm^{-1}; nmr (CCl_4) δ 1.84 (d, 6, CH_3), 4.68 (m, 2, CHBr), 6.03 (d d, 2, CH=CH). A similar recrystallization of the bromination product from the *E*,*E* isomer gave **12** (98% pure by vpc): a liquid; ir (CCl_4) trans CH=CH, 960 cm^{-1}; nmr (CCl_4) δ 1.84 (d, 6, CH_3), 4.68 (m, 2, CHBr), 6.06 (d d, 2, CH=CH). Both **11** and **12** rearranged when heated in sealed tubes for several days at 80° to identical mixtures of dibromides.

Assignments of stereochemical structures to **11** and **12** were based on the reactions described in Scheme I above. Dibromides **11** and **12** were converted to glycols by reaction with permanganate in aqueous ethanol at −30° according to the procedure of Winstein.[10a] For example, 2 g of **11** yielded 2 g of crude product which melted at 103.5–105° after washing with pentane. The product from **12** melted at 90–92° after similar treatment. Both products showed strong ir absorption at 3400 cm^{-1} (KBr disk).

Conversion of the glycols from **11** and **12** to diepoxides was accomplished as follows. For example, 1.0 g of the glycol from **11** was stirred with 9.3 ml of 0.77 *M* NaOH for a few minutes at 0°. Titration of an aliquot showed that 2 equiv of base was consumed. The diepoxide was isolated by repeated ether extraction. After distillation of ether, the residue was distilled, yielding 0.3 ml, bp 80–82° (30 mm) [reported for a mixture of hexadiene diepoxides,[33] 175–177° (760 mm)]. The diepoxide from **12** was obtained in similar quantity with similar boiling point.

Vpc analysis (DEGS, 8 ft × 0.25 in., 60°) of the diepoxide from **11** showed a single peak (retention time 11.5 min) identical in ir spectrum and retention time with the minor diepoxide obtained by reaction of (*E*,*Z*)-2,4-hexadiene with peroxy acid.[34] The diepoxide from **12** showed two peaks, A and B, in its vpc in a ratio (A:B) of 0.13, retention times 9.7 and 12.1 min, respectively. Diepoxides A and B were isolated and found to be identical (retention times and ir) with the minor diepoxides obtained from (*E*,*E*)- and (*Z*,*Z*)-2,4-hexadiene (and peroxy acid), respectively.

4,5-Dibromo-2-hexenes (7, 8, 9, and 10).—The 1,2-dibromides were isolated by preparative vpc. The compounds collected from a (*Z*,*Z*)-2,4-hexadiene bromination product were identified as a mixture of **7** and **8** by the ir spectra: cis CH=CH (CS_2), 740 cm^{-1} (strong). Similarly, the collected compounds from the (*E*,*E*)-2,4-hexadiene bromination product were identified as **9** and **10** by the ir spectra: trans CH=CH (CS_2), 960 cm^{-1} (strong). Also, each of the collected 1,2-dibromides rearranged upon heating in CCl_4 at 80° to give the identical equilibrium mixtures of **7**, **8**, **9**, **10**, **11**, and **12** as were formed on equilibration of **11** and **12** under identical conditions.

Further proof for the structures of the 1,2-dibromides was obtained by converting them to known crotonaldehyde dibromides as outlined in Scheme II above. For example, 3.20 g of the crude dibromide mixture [from bromination of (*Z*,*Z*)-2,4 hexadiene] was oxidized to a glycol mixture as described for **11** and **12** above. The glycol was isolated, it was dissolved in 25 ml of water and 15 ml of alcohol, a solution of 3.5 g of periodic acid in 10 ml of water was added, and the mixture was stirred at 25° for 30 min. The crotonaldehyde dibromides were extracted from the reaction mixture with ether and isolated by preparative vpc [6 ft × 0.25 in., 2.5% SE-30 on 60/80 mesh Chromosorb W (AW-DMCS), 42°, 125 ml/min (N_2)]. The crotonaldehydes obtained from dibromide mixtures and authentic crotonaldehyde dibromides were found to have identical retention times (erythro, 12.6 and threo, 14.0 min) and ir spectra: (CCl_4) HC=O, 2820 and 2720 cm^{-1}, and C=O, 1740 cm^{-1}. The authentic crotonaldehyde dibromides were prepared by bromination of commercial crotonaldehyde and were obtained, bp 95–97° (30 mm) [lit.[35] by 75–82° (14 mm)], in a ratio of 6:1 (erythro:threo).

Cyclopentadiene Dibromides (1, 2, and 3).—Winstein, *et al.*,[10a] have previously identified **1**, **2**, and **3** as products in the bromination of cyclopentadiene. Samples of **1** (5% **2**) and **3** (99%) were obtained using essentially the procedure of Winstein, *et al.* A mixture of **1** and **2** containing 70% **2** was obtained. Nmr measurements at 60 MHz in CCl_4 gave the following: **1**, 2.72 [dd, 1, cis CBrC(H)H, J = 20.3 Hz, other fine coupling], 3.31 [dd, 1, trans CBrC(H)H, J = 20.3, J' = 5.4 Hz, other fine coupling], 4.72 (d, 1, CH_2CHBr, J = 5.4 Hz, other fine coupling), 5.22 (s, 1, CH=CHCHBr, fine coupling), 6.05 (s, 2, CH=CH, fine coupling); **2**, 2.96 (t, 2, CH_2, J = 5.5 Hz), 5.12 [d t, 1, CBr(H), J = 5.5, J' = 1.1 Hz], 6.12 (d, 2, CH=CH, J = 1.1 Hz); **3**, 2.62 [d t, 1, cis CBrC(H)H, J = 17.4, J' = 2.2 Hz], 3.09 [d t, 1, trans CBrC(H)H, J = 17.4, J' = 6.6 Hz], 5.01 [d of dd, C(H)-Br, 2, J = 6.6, J' = 2.2, J'' = 1.5 Hz], 6.06 (d, 2, CH=CH, J = 1.5 Hz).

Cyclohexadiene Dibromides (4, 5, and 6).—These dibromides were prepared essentially as described previously.[10b] The liquid

(32) Control experiments were performed to show that rearrangement of isomers did not occur under conditions of bromination. Cyclopentadiene was brominated in the presence of pure **11** and also in the presence of a hexadiene dibromide mixture; (*E*,*Z*)-2,4-hexadiene was brominated with pure **3** added. No rearrangement of the above added dibromides was detected in these experiments. The absence of rearrangement during vpc analyses is established as follows. (a) Single vpc peaks were obtained from purified isomers, showing no injection port rearrangement. (b) Samples collected from the vpc showed the same composition after reinjection, demonstrating absence of injection-port and column rearrangement. The routine observation of a sharply returning base line between well-separated peaks of isomers also rules out on-column rearrangement.

(33) J. L. Everett and G. A. R. Kon, *J. Chem. Soc.*, 3131 (1950).

(34) The 2,4-hexadienes were converted to diepoxides by reaction for 3 days at 0° with excess *m*-chloroperoxybenzoic acid in chloroform. Each diene yielded two diepoxides in about 2:1 ratio. Each of the six diastereoisomeric diepoxides was isolated in pure form and an ir and nmr spectrum was obtained for each compound. The isomers are readily distinguished by their spectra. A paper is in preparation which will report the details of this study.

(35) P. L. Viguir, *C. R. Acad. Sci.*, **150**, 1431 (1910).

dibromide was isolated by removing through fractional recrystallization (of a bromination product) at Dry Ice temperature (*n*-pentane) as much of the solid 3,6 isomers as possible and then flash distilling [bp 40° (0.07 mm)] a small amount of the liquid. Only a very small amount of the pure isomer (nearly free of the 3,6 isomers) could be isolated with each distillation. The liquid (pure) was found to be extremely labile and rearranged to the 3,6 isomers.

The liquid dibromide was assigned the trans 3,4 structure (**4**) on the following basis: its boiling point was essentially identical with those of the 3,6 isomers; its melting point was much lower than those of the 3,6 isomers, which suggests lower molecular symmetry; the C–H absorption bands in the ir spectrum were very similar to those of the 3,6 isomers; and it (**4**) rearranged on standing in CCl_4 to give **5** and **6**. [The liquid isomer (**4**), **5**, and **6** all rearranged to identical equilibrium mixtures.] Also, nmr spectra of mixtures containing **4** did not show any signals inconsistent with its structure. Unfortunately, signals attributable to it were masked by the overlapping signals from the other two isomers, even at 220 MHz. Nmr spectra of both pure solid dibromides were recorded in CCl_4 at 60, 100 (see Figure 1), and 220 MHz: **5**, 4.304 (complex multiplet, 2, $-CH_2CH_2-$protons), 4.8268 (complex multiplet, 1, –CHBr–), 5.942 (broad d, J = 3 Hz, 1, –CH=CH–); **6**, 2.224 (complex multiplet, 1, $-CH_2CH_2-$ protons), 4.700 (complex multiplet, 1, –CHBr–), 5.906 (sharp d, J = 1.7 Hz, 1, –CH=CH–). The infrared spectra (CCl_4) of **4**, **5**, and **6** all showed a fairly similar C–H stretching region (3150–2850 cm^{-1}) and additional strong–medium absorptions as follows: **4**, 1435, 1440, 1280, 1210, 1222, 1145, 1018, 922, 730, 655, 590, 545 cm^{-1}; **5**, 1440, 1400, 1291, 1080, 995, 565 cm^{-1}; **6**, 1450, 1440, 1350, 1301, 1214, 1165, 1175, 1130, 1068, 980, 887, 730, 668 cm^{-1}.

Equilibration Studies.—The equilibrium mixtures shown in Table III were obtained in every case by approaching the equilibrium position from more than one direction; *e.g.*, pure samples of two of the three cyclohexadiene dibromides (**5** and **6**) and nearly pure samples of **4** in carbon tetrachloride were allowed to stand at room temperature until each showed the same composition of dibromides (about 3 months). Equilibration times at room temperature for the other dibromides follow: cyclopentadiene dibromides, 1–2 months; 2,4-hexadiene dibromides, 75% complete in 3 months (CCl_4); bromination mixtures (in CH_3NO_2) from (*E,Z*)- and (*E,E*)-2,4-hexadiene, 1.5 months. Heating at 78–80° caused equilibration of all of the dibromides within 1–2 weeks.

Acknowledgment.—Support for this work was provided by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Union Oil Co. of California Foundation, Brea, Calif., and the Jet Propulsion Laboratory Director's Discretionary Fund. This paper presents results of one phase of research carried out at the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. NAS 7-100, sponsored by the National Aeronautics and Space Administration. We wish to thank Professor S. I. Chan, Department of Chemistry, Cal Tech, for access to the SC-220 spectrometer.

Registry No.—**1**, 42086-50-0; **2**, 42086-51-1; **3**, 17040-70-9; **4**, 42086-52-2; **5**, 42086-53-3; **6**, 42086-54-4; **7**, 42086-55-5; **8**, 42086-56-6; **9**, 42086-57-7; **10**, 42086-58-8; **11**, 42086-59-9; **12**, 42086-60-2; 1,3-cyclohexadiene, 592-57-4; cyclopentadiene, 542-92-7; (*Z,Z*)-2,4-hexadiene, 6108-61-8; (*E,Z*)-2,4-hexadiene, 5194-50-3; (*E,E*)-2,4-hexadiene, 5194-51-4.

Study of a Cope-Related System. *trans,trans*-1,5-Cyclodecadiene and *trans*-1,2-Divinylcyclohexane[1,2]

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Rate constants were determined for the forward and reverse rearrangements of the Cope-related pair, *trans,trans*-1,5-cyclodecadiene (**3**) and *trans*-1,2-divinylcyclohexane (**4**). The rate of **4** → **3** was determined from the rate of racemization of (+)-**4** (the two rate constants are identical), an indirect approach necessitated by the large equilibrium constant favoring **4**; the ratio of forward and reverse rate constants yielded $K_{200°} = 2 \times 10^4$ with $\Delta G_{200°} = 9.4$ kcal mol^{-1}. The individual rate constants yielded $E_a = 25.0$ and 31.6 kcal mol^{-1} for **3** → **4** and **4** → **3**, respectively. The ring strain of **3** is estimated to be 12 kcal mol^{-1} relative to **4**.

trans,trans-1,5-Cyclodecadienes and *trans*-1,2-divinylcyclohexanes are formally interconvertible *via* the Cope rearrangement, and several such related pairs are now known as a result of the isolation of many sesquiterpene cyclodecadienes. In some instances there is an observable equilibrium, *e.g.*, **1**–**2**, as a result of differential effects of methyl substitution of the double bonds and the presence of a trans-fused lactone[3] which offset the strain of the cyclodecadiene. For the unsubstituted pair **3**–**4** there is insufficient counterbalancing of the high energy of the medium ring and the conversion to **4** is virtually complete. It is nevertheless still possible to explore the relationship from both sides. The rate constant k_1 for the forward Cope rearrangement can be measured directly; and the rate constant k_{-1} for the reverse Cope rearrangement can be obtained from the rate of racemization of optically active **4**, which involves Cope rearrangement to an optically active conformation of **3**, racemization of the cyclodecadiene (a relatively rapid process[4]), and reversion of the Cope rearrangement.[5] For this relationship $k_{obsd} = k_{rac} = k_{-1}$. The present paper reports on the determination of these rate constants and related thermodynamic parameters.

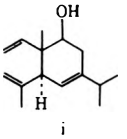
(1) The investigation was supported by Public Health Service Research Grants GM 14133 and 16338 from the Division of General Medical Sciences, U. S. Public Health Service.

(2) The article is abstracted from the Ph.D. Thesis of D. W. J., University of Wisconsin, 1970. The last year of research was carried out at Wesleyan University.

(3) T. C. Jain, C. M. Banks, and J. E. McCloskey, *Tetrahedron Lett.*, 841 (1970).

(4) For 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene, interconversion of enantiomeric conformations has been shown to be fast on the nmr time scale between temperatures of 40 and 90°. It is therefore not possible for the energy of activation for interconversion of enantiomeric conformations of **3** to be rate determining. See ref 6.

(5) This sequence corresponds to the interconversion at 200° of δ- and epi-δ-elemenol (i and ii) reported by K. Morikawa and Y. Hirose, *Tetrahedron Lett.*, 869 (1969).



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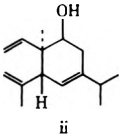

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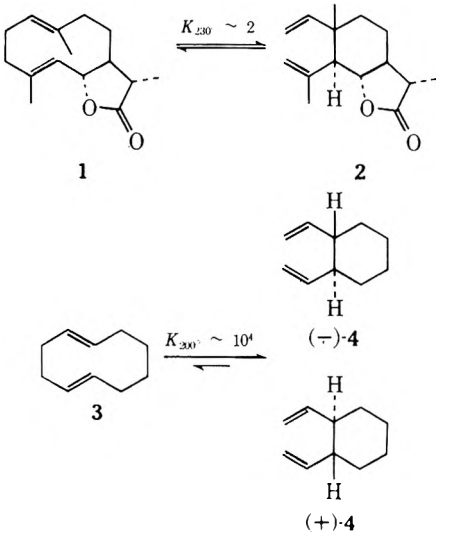
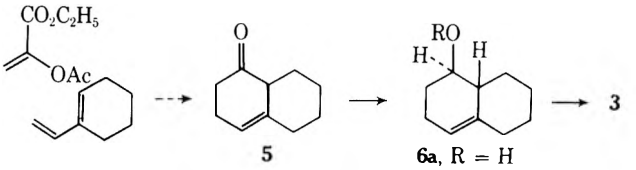


trans,trans-**1,5-Cyclodecadiene.**—Experience gained in the synthesis of 1,5-dimethyl-*trans,trans*-1,5-cyclodecadienes[6,7] was responsible for our use of the same overall route to the unsubstituted ring (see Scheme I). A possible preparative route involving its reported

SCHEME I



formation *via* Hofmann elimination of the 1,6-bisquaternary ammonium salt of cyclodecane[8] was not examined.

Combination of ethyl acetoxyacrylate and 1-vinylcyclohexene yielded a mixture of 1,4 cycloadducts in 86% yield. Reduction of the mixture with lithium aluminum hydride and crystallization of the resulting sludge gave a white solid, mp 75–93°, in 75% yield. That this solid was solely a mixture of epimers was shown by periodate oxidation, which afforded a single β,γ-unsaturated ketone (**5**) in 98% yield. By contrast, periodate oxidation of the total sludge of diols gave two glpc components in a ratio of 88:12, presumably corresponding to the two β,γ-unsaturated ketones obtainable from the two possible regioisomeric modes of cycloaddition.

Hydride reductions of **5** gave mixtures of anti (**6a**) and syn alcohols of variable composition. Sodium borohydride in alcohol at room temperature yielded a highly unfavorable 25:75 ratio and lithium aluminum hydride in ether at room temperature was only slightly better (35:65). Several other variations were tested, with the best (70:30) consisting of a combination of lithium aluminum hydride in diglyme at −78° which was allowed to warm slowly to room temperature. The mixture thus obtained could be enriched to 93 anti:7 syn, with 65% recovery, by acetylation of the alcohol, fractional distillation, and saponification; and this enriched product was sufficiently pure to yield anti tosylate (**6b**) without difficulty in 82% yield after two crystallizations.

Conversion of **6b** to *trans,trans*-1,5-cyclodecadiene (**3**) was effected by Marshall's method:[9] addition of diborane to the double bond and base-promoted fragmentation of the intermediate thus formed. Best results were obtained with 5 *N* sodium hydroxide for 48 hr at room temperature, the undistilled oily product consisting of 94% **3**, 1% *trans*-1,2-divinylcyclohexane (**4**), and 5% of another component (probably the expected cyclopropane[9]) in an overall yield of 65% as determined by glpc analysis.

Isolation of **3** from the crude product was complicated by the substantial losses which occurred in recovery from solutions because of its great volatility, and by the case with which it rearranged to **4** (half-lives of 30 min at 90° and 145 hr at 40° were subsequently determined). However, it was eventually found that samples >99% pure by glpc could be reproducibly obtained by silica gel chromatography at 5° using 2-methylbutane as eluent and subsequent careful removal of solvent and low-temperature distillation.[10]

The Cope rearrangement of **3** was found to proceed at conveniently measurable rates at temperatures between 40 and 90°. Kinetics runs in *n*-decane, which served as both solvent and internal glpc standard, afforded the rate constants given[11] in Table I and a value of $E_a = 25.0 \pm 0.3$ kcal mol^{-1}.

TABLE I

RATE CONSTANTS FOR THE CONVERSION **3** → **4**

Temp, °C	k, sec^{-1}
39.78	1.35×10^{-6}
60.09	1.55×10^{-5}
75.00	7.69×10^{-5}
90.90	3.83×10^{-4}

trans-**1,2-Divinylcyclohexane.**—The isolation of **3** involved a chromatography which cleanly removed the minor saturated component and yielded fractions containing either pure **3** or mixtures of **3** and **4**. It was a simple matter to obtain pure **4** (>99.9% by glpc) by heating such fractions at 100°.

Partial resolution of **4** was effected by treatment of the racemic mixture with 0.5 equiv of optically active diisopinocampheylborane.[12] The volatile hydrocarbon product so obtained was found to contain much α-pinene, but this could be completely removed from pentane solutions by silica gel impregnated with silver nitrate. The final distilled product was shown to be >99.9% pure by glpc and yielded rotations as high as $[\alpha]_D$ +3.6° and $[\alpha]_{436}$ +7.5°.

Optically active **4** was found to racemize with unimolecular kinetics at conveniently measurable rates

(6) P. S. Wharton, Y. C. Poon, and H. C. Kluender, *J. Org. Chem.*, **38**, 735 (1973).

(7) P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.*, **37**, 34 (1972).

(8) C. A. Grob, H. Link, and P. W. Schiess, *Helv. Chim. Acta*, **46**, 483 (1963).

(9) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 854 (1967).

(10) It may be noted that the corresponding preparation of 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene was very much simpler.[6] Each of the methyl groups afforded higher stereoselectivity during the synthesis: the C-5 methyl enhanced the regiospecificity of cycloaddition and the C-1 methyl directed hydride reduction of the octalone in the desired sense. Furthermore, the two methyl groups together were responsible for straightforward isolation of the cyclodecadiene by diminishing both its volatility and tendency to rearrange.

(11) The limits were calculated at the 95% confidence level.

(12) See H. C. Brown and N. R. Ayyangar, *J. Amer. Chem. Soc.*, **86**, 397, 1071 (1964). The procedure followed was identical with that used for the partial resolution of **7**; see ref 14.

between 150 and 200°. Kinetic runs afforded the rate constants[11] given in Table II and a value of $E_a = 31.6 \pm 0.9$ kcal mol^{-1}.

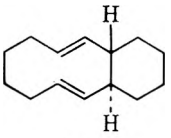
TABLE II
RATE CONSTANTS FOR THE RACEMIZATION OF (+)-4

Temp, °C	k, sec^{-1}
147.48	6.8×10^{-7}
170.44	6.12×10^{-6}
190.61	2.57×10^{-5}
200.18	4.96×10^{-5}

Discussion

The equilibrium constants for the rearrangement **3** ⇄ **4** obtained from the extrapolated rate constants of Tables I and II are 2.1 and 80 × 10^4 at 200 and 40°, respectively. The corresponding free energy differences are 9.4 and 8.5 kcal mol^{-1}. The difference in internal energy between **3** and **4**, derived from the difference in activation energies, is ~7 kcal mol^{-1}; a substantial entropy difference favoring the divinylcyclohexane is revealed.

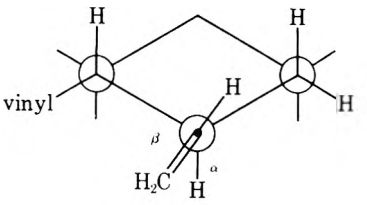
The rate of the Cope rearrangement of **4** → **3** is not very different from that of an acyclic diene: the observed E_a of 31.6 can be compared with 34.2 kcal mol^{-1} reported for 3-methyl-1,5-hexadiene.[13] By contrast the rate of the rearrangement **3** → **4** is very facile and the observed E_a of 25.0 kcal mol^{-1} is identical with that of the degenerate Cope rearrangement of **7**.[14] This correspondence is almost certainly not fortuitous because both **3** and **7** exist in a ground-state chair conformation



(−)-**7**

which is geometrically closely related to the transition state of the Cope rearrangement.[15] By contrast, the double bonds of **4** can rotate and thereby relieve the repulsive interaction of this conformation without generating additional interactions, as shown in the Newman projections **8** and **9**.

The difference in ground-state geometries of **7** and **4** shows up in an interesting way in their partial resolutions using (−)-diisopinocampheylborane. Both dienes can be converted *via* ozonolysis to dimethyl *trans*-1,2-cyclohexanedicarboxylate (**10**).[16] Partially resolved **7** and **4** yield **10** with negative and positive rotations in 45 and 25% optical purity, respectively.[17] Thus partial resolution preferentially destroys enantiomers of opposite bridgehead trans configuration in the



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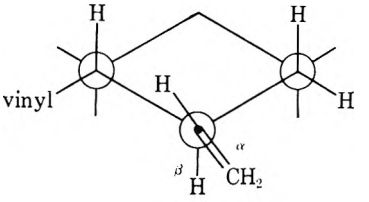

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two series. An explanation for these observations can be advanced on the basis that diene **7** is restricted to conformation **8**, in which each double bond presents only the α face toward an attacking reagent; the β face is shielded by the transannular double bond. By contrast, the double bonds of **4** are freer and prefer to exist substantially in conformation **9** in which the β face is not only not shielded by the adjacent double bond but is totally less hindered to an approaching reagent. Consistent with this explanation are the very different magnitudes of the specific rotations of **4** and **7**, $[\alpha]_D$ 14 and 176°, respectively.

The magnitude of the ring strain in **3** relative to **4** is considerable and can be crudely evaluated as 12 kcal mol^{-1} by adding the experimentally determined difference in internal energy of 7 kcal mol^{-1} and a 5 kcal mol^{-1} term which takes into account the differential effects of alkyl substitution of the double bonds.[18]

It is now possible to contribute to the explanation of the intriguing observation that base-induced fragmentation of boranes (as in the present synthesis), which could in principle lead to cleavages of both internal (→**3**) and peripheral bonds (→**4**), in fact, proceeds almost exclusively *via* the internal mode despite the fact that the product thus generated is much less stable than the product which would be derived from peripheral cleavage.[9,19] In both internal and peripheral cleavage, as the carbon–carbon bond breaks, there is a disrotation of the two incipient double bonds. The transition state for internal cleavage necessarily resembles the crossed chair geometry of **3** but at the corresponding point in peripheral cleavage there is no sensing of the stability of **4**; this is gained only by subsequent rotation. Thus for comparable transition-state geometries, product control is exercised by alkyl stabilization of the incipient double bonds, as suggested by Marshall. Our observation that **4** is kinetically formed to the extent of 1% or less suggests that at the transition state

(13) See H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969).

(14) P. S. Wharton and R. A. Kretchmer, *J. Org. Chem.*, **33**, 4258 (1968).

(15) It has been shown from nmr data that the crossed (chair) conformation of 1,5-dimethyl-**3** is no less stable than any other conformation despite the fact that it is specifically disfavored by a severe methyl–methyl repulsion (see ref 6). It can therefore be concluded that the crossed (chair) conformation of **1**, which lacks such methyl groups, is substantially more stable than other conformations. Models show that the trans bicyclic fusion present in **7** further stabilizes the crossed conformation relative to others.

(16) A. Werner and H. E. Conrad, *Chem. Ber.*, **32**, 3046 (1899). The absolute configuration of (+)-**10** was determined by D. E. Applequist and N. D. Werner, *J. Org. Chem.*, **28**, 48 (1963), and is the basis for the designations of configurations of optically active **4** and **7**.

(17) The 45% figure was established by H. C. Kluender. The rotations of optically pure **10** were determined by Werner and Conrad.[16]

(18) The value of 5 kcal mol^{-1} is obtained from Kistiakowsky's widely cited values for heats of hydrogenation of various alkyl-substituted olefins. Consideration of the effect of the additional alkyl substitution of 1,5-dimethyl-**3** (a pattern common to many sesquiterpenes) suggested that the amount of this cyclodecadiene present at equilibrium might be directly observable: the free energy difference of 9.4 kcal mol^{-1} found for the pair **3**, **4** at 200° should be reduced to ~4.7 kcal mol^{-1} assuming that there is no other differential effect of methyl substitution. Indeed, it has been found experimentally that there is 0.35% of 1,5-dimethyl-**3** present at equilibrium at 200°, an amount obtained starting from both higher and lower values. The free energy difference of 5.3 kcal mol^{-1} corresponding to this equilibrium is perhaps fortuitously close to that calculated (Y. C. Poon, Ph.D. Thesis, Wesleyan University, 1971; see also ref 6).

(19) J. A. Marshall and J. H. Babler, *Tetrahedron Lett.*, 3861 (1970); *J. Org. Chem.*, **34**, 4186 (1969).

there is operative at least half of the 5 kcal mol^{-1} influence of alkyl substitution[18] stabilizing the double bonds of **3** relative to **4**.

Experimental Section

Physical Data.—Melting points were determined using a Thomas Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded on Beckman IR-8 and Perkin-Elmer Infracord Model 137 spectrometers. The ultraviolet spectrum was recorded on a Cary Model 14 spectrometer. Nmr spectra were recorded using a Varian A-60A spectrometer with tetramethylsilane as an internal reference. Unless otherwise stated glpc data were obtained using 150 ft × 0.01 in. stainless steel columns in conjunction with a Perkin-Elmer Model F-11 unit, with flame ionization detection, and Disc chart integration. Fractional distillations were performed using a 24-in. Nester-Faust NFT-50 Teflon spinning bond column. Ozone was generated by a Welsbach Ozonator, Model T-408. Optical rotations were obtained at 25° using 1-dm cells in conjunction with a Rudolph Model 80 polarimeter (which happened to be modified to record *via* the faraday effect). The constant-temperature bath used in kinetic studies consisted of an insulated drum containing 12 gal of Dow Corning 510 silicone fluid, stirred with a Lightnin Model L stirrer and regulated by a YSI Model 63RA unit.

Materials.—Organic extracts were dried with either magnesium or sodium sulfate. Solvents were distilled before use (after drying when necessary) with the exceptions of anhydrous ether and alcohol. α-Pinene (Aldrich) was subjected to careful fractional distillation and a fraction was used with bp 88.0–88.5° (100 mm), >99.9% by glpc. *p*-Toluenesulfonyl chloride, *p*-nitrobenzoyl chloride, and 3,5-di-*tert*-butylcatechol were crystallized from hexane. The silica gel used was Grace, Grade 950, 80–200 mesh. For impregnation with silver nitrate 225 g of silica gel was mixed with 250 ml of 10% aqueous silver nitrate in a flask blackened externally and the water was removed at 80° on a rotary evaporator. Activation of the silica gel was accomplished by heating at 100° for at least 12 hr before use.

$\Delta^{4(10)}$-1-Octalone (5).—A mixture of 142.7 g (1.32 mol) of 1-vinylcyclohexene,[20] 186.0 g (1.18 mol) of ethyl α-acetoxyacrylate,[21] and 7.5 g of 3,5-di-*tert*-butylcatechol was heated under nitrogen at 130° for 50 hr. After cooling, distillation yielded 269.1 g (86%) of a highly viscous, colorless liquid: bp 108–110° (0.4 mm); ir (neat) 5.74 μ; nmr (CCl_4) δ 5.36 (1, broad), 4.13 (2, q, J = 7 Hz), 2.01 and 1.98 (3 total, singlets), and 1.24 ppm (3, t, J = 7 Hz).

A solution of the distillate in 1000 ml of ether was added slowly, with stirring and cooling, under nitrogen, to a mixture of 60 g (1.5 mol) of lithium aluminum hydride in 200 ml of ether. After the addition was complete the mixture was stirred for 15 hr at room temperature. Saturated magnesium sulfate solution (75 ml) was then added slowly with stirring and cooling and the mixture was allowed to stand until it was almost white (24 hr). It was then poured onto 2000 ml of ice–water, and concentrated hydrochloric acid was added to dissolve all solid. Extraction with five 500-ml portions of ether and further work-up yielded a crude product which was dissolved in ether and allowed to crystallize at 5°, affording from these repetitions a combined total of 150 g of a greenish-white solid. Crystallization of this solid from acetone gave 138.8 g (75%) of white solid: mp 75–93°; ir (CCl_4) 2.93, 6.02, and 11.64 μ; nmr (CCl_4) δ 5.30 (1, broad), and 4.0–3.0 ppm (4, broad).

To a solution of this solid (0.76 mol) in 2000 ml of 50% aqueous alcohol was added, with cooling and stirring under nitrogen, 182.8 g (0.795 mol) of sodium metaperiodate in one portion. After the solution was stirred at room temperature for 1.5 hr, 2000 ml of water was added and the mixture was extracted with two 500-ml portions of pentane. The aqueous phase was then diluted to 8000 ml and extracted with four 1000-ml portions of pentane. The combined pentane extracts were washed with 500 ml of water, 500 ml of 0.5 *N* sodium thiosulfate solution, 500 ml of water, and 500 ml of saturated sodium chloride solution. Drying and removal of solvent yielded 112.6 g (98.5%) of a colorless liquid: ir (neat), 5.85 and 8.34 μ; uv max (95% ethanol) 285 nm (ε 30.5); nmr (CCl_4) δ 5.50 ppm (1, broad).

anti-$\Delta^{4(10)}$-1-Octalol and Its Derivatives (6).—To a mixture of 11.0 g (275 mmol) of lithium aluminum hydride in 2000 ml of diglyme, cooled to −78° in a Dry Ice–acetone bath, was added over a period of 1.5 hr, with stirring, under nitrogen, a solution of 112.6 g (0.749 mol) of $\Delta^{4(10)}$-1-octalone in 500 ml of diglyme. After stirring for an additional 5 hr at −78° the mixture was allowed to warm to room temperature. Saturated magnesium sulfate solution (75 ml) was then added slowly, with cooling, and the mixture was allowed to stand until it was nearly white (24 hr). Addition of 450 g of powdered anhydrous magnesium sulfate yielded a mixture which could be filtered easily. The separated solid was washed thoroughly with ether. The combined organic solutions were distilled, eventually at 50 mm, until the head temperature reached 87°, in order to remove most of the diglyme. The residue was diluted with 1000 ml of water and then extracted with three 500-ml portions of pentane. The combined pentane extracts were washed with four 500-ml portions of water and 250 ml of saturated sodium chloride solution. After drying, removal of solvent afforded 105.2 g (92%) of a yellow oil: nmr (CCl_4) δ 3.85 and 3.38 ppm (1 total, complex), attributable to syn and anti isomers, respectively, in a 31:69 ratio (best determined after removal of the OH absorption by adding D_2O).

To a solution of this yellow oil in 1000 ml of pyridine was added 400 ml of acetic anhydride. After 30 hr at room temperature the solution was poured over ice and the mixture was stirred for 1 hr. Addition of 3000 ml of water and extraction with four 500-ml portions of ether gave, after further work-up and a rapid distillation at 0.5 mm, 128.8 g (96%) of a colorless, fragrant liquid. The distillation product was then subjected to a careful fractional distillation at 0.3 mm (head temperature *ca.* 60°) and the per cent anti alcohol in the distillate was determined by glpc at 160° (Apiezon L): fraction 1, 45.2 g (95.4%); fraction 2, 25.6 g (91.2%); fraction 3, 30.9 g (74.8%); fraction 4, 26.3 g[22] (3.2%). Redistillation of fraction 3 afforded a further 20.0 g (96.5%) which was combined with fractions 1 and 2 (totaling 90.8 g, 94.5% anti).

This combined distillate (90.8 g) was saponified in a solution of 1250 ml of methanol and 125 ml of water containing 75 g of 85% potassium hydroxide. After 14 hr at 40° under nitrogen, the methanol was removed under reduced pressure, 2000 ml of water was added, and the mixture was extracted with four 500-ml portions of ether. Further work-up yielded 75.4 g of a yellow oil which afforded, upon distillation, 67.5 g (95%) of a colorless oil: bp 70.7–73.0° (0.7 mm); nmr (CCl_4) δ 5.27 (1, broad) and 3.38 ppm (1, m). A small portion yielded crystals from a pentane solution at −78°; and further crystallization from pentane at −20° gave a white solid, mp 40.1–42.2°.

From the distilled oil, a crystalline *p*-nitrobenzoate was obtained by a standard procedure, mp 71.0–71.3°.

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.67; H, 6.36; N, 4.65. Found: C, 67.87; H, 6.13; N, 4.66.

The *p*-toluenesulfonate was prepared from 40.0 g (0.263 mol) of the distilled oil, which was dissolved in 300 ml of pyridine and treated with 55.0 g (0.288 mol) of *p*-toluenesulfonyl chloride. The solution was allowed to stand at 5° for 80 hr. Excess *p*-toluenesulfonyl chloride was then destroyed by the addition of 5 ml of water. Further work-up afforded 80.6 g of a white solid which gave, after two crystallizations from methanol at −20°, with pentane washing, 65.9 g (82%) of white crystals: mp 44.7–45.4°; nmr (CCl_4) δ 5.28 (1, broad) and 4.34 (1, m).

Anal. Calcd for $C_{17}H_{22}O_3S$: C, 66.65; H, 7.24; S, 10.44. Found: C, 66.79; H, 7.28; S, 10.36.

***trans*,*trans*-1,5-Cyclodecadiene (3) and *trans*-1,2-Divinylcyclohexane (4).**—To a solution of 20.0 g (65.2 mmol) of *anti*-$\Delta^{4(10)}$-1-octalyl *p*-toluenesulfonate in 50 ml of tetrahydrofuran, stirred and cooled in an ice–water bath and under nitrogen, was added, over a period of 15 min, 70 ml of a solution of 1 *M* borane in tetrahydrofuran (Alfa). The mixture was stirred for an additional 90 min at room temperature. To it was added cautiously,

(20) 1-Vinylcyclohexene was prepared from 1-ethynylcyclohexanol *via* the sequence elimination–reduction (not the converse) described by E. D. Bergman and A. Becker, *J. Amer. Chem. Soc.*, **81**, 225 (1959).

(21) Ethyl α-acetoxyacrylate was prepared according to the procedure described for the methyl ester by J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3598 (1964).

(22) This fraction was characterized as *syn*-$\Delta^{4(10)}$-1-octalyl acetate and yielded *syn*-$\Delta^{4(10)}$-1-octanol, mp 50–51°, and *syn*-$\Delta^{4(10)}$-1-octalyl *p*-toluenesulfonate, mp 58.6–59.3° dec.

with cooling in an ice–water bath, first 15 ml of water and then 25 ml of 5 *N* sodium hydroxide solution. The mixture was stirred at room temperature for 48 hr and then 25 ml of 30% hydrogen peroxide was added with external cooling. The mixture was stirred for an additional 3 hr at room temperature. Work-up involved addition of 500 ml of water and extraction with five 100-ml portions of 2-methylbutane. The combined 2-methylbutane extracts were extracted with four 100-ml portions of water and then dried. Removal of most of the solvent was effected by fractional distillation and the residue was chromatographed on a 250-g column of silica gel; 100-ml fractions of 2-methylbutane eluent were collected and the solvent was removed by fractional distillation. Fraction 2 yielded a mixture probably containing tricyclo[5.3.0.$0^{1,6}$]decane: ir (film) 3.35 and 9.80 μ; nmr (CCl_4) δ 0.95–0.5 ppm (2, complex). Fraction 3 gave 1.22 g of a colorless liquid which was shown to be a mixture of 70% **3** and 30% **4** by glpc at 50° (SF-96). Fraction 4 afforded 4.67 g of a colorless liquid which was shown to be **3** containing less than 2% of **4** by glpc. Fractions 5 and 6 yielded oils similar in composition to fraction 4. Fractions 3–6 were combined and heated overnight at 100° under nitrogen. Short-path distillation of the resulting oil gave 5.50 g (62%) of *trans*-1,2-divinylcyclohexane (**4**) (>99.9% by glpc): bp 46.0–46.5° (10 mm); ir (film) 3.28, 5.50, 6.10, 10.10, and 11.01 μ; nmr, ratio of olefinic to paraffinic hydrogens, 6:10.

From similar runs *trans,trans*-1,5-cyclodecadiene (**3**) was obtained from individual fractions. For example, a 2.78-g chromatography fraction (>98% **3** by glpc) afforded 1.58 g of **3** (99% by glpc) upon short-path distillation at room temperature and 0.3 mm: ir (film) 3.36, 6.02, 10.11, 10.41, 12.78, and 13.65 μ; nmr (CCl_4), ratio of olefinic to paraffinic hydrogens, 4:12, main olefinic H signal a broad band centered at δ 4.7 ppm with $W_{1/2}$ = 14 Hz.

(+)-*trans*-**1,2-Divinylcyclohexane.**—To a solution of 0.997 g (26.4 mmol) of sodium borohydride and 9.60 g (70.2 mmol) of α-pinene, $[\alpha]_D$ +53.4° (95% ethanol), in 75 ml of diglyme, cooled to −10 to −20° in an ice–salt bath, was added slowly, with stirring under nitrogen, 4.98 g (35.1 mmol) of boron trifluoride etherate. The mixture was stirred for an additional 4 hr at −10 to −20°. Racemic **4** (9.58 g, 70.2 mmol) was added in one portion and the mixture was stirred at −10 to −20° until it became homogeneous (6 hr). To the cold solution was added cautiously first 5 ml of water and then 20 ml of 5 *N* sodium hydroxide solution. The ice–salt bath was removed, 20 ml of 30% hydrogen peroxide was added, and the mixture was allowed to stand overnight with stirring. It was then poured into 500 ml of water. Further work-up afforded 6.85 g of a colorless oil, bp 50–60° (10 mm), glpc analysis (SF-96) showing it to be a 65:34 mixture of **4** and α-pinene. The mixture was placed on a 180-g column of silica gel impregnated with 10% silver nitrate. Pentane was passed through the column until no trace of pinene in the eluent could be detected by glpc (this required 600 ml of pentane). The pentane in the column was displaced by 2-methylbutane and the column packing was then dumped into 400 ml of cold, concentrated ammonium hydroxide. Extraction with three 150-ml portions of 2-methylbutane and further work-up afforded, after distillation, 2.17 g of a colorless oil: bp 43–45° (10 mm); >99.9% **4** by glpc; $[\alpha]_{436}$ +9.00° (cyclohexane).

Configurational Correlation of (+)-4 with (+)-Dimethyl *trans*-1,2-Cyclohexanedicarboxylate.—One sample of (+)-**4**, 61 mg (0.448 mmol), $[\alpha]_D$ +3.61°, $[\alpha]_{436}$ +7.53° (cyclohexane), in 25 ml of methylene chloride was cooled to −78° and treated with an excess of ozone. The solution was allowed to warm to room temperature and remain at that temperature for 60 min. Solvent was then removed and to the residue was added 3 ml of 5 *N* sodium hydroxide solution and 2 ml of 30% hydrogen peroxide. The mixture was stirred overnight and excess peroxide was then destroyed with a small amount of 5% palladium on carbon. Further work-up yielded 20 mg (26%) of a white, solid acid.

A second sample of (+)-**4**, 59 mg (0.435 mmol), $[\alpha]_D$ +3.61°, $[\alpha]_{436}$ +7.53° (cyclohexane), in 2 ml of chloroform at −30° was treated with an excess of ozone. The solution was then allowed to stand at room temperature for 60 min. Thereafter the chloroform was removed by dropwise addition to 10 ml of water maintained at 95°. The aqueous mixture was then cooled slightly before adding to it 0.5 g of silver oxide and 1 ml of 5 *N* sodium hydroxide solution. This mixture was heated at 90° for 1 hr and then filtered hot. Further work-up afforded 17 mg (23%) of a slightly yellow oily acid.

The acidic products obtained from the two ozonolyses were combined, 38 mg, and esterified with an ethereal solution of diazomethane. Work-up gave 44 mg of a yellow oil which, subjected to preparative glpc at 150° (5 ft × 0.25 in. column packed with 5% Carbowax 20M on 40/60 Chromosorb T) afforded 29 mg of a colorless oil with ir and glpc characteristics indistinguishable from those of authentic dimethyl *trans*-1,2-cyclohexanedicarboxylate, $[\alpha]_D$ +7.29°, $[\alpha]_{436}$ +12.89° (acetone).

Kinetic Studies. A. Cope Rearrangement.—Samples of **3** in *n*-decane were degassed and then sealed under nitrogen and heated in a constant-temperature bath (±0.01°). Over the period of observation (approximately 2 half-lives) no side reactions could be detected by glpc and no residue was left upon distillation. The extent of conversion was determined by glpc analysis (50°, SF-96), each analysis in duplicate or triplicate, using the *n*-decane as a reference in two independent determinations: (1) the rate of disappearance of **3** and (2) the rate of appearance of **4**. At each of four temperatures two runs were made; for each run approximately ten sample tubes were heated. The glpc areal ratios were slightly changed by using a correlation line obtained with standard weighed mixtures; inexplicably, this did not quite pass through the origin for the mixture of **3** and *n*-decane. A good value of $[\mathbf{4}]_\infty$ was difficult to obtain directly (it was probably obscured by polymerization) and it was finally assigned the value of $[\mathbf{3}]_0$; varying this value by ±5% was found to have a negligible effect on the results. The total set of rate constants thus obtained yielded Arrhenius parameters from a General Electric Mark I computer using the least squares program SIXCR$.

B. Racemization.—Samples of (+)-**4** were degassed and then sealed under vacuum and heated in a constant-temperature bath (±0.02°). Approximately ten samples were analyzed for each run, which extended over approximately 2 half-lives (except at the lowest temperature when there were only four observations taken up to ~20% conversion). Each sample tube was cooled and opened and the contents were distilled from the tube at room temperature and 0.3 mm into a small Dry Ice–acetone trap. The contents of the trap were removed with a small amount of cyclohexane and their weight was determined by difference. For determination of rotations each cyclohexane solution was made up to 1 ml in a volumetric flask. The specific rotation at t_∞ was taken to be zero and was actually found to be $[\alpha]_{436}$ 0.000 ± 0.004° after 10 half-lives. For each separate determination of rotation an individual rate constant was calculated from the first-order rate equation, yielding an average rate constant for each temperature. The total set of rate constants thus obtained yielded Arrhenius parameters from the computer program referred to above.

Registry No.—**3**, 10573-77-0; (±)-**4**, 41727-77-9; (+)-**4**, 41727-78-0; **5**, 41718-12-1; **6a**, 41727-79-1; *syn*-**6a**, 41727-80-4; **6a** *p*-nitrobenzoate, 41727-81-5; *syn*-**6a** acetate, 41727-82-6; **6b**, 41727-83-7; *syn*-**6b**, 41727-84-8; 1-vinylcyclohexene, 2622-21-1; ethyl α-acetoxyacrylate, 22807-79-0; 1,4-cycloadduct regioisomer A, 41718-15-4; 1,4-cycloadduct regioisomer B, 41718-16-5; epimer A, mp 75–93°, 41727-85-9; epimer B, mp 75–93°, 41727-86-0; tricyclo[5.3.0.$0^{1,6}$]decane, 41718-17-6; (+)-α-pinene, 7785-70-8.

Solvolytic Behavior of the *cis*- and *trans*-1-Tosyloxycyclopentane 3,4-Epoxides. The Absence of Neighboring Epoxy Group Participation[1]

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The epimeric *cis*- and *trans*-1-tosyloxycyclopentane 3,4-epoxides have been synthesized and their solvolytic behavior has been studied in buffered acetic acid. The acetolysis rate of the cis epimer exceeded that of the trans epimer by only a factor of 3.3. Comparison with model compounds showed little, if any, rate acceleration. Analysis of the complex product mixtures has shown that each epimer gave predominantly acetate of inverted configuration. These acetates were unstable to the reaction conditions and underwent rapid opening of the epoxide ring, with a minor amount of 1,3-acetoxyl neighboring group participation in the case of the trans acetate. No indication of neighboring epoxide group participation was found in the solvolysis of the tosylates.

Recently there has been considerable interest in the solvolytic behavior of heterocyclic analogs of cyclopropyl carbinyl systems.[2] The solvolytic behavior of oxiranes[2a-c,g] (**1a**), aziridines[2d-f] (**1b**), and thiiranes[2b,h] (**1c**) has been reported. While these systems resemble the cyclopropyl carbinyl system (**1d**) which has been postulated to give rise to a nonclassical carbonium ion,[3] their behavior is best explained by the intermediacy of heterocyclic bicyclobutonium cations (**2**),[2a,b,d,f,h,i] aris-

1a, X = O
b, X = NR
c, X = S
d, X = CH_2

L = leaving group

2

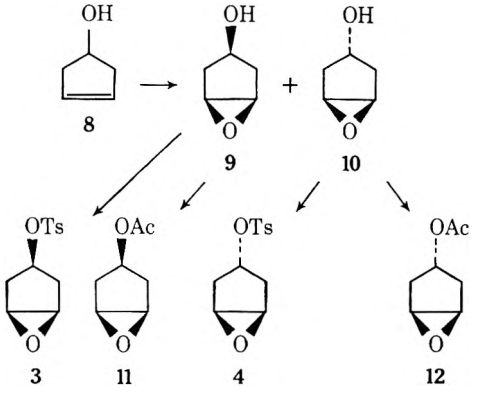
ing from participation of the unshared pair of electrons on the heteroatom. Only in one of these cases has participation of the carbon–carbon bond of the heterocyclic ring been postulated.[2c]

We wish to report our studies on *cis*- and *trans*-1-tosyloxycyclopentane 3,4-epoxides (**3** and **4**). These are the oxa analogs of the 3-tosyloxybicyclo[3.1.0]-hexanes studied by Winstein and Sonnenberg[4] and postulated to give rise to the intriguing "trishomocyclopropenyl cation" (**5**). If participation were to occur in the solvolysis of **3** or **4**, it would necessarily involve the 3,4 carbon–carbon bond and could give rise to the nonclassical cation **6**.[5] Direct migration to produce stabilized cation **7** is an additional possibility.

Synthesis and Solvolysis.—The desired *cis*- and *trans*-cyclopentan-1-ol 3,4-epoxides[6] (**9** and **10**) were

5 **6** **7**

synthesized by epoxidation of Δ-3-cyclopentenol[7] with *m*-chloroperbenzoic acid. The stereochemistries of **9** and **10** have been established by Darby, Henbest, and McClenaghan[6] by the presence of dilution-independent intramolecular hydrogen bonding (band at 3546 cm^{-1} in the infrared) in **9** which was absent in **10**, and by chemical studies. Reaction of **9** with tosyl chloride and acetyl chloride gave *cis*-1-tosyloxycyclopentane 3,4-epoxide (**3**) and *cis*-1-acetoxycyclopentane 3,4-epoxide (**11**), respectively. Upon reaction with tosyl chloride and acetic anhydride, **10** gave the trans isomers **4** and **12**, respectively.



The rates of solvolysis of compounds **3** and **4** in acetic acid buffered with sodium acetate are given in Table I. Both compounds gave good first-order kinet-

TABLE I

ACETOLYSIS RATES OF 1-TOSYLOXYCYCLOPENTANE 3,4-EPOXIDES

Compd	Temp, °C	Rate, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
3	100.0 ± 0.02	(1.81 ± 0.06) × 10^{-4}	20.1	−22.2
	90.0 ± 0.02	(8.19 ± 0.10) × 10^{-5}		
	80.0 ± 0.02	(3.68 ± 0.02) × 10^{-5}		
	(25)[a]	1.55 × 10^{-7}		
4	110.0 ± 0.02	(1.80 ± 0.01) × 10^{-4}	24.8	−11.4
	100.0 ± 0.02	(7.53 ± 0.02) × 10^{-6}		
	90.0 ± 0.02	(2.84 ± 0.04) × 10^{-5}		
	(25)[a]	1.31 × 10^{-8}		

[a] Extrapolated from higher temperatures.

(1) Presented in part at the 165th National Meeting of the American Chemical Society, Dallas, Tex., April 1973.

(2) (a) H. G. Richey, Jr., and D. V. Kinsman, *Tetrahedron Lett.*, 2505 (1969); (b) H. Morita and S. Oae, *ibid.*, 1347 (1969); (c) D. L. Whalen, *J. Amer. Chem. Soc.*, **92**, 7619 (1970); (d) V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970); (e) V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968); (f) J. A. Deyrup and C. L. Moyer, *ibid.*, 6179 (1968); (g) J. M. Coxon, R. P. Garland, M. P. Hartshorn, and G. A. Lane, *Chem. Commun.*, 1506 (1968); (h) J. C. Martin and D. J. Anderson, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, Abstract 31-O; (i) R. H. Higgins and N. H. Cromwell, *J. Amer. Chem. Soc.*, **95**, 120 (1973).

(3) See R. Breslow in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 233–294.

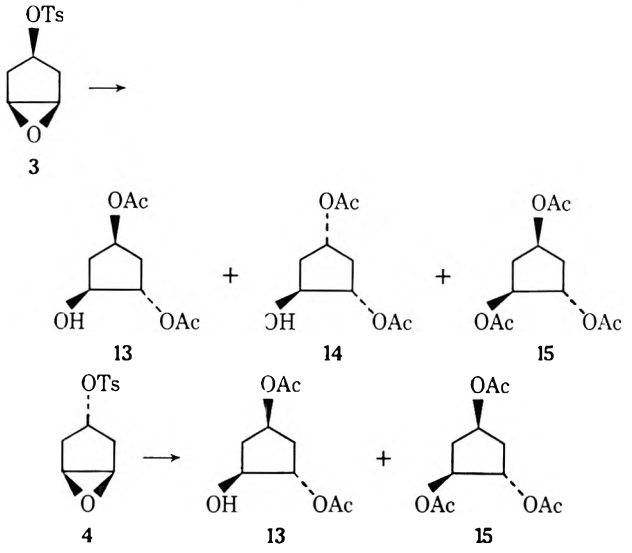
(4) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235, 3244 (1961).

(5) Cation **6** would be destabilized relative to **5** because of the inductive withdrawal of electrons by oxygen. However, resonance donation of the nonbonded electrons on oxygen could provide a stabilizing contribution.

(6) A. C. Darby, H. B. Henbest, and I. McClenaghan, *Chem. Ind. (London)*, 462 (1962).

(7) E. L. Allred, J. Sonnenberg, and S. Winstein, *J. Org. Chem.*, **25**, 26 (1960); for a procedure with higher yield see H. M. Hess and H. C. Brown, *ibid.*, **32**, 4138 (1967).

ics through at least two half-lives. The product mixtures obtained from the solvolysis of **3** and **4** were complex. Analysis of the product mixture from **3** by glpc showed 10% of *trans*-2-*cis*-4-diacetoxycyclopentanol (**13**), 24% of *trans*-2-*trans*-4-diacetoxycyclopentanol (**14**), 41% of *trans*-2-*cis*-4-triacetoxycyclopentane (**15**),



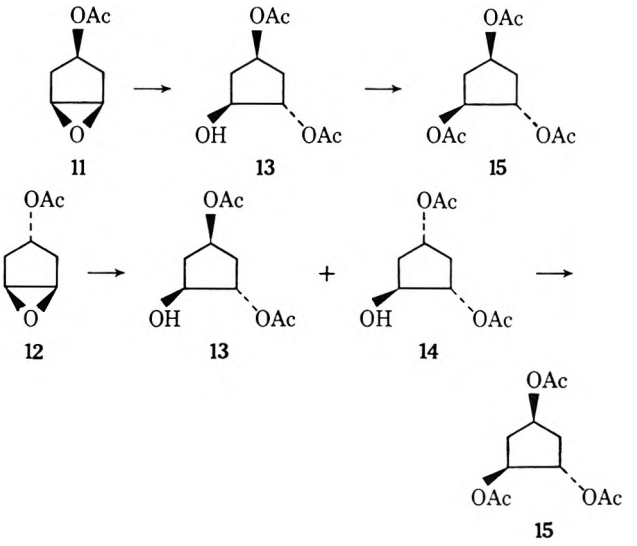
and 25% of seven unidentified components. Analysis of the product mixture from **4** by glpc showed 18% of **13**, 61% of **15**, and 21% of five unidentified components. Although no **14** was detected, amounts of less than *ca.* 5% would not have been resolved from **13**.

The structure of **15** was suggested by its nmr spectrum, which showed a singlet superimposed on a multiplet at τ 7.85 (relative area of 13) assigned to the nine methyl and four methylene hydrogens, and a broad multiplet at τ 4.60 (relative area of 3) assigned to the hydrogens adjacent to oxygen. The structure was proven by comparison of spectral properties (ir, nmr) and glpc retention time with those of an authentic sample of **15** prepared by reaction of the known[8] *trans*-2,*cis*-4-trihydroxycyclopentane with acetic anhydride.

Although stereoisomers **13** and **14** could be partially resolved by analytical glpc, they could not be separated by preparative glpc and were therefore analyzed as a mixture. Their structures were suggested by the infrared spectrum of the mixture (showing absorptions for both hydroxyl and carbonyl groups) and the nmr spectrum, which showed two singlets superimposed on a broad multiplet at τ 7.85 (relative area of 10) assigned to the six methyl hydrogens and the four methylene hydrogens, a broad peak at τ 6.45 (relative area of 1) assigned to the hydroxyl hydrogen, and a group of broad multiplets at τ 4.5–5.5 (relative area of 3) assigned to the three hydrogens adjacent to oxygen. Upon reaction with acetic anhydride, the mixture produced a single compound which was identified as **15** by comparison with an authentic sample. These data limit the possible structures of the two products to **13**, **14**, and *trans*-3-*cis*-4-diacetoxycyclopentanol. Mechanistic considerations strongly suggested **13** and **14** as the correct structures. Definitive evidence for this assignment and for the individual stereochemistries of the isomers was obtained from the acetic acid mediated cleavage of epoxy acetates **11** and **12** (*vide infra*).

(8) R. Steyn and H. Z. Sable, *Tetrahedron*, **25**, 3579 (1969).

In order to determine if the observed products were arising *via* the intermediacy of epoxy acetates **11** and **12**, the stability of these compounds to the acetolysis conditions was determined. Upon heating at 100° in acetic acid buffered with sodium acetate, the disappearance of **11** with a rate constant[9] of 6×10^{-4} sec^{-1} was observed. Diacetate **13**[10] was formed at the same rate and then disappeared at a slower rate to produce **15**. Epoxy acetate **12** was similarly observed to decompose with a rate constant[9] of 8×10^{-4} sec^{-1} to give a 1:8 mixture of **13** and **14**,[10] which then reacted more slowly to give **15**.



Additional evidence supporting the intermediacy of **11** and **12** in the acetolysis of **3** and **4** was provided by examination of the product composition after reaction for approximately one half-life of the tosylates. The products from acetolysis at 100° of cis tosylate **3** showed the presence of 26% of trans acetate **12** after 30 min.[11] Isolation of the solid product after 60 min gave material whose infrared spectrum was identical with that of authentic cis tosylate **3**. Approximately 2% of **11** could be detected in the acetolysis products of trans tosylate **4** after 60 min at 100°.[11] Only minor amounts of **15** were detected in either case at this stage of reaction.

Discussion

Inversion of configuration in the opening of epoxides by acids to give trans products is a well-documented reaction.[12] Thus, the expected product from the opening of cis epoxide **11** in acetic acid is **13**. This evidence provides confirmation of the general structural assignment and also establishes the stereochemistry of **13**. The expected product from the opening of trans epoxide **12** in acetic acid is **14**.[12] We assigned this structure to the major product observed in the reaction of **12** with acetic acid. The minor product was identical with the major product in the reaction of **11** and thus is **13**. This stereoisomer must arise by inversion at the initial acetate position in addition to opening of the

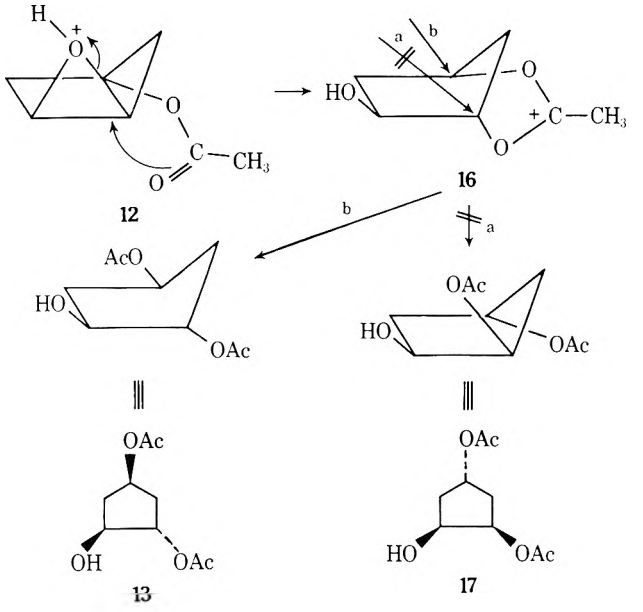
(9) Rates were determined by analysis of aliquots by glpc (see Experimental Section).

(10) See Discussion for assignment of structures to these products.

(11) The half-life of **3** at 100° is *ca.* 1 hr. The half-life of **4** at 100° is *ca.* 2.5 hr.

(12) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959); see especially pp 757–762.

epoxide ring with inversion. A possible mechanism for the formation of this product involves neighboring group participation.[13] Thus 1,3-acetoxyl participation[14-18] in the opening of **12** would give acetoxonium ion **16**. Nucleophilic attack on **16** could occur *via* path a to give *cis*-2,*trans*-4-diacetoxycyclopentanol (**17**) or



via path b to give **13**. The failure to observe **17** in the product mixture implies steric hindrance to path a attack in **16** by the hydroxyl group. The product ratio shows that intramolecular participation is only one eighth as fast as direct solvent displacement in this system.[19]

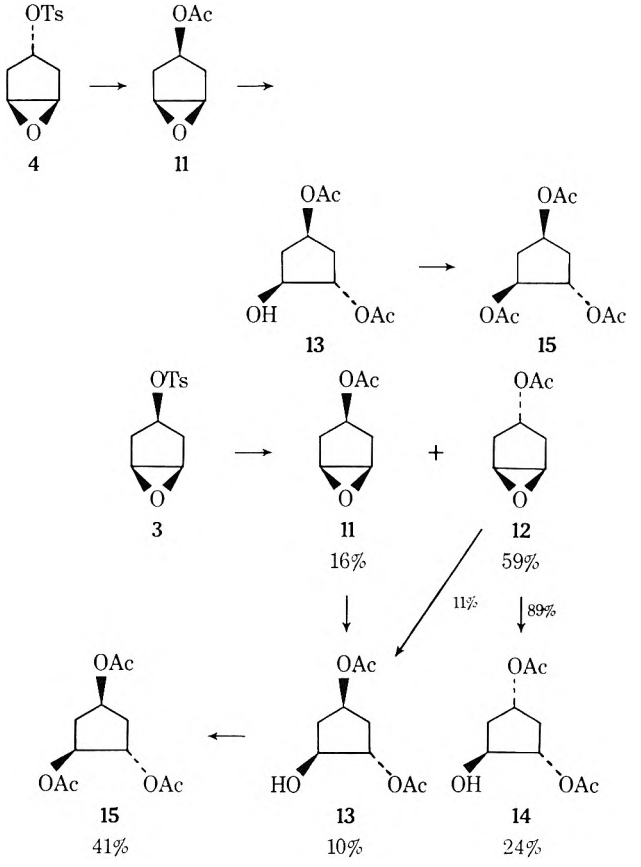
Reaction rates greater than expected and unusual product compositions (rearrangements, retention of configuration, etc.) are usually taken as evidence of neighboring group participation in solvolysis reactions.[20] Considering the question of rates first, it is difficult to find a good model for this system. Table II lists relative relative rates for **3**, **4**, and 4-tosyloxytetrahydropyran (**18**).[21] It is seen that the solvolysis rate of **3** is enhanced over that of **18** by a factor of 15. However, this rate difference may not be meaningful since bridging carbons 2 and 6 in **18** should also increase the amount of strain relieved upon ionization and thus increase the solvolysis rate of **3** and **4** relative to **18**. For example, cyclopentyl tosylate undergoes acetolysis some 20 times faster than cyclohexyl tosylate at 50°.[4] If the solvolysis rate of trans tosylate **4** is used as a model for that of **3**, a modest rate acceleration of 3.3 at 84.8°[22] is seen.[23] It must be concluded, therefore, that rate acceleration in **3** due to neighboring group participation is small, if present at all.

TABLE II
ACETOLYSIS RATES AT 84.8°

Compd	Rate, sec^{-1}	Relative rates
3	5.6×10^{-5} [a]	15
4	1.7×10^{-5} [a]	4.6
		
18	3.7×10^{-6} [b]	1

[a] Extrapolated from other temperatures. [b] See ref 21.

We propose the scheme presented below to explain the identified solvolysis products of **3** and **4**. Upon acetolysis, trans tosylate **4** produces 79% of cis acetate **11** and only a small amount, if any, of trans acetate **12** in addition to 21% of unidentified products. Acetate **11** completely decomposes to produce **13** during the course of the reaction so that **13** and its esterification product **15** are the only isolable products. In the case



of cis tosylate **3**, both cis and trans acetates **11** and **12** are initially produced in the amounts of 16 and 59%, respectively. Both acetates decompose completely during the course of the reaction, **11** giving only **13** and **12** giving **13** and **14** in a 1:8 ratio. This results in a

(13) For an example of neighboring carbonyl participation in epoxide opening, see H. O. House, *J. Org. Chem.*, **21**, 1306 (1966); also see ref 12, p 763.
(14) L. J. Dolby, C. N. Lieske, D. R. Rosencrantz, and M. J. Schwartz, *J. Amer. Chem. Soc.*, **85**, 47 (1963).
(15) L. J. Dolby and M. J. Schwartz, *J. Org. Chem.*, **30**, 3581 (1965).
(16) R. J. Ouellette and R. D. Robins, *Tetrahedron Lett.*, 397 (1968).
(17) P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 5200 (1972).
(18) O. Kovacs, G. Schneider, and L. K. Lang, *Proc. Chem. Soc.*, 374 (1963).
(19) See ref 15 for evidence that 1,3-acetoxyl participation is less favorable than 1,2-acetoxyl participation.
(20) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).
(21) D. S. Tarbell and J. R. Hazen, *J. Amer. Chem. Soc.*, **91**, 7657 (1969).
(22) This acceleration increases to a factor of 12 at 25°.
(23) It might be argued that the rate of **4** is accelerated by direct participation of the oxygen nonbonded electrons. Such participation is highly unlikely due to the large amount of strain that would be incorporated during such participation and the rarity of R_2O-4 participation.[21,24,25] In addition product studies discount this possibility (*vide infra*).
(24) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958); L. A. Paquette and M. K. Scott, *J. Amer. Chem. Soc.*, **94**, 6751 (1972).
(25) For examples of proposed R_2O-4 participation see P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429, 2433 (1968), and L. A. Paquette and M. K. Scott, *J. Amer. Chem. Soc.*, **94**, 6760 (1972).

3:7 ratio of **13** to **14**, both of which undergo slow conversion to **15**.[26]

It can be seen that both **3** and **4** give predominantly acetolysis products resulting from inversion of configuration. Inversion is incompatible with neighboring group participation, but it is not unusual in the absence of participation. For example, the unrearranged ester from acetolysis of cyclohexyl tosylate is entirely of inverted configuration.[27] These observations and the absence of significant rate acceleration force the conclusion that neighboring group participation is not an important pathway in the acetolysis of **3** and **4**.

Although *cis*-3-tosyloxybicyclo[3.1.0]hexane has been postulated to undergo solvolysis *via* the "trishomocyclopropenyl cation" (**5**), the driving force for the proposed participation is not large, as evidenced by the only modest enhancement of the solvolysis rate.[4,28] In the oxa analog, **3**, the inductive withdrawal of electrons from the carbon–carbon σ bond by oxygen overwhelms the weak driving force for neighboring group participation in the solvolysis reaction. This system provides another example of the inefficacy of resonance donating but inductive withdrawing substituents in stabilizing the transition states leading to σ delocalized cations.[30]

Experimental Section[31]

cis- and *trans*-**Cyclopentan-1-ol 3,4-Epoxides (9 and 10).**—The epoxides **9** and **10** were prepared by a modification of the procedure of Darby, Henbest, and McClenaghan.[6] A solution of 18.0 g (0.215 mol) of Δ^3-cyclopentenol[7] in 20 ml of tetrahydrofuran was added to an ice-cooled solution of 43.5 g (0.215 mol) of 85% *m*-chloroperbenzoic acid in 100 ml of tetrahydrofuran at such a rate that the temperature remained below 20°. After standing overnight at 5°, the solution was diluted with 1.5 l. of water and 5 g of sodium bisulfite was added followed by 30 g of sodium bicarbonate. The aqueous solution was continuously extracted with ether and the ether solution was dried over anhydrous magnesium sulfate. Distillation through a 6 in. Vigreux column at 62 mm gave the following fractions: fraction 1, bp 30–45°, forerun; fraction 2, 4.2 g, bp 87–91°, pure **9**; fraction 3, 2.2 g, bp 94–99°, pure **9**; fraction 4, 0.5 g, bp 100–126°, mixture containing predominantly **9** and some **10**; fraction 5, 1.4 g, bp 127–134°, mixture containing 70% **10** and 30% **9**. Fractions were analyzed by glpc (6 ft × 0.125 in., 3% SE-52 on 80/100 Chromosorb W at 80°). The yield of cis epoxy alcohol **9** was 35% and of trans epoxy alcohol **10** was 5%. An additional 2.1 g (10%) of product mixture was obtained from two additional continuous extractions of the aqueous solution. Distillation fractions containing **10** from several runs were combined and chromatographed on silica gel using 25% ether in hexane as eluent. The fractions containing **10**, which eluted after **9**, were combined and distilled to give pure trans alcohol **10**, bp 132–133° (67 mm).

cis-**1-Tosyloxycyclopentane 3,4-Epoxide (3).**—To an ice-cold solution of 3.0 g (0.030 mol) of **9** in 30 ml of pyridine was added 9.5 g (0.05 mol) of *p*-toluenesulfonyl chloride. After standing overnight at 5°, the solution was diluted with 500 ml of water and extracted with three 150-ml portions of chloroform. The combined extracts were washed twice with dilute aqueous hydrochloric acid, then with aqueous sodium bicarbonate, and finally with water and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to leave 7.7 g of oil which crystallized on standing. Two recrystallizations from hexane–methylene chloride gave 5.0 g (66%) of **3**, mp 87.5–89°.

Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61. Found: C, 56.66; H, 5.48; S, 12.54.

trans-**1-Tosyloxycyclopentane 3,4-Epoxide (4).**—The trans tosylate **4** was prepared from **10** in the manner described for **3** in 61% yield, mp 66.5–67.5.

Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61. Found: C, 56.61; H, 5.48; S, 12.60.

cis-**1-Acetoxycyclopentane 3,4-Epoxide (11).**—To an ice-cold solution of 0.50 g (5.0 mmol) of **9** in 15 ml of pyridine was added 0.8 g (10 mmol) of acetyl chloride. After standing overnight at 5°, the solution was diluted with 250 ml of water and extracted with three 50-ml portions of chloroform. The combined extracts were washed twice with dilute aqueous hydrochloric acid, then with aqueous sodium bicarbonate, and finally with water, then dried over anhydrous magnesium sulfate. Distillation gave 0.51 g (72%) of **11**, bp 122–125° (29 mm). Preparative glpc (5 ft × 0.25 in., 15% Carbowax 20M on 60/80 Chromosorb W at 148°) followed by distillation gave an analytical sample, mp 30–31°.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.14; H, 6.93.

trans-**1-Acetoxycyclopentane 3,4-Epoxide (12).**—The trans acetate **12** was prepared from **10** by the procedure described for the preparation of **11** with the exception that acetic anhydride was used in place of acetyl chloride. This procedure gave a 79% yield of **12**, bp 107–108° (31 mm). Preparative glpc (same column as for **11**) at 135° followed by distillation gave an analytical sample, mp 44–45°.

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.16; H, 7.06.

trans-2,*cis*-**4-Triacetoxycyclopentane (15).**—*trans*-2,*cis*-4-Trihydroxycyclopentane was prepared by the procedure of Steyn and Sable[8] and carried on directly to the triacetate.

A solution of 2.02 g (20.2 mmol) of **9** in 50 ml of 0.05 *N* aqueous sulfuric acid was heated in a boiling water bath for 1.5 hr. Two grams of barium carbonate were added and the solution was filtered through Celite. The water was removed by distillation to leave yellow oily triol.

Acetyl chloride (5 g, 0.064 mol) was added dropwise to an ice-cold solution of the triol in 25 ml of pyridine. After standing overnight at 5°, the solution was diluted with 250 ml of water and extracted with ether. The extracts were washed twice with dilute aqueous hydrochloric acid, then with aqueous sodium bicarbonate, and finally with water, then dried over anhydrous magnesium sulfate. Distillation gave 1.96 g (40% from **9**) of **15**, bp 112–114° (0.4 mm).

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.76; H, 6.54.

Kinetics. Reagents.—Anhydrous acetic acid was prepared by refluxing a solution of acetic anhydride and sodium acetate in glacial acetic acid for 24 hr and subsequent fractional distillation in a dry atmosphere. Standard sodium acetate in acetic acid (*ca.* 0.1 *M*) was prepared by the careful addition of anhydrous acetic acid to a solution of anhydrous sodium carbonate in acetic anhydride, such that *ca.* 1% acetic anhydride remained after the water of neutralization was removed, followed by refluxing in a dry atmosphere for 5 hr[32] (calculated to be 1.325 g of anhydrous sodium carbonate and 3.78 g of acetic anhydride diluted to 250 ml with anhydrous acetic acid). Standard perchloric acid in acetic acid (*ca.* 0.02 *M*) used in titrating acetolysis aliquots was prepared by the careful addition of 70% perchloric acid to a solution of anhydrous acetic acid and acetic anhydride, such that 1% acetic anhydride remained after the water was removed (calculated to be 2.8756 g of 70% perchloric acid and 14.920 g of acetic anhydride diluted to 1 l. with anhydrous acetic acid),

(26) In this analysis it is assumed that **13** and **14** are converted to **15** at similar rates.

(27) J. B. Lambert, G. J. Putz, and C. E. Mixan, *J. Amer. Chem. Soc.*, **94**, 5132 (1972); J. E. Nordlander and T. J. McCrary, Jr., *ibid.*, **94**, 5133 (1972).

(28) The intermediacy of the "trishomocyclopropenyl cation" has been questioned[29] because of the observation that 1,5-diphenyl substitution does not lead to an enhanced solvolysis rate. However, it has recently been demonstrated by Wilcox and Banks[30] that phenyl substituents are unable to stabilize the transition states leading to σ delocalized ions.

(29) E. J. Corey and H. Uda, *J. Amer. Chem. Soc.*, **85**, 1788 (1963).

(30) C. F. Wilcox, Jr., and H. D. Banks, *J. Amer. Chem. Soc.*, **94**, 8231, 8232 (1972).

(31) Boiling points and melting points are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian Model EM-360 or Varian Model DP-60 spectrometer. Gas–liquid partition chromatographic work was performed with a Hewlett-Packard Model 5750 research chromatograph and an Aerograph Model A-700 preparative chromatograph. Elemental analyses were obtained from Spang Microanalytical Laboratory, Ann Arbor, Mich.

(32) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960).

followed by standing at room temperature for 12 hr. The molarity of the standard perchloric acid in acetic acid was determined by titrating an aliquot *vs.* potassium acid phthalate (primary standard) in anhydrous acetic acid using Bromophenol Blue as the indicator.

Procedure.—The kinetic procedure followed was essentially that of Winstein and coworkers.[33] All rates were determined in duplicate using infinity titers.[34]

Acetolysis Product Analysis of *cis*-1-Tosyloxycyclopentane 3,4-Epoxide (3).—A solution of 1.002 g (3.94 mmol) of **3** in 50 ml of 0.09413 *M* sodium acetate in acetic acid was heated to 100° for 11 hr (*ca.* 10 half-lives). The solution was diluted with 500 ml of water and neutralized by the careful addition of 150 g of sodium bicarbonate. The solution was ether extracted and the extracts were dried over anhydrous magnesium sulfate. The solvent was removed by distillation. Analysis of the residue by glpc (6 ft × 0.125 in., 10% silicone gum rubber UC-W 982 on 80/100 Porapak S, temperature-programmed run, 100–156° and 10 ft × 0.125 in., 20% Carbowax 20M on 80/100 Chromosorb P at 180°) showed a complex mixture of products containing 41% of **15**, 10% of **13**, 24% of **14**, and 25% of seven unidentified compounds. Preparative glpc (5 ft × 0.25 in., 15% Carbowax 20M on 60/80 Chromosorb W at 166°) allowed isolation of pure **15** and a mixture of **13** and **14**. The triacetate **15** was identified by comparison of its nmr spectrum, infrared spectrum, and glpc retention times on three different columns (the two columns listed above and 5 ft × 0.125 in., 10% butanediol succinate on 80/100 Chromosorb P at 173°) with those of an authentic sample.

The diacetate alcohols **13** and **14** were identified by the infrared (hydroxyl and carbonyl) and nmr spectra of the mixture and conversion of the mixture to **15** by treatment with acetic anhydride as described below.

To an ice-cold solution of 39 mg (0.2 mmol) of the **13** and **14** mixture in 5 ml of pyridine was added 0.3 g (2.9 mmol) of acetic anhydride. After standing overnight at 5°, the solution was diluted with 100 ml of water and ether extracted. The extracts were washed twice with dilute hydrochloric acid, then with sodium bicarbonate, and finally with water, then dried over anhydrous magnesium sulfate. The solvent was removed by distillation. The residue showed only one component with retention time identical with that of **15** on three different glpc columns (columns and conditions as above). Preparative glpc (as above) gave a pure sample which had an infrared spectrum identical with that of authentic **15**. The relative stereochemistries were established by comparison with the decomposition products of **11** and **12** by glpc (three different columns described above).

Samples which had not been solvolyzed to completion were also analyzed for products. Two-milliliter aliquots of a solution of 0.0949 g (0.374 mmol) of **3** in 10 ml of 0.09413 *N* sodium acetate in acetic acid were sealed in tubes and placed in a bath at 100.0°. Duplicate tubes were withdrawn after 30 and 60 min (half-life is 1 hr at 100°). The contents were diluted with 40 ml of water, neutralized with 5 g of sodium bicarbonate, and ether extracted. Analysis by glpc (UCW column described above, temperature-programmed run, 100–155°) showed the presence of **12** (26% after 30 min, 7% after 60 min). Cis acetate **11** may have been present in small amounts. The triacetate **15** was not observed in the 30-min run and was present only in 1% in the 60-min run. The identity of **12** was established by comparison of glpc retention times on three different columns (UCW column and conditions described above; Carbowax 20M column, described above, at 129°; 6 ft × 0.125 in., 3% OV-17 on 100/120 Chromosorb W at 96°.

Acetolysis Product Analysis of *trans*-1-Tosyloxycyclopentane 3,4-Epoxide (4).—A solution of 0.764 g (3.00 mmol) of **4** and 0.4 g of sodium acetate in 40 ml of anhydrous acetic acid was heated to 100° for 25.5 hr (10 half-lives). The solution was diluted with 500 ml of water and neutralized with 100 g of sodium bicarbonate. The solution was ether extracted and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation. Analysis of the residue by glpc (as for the products from **3**) showed a mixture of products containing 61% of **15**, 18% of **13**, and 21% of five unidentified compounds. The diastereomeric **14** may have been present in less than 5%. Preparative glpc (conditions as above) allowed isolation of pure **15** and **13**. The triacetate **15** was identified by comparison of its infrared spectrum and glpc retention times with those of an authentic sample (*vide supra*). The diacetate alcohol **13** was identified by comparison of its infrared spectrum and glpc retention times on three different columns (*vide supra*) with those of the mixture of **13** and **14** obtained from acetolysis of **3**. The stereochemistry was established by comparison with the decomposition products of **11** and **12** (three different columns as described above).

Samples which had not been solvolyzed to completion were also analyzed for products as described above for **3**. Reaction times were 60 and 120 min (half-life is 2.56 hr at 100°). Analysis as above showed *ca.* 2% of **11** present in the 60-min runs. No **15** was found in the 60-min run and *ca.* 2% was found in the 120-min run. The cis acetate **11** was identified by comparison of glpc retention times on two of the columns (UCW and Carbowax columns, conditions described above).

Decomposition of *cis*-1-Acetoxycyclopentane 3,4-Epoxide (11) in Acetic Acid.—A solution of 24.94 mg (0.176 mmol) of **11** was diluted to 10.0 ml with 0.09413 *N* sodium acetate in acetic acid. Aliquots (1.2 ml) of this solution were sealed in solvolysis tubes and placed in a constant-temperature bath at 100.0°. The tubes were withdrawn at timed intervals (0, 10, 30, 60, 120, 180, 300, 420 min) and quenched in ice water. Aliquots (1.0 ml) from each tube were added to 20 ml of water. The solutions were neutralized with 2.5 g of sodium bicarbonate. To this solution was added 1.0 ml of a solution of 0.02804 g of naphthalene diluted to 10.0 ml with tetrahydrofuran. The solutions were then ether extracted. Analysis by glpc (UCW column described above, temperature-programmed run, 100–156°) showed that **11** decomposed with a rate constant of 6×10^{-1} sec^{-1} and **13** appeared initially at approximately the same rate and then reacted further to produce **15** at a slower rate. Identity of **13** was established by comparison of its glpc retention times with those of the solvolysis products of **3** and **4** on three different columns (as described above). Stereochemistry was established by assuming trans opening of the epoxide ring (see Discussion).

Decomposition of *trans*-1-Acetoxycyclopentane 3,4-Epoxide (12) in Acetic Acid.—The decomposition of trans acetate **12** was analyzed as described for **11**. It was found that **12** decomposed with a rate constant of 8×10^{-4} sec^{-1} at 100.0° and an 89:11 mixture of **14** and **13**, respectively, appeared initially at approximately the same rate, then reacted further to produce **15** at a slower rate. Product identities were established as described above.

Acetolysis of *cis*-1-Tosyloxycyclopentane 3,4-Epoxide (3) for One Half-Life.—A solution of 0.500 g (1.97 mmol) of **3** and 0.26 g (3.2 mmol) of sodium acetate in 20 ml of anhydrous acetic acid was heated to 100.0° for 1 hr (half-life is 1.06 hr). The solution was diluted with 500 ml of water and neutralized with 50 g of sodium bicarbonate. The solution was ether extracted and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to leave 0.398 g of an oily mixture of tosylate and solvolysis products. Crystallization from ether–hexane gave 0.122 g (49% of theoretical) solid tosylate. The infrared spectrum of this material was identical with that of **3**.

Registry No.—**3**, 42142-25-6; **4**, 42142-26-7; **9**, 25494-14-8; **10**, 25494-15-9; **11**, 34310-94-6; **12**, 25494-20-6; **15**, 42142-31-4; Δ^3-cyclopentenol, 14320-38-8; *trans*-2,*cis*-4-trihydroxycyclopentane, 42142-32-5.

(33) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

(34) The amount of acid produced as measured titrimetrically in each kinetic run was in excellent agreement with the theoretical amount (average difference of less than 2%).

Acetolysis of the 3-Phenyl-, 3-*p*-Anisyl-, and 7-Phenyl-2-norbornyl Tosylates

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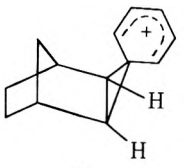
The acetolysis rates of the four 3-phenyl-, the four 3-*p*-anisyl-, and the four 7-phenyl-2-norbornyl tosylates have been determined. It appears that the 3-*endo*-phenyl- and 7-*anti*-phenyl-2-*exo* isomers acetolyze *via* a transition state of approximately equivalent energy relative to tosylate reactant. The 7-*syn*-phenyl-2-*exo* tosylate acetolyzes 33 times as fast as the 3-*exo*-phenyl-2-*exo* compound. That the 3-*endo*-phenyl-2-*endo* isomer reacts faster than its unsubstituted 2-endo parent is attributed to steric acceleration in the former case. The extremely slow rate for the 3-*exo*-phenyl-2-*endo* isomer may be due to steric inhibition to solvation of the developing positive charge in the transition state. The rate retardation in the 3-*exo*-phenyl-2-*exo* compound may result from phenyl π-cloud-developing anion transition-state destabilization. The same effect may be operative in the 1-phenyl-2-*exo* tosylate. Rate increases by the *p*-anisyl group relative to phenyl ranged from 1.1 to 2.7 for the compounds studied.

Our initial interest in the solvolyses of phenyl-substituted norbornyl tosylates stemmed from a desire to assess the geometrical requirement for aryl participation to a phenonium ion intermediate (**1** or **2**) of the



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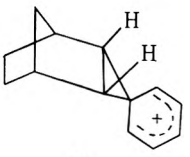

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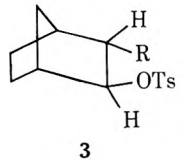
type frequently postulated for solvolyses in acyclic systems.[2] We also anticipated that studies involving fixed geometries with known dihedral angles between aryl and departing tosylate groups might provide insight as to relationships between geometries and the rate-retarding inductive effects of aryl substituents, steric hindrance to ionization, and steric acceleration. In addition, comparison of the rate data from 3-substituted 2-norbornyl tosylates with the related 7-substituted 2-norbornyl derivatives might provide information as to the amount of participation of the C_1–C_6 bond in the transition state for the exo compounds. For example, if the transition state for solvolysis of **3** involves significant σ bond participation with charge delocalization to C-1, then, assuming that the ground states are of identical energy, the inductive effect of the substituent at C-3 should not differ markedly from its effect at C-7 (as in **4**). Conversely, if there is no



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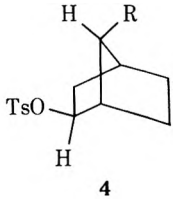

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significant σ participation in the transition states, then the inductive effect of a substituent at C-3 (**3**) on the rate of solvolysis of *exo*-norbornyl tosylate should be similar in magnitude to its effect on the solvolysis rate of *endo*-norbornyl tosylate. Positional responses of the exo/endo rate ratios are generally considered to be one of the most concise methods of analyzing the results in the norbornyl system.[3]

The effects of geminal dimethyl groups at C-3, C-5, C-7,[4] and at C-6[5] on the acetolysis rates of norbornyl tosylates have been reported. Dimethyl substitution at C-3 retards the acetolysis rate of the exo tosylate by a factor of 23 in comparison with its C-7 dimethyl-substituted isomer of Wagner–Meerwein rearrangement. The retardation factor is reduced to 5.8 when the rate data for the C-3 and C-7 dimethyl-substituted endo tosylates are compared. These examples serve to illustrate the involvement of factors other than inductive effects, since inductive effects alone would lead one to an *a priori* expectation of a greater accelerating influence by the more proximate C-3 methyl substituents. While rate and product studies of the effects of chloro and oxygenated substituents at the C-7 position[6] and of methoxy substituents at the C-4, C-5, C-6, and C-7 positions[3] on the acetolyses of 2-norbornyl tosylates have appeared prior and subsequent to our initial communication,[7] the only datum reported on Wagner–Meerwein rearrangement isomers with these substituents is the report that the rate of acetolysis of *cis-exo*-3-chloronorbornyl tosylate is at least 239 times slower than that of 7-*anti*-chloro-2-norbornyl tosylate.[8] This result suggests little generation of positive charge at C-1 in the transition state; *i.e.*, the positive charge is developing largely at C-2, where the rate-retarding inductive effect of the 3-chloro substituent in the former operates maximally and in the latter operates minimally.

Determinations of the acetolysis rates for the four 3-phenyl-2-norbornyl tosylates and the four 7-phenyl-2-norbornyl tosylates should reflect the relative effects of phenyl substituents on the acetolyses of *exo*- and *endo*-norbornyl tosylates. Herein we report the summations of these rate studies along with rate data on

(1) National Aeronautics and Space Administration (NASA) Fellow, 1966–1968.

(2) It would be impractical to list all phenonium ion references. The following references may be considered as representative evaluations of the phenonium ion problem: (a) D. J. Cram, *J. Amer. Chem. Soc.*, **86**, 3767 (1964); (b) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *ibid.*, **87**, 2137 (1965); (c) J. E. Nordlander and W. G. Deadman, *ibid.*, **90**, 1590 (1968).

(3) P. v. R. Schleyer, P. J. Stang, and D. J. Raber, *J. Amer. Chem. Soc.*, **92**, 4725 (1970).

(4) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *J. Amer. Chem. Soc.*, **87**, 378 (1965).

(5) P. v. R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Amer. Chem. Soc.*, **87**, 375 (1965).

(6) (a) P. G. Gassman and J. H. Hornback, *J. Amer. Chem. Soc.*, **91**, 4280 (1969); (b) P. G. Gassman, J. L. Marshall, J. G. Macmillan, and J. H. Hornback, *ibid.*, **91**,, 4282 (1969); (c) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2822 (1966); (d) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429, 2433 (1968); (e) P. G. Gassman and J. G. Macmillan, *J. Amer. Chem. Soc.*, **91**, 5527 (1969); P. G. Gassman and J. M. Hornback, *ibid.*, **94**, 7010 (1972).

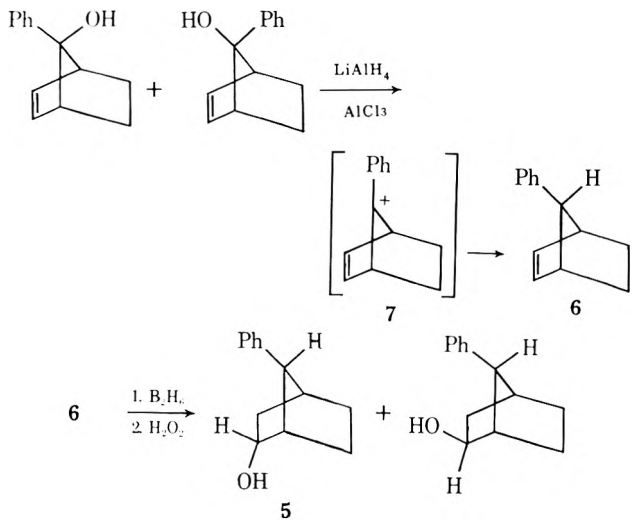
(7) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, and T. E. Dye, *J. Amer. Chem. Soc.*, **88**, 5350 (1966).

(8) H. L. Goering and M. J. Degani, *J. Amer. Chem. Soc.*, **91**, 4506 (1969).

the four 3-*p*-anisyl-2-norbornyl tosylates. In subsequent publications we shall deal with detailed analyses of the acetolysis products[9] and a study of the influence of cyclohexyl substituents on the acetolysis rates.[10]

Synthesis of Compounds.—The preparation and characterization of the four 3-phenyl-2-norbornanols were described previously.[11] The four *p*-anisyl analogs were prepared in a similar fashion. The alcohols 7-*syn*-phenyl-2-*exo*-norbornanol and 7-*anti*-phenyl-2-*exo*-norbornanol were isolated and characterized as products of the acetolyses after reduction with $LiAlH_4$.[12] Reduction with $LiAlH_4$ of 7-*anti*-phenyl-2-norbornanone, prepared by oxidation of the exo alcohol, afforded 7-*anti*-phenyl-2-*endo*-norbornanol.

A convenient route to 7-*syn*-phenyl-2-*endo*-norbornanol (**5**) was not so accessible. As expected by analogy with other syn-7-substituted norbornanones,[13] $LiAlH_4$ reduction of 7-*syn*-phenyl-2-norbornanone gave exclusively attack from the endo direction to re-form the exo alcohol. The key intermediate in the preparation of **5** was 7-*syn*-phenyl-2-norbornene (**6**). Reduction with $LiAlH_4$–$AlCl_3$ by the method of Nystrom and Berger[14] of the mixture of *syn*- and *anti*-phenyl-7-norbornenols formed *via* phenyllithium addition to 7-norbornenone gave only alkene **6**. Evidently the 7-



phenylnorbornenyl cation (**7**) suffers attack by hydride solely from the anti direction, a reaction mode consistent with the necessity for π-bond stabilization of cation **7**.[15] Oxymercuration of **6** gave only the exo alcohol, which was a more convenient preparation than that previously reported.[12] Hydroboration of **6**, on the other hand, gave a *ca.* 3.0:2.0 mixture of exo to endo alcohol, separable by column chromatography. The larger percentage of exo alcohol obtained from hydroboration contrasts with the results from norbornenes with syn methyl substituents[16] in which approximate 1.0:3.5 ratios of exo to endo alcohols were obtained.

Results and Discussion

Rate data for the acetolyses of the eight phenylnorbornyl tosylates and the four *p*-anisyl compounds determined by us are listed in Tables I and II. The data for *exo*- and *endo*-norbornyl tosylates[17] and their 1-phenyl and 1-*p*-anisyl derivatives[18] are included for comparative purposes.

The acetolysis rates for the Wagner–Meerwein rearrangement isomers, 3-*endo*-phenyl- and 7-*anti*-phenyl-2-*exo*-norbornyl tosylates (**9a** and **11**), are practically the same. That isomerization (internal return) of **9a** to **11** competes with acetolysis of **9a** was shown by interrupting its acetolysis after *ca.* 30% reaction and obtaining an equimolar mixture of the two tosylates. A similar experiment starting with pure **11** gave no appreciable amount of **9a**. Since there was a small decrease in rate with progress of time for **9a**, the rate reported was obtained by determinations up through little more than 10% solvolysis and by extrapolation to zero time. One might expect the acetolysis of **9a** to proceed with some steric acceleration resulting from partial relief of unfavorable interactions between an *o*-phenyl hydrogen and the endo-5 hydrogen. Essentially complete isomerization of *endo*-5,6-trimethylene-2-*exo*-norbornyl tosylate to *exo*-5,6-trimethylene-2-*exo*-norbornyl tosylate occurs after about 23% reaction;[19] the acetolysis rate of the former tosylate exceeds the latter by a factor of 3.7, presumably owing to steric acceleration in the former compound. Such steric acceleration does not contribute significantly to the ionization of **9a** relative to that exhibited by the endo trimethylene compound, since steric interactions can be minimized in **9a** by rotation of the benzene ring away from the endo-5 hydrogen.

Thus data analysis of the *endo*-phenyl and *anti*-phenyl isomers, **9a** and **11**, suggests that acetolysis occurs *via* a common intermediate with the two transition states being of approximately equal energy and whose structures lie on the reaction coordinate at positions close to that of the intermediate. The effect of the phenyl on their acetolysis rates is practically the same: *i.e.*, the β-phenyl and γ-phenyl substituent effects are identical. The choice of a suitable model for the rate-retarding inductive effect of phenyl is a difficult one. Winstein, in a number of his publications,[20] has estimated the effect of a β-phenyl substituent to be worth a retardation factor of *ca.* 10. An appropriate monocyclic model with sufficiently remote substituents might be the relative acetolysis rate of *trans*-2-phenylcyclopentyl tosylate *vs.* cyclopentyl tosylate of 0.18.[21] A

(9) D. C. Kleinfelter, M. B. Watsky, and W. E. Wilde, *J. Org. Chem.*, **38**, 4134 (1973).

(10) D. C. Kleinfelter and J. M. Miller, Jr., *J. Org. Chem.*, **38**, 4142 (1973).

(11) D. C. Kleinfelter, T. E. Dye, J. E. Mallory, and E. S. Trent, *J. Org. Chem.*, **32**, 1734 (1967).

(12) D. C. Kleinfelter, *J. Org. Chem.*, **32**, 3526 (1967).

(13) S. Beckmann and R. Mezger, *Chem. Ber.*, **89**, 2738 (1956).

(14) R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

(15) P. G. Gassman and A. F. Fentiman, Jr., *J. Amer. Chem. Soc.*, **92**, 2549 (1970); **91**, 1545 (1969).

(16) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 1990 (1970).

(17) Reference 3 has listed values calculated from data in R. Heck and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3432 (1957).

(18) D. C. Kleinfelter and P. v. R. Schleyer, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, Abstracts, p 432; D. C. Kleinfelter, *Diss. Abstr.*, **22**, 428 (1961); J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 182.

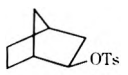
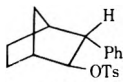
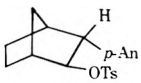
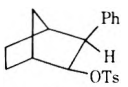
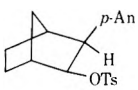
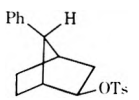
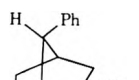
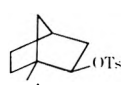
(19) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Jap.*, **38**, 1318 (1965).

(20) *Cf.* S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948); S. Winstein, B. K. Morse, E. Grunwald, K. C. Schreiber, and J. Corse, *ibid.*, **74**, 1113 (1952).

(21) C. J. Kim and H. C. Brown, *J. Amer. Chem. Soc.*, **91**, 4287 (1969).

TABLE I

KINETIC DATA FOR THE ACETOLYSES OF PHENYL (Ph) AND *p*-ANISYL (*p*-An) SUBSTITUTED 2-*exo*-NORBORNYL TOSYLATES

Exo tosylate	Temp, °C	k_1, sec^{-1}	k_{rel} at 25°	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
 8	25.0[a]	2.40×10^{-5}	1.00	22.4	−4.6
 9a	25.0[b]	6.93×10^{-6}	0.289	23.3	−4.0
	30.0	$(1.42 \pm 0.05) \times 10^{-5}$			
	50.0	$(1.35 \pm 0.11) \times 10^{-4}$			
	70.0	$(1.37 \pm 0.03) \times 10^{-3}$			
 9b	25.0	$(1.03 \pm 0.05) \times 10^{-5}$	0.429	22.9	−4.9
	50.0	$(2.23 \pm 0.03) \times 10^{-4}$	(1.49)[c]		
 10a	25.0[b]	1.82×10^{-7}	0.00758	25.5	−3.8
	75.0	$(1.02 \pm 0.05) \times 10^{-4}$			
	95.0	$(7.92 \pm 0.11) \times 10^{-4}$			
 10b	25.0[b]	2.57×10^{-7}	0.0107	24.7	−5.7
	50.0	$(7.05 \pm 0.16) \times 10^{-6}$	(1.41)[c]		
	75.0	$(1.20 \pm 0.04) \times 10^{-4}$			
 11	25.0	$(5.68 \pm 0.13) \times 10^{-6}$	0.237	24.5	−0.2
	50.0	$(1.52 \pm 0.05) \times 10^{-4}$			
 12	25.0	$(6.04 \pm 0.08) \times 10^{-6}$	0.252	23.5	−3.6
	50.0	$(1.41 \pm 0.03) \times 10^{-4}$			
 13a	25.0[d]	9.55×10^{-5}	3.98	22.8	−0.3
 13b	25.0[d]	1.88×10^{-4}	7.83 (1.97)[c]	22.1	−1.6

[a] Reference 17. [b] Extrapolated from higher temperature. Hence, k_1 and k_{rel} are probably reliable to two significant figures. [c] k_{rel} to the Ph analog. [d] Reference 18.

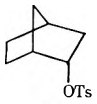
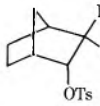
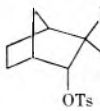
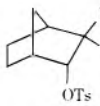
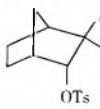
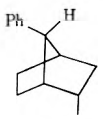
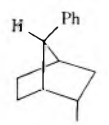
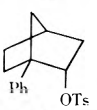
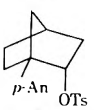
similar, presumably remotely substituted model in a bicyclic system would be 1-phenyl-2-*endo*-norbornyl tosylate (**19a**), whose rate is *ca.* 0.70 times that of *endo*-norbornyl tosylate (**14**).[18] The rate-retarding effects of the phenyl groups in **9a** and **11** of 3.5 and 4.2, respectively, fall within the 1.4–5.5 range for **19a** and the *trans*-2-phenylcyclopentyl system.

The acetolysis rate for the *anti*-phenyl endo tosylate (**17**) relative to its unsubstituted parent (**14**) of 0.29 is approximately equal to the epimeric tosylate (**11**) to exo parent (**8**) ratio of 0.24. In **17** the phenyl is attached γ to the incipient positive charge generated at C-2. If σ participation is involved in **11** with partial positive charge generation at C-1, then one might expect the phenyl to exert a greater rate-retarding inductive effect, since it would be closer to said positive charge than in **17**. Based on such an interpretation, the results would offer dubious evidence for σ participation. Gassman and coworkers[6a] have shown that the rate-retarding effect of an *anti*-chloro substituent on the acetolysis rate of *exo*-norbornyl tosylate ($^1/_{531}$) is only 3.4 times its effect on the acetolysis rate of *endo*-norbornyl tosylate ($^1/_{155}$). The relative effect of phenyl, the rate of **11** *vs.* **8** compared to **17** *vs.* **14**, of only 1.2 is then not surprising when one considers that the chlorine ($\sigma^* = +1.05$) is known to exert a greater inductive effect than phenyl ($\sigma^* = +0.215$). Hence, while the factor of 1.2 is not large, it is in line with the relatively small differences attributed to electron-withdrawing substituents on exo *vs.* endo solvolyses.[6b]

The cis,endo tosylate **15a** undergoes acetolysis at a rate *ca.* 2.4 times that of **14**. This relative rate of 2.4 is presumably due to a combination of steric acceleration and phenyl inductive retardation. From the inductive retardation factor of 0.29 from **9a** one may assign a rate increase for **15a** of 8.1 attributable to steric acceleration. The steric acceleration factor in the 2-phenylcyclopentyl system, the relative rate of *cis- vs. trans*-2-phenylcyclopentyl tosylate, is 4.7. That the effect appears more pronounced in the norbornyl system may stem from the known greater proximity of the cis substituents with dihedral angles of *ca.* 0°. In the

TABLE II

KINETIC DATA FOR THE ACETOLYSES OF PHENYL (Ph) AND *p*-ANISYL (*p*-An) SUBSTITUTED 2-*endo*-NORBORNYL TOSYLATES

Endo tosylate	Temp, °C	k_1, sec^{-1}	k_{rel}, 25°	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
 14	25.0[a]	8.14×10^{-8}	1.00	26.5	−2.0
 15a	25.0[b]	1.91×10^{-7}	2.35	25.3	−4.5
	50.0	$(5.61 \pm 0.06) \times 10^{-6}$			
	75.0	$(1.10 \pm 0.05) \times 10^{-4}$			
 15b	25.0[b]	2.86 ± 10^{-7}	3.51	26.1	−0.9
	50.0	$(9.37 \pm 0.16) \times 10^{-6}$	(1.49)[c]		
	75.0	$(1.86 \pm 0.04) \times 10^{-4}$			
 16a	25.0[b]	3.19×10^{-10}	0.00392	29.5	−3.0
	80.0	$(8.79 \pm 0.05) \times 10^{-7}$			
	95.0	$(5.51 \pm 0.05) \times 10^{-6}$			
	110.0	$(2.52 \pm 0.03) \times 10^{-5}$			
 16b	25.0[b]	8.50×10^{-10}	0.0104	29.1	−2.5
	75.0	$(1.13 \pm 0.05) \times 10^{-6}$	(2.65)[c]		
	90.0	$(6.72 \pm 0.15) \times 10^{-6}$			
	110.0	$(5.70 \pm 0.06) \times 10^{-5}$			
 17	25.0[b]	2.34×10^{-8}	0.286	26.6	−4.4
	75.0	$(1.68 \pm 0.05) \times 10^{-5}$			
	100.0	$(2.32 \pm 0.08) \times 10^{-4}$			
 18	25.0[b]	2.99×10^{-8}	0.367	25.8	−6.5
	80.0	$(3.90 \pm 0.06) \times 10^{-5}$			
	100.0	$(2.93 \pm 0.08) \times 10^{-4}$			
 19a	25.0[d]	5.66×10^{-8}	0.695	25.0	−7.7
 19b	25.0[d]	6.23×10^{-8}	0.765 (1.10)[c]	25.5	−6.1

[a] Reference 17. [b] Extrapolated from higher temperatures. Hence, k_1 and k_{rel} are probably reliable to two significant figures. [c] k_{rel} to the Ph analog. [d] Reference 18.

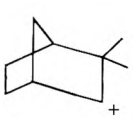
cyclopentyl system the cis substituents are presumably moved further apart with a corresponding smaller effect on the ground-state energy.

The rates of the *syn*-7-phenyl tosylates, **12** and **18**, are only 1.2 and 1.4 times those of their respective *anti*-phenyl isomers, **11** and **17**. This approximate equivalence in rates between the two systems points to the operation of similar effects of the phenyls.

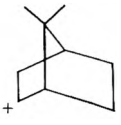
The value of the H–C_2–C_3–H dihedral angle in 3-*exo*-phenyl-2-*endo*-norbornyl tosylate (**16a**) should be near that approximated for **9a**, namely 120°, and no *a priori* effect from the *exo*-3-phenyl other than a rate-retarding inductive one would be anticipated. The observed relative rate of 0.0038 for **16a** when compared with that of **14** is too large a retardation to be ascribed to the inductive factor alone. A retardation factor in the neighborhood of 10^2 must be due to some other cause. An assignment of this factor to some known cause is not intuitively obvious. A tentative hypothesis is that of steric inhibition by phenyl to solvation of the developing positive charge in the transition state for **16a**. Carbonium ions owe a large measure of their inherent stability to stabilization by solvent.[22] Car-

(22) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 315.

bonium ions in the bicyclo[2.2.1]heptyl system are stabilized by solvent preferentially from the exo side. If this solvation were inhibited in the transition state, then the activation energy could be raised sufficiently to account for the rate retardation. *syn*-7-Methyl substituents alter the normal mode of exo approach in additions to norbornanones[13] and in additions to norbornenes involving cyclic processes.[23] The effect of exo 3 substituents has received far less attention. That an *exo*-3-phenyl substituent exerts a smaller steric effect to exo attack than a *syn*-7-phenyl substituent is evidenced by the formation of a 2:1 ratio of endo to exo alcohol from $LiAlH_4$ reduction of 3-*exo*-phenyl-2-norbornanone, which contrasts with the exclusive formation of exo alcohol from 7-*syn*-phenyl-2-norbornanone. Extension of these data to the acetolyses of the endo isomers, **18** and **16a**, fosters the prediction of a slower rate for the *syn*-7-phenyl compound (**18**) if steric inhibition to solvation were involved in the acetolysis of **16a**. The rate ratio for **18** to **16a**, however, is actually 94:1.0. Brown[24] has pointed out the need for caution in extrapolating ketone reduction results to the behavior of carbonium ions in the bicyclo[2.2.1]heptyl system. Although syn substituents may cause ketone reductions to proceed by endo attack, they need not significantly alter the general rule of exo approach of solvent to carbonium ions. If the transition state for solvent approach to a carbonium ion resembles the transition state for tosylate departure, as may be inferred from the familiar Goering–Schwene diagram,[25] then a smaller inhibition to solvation by a syn 7 substituent relative to an exo 3 substituent is not exceptional. The low proportion of acetic acid solvent reaction at the 2 position in the camphenilyl ion (**20**) relative to the aposantenyl ion (**21**), 1:50, has been attributed to steric hindrance in the former ion.[26]



20



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The invocation of steric inhibition to transition state solvation to explain the slow rate for the cis,exo tosylate (**10a**) relative to **8** of 0.0076 is unwarranted. The p orbital being formed in the solvolysis of an exo tosylate would develop beneath the C_1–C_2 bond axis, and solvation difficulties encountered in the transition state for **10a** should not differ appreciably from those of other exo tosylates. In addition, the steric acceleration invoked to explain the rate acceleration of the cis,endo isomer (**15a**) is obviously not operating in the cis,exo isomer (**10a**), although the dihedral angles between the substituents are presumably the same. However, one is forced to conclude that there are increased unfavorable interactions, steric and/or polar, in the transition state for **10a** but not for **15a**.

The slow solvolysis rate of most endo tosylates has been ascribed to steric hindrance to ionization resulting from the necessity for the leaving group to depart in the direction of the endo 6 substituent, H, alkyl, or aryl, as amply demonstrated by Brown and coworkers.[27] The approach of solvent to the developing p orbital in the transition state for the solvolysis of an exo tosylate should also be inhibited by the endo 6 substituent. Counterbalancing this inhibition to solvent coordination is the perfectly aligned C_1–C_6 σ bond which, acting like a solvent nucleophile, stabilizes the developing positive charge by overlapping with the developing p orbital at C-2.[28] This concept implies a bridged, or at least partially bridged, transition state for the departure of most exo tosylates for a secondary norbornyl compound *but* does not require a bridged carbonium ion intermediate. The reaction of solvent with the carbonium ion(s) to give product(s) need not be the microscopic reverse of the generation of the ion(s) from the tosylate. The transition state for the solvent capture may not require carbon bridging.

If for some reason carbon bridging were impeded in the transition state for tosylate departure, then the solvolysis rate might be significantly reduced. Increased steric and/or polar interactions between a phenyl group and leaving tosylate (or other substituent in the molecule) in the transition state could effectively dampen σ participation and retard the rate.[29] The large rate retardation in the cis,exo compound (**10a**) may be due to repulsion between the leaving tosylate anion with its partial negative charge on oxygen and the π cloud of the orientationally restricted phenyl ring. The rigid norbornane skeleton does not possess the conformational mobility of acyclic and simple monocyclic systems like cyclopentane and cyclohexane.[30] Consequently, this rigid three-dimensional structure may provide an ideal system for the investigation of large steric effects. Along with this rigidity one may have preferred orientations of the phenyl ring in the ground state of a reactive species, which may remain so preferred in the transition state. In previous publications[11,12,31] we have demonstrated orientational preferences for exo, endo, 7-syn, and 1-phenyl substituents with and without groups other than H in a cis relationship. This was accomplished *via* compilation of infrared and nmr data for the phenylnorbornanols and nmr data for their *p*-nitrobenzoates and tosylates.

The three exo compounds that exhibited the greatest amount of interaction between the phenyl π cloud and

(23) H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **93**, 7335 (1971); H. C. Brown, J. H. Kawakami, and K.-T. Liu, *ibid.*, **95**, 2209 (1973).

(24) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966), and subsequent references.

(25) H. L. Goering and H. L. Schewene, *J. Amer. Chem. Soc.*, **87**, 3516 (1965).

(26) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 148.

(27) S. Ikegami, D. L. Vander Jagt, and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 7124 (1968), and references cited therein.

(28) H. C. Brown and coworkers have accumulated a wealth of data supporting the view that tertiary 2-norbornyl derivatives solvolyze *via* nonbridged transition states to classical cation intermediates; *e.g.*, see K. Takeuchi and H. C. Brown, *J. Amer. Chem Soc.*, **90**, 2693 (1968), and prior references. Professor Brown has admitted that the available data do not permit a definitive answer to the question of whether σ participation is present in norbornyl (*i.e.*, secondary norbornyl) itself. The contrast between the lack of bridging in the transition state for the tertiary systems *vs.* the existence of bridging in the transition state for the secondary systems may be resolved by proper assessment of transition state solvation in the two systems. Secondary carbonium ions would require greater stabilization by solvent than the tertiary ions.

(29) One might argue that in the absence of σ participation, *i.e.*, with sole involvement of positive charge generation at C-2, there still could be increased interactions between phenyl and tosylate groups leading to rate retardation. Support of our hypothesis from solvolysis data of the 6-phenyl-2-norbornyl system will be the subject of a future publication.

(30) H. C. Brown and S. Ikegami, *J. Amer. Chem. Soc.*, **90**, 7122 (1968), and ref 24.

(31) D. C. Kleinfelter, *J. Amer. Chem. Soc.*, **89**, 1734 (1967).

O–X substituent (X = H, Ts, and PNB) were the 1-phenyl, *exo*-3-phenyl, and *syn*-7-phenyl derivatives. In the 1-phenyl compounds the preferred phenyl orientation was shown to be that in which the plane of the phenyl ring bisected the 7-bridge protons. In the *exo*-3-phenyl compounds the preferred phenyl orientation is one in which the phenyl plane is orthogonal to the exo C_2–OX bond axis. In 3-*exo*-phenyl-2-*exo*-norbornyl tosylate (**10a**) with the 0° dihedral angle between substituents one might expect to find the greatest destabilization of the transition state owing to interaction between the π cloud and the developing anion. In the *endo*-3-phenyl compounds, however, the preferred phenyl orientation is not that in which the phenyl plane is orthogonal to the endo C_2–OX bond axis. The ir and nmr data reveal considerably less interaction between the π cloud and X substituent. This decreased interaction is a result of the rotation of the phenyl ring away from the unfavorable interaction between an *o*-phenyl hydrogen and the endo-5 hydrogen. Evidently this rotation is sufficient enough to cause some interaction between the phenyl plane and the endo 2 substituent in the ground state which is relieved in its transition state, *viz.*, steric acceleration.

Although the dihedral angle between the 1-phenyl and *exo*-2-tosylate substituents is much larger than 0° (*ca.* 44°), there may still be a fair degree of transition-state destabilization in this system, as revealed by its unexpectedly slow rate of acetolysis[32] in comparison with the 1-alkyl substituted analogs. This interaction in the 1-phenyl compound (**13a**) may lessen the extent of participation by the C_1–C_6 σ bond and consequently the degree of positive charge accumulation at C-1 in its transition state. Where such interaction is not operating, as in the 1-alkyl analogs, σ participation and positive charge development at C-1 are much more evident. The differences between β-alkyl and β-phenyl substituents in stabilizing by resonance a charge-delocalized transition state, as is found in participating systems, have been summarized recently.[33] One would presume that the more the positive charge resides at C-2 in the solvolysis transition state, the greater the ability of phenyl to retard the rate by its inductive effect.

In the *syn*-7-phenyl compounds the preferred phenyl orientation approaches that in which the plane of the benzene ring and the exo C_2 and C_3 substituents are parallel. The C_7–phenyl ring bond bisects the C_2–C_3 bond. If the interaction between the phenyl ring and the 2 substituent is an energetically favorable one, as it presumably is in the OH π bonding case for the alcohol, and as it may be for the *p*-nitrobenzoate and tosylate (a type of weak charge transfer complex between the 7-phenyl and substituent phenyl protons), then the substitutent would orient itself toward the 7-phenyl π cloud. In the tosylate solvolysis, however, the negative charge buildup is on the oxygen directly attached to C-2, and this oxygen with its partial charge may leave in a direction away from the 7-phenyl ring or at least in a manner in which there is no significant transition-state destabilization.

The four 3-*p*-anisyl-2-norbornyl tosylates were solvolyzed with the purpose of determining whether any directional (dihedral angle) effect operates on the ability of the aryl substituent to transmit its electronic effect to the reaction site. With inclusion of the 1-*p*-anisyl-2-norbornyl tosylates, the compounds and the dihedral angles between the aryl and tosylate substituents are **9b** and **16b**, 120°; **10b** and **15b**, 0°; **13b**, 44°; **19b**, 79°. As can be seen from examination of Tables I and II, the increases in rate afforded by the *p*-anisyl group relative to phenyl range from 1.10 to 2.65. That the minimum effect of the *p*-methoxy substituent is evidenced where the dihedral angle is the closest to 90° (**19b**, ϕ = *ca.* 79°) may be significant. Vicinal coupling constants in the nmr are known to be at a minimum when the dihedral angle is around 90°.[34] Both relative rates with dihedral angles of *ca.* 0° and one of the two with 120° are about the same. The relative rate at 44° for **13b** may be anomalous owing to some partial positive charge buildup at C-1 in the transition state for its acetolysis. The products in this case are derived from the tertiary arylnorbornyl cation.[18] The largest rate increase attributable to the *p*-methoxy substituent of 2.65 is shown by 3-*exo*-*p*-anisyl-2-*endo*-norbornyl tosylate (**16b**), in which the dihedral angle between substituents is *ca.* 120°. Although the ideal dihedral angle for aryl participation of 180° is far from attained in this compound, the fact that the phenyl isomer (**16a**) solvolyzes so slowly may indicate a sufficient driving force for some small degree of aryl participation in **16b**. However, significant aryl participation is unlikely, since *p*-anisyl substituents normally provide far greater rate accelerations relative to phenyl.[35] Attempts to ascribe relative rate differences observed between *p*-anisyl- and phenyl-substituted norbornyl tosylates to differences in dihedral angles would be quite speculative at present.

Experimental Section

Melting points were determined in soft capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are uncorrected. Infrared spectra for the 3-μ region were recorded on a Perkin-Elmer Model 421 grating spectrometer. A Varian A-60 nmr spectrometer, calibrated with tetramethylsilane (δ 0) and chloroform (δ 436.5 Hz), was used for the nmr determinations. Chemical shifts are presumed correct to ±0.01 ppm. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., and by F. B. Strauss Microanalytical Laboratory, Oxford, England.

Unless otherwise specified, all ether and ligroin solutions of products were dried over anhydrous sodium sulfate prior to removal of solvent. Ligroin was distilled over potassium permangamate, bp 40–55°.

7-*anti*-Phenyl-2-norbornanone.—To a stirred solution of 7-*anti*-phenyl-2-*exo*-norbornanol (1.46 g, 0.00775 mol), mp 89–90°,[12] in acetone (25 ml) held at 0° was added 8 *N* chromic acid (3.0 ml). Sodium bisulfite was added to consume excess chromic acid, the green chromate sludge was removed by filtration, and the resulting acetone solution of the ketone was dried over anhydrous magnesium sulfate. Evaporation of the acetone left 1.40 g (97.1%) of oily ketone. The 2,4-dinitrophenylhydrazone, prepared in the usual manner,[36] gave mp 224–225° from ethanol–ethyl acetate. *Anal.* Calcd for $C_{19}H_{18}N_4O_4$: C, 62.28; H, 4.95. Found: C, 62.17; H, 4.80.

(32) The factor of *ca.* 4.0 for **13a** over **8** is reduced to unity when one considers rates of ionization rather than rates of solvolysis. We wish to thank Professor H. C. Brown for pointing this out to us. Presumably internal return is inoperative in **13a**.

(33) W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **94**, 133 (1972).

(34) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(35) For example, see P. v. R. Schleyer and C. J. Lancelot, *J. Amer. Chem. Soc.*, **91**, 4297 (1969), and references cited therein.

(36) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 247.

7-*anti*-Phenyl-2-*endo*-norbornanol.—Reduction of 7-*anti*-phenyl-2-norbornanone (1.38 g, 0.00741 mol) with lithium aluminum hydride in ether in the standard manner[37] gave the endo alcohol (1.32 g, 95.3%): mp 68.5–69.5° from ligroin (*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.69; H, 8.34.); nmr (CCl_4) δ 7.16 (5 H, s, Ar H's), 4.30 (1 H, t, H-2*x*), 3.50 (1 H, s, exch, CH), 2.88 (1 H, b s, H-7*s*), 2.52 (2 H, m, H-1 and H-4), 2.3–0.8 (6 H, m, remaining H's). The *p*-toluenesulfonate derivative, prepared in the usual manner,[38] gave mp 84–85° from ether. *Anal.* Calcd for $C_{20}H_{22}SO_3$: C, 70.16; H, 6.48. Found: C, 70.21; H, 6.50.

Hydroboration of 7-*syn*-phenylnorbornene (6).—The alkene 6 was prepared from an approximate 50:50 mixture of 7-*syn*-phenyl- and 7-*anti*-phenyl-2-norbornen-7-ols by the method of Nystrom and Berger[14] using lithium aluminum hydride and aluminum chloride in ether solution.[39] Hydroboration of 6 was accomplished by the method of Brown and Zweifel.[40] To a solution of 45 ml of 1.0 *M* sodium borohydride in diglyme and unpurified 6 (25.0 g, 0.147 mol) in 50 ml of diglyme was added dropwise 13 ml of boron trifluoride etherate over a period of 1 hr. After the mixture was stirred for an additional 4 hr, water (10 ml), 3 *N* sodium hydroxide (16 ml), and 30% hydrogen peroxide (16 ml) were added in that order. The mixture was poured into water and extracted with ether, and the ether extracts were washed several times with water to remove the diglyme. After removal of the ether, 24.5 g of an oil remained. Integration of the H-2*x* signal at δ 4.07 in 5 and an H-2*n* signal at δ 3.60 in 7-*syn*-phenyl-2-*exo*-norbornanol gave a 40:60 ratio of alcohol products. Separation of 5 from its exo isomer was attained by chromatography on F-20 alumina with ligroin and ligroin–ether eluents. The exo isomer was largely eluted prior to 5. The weight of pure 5 plus the weight calculated from the overlapping eluted portions amounted to 40% of the total alcohol collected. Pure 5 had mp 64–65° when recrystallized from ligroin (*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.94; H, 8.58.); nmr (CCl_4) δ 7.15 (5 H, s, Ar H's), 4.07 (1 H, tp, H-2*x*), 3.20 (1 H, s, exch, OH), 3.03 (1 H, b s, H-7*a*), 2.54 (s H, m, H-1 and H-4), 2.3–0.7 (6 H, m, remaining H's). The *p*-toluenesulfonate derivative gave mp 87–88.5° from ether. *Anal.* Calcd for $C_{20}H_{22}SO_3$: C, 70.16; H, 6.48. Found: C, 70.01; H, 6.46.

3-*endo*-*p*-Anisyl-2-*exo*-norbornanol.—The procedure was similar to that employed for the preparation of the phenyl analog[11,41] and for 5 described above. To a mixture of 2-*p*-anisylnorbornene (100 g, 0.500 mol), sodium borohydride (15.7 g, 0.429 mol), and 350 ml of diglyme was added dropwise 64.3 g of boron trifluoride etherate. After the mixture was stirred for 4 hr, 3 *N* sodium hydroxide (107 ml) and 30% hydrogen peroxide (107 ml) were added. The mixture was poured into *ca.* 2 l. of ice water and a white solid precipitated within 15–20 min. Filtration, suction drying, and recrystallization from ligroin gave the desired alcohol (84.6 g, 81.9%): mp 69–70° (*Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.14; H, 8.42.); nmr (CCl_4) δ 7.10–6.65 (4 H, AA'BB' system, Ar H's), 3.77 (1 H, largely hidden by OCH_3 signal, H-2*n*), 3.72 (3 H, s, OCH_3), 2.77 (1 H, t, $J_{2n,3x} = J_{3x,4} = 3.5$ Hz, H-3*x*), 2.50 (1 H, s, exch, OH), 2.33 (1 H, m, H-4), 2.12 (1 H, m, H-1), 1.85 (1 H, d m, H-7*s*), 1.5–1.0 (5 H, m, remaining H's); ir (CCl_4, dilute) 3616 cm^{-1} (OH). The *p*-toluenesulfonate gave mp 79–79.5° from ether. *Anal.* Calcd for $C_{21}H_{24}SO_4$: C, 67.73; H, 6.50. Found: C, 67.83; H, 6.70.

2-*endo*-*p*-Anisylnorbornane-2,3-*cis*-*exo*-diol.—To a stirred solution of 2-*p*-anisylnorbornene (30.0 g, 0.150 mol) and chloroform (100 ml) maintained at 5–10° was added slowly a mixture of 30% peracetic acid (77.8 g, 0.301 mol) and sodium acetate (22.9 g). After the yellow reaction mixture was stirred for 12 hr at room temperature, excess sodium bisulfite was added, and the resulting mixture was added to 250 ml of heavily salted (NaCl) water and extracted three times with 200-ml portions of ether. The combined ether extracts were washed once with dilute sodium carbonate and once with water, and then dried. Flash evaporation of the ether and chloroform left 42.0 g of residual orange oil. This orange oil was reduced with lithium aluminum hydride (5.70 g, 0.150 mol) in ether solution in the standard manner.[37] The reaction mixture was refluxed for 12 hr to ensure complete reduction. The ether solution was concentrated to a volume of 85 ml and poured into 250 ml of ligroin to give white, flocculent diol (20.4 g, 58.1%): mp 98–98.5° from ether–ligroin (*Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 72.01; H, 7.89.); nmr ($CDCl_3$) δ 7.48–6.80 (4 H, AA'BB' system, Ar H's), 4.10, 3.98 (2 H, s, exch, OH's), 3.98 (1 H, d, $J_{3n,7a} = 1.6$ Hz, H-3*n*), 3.80 (3 H, s, OCH_3), 2.48 (1 H, m, H-1), 2.12 (2 H, m, H-4 and H-7*s*), 1.6–0.9 (5 H, m, remaining H's); ir (CCl_4, dilute) 3606, 3517 cm^{-1} (2 OH's).

3-*endo*-*p*-Anisyl-2-norbornanone.—A mixture of 2-*endo*-*p*-anisylnorbornane-2,3-*cis*,*exo*-diol (50.3 g, 0.215 mol) and 70% perchloric acid (500 ml) was stirred at room temperature until all the diol had dissolved (*ca.* 1 hr). The resulting light brown solution was poured into 750 ml of ice water and was allowed to stand for 1 hr until crystallization was complete. The solid was filtered, dissolved in ether, and washed with aqueous sodium carbonate. Evaporation of the ether afforded an oil which crystallized upon addition of ligroin. Recrystallization from ligroin gave the ketone (39.6 g, 85.5%): mp 63.5–64.5° (*Anal.* Calcd for $C_{14}H_{16}O_2$: C, 77.55; H, 6.41. Found: C, 77.75; H, 6.46.); nmr (CCl_4) δ 7.15–6.70 (4 H, AA'BB' system, Ar H's), 3.71 (3 H, s, OCH_3), 3.30 (1 H, d, $J_{3x,4} = 4.4$ Hz, H-3*x*), 2.75, 2.60 (2 H, m, H-4 and H-1), 2.0–1.2 (6 H, m, remaining H's). The 2,4-dinitrophenylhydrazone gave mp 181–182° from ethanol–ethyl acetate. *Anal.* Calcd for $C_{20}H_{20}O_5N_4$: C, 60.60; H, 5.09. Found: C, 60.70; H, 5.22.

The ketone could also be prepared by reaction of the diol with concentrated sulfuric acid at 0°, but the yields were much less (max 50.0%, average *ca.* 25%), presumably owing to sulfonation of the aryl ring.

3-*endo*-*p*-Anisyl-2-*endo*-norbornanol.—Reduction of 3-*endo*-*p*-anisyl-2-norbornanone (3.85 g, 0.0178 mol) with lithium aluminum hydride in ether in the standard manner[37] gave the endo alcohol (3.90 g, 100%): mp 51.0–52.0° from ligroin (*Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 831. Found: C, 77.14; H, 8.42.); nmr (CCl_4) δ 7.20–6.65 (4 H, AA'BB' system, Ar H's), 4.16 (1 H, d p, $J_{2x,3x} = 9.8$, $J_{2x,1} = 4.4$ Hz, H-2*x*), 2.91 (1 H, d p, $J_{2x,3x} = 9.8$, $J_{3x,4} = 3.8$ Hz, H-3*x*), 2.30 (2 H, m, H-1 and H-4), 1.90 (1 H, s, exch, OH), 2.0–1.1 (6 H, m, remaining H's); ir (CCl_4, dilute) 3609 cm^{-1} (OH). The *p*-toluenesulfonate gave mp 90.0–91.0 from ether. *Anal.* Calcd for $C_{21}H_{24}SO_4$: C, 67.73; H, 6.50. Found: C, 67.70; H, 6.45.

3-*exo*-*p*-Anisyl-2-*endo*-norbornanol.—A solution of 3-*endo*-*p*-anisyl-2-norbornanone (50.3 g, 0.234 mol), ethylene glycol (1200 ml) and potassium hydroxide (51.0 g, 0.910 mol) was refluxed for 12 hr and then worked up according to the procedure reported[42] for the phenyl analog. Distillation gave a clear oil (32.8 g, 65.0%), bp 120–140° (0.25 mm), which was shown by nmr integration to be *ca.* 61% 3-*exo*-*p*-anisyl-2-*endo*-norbornanol, 31% 3-*endo*-*p*-anisyl-2-*endo*-norbornanol, and 8% 3-*exo*-*p*-anisyl-2-*exo*-norbornanol. Chromatography over F-20 alumina with ligroin–ether eluent gave 12.2 g of a mixture of cis alcohols which could not be separated, and a second portion, 19.6 g of 3-*exo*-*p*-anisyl-2-*endo*-norbornanol: mp 64–65° from ether–ligroin (*Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.80; H, 8.10.); nmr (CCl_4) δ 7.15–6.60 (4 H, AA'BB' system, Ar H's), 3.98 (1 H, t, $J_{1,2x} = J_{2x,3n} = 4.1$ Hz, H-2*x*), 2.90 (1 H, s, exch, OH), 2.20 (3 H, m, H-3*n*, H-1, and H-4), 2.1–1.1 (6 H, remaining H's); ir (CCl_4, dilute) 3622 cm^{-1} (OH). The *p*-toluenesulfonate gave mp 99.5–100.5 from ether. *Anal.* Calcd for $C_{21}H_{24}SO_4$: C, 67.73; H, 6.50. Found: C, 67.64; H, 6.51.

3-*exo*-*p*-Anisyl-2-norbornanone.—The procedure employed was similar to that used for the preparation of 7-*anti*-phenyl-2-norbornanone from the alcohol. From 3-*exo*-*p*-anisyl-2-*endo*-norbornanol (8.12 g, 0.0376 mole) and 8 *N* chromic acid (7.0 ml) in 25 ml of acetone there was obtained the desired ketone (4.60 g, 56.2%): mp 68–69° from ether–ligroin (*Anal.* Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.67; H, 7.66.); nmr (CCl_4) δ 7.20–6.65 (4 H, AA'BB' system, Ar H's), 3.70 (3 H, s, OCH_3), 2.91 (1 H, d, $J_{3n,7a} = 3.1$ Hz, H-3*n*), 2.78, 2.52 (2 H, m, H-4 and H-1), 2.1–1.2 (6 H, m, remaining H's). The 2,4-dinitrophenylhydrazone melted over a 20° range after repeated recrystallization from ethanol–ethyl acetate. By analogy

(37) W. G. Brown, *Org. React.*, **6**, 469 (1951).

(38) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1180.

(39) The characterization of **6**, its spectral properties, and those of other hydrocarbon by-products from this and analogous reactions will be the subject of a future publication.

(40) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

(41) C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *J. Amer. Chem. Soc.*, **86**, 4913 (1964).

(42) D. C. Kleinfelter, *J. Org. Chem.*, **32**, 840 (1967).

with the phenyl analog[43] it was assumed that a mixture of 2,4-dinitrophenylhydrazones of the *exo*-*p*-anisyl and *endo*-*p*-anisyl ketones was formed.

3-*exo*-*p*-Anisyl-2-*exo*-norbornanol.—Reduction of 3-*exo*-*p*-anisyl-2-norbornanone (4.60 g, 0.0213 mol) with lithium aluminum hydride in ether in the standard manner[37] gave a mixture of 3-*exo*-*p*-anisyl-2-*endo*-norbornanol and 3-*exo*-*p*-anisyl-2-*exo*-norbornanol (4.40 g, 94.8%), in an approximate 2:1 ratio (nmr integration). The di exo alcohol was eluted first with 5% ether–95% ligroin. This alcohol gave mp 51.0–51.5° from ligroin (*Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.22; H, 8.50.); nmr (CCl_4) δ 7.12–6.85 (4 H, AA'BB' system, Ar H's), 3.76 (1 H, largely hidden by OCH_3 signal, H-2*n*), 3.70 (3 H, s, OCH_3), 2.73 (1 H, d m, $J_{2n,3n}$ = 6.9 Hz, H-3*n*), 2.33, 2.21 (2 H, m, H-4 and H-1), 1.97 (1 H, d m, $J_{7s,7a}$ = *ca.* 10 Hz), 0.80 (1 H, b s, exch, OH), 1.7–0.9 (5 H, m, remaining H's); ir (CCl_4, dilute) 3582 cm^{-1} (OH). The *p*-toluenesulfonate gave mp 83–84° from ether. *Anal.* Calcd for $C_{21}H_{24}SO_4$: C, 67.73; H, 6.50. Found: C, 67.58, H, 6.59.

Kinetic Procedures.—Anhydrous acetic acid was prepared by distillation from acetic anhydride. Substrate concentrations for titrimetric kinetics were generally 0.015–0.030 *M* except for 9a and 9b, which were also acetolyzed at concentrations of *ca.* 0.10 *M* to obtain kinetics *via* extrapolation. This change in concentration did not affect the rate constants obtained. The method of Winstein[44] was employed for the titrimetric tosylate acetolyses. Bromthymol Blue and Crystal Violet were used as indicators. All tosylates displayed good first-order kinetics. Eight titrimetric points were usually taken per kinetic run and most acetolyses were followed to 70% reaction or greater.

(43) D. C. Kleinfelter and P. v. R. Schleyer, *J. Amer. Chem Soc.*, **83**, 2329 (1961).

(44) S. Winstein, C. Hansen, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948).

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Registry No.—**5**, 41770-08-5; *exo*-**5**, 14181-14-7; **6**, 29266-12-4; **8**, 959-42-2; **9a**, 10561-82-7; **9b**, 41770-13-2; **10a**, 10472-63-6; **10b**, 41770-15-4; **11**, 14181-18-1; **12**, 14181-15-8; **13a**, 14182-95-7; **13b**, 41770-19-8; **14**, 840-90-4; **15a**, 10472-58-9; **15b**, 41770-22-3; **16a**, 10561-85-0; **16b**, 41770-24-5; **17**, 41770-25-6; **18**, 41770-26-7; **19a**, 14182-98-0; **19b**, 41770-28-9; 7-*anti*-phenyl-2-norbornanone, 41770-29-0; 7-*anti*-phenyl-2-norbornanone 2,4-dinitrophenylhydrazone, 41770-30-3; 7-*anti*-phenyl-2-*exo*-norbornanol, 14181-16-9; 7-*anti*-phenyl-2-*endo*-norbornanol, 41770-32-5; 3-*endo*-*p*-anisyl-2-*exo*-norbornanol, 41770-33-6; 2-*p*-anisylnorbornene, 24920-37-4; 2-*endo*-*p*-anisylnorbornane-2,3-*cis*-*exo*-diol, 10381-57-4; 3-*endo*-*p*-anisyl-2-norbornanone, 10381-58-5; 3-*endo*-*p*-anisyl-2-norbornanone 2,4-dinitrophenylhydrazone, 41770-37-0; 3-*endo*-*p*-anisyl-2-*endo*-norbornanol, 10381-60-9; 3-*exo*-*p*-anisyl-2-*endo*-norbornanol, 41770-39-2; 3-*exo*-*p*-anisyl-2-norbornanone, 41770-40-5; 3-*exo*-*p*-anisyl-2-*exo*-norbornanol, 41770-41-6.

Acetolysis Products from Some Phenylnorbornyl Tosylates

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Kinetic product analyses were obtained for 3-*endo*-phenyl-2-*exo*-, 3-*endo*-phenyl-2-*endo*-, 3-*exo*-phenyl-2-*endo*-, 7-*anti*-phenyl-2-*exo*-, 7-*syn*-phenyl-2-*exo*-, and a mixture of 5-*endo*-phenyl-2-*exo*- and 5-*exo*-phenyl-2-*exo*-norbornyl tosylates. Thermodynamic product analyses were obtained for 3-*endo*-phenyl-2-*exo*-, 3-*endo*-phenyl-2-*endo*-, and 1-phenyl-2-*exo*-norbornyl tosylates. The results from the kinetic analyses were compared with those obtained from the 7-chloro-, 3-methyl-, and 3-*endo*-phenyl-3-*exo*-hydroxy-2-norbornyl tosylates. The preference of 7-*syn*-phenyl-2-*exo* product over 3-*exo*-phenyl-2-*exo* product is attributed to steric inhibition to solvent approach to the 3-*exo*-phenyl-2-norbornyl cation. Under thermodynamic conditions amounts of 1-phenyl-2-*exo* and 4-phenyl-2-*exo* products were detected. With sufficient reaction time the products formed under thermodynamic conditions approach the same equilibrium mixture.

Carbonium ions generated in the norbornyl system have been extensively studied.[1] In any significant investigation involving solvolysis rate determinations one must also consider the products of the solvolyses. In a previous paper[2] we have reported upon the acetolysis rates for the four 3-phenyl-2-norbornyl tosylates, their *p*-anisyl analogs, and the four 7-phenyl-2-norbornyl tosylates in order to determine the relative effects of the aryl substituents on the acetolysis rates. In this paper we report upon the acetolysis products obtained from a number of these phenylnorbornyl tosylates.

If the effect of an aryl group on the energy of the transition state leading from starting tosylate to the carbonium ion intermediate is similar in magnitude to the energy of the transition state leading from said intermediate to a solvolysis product, as has been represented[3] and supported[4] by Goering and Schewene diagrams, then there should be some correlation between the acetolysis rates and product distributions. Since the endo transition state energies for both the tosylate departure and solvent capture are considered to be so high relative to their exo counterparts, no endo products should be obtained.

The tosylates for which acetolysis products were determined are 3-*endo*-phenyl-2-*exo*-norbornyl tosylate (**1**), 3-*endo*-phenyl-2-*endo*-norbornyl tosylate (**2**), 3-*exo*-phenyl-2-*endo*-norbornyl tosylate (**3**), 7-*anti*-phenyl-2-*exo*-norbornyl tosylate (**4**), and 7-*syn*-phenyl-2-*exo*-norbornyl tosylate (**5**). The preparation and characterization of these tosylates and their alcohol precursors have been described previously.[5] In addition, 5-*endo*-phenyl-2-*exo*-norbornyl tosylate (**6**), contam-

(1) J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963; G. D. Sargent, *Quart. Rev., Chem Soc.*, **20**, 301 (1966); P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1966; H. C. Brown, *Chem. Eng. News*, **45**, 87 (1967).

(2) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, T. E. Dye, and J. H. Long, Jr., *J. Org. Chem.*, **38**, 4127 (1973).

(3) H. L. Goering and H. L. Schewene, *J. Amer. Chem. Soc.*, **87**, 3516 (1965).

(4) H. C. Brown, *Chem. Brit.*, **2**, 199 (1966); H. C. Brown and K. Takeuchi, *J. Amer. Chem. Soc.*, **90**, 2690, 5270 (1968); H. C. Brown and M. H. Rei, *ibid.*, **90**, 6216 (1968); H. C. Brown, P. v. R. Schleyer, R. C. Fort, and W. E. Watts, *ibid.*, **91**, 6848 (1969).

(5) D. C. Kleinfelter, T. E. Dye, J. E. Mallory, and E. S. Trent, *J. Org. Chem.*, **32**, 1734 (1967); D. C. Kleinfelter, *ibid.*, **32**, 3526 (1967).

TABLE I

PRODUCT PERCENTAGES (MOLE PER CENT) OBTAINED FROM THE KINETIC ACETOLYSES

	Hydrocarbons		Alcohols						
Norbornyl tosylate	8	9	2-*n*-Ph 10	3-*x*-Ph 11	7-*s*-Ph 12	3-*n*-Ph 13	7-*a*-Ph 14	5-*n*-Ph 15	5-*x*-Ph 16
3-*n*-Ph-2-*x*[a]	14	6.7	0	0	5.0	23	44	3.6	3.9
3-*n*-Ph-2-*x*[b]	8.0	0	0	0	5.5	27	51	4.5	4.5
3-*n*-Ph-2-*n*[a]	15	18	2.0	0	4.2	24	28	3.6	4.7
3-*x*-Ph-2-*n*[a]	19	2.0	0	1.7	15	15	26	10	11
3-*x*-Ph-2-*n*[c]	33	0	0	1.3	13	13	22	8.7	9.4
7-*a*-Ph-2-*x*[d]	20	6.4	0	0	4.8	21	42	2.2	3.3
7-*s*-Ph-2-*x*[d]	28	0	0	Trace	14	14	30	5.8	7.2
5-*n*-Ph-2-*x*[e]	19	11	0	0	1.5	7.3	15	32	18

[a] Acetolysis was conducted for greater than 10 half-lives at or above the higher (highest) of the temperatures at which the rate data were obtained.[2] Unless otherwise noted the reported percentages are the averages for three different determinations. [b] 110 hr at the reflux temperature of acetic acid. [c] Acetolysis conducted to *ca.* 90% completion. [d] One determination only. [e] One determination only; tosylate was contaminated with *ca.* 20% of the 5-*exo*-phenyl isomer.

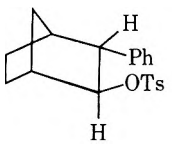
TABLE II

PRODUCT PERCENTAGES (MOLE PER CENT) OBTAINED FROM THE THERMODYNAMIC ACETOLYSES

	Hydrocarbons[a]	Alcohols				
Norbornyl tosylate	9 + 17	7-*s*-Ph + 3-*n*-Ph 12 + 13	1-Ph 18	7-*a*-Ph 14	4-Ph + 5-*n*-Ph 19 + 15	5-*x*-Ph 16
3-*n*-Ph-2-*x*[b]	0	26	9.5	49	9	6
3-*n*-Ph-2-*x*[c]	0	4	41	10	36	8
3-*n*-Ph-2-*n*[d]	0	26	22	38	8	6
3-*n*-Ph-2-*n*[c]	3	6.3	34	15	28	14
1-Ph-2-*x*[e]	69 (29) 31	?	67	?	?	0
1-Ph-2-*x*[f]	Trace	8	34	21	32	5

[a] No 8 was found. [b] Acetolysis conducted for 3 hr at 70°. [c] 13 hr at reflux temperature of acetic acid. [d] 17.5 hr at 70°. [e] 0.3 hr at 70°; 4% of alcohols unidentified but assumed (vpc) to be a mixture of all possibilities other than 15 and 16. [f] 16 hr at reflux temperature of acetic acid.

inated with some 5-*exo*-phenyl-2-*exo*-norbornyl tosylate, was acetolyzed. All these product studies were conducted with *at least* 1 mol excess of sodium acetate, *i.e.*, 2 mol of sodium acetate/mol of tosylate, in glacial acetic acid solvent to give the kinetically controlled products. Tosylates **1**, **2**, and 1-phenyl-2-*exo*-norbornyl tosylate (**7**) were also run in acetic acid alone to give the thermodynamically controlled products caused by the accumulation of the *p*-toluenesulfonic acid generated in the acetolyses. The acetolysis of **7** in the presence of sodium acetate has been reported elsewhere.[6]



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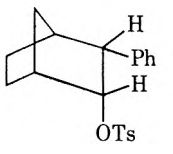

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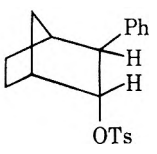

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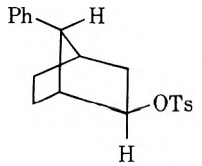

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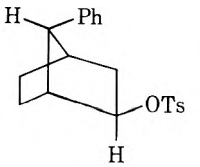

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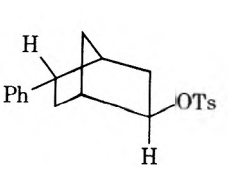

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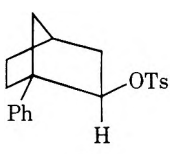

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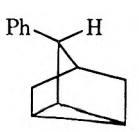
The results of the kinetic and thermodynamic acetolyses are reported in Tables I and II. The acetolysis products were routinely reduced with $LiAlH_4$ in ether prior to their attempted separation. Hence, in the tables and subsequent discussion the nonhydrocarbon products are referred to as alcohols rather than acetates.

Separation and Identification of Products. Kinetic Conditions.—After reduction with $LiAlH_4$ the products were chromatographed over alumina. Hydrocarbons **8** and **9** eluted simultaneously. An nmr spectrum of this mixture was obtained, and integration of the H-3 proton of **9** at δ 6.21[5] and the benzylic proton of **8** at δ 2.75 allowed the relative percentages to be determined. Integration of the H-1 and H-4 protons of **9** at δ 3.25 and 2.92 confirmed the percentages. These data could also be checked by vpc analysis, since the retention times of **8** and **9** differed slightly.



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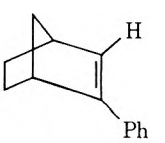
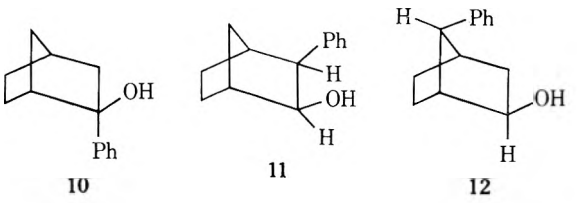


9

Only in the product study from 3-*endo*-phenyl-2-*endo*-norbornyl tosylate (**2**) was there any tertiary alcohol (**10**) obtained. It was eluted simultaneously with **12**, and, since it had no benzylic or carbinol CH atoms, its percentage in the mixture could be obtained by nmr integration of the phenyl region and the H-2*n* (δ 3.58) and H-7*a* (δ 2.90) protons of **12**.[5] As **10** thermally dehydrated to 1-phenylnortricyclene (**17**) and **9** upon vpc

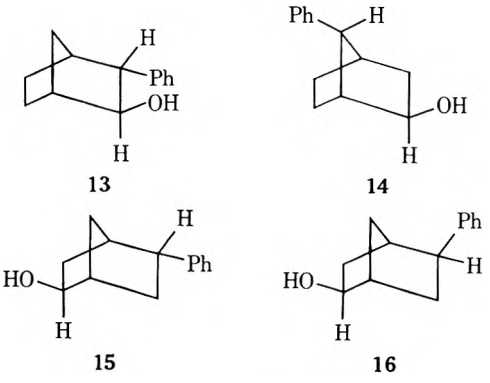
(6) D. C. Kleinfelter, Ph.D. Thesis, Princeton University, 1960, p 301.



10 11 12

analysis, a confirmation of the nmr data could be obtained. In only the product study from 3-*exo*-phenyl-2-*endo*-norbornyl tosylate (**3**) was there any 3-*exo*-phenyl-2-*exo*-norbornanol (**11**) obtained. It also eluted simultaneously with **12**. The H-2*n* proton of **12** masked half of the H-2*n* triplet pair of **11** centered at δ 3.87. Twice the unmasked triplet integration divided by the total H-2*n* absorption gave the mole fraction of **11** in the mixture.

In the other product studies the order of eluted alcohols was **12**, 3-*endo*-phenyl-2-*exo*-norbornanol (**13**), 7-*anti*-phenyl-2-*exo*-norbornanol (**14**), and the 5-phenyl-2-norbornanols, 5-*endo*-phenyl-2-*exo*-norbornanol (**15**) and 5-*exo*-phenyl-2-*exo*-norbornanol (**16**). Wherever

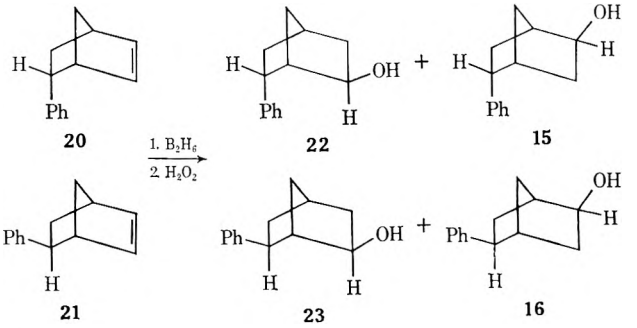


possible, pure compounds were obtained by crystallization or recrystallization of mixtures to minimize the obtaining of product percentages *via* nmr integration. In most cases some **12** could be obtained uncontaminated with **13**, but later mixtures of **12** and **13** could be not be avoided. The benzylic protons of both **12** and **13** absorb at *ca.* δ 2.85. However, the H-1 and H-4 protons of **12** are broad singlets at δ 2.67. Since no protons of **13** absorbed in that region, the percentages of both compounds could be obtained. One-half the δ 2.67 integration divided by the δ 2.85 integration gave the mole ratio of **12** in the mixtures. After small amounts of pure **13** were obtained, mixtures of **13** and **14** were eluted. Integration of the H-3*x* signal of **13** at δ 2.85 and the 7*s* signal of **14** at δ 3.25 gave their relative percentages.

In initial fractions these 3*n* and 7*a* integrations summed to the integration of their H-2*n* absorptions centered at *ca.* δ 3.80. However, with later fractions their sum fell short of the δ 3.80 integration. At the same time a second distinct phenyl singlet appeared at δ 7.09. (The phenyl absorptions for both **13** and **14** coincide as a singlet at δ 7.12.) Somewhat fortuitously, the peak height at δ 7.09 gave a fairly good approximation of the relative per cent of the last two alcohols, **15** and **16**, in these mixtures.

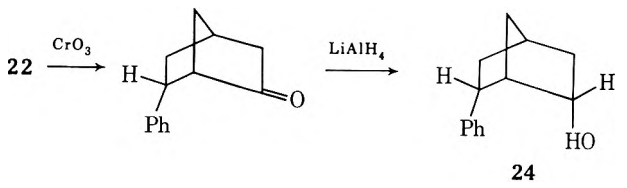
Vapor phase chromatography (vpc) did not afford the desired separation of the isomeric phenylnorbornanols. For example, mixtures of **12**, **13**, **14**, and **15** were eluted as one peak on the chromatogram. Since certain anomeric sugars had been separated successfully by gas chromatography after reaction with hexamethyldisilane (HMDS) and trimethylchlorosilane (TMCS) to form their trimethylsilyl (TMS) ethers,[7] we attempted to extend this application to our compounds. Alcohols **11** and **12** could not be separated as their TMS ethers. However, nmr analysis gave satisfactory percentages for these two isomers when they were eluted together. The TMS ethers of **13**, **14**, and **16** separated cleanly, but the TMS ethers of **14** and **15**, although giving a somewhat unsymmetrical peak on the chromatogram, could not be separated. Fortunately, integration of the isolated downfield H-7*s* signal in **14** gave its percentage, and the percentage of **15** could be obtained from the chromatogram after subtraction of the **14** percentage. Hence, by combined nmr and vpc analyses the per cents of all the acetolysis products were determined. Product percentages from tosylates **1**, **2**, and **3** were obtained three times each, and the deviation between determinations was less than 1.0%.

While compounds **15** and **16** were likely products to have been formed during these solvolyses by analogy with the data from the methylnorbornyl cations,[8] it was necessary to prove their structures. Hydroboration of the Diels–Alder adducts of styrene and cyclopentadiene,[9] a mixture of 5-*endo*-phenyl-2-norbornene (**20**) and 5-*exo*-phenyl-2-norbornene (**21**), gave a mixture of the four alcohols shown below. A vpc analysis of the



TMS ethers of this mixture gave three peaks in the ratio of 44:47:9. The retention time for the 44% peak was identical with that of the TMS derivative of 3-*endo*-phenyl-2-*exo*-norbornanol (**13**) and therefore could not belong to **15** or **16**. Some of the alcohol whose TMS ether corresponded to this 44% peak was isolated by chromatography over alumina. In its nmr spectrum the absorptions at δ 3.05 and δ 3.53 indicate exo benzylic and endo carbinol protons, respectively. The upfield shift of this latter signal relative to the same proton signal in 2-*exo*-norbornanol of δ 3.66[10] suggests some diamagnetic shielding by a proximate phenyl. These data are consistent with the structural assignment of 6-*endo*-phenyl-2-*exo*-norbornanol (**22**). Confirmation of this assignment was accomplished by oxidation of **22** to the ketone, which was reduced with $LiAlH_4$ to the epimeric alcohol, 6-*endo*-phenyl-2-*endo*-norbornanol (**24**). The structural assignment of **24** was proven by analysis of its nmr and ir spectra. In the nmr spectrum the phenyl region was found to be highly split. The

(7) C. C. Sweenley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).
(8) J. A. Berson, A. W. McRowe, and R. G. Bergman, *J. Amer. Chem. Soc.*, **89**, 2573 (1967).
(9) K. Alder and H. F. Rickert, *Ber.*, **71**, 373 (1938).
(10) E. W. C. Wong and C. C. Lee, *Can. J. Chem.*, **42**, 1245 (1964).



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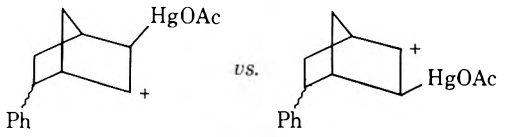
only other secondary 2-norbornanol bearing a phenyl substituent which exhibits this type of splitting is 7-*syn*-phenyl-2-*exo*-norbornanol (**12**), whose phenyl and hydroxyl groups are situated in similar proximate positions. The ir spectrum (dilute solution in CCl_4) of **24** showed no free OH absorption but only a bonded peak at 3594 cm^{-1}. From the free peak of 2-*endo*-norbornanol at 3622 cm^{-1} one obtains a $\Delta\nu$ (OH–π) of 28 cm^{-1}, identical with the value found for **12**.

The 47% peak was somewhat unsymmetrical, suggesting the presence of two components. The mixture of 5-phenyl-2-norbornenes is richer in the 5-*endo*-phenyl component (*ca.* 82%), as shown by integration of the benzylic proton signals in the 2-phenylnorbornanes formed by hydrogenation. Hence, the major component of the 47% peak should be 5-*endo*-phenyl-2-*exo*-norbornanol (**15**). The sum of the **15** and **22** percentages should equal the per cent of the norbornene precursor (**20**).

To assist in the remaining structural assignments the alkene mixture was also oxymercurated according to the procedure of Brown.[11] Vpc analysis gave the same three peaks as the hydroboration product mixture but in a distinctly different ratio of 16:73:11. Oxymercuration affords considerably less 6-*endo*-phenyl-2-*exo*-norbornanol (**22**) and thereby less 6-phenyl-2-norbornanols than 5-phenyl-2-norbornanols. This selectivity may be attributed to the electron-withdrawing effect of the phenyl group, which would inhibit positive charge buildup at the more proximate 6 position, as shown below. Traylor[12] has treated 5-*endo*-cyanonorbornene



with mercury acetate and obtained only 5-*endo*-cyano-2-*exo*-norbornyl acetate or its alcohol. The absence of 6-*endo*-cyano-2-*exo* products was explained by the inductive or field effect of the cyano group making the 2 position of the unsymmetrical transition state less susceptible to positive charge accumulation.

The major component of the 73% peak is then the TMS ether of 5-*endo*-phenyl-2-*exo*-norbornanol (**15**). If only 16% of **22** forms in the oxymercuration, one must obtain much more than 11% 5-*endo*-phenyl-2-*exo*-norbornanol (**15**) and much less than 11% 6-*exo*-phenyl-2-*exo*-norbornanol (**23**). The only possible assignment to the 11% peak is that of the TMS ether of 5-*exo*-phenyl-2-*exo*-norbornanol (**16**). Consequently, the peak for the TMS ether of **23** is largely masked by the peak for the TMS ether of **15**. It has recently been shown that the TMS ether of pure **23** has a retention time on the low side of the midpeak of these chromatograms, which is the side of the aforementioned peak distortion.[13]

From a mixture of approximately 80% **15** and 20% **16** obtained from chromatography of the alcohols obtained from oxymercuration, a sample of essentially pure **15** was obtained by repeated recrystallizations. Its properties were identical with those of an authentic sample prepared *via* a different route.[14] The TMS ethers of this mixture of alcohols (**15** and **16**) gave chromatograms whose retention times were identical with those of the latter two alcohols of our solvolysis product study. Thus all the products of the kinetic studies were identified and their percentages were obtained.[15]

Discussion of the Kinetic Acetolyses.—Of the multitude of product studies on norbornyl systems recorded in the literature we have chosen to compare our results with those of Gassman and Hornback,[16] who performed rate and product studies with the 7-chloro-2-norbornyl tosylates, with those of Berson and coworkers,[8] who determined product ratios from the 3-methyl-2-norbornyl brosylates, and with those of Collins and Benjamin,[17] who obtained product percentages from the hydrolysis of 3-*endo*-phenyl-3-*exo*-hydroxy-2-*exo*-norbornyl tosylate and its Wagner–Meerwein partner. This allows us to compare our results (phenyl) with a strongly inductive withdrawing substituent (chlorine), a mild electron-releasing group of moderate bulk (methyl), and a phenyl substituent plus a strongly inductive withdrawing group (hydroxyl) on the same carbon atom. Only with the chloro compounds have both rate and product studies been accomplished.

From Table I the Wagner–Meerwein product ratios of **25a** to **26a** were found to be *ca.* 1.0:2.0 except for the acetolysis of 3-*endo*-phenyl-2-*endo*-norbornyl tosylate (**2**), in which case the ratio was *ca.* 1.0:1.2. Of the two carbonium ion intermediates, the 3-*endo*-phenyl-2-norbornyl cation and the 7-*anti*-phenyl-2-norbornyl cation, the former should be less stable owing to the closer proximity of the inductively destabilizing phenyl substituent. In the solvolysis of the chloro- and phenylhydroxy-substituted compounds no product analogous to **25a**, namely **25b** or **25d**, derived from the 3-substituted 2-norbornyl cation was isolated, although a small amount of **25b** may have been present in the unidentified products from the chloro derivatives.[16] In the acetolysis of the methyl-substituted compounds virtually no selectivity existed between the products **25c** and **26c**. The increase in the amount of **25a** formed from acetolysis of the di endo compound (**2**) suggested the involvement of some SN2 displacement competing with unimolecular acetolysis. When **2** was acetolyzed with a 30-mol excess of sodium acetate, the per cent of

(11) H. C. Brown and P. R. Geoghegan, *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(12) A. Factor and T. G. Traylor, *J. Org. Chem.*, **33**, 2607 (1968).

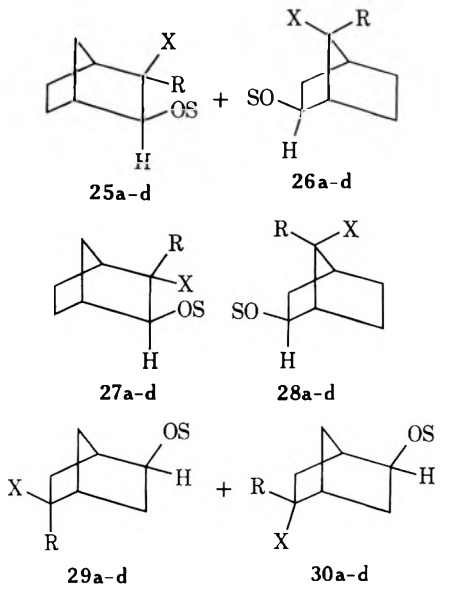
(13) R. A. Ralston, unpublished results.

(14) B. M. Benjamin, Oak Ridge National Laboratories, Oak Ridge, Tenn., kindly furnished us with the properties of his compound (**15**).

(15) The presence of a small amount of 6-*exo*-phenyl-2-*exo*-norbornanol (**23**) is not precluded by these data, since we have recently learned[13] that the acetolysis of the 6-*endo*-phenyl-2-*exo* tosylate under kinetic conditions gives *ca.* ten times as much 6-*exo*-phenyl product as 6-*endo*-phenyl product. The formation of any 6-phenyl products in our solvolysis studies would require a 3,2 exo hydride shift. Since very little such 3,2 shift occurs from a secondary to a tertiary cation in our systems, a secondary–secondary 3,2 shift should be quite unlikely.

(16) P. G. Gassman and J. M. Hornback, *J. Amer. Chem. Soc.*, **91**, 4280 (1969); **94**, 7010 (1972).

(17) C. J. Collins and B. M. Benjamin, *J. Amer. Chem. Soc.*, **89**, 1652 (1967).



a, X = H; R = Ph; b, X = H; R = Cl;
c, X = H; R = CH_3; d, X = OH; R = Ph.

25a was increased from 24 to 32% and the elimination products were increased from 33 to 41%. Within the elimination products the ratio of 2-phenylnorbornene (**9**) to the phenylnortricyclene (**8**) was increased from 1.2:1.0 to 2.1:1.0. SN2 displacement accounted for 7–8% of the product in the acetolysis of 2-*endo*-norbornyl tosylate.[18]

It was also noted that some 3,2-hydride shift occurred in the acetolysis of **2** to produce 2-*endo*-phenyl-2-*exo*-norbornanol (**10**). Such a production is apparently due to the favorable geometry. The exo-3 hydrogen may concertedly migrate to the 2 position, concomitant with *endo*-2-tosylate departure. The tertiary aryl substituted cation formed by this migration may react with solvent to give tertiary product or lose a proton to produce the olefin **9**. The greater amount of **9** relative to tricyclene (**8**) formed in this acetolysis is presumably due to the operation of this vicinal hydride shift.

The Wagner–Meerwein product ratio of **27a** to **28a** was found to be *ca.* 1.0:9.0. Only in the acetolysis of 3-*exo*-phenyl-2-*endo*-norbornyl tosylate (**3**) was any **27a** (**11**) isolated. This product may have been present in the other product studies, but the minute amount, 0.7% or less, was insufficient to allow detection.[19] That the formation of **11** was presumably not *via* any SN2 displacement was substantiated by no greater formation when the acetolysis was conducted in a tenfold excess of sodium acetate. To ascribe this position selectivity of **28a** over **27a** to only the inductive effect of phenyl seems unwarranted in light of the results discussed previously on **25a** and **26a**. The large preference of **28a** over **27a** is apparently due to a larger steric inhibition to solvent approach to the 3-*exo*-phenyl-2-norbornyl cation and the resulting partial attachment in the transition state leading to **27a**. The preference of **28c** over **27c** in the methylnorbornyl system has been shown to be at least 5.6:1.0. In the only acetolysis in which **27c** was isolated the noninvolvement of SN2 displacement was not determined.

No apparent selectivity for **29a** over **30a** was established in our studies except for the acetolysis of the 5-phenyl-2-norbornyl tosylate mixture, which gave a selectivity of 1.8 parts **29a**:1.0 part **30a**. In the other acetolyses a slight preference of **30a** over **29a** was observed. No apparent selectivity was observed in the hydroxyphenyl or the methylnorbornyl systems, although a slight preference of 1.3:1.0 for **29c** over **30c** was obtained in the acetolysis of 5-*endo*-methyl-2-*exo*-norbornyl tosylate. A preference for the 5-*exo*-chloro product (**30b**) apparently existed in the chloronorbornyl acetolyses. In some cases this preference was at least 3:1. Whatever may be causing the preference of one product over another in these product pairs, the difference may be considered to be significant only in the chloronorbornyl studies.

The values listed in Table III are for the ratios of products resulting from a 6,2-hydride shift relative to products resulting from solvent capture of the original cation or its Wagner–Meerwein partner. The values for the hydroxyphenyl, chloro, and methylnorbornyl systems are included where the data are available or calculable. The ratios of 6,2-hydride shift products to initial solvent-captured products are largest for the exo 3-substituted and syn 7-substituted tosylates, the largest ratio being displayed by the phenyl substituted compounds. Also, the smallest ratio for the endo 3- and anti 7-substituted compounds studied is exhibited by the phenyl-substituted compounds. These effects by phenyl strongly support the tenet of steric inhibition by the *exo*-3-phenyl group to solvation of the transition state leading to ionization of the tosylate and steric inhibition to solvent approach in the transition state leading from the intermediate 3-*exo*-phenyl-2-norbornyl cation to acetate product. The greater amount of 7-*anti*-phenyl-2-*exo* product relative to 7-*syn*-phenyl-2-*exo* product, *ca.* 9:1 starting with the *endo*-3-phenyl or *anti*-7-phenyl tosylates and 2:1 from the *exo*-3-phenyl or *syn*-7-phenyl tosylates, indicates appreciable steric inhibition to solvent capture of the 7-*syn*-phenyl-2-norbornyl cation. That the two tosylates, 7-*anti*-phenyl- (**4**) and 7-*syn*-phenyl-2-*exo*-norbornyl tosylate (**5**), acetolyzed at approximately the same rate may be due to the involvement of some steric acceleration in the latter compound. Although participation by methoxyl has been demonstrated in the acetolysis of 7,7-dimethoxy-2-*endo*-norbornyl tosylate,[20] attributing aryl participation to the syn isomer to explain the near identity in rates of the two 7-phenyl-2-*endo*-tosylates seems unwarranted. Finally, it should be noted that, while 3-*endo*-phenyl-2-*exo*-norbornyl tosylate (**1**) suffers internal return to 7-*anti*-phenyl-2-*exo*-norbornyl tosylate (**4**),[1] neither the 3-*exo*-phenyl nor 7-*syn*-phenyl tosylates displayed any internal return. Evidently the steric bulk of the phenyl substituents is such that the tosylate group departs in a direction away from said phenyl substituents so that internal return cannot operate.

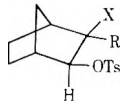
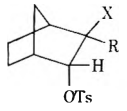
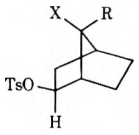
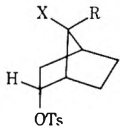
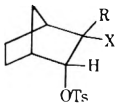
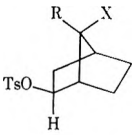
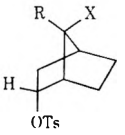
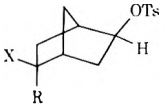
As mentioned in our prior publication,[1] a *syn*-7-phenyl substituent exerts a larger steric effect than an *exo*-3-phenyl substituent to $LiAlH_4$ reduction of a

(18) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1147, 1154 (1952).

(19) Even in the largest scale acetolysis of the other tosylates, *e.g.*, **1** (see Experimental Section), the maximum anticipated amount of **11** would be 70 mg or less.

(20) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429 (1968).

TABLE III
RATIOS OF 6,2-HYDRIDE SHIFT PRODUCT TO INITIAL SOLVENT CAPTURE[a]

Norbornyl tosylate[b]	R = Ph; X = H	R = Cl; X = H	R = Me; X = H	R = Ph; X = OH
	0.19		0.52	0.45
	0.24			
	0.16	0.37		0.43
		0.35		
	3.7		2.0	
	4.0	1.2[c]		
		2.4		
	0.47		0.74	

[a] Hydrocarbon products like 8 and 9 are ignored in these calculations. As a sample calculation the value of 0.19 for the first tosylate (R = Ph; X = H) is obtained by dividing the mole per cent of 25a and 26a (67%) into the mole per cent of other products, 27a–30a. [b] Where R = Me, OTs should be OBs. [c] Goering and Degani report 49.4% anti-chloro and 33.4% syn-chloro products, while Gassman and Hornback[16] report 42 and 49%. If Goering and Degani's data are used, this ratio of 6,2-hydride shift to solvent capture becomes 1.8. These groups are in virtual agreement on the anti-chloro product studies.

2-norbornanone. However, as pointed out by Brown,[21] although syn substituents may cause ketone reductions to proceed by endo attack, they need not significantly alter the general rule of exo approach of solvent to carbonium ions. If the transition state for tosylate departure leading to a carbonium ion resembles the transition state for solvent approach to a carbonium ion to give product, then a smaller inhibition to solvation by a syn 7 substituent relative to an exo 3 substituent would not be exceptional. If one were to assume that these latter transition states resembled the products and that the steric interactions were present in the products, then one's tenets could be supported by showing that greater interaction existed between an *exo*-3-phenyl and an exo 2 substituent than between a *syn*-7-phenyl and an exo 2 substituent.

Since the trimethylsilyl group is extremely bulky, it was hoped that the relative rates of formation of the TMS ethers of 7-*syn*-phenyl-2-*exo*-norbornanol *vs.* 3-*exo*-phenyl-2-*exo*-norbornanol might afford an opportunity to assess the degree of steric interaction between the substituents. At room temperature, the alcohols were mixed with a 20-mol excess of the silylating reagents, HMDS and TMCS, in an attempt to produce pseudo-first-order kinetics. Conclusive evidence for the silylation mechanism is lacking, but most authors agree that the rate-determining step is bimolecular involving nucleophilic substitution on silicon.[22] The progress of the reactions was followed by vpc analysis. The alcohols employed were 7-*anti*-phenyl-2-*exo*-norbornanol (**14**) and the 7-*syn*-phenyl (**12**), 3-*exo*-phenyl (**11**), and 1-phenyl (**18**) isomers. In **14**, in which the phenyl and hydroxy substituents are quite remote, the silylation proceeded quite rapidly with approximately 90% completion in 20 min reaction time. The other three isomers silylated slowly enough for sufficient data accumulation. Each reaction seemed to follow first-order kinetics up to a certain point, after which it began to level off. The 7-*syn*-phenyl isomer reacted approximately four times faster than the 3-*exo*-phenyl isomer, thus lending support to our hypothesis that greater interaction exists between an *exo*-3-phenyl and an exo 2 substituent than between a *syn*-7-phenyl and an exo 2 substituent. The 1-phenyl isomer reacted just slightly (1.1:1.0) faster than **11**, demonstrating considerable steric interaction to exist between phenyl and the exo substituent even though the dihedral angle between the substituents is *ca.* 44°.[23]

In order to illustrate further the relative steric interactions between a phenyl and an exo substituent, the methyl signals in the nmr spectra of the acetates of **12**, **11**, and **18** were obtained. These methyl signals were located at δ 1.46, 1.34, and 1.59, respectively. The methyl signal for an acetate in which phenyl is not affecting the chemical shift by a ring current effect is in the neighborhood of δ 2.06 (benzyl acetate) to δ 2.03 (ethyl acetate).[24] Evidently the phenyl group is significantly shielding the acetate methyl group in the three acetates of interest. The greatest interaction is seen in the case of the 3-*exo*-phenyl-2-*exo* acetate. By analogy with the silylation rate data one might expect the phenyl–methyl interaction to be considerably greater in the 1-phenyl isomer than the 7-*syn*-phenyl analog. However, the interaction is actually greater in the 7-*syn*-phenyl compound. One must consider that the methyl protons of the acetate are four bonds removed from C-2 of the norbornane skeleton while the reacting O atom of the alcohol in the silylation reaction is only one bond removed from C-2. Thus, the methyl shielding in the nmr spectra of the acetates should not necessarily reflect the steric effect of the phenyl groups as well as the silylation rate data.

Results of the Thermodynamic Solvolyses.—When

(21) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966), and subsequent references.

(22) A. E. Pierce, "Silylation of Organic Compounds," Pierce Chemical Co., Rockford, Ill., 1968.

(23) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(24) N. S. Bhacca, D. P. Hollis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "NMR Spectra Catalog, No. 530," Varian Associates, 1962 and 1963, lithographed by the National Press.

tosylates **1**, **2**, and **7** were acetolyzed in unbuffered acetic acid, in addition to the products observed under kinetic conditions, quantities of 1-phenyl-2-*exo*-norbornanol (**18**) and what is presumed to be 4-phenyl-2-*exo*-norbornanol (**19**) were detected. The percentage of **18** could be obtained from vpc analysis of the alcohol product mixtures, since it had a retention time different from those of the other alcohol products. The TMS ethers of **14**, **15**, and **19** had nearly identical retention times. As mentioned previously, the percentage of **14** could be obtained by integration of the 7-syn-benzylic hydrogen signal in the nmr spectrum. An approximate percentage of **19** could be obtained from vpc analysis of the alcohol products in that its retention time differed from those of the other alcohols except for some small overlap with the peaks of the 7-*syn*- and 3-*endo*-phenyl compounds (**12** and **13**). Distinguishing features in the nmr spectra of **18** and **19** were the absence of any downfield signals due to benzylic protons which are present in all of the other secondary alcohol products.

Although little 3,2-hydride shift occurred in the kinetic acetolyses, such is obviously not the case under thermodynamic conditions. Evidently sufficient driving force is operating to produce the tertiary 2-phenylnorbornyl cation under these conditions. The tertiary acetate formed from this ion should be quite labile in the acetic acid–*p*-toluenesulfonic acid medium and would reionize and then rearrange to the 1-phenyl-2-*exo*-norbornyl cation, which would afford the more stable secondary acetate. The nearly exclusive product from the buffered acetolysis of **7** is 2-phenylnorbornene (**9**). This contrasts with the changeover to 1-phenyl-2-*exo*-norbornyl acetate under thermodynamic conditions. Given sufficient reaction time even the 1-phenyl-2-*exo*-acetate will react to give a mixture of secondary acetates of 6,2, 3,2, and Wagner–Meerwein rearrangements. In fact it appears that all tosylates studied approach the same equilibrium mixture of acetates with sufficient reaction time. Of the alcohol products obtained from heating **7** at 70° in acetic acid for 20 min, 94% was **18**. Refluxing **7** for 16 hr in acetic acid reduced the amount of **18** to 34% and gave *ca.* 27% of **19**. Acetolysis of **1** at 70° for 3 hr gave *ca.* 13% of **18** and **19**, while refluxing **1** in acetic acid for 13 hr increased the percentages of these products to nearly 70%. The amount of **13** and **14** produced under these conditions decreased from *ca.* 75% in the former case to *ca.* 14% in the latter. Similar accumulation of 1- and 4-substituted products was obtained in the methylnorbornyl systems studied under the thermodynamic conditions.[8]

Experimental Section

Melting points were determined in soft capillary tubes using a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are uncorrected. Infrared spectra for the 3-μ region were recorded on a Perkin-Elmer Model 421 grating spectrometer. A Varian A-60 nmr spectrometer, calibrated with tetramethylsilane (δ 0) and chloroform (δ 436.5 Hz), was used for the nmr determinations. Chemical shifts are presumed correct to $\pm$0.01 ppm. A Varian Aerograph A90-P3 gas chromatograph equipped with a 6 ft $\times$ 0.25 in. 20% SE-30 Chromosorb W column was used for gas chromatographic determinations of product mixtures. A Varian A600-D flame ionization detector gas chromatograph equipped with a 5 ft $\times$ 0.125 in. 3% SE-30 Chromosorb W column was used in studying the rates of formation of some of the trimethylsilyl (TMS) ethers. In all chromatographic work the column temperature was *ca.* 190° with a helium flow rate of 75 ml/min. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Unless otherwise specified, all ether and ligroin solutions of products were dried over anhydrous sodium sulfate prior to removal of solvent. Ligroin was distilled over potassium permangamate and had bp 40–55°.

Acetolyses (kinetic) were carried out under the conditions given in Table I. The tosylates were dissolved in the acetic acid (reagent, 99.9%) containing the sodium acetate; the initial concentrations of tosylate and sodium acetate were *ca.* 0.2 *M* in substrate and 1.0 *M* in base except for two acetolyses, those of **1** and **3** (not reported in Table I), in which the base concentration was much greater (see text). After acetolyses were judged to be complete the reaction solutions were cooled and poured into a large volume (1 l. or more) of ice water. The oily product mixtures were extracted with ligroin and with ether; the combined extracts were washed with aqueous sodium carbonate and dried, and the solvent was removed by flash evaporation. The oily residues were dissolved in anhydrous ether and reduced with lithium aluminum hydride in the standard manner.[25] After removal of the ether solvent, ligroin was added and the ligroin solution was refrigerated for several days. The white solid of 7-*anti*-phenyl-2-*exo*-norbornanol (plus small amounts of 3-*endo*-phenyl-2-*exo*-norbornanol) that formed in most instances was filtered, analyzed by vpc and nmr, and weighed. The filtrates were chromatographed over F-20 alumina using ligroin and ligroin–ether mixtures as eluents. Analyses of these chromatographs are discussed in the text. The material balances (moles of reactants, moles of products, percentage yields) are listed in Table IV.

TABLE IV

YIELD DATA FOR KINETIC ACETOLYSES

Norbornyl tosylate	Moles of reactant	Reaction time, hr	Moles of product	Yield, %
1	0.0731	12.5	0.0644	88.1
	0.0731	13.0	0.0632	85.2
	0.0141	110	0.0125	89.5
2	0.0731	13.0	0.0519	71.0
	0.0585	13.0	0.0467	29.8
3	0.0518	110	0.0451	87.1
	0.0535	110	0.0460	86.0
	0.3515	110	0.0455	87.5
	0.0608	8.5	0.0498	81.2
4	0.0206	10.0	0.0187	91.0
5	0.0224	10.0	0.0201	89.7
6	0.0291	10.0	0.0271	93.1

Acetolyses (thermodynamic) were carried out under the conditions given in Table II. The initial concentrations of tosylate were *ca.* 0.2 *M* in substrate. The product work-up was accomplished in the same manner as that described for the kinetic acetolyses. The material balances are listed in Table V.

TABLE V

YIELD DATA FOR THERMODYNAMIC ACETOLYSES

Norbornyl tosylate	Moles of reactant	Reaction time, hr temp, °C	Moles of product	Yield, %
1	0.0400	13 (reflux)	0.0320	80.0
	0.0145	3 (70)	0.0115	79.5
2	0.0155	13 (reflux)	0.0123	79.9
	0.0150	17.5 (70)	0.0119	79.8
7	0.0249	16 (reflux)	0.0210	84.0
	0.0160	0.3 (70)	0.0135	84.5

5-*endo*-Phenyl- and 5-*exo*-Phenyl-2-norbornenes (20 and 21).—The reaction was carried out in a manner similar to that reported,[9] but with the following modifications. A mixture of dicyclopentadiene (132 g, 1.00 mol), styrene (104 g, 1.00 mol), and hydroquinone (4.0 g) was heated at 140–150° for 4 hr, then cooled, and the hydroquinone was removed by filtration. The remaining solution was distilled *in vacuo* to give a clear, colorless liquid (87.5 g, 51.5%), bp 80–85° (1 mm) [lit.[9] bp 121–125° (11

(25) W. G. Brown, *Org. React.*, **6**, 469 (1951).

mm)]. A small sample (*ca.* 2.0 g) of this product was hydrogenated with PtO_2 catalyst in a Paar bomb. Integration of the benzylic protons at δ 3.13 and 2.65 in the two phenylnorbornanes produced gave a percentage of 20:21 of 82:18. The relative percentages of 20:21 varied somewhat with reflux time and temperature.

Hydroboration of 20 and 21 and Isolation of 6-*endo*-Phenyl-2-*exo*-norbornanol (22).—The procedure employed was that of Brown and Zweifel[26] as applied to that reported for the hydroboration of 7-*syn*-phenylnorbornene.[2] From a mixture of **20** and **21** (18.7 g, 0.111 mol), sodium borohydride (4.20 g, 0.111 mol), and 17.0 g of boron trifluoride etherate, there was obtained after treatment with 3 *N* sodium hydroxide and 30% hydrogen peroxide and subsequent work-up a clear, oily alcohol mixture (17.1 g, 82.2%). Attempted distillation of this oil *in vacuo* resulted in decomposition. The analysis of the product composition is discussed in the text. The alcohol mixture (9.44 g, 0.0500 mol) was dissolved in 90:10 ligroin–ether and chromatographed over F-20 alumina. **22** was eluted with 75:25 ligroin–ether. One recrystallization from ligroin gave pure **22** (2.88 g, 30.4%): mp 65–66° (*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.74; H, 8.53.); nmr (CCl_4) δ 7.12 (5 H, s, Ph H's), 3.53 (1 H, m, H-2*n*) 3.05 (1 H, m, H-6*x*), 2.65 (1 H, s, b, exch, OH) 2.24 (2 H, m, H-1 and H-4), 1.9–1.1 (6 H, m, remaining H's).

6-*endo*-Phenyl-2-*endo*-norbornanol (24).—From **22** (1.00 g, 0.00532 mol) and 8 *N* chromic acid (3 ml) in 10 ml of acetone there was obtained the ketone, 6-*endo*-phenyl-2-norbornanone (0.71 g, 71%). This oily ketone was reduced with lithium aluminum hydride in the standard manner.[26] After removal of the ether solvent there was obtained **24** (0.525 g, 73% based on ketone): mp 49.5–51° from ligroin (*Anal.* Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 82.86; H, 8.59.); nmr (CCl_4) δ 7.3–7.0 (5 H, m, Ph H's), 4.05 (1 H, m, H-2*x*), 3.33 (1 H, m, H-6*x*), 2.67 (1 H, m, H-1), 2.25 (1 H, m, H-4), 0.80 (1 H, s, exch, OH), 2.15–0.70 (6 H, m, remaining H's); ir (CCl_4, dilute) 3594 cm^{-1} (OH).

Oxymercuration of 20 and 21 and Isolation of 5-*endo*-Phenyl-2-*exo*-norbornanol (15).—The procedure employed was similar to that of Brown and Geoghegan.[11] To a stirred solution of mercuric acetate (19.0 g, 0.0596 mol) in water (50 ml) and tetrahydrofuran (50 ml) were added **20** and **21** (8.50 g, 0.0500 mol). The reaction mixture immediately turned deep yellow; after 100 sec the color faded, but stirring was continued for another 400 sec. To the cloudy white mixture was added 3.0 *N* sodium hydroxide (50 ml) and a solution (50 ml) of 0.5 *M* sodium borohydride in 3.0 *N* sodium hydroxide. After 5 min of stirring, the mixture was extracted with three 50-ml portions of ether. The ether extracts were washed four times with water to remove the tetrahydrofuran. The dried ether solution was treated with lithium aluminum hydride (1.00 g) in the standard manner[26] to reduce the acetate that had formed. After removal of the ether solvent, 8.65 g of colorless oil remained. Vpc analysis revealed 5.0% unreacted **20** and **21**. The yield of alcohol products was 8.2 g (87%). The analysis of the product composition is discussed in the text. The reaction products (8.60 g) were dissolved in 25 ml of ligroin and chromatographed over F-20 alumina. The unreacted **20** and **21** were eluted quickly with ligroin. A small amount of **22** was eluted with 75:25 ligroin–ether. The desired alcohol (**15**) and 5-*exo*-phenyl-2-*exo*-norbornanol (**16**) were eluted simultaneously with 70:30 ligroin–ether. From this mixture there was obtained 0.41 g of **15** after crystallization from ligroin in a Dry Ice–acetone bath, vacuum sublimation, and recrystallization from ligroin. The solid gave mp 55–57° (compared to mp 60–61° for that of Benjamin[14]); the nmr spectrum in CCl_4 solution superimposed on the spectrum provided by Benjamin. The H-2*n* and H-5*x* signals (multiplets) absorb at δ 3.63 and 3.02, respectively. The mixture of **15** and **16** [with perhaps a trace of 6-*exo*-phenyl-2-*exo*-norbornanol (**23**)] was converted to the tosylate mixture, an oil, in the usual manner. This oil was used for the acetolysis product study.

Preparation of the TMS Derivatives.—The method of preparation was similar to that of Sweenley and coworkers.[7] Alcohol (or alcohol mixture, *ca.* 40 mg) and 0.1 ml of CCl_4 were placed in a small screw top vial. To this solution were added a 0.1 ml of HMDS and 0.05 ml of TMCS. The mixture was heated for 5–10 min over a steam bath to ensure complete reaction.

To measure the rates of TMS ether formation, 10.0 mg (5.32×10^{-5} mol) of alcohol was dissolved in 0.10 ml of CCl_4. To this solution were added 0.200 ml (0.210 g, 0.00124 mol) of HMS and 0.100 ml (0.128 g, 0.00117 mol) of TMCS. The densities of HMDS and TMCS as determined with the use of a Mettler 1–911 Gram-Atic balance were found to be 1.05 and 1.27 g/ml, respectively. The amount of TMS ether derivative formed and the amount of alcohol unreacted were obtained by vpc analysis. The rate constants for TMS ether formation were obtained by plotting ln [TMS ether] *vs.* time and by calculation.

Registry No.—**1**, 10561-82-7; **2**, 10472-58-9; **3**, 10561-85-0; **4**, 14181-18-1; **5**, 14181-15-8; **6**, 41914-80-1; **7**, 14182-95-7; **8**, 41894-48-8; **9**, 4237-08-5; **10**, 17989-93-4; **11**, 10472-45-4; **12**, 14181-14-7; **13**, 944-56-9; **14**, 14181-16-9; **15**, 41914-87-8; **16**, 41914-88-9; **17**, 4601-86-9; **18**, 14182-93-5; **19**, 41919-90-3; **20**, 41914-91-4; **21**, 26280-24-0; **22**, 41914-92-5; **24**, 41914-93-6.

(26) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

Acetolysis of Some Cyclohexylnorbornyl Tosylates and the Case for Dipolar Effects in Cis–Exo Norbornanes

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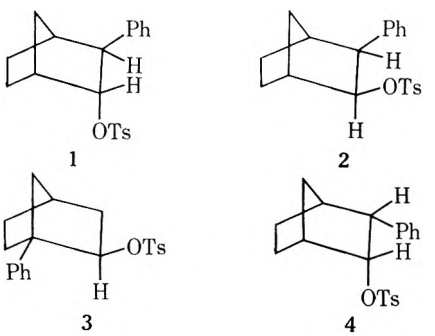
The acetolysis rates of the 3-cyclohexyl-, the 7-cyclohexyl-, and the 1-cyclohexyl-2-norbornyl tosylates have been determined. That 3-*exo*-cyclohexyl-2-*exo*-norbornyl tosylate reacted at about the same rate as the unsubstituted parent supports the explanation of an unfavorable dipolar interaction in the *exo*-3-phenyl analog causing its rate retardation. The 1-cyclohexyl-2-*exo* isomer reacted 146 times as fast as the unsubstituted parent, demonstrating again a significant positive charge accumulation at C-1 in the transition state for the 1-alkyl-2-*exo* tosylates. In the endo series the 3-*exo*-cyclohexyl isomer reacted 0.0910 times the rate of its unsubstituted parent, a retardation ascribed to steric inhibition to solvation of the developing positive charge in the transition state. The 3-*endo*-cyclohexyl- and 1-cyclohexyl-2-*endo* isomers reacted, respectively, 21 and 9.0 times as fast as their parent attributed to steric acceleration. A comparison of kinetic data for some 3-exo-substituted 2-*exo*-norbornyl tosylates with the data from some identically substituted 2-cyclohexyl brosylates revealed a greater rate depression in the norbornyl system. This supports the operation of a significant dipolar repulsive interaction in the acetolyses of the norbornyl compounds.

In prior papers we have reported upon the acetolysis rates for the four 3-phenyl-2-norbornyl tosylates, the four 3-*p*-anisyl-2-norbornyl tosylates, and the four 7-phenyl-2-norbornyl tosylates[1] as well as detailed analyses of the acetolysis products under kinetic and thermodynamic conditions.[2] These studies were conducted in order to assess the relationships between fixed geometries with definite dihedral angles and the rate-retarding inductive effects of aryl substituents, steric hindrance to ionization, and steric acceleration. In addition we anticipated that comparison of the rate data from 3-substituted norbornyl tosylates with the related 7-substituted compounds might provide information as to the amount of participation of the C_1–C_6 bond in the transition state for the exo compounds. Three of the reported relative rates were attributed to some "special effect" of phenyl not generally invoked to explain rate data: (1) 3-*exo*-phenyl-2-*endo*-norbornyl tosylate (**1**) acetolyzed at a rate 0.00392 times that of *endo*-norbornyl tosylate owing to steric inhibition to solvation of the developing positive charge in the transition state for the phenyl-substituted compound; (2) 3-*exo*-phenyl-2-*exo*-norbornyl tosylate (2) acetolyzed at a rate 0.00758 times that of *exo*-norbornyl tosylate owing to transition-state destabilization caused by a dipolar repulsive interaction between the phenyl π cloud and the developing tosylate anion; (3) if one compares ionization rates rather than acetolysis rates, the phenyl substituent in 1-phenyl-2-*exo*-norbornyl tosylate (**3**) has virtually no effect on the acetolysis rate of *exo*-norbornyl tosylate even though participation of the C_1–C_6 bond could lead to a transition state with positive charge generation at the tertiary benzylic position, which one would presume to be an energetically favorable process. This observed small effect of phenyl may also be due to the aforementioned dipolar repulsive interaction.



The rigid norbornane skeleton does not possess the conformational mobility of acyclic and simple monocyclic systems like cyclopentane and cyclohexane, and this rigid three-dimensional structure may provide an ideal system for the investigation of large steric effects.[3] As a consequence of this rigidity a preferred phenyl orientation in the ground state of a reacting species may remain so preferred in the transition state and lead to a rate retardation due to the preferential alignment. A different preferred phenyl orientation could lead to a rate acceleration, *viz.*, steric acceleration. For example, the overall effect of phenyl in the *cis-endo*-phenyl substituted isomer (**4**) is one of steric acceleration in which steric interactions are relieved in the transition state. In **4** the phenyl plane is presumably oriented in such a way that the dipolar repulsive interaction in the transition state is much less than that operating in **2**. Such preferential alignments of phenyls in **2**, **3**, and **4** have been demonstrated *via* compilation of nmr and ir spectral data.[4]

In an attempt to verify these factors contributing to the effects of the phenyl substituents on the acetolysis rates, we wished to determine acetolysis rates for substituted norbornyl tosylates lacking the phenyl substituent. Since the phenyl ring could be hydrogenated readily, we prepared the cyclohexyl derivatives from the available and characterized phenylnorbornanols. The cyclohexyl ring should have approximately the same bulk as phenyl and should transmit only a slight inductive electron-releasing effect to the reaction site. Herein we report the summations of our studies on the effects of cyclohexyl substituents on the acetolysis rates of *exo*- and *endo*-norbornyl tosylates.

All of the cyclohexyl derivatives were prepared by catalytic hydrogenation of the phenylnorbornanols with platinum oxide in acetic acid. One side reaction, that of partial esterification of the alcohol, frequently

(1) D. C. Kleinfelter, E. S. Trent, J. E. Mallory, T. E. Dye, and J. H. Long, Jr., *J. Org. Chem.*, **38**, 4127 (1973).

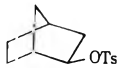
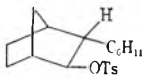
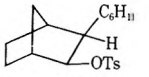
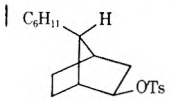
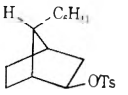
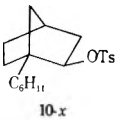
(2) D. C. Kleinfelter, M. B. Watsky, and W. E. Wilde, *J. Org. Chem.*, **38**, 4134 (1973).

(3) H. C. Brown and S. Ikegami, *J. Amer. Chem. Soc.*, **90**, 7122 (1968).

(4) (a) D. C. Kleinfelter, T. E. Dye, J. E. Mallory, and E. S. Trent, *J. Org. Chem.*, **32**, 1734 (1967); (b) D. C. Kleinfelter, *ibid.*, **32**, 3526 (1967); (c) D. C. Kleinfelter, *J. Amer. Chem. Soc.*, **89**, 1734 (1967).

TABLE I

KINETIC DATA FOR THE ACETOLYSES OF CYCLOHEXYL- (C_6H_{11}) SUBSTITUTED 2-*exo*-NORBORNYL TOSYLATES

Exo tosylate	Temp, °C	k_1, sec^{-1}	k_{rel} at 25°	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
 5-*x*	25.0[a]	2.40×10^{-5}	1.00	22.4	−4.6
 6-*x*	25.0[b] 50.0	3.64×10^{-5} 7.37×10^{-4}	1.52 (0.289)[c]	22.4	−3.6
 7-*x*	25.0 50.0	$2.50 \pm 0.16 \times 10^{-5}$ $6.02 \pm 0.16 \times 10^{-4}$	1.04 (0.00758)	23.8	+0.14
 8-*x*	25.0 50.0	$2.73 \pm 0.08 \times 10^{-5}$ $6.11 \pm 0.10 \times 10^{-4}$	1.14 (0.237)	23.3	−1.6
 9-*x*	50.0 50.0	4.37×10^{-5} 9.68×10^{-4}	1.82 (0.252)	23.1	−0.91
 10-*x*	25.0	3.51×10^{-3}	146 (3.98)		

[a] P. v. R. Schleyer, P. J. Stang, and D. J. Raber, *J. Amer. Chem. Soc.*, 92, 4275 (1970). [b] Rate constants recorded without uncertainties (±) are extrapolated values reported due to some apparent internal return being involved. [c] Relative rates in parentheses are for the corresponding phenyl analogs.

occurred; therefore, the reaction product mixture was routinely treated with lithium aluminum hydride. Only 1-cyclohexyl-2-*endo*-norbornanol was not isolated as a pure compound. A small amount of epimeric exo alcohol was present. The sample of impure alcohol was converted to the tosylate mixture. After the mixture was allowed to sit for several days, all of the exo tosylate decomposed, leaving the endo tosylate unaffected. This partially decomposed mixture was used for the kinetic determinations without further purification.

Rate Data and Discussion.—Rate data for the acetolyses of the ten cyclohexylnorbornyl tosylates determined by us are listed in Tables I and II. The data for *exo*- and *endo*-norbornyl tosylates and relative rates for the analogous phenyl-substituted compounds are included for comparative purposes.

All of the 3- and 7-cyclohexyl-2-*exo*-norbornyl tosylates acetolyzed at rates *ca.* 1.0–1.8 times the rate of the unsubstituted parent (**5**-*x*). In the absence of any steric contribution to the reaction rates, one would predict a small inductive acceleration by virtue of the known electron-releasing effect of β and γ alkyl groups like cyclohexyl (δ^* for $C_6H_{11}CH_2$ −0.06; σ^* for $C_6H_{11}CH_2CH_2$ −0.03).[5] Two exo tosylates, **7**-*x* and **10**-*x*, deserve special consideration. The slow acetolysis rate for **2** of 0.00758 relative to **5**-*x* was attributed to the dipolar repulsive interaction. When the phenyl has been replaced by cyclohexyl as in **7**-*x*, the acetolysis rate is practically identical with that of **5**-*x*. When methyl and ethyl substituents are attached in the 1 position, rate increases relative to **5**-*x* of 51 and 78 are observed.[6] In these tosylates there must be significant positive charge buildup at C-1 in the transition state, contrary to the effect of the 1-phenyl substituent. The 1-cyclohexyl substituent in **10**-*x* causes a rate increase of 146 relative to **5**-*x*. The order of cyclohexyl (σ^* −0.15) > ethyl (σ^* −0.100) > methyl (σ^* 0.000) is the order of inductive effects of the groups rather than the Baker–Nathan order.[7] Streitweiser[8] has found that the rates of solvolysis of tertiary chlorides in 80% ethanol follow the inductive order, *i.e.*, the σ^* values for the R substituent groups. Relief of steric interactions between the 1-alkyl groups and the exo tosylate substituent may also accelerate the acetolysis rates relative to **5**-*x*. The order of steric substituent constants (E_s)[9] of cyclohexyl (−0.79) > ethyl (−0.07) > methyl (0.00) is also in line with the relative rates observed. Regardless of the effects contributing to cause the acceleration by the cyclohexyl over that of the methyl and ethyl groups, by analogy with the modest effect of a 3-cyclohexyl group on the acetolysis of an exo tosylate there must be significant positive charge generation at C-1 in the transition state for all of the 1-alkyl substituted 2-exo tosylates.

Of the four 3- and 7-cyclohexyl-2-*endo*-norbornyl tosylates, the 7-anti substituted compound (**8**-*n*) and

(5) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 619; σ^* for $C_6H_{11}CH_2CH_2$ is obtained by dividing σ^* for $C_6H_{11}CH_2$ by 2.8 (see p 592).

(6) D. C. Kleinfelter and P. v. R. Schleyer, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, Abstracts, p 432; D. C. Kleinfelter, *Diss. Abstr.*, **22**, 428 (1961); J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 182.

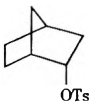
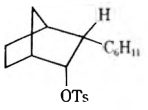
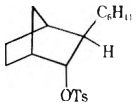
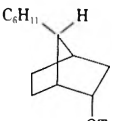
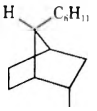
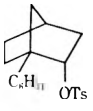
(7) J. W. Baker and W. S. Nathan, *J. Chem. Soc.*, 1840, 1844 (1935).

(8) A. Streitweiser, Jr., *J. Amer. Chem. Soc.*, **78**, 4935 (1956).

(9) Reference 5, p 598.

TABLE II

KINETIC DATA FOR THE ACETOLYSES OF CYCLOHEXYL- (C_6H_{11}) SUBSTITUTED 2-*endo*-NORBORNYL TOSYLATES

Endo tosylate	Temp, °C	k_1, sec^{-1}	k_{rel} at 25°	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
 5-*n*	25.0[a]	8.14×10^{-8}	1.00	26.5	−2.0
 6-*n*	25.0[b] 50.0 75.0	1.70×10^{-6} 5.81×10^{-5} 1.21×10^{-3}	20.9 (2.35)[c]	26.6	+4.1
 7-*n*	25.0[b] 75.0 100.0	7.40×10^{-9} $8.27 \pm 0.10 \times 10^{-6}$ $1.38 \pm 0.01 \times 10^{-4}$	0.0910 (0.00392)	28.3	−0.72
 8-*n*	25.0[b] 75.0 100.0	1.12×10^{-7} $7.45 \pm 0.08 \times 10^{-5}$ $9.92 \pm 0.16 \times 10^{-4}$	1.38 (0.286)	26.2	−2.6
 9-*n*	25.0[b] 75.0 100.0	6.17×10^{-8} $4.93 \pm 0.03 \times 10^{-5}$ $7.17 \pm 0.11 \times 10^{-4}$	0.758 (0.367)	27.1	−0.72
 10-*n*	25.0[b] 75.0 100.0	7.32×10^{-7} $3.43 \pm 0.07 \times 10^{-4}$ $4.00 \pm 0.10 \times 10^{-3}$	8.99 (0.695)	24.8	−3.5

[a] See footnote *a*, Table I. [b] Extrapolated from higher temperatures; also see footnote *b*, Table I. [c] See footnote *c*, Table I.

the 7-syn substituted compound (**9**-*n*) acetolyzed at rates close to that of the unsubstituted parent (**5**-*n*). The acetolysis rate for 3-*exo*-cyclohexyl-2-*endo*-norbornyl tosylate (**7**-*n*) is 0.0910 times that of **5**-*n*. However, this rate is still *ca.* 23 times faster than that of the phenyl analog (**1**). Of course, some of the phenyl rate retardation is due to the inductive effect of the substituent group. The E_s substituent constants for phenyl and cyclohexyl are −0.90 and −0.79, respectively;[9] *i.e.*, the bulk of a phenyl is presumed to be greater than that of a cyclohexyl. The relative steric effects of these substituents should depend on their rotational alignments with respect to the interacting reaction center. In the cyclohexane system the conformational free-energy differences, $-\Delta G_x^{\circ}$ values in kcal/mol, for methyl, ethyl, and isopropyl are within the same range.[10] Presumably the methyls of an axial ethyl or isopropyl group may be rotated into positions where they cause no extra interference with the syn-axial ring hydrogens. On this basis the bulk of a cyclohexyl group should not be significantly different from that of an isopropyl group. The ortho hydrogens of phenyl can also be oriented away from axial hydrogens by rotation about the phenyl to cyclohexane bond axis. The $-\Delta G^{\circ}$ values for phenyl and isopropyl by the same experimental method of equilibration in anhydrous ether are *ca.* 2.6[11] and 1.84–2.20,[12] respectively. The values for cyclohexyl and isopropyl by the nmr method in CCl_4 are 2.5[13] and 2.22 ± 0.08.[14] On the basis of these data a phenyl is slightly larger than a cyclohexyl substituent and a greater steric effect by the former might be expected. The relative steric effects of a 3-*exo*-phenyl *vs.* a 3-*exo*-cyclohexyl substituent on $LiAlH_4$ reduction of a 2-norbornanone may be obtained from the relative amounts of exo and endo alcohols formed. Reduction of 3-*exo*-phenyl-2-norbornanone gave an approximate 2.0:1.0 ratio of endo to exo alcohol, while reduction of the 3-exo-cyclohexyl analog gave only endo alcohol. Through this analogy one might expect a greater inhibition to solvation by the phenyl group.[15] Regardless of the magnitude of the difference between phenyl and cyclohexyl, the rate retardation demonstrated by **7**-*n* may be attributed to steric inhibition to solvation of the developing positive charge in the transition state.

While 3-*exo*-phenyl-2-*exo*-norbornyl tosylate (**2**) undergoes acetolysis quite slowly, presumably owing to

(10) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 44.

(11) E. L. Eliel and M. N. Rerick, *J. Amer. Chem. Soc.*, **82**, 1367 (1960).

(12) E. L. Eliel and T. J. Brett, *J. Amer. Chem. Soc.*, **87**, 5039 (1965).

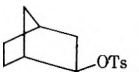
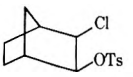
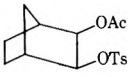
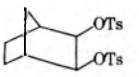
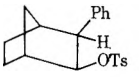
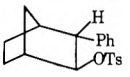
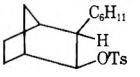
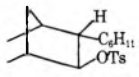
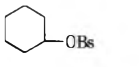
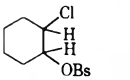
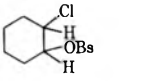
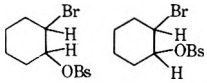
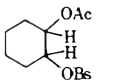
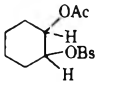
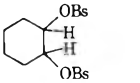
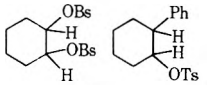
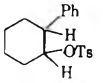
(13) J. Reisse, J. C. Celotti, D. Zimmermann, and G. Chiurloglu, *Tetrahedron Lett.*, 741 (1962).

(14) A. H. Lewin and S. Winstein, *J. Amer. Chem. Soc.*, **84**, 2464 (1962).

(15) The problems associated with attempts to equate ketone addition reactions with nucleophilic solvent approach to carbonium ions have been cited previously. See ref 1 and H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966). These problems should be minimized when the comparisons are made between two substituents on the same carbon atom.

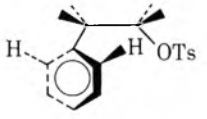
TABLE III

KINETIC DATA FOR THE ACETOLYSES OF SOME 3-SUBSTITUTED 2-*exo*-NORBORNYL TOSYLATES AND SOME 2-SUBSTITUTED CYCLOHEXYL BROSYLATES AND TOSYLATES

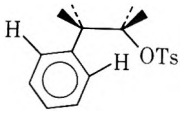
Compd	 5-*x*	 12	 13	 14
k_{rel} at 75°	1.00[a]	3.25×10^{-5} [b]	5.10×10^{-5} [a]	2.89×10^{-6} [a]
Compd	 2	 15	 7-*x*	 6-*x*
k_{rel} at 75°	1.73×10^{-2}	3.81×10^{-1}	1.58	1.62
Compd				
k_{rel} at 74.9°	1.00[c]	4.8×10^{-4}	1.3×10^{-4}	1.05×10^{-1} 1.3×10^{-4}
Registry no.		41914-94-7	41914-95-8	41914-96-9 41914-97-0
Compd				 
k_{rel} at 74.9°	2.40×10^{-1}	3.8×10^{-4}	6.9×10^{-5}	7.7×10^{-5} 1.21×10^{-1} [d] 1.93[d]
Registry no.	41914-98-1	41914-99-2	41915-00-8	27892-06-4 (75°) (75°)

[a] J. R. Lambert and A. G. Holcomb, *J. Amer. Chem. Soc.*, **93**, 2994 (1971); the k_1 for 5-*x* reported in this reference is 5.88×10^{-3} sec^{-1} while that calculated from 5-*x* using the data in Table I is 6.31×10^{-3} sec^{-1}. Since we are using the k_{rel} for two of the compounds from Lambert and Holcomb, we are employing their value for 5-*x*. [b] H. L. Goering and M. J. Degani, *J. Amer. Chem. Soc.*, **91**, 4506 (1969); the listed k_{rel} was calculated from this reference and from data found in P. G. Gassman and J. M. Hornback, *J. Amer. Chem. Soc.*, **94**, 7010 (1972). Goering and Degani report a k_{rel} to 7-*syn*-chloro-2-*exo*-norbornyl tosylate at 78.2°, and Gassman and Hornback list data for this syn isomer from which a *k* at 75° was calculated. Then a *k* for **12** was calculated by assuming that the k_{rel} to the syn isomer would not be changed by the difference of only 3.2°. [c] S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948); E. Grunwald, *ibid.*, **73**, 5458 (1951). [d] H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965); the data are relative to cyclohexyl tosylate at 75°. No correction was attempted for the different leaving group or the temperature difference of 0.1°.

the unfavorable dipolar interaction, a similar effect of equivalent magnitude cannot be operating in the endo isomer (**4**) since a rate acceleration (2.35 times) relative to 5-*n* is observed. If the C–OTs bond is located directly below the plane of the benzene ring (see **11**-*x* below), then the destabilization of the transition state is presumed to be at a maximum. Such an arrangement would be approached by the exo isomer (**2**). If the C–OTs bond is located in the same plane as that defined by the benzene ring (see **11**-*n* below), then the dipolar



11-*x*



11-*n*

contribution to the destabilization of the transition state should be at a minimum with only the inductive effect through the σ bonds affecting the rate. In this latter case steric acceleration should be at a maximum. Since there is some ground-state interaction between the endo phenyl π cloud and the cis-endo substituent, as shown from nmr and ir studies,[4] then the rate of the endo tosylate **4** reflects all three possible rate-influencing factors operating simultaneously, *i.e.*, the inductive effect through the σ framework (rate retardation), the dipolar effect through space, or field effect (rate retardation), and the steric effect (rate acceleration). If one were to accept the premise that a phenyl is larger than a cyclohexyl group, then the observed rates for **4** and 6-*n* should be close to one another if no dipolar field effect were operating in **4**. That this effect is influencing the rate to some extent is revealed by the acetolysis rate for the cyclohexyl compound (6-*n*), which is *ca.* 21 times faster than that of 5-*n*.

Finally, one of the most surprising rates was that exhibited by 1-cyclohexyl-2-*endo*-norbornyl tosylate (**10**-*n*), which acetolyzed *ca.* 9.0 times faster than 5-*n*. Both the 1-methyl- and 1-ethyl-2-*endo* tosylates acetolyzed at the same rate (1.13 times 5-*n*).[6] Since the dihedral angle between the 1- and 2-endo substituents is considered to be *ca.* 79°,[16] steric interactions between said substituents would presumably be slight. However, the only tenable explanation for the observed rate of **10**-*n* is that of some relief of ground-state interactions between the cyclohexyl and OTs substituents in the transition state, *viz.*, steric acceleration. In the 1-ethyl compound the CH_3 may be rotated away from any potentially unfavorable interaction at the 2 position. However, when one of the CH_2 protons is replaced by CH_3 as in isopropyl, or in the structurally analogous cyclohexyl case (here a CH_2 proton is replaced by CH_2R), then some steric interaction may be present. The norbornane ring should be equatorially attached to the cyclohexane ring. By positioning the tertiary axial proton toward C-2 of the norbornane ring, the cyclohexane's 2-methylene group may then interact with the C-2 endo-OTS substituent. The equatorial attachment of isopropyl or cyclohexyl to a cyclohexane ring with the tertiary axial hydrogen directed toward a 2-positioned substituent would not cause a similar unfavorable interaction.[17]

The Case for Dipolar (Field) Effects in Cis–Exo Norbornanes.—Table III lists some relative rates for

(16) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(17) This difference can be seen best with the aid of molecular models. In a previous paper (ref 4b) it was shown that there is some interaction between a 1-phenyl substituent and the 2-tosylate aromatic protons. The tosyloxy protons appear at δ 7.83 and 7.31 in 7-*anti*-phenyl-2-*exo*-norbornyl tosylate (no interaction possible), while the same protons appear at δ 7.45 and 7.04 in 1-phenyl-2-*endo*-norbornyl tosylate.

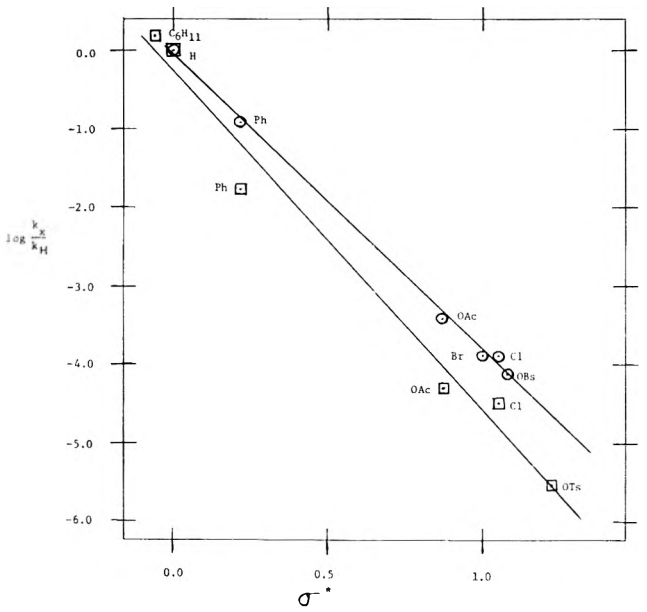


Figure 1.—Plot of log k_x/k_H *vs.* σ^* for the acetolysis of 2-substituted cyclohexyl brosylates (○) and 3-exo-substituted 2-*exo*-norbornyl tosylates (□). $\rho = -3.77$, $r = -0.99$ for cyclohexyl compounds; $\rho = -4.34$, $r = -0.985$ for the norbornyl compounds. σ^* for OAc of 0.87 was calculated from the σ_I of 0.39 using the formula $\sigma_I = (0.45)\sigma^*_{XCH_2}$; see ref 5, p 594. Although σ^* values for OBs and OTs are not listed in the literature, they have been included in the plots. Using these data, σ^* values of −1.08 and −1.22 for OBs and OTs, respectively, may be obtained.

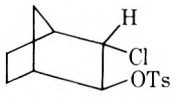
some *exo*-norbornyl tosylates and some cyclohexyl brosylates and tosylates. We offer a rationalization of these data which will support our hypothesis that an adverse dipolar or field effect is operating to a large extent in the acetolyses of **2** and **3**. Four of the 3-exo-substituted tosylates listed can exhibit rate retardation *via* inductive effects through the σ system as well as through space (field effect). The relative rates shown, Ph > OAc > Cl > OTs, are what one would expect based on σ^* substituent constants (XCH_2). The only cis and trans compounds studied bearing one of these substituents (Ph) are **2** and 3-*endo*-phenyl-2-*exo*-norbornyl tosylate (**15**). The rate of **2** is 22 times slower than that of **15** at 75°. The problem with the other 3-exo-substituted tosylates revolves around estimates of what one would expect the cis substituents to exert on the acetolysis rates; *i.e.*, how much slower should their rates be relative to their trans (3-endo-substituted) isomers.

Since the rigid norbornane system does not enjoy the flexibility of acyclic or alicyclic systems, the unfavorable dipolar effect is presumably at a maximum in the cis–exo-substituted norbornanes. In the cyclohexane system where the dihedral angles between adjacent substituents are 60° or more, such a dipolar effect should operate to a smaller extent. The cis cyclohexane compounds represent the best model compounds for measuring the overall inductive effects, since neighboring-group participation is inoperative in these stereoisomers. The rates of the two dibrosylates are practically the same, since no neighboring-group participation operates in the trans isomer as well. Once again the relative rates shown, Ph > OAc > Cl = Br > OBs, are what one would expect based on σ^* substituent constants. The relative effects of the substituents in the two systems may be revealed by the $\rho\sigma^*$ plots shown in Figure 1. This figure illustrates that the rate depressions caused by exo Ph, OAc, Cl, and OTs substituents in the norbornane system are greater than those observed by the same substituents (OBs rather than OTs) in the cyclohexane system. The magnitude of these relative rate depressions in the two systems ranges from 2.7 (OBs or OTs) to 7.5 (OAc). The cis cyclohexane system may be complicated somewhat by the possibility of the leaving brosylate (or tosylate) occupying either the equatorial or axial position. The interaction of an axial tosylate group with the syn-axial hydrogens is relieved when one goes to the carbonium ion intermediate or to the corresponding transition state which resembles the intermediate.[18] Hence, the greater the percentage of molecules reacting with the OTs or OBs groups axial, the faster will be the rate. This complication is maximized in the *cis*-2-phenylcyclohexyl tosylate, where the free energy difference between Ph and OTs is such that most of the reacting molecules would have the OTs in the axial position. In addition, some of the rate acceleration in this tosylate has been ascribed to steric acceleration combined with H participation.[19] For these reasons we have used the relative rate for the *trans*-2-phenylcyclohexyl tosylate in our $\rho\sigma^*$ plot.[20] Neighboring phenyl group participation is inoperative in the acetolysis of this compound.

Goering and Degani[21] have mentioned that the rate difference between 3-*exo*-chloro-2-*exo*-norbornyl tosylate (**12**) and 3-*endo*-chloro-2-*exo*-norbornyl tosylate (**16**) should be less than the *ca.* 4 difference in the cyclohexyl system. Since the two dibrosylates acetolyze with approximately the same rates, the difference in the 2-chlorocyclohexyl brosylates may be attributed to some small amount of neighboring chloro participation in the trans compound. As mentioned previously, tosylate **2** acetolyzes at a rate which is 22 times slower than that of **15**. Based on our previous rationale, the difference in rates between **12** and **16** may actually turn out to be significantly greater than 4.

In the 1-substituted 2-*exo*-norbornyl system a phenyl substituent accelerates the acetolysis rate by a factor of only 3.91 while an alkyl group causes a rate increase of 51–146, indicative of significant positive charge generation in the transition state for the 1-alkyl substituted compounds. The lack of significant rate enhancement in **3** may also be explained by the unfavorable dipolar effect previously discussed with reference to the cis–exo isomer (**2**). A dipolar effect may be used to explain why a 1-methoxy substituent in **17** exerts a much smaller rate-accelerating effect than a 1-methyl substituent[22] whereas in other systems methoxy prevails over methyl in their abilities to delocalize positive charge. A dipole–dipole repulsive interaction has been suggested as a possible explanation for the small (2.9) exo:endo ratio in the acetolysis rates of the 1-cyanoapoisobornyl (**18**) and 1-cyanoapobornyl (**19**) brosylates,[23] in which the rate of the exo brosylate is

(18) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955); see, *e.g.*, ref 10, p 84.
(19) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965).
(20) When the *trans*-2-phenylcyclohexyl tosylate is not included, a ρ of −3.81 is obtained, $r = -0.999$.
(21) H. L. Goering and M. J. Degani, *J. Amer. Chem. Soc.*, **91**, 4506 (1969).
(22) Footnote *a*, Table I.
(23) R. Muneyuki and T. Yano, *J. Amer. Chem. Soc.*, **92**, 746 (1970).



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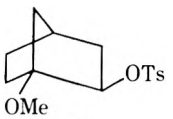

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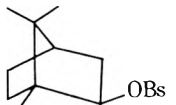

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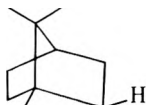

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retarded by a factor of 1.71×10^{-7} (relative to apoisobornyl) while for the endo brosylate this difference (relative to apobornyl) is reduced to 2.43×10^{-4}. Presumably the dipolar effect is quite small in the endo brosylate (ϕ between CN and OBs is *ca.* 79°) wherein the inductive effect through the σ system exerts the greater influence. We intend to determine the acetolysis rates of the 3-endo-substituted 2-exo isomers of **12**, **13**, and **14** to test the hypotheses set down in this publication.

Experimental Section

Melting points were determined in soft capillary tubes using a Hoover capillary melting point apparatus (Arthur H. Thomas Co., Philadelphia, Pa.) and are uncorrected. A Varian A-60 nmr spectrometer, calibrated with tetramethylsilane (δ 0) and chloroform (δ 436.5 Hz), was used for the nmr determinations. Chemical shifts are presumed correct to ±0.01 ppm. Microanalyses were carried out by F. B. Strauss Microanalytical Laboratory, Oxford, England. All ether and ligroin solutions of products were dried over anhydrous sodium sulfate prior to removal of solvent. Ligroin was distilled over potassium permanganate and had bp 40–55°.

Preparation of the Cyclohexylnorbornanols.—All of the cyclohexylnorbornanols were prepared from the known phenylnorbornanols by catalytic hydrogenation. A typical procedure follows. The phenylnorbornanol (*ca.* 5 g) was dissolved in a minimum amount of acetic acid. Platinum oxide (*ca.* 200 mg) was added, and the mixture was subjected to *ca.* 40 psi of hydrogen in a Paar bomb apparatus for 24 hr or until no more hydrogen was taken up. After filtration the acetic acid solution was poured into water. If the product solidified it was filtered and washed with dilute sodium hydroxide and then with water. If the product did not solidify, the oil was extracted with ligroin, the ligroin solution was washed with dilute sodium hydroxide and dried, and the solvent was removed at reduced pressure. The resultant solid or oil was dissolved in ether, stirred with $LiAlH_4$ (*ca.* 1.0 g) to reduce any acetate that formed, and worked up in the standard manner. The cyclohexylnorbornanol was crystallized and/or recrystallized from ligroin. The melting points and chemical shifts of the H-2 protons are listed in Table IV. The *p*-toluenesulfonates were prepared in the usual manner.[24] Their melting points are listed in Table V.

Reduction of 3-*exo*-Cyclohexyl-2-norbornanone.—An ether solution of 3-*exo*-cyclohexyl-2-norbornanone (0.83 g, 0.0043 mol), prepared by the oxidation of 3-*exo*-cyclohexyl-2-*endo*-norbornanol with 8 *N* chromic acid in acetone held at 0°, was reduced with 0.5 g of $LiAlH_4$ in the standard manner.[25] Nmr analysis showed only the H-2 absorption at δ 3.87, characteristic of the endo isomer. No appreciable absorption at δ 3.73 for the exo isomer was observed.

TABLE IV

PHYSICAL DATA FOR CYCLOHEXYLNORBORNANOLS

Registry no.	—Norbornanol[a]— Cyclohexyl	OH	Mp, °C	Nmr[b] (H-2), ppm
38935-69-2	3-*n*	2-*x*	70.5–71.5	3.13
38935-68-1	3-*n*	2-*n*	57.0–57.5	4.21
38935-70-5	3-*x*	2-*x*	Oil	3.73
38935-71-6	3-*x*	2-*n*	65–67	3.87
38935-72-7	7-*a*	2-*x*	78–79	3.71
38935-73-8	7-*a*	2-*n*	83–86	4.04
38935-74-9	7-*s*	2-*x*	116–117	3.80
38935-75-0	7-*s*	2-*n*	101.0–101.5	4.34
41915-10-0	1	2-*x*	71–73	3.63
41915-11-1	1	2-*n*	Semisolid	3.87

[a] Satisfactory combustion analytical data for C, H (±0.4%) were reported for these compounds: Ed. [b] CCl_4 solution.

TABLE V

PHYSICAL DATA FOR CYCLOHEXYLNORBORNYL TOSYLATES

Tosylate[a]	Mp, °C
6-*x*	78–80
6-*n*	103–106
7-*x*	61–62.5
7-*n*	111–112
8-*x*	55–57
8-*n*	80–81
9-*x*	58.5–59
9-*n*	102–103
10-*x*	105–107
10-*n*	110–111

[a] Satisfactory combustion analytical data for C, H (±0.3%) were reported for these compounds: Ed.

Kinetic Procedures.—Anhydrous acetic acid was prepared by distillation from acetic anhydride. Substrate concentrations for tritrimetric kinetics were generally 0.040 ± 0.010 *M*. The method of Winstein[26] was employed for the titrimetic tosylate acetolyses. Bromthymol Blue and Crystal Violet were used as indicators. All tosylates displayed good first-order kinetics. Eight titrimetric points were usually taken per kinetic run and most acetolyses were followed to 70% reaction or greater.

Acknowledgment.—We wish to thank Mr. R. A. Ralston for the least-squares analysis for Figure 1. J. M. M. wishes to acknowledge support by a Union Carbide Fellowship (1967–1968) and a Petroleum Research Fellowship (1968–1969).

Registry No.—**2**, 10472-63-6; **5-*x***, 959-42-2; **5-*n***, 840-90-4; **6-*x***, 41915-15-5; **6-*n***, 41915-16-6; **7-*x***, 41939-31-5; **7-*n***, 41915-17-7; **8-*x***, 41915-18-8; **8-*n***, 41915-19-9; **9-*x***, 41915-20-2; **9-*n***, 41915-21-3; **10-*x***, 41915-23-5; **10-*n***, 41915-22-4; **15**, 10561-82-7; 3-*endo*-phenyl-2-*exo*-norbornanol, 944-56-9; 3-*endo*-phenyl-2-*endo*-norbornanol, 10381-59-6; 3-*exo*-phenyl-2-*exo*-norbornanol, 10472-45-4; 3-*exo*-phenyl-2-*endo*-norbornanol, 10561-84-9; 7-*anti*-phenyl-2-*exo*-norbornanol, 14181-16-9; 7-*anti*-phenyl-2-*endo*-norbornanol, 41770-32-5; 7-*syn*-phenyl-2-*exo*-norbornanol, 14181-14-7; 7-*syn*-phenyl-2-*endo*-norbornanol, 41770-08-5; 1-phenyl-2-*exo*-norbornanol, 14182-93-5; 1-phenyl-2-*endo*-norbornanol, 14182-96-8.

(24) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1180.

(25) W. G. Brown, *Org. React.*, **6**, 469 (1951).

(26) S. Winstein, C. Hansen, and E. Grunwald, *J. Amer. Chem. Soc.*, **70**, 812 (1948).

Chemistry of α-Haloaldehydes. III.[1] Reaction of 2-Halo-2-methylpropanal with Malonic Esters in the Presence of Potassium Carbonate (Synthesis of γ-Butyrolactones)

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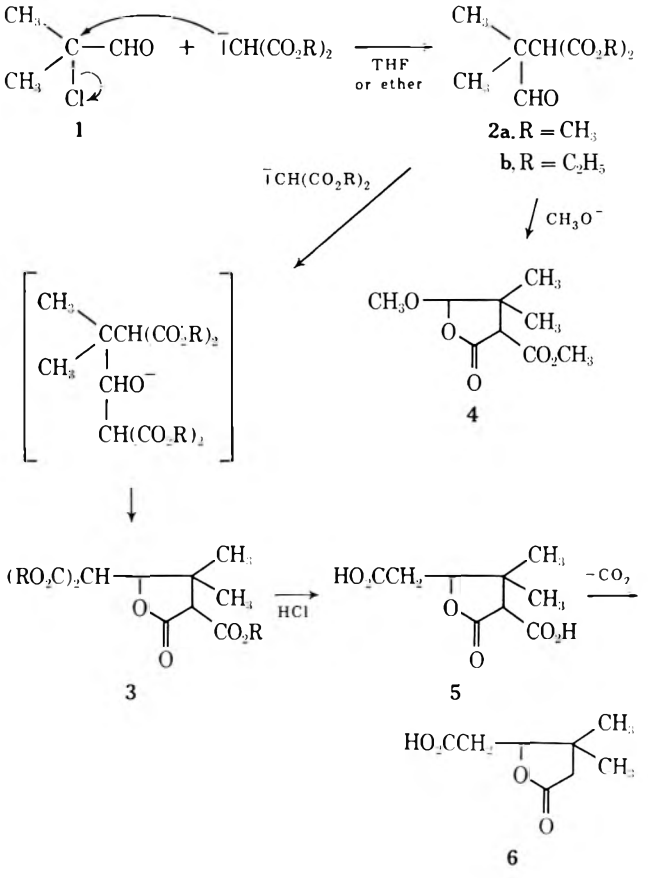
A new method for the preparation of γ-butyrolactone has been described. The reaction of 2-chloro-2-methylpropanal (1) with dimethyl malonate in the presence of potassium carbonate carried out under mild conditions gave γ-butyrolactone derivatives in good yields. The reaction of 1 with dimethyl malonate in tetrahydrofuran (THF) affords a mixture of methyl 3-formyl-2-methoxycarbonyl-3-methylbutanoate (2a) and α-methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (3). The yield of the lactone 3 was greatly improved when 2 equiv of dimethyl malonate in THF was used. Treatment of 2a with sodium methoxide gave α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (4). Aldehyde 2a further reacted with dimethyl sodiomalonate giving the lactone 3. Aldehyde 1 reacted with 2 equiv of dimethyl malonate in aqueous potassium carbonate to give predominantly α-methoxycarbonyl-β-dimethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (10). The hydrolysis of the lactone 10 with concentrated HCl gave α-carboxy-β-carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (11), which was decarboxylated to *dl*-terpenylic acid (12) by heating.

In previous papers[1,2] we reported the base-catalyzed condensation of α-haloaldehydes with dichloro- and monochloroacetates to afford corresponding halo-epoxyalkanoates. The present paper describes the result of the title reaction attempted for the synthesis of γ-butyrolactone derivatives as is exemplified by the reaction of 2-chloro-2-methylpropanal (1) which was carried out under various conditions using potassium carbonate as a catalyst.

When the reaction was conducted at room temperature in tetrahydrofuran (THF) using 1 equiv each of dimethyl malonate and the aldehyde 1, methyl 3-formyl-2-methoxycarbonyl-3-methylbutanoate (2a) was obtained in a 60% yield together with α-methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (3, 26%). The lactone 3 has been confirmed to be derived by the subsequent reaction of 2a with dimethyl malonate by a separate experiment. Thus the yield of the lactone 3 was significantly improved when 2 equiv of malonate in THF were used. On the other hand, the reaction of the formylbutanoate 2a with methoxide ion similarly resulted in an intramolecular cyclization to afford α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (4) in a 65% yield. The analogous reaction of 1 with dimethyl malonate in ether afforded the methoxylactone 4 (20% yield) and the lactone 3 (46% yield). The reaction sequence for the formation of the lactones 3, and 4 is shown in Scheme I. The structural assignment of these products was made on the basis of ir and nmr data. Ir absorptions of 3 at 1790, 1760, and 1728 cm^{-1} indicate the presence of γ-butyrolactone ring and two ester groups, respectively. The lactone ring skeleton is also supported by the nmr spectrum taken in $CDCl_3$, which exhibited a singlet at δ 3.28 ppm (α-methine proton) and two doublets at δ 5.04 and 3.67 ppm (1 H each, J = 10.5 Hz, γ-methine proton and δ-methine proton). The structure of 2a was determined by nmr and mass spectrum [m/e 174 (M^+ − CO) and 171 (M^+ − OCH_3)]. Although the nmr signal of 2a observed at 3.74 ppm as a singlet apparently is due to its methine proton, it was hardly distinguishable from the very close-lying singlet at 3.72 ppm due to two ester methyl protons. On the contrary, the nmr spectrum of ethyl 2-ethoxycarbonyl-3-methyl-3-formylbutanoate (2b) measured in $CDCl_3$ showed a sharp singlet at δ 3.60 ppm (methine proton) and the ethyl ester patterns at δ 1.26 and 4.17 ppm.

SCHEME I



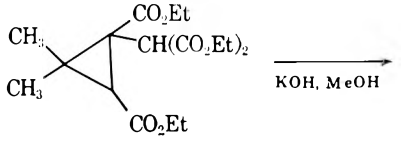
The ester cleavage[3] of the lactone 3 to α-carboxy-β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (5) was effected in a 97% yield by heating with concentrated hydrochloric acid at 70–80° for 24 hr. The nmr spectrum of the lactone acid 5 in trifluoroacetic acid showed four singlets at δ 1.13, 1.30, 1.32, and 1.45 ppm due to β,β-dimethyl protons and two singlets at δ 3.63

(1) Preceding paper: A. Takeda, S. Tsuboi, and T. Hongo *Bull. Chem. Soc. Jap.*, **46**, 1844 (1973).

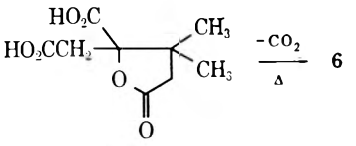
(2) A. Takeda, S. Tsuboi, S. Wada, and H. Kato, *Bull. Chem. Soc. Jap.*, **45**, 1217 (1972).

(3) Neither alkaline hydrolysis nor heating with 20% H_2SO_4 was effective.

and 3.83 ppm due to α-methine proton. This rather complicated pattern indicates that the product consists of a diastereomeric mixture. This estimation is compatible with the fact that the lactone acid **5** was decarboxylated to a uniform product, β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (**6**), mp 89.5–90°. The nmr spectrum of **6** in trifluoroacetic acid showed a clear pattern involving two singlets at δ 1.22 and 1.37 ppm due to two methyl protons, a singlet at δ 2.73 ppm due to α-methylene protons, a doublet (J = 7 Hz) at δ 2.93 ppm due to branched methylene protons, and a triplet (J = 7 Hz) at δ 4.98 ppm due to γ-methine proton. In 1901, Perkin and Thorpe reported the synthesis of the lactone **6** with the mp 154–156°.[4] They noted that the hydrolysis of diethyl (1,3-diethoxycarbonyl-2,2-dimethylcyclopropyl)malonate (**7**) with boiling methanolic potassium hydroxide afforded β,β-dimethyl-γ-carboxy-γ-carboxymethyl-γ-butyrolactone (**8**) which was then decarboxylated to the compound **6**.



7



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In order to solve the question about the discrepancy of melting points we reexamined their experiment. Both spectral data and analysis did not support such structures as they reported. The results of the reinvestigation of Perkin's experiment on the synthesis of compound **6** will be published elsewhere.[4]

The reaction of **1** with malonic esters conducted in aqueous potassium carbonate proceeded in different ways. It gave α-alkoxycarbonyl-β-dialkoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (**10**) in good yields (70–82%). The formation of the lactone **10** may be well explained by assuming the intermediate **9**, which further reacted with malonate as is shown in Scheme II. The reaction carried out in dry methanol gave a mixture of lactone **4** (22% yield) and **10a** (17% yield).

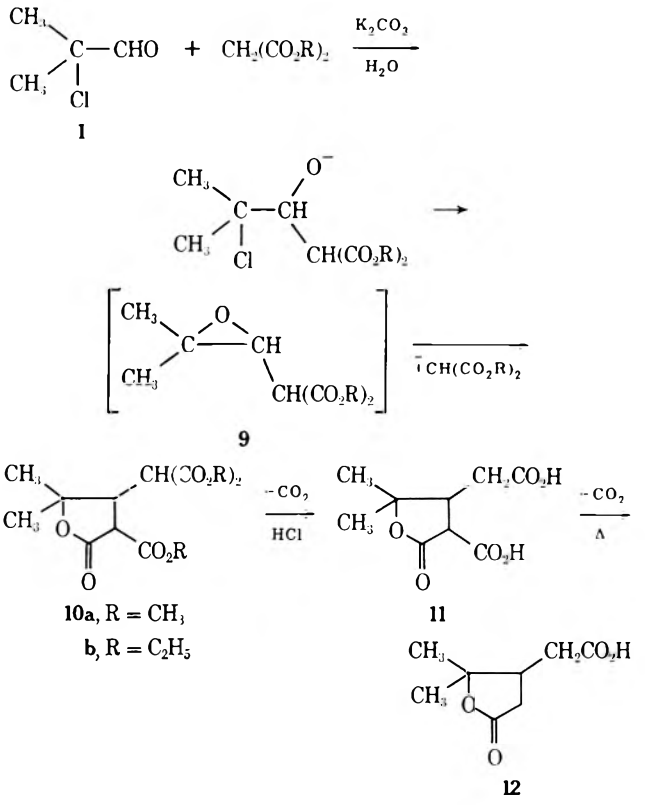
The hydrolysis of the lactone **10** with concentrated hydrochloric acid gave the free acid **11** in a 98% yield. When heated at 172–180°, compound **11** was transformed to terpenylic acid (**12**)[5] quantitatively, with the loss of carboxyl group attached to the α carbon. Terpenylic acid is usually prepared by the oxidation of α-terpineol. The yield is not satisfactory, however, because of the formation of several by-products. Accordingly, the route by way of compound **11** described here provides us with a convenient procedure for the synthesis of terpenylic acid. It has been reported by Franke and Groeger[6] that 2-bromo-2-methylpropanal reacted with diethyl sodiomalonate in ethanol to

(4) W. H. Perkin and J. F. Thorpe, *J. Chem. Soc.*, **79**, 763 (1901).

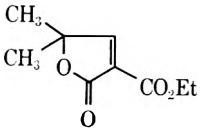
(5) C. Hempel, *Justus Liebigs Ann. Chem.*, **180**, 79 (1875). Compound **12** isolated by us melts at 88–89° (lit. mp 89–90°).

(6) A. Franke and G. Groeger, *Monatsh. Chem.*, **43**, 55 (1922).

SCHEME II



give α-ethoxycarbonyl-γ,γ-dimethyl-$\Delta^{\alpha,\beta}$-γ-butenolide (**13**). In reinvestigating their experiment, we followed



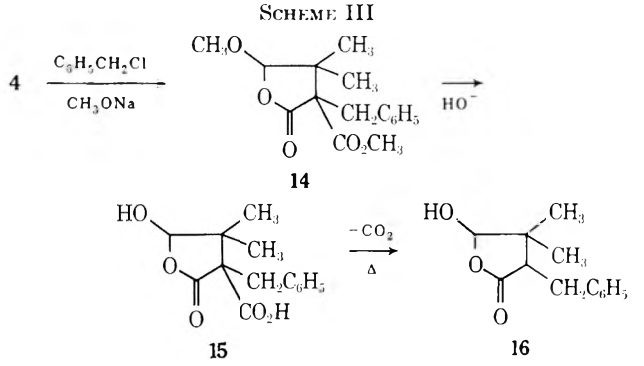
13

the procedure literally, but we failed to isolate the butenolide **13** and obtained only the lactone **10b** in a 53% yield. Therefore, there remains some doubt as to the actual isolation of the compound **13** as reported by Franke, *et al.* The structure of **10** was determined by analysis and spectral data. The ir band of **10a** at 1760 cm^{-1} is characteristic of γ-butyrolactone. The nmr spectrum in $CDCl_3$ showed two singlets at δ 1.33 and 1.52 ppm due to methyl protons, three singlets at δ 3.69, 3.75, and 3.78 ppm due to three methyl ester protons, and a multiplet at δ 3.25–4.0 ppm due to α-, β-, and branched methine protons, while no signals appeared at around 5.04 ppm indicating the absence of γ-methine proton. The nmr spectrum of **11** in trifluoroacetic acid showed unambiguous patterns. Two methine protons of the lactone ring appeared at δ 3.37 ppm (dd, 1 H, J = 6 and 11 Hz) and δ 4.01 ppm (d, 1 H, J = 11 Hz), respectively. The geometry of **11** is deduced to be trans from the large coupling constant ($J_{\alpha,\beta}$ = 11 Hz).

To obtain a firm support for the structures and also to study the reactivity of their α carbon, we carried out the reaction of the lactones **3**, **4**, and **10** with benzyl chloride in the presence of sodium methoxide. While the lactones **3** and **10** were recovered unreacted, the methoxylactone **4** gave α-benzyl-α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (**14**) in a 28% yield. The nmr spectrum of **14** in CCl_4 showed a

singlet at δ 7.09 ppm due to phenyl protons and no signals at around δ 3.53 ppm due to the α-methine proton. Hydrolysis of the benzyllactone **14** with methanolic sodium hydroxide gave hydroxylactone **16** (50% yield) and lactone acid **15** (42% yield). On heating at 180°, **15** underwent decarboxylation to afford **16** in a quantitative yield. In nmr spectrum of **15** and **16**, resonances of the γ proton appeared at δ 5.60 and 5.18 ppm, respectively. The reaction sequence for the formation of the lactones **14**, **15**, and **16** is shown in Scheme III. These unusually high δ values

SCHEME III



are attributable to the deshielding effects of the hydroxyl group and the lactone ring oxygen. The signals of β-methyl protons in **16** appear upfield (0.86–1.01 ppm) from those of **4**, as a result of the shielding effect of the phenyl group.

On the whole, it might be concluded that in aprotic solvents such as THF the carbanion of malonic esters becomes more nucleophilic than in protic solvent so that it attacks the α carbon of the α-haloaldehyde, thus forming C–C bond by SN reaction followed by an intramolecular cyclization to afford γ-lactones **3** and **4**, whereas, in protic solvents such as H_2O, the carbanion attacks the carbonyl carbon polarized by solvent molecule forming C–C bond by nucleophilic addition followed by an intramolecular cyclization to afford γ-lactone **10**.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano. Analytical determinations by glpc were performed on a Hitachi K-53 model gas chromatograph (3 mm o.d. × 1 m, 10% Apiezon Grease L on Chromosorb W). The mass spectra were obtained with a Hitachi RMS-4 mass spectrometer (70 eV). We are indebted to Mr. Hiroshi Ooyama, Hokko Chemical Industry Co., Ltd., and Mr. Heizan Kawamoto and Miss Hiromi Ootani for the nmr measurements (60 MHz).

2-Chloro-2-methylpropanal (**1**) was prepared by the method of Stevens[7] by treating aldehydes with sulfuryl chloride, bp 86–90° (lit.[7] bp 86–88°), yield 86%. 2-Bromo-2-methylpropanal was prepared by brominating 2-methylpropanal in the presence of calcium carbonate in ether, bp 105–112° [lit.[8] bp 48° (8 mm), lit.[9] bp 112–113°], yield 43%.

Methyl 3-Formyl-2-methoxycarbonyl-3-methylbutanoate (**2a**).—To a solution of 22.3 g (0.17 mol) of dimethyl malonate in 100 ml of dry THF was added 23.4 g (0.17 mol) of potassium carbonate at room temperature. A solution of 18 g (0.17 mol) of **1** in 50 ml of dry THF was then added to the mixture. After being stirred at room temperature for 6 days, the mixture was poured into water. It was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal extract was washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue, on distillation, gave 20.5 g (60%) of **2a**: bp 96–97° (3 mm); ir (neat) 2760 (CHO), 1740 (C=O), 1438, 1340, 1260, 1170, 1050, 902 cm^{-1}; nmr (CCl_4) δ 1.17 (s, 6, 2 CH_3), 3.72 [s, 6, $(CO_2CH_3)_2$], *ca.* 3.74 [s, 1, $CH(CO_2CH_3)_2$], 9.53 (s, 1, CHO); mass spectrum *m/e* (rel intensity) 174 (4, $M^+ - CO$), 171 (6, $M^+ - OCH_3$), 159 (3), 142 (20), 139 (46), 115 (55), 114 (70), 83 (100), 59 (38), 32 (10), 29 (34), 28 (56).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.50; H, 6.82.

The undistillable material was recrystallized from benzene to give 6.7 g (26%) of **3**.

α-Methoxycarbonyl-β,β-dimethyl-γ-dimethoxycarbonylmethyl-γ-butyrolactone (**3**) showed mp 120–120.5°; ir (Nujol) 1790 (lactone C=O), 1760, and 1728 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.14 (s, 3, C-β CH_3), 1.21 (s, 3, C-β CH_3), 3.28 (s, 1, C-α H), 3.67 [d, 1, J = 10.5 Hz, $CH(CO_2CH_3)_2$], 3.77 (s, 9, 3 CO_2CH_3), 5.04 (d, 1, J = 10.5 Hz, C-γ H).

Anal. Calcd for $C_{13}H_{18}O_8$: C, 51.66; H, 6.00. Found: C, 52.00; H, 5.94.

Ethyl 3-Formyl-2-ethoxycarbonyl-3-methylbutanoate (**2b**).—From a mixture of **1** (5 g, 0.047 mol), diethyl malonate (7.5 g, 0.047 mol), potassium carbonate (6.5 g, 0.047 mol), and dry THF (80 ml), 4.7 g (44%) of a liquid distilling at 114–115° (4.5 mm) was obtained by the same treatment as described in the preparation of **2a**: ir (neat) 2760 (CHO), 1740 (C=O), 1478, 1380, 1334, 1255, 1165, 1050, 901 cm^{-1}; nmr (CCl_4) δ 1.19 (s, 6, 2 CH_3), 1.26 (t, 6, J = 7.5 Hz, 2 $CO_2CH_2CH_3$), 3.60 [s, 1, $CH(CO_2C_2H_5)_2$], 4.17 (q, 4, J = 7.5 Hz, 2 $CO_2CH_2CH_3$), 9.5 (s, 1, CHO).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.30; H, 8.26.

Reaction of 2a with Dimethyl Malonate.—To a solution of 3.8 g (0.029 mol) of dimethyl malonate in 30 ml of dry ether was added 1.6 g (0.029 mol) of sodium methoxide at room temperature. A solution of 5.8 g (0.029 mol) of **2a** in 20 ml of dry ether was added dropwise at 0–5° and the mixture was then stirred for 30 min. After standing overnight at room temperature, the mixture was refluxed for 6 hr. An equivalent amount of water was added to the mixture and then the ethereal layer was separated. When the aqueous layer was acidified with 10% HCl, white crystals precipitated. The solid was collected, thoroughly washed with water, and air dried to give 3.3 g (38%) of white crystals, mp 119–120°. It was identified as **3** by comparison of ir and nmr spectra with those of the authentic sample. The ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residual oil was distilled to yield 1.3 g of dimethyl malonate, bp 48–50° (4 mm), and 1.1 g of **2a**, bp 104–105° (3.5 mm).

Reaction of 1 with Two Equivalents of Dimethyl Malonate.—To a solution of 32.2 g (0.244 mol) of dimethyl malonate in 100 ml of dry THF was added 33.8 g (0.244 mol) of potassium carbonate at room temperature. Then a solution of 13 g (0.122 mol) of **1** in 20 ml of dry THF was added to the mixture. After being stirred at room temperature for 3 days, the mixture was poured into a large quantity of water and acidified with 10% HCl. The organic layer was extracted with ether, and then 14.3 g of **3** precipitated. The ethereal layer was washed with water and dried over $MgSO_4$ for 2 hr. After removal of the solvent, the residue, on distillation, gave 12 g of dimethyl malonate and 7 g (28%) of **2a**, bp 96–99° (3 mm). The undistillable material was washed with ether to give 0.9 g (total yield 41%) of white crystals whose ir and nmr spectra were identical with those of an authentic sample of **3**.

α-Methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (**4**).—To a solution of 1 g (0.005 mol) of **2a** in 30 ml of dry ether was added 0.27 g (0.005 mol) of sodium methoxide at room temperature. After being refluxed for 18 hr, the mixture was cooled and acidified with 5% HCl. The ethereal layer was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent, 0.65 g (65%) of colorless needles was obtained: mp 53–55° (from benzene); ir (Nujol) 1790 (lactone C=O), 1730 (ester C=O), 1435, 1340, 1200, 1110, 960, 740 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (s, 3, β-CH_3), 1.25 (s, 3, β-CH_3), 3.50 (s, 3, OCH_3), 3.53 (s, 1, α-H), 3.76 (s, 3, CO_2CH_3), 4.96 (s, 1, γ-H); mass spectrum *m/e* 201 ($M^+ - 1$), 171 ($M^+ - OCH_3$), 143 ($M^+ - CO_2CH_3$), 139, 127, 115, 114, 111, 95, 83, 82, 75, 73, 71, 67, 55.

(7) C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, **79**, 3448 (1957).

(8) T. A. Favorskaya and D. A. Shkurgina, *J. Gen. Chem. USSR*, **25**, 713 (1955); *Chem. Abstr.*, **50**, 2427 (1956).

(9) L. A. Yanovskaya and A. P. Terent'ev, *Zh. Obshch. Khim.*, **22**, 1598 (1952); *Chem. Abstr.*, **47**, 9258 (1953).

Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.37; H, 7.10.

Reaction of 1 with Dimethyl Sodiomalonate in Ether.—Sodium (2.3 g, 0.1 mol) was dissolved in 60 ml of absolute methanol with moderate cooling. To the solution was added 13.2 g (0.1 mol) of dimethyl malonate at 30–40°. Removal of the solvent left 15.4 g (0.1 mol) of dimethyl sodiomalonate. To a solution of 10.6 g (0.1 mol) of **1** in 55 ml of dry ether was added in several portions 15.4 g (0.1 mol) of dimethyl sodiomalonate at −3 to 3° with stirring. The mixture was stirred for 1 hr at 0° and then for 3 hr at room temperature. After standing overnight, it was refluxed for 6 hr. After being cooled, it was poured into a large quantity of water. The organic layer was extracted with ether. The ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent the residue, on distillation, gave 4.1 g (20%) of **4**, bp 122–124° (5 mm), mp 53–55° (benzene). Ir and nmr spectra were identical with those of the authentic sample. The aqueous layer was acidified with 1 *N* HCl. The precipitated crystals were collected, washed with water and ether, and air dried to give 6.9 g (46%) of **3**, mp 118–119° (chloroform–ether). Ir and nmr spectra were identical with those of the authentic sample.

α-Carboxy-β,β-dimethyl-γ-carboxymethyl-γ-butyrolactone (5).—A mixed solution of 3.9 g (0.013 mol) of **3** in 20 ml of concentrated HCl was stirred at 70–80° for 24 hr. Removal of concentrated HCl gave 2.7 g (97%) of **5**. An analytical sample was obtained by recrystallization from acetone–ether: mp 146–148°; ir (KBr) 2650 (COOH), 1780 (lactone C=O), 1700 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.13 (s, β-CH_3), 1.30 (s, β-CH_3), 1.32 (s, β-CH_3) and 1.45 (s, β-CH_3) (cis–trans mixture, 6), 2.88 (d, 2, J = 6.5 Hz, CH_2CO_2H), 3.63 (s, α-H) and 3.83 (s, α-H) (cis–trans mixture, 1), 4.89 (m, 1, γ-H).

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.03; H, 5.32.

β,β-Dimethyl-γ-carboxymethyl-γ-butyrolactone (6).—Compound **5** (0.14 g, 0.63 mmol) was heated at 180–200° for 30 min. Crude **6** was recrystallized from ether–acetone to give 0.11 g (98%) of pure **6**: mp 89.5–90° (benzene) (lit.[4] mp 154–156°); ir (KBr) 2950, 2650 (CO_2H), 1780 (lactone C=O), 1700 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.22 (s, 3, cis CH_3), 1.37 (s, 3, trans CH_3), 2.73 (s, 2, α-H), 2.93 (d, 2, J = 7 Hz, CH_2CO_2H), 4.98 (t, 1, J = 7 Hz, γ-H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.79; H, 6.84.

α-Methoxycarbonyl-β-dimethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (10a).—To a solution of 13.8 g (0.1 mol) of potassium carbonate in 56 ml of water was added 13.2 g (0.1 mol) of dimethyl malonate. Aldehyde **1** (10.7 g, 0.1 mol) was added and the mixture was stirred at room temperature for 30 hr. After addition of ether, the mixture was acidified with 10% HCl. The precipitated crystals were collected, washed with water and ether, and air dried to give 6.9 g of **10a**. The filtrate was extracted with ether and the ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residual oil crystallized. The solid was recrystallized from *n*-hexane–benzene (1:1) to give 5.5 g of **10a**. The total yield of **10a** was 82%: mp 87–89°; ir (Nujol) 1760 (lactone C=O), 1738 cm^{-1} (ester C=O); nmr ($CDCl_3$) δ 1.33 (s, 3, γ-CH_3), 1.52 (s, 3, γ-CH_3), 3.69 (s, 3, CO_2CH_3), 3.75 (s, 3, CO_2CH_3), 3.78 (s, 3, CO_2CH_3), 3.25–4.0 [m, 3, γ-H, β-H and $CH(CO_2CH_3)_2$].

Anal. Calcd for $C_{13}H_{18}O_8$: C, 51.66; H, 6.00. Found: C, 51.86; H, 6.11.

α-Ethoxycarbonyl-β-diethoxycarbonylmethyl-γ,γ-dimethyl-γ-butyrolactone (10b).—A mixture of **1** (61.9 g, 0.58 mol), diethyl malonate (186 g, 1.16 mol), potassium carbonate (161 g, 1.16 mol), and water (250 ml) was stirred at 35–40° for 20 hr. The mixture was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal layer was washed with water and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue, on distillation, gave 140 g (70%) of **10b**: bp 188–191° (1.2 mm); ir (neat) 1770 (lactone C=O), 1730 cm^{-1} (ester C=O); nmr (CCl_4) δ 1.12–1.42 (m, 9, 3 $CO_2CH_2CH_3$), 1.20 (s, 3, γ-CH_3), 1.42 (s, 3, γ-CH_3), 3.22 (m, 1, β-H), 3.43 (d, 1, J = 11 Hz, α-H), *ca.* 3.65 [d, 1, J = 11 Hz, $CH(CO_2C_2H_5)_2$], 4.03 (m, 6, 3 $CO_2CH_2CH_3$).

Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: C, 56.15; H, 7.10.

Reaction of 1 with Dimethyl Malonate in the Presence of Sodium Methoxide in Absolute Methanol.—To a solution of 10.6 g (0.1 mol) of **1** in 30 ml of absolute methanol was added a methanol solution of dimethyl sodiomalonate prepared from absolute methanol (60 ml), sodium (2.3 g, 0.1 mol), and dimethyl malonate (13.2 g, 0.1 mol). After addition was completed, the mixture was stirred for 1 hr at 0° and then for 1.5 hr at room temperature. After being refluxed for 7 hr with stirring, the mixture was filtered to remove the precipitated sodium chloride. After removal of the solvent, the residue was extracted with ether and the ethereal solution was washed with water and dried over Na_2SO_4. Removal of the solvent left a clean oil which on distillation gave 3.9 g (22%) of **4**, bp 128–129° (4 mm), and 2.5 g (17%) of **10a**, bp 160–170° (0.25 mm): mp 87–89° (*n*-hexane–acetone). Each component was identified by comparison of ir and nmr spectra with those of the authentic samples.

α-Carboxy-β-carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (11).

A. From 10a.—A mixed solution of 10 g (0.033 mol) of **10a** in 30 ml of concentrated HCl was stirred at 60° for 13 hr and then at 70–75° for 6 hr. Removal of concentrated HCl gave 7 g (98%) of **11** which, on tlc analysis,[10] showed one clean spot with the R_f value of 0.23: mp 161–163° (acetone); ir (KBr) 2650 (CO_2H), 1765 (lactone C=O), 1715 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.47 (s, 3, cis CH_3), 1.70 (s, 3, trans CH_3), 2.85 (d, 2, J = 6 Hz, CH_2CO_2H), 3.37 (dd, 1, J = 6 and 11 Hz, β-H), 4.01 (d, 1, J = 11 Hz, α-H).

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.09; H, 5.77.

B. From 10b.—The mixed solution of 4.2 g (0.012 mol) of **10b** in 20 ml of concentrated HCl was stirred at 70–80° for 24 hr. After removal of concentrated HCl the residue was washed with ether to give 0.8 g (35%) of **11**, mp 161–163° (acetone). Ir (Nujol) and nmr (CF_3CO_2H) spectra were identical with those of the authentic sample prepared from **10a**.

β-Carboxymethyl-γ,γ-dimethyl-γ-butyrolactone (12).—Compound **11** (0.11 g, 0.52 mmol) was heated at 175–180° until evolution of carbon dioxide ceased and 0.089 g (100%) of **12**[11] was obtained: mp 88–89° (acetone–ether) (lit.[5] mp 89–90°); ir (KBr) 3000, 1750 (lactone C=O), 1710 cm^{-1} (acid C=O); nmr (CF_3CO_2H) δ 1.42 (s, 3, cis CH_3), 1.62 (s, 3, trans CH_3), 2.74 (d, 2, J = 12 Hz, CH_2CO_2H), 2.69–3.31 (m, 3, α-H and β-H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 56.01; H, 7.19.

Reaction of 2-Bromo-2-methylpropanal with Diethyl Sodiomalonate.[6]—Sodium (3.2 g, 0.14 mol) was dissolved in 65 ml of absolute ethanol with moderate cooling. A solution of 48 g (0.3 mol) of diethyl malonate in 10 ml of absolute ethanol was then added dropwise at 20° with stirring. To the resulting solution was added dropwise 13.5 g (0.089 mol) of 2-bromo-2-methylpropanal at room temperature. After stirring was continued for 14 hr at room temperature, the mixture was refluxed for 1 hr. After being cooled, it was poured into 300 ml of water. The mixture was acidified with 10% HCl and the organic layer was extracted with ether. The ethereal solution was washed with water, dried over $MgSO_4$, and evaporated. The residual oil was distilled at 166–170° (0.2 mm) [lit.[6] bp 177–178° (25 mm)] to give 18.2 g (53%) of a clean oil, of which the ir and nmr spectra were identical with those of the authentic sample of **10b**.

α-Benzyl-α-methoxycarbonyl-β,β-dimethyl-γ-methoxy-γ-butyrolactone (14).—Sodium (0.3 g, 0.013 g-atom) was dissolved in 10 ml of absolute methanol with moderate cooling. To the resulting solution was added 1.5 g (0.0074 mol) of **4** and then 1.9 g (0.015 mol) of benzyl chloride at room temperature with stirring. After stirring was continued for an additional 5 hr at room temperature, the mixture was refluxed for 1 hr. After evaporation of the most of methanol, 100 ml of water was added with cooling. After being acidified with dilute H_2SO_4, the mixture was extracted with ether. The ethereal solution was washed with water and dried over Na_2SO_4. Removal of the solvent gave 0.6 g (28%) of **14**: mp 105–107° (ether); ir (Nujol) 1783 (lactone C=O), 1729 (ester C=O), 1600 cm^{-1} (benzene ring); nmr (CCl_4) δ 1.03 (s, 3, β-CH_3), 1.19 (s, 3, β-CH_3), 3.17 (s, 2, $C_6H_5CH_2$–), 3.52 (s, 3, OCH_3), 3.57 (s, 3, CO_2CH_3), 4.75 (s, 1, γ-H), 7.09 (s, 5, C_6H_5–).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.68; H, 7.06.

α-Benzyl-β,β-dimethyl-γ-hydroxy-γ-butyrolactone (16).—To 5

(10) Condition of tlc: support, silica gel GF_{254} (E. Merck AG, Darmstadt), 0.2 mm; developer, benzene–methanol–acetic acid (10:1:1); spray, Bromocresol Green (B. C. G.).

(11) Tlc analysis showed one spot. Conditions of tlc: support, silica gel GF_{254} (E. Merck AG, Darmstadt), 0.2 mm; developer, benzene–methanol–acetic acid (9:1:1); spray, B. C. G.; R_f value 0.46.

ml of methanol was added 0.22 g (0.0054 mol) of sodium hydroxide dissolved in a small amount of water. To the resulting solution was added 0.8 g (0.0027 mol) of **14** and the mixture was then stirred at 30–40° for 2 days. After being acidified with dilute H_2SO_4, the mixture was extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate and then with water, and dried over Na_2SO_4. Removal of the solvent left 0.5 g of a light yellow oil which, on tlc analysis,[12] showed two spots at the R_f values of 0.36 and 0.58, in a ratio of 3:2. A compound with the R_f value of 0.36 was collected by preparative tlc[13] and identified as **16**: yield 50%; mp 83–84° (ether); ir (Nujol) 3320 (OH), 1760 (lactone C=O), 1598 cm^{-1} (benzene ring); nmr (CCl_4) δ 0.86 (s, 3, cis CH_3 to $C_6H_5CH_2$–), 1.01 (s, 3, trans CH_3 to $C_6H_5CH_2$–), 2.50–3.30 (m, 3, mixture of α-H and benzyl methylene), 4.60 (broad s, 1, OH), 5.18 (s, 1, γ-H), 7.19 (s, 5, $C_6H_5CH_2$–).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.06; H, 7.00.

The aqueous layer was acidified with silute H_2SO_4 to give 0.3 g (42%) of **15**.

α-Benzyl-α-carboxy-β,β-dimethyl-γ-hydroxy-γ-butyrolactone (**15**) showed mp 135–137° (benzene); ir (Nujol) 3400 (OH), 2800–2500 (COOH), 1763 (lactone C=O), 1695 (acid C=O), 1600 cm^{-1} (benzene ring); nmr [$(CD_3)_2CO$] δ 1.22 (s, 6, 2 CH_3), 3.33 (s, 2, $C_6H_5CH_2$–), 5.48 (s, 2, COOH and OH), 5.60 (s, 1, γ-H).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 64.00; H, 6.25.

Registry No.—**1**, 917-93-1; **2a**, 42203-05-4; **2b**, 42203-07-6; **3**, 42203-06-5; **4**, 42203-08-7; *cis*-**5**, 42203-09-8; *trans*-**5**, 42203-10-1; **6**, 42203-11-2; **10a**, 42203-12-3; **10b**, 42203-13-4; **11**, 42203-14-5; **12**, 116-51-8; **14**, 42203-16-7; **15**, 42203-17-8; **16**, 42203-18-9; dimethyl malonate, 108-59-8; diethyl malonate, 105-53-3; dimethyl sodiomalonate, 18424-76-5; diethyl sodiomalonate, 996-82-7; 2-bromo-2-methylpropanal, 13206-46-7.

(12) Conditions of tlc: support, silica gel G (E. Merck AG, Darmstadt), 0.1 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); spray reagent, H_2SO_4–$KMnO_4$ (7:3 w/w). The spot of **14** on tlc appeared at R_f 0.58.

(13) Conditions of preparative tlc: support, silica gel G (E. Merck AG; Darmstadt), 0.8 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); eluent, acetone.

Mass Spectrometry in Structural and Stereochemical Problems. CCXXXIV.[1] Alkyl Pyridyl Ketones

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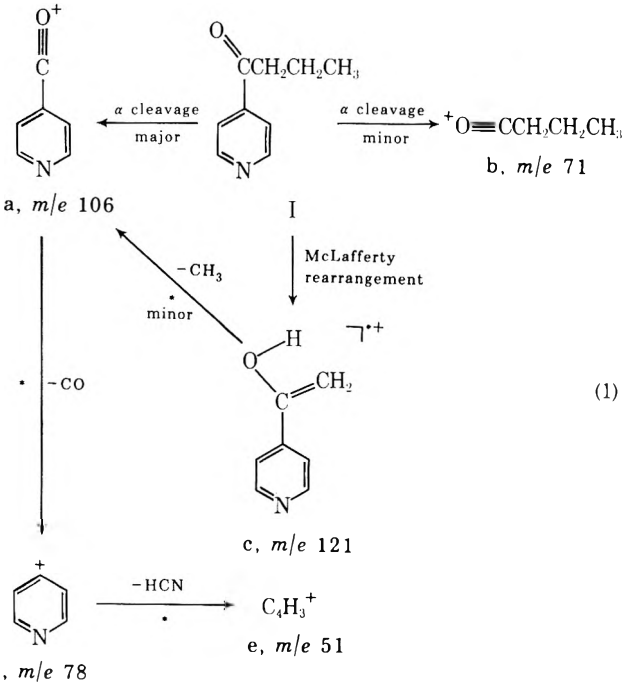
The mass spectra of the three isomeric propyl pyridyl ketones are reported. Negligible influence by the ring nitrogen was observed in the 3 and 4 isomers. Fragmentation of the McLafferty rearrangement ion is observed to occur without prior ketonization. The mass spectrum of propyl 2-pyridyl ketone is markedly different owing to interactions of the side chain with the ring nitrogen. A similar behavior is noted in the higher homologs.

Although the mass spectra of alkyl phenyl ketones have been extensively studied,[2] very little attention has been directed toward the unimolecular decomposition of alkyl pyridyl ketones upon electron impact. This is somewhat surprising in view of much other work on the significant influence of heteroatoms on the fragmentation pattern of many substituted pyridine ions.[3] In light of this and our interest in the electron impact induced fragmentations of ketones,[4] we considered it informative to examine the electron impact induced fragmentations of alkyl pyridyl ketones, specifically the three isomeric propyl pyridyl ketones (I, II, III) and some of their labeled analogs.

Propyl 4-Pyridyl Ketone (I).—The mass spectrum of propyl 4-pyridyl ketone (I) is shown in Figure 1. The major fragmentation pathways are illustrated in eq 1. The elemental composition of the ions was substantiated by high-resolution mass measurements. Its behavior is quite similar to that of butyrophenone with the two major fragmentation pathways being simple cleavage α to the carbonyl group, yielding ions a (*m/e* 106) and b (*m/e* 71) and a McLafferty rearrangement to



(1)

form the ion c of mass 121. Exact mass measurements showed that the expulsion of CO from the molecular ion makes only a 3% contribution to the *m/e* 121 peak. Specific labeling of the three propyl carbons with deuterium also confirms the fragmentation scheme. The McLafferty rearrangement ion c fragments by loss of CH_3 as verified by the observation of the appropriate metastable peak. Examination of the metastable

(1) For the previous paper, see S. Hammerum and C. Djerassi, *J. Amer. Chem. Soc.*, submitted for publication.

(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(3) (a) E. V. Brown and M. B. Shambhu, *Org. Mass. Spectrom.*, **6**, 479 (1972); (b) C. S. Barnes, R. J. G. Goldrach, J. Halbert, J. G. Wilson, R. J. Lyall, and S. Middleton, *Tetrahedron Lett.*, 705 (1973); (c) R. G. Cooks, R. N. McDonald, P. T. Cranor, H. E. Petty, and N. L. Wolfe, *J. Org. Chem.*, **38**, 1114 (1973); (d) G. H. Kellen, L. Bauer, and L. L. Bell, *J. Heterocycl. Chem.*, **5**, 647 (1968); (e) R. J. Moser and E. V. Brown, *Org. Mass Spectrom.*, **4**, 555 (1970); (f) C. P. Whittle, *Tetrahedron Lett.*, 3689 (1968); (g) E. V. Brown and R. J. Moser, *J. Heterocycl. Chem.*, **8**, 189 (1971).

(4) K. B. Tomer and C. Djerassi, *Org. Mass Spectrom.*, **6**, 1285 (1972).

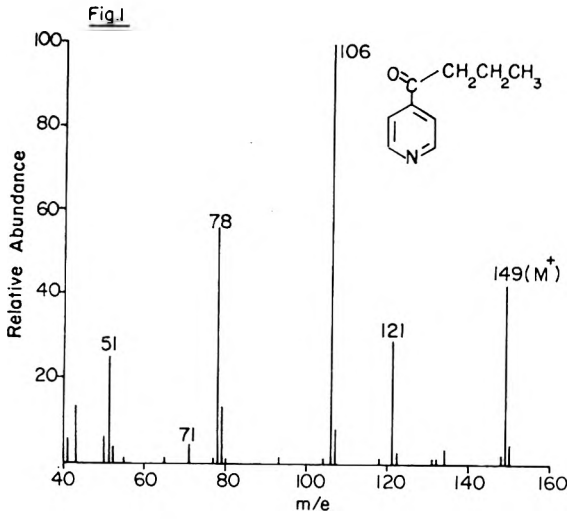


Figure 1.—70-eV mass spectrum of propyl 4-pyridyl ketone (I).

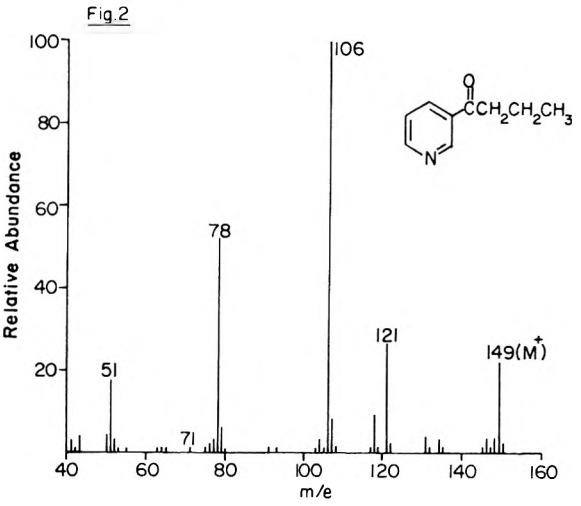
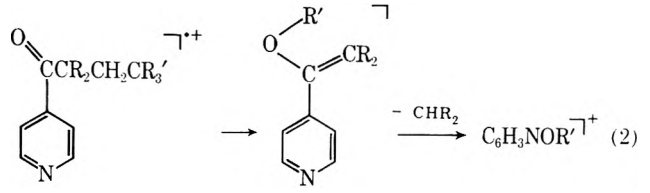


Figure 2.—70-eV mass spectrum of propyl 3-pyridyl ketone (II).

peaks for this process in the mass spectra of the labeled ketones showed that the loss of CH_3 does not involve the itinerant hydrogen (eq 2). Thus, this ion does



(2)

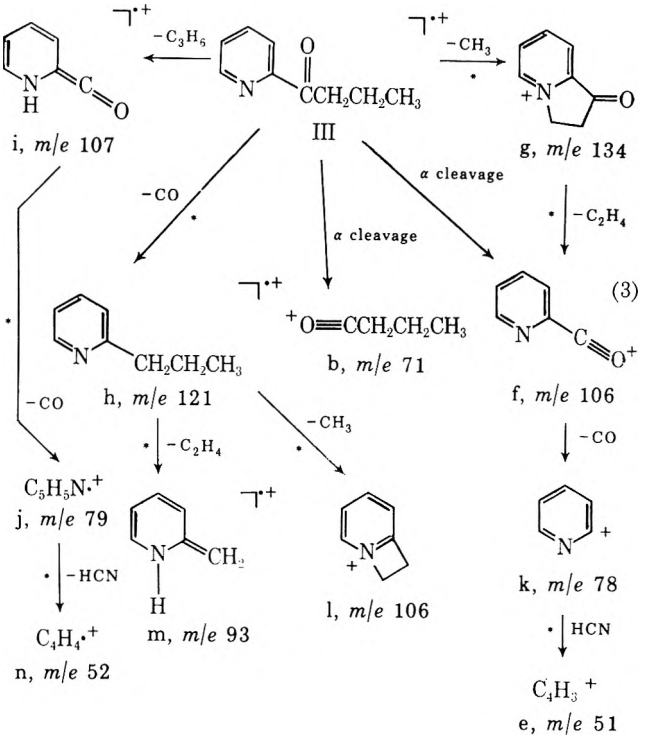
I′, R = D; R′ = H c′, R = D; R′ = H
I″, R = H; R′ = D c″, R = H; R′ = D

not reketonize prior to CH_3 expulsion, but must lose a ring hydrogen in this process. Identical results were observed for the expulsion of CH_3 from the McLafferty rearrangement ion of butyrophenone.[4] The deuterium labeling also show that this methyl loss is a minor process in the formation of the $C_6H_4NO^+$ ion a in the 70-eV spectrum (~1%).

Propyl 3-Pyridyl Ketone (II).—The mass spectrum of propyl 3-pyridyl ketone (II) is shown in Figure 2. A comparison of Figures 1 and 2 as well as the behavior of the deuterium-labeled analogs show that the mass spectra exhibit only minor differences. The major fragmentation pathways are, therefore, the same as those for the 4 isomer (eq 1). High-resolution mass measurements indicate no contribution from CO loss to the *m/e* 121 peak.

Propyl 2-Pyridyl Ketone (III).—The mass spectrum (Figure 3a and 3b) of propyl 2-pyridyl ketone (III) shows striking differences from those (Figures 1 and 2) of the 3 and 4 isomers. High-resolution mass measurements show that, in this compound, the *m/e* 121 peak results from CO expulsion ($C_8H_{11}N$; 94%) rather than from a McLafferty rearrangement (C_7H_7NO; 6%). The *m/e* 106 peak, much reduced in importance in comparison to that found in the spectra of the 3 and 4 isomers, is also revealed to be a doublet [51% C_6H_4NO (f); 49% C_7H_8N (l)]. With the aid of deuterium labeling (Table I), high-resolution mass measurements, and the presence of metastable ions, the fragmentation pattern in eq 3 is proposed which encompasses several fragmentations attributable to involvement of the pyridyl nitrogen.

[M − CH_3]·+.—The loss of methyl (unimportant in



(3)

I and II) is shown by deuterium labeling to involve only the terminal methyl group of the propyl chain. This peak increases in importance as the ionizing energy is decreased and the reaction is marked by an abundant (70 eV) metastable peak (*m/e* 120.8).

Thus a cyclization reaction is implicated rather than a simple cleavage. This ion is not observed in the mass spectrum (Figure 4) of ethyl 2-pyridyl ketone (IV) (Figure 4) but loss of hydrogen in IV is more important than in III. In accordance with these observations, butyl 2-pyridyl ketone (V) and pentyl 2-pyridyl ketone (VI) lose ethyl (Figure 5) and propyl (Figure 6) fragments. Thus cyclization to form a five-membered ring is preferred over other ring sizes (eq 4). This is in contrast to the observation of preferential four-membered ring formation in simple 2-alkyl pyridines and quinolines.[2,5] Since this cyclization process is not important in the 3 and 4 isomers, interaction of the ring

(5) S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

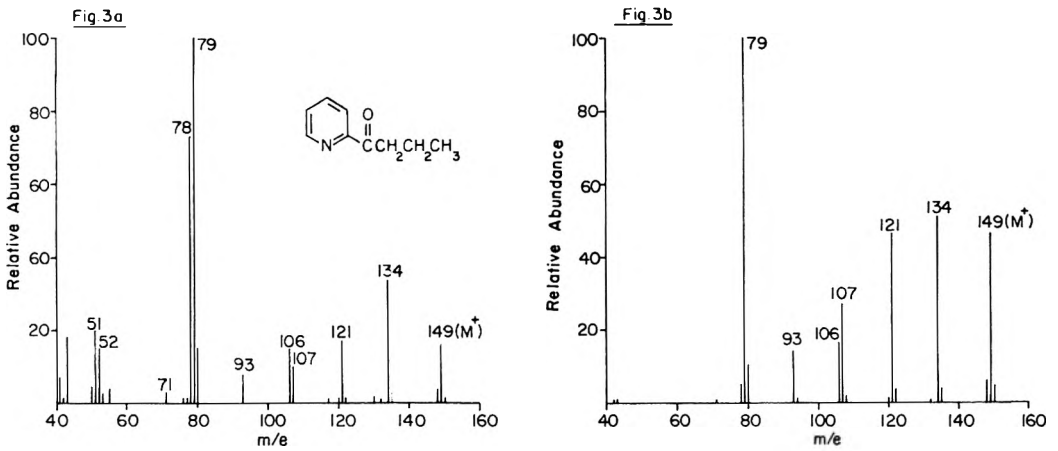


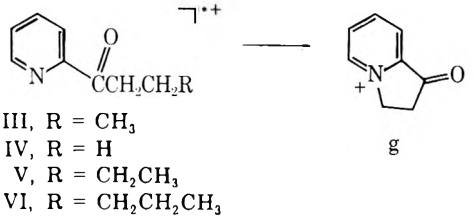
Figure 3.—(a) 70-eV mass spectrum of 2-pyridyl ketone (III); (b) 12-eV mass spectrum of 2-pyridyl ketone (III).

TABLE I

COMPARISON OF MASS SHIFTS ENCOUNTERED IN THE MAIN PEAKS OF THE SPECTRA OF LABELED PROPYL 2-PYRIDYL KETONES AT 70 AND 12 eV[a]

		% m/e 134 which shifts to[b]			% m/e 121 which shifts to[b]			% m/e 107 which shifts to[b]			% m/e 106 which shifts to[b]			% m/e 93 which shifts to[b]			% m/e 79 which shifts to[b]			% m/e 78 which shifts to[b]		
eV		135	136	137	122	123	124	108	109	110	107	108	109	94	95	96	80	81	82	79	80	81
70	α-d_2	0	100	0	0	100	0	0	0	0	0	55	0	0	83	0	15	0	0	0	0	0
	β-d_2	0	100	0	4	96	0	100	0	0	0	20	0	20	0	0	60	0	0	0	0	0
	γ-d_3	0	0	0	5	0	95	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0
12	α-d_2	0	100	0	0	100	0	0	0	0	0	84	0	0	90	0	7	0	0	0	0	0
	β-d_2	0	100	0	0	94	0	100	0	0	12	62	0	16	0	0	90	0	0	0	0	0
	γ-d_3	0	0	0	2	0	98	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0

[a] All compounds have been corrected to 100% isotopic purity. [b] ±5%.

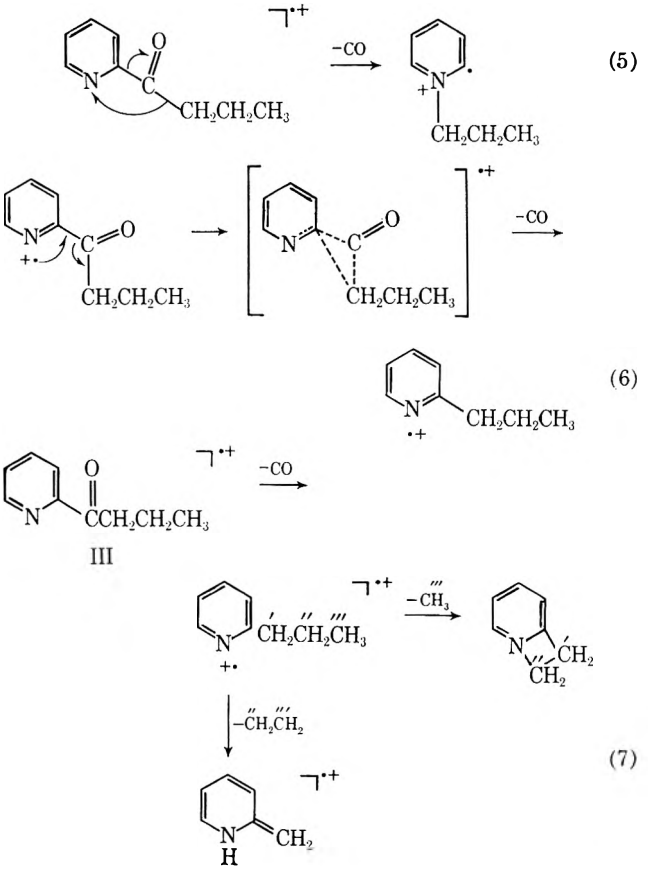


(4)

nitrogen with the side chain is invoked to initiate this reaction.

[M − CO]·+.—Brown and Shambhu[3a] and Barnes and coworkers[3b] have observed the expulsion of CO from phenyl 2-pyridyl ketones but not from the 3 and 4 isomers. The mass spectrum of 2-acetylpyridine has been reported[6] and a peak corresponding to loss of 28 mass units observed (Figure 7). The occurrence of this fragmentation in 2-acetylpyridine (VII) and ethyl 2-pyridyl ketone (IV) (Figure 4) in addition to the higher homologs (Figure 5 and 6) demonstrates that chain length is not a significant factor in the reaction. Two mechanisms can be drawn for this reaction involving either propyl migration to nitrogen (eq 5) or extrusion of CO with bonding between the 2 position and the propyl moiety (eq 6).

The [M − CO] ion fragments further by loss of CH_3 or C_2H_4. The deuterium labeling results (Table I) show that the loss of CH_3 involves the terminal CH_3 group of the propyl chain and the C_2H_4 loss involves hydrogen transfer from C-3 of the propyl group with loss of C-2 and C-3 (eq 7). The appropriate metastable peaks for these reactions were observed. The fragmentation pattern of 2-propylpyridine[2] is



similar and on this basis the mechanism in eq 6 is assigned to this reaction.

[M − C_3H_6]·+.—The deuterium-labeling results (Table I) show that expulsion of C_3H_6 occurs with site-specific hydrogen transfer from the β carbon of the

(6) A. Ferretti and V. P. Flanagan, *J. Agr. Food Chem.*, **19**, 245 (1971).

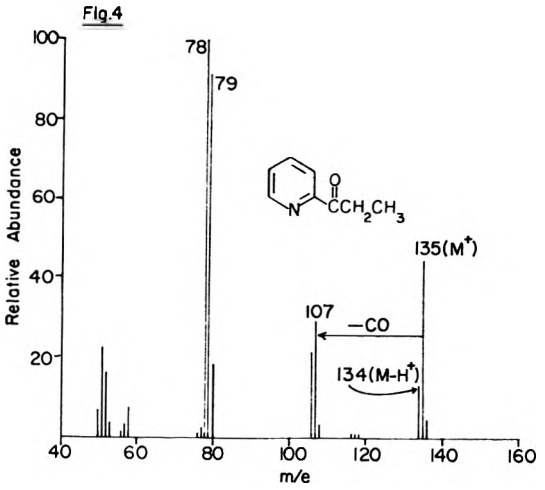


Figure 4.—70-eV mass spectrum of ethyl 2-pyridyl ketone (IV).

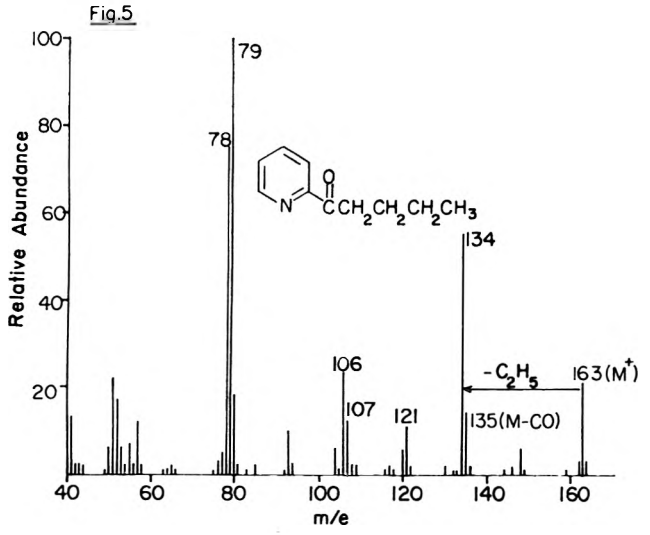


Figure 5.—70-eV mass spectrum of butyl 2-pyridyl ketone (V).

propyl group. On this basis, the structure i in scheme 3 is assigned to this ion. Fragmentation of this ion occurs by CO expulsion giving rise to an ion of composition $C_5H_5N\cdot^+$. This then expels HCN as expected for pyridine ions. When the itinerant hydrogen is replaced by deuterium, much greater HCN loss than DCN loss occurs in the second field-free region. This is consistent with the observation of Williams and Ronayne[7] that the hydrogens in the pyridine molecular ion become scrambled prior to HCN expulsion. The deuterium-labeling results (Table I) also show that the hydrogen transferred from the propyl chain to eventually form the $C_5H_5N\cdot^+$ ion arises largely from the β carbon. Thus, the expulsion of C_3H_6 initiates the major fragmentation pathway in propyl 2-pyridyl ketone.

The mass spectrum of butyl 2-pyridyl ketone (Figure 5) shows that when the McLafferty rearrangement to oxygen (*m/e* 121) involves transfer of a secondary hydrogen, it can compete with the McLafferty rearrangement to nitrogen (*m/e* 107). Although the *m/e* 121 and *m/e* 107 peaks are of similar intensity, the evidence for extensive further fragmentation of these ions (scheme 3) makes further comparisons of the two pathways dangerous.

In conclusion, propyl 2-pyridyl ketone exhibits

(7) D. H. Williams and J. Ronayne, *Chem. Commun.*, 1129 (1967).

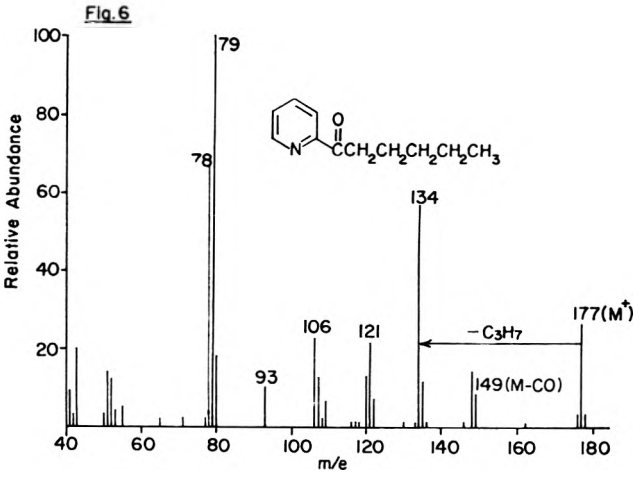


Figure 6.—70-eV mass spectrum of pentyl 2-pyridyl ketone (VI).

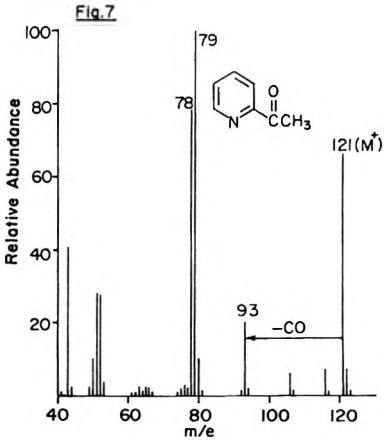


Figure 7.—70-eV mass spectrum of 2-acetylpyridine (VII).

fragmentation patterns strikingly different from those of the 3 and 4 isomers. These differences are attributable to interaction between the substituent and ring nitrogen.

Experimental Section

Low-resolution mass spectra were run on an AEI MS-9 spectrometer using a heated inlet system. High-resolution mass spectra were run on a Varian MAT 711 instrument. Technical assistance was provided by Mr. R. Ross and Miss A. Wegmann. All ionizing voltages are nominal.

The alkyl pyridyl ketones[8a,b] were prepared by reaction of the appropriate alkylmagnesium bromide with the appropriate cyanopyridine (Aldrich Chemical Co.) followed by acidic hydrolysis.[8b,9] The ketones were purified by glc.

The α-d_2 propyl pyridyl ketones were prepared by exchange of the unlabeled ketones on a 10% KOD/10% carbowax 6000 glc column.[10] β-d_2 and γ-d_3 propyl pyridyl ketones were prepared by reaction of the appropriate labeled propylmagnesium bromide and the appropriate cyanopyridine. After acidic hydrolysis, the ketones were purified by glc.

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Registry No.—I, 1701-71-9; II, 1701-70-8; III, 22971-32-0; IV, 3238-55-9; V, 7137-97-5; VI, 42203-03-2; VII, 1122-62-9.

(8) (a) *Beilstein*, XXI, pp 280–282; (b) J. F. Geldard and F. Lions, *Inorg. Chem.*, **2**, 270 (1963).

(9) (a) F. B. LaForge, *J. Amer. Chem. Soc.*, **50**, 2477 (1928); (b) C.-C. Chu and P. C. Teague, *J. Org. Chem.*, **23**, 1578 (1958); (c) I. Suzuki, *Chem. Pharm. Bull.*, **4**, 1479 (1956).

(10) M. Senn, W. J. Richter, and A. I. Burlingame, *J. Amer. Chem. Soc.*, **87**, 680 (1965).

SRN1 Phenylation of Nitrile Carbanions, and Ensuing Reactions. A New Route to Alkylbenzenes[1,2]

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Under stimulation by solvated electrons, the anions of aliphatic nitriles react with halobenzenes, phenyl diethyl phosphate, or phenyltrimethylammonium ion to form the α-phenyl derivative of the nitrile, the alkylbenzene that would result from decyanation thereof, and a benzylic radical dimer (*e.g.*, 1,2-diphenylethane when the cyanomethyl anion is used), as well as minor products. In the postulated mechanism, a phenyl radical combines with the nitrile anion to form the radical anion of an α-phenyl nitrile. The latter may lose an electron to appear as the nitrile, or it may expel cyanide ion forming a benzylic radical which dimerizes or is reduced to an alkylbenzene. The reaction has potential value in synthesis for the purpose of installing an alkyl group on an aromatic ring in place of a nucleofugic substituent or an amino or hydroxy group.

Aryl *radicals* are intermediates in the recently recognized SRN1 mechanism of aromatic nucleophilic substitution.[4] Supply of an electron to a substituted benzene, in which the substituent is a halogen or other suitable leaving group, forms a radical anion which then ejects the nucleofugic substituent, emerging as an aryl radical. The radical combines with a nucleophile to form a new radical anion which, upon getting rid of a surplus electron, becomes a stable nucleophilic substitution product.

An alkali metal dissolved in liquid ammonia exists for the most part as alkali metal cations and solvated electrons,[5] and is effective in provoking SRN1 reactions. Among the nucleophiles successfully involved in substitutions by this mechanism are the amide ion,[6,7] ketone enolate ions,[8,9] and hydrocarbon-derived carbanions such as the fluorenide ion.[10]

Heretofore, aromatic SRN1 reactions involving α-cyanocarbanion nucleophiles have received only preliminary attention. Kim and Bunnett[6] observed chlorobenzene to react with the cyanomethyl anion and potassium metal in liquid ammonia to form phenylacetonitrile, toluene, benzene, and aniline. Rossi[11] conducted a similar experiment, with iodobenzene instead of chlorobenzene, and obtained a substantial amount of 1,2-diphenylethane (DPE)[12] as well as the other products mentioned.

We now report a study of several reactions of this general type, involving six monosubstituted benzenes and the carbanions from seven aliphatic nitriles. The results are of interest to preparative chemistry. Also, they illuminate significant features of the reaction mechanism.

Most of our observations conform to the generalized scheme of eq 1.

$$\mathrm{PhX} + \underset{\mathrm{CN}}{\mathrm{RCH^-}}\,\mathrm{K^+} \xrightarrow[\mathrm{NH_3}]{\mathrm{K}} \mathrm{PhCHR} + \mathrm{PhCH_2R} + \underset{\mathrm{CN}}{\mathrm{Ph_2CHR}} + \underset{\mathrm{R}\quad\mathrm{R}}{\mathrm{PhCH{-}CHPh}} + \mathrm{C_6H_6} + \mathrm{C_6H_5NH_2} \quad (1)$$

Results

Our two principal series of experiments are summarized in Tables I and II.

Table I concerns several experiments involving the cyanomethyl anion, from reaction of acetonitrile with an equimolar amount of KNH_2. The several runs differ in the identity of the monosubstituted benzene employed, in the temperature, in the proportions of reactants, and in the method for conducting the experiment. In some runs, solvated electrons (from the dissolved potassium metal[5]) were constantly in large excess over the aromatic substrate, while in others the concentration of solvated electrons was kept quite low.

The products obtained from reactions with cyanomethyl anion (eq 1, R = H) are those described by earlier workers, as mentioned, plus a small amount of diphenylmethane (DPM).[12] Toluene is prominently formed, in yields ranging from 14 to 49%. Benzene is also prominent, in yields from 8 to 44%. DPE is formed in considerable amount in some runs but to a minor extent in others; yields vary from 3 to 40%. The same can be said for phenylacetonitrile (PAN), the yields of which are from 2 to 31%. The highest yield of DPM encountered was 7%, and in some runs only trace amounts were formed. Aniline yields are also very small.

Despite the considerable differences in conditions and in results among the several runs of Table I, it is difficult to correlate product patterns with experimental variables. It should be noted that our procedures for the addition of potassium metal and/or aromatic substrate during the course of a run were not such as to provide close control of addition rates or of solvated electron concentration in the reaction mixture. In consequence, there may have been substantial variation of the concentration of solvated electrons and/or of reaction intermediates, even between runs ostensibly conducted by the same technique. For exceedingly fast reactions, as these are, such variation plausibly would have a significant effect on product proportions.

The experiments of Table II concern carbanions derived from other nitriles. Again there is substantial variation of product patterns between runs, and again

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(3) Grateful recipient of a fellowship, 1971–1972, from the Schweizerische Stiftung für Stipendien auf dem Gebiete der Chemie.

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(12) Glossary of acronyms: BME, benzyl methyl ether; DPE, 1,2-diphenylethane; DPM, diphenylmethane; MPAN, 3-methylphenylacetonitrile; $MPAN^-$, anion of MPAN; PAN, phenylacetonitrile; PBN, α-phenylbutyronitrile.

TABLE I

REACTIONS OF MONOSUBSTITUTED BENZENES WITH CYANOMETHYL ANIONS, PROVOKED BY POTASSIUM METAL IN LIQUID AMMONIA

Run no.	Registry no.	Substituent	PhX, mmol	CH_2CNK, mmol	K, mmol	NH_3, ml	Temp, °C	Method[a]	Ether, ml	Yield, % Toluene	PAN[b]	DPM[c,e]	DPE[d,e]	C_6H_6	Aniline
1	462-06-6	F	25	115	63	150	−33	A[f]	80	44	2	Trace	8	31	~1
2		F	14	76	40	110	−33	A[g]	65	30	3	0.7	3	44	*h*
3		F	40	123	107	250[i]	−78	AB[j]		49	3	4	23	10	2
4	108-90-7	Cl	22	87	55	130	−33	A[k]	70	40	7	2	12	20	~2
5		Cl	60	150	69	50	−33	A[l]		18	31	~2	5	17	*m*
6		Cl	64	160	95	50	−33	B		24	24	~3	9	17	*m*
7		Cl	63	75	110	50	−33	B		16	19	5	3	27	*m*
8		Cl	165	165	330	50	−78	B		14	19	3	5	30	
9		Cl	67	80	81	50	−78	B		31	18	5	14	26	*m*
10		Cl	30	88	37 (15)[n]	60	−78	B		27	12	2	40	8	
11		Cl	64	80	87 (34)[o]	60 (150)	−78	AB		35	22	7	12	18	
12		Cl	146	49	254 (85)[p]	50 (250)	−33	AB		46	3	3	7	22[q]	10[q]
13	108-86-1	Br	27	106	69	150	−33	B	70	26	5	3	14	43	~1
14	591-50-4	I	25	95	64	150	−33	B	70	14	5	4	25	32	*m*
15	2510-86-3	$OPO(OEt)_2$	50	80	90 (25)[r]	50	−78	AB		43	3	1	7	11	~3[s]
16	98-04-4	$N(CH_3)_3{}^+I^-$	63	78	85	50	−78	AB[t]		26	5	4	19	21	~7

[a] Methods: A, the monosubstituted benzene, neat or in solution, was slowly added to a solution of CH_2CNK and K metal; AB, the monosubstituted benzene, neat or in solution, was slowly added to a solution of CH_2CNK, and K metal was added slowly in small portions so as to keep K metal in more or less constant excess; B, to a solution of CH_2CNK and the monosubstituted benzene, a small piece of K metal was added and then, after the blue color had vanished, another small piece, etc. [b] PAN = phenylacetonitrile. [c] DPM = diphenylmethane. [d] DPE = 1,2-diphenylethane. [e] The yield calculation takes account of the fact that 2 mol of C_6H_5X are required to form 1 mol of DPM or DPE. [f] C_6H_5F in ether (5 ml) added during 30 min; quenched with C_6H_5COONa, then NH_4Cl. [g] C_6H_5F in ether (40 ml) added. [h] Not sought. [i] Not distilled before use. [j] C_6H_5F in NH_3 (150 ml) added during 90 min; quenched with C_6H_5COONa, then NH_4Cl. [k] C_6H_5Cl in ether (5 ml) added during 40 min. [l] C_6H_5Cl added as fast as possible (during 5 min); vigorous refluxing. [m] A tiny peak at the retention time for aniline. [n] After addition of 37 mmol of K in especially small pieces, ice was added until the orange color faded, and then a further 15 mmol of K. [o] Half the C_6H_5Cl was added, then about 44 mmol of K, then the rest of the C_6H_5Cl, then about 43 mmol of K, then 390 mmol of ice (causing the orange color to fade), then 34 mmol of K. [p] After addition of 254 mmol of K, 670 mmol of ice and 200 ml of ammonia were added, and then 85 mmol of K (with shaking of the thick slurry). [q] Based on C_6H_5Cl. [r] After addition of 90 mmol of K, ice was added and then 25 mmol of K. [s] 4% of phenol also obtained. [t] K added in two portions, each followed by half the substrate.

TABLE II

REACTIONS OF MONOSUBSTITUTED BENZENES WITH ANIONS FROM NITRILES OF STRUCTURE RCH_2CN, PROVOKED BY POTASSIUM METAL IN LIQUID AMMONIA

Run no.	R	X of C_6H_5X	Registry no.	[RCHCN⁻], M	$[C_6H_5X]$, M	K, M[b]	Temp, °C	Method[a]	Yield, % Ph-CH_2R	PhCH-RCN	Ph_2-CHR	Ph-CHCRHRPh[c] Meso	Rac	C_6H_6	Aniline
17	CH_3	Cl	42117-12-4	1.38	0.87	2.0 (0.65)	−78	AB	22	*d*	*d*	5	5	34	5
18	CH_3	Cl		1.40	2.80	3.98	−33	AB	34	6	7	6	6	38[e]	10[e,f]
19	CH_3	$OPO(OEt)_2$		1.16	0.73	1.7 (0.1)[g]	−78	AB	14	*d*	*d*	7	7	35	5[h]
20	CH_3	$N(CH_3)_3{}^+I^-$		1.07	0.67	1.26	−78	AB[i]	8	*d*	*d*	8	8	36	3
21	C_2H_5	F	42117-13-5	1.28	0.43	1.09	−78	AB[j]	28	4	*d*	13	13	35	13
22	C_2H_5	Cl		1.37	4.1	6.04	−33	AB[k]	37	0.5	13			27[e]	3[e]
23	C_2H_5	I		0.30	0.16	0.20	−33	A	6	29	2	12	12	27	*l*
24	C_2H_5	$OPO(OEt)_2$		1.04	0.15	0.30	−33	B	28	4	0.2	1	1	20	*n*
25	$(CH_3)_2$[o]	Br	42117-14-6	0.98	2.94	5.3	−33	AB	27					31	7
26	*n*-C_3H_7	Cl	42117-15-7	1.09	3.30	6.3 (1.7)	−33	AB	56	*d*	*m*	*m*	*m*	38[e]	14[e]
27	*n*-C_3H_7	$OPO(OEt)_2$		1.58	0.60	1.45 (0.2)	−33	BA[p]	38	10	*d*	*d*	*d*	27	*q*
28	$(CH_3)_2CH$	Cl	42117-16-8	1.64	3.2	4.9	−33	AB	37[r]	19[r]	12	*d*	*d*	31[e]	~5[e]
29	$(CH_3)_2CH$	$OPO(OEt)_2$		1.80	0.72	1.48	−78	B	20	7				36	~2[s]
30	$(CH_3)_2CH$	$OPO(OEt)_2$		1.30	0.52	0.85 (0.23)	−33	BA[p]	31	10	*d*	*d*	*d*	32	*d*
31	$(CH_3)_2CH$	$OPO(OEt)_2$		0.63	0.20	0.70	−78	AB[j]	22	15	*d*	*d*	*d*	41	2
32	C_6H_5	$OPO(OEt)_2$	18802-89-6	1.44	1.12	1.47	−78	AB	12	3[t]	6			25	1[u]
33	C_6H_5	$N(CH_3)_3{}^+I^-$		1.50	1.19	2.08	−78	AB	17		12			43	1[v]

[a] See footnote *a*, Table I. [b] Concentration that would have prevailed had there been no reaction; the K indicated in parentheses was added after ice. [c] The glpc peaks for racemic and meso stereoisomers were not fully resolved, but were approximately equal in area; the sum of the two could be measured accurately, and was arbitrarily allocated in equal parts to meso and racemic. [d] A tiny peak at the expected retention time. [e] Based on C_6H_5Cl. [f] 4% of C_6H_5Cl recovered. [g] The K indicated in parentheses was added after ice and 150 ml of ether. [h] Phenol (2%) also formed. [i] Excess K present at the end was destroyed by addition of ice. [j] The C_6F_5X, in 150 ml of NH_3, was added during 90 min. [k] After reaction, NH_3 was added to increase the volume from *ca.* 50 ml to 200 ml, followed by 10 g of ice and 75 mmol of K. [l] 12% of C_6H_5I recovered. [m] Detected qualitatively. [n] Phenol (29%) and some 4-amino-3-cyano-3-heptene also formed. [o] Isobutyronitrile. [p] Method BA: the C_6H_5X and K metal were both added in portions, but so as always to keep C_6H_5X in excess. [q] Phenol (8%) also formed. [r] After decyanation of the isolated product mixture, 50% of isobutylbenzene and a mere trace of 2-phenyl-3-methylbutanonitrile were obtained. [s] Phenol (6%) also formed. [t] Identification solely by glpc retention time. [u] Phenol (12%) also formed; 80% of PAN recovered. [v] 76% of PAN recovered.

the variation is often difficult to correlate with differences in reaction participants or conditions. Alkylbenzenes, $PhCH_2R$, corresponding to toluene in Table I, are prominent products of most runs, as is benzene. Phenyl derivatives of the starting nitriles are formed in significant amounts in some runs but only in trace amounts in others. 1,1-Diphenylalkanes, Ph_2CHR, appear to a significant extent in only a few runs, most of which involve the aromatic substrate in excess. Dimeric products, meso and racemic PhCHRCHRPh, are formed in amounts totalling as high as 26% in reactions of the anions from propio- and butyronitrile, but only in minor amounts in the other runs. The yields of aniline are variable, but never large.

Photostimulated Reactions.—Inasmuch as SRN1 reactions of halobenzenes with acetone enolate ion

TABLE III

REACTIONS OF BROMOBENZENE WITH CYANOMETHYL ANION, AND REACTIONS WITH MIXED CYANOMETHYL AND ACETONE ENOLATE IONS, IN LIQUID AMMONIA AT −33°

Run no.	[C_6H_5Br], M	[KNH_2], M[a]	[CH_3CN], M[a]	[Acetone], M[a]	Reaction time, min	Promoter	Yield, % C_6H_5Br[b]	C_6H_6	Toluene	PAN	DPM	DPE	Phenylacetone
34	0.08	0.46	0.46		120	Dark	98	1					
35	0.08	0.52	0.54		120	$h\nu$	62	1	2	8	1	18	
36	0.07	0.74	0.68	0.07	125	$h\nu$	44	3	2	14	1	36	<0.3
37	0.07	0.92	0.46	0.46	120	$h\nu$	55	2	3	8	0.6	19	<2[c]
38	0.07	0.90	0.46	0.46	~5[d]	K[d]		4	22	12	1	32	<2[c,e]

[a] Concentration that would have prevailed had there been no reaction of CH_3CN or acetone with KNH_2. [b] Recovered. [c] Precise glpc yield determination difficult because of partial overlap with other peaks. [d] Potassium metal (0.15 mol) added bit by bit. [e] 1-Phenyl-2-propanol (*ca.* 5%) also obtained.

TABLE IV

ATTEMPTS TO OBSERVE REACTIONS OF BENZYL RADICALS WITH THE ANION OF 3-METHYLPHENYLACETONITRILE IN REFLUXING AMMONIA

Run no.	Radical source: Identity	Concn, M	[MPAN$^-$], M[a]	[K], M[b]	Method[c]	Yield, % Toluene	PAN	DPE	Other products
40	BME[d]	0.30		0.78	B	71		29	
41	BME[d]	0.32	0.32	0.60	B	70	*e*	26	*f*
42	C_6H_5Cl / CH_2CN^-	0.45 / 1.35	0.45	0.79	B	42	5[g]	29	*h*

[a] MPAN$^-$ = anion of 3-methylphenylacetonitrile. [b] Concentration that would have prevailed had there been no reaction. [c] See footnote *a*, Table I. [d] BME = benzyl methyl ether. [e] 3-Methylphenylacetonitrile (73%) recovered. [f] Benzyl methyl ether (1%) recovered. [g] 3-Methylphenylacetonitrile (93%) recovered. [h] Also obtained were C_6H_5Cl (8%) and C_6H_6 (15%).

occur not only as provoked by solvated electrons,[8] but also with great facility under stimulation by near-ultraviolet light,[9] the action of light on mixtures of bromobenzene and cyanomethyl anion was investigated. Table III provides an overview of the results.

Negligible reaction occurs in the dark (run 34). However (run 35), there is appreciable reaction during 2 hr of exposure to near-ultraviolet radiation in the photochemical reactor. The reaction is sluggish, though, for only 38% of the bromobenzene reacts under those conditions. In contrast, the reaction of bromobenzene with acetone enolate ion under similar conditions is complete within 50 min or less.[9] The product pattern resembles that from potassium metal stimulated reactions of the cyanomethyl anion with bromobenzene, with the important exception that the benzene and toluene yields are quite small relative to those of PAN and DPE.[12]

It was thought that photochemical reaction of bromobenzene with mixtures of the cyanomethyl and acetone enolate ions might occur more readily than with the cyanomethyl anion alone. There was found to be a somewhat greater consumption of bromobenzene in reaction with mixtures of the carbanions (runs 36 and 37) than with the cyanomethyl anion alone (run 35), but the increase was slight. Remarkably, the photochemical reactivity of bromobenzene with acetone enolate ion is severely depressed by admixture of cyanomethyl anions; compare run 37 with typical runs reported by Rossi and Bunnett.[9]

Comparison of Reactivity toward Phenyl Radical.—The products obtained from photochemical reaction of bromobenzene with an equimolar mixture of the cyanomethyl and acetone enolate ions are mainly those attributable to reaction with the former of these species. The same qualitative result was obtained from potassium metal stimulated reaction of bromobenzene with a mixture of these nucleophiles (run 38). The reactivity of the cyanomethyl anion toward the phenyl radical is thus demonstrated to be much greater than that of acetone enolate ion.

It is noteworthy that the phenylacetone–1-phenyl-2-propanol product ratio from potassium metal stimulated reaction of bromobenzene with this mixture of nucleophiles (run 38) was *ca.* 0.4, much lower than observed[8] in reaction with acetone enolate ion uncontaminated with cyanomethyl anion.

Attempts to Observe Reactions of Benzyl Radicals with a Carbanion.—Conceivably (*vide infra*), DPE might have been formed by a reaction pathway involving combination of benzyl radical with the phenylacetonitrile anion. In order to check this possibility, the experiments outlined in Table IV were performed.

Run 40 concerns the action of potassium metal on benzyl methyl ether. The formation of DPE in 29% yield indicates that benzyl radicals are, at least in part, intermediates in this reaction.[13]

The objective of runs 41 and 42 was to see whether benzyl radicals are able to combine with the anion of 3-methylphenylacetonitrile (MPAN) rapidly enough to compete with other processes. As discussed below, such combination would be expected to lead ultimately to 1-(3′-methylphenyl)-2-phenylethane. In run 41,

(13) Schorigin and Skoblinskaya[14a] obtained DPE from the action of sodium in ammonia on benzyl phenyl ether. They, and later Burwell,[14b] attributed this result to two-electron cleavage of the ether to phenoxide and benzyl anions, followed by S$_N$2 reaction of benzyl anion with the ether, displacing phenoxide ion. However, that explanation would require the S$_N$2 reaction to be faster than proton capture by benzyl anion from the ammonia solvent, which is unlikely. Waters[15] perceived years ago that one-electron cleavage of benzyl ethers, to generate benzyl radicals, can occur. The sodium–ammonia cleavage of benzyltrimethylammonium ion to form bibenzyl in yield as high as 70% has been interpreted preferentially in terms of a radical mechanism.[16]

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TABLE V
REACTIONS OF PHENYLACETONITRILE (PAN) AND α-PHENYLBUTYRONITRILE (PBN) WITH ALKALI METALS IN LIQUID AMMONIA AT −33°

Run no.	Substrate	[Substrate], M	Alkali metal	[K] or [Na], M[a]	Other substance: Identity	Other substance: Concn, M	Method[b]	Quench	Yield, %: Educt[c]	Yield, %: Toluene
43	PAN	0.10	K	0.11			B	NH_4Cl	46	52[d]
44		0.22	Na	0.45			A	C_6H_5COONa[e]	51	52[d]
45		0.21	Na	0.43			A	Ice	9	91[d]
46		0.25[f]	K	0.63	KNH_2	0.5[f]	B	[g]	100	0.4
47		0.30[f]	K	0.85	KNH_2	0.65[f]	[h]	Ice	49	49
48		0.20	Na	0.44	H_2O	2.0	B			98
49		0.20	Na	~0.87	H_2O	2.0	B			36[i]
50	PBN	0.20	K	0.25			B	NH_4Cl	48	45[j]
51		0.10	K	0.20	$(NH_4)_2SO_4$	0.025[k]	B		36	53[j]
52		0.10	K	0.22	$(NH_4)_2SO_4$	0.17[k]	B		6	67[j]
53		0.10	K	0.23	CH_3OH	[l]	B[l]	[l]		73[j]

[a] Concentration that would have prevailed had there been no reaction. [b] See footnote *a*, Table I. [c] PAN or PBN. [d] 1–2% of DPE also formed. [e] Followed by NH_4Cl. [f] Concentration that would have prevailed at start had there been no reaction of PAN with KNH_2. [g] After 45 min, the blue color had vanished, and NH_4Cl was added to neutralize. [h] To PAN and KNH_2 in NH_3, K metal was added all at once, followed quickly by ice. [i] *Ca.* 56% of another product, probably 2,5-dihydrotoluene,[21] was obtained. [j] 1-Phenylpropane. [k] $(NH_4)_2SO_4$ is insoluble; the concentration that would have prevailed had it dissolved is given. [l] Enough K metal to give a persistent blue color was added, then enough CH_3OH to discharge the color, then more K metal, etc.; total CH_3OH about 5 ml.

the benzyl radical was generated by reaction of potassium metal with benzyl methyl ether and, in run 42, by the action of potassium metal on a mixture of chlorobenzene and cyanomethyl anion (see the discussion below). Although DPE was a prominent product of both reactions, no 1-(3′-methylphenyl)-2-phenylethane was detectable as a product in run 41 or 42. We established that as little as 0.1% of this product would have been detectable. We conclude that benzyl radical is unreactive with the anion of MPAN.

Decyanation of Nitriles.—We found it necessary to give some experimental attention to this topic, which is relevant both to experimental procedures for our reactions and to theoretical interpretation.

Although instances of the decyanation of nitriles (RCN → RH) through the action of alkali metals were recorded decades ago,[17] only in recent years has the reaction received much forthright attention.[18–20]

We investigated the decyanation of phenylacetonitrile (PAN) and α-phenylbutyronitrile (PBN) in liquid ammonia medium. Results are summarized in Table V.

Runs 44 and 45 are especially illuminating. The conditions for these runs closely resemble those for an experiment of Arapakos, *et al.*,[18b] but they differ in the manner of quenching the reaction mixture at the end of the experiment. Run 44 was treated first with excess sodium benzoate, which destroys solvated electrons,[21,22] and then neutralized with NH_4Cl. Run 45 was quenched directly with ice, while the reaction mixture was still blue owing to solvated electrons; Arapakos, *et al.*,[18b] also quenched with ice. The sodium benzoate quenched reaction gave a 52% yield of decyanation product (toluene), in nearly perfect accord with the balanced equation (eq 2). The ice-quenched reaction

$$2RCH_2CN + 2Na \longrightarrow RCH_3 + RCHCN^-Na^+ + NaCN \quad (2)$$

afforded 91% of toluene, in agreement with the 90% reported by Arapakos, *et al.*

These experiments imply, first, that the conjugate base of the nitrile resists decyanation by solvated electrons in ammonia. This implication is confirmed by run 46, in which a twofold excess of KNH_2 with respect to PAN was present. Such an excess converted the PAN entirely to its conjugate base. An excess of potassium metal was employed, but the reaction mixture was allowed to stand until the metal had all reacted to form KNH_2 under catalysis by the iron present in the medium; iron had been used to catalyze formation of KNH_2 in the beginning of the experiment. When the blue color had vanished, the mixture was neutralized with NH_4Cl and it was possible to recover nearly all the PAN originally introduced. A mere trace of toluene was formed.

A further implication of runs 44 and 45 is that a substantial amount of decyanation of the nitrile conjugate base occurs during quenching with ice if solvated electrons are still present. Substantiation is provided by the results of run 47 which, like run 46, had excess KNH_2 present at the time the potassium metal was introduced, but which was quenched by ice before there had been time for much of the metal to be converted to KNH_2. In run 47, half of the PAN was decyanated and half was recovered.

Run 48 was organized so that excess water was present during addition of alkali metal. It gave a superb yield (98%) of toluene. However, when decyanation is conducted in wet ammonia with use of more than 2 mol of alkali metal per mole of nitrile, a complication of Birch reduction of an unsaturated decyanation product can become serious, as demonstrated by run 49.

These experiments indicate that decyanation in liquid ammonia is optimally conducted by dissolving the nitrile in ammonia containing water and adding just 2 mol of alkali metal per mole of nitrile. We had occasion to employ approximately these conditions of decyanation in our synthesis of 1-(3′-methylphenyl)-2-

(17) M. M. Rising and E. W. Lowe, *J. Amer. Chem. Soc.*, **52**, 2524 (1930); L. A. Walter and S. M. McElvain, *ibid.*, **56**, 1614 (1934); L. I. Smith and L. J. Spillane, *ibid.*, **65**, 202 (1943).

(18) (a) P. G. Arapakos, *J. Amer. Chem. Soc.*, **89**, 6794 (1967); (b) P. G. Arapakos, M. K. Scott, and F. E. Huber, Jr., *ibid.*, **91**, 2059 (1969).

(19) S. Bank and S. P. Thomas, *Tetrahedron Lett.*, 305 (1972).

(20) C. Fabre and Z. Welvart, *Bull. Soc. Chim. Fr.*, 2620 (1965); *C. R. Acad. Sci., Ser. C*, **270**, 1887 (1970); H. Thies, H. Schoenenberger, and P. K. Qasba, *Arch. Pharm. (Weinheim)*, **302**, 897 (1969); T. Cuvigny, M. Larcheveque, and H. Normant, *C. R. Acad. Sci.*, **274**, 797 (1972); A. R. Doumaux, Jr., *J. Org. Chem.*, **37**, 508 (1972).

(21) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(22) S. S. Hall, S. D. Lipsky, F. J. McEnroe, and A. P. Bartels, *J. Org. Chem.*, **36**, 2588 (1971).

phenylethane, described in the Experimental Section; this product was obtained in 78% yield by decyanation of 2-(3′-methylphenyl)-3-phenylpropanonitrile.

As for the experiments with PBN in Table V, run 50 resembles run 43 in that only a little more than 1 mol of alkali metal was used per mole of nitrile; both runs gave about about 50% decyanation, in accordance with eq 2. Runs 51–53 test the efficacy of decyanation when proton donors other than water are present during addition of the alkali metal; they suggest that ammonium sulfate and methanol are inferior to water for that purpose.

Discussion of Reaction Mechanisms

The SRN1 mechanism,[4] adapted to the present situation, is sketched in eq 3–6. First (eq 3) an elec-

$$\mathrm{PhX} + \text{electron source} \longrightarrow [\mathrm{PhX}]\cdot^- + \text{residue} \quad (3)$$

$$[\mathrm{PhX}]\cdot^- \longrightarrow \mathrm{Ph}\cdot + \mathrm{X}^- \quad (4)$$

$$\mathrm{Ph}\cdot + \mathrm{RCHCN}^- \longrightarrow \left[\mathrm{PhCHCN}\right]\cdot^- \quad (5)$$

$$\left[\mathrm{PhCHCN}\right]\cdot^- + \mathrm{PhX} \longrightarrow \mathrm{PhCHCN} + [\mathrm{PhX}]\cdot^- \quad (6)$$

tron source, which is the solvated electron in most of our experiments, furnishes an electron to the aromatic substrate. The resulting radical anion (eq 4) undergoes scission, ejecting the nucleofugic group and appearing as an aryl radical. Then (eq 5) the radical combines with an α-cyanoalkyl anion. The new radical anion thereby formed is metastable, and may transfer a surplus electron to another molecule of the aromatic substrate (eq 6), forming an α-phenyl nitrile, an observed product, as well as the same radical anion generated in eq 3. Because it is relatively acidic, the nitrile will then undergo the acid–base reaction of eq 7 rather completely.

$$\mathrm{PhCHCN} + \mathrm{RCHCN}^- \rightleftharpoons \mathrm{PhC{=}CN}^- + \mathrm{RCH_2CN} \quad (7)$$

Further steps are required in order to account for the other products actually formed (*cf.* eq 1). The steps of eq 8–18 are postulated. The key step (eq 8) is one

$$\left[\mathrm{PhCHCN}\right]\cdot^- \longrightarrow \mathrm{PhCH}\cdot + \mathrm{CN}^- \quad (8)$$

$$\mathrm{PhCH}\cdot + \mathrm{PhCH}\cdot \longrightarrow \mathrm{PhCH{-}CHPh} \quad (9)$$

$$\mathrm{PhCH}\cdot + \mathrm{e}^-_{\mathrm{sol}} \longrightarrow \mathrm{PhCH}{:}^- \quad (10)$$

$$\mathrm{PhCH}{:}^- + \mathrm{NH_3} \longrightarrow \mathrm{PhCH_2R} + \mathrm{NH_2}^- \quad (11)$$

$$\mathrm{Ph}\cdot + \mathrm{e}^-_{\mathrm{sol}} \longrightarrow \mathrm{Ph}{:}^- \quad (12)$$

$$\mathrm{Ph}{:}^- + \mathrm{NH_3} \longrightarrow \mathrm{C_6H_6} + \mathrm{NH_2}^- \quad (13)$$

$$\mathrm{PhCH}\cdot + \mathrm{Ph}\cdot \longrightarrow \mathrm{Ph_2CHR} \quad (14)$$

$$\mathrm{PhC{=}CN}^- + \mathrm{Ph}\cdot \longrightarrow \left[\mathrm{Ph_2CCN}\right]\cdot^- \quad (15)$$

$$\left[\mathrm{Ph_2CCN}\right]\cdot^- \longrightarrow \mathrm{Ph_2C}\cdot + \mathrm{CN}^- \quad (16)$$

$$\mathrm{Ph_2C}\cdot + \mathrm{e}^-_{\mathrm{sol}} \longrightarrow \mathrm{Ph_2C}{:}^- \quad (17)$$

$$\mathrm{Ph_2C}{:}^- + \mathrm{NH_3} \longrightarrow \mathrm{Ph_2CHR} + \mathrm{NH_2}^- \quad (18)$$

in which the nitrile radical anion which was formed in step 5 ejects cyanide ion and thereby is transformed into a benzylic radical. In steps 9 and 14, the benzylic radical dimerizes or combines with phenyl radical to form products such as reported in Tables I and II.

No doubt the scheme should be expanded to include a step, parallel to eq 9, in which the two benzylic radicals (except when R = H) react by disproportionation, but it is known[23] that disproportionation of α-alkylbenzyl radicals occurs only about one tenth as fast as combination.

The formation of toluene and other products of type $\mathrm{PhCH_2R}$ is attributed to acquisition of an electron by the benzylic radical (eq 10) to form an anion, which then takes (eq 11) a proton from the ammonia solvent. Likewise, the genesis of benzene is ascribed to the sequence of steps 12 and 13. Steps analogous to eq 10 and 12 have been proposed in other studies.[24]

Two routes to DPM and other products of type $\mathrm{Ph_2CHR}$ are postulated. One route is combination of phenyl radical with a benzylic radical (step 14). The other involves phenylation (in step 15) of the anion of the α-phenylated nitrile produced in steps 3–6, spontaneous scission (in step 16) of the radical anion thus formed, and finally reduction (in steps 17 and 18) of the benzhydrylic radical so generated. The feasibility of the second route is indicated by runs 32 and 33 of Table II in which the starting nitrile has an α-phenyl substituent. However, we see no grounds to exclude the first route.

Two further steps (19 and 20) likely play some part

$$\mathrm{PhCH}\cdot + \mathrm{R'H} \longrightarrow \mathrm{PhCH_2R} + \mathrm{R}\cdot' \quad (19)$$

$$\mathrm{Ph}\cdot + \mathrm{R'H} \longrightarrow \mathrm{C_6H_6} + \mathrm{R}\cdot' \quad (20)$$

when diethyl ether or other good hydrogen atom donor is a component of the system. These are plausible, but we cannot assert that our experiments provide evidence for them because the same products (*e.g.*, benzene and toluene) are formed in comparable yield when ether is absent.

The production of aniline is ascribed to combination of phenyl radical with amide ion followed by disposal of a surplus electron. That aromatic primary amines are readily formed in SRN1 reactions is reported elsewhere.[6,7]

It is possible to exclude some conceivable steps. The possibility that phenyl radical abstracts a hydrogen atom from ammonia to form benzene (step 21) is rejected because photostimulated SRN1 reactions of bromobenzene with acetone enolate ion in liquid ammonia afford phenylacetone in high yield without appreciable formation of benzene as a by-product, unless a good hydrogen atom donor (such as isoprop-

(23) M. J. Gibian and R. C. Corley, *J. Amer. Chem. Soc.*, **94**, 4178 (1972).
(24) J. F. Garst, *Accounts Chem. Res.*, **4**, 400 (1971); G. D. Sargent, *Tetrahedron Lett.*, 3279 (1971).

$$Ph\cdot + NH_2^- \not\rightarrow C_6H_6 + H_2N\cdot \quad (21)$$

$$Ph\cdot + Ph\cdot \not\rightarrow Ph\text{–}Ph \quad (22)$$

$$PhC(R)=CN^- + PhCH(R)\cdot \not\rightarrow \left[PhCH(R)\text{–}C(CN)Ph\right]\cdot^- \quad (23)$$

oxide ion) is also present.[9] That phenyl radical dimerization (step 22) plays no substantial role is shown by the undetectability of biphenyl as a product. The possibility that DPE and other benzylic radical dimers are formed by alkylation of an α-phenyl nitrile anion (step 23) followed by cyanide ion loss, etc., is discarded because of the unreactivity of benzyl radical with the anion (MPAN$^-$) of 3-methylphenylacetonitrile, as shown by runs 41 and 42, Table IV.

Relationship of Product Distribution to Nucleofugic Group.—The chief products of potassium metal stimulated reaction of halobenzenes with acetone enolate ion are phenylacetone and 1-phenyl-2-propanol.[8] There is a remarkable relationship between the phenylacetone–1-phenyl-2-propanol product ratio and the nucleofugic substituent, in the sense that mainly the ketone is obtained from iodobenzene and mainly the secondary alcohol from fluorobenzene, with the others falling between. This has been attributed to competition between two reaction pathways available to the radical anion formed by addition of phenyl radical to the enolate ion: it may be reduced to alkoxide ion, or it may transfer an electron to another halobenzene molecule (in a step analogous to eq 6) and appear as ketone.[8] The latter pathway is more rapidly traversed the larger the halogen,[25] and that accounts for the predominance of the ketone product from iodobenzene.

One might anticipate a similar competition in the present series of reactions, specifically, between steps 6 and 8. Accordingly, one might expect, in reactions of halobenzenes with the cyanomethyl anion (Table I), to get relatively more phenylacetonitrile with larger halogens and relatively more of products derived from benzyl radical (toluene and DPE)[12] with smaller halogens. (Since DPM might be formed either from benzyl radical or from the anion of PAN and is a minor product anyhow, let us for the moment ignore it.) Very crudely the observed yields conform to these expectations: the lowest yields of PAN and relatively high yields of toluene and DPE are obtained from fluorobenzene. However, there is no clear trend in the product patterns from chloro-, bromo-, and iodobenzenes. Evidently other factors, perhaps details of reagent addition technique, exert a greater influence on product proportions.

Decyanation of Nitriles.—The action of solvated electrons on nitriles to effect decyanation is accounted for by an initial step in which the nitrile accepts an electron to become a radical anion analogous to that formed in step 5, followed by scission to radical and cyanide ion (step 8) and reduction of the radical to hydrocarbon (steps 10 and 11). The amide ion formed in step 11 undergoes an acid–base reaction with the nitrile, converting it to its anion which is resistant to solvated electrons (*cf.* run 46, Table V). Therefore the stoichiometry of eq 2 prevails.

However, during quenching with water the anion can be reconverted to the molecular nitrile which can accept solvated electrons, etc., enabling overall decyanation yields to exceed the 50% called for by eq 2. It should be noted that run 44, in which sodium benzoate was added to absorb electrons before acidification (with NH_4Cl), conforms closely to the specifications of eq 2. Also, if an acid (*e.g.*, water) is present during reaction of the nitrile with the alkali metal, it prevents the nitrile from being tied up as its conjugate base, and decyanation is facilitated.

It is remarkable that very little DPE appeared as a product of decyanation of PAN (Table V), in contrast to the substantial amounts formed in the SRN1 phenylation of cyanomethyl anion (Table I). At most, 2% of DPE was obtained in the decyanation experiments, and DPE was not detectable as a product of the decyanations which occurred in the presence of water. Presumably both phenylation of cyanomethyl anion and decyanation of PAN occur *via* PAN radical anions. If two reactions involve the same intermediate, they ought to give the same products under the same conditions. We are puzzled.

Photostimulated Reactions.—Whereas bromobenzene reacts rapidly and efficiently with acetone enolate ion under photostimulation,[9] its reaction with the cyanomethyl anion responds only sluggishly to illumination; see Table III. Responsible for the difference is the proclivity of the $[PhCH_2CN]\cdot^-$ radical anion to expel cyanide ion and form benzyl radical (eq 8). In this system, the benzyl radical is rather ineffective in propagating a reaction chain. It is not very reactive with nucleophiles, as we have shown in other studies, and tends to accumulate until it dimerizes (eq 9) or takes an electron and is reduced (eq 10); both are termination steps.

Thus while the photochemical reaction of bromobenzene with acetone enolate ion has a long propagating chain, as shown by its sensitivity to radical trapping agents,[9] its reaction with cyanomethyl anion leads largely to radicals of low reactivity which engage mainly in termination steps. Moreover, because the cyanomethyl anion is more reactive than acetone enolate ion toward the phenyl radical, its net effect is that of a radical scavenger when present during reaction of the enolate ion with bromobenzene.

That little benzene or toluene was formed in photochemical run 35 (Table III) is consistent with the interpretation offered above for the genesis of these products. In a system providing few if any solvated electrons, steps 10 and 12 would necessarily be insignificant.

Discussion of Potentialities in Synthesis

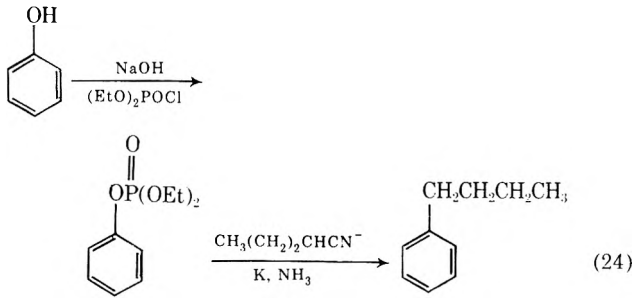
The reactions we describe constitute a method for installing an alkyl group on a benzene ring in place of a nucleofugic substituent. Examples that we report (in Table II) concern the introduction of ethyl, propyl, isopropyl, butyl, isobutyl, and benzyl groups, as well as the methyl group (Table I).

Although in our experience the yields of alkylbenzenes (reckoned on the basis of substituted benzene, with the nitrile anion in excess) were always less than

(25) M. Anbar and E. J. Hart, *J. Amer. Chem. Soc.*, **86**, 5633 (1964), report that rates of reactions of the hydrated electron with monohalobenzenes increase with the size of the halogen.

50%, the method may nevertheless be useful in synthesis. First, the alkyl group is introduced specifically at the site vacated by the nucleofugic substituent.[26] In contrast, introduction of an alkyl group by Friedel–Crafts alkylation or acylation (followed by reduction) is at the mercy of the orienting effects of other nuclear substituents. Second, the alkyl group is installed without rearrangement, whereas the introduction of straight-chain or β-branched alkyl groups by the Friedel–Crafts method is severely complicated by isomerization within the alkyl group.[27]

A third attractive feature is that the alkyl group can, with the interposition of one additional step, be introduced in place of a phenolic hydroxy group or an amino group. Phenols are readily converted in high yield to their diethyl phosphate esters.[7] The sequence of two operational steps depicted in eq 24 effects, for example,



(24)

the transformation of phenol to *n*-butylbenzene in an overall yield of 33%; the yield is 87% in the esterification step[7] and 38% in the alkylation step (run 27, Table II). As for aromatic primary amines, they are easily quaternized, and the trimethylammonio group is suitably nucleofugic (*cf.* run 16, Table I).

For the purpose of installing an alkyl group in place of a nucleofugic aromatic substituent, the α-phenyl nitrile by-product is not utterly lost because it can be converted to the desired product by decyanation. It struck us that such decyanation might be caused to occur in the same pot by quenching the reaction mixture with ice and then adding more potassium metal. Runs 10, 11, 12, and 15 of Table I and runs 26, 27, and 30 of Table II were conducted in that way, but the result was only partially as desired. There was some improvement in the yield of toluene or other product of type $PhCH_2R$ but, except in run 25, a significant amount of the α-phenyl nitrile nevertheless survived.

Consideration of the postulated reaction mechanism, with particular attention to steps 9 and 10, suggests that the yield of toluene or other $PhCH_2R$ product should be improved, relative to that of DPE or other benzylic radical dimer, by having a rich supply of solvated electrons constantly available. However, if solvated electrons are freely available, step 12, which (with step 13) produces benzene, should also be favored with consequent reduction of the yield of alkylbenzene. These concepts notwithstanding, we find in our experiments little relationship of the product pattern to the technique used for mixing reactants. Nevertheless, we have faith that, with effort, conditions could be defined that would afford reproducibly higher yields of alkylbenzene products than we actually got.

If the synthetic objective were to replace a cyano group in a precious nitrile by a phenyl group, the phenylating reagent (*e.g.*, chlorobenzene) would be used in excess and losses of phenyl radicals to benzene would be of little consequence. Runs 22, 26, and 28 (Table II) were conducted with chlorobenzene in excess and they did give products of type $PhCH_2R$ in somewhat higher yields than when the nitrile anion was in excess.

For the purpose of installing an α-phenyl group in the α position of an aliphatic nitrile, SRN1 phenylation appears to be inferior to benzyne phenylation of the nitrile anion.[28] Benzyne phenylation followed by decyanation would furnish an alkylbenzene, but synthetically such a method would suffer some disadvantages: benzyne is not readily generated from monosubstituted benzenes in the presence of carbanions when the substituent has oxygen or nitrogen as first atom, and arylation by substituted benzynes sometimes gives mixtures of positional isomers.

Our experiments, especially run 48, Table V, support other indications[18b,20] that nitrile decyanation through the action of solvated electrons is a useful synthetic transformation.

Experimental Section

Phenylation of Nitrile Anions, Stimulated by Alkali Metal.—A procedure for phenylation of cyanomethyl anion is representative. The reaction was carried out in a three-neck, round-bottom flask fitted with a solid CO_2–isopropyl alcohol condenser, stirred by a magnetic stirrer and constantly swept by a slow stream of dry nitrogen. Ammonia from a commercial cylinder was dried with potassium and 50 ml was distilled into the reaction flask in a current of dry nitrogen. Potassium (0.080 mol) and a little ferric nitrate were added to catalyze the formation of KNH_2. After the metal had all reacted (care was taken to rinse back into the solution the amide splashed up and deposited on the walls of the flask), the solution was cooled to −78° and acetonitrile (0.080 mol) was added dropwise.[29] After a few minutes, 0.067 mol of chlorobenzene was added, and then potassium metal (0.081 mol) in small pieces. Some sodium benzoate was added and then the brownish-red mixture was neutralized by adding excess NH_4Cl, which caused the color to fade. Diethyl ether (50 ml) and internal standards (ethylbenzene and biphenyl) were added, and the ammonia was allowed to evaporate. Water was added, the two layers were separated, the aqueous phase was extracted with ether, and the combined ether fractions were washed neutral and dried over anhydrous sodium sulfate. The solution was analyzed by glpc on a column of 10% Carbowax 20M on Chromosorb P.

Identification of Products.—Analysis was performed on samples collected by preparative glpc on columns of either 10% silicone rubber SE-54 or 10% Carbowax 20M on Chromosorb P.

Unreacted starting material, benzene, alkylbenzenes, α-phenyl nitriles, diphenylmethane, triphenylmethane, 1,2-diphenylethane, aniline, and phenol were identified by comparison of their glpc retention times and ir spectra with those of authentic samples, unless otherwise stated. Evidence for the identity of other products is now presented.

α-Phenylvaleronitrile had ir (CCl_4) 2250 cm^{-1}; mass spectrum[30] *m/e* (rel intensity) 159 (molecular ion, 17), 133 (10), 117 (100), 116 (20), 91 (50), 77 (10).

α-Phenylisovaleronitrile had ir (CCl_4) 2250, 1390, 1365 cm^{-1};

(26) The absence of cine substitution in reactions by the SRN1 mechanism has been demonstrated in other studies.[6,8] In the present work, a run with *p*-bromotoluene and the cyanomethyl anion under conditions similar to those of run 13, Table I, afforded p-xylene (17%) uncontaminated by ortho or meta isomers.

(27) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965, pp 157–173.

(28) V. Dryanska, K. Ivanov, and V. Lachkova, *God. Sofii. Univ., Khim. Fak.*, **64**, 445 (1969–1970); *Chem. Abstr.*, **78**, 135,838 (1973).

(29) For reactions at −78°, the flask was immersed in a solid CO_2–isopropyl alcohol bath, and, for reactions at −33°, there was no cooling.

(30) The mass spectra were obtained on a Hitachi RMU-GE spectrometer at an ionization potential of 80 eV.

TABLE VI

NMR DATA OF DIPHENYLALKANES[a]

Compd	Methyl protons: Pattern	Methyl protons: δ, ppm	Methyl protons: J_{A_3-B}, Hz	Aromatic protons: Pattern	Aromatic protons: δ, ppm
meso-2,3-Diphenylbutane	"d"	1.02	6.5	"s"	7.17
rac-2,3-Diphenylbutane	d	1.21	6.5	"s"	6.93
Mixture of *meso*- and *rac*-3,4-diphenylhexane[b,c]	t	0.51	6.5[d]	m	~7
	t	0.72	6.5[d]	"s"	7.2
Mixture of *meso*- and *rac*-4,5-diphenyloctane[c]	"t"	~0.7		m	~6.9
	"t"	~0.85		"s"	~7.13

[a] All nmr spectra were run on a Varian A56/60 spectrometer. [b] Although small amounts of *meso*- and *rac*-3,4-diphenylhexane sufficient for ir and mass spectral analysis could be isolated by glpc, it was practicable to isolate the larger amount needed for nmr only as a mixture of isomers. [c] Each line refers to a different isomer. [d] Refers to CH_2–CH_3 splitting in the ethyl groups.

mass spectrum *m/e* (rel intensity) 159 (molecular ion, 3), 118 (10), 117 (100), 116 (9), 91 (5), 90 (16), 89 (12), 77 (4).

1,1-Diphenylethane had ir (CCl_4) 3100–2880, 1590, 1480, 1440, 1350, 695 cm^{-1}; mass spectrum *m/e* (rel intensity) 182 (molecular ion, 25), 167 (100), 166 (11), 165 (28), 152 (16), 105 (7), 103 (10), 91 (9), 77 (22), m* 138.3 (167 → 152).

1,1-Diphenylpropane had ir (CCl_4) 3100–2870, 1600, 1490, 1450, 1375, 695 cm^{-1}; mass spectrum *m/e* (rel intensity) 196 (molecular ion, 7), 167 (100), 165 (38), 152 (20), 115 (10), 91 (16), 77 (9), m* 142.3 (196 → 167), m* 138.3 (167 → 152).

1,1-Diphenylbutane had ir ($CHCl_3$) 3100–2870, 1600, 1490, 1450, 695 cm^{-1}; mass spectrum *m/e* (rel intensity) 210 (molecular ion, 9), 167 (100), 165 (20), 152 (12), 115 (4), 91 (6), 77 (4), m* 138.3 (167 → 152), m* 132.8 (210 → 167).

1,1-Diphenyl-2-methylpropane had ir (CCl_4) 3100–2880, 1595, 1490, 1450, 1375, 1360, 695 cm^{-1}; mass spectrum *m/e* (rel intensity) 210 (molecular ion, 3), 167 (100), 165 (25), 152 (13), 115 (7), 91 (8), 77 (6), m* 138.3 (167 → 152), m* 132.8 (210 → 167).

***meso*-2,3-Diphenylbutane**.—The product crystallized after evaporation of the ether from run 19: mp 125–126° (lit.[31] mp 128°); ir (CCl_4) 3120–2880, 1600, 1490, 1450, 1370, 695 cm^{-1}; nmr, see Table VI; mass spectrum *m/e* (rel intensity) 210 (molecular ion, 0.4), 115 (2), 106 (57), 105 (100), 104 (29), 91 (8), 79 (19), 77 (22), m* ~101 (131 → 115), m* 59.5 (105 → 79).

***rac*-2,3-Diphenylbutane** had an ir (CCl_4) differing slightly from the spectrum of the meso form between 1300 and 800 cm^{-1}; nmr, see Table VI; mass spectrum virtually identical with the spectrum of the meso compound.

***meso*-3,4-Diphenylhexane** had ir ($CHCl_3$) 3110–2870, 1600, 1490, 1450, 1375 cm^{-1}; nmr, see Table VI; mass spectrum *m/e* (rel intensity) 238 (molecular peak, not detected), 119 (100), 118 (41), 115 (12), 91 (87), 77 (20), m* 69.6 (119 → 91), m* 46.5 (91 → 65).

***rac*-3,4-Diphenylhexane** had an ir ($CHCl_3$) fingerprint region slightly different from the spectrum of the meso compound; nmr, see Table VI; mass spectrum virtually identical with the spectrum of the meso form.

***meso*- and *rac*-4,5-Diphenyloctane**.—The compounds were not separated under the conditions of our glpc sampling: ir ($CHCl_3$) 3110–2870, 1600, 1490, 1450, 1370, 695 cm^{-1}; nmr, see Table VI; mass spectrum *m/e* (rel intensity) 266 (molecular peak, <0.01), 167 (8), 133 (88), 132 (70), 117 (10), 115 (8), 104 (9), 92 (29), 91 (100), 77 (10), m* 62.2 (133 → 91), m* 46.5 (91 → 65).

Reactions of Table III.—For photostimulated reactions, the reaction mixtures were prepared as described above. The reaction flask was then placed into a Rayonet photochemical reactor and the mixture was irradiated by "350-nm" lamps. For run 38, the experimental procedure was the same as for the phenylation of nitrile anions. Phenylacetone was identified by comparison of its glpc retention time and mass spectrum with those of an authentic sample. 1-Phenyl-2-propanol was identified by ir ($CHCl_3$), 3600, 3450, 3110–2850, 1600, 1490, 1450, 1370, 690 cm^{-1}, and nmr (CCl_4), δ 1.08 (d, J = 6.5 Hz, 3 H), 2.6 (d, J = 6.5 Hz, 1 H), 2.64 (d, J = 6.5 Hz, 1 H), 3.7 (s, 1 H, exchanged with D_2O), ~3.85 (m, J = 6.5 Hz, 1 H), 7.12 (s, 5 H).

Aldol-type condensation products were also found. 4-Hydroxy-4-methyl-2-pentanone and 3-hydroxy-3-methylbutanonitrile were formed in all competitive reactions and were identified by their nmr, ir, and mass spectrum. In the photoreaction 37, about 4% of 3-hydroxy-3-methyl-4-phenylbutanonitrile was also formed, by condensation of phenylacetone and cyanomethyl anion: nmr (CCl_4) 1.23 (s, 3 H), 2.29 (s, 2 H), 2.78 (s, 2 H), 3.14 (s, 1 H), 7.18 (s, 5 H); ir (neat) 3460, 3090–2930, 2250, 1600, 1500, 1450, 1380, 700 cm^{-1}; mass spectrum *m/e* (rel intensity) 175 (molecular peak, ~0.2), 160 (0.8), 159 (1.2), 135 (7), 117 (4), 115 (3), 92 (100), 91 (83), 77 (3), m* 101.3 (135 → 117), m* 46.5 (91 → 65).

From the potassium-stimulated reaction 38, *ca.* 2% of 1,3-diphenyl-2-methyl-2-propanol was isolated. It was probably formed by condensation of phenylacetone with the anion of phenylacetonitrile, followed by decyanation: nmr (CCl_4) δ 0.96 (s, 3 H), 1.67 (s, 1 H), 2.7 (s, 4 H), 7.16 (s, 10 H); ir ($CHCl_3$) 3585, 3460, 3080–2850, 1600, 1490, 1445, 1370 cm^{-1}; mass spectrum *m/e* (rel intensity) 226 (molecular peak, not detected), 211 (1), 208 (6.5), 193 (67), 136 (11), 135 (100), 134 (22), 117 (30), 115 (14), 92 (50), 91 (85), 77 (11), m* 101.3 (135 → 117), m* 46.5 (91 → 65), m* 24 (77 → 43).

Reactions of Benzyl Radicals (Table IV).—The runs designed to find reaction of benzyl radical with anions were performed in the same way as the phenylations of nitrile anions. An authentic sample of 1-(3′-methylphenyl)-2-phenylethane was prepared by our new decyanation method: 3.5 g of 2-(3′-methylphenyl)-3-phenylpropanonitrile, obtained by the method of Ganellin and Stolz,[32] was added to a mixture of ammonia (100 ml) and diethyl ether (50 ml); 3.6 g of ice was added, followed by sodium (0.89 g) in small bits. Ammonium chloride was added and the ammonia was evaporated. After the usual work-up the ether was removed. From the residue 2.4 g (78%) of the product was obtained by distillation: bp 91–94° (0.2 Torr); nmr (CCl_4) δ 2.25 (s, 3 H), 2.80 (s, 4 H), ~6.8 (m, 4 H), 7.06 (s, 5 H); mass spectrum *m/e* (rel intensity) 196 (molecular peak, 31), 106 (16), 105 (100), 91 (74), 79 (16), 77 (30), m* 59.5 (105 → 79), m* 56.3 (196 → 105), m* 46.5 (91 → 65).

Decyanation Reactions of Table V.—These reactions were conducted similarly to the phenylations of nitrile anions. The ammonia, however, was not distilled and air was not excluded.

Registry No.—CH_2CNK anion, 2932-82-3; BME, 538-86-3; $MPAN^-$, 42117-18-0; PAN, 140-29-4; PBN, 769-68-6; K, 7440-09-7; Na, 7440-23-5; α-phenylvaleronitrile, 5558-78-1; α-phenylisovaleronitrile, 5558-29-2; 1,1-diphenylethane, 612-00-0; 1,1-diphenylpropane, 1530-03-6; 1,1-diphenylbutane, 719-79-9; 1,1-diphenyl-2-methylpropane, 1634-11-3; *meso*-2,3-diphenylbutane, 4613-11-0; *rac*-2,3-diphenylbutane, 2726-21-8; *meso*-3,4-diphenylhexane, 39952-67-5; *rac*-3,4-diphenylhexane, 42087-02-5; 4,5-diphenyloctane, 42117-21-5; 1-phenyl-2-propanol, 698-87-3; 3-hydroxy-3-methyl-4-phenylbutanonitrile, 42117-22-6; 1,3-diphenyl-2-methyl-2-propanol, 42117-23-7; 1-(3′-methylphenyl)-2-phenylethane, 34403-06-0.

(31) F. v. Wessely and H. Welleba, *Chem. Ber.*, **74**, 777 (1941).

(32) C. R. Ganellin and J. C. S. Stolz, *J. Chem. Soc. C*, 2132 (1969).

(*E*)-3-Benzylidenephthalides

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Tributyl(3-phthalidyl)phosphonium bromide (**1a**) and triphenyl(3-phthalidyl)phosphonium bromide (**1b**) were prepared from 3-hydroxyphthalide, the appropriately substituted phosphine, and hydrogen bromide in acetic acid. Triethylamine-catalyzed Wittig reactions of **1a** with aromatic aldehydes in methylene chloride solution produced, in nearly quantitative yields, *E*–*Z* mixtures of 3-benzylidenephthalides in which the *E* isomers predominated (80–91%). Pure *E* isomers **3a–e** were obtained in 40–49% yields by simple fractional crystallization procedures. This method constitutes the first practical synthesis of (*E*)-3-benzylidenephthalides. Triethylamine-catalyzed reaction of **1a** with aromatic nitroso compounds resulted in 3-aryliminophthalides **5a** (73% yield) and **5b** (82% yield).

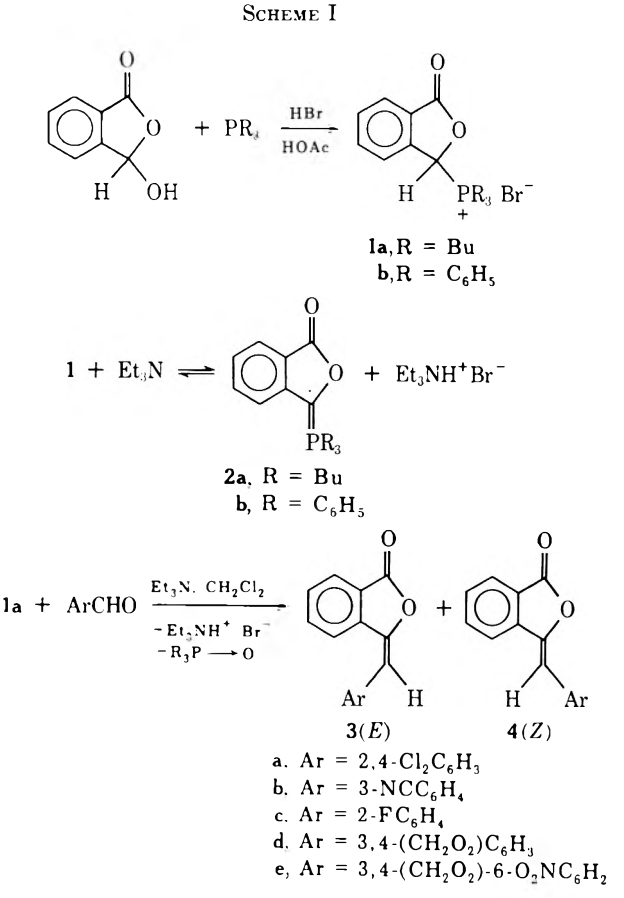
(*E*)-3-Benzylidenephthalides have been the subject of numerous publications throughout the years. These compounds have served extensively as intermediates for syntheses of drug candidates.[1] Generally, 3-benzylidenephthalides are prepared by condensation of phthalic anhydride with arylacetic acids at 230–250°, a method that leads very predominantly to the *Z* isomers.[1b,g,2–4] Recently, a new synthesis was reported in which (*Z*)-3-benzylidene-6-nitrophthalides were prepared by condensation of diphenyl 6-nitrophthalide-3-phosphonate and aromatic aldehydes using sodium hydride in *N*,*N*-dimethylformamide.[5] (*E*)-3-Benzylidenephthalides have appeared only rarely in the chemical literature[3b,4] and have been isolated with difficulty from *E*–*Z* mixtures in which the more stable *Z* isomers predominated. No preparative method for synthesis of the *E* isomers appears to have been reported previously. We describe here a practical method of wide scope for the preparation of (*E*)-3-benzylidenephthalides.

The phthalidylphosphonium salts **1a** and **1b** were prepared as shown in Scheme I. These salts are remarkably acidic. Treatment of **1a** with 1 equiv of triethylamine in methylene chloride results in *ca.* 10–20% formation of yellow ylide **2a** and triethylammonium bromide, based on the intensity of the $Et_3NH^+Br^-$ ir bands at 3.85 and 4.05 μ. Inductive effects undoubtedly play a major role in the acidity of **1a**; however, extended conjugation through the π electron system of the ylide lactone ring may also be a contributing factor.

Dropwise addition of 1 equiv of triethylamine to **1a** and 2,4-dichlorobenzaldehyde in methylene chloride resulted with each drop in a fleeting yellow color that rapidly discharged as the yellow ylide **2a** reacted with the aldehyde. After 1.5 hr at 23°, ir analysis of the solution revealed that all the aldehyde was consumed and that 1 equiv of triethylammonium bromide had formed. Extraction of the solution with water and nmr analysis of the aqueous extracts, using DMSO as a quantitative internal standard, revealed that triethylammonium bromide had formed in 96% yield. Quantitative gc analysis of the methylene chloride solution revealed that tributylphosphine oxide had formed in 100% yield and that a 91:9 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides had been produced in 98% yield. Similar reaction of **1b** with 2,4-dichlorobenzaldehyde gave triphenylphosphine oxide in 95.5% yield and an 87:13 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides in 93% yield.

The reaction appears general for aromatic aldehydes as demonstrated by the preparation of **3a–e** from **1a**.[6] With 3-cyanobenzaldehyde, an 86:14 mixture of **3b** and **4b** was obtained. 2-Fluorobenzaldehyde gave an 83:17 mixture of **3c** and **4c**. From piperonal, an 80:20 mixture of **3d** and **4d** was obtained. Use of 6-nitropiperonal resulted in formation of a mixture of **3e** and **4e** in which the *E* isomer amounted to ≥85%.

SCHEME I



(1) (a) U. S. Patent 3,274,185 (1966); (b) Z. J. Vejdelek, O. Nemecek, V. Musil, and A. Simek, *Collect. Czech. Chem. Commun.*, **29**, 776 (1964); (c) Swiss Patent 356,759 (1961); *Chem Abstr.*, **59**, 5104 (1963); (d) Czechoslovakian Patent 102,062 (1961); *Chem. Abstr.*, **57**, 16521 (1962); (e) P. Hrnciar and V. Kovalcik, *Chem. Zvesti*, **16**, 96, 200 (1959); *Chem. Abstr.*, **59**, 2731 (1963); (f) East German Patent 17,075 (1961); *Chem. Abstr.*, **55**, 2700 (1961); (g) C. van der Stelt, A. F. Harms, and W. T. Nauta, *J. Med. Pharm. Chem.*, **4**, 335 (1961).

(2) According to recent nomenclature rules [*J. Org. Chem.*, **35**, 2849 (1970)], the old cis and trans steroisomeric terms[3b,4] for 3-benzylidenephthalides are to be replaced by *E* and *Z* descriptors, respectively.

(3) (a) R. Weiss, *Org. Syn.*, **13**, 10(1933); (b) G. Berti, *Gazz. Chim. Ital.*, **86**, 655 (1956); *Chem Abstr.*, **52**, 1958 (1958).

(4) J. Rigaudy and P. Derible, *Bull. Soc. Chim. Fr.*, 3047 (1965).

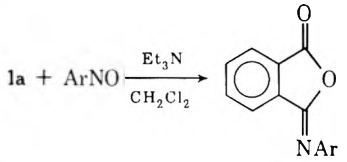
(5) A. Yamaguchi and M. Okazaki, *Nippon Kagaku Kaishi*, 110 (1973).

(6) Attempts to condense the ylide with acetone and with acetophenone were unsuccessful.

Compounds **3a–e** were each obtained in 100% purity by fractional crystallizations. Yields of pure *E* isomers **3a–e** ranged from 40 to 49%.

Pure samples of the *Z* isomers **4a–e** were prepared by iodine-catalyzed isomerizations of the corresponding *E* isomers. Compounds **4a**,[1b] **4c**,[7] and **4d**[8] have been prepared previously. Correspondence of the physical properties of our samples of **4a**, **4c**, and **4d** with the literature values for these compounds and conversion of the *E* isomers to the *Z* isomers adds confirmation to the nmr and ir spectral assignments for the structures of the (*E*)-benzylidenephthalides **3a–e**.

Ylide **2a** reacts very rapidly (5–15 min at 10–30°) with aromatic nitroso compounds to produce 3-arylaminophthalides in good yields (73% for **5a**, 82% for



5a, Ar = C_6H_5
b, Ar = 2-$CH_3C_6H_4$

5b).[9] The very mild reaction conditions involved in this reaction allow isolation of these somewhat unstable materials that are prone toward isomerization[10] to *N*-arylphthalimides.

The stereochemical outcome of any Wittig reaction depends on the interactions of several factors, including the ratio of epimeric betaine intermediates formed, the rates of reversion of the betaines to starting materials, and the rates of conversion of the epimeric betaines to *E* and *Z* olefins. In most cases of the phosphonate version of the Wittig reaction with aldehydes, these factors combine in such a fashion as to produce predominantly the more stable olefin.[11] In the reaction of phosphonium ylides with aldehydes, the betaine that produces the less stable olefin is formed predominantly, for reasons that are not entirely clear, under conditions of kinetic control.[11] When these conditions prevail and, in addition, when the epimeric phosphonium betaines collapse to olefin products faster than they revert to starting materials, the less stable olefin is produced predominantly.[11] Such appears to be the case in the reactions of **2a** and **2b** with aromatic aldehydes; restated, $k_1 > k_3$ and $k_2 > k_{-1}$ in Scheme II.[12,12a]

(7) U. S. Patent 3,641,153 (1972).

(8) M. Furdik and I. Pastorek, *Acta Fac. Rerum Natur. Univ. Comenianae, Chim.*, No. 11, 47 (1966); *Chem. Abstr.*, **68**, 12742 (1968).

(9) Condensation of diphenyl 6-nitrophthalide-3-phosphonate with aromatic nitroso compounds using sodium hydride in *N,N*-dimethylformamide led to *N*-arylphthalimides, presumably *via* intermediate 3-arylimino-6-nitrophthalides which rearranged under the reaction conditions: ref 5.

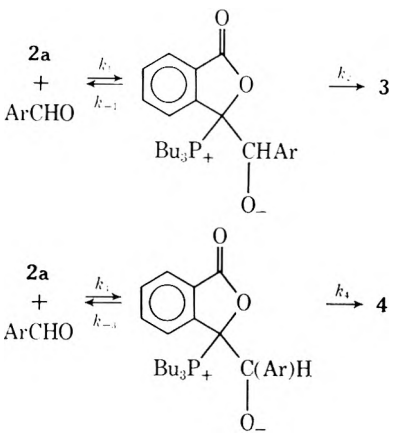
(10) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).

(11) M. Schlosser in "Topics in Stereochemistry," Vol. 5, E. Eliel and N. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1970, pp 1–30.

(12) Similar results have been found in the reaction of certain carbonyl-stabilized phosphonium ylides with phthalic anhydride: P. S. Chopard, R. F. Hudson, and R. J. G. Searle, *Tetrahedron Lett.*, 2357 (1965).

(12a) NOTE ADDED IN PROOF.—In a recent paper, E. Vedejs and K. A. J. Snoble [*J. Amer. Chem. Soc.* **95**, 5778 (1973)] have provided direct evidence for the intermediacy of oxaphosphetanes in the Wittig reactions of certain nonstabilized phosphonium ylides with aldehydes. Possible betaine intermediates were not detected (<1%) and were considered to be considerably less stable than the cyclic oxaphosphetanes. Vedejs and Snoble proposed that the oxaphosphetane is formed by concerted $\pi 2_s + \pi 2_a$ cycloaddition of ylide and aldehyde; predominant cycloaddition *via* the least hindered orientation of ylide and aldehyde would lead directly to the most hindered oxaphosphetane and thus would result in selective cis olefin formation. This mechanism could account quite nicely for our results in the phthalidyl system.

SCHEME II



Neither the triethylamine nor the product triethylammonium bromide appears to influence significantly the stereochemical results of the reaction of **2a** with aldehydes as determined from an experiment in which a solution of **1a** and 2,4-dichlorobenzaldehyde in methylene chloride was shaken with excess aqueous sodium hydroxide at 0–5°. Reaction was nearly instantaneous under these conditions, in which ylide **2a** presumably is generated in the presence of the aldehyde and in the absence of any salts. Products **3a** and **4a** were obtained in a 93:7 ratio in 94% total yield.

Experimental Section[13]

Tributyl(3-phthalidyl)phosphonium Bromide (1a).—A mixture of 30 g (0.20 mol) of 2-carboxybenzaldehyde, 57 g (0.211 mol of HBr) of 30% HBr in acetic acid, and 40.4 g (0.20 mol) of tributylphosphine was stirred under N_2 at 90° for 22 hr and then was concentrated under vacuum. The residue was stirred with 250 ml of ether, and seed crystals were added. The resultant semisolid was triturated with 250 ml of fresh ether to give 75.8 g of pale yellow solid, mp 135–146°. The solid was crystallized from CH_3CN–EtOAc to give 34.6 g of white solid, mp 151–152.5°. An additional 18.1 g of solid, mp 149–151°, was obtained from the filtrate. The total yield was 63.5%: ir (mineral oil mull) 5.61 μ; nmr ($CDCl_3$) δ 7.9 (m, 5, ArH + ArCHP), 2.68 (m, 6, PCH_2), 1.50 (m, 12, $PCH_2CH_2CH_2CH_3$), 0.91 (m, 3, CH_3).

Anal. Calcd for $C_{20}H_{32}BrO_2P$: C, 57.83; H, 7.77. Found: C, 57.61; H, 7.82.

Triphenyl(3-phthalidyl)phosphonium Bromide (1b).—A solution of 45 g (0.30 mol) of 2-carboxybenzaldehyde, 78.6 g (0.30 mol) of triphenylphosphine, 81.0 g (0.30 mol of HBr) of 30% HBr in acetic acid, and 60 ml of acetic acid was stirred at 90° under N_2 for 48 hr. The reaction mixture was allowed to cool and was seeded with pure product obtained from an aliquot. The resultant 106.6 g of solid was boiled with 1400 ml of CH_3CN, and the mixture was allowed to cool and was filtered to give 64.6 g of white solid, mp 258–260°. An additional 37.7 g of solid, mp 258–260°, was obtained from the filtrate (72% total yield): ir (mineral oil mull) 5.65 μ.

Anal. Calcd for $C_{26}H_{20}BrO_2P$: C, 65.70; H, 4.24. Found: C, 65.86; H, 4.22.

(*E*)-3-(2,4-Dichlorobenzylidene)phthalide (3a).—To a solution of 4.15 g (0.010 mol) of tributyl(3-phthalidyl)phosphonium bromide and 1.75 g (0.010 mol) of 2,4-dichlorobenzaldehyde (recrystallized) in 60 ml of CH_2Cl_2 was added dropwise with stirring 1.01 g (0.010 mol) of triethylamine. The solution was stirred for 1.5 hr, and then 40 ml of CH_2Cl_2 was added. The solution was extracted with three 50-ml portions of water. The aqueous layers were combined, and 0.010 mol of DMSO was added. Nmr analysis of this solution, using the DMSO as a quantitative internal standard, indicated a 96% yield of triethylammonium bromide. Gc analysis of the CH_2Cl_2 solution using bis(*p*-bromophenyl) ether as an internal standard revealed that tributyl-

(13) Melting points were taken in open capillaries in a Mel-Temp apparatus and are corrected.

phosphine oxide had formed in 100% yield and a mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides was formed in 98% yield (analysis on a 2-ft column of 10% SE-30 at 230°). Gc analysis on a 2-ft column of 2% XE-60 at 220° (injector port at 250°) indicated the *E* to *Z* ratio to be 91:9 (under these latter gc conditions <1% isomerization of *E* to *Z* isomer occurred). Nmr analysis of the CH_2Cl_2 solution indicated a 92:8 *E* to *Z* isomer ratio by comparison with a standard 92:8 mixture prepared from the pure isomers. The analysis was made possible by the fact that the *Z* isomer has a one-proton doublet at δ 8.25 that is at lower field than the rest of the proton signals of the *E* and *Z* isomers.

The CH_2Cl_2 solution was concentrated under vacuum to 5.0 g of solid (98% of theory for tributylphosphine oxide plus the phthalides). The solid was treated twice with hot hexane. The undissolved solid, 1.8 g (62% yield), mp 143–144°, was >98% pure (*E*)-3-(2,4-dichlorobenzylidene)phthalide (ir analysis). Two crystallizations of the solid from ethanol gave 1.22 g (42% yield) of 100% pure *E* isomer (nmr, ir, and gc analyses): mp 145.5–146°; ir (mineral oil mull) 5.62 (s), 6.02 (w), 6.31 μ (w); nmr ($CDCl_3$) δ 7.93 (m, 1, ArH), 7.53 (m, 6, ArH), 6.78 (s, 1, ArCH=C).

Anal. Calcd for $C_{15}H_8Cl_2O_2$: C, 61.88; H, 2.77. Found: C, 61.97; H, 2.78.

A similar reaction in which triphenyl(3-phthalidyl)phosphonium bromide was employed gave triphenylphosphine oxide in 95.5% yield and an 87:13 mixture of (*E*)- and (*Z*)-3-(2,4-dichlorobenzylidene)phthalides in 93% yield.

(*Z*)-**3-(2,4-Dichlorobenzylidene)phthalide** (**4a**).—A solution of 1.1 g of (*E*)-3-(2,4-dichlorobenzylidene)phthalide and *ca.* 10 mg of I_2 in 20 ml of nitrobenzene was held at reflux under N_2 for 30 min. Methylene chloride was added, and the solution was washed twice with dilute sodium thiosulfate solution. Gc analysis indicated a 5:95 ratio of *E* to *Z* isomers. The solution was concentrated under vacuum to a brown solid, which was crystallized from methylcyclohexane (charcoal) to give 0.63 g of solid, mp 180–181° (lit.[1b] mp 181°), which was 100% pure (gc assay) *Z* isomer: ir (mineral oil mull) 5.60 (s), 6.02 (w) 6.32 μ (w); nmr ($CDCl_3$) δ 8.25 (d, 1, J = 8 Hz, 6-H of 2,4-$Cl_2C_6H_3$ ring), 8.0–7.2 (m, 6, ArH), 6.80 (s, 1, ArCH=C).

(*E*)-**3-(*m*-Cyanobenzylidene)phthalide** (**3b**).—To a solution of 5.15 g (0.0393 mol) of 3-cyanobenzaldehyde and 16.3 g (0.0393 mol) of **1a** in 150 ml of CH_2Cl_2 stirred under N_2 was added 3.97 g (0.0393 mol) of triethylamine during 5 min. The resultant mixture was stirred for another 15 min and then was diluted to 600 ml to obtain a homogeneous solution. The solution was washed with water and was analyzed by gc (2-ft 2% XE-60 column at 250°); the ratio of *E* and *Z* isomers was 86:14. The solvent was removed under vacuum and the residue was triturated with 125 ml of hexane to remove tributylphosphine oxide. The hexane-insoluble solid, 9.40 g (97%), was dissolved in hot $CHCl_3$, and the solution was allowed to cool and was seeded with pure *Z* isomer. After needles of the *Z* isomer formed, the mixture was rapidly filtered. The filtrate was reheated to boiling, was allowed to cool somewhat, was seeded with pure *E* isomer, and was diluted to *ca.* four times the volume with CCl_4. The mixture was filtered rapidly after two minutes to give *E*-rich solid. Recrystallizations of this material from $CHCl_3$–CCl_4 gave pure *E* isomer. In this way, a total of 4.27 g (44%) of 100% pure (gc assay) (*E*)-3-(*m*-cyanobenzylidene)-phthalide, mp 206–207°, was obtained: ir (mineral oil mull) 4.50, 5.64 μ; nmr ($CDCl_3$) δ 8.07–7.3 (m, 8, ArH), 6.83 (s, 1, ArCH=C).

Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.70. Found: C, 77.90; H, 3.81.

A total of 0.63 g (6.5%) of fairly pure *Z* isomer **4b**, mp 247–249°, was also obtained.

(*Z*)-**3-(*m*-Cyanobenzylidene)phthalide** (**4b**).—A solution of 2.0 g of **3b** and 20 mg of I_2 in 20 ml of nitrobenzene was held at reflux under N_2 for 30 min and then was allowed to cool. The resultant solid was collected, washed with methanol, and crystallized twice from 1,2 dichloroethane to give 1.54 g (77%) of 100% pure (gc assay) *Z* isomer **4b**: mp 249–250°; ir (mineral oil mull) 4.50, 5.58 μ; nmr ($CDCl_3$) δ 8.13–7.43 (m, 8, ArH), 6.37 (s, 1, ArCH=C).

Anal. Calcd for $C_{16}H_9NO_2$: C, 77.72; H, 3.70. Found: C, 77.92; H, 3.78.

(*E*)-**3-(*o*-Fluorobenzylidene)phthalide** (**3c**).—A solution of 4.96 g (0.040 mol) of *o*-fluorobenzaldehyde, 16.6 g (0.040 mol) of **1a**, and 4.04 g (0.040 mol) of triethylamine in 200 ml of CH_2Cl_2 was stirred under N_2 for 44 hr and then was washed with water. Gc analysis of the solution revealed an 83:17 mixture of *E* and *Z* isomers. The solvent was removed under vacuum, and the residue was triturated with two 50-ml portions of hexane. The hexane-insoluble solid, 7.60 g (79%), was crystallized from 600 ml of hexane to give 4.2 g (44%) of 100% pure *E* isomer **3c** as white needles, mp 119–120°. An additional 0.43 g (4.5%) of **3c**, mp 119–120°, was recovered from the hexane extracts and filtrate: ir (mineral oil mull) 5.60 μ; nmr ($CDCl_3$) δ 8.07–7.10 (m, 8, ArH), 6.78 (s, 1, ArCH=C).

Anal. Calcd for $C_{15}H_9FO_2$: C, 75.00; H, 3.78. Found: C, 75.22; H, 3.90.

(*Z*)-**3-(*o*-Fluorobenzylidene)phthalide** (**4c**).—Iodine-catalyzed isomerization of 1.5 g of **3c** in nitrobenzene at reflux under N_2 for 45 min and crystallization of the product from ethanol gave 0.63 g (42%) of **4c** as yellow needles: mp 151–152.5° (lit.[7] mp 148–151°); ir (mineral oil mull) 5.58 μ; nmr ($CDCl_3$) δ 8.53–7.0 (m, 8, ArH), 6.71 (s, 1, ArCH=C).

(*E*)-**3-Piperonylidenephthalide** (**3d**).—A solution of 8.30 g (0.020 mol) of **1a**, 3.0 g (0.020 mol) of piperonal, and 2.02 g (0.020 mol) of triethylamine in 120 ml of CH_2Cl_2 was stirred under N_2 for 29 hr, was diluted to 150 ml with CH_2Cl_2, and was washed with water. Gc analysis of the solution revealed the *E* to *Z* product ratio to be 82:18. The solution was concentrated under vacuum, and the solid residue was triturated with 50 ml of hexane. The hexane-insoluble solid, 5.0 g (94%), was crystallized from 30 ml of $CHCl_3$ at 5° (seeding with pure *Z* isomer) to give 0.59 g of 96% *Z* isomer, mp 196–200°. Recrystallization of this solid from 1,2-dichloroethane gave 0.42 g (8%) of pure *Z* isomer **4d**, mp 202–204° (lit.[8] mp 206–207.5°).

The $CHCl_3$ filtrate was concentrated somewhat and was cooled in ice to give 2.33 g of 96% *E* isomer, mp 137–140°. The filtrate was diluted with CCl_4 and was seeded with *Z* isomer to give 0.17 g of *E*–*Z* mixture. Concentration of the filtrate and seeding with *E* isomer gave 0.33 g of 95% *E* isomer. The 2.66 g (50%) of *E* isomer was dissolved in hot CCl_4. The solution was seeded with *E* isomer and was cooled rapidly to 20°. The resultant 2.31 g of 98% *E* isomer, mp 137–139°, was recrystallized in the same way to give 2.11 g (40%) of pale yellow solid, mp 139–140°, that was 100% pure *E* isomer **3d**: ir (mineral oil mull) 5.65 μ; nmr ($CDCl_3$) δ 7.87 (m, 1), 7.7–7.43 (m, 3), 6.90 (s, 3), 6.80 (s, 1, ArCH=C), 6.03 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.98; H, 3.84.

(*Z*)-2-**Piperonylidenephthalide** (**4d**).—A solution of 1.0 g of *ca.* 82:18 *E*:*Z* mixture of 3-piperonylidenephthalide and a few milligrams of iodine in 25 ml of nitrobenzene was held at reflux for 45 min and was concentrated under vacuum. The residue was triturated with methanol to give 0.90 g (90%) of solid, mp 201–203°. Recrystallization of this material from 1,2-dichloroethane gave 0.74 g of 100% pure *Z* isomer **4d** as a beige solid: mp 202.5–204° (lit.[8] mp 206–207.5°); ir (mineral oil mull) 5.63 and 5.68 μ; nmr ($CDCl_3$) δ 8.0–7.2 (m, 6), 6.82 (d, 1, J = 8 Hz, 5-H of piperonyl ring), 6.33 (s, 1, ArCH=C), 6.00 (s, 2, OCH_2O).

(*E*)-**3-(6-Nitropiperonylidene)phthalide** (**3e**).—A solution of 4.15 g (0.010 mol) of **1a**, 1.95 g (0.010 mol) of 6-nitropiperonal, and 1.01 g (0.010 mol) of triethylamine in 50 ml of CH_2Cl_2 was stirred under nitrogen for 30 hr, and the resultant mixture was diluted to 220 ml with CH_2Cl_2 to obtain a homogeneous solution. The solution was washed with water and was dried ($CaSO_4$). An aliquot was concentrated under vacuum, and the residue was dissolved in $CDCl_3$ for an nmr assay, which revealed that there was less than 15% of the *Z* isomer in the *E* product.

The $CDCl_3$ solution was combined with the CH_2Cl_2 solution, and the solvents were removed under vacuum to give a yellow solid. The solid was crystallized from 1,2-dichloroethane–hexane to give 2.73 g (88%) of solid, mp 197–201°. This material was fractionally recrystallized from 1,2 dichloroethane to give 1.36 g (44%) of pure *E* isomer **3e**: mp 203–204° (above 204°, the solid recrystallizes and then decomposes at 262–264° owing to isomerization to the *Z* isomer); ir (mineral oil) mull) 5.65 μ; nmr ($CDCl_3$) δ 8.0–6.9 (m, 7), 6.20 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_9NO_6$; C, 61.74; H, 2.91. Found: C, 61.56; H, 2.93.

(*Z*)-**3-(6-Nitropiperonylidene)phthalide** (**4e**).—A solution of 0.50 g of **3e** and *ca.* 1 mg of iodine in 10 ml of nitrobenzene was held at reflux for 5 min under nitrogen and then was concentrated under vacuum. The residue was triturated with methanol to give 0.47 g (94%) of solid, mp 266–267° dec. This material was recrystallized from 1,2-dichloroethane to give 0.34 g (68%) of **4e**

as a yellow solid: mp 269.5–270°; ir (mineral oil mull) 5.60 μ; nmr ($CDCl_3$) δ 8.1–7.4 (m, 6), 7.05 (s, 1, ArCH=C), 6.13 (s, 2, OCH_2O).

Anal. Calcd for $C_{16}H_9NO_6$: C, 61.74; H, 2.91. Found: C, 61.58; H, 2.83.

3-(Phenylimino)phthalide (5a).—To a solution of 4.15 g (0.010 mol) of **1a** and 1.07 g (0.010 mol) of nitrosobenzene in 30 ml of CH_2Cl_2 was added dropwise, during 3 min, 1.01 g (0.010 mol) of triethylamine with stirring at 25 ± 2° (ice-bath cooling required). The solution was stirred another 7 min at 10–25°, and then 20 ml of CH_2Cl_2 was added. The solution was extracted with three 25-ml portions of ice water, dried ($CaSO_4$), and concentrated under vacuum at 20° to 4.5 g of yellow solid. The solid was stirred with 15 ml of methanol, collected, and washed with 5 ml of methanol. The resultant 2.83 g of pasty solid was dissolved in 45 ml of CH_3CN, the solution was filtered, and 25 ml of ice water was added to the filtrate to give 1.63 g (73% yield) of yellow solid: mp 120–121.5° (lit.[10] mp 119–120°, lit.[14] mp 120–122°); ir (mineral oil mull) 5.60, 5.89 μ.

In preliminary experiments, crystallizations of the product from hot hexane gave solid of constant mp 114–115.5°. Examination of the ir spectrum of this material revealed weak extraneous absorptions at 7.26, 8.98, 11.33, and 13.89 μ due to small amounts of *N*-phenylphthalimide.

3-(*o*-Tolylimino)phthalide (5b).—To a solution of 8.30 g (0.020 mol) of **1a** and 2.42 g (0.020 mol) of 2-nitrosotoluene in 60 ml of CH_2Cl_2 was added dropwise, during 4 min, 2.02 g (0.020 mol) of triethylamine with stirring at 25–30° (ice-bath cooling). The solution was stirred for another 15 min at 5–15°, and then 40 ml of CH_2Cl_2 was added. The solution was extracted with three 50-ml portions of ice water, dried ($CaSO_4$), and concentrated under vacuum at 20° to a yellow solid. The solid was swirled with methanol and collected to give 3.90 g (82% yield) of yellow solid: mp 136–138° (lit.[15] mp 136–137°, lit.[16] mp 136°); ir (mineral oil mull) 5.51 (sh), 5.60, 5.88 μ. There was no trace of the isomeric phthalimide present as judged from the absence of absorptions at 11.65 and 13.89 μ, bands that are strong in the spectrum of *N*-(*o*-tolyl)phthalimide.

Reaction of 1a and 2,4-Dichlorobenzaldehyde Using Sodium Hydroxide as the Base.—A solution of 4.15 g (0.010 mol) of **1a** and 1.75 g (0.010 mol) of 2,4-dichlorobenzaldehyde in 60 ml of methylene chloride was extracted at 0–5° with two 20-ml portions of 0.5 *M* aqueous sodium hydroxide and 20 ml of water. The very pale, yellow-green methylene chloride solution was dried ($CaSO_4$) and analyzed by ir within 5 min; no residual aldehyde was present. Glc analysis of the solution indicated that **3a** and **4a** had formed in a 93:7 ratio in 94% total yield.

Registry No.—**1a**, 42116-85-8; **1b**, 42116-86-9; **3a**, 42086-67-9; **3b**, 42086-68-0; **3c**, 42086-69-1; **3d**, 42086-70-4; **3e**, 42086-71-5; **4a**, 42086-72-6; **4b**, 42086-73-7; **4c**, 42086-74-8; **4d**, 42086-75-9; **4e**, 42086-76-0; **5a**, 487-42-3; **5b**, 42116-88-1; 2-carboxybenzaldehyde, 119-67-5; tributylphosphine, 998-40-3; triphenylphosphine, 603-35-0; 2,4-dichlorobenzaldehyde, 874-42-0; 3-cyanobenzaldehyde, 24964-64-5; *o*-fluorobenzaldehyde, 446-52-6; piperonal, 120-57-0; 6-nitropiperonal, 712-97-0.

(14) S. Hoogewerff and W. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **21**, 339 (1902).

(15) *Beilstein*, **17**, I 253.

(16) W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, **28**, 2018 (1963).

11-Aminoacridizinium Derivatives[1]

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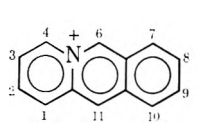
Acid-catalyzed cyclization of the 1-benzyl-2-cyanopyridinium ion and its congeners has provided a means for the synthesis of some 11-aminoacridizinium salts. Hydrolysis of the 11-aminoacridizinium ion afforded the 11-hydroxyacridizinium ion while diazotization effected ring opening and closing to form a 3-*v*-triazolo[1,5-*a*]pyridine derivative.

The relatively large number of acridizinium derivatives (**1**) which have been synthesized[2] includes only one amine, the 6-aminoacridizinium ion, obtained by the cyclization of *o*-(2-pyridylmethyl)benzonitrile (**2**).[3]



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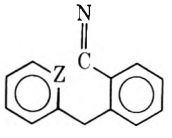
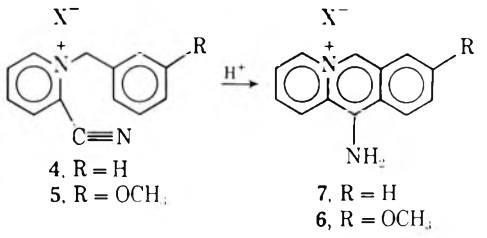


2, Z = N
3, Z = CH

This nitrile cyclization as well as the earlier cyclization[4] of *o*-benzylbenzonitrile (**3**) suggested that 11-aminoacridizinium salts (**6**) might be obtained by acid-catalyzed cyclization of 1-benzyl-2-cyanopyridinium salts (**4**).

While a variety of acidic cyclization reagents, including trifluoroacetic acid, polyphosphoric acid, fluorosulfonic acid, and hydrogen chloride in acetic acid,



4, R = H
5, R = OCH_3

7, R = H
6, R = OCH_3

were tried, under a variety of conditions, nothing appeared superior to concentrated sulfuric acid (at 100° for 15 min) and yields of **6** did not surpass 35%. An important side reaction was cleavage of the quaternary salt **4**; for example, the cyclization attempt using hydrogen chloride afforded a good yield of 2-picolinamide hydrochloride.

Since the cyclization reaction can be regarded as an internal Hoesch[5] reaction, it is not surprising that introduction of a methoxyl group para to the position of expected cyclization (**5**) resulted in an improved (70%) yield. Efforts to prepare benzologs of **6** by the cyclization of 1α- or 1β-naphthylmethyl-2-cyanopyridinium salts failed.

An alternate approach to the synthesis of benzologs of the 11-aminoacridizinium system **6** was through the

(1) This research was supported by Grant No. CA-05509 of the National Cancer Institute of the U. S. Public Health Service.

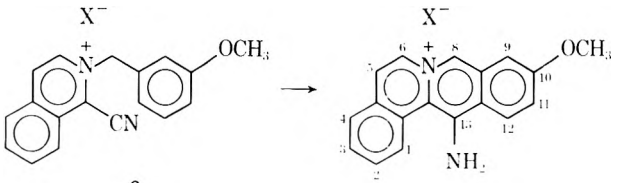
(2) C. K. Bradsher, *Accounts Chem. Res.*, **2**, 181 (1969). One aminophenol has been reported: D. L. Fields and J. B. Miller, *J. Heterocycl. Chem.*, **7**, 91 (1970).

(3) C. K. Bradsher and J. P. Sherer, *J. Org. Chem.*, **32**, 733 (1967).

(4) C. K. Bradsher and D. J. Beavers, *J. Org. Chem.*, **21**, 1067 (1956).

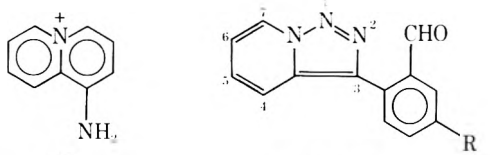
(5) P. E. Spoerri and A. S. DuBois, "Organic Reactions," Vol. 5, Wiley, New York, N. Y., 1949, p 387.

use of 1-cyanoisoquinoline,[6] which can be quaternized with *m*-methoxybenzyl bromide to yield **8**, X = Br. Cyclization of the tetrafluoroborate salt (**8**, X = BF_4) in 100% phosphoric acid at 130° gave an 88% yield of **9**.



8 **9**

As might be expected from the reported behavior[7] of the 1-aminoquinolizinium ion (**10**), the new 11-aminoacridizinium ion (**6**) shows very weak basicity, but can be acetylated. Diazotization of 11-aminoacridizinium perchlorate (**6**) brings about (in good yield) a complex ring opening and recyclization reaction leading to a neutral, nonionic species. From its physical and chemical properties and by analogy to the diazotization of 1-aminoquinolizinium[8] ion, the new compound was characterized as 2-(3-*v*-triazolo[1,5-*a*]-pyridyl)benzaldehyde (**11**). The 8-methoxy-11-aminoacridizinium ion behaved similarly on diazotization, affording **12**.

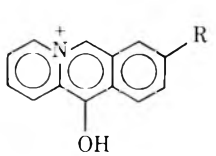


10

11, R = H
12, R = OCH_3

The amino group of 11-aminoacridizinium ion is too weakly basic to be alkylated by dimethyl sulfate or methyl iodide, nor would it form a Schiff base by reaction with 2,4-dinitrobenzaldehyde.

Hydrolysis of the amino group of **6** to afford the unknown 11-hydroxyacridizinium ion (**13**) is easily accomplished by heating **6** in dilute hydrochloric acid. The new hydroxy acridizinium salt **13** evidently exists as a betaine in neutral or alkaline solution, since on acidification there is a characteristic hypsochromic shift in the uv absorption spectrum. Similar behavior was noted for the 8-methoxy-11-hydroxyacridizinium salt **14** derived from **7**. The hydroxy group of **13**



13, R = H
14, R = OCH_3

could be acetylated, but it could not be replaced by chlorine using phosphorus oxychloride alone or admixed with phosphorus trichloride.

(6) J. J. Padbury and H. G. Lindwall, *J. Amer. Chem. Soc.*, **67**, 1268 (1945).
(7) A. R. Collicutt and G. Jones, *J. Chem. Soc.*, 4101 (1960).
(8) L. S. Davies and G. Jones, *J. Chem. Soc. C*, 688 (1970).

Experimental Section

Elemental analyses were carried out by the M-H-W Laboratories, Garden City, Mich. The melting points (uncorrected) determined in capillaries using a Hoover melting point apparatus. Spectra data were recorded as follows: uv, Beckman D. B. spectrometer; ir, Perkin-Elmer 137 or 237 spectrometer; nmr, Varian T-60 spectrometer. Chemical shifts, δ (parts per million) were determined using tetramethylsilane as an internal standard, except when D_2O was the solvent and when tetramethylsilane in carbon tetrachloride was used as an external standard. Mass spectra were recorded on an AEI MS902 spectrometer through the cooperation of the Research Triangle Mass Spectrometry Center, which is sponsored by Grant No. FR-0330-02, National Institutes of Health.

1-Benzyl-2-cyanopyridinium Bromide[9] (**4**, **X = Br**).—A solution of 2-cyanopyridine (20 g, 0.19 mol) and benzyl bromide (35 g, 0.20 mol) in sulfolane (20 ml) was allowed to stand for 24 hr at 45°. The solid which formed was triturated with ethyl acetate and then recrystallized from methanol–ethyl acetate as colorless plates, mp 136–137°, yield 37.5 g (72%).

Anal. Calcd for $C_{13}H_{11}BrN_2$: C, 56.74; H, 4.03; N, 10.18. Found: C, 56.69; H, 4.19; N, 10.05.

The tetrafluoroborate salt, prepared by addition of a saturated solution of sodium tetrafluoroborate to an aqueous solution of **4** bromide, crystallized from water as needles, mp 95–97°.

Anal. Calcd for $C_{13}H_{11}BF_4N_2$: C, 55.36; H, 3.93; N, 9.93. Found: C, 55.48; H, 3.80; N, 9.54.

11-Aminoacridizinium Perchlorate (**6**, **X = ClO_4**).—The reaction flask (under nitrogen) containing 10 g of the bromide salt (**4**, X = Br) was cooled in an ice–water bath while 40 ml of concentrated sulfuric acid was added slowly. A vigorous stream of nitrogen was passed through the solution throughout in order to sweep out the hydrogen bromide and bromine formed. Fifteen minutes after addition was complete the mixture was heated for 15 min on a steam bath. The cooled solution was added to ice-cold anhydrous ether, precipitating a brown oil. The ether (containing the sulfuric acid) was decanted and the oil was taken up in 150 ml of water. The filtered aqueous solution was made basic with sodium bicarbonate and the resulting solution was washed several times with chloroform. To the aqueous solution an excess of saturated sodium perchlorate solution was added and the resulting yellow solid collected and dried in a vacuum desiccator, affording 3.8 g (35%). The analytical sample was crystallized from water as yellow needles: mp 247–250° dec; uv max (95% C_2H_5OH) 245 nm (log ε 4.90), 418 (4.71); nmr (CD_3CN) δ 6.1 (s, br, 1, NH_2), 7.3–8.1 (m, 7, aromatic), 8.3–8.5 (m, 1, H-4), 8.75 ppm (s, 1, H-6).

Anal. Calcd for $C_{13}H_{11}ClN_2O_4$: C, 52.99; H, 3.76; N, 9.51. Found: C, 53.09; H, 3.55; N, 9.86

1-(*m*-Methoxybenzyl)-2-cyanopyridinium Bromide (**5**, **X = Br**).—The reaction of *m*-methoxybenzyl bromide[10] with 2-cyanopyridine was carried out as in the preparation of **4** (84% yield). It was recrystallized from water as yellow needles, mp 151–152°

Anal Calcd for $C_{14}H_{13}N_2BrO$: C, 55.10; H, 4.29; N, 9.17. Found: C, 55.07; H, 4.23; N, 9.13.

The tetrafluoroborate of **5**, prepared as in the case of **4**, afforded a 93% yield of product which crystallized from water as needles, mp 116–118°.

Anal. Calcd for $C_{14}H_{13}BF_4N_2O$: C, 53.88; H, 4.20; N, 8.98. Found: C, 53.70; H, 4.15; N, 8.67.

11-Amino-8-methoxyacridizinium Bisulfate (**7**, **X = HSO_4**).—A solution of 5 g of the tetrafluoroborate salt (**5**, X = BF_4) in concentrated sulfuric acid (15 ml) was heated for 1 hr on a steam bath while a vigorous stream of nitrogen was passed through the solution, entraining a considerable quantity of hydrogen fluoride and boron trifluoride. The cooled solution was poured into 1 l. of anhydrous ether, the ether was decanted, and the yellow product was triturated with water (20 ml). The yellow solid was collected, dried, and suspended in methanol (150 ml). To the suspension enough triethylamine was added to make the solution basic, the resulting solution was filtered, and the filtrate was poured into 1 l. of anhydrous ether. The product was collected and washed with hot chloroform to remove any triethylamine

(9) This preparation was first described by J. D. Turner, Ph.D. Dissertation, Duke University, 1965, p 91.
(10) W. Q. Beard, D. N. Van Enam, and C. R. Hauser, *J. Org. Chem.*, **26**, 2310 (1961).

salt. The salt (5, X = HSO_4) crystallized from aqueous ethanol as yellow needles, mp 274–277° dec, yield 3.6 g (70%).

Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.27; H, 4.69; N, 8.54.

The perchlorate (7, X = ClO_4) was prepared by addition of an aqueous solution of sodium perchlorate to an aqueous solution of the bisulfate (7, X = HSO_4) and crystallized from water as yellow prisms: mp 222–224° dec; uv max (95% C_2H_5OH) 250 nm (log ϵ 4.77), 266 (4.76), 305 sh, 342 sh, 420 (4.75); nmr (CF_3COOH) δ 4.20 (s, 3, CH_3), 7.4–9.2 ppm (m, 8, aromatic).

Anal. Calcd for $C_{14}H_{13}ClN_2O_5$: C, 51.79; H, 4.03; N, 8.63. Found: C, 51.69; H, 3.82; N, 8.38.

1-(2-Naphthylmethyl)-2-cyanopyridinium Tetrafluoroborate.—This salt was prepared from 2-bromomethylnaphthalene[11] in essentially the same way as was 4, X = BF_4. It crystallized from acetone–ethyl acetate as prisms: mp 147–148°; yield 81%; nmr (CF_3CO_2H) δ 6.20 (s, 1, CH_2), 7.3–8.9 (m, 10 aromatic), 9.10 ppm (d, 1, pyridyl 6-H).

Anal. Calcd for $C_{17}H_{13}BF_4N_2$: C, 61.48; H, 3.94; N, 8.44. Found: C, 61.75; H, 4.05; N, 8.25

1-(1-Naphthylmethyl)-2-cyanopyridinium Iodide.—A solution of 17.7 g (0.1 mol) of 1-chloromethylnapthalene and 15 g (0.1 mol) of sodium iodide in 150 ml of acetone was allowed to stand at room temperature for 5 hr. To the filtered solution 10.4 g (0.1 mol) of 2-cyanopyridine was added and the solvent was removed under reduced pressure. The residue was allowed to stand for 3 days at 45°. The iodide crystallized from water as red needles, mp 105–106°, yield 17.4 g (47%).

Anal. Calcd for $C_{17}H_{13}IN_2$: C, 54.84; H, 3.52; N, 7.55. Found: C, 54.74; H, 3.64; N, 7.42.

The tetrafluoroborate salt crystallized from water as orange plates, mp 159–160°.

Anal. Calcd for $C_{17}H_{13}BF_4N_2 \cdot H_2O$: C, 58.31; H, 4.32; N, 8.00. Found: C, 58.44; H, 3.86; N, 8.07

Although cyclization of both of the naphthylmethyl-2-cyanopyridinium tetrafluoroborates was attempted, using concentrated sulfuric acid or 100% phosphoric acid, only dequaternization and decomposition were observed.

1-Cyano-2-(*m*-methoxybenzyl)isoquinolinium Tetrafluoroborate (8, X = BF_4).—The quaternization of 9.6 g of 1-cyanoisoquinoline[5] with *m*-methoxybenzyl bromide was carried out in the usual way. The tetrafluoroborate salt (8, X = BF_4) crystallized from acetone as prisms, mp 181–182°, yield 40%.

Anal. Calcd for $C_{18}H_{15}BF_4N_2O$: C, 59.70; H, 4.17; N, 7.74. Found: C, 59.41; H, 4.12; N, 7.54.

10-Methoxy-13-aminobenz[*a*]acridizinium Tetrafluoroborate (9, X = BF_4).—To a 100% phosphoric acid solution, prepared by the addition of 14 g of phosphorus pentoxide to 31 g of 85% phosphoric acid, 5 g of 2-(*m*-methoxybenzyl)-1-cyanoisoquinolinium tetrafluoroborate was added and the mixture was heated at 130° for 1 hr. The red mixture was poured into ice water containing 5 ml of concentrated tetrafluoroboric acid. The resulting yellow solid was crystallized from aqueous acetone: yield 4.4 g (88%); mp 229–231° dec; uv max (95% C_2H_5OH) 237 nm (log ϵ 4.72), 281 sh, 290 (4.74), 320 (4.71), 330 (4.71) 390 sh, 420 sh, 440 (4.69); nmr (CF_3CO_2H) δ 4.15 (s, 3, CH_3), 7.6–8.6 (m, 9, aromatic), 9.25 ppm (s, 1, H-6).

Anal. Calcd for $C_{18}H_{15}BF_4N_2O$: C, 59.70; H, 4.18; N, 7.74. Found: C, 59.42; H, 4.43; N, 7.42.

11-Acetamidoacridizinium Perchlorate. A. By Use of Acetic Anhydride.—A solution of 11-aminoacridizinium perchlorate (6, X = ClO_4) in 25 ml of acetic acid and 10 ml of acetic anhydride was refluxed under nitrogen for 2 hr. Addition of ethyl acetate to the cooled solution precipitated the 11-acetamidoacridizinium perchlorate (0.43 g, 75%) which crystallized from water as yellow prisms: mp 263–265° dec; uv max (95% C_2H_5OH) 224 nm (log ϵ 4.80), 370 (4.76), 387 (4.76), 408 (4.76); ir (KBr) 1700 cm^{-1} (amide C=O); nmr (CF_3CO_2H) δ 2.2 (s, 3, CH_3), 7.2–8.0 (m, 7, aromatic), 8.5 (d, 1, H-4), 9.4 ppm (s, 1, H-6).

B. By Action of Acetic Acid–Hydrogen Chloride.—A solution of 6, X = ClO_4, in 30 ml of acetic acid was refluxed for 2 hr while hydrogen chloride was passed through the solution. The product, isolated and crystallized as before, afforded 0.35 g (61.3%).

Anal. Calcd for $C_{15}H_{13}ClN_2O_5$: C, 53.50; H, 3.90; N, 8.32. Found: C, 53.35; H, 3.93; N, 8.12.

2-(3-*v*-Triazolo[1,5-*a*]pyridyl)benzaldehyde (11).—A solution of 0.5 g of 11-aminoacridizinium perchlorate (6, X = ClO_4) in 50 ml of water at 5° was treated with an excess of a saturated aqueous sodium nitrite solution and then with 5 ml of 1 *N* hydrochloric acid. The solution was allowed to warm to room temperature (30 min) and the insoluble product was collected. The aldehyde 11 was obtained as a tan solid (0.3 g, 79%) which was crystallized from ethanol (charcoal) as needles: mp 191.5–192.5; uv max (95% C_2H_5OH) 246 nm (log ϵ 4.55), 288 (4.51), 318 (4.51); ir (KBr) 1680 cm^{-1} (CH=O); nmr ($CDCl_3$) δ 7.0–8.0 (m, 6, aromatic), 8.2 (d, 1, H-4), 8.9 (d, 1, H-7), 10.4 ppm (s, 1, CHO); mass spectrum *m/e* 223.0741 (M^+), 195, 167, 140, 139.

Anal. Calcd for $C_{13}H_9N_3O$ (223.0745): C, 69.95; H, 4.06; N, 18.82. Found: C, 69.98; H, 3.78; N, 18.69.

The 2,4-dinitrophenylhydrazone of 11 crystallized from xylene as a red solid, mp 269–270° dec.

Anal. Calcd for $C_{19}H_{13}N_7O_4$: C, 56.56; H, 3.25; N, 24.30. Found: C, 56.78; H, 3.50; N, 24.08.

2-(3-*v*-Triazolo[1,5-*a*]pyridyl)-5-methoxybenzaldehyde (12).—The addition of 1 ml of concentrated hydrochloric acid to a solution of 0.5 g (15.5 mmol) of 11-amino-8-methoxyacridizinium bisulfate (7, X = HSO_4) caused the formation of a precipitate. When the solution was cooled to 0° and treated dropwise with a solution containing 0.5 g (72 mmol) of sodium nitrite in 5 ml of water, the precipitate dissolved to give a deep red solution. The solution was stirred for an additional 30 min at 0–5° and then allowed to warm to room temperature. The solution was extracted with chloroform and the dried (Na_2SO_4) extract was evaporated to dryness under reduced pressure. The residue crystallized as needles from aqueous ethanol (0.33 g, 41%): mp 176–177°; uv max (95% C_2H_5OH) 241 nm (log ϵ 4.70), 293 (4.67), 333 (4.67); ir (KBr) 1675 cm^{-1} (CH=O); nmr ($CDCl_3$) δ 4.0 (s, 3, CH_3), 6.9–7.9 (m, 6, aromatic), 8.9 (d, 1, H-7), 10.3 ppm (s, 1, CHO).

Anal. Calcd for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.37; N, 16.59. Found: C, 66.51; H, 4.43; N, 16.50.

11-Hydroxyacridizinium Perchlorate (13, X = ClO_4).—A solution of 11-aminoacridizinium perchlorate (1 g) in 20 ml of 1 *N* hydrochloric acid was heated for 30 min on a steam bath. When the hot solution was filtered and allowed to cool, 11-hydroxyacridizinium perchlorate (13, X = ClO_4) crystallized as yellow needles: yield 0.85 g (85%); mp 110° (unchanged by recrystallization); nmr (CF_3CO_2H) δ 7.7–9.0 (m, 8, aromatic), 9.45 ppm (s, 1 H, H-6).

Anal. Calcd for $C_{13}H_{10}ClNO_5$: C, 52.81; H, 3.41; N, 4.74. Found: C, 52.70; H, 3.43; N, 4.81.

Betaine of 11-Hydroxyacridizinium Ion.—A solution of 1 g of 11-hydroxyacridizinium perchlorate in 25 ml of water was made basic by addition of solid sodium bicarbonate and the solution was extracted several times with chlororm. The combined extracts were dried (sodium sulfate) and concentrated and the red residue was recrystallized from methanol–ether to give the betaine as a yellow solid (0.32 g, 32%): mp 260–265° dec; uv max (95% C_2H_5OH) 243 nm (log ϵ 4.79), 418 (4.72); mass spectrum 195.0716 (M^+) (calcd for $C_{13}H_9NO$, 195.06841), 167, 139.

11-Acetoxyacridizinium Perchlorate.—A solution of 0.3 g of 13, X = ClO_4, in 20 ml of acetic anhydride was heated for 15 min on a steam bath. Addition of ether to the cooled solution precipitated the acetate as a yellow solid, 0.29 g (84%). The solid crystallized from aqueous acetone as yellow needles: mp 220–224° dec; uv max (95% C_2H_5OH) 250 nm (log ϵ 4.87), 371 (4.67), 388 (4.68), 411 (4.67); ir (KBr) 1775 cm^{-1} (ester C=O); nmr (CF_3CO_2H) δ 2.5 (s, 3, CH_3), 7.45–8.4 (m, 7, aromatic), 8.85 (d, 1, H-4).

11-Hydroxy-8-methoxyacridizinium Bisulfate (14, X = HSO_4).—The hydrolysis of 1 g of 7 bisulfate was carried out essentially as in the hydrolysis of 6: yield 70% of yellow needles; mp 146–148°; uv max (95% C_2H_5OH) 245 nm (log ϵ 4.82), 262 sh, 286 (4.79), 302 (4.78), 334 (4.76), 418 (4.80); nmr (D_2O) δ 3.5 (s, 3, CH_3), 6.0–8.3 ppm (m, 8, aromatic).

Biological Testing.—Screening tests carried out by agencies under contract to the Drug Research and Development branch of the National Cancer Institute have demonstrated that compound 9, X = BF_4, has reproducible minimal activity in the KB cell culture test.

Registry No.—4 (X = Br), 6318-97-4; 4 (X = BF_4), 42031-31-2; 5 (X = Br), 42031-32-3; 5 (X = BF_4), 42031-33-4; 6 (X = ClO_4), 42031-34-5; 7 (X = HSO_4), 42031-35-6; 7 (X = ClO_4), 42031-36-7; 8 (X = BF_4), 42031-37-8; 9 (X = BF_4),

(11) N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 5044 (1952).

42031-38-9; 11, 42031-39-0; 11 2,4-DNP, 42031-40-3; 12, 42031-41-4; 13 (X = ClO_4), 42031-42-5; 13 betaine, 42031-43-6; 14 (X = HSO_4), 42031-44-7; 1-(2-naphthylmethyl)-2-cyanopyridinium tetrafluoroborate, 42031-45-8; 1-(1-naphthylmethyl)-2-cyanopyridinium iodide, 42031-46-9; 1-(1-naphthylmethyl)-2-cyanopyridinium tetrafluoroborate, 42133-37-9; 11-acetamidoacridizinium perchlorate, 42031-47-0; 11-acetoxyacridizinium perchlorate, 42031-48-1.

Studies on the Synthesis of Benzo[*b*]quinolizinium Salts

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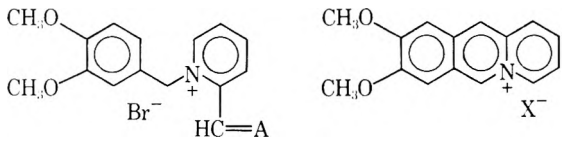
An improved procedure for the preparation of 8,9-dimethoxybenzo[*b*]quinolizinium bromide and a method for the preparation of selected 11-aminobenzo[*b*]quinolizinium bromides are described.

As a consequence of our work on derivatives of 1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (**1**),[1] we became interested in the synthesis of derivatives of the parent aromatic system **2**.[2] These latter sub-

1 **2**

stances have been studied extensively by Bradsher and his coworkers,[3] but our findings differ significantly from those reported.

Bradsher and Dutta[4] reported that cyclization of the pyridinium salt **3a** in concentrated hydrochloric acid at 100°, followed by ion exchange, gave the quaternary chloride **4a**. However, in agreement with the report



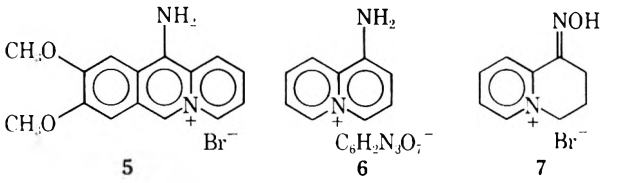
3a, A = O
b, A = NOH

4a, X = Cl
b, X = Br

of Kupchan, Flouret, and Matuszak,[5] we found that the cyclization reaction was accompanied by demethylation, and that we were unable to obtain a pure product.

We decided to modify the procedure of Bradsher and Dutta[4] by using hydrobromic acid to avoid the necessity for ion exchange. We found that cyclization could be effected in 5 min at 75° in the concentrated acid. Pouring the reaction mixture into tetrahydrofuran precipitated the product **4b** as a yellow solid which could be obtained analytically pure after one recrystallization.

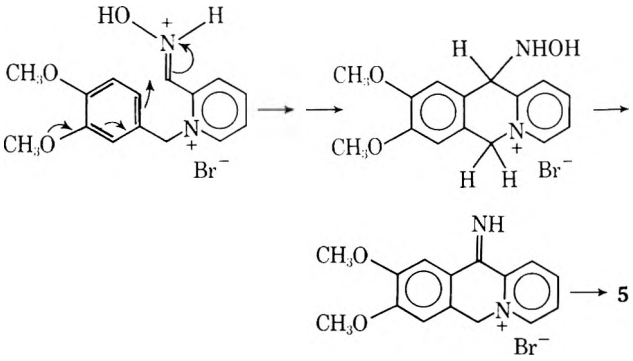
Bradsher has also advocated the preparation of benzo[*b*]quinolizinium salts by cyclization of the appropriate quaternary oxime,[6] and we attempted to prepare **4b** from **3b**. Conducting the reaction in hydrobromic acid as described above gave a product the nmr spectrum of which shows two equivalent exchangeable protons and only seven aromatic protons. Microanalysis indicated the presence of an additional nitrogen atom. These data suggested that the product is the 11-amino derivative **5**. This structure is analogous to that of the bicyclic primary amine picrate salt **6** prepared by Collicut and Jones[7] by treatment of the quaternary oxime **7** with acetic anhydride and con-



5 **6** **7**

centrated sulfuric acid, followed by hydrolysis of the acetamide of **6**.

It is tempting to suggest that the conversion of **3b** to **5** proceeds by way of the nitrile,[8] but dehydration of an aldoxime with aqueous acid is unprecedented. Normally an oxime would be hydrolyzed under these conditions. In this case we suggest that instead of being attacked by water, the protonated oxime cyclizes. The resulting intermediate then dehydrates to the imine, which is a tautomer of **5**. Presumably such a



dihydroaromatic hydroxylamine derivative is also involved in the acid-promoted conversion of 3,5-dimethylcyclohexenone oxime to 3,5-xylylamine,[9] and transformations similar to the above are involved in Semmler–Wolff aromatizations in general.[7,10]

The oximes **8a** and **8b** underwent cyclization to the 11-amino derivatives **9a** and **9b**, respectively. How-

(1) J. W. H. Watthey and K. J. Doebel, U. S. Patent 3,484,443 (1969) [*Chem. Abstr.*, **72**, 3396f (1970)].

(2) K. J. Doebel and J. W. H. Watthey, S. African Patent 6,707,635 [*Chem. Abstr.*, **70**, 96652h (1969)].

(3) For a review see C. K. Bradsher, *Accounts Chem. Res.*, **2**, 181 (1969).

(4) C. K. Bradsher and N. L. Dutta, *J. Amer. Chem. Soc.*, **82**, 1145 (1960).

(5) S. M. Kupchan, G. R. Flouret, and C. A. Matuszak, *J. Org. Chem.*, **31**, 1707 (1966).

(6) C. K. Bradsher, T. W. G. Solomons, and F. R. Vaughan, *J. Org. Chem.*, **25**, 757 (1960).

(7) A. R. Collicut and G. Jones, *J. Chem. Soc.*, 4101 (1960).

(8) Cyclization of analogous nitriles to 11-aminobenzo[*b*]quinolizinium salts is described in the accompanying paper: C. K. Bradsher and L. S. Davies, *J. Org. Chem.*, **38**, 4167 (1973).

(9) L. Wolff, *Justus Liebigs Ann. Chem.*, **322**, 351 (1902).

(10) M. V. Bhatt, *Experientia*, **13**, 70 (1957).

TABLE I

1-BENZYLPYRIDINIUM BROMIDES[a]

Compd	Yield, %	Mp, °C	Calcd, % C	H	Br	N	Found, % C	H	Br	N
3b	85	168–171.5	50.99	4.85	22.63	7.93	51.29	4.96	22.51	7.86
8a[b]	86	149–150	50.99	4.85	22.63	7.93	50.83	5.00		8.09
8b	68	155–157.5	52.32	5.22	21.76	7.63	52.32	5.22	21.49	7.63
8c	91	166.5–168	50.14	5.00	20.85	7.32	50.18	4.79	21.04	7.30

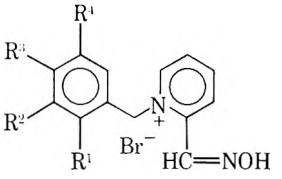
[a] The benzyl bromide starting materials were obtained as follows: 3,4-dimethoxy-, ref 13; 2,3-dimethoxy-, R. D. Haworth and W. H. Perkin, *J. Chem. Soc.*, **127**, 1437 (1925); 3,4-dimethoxy-2-methyl-, see below; 3,4,5-trimethoxybenzyl bromide was prepared by the method Haworth and Perkin used for the 2,3-dimethoxy compound and was used without purification. [b] Recrystallized from methanol–ethyl acetate.

TABLE II

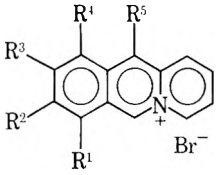
BENZO[b]QUINOLIZINIUM BROMIDES

Compd	Yield, %	Mp, °C	Calcd, % C	H	Br	N	Found, % C	H	Br	N
5[a]	89	267–267.5	53.75	4.51	23.84	8.36	53.85	4.45	23.67	8.66
9a	66	252–255	53.75	4.51	23.84	8.36	54.02	4.60	23.70	8.64
9b	70	223–223.5	52.61	4.69	21.88	7.67	52.53	4.90	21.75	7.62
9c[b]	62	228–231	57.49	4.83	23.92	4.18	57.19	4.66	23.73	4.49
9e	72	258–260	56.27	4.41	24.96	4.38	56.46	4.51	25.13	4.33

[a] Recrystallized from methanol–ethanol. [b] The mother liquor yielded a small amount of the 11-NH_2 derivative **9d**, mp 259.5–260°. *Anal.* Calcd: C, 55.02; H, 4.91; Br, 22.88; N, 8.02. Found: C, 54.82; H, 4.88; Br, 22.90: N, 7.86.



8a, $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$
b, $R^1 = H$; $R^2 = R^3 = R^4 = OCH_3$
c, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = H$
d, $R^1 = R^4 = OCH_3$; $R^2 = R^3 = H$



9a, $R^1 = R^2 = OCH_3$; $R^3 = R^4 = H$; $R^5 = NH_2$
b, $R^1 = H$; $R^2 = R^3 = R^4 = OCH_3$; $R^5 = NH_2$
c, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = R^5 = H$
d, $R^1 = CH_3$; $R^2 = R^3 = OCH_3$; $R^4 = H$; $R^5 = NH_2$
e, $R^1 = R^4 = OCH_3$; $R^2 = R^3 = R^5 = H$
f, $R^1 = R^4 = OH$; $R^2 = R^3 = R^5 = H$

ever, cyclization of the oxime **8c** gave almost exclusively **9c**, although a small quantity of the amine **9d** was isolated in a pure state.

Cyclization of **8d**[11] gave exclusively the substance lacking the amino group **9e**. Bradsher and Barker[11] obtained this substance as the mixed salt with hydroxylamine hydrobromide. Ion exchange of the picrate gave the bromide salt; we obtained the bromide directly—one recrystallization gave the pure salt.

Those substances which cyclize to give only the amino derivative have a methoxy group para to the site of cyclization, flanked by a methoxy group and a hydrogen atom. Those substances which gave little or no amino compound presumably react more slowly, enabling oxime hydrolysis to occur. In **8c** the steric requirements of the methyl group will reduce the resonance effect of the adjacent methoxy group. In the case of **8d** the results can be rationalized by consideration of the steric effects of the methoxy group ortho to the site of cyclization.

In contrast to an earlier report,[11] demethylation of **9e** was found to proceed normally in concentrated hydrobromic acid, to give the known hydroquinone derivative **9f**.[12]

Experimental Section

All melting points (uncorrected) were determined on a Thomas-Hoover Uni-melt capillary melting point apparatus. Nmr spectra were obtained on a Varian A-60A spectrometer (Me_4Si).

1-(3,4-Dimethoxybenzyl)-2-formylpyridinium Bromide (3a).[4]—A solution of 3,4-dimethoxybenzyl bromide[13] (65 g) and freshly distilled 2-picolinaldehyde (31 g) in dimethylformamide (10 ml) was maintained at 30° for 18 hr. The solid was slurried in ethyl acetate (250 ml), filtered, and dried, giving 81 g of **3a**, mp 118–128°.

Anal. Calcd for $C_{15}H_{16}BrNO_3$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.08; H, 5.07; N, 4.37.

8,9-Dimethoxybenzo[b]quinolizinium Bromide (4b)—**3a** (10 g) was finely ground and added to 48% hydrobromic acid (25 ml) previously heated to 75°. After 5 min at 75° the solution was poured into tetrahydrofuran (400 ml) with stirring. The yellow solid was recrystallized from methanol–ethanol to give 6.3 g of **4b**: mp 247–250°; nmr (DMSO-d_6) δ 10.13 (s, 1), 9.21 (m, 1) 8.81 (s, 1), 8.36 (m, 1), 7.82 (m, 2), 7.64 (s, 2), 4.08 (s, 3), 4.03 (s, 3).

Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27: H, 4.41; Br, 24.96; N, 4.38. Found: C, 56.01; H, 4.56; Br, 24.81; N, 4.34.

The 1-benzylpyridinium bromides 3b and 8a–c were obtained by the method used by Bradsher and Barker[11] for the preparation of **8d**. Details are given in Table I. Reaction time was 18 hr at 30°; recrystallization was from methanol.

The benzo[b]quinolizinium bromides 5 and 9a–c,e were obtained from **3b** and **8a–d**, respectively, using the general method employed for the conversion of **3a** to **4b**. Details are given in Table II. Recrystallization was from ethanol.

7,10-Dihydroxybenzo[b]quinolizinium Bromide (9f).[12]—A solution of 6.4 g of **9e** in 25 ml of 48% hydrobromic acid was refluxed for 3 hr. The reaction mixture was cooled and the product was recrystallized twice from 48% hydrobromic acid, extracted exhaustively with methanol in a Soxhlet apparatus (leaving a small

(11) C. K. Bradsher and M. W. Barker, *J. Org. Chem.*, **29**, 61 (1964).

(12) D. F. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **30**, 252 (1965).

(13) L. D. Haworth, W. H. Perkin, and J. Rankin, *J. Chem Soc.*, **127** 1445 (1925).

amount of a black, insoluble substance), and finally recrystallized from methanol to give 2.3 g of **9f**, mp 315–318° dec.

Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.44; H, 3.46; Br, 27.36; N, 4.80. Found: C, 53.37; H, 3.50; Br, 27.30; N, 4.84.

3,4-Dimethoxy-2-methylbenzyl Bromide.—A mixture of 2,3-dimethoxytoluene (80 g), bromomethyl methyl ether (137 g), and glacial acetic acid (88 ml) was maintained at 30° for 8 hr. The reaction mixture was poured into ice–water and the solid was recrystallized from hexane to give 73 g of the benzyl bromide, mp 66–68°. Structural assignment was by analogy with the corresponding chloro compound.[14]

(14) E. D. Hornbaker and A. Burger, *J. Amer. Chem. Soc.*, **77**, 5314 (1955).

Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35; Br, 32.39. Found: C, 48.97; H, 5.40; Br, 32.39.

Acknowledgments.—We thank Dr. V. Boekelheide for useful discussions, and the Analytical Research Department for analyses and spectral data.

Registry No.—**3a**, 42031-49-2; **3b**, 21852-33-5; **4b**, 24403-47-2; **5**, 21852-31-3; **8a**, 42031-53-8; **8b**, 21852-51-7; **8c**, 21831-11-8; **9a**, 42031-56-1; **9b**, 21852-49-3; **9c**, 21831-08-3; **9d**, 21852-24-4; **9e**, 42031-60-7; **9f**, 3919-24-2; 3,4-dimethoxy-2-methylbenzyl bromide, 21831-10-7; 2,3-dimethoxytoluene, 4463-33-6; bromomethyl methyl ether, 13057-17-5.

Kinetics in the Thermolysis of 1-Arylethyldimethylamine Oxides in Aqueous Media[1]

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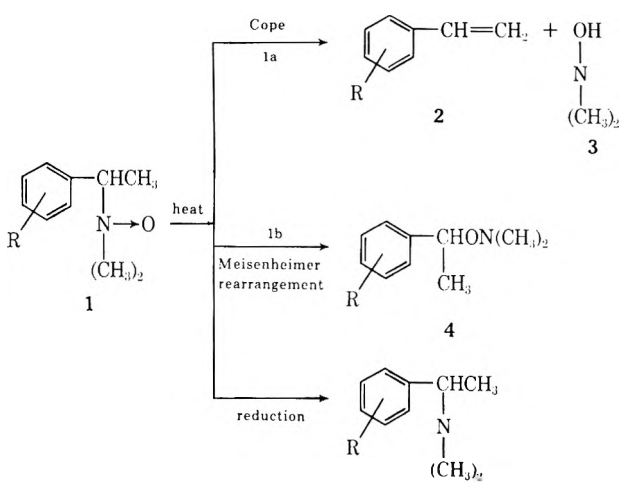
The kinetics of the thermolysis of unsubstituted and 1-(*p*-methoxy, *o*-methoxy, *p*-methyl, *o*-methyl, *p*-chloro, and *p*-nitro)phenylethyldimethylamine oxides, **1**, at 94° in aqueous media have been determined by nuclear magnetic resonance spectroscopy. Essentially only the Cope elimination reaction occurred with all amine oxides except in the last two cases, those containing *p*-Cl and *p*-NO_2 substituents. With amine oxides possessing electron-withdrawing substituents, the Meisenheimer rearrangement and the formation of the free tertiary amine complicated the evaluation of the rate of the Cope elimination reaction. Good agreement was obtained between log k/k_0 with Hammett's σ constants for the amine oxides possessing electron-donating substituents which showed a ρ of −6.5. Activation parameters for the *p*-OMe derivative in the Cope thermolysis are E_a = 39.6 kcal/mol and $\Delta S^\dagger$ = 32 eu. Mechanistic implications of the Cope reaction are discussed in light of these data.

Several studies have shown that during the thermolysis of benzyl tertiary amine oxides **1** there are at least three main competing reactions occurring (Scheme I),

SCHEME I



the Cope elimination, 1a, the Meisenheimer rearrangement, 1b, and reduction to the tertiary amine. In the Cope elimination the olefin **2** and dimethylhydroxylamine **3** are formed. The Meisenheimer rearrangement involves a migration of benzyl group from nitrogen to oxygen yielding **4**.[2a]

The competition between these three reactions is markedly affected by the nature of the groups on the tertiary amine oxides. Essentially, only the Cope reaction occurs unless benzyl or allyl groups are involved. In cases where the Cope elimination reaction cannot occur, it has been shown that the electron-withdrawing groups on the benzyl group (*e.g.*, NO_2) enhance the Meisenheimer reaction.[2b] No reports, however, have appeared of a substituent effect study where the two reactions compete from the same starting material.

This study has been directed to the kinetics of the Cope reaction, a Hammett $\rho\sigma$ study, a determination of Arrhenius activation parameters, effects of water on the reaction rate constants, and proximity effects in the Cope reaction. These aspects of the Cope reaction have not been reported. Also reported is additional esr evidence for a radical intermediate in the Meisenheimer rearrangement.

Results

Aqueous Media.—The thermolysis of the tertiary amine oxides was carried out in aqueous media for various reasons. Amine oxides are difficult to obtain pure, since they readily form hydrates. The removal of the water from the hydrate is difficult without partial decomposition of the amine oxide, even at reduced pressure.[3] Lepley, Cook, and Willard[3b] attempted to remove all water from the oxide of *N*,*N*-dimethylbenzylamine by a freeze-drying process at 0.01 Torr. The hydroscopic, free-flowing white powder proved to be the monohydrate with an nmr ($CHCl_3$) peak at δ 5.03. This is also the position found for the water

(1) This paper was presented in part at the 28th Annual Northwest Regional Meeting of the American Chemical Society, Pullman, Wash., June 1973, Abstract ORGN, 26.

(2) (a) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Amer. Chem. Soc.*, **71**, 3929 (1949); (b) U. Schöllkopf, U. Ludwig, M. Patsch, and W. Franken, *Justus Liebigs Ann. Chem.*, **703**, 77 (1967).

(3) (a) G. P. Shulman, P. Ellgen, and M. Connor, *Can. J. Chem.*, **43**, 3459 (1965); (b) A. R. Lepley, P. M. Cook, and G. F. Willard, *J. Amer. Chem. Soc.*, **92**, 1101 (1970).

TABLE I

EFFECT OF VARYING THE WATER CONCENTRATIONS OF THE THERMOLYSIS OF TERTIARY AMINE OXIDES[a]

Registry no.	1-Arylethyldimethylamine oxide Substituent	$k \times 10^5$, sec^{-1} (94.5°) About 33% water[b]	65–70% water	75–80% water
42142-05-2	*p*-OCH_3	117, 115, 117[c]	86.6, 86.6[d]	79.0, 79.0[d,e]
42142-06-3	*p*-CH_3	31.0, 31.1[c]	17.2	14.6[e]
42142-07-4	H	6.0, 5.8[c]	1.5	1.47
42142-08-5	*p*-Cl	53.0, 62.2[c,f]	14.0, 12.2[c,f]	
42142-09-6	*p*-NO_2	6.93, 7.1[c,f]	10.0, 10.7[c,f]	
42142-10-9	*o*-OCH_3		12.7, 12.7[d]	
42142-11-0	*o*-CH_3			13.47, 13.88[c]

[a] Based on the loss of starting amine oxide as measured by nmr. The precision of the experiments was greater than 10%. [b] Attempts were made to remove all of the water *in vacuo* in a rotatory evaporator. However, not all of the water could be removed by this technique owing to decomposition. The final traces of water most likely could not be removed even by freeze drying.[3] [c] Multiple determinations. [d] The same value was obtained for the rate constant as measured by the loss of amine oxide or the formation of the dimethylhydroxyl amine. [e] 94.0°. [f] These values represent the sum of three rate constants: Cope elimination, Meisenheimer rearrangement, and the reduction of the amine oxide to the free amine by the hydroxylamine product. Therefore, it was not feasible to determine quantitatively the several reaction rates.

absorption in our experiments. The advantage of using water is that the amine oxides dissolve readily in water and yet decompose below 100°. Therefore, a study of their thermolysis is readily attainable in aqueous media. A driving force in the Cope elimination may be a basic attack by an unshared electron pair of the oxygen on the β hydrogens. This is supported by the fact that addition of water reduces the rate of reaction, as shown in Table I. However, when sufficient water is added, the rate is not so dependent on the water concentration. Hence, kinetic studies were made at water concentrations where small changes in concentration did not influence the rate. The water concentration appears also to reduce the rate of the Miesenheimer rearrangement. However, mechanistically these reactions are different.

Rate Measurements by Nmr.—The two methyl groups on the unpyrolyzed 1-arylethyldimethylamine oxide (~3.05) have different shifts than the same methyl groups which appear in the product, dimethylhydroxylamine (2.77 ppm). These strongly absorbing hydrogens provided an ideal means to follow the kinetics of the Cope elimination with nmr. [The nmr spectrum for a representive compound, 1-(*p*-methoxyphenyl)-ethyl-*N*,*N*-dimethylamine oxide, and a table listing the absorptions in the nmr spectra for the amine oxides are given in supplementary microfilm material.] Furthermore, measuring the rate of disappearance of the starting amine oxide and the appearance of the dimethylhydroxylamine considerably reinforced the precision of the rate measurement where the competing reactions, the Meisenheimer rearrangement and the reduction of the tertiary amine, were not important.

The kinetic results are shown in Table I. 1-*p*-Methoxyphenylethyldimethylamine oxide in aqueous solution pyrolyzes cleanly to two products, *p*-methoxystyrene and dimethylhydroxylamine. Nmr did not indicate any Meisenheimer rearrangement product from this compound. Therefore, Arrhenius measurements were obtainable for this compound (Table II). No Meisenheimer product resulted from the *o*-methoxy derivative as well. A first-order kinetics plot for the thermolysis of the *p*-methoxy derivative is given in the supplementary microfilm material.

Nmr showed that the *o*- and *p*-methoxy derivative proceeded exclusively to the Cope elimination product with no indication of the Meisenheimer product; the *o*- and *p*-methyl derivative gave 98–99% Cope product and the unsubstituted 1-phenylethyldimethylamine oxide pyrolyzed 95–97% *via* the Cope reaction and 3–5% *via* the Meisenheimer rearrangement. With the *p*-Cl and *p*-NO_2 derivatives, the extent of the Meisenheimer rearrangement and the reduction to the free tertiary amine increased appreciably and for these reasons, evaluation of the extent of the Cope reaction could not be suitably obtained.

TABLE II

RATE OF THERMOLYSIS OF 1-*p*-METHOXYPHENYLDIMETHYLAMINE OXIDE AS A FUNCTION OF TEMPERATURE[a]

Temp, °K	351.5	360.0	363.0	367.0	367.5
$k \times 10^5$, sec^{-1}	7.46	18.6	30.4	79.0	86.6

[a] These rate data were determined by nmr by noting the disappearance of the amine oxide and the rate of formation of the dimethylhydroxylamine. The decomposition followed excellent first-order kinetics at each temperature. The Arrhenius activation parameters calculated, using a computer, from these data are E_a = 39.6 kcal/mol and $\Delta S^\dagger$ = 32 eu.

Electron spin resonance studies revealed that the free radical $(CH_3)_2NO\cdot$ was formed in all of the thermolyses even in the case where no nmr evidence of a Meisenheimer rearrangment was found, *e.g.*, with the *o*- and *p*-methoxybenzyl derivatives. This is a very stable free radical and one that is readily characterizable with esr. The splitting into 21 peaks is as theory predicts for this radical. The a_H splitting was determined to be 14.2 G and the a_N was 16.6 G. As the temperature was lowered the radical signal gradually disappeared. This very sensitive method of detecting free radicals (one part per 100 million) concurs that the Meisenheimer rearrangement occurs *via* a radical cleavage–recombination mechanism, and furthermore that, although nmr did not reveal a Meisenheimer reaction in the case of the *o*- and *p*-methoxy derivative, it was shown to occur to a very limited extent. (See paragraph at the end of paper about supplementary material.)

Hammett $\rho\sigma$ Plot.—The results in Table I clearly demonstrate that electron-releasing groups activate the Cope rearrangement in arylethyldimethylamine oxides. From the rate of loss of starting amine oxide and the rate of formation of dimethylhydroxylamine, it was evident that electron-withdrawing groups enhance the Meisenheimer rearrangement. A limited Hammett

$\rho\sigma$ plot of the Cope elimination using only data from those compounds in which the radical rearrangement occurred to less than 5% showed a ρ value of -6.5. The limits of error for this result are less than ± 2. A better plot was obtained with σ than with σ^+.

Arrhenius Parameters.—As stated, the 1-*p*-methoxyphenyldimethylamine oxide pyrolyzed almost exclusively *via* the Cope elimination reaction. Therefore, Arrhenius activation parameters for this reaction were attainable and were found to be E_a = 39.6 kcal/mol and $\Delta S^\dagger$ = 32 eu. The data from which these activation parameters were calculated, using a computer, are shown in Table II.

Para to ortho ratio in the Cope elimination reaction rates showed (Table I) an appreciable proximity effect for the methoxy substituent (p-OCH_3/o-OCH_3 = 6.8) but no proximity effect was observed for the methyl substituent (p-CH_3/o-CH_3 = 1.1). This, very likely, is another example of steric inhibition of resonance.

Experimental Section

Materials.—The amine oxides were prepared through several steps starting from the corresponding acetophenones which were available from Aldrich Chemical Co. The purity was checked using melting points and refractive indices. They follow: p-Cl, n^{20}_4 1.544; p-CH_3, n^{20}_4 1.5334; o-CH_3, n^{20}_4 1.5322; o-OCH_3, n^{20}_4 1.5393; p-NO_2, mp 78–80°; p-OCH_3, mp 34–37°. Acetophenone (98.8%) was obtained from Baker Analyzed Reagent Co.

1-Arylethylamines were synthesized by following the procedure described by Ingersoll[4] starting with the acetophenone derivative and ammonium formate. Ammonium formate was prepared from ammonium carbonate and formic acid. The amines were also identified by ir spectroscopy and mass spectral analysis, and were shown to be pure. (See paragraph at end of paper for supplementary material on yields, nmr chemical shifts, boiling points, etc.)

1-Arylethyldimethylamines were formed from the primary amines by the action of formaldehyde in the presence of formic acid.[5] Yields, nmr chemical shifts, and boiling points are given in the supplementary material. The amines were also identified by ir spectroscopy and mass spectral analysis.

1-Arylethyldimethylamine Oxides.—The tertiary amines were dissolved in an equal volume of methanol. To this solution was added slowly four volumes of a 30% solution of hydrogen peroxide. The mixture was stirred magnetically at room temperature for 96 hr. After the oxidation was completed, 50 mg of platinum black (Fischer) was added to decompose the excess hydrogen peroxide and the mixture was stirred at room temperature for an additional 48 hr. Potassium iodide–starch test paper was used to confirm the complete absence of hydrogen peroxide. The black suspension was filtered over Whatman No. 1 filter paper (this grade proved to be necessary) and the filtrate was evaporated at room temperature in a rotary evaporator to $\frac{1}{2}$–$\frac{1}{3}$ volume. The concentration of amine oxide was shown by nmr to be about 33% (aqueous solution). Although the per cent yield could not be determined accurately, the tertiary amine in each case appeared to be converted quantitatively to its amine oxide, as no unreacted tertiary amine, or any other organic material, was detectable by nmr.

As stated, the nmr showed no sign of an organic impurity. Carbon, hydrogen, and nitrogen analyses were not feasible because the oxides were in their hydrate form. Mass spectrographic analyses showed a small molecular ion with a base peak of M − 61, the loss of dimethylhydroxylamine. These data clearly characterize the purity of the amine oxides.

Kinetic Experiments. Sample Preparation.—The hydrated amine oxides were further diluted with water (see Table I) before introduction into an nmr tube. The tube was filled to a height of 50 mm. The dilution and amount placed in the tube proved to be important. The olefin formed during the course of the reaction is water insoluble and does not dissolve in the aqueous phase. It is critical that the radiowave pass through the aqueous phase only containing the water-soluble tertiary amine oxide reactant and most of the dimethylhydroxylamine product as it is formed. The olefin formed (except in the case of the p-nitro derivative) was less dense than the aqueous medium and formed a thin layer at the top of the nmr tube.

Instrument Calibration.—Nmr spectra were taken on a Varian Associates A-60 analytical nmr spectrometer equipped with a V-6040 nmr variable-temperature controller. The instrument was tuned, the field homogeniety was checked, and the temperature and the integrator were calibrated *before* and *after* each kinetic run. Field width calibration at 500 cycles were taken using the Varian 943346-07 standard with a chemical shift of chloroform of 434.5 cycles with respects to an internal standard of TMS. Integration calibrations were made using Varian test integrator 943346-15 containing 5% ethylbenzene. High-temperature calibrations and tuning were done using ethylene glycol.

The temperature was controlled by a Varian V-6040 variable controller to within ±1° and measured using Varian 943346-05 ethylene glycol standard. The dial of the variable controller was calibrated prior to each kinetic run. Sufficient time (30–40 min) was used to allow the probe area to reach equilibrium temperature. After the ethylene glycol sample was placed in the probe, special care was taken to ensure the best temperature control possible by doubling the recommended stabilization time from 5 to 10 min. After 4 min the $\Delta\delta$ for the ethylene glycol standard held constant. Temperature measurements (using ethylene glycol) were taken immediately before and after each experiment and the results were discarded if the variation in temperature was greater than 1°.

Rate Measurements.—The nmr tubes were left open during the kinetic runs to avoid explosions in the nmr probe. No change in volumes was observed during the kinetic runs. After the sample was placed in the probe, sufficient time (>180 sec) was used to equilibrate the temperature to the operation temperature (94°) before kinetic readings were made. The rate of the disappearance of the reactant, the tertiary amine oxide, was followed by recording the change in intensity of the two singlets at just above 3 ppm with time.

Kinetic measurements (integration of the two singlets) was commenced after a sufficient temperature stabilization period (180 sec). As the peak height decreases, the new height was represented by a_t; therefore

$$\ln a_0/a_t = kt$$

which rearranges to

$$\ln a_t = -kt + \ln a_0$$

A plot of $\ln a_t$ *vs.* t resulted in the evaluation of k (Table I and II). It was not necessary to evaluate a_0.

Similarly, the rate of formation of dimethylhydroxylamine was measured by noting the change in the integration of the singlet at 2.7 ppm and noting its change with time. In the studies of o- and p-methoxy derivatives, where no measureable amount of Meisenheimer rearrangement occurred, the rate constants were the same by both analytical methods (Table I).

Esr Measurement.—The esr measurements were taken on a Varian Associates epr spectrometer No. V-4500 equipped with a 100 KC modulation. The esr spectrum of the free radical $(CH_3)_2$-NO· formed in the thermolysis of 1-aryldimethylamine oxide resulting from a Meisenheimer reaction is given in the supplementary material. The hyperfine splitting values (a_H = 14.2 G and a_N = 16.6 G) were readily measurable from the spectrum. The radical formation was detected at lower temperatures and after shorter times when a p-nitro or p-chloro substituent was present than with amine oxides bearing a methyl or methoxy substituent.

Discussion

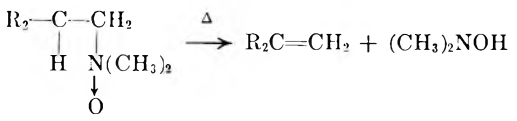
The value of pyrolysis of tertiary amine oxides (the Cope elimination reaction) as a preparative method of alkenes has been reviewed by Cope and Trumbull.[6] In this review, Cope and Trumbull commented briefly

(4) A. W. Ingersoll in "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 503.

(5) H. T. Clark, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

(6) A. C. Cope and E. R. Trumbell in "Organic Reactions," Vol. 2, R. Adams, Ed., Wiley, New York, N. Y., 1960, p 317.

on the mechanism of this elimination reaction and stated that the stereochemical evidence presented by Cram and McCarty[7] (stereoselective cis elimination) "establishes an intramolecular mechanism (for this reaction) involving a planar five-membered cyclic transition state (which) resembles the Chugaev reaction and the pyrolysis of esters." There has been no additional evidence given to support or challenge this mechanism, although all references to the mechanism of this reaction quote Cope and Trumbull's mechanism.



The first-order kinetics reported in this paper supports the intramolecular nature of this reaction, but the large negative ρ (−6.5), the large positive $\Delta S^{\dagger}$ value (+32 eu), and the effect of solvent challenge the simplicity of the mechanism described by Cope and Trumbull for the pyrolysis of tertiary amine oxides in aqueous medium. The data is more in line with a heterolytic cleavage than a quasi-five-membered ring transition. The size and sign of the ρ value argues for a very polarized benzylic carbon in the course of pyrolysis of 1-arylethyldimethylamine oxides. The extent of this charge is appreciably more advanced at the transition state than in the pyrolysis of esters or xanthates.

Amine oxides are particularly polar. Therefore, protic solvents have a major influence on their rate of pyrolysis. The importance water has on the reaction rate is evidenced from the data shown in Table I but is perhaps even more dramatically shown by the work of Cram, *et al.*[8] They reported the ratio of the rate constants (k_{DMSO}/k_{H_2O}) in the pyrolysis of 2-*N*,*N*-dimethylamino-3-phenylbutane oxides as approximately 10^5 for the threo and 10^4 for the erythro isomer. Even larger ratios were reported when tetrahydrofuran was used as solvent.

There are several ways protic solvents can alter the reaction rate. Hydration reduces the nucleophilic attack of the oxygen at the β hydrogen. Furthermore, it reduces the magnitude of the positive charge at nitrogen, which in effect strengthens the C–N$^+$ bond which has the effect of raising the activation energy. The high positive entropy of activation (+32 eu) is associated with the loss of hydration in going from the ground state to the activated state. Heterolysis of the C–N$^+$ bond would also account for part of the large $+\Delta S^{\dagger}$. The high $+\Delta S^{\dagger}$ (32 eu) found for this reaction argues against the formation of a five-membered cyclic transition state as proposed by Cope and Trumbull. The cyclic mechanism is associated with a negative entropy of activation. If indeed a cyclic mechanism is involved, the increase in $\Delta S^{\dagger}$ resulting from the loss of solvation overshadows the small negative $\Delta S^{\dagger}$ brought about from the formation of a cyclic transition state.

As stated above, the significantly negative ρ value (−6.5) indicates that considerable charge develops on the benzylic carbon in the transition state. This is in line with the large $\Delta S^{\dagger}$ and can be interpreted to mean that ions are actually formed in the benzylic system. The large entropy of activation for this reaction when an excess of water is used is in marked contrast to that found by Cram, *et al.*,[8] who studied the effects of water on the Cope elimination reaction in THF and DMSO. Apparently the benzylic system, being capable of developing ions in the Cope reaction, orders the solvent in a different manner than the *N*,*N*-dimethyl-3-phenyl-2-butylamine oxide, which Cram, *et al.*, studied. Although the value of ρ is not so precise as it would have been had more points on the Hammett plot been obtainable, the data are sufficient to set the ρ value between −4.5 and −8.5. Because the medium stabilized the developed charge on carbon, it is not necessary for there to be *enhanced* stabilization by methoxy substituents on the ring; therefore, σ gives a better plot than σ^+.

Further evidence for a highly developed charge in the transition state comes from a proximity effect study. A careful study was made of the para/ortho ratio for OCH_3 and CH_3 in the pyrolysis of 1-arlethyldimethylamine oxides. The para/ortho ratio for OCH_3 was 6.8 and for CH_3 was 1.1. This demonstrates that the reaction is sensitive to the conformation of the methoxy substituent. When a methoxy substituent is placed ortho to the reacting site, it cannot rotate into its most favorable conformer for charge delocatization. The conformation is not critical for methyl. As stated, this reinforces the concept of a highly developed charge in the transition state. A similar study in gas-phase pyrolysis of esters where the ρ value is only −0.67 revealed the para/ortho ratio for methoxy to be 1.67.[9]

Based on these data, the following mechanism for the Cope elimination is proposed. Heating causes a less ordered transition state by the loss of water, which is the major cause for the large positive $\Delta S^{\dagger}$. As water is lost, the C–N$^+$ bond is weakened and the carbon atoms develops a positive charge. The extent of this charge must be sufficient to account for the large negative ρ value, and if ions are formed this would help account for the positive $\Delta S^{\dagger}$. The stereochemistry (cis elimination) that Cram, *et al.*, observed may not persist in cases such as studied here where heterolysis occurs at the benzylic carbon. If it is determined by further investigation that the reaction is stereoselective with systems containing a benzylic carbon attached to nitrogen, then, in some way (perhaps by a solvent cage), stereoselective loss of a β hydrogen must occur. In the Stevens rearrangement, it has been suggested that a solvent cage has been invoked to explain the retention of configuration.[10a] By removing water molecules, the oxygen becomes sufficiently basic to abstract a β hydrogen. If a quasi-five-membered ring transition state is formed, the polarity around the C–N bond must be sufficient to account for the large negative ρ value. The entropy loss in going through a confined five-membered ring would be overshadowed by the entropy gained due to the loss of water molecules of hydration. The difference between amine oxide pyrolyses and the pyrolyses of esters centers around the extent of charge build-up on the benzylic carbon atom

(7) (a) D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, **76**, 5740 (1954); (b) A. C. Cope and C. L. Bumgardner, *ibid.*, **79**, 960 (1957).

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(10) (a) R. A. W. Johnstone, *Mech. Mol. Migr.*, **2**, 249 (1969); (b) R. D. Bach, D. Andrzejewski, and L. R. Dusold, *J. Org. Chem.*, **38**, 1742 (1973); (c) A. R. Lepley and A. G. Giumanni, *Mech. Mol. Migr.*, **3**, 297 (1971); (d) W. K. Musker *Fortschr. Chem. Forsch.*, **14**, 295 (1970).

and also the effects brought upon by the solvent. Further studies using other solvents such as DMSO and THF will assist in substantiating or challenging these conclusions.

Bach, *et al.*,[10b] have recently discussed the mechanism of the Cope reaction in cyclooctyldimethylamine oxide. With such systems polarization of the C–N bond in the transition state would not be so likely as with the systems discussed in this paper.

The Meisenheimer Rearrangement.—The mechanism of the Meisenheimer rearrangement and similar reactions, which has been debated for many years, has recently been reviewed,[10] and will only be discussed briefly here. However, since the Meisenheimer reaction accompanies the Cope reaction in several cases, it is appropriate that a few comments be made. For many years the Meisenheimer reaction has been linked to the Wittig rearrangement of ethers[11] and the Stevens rearrangement of quaternary ammonium salts.[12] An SNi mechanism has been seriously considered for all three of these reactions, but the present thinking is that they all occur *via* a cleavage–recombination process. The Meisenheimer reaction most likely follows a radical cleavage–recombination mechanism. The detection by esr of the dimethylamine oxide radical found in this study is further evidence that a radical is formed in the Meisenheimer isomerization. This is the first detection by esr of a radical in the *thermally* induced Meisenheimer reaction.

Wragg, *et al.*,[13] reported first-order kinetics for this reaction. Schöllkopf, *et al.*,[2b] reported activation energies between 33 and 40 kcal for the isomerization of benzylmethylaniline oxides in the aqueous alcohol and activation entropies between 19 and 41 eu. Shulman, *et al.*,[3a] have reported an E_a value of 34.2 ± 1 kcal and an entropy of activation of +7.9 ± 2.5 eu for the rearrangement of benzyldimethylamine oxide. In itself, this strongly implies that a cleavage–recombination mechanism operates and that no cyclic transition state (SNi or SNi′) is involved. It was reported, however, that the amount of water present altered the $\Delta S^{\dagger}$ in this reaction (the higher the concentration of water, the larger the $\Delta S^{\dagger}$). Therefore, the significance of the large $\Delta S^{\dagger}$ as evidence for a cleavage mechanism should be attenuated. In addition to these data, Schöllkopf and coworkers have shown that extensive racemization occurs during isomerization of α-deuteriobenzyldimethylamine oxide[14,15] and that a radical intermediate $CH_3N(O\cdot)C_6H_5$ has been detected by esr during the course of this reaction when initiated photochemically.[16] It is significant, as shown in this work, that this same radical can be thermally induced and that it forms appreciably more readily with amine oxides bearing electron-withdrawing substituents, *e.g.*, NO_2 and Cl. Schöllkopf, *et al.*, reported a ρ value of 0.9 in the isomerization of substituted benzylmethylaniline oxides[13] and a ρ of 1.3 in the thermal isomerization of benzylmethylaniline oxides substituted in the aniline ring.[17] They have submitted these results in support of a cleavage–recombination mechanism.

Schöllkopf and coworkers stated that these ρ values are too small for a carbanion mechanism. Lorand and coworkers[18] have presented additional evidence for a radical cage mechanism. They studied the effect of oxygen on the isomerization of *N*-benzyl-*N*-methylaniline *N*-oxide in ethanol–water solution and found that oxygen greatly reduced the yield of the Meisenheimer product (a drop from 89% to 33%); yet the rate constant stayed the same with or without oxygen. Lorand and O'Connell[19] have attempted to generate a 1-adamantyl radical *via* a Meisenheimer rearrangement reaction of 1-dimethylaminoadamantane *N*-oxide without success. Tabushi and associates[20] have provided additional evidence for a radical mechanism by showing that BuSH prohibited the reaction effectively. Allyl groups isomerize in the radical form before recombination.

It is important to realize that radical detection in itself does not establish that the thermally induced Meisenheimer isomerization takes place by a radical-recombination mechanism, since its formation could occur through a side reaction, the oxidation of a dialkylhydroxyl amine, a product of the Cope reaction.

Perhaps the most convincing evidence for an intramolecular rearrangement mechanism in the Meisenheimer reaction comes from the observations by Lepley, *et al.*,[3b] and Ostermann and Schöllkopf,[21] who have observed proton magnetic resonance emission spectra for the nitroxyl and benzyl radicals. Pine[22] has discussed the value and also the cautions to be applied to these results. Craig, *et al.*,[23] supplied evidence for an intermolecular mechanism for the Meisenheimer reaction. Taken as a whole, the evidence for a radical cleavage–recombination mechanism is convincing.

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Registry No.—*p*-Chloroacetophenone, 99-91-2; *p*-methylacetophenone, 122-00-9; *o*-methylacetophenone, 577-16-2; *o*-methoxyacetophenone, 579-74-8; *p*-nitroacetophenone, 100-19-6; *p*-methoxyacetophenone, 100-06-1; acetophenone, 98-86-2.

Supplementary Material Available.—The nmr data for the amine oxides and the primary and tertiary amines are tabulated in three tables and will appear following these pages in the microfilm

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(12) T. S. Stevens, *J. Chem. Soc.*, 3193 (1928); (b) S. H. Pine in "Organic Reactions," Vol. 18, J. R. Adams, Ed., Wiley, New York, N. Y., 1971, p 403.

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(19) J. P. Lorand and E. M. O'Connell, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 9–14, 1972, Abstract ORGN-142.

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edition of this volume of the journal. Also included in the supplement are the nmr spectrum of a representative amine oxide, 1-(*p*-methoxyphenyl)ethyldimethylamine oxide, the first-order kinetics plot for the Cope elimination reaction for this compound, and the esr for the free radical, $(CH_3)_2NO\cdot$. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4172.

Phosphorus-Containing Products from the Reaction of Propargyl Alcohols with Phosphorus Trihalides. II. The Crystal and Molecular Structure of 2-Hydroxy-3,5-di-*tert*-butyl-1,2-oxaphosphol-3-ene 2-Oxide[1,2]

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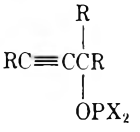
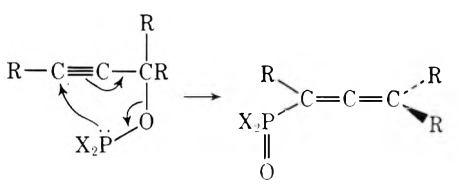
The reactions of 1,3-di-*tert*-butylpropargyl alcohol (2) with PBr_3 in chloroform or carbon tetrachloride gave the expected propargyl and allenic halides plus a 10–20% yield of 2-bromo-3,5-di-*tert*-butyl-1,2-oxaphosphol-3-ene 2-oxide (3-Br). In dioxane or hexane the product was 2,2,6,6-tetramethyl-3,4-heptadiene-3-phosphonic acid (5-OH). Mild hydrolysis of 3-Br led to the title compound, 3-OH, an isomer of 5-OH. Attempts to interconvert 3-OH and 5-OH gave phosphonic anhydride 6. The intermediate, dibromophosphite 4, was observed by nmr. The reaction of 2 with PCl_3 in chloroform afforded 3-Cl in 6% yield. The crystal structure of 3-OH was determined by X-ray crystallography. The constraint inherent in the essentially planar unsaturated five-membered ring distorts the atoms bonded to phosphorus away from their normal tetrahedral positions. The P–O bond lengths for the two exocyclic oxygen atoms are identical (1.51 Å), suggesting that the acid proton is intramolecularly hydrogen bonded equally to both atoms.

The reaction of propargyl alcohols with phosphorus trihalides has long been recognized as a general source of propargyl and allenic halides.[3] These transformations are believed to involve preliminary formation of the corresponding dihalophosphite ester (1). This



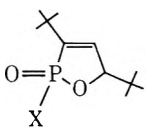
1

normally reacts with two additional alcohol molecules to give a trialkyl phosphite, which is then partitioned to allenic and propargyl products through nucleophilic attack by external halide ion. The possibility exists, however, that the phosphorus atom, with its nonbonding pair of electrons, might function as a competitive *internal* nucleophile. Precedents for such processes include the rearrangement, upon standing, of dialkyl propargyl phosphites to allenic phosphonates,[4] and similar rearrangements during the reaction of phosphorus trichloride (PTC) with propargyl alcohols in the presence of amines.[5,6] Mechanistic data about such transposition has been interpreted in two ways. The fact that the rate of rearrangment seemed to parallel the expected carbonium ion stability of the propargyl fragment led to the postulation of an SNi′ (ion-pair) mechanism.[4] However, absence of the isomeric propargyl phosphonate has been taken as evidence for a concerted mechanism.[5]



(1)

There are three mechanistic extremes for such a rearrangement: stepwise with preliminary C–O heterolysis (SNi′ ion pair), concerted [3,2] sigmatropic shift (thermally allowed in the all-suprafacial mode), or stepwise with preliminary P–C bond formation *via* nucleophilic attack by phosphorus on the triple bond. We recently reported[2] that the reaction of 1,3-di-*tert*-butylpropargyl alcohol (2) with phosphorus tribromide (PTB), either neat or in chloroform, afforded a 10–20% yield of a crystalline, phosphorus-containing compound, in addition to the expected propargyl and allenic bromides. Based on its spectral and chemical properties, this compound was believed to be the novel five-membered oxaphospholene 3-Br. Clearly, the



(3-Br, X = Br, etc.)

occurrence of such a product argues strongly for P–C bond formation preceding C–O bond rupture, even though the 1,3-di-*tert*-butylpropargyl system is quite solvolytically reactive under SN1 conditions.[7] We present here further details of these and related reactions as regards their mechanisms and synthetic utility. In addition we report the results of an X-ray crystallographic study on a derivative of 3-Br, which fully confirms previous and present structural assignments.

(1) This work was presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Sept 1972, Abstract ORGN-117.

(2) Preliminary report: R. S. Macomber, *J. Org. Chem.*, **36**, 2713 (1971).

(3) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967).

(4) V. Mark, *Tetrahedron Lett.*, 281 (1962).

(5) A. P. Boisselle and N. A. Meinhardt, *J. Org. Chem.*, **27**, 1828 (1962).

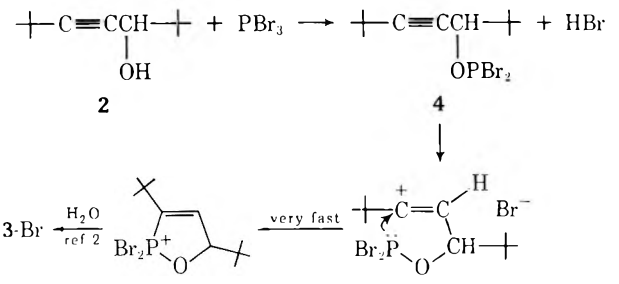
(6) M. Verny and R. Vessiere, *Bull. Soc. Chim. Fr.*, 3004 (1968).

(7) R. S. Macomber, *Tetrahedron Lett.*, 4639 (1970).

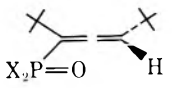
Results and Discussion

The reactions of propargyl alcohols with phosphorus trihalides are usually carried out in the presence of an amine to neutralize the acid liberated during formation of the initial intermediate **1**. However, when the reaction is carried out neat or in chloroform, acid will accumulate and it is not unreasonable to expect the relatively strong HX to protonate the weakly basic sites of reactants and products. As shown in Scheme I,

SCHEME I



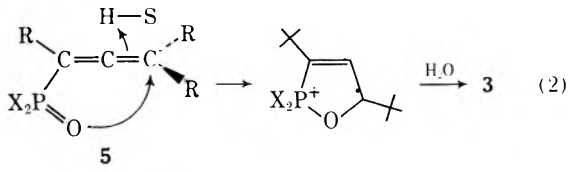
protonation of intermediate **4** would lead to a vinyl cation,[8] which could be easily trapped through internal nucleophilic attack by phosphorus. Because **3**-Br was isolated under these acidic conditions,[2] we attempted to determine the effect on cyclization of variations in the basicity of the medium. In weakly basic dioxane the major products were again the propargyl and allenic bromides, but another colorless, crystalline product was isolated in 15% yield. This new compound decolorized bromine, was soluble in polar organic solvents, and was found to have the molecular formula $C_{11}H_{21}O_3P$. The spectral data[9] immediately rule out heterocyclic derivatives of **3**. Of particular significance were infrared bands indicating an allenic system (1949 cm^{-1}) and a phosphonic acid (1010 and 920 cm^{-1}).[10] The ^{31}P chemical shift substantiated the presence of a phosphonic acid,[11] while the pmr spectrum showed two different *tert*-butyl groups, two equivalent acidic protons, and an olefinic proton coupled to phosphorus. The above data indicate the compound to be 2,2,6,6-tetramethyl-3,4-heptadiene-3-phosphonic acid (**5**-OH). The magnitude of the four-bond P–H coupling constant in **5**-OH (13 Hz) is another example of effective transmission of spin information across an allenic linkage,[12,13] presumably a consequence of some type of "homohyperconjugative" interaction.[14] The complete hydrolysis of the bromines in presumed intermediate **5**-Br, compared with only partial hydrolysis of the cyclic precursor of **3**-Br (Scheme I), is not surprising because the deterrent to pseudorotation present in the latter (the small ring) is absent in **5**-Br.[2]



5

(**5**-OH, X = OH, etc.)

This result suggested the possibility that type **3** products might arise *via* preliminary concerted rearrangement of **4** to **5**-Br (reaction 1), followed by (acid-catalyzed) nucleophilic attack of oxygen on the terminal carbon of the allene system,[15] the latter step being suppressed in dioxane.



Evidence against the intermediacy of **5** in reactions which yield type **3** products came from the observation that exposure of **5**-OH to perchloric acid in THF (18 hr, 25°) or to chloroform–water containing *p*-toluenesulfonic acid for 54 hr at 25° afforded only unchanged starting material. No products could be detected.

There was also the possibility that the formation of **5** in dioxane was a result not of the operation of concerted reaction 1, but rather of base- (solvent-) catalyzed "eliminative" ring opening of first-formed **3**-Br.[17] This was ruled out by the finding that hydrolysis of **3**-Br in 90% aqueous dioxane (with or without suspended sodium bicarbonate) led not to derivatives of **5**, but rather to another new crystalline compound. The elemental analysis and mass spectrum[9] indicated it to be an isomer of **5**-OH, and, although many peaks were common to the mass spectra of both compounds, the relative abundances differed widely.[18] The infrared and nmr spectra[9] of the new compound were closely similar to those of **3**-Br[2], identifying it as **3**-OH, the hydrolysis product of **3**-Br, another member of the unique ring system family.[19–21]

(8) P. J. Stang, *Progr. Phys. Org. Chem.*, **10**, 276 (1973).

(9) See Experimental Section.

(10) Phosphonic acids generally display a strong P=O band at 1150–1220 cm^{-1}, as well as pairs of P–O–H bands at 972–1030 and 917–950 cm^{-1}: L. C. Thomas and R. A. Chittendon, *Spectrochim. Acta*, **20**, 467, 489 (1964); see also ref 11.

(11) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 295 (1967): ^{31}P chemical shifts for several allenic phosphonates occur in the region $\delta -16.0 \pm 2.0$.

(12) R. S. Macomber, *J. Org. Chem.*, **36**, 999 (1971).

(13) D. F. Koster and A. Danti, *J. Phys. Chem.*, **69**, 486 (1965).

(14) T. L. Jacobs and R. S. Macomber, *J. Org. Chem.*, **33**, 2988 (1968); M. Karplus, *J. Amer. Chem. Soc.*, **82**, 4431 (1960).

(15) Such a process is probably no more geometrically constrained from being concerted than is reaction 1; bond lengths and angles are comparable in both cases. Moreover, preliminary protonation at the central carbon would facilitate cyclization, by collapsing the C–C–C angle.[16]

(16) *Bona fide* electrophilic additions to allenes normally occur with attachment in this orientation. See, for example, T. L. Jacobs, R. S. Macomber, and D. Zunker, *J. Amer. Chem. Soc.*, **89**, 7001 (1967).

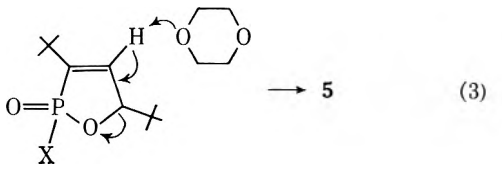
(17) Evidence against the generality of the concerted E1 elimination has recently been summarized: F. G. Bordwell, *Accounts Chem. Res.*, **5**, 374 (1972).

(18) The mass spectra of **5**-OH, **3**-OH, **6**, and **3**-Cl (as well as **3**-Br[2]) are all dominated by fragmentations of the *tert*-butyl groups: loss of methyl, loss of isobutylene, and *tert*-butyl cations. It is interesting that **3**-OH and **3**-Cl, like **3**-Br[2], exhibited no parent ion, but rather M + 1 peaks for protonated material. This may be a manifestation of the basicity and hygroscopicity of the heterocyclic ring system. The differences between the mass spectra of **3**-OH and **5**-OH show that the two systems do not equilibrate under electron impact.

(19) As observed previously,[2] **3**-Br is hydrolytically quite unreactive, requiring 30 hr in aqueous dioxane or several days in moist air to be transformed into **5**-OH.

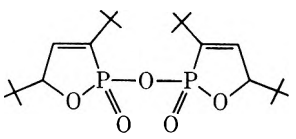
(20) During the course of this work, the preparation of a related oxaphospholene was reported: C. F. Garbers, J. S. Malherbe, and D. F. Schneider, *Tetrahedron Lett.*, 1421 (1972).

(21) A unique feature of the ring system in **3** is the presence of two chiral centers (phosphorus and saturated carbon) which leads to the possible existence of two diastereomeric *dl* pairs. Apparently only one (pair) is formed in the case of **3**-Br.[2] In the case of **3**-OH, however, there is reason to believe that only one *dl* pair is possible, since mere prototropic shift renders the two exocyclic oxygens equivalent. Evidence for this is presented below with the X-ray structural data.



3

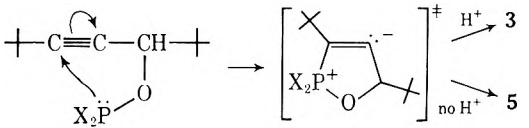
Additionally, we have been unable to effect the 3-OH → 5-OH isomerization[22] under any of the following conditions: electron impact,[18] thermolysis at 200°, *n*-butyllithium in ether, sodium hydride in hexane, and potassium hydroxide in aqueous dioxane. However, under several sets of these conditions, most notably the last, we isolated in varying yield still another new compound, **6**. The mass spectrum[9] showed a parent ion at *m/e* 446, corresponding to two molecules of **3**-OH or **5**-OH minus a molecule of water—a phosphonic anhydride. Whether **6** was an anhydride of **3**-OH or **5**-OH or a mixed anhydride was readily established by its infrared and pmr spectra,[9] which closely resembled those of **3**-Br[2] and **3**-OH.[25] As with **3**,[21] the presence of



6

multiple chiral centers (four in the case of **6**) complicates the picture, since four *dl* pairs and two meso stereoisomers are possible. Although elemental analysis, thin layer chromatography, and infrared spectroscopy showed that **6** was free from other compounds, its melting point was broad (217–223°) after recrystallization and sublimation, and its pmr spectrum[9] clearly indicated the presence of at least three diastereomers. We have, as yet, been unable to separate these, owing to their close chemical similarity.

From the fact that cyclic compounds **3** do not interconvert with their acyclic isomers **5** under typical reaction conditions (*vide supra*), it is reasonable that they arise from mutually exclusive mechanisms, with common starting point **4**. That compounds **3** can be isolated at all is evidence that the SNi′ (ion pair) mechanism is *not* operative. The fact that substitution at the propargyl carbon increases the facility of these reactions[4] is probably not due to an increase in carbonium ion stability. Rather, this order is due to steric effects of these added groups, which give rise to strain that is partially relieved upon rearrangement, and which favor conformations from which such processes are accessible (*cf. gem*-dimethyl effect). Evidence for the near concert of protonation and phosphorus attack can be adduced from the lack of methyl migration to the incipient positively charged carbon atom, as found when vinyl cations are not efficiently trapped by nucleophile.[7,8] We are left with the likelihood that **5**-Br is formed in a concerted fashion from **4** (reaction 1). We have no evidence that the third alternative (*vide supra*), preliminary nucleophilic attack by phosphorus leading to zwitterion **7**, is occurring *except* when **4** has been previously or simultaneously protonated. We conclude



4 7

that the outcome of the reaction of **4** (and hence the reaction of propargyl alcohols with phosphorus trihalides in general) depends critically on the availability of protons as the phosphorus atom approaches the triply bonded carbon. If **7** (or **4**) can be readily protonated, cyclization results; in the absence of protons (*i.e.*, the presence of base or basic solvent) formation of the new P–C bond is accompanied by concerted C–O bond fission. Thus, the nature of the phosphorus-containing products seems to be controlled by the acidity of the medium.

An explicit foregone assumption throughout this entire work regards the intermediacy of dibromophosphite **4**. We have been able to substantiate its formation by low-temperature pmr spectroscopy. At −53° (but not at room temperature[26]) the pmr spectrum of **2**[27] shows two *tert*-butyl singlets (δ 0.96 for the alkyl *tert*-butyl group and δ 1.20 for the ethynyl *tert*-butyl group[28]) as well as *doublets* (J = 4.5 Hz) for the hydroxyl (δ 2.25) and methine (δ 3.94) protons, the coupling due to slowed O–H exchange. Immediately upon addition of a precooled deuteriochloroform solution of PTB (1.2 mol/mol of **2**), the O–H resonance *completely disappeared*, the methine resonance collapsed to a singlet and shifted to δ 4.50, and the *tert*-butyl resonances shifted to δ 0.95 and 1.22, respectively.[29] However, in addition to these, a new set of resonances appeared, though initially less intense than those from **2** (or **8**[29]), comprising *tert*-butyl singlets at δ 1.05 and 1.19 and a methine doublet (J_{PH} = 13.5 Hz) at δ 4.78. We attribute these peaks to intermediate **4**. Over the next 2.5 hr, during which time the temperature was allowed to rise to −33°, the second set of absorptions gradually but completely replaced the original set. During the next 1.5 hr, with the temperature allowed to slowly rise to ambient temperature, the resonances attributed to **4** slowly decreased, while those of 1,3-di-*tert*-butyl-

(22) Comparing only bond strengths,[23] compound **3**-OH might be expected to be *ca.* 5 kcal/mol more thermodynamically stable than **5**-OH, but ring strain[24] probably more than offsets this order.

(23) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968.

(24) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970), lists a strain in cyclopentene of ~6–7 kcal/mol.

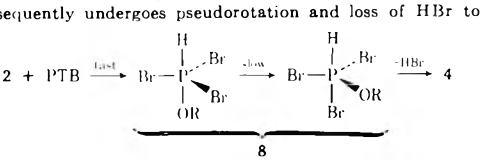
(25) Compound **6** could be best prepared from the reaction of the conjugate base of **3**-OH with **3**-Br (see Experimental Section). Under the other conditions **6** was contaminated with **3**-OH, and the separation was not an easy one.

(26) R. S. Macomber, *J. Org. Chem.*, **37**, 1205 (1972).

(27) Deuteriochloroform solution, internally locked on 20% benzene, referred to 3% internal TMS.

(28) These assignments were made previously[26] and have since been confirmed by the observation of a 10.7% nuclear Overhauser effect enhancement on the methine proton resonance upon irradiation of the *upfield tert*-butyl resonance, whereas irradiation of the *downfield tert*-butyl peak leads to a decrease of 0.6%.

(29) These initial changes seem too dramatic for a simple medium effect of added PTB. We cannot resist the temptation to ascribe the *disappearance* of the OH absorption and collapse of the methine resonance to the formation of something resembling pentacoordinated phosphorus compound **8**, which subsequently undergoes pseudorotation and loss of HBr to give **4**.



8

The absence of a PH resonance and of POCH coupling may be due to rapid exchange or equilibrium between **8** and its ion-pair form.

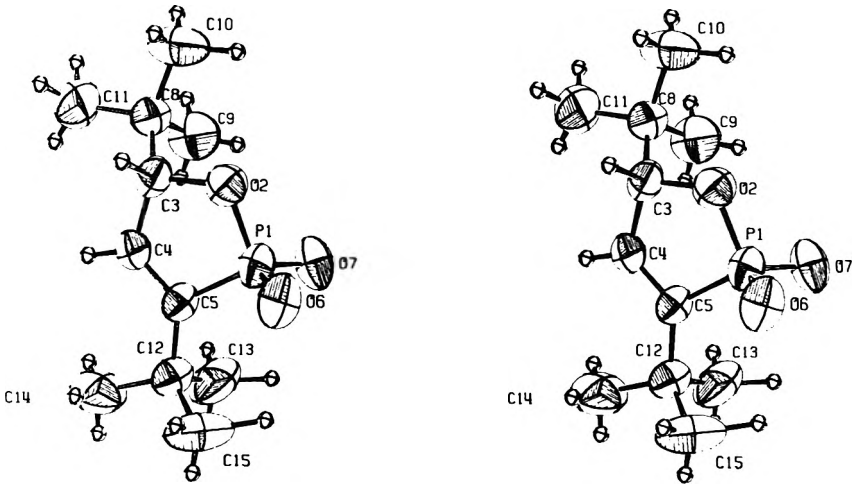
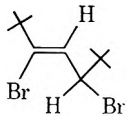


Figure 1.—Stereoscopic view of a molecule of the title compound, 3-OH.

propargyl bromide (the major product[2]) began to appear at δ 1.09, 1.19, and 4.32. Also observable was a weak doublet of doublets (δ 5.10, J_{PH} = 6 Hz, J_{HH} = 1.5 Hz) characteristic of type **3** products (Experimental Section and ref 2), probably due to the as yet unhydrolyzed cyclic precursor of **3**-Br (Scheme I).[30] The intermediacy of **4** under these conditions is thus strongly supported.

A study is presently underway to examine the effects of structural and reaction variables on the inclusion of phosphorus into the products of these reactions. For example, the reaction of PTB and **2** in carbon tetrachloride afforded **3**-Br in 10% yield. With hexane as solvent, only **5**-OH could be isolated (6% yield). Substitution of PTC for PTB (chloroform) had a slight depressing effect on the yield (6%) of cyclized **3**-Cl, while in dioxane neither **3**-Cl nor **5**-OH could be isolated. Further, it has been discovered that in virtually all reactions involving PTB, a dibromide believed to be **9** is formed, presumably *via* addition of HBr to



9

the allenic monobromide.[9] The yield of **9** varied from *ca.* 20% in nonbasic chloroform to 3% in dioxane, as would be expected for a reaction involving free HBr (*vide supra*).

The reaction of **2** with PI_3 was complex and greatly affected by laboratory light. The strength of the P–I bond (51 kcal/mol[31]) may explain the photolability of PI_3 and of intermediates such as **4** (X = I) and **3**-I. In order to determine whether products analogous to **3** or **5** were being formed, the reaction was carried out in the dark, then hydrolyzed with aqueous silver ion to convert all P–I bonds to P–O–H linkages (conditions under which the heterocyclic system is known to survive[2]). Unfortunately, we were unable to detect **3**-OH, **5**-OH, or any other phosphorus-containing products from the complex mixture which resulted.

X-Ray Crystallographic Study.—The novelty of the ring system in compound **3** made an X-ray structural investigation highly desirable, both for acquiring exact geometrical parameters and as unequivocal confirmation of the assigned structures. Compound **3**-Br was initially investigated. Precession photographs of a needlelike crystal [from 3:1 (v/v) heptane–chloroform] showed systematic absences at $h + l = 2n + 1$ for the $h0l$ layer, $h = 2n + 1$ for the $h00$ line, and $l = 2n + 1$ for the $00l$ line, indicating an orthorhombic system of space group C_{2v}^{7}-$Pmn2_1$,[32a] with lattice constants a = 17.32 (3), b = 11.85 (2), and c = 6.94 (1) Å. Density measurements [D_m = 1.36 (1), D_c = 1.38 g/cm^3] indicated four molecules per unit cell. Unfortunately, further examination revealed that the crystals were uniformly twinned (confounding but not precluding complete structural solution) and they slowly decomposed in air[19] during the study. Fortuitously, the simultaneous isolation of **3**-OH (*vide supra*) afforded crystals which proved ideal for the X-ray study.

A stereoscopic view of **3**-OH, which comprises the asymmetric unit of the cell, is shown in Figure 1.[33] Bond lengths and angles are given in Tables I and II, respectively. Clearly this structure is totally consistent with the structural assignments made during this study. The five-membered ring is very slightly envelope shaped, with the $P_1O_2C_3$ plane tipped 0.66° away from the $C_3C_4C_5P_1$ plane. The four atoms bonded to phosphorus are somewhat distorted away from their normal tetrahedral positions owing to the constraint imposed by the unsaturated ring system. The carbon–carbon single bond distances in **3**-OH (Table I) range from 1.494 Å (C_3–C_4) to 1.537 Å (C_8–C_{10}), falling within the normal limits[34] which are a function of s-character effects. The carbon–carbon double bond length is 1.324 Å, slightly shorter than the normal value of

(30) There were several other peaks observed during the course of this experiment, among these several pairs of weak *tert*-butyl singlets which grew throughout the reaction. Some of these undoubtedly belong to the precursor described above. There was also a transient singlet at δ 3.44, which reached maximum intensity (1/3 that of **4**) after 3 hr (−13°). As yet, we have no assignment for this resonance.

(31) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," 2nd ed, Wiley, New York, N. Y., 1966.

(32) (a) "International Tables for X-Ray Crystallography," Vol. I, 3rd ed, Kynoch Press, Birmingham, England, 1969, p 117; (b) p 99; (c) Vol. III, 2nd ed, 1968, p 201.

(33) This drawing was made with the program ORTEP II (C. K. Johnson, "A FORTRAN Thermal Ellipsoid Plot Program for Crystal Structure Illustration," Report ORNL-3794, 2nd revision, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1970) implemented at the University of Cincinnati by R. C. Elder. The thermal ellipsoids show 50% probability.

(34) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960.

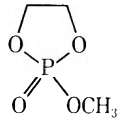
TABLE I

BOND LENGTHS IN 3-OH[a]

Bond	Length, Å	Bond	Length, Å
P(1)-O(2)	1.586 (3)	C(10)-H(2)	1.18 (8)
P(1)-C(5)	1.784 (4)	C(10)-H(5)	1.01 (6)
P(1)-O(6)	1.514 (3)	C(10)-H(8)	0.91 (5)
P(1)-O(7)	1.509 (3)	C(11)-H(4)	1.09 (6)
O(2)-C(3)	1.459 (5)	C(11)-H(15)	0.89 (6)
C(3)-H(1)	1.06 (4)	C(11)-H(18)	1.08 (6)
C(3)-C(4)	1.494 (6)	C(12)-C(13)	1.52 (1)
C(3)-C(8)	1.534 (7)	C(12)-C(14)	1.53 (1)
C(4)-H(14)	0.95 (4)	C(12)-C(15)	1.532 (9)
C(4)-C(5)	1.324 (6)	C(13)-H(6)	0.85 (5)
C(5)-C(12)	1.512 (6)	C(13)-H(9)	1.22 (9)
C(8)-C(9)	1.529 (8)	C(13)-H(13)	0.91 (7)
C(8)-C(10)	1.537 (9)	C(14)-H(7)	0.87 (6)
C(8)-C(11)	1.527 (9)	C(14)-H(19)	1.05 (7)
C(9)-H(3)	1.06 (6)	C(14)-H(20)	0.97 (7)
C(9)-H(11)	1.00 (5)	C(15)-H(10)	0.83 (5)
C(9)-H(17)	0.93 (6)	C(15)-H(12)	1.34 (8)
		C(15)-H(16)	0.94 (7)

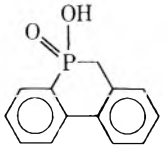
[a] Estimated standard deviations in the last quoted digit appear in parentheses. This notation is used throughout the paper.

~1.34 Å.[34-36] The endocyclic P–O_2 distance of 1.586 Å compares favorably with the value of 1.57 and 1.59 Å for the endocyclic P–O bond lengths of cyclic phosphate **10**.[37] More interesting is a comparison of the



10

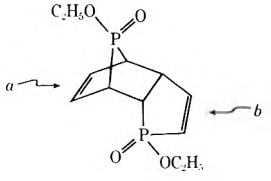
essentially equal P–O_6 and P–O_7 bond lengths in **3**-OH (1.514 and 1.509 Å, respectively) with their counterparts in **10** (P=O, 1.44 Å; P–O, 1.54 Å)[36] and 9,10-dihydro-9-hydroxyphosphaphenanthrene 9-oxide (**11**,



11

P=O, 1.47 Å; P–O, 1.57 Å).[38] Compound **11** (but not **10**) is *inter*molecularly hydrogen bonded, but the distinguishability between exocyclic P–O bonds persists. With **3**-OH, however, the *tert*-butyl group bonded to C_5 inhibits intermolecular hydrogen bonding, and *intra*molecular hydrogen bonding, which would render the two oxygens identical, thus becomes favored, effectively averaging the P–O bond lengths

(35) The C=C bond lengths in the molecule below are a = 1.39 (4) and b = 1.37 (2) Å: Y. H. Chin and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **91**, 4150 (1969).



(36) The C=C bond lengths in 1-benzylphosphole (presumably slightly lengthened by resonance) are 1.343 (5) Å: P. Coggon, J. F. Engel, A. T. McPhail, and L. D. Quin, *J. Amer. Chem. Soc.*, **92**, 5779 (1970).

(37) T. A. Steitz and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **87**, 2488 (1965), and ref 35.

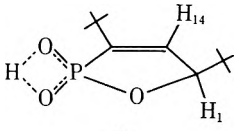
(38) P. J. Wheatley, *J. Chem. Soc.*, 3733 (1962).

TABLE II

BOND ANGLES IN 3-OH

Unit	Angle, deg
O(2)-P(1)-C(5)	96.5 (2)
O(2)-P(1)-O(6)	109.6 (2)
O(2)-P(1)-O(7)	110.1 (2)
C(5)-P(1)-O(6)	114.4 (2)
C(5)-P(1)-O(7)	113.3 (2)
O(6)-P(1)-O(7)	111.8 (2)
P(1)-O(2)-C(3)	113.6 (2)
O(2)-C(3)-C(4)	105.8 (3)
O(2)-C(3)-C(8)	109.1 (4)
C(4)-C(3)-C(8)	116.8 (4)
C(3)-C(4)-C(5)	117.7 (4)
P(1)-C(5)-C(4)	106.3 (3)
P(1)-C(5)-C(12)	125.2 (3)
C(4)-C(5)-C(12)	128.5 (4)
C(3)-C(8)-C(9)	111.0 (4)
C(3)-C(8)-C(10)	109.0 (5)
C(3)-C(8)-C(11)	108.4 (5)
C(9)-C(8)-C(10)	109.3 (5)
C(9)-C(8)-C(11)	110.0 (6)
C(10)-C(8)-C(11)	109.2 (5)
C(14)-C(12)-C(15)	109.4 (6)
C(14)-C(12)-C(5)	110.6 (5)
C(14)-C(12)-C(13)	110.2 (7)
C(15)-C(12)-C(5)	109.1 (4)
C(15)-C(12)-C(13)	109.2 (6)
C(5)-C(12)-C(13)	108.3 (5)

[$\frac{1}{2}$(1.57 + 1.47) = 1.52 Å]. There are two possible explanations for this averaging: either there is a 50:50 distribution within the crystal of molecules with the proton on O_6 or O_7, or the proton is bridging the two oxygens as in **12** (either of these accounting for the



12

inability to locate this proton in the crystal structure). Evidence for latter alternative can be adduced from the thermal ellipsoids for O_6 and O_7 (Figure 1), the longest dimensions of which are perpendicular to the P–O bond vectors, in contrast to what would be expected for the first alternative. This averaging removes the contribution of phosphorus to the stereochemistry of **3**-OH.[21] The P–C_5 distance of 1.784 Å in **3**-OH agrees with values of 1.79 and 1.80 Å in **11**.[38] The bond lengths and angles of the *tert*-butyl groups compare favorably with the usual values.[39]

Finally, it was of interest to examine certain aspects of the structure of **3**-OH, in light of its rather interesting nmr spectral behavior.[2,9] Of special significance were the values of $^3J_{\text{trans P-H}_{14}}$ (56.5 Hz in **3**-Br, 46 Hz in **3**-OH) and $^3J_{H_1-H_{14}}$ (1.8 Hz in **3**-Br, 1.7 Hz in **3**-OH). The rather large magnitude of the vicinal ^{31}P–H coupling is apparently a result of the intervening π system and the PC=CH linkage trans configuration.[40] The previously noted[2] small magnitudes of the vicinal coupling between the ring hydrogens can be rational-

(39) T. Brennan, E. F. Putkey, and M. Sundaralingam, *Chem. Commun.*, 1490 (1971); J. Sletten, *Acta. Chem. Scand.*, **25**, 3586 (1971).

(40) This magnitude for $^3J_{\text{trans PH}}$ has precedent [M. P. Williamson, S. Castellano, and C. E. Griffin, *J. Phys. Chem.*, **72**, 175 (1968); T. Ikeda, Ph.D. Thesis, University of Toledo, 1972], while $^3J_{\text{cis PH}}$ is normally less than half these values.

ized by the Karplus relationship,[41] which predicts a dihedral angle of 60 ± 1° for $^3J_{H-H}$ = 1.7 ± 0.1 Hz. This agrees quite well with the experimental value of 66.5°, considering the uncertainty in this value and the approximate nature of the Karplus relationship.

The effect of changing the steric requirements of the propargyl fragment is under investigation, as is the possibility that appropriately substituted allylic alcohols may undergo these reactions to yield saturated analogs of **3**.

Experimental Section

General.—The instruments and general methods have been previously described.[2] Microanalyses were performed by Chemalytics, Tempe, Ariz. Melting points (oil bath) and boiling points are uncorrected. The preparation of 1,3-di-*tert*-butylpropargyl alcohol (**2**) has been published.[42] Other reagents were commercially available.

Reaction of 2 with PTB. A. Chloroform.—This reaction has been described in detail previously.[2] The yield of **3**-Br was 10–15% after purification. In addition to the propargyl and allenic bromides, another less volatile product was detected by glc of the liquid portion of the product mixture. Careful distillation provided material, bp 48° (0.35 mm), with the following spectral properties: pmr[43] δ 1.07 (s, 9 H), 1.23 (s, 9 H), 4.78 (d, *J* = 10.5 Hz, 1 H), 5.95 (d, *J* = 10.5 Hz, 1 H); ir[43] 2960 (s), 1630 (w), 1480 (m), 1470 (m), 1400 (w), 1370 (m), 1250 (m), 960 cm^{-1} (w); mass spectrum (14 eV) *m/e* (rel intensity) 310, 312, 314 (1:3:1, 2%), 230, 232 (1:1, 100%, M − HBr).[44] We believe this to be 3,5-dibromo-2,2,6,6-tetramethyl-3-heptene, which exactly fits the pmr spectrum, because the material does not undergo silver-promoted hydrolysis to 2,2,6,6-tetramethyl-4-hepten-3-one, as would be expected if the dibromide were instead 5,5-dibromo-2,2,6,6-tetramethyl-3-heptene.[45] When gaseous HBr was bubbled through a 70:30 mixture of allenic-propargyl bromides, the former was completely consumed, while the latter was essentially stable. Propargyl monobromide was removed by evacuation of the mixture at room temperature (1 mm) overnight, leaving dibromide **9** in 95% purity.

B. Dioxane.—A solution of 1.68 g (10.0 mmol) of **2** in 20 ml of dry dioxane was added at once to a solution of 2.71 g (10.0 mmol) of PTB in 20 ml of dry dioxane under nitrogen. The solution was stirred for 19.5 hr at ambient temperature, then hydrolyzed with two 10-ml portions of saturated aqueous sodium chloride. The combined brine solutions were back-extracted with three 25-ml portions of ether, and the combined organic phases were dried over 5-Å molecular sieve. Rotary evaporation left a yellow oil which, upon standing at −20°, deposited colorless crystals. Recrystallization from 1:1 (v/v) acetone–acetonitrile provided 340 mg (15%) of **5**-OH from three crops: mp 173.5–175.0°; mass spectrum[46] (70 eV) *m/e* (rel intensity) 232 (99), 217 (43), 177 (62), 176 (100), 162 (93), 161 (100), 151 (23), 143 (35), 137 (43), 135 (92), 128 (102), 127 (100), 121 (33), 120 (46), 119 (28), 97 (34), 96 (79), 91 (67), 83 (28), 81 (77), 79 (64), 77 (86), 73 (17), 71 (21), 69 (35), 67 (42), 65 (31), 57 (104), 55 (62), 53 (26), 45 (24), 43 (30), 41 (75); ir[43] 3500–2000 (br), 2962 (s), 1949 (m), 1476 (m), 1462 (m), 1394 (m), 1373 (m), 1232 (s), 1115 (vs), 1010 (vs), 920 (s), 651 (w), 607 (m), 547 cm^{-1} (m); pmr (acetone-d_6, internal TMS) δ 1.04 (s, 9 H), 1.19 (s, 9 H), 5.31 (d, J_{P-H} = 13 Hz, 1 H), 6.31 (s, 2 H);[47] ^{31}P nmr (acetone, external H_3PO_4) δ[48] −16.1 (d, J_{P-H} = 12 ± 1 Hz). *Anal.*[49] Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.33. Found: C, 56.80; H, 9.12; P, 13.05.

Hydrolysis of 3-Br.—To a solution of 100 mg (0.34 mmol) **3**-Br in 5 ml of dioxane was added 5 ml of 80% (v/v) aqueous dioxane (20% water). This solution was stirred for 30 hr at room temperature (by which time it had become yellow); then 28 mg of sodium bicarbonate was added. The mixture was stirred for an additional 14 hr, then rotary evaporated to dryness. The residue was triturated with hot acetone–acetonitrile (1:1 v/v), and the undissolved material (mostly sodium bromide) was discarded. The combined triturant solutions were concentrated and cooled to −20°, providing two crops of **3**-OH totalling 70 mg (89%): mp 162–164°; mass spectrum (70 eV) *m/e* (rel intensity) 233 (2), 217 (5), 177 (14), 176 (100), 162 (9), 161 (90), 97 (5), 96 (4), 91 (3), 81 (3), 79 (4), 77 (4), 69 (2), 67 (3), 65 (2), 57 (8), 55 (3), 41 (5); ir[50] 3200–2000 (br), 2990 (w),*[51] 2950 (vs),* 1615 (w),* 1477 (m),* 1370 (s),* 1309 (m),* 1280 (m),* 1260 (w),* 1185 (s), 1063 (s),* 1009 (vs),* 984 (vs),* 933 (w),* 902 (w),* 864 (m),* 848 (m),* 650 (m),* 618 (m),* 538 cm^{-1} (m)*; pmr[52] δ 0.97 (s, 9 H), 1.31 (s, 9 H), 4.48 (d of d, J_{HH} = 1.7, J_{PH} = 4.7 Hz, 1 H), 6.57 (d of d, J_{HH} = 1.7, J_{PH} = 46 Hz, 1 H), 13.00 (s, 1 H); ^{31}P nmr[48] (chloroform, external H_3PO_4) δ −42.0 (d of d, J_{PH_1} = 46, J_{PH_2} = 4.5 ± 0.3 Hz).

Anal. Calcd for $C_{11}H_{21}O_3P$: C, 56.88; H, 9.11; P, 13.33. Found: C, 57.09; H, 8.94; P, 13.60.

Attempted Cyclization of 5-OH to 3-OH.—To a mixture of 100 mg (0.43 mmol) of **5**-OH and 30 mg of *p*-toluenesulfonic acid in 6 ml of chloroform was added 1 ml of water. The heterogeneous mixture was shaken for 51 hr at room temperature, then the organic phase was separated, washed with water, and dried. The residue, after rotary evaporation, was examined by pmr, and showed only unreacted **5**-OH. Recovery was 62%.

Similarly, a mixture of 100 mg of **5**-OH and 3 drops of 72% perchloric acid in 10 ml of THF was stirred at ambient temperature for 18 hr. Starting material could be recovered in 90% yield; no other products were detected.

Attempts to Open 3-OH to 5-OH. A. Thermally.—A 40-mg sample of **3**-OH was sealed into a glass tube and heated in an oil bath to 200° for 16 hr. By this time some darkening of the material had occurred. However, only starting material could be detected by pmr.

B. Alkyllithium.—To 34 mg (0.15 mmol) of **3**-OH in 10 ml of dry ether was added 0.13 ml (0.29 mmol) of 2.2 *M* *n*-butyllithium in hexane. After stirring at room temperature for 12 hr, the solution was hydrolyzed with 2 ml of 0.5 *N* HCl. The organic phase was separated, and the aqueous phase was extracted with two 5-ml portions of ether. The combined ether phases were dried over molecular sieve, then rotary evaporated to give 25 mg (74% recovery) of **3**-OH. No **5**-OH could be detected.

C. Sodium Hydride.—To 30 mg (0.13 mmol) of **3**-OH in 10 ml of ether was added 14 mg (0.33 mmol) of 57% sodium hydride (oil dispersion). After 37 hr of stirring at room temperature, the suspension was hydrolyzed with 2 ml of 0.5 *N* HCl and worked up as in B above. Starting material was recovered in 66% yield. No **5**-OH was detected by pmr.

D. Potassium Hydroxide.—To 30 mg (0.13 mmol) of **3**-OH in 3.5 ml of 90% aqueous dioxane (9:1 dioxane–water) was added 39 mg (0.60 mmol) of KOH. After 67 hr of stirring at room temperature, the mixture was neutralized with 2 ml of HCl and the

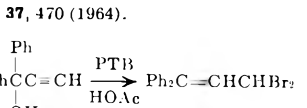
(41) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963): ^3J = 4.22 − 0.5 cos θ + 4.5 cos 2θ.

(42) W. T. Borden and E. J. Corey, *Tetrahedron Lett.*, 313 (1969).

(43) Carbon tetrachloride solution, internal TMS for pmr samples.

(44) The mass spectrum of **9** was anomalous. Not only were the parent ions almost imperceptible, but peaks at 382, 384 (1:1), 326, 328 (1:1), and 302 (single peak) indicated the presence of a higher mass compound, probably a dimer of 1-bromo-1,3-di-*tert*-butylallene (*m/e* 230, 232), resulting from loss of HBr from **9**. Such dimers do not, however, fit the other spectral data for **9**.

(45) Propargyl alcohol i has been reported to give *gem*-dibromide ii in 45% yield upon treatment with PTB in acetic acid: H. Tani and F. Toda, *Bull. Chem. Soc. Jap.*, **37**, 470 (1964).



i ii

However, the pmr spectrum reported for ii [τ 2.75 (s), 3.60 (q), 7.90 (s)] does not fit the structure given. We are reinvestigating this reaction.

(46) The relative abundances for **5**-OH are expressed as a per cent of the *m/e* 176 peak to facilitate comparison with the spectrum of **3**-OH.

(47) That the δ 6.31 singlet in the pmr spectrum of **5**-OH was indeed due to the acidic OH protons was confirmed by three observations: the intensity of the absorption increased instantaneously when a small amount of HOD was initially present in the acetone-d_6 solvent, the absorption disappeared completely when the solution was warmed to 65° for 3 days, owing to H–D exchange, and the band position shifts to δ 10.0 in deuteriochloroform.

(48) Positive δ is *upfield* for ^{31}P resonances.

(49) Phosphonic acid **5**-OH is, not unexpectedly, fairly hygroscopic, and has a tendency to form a solvate with water. This was shown by its pmr spectrum[47] and the fact that only after preliminary drying (50° for 4 hr) did the elemental analysis match the calculated values.

(50) Chloroform solution.

(51) Ir bands marked with an asterisk are common to **3**-Br,[2] **3**-OH, **3**-Cl, and **6**.

(52) Deuteriochloroform, internal TMS.

TABLE III

PHOSPHORUS-CONTAINING PRODUCTS FROM THE REACTIONS OF 2 WITH PHOSPHORUS TRIHALIDES

Registry no.	Reactant	Solvent	Temp, °C	Time, hr	Product[a]	Yield, %
7789-60-8	PTB	CCl_4	25	26	3-Br	4.1
	PTB	Heptane[b]	25	21.5	5-OH	5.7
7719-12-2	PTC	$CHCl_3$	25	40	3-Cl[c]	5.5
	PTC	Dioxane	25	24	None	
13455-01-1	PTI	$CHCl_3$ or dioxane	25	24	*d*	

[a] The remaining products comprised mixtures of the allenic and propargyl halides (with the ratio ranging from 1:17 in chloroform to 1:1 in carbon tetrachloride), together with varying amounts of 9 in the cases of PTB. [b] Crude product mixture required 2 months at room temperature to deposit crystalline material. [c] Properties given below. [d] See text for a description of this reaction.

solution was evaporated to dryness. The residue was triturated with acetone, and the insoluble material was discarded. Evaporation of the acetone left 3-OH in recoveries as high as 90%. If aqueous NaOH was substituted for the KOH, varying amounts of a higher melting (220–230°) solid could be isolated in addition to 3-OH. This was later shown to be anhydride 6 by independent synthesis (*vide infra*).

Reactions of PTX with 2 in Various Solvents.—Using the procedure described above for the PTB–dioxane reaction, trials were carried out under other exploratory conditions. These are summarized in Table III.

Properties of 3-Cl follow: mp 147–148° after recrystallization (heptane–chloroform, 1:1 v/v) and sublimation (83°, 0.35 mm); mass spectrum (70 eV) *m/e* (rel intensity) 253 (9), 251 (32), 237 (15), 235 (44), 215 (30), 196 (92), 194 (97), 182 (34), 181 (86), 180 (100), 179 (82), 178 (41), 163 (16), 153 (15), 143 (31), 135 (49), 121 (19), 120 (13), 119 (32), 111 (16), 109 (13), 107 (48), 105 (44), 97 (37), 96 (16), 95 (50), 94 (22), 93 (24), 91 (83), 83 (15), 81 (47), 80 (16), 79 (29), 78 (29), 77 (27), 69 (36), 67 (86), 65 (53), 57 (66), 56 (26), 55 (31), 53 (79), 47 (24), 41 (57), 39 (35), 36 (27); ir[50,51] 3000 (s),* 2950 (vs), 1620 (w),* 1475 (s),* 1400 (m),* 1370 (s),* 1310 (m),* 1280 (vs),* 1255 (vs),* 1210 (s), 1075 (m),* 1012 (s),* 965 (s),* 937 (m),* 908 (s),* 871 (s),* 849 (s),* 817 (m), 750 (vs), 656 (vs),* 613 (vs),* 539 cm^{-1} (s);* pmr[43] δ 1.09 (s, 9 H), 1.33 (s, 9 H), 4.71 (d of d, J_{HH} = 1.9, J_{PH} = 5.8 Hz, 1 H), 6.67 (d of d, J_{HH} = 1.9, J_{PH} = 53 Hz, 1 H); ^{31}P nmr (chloroform, external H_3PO_4)[48] δ −46.2 (d of d, J_{PH_1} = 53 ± 1, J_{PH_2} = 6 ± 1 Hz).

Anal. Calcd for $C_{11}H_{20}O_2PCl$: C, 52.70; H, 8.04; P, 12.35. Found: C, 52.71; H, 7.96; P, 12.33.

Preparation of Anhydride 6.—To a solution of 79.5 mg (0.34 mmol) of 3-OH in 5.0 ml of dioxane was added 0.34 ml of 1.0 *N* NaOH, followed by a solution of 100.4 mg (0.34 mmol) of 3-Br in 5.0 ml of dioxane. After stirring at room temperature for 22.5 hr, the yellow solution was rotary evaporated to dryness, and the acetone-soluble portion of the residue was recrystallized from heptane–chloroform (2:1, v/v) at −20°. The first crop (50.3 mg), isolated after 4 days of standing, had mp 217–223°. The spectral properties of this mixture of stereoisomers are given below. Subsequent crops contained considerable 3-OH, and exhibited depressed melting points. Some difficulties were encountered in attempts to reproduce this reaction. Large amounts of 3-OH often precluded purification of the 6: mass spectrum (70 eV) *m/e* (rel intensity) 446 (21), 431 (14), 390 (100), 375 (18), 215 (27), 161 (12), 149 (10); ir[50,51] 2990 (m),* 2955 (vs),* 1615 (w),* 1470 (m),* 1370 (s),* 1310 (m),* 1280 (vs),* 1260 (vs),* 1080 (m),* 1011 (m),* 974 (m),* 943 (vs),* 930 (m),* 907 (w),* 872 (m),* 852 (m),* 656 (m),* 611 (m),* 528 cm^{-1} (m);* pmr[52] δ 0.97, 0.99, 1.00 (singlets of approximately equal intensity), 1.31, 1.33, 1.35 (singlets of approximately equal intensity), 4.4–4.9 (complex m), 6.2–7.1 (complex m); ^{31}P nmr (chloroform, external H_3PO_4) δ −28.4 (complex m, 160-Hz width).

Anal. Calcd for $C_{22}H_{40}O_5P_2$: C, 59.18; H, 9.03. Found: C, 58.85; H, 9.10.

X-Ray Method.—Optical and preliminary X-ray examinations showed that crystals of 3-OH [from acetone–acetonitrile (1:1 v/v)] belong to the monoclinic system. Systematic absences in the precession photographs of the *h*0*l*, 0*kl*, *h*1*l*, and 1*kl* layers were observed at $l = 2n + 1$ for the *h*0*l* layer and $k = 2n + 1$ for the 0*k*0 line, which is consistent with space group C_{2h}^5-$P2_1/c$.[32b] Lattice constants were obtained by least-squares refinement of the setting angles of 15 reflections which had been centered on a Syntex P1 four-circle diffractometer, using Mo K_α radiation (λ 0.71069 A) at room temperature (20 ± 2°). Their values were a = 9.910 (4), b = 12.155 (7), c = 11.886 (7) Å and β = 98.19 (2)°. A density of 1.11 (1) g/cm³, determined by floatation in benzene–carbon disulfide, agreed with a value of 1.10 g/cm³ calculated for four molecules in the unit cell.

The crystal used for data collection was a rectangular prism (0.18 × 0.18 × 0.41 mm) mounted along its long dimension, the *a* axis. A take off angle of 4° and a graphite crystal monochromator were used during data measurement. A 1-mm-diameter collimator was used on the incident beam side of the crystal, and a 2-mm-diameter circular aperture on the diffracted beam side. The source-to-crystal and crystal-to-counter distances were 45 and 90 mm, respectively. Alignment procedures for the diffractometer have been previously described.[53] A θ–2θ scan mode was employed with 2θ ranging from 3.5 to 38.0°. The scan rate was varied from 1 to 12°/min depending on peak intensity. Four check reflections were observed after each 36 data reflections; intensities were processed as previously described.[53] A total of 1298 reflections, of which 1278 were unique, was used in the solution and refinement of structure (*vide infra*). The linear absorption coefficient, μ, for the crystal was calculated to be 1.9 cm^{-1}. Since the relative error introduced into the intensity measurements was less than 2%, no absorption corrections were applied to the data.

Structure Determination and Refinement.—The structure of 3-OH was solved using conventional heavy-atom methods. A sharpened three-dimensional Patterson function map clearly showed the phosphorus vector. A trial structure based on this vector gave an *R* value[54] of 0.547. Unit weights were used throughout the refinement. Atomic scattering factors for carbon, hydrogen, oxygen, and phosphorus were taken from standard tables.[32c] The initial Fourier map gave coordinates for all 15 nonhydrogen atoms in the molecule. A calculation based on this model yielded an *R* value of 0.308. Seven cycles of full-matrix least-squares refinement of positional and isotropic temperature factors gave an *R* of 0.153. Anisotropic refinement for six cycles reduced *R* to 0.077. From a difference Fourier synthesis, all but one of the hydrogen atoms were located (*vide infra*). Seven additional refinement cycles provided a final *R* factor of 0.036, at which time the maximum shift/error was 0.6 σ for hydrogen atoms and 0.4 σ for nonhydrogen atoms. Bond lengths and angles are given in Tables I and II.

Acknowledgment.—We thank Mr. Jim Schmidt for performing the NOE experiment.[28] E. R. K. gratefully acknowledges an NSF Traineeship, 1971 to present. Acknowledgment is further made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Registry No.—**2**, 30338-48-8; **3**-Cl, 42087-74-1; **3**-Br, 30338-49-9; **3**-OH, 42087-75-2; **5**-OH, 42087-76-3; **6**, 42087-86-5; **9**, 42087-87-6.

Supplementary Material Available.—Atomic fractional coordinates, final thermal parameters, and structure factors will appear following these pages in the microfilm edition of this

(53) R. C. Elder, L. R. Florian, R. E. Lake, and A.M. Yacynych, *Inorg. Chem.*, **12**, 2690 (1973). All programs used in the present study were taken from "The X-Ray System," edited by J. M. Stewart, F. A. Kundell and J. C. Baldwin, University of Maryland. The programs were implemented at the University of Cincinnati by R. C. Elder.

(54) $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$.

volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4177.

Photochemistry of Thianaphthene 1,1-Dioxide. Addition of Alkenes

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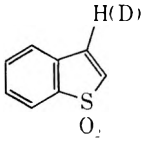
The photocycloaddition of thianaphthene 1,1-dioxide to various unsymmetrically substituted olefins gives products with orientational and stereochemical specificity. The mechanism appears to involve a resonance stabilized 1,4-diradical intermediate.

Photochemically induced cycloaddition reactions of mixed alkene partners have received considerable attention as routes to theoretically interesting compounds and natural products as well as for their mechanistic properties.[2] While a number of alkene systems have been examined, there is little known concerning the role that α heteroatoms may have on the coupling mode. Accordingly, we have studied the addition of several alkene derivatives to thianaphthene 1,1-dioxide (**1**, benzo[*b*]thiophene 1,1-dioxide).[3]



1a, H
b, D

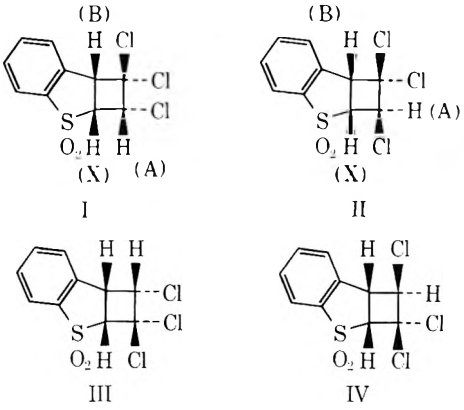
Results and Discussion

Reaction solutions were irradiated with light of wavelength 300 nm and greater; thianaphthene 1,1-dioxide (**1a**) absorbs 99% of the emitted radiation while the olefins absorb no more than 1%.

Cycloaddition to Trichloroethene.—Thianaphthene 1,1-dioxide (**1a**) was dissolved in trichloroethene, purged with dry nitrogen, and irradiated for 3 hr. Fractional crystallization from benzene gave adduct **2a** (52%) and the two photodimers of **1a** (48%).[3a]

Analysis of the mass spectrum (*m/e* 296, parent) and ir [$\bar{\nu}$ at 1320 and 1160 (SO_2) and 670 cm^{-1} (CCl)] indicated a 1:1 adduct with the possible structures I–IV. Photoadducts with trans stereochemistry at the junction of the five- and four-membered ring are unlikely, particularly considering the two-step process proposed by Corey.[4] Isomerization of a possible trans ring juncture cannot be performed because of rapid hydrohalide elimination from the substrate (*vide infra*).

The structure and stereochemistry of **2** were determined by a comparison analysis of cycloadducts **2a** and **2b**. Adduct **2b** was formed by using 3-deuteriothianaphthene 1,1-dioxide (**1b**). Resonances appearing in the nmr spectrum of **2b** were τ 2.18 (4 H, aromatic), 5.18 (1 H, d, J_{AX} = 8.0 Hz, CH), and 5.69 (1 H, d, J_{AX} = 8.0 Hz, CH). This spectrum is consistent with structure I or II. If structure III or IV were correct, the coupling between the chloro proton (A) and the SO_2 proton (X) would be expected to be of the order of 0–2.5 Hz instead of 8.0 Hz (cross-ring coupling constants higher than 2.5 Hz have been recorded only for rigid bicyclobutane derivatives[5]). The nmr spectrum of compound **2a** consists of a multiplet at τ 2.18 (4 H, m, aromatic) and an ABX multiplet in which the AB portion is centered at τ 5.18 (2 H) and the X part at τ 5.69 (1 H). Examination of the ABX signals revealed J_{AB} = 1.5 Hz (cross-ring coupling) and $J_{AX} + J_{BX}$ = 15.5 Hz. Because the AB section (expanded scale) of the spectrum has only six recognizable peaks, it was not possible to determine values for D^+, D^-, and $^1/_2(J_{AX} + J_{BX})$;[6] hence J_{AB} and $J_{AX} - J_{BX}$ could not be calculated. However, from ($J_{AX} + J_{BX}$) and J_{AX} = 8 Hz (determined from nmr spectrum of deuterated adduct **2b**), a value of J_{BX} (7.5 Hz) was determined. The X section of the ABX spectrum contained four peaks; thus J_{AX} and J_{BX} have the same sign.[5]



The nmr data obtained for compound **2a** are consistent with structure I rather than II. It has been observed[7] for vicinal protons that $J_{cis}/J_{trans} > 1$. Hence, J_{BX} = 7.5 Hz for the vicinal cis benzylic and sulfonyl protons and J_{AX} = 8.0 Hz, $J_{BX(cis)}/J_{AX} < 1$, supports cis stereochmistry for protons A and X.

(1) NRCC Bursary Holder, 1968–1970.

(2) For leading references see P. de Mayo, *Accounts Chem. Res.*, **4**, 41 (1971); P. G. Bauslaugh, *Syntheses*, **2**, 287 (1970).

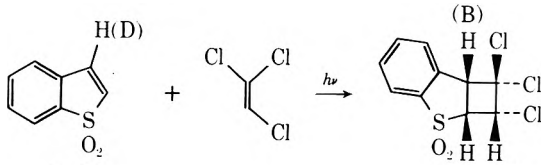
(3) For previous papers on the photochemistry of **1** see (a) D. N. Harpp and C. Heitner, *J. Org. Chem.*, **35**, 3256 (1970); (b) D. N. Harpp and C. Heitner, *J. Amer. Chem. Soc.*, **94**, 8179 (1972).

(4) E. J. Corey, J. D. Bass, R. La Mahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(5) R. M. Dodson and A. G. Zielske, *J. Org. Chem.*, **32**, 28 (1967).

(6) C. N. Banwell, "Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press, New York, N. Y., 1967, p 85.

(7) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).

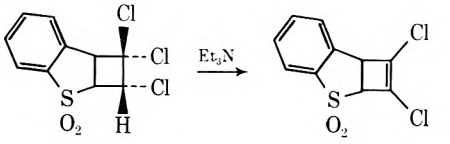


1a, H
b, D

2a, H
b, D

Since cross-ring coupling constants for protons with 1,3 cis stereochemistry range from 0.9 to 2.5 Hz for cyclobutane compounds and cross-coupling constants for protons with trans stereochemistry are 0.5 Hz,[6] the value for J_{AB} of 1.5 Hz provides further evidence that protons A, B, and X have cis stereochemistry.

The elemental analysis for compound **2a** was not completely satisfactory. This is most likely due to slow decomposition (dehydrohalogenation) on standing. Characterization of a stable derivative was therefore necessary. Dehydrohalogenation of **2a** in refluxing triethylamine gave dihalide **3**: nmr (C_6D_6) τ 2.60–3.35 (4 H, m, aromatic), 6.35 (2 H, AB q, $\Delta\nu$ = 20.1, J_{AB} = 4.0 Hz, CH); ir $\bar{\nu}$ 1680 (C–C), 1320 and 1150 (SO_2), 650 cm^{-1} (CCl). The above data are consistent with the loss of HCl to give cyclobutene derivative **3**.



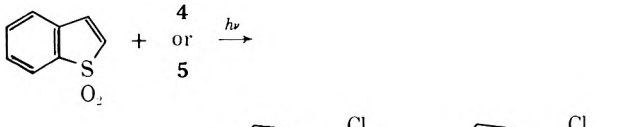
2a 3

Purging the trichloroethene solution of **1a** with O_2 completely inhibited cycloaddition, indicating a triplet excited state as intermediate.

Cycloaddition to *cis*- and *trans*-Dichloroethene.—Thianaphthene 1,1-dioxide (**1a**) was dissolved in *cis*- (**4**) or *trans*-dichloroethene (**5**) and irradiated. The solvent was then evaporated and the reaction mixture was crystallized (ethanol, *cis*-dichloroethene adduct; benzene, trans adduct). Examination of the crude reaction mixture by vpc, nmr, and ir techniques revealed the same two products for each reaction.

The crystals obtained from photoaddition of dioxide **1a** to *cis*-dichloroethene (**4**) were separated on a silica gel column. The first fraction was pure **6** [nmr τ 2.3 (4 H, aromatic), 5.0 (m), 5.5 (m)]; the second fraction contained a mixture of **6** and **7** and was crystallized from CCl_4 to give pure **7** [nmr τ 2.3 (4 H, aromatic), 5.1–5.9 (m)].

Consideration of the spectral data has led to structure assignments for **6** and **7** as shown below. It has been



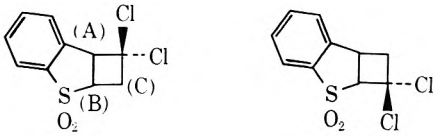
6 7

	%6	%7
4 (cis)	53	47
5 (trans)	23	77

observed that halogen atoms shield protons that are cis to them.[6] The lower field signals appear to move into the envelope while peaks have been shifted to high field out of the envelope (in comparing cis with trans). Hence, a tentative structure as illustrated by **6** and **7** can be proposed without defining the relative stereochemistry of the ring junction protons.

By comparing the integration for the nmr signal that is unique to each of **6** and **7** in the reaction mixtures, ratios of **6**:**7** = 53:47 and 23:77 were estimated for cycloadditions of **1a** to *cis*- and *trans*-1,2-dichloroethylene, respectively. It is of interest to note that, in these cycloaddition reactions, only two of the four possible products were observed. The photocycloaddition of *cis*- and *trans*-1,2-dichloroethylene to thianaphthene and cyclopentenone gave four products.[8,9]

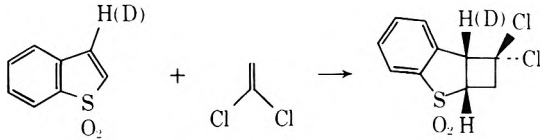
Cycloaddition to 1,1-Dichloroethene (8).—Thianaphthene 1,1-dioxide (**1a**) and 1,1-dichloroethene (**8**) were irradiated in benzene. Work-up and recrystallization from ethanol gave 77% of **9a** as the only product. Spectroscopic evidence [nmr τ 2.2 (4 H, aromatic), 5.20 (1 H, m), 5.73 (1 H, m), 6.25–7.0 (2 H, m)] indicates that the compound is a 1:1 adduct between thianaphthene 1,1-dioxide and 1,1-dichloroethane as represented by either structure V or VI.



V VI

Irradiation of the resonance at τ 6.25–7.0 (proton C) causes the peaks at τ 5.20 (proton A) to collapse to a doublet (J = 8.0 Hz). This same signal (τ 5.20) collapsed to a doublet (J = 2.5 Hz) and the multiplet at τ 6.25–7.01 into a distorted quartet when the resonance at τ 5.75 (proton B) was irradiated. This indicates that proton A is strongly coupled to proton B while B is similarly coupled to C; proton A is weakly coupled to proton C. The assignments for A, B, and C will then lead to the elucidation of the structure of adduct **9a**. Final evidence for this assignment is derived from the product of the irradiation of 3-deuteriothianaphthene 1,1-dioxide (**1b**) in 1,1-dichloroethene. Photolysis of **1b** in the presence of **8** under the same conditions as for **1a** gave compound **9b** (melting point identical with that of **9a**).

Examination of the nmr spectrum revealed that the



1a, H
b, D

9a, H
b, D

(8) D. C. Neckers, J. H. Dopper, and H. Wynberg, *J. Org. Chem.*, **35**, 1582 (1970). Although this paper by Neckers produced more cycloaddition products than the present study in the reactions of methyl-substituted benzo[*b*]thiophenes with *cis*- and *trans*-1,2-dichloroethene, in the one comparable case to our work (2,3-dimethylbenzo[*b*]thiophene) the cis/trans ratio of products was very similar (cis olefin 51:48 *vs.* 53:47; trans olefin 72:28 *vs.* 77:23.

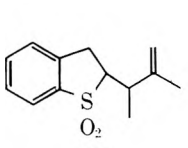
(9) W. L. Dilling, T. E. Tabor, F. P. Boer, and P. P. North, *J. Amer. Chem. Soc.*, **92**, 1399 (1970). de Mayo has recently reported four.[9b] (b) R. O. Loutfy and P. de Mayo, *Can. J. Chem.* **50**, 3465 (1972).

resonance at τ 5.73 (B) had collapsed to a triplet (J = 8.0 Hz). In addition, the signal at τ 6.25–7.0 (C) appeared as a pair of doublets (τ 6.53, J = 8.0 Hz, and τ 6.61, J = 8.0 Hz). Thus, A is the benzylic proton and B is the sulfonyl proton; the above results are consistent with **9a** having structure V.

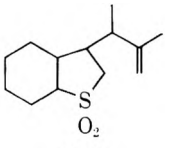
Cycloaddition of Thianaphthene 1,1-Dioxide (1a) to Tetrachloroethene.—Thianaphthene 1,1-dioxide was irradiated in the presence of tetrachloroethene; the only materials recovered after all of compound **1a** was consumed were the two photodimers of **1a**.[3a]

Cycloaddition of Thianaphthene 1,1-Dioxide (1a) to 2-Methyl-2-butene (10).—Compound **1a** was irradiated in the presence of 2-methyl-2-butene in benzene for 1 hr. Analysis of the reaction mixture by vpc and tlc indicated that two products formed. The components of the reaction mixture were separated by preparative tlc developed by cyclohexane–ethyl acetate (4:1).

The first fraction, after recrystallization from ethanol, showed nmr τ 2.4 (m, aromatic), 5.0 (s, 2 H, $=CH_2$), 6.3–7.2 (m, 4 H), 8.2 (s, 3 H, CH_3), 8.4 (d, 3 H, $CHCH_3$), and m/e 236 (molecular ion). The above data are consistent with a 1:1 adduct of compound **1a** and 2-methyl-2-butene of structure VII or VIII. The second fraction, **12a**, showed nmr τ 2.5

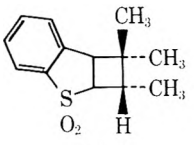


VII

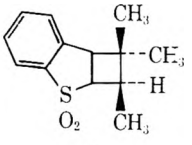


VIII

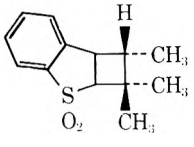
(m, 4 H), 6.4 (m, 2 H), 7.7 (m, 1 H), 8.8 (d, 3 H), 9.3 (s, 3 H), and m/e 236 (molecular ion). The structures that are consistent with the spectral properties listed above are 1:1 adducts IX–XII shown below.



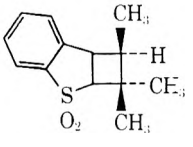
IX



X



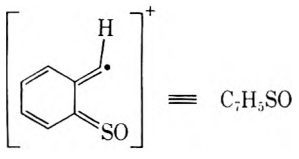
XI



XII

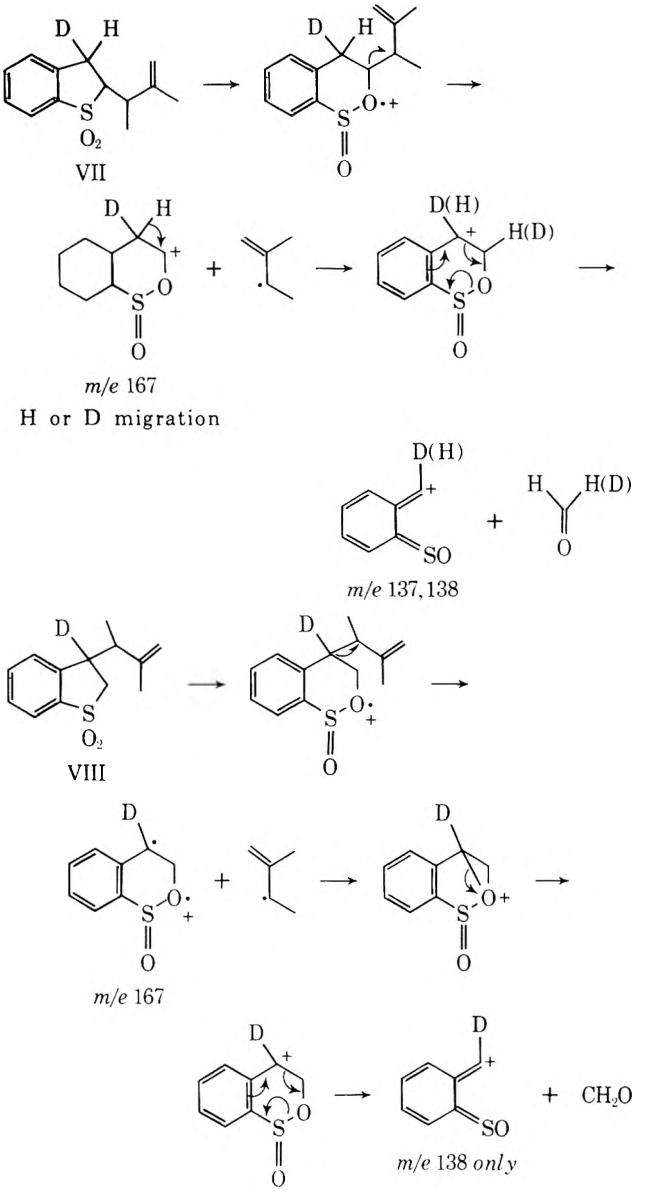
In order to facilitate mass spectra and nmr interpretations, 3-deuteriothianapthene 1,1-dioxide (**1b**) was used as a substrate for the previous photochemical reaction. The two 3-deuterio products (**11b** and **12b**) were separated as before.

One of the consistently prominent peaks in the mass spectra of thianaphthene 1,1-dioxide (**1a**) and its derivatives, photodimers, and adducts **2a**, **6**, **7**, **9a**, **11a**, and **12a** occurs at m/e 137.006 (C_7H_5SO). This



peak can be envisioned to arise from either VII or VIII *via* ions with m/e 167 as illustrated in Scheme I. Com-

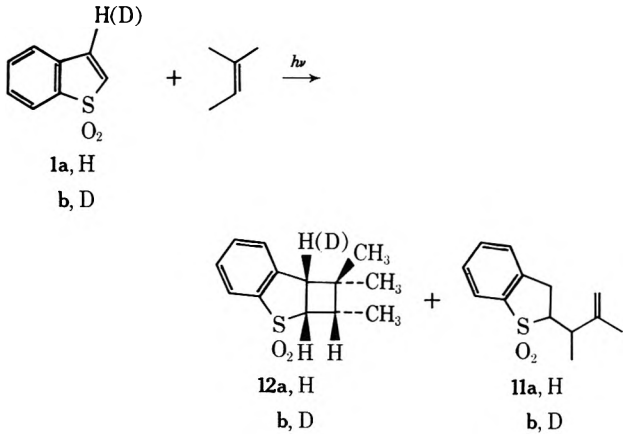
SCHEME I



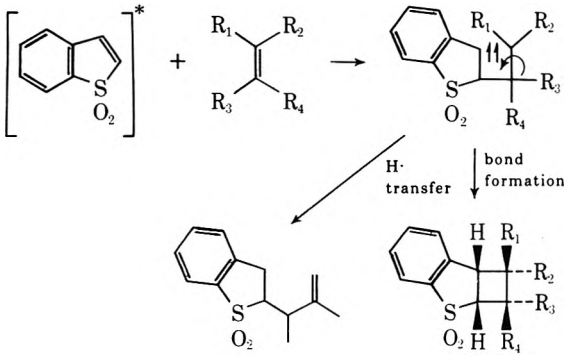
pound **11b** (deuterium in the benzylic position) has a mass spectrum in which peaks at m/e 137 and 138 are prominent. This observation is consistent with **11a** having structure VII. If compound **11a** had structure VIII, one would expect to find only a very small peak for m/e 137 in the mass spectra of the 3-deuterio derivative (**11b**).

The nmr of compound **12b** (the 3-deuterio derivative of compound **12a**) was identical with that of compound **12a** except that the resonance at τ 6.20–6.56 collapsed to a doublet at τ 6.35 (J = 9.0 Hz). This means that the α sulfonyl proton is vicinal to the α methyl proton, since the broad quintet at τ 7.58 did not collapse to a first-order quartet. The vicinal coupling constant (9.0 Hz) is consistent with all methine protons being cis (if one assumes that protons at the junction of five- and four-membered rings formed by a two-step process are cis). Therefore, the data given are consistent with compound **12a** having structure IX. The

reaction to produce compounds **11a** and **12a** is summarized below.



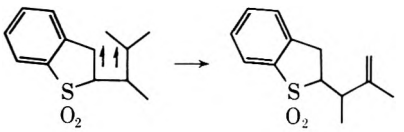
The results obtained for the photocycloaddition of thianaphthene 1,1-dioxide (**1a**) to olefins are consistent with a resonance-stabilized 1,4-diradical intermediate. The initial addition appears to involve bond formation between the 2 position of compound **1a** and the least



substituted carbon atom of the olefins (analogous to free-radical attack on an alkene).[10] The resulting intermediate thus is the most stabilized diradical (benzylic and tertiary). The hypothesis is borne out by the fact that photocycloaddition of **1a** to trichloroethane and 2-methyl-2-butene gives only one cyclobutane derivative. If attack occurred from the 3 position to the highly substituted carbon atom of the olefin (carbon atom with two chlorine or two methyl groups), then rotation around the C–C bond of the substrate moiety would cause two stereoisomers to form. The occurrence of this type of rotation during photocycloaddition was found in the case of *cis*- and *trans*-1,2-dichloroethene, where cycloaddition to both the cis and trans isomers resulted in a mixture of two adducts identical in structure except for the stereochemistry of the chlorine atoms. The products of cycloaddition of dioxide **1a** to 1,1-dichloroethene is also consistent with a free-radical attack by the 2 position of the excited state of **1a** on the least substituted carbon atom.[10]

The fact that tetrachloroethene does not add to the excited state of **1a** can be attributed to steric hindrance by the four chlorine atoms to attack on the π bond. This results in photodimerization being much faster than mixed cycloaddition.

The isolation of compound **11a** from the photocycloaddition of dioxide **1a** to 2-methyl-2-butene provides evidence for the existence of 1,4-diradical intermediate **13**. Compound **11a** was likely formed by a hydrogen



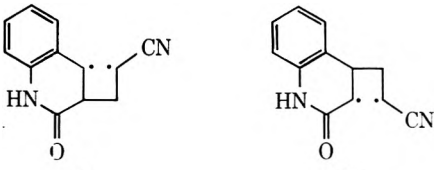
abstraction from the methyl group of the 2-methyl-2-butene moiety by the benzylic position.[11]

Thianaphthene 1,1-dioxide (**1a**) reacts under similar conditions as cyclic enones[4,10,12] and indenes[13,14] to give comparable compounds. The photocycloaddition of cyclic enones to unsymmetrical olefins gives two cyclic products with each possible orientation in which one orientation predominates,[4,12] while indene,[14] 1,1-dimethylindene,[13] carbostryil,[15] and thianaphthene 1,1-dioxide (**1a**) give one product. These results can be explained by invoking resonance-stabilized diradical intermediates for those olefins that are fused and conjugated to aromatic systems. Such intermediates are not involved in the case of cyclic enones.

It has been suggested that most of the products formed by cycloaddition of cyclic α,β-unsaturated ketones to unsymmetrical olefins can be rationalized by a two-stage mechanism.[4,12] While controversy exists concerning aspects of this proposal,[9a,b] it generally accounts for the orientational selectivity of cycloadditions of unsymmetrical alkenes and the lack of stereospecificity of addition of cis and trans alkenes. This mechanism, however, does not account for the orientation of the cycloadducts of carbostyril,[15] indene,[13] and 1,1-dimethylindene to acrylonitrile.[13]

Acrylonitrile adds to an opposite orientation to that predicted by Corey's mechanism.[4] It has been well established that a change in polarity occurs in an $n-\pi^*$ transition (for cyclic enones) while no such change has been observed for $\pi-\pi^*$ transition (carbostyril, indene, 1,1-dimethylindene).[16]

These latter results can be well explained by considering the stabilization of the resulting 1,4-diradical intermediate. The 1,4 diradical **14** with a resonance-stabilized benzylic free radical would be expected to be more stable than diradical **15** (with a less stabilized



(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Reinhart and Winston, New York, N. Y., 1959, p 732.

(11) A referee has noted that the likely involvement of diradical **13** rather than alternative intermediates may possibly be indicative of the tendency of the sulfone group to destabilize adjacent radical centers.

(12) O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson, and E. L. Brown, *J. Amer. Chem. Soc.*, **90**, 1657 (1968); T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969).

(13) J. J. McCullough and C. W. Huang, *Can. J. Chem.*, **47**, 757 (1969).

(14) W. Metzner, *Tetrahedron Lett.*, 1321 (1968).

(15) G. R. Evanega and D. L. Fabing, *J. Org. Chem.*, **35**, 1757 (1970).

(16) G. Porter, "Reactivity of the Photoexcited Molecule," Proceedings of the Thirteenth Conference on Chemistry, Interscience, New York, N. Y., 1967, p 79.

free radical). This hypothesis also accounts for the observations of Corey.[4]

Experimental Section

Apparatus.—Infrared spectra of KBr pellets were measured with a Perkin-Elmer 337 spectrometer, nmr spectra were obtained from a Varian Associates T-60 instrument, and mass spectra were recorded on an AEI MS 902 spectrometer. Melting points were taken on a Gallenkamp apparatus and are not corrected. The vpc data were obtained on a Hewlett-Packard F & M series 5670 research chromatograph. A Hanovia medium-pressure mercury vapor lamp (type L, 450 W) in a Pyrex water-cooled immersion apparatus, surrounded by the reaction mixture, was used for all photocycloadditions. With the exception of the reaction with 2-methyl-2-butene (34%) an excellent material balance was obtained (77–100%) for each reaction.

Thianaphthene 1,1-Dioxide (1a).—This compound was prepared and purified as previously described.[3a]

3-Bromothianaphthene.—This material was synthesized according to the method of von Komppa.[17]

3-Deuteriothianaphthene.—This compound was synthesized by slowly adding 2.0 g of D_2O to thianaphthene-3-magnesium bromide. The latter was formed by adding 6.4 g (0.032 mol) of 3-bromothianaphthane in 20 ml of tetrahydrofuran to 0.76 g (0.32 mol) of magnesium turnings in 20 ml of tetrahydrofuran. Normal work-up and fractional distillation at 78–80° (2 mm) gave 2.5 g (0.018 mol, 62% yield) of 3-deuteriothianaphthene (80% deuterated as determined by mass spectra).

3-Deuteriothianaphthene 1,1-Dioxide (1b).—This compound was prepared in the same way as compound **1a** (mp 142–142.5°; mp of **1a** 142–142.5°).

Photocycloaddition of Thianaphthene 1,1-Dioxide (1a) to Trichloroethene.—Thianaphthene 1,1-dioxide (3.5 g, 0.021 mol) was dissolved in 500 ml of reagent-grade trichloroethene (distilled at 86–86.5°), and the solution was purged with dry nitrogen for 45 min and irradiated for 3 hr. After the solution was evaporated and the resultant oil was refluxed in CCl_4, 5.1 g of a white solid containing three compounds (tlc on silica gel developed by $CHCl_3$ and glpc on 6 ft × 0.125 in., 10% Apiezon L column of reaction mixture) was obtained. Fractional crystallization in 50 ml of benzene gave 1.7 g (0.005 mol, 48% yield) of the photodimers of **1a** and 3.4 g (0.013 mol, 52% yield) of compound **2a**: mp 142–144°; ir $\bar{\nu}$ 1320 and 1160 (SO_2), 670 cm^{-1} (CCl); nmr ($CDCl_3$) τ 218 (4 H, multiplet, aromatic), 5.18 (2 H, AB part of ABX spectrum, CH), 5.69 (1 H, X part of ABX spectrum, CH); mass spectrum *m/e* 296 (molecular ion).

Anal. Calcd for $C_{10}H_7SO_2Cl_3$: C, 40.33; H, 2.43; S, 10.76; Cl, 35.80. Found: C, 41.01; H, 2.42; S, 10.93; Cl, 34.60.

Dehydrochlorination of Adduct 2a.—Compound **2a** (3.0 g, 0.009 mol) was dissolved in 50 ml of triethylamine (reagent grade) and refluxed for 20 hr. Evaporation of solvent and recrystallization from ethanol–activated charcoal gave **3** (2.0 g, 0.008 mol, 89% yield): mp 169–170°; nmr (C_6D_6) τ 2.60–3.35 (4 H, aromatic), 6.35 (2 H, AB q, $\Delta\nu$ = 20.1, $J_{AB'}$ = 4.0 Hz, CH); ir $\bar{\nu}$ 1680 (C=C), 1320 and 1150 (SO_2), 650 cm^{-1} (CCl).

Anal. Calcd for $C_{10}H_6SO_2Cl_2$: C, 45.98; H, 2.30; S, 12.25; Cl, 27.20. Found: C, 45.97; H, 2.34; S, 12.24; Cl, 27.21.

Photocycloaddition of 3-Deuteriothianaphthene 1,1-Dioxide (1b) to Trichloroethane.—A 150-ml trichloroethene solution of 3-deuteriothianaphthene 1,1-dioxide (**1b**, 0.5 g, 0.003 mol) was irradiated for 30 min. The product was isolated and purified as above and resulted in compound **2b** (0.5 g, 0.0014 mol, 47%): mp 142–144°; nmr ($CDCl_3$) τ 2.18 (4 H, m, aromatic), 5.18 (1 H, *J* = 8.0 Hz, CH), 5.70 (1 H, *J* = 8.0 Hz, CH); mass spectrum *m/e* 297 (molecular ion).

Photocycloaddition of Thianaphthene 1,1-Dioxide (1a) to *cis*-1,2-Dichloroethene.—Thianaphthene 1,1-dioxide (**1a**, 1.75 g, 0.0105 mol) was dissolved in 350 ml of *cis*-1,2-dichloroethene (reagent grade) and irradiated for 9 hr under nitrogen atmosphere. Dichloroethene was removed by distillation and ethanol was added to the oily residue, resulting in white crystals (2.0 g). The unreacted starting material (0.7 g) was separated from the products by filtering from boiling water. The resulting solid (1.3 g, 0.005 mol, 79% yield based on unreacted starting material) was examined by vpc (6 ft × 0.125 in., 10% Apiezon L on Chromosorb W) and was found to contain two compounds, **6** and **7**. This mixture was chromatographed over silica gel by $CHCl_3$ and partial separation was obtained. The first fraction contained 0.2 g (13% yield based on the amount of compound **1a** consumed) of compound **6**: mp 144.5–146.5°; ir $\bar{\nu}$ 1320 and 1170 (SO_2), 665 cm^{-1} (CCl); nmr ($CDCl_3$) τ 2.00–2.50 (4 H, aromatic), 4.94–5.15 (1 H, m, CH), 5.33–5.60 (3 H, CH).

Anal. Calcd for $C_{10}H_8SO_2Cl_2$: C, 45.63; H, 3.04; S, 12.17; Cl, 27.00. Found: C, 45.61; H, 3.09; S, 12.26. Found: C, 45.95; H, 3.20; S, 12.23; Cl, 26.26.

The ratio of compounds **6** and **7** in the original mixture was estimated by comparing the integration of the resonances at τ 4.94–5.15 for **6** with that at τ 5.80–6.00 for **7**, found 53:47.

Photocycloaddition of Thianaphthene 1,1-Dioxide (1a) to *trans*-1,2-Dichloroethene.—A solution of thianaphthene 1,1-dioxide (0.134 g, 0.8 mmol) in 150 ml of *trans*-1,2-dichloroethene was irradiated for 45 min. Distillation of the dichloroethene and crystallization in ethanol–hexane (4:1) gave 0.185 g (87% yield) of compounds **6** and **7**. Fractional crystallization in ethanol gave 40 mg (29% yield) of compound **7** (mp 170–171°, mixture melting point with **7** from photoaddition of *cis*-1,2-dichloroethene was not depressed). The ratio of compound **6** and **7** by vpc analysis was found to be 23:77.

Photocycloaddition of Thianaphthene 1,1-Dioxide (1a) to 1,1-Dichloroethene.—Thianaphthene 1,1-dioxide (0.5 g, 0.003 mol) and 1,1-dichloroethene (12 g, 0.12 mol) in 150 ml of benzene were irradiated for 3 hr. The polymeric material that had formed was filtered, an additional 12 g of 1,1-dichloroethene was added, and the irradiation was continued for 3 hr. At this point glpc analysis (6 ft × 0.125 in., 10% UC-W98 on Diatoport S) indicated complete reaction and together with tlc (silica gel developed by $CHCl_3$) indicated only one product. Recrystallization in ethanol gave compound **9a** (mp 139.5–140.5°, 0.6 g, 0.0023 mol, 77% yield): ir $\bar{\nu}$ 1310 and 1160 (SO_2) and 615 cm^{-1} (CCl); nmr ($CDCl_3$) τ 2.10–2.50 (4 H, m, aromatic), 5.20 (1 H, $J_{2,3}$ = 8.0, $J_{3,5}$ = 2.5 Hz, CH), 5.73 (1 H, *J* = 8.0 Hz, CH), 6.25–7.00 (2 H, CH_2); mass spectrum *m/e* 262 (molecular ion).

Anal. Calcd for $C_{10}H_8SO_2Cl_2$: C, 45.63; H, 3.04; S, 12.17; Cl, 27.00. Found: C, 45.87; H, 3.05; S, 12.42; Cl, 26.18. Exact mass measurement of the molecular ion (calcd for $C_{10}H_8O_2SCl_2$, 261.9622), 261.9631.

Photocycloaddition of 3-Deuteriothianaphthene 1,1-Dioxide (1b) to 1,1-Dichloroethene.—Thianaphthene 1,1-dioxide (1.7 g, 0.01 mol) and tetrachloroethene (108 g, 0.8 mol) in 170 ml of benzene was irradiated until all of the starting material was consumed (6 hr). Evaporation of the benzene and tetrachloroethylene gave white crystals which tlc (silica gel developed by acetone) and glpc (6 ft × 0.125 in., 10% Apiezon L on Chromosorb W) revealed to be the photodimers of **1a** (1.7 g, 100% yield). No mixed cycloadduct was observed.

Photocycloaddition of Thianaphthene 1,1-Dioxide to 2-Methyl-2-butene.—Compound **1a** (0.35 g, 2.1 mmol) and 2-methyl-2-butene (14 g, 0.2 mol) were irradiated in benzene for 1 hr under nitrogen atmosphere. Evaporation of the solvent left 0.49 g of an oily material (theoretical yield for 100% cycloaddition is 0.46 g). Examination of the reaction mixture by tlc [silica gel developed by cyclohexane–ethyl acetate (4:1)] and glpc (6 ft × 0.125 in., 10% UX-W98 silicone rubber on Diatoport S) showed that two products were formed. The reaction mixture was then chromatographed on preparative tlc plates (0.75 mm thick) of silica gel with cyclohexane–ethyl acetate (4:1) (development was repeated until separation occurred). Fraction 1 (recrystallization with ethanol) gave **11a** (39 mg, 0.089 mmol, 9% yield, mp 145–145.5°): ir $\bar{\nu}$ 1670 (C=C), 1305 and 1152 cm^{-1} (SO_2); nmr ($CDCl_3$) τ 2.18–2.58 (4 H, aromatic), 5.08 (2 H, broad, vinylidene), 6.40–7.20 (3 H, CH_2 and CH), 8.23 (3 H, *J* = 1.0 Hz, CH_3), 8.55 (3 H, *J* = 6.0 Hz, CH_3); mass spectrum *m/e* 236 (molecular ion).

Anal. Calcd for $C_{13}H_{16}SO_2$: C, 66.10; H, 6.78; S, 13.56. Found: C, 65.84; H, 6.83; S, 13.36.

Fraction 2 (recrystallization from ethanol) gave compound **12a** (115 mg, 0.5 mmol, 25%, mp 131.5–132°): ir $\bar{\nu}$ 1470 cm^{-1} (CCH_3); nmr τ 2.11–2.75 (4 H, aromatic), 6.20–6.56 (2 H, m, CH), 7.58 (1 H, *J* = 7.0 Hz, CH), 8.70 (3 H, s, CH_3), 8.88 (3 H, *J* = 7.0 Hz, CH_3), 9.20 (3 H, CH_3); mass spectrum *m/e* 236 (molecular ion).

Anal. Calcd for $C_{13}H_{16}SO_2$: C, 66.10; H, 6.78; S, 13.56. Found: C, 66.03; H, 6.97; S, 13.41.

Photocycloaddition of 3-Deuteriothianaphthene 1,1-Dioxide (1b) to 2 Methyl-2-butene.—This experiment was executed in exactly the same way as was the cycloaddition of compound **1a**

(17) G. von Komppa, *J. Prakt. Chem.*, **622**, 319 (1929).

to 2-methyl-2-butene. The resulting products were compound **11b** (mp 145–145.5°), mass spectrum *m/e* 237 (molecular ion), and **12b** (mp 131.5–132°): nmr ($CDCl_3$) τ 2.11–2.75 (4 H, aromatic), 6.35 (1 H, J = 9.0 Hz, CH), 7.58 (1 H, J = 7.0 Hz, CH), 8.70 (3 H, CH_3), 8.88 (3 H, J = 7.0 Hz, CH_3), 9.20 (3 H, CH_3); mass spectrum *m/e* 237 (molecular ion).

Acknowledgment.—We are grateful to Dr. John G. Gleason for spin-decoupling experiments and to the National Research Council of Canada for financial support.

Registry No.—**1a**, 825-44-5; **1b**, 41674-77-5; **2a**, 41674-78-6; **2b**, 41674-79-7; **3**, 41674-80-0; **4**, 156-59-2; **5**, 156-60-5; **6–7**, 41674-81-1; **8**, 75-35-4; **9a**, 41674-82-2; **11a**, 41674-83-3; **11b**, 41674-84-4; **12a**, 41674-85-5; **12b**, 41674-86-6; 3-deuteriothianaphthene, 15816-45-2; 3-bromothianaphthene, 7342-82-7; trichloroethylene, 79-01-6; 2-methyl-2-butene, 513-35-9.

Directed Metalation Reactions. V.[1] Metalation and Rearrangement in Substituted 2-Thiophenesulfonamides

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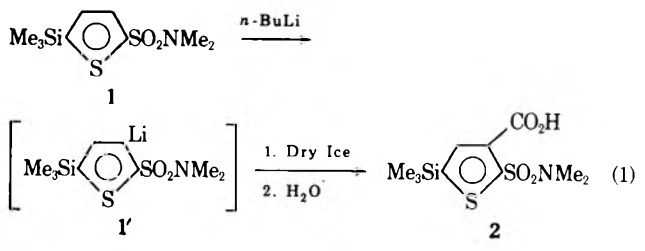
Metalation of several 2-*N*,*N*-dialkylthiophenesulfonamides with *n*-butyllithium has revealed some diverse behavior. Whereas metalation of 5-trimethylsilyl-*N*,*N*-dimethyl-2-thiophenesulfonamide (**1**) gave 3 metalation only, metalation of the diethyl analog (**4**) produced 3 metalation accompanied by loss of the trimethylsilyl group when the lithio intermediate **4′** was condensed with Dry Ice. When other reagents were condensed with **4′**, loss of the trimethylsilyl group was not observed and 3-substituted derivatives of **4** were produced. Moreover, when dimethylsulfonamide **1** was treated with *n*-butyllithium–TMEDA complex, a rearrangement ensued which produced 2-trimethylsilyl-4-*N*,*N*-dimethylthienylamine (**3**).

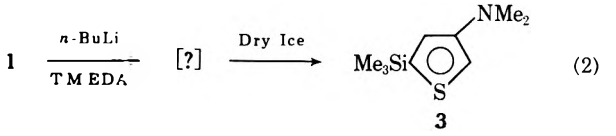
Ortho metalation of both *N*-methyl- and *N*-phenylbenzenesulfonamide has been demonstrated.[2a] Similarly, *N*,*N*-dimethylbenzenesulfonamide was found[2b] to undergo metalation ortho to the sulfonamide group and to give good yields of various condensation products. Such studies involving the metalation of thiophenesulfonamides have not been reported in the literature. However, it has been shown by Stoyanovitch and Fedorov[3] that *tert*-butyl 2-thienyl sulfone was dimetalated in the 3 and 5 positions with excess *n*-butyllithium. Similar results were anticipated in the metalation of the thiophenesulfonamides, but, as described below, other processes intervened at times.

Initial attempts to effect metalation of *N*,*N*-dimethyl-2-thiophenesulfonamide in the 3 or 3,5 positions were unsuccessful, metalation occurring only at the 5 position. This observation prompted the introduction of a blocking group into the 5 position of the thiophenesulfonamide with the result that 5-trimethylsilyl-*N*,*N*-dimethyl-2-thiophenesulfonamide (**1**) was prepared. Metalation of **1** with *n*-butyllithium followed by condensation of the lithio intermediate (**1′**) with Dry Ice afforded a 10% yield of 5-trimethylsilyl-3-carboxyl-*N*,*N*-dimethyl-2-thiophenesulfonamide (**2**) (eq 1) and 75% recovery of starting material. An ir spectrum of **2** exhibited bands between 3000 and 2450 and at 1710 cm^{-1} characteristic of a carboxyl group. In addition, its nmr spectrum showed a singlet at 7.66 ppm for the lone remaining thiophene ring proton and singlet peaks for the methyl groups attached to the sulfonamide group and silicon atom at 2.94 and 0.37 ppm, respectively. The site of metalation is postulated as being the 3 position, in analogy to the results for *N*,*N*-dimethylbenzenesulfonamide[2] and also as a result of a deuterium labeling experiment. When lithio intermediate **1′** was quenched with D_2O, a deuterated disubstituted thiophene resulted which exhibited attenuation of the more downfield signal, the signal which was assigned to the 3-position proton since it was adjacent to the highly deshielding sulfonamide group. A similar deshielding has been observed for SO_2R derivatives of cymantrene and ferrocene.[4]



(1)

In order to possibly increase the yield of condensation product, sulfonamide **1** was metalated with *n*-butyllithium–*N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA) at −30° and condensed with Dry Ice. No carboxylic acid condensation product was isolated but rather a rearranged aminothiophene identified as 2-trimethylsilyl-*N*,*N*-dimethyl-4-thienylamine (**3**) was obtained in 39% yield (eq 2). Attempts to eliminate



(2)

Dry Ice from the reaction with substitution of ice water led to much lower yields of amine **3**. The structure of amine **3** was deduced from examination of its ir and nmr spectra. Its ir spectrum exhibited two bands at 2800 and 1250 cm^{-1} characteristic of tertiary aryl amines,[5] whereas the intense sulfonamide bands at 1350 and

(1) For paper IV in this series, *cf.* D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).

(2) (a) H. Watanabe, R. L. Gay, and C. R. Hauser, *J. Org. Chem.*, **33**, 900 (1968); (b) H. Watanabe, R. A. Schwarz, C. R. Hauser, J. Lewis, and D. W. Slocum, *Can. J. Chem.*, **47**, 1543 (1969).

(3) F. M. Stoyanovitch and B. P. Fedorov, *Khim. Geterotsikl. Soedin.*, **5**, 823 (1967); *Chem. Abstr.*, **69**, 7119 (1968).

(4) (a) D. W. Slocum and C. R. Ernst, *Organometal. Chem. Rev., Sect. A*, **6**, 283 (1970); (b) D. W. Slocum and C. R. Ernst, *Advan. Organometal. Chem.*, **10**, 79–114 (1972).

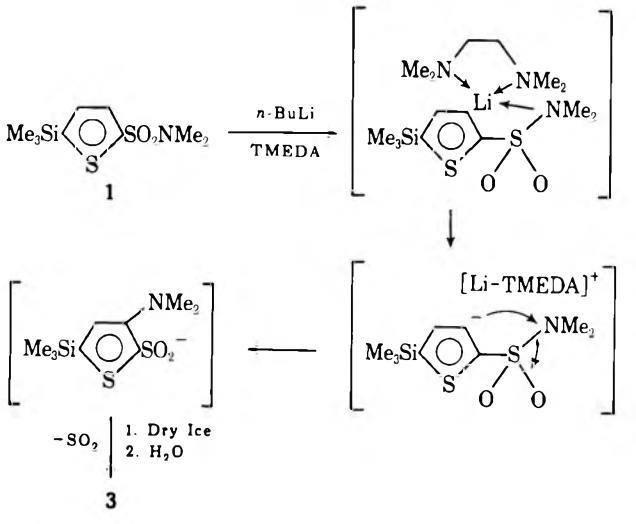
(5) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, pp 38 and 40.

1160 cm^{-1} were absent. The postulation of a 2,4 orientation of the substituents is based primarily on the compound's nmr spectrum, which exhibited a well-resolved AB pattern for the two ring protons. The observed coupling constant of 1.3 Hz for the two protons is reported to be characteristic of 2,4-disubstituted thiophenes.[6] A coupling constant of 1.5 Hz has recently been reported for a series of 2,4-thiophenediamines.[7]

Although the instability of thienylamines has long been recognized,[8] some stability is imparted to such systems if the amines are present in tertiary form. Thus, several examples of *N,N*-dialkyl-3-thienylamines have been reported,[9,10] and a unique series of 2,4-tetraalkylthiophenediamines.[7] More to the point, *N,N*-dimethyl-3-thienylamine has been prepared by a reductive method but the same technique failed to produce any of the 2 isomer.[10] Thus, the fact that amine **3** has the amine substituent in the β rather than the α position appears to be consistent with current data for thienylamines.

A possible mechanism leading to the formation of amine **3** may begin with coordination of the lithiated intermediate with TMEDA as shown in Scheme I.

SCHEME I



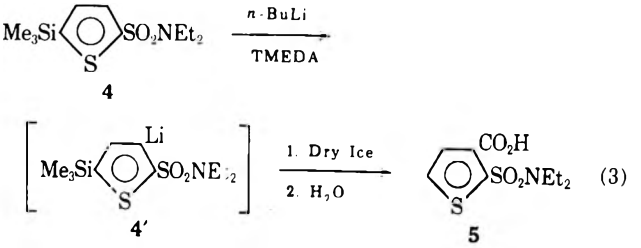
1 3

This, in turn, may enhance the carbanionic activity of the 3-position carbon–lithium bond sufficiently to effect a nucleophilic displacement reaction on nitrogen with the thiophenesulfinate anion functioning as a leaving group. Condensation with Dry Ice would not be expected to yield any stable product from the sulfinate intermediate but the subsequent hydrolysis step should yield the sulfinic acid derivative. Loss of SO_2 would then yield the rearrangement amine, **3**. As mentioned previously, Dry Ice was not necessary for the production of amine **3**, but yields were much poorer when it was omitted.

This last step is lent some credence by a number of reports of the instability of aromatic sulfinic acids. For example, 2-thiophenesulfinic acid prepared from 2-thienyllithium and sulfur dioxide has been reported to be "somewhat unstable."[11] Moreover, all attempts to convert lithium 2-furansulfinate to the free sulfinic acid failed.[11] Benzyhydryllithium sulfinate upon acidification at 0° gave the free acid but this decomposed at 25° to sulfur dioxide and diphenylmethane.[12] Heating 2,4-dinitrobenzenesulfonhydrazine (a reaction known to lead to sulfinic acids with other arylsulfonhydrazides) gave a quantitative yield of *m*-dinitrobenzene.[13]

Other possible rearrangement pathways were deemed less likely since they all would have given ring lithiated intermediates which under these conditions should have given a condensation product with Dry Ice–ether.

Further testing of the scope of this rearrangement was attempted by the metalation with *n*-butyllithium–TMEDA of 5-trimethylsilyl-*N,N*-diethyl-2-thiophenesulfonamide (**4**) with the idea of preparing the diethyl analog of **3**. No rearrangement product was detected after this system was treated with Dry Ice. Rather directed metalation as observed for sulfonamide **1** with uncomplexed butyllithium occurred, accompained by loss of the trimethylsilyl group with the resulting isolation of a single product, 3-carboxyl-*N,N*-diethyl-2-thiophenesulfonamide (**5**) in 44% yield (eq 3). The site



4 4′ 5 (3)

of metalation was ascertained from the product's nmr spectrum, which exhibited a well-resolved AB pattern for the two ring protons. The coupling constant of these protons was 4.9 Hz, which falls in the region reported for a large number of 2,3-disubstituted thiophenes.[5] Separate synthesis of the 2,5 isomer established unequivocally that this was not the structure of **5** (*cf.* Experimental Section).

The absence of rearrangement amine product could be associated with steric effects of the larger ethyl groups which may hinder close approach of the diethylamino group to the carbanionic site. Loss of the trimethylsilyl group could not be explained but was thought perhaps to be associated with the particular condensation reagent or work-up procedure. In order to explore this possibility, metalation of sulfonamide **4** with *n*-butyllithium–TMEDA was repeated but the lithio intermediate was hydrolyzed with D_2O. Deuterated sulfonamide **4** was obtained in 70% recovery and with no loss of the trimethylsilyl group. Nmr integration indicated that one deuteron had been incorporated into the thiophene ring with the site of deuteration and, hence, of metalation being assigned the 3 position. Assignment of the site of deuteration was based on the nearly total attenuation of the downfield proton resonance. Of the two thiophene ring resonances this would correspond to the proton adjacent to the deshielding sulfonamide system.

The lithio intermediate of sulfonamide **4** was also

(6) R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1960).
(7) J. P. Chupp, *J. Heterocycl. Chem.*, **7**, 285 (1970).
(8) H. D. Hartough, "Thiophene and Its Derivatives," Interscience, New York, N. Y., 1952, pp 228–235.
(9) F. A. Biuter, J. H. Sperma Weiland, and H. Wynbert, *Recl. Trav. Chim. Pays-Bas*, **83**, 1160 (1964).
(10) J. B. Sullivan and W. C. McCarthy, *J. Org. Chem.*, **30**, 662 (1965).
(11) W. E. Truce and E. Wellisch, *J. Amer. Chem. Soc.*, **74**, 5177 (1952).
(12) E. Wellisch, E. Gipstein, and O. T. Sweeting, *J. Org. Chem.*, **27**, 1810 (1962).
(13) H. Bradbury and F. J. Smith, *J. Chem. Soc.*, 2943 (1952).

condensed with dimethylformamide to give an estimated 14% yield of the carboxaldehyde derivative.[8] Again, no loss of the trimethylsilyl group was observed. Since the site of deuteration was in the 3 position, assignment of the carboxaldehyde functional group to the 3 position was deemed justified. Otherwise the structure **6** was supported by the usual spectral and analytical data but the compound was not obtained free of starting material.

Several attempts at acid hydrolysis of the thiophene–trimethylsilyl bond were attempted with the idea that the trimethylsilyl group would serve as a blocking group during the synthesis of 2,3-disubstituted thiophenes. All such attempts failed. Interestingly, cleavage of the trimethylsilyl–thiophene ring bond did occur upon carbonation of lithiated sulfonamide **4** but the reaction was not able to be generalized and at present remains inexplicable.

Experimental Section

n-Butyllithium (1.6 *M* in hexane) used in the following experiments was purchased from Foote Mineral Co. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Co. and stored over KOH pellets. The ether used as a reaction solvent was Matheson Coleman and Bell "absolute" grade and was stored over Linde 3A Molecular Sieves or sodium metal.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratories, Mulheim, West Germany. Melting points were determined on a Hoover melting point apparatus and have been corrected. Ir spectra were obtained on a Perkin-Elmer Model 137 Infracord spectrometer using the 5.14-μ and 11.03-μ bands of polystyrene as references. Nmr spectra were obtained on a Varian A-56/60 spectrometer using tetramethylsilane (TMS) as an internal standard.

***N,N*-Dimethyl-2-thiophenesulfonamide.**—2-Thiophenesulfonyl chloride was prepared in 24% yield from thiophene (25 ml, 0.32 mol) and chlorosulfonic acid (100 g, 0.86 mol), according to the procedure of Blatt, *et al.*,[14] bp 58–60° (0.7 mm) [lit.[14] bp 99–101° (6.0 mm)]. The sulfonyl chloride (14 g, 0.77 mol) was then added dropwise to 100 ml of absolute dimethylamine with the reaction mixture kept at −20°. After addition was complete, excess dimethylamine was boiled off on the steam bath, leaving a tan-colored, crystalline material. The yield of *N,N*-dimethyl-2-thiophenesulfonamide was 10.2 g (69%): mp 67–69°; ir 1360, 1160 cm^{-1} ($SO_2N<$); nmr ($CDCl_3$) δ 2.92 [s, 6, $N(CH_3)_2$], 7.42–8.10 (m, 3, aromatic CH).

Anal. Calcd for $C_6H_9NO_2S_2$: C, 37.68; H, 4.74; N, 7.32. Found: C, 37.60; H, 4.64; N, 7.25.

6-Trimethylsilyl-*N,N*-dimethyl-2-thiophenesulfonamide (1).—*N,N*-Dimethyl-2-thiophenesulfonamide (5.7 g, 0.03 mol) was dissolved in 100 ml of dry THF under argon and 22.7 ml (0.036 mol) of 1.6 *M* *n*-butyllithium was added. After 20-min stirring, chlorotrimethylsilane (3.9 g, 0.036 mol) was added. The flask was tightly stoppered and the reaction mixture was stirred for 5 hr. Water was added and the organic layer was separated, combined with the ether extracts of the aqueous phase, dried over $MgSO_4$, and stripped. The resultant brown solid was recrystallized from petroleum ether (bp 30–60°) to give 3.24 g (41%) of 5-trimethylsilyl-*N,N*-dimethyl-2-thiophenesulfonamide (1): mp 75–77°; ir 1350, 1160 cm^{-1} (SO_2N); nmr ($CDCl_3$) δ 1.50 [s, 9, $Si(CH_3)_3$], 2.75 [s, 6, $SO_2N(CH_3)_2$], 7.21, 7.56 (AB, J_{34} = 3.5 Hz, 2, aromatic CH).

Anal. Calcd for $C_9H_{17}O_2NS_2Si$: C, 41.03; H, 6.50; N, 5.32. Found: C, 40.91; H, 6.62; N, 5.21.

Metalation of 5-Trimethylsilyl-*N,N*-dimethyl-2-thiophenesulfonamide (1). A. With *n*-Butyllithium. Condensation with Dry Ice.—Sulfonamide 1 (2.00 g, 0.0076 mol) was dissolved in 75 ml of dry ether under argon and the solution was cooled to 0°; then 9.6 ml (0.015 mol) of 1.6 *M* *n*-butyllithium in hexane was added. After the reaction mixture was stirred for 6 hr at 0–4°, it was poured over a slurry of Dry Ice in ether. Water (100 ml) was later added to the suspension and the resulting two layers were separated. The aqueous layer was treated with 100 ml of 3 *N* HCl and extracted twice with ether. The ether extracts were combined, dried over $MgSO_4$, and stripped to give a brown oil. Repeated washings of the oil with petroleum ether gave a brown solid. Recrystallization from 1:1 absolute ethanol–petroleum ether gave 0.23 g (9.8% yield) of 5-trimethylsilyl-3-carboxyl-*N,N*-dimethyl-2-thiophenesulfonamide (2), mp 119–121° dec.

The original ether layer was dried over $MgSO_4$ and stripped to give 1.5 g (75%) of recovered material, mp 74–77°. The ir spectrum of the recovered material was identical with that of the sulfonamide 1. The ir spectrum of 2 showed bands at 3000–2450, 1710 (COOH), 1345, and 1150 cm^{-1} ($SO_2N<$); nmr ($CDCl_3$) δ 0.37 [s, 9, $Si(CH_3)_3$], 2.94 [s, 6, $SO_2N(CH_3)_2$], 7.66 (s, 1, aromatic CH), 10.70 (s, 1, COOH).

Anal. Calcd for $C_{10}H_{17}NO_4S_2Si$: C, 39.06; H, 5.57; N, 4.56. Found: C, 39.48; H, 5.63; N, 4.67.

B. With *n*-Butyllithium–TMEDA. Condensation with Dry Ice.—Tetramethylethylenediamine (2.07 g, 0.0023 mol) was dissolved in 40 ml of 1:1 ether–hexane solution and treated with 1.28 ml (0.0023 mol) of 1.6 *M* *n*-butyllithium in hexane under argon. After being stirred for 15 min, the reaction mixture was cooled to −30° and sulfonamide 1 (0.5 g, 0.0019 mol) was added. The stoppered flask was stirred for 5 hr at −30°; then the contents of the flask were poured over a slurry of Dry Ice in ether. After excess Dry Ice had evaporated, the white suspension was stirred with 100 ml of H_2O and the resulting two layers were separated. The aqueous layer was treated with 100 ml of 3 *N* HCl and extracted twice with ether; the combined ether extracts were dried over $MgSO_4$ and stripped. No carboxylic acid product was obtained. The original ether layer was dried over $MgSO_4$ and stripped to give a brown oil. Vacuum distillation of the crude oil gave 0.15 g (39%) of the rearranged amine, 2-trimethylsilyl-*N,N*-dimethyl-4-thienylamine (3), bp 62–64° (1.5 mm), methiodide derivative mp 229–231°.

The following data support the structure of the rearranged amine 3: ir 2800 [$N(CH_3)_2$], 1250 cm^{-1} ($ArN<$); nmr ($CDCl_3$) δ 2.95 [s, 9, $Si(CH_3)_3$], 6.35 (d, $J_{2,4}$ = 1.3 Hz, 1, aromatic CH), 7.05 (d, $J_{2,4}$ = 1.3 Hz, 1, aromatic CH); mass spectrum M^+ at *m/e* 199.

Anal. Calcd for $C_9H_{17}NSSi$: C, 54.21; H, 8.59. Found: C, 54.12; H, 8.48.

5-Trimethylsilyl-*N,N*-diethyl-2-thiophenesulfonamide (4).—2-Thiophenesulfonyl chloride was prepared as described at the beginning of this Experimental Section. The sulfonyl chloride (9.0 g, 0.038 mol) was added dropwise to excess diethylamine (25 ml) with stirring. After the addition was completed, excess diethylamine was stripped, and the resulting white solid was washed with petroleum ether. The product was vacuum distilled at 1.3 mm to give a single fraction boiling between 99 and 102° which weighed 6.5 g (78%): ir 1330, 1155 cm^{-1} ($SO_2N<$); nmr ($CDCl_3$) δ 1.25 (t, 6, CH_3), 3.40 (q, 4, CH_2), 7.33–7.97 (m, 3, aromatic CH).

Anal. Calcd for $C_8H_{13}NO_2S_2$: C, 43.81; H, 5.98; N, 6.39. Found: C, 43.78; H, 5.92; N, 6.27.

The sulfonamide (6.5 g, 0.03 mol) was dissolved in 200 ml of dry ether under argon and 22.7 ml (0.036 mol) of 1.6 *M* *n*-butyllithium was added. After 30-min stirring, chlorotrimethylsilane (7.8 ml, 0.72 mol) was added. The mixture was stirred for 20 min and hydrolyzed with H_2O, whereupon the ether layer was separated, washed once with H_2O, dried over $MgSO_4$, and stripped. The resultant reddish-brown oil was vacuum distilled at 0.8 mm. A single fraction, bp 133–137°, was collected to give 6.9 g (79%) of 5-trimethylsilyl-*N,N*-diethyl-2-thiophenesulfonamide (4): ir 1345, 1150 cm^{-1} ($SO_2N<$); nmr ($CDCl_3$) δ 0.35 [s, 9, $Si(CH_3)_3$], 1.17 (t, J = 7.0 Hz, 6, CH_3), 3.22 (q, J = 7.0 Hz, 4, CH_2), 7.17 (d, $J_{3,4}$ = 3.5 Hz, 1, aromatic CH), 7.50 (d, $J_{3,4}$ = 3.5 Hz, 1, aromatic CH).

Anal. Calcd for $C_{11}H_{21}NO_2S_2Si$: C, 45.32; H, 7.26; N, 4.80. Found: C, 45.51; H, 7.25; N, 4.69.

Metalation of 5-Trimethylsilyl-*N,N*-diethyl-2-thiophenesulfonamide (4) and Condensation with Electrophilic Reagents. A. Condensation with Dry Ice.—To a solution of TMEDA (0.56 g, 0.005 mol) in 45 ml of dry ether was added 3.1 ml (0.005 mol) of 1.6 *M*-*n*-butyllithium in hexane under argon. After 15-min stirring, the reaction mixture was cooled to 0° and sulfonamide 4 (1.27 g, 0.0045 mol) was added. The tightly stoppered flask was stirred for 6 hr at approximately −30°, after which the contents of the flask was poured over a slurry of Dry Ice in ether. Water

(14) A. H. Blatt, S. Bach, and L. W. Kresch, *J. Org. Chem.*, **22**, 1693 (1957).

(100 ml) was added, and the aqueous layer was separated, acidified with 100 ml of 10% HCl, and extracted twice with ether. The combined ether extracts were dried over $MgSO_4$ and stripped to give 0.52 g (44%) of 3-carboxyl-*N*,*N*-diethyl-2-thiophenesulfonamide (5), mp 147–149°.

The original ether layer was dried over $MgSO_4$ and stripped to give 0.30 g (22% recovery) of starting material whose ir spectrum was superimposable on that of sulfonamide **4**.

The ir spectrum of compound **5** (Nujol) exhibited bands at 3000–2450, 1715 (COOH), 1340, 1140 cm^{-1} ($-SO_2N<$); nmr (DMSO-d_6) δ 1.07 (t, 6, CH_3), 3.40 (q, 4, CH_2), 7.55, 8.05 (AB, J_{AB} = 4.9 Hz, 2, aromatic CH).

Anal. Calcd for $C_9H_{13}NO_4S_2$: C, 41.05; H, 4.98; N, 5.32. Found: C, 41.03 (41.40); H, 5.01; N, 4.79 (4.96).

Metalation of *N*,*N*-Diethyl-2-thiophenesulfonamide.—To a solution of *N*,*N*-diethyl-2-thiophenesulfonamide (2.0 g, 0.0093 mol) in 50 ml of dry ether under argon was added 6.3 ml (0.01 mol) of 1.6 *M* *n*-butyllithium with stirring. After 1 hr, the contents of the reaction flask was quickly added to a slurry of excess Dry Ice in ether. The mixture was later hydrolyzed with 100 ml of water. Solid NaOH was added until the mixture was strongly basic. The aqueous layer was separated, washed once with ether, and then neutralized with 10% HCl. Ether extracts of the neutralized aqueous layer were dried over $MgSO_4$ and stripped to give 1.97 g (82%) of 5-carboxyl-*N*,*N*-diethyl-2-thiophenesulfonamide. Recrystallization from dry ether gave an analytical sample: mp 128–130°; ir (Nujol) 2700–2450, 1700 (COOH), 1360, 1145 cm^{-1} ($-SO_2N<$).

Anal. Calcd for $C_9H_{13}NO_4S_2$: C, 41.05; H, 4.98; N, 5.32. Found: C, 41.04; H, 4.89; N, 5.14.

B. Condensation with Deuterium Oxide.—Lithio intermediate **4′** was prepared as described at the beginning of this section using 2.0 g (0.007 mol) of sulfonamide **4**, 5.0 ml (0.008 mol) of 1.6 *M* *n*-butyllithium in hexane, and 0.90 g (0.008 mol) of TMEDA. After being stirred for 6 hr, the reaction mixture was hydrolyzed with 1.0 ml of D_2O. The ether layer was separated, washed with H_2O, dried over $MgSO_4$, and stripped. The resulting oil was vacuum distilled to give 1.4 g (70% recovery of material), bp 130–132° (0.65 mm). An nmr spectrum indicated that 1.0 deuterium atom was incorporated into the aromatic ring by the absence of a proton resonance corresponding to the chemical shift of the downfield ring proton (δ 7.50) in the undeuterated sulfonamide **4**. The ir spectrum of deuterated sulfonamide **4** was identical with that of the starting material. The C–D stretching vibration that should be present for this compound was not in evidence on an instrument with the sensitivity of the Infracord 137.

C. Condensation with Dimethylformamide.—To a solution of TMEDA (0.70 g, 0.006 mol) in 30 ml of dry ether was added 3.8 ml (0.006 mol) of 1.6 *M* *n*-butyllithium in hexane under argon. After being stirred for 15 min, the reaction mixture was cooled to 0°, sulfonamide **4** (1.45 g, 0.005 mol) was added, and the mixture was stirred for 24 hr at 0–4°. Dimethylformamide (0.88 g, 0.012 mol) was added to the mixture and stirred for 6 hr. After the reaction mixture was hydrolyzed, the ether layer was separated, combined with ether extracts of the aqueous layer, dried over $MgSO_4$, and stripped. Vacuum distillation of the resultant crude oil gave 0.10 g of a yellow oil boiling at 80–82° (1.25 mm) and 0.39 g of a product mixture boiling at 156° (1.25 mm). Ir and nmr spectra for the first fraction did not conform with any predicted product or products; ir spectrum showed bands at 2910, 1240, 1000, 833, and 745 cm^{-1}; nmr ($CDCl_3$) δ 1.05–1.53 (m, 8.5 H), 2.40–3.00 (m, 2.2 H), 6.76 (s, 1, aromatic CH).

An nmr analysis of the second fraction showed it to be 43% starting sulfonamide **4** and 57% 5-trimethylsilyl-3-formyl-2-*N*,*N*-diethylthiophenesulfonamide (**6**) by comparison of the relative peak areas at 7.50 ppm for **4** and 10.30 ppm for compound **6**. The nmr data corresponded to 12% recovery and a 14% yield, respectively, of the two compounds. An ir spectrum for the mixture showed bands at 1695 (C=O), 1330, and 1140 cm^{-1} (SO_2N); nmr (CCl_4) δ 0.37 [s, unresolved, $Si(CH_3)_3$], 1.20 (t, unresolved, CH_3), 3.27 (q, unresolved, CH_2), 7.50 (d, J_{34} = 3.5 Hz, aromatic CH), 7.58 (s, aromatic CH), 10.30 (s, CHO).

An unsuccessful attempt was made to separate the mixture on a 30-ft preparative scale gas chromatographic column containing Carbowax 4000.

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Registry No.—**1**, 41895-02-7; **2**, 41895-03-8; **3**, 41895-04-9; **3** methiodide derivative, 41895-05-0; **4**, 41895-06-1; deuterated **4**, 41895-07-2; **5**, 41895-08-3; **6**, 41895-09-4; *N*,*N*-dimethyl-2-thiophenesulfonamide, 41895-10-7; dimethylamine, 124-40-3; chlorotrimethylsilane, 75-77-4; diethylamine, 109-89-7; *N*,*N*-diethyl-2-thiophenesulfonamide, 41895-11-8; 5-carboxy-*N*,*N*-diethyl-2-thiophenesulfonamide, 41895-12-9; dimethylformamide, 68-12-2.

Complexation as a Factor in Metalation Reactions. Metalation of 1-Methoxy-2-phenoxyethane

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The effect of side-chain chelation on the rate of metalation of aryl rings by *n*-butyllithium was investigated by allowing anisole and 1-methoxy-2-phenoxyethane (MPE) to compete for excess base. The ratio of MPE to anisole metalation was found to be 13.9:1 and 14.4:1 in ether and hexane, respectively. MPE gave phenol and phenyl vinyl ether as minor products during the reaction. Labeling experiments showed the phenol to be derived from both inter- and intramolecular routes. Evidence for a 2:1 complex between *n*-butyllithium and MPE was presented.

The metalation reaction continues to attract attention both with regard to the mechanism of proton removal as well as synthetic utility.[1] In the latter context we became interested in the relative importance of heteroatom chelation as a directing and activating influence during the metalation of aromatics. Here we report a quantitation of this effect for oxygen in the metalation of benzene rings by *n*-butyllithium.

During the past few years evidence has been accumulating which clearly shows that heteroatoms either in the solvent or on reactants enhance the reactivity of lithium alkyls and influence site selection for proton removal. Thus, while generally unreactive to *n*-butyllithium, benzene can be quantitatively metalated by this base in the presence of simple tertiary amines.[2] Good chelating bases such as sparteine or

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(2) C. G. Screttas and J. F. Eastham, *J. Amer. Chem. Soc.*, **87**, 3276 (1965).

N,N,N',N'-tetramethylethylenediamine are especially effective and the degree of enhanced reactivity was found to be proportional to base strength.[3] Similarly, chelation of ethers has been invoked to explain the fragmentation of self-associated lithium alkyls to smaller and more reactive species.[4]

Prior coordination of the lithium alkyl to a substituent heteroatom appears to explain the selective ortho metalation of γ-phenylpropyldimethylamine by *n*-butyllithium[5a] as well as similar results observed with dimethylaminomethylferrocenes,[5b] alkoxymethylferrocenes,[5c] and related thiophenes.[5d] In the case of *p*-methoxybenzyldimethylamine, proton removal occurs at the position meta to the methoxyl group in spite of the virtually selective metalation of anisole at the ortho position.[6]

This situation is not universally true, however, since triphenylamine has been shown to meta metalate[7] and ethylphenyl sulfide yielded as much as 18.5% of meta proton removal.[8] Further, while prior coordination of the base should be reflected in a steric hindrance effect due to alkyl substituents on the heteroatom, a competitive metalation of anisole and phenyl *tert*-butyl ether using *tert*-butyllithium showed no difference in metalation rate.[9] On the other hand, what appears to be a distinct steric effect in the metalation of *o-tert*-butylanisole has recently been observed.[10] Alternate explanations for site-selective metalation and increased reactivity in aromatics include enhanced inductive effects operating on the ortho carbon due to electronegative substituents[7] and a multistep free-radical mechanism.[9]

The work described here was aimied at studying the influence of chelation under careful control of variables. It was reasoned that a good measure of the effect of reagent chelation would be obtained by keeping the electronic characteristics of the aryl ring constant while varying the chelating ability of the ring substituent.

Experimental Section

Nmr spectra were obtained on a Varian A-60A instrument with chemical shifts in δ units relative to internal tetramethylsilane. Deuterium incorporation was determined by mass spectrometry using a Finnigan 1015 instrument coupled to a Varian 1700 gas chromatograph. Errors in these measurements were estimated as ±1%. Quantitative analysis of product mixtures was accomplished with a Varian Aerograph 1800 instrument with flame ionization detectors and a 6 ft × 0.125 in. 10% Apiezon L column at 200°. Infrared spectra were recorded on neat films using a Beckman IR-5A instrument.

n-Butyllithium in hexane (15.03 and 21.4%) was obtained from Matheson Coleman and Bell and Alfa Inorganics Inc., respectively. The concentration was determined by a previously described method.[11] Lithium aluminum hydride and lithium aluminum deuteride ($LiAlD_4$) were obtained from Alfa Inorganics Inc. 2-Phenoxyethanol and 2,3-benzofuran were obtained from Aldrich Chemical Co. and were purified by distillation. Phenoxyacetic acid was obtained from Eastman Organic Chemicals. Pyridine was purified before use by distillation from barium oxide.

Preparation of 1-Methoxy-2-phenoxyethane-*1,1*-d_2 (MPE-*1,1*-d_2).—To a solution of 10 g (58.0 mmol) of *p*-toluenesulfonic acid in 500 ml of benzene was added 15.2 g (0.1 mol) of phenoxyacetic acid and 17.6 ml (0.3 mol) of absolute ethanol. The reaction mixture was refluxed with continuous removal of water until no further water evolution was evident (2 hr) and then concentrated by evaporation *in vacuo*. The concentrate was added to saturated sodium carbonate and extracted twice with ether. The ether extracts were combined, dried with magnesium sulfate, and evaporated *in vacuo* until free of solvent, affording 13.6 ml (83.5 mmol, 83.5%) of phenoxyacetic acid ethyl ester which was 100% pure by glc, and characterized in the ir by the absence of a carboxylic acid peak and the presence of strong unconjugated ester peaks at 1725 and 1200 cm^{-1}.

To 50 ml of diethyl ether in a flame-dried 100-ml three-necked round-bottomed flask fitted with a reflux condenser was added 0.575 g (13 7 mmol) of $LiAlD_4$. To this mixture a 25-ml diethyl ether solution of 3 ml (18.3 mmol) of the above-prepared phenoxyacetic acid ethyl ester was slowly added *via* a dropping funnel and then allowed to reflux for 24 hr. After the reaction was complete, a saturated water solution of Rochelle salt was added dropwise to the reaction vessel until precipitation was initiated. The reaction mixture was filtered and the residue was washed twice with ether. The ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* at room temperature until free of solvent. The crude product was redistilled under high vacuum, affording 1.952 g (76%) of 2-phenoxyethanol-*1,1*-d_2 which was 100% pure on glc and characterized by ir and nmr comparisons with an authentic sample of 2-phenoxyethanol.

To a flame-dried flask containing 0.70 g (16.7 mmol) of a sodium hydride suspension in oil was added 30 ml of dimethoxyethane (DME) after several prior washings of the hydride suspension with DME to remove excess oil. Once a fine suspension was achieved, a 20-ml DME solution of 1.952 g (13.9 mmol) of the above-prepared 2-phenoxyethanol-*1,1*-d_2 was added with an oven-dried syringe. After 1 hr a 10-ml DME solution of 1.04 ml (16.7 mmol) of iodomethane was added to the flask with an oven-dried syringe and the reaction was allowed to reflux overnight. The unreacted sodium hydride was decomposed by a dropwise addition of saturated aqueous ether. The reaction mixture was added to water and extracted three times with ether. The ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* until free of solvent. The crude isolated product was distilled under high vacuum, affording 1.875 g (87%) of 1-methoxy-2-phenoxyethane-*1,1*-d_2 which was 100% pure on glc: nmr (CCl_4) δ 4.00 (s, 2, OCH_2CD_2–), 3.34 (s, 3, OCH_3), and 6.7–7.4 (m, 5, phenyl H).

The 3350-cm^{-1} band was absent from the ir spectrum. The molecular weight was determined by mass spectrometry to be 154 with nearly quantitative incorporation of two D atoms.

Preparation of 1-Methoxy-2-phenoxyethane (MPE).—Using the above procedure MPE was prepared in 90% yield from 2-phenoxyethanol. The isolated product was 100% pure by glc: nmr (CCl_4) δ 4.04 (t, 2, $C_6H_5OCH_2$–), 3.65 (t, 2, CH_2OCH_3), 3.37 (s, 3, OCH_3), 6.7–7.4 (m, 5, phenyl H). The 3350-cm^{-1} hydroxyl peak was absent from the ir spectrum.

Preparation of Coumaran (2,3-Dihydrobenzofuran).—A 5-ml solution of 0.250 g (2.12 mmol) of 2,3-benzofuran in glacial acetic acid was added to a dry 100-ml round-bottomed hydrogenation flask containing a 20-ml solution of 0.500 g of 5% Pd/C in glacial acetic acid and under hydrogen at atmospheric pressure and temperature. The reactants were stirred vigorously until 47.5 ml (2.12 mmol) of hydrogen gas was consumed (~4.5 hr). The reaction mixture was filtered through Kieselguhr, neutralized with saturated sodium carbonate, and extracted four times with ether. The diethyl ether layers were combined, dried with magnesium sulfate, and evaporated *in vacuo* at room temperature until free of solvent. The crude isolated product was distilled, affording 0.113 g (44%) of coumaran: bp 104° (0.1 mm); nmr ($CDCl_3$) δ 3.18 (t, 2, $CH_2C_6H_4$), 4.56 (t, 2, $C_6H_4OCH_2$), and 6.7–7.4 (m, 4, C_6H_4).

Anal. Calcd for C_8H_8O: C, 79.97; H, 6.71. Found: C, 79.93; H, 6.76.

Preparation of Phenyl Vinyl Ether.—(2-Chloroethoxy)benzene was prepared by a modification of the method of Brooks and

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(4) H. L. Lewis and T. L. Brown, *J. Amer. Chem. Soc.*, **92**, 4664 (1970).
(5) (a) R. L. Vaulx, F. N. Jones, and C. R. Hauser, *J. Org. Chem.*, **30**, 58 (1965); (b) D. W. Slocum, B. W. Rockett, and C. R. Hauser, *J. Amer. Chem. Soc.*, **87**, 1241 (1965); (c) D. W. Slocum and B. P. Koonsvitzky, *Chem. Commun.*, 846 (1969); (d) D. W. Slocum and P. L. Gierer, *ibid.*, 305 (1971).
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(9) D. A. Shirley and J. P. Hendrix, *J. Organometal. Chem.*, **11**, 217 (1968).
(10) D. W. Slocum and B. P. Koonsvitsky, *J. Org. Chem.*, **38**, 1675 (1973).
(11) R. A. Ellison, R. Griffin, and F. N. Kotsonis, *J. Organometal. Chem.*, **36**, 209 (1972).

Snyder.[12] Into a flame-dried flask fitted with a reflux condenser and containing 36.4 ml (0.29 mol) of 2-phenoxyethanol and 25.6 ml (0.32 mol) of pyridine cooled with an ice bath was slowly added 21.6 ml (0.30 mol) of thionyl chloride with an oven-dried syringe. Once addition was complete, the ice bath was removed and the reaction was allowed to proceed with continuous stirring for 12 hr. The reaction mixture was added to 300 ml of ether and washed with saturated aqueous sodium carbonate and twice with water. The ether layer was dried with magnesium sulfate and evaporated *in vacuo* until free of solvent. The crude product was distilled under high vacuum, affording 37.42 g (82.5%) of (2-chloroethoxy)benzene which was 100% pure by glc and had an nmr spectrum identical with that of a reference spectrum.[13]

This product was treated with powdered KOH according to the method of Fauer and Spielman[14] to give an oil which was purified by distillation: bp 147–153° (760 mm); nmr ($CDCl_3$) δ 4.42 (1 H, d, d, J = 6, 1.5 Hz), 4.77 (1 H, d, d, J = 14, 1.5 Hz), 6.62 (1 H, d, d, J = 14, 6 Hz), 7.15 (5 H, m); mass spectrum m/e (rel intensity) 120 (49), 91 (100), 39 (75), 27 (78).

General Metalation Procedure.—All experiments involving *n*-butyllithium were performed in flame-dried, three-neck, 100-ml, round-bottomed flasks fitted with serum caps. The reactions were run at room temperature with a positive pressure of argon being maintained in the flasks throughout the reaction period. *n*-Butyllithium in hexane solution was delivered to the flasks by means of an oven-dried standard B-D Yale type syringe. After 2 hr reactions were quenched with D_2O (99.7%, Merck and Co.) and added to 50 ml of 1 *N* HCl, then extracted four times with ether. The ether extracts were combined, dried over magnesium sulfate, and evaporated *in vacuo* at room temperature. Control experiments showed no incorporation of deuterium into phenol under these quenching conditions.

The following metalation experiments were conducted using the quantities and times indicated. The yields of isolated products were obtained by glc and combined glc–mass spectrometry.

Anisole.—Anisole (0.356 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (3 ml, 2.1 *M*, 6.2 mmol) were used. The recovered anisole (0 349 g, 97%) contained 29.5% anisole-d_1.

1-Methoxy-2-phenoxyethane (MPE) in Ether.—MPE (0.542 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 2.1 *M*, 4.2 mmol) were used. The product mixture (0.491 g) contained phenyl vinyl ether, 0.034 g (0.287 mmol, 8.1%), phenol, 0.039 g (0.417 mmol, 11.7%), and MPE, 0.418 g (2.74 mmol, 77%) containing 67.5% MPE-d_1. Total recovered material (mmol) was 96.8%.

MPE in Tetrahydrofuran (THF).—MPE (0.152 g, 1.0 mmol), THF (50 ml), and *n*-butyllithium (0.66 ml, 1.67 *M*, 1.1 mmol) were used. The recovered MPE (86%) contained less than 1% MPE-d_1.

1-Methoxy-2-phenoxyethane-*1,1-d*$_2$ (MPE-*1,1-d*$_2$) in Ether.—MPE-*1,1-d*$_2$ (0.432 g, 2.8 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The product mixture (0.380 g) contained phenyl vinyl ether-d_2, 0.032 g (0.264 mmol, 9.4%), phenol, 0.006 g (0.064 mmol, 2.3%) containing 15.7% phenol-d_1, and MPE, 0.341 g (2.204 mmol, 79%) containing MPE-d_2 (37.3%) and MPE-d_3 (62.7%). Total recovered material (mmol) was 90.7%.

MPE-*1,1-d*$_2$ in Hexane.—MPE-*1,1-d*$_2$ (0.432 g, 2.80 mmol), hexane (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The recovered product mixture (0.378 g) contained phenol, 0.045 g (0.48 mmol, 17.1%) containing 2.5% phenol-d_1, MPE, 0.290 g (1.90 mmol, 68%) containing MPE-d_2 (59.5%) and MPE-d_3 (40.5%), and unknown, 0.043 g. No phenyl vinyl ether was detected. Total recovered material (material balance) was 87.5%.

Competition between MPE and Anisole in Ether.—MPE (0.542 g, 3.57 mmol), anisole (0.386 g, 3.57 mmol), ether (50 ml), and *n*-butyllithium (2 ml, 2.1 *M*, 4.2 mmol) were used. The product mixture (0.750 g) contained anisole, 0.314 g (2.90 mmol, 79%) containing 4.0% anisole-d_1, phenol, 0.039 g (0.417 mmol, 11.7%), phenyl vinyl ether, 0.034 g (0.287 mmol, 8.05%), and MPE, 0.393 g (2.59 mmol, 72.6%) containing 66.0% MPE-d_1. Total recovered material (mmol) was 87%.

Competition between MPE and Anisole in Hexane.—MPE (0.425 g, 2.80 mmol), anisole (0.302 g, 2.80 mmol), hexane (50 ml), and *n*-butyllithium (2 ml, 1.67 *M*, 3.34 mmol) were used. The recovered product mixture consisted of anisole, 0.255 g (2.36 mmol, 84.3%) containing 2.0% anisole-d_1, phenol, 0.061 g (0.65 mmol, 23%), MPE, 0.310 g (2.03 mmol, 72.5%) containing 39.0% MPE-d_1, and unknown, 0.034 g. Total recovered material (mmol) was 90%.

Results and Discussion

Anisole and 1-methoxy-2-phenoxyethane (MPE, **2**) were chosen for comparison in order to maintain aro-

1, R = CH_3
2, R = $CH_2CH_2OCH_3$

matic rings which were comparable electronically while at the same time displaying differences in complexing ability of the substituent heteroatoms. The vicinal oxygen atoms in **2** might be expected to behave somewhat like 1,2-dimethoxyethane.[15] Since **1** metalates almost exclusively in the ortho position,[16] the chelation effect, if any, would be reflected in an enhanced reactivity for **2** which could be quantitated by competition with **1** for base.

Metalation of 1.—Treatment of **1** with excess *n*-butyllithium in ether for 2 hr followed by quenching with deuterium oxide gave a 97% recovery of anisole of which 29.5% was monodeuterated. No bisdeuterated material was detected. Under the same conditions in tetrahydrofuran (THF) only a trace of metalated product was detected reflecting the competing decomposition of THF by *n*-butyllithium.

Metalation of 2.—The analogous metalation of **2** proved to be more complex than anticipated but could be analyzed to provide data for the competition study. Thus, treatment of **2** with 1.2 molar equiv of *n*-butyllithium in ether followed by quenching with deuterium oxide gave phenol and phenyl vinyl ether (**10**) as products in addition to MPE-d_1. The results are shown in Table I and the corresponding pathways are presented in Scheme I. The position of metalation in **4**

SCHEME I

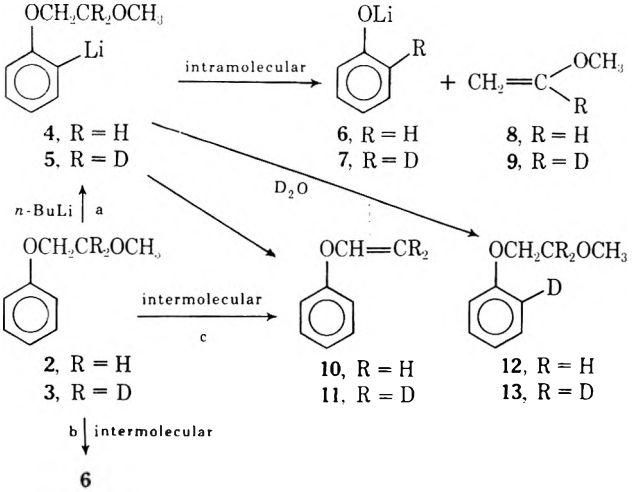

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TABLE I
METALATION OF MPE (2) AND MPE-d_2 (3)

MPE (2)		MPE-d_2 (3)		
	% yield (% D incorpn)[a,b]		% yield (% D incorpn)[a,b]	
Product	of ether	Product	Ether	Hexane
MPE	77.0 (67.5)	MPE-*1,1*-d_2	79.0 (62.7)	68.0 (40.5)
Phenol	11.7 (0)	Phenol	2.3 (15.7)	17.1 (2.5)
Phenyl vinyl ether	8.1	Phenyl vinyl ether-d_2	9.4	0

[a] The reaction was quenched with D_2O. [b] Isotope composition was determined by combined glc–mass spectrometry.

and **5** was assumed to be ortho in analogy with anisole. The structure of phenyl vinyl ether was verified by chromatographic and spectrographic comparison with an authentic sample unambiguously prepared. Since the fragmentation products could arise from either intra- or intermolecular elimination (see Scheme I) it was necessary to distinguish between these two routes. This was accomplished by metalation of the bisdeuterated analog of **2** (**3**). From this reaction the extent of aryl metalation was determined from the sum of all products derived from the intermediate anion **5** (*i.e.*, **7** + **13** + intramolecularly derived **11**). A blank run showed that under the work-up conditions **7** could only arise *via* intramolecular deuterium exchange.

With ether as solvent, intramolecular phenol formation (**3** → **5** → **7**) proceeded to the extent of 15.7% and this value was accepted as valid for the same reaction with **2**. The lower yield of phenol from **3** as opposed to **2** is ascribed to the deuterium isotope effect during elimination. With the compounds at hand it was not possible to determine the amount of **11** obtained from **5**. However, in spite of the different transition states involved, this was taken to be comparable with that for **7** derived from **5** (*i.e.*, 15.7%). Owing to the relatively small amount of phenyl vinyl ether obtained, this assumption does not seriously affect the results. On this basis total metalation of **2** was found to exceed intermolecular elimination by a factor of 3.1. This result and those from the competition experiments below are valid only if some *n*-butyllithium remains when the reaction is quenched; otherwise **7** would continue to accumulate at the expense of **6**. That this is the case is evidenced by the fact that *n*-butyllithium is stable to diethyl ether under the reaction conditions[17] and that less than 1 equiv of material was treated with the base.

When the same reaction was conducted in hexane as solvent the amount of phenol derived from intramolecular elimination was some six times less than in ether, although the overall production of phenol was greater. Interestingly, no **11** was formed but rather a small amount of a new product which was not identified. One possible product is 2,3-dihydrobenzofuran. However, comparison of the gas chromatographic retention time of the product with that of synthetically prepared material showed this not be the case. Generally however, the results in hexane were similar to those in ether.

Competitive Metalation.—The results of allowing equimolar amounts of **1** and **2** to compete for an excess of *n*-butyllithium in both ether and hexane are shown in Table II. The ratio of MPE metalation to that of anisole was found to be 13.9:1 and 14.4:1 in the respective solvents, although the presence of a small amount of unidentified product in the hexane run makes that value somewhat uncertain. It is clear, however, that the presence of the second oxygen atom in the side chain significantly influences the rate of metalation of the aryl ring.

TABLE II
COMPETITION OF ANISOLE AND MPE FOR *n*-BUTYLLITHIUM

	% yield (% D incorpn)[a]	
Product	Ether	Hexane
Anisole	79 (4.0)	84.3 (2.0)
MPE	72.6 (66.0)	72.5 (39.0)
Phenol	11.7 (15.7)	23.2 (2.5)
Phenyl vinyl ether	8.1	0[b]
% total MPE metalation	55.6[c]	28.7[d]

[a] Yields were determined by combined glc–mass spectrometry. [b] A small amount of unidentified material was also detected. [c] Calculated as recovered MPE-d_1 + 0.157 × recovered (**6** + **10**) and then normalized to 100%. [d] Based on 95.7% material balance.

The change in solvent from ether to hexane does not significantly alter the ratio of metalation rates but does result in a twofold decrease in overall rate for both **1** and **2**.

Evidence for Complexation.—In order to obtain evidence for a complex between *n*-butyllithium and **2**, increasing quantities of **2** were added to *n*-butyllithium in hexane and the chemical shift of the methylene protons α to lithium was observed. This technique has been used to demonstrate the existence of a 1:1 complex between *n*-butyllithium and **1**.[18] The results are shown in Table III. Starting from −50.5 Hz a maximum upfield shift is observed at −57.0 Hz at a molar ratio of MPE to base of 1:2. This stoichiometry has previously been observed for the complex between *n*-butyllithium and diethyl ether.[19] Unlike the latter case, further addition of MPE caused a decrease in the observed chemical shift. This is possibly due to the intervention

TABLE III
COMPLEXATION OF MPE (2) WITH *n*-BUTYLLITHIUM IN HEXANE

			Observed chemical shift, Hz[a,b]	
Expt	[MPE] × [*n*-BuLi][c]	[MPE]/[*n*-BuLi]	*n*-BuLi	*n*-BuLi + MPE
1	0.543	0.25	−50.5	−54.6
2	0.550	0.33	−50.5	−56.5
3	0.545	0.50	−50.5	−57.0
4	0.546	1.0	−50.5	−54.0
5	0.552	2.0	−51.0	−52.5

[a] Methylene protons α to Li. [b] Relative to internal tetramethylsilane. [c] The rate of metalation (k[MPE][*n*-BuLi]) was held constant and values were read at the same time into the run.

(17) G. E. Coates, M. L. H. Green, and K. Wade, "Organometallic Compounds, Vol. 1. The Main Group Elements," 3rd ed, Methuen, London, 1967, p 9.

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of new equilibria, but no further evidence is available on this point.

The rapid reaction of **2** with *n*-butyllithium was evident from observation of the nmr spectrum in the region downfield from tetramethylsilane. Shortly after addition of **2** a new singlet appeared upfield from that assigned to MPE which was attributed to the methoxyl protons of the metalated derivative. During the course of the reaction both singlets gradually moved upfield, indicating that these species were also involved in changing equilibria. Because the chemical shift of the methylene protons α to lithium also changed with time, it was necessary to adjust concentrations of *n*-butyllithium and **2** so as to maintain a constant reaction rate for all spectra and to record each at the same time into the run.

While the details are undoubtedly complex, it seems likely that the 14-fold increase in reactivity of **2** relative to **1** can be explained in part by the change in base–ether ratio from 1:1 in the case of **1** to 2:1 in the case of **2**.

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Registry No.—**1**, 100-66-3; **2**, 41532-81-4; **3**, 41894-71-7; **10**, 766-94-9; phenoxyacetic acid, 122-59-8; phenoxyacetic acid ethyl ester, 2555-49-9; 2-phenoxyethanol-*1,1-d*$_2$, 21273-38-1; 2-phenoxyethanol, 122-99-6; 2,3-benzofuran, 271-89-6; 2,3-dihydrobenzofuran, 496-16-2; (2-chloroethoxy)benzene, 622-86-6.

1-Butanol–Hydrogen Chloride. An Allegedly Anhydrous Esterification Reagent

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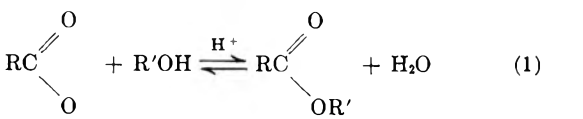
The stability of a common Fischer esterification reagent used extensively for preparation of amino acid and carboxylic acid esters, 2.1 *M* HCl–1-butanol, has been studied in detail. After 2 hr at 100 and 150°, the concentrations of 1-chlorobutane, di-1-butyl ether, and water in this reagent are 0.71, 0.04, and 0.75, and 2.36, 0.22, and 2.58 *M*, respectively. Approximate rate constants for formation of these products at 100 and 150° have been determined. It is concluded that esterifications with this reagent should be carried out below 100° to achieve best yields. An equilibrium constant of 0.15 ± 0.03 has been measured in the esterification of a typical aliphatic amino acid, leucine. The significance of the production of water in this esterification reagent is discussed especially in light of its use in amino acid esterification procedures where the carboxylic acid concentrations may be at the millimolar or lower concentration level.

The importance of amino acid chemistry and general lack of detailed quantitative studies of amino acid esterification reactions suggested to us that the latter problem deserves more extensive investigation. Herein we describe an investigation of some of the properties of the Fischer esterification reagent, 1-butanol–hydrogen chloride in our case, or in general an alcohol mixed with a strong acid, and its use for esterification of amino acids.

The Fischer esterification procedure for carboxylic acids was introduced in 1895[1] and synthetic procedures for esterification of amino acids by this method were published in 1901.[2] The mechanism of the reaction has been widely investigated and discussions of it may be found in most organic chemistry texts.[3] It is well known that, for equimolar quantities of reactant, the equilibrium in this reaction lies quite short of completion. To obviate this, an excess of alcohol or acid, product removal by distillation, or addition of a water scavenger is generally employed to shift the equilibrium in favor of the product.[3]

Recently, methods have been reported[4–8] utilizing Fischer esterification, usually with 1-butanol–HCl, and subsequent trifluoroacylation to render amino acids amenable to quantitative analysis by gas chromatography. Examination of the literature indicates that little systematic investigation has been directed toward the esterification reaction at concentration levels usually encountered in amino acid analysis. The quantitative yield of volatile amino acid derivatives is dependent upon the reproducibility and completeness of the derivatization reactions. Equilibrium constants, concomitant reactions of the esterification reagent, and the relationship of these to the total reaction become, therefore, important considerations in these analytical procedures and should be considered in any syntheses involving an expensive and/or small amount of carboxylic acid.

With few exceptions,[9,10] the esterification reagent has been generally considered anhydrous in that it contributes little or no water to the reaction. On this basis, it has been accepted that maximum water concentration at equilibrium would be equal to amino acid ester concentration according to eq 1. With a carboxylic acid



$$RC(=O)O^- + R'OH \overset{H^+}{\rightleftharpoons} RC(=O)OR' + H_2O \qquad (1)$$

(1) E. Fischer and A. Speier, *Ber.*, **28**, 3242 (1895).
(2) E. Fischer, *Ber.*, **34**, 433 (1901).
(3) See, for example, L. F. Feiser and M. Feiser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, pp 371–376; C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1963, pp 752–781; V. M. Migrdichian, "Organic Synthesis," Vol. 1, Reinhold, New York, N. Y., 1957, pp 311–332; J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, pp 389–390, 519–521.
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concentration at or below the millimolar level, a large excess of alcohol has been considered sufficient to drive the reaction to completion. However, the results reported here indicate that several orders of magnitude more water can be produced from the conversion of 1-butanol to 1-chlorobutane and di-1-butyl ether than is produced by the esterification reaction alone. The implications of the presence of large amounts of water in a quantitative esterification reaction are obvious. To assess the effect of these side reactions, we have examined and report here the degree and rate of production of 1-chlorobutane, di-1-butyl ether, and water from 1-butanol–HCl at times and temperatures most often used in amino acid esterification. We also report the equilibrium constant for the esterification of leucine, a typical aliphatic amino acid, at 60° in order to assay the magnitude of the effect of water formation on its esterification equilibrium.

Experimental Section

Materials.—Leucine was Calbiochem A Grade and used as received. 1-Butanol was Analabs pesticide grade, dried over and distilled from magnesium turnings in an all-glass system under dry nitrogen and subsequently acidified with Matheson anhydrous hydrogen chloride. The hydrogen chloride gas was added slowly and with cooling to reduce heat liberation and possible side reactions.

Instrumentation.—A Varian Model 1440 gas chromatograph with flame ionization detector and Hewlett-Packard 3370A digital integrator were used for all quantitative determinations. Combined gas chromatogaphy–mass spectrometry was performed on a Victoreen 4000 series gas chromatograph using a 10 ft × 0.050 in. Poropak Q column coupled through a single-stage Ryhage-type separator into a Hitachi Perkin-Elmer RMS-4 mass spectrometer.

Synthesis.—Leucine 1-butyl ester hydrochloride was prepared by refluxing leucine in 1-butanol–2.7 *N* HCl for 15 min. The resultant mixture was taken to dryness on a glass–Teflon rotary evaporator. The solid (1-butyl)leucine 1-butyl ester hydrochloride was dissolved in 0.1 *N* KOH and sufficient base was added to ensure alkalinity. The free leucine 1-butyl ester was extracted into dichloromethane, washed twice with water, and reacidified with HCl gas. The dichloromethane was evaporated and the resultant leucine 1-butyl hydrochloride was recrystallized twice from hot diethyl ether, mp 94.5–95.5° (not previously reported). The chloride content was determined by potentiometric titration using silver nitrate. *Anal.* Calcd for $C_{10}H_{22}ClNO_2$: Cl, 15.87. Found: Cl, 15.7 ± 0.3.

Leucine–Leucine 1-Butyl Ester Equilibrium Standardization.—Accurately weighed amounts of leucine, leucine 1-butyl ester hydrochloride, and dodecane (internal standard) were added to 1 ml of 1-butanol–2.7 *N* HCl. This mixture was partitioned between 4 ml of petroleum ether (bp 20–40°) and 20 ml of 0.2 *N* KOH. The organic layer was chromatographed and molar responses relative to dodecane were determined. The precision of the relative molar response determinations was ±1.9% coefficient of variation. Chromatography was effected on a 6 ft × 2 mm glass column packed with 80/100 mesh GLC-110 coated with 0.2% OV-7, isothermal at 90° with a 20-ml/min helium flow.

Equilibration.—Accurately weighed amounts of leucine and dodecane were added to 1 ml of 2.7 *N* HCl–1-butanol and the mixture was sealed in ampoules. The ampoules were heated in an oil bath at 60° for 30, 60, and 90 min and the contents of each were subsequently extracted and analyzed exactly as for the standardization. Some experiments were done at 25° where the above mixture was sampled periodically, extracted, and analyzed.

Analysis of Products Found in 2.7 *N* HCl–1-Butanol. 1-Chlorobutane and Di-1-butyl Ether.—Accurately weighed amounts of 1-chlorobutane, di-1-butyl ether, and decane (internal standard) were dissolved in 1 ml of freshly prepared 1-butanol–2.7 *N* HCl and extracted as above, and relative molar responses were determined. Aliquots (1.5 ml) of 1-butanol–2.7 *N* HCl with a known amount of internal standard were sealed in ampoules and heated at 100 or 150° for 15, 30, 60, and 120 min. For analysis, 1-ml aliquots were removed and extracted. Chromatography was performed using a 20 × 0.125 in. stainless steel column packed with 80/100 mesh Poropak T programmed from 165 to 195° at 8°/min. Flow rate was 25 ml/min. To detect the possible product 1-butene, 1 ml of 2.7 *N* HCl–1-butanol was heated in a septum-capped vial for 3 hr at 100°. The head space vapor was sampled several times with a syringe and analyzed by combined gas chromatography–mass spectrometry. The limit of detectability was estimated to be about 0.1% for 1-butene and none was detected in these experiments.

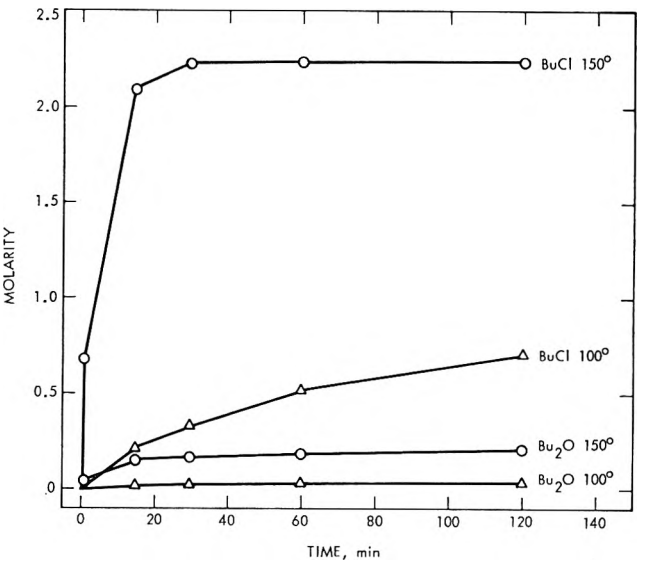

Figure 1.—Conversion of 2.7 *M* HCl–1-butanol to 1-chlorobutane and di-1-butyl ether at 100 and 150°.

Results

Rates of Production of 1-Chlorobutane and Di-1-butyl Ether.—In a mixture of 1-butanol and hydrogen chloride, the 1-chlorobutane and di-1-butyl ether are formed according to eq 2 and 3. Each of these reactions

$$CH_3CH_2CH_2CH_2OH + HCl \rightleftharpoons CH_3CH_2CH_2CH_2Cl + H_2O \quad (2)$$

$$2CH_3CH_2CH_2CH_2OH + H^+ \rightleftharpoons (CH_3CH_2CH_2CH)_2O + H_2O \quad (3)$$

is acid catalyzed and each produces water. However, reaction 2 consumes acid, while reaction 3 does not. Each represents a reversible equilibrium, the reaction producing 1-chlorobutane being considerably more rapid than that producing di-1-butyl ether. Examination of Figure 1 and Table I reveals some of the details of these reactions. The 1-butanol is converted to 1-chlorobutane approximately ten times more rapidly than di-1-butyl ether. Starting with 2.7 *M* HCl in 1-butanol at 150°, an equilibrium amount of approximately 2.3 *M* 1-chlorobutane is produced along with an equivalent amount of water. In this process the HCl concentration is reduced from 2.7 to 0.4 *M*.

It appears that reaction 2 has reached equilibrium within 30 min at 150° while reaction 3 has not gone to completion within 2 hr. Di-1-butyl ether is formed quite rapidly in the first few minutes, as shown in Table I, but, as the acid is consumed by reaction 2, the rate drops rapidly. At 100° similar behavior is observed, but the rates are approximately ten times slower.

The high concentrations of reactants in this system cause the characteristics of the reaction medium to change markedly during the course of the reaction; consequently, only estimates can be made of the rate

TABLE I

CONVERSION OF 2.7 *M* HCl–1-BUTANOL TO BUTYL CHLORIDE AND DI-1-BUTYL ETHER

Temp	Time, min	[BuCl], *M*	[Bu_2O], *M*	Sum, *M*[a]
100°	0	0.010	0.008	0.018
	15	0.214	0.015	0.229
	30	0.330	0.027	0.357
	60	0.519	0.031	0.550
	120	0.709	0.042	0.751
150°	0	0.010	0.02	0.03
	1	0.68	0.05	0.73
	15	2.10	0.16	2.26
	30	2.23	0.17	2.40
	60	2.30	0.19	2.49
	120	2.36	0.22	2.58

[a] The sum of BuCl and Bu_2O concentrations represents the concentration of water formed.

TABLE II

ESTIMATION OF RATE CONSTANT FOR ACID-CATALYZED CONVERSION OF 1-BUTANOL TO DI-1-BUTYL ETHER AT 100°

Time, min	[Bu_2O], *M*	[HCl], *M*[a]	[BuOH], *M*[b]	10^3 k,[c] M^{-2} sec^{-1}
0	0.020	2.69	10.9	2.6
1	0.05	2.48	10.7	4.9
15	0.16	2.36	10.5	0.9
30	0.17	2.17	10.4	1.4
60	0.19	1.98	10.3	2.7
120	0.22	1.72	9.8	2.5 ± 1.1

[a] HCl concentration calculated from the initial concentration of acid minus the amount of butyl chloride formed. [b] Butanol concentration calculated from initial concentration and corrected for total products formed. [c] Rate constant calculated from the following expression: $d[BuOH]/dt = k[BuOH]^2[HCl]$.

constants. These constants for the two reactions at both temperatures are estimated from the data of Figure 1 and Tables I and II, and the calculations are based on eq 4 and 5.

$$d[BuCl]/dt = k[BuOH][HCl] \quad (4)$$

$$d[Bu_2O]/dt = k[BuOH]^2[HCl] \quad (5)$$

Table III summarizes these data at the two temperatures and includes the rate constants extrapolated to 60°. The rate of production of water at this lower temperature is important since the esterification equilibrium constant for conversion of leucine to leucine 1-butyl ester was measured at that temperature.

Equilibrium Constant for Esterification of Leucine.— The equilibrium constant for esterification of leucine hydrochloride in 2.7 *M* HCl–1-butanol was determined at 60°. Since under these conditions the conversion of the amino acid to ester is almost complete (97–98%), considerable attention was paid to the precision and accuracy of the analytical procedure. The difference between 98 and 99% represents approximately a factor of two in the equilibrium constant, while the difference between 99 and 99.9% represents a factor of ten. Also, owing to the inaccuracies inherent in chromatographic methods, 99% is indistinguishable from 99.9% and higher per cent conversions, and the equilibrium constant becomes essentially indeterminant. As shown by Table IV and the Experimental Section, the gas chromatographic analytical precision was on the order of 2%, coefficient of variation. In all cases, the per cent conversion of leucine to its ester was less than 98%. The error ranges in Table II represent standard

TABLE III

SUMMARY OF ESTIMATED RATE CONSTANTS AND ACTIVATION ENTHALPY AT 150 AND 100° EXTRAPOLATED TO 60° FOR CONVERSION OF 1-BUTANOL TO BUTYL CHLORIDE AND DI-1-BUTYL ETHER

Temp, °C	Reaction	*k*, M^{-1} sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}
150	$ROH + HCl \rightleftharpoons RCl + H_2O$	8×10^{-6} [a]	29.5
100		8×10^{-6} [a]	
60		(7×10^{-7})[b]	
	H_2	*k*, M^{-2} sec^{-1}	
150	$2\,ROH \rightleftharpoons R_2O + H_2O$	4×10^{-7} [c]	32.5
100		2.5×10^{-8} [d]	
60		(1×10^{-9})[b]	

[a] Rate constant estimated from initial slope of [BuCl] *vs.* time (Figure 1) and calculated from the expression $d[BuCl]/dt = k[BuOH][HCl]$. [b] Rate constants extrapolated from data at 100 and 150°. [c] Rate constant estimated from the average slope of [Bu_2O] *vs.* time (Figure 1) after 15-min reaction, calculated from the expression $d[Bu_2O]/dt = k[BuOH]^2[HCl]$. [d] Rate constant estimated from data in Table III.

TABLE IV

ESTERIFICATION OF LEUCINE HCl AT 60° WITH 2.7 *M* HCl–1-BUTANOL

Time, min[a]	Initial[b] leucine HCl, m*M*	(1-Butyl)leucine, m*M*[c]		Conversion, %	K_{eq}
30	37.02	35.5			
		36.6	36.2 ± 3.5	97.7 ± 1.3$_5$	0.146
		36.6			
		36.2			
60	53.7	52.1			
		51.6			
		54.3	52.4 ± 1.3	97.4 ± 2.3$_7$	0.178
		51.6			
120	45.7	43.7			
		43.1			
		44.1	44.3 ± 1.1	96.9 ± 2.4$_1$	0.128
		44.8			
		46.0			0.151 ± .026

[a] Esterification time at 60°. [b] Amount of leucine HCl weighed out. [c] Amount of (1-butyl)leucine extracted and quantitated by gas chromatography.

deviations, and the error in the average equilibrium constant is a reasonable estimate of the cumulative errors associated with its measurement. Thus, the precision and accuracy of the data are sufficiently high to establish that the per cent conversion of the amino acid to its butyl ester is less than and distinguishable from 100%.

To minimize the production of water by reactions 2 and 3, the equilibrium constant for the esterification of leucine was measured at a temperature (60°) significantly lower than the 100–150° at which amino acid esterifications are carried out in several currently used analytical procedures.[4–8] Because the effect of temperature on this equilibrium is unknown, in the following discussions of the effect of water it will be assumed that the equilibrium constant is essentially invariant over the temperature range discussed here.

Figure 2 shows some calculations of the per cent amino acid ester which would be present at equilibrium in 1-butanol–HCl for a number of different initial concentrations of water and for three equilibrium constants. The dotted lines below and associated with each curve represent the per cent ester formed as a

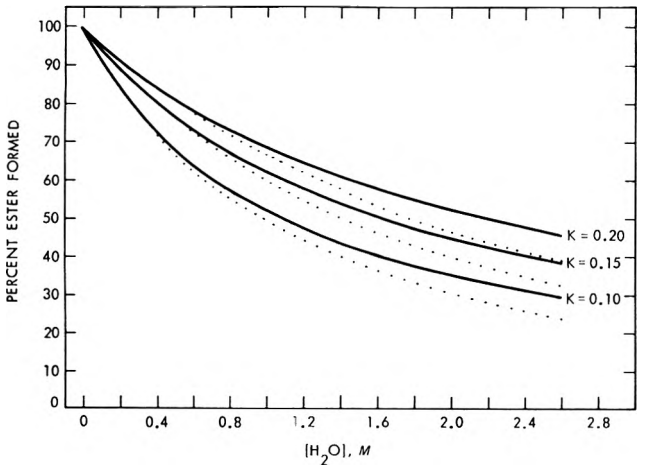

Figure 2.—Calculated per cent amino acid ester present at equilibrium for a number of different initial water concentrations. Dotted line below and associated with each curve represent the per cent ester formed if the initial water present were produced by the 1-butanol (see Results).

function of initial water concentration if the water were produced from the 1-butanol. That is, the initial 1-butanol concentration (10.9 *M*) is reduced by the amount of water "formed." Calculations for initial amino acid concentrations ranging from 10^{-6} to 10^{-2} *M* gave curves which were essentially the same. The initial 1-butanol concentration of 10.9 *M* was calculated from the density of 1-butanol at 25°. No correction was made for density changes with temperature.

Rate of Esterification.—As indicated by Table IV, leucine esterification is essentially complete in less than 30 min at 60°. Additional qualitative evidence suggests that esterification is quite rapid even at 25° in 2.7 *M* HCl–BuOH. In fact the rate of esterification of solid leucine hydrochloride may be limited by the rate of solution of the solid amino acid hydrochloride in 1-butanol–HCl. In one experiment, leucine hydrochloride was placed in a Teflon capped glass vial and 2.7 *M* HCl–1-butanol was added. The tube was agitated, at room temperature, with a Vortex mixer until the visible traces of solid amino acid hydrochloride were just gone. This took approximately 15 min. The excess 1-butanol–HCl was evaporated at room temperature under a stream of dry nitrogen. Analysis of the residue indicated that approximately 30–40% of the amino acid had been converted to the 1-butyl ester under these conditions.

Discussion

Under conditions normally employed for direct esterification of amino acids, the esterifying reagent, HCl–1-butanol, reacts to produce 1-chlorobutane, di-1-butyl ether, and water.[11] The water produced in this reaction interferes in the quantitative conversion of the amino acids to their esters. The maximum magnitude of the problem is related to how much water is produced at equilibrium (equilibrium between 1-butanol–HCl and 1-chlorobutane, di-1-butyl ether and water), and the equilibrium constant for esterification of the amino acid. Thus, the importance of the rate of esterification

(11) Water could also be produced by dehydration of 1-butanol to form 1-butene, although this reaction is unlikely for a primary alcohol under the conditions discussed here, and none was detected in this work as mentioned in the Experimental Section.

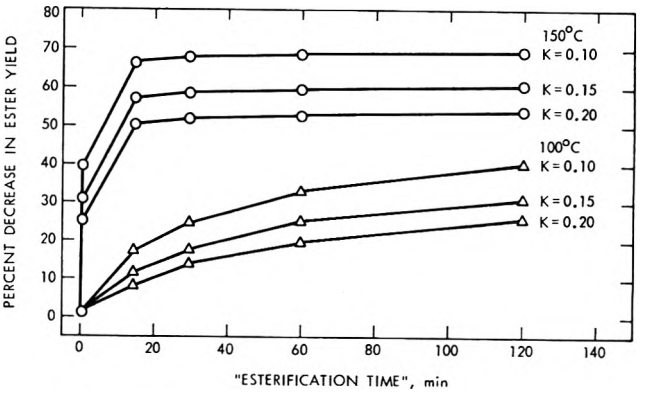

Figure 3.—Per cent decreases in ester yield as a function of time. Time is a measure of the amount of water formed by the HCl–1-butanol reactions.

relative to the rate of water production needs to be realized.

Some assessment of the interaction of these two rate and equilibrium effects on the final ester yield is given by Figure 3. This figure is a plot of calculations of the per cent decrease in ester yield as a function of "esterification time" using the kinetic data obtained in this work for reactions 2 and 3. The decrease in ester yield is the difference between amino acid ester which would be formed if there were no water present in the HCl–1-butanol reagent (aside from the water formed as a result of the esterification reaction) and the amount of ester which would be formed at equilibrium if there were as much water in the esterifying reagent as would be formed if the reagent had been held at the given temperature, 100 or 150°, for the various times. This plot might be thought of as the equilibrium ester concentrations as a function of the kinetic water concentrations. The ester concentrations were calculated for three equilibrium constants at the two temperatures indicated.

As we noted earlier, the esterification reaction is probably quite rapid once the amino acid hydrochloride is in solution, but the rate of solution is, under some conditions, slow. The rate of esterification is even more complicated, since, not only is the final ester yield influenced by the water produced by the HCl–butanol reaction, but the esterification reaction is acid catalyzed. The conversion of 1-butanol to 1-chlorobutane consumes acid and the acid-catalyzed rate consequently drops. This slower rate then demands an even longer esterification time for equilibration, hence more time for an additional amount of water to be produced and an even lower yield of ester.

Some of the previous argument is based on data obtained for the amino acid leucine. We expect that esterification equilibrium data for most of the other amino acids should be similar, although we were surprised to find no other quantitative data in the literature of a similar nature for other amino acids. Steric effects undoubtedly play a role in the amino acid esterification as they do in aliphatic carboxylic acid systems.[12] However, most of the amino acids are already α,β-substituted acids and subsequently the effect of changing the size of the β substituent will be much less pronounced than if the amino acids were not already

(12) M. S. Newman, *J. Amer. Chem. Soc.*, **72**, 4783 (1950); K. L. Loening, A. B. Garrett, and M. S. Newman, *ibid.*, **74**, 3929 (1952).

so highly substituted. The effect of the α-amino group should be essentially the same for most amino acids except perhaps for tryptophane or proline. In any event, the variation in esterification rates for the amino acids will act mainly to demand increased esterification time to reach equilibrium. The importance of the amino acids would seem to warrant some studies along these lines.

It has been our experience that an important difference in behavior between the amino acids is the rates of solution of their hydrochloride salts.[13] The magnitude of this feature has not as yet been investigated in a systematic manner. In any case it is clear from the preceding data that increasing the temperature of the esterification reagent to speed the rate of solution of amino acid hydrochlorides may not be a wise approach. With the thought in mind that a salt with an anion larger than chloride would dissolve more rapidly, we observed the rate of solution of a mixture of amino acid hydrobromides and found no dramatic increase in solubility rate. Sulfate salts do dissolve rapidly[14] but the acid, H_2SO_4, is not volatile and would interfere with steps subsequent to esterification. Gehrke[9] has suggested sonic energy to aid in dissolving the amino acid hydrochlorides.

Clearly, then, esterification of amino acid hydrochlorides at 100° is marginal with respect to reproducible quantitative conversion to esters. If the acids are esterified within less than 5–10 min the water produced at 100° can cause at most a 2–10% decrease in the yield of ester formed depending on esterification equilibrium constant. A rapidly dissolving and esterifying amino acid would be little influenced by the water from the 1-butanol–HCl.

(13) Unpublished work of J. P. Hardy and S. L. Kerrin.
(14) G. E. Pollock, private communication.

Conclusions

It has been shown that, above 100°, 2.7 *M* HCl–1-butanol Fischer esterification reagent produces considerable water in a time comparable to the times required for esterification of the amino acids and probably other carboxylic acids. Thus, to realize good yields or satisfactory quantitative results in esterification reactions with Fischer-type reagents, the reactions should be carried out at temperatures below 100° and for times long enough to ensure complete solution of the amino acid hydrochlorides. To ensure reproducible quantitation of amino acids by gc analysis of their volatile derivatives, such as the *N*-trifluoroacetyl-*O*-butyl esters,[4-8] *N*-trimethylsilyl-*O*-1-butyl esters,[15] and other ester derivatives, the initial esterification step with a Fischer-type reagent should be carried out at temperatures below 100°.

Acknowledgment.—The authors wish to thank Dr. E. A. Cohen for assistance in putting together the Hewlett-Packard 2116 computer program to perform the equilibrium calculations. This paper presents the results of one phase of research carried out at the Jet Propulsion Laboratory, California Institute of Technology, under Contract No. NAS 7-100, sponsored by the National Aeronautics and Space Administration.

Registry No.—1-Butanol–HCl, 42031-19-6; leucine 1-butyl ester hydrochloride, 42031-13-0; 1-chlorobutane, 109-69-3; di-1-butyl ether, 142-96-1; 1-butanol, 71-36-3; leucine HCl, 760-84-9.

(15) J. P. Hardy and S. L. Kerrin, *Anal. Chem.*, **44**, 1497 (1972).

Notes

O-Carbamoyloximes[1]

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Shortly after the turn of the century, a general azoxirane synthesis was reported by Conduché.[2] The method for realizing these compounds (**1**) involved careful treatment of an aqueous suspension of aldehyde with hydroxyurea (presumably generated *in situ* from hydroxylamine hydrochloride and potassium cyanate) or, alternatively, of the hydrogen chloride salt of the oxime of the aldehyde with potassium cyanate.

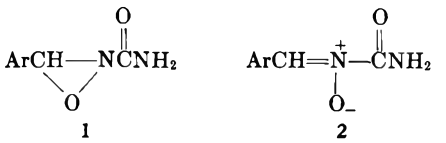
The same products were reportedly obtained by Bellavita and Cagnoli[3] utilizing the first method of Conduché, although the structural class was modified to that of the nitrones (**2**). The new structures were preferred largely because the compounds appeared more stable than would be expected were their structures **1** and, so it was reported, treatment of the compounds **2** with cyanide ion in aqueous solution resulted in formation of the ureides **3**.

The alternative structure **4**, *i.e.*, an *O*-carbamoyloxime, for the original azoxirane was considered possible by Grammaticakis,[4] but clearly this would not satisfy the ureide formation of Bellavita and Cagnoli[3] and he concluded (largely on the basis of ultraviolet spectral comparisons with oximes) that **4** could be rejected.

Finally, however, the elegant interpretation of the available spectral and chemical data by Exner[5] sug-

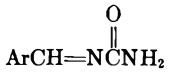
(1) A communication dealing with a portion of the material contained herein has appeared: D. R. Dalton, H. G. Foley, K. N. Trueblood, and M. R. Murphy, *Tetrahedron Lett.*, 779 (1973).
(2) A. Conduché, *Bull Soc. Chim. Fr.*, [3] **35**, 418 (1906); *Ann. Chim. Phys.*, [8] **12**, 533 (1970); [8] **13**, 5 (1908).
(3) V. Bellavita and N. Cagnoli, *Gazz. Chim. Ital.*, **69**, 583, 602 (1939).
(4) P. Grammaticakis, *Bull. Soc. Chim. Fr.*, **8**, 101 (1941).
(5) O. Exner and M. Horack, *Collect. Czech. Chem. Commun.*, **24**, 2992 (1959), and earlier papers.

gested that the *O*-carbamoyloxime structure (**4**) was correct after all. The formation of the ureides reported by Bellavita and Cagnoli[3] was, however, ignored by Exner and he did confess that his proof was based upon the "proper interpretation of ... the ultraviolet spectra" and examination of the products of reduction with lithium aluminum hydride on the one hand and aluminum amalgam on the other. However, his work has been largely ignored, particularly as regards the nitrones **2**[6] and, indeed, definitive proof was lacking.



1

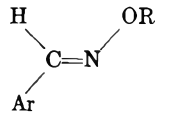
2



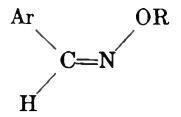
3

ArCHO

5a–d



(*E*)-**4a–d**, R = $CONH_2$
(*E*)-**6a–d**; R = H



(*Z*)-**4a–d**, R = $CONH_2$
(*Z*)-**6a–d**, R = H

4a, 5a, 6a, Ar = *p*-bromophenyl
4b, 5b, 6b, Ar = *p*-chlorophenyl
4c, 5c, 6c, Ar = *m*-nitrophenyl
4d, 5d, 6d, Ar = 3-ethoxy-4-hydroxyphenyl

Our initial interest in this problem stemmed from the reported facile synthesis of ureides through the unprecedented reaction with cyanide ion (*vide supra*).[3] As might be expected, the report is spurious.

Results and Discussion

On treatment of an aqueous solution of hydroxylamine hydrochloride and potassium cyanate with representative aldehydes (**5a–d**) under the original conditions of Conduché[2] a mixture of oximes [(*E*)- and (*Z*)-**6a–d**] and "azoxirane" is obtained. Elemental analyses are in accord with all of the possible formulations presented (**1**, **2**, and **4**) for the "azoxirane."

Mass spectrometric[7] examination of the compound obtained, for example, from *m*-nitrobenzaldehyde (**5c**) is also in concert, potentially, with the formulations **1**, **2**, and **4**. Thus, the molecular ion, *m/e* 209, accords the compound a monomeric nature and the base peak, *m/e* 166, corresponds to that of the *E* oxime [(*E*)-**6c**], as does the remainder of the spectrum. All three formulations, *i.e.*, **1**, **2**, and **4**, could, *a priori*, fragment to generate such a pattern.

The infrared spectra of the compounds prepared by Conduché's method revealed that the 1170–1280-cm^{-1} absorption characteristic of nitrones[8] was absent. Nevertheless, structure **2** could not be eliminated because its unusual nature, *i.e.*, a carbonyl directly attached to the nitrogen of the nitrone, might result in an anomalous shift.

Reduction of the presumed "azoxiranes" with diborane in tetrahydrofuran solution generated the corresponding benzylamines. This result is not in accord with structures **1** and **2**, since nitrogen–oxygen, but not nitrogen–carbon, bond cleavage is expected under these conditions.[9] The same conclusion was reached by Exner[5] concerning lithium aluminum hydride reduction of similar compounds and we therefore concur with his opinion that structure **4** (the *O*-carbamoyloximes) represents the correct formulation for the presumed azoxiranes.

We suggest further that the *O*-carbamoyloximes are formed from isohydroxyurea present in the initial reaction mixture and that the oximes which accompany them are derived from the reaction between aldehyde and hydroxyurea (see Experimental Section). Both hydroxy- and isohydroxyurea are formed on mixture of hydroxylamine hydrochloride and potassium cyanate. The nature of this essentially irreversible reaction (at 0°) to generate two urea derivatives was established unequivocally by Kofod,[10] who also demonstrated that aqueous solutions of the isolable products involved "no decomposition involving formation of ions" on prolonged standing at 0° in water; the structure of isohydroxyurea has been established by X-ray crystal analysis.[11]

As to the ureides of Bellavita and Cagnoli,[3] careful inspection of the experimental data presented by them indicates that the melting points for the reported ureides are, within experimental error, identical with the reported values of the corresponding *E* oximes.[12] The comparison is presented in Table I. We suggest that cyanide ion attacks the carbon of the carbonyl of the *O*-carbamoyloxime (**4**), liberating the oxime. If this is correct, it implies that all of the *O*-carbamoyloximes possess the *E* configuration.

In an effort to determine the configuration unequivocally, oximes (*E*)- and (*Z*)-**6a,b** were treated with chlorosulfonyl isocyanate[13] and the resulting unstable[14] carbamoyl chlorosulfonates were hydrolyzed directly to the corresponding *O*-carbamoyloximes. Regardless of the geometry of the starting oxime (*E* or *Z*) the same *O*-carbamoyloxime was obtained. Attempted examination of the *O*-carbamoyl chlorosulfonates from any pair of oximes was hampered by their rapid decomposition in solution. After only a few minutes at ambient temperatures in acetone-d_6 only the spectrum of the *E* oxime could be observed (regardless of the configuration of the starting oxime). We suggest, therefore, that rapid isomerization of the *O*-carbamoyl chlorosulfonate occurs, concomitant with hydrolysis to the oxime and the

(6) In particular, see (a) J. Hammer and A. Malacuso, *Chem. Rev.*, **46**, 473 (1964), and (b) G. R. Delpierre and M. Lamchen, *Quart. Rev. Chem. Soc.*, **19**, 329 (1965). The latter authors state "If ... a carbonyl group is attached to the nitrogen atom, its −I effect influences the nitrone system to lose oxygen; thus potassium cyanide reacts with the nitrone ... to give the deoxygenated product ... and potassium cyanate."

(7) Mass spectra were obtained on an AEI MS-9 at 70 eV. We gratefully acknowledge the aid of Dr. S. Schrader in obtaining these spectra.

(8) P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).

(9) See, *e.g.*, H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).

(10) H. Kofod, *Acta Chem. Scand.*, **7**, 938 (1953).

(11) I. K. Larsen, *Acta Chem., Scand.*, **22**, 843 (1968).

(12) It should be pointed out that the authors were aware that the elemental analyses for the ureides were unacceptable. However, the analyses were reported as being correct, and only later was the problem noted. See V. Bellavita, *Atti X Congr. Int. Chim.*, **3**, 33 (1939); *Chem. Abstr.*, **34**, 10,043 (1940).

(13) R. Graf, *Ber.*, **96**, 56 (1963).

(14) The crystalline materials slowly decompose with evolution of HCl on standing in closed vials at room temperature for several hours. We suspect adventitious moisture responsible but made no effort to keep the carbamoyl chlorosulfonates for extended periods.

TABLE I

Aldehyde RCHO, R	Registry no.	Ureide[a] (presumed) RCHNCOCH$_2$ mp, °C	*E* oxime[b] mp, °C	Registry no.	*Z* oxime[c] mp, °C	Registry no.
C_6H_5	100-52-7	Oil	35	622-31-1		
$C_6H_5CH=CH$	104-55-2	75–77	72–73[d]	21737-13-3		
o-$NO_2C_6H_4$	552-89-6	103	102–103[e]	4836-00-4		
m-$NO_2C_6H_4$	99-61-6	123.5	121–123[e]	3717-29-1	121–123	3717-30-4
p-$NO_2C_6H_4$	555-16-8	131	129[e]	3717-19-9	171–172	
p-ClC_6H_4	104-88-1	112	110–111	3717-24-6	157–158	3717-23-5
p-BrC_6H_4	1122-91-4		115–116	40979-16-6	166–167	25062-46-8
p-$CH_3OC_6H_4$	123-11-5	66–67	65[e]	20747-40-4		
3,4-$CH_2O_2C_6H_3$	120-57-0	113.5	110	20747-41-5		
p-$(CH_3)_2CHC_6H_4$	122-03-2	110	112[e,f]	30950-38-0		
p-$(CH_3)_2NC_6H_4$	100-10-7	147	144[e,g]	37961-71-0		

[a] All melting points obtained from ref 3 and subsequent papers. [b] Unless otherwise specified, all melting point data are from R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965 [c] Values are given only for compounds referred to in this paper. [d] B. Unterhalt, *Arch. Pharm.* (*Weinheim*), **303**, 661 (1970). [e] These materials are often considered to have the configuration opposite to the one assigned here. However, the assignment is correct as presented here. See R. J. Crawford and C. Woo, *Can. J. Chem.*, **43**, 3178 (1965), and data therein. [f] H. Goldschmidt, *Ber.*, **23**, 2175 (1890). [g] J. C. Duff, *J. Chem. Soc.*, 276 (1945).

O-carbamoyloxime in aqueous solution, and that this too implies that the latter possesses the *E* configuration.

Finally, the *O*-carbamoyloximes (**4a–d**) were identified as indeed possessing the *E* configuration by X-ray crystal analysis of **4a**[15] and correlation of the proton magnetic resonance (pmr) spectra of the analogous **4b–d** with **4a**.[16] In all of these compounds, as with the corresponding oximes, the chemical shift of the benzylic proton is downfield of the aromatic protons (oximes 8.0–8.7 ppm, acetone-d_6, TMS 0.00; *O*-carbamoyloximes 8.0–8.7 ppm, acetone-d_6, TMS 0.00) while in the *Z* oximes, all benzylic proton resonances are upfield (7.3–7.6 ppm, acetone-d_6, TMS 0.00) of the aromatic protons.

We are currently attempting to prepare the (*Z*)-*O*-carbamoyloximes and materials corresponding to the nitrone 2.

Experimental Section

Aldehydes were obtained from the Aldrich Chemical Co. and used as received. Hydroxylamine hydrochloride and potassium cyanate were Fisher Certified Reagent and used as received. Thin layer chromatography (tlc) was performed on precoated silica gel, GF, 250-μ plates obtained from Analtech, Inc. Infrared spectra were run on a Beckman IR-5A spectrophotometer[17] and proton magnetic resonance (pmr) spectra on a Varian XL-100-15 spectrometer. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were obtained on a Fisher-Thomas melting point apparatus and are uncorrected.

Preparation of *O*-Carbamoyloximes (4a–d).—These compounds were prepared according to the procedure of Conduché.[2] ***p*-Bromobenzaldehyde *O*-carbamoyloxime (4a)**, mp 164–165°, was accompanied by a mixture of the corresponding *E* and *Z* oximes. Tlc (2:1 benzene–ether) showed the presence of all three species, *E* oxime, R_f 0.77, *Z* oxime, R_f 0.56, and *O*-carbamoyloxime, R_f 0.21. Fractional crystallization (CH_2Cl_2) of the solid residue from the above reaction permitted removal of the mixture of oximes (*E*/*Z* > 95/5):[18] ir (KBr) 1695 cm^{-1} (C=O); pmr (acetone-d_6, TMS 0.00) δ 6.50 (s, 2 H), 7.67 (m, 4 H), 8.41 ppm (s, 1 H). *Anal.* Calcd. for $C_8H_7N_2O_2Br$: C, 39.50; H, 2.88; N, 11.52. Found: C, 39.77; H, 3.10; N, 11.75. This compound forms monoclinic needles, space group $P2_1/c$, with a = 14.39, b = 5.101, c = 12.5 Å, β = 99.51°, and four molecules in the unit cell.[15]

***p*-Chlorobenzaldehyde *O*-carbamoyloxime (4b)** had mp 159–160°; R_f 0.29 (2:1 benzene–ether) (lit.[1] mp 132–135°); ir (Nujol) 1712 cm^{-1} (C=O); pmr (acetone-d_6, TMS 0.00) δ 6.50 (s, 2 H), 7.64 (m, 4 H), 8.42 ppm (s, 1 H). *Anal.* Calcd for $C_8H_7N_2O_2Cl$: C, 48.36; H, 3.52; N, 14.10. Found: C, 48.31; H, 3.65; N, 14.26.

***m*-Nitrobenzaldehyde *O*-carbamoyloxime (4c)** had mp 192° (lit.[1] mp 180°); R_f (2:1 benzene–ether) 0.28; ir (Nujol) 1786 cm^{-1} (C=O); pmr (DMSO-d_6) δ 7.27 (s, 2 H), 8.31 (m, 4 H), 8.73 ppm (s, 1 H). *Anal.* Calcd for $C_8H_7N_3O_4$: C, 45.93; H, 3.35; N, 20.09. Found: C, 45.95; H, 3.63; N, 20.21.

3-Ethoxy-4-hydroxybenzaldehyde *O*-carbamoyloxime (4d) had mp 143–144° (lit.[1] mp 139–140°); R_f (2:1 benzene–ether) 0.14; ir (Nujol) 1724 cm^{-1} (C=O); pmr (acetone-d_6) δ 1.36 (t, 3 H), 2.7 (s, 2 H), 4.1 (q, 4 H), 6.46 (s, 1 H), 7.14 (m, 3 H), 8.27 ppm (s, 1 H). *Anal.* Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.35; N, 12.50. Found: C, 53.37; H, 5.41; N, 12.23.

Attempted Preparation of the Ureides (3).—The compounds obtained above (**4a–c**) were treated with potassium cyanide under the conditions of Bellavita and Cagnoli.[3] The insoluble precipitate which formed was removed by filtration and evaporation of the filtrate yielded, in each case, *E* oxime: *p*-bromobenzaldehyde (*E*)-oxime, mp 115–116° (lit.[19] mp 110–111°), 85%; *p*-chlorobenzaldehyde (*E*)-oxime (**6b**), mp 107–108° (lit.[19] mp 110–111°), 91%; *m*-nitrobenzaldehyde (*E*)-oxime (**6c**), mp 119.5–120° (lit.[19] mp 121–122°); 69%.

Reduction of the *O*-Carbamoyloximes with Diborane.—The procedure of Fauer and Braunstein[9] was followed. *p*-Bromobenzaldehyde *O*-carbamoyloxime (**4a**) yielded *p*-bromobenzylamine (86%); *p*-chlorobenzaldehyde *O*-carbamoyloxime (**4b**) yielded *p*-chlorobenzylamine (100%); *m*-nitrobenzaldehyde *O*-carbamoyloxime (**4c**) yielded *m*-nitrobenzylamine (83%); and 3-ethoxy-4-hydroxybenzaldehyde *O*-carbamoyloxime (**4d**) yielded 3-ethoxy-4-hydroxybenzylamine (80%). The amines were identified by comparison of their spectra with those previously reported where

(15) Compound **4a** forms monoclinic needles, space group $P2_1/c$ with a = 14.39, b = 5.101, c = 12.5 Å, β = 99.51°, and four molecules in the unit cell. The structure was solved by Patterson and Fourier methods and full-matrix least-squares refinement is in progress. The crystal and molecular structure will be the subject of a future communication.

(16) See, *e.g.*, L. M. Jackman and S. Sternhall, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N.Y., 1969, p 226.

(17) The spectrophotometer was purchased from funds provided by a grant (CA 08841) from the National Cancer Institute, National Institutes of Health. We gratefully acknowledge this financial assistance.

(18) While the *Z* oxime could be detected by tlc (comparison with an authentic sample) it proved unreasonable to isolate it. In addition, it could not be detected by pmr spectroscopy of the reaction mixture. Therefore, since we are confident that we could detect 5% of this material were it present by the latter method, we believe its concentration to be far smaller than that indicated.

(19) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1965.

available.[20] Alternatively, they were analyzed as their HCl salts.

Preparation of the Oximes (*E*)- and (*Z*)-6a–d.—The *E* oximes were prepared by standard procedures[19] and isomerized to their *Z* counterparts by the method of Crawford and Woo.[21] The melting point data are given in Table I.

Reaction of *E* and *Z* Oximes 4a and 4b with Chlorosulfonyl Isocyanate.—Each of the oximes (0.01 mol) was dissolved in anhydrous benzene and treated with chlorosulfonyl isocyanate (0.01 mol) at room temperature. The precipitate that formed was collected by filtration and washed with hexane. The adducts were permitted to stand in aqueous solution (20 ml) overnight and filtered and the solids obtained were examined by pmr (acetone-d_6) spectroscopy. *E* oxime and *O*-carbamoyloxime (2:1, respectively, by comparison to known mixtures) were found in each case.

Reaction of Aldehydes with Hydroxyurea.—*p*-Bromobenzaldehyde (1.0 g, 5.4 mmol) and *N*-hydroxyurea (814 mg, 10.7 mmol) were mixed, at room temperature, in ethanol–water (2:1) (25 ml), and acid (1.9 ml, 1 *N* HCl) was added. The solution was heated to reflux for 1 hr and poured over ice. The solid so generated (67%) was identified as (*E*)-*p*-bromobenzaldehyde oxime by comparison with a known sample (*vide supra*). In a similar fashion, but without heating, *m*-nitrobenzaldehyde yielded crystalline (*E*)-*m*-nitrobenzaldehyde oxime (83%). It should be pointed out for this latter material that tlc (2:1 benzene–ether) always demonstrates a small amount of *Z* contaminant. The *Z* isomer cannot be detected by pmr.

Acknowledgment.—One of us (H. G. F.) gratefully acknowledges financial assistance from the Fund for Scientific Education, Inc., Philadelphia, Pa.

Registry No.—**4a**, 41514-42-5; **4b**, 41514-43-6; **4c**, 41514-44-7.

(20) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1972.

(21) R. J. Crawford and C. Woo, *Can. J. Chem.*, **43**, 3178 (1965).

Conversion of 1,2-Diols *via* Cyclic Ortho Acetates to Acetates of Chlorohydrins by Treatment with Trimethylsilyl Chloride[1]

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Received July 23, 1973

In earlier papers, the conversion of 1,2-diols, **1**, into esters of the corresponding chlorohydrins, **2**, was accomplished by two methods: A, reaction with an α-keto acid to produce a ketal acid, **3**, followed by treatment of the latter with phosphorus pentachloride or thionyl chloride,[3] and B, reaction with trimethyl orthoacetate to form a cyclic ortho ester, **4**, followed by treatment with triphenylmethyl (trityl) chloride.[4] In both cases the reactions were shown to be highly regio- and stereospecific. Since the chlorohydrin esters are readily converted into epoxides by suitable treatment with bases, the synthesis of optically active epoxides is readily accomplished.

A disadvantage of method A is that the yields of **3** based on **1** lie in the 50–70% range. The yields of **4** in method B are excellent but the removal of methyl trityl ether can be troublesome. In this paper we describe method C, in which the disadvantages of methods A and B are overcome. The new method consists of heating the ortho esters, **4**, in methylene chloride with excess trimethylsilyl chloide[5] (much less expensive than trityl chloride). The conversions of **4** to **2** are of the same excellence as the corresponding steps in methods A and B. The removal of excess trimethylsilyl chloride and methyl trimethylsilyl ether is easily accomplished by distillation. The stereochemical results are the same as those reported.[3,4]

(1) This work was supported by Grant CA-07394 from the National Institutes of Health.

(2) Postdoctoral research associate.

(3) (a) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, **94**, 2149 (1972); (b) *J. Org. Chem.*, **38**, 1173 (1973).

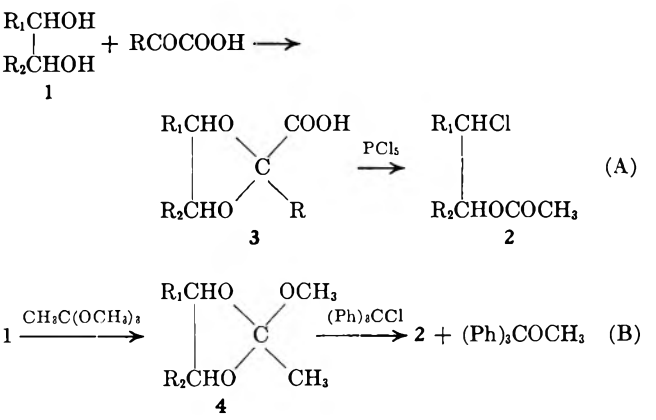
(4) M. S. Newman and C. H. Chen, *J. Amer. Chem. Soc.*, **95**, 278 (1973).

TABLE I

REACTIONS OF CYCLIC ORTHO ESTERS WITH $(CH_3)_3SiCl$

Cyclic ortho ester 4	Time, hr	Ortho ester, mmol	$(CH_3)_3SiCl$, mmol	Yield, % 2
4a, $R_1 = CH_3$; $R_2 = H$	2	20.3	33	86[a]
4b, $R_1 = Ph$; $R_2 = H$	1.5	17.8	28	91[b]
4b, $R_1 = Ph$; $R_2 = H$	2	11.3	12	92[c]
4c, $R_1 = R_2 = CH_3$	1.7	11.8	19	97[d]
4c, $R_1 = R_2 = CH_3$	5	35	37	73[e]
$(CH_3)_2CO$ OCH_3 / H_2CO CH_3	0.5	20.6	26	89[g]

[a] Bp 48–49° (25 mm). This compound was 1-chloro-2-propyl acetate as shown by nmr. However, no europium shift reagent was used as was the case when the same compound was obtained previously and shown to contain about 6% of 2-chloro-1-propyl acetate (see footnote 7 in ref 4). [b] Bp 83–85° (0.2 mm), inactive, mixture of about 95% 2-chloro-2-phenyl acetate and 5% 2-chloro-1-phenyl acetate. [c] $[\alpha]^{25}D$ 86 ± 1° (*c* 3.550, $CHCl_3$). Treatment with sodium hydroxide gave (*R*)-(−)styrene oxide, $\alpha^{25}D$ 34.1° neat, 1 dm, of 97% optical purity [the highest rotation for styrene oxide, 35.2° neat, 1 dm, is reported by C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, **93**, 5303 (1971)], $[\alpha]^{25}D$ −22.5 ± 0.2° (*c* 2.39, $CHCl_3$). [d] Bp 83–84° (52 mm), inactive. [e] The center cut only, bp 75.5–76.0° (34 mm), was taken for measurement of optical activity, $\alpha^{25}D$ 13.32°, neat, 1 dm. Treatment with sodium hydroxide gave D-(+)-2,3-epoxybutane, $\alpha^{25}D$ 45.6°, neat, 1 dm [P. J. Leroux and H. J. Lucas, *J. Amer. Chem. Soc.*, **73**, 41 (1951), report $\alpha^{25}D$ 46.75°]. [f] Bp 82.0–82.5° (85 mm); nmr [CCl_4, $(CH_3)_4Si$] δ 3.75 (s, 2, CH_2), 3.22 (s, 3, OCH_3), 1.45, 1.35 [2 singlets, 6, $(CH_3)_2C$], 1.27 [s, 3, $OC(CH_3)O$]; molecular ion, 146. *Anal.* Calcd for $C_7H_{14}O_3$: C, 57.5; H, 9.7. Found (analysis by Galbraith Laboratories, Knoxville, Tenn.): C, 57.5; H, 9.6. This new compound was prepared by the method described.[4] [g] Bp 63.5–64.5° (23 mm) [A. Bruylants, M. Tits, C. Dieu, and R. Gauthier, *Bull. Soc. Chim. Belg.*, **61**, 366 (1952), give bp 90–91°]. No isomer detected (see footnote 7 in ref 4). Nmr [CCl_4, $(CH_3)_4Si$] δ 4.09 (s, 2, CH_2), 2.40 (s, 3, CH_3CO), 1.77 [s, 6, $(CH_3)_2C$].



$$4 + (CH_3)_3SiCl \longrightarrow 2 + (CH_3)_3SiOCH_3 \qquad (C)$$

In a typical reaction a solution of 3.46 g (17.8 mmol) of inactive 2-methoxy-2-methyl-4-phenyl-1,3-dioxolane[4]

(5) The use of $(CH_3)_3SiCl$ was first demonstrated by Dr. Paul Tornstrom in our laboratory.

(**4b**, R_1 = H; R_2 = Ph) and 3 g (28 mmol) of trimethylsilyl chloride in 8 ml of methylene chloride was held at reflux for 1.5 hr. On distillation there was obtained 3.22 g (91%) of a 95:5 mixture of 2-chloro-2-2-phenylethyl acetate, **2** (R_1 = C_6H_5; R_2 = H), and 2-chloro-1-phenylethyl acetate, **2** (R_1 = H; R_2 = C_6H_5), respectively. This and other compounds prepared by the new procedure are listed in Table I.

It should be pointed out that, while the yields of 1,2-chlorohydrin acetates obtained from 1,3-dioxolanes by method C are comparable to those by method B, the reaction of trimethylsilyl chloride with 2-methoxy-2,5,5-trimethyl-1,3,-dioxane (compound **4** in ref 4) and with 2-methoxy-2-methyl-1,3-dioxepane (compound **5** in ref 4) did not take place to give the expected chloro esters in good yield.

Registry No.—**2a**, 627-68-9; **2b**, 6509-95-1; **2c**, 760-86-1; **2** [R_1 = $(CH_3)_2$; R_2 = H], 6509-93-9; **4a**, 39834-09-8; **4b**, 39904-21-7; **4c**, 42077-65-6; **4** [R_1 = $(CH_3)_2$; R_2 = H], 42077-66-7; trimethylsilyl chloride, 75-77-4.

Structure of the Metabolite LL-S490β from an Unidentified *Aspergillus* Species

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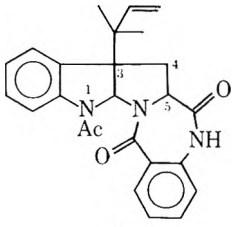
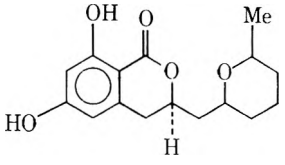
In relation to a screening program seeking useful biologically active mold metabolites, we examined fermentations of an unidentified *Aspergillus* species. We describe here the structure of a novel benzodiazepinedione (I) designated LL-S490β. In addition to I, we isolated cladosporin[1] (asperentin,[2] II), an antifungal



I



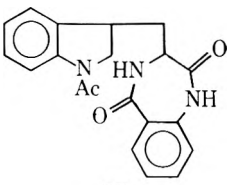
II

metabolite recently obtained from *Cladosporium cladosporiodes*[1] and *Aspergillus flavus*.[2]

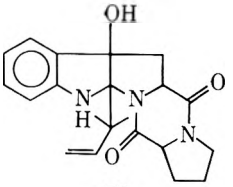
LL-S490β, $C_{25}H_{25}N_3O_3$, mp 238–240°, $[\alpha]_D$ +425° (MeOH), exhibits a mass spectrum characterized by a strong molecular ion at *m/e* 415 in addition to significant peaks at *m/e* 373 (M − 42), 346 (M − 69), and the base peak at 304 [M − (42 + 69)]. A high-intensity peak at *m/e* 130 is assigned to the indoline-3-methylene ion.[3] The general appearance of the uv spectrum [λ_{max} 210 (ε 61,000), 245 (22,000), and 284 nm (sh, 3940)] is very reminiscent of the *N*-acylindoline chromophore,[4] although the high extinction values indicate the presence of an additional chromophoric unit.

The nmr spectrum of I discloses the presence of eight aromatic proton signals between δ 6.83 and 8.17. A sharp 3-H singlet at δ 2.60 is assigned to the methyl of an *N*-acetyl group. Two tertiary *C*-methyl signals resonate at δ 1.02 and 1.21 and, in conjunction with the loss of 69 mass units in the mass spectrum, are assigned to the inverted γ,γ-dimethylallyl group. Consistent with this is the appearance of the very characteristic ABX pattern of the three vinyl protons of the C_5 moiety between δ 5.16 and 5.92.[5]

The ir spectrum of I shows absorption at 3300, 1689, and 1647 cm^{-1} assigned to NH and amide functionalities, respectively. In fact the latter two absorptions strongly suggest the presence of a dipeptide system.[6] Consideration of the molecular formula and the functionality described above suggests the combination of a tryptophane portion with anthranilic acid to give the partial structure III below. The uv of 3,4-dihydro-



III



IV

4-methyl-1*H*-1,4-benzodiazepine-2,5-dione [λ_{max} 215 nm (ε 32,100) and 291 (2180)][7] superimposed with that of the *N*-acylindoline system accounts for the observed uv spectrum of I.

The final molecular assembly was arrived at by examination of an ABX pattern in the nmr spectrum between δ 2.46 and 3.90 assigned to the geminal protons at C-4 and the methine hydrogen at C-5. The geminal pair resonate as four-line patterns at δ 2.46 and 3.42 with J_{AB} = 14, J_{AX} = 8.5, and J_{BX} = 8.0 Hz. The H-5 signal appears at δ 3.90 as an apparent triplet (J = 8 Hz). The similar J values of the corresponding nmr system in brevianamide E[5] (IV) provide a good analogy.

Placement of the inverted terpene unit at C-3 is dictated by the fact that the aforementioned geminal hydrogens are spin coupled only to the C-5 methine hydrogen. A sharp 1-H singlet at δ 6.00 is assigned to the C-2 methine hydrogen on comparison with the spectrum of a model compound.[4b] The singlet nature of this signal supports the absence of a proton at C-3.

An exchangeable 1-H singlet (br d) at δ 8.5 is attributable to the NH of the benzodiazepinedione ring.

The occurrence of I with the inverted C_5 unit at C-3 is unusual and raises the question as to the mode of incorporation of the terpene moiety into the indolyl system. A chemical precedent comes from the work of Bycroft and Landon,[8] who incorporated the inverted C_5 grouping at C-3 by a thio-Claisen rearrange-

(1) P. M. Scott, W. van Walbeek, and W. M. MacLean, *J. Antibiot.*, **24**, 747 (1971).

(2) J. F. Grove, *J. Chem. Soc., Perkin Trans. 1*, 2400 (1972).

(3) J. H. Benyon, R. A. Sanders, and A. E. Williams, "The Mass Spectra of Organic Molecules," Elsevier, New York, N. Y., 1968, p 303.

(4) (a) A. I. Scott, "Ultraviolet Spectra of Natural Products," Pergamon Press, Oxford, 1964, p 298; (b) M. Ohno, T. F. Spande, and B. Witkop, *J. Amer. Chem. Soc.*, **92**, 343 (1970).

(5) A. J. Birch and J. J. Wright, *Tetrahedron*, **26**, 2329 (1970).

(6) K. Blaha, J. Smolikova, and A. Vitek, *Collect. Czech. Chem. Commun.*, **31**, 4296 (1966).

(7) P. K. Martin, H. Rapoport, H. W. Smith, and J. L. Wong, *J. Org. Chem.*, **34**, 1359 (1969).

(8) B. W. Bycroft and W. Landon, *Chem. Commun.*, 967 (1970).

ment of a dimethylallyl 2-indolyl sulfonium salt. It is of interest that a number of related metabolites, such as euchinulin,[9] the brevinamides,[5] and austamide,[10] contain the inverted C_5 unit at C-2.[11]

Experimental Section

The melting points were determined on a Fisher-Johns melting point block. Nmr spectra were recorded with a Varian A-60D in $CDCl_3$; shifts are expressed in δ values (parts per million) from tetramethylsilane as internal standard, and coupling constants are expressed in cycles per second (hertz). In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet, and q = quartet. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord and ultraviolet spectra on a Cary Model 11.

Isolation of I.—The whole mash from a 30-l. fermentation was extracted with an equal volume of ethyl acetate at pH 5.0. The extract was concentrated to dryness and the residue was partitioned between methanol and heptane to remove fatty material. Evaporation to dryness of the methanol portion gave ~25 g of a crude residue. Twelve grams of this residue was chromatographed over a 500-g silica gel column (acid washed) packed in methylene chloride. A gradient elution between 0.5% methanol–methylene chloride and 3% methanol–methylene chloride provided cladosporin (II, 110 mg) after evaporation of the solvent and crystallization from ethyl acetate–benzene, mp 186–187°. Further elution gave the benzodiazepinedione I (185 mg) after removal of the solvent and crystallization from ethyl acetate–benzene: mp 238–240°; $[\alpha]D$ +425° (*c* 0.20, MeOH); ir (KBr) 3300, 1689, and 1647 cm^{-1}; λ_{max}^{MeOH} 210 nm (ϵ 61,000), 245 (22,000), and 284 (sh, 3940); nmr ($CDCl_3$) δ 1.02 and 1.21 (3 H, s), 2.60 (3 H, s), 2.46 (q, J_{AB} = 14, J_{AX} = 8.0 Hz), 3.42 (q, J_{AB} = 14, J_{BX} = 8.5 Hz), 3.90 (t, J = 8 Hz), 5.16 (m, AB of vinylidene), 5.92 (q, J_{trans} = 18, J_{cis} = 9.5 Hz, X of vinylidene), 6.00 (1 H, s), 6.83–8.17 (8 H, m), and 8.45 (1 H, s); mass spectrum *m/e* 415.18919 (calcd for $C_{25}H_{25}N_3O_3$, 415.18959).

Chromatography of the remaining portion of the crude ethyl acetate concentrate gave a total of 225 mg of II and 389 mg of I.

Acknowledgments.—We wish to thank Dr. H. Tresner and Miss Jean Hayes for culture isolation and identification, Mr. A. Shay for large-scale fermentations, Mr. M. Dann for large-scale work-ups, Mr. W. Fulmor and Mr. G. Morton for the uv and nmr spectra, and Dr. G. Van Lear for the mass spectrum [direct inlet MS 9 (AEI)].

Registry No.—I, 42230-55-7; II, 35818-31-6.

(9) A. Quilico, *Res. Progr. Org.-Biol. Med. Chem.*, **1**, 1964 (1964); for a recent study on the biosynthesis of echinulin, see C. M. Allen, Jr., *Biochemistry*, **11**, 2154 (1972).

(10) P. S. Steyn, *Tetrahedron Lett.*, 3331 (1971).

(11) A proposal for the echinulin-type metabolites has been put forth by Cosnati and Pochini [*Chem. Commun.*, 1328 (1970)]. On the basis of model reactions, they point out the feasibility of a primary attack at N-1 (*e.g.*, lanosulin[12]) followed by rearrangement to introduce the inverted γ,γ-dimethylallyl group at C-2. This postulate does not appear to be relevant to the introduction of the C_5 moiety at C-3.

(12) D. T. Dix, J. Martin, and C. E. Moppett, *Chem. Commun.*, 1168 (1972).

Cyclization of Azidoformates

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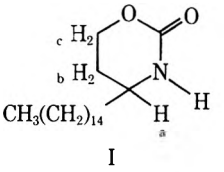
The major product of the thermolysis of *n*-octadecyl azidoformate in cyclohexane is *n*-octadecyl *N*-cyclohexylcarbamate. In addition, two isomeric minor products, with the empirical formula $C_{19}H_{37}O_2N$, are found. One, obtained in 5% yield, is the five-membered ring compound formed by "backbiting" of the nitrene, 4-*n*-hexadecyloxazolidin-2-one, as shown by comparison of its infrared and nmr spectra with those of an authentic sample of the 4-ethyl derivative.[2,3]

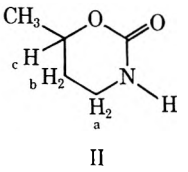
Although common sense dictated that the other isomer, obtained in 8% yield, should be the corresponding six-membered ring compound, 4-*n*-pentadecyltetrahydro-2*H*-1,3-oxazin-2-one (I), the nmr spectrum in comparison with an "authentic" sample of the corresponding 4-methyl derivative seemed to eliminate this possibility; the difficulty arose because in the "4-methyl derivative" spectrum the two protons adjacent to O are upfield from the one adjacent to N, whereas in the octadecyl compound the reverse is true.[2]

Edwards[4] suggested that the large alkyl group in I imparts conformational rigidity to the ring and causes the signal of one of the hydrogens in the 6 position to overlap that of the hydrogen in the 4 position, adjacent to the N atom. We did not consider this a very likely explanation and decided to reinvestigate the problem.[5]

There is now no doubt that the unknown is indeed the six-membered ring isomer (I), whereas the "authentic 4-methyl derivative" is 6-methyltetrahydro-2*H*-1,3-oxazin-2-one (II). Table I summarizes the nmr chemi-



I



II

TABLE I

NMR SPECTRA AND PEAK ASSIGNMENTS FOR ISOMERIC ALKYL-2*H*-1,3-OXAZIN-2-ONES

Proton group	δ, ppm from TMS (rel area) I	II
H_a	3.4 (1)	3.36 (2.1)
H_b	1.9 (1.8)	1.9 (2)
H_c	4.23 (2)	4.41 (1.0)
NH	6.45 (0.8)	7.1

cal shifts observed for the various proton groups in the two compounds. Time averaging in the presence of $Eu(dpm)_3$ showed H_a in I to be a quintet, consistent with the assigned structure. The fact that the H_c protons occur as a narrow (*ca.* 13 Hz) multiplet is consistent with a six-membered ring, as is the absence of an amide II band in the infrared spectrum.[2] The fact that the single proton (H_a) occurs at higher field than the two

(1) Hercules Research Center Contribution No. 1617.

(2) D. S. Breslow, T. J. Prosser, A. F. Marcantonio, and C. A. Genge, *J. Amer. Chem. Soc.*, **89**, 2384 (1967).

(3) Our recent nmr studies have shown that the nmr chemical shift assignments given in ref 1 for 4-*n*-hexadecyloxazolidin-2-one and the corresponding ethyl derivative, which were based on poorly resolved spectra obtained on a primitive instrument, were in error. Spectra run on a modern high-resolution instrument, confirmed by proton decoupling and the use of lanthanide shift reagents, show that the ring methylene protons adjacent to oxygen are nonequivalent and occur at δ 4.0 and 4.6. The ring methyne proton adjacent to nitrogen is observed at δ 3.8.

(4) O. E. Edwards, "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, p 236.

(5) We are indebted to Dr. C. A. Genge and Mrs. E. I. Edwards of the Hercules Research Center for the preparation and isolation of a fresh sample of isomer.

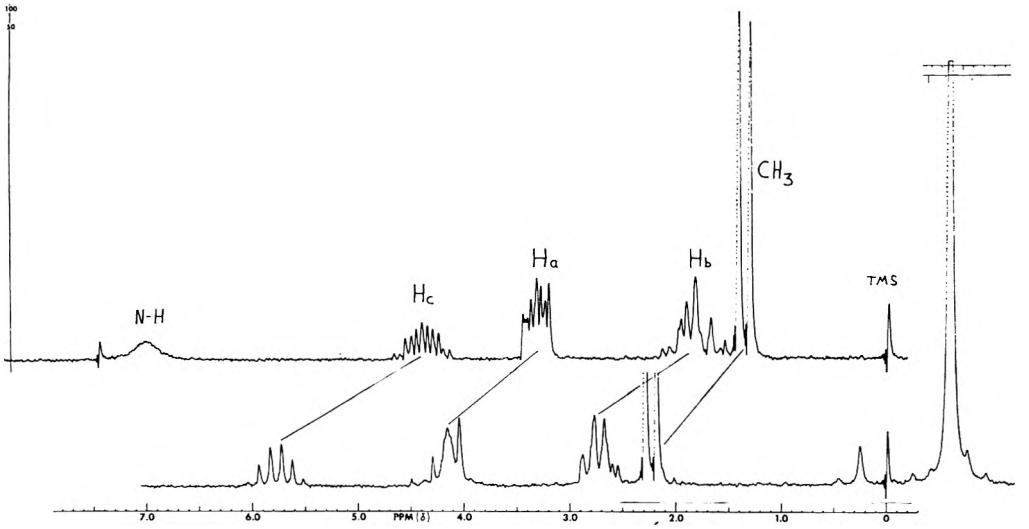


Figure 1.—Effect of Eu(dpm)$_3$ on the nmr spectrum of 6-methyltetrahydro-2*H*-1,3-oxazin-2-one: upper spectrum, no shift reagent; lower spectrum, Eu/substrate = 0.148.

protons (H_c) leaves little doubt as to the assigned structure; $-CH_2NHC{=}O$ is reported in the range of δ 3.0–3.5, whereas $-CH_2OC{=}O$ is reported at δ 4.1–4.3.[6]

Proton assignments in II were confirmed by proton–proton decoupling studies and shift enhancement with Eu(dpm)$_3$. The paramagnetic shift reagent was particularly useful in this work because it provided simplification of the complex, non-first-order spectra of the ring protons as well as resolution of overlapping multiplets. As an example, Figure 1 shows the unshifted and shifted spectra of II. In the shifted spectrum, run at a molar ratio of Eu/substrate of only 0.148, the NH proton occurs at δ 9.3, off the low-field end of the spectrum. H_c, shifted from δ 4.4 to 5.8, is clearly a sextet, coupled to the methyl group and the H_b methylene protons. The H_b multiplet, shifted from δ 1.9 to 2.7, is now clearly recognizable as a quartet, although some evidence of non-first-order coupling is still present at this Eu/substrate ratio. In the case of I, run at a similar Eu(dpm)$_3$/substrate ratio, the NH proton was observed at δ 9.1 and H_a was shifted from δ 1.9 to 2.9 and H_c from δ 4.2 to 5.8. In the shifted spectrum of I, the proton multiplets were also simplified, although they were not completely first order, and area measurements were significantly improved.

The only synthesis of 4-methyltetrahydro-2*H*-1,3-oxazin-2-one in the literature involves the condensation of 1,3-butanediol with urea.[7] Since this reagent would be expected to yield a mixture of isomers, and in any case could not be considered an unequivocal synthesis, we chose to prepare it by the reaction of diethyl carbonate and purchased "3-amino-1-butanol."[8] It is most unlikely that an isomerization would take place under the reaction conditions used, and, since there is no doubt that the product obtained is the 6-methyl isomer, the starting material must therefore have been 4-amino-2-butanol.[9]

(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 164.

(7) A. M. Paquin, *Z. Naturforsch.*, **1**, 518 (1946).

(8) K & K Laboratories, Inc.

(9) Unfortunately, the structure of the amino alcohol was not investigated at the time the preparation was run, and the compound is no longer available.

Experimental Section

6-Methyltetrahydro-2*H*-1,3-oxazin-2-one (II).—To a solution of 12.3 g (0.14 mol) of "1-amino-3-butanol"[8] in 35.1 g (0.30 mol) of diethyl carbonate was added 10 mg of sodium. The reaction was heated at 130–140° and ethanol was distilled off through a short Vigreux column as it formed. The white crystals which formed on cooling in a deep freeze were filtered and recrystallized once from acetone, mp 91–92° (6.30 g, 39% of theory). One recrystallization from benzene raised the melting point to 98.5–99.5° (lit.[6] mp 91°).

Anal. Calcd for $C_5H_9O_2N$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.15, 52.10; H, 7.98, 7.80; N, 12.05, 12.23.

Nmr spectra were run at 90 MHz on a Bruker HFX-90 spectrometer and at 60 MHz on a Varian A-60A spectrometer in standard 5-mm-o.d. sample tubes, using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference and lock signal.

Registry No.—I, 42202-88-0; II, 42202-89-1; *n*-octadecyl azidoformate, 822-04-8; *n*-octadecyl *N*-cyclohexylcarbamate, 16307-63-4; 4-*n*-hexadecyloxazolidin-2-one, 16392-84-0; 1-amino-3-butanol, 39884-48-5.

Quinazolines and 1,4-Benzodiazepines. LXII.[1] Reaction of Oxaziridines with Water or Alcohols Catalyzed by Iron Salts

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We have reported[2–4] on the preparation and chemistry of oxazirinobenzodiazepinones **1** and **5**. It was found[3] that **5** undergoes ring contraction reactions to form quinazolinones when alcoholic or aqueous solutions were simply allowed to stand at room temperature. We wish to report here that, when ferrous sulfate or

(1) Paper LXI: R. Y. Ning, P. B. Madan, and L. H. Sternbach, *J. Heterocycl. Chem.*, in press.

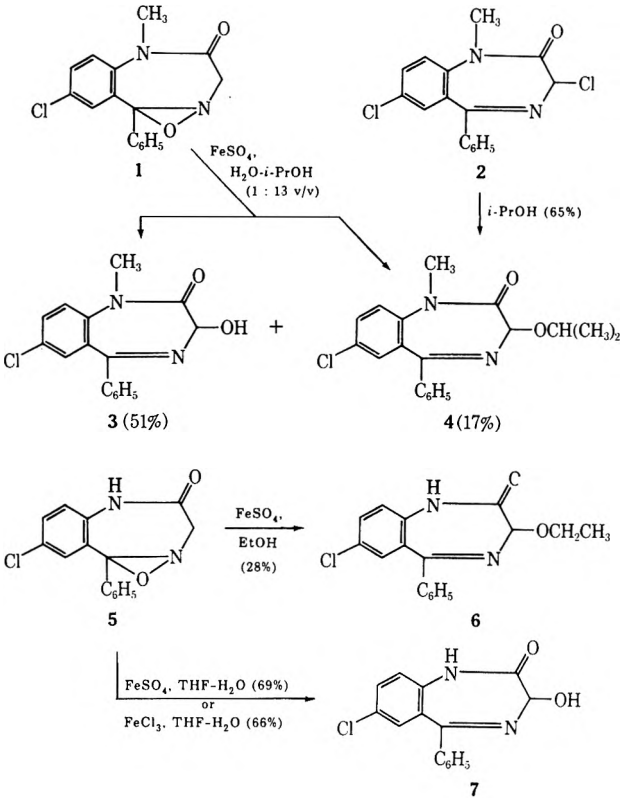
(2) R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.*, **7**, 475 (1970).

(3) R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **36**, 2243 (1970).

(4) R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Org. Chem.*, **36**, 1064 (1971).

ferric chloride is added to solutions of **1** or **5** in alcohol or aqueous tetrahydrofuran, 3-alkoxy- or 3-hydroxybenzodiazepinones of types **3**, **4**, **6**, and **7** are formed as main products. Other oxaziridines have been reported[5-11] to react with ferrous salts, in one-electron-transfer chain reactions, to yield carbonyl compounds and, in many cases, complex mixtures. The reaction of **1** and **5** with ferrous sulfate appeared sluggish and required more than 1 equiv of the ferrous salt to bring about complete reactions.

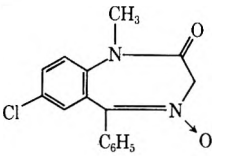
When a solution of 7-chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrachloro-2*H*-1,4-benzodiazepin-2-one (**1**) in isopropyl alcohol containing a small amount of water and 1.5 mol equiv of ferrous sulfate was stirred at room temperature for 2 days, two major products were formed. One, isolated in 51% yield, was found to be 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**3**)[12] and the other, isolated in 17% yield, was 7-chloro-1,3-dihydro-3-isopropyloxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**4**). The structure of **4**, indicated by spectral data, was confirmed by a synthesis from the reaction of



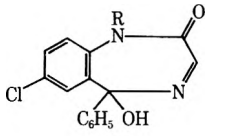
the corresponding 3-chloro compound 2[4] with isopropyl alcohol. Analogously, the treatment of 7-chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (**5**) with ferrous sulfate in aqueous ethanol afforded the 3-ethoxy compound **6** (28%). Although the 3-hydroxy compound **7** appeared, by tlc, to be the other major product of this reaction, we did not isolate it. By replacing aqueous ethanol with aqueous tetrahydrofuran, **5** was converted to **7** by ferrous sulfate in at least 69% yield.

Being aware of the special sensitivity of some oxaziridines to ferrous salts,[5-11] we proceeded to study this reaction with ferric chloride, nickel chloride ($NiCl_2$), cupric sulfate, and cobalt chloride ($CoCl_2$) in place of ferrous sulfate. Under the same reaction conditions, (aqueous tetrahydrofuran), **5** was quite stable toward the latter three salts. With ferric chloride, however, the conversion to **7** proceeded just as well as it did with ferrous sulfate.

We have ruled out the formation of nitrones,[13] such as **8**, as intermediates in these reactions. **8**[12] was quite stable toward ferrous sulfate under these conditions. It is likely[4] that the 1,5-dihydrobenzodiazepinones **9** are



8



9

intermediates in these reactions. An attempt at the preparation of **9** by treating **5** with ferric chloride hexahydrate in tetrahydrofuran without added water resulted only in the 3-hydroxy compound **7**.

Experimental Section[14]

7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[12] (**3**) **and 7-Chloro-1,3-dihydro-3-isopropyloxy-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one** (**4**).—To a solution of 7-chloro-4,5-epoxy-1-methyl-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one[3] (**1**, 200 mg, 0.67 mmol) in isopropyl alcohol (90 ml) was added an aqueous solution of ferrous sulfate heptahydrate (Baker reagent grade, 1.0 mmol in 7 ml of water). The mixture was stirred at room temperature for 2 days under nitrogen. The reaction mixture was evaporated to dryness. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was washed with water and dried (Na_2SO_4). The methylene chloride was evaporated to dryness. The residue was separated by preparative tlc (four silica gel plates measuring 20 cm × 20 cm × 1.5 mm; ethyl alcohol–pentane–ether in 1:2:7 ratio of volumes used as developer).

3 (R_f 0.4), obtained as colorless needles after recrystallization from ether–pentane, weighed 103 mg (51%), mp 125–126°. It was found to be identical (ir, tlc, mixture melting point) with an authentic sample of **3** prepared by the method of Bell and Childress.[12]

4 (R_f 0.5), obtained as colorless prisms after recrystallization from ether–pentane, weighed 40 mg (17%): mp 210–212°;

(5) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(6) E. Schmitz, *Advan. Heterocycl. Chem.*, **2**, 83 (1963).
(7) W. D. Emmons in "The Chemistry of Heterocyclic Compounds, A. Weissberger, Ed., Vol. 19, Part I, Interscience, New York, N.Y., 1964, Chapter 4.
(8) J. F. Dupin, *Bull. Soc. Chim. Fr.*, 3085 (1967).
(9) E. Schmitz and D. Murawski, *Chem. Ber.*, **98**, 2525 (1965).
(10) F. Minisci, M. Cerere, and R. Galli, *Chim. Ind. (Milan)*, **50**, 225 (1968).
(11) F. Minisci, M. Cerere, and R. Galli, *Gazz. Chim. Ital.*, **98**, 358 (1968).
(12) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).
(13) Oxaziridines rearrange readily to nitrones under some conditions; see ref 6–8.
(14) General experimental details are as noted in the corresponding footnote in ref 4. Thin layer chromatography was performed on glass plates coated with Mallinckrodt silica 7GF5 (with fluorescent indicator) in the case of analytical tlc and Merck silica gel PF254 in the case of preparative tlc. All plates were activated by heating to 100° for 1 hr and then stored at 20–50°. The chromatograms were developed over a distance of 10 cm and then viewed or photographed under uv light.

ir (KBr) 1680 cm^{-1} (CO); uv max (CH_3CN) 231 nm (ϵ 33,900), 255 (sh) (17,500), 317 (2740); nm ($CDCl_3$) δ 1.33 (t, 6, 2 CH_3), 3.43 (s, 3, NCH_3), 4.12 (m, 1, $CH(CH_3)_2$), 4.88 (s, 1, H-3), 7.2–7.8 ppm (m, 8, aromatic); molecular ion m/e 342 (calcd 342).

Anal. Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.56; H, 5.58; N, 8.17; Cl, 10.34. Found: C, 66.60; H, 5.84; N, 8.04; Cl, 10.43.

The structure of **4** was confirmed by a synthesis from the corresponding 3-chloro compound **2**[4] as shown.

A solution of 3,7-dichloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one[4] (**2**, 164 mg, 0.50 mmol) in isopropyl alcohol (20 ml) was heated on a steam bath for 20 min. The solution was evaporated to dryness. Crystallization of the residue from ether–pentane afforded 112 mg (65%) of **4** as prisms, mp 210–211°, identical with that prepared above by ir, tlc, and mixture melting point.

7-Chloro-1,3-dihydro-3-ethoxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (6).[12]—To a solution of 7-chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one[2] (**5**, 574 mg, 2.0 mmol) in ethyl alcohol (500 ml) was added an aqueous solution of ferrous sulfate heptahydrate (834 mg, 3.0 mmol, in 10 ml of water). The mixture was stirred at room temperature for 20 hr under nitrogen. Solvent was evaporated. The residue was partitioned between methylene chloride and brine. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was applied to a column of 50 g of Florisil with methylene chloride. Elution with 1.5 l. of ethyl acetate followed by 500 ml of acetone afforded pure **6** (R_f 0.37 on silica gel tlc, using ether). Crystallization from methylene chloride–ether afforded 180 mg (28%) of colorless flakes, mp 222–224°, identical (tlc and mixture melting point) with a sample of **6** prepared by the literature procedure.[12]

7-Chloro-1,3-dihydro-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (7).[12] **A. With Aqueous Ferrous Sulfate.**—To a solution of 7-chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one[2] (**5**, 143 mg, 0.50 mmol) in tetrahydrofuran (100 ml) was added an aqueous solution of ferrous sulfate heptahydrate (208 mg, 0.75 mmol, in 20 ml of water). The mixture was stirred under nitrogen at room temperature for 3 days. The solvent was evaporated. The residue was partitioned between methylene chloride and saturated brine. The methylene chloride layer was washed with water, dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residue from ether afforded 100 mg (69%) of **7** as colorless prisms, mp 208–210°. This material was found identical (ir, tlc, mixture melting point) with a sample of **7** prepared by the known[12] procedure.

B. With Aqueous Ferric Chloride.—To a solution of **5** (144 mg, 0.50 mmol) in tetrahydrofuran (150 ml) was added an aqueous solution of ferric chloride hexahydrate (Baker reagent grade, 0.75 mmol, in 20 ml of water). The mixture was stirred under nitrogen at room temperature for 7 days. The product was isolated in the same manner as described above in A. The yield of **7**, isolated as colorless prisms from ether, was 94 mg (65%), mp 206–208°. It was identified by ir, tlc, and mixture melting point.

C. With Ferric Chloride Hexahydrate.—To a solution of **5** (1.44 g, 5.0 mmol) in tetrahydrofuran (800 ml) was added solid ferric chloride hexahydrate (2.03 g, 7.5 mmol). The mixture was stirred under nitrogen at room temperature for 1 day. Isolation of the product in the same manner as described in A afforded 580 mg (40%) of **7**, identified by ir, tlc, and mixture melting point.

Stability of 7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (8) toward Ferrous Sulfate.—To a solution of 1.5 g (5.0 mmol) of **8** in 1 l. of isopropyl alcohol was added an aqueous solution of ferrous sulfate heptahydrate (2.09 g, 7.5 mmol, in 50 ml of water). After 2 days of stirring at room temperature, under nitrogen, tlc indicated no signs of reaction. After evaporation of solvent and partitioning the residue between methylene chloride and water, **8** was quantitatively recovered.

Acknowledgment.—We thank Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. W. Benz for mass spectra, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv measurements, Mr. S. Traiman for ir spectra, and Dr. T. Williams for nmr spectra.

Registry No.—**1**, 24605-70-7; **2**, 23433-96-7; **3**, 846-50-4; **4**, 42077-69-0.

Addition of Trimethyl Phosphite to β-Nitrostyrene

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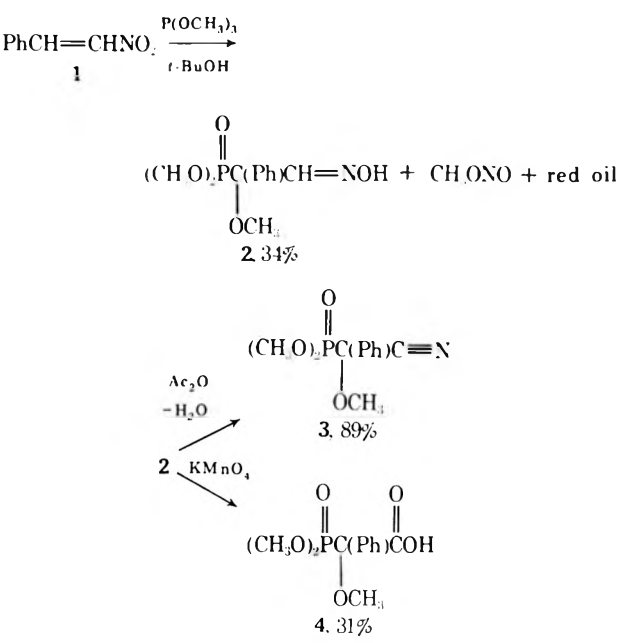
In connection with a general study of the deoxygenation of nitroalkenes with trivalent phosphorus compounds, β-nitrostyrene (**1**) was treated with trimethyl phosphite in *tert*-butyl alcohol at room temperature. The exothermic reaction formed a white solid in 34% yield. This solid was not the product of the intermediate nitrene expected of deoxygenation, nor was it similar to the product of the reaction of β-nitrostyrene with triethyl phosphite.[1] The chemical and physical data support **2** as the structure of this compound; the other products of this reaction include an unidentified red oil and an undetermined amount of methyl nitrite[2] (Chart I).

CHART I



Elemental analyses gave an empirical formula of $C_{11}H_{16}NO_5P$, a 1:1 adduct of the starting materials, and was in agreement with the mass spectrum which showed a molecular ion of M^+ 273. The presence of the phosphonate ester group was established by the ^{31}P nmr, δ −20.5 ppm (heptet, J_{H-P} = 10.6 Hz), by ^1H nmr (Table I), by the mass spectrum with a base peak at m/e 164, corresponding to the loss of O=P-$(OCH_3)_2$,[3] and by the infrared spectral bands at 1280 (vs) and 1065 cm^{-1} (vs). The ^1H nmr also indicated the presence of a third methoxyl at 3.48 ppm.

(1) G. L. Behelfer, J. R. Maloney, and W. E. Krueger, Abstracts, 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972, ORGN-157.

(2) The determination of yield of methylnitrite was complicated by the fact that nitrites react with phosphites: J. H. Boyer and J. D. Woodyard, *J. Org. Chem.*, **33**, 3329 (1968).

(3) J. L. Occolowitz and J. M. Swan, *Aust. J. Chem.*, **19**, 1187 (1966).

TABLE I
PMR CHEMICAL SHIFTS

Compd	$COCH_3$	$POCH_3$	-CH=NOH	OH
2	3.48	3.55, 3.75	7.71	10.8
3	3.28	3.53, 3.75		11.2
4	3.45	3.68, 3.74		

Compound 2 reacted smoothly with refluxing acetic anhydride in a reaction typical of aldoximes to give the nitrile 3 in 89% yield. Further evidence for the oxime function in 3 was provided by the ^1H nmr, δ 10.8 (s, exchangeable) and 7.71 ppm (s), and by the infrared spectrum, ν 3550 (w) and 3220 cm^{-1} (s, broad).

The oxidation of 2 with cold, dilute, neutral potassium permanganate gave an acidic product, 4, whose elemental analyses were consistent with an empirical formula of $C_{11}H_{15}O_6P$. This was in good agreement with the mass spectrum, which showed a molecular ion at M^+ 274. That carbon was not lost in this reaction and that the product was an acid indicated that the third methoxyl was on the carbon α to the phenyl group. This is also in agreement with the observed singlet for the aldoximino proton of 2 at 7.71 ppm. These data are consistent only with 2-dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde oxime as the structure of 2.

The mechanistic implications of these results currently are being investigated.

Experimental Section[4]

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetaldehyde Oxime (2).—A solution of 30 g (0.2 mol) of β-nitrostyrene (1) in 300 ml of *tert*-butyl alcohol was placed in a three-neck flask equipped with a condenser, pressure-equalizing dropping funnel, and thermometer and 62 g (0.5 mol) of trimethyl phosphite was run in. An initial cooling of 4° was observed followed by a slow increase in temperature to a maximum of 65–75° usually within 20 min. The reaction was accompanied by a slight darkening and a barely discernible gas evolution at higher temperatures. After 3 hr the solvent was removed by rotary evaporation, the residue was cooled and seeded, and the walls of the vessel were scratched. Slow crystallization from the red oil began immediately. After standing overnight the crystals were filtered, washed twice with 20 ml of toluene, and recrystallized from 1,2-dimethoxymethane to give 16.63 g of white, crystalline 2, mp 134–136°. A second crop from the reaction mixture treated in the same way gave an additional 1.92 g for a total yield of 34%: mass spectrum *m/e* (rel intensity) M^+ 273 (0.5), 243 (18), 164 (100), 132 (83), 105 (37), 77 (42); ^1H nmr ($CDCl_3$) δ 3.47 and 3.48 (pair of singlets, 3, $COCH_3$), 3.55 (d, 3, J_{HP} = 10.6 Hz, $POCH_3$), 3.75 (d, 3, J_{HP} = 10.6 Hz, $POCH_3$),[5] *ca.* 7.40 (m, 5, C_6H_5–), 7.71 ppm (s, 1, -CH=N), 10.8 (s, 1, OH); ^{31}P nmr ($CHCl_3$) δ −20.5 ppm [heptet, J_{HP} = 10.6 Hz, P(O)-$(OCH_3)_2$]; ir ($CHCl_3$) 3550 (w) and 3220 (s, br, OH), 1280 (vs, P=O), 1065 cm^{-1} (vs, POC). *Anal.* Calcd for $C_{11}H_{16}NO_5P$: C, 48.35; H, 5.90; N, 5.13; P, 11.33. Found: C, 48.20; H, 5.91; N, 5.15; P, 11.83.

The red oil that remained was not distillable at pressures of 0.25 mm and temperatures of 180–200°.

The reaction also produced an undetermined amount of a colorless gas which was trapped with a Dry Ice–acetone cold finger distillation head placed at the top of the water-jacketed condenser: nmr (CCl_4) δ 3.98 ppm (s, CH_3ONO); ir (CCl_4) 1665 (s) and 1610 cm^{-1} (s, -ONO).

These spectra were identical with those of an authentic sample of methyl nitrite prepared by reaction of methyl iodide with sodium nitrite in dimethylformamide.

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetonitrile (3).—The white solid 2, 5.4 g (0.02 mol), and 20 ml of acetic anhydride were placed in a round-bottom flask with condenser and heated at reflux for 8 hr. The volatile materials were removed at aspirator pressure and the residue was distilled to give 4.54 g (89%) of a water-white liquid, bp 140–144° (0.7 mm). Redistillation gave an analytical sample: bp 133–135° (0.25 mm); ir (CCl_4) 2250 cm^{-1} (vw, C≡N);[6] nmr (CCl_4) δ 3.28 (s, 3, $COCH_3$), 3.53 (d, 3, J_{HP} = 10.5 Hz, $POCH_3$), 3.75 (d, 3, J_{HP} = 10.5 Hz, $POCH_3$),[5] 7.41 ppm (m, 5, C_6H_5); mass spectrum *m/e* (rel intensity) 255 (0.5), 146 (100), 109 (8), 105 (49), 77 (12). *Anal.* Calcd for $C_{11}H_{14}NO_4P$: C, 51.72; H, 5.53. Found: C, 51.59; H, 5.53.

2-Dimethoxyphosphinyl-2-methoxy-2-phenylacetic Acid (4).—A solution of 2.73 g (0.01 mol) of 2 in 150 ml of water, which was prepared by warming the water until the solid 2 just dissolved, was added to a solution of 1.58 g of $KMnO_4$ in 150 ml of H_2O in such a way that the temperature did not go above 35°. After 0.5 hr the mixture was filtered and the water was removed under vacuum. The solid–oil mixture that resulted was taken up in $CHCl_3$ and extracted three times with 20 ml of 10% K_2CO_3 solution. The combined water layers were extracted once with 15 ml of $CHCl_3$ and neutralized with excess HCl. The turbid mixture was extracted three times with 20 ml of $CHCl_3$ and the combined organic layers were dried over $MgSO_4$ and evaporated to give 1.44 g of a yellow oil Trituration in benzene gave a white solid which was collected by filtration Recrystallization from toluene gave 0.86 g (31%) of 4 as a white solid: mp 148–150°; mass spectrum *m/e* (rel intensity) 274 (0.5), 230 (18), 215 (15), 165 (61), 121 (94), 105 (100), 77 (61); ir 1750 (s, C=O), 1240 (s, P=O), 1060 cm^{-1} (s, POC); nmr ($CDCl_3$) δ 3.45 (s, 3, $COCH_3$), 3.68 (d, 3, J = 10.5 Hz, $POCH_3$), 3.74 (d, 3, J = 10.5 Hz, $POCH_3$),[5] *ca.* 7.5 (m, 5, C_6H_5), 11.2 ppm (s, 1, CO_2H). *Anal.* Calcd for $C_{11}H_{15}O_6P$: C, 48.18; H, 5.51; P, 11.29. Found: C, 48.31; H, 5.22; P, 11.16.

Acknowledgments.—We acknowledge the support of donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Foundation of the State University of New York for their partial support of this research.

Registry No.—1, 102-96-5; 2, 42151-03-1; 3, 42151-04-2; 4, 42151-05-3.

(4) Infrared spectra were determined on a Perkin-Elmer Model 221G spectrophotometer, nmr spectra on a Hitachi Perkin-Elmer R-20B, and mass spectra on a Du Pont Model 21-491 gc–mass spectrometer.

(5) The nonequivalence of methoxyl groups is expected of phosphinyl groups attached to a carbon bearing three different substituents and further supports structures 2, 3, and 4: R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 75; J. H. Boyer and R. Selvarajan, *J. Org. Chem.*, 35, 1229 (1970).

(6) The nitrile infrared band may disappear altogether when attached to a carbon bearing an oxygen: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, p 266.

Convenient, High Yield Conversion of Androst-5-ene-3β,17β-diol to Dehydroisoandrosterone

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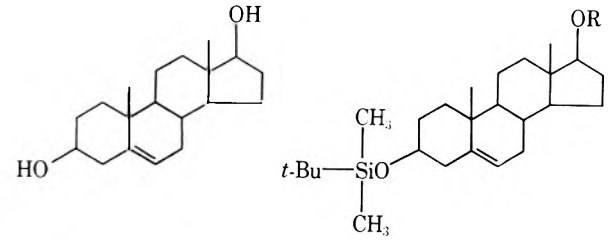
In connection with the investigation of the mechanism of steroid biotransformations we required dehydroisoandrosterone labeled with tritium in specific locations and orientation. To prepare these substrates with adequate specific activities, a convenient and high yield method of converting androst-5-ene-3β,17β-diol which is readily obtainable from androstenedione or testosterone to dehydroisoandrosterone was required. Since direct selective oxidation of the

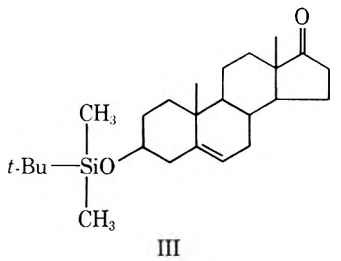
17-hydroxyl function was not promising,[1] selective protection of the 3β-hydroxyl group appeared to offer the best chance of success. Kupfer, *et al.*,[2] have previously used digitonin complexes for the selective protection of the 3β-hydroxyl in 3,17-diols followed by subsequent oxidation. The yields, however, were variable and the method was therefore deemed not suitable for a radiochemical synthesis where high yields were essential. In this communication we wish to report a convenient synthesis of dehydroisoandrosterone from androst-5-ene-3β,17β-diol which proceeds with high yield and is applicable to small-scale radioactive preparations.

Dimethyl-*tert*-butylsilyl chloride has been used as protective group for hydroxyl function by Corey and Venkateswarlu[3] in their prostaglandin syntheses. The principal advantages of this reagent are the lack of a chiral center and the ease of removal under mild conditions. Of particular interest to us was the large bulk of the reagent suggesting that it may lead to selective derivatization in the case of androstenediol (I).

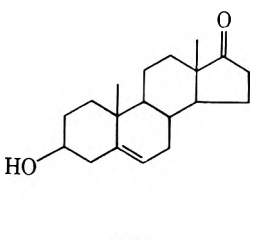


I

IIa, R = H
b, R = $Si(CH_3)_2 \cdot t$-Bu



III



IV

Reaction of 60 mg of androstenediol (I) with 110 mg of dimethyl-*tert*-butylsilyl chloride in 2 ml of dimethylformamide in the presence of imidazole yielded the desired androst-5-ene-3β,17β-diol 3-dimethyl-*tert*-butylsilyl ether (IIa) in 71% yield. Evidence for the highly selective silylation at C-3 was observed by conversion to dehydroisoandrosterone 3-dimethyl-*tert*-butylsilyl ether (III), identical with that obtained from dehydroisoandrosterone. Although the 3β,17β-disilyl ether (IIb) was formed in 28% yield, only trace material with the expected mobility of the 17β-monosilyl derivative was observed.

Oxidation of IIa with the CrO_3–pyridine complex gave dehydroisoandrosterone 3-dimethyl-*tert*-butylsilyl ether (III) in quantitative yield, while oxidation with the Jones reagent was less successful giving a yield of only 40%.

Cleavage of the 3β-dimethyl-*tert*-butylsilyl group of III was performed in a mixture of AcOH–H_2O–THF or by exposure to tetra-*n*-butylammonium fluoride. Dehydroisoandrosterone (IV) was generated quantitatively in the both instances.

The overall yield of IV from I was at least 64%. When the sequence was repeated starting with 0.6 mg of [4-^{14}C]androst-5-ene-3β,17β-diol the final overall yield of [4-^{14}C]dehydroisoandrosterone was 51%.

(1) M. Gut and M. Uskoković, *J. Org. Chem.*, **24**, 673 (1959).

(2) D. Kupfer, E. Forchielli, and R. I. Dorfman, *J. Amer. Chem. Soc.*, **82**, 1257 (1960).

(3) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 6190 (1972).

Experimental Section[4]

Androst-5-ene-3β,17β-diol 3-Dimethyl-*tert*-butylsilyl Ether (IIa).—To a solution of androst-5-ene-3β,17β-diol (60 mg) in DMF (2 ml) were added dimethyl-*tert*-butylsilyl chloride (110 mg) and imidazole (140 mg) at 0°. The solution was shaken for 5 min and allowed to stand at room temperature for 20 min. The reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4, and the solvent was evaporated at 40° under reduced pressure. Purification of the crystalline product by preparative tlc using cyclohexane–AcOEt (4:1) as developing solvent gave 59 mg (71%) of IIa: mp 171–172° (from MeOH); R_f 0.41; $[\alpha]^{23}D$ −43.5° ($CHCl_3$); ir (KBr) 3400, 1670, 1260, 1100, 840, 775 cm^{-1}; nmr ($CDCl_3$) δ 0.05 (6 H), 0.75 (3 H), 0.88 (9 H), 1.00 (3 H), 3.2–3.7 (2 H), 5.32 (1 H).

Anal. Calcd for $C_{25}H_{44}O_2Si \cdot {}^1/_2H_2O$: C, 72.58; H, 10.96. Found: C, 72.73; H, 10.75.

Elution of less polar fraction (R_f 0.75) gave 30 mg of androst-5-ene-3β,17β-diol of di(dimethyl-*tert*-butylsilyl) ether (IIb, 28%): mp 113–115° (from ether–MeOH); $[\alpha]^{22}D$ −31.9° ($CHCl_3$); ir (KBr) 1672, 1250, 1110, 840, 775 cm^{-1}; nmr ($CDCl_3$) δ 0.02 (6 H), 0.05 (6 H), 0.72 (3 H), 0.88 (18 H), 1.00 (3 H), 3.2–3.7 (2 H), 5.32 (1 H).

Anal. Calcd for $C_{31}H_{58}O_2Si_2$: C, 71.74; H, 11.27. Found: C 71.94; H, 10.91.

Trace material was observed with a R_f (0.34), which probably was the 17-monosilyl ether. There was insufficient amount for further identification.

3β-Hydroxyandrost-5-en-17-one 3-Dimethyl-*tert*-butylsilyl Ether (III). A. From Dehydroisoandrosterone.—To a solution of dehydroisoandrosterone (200 mg) in DMF (5 ml) were added dimethyl-*tert*-butylsilyl chloride (370 mg) and imidazole (470 mg), and the solution was allowed to stand at room temperature for 1 hr. The reaction mixture was worked up in the usual way to give III (265 mg, 96%): mp 146–147° (from MeOH); $[\alpha]^{23}D$ +7.7° ($CHCl_3$); ir (KBr) 1750, 1670, 1260, 1100, 840, 776 cm^{-1}; nmr ($CDCl_3$) δ 0.05 (6 H), 0.88 (12 H), 1.00 (3 H), 3.2–3.7 (1 H), 5.32 (1 H).

Anal. Calcd for $C_{25}H_{42}O_2Si$: C, 74.56; H, 10.51. Found: C, 74.67; H, 10.23.

B. From Oxidation of IIa.—A solution of IIa (50 mg) in pyridine (1 ml) and 0.4 ml of CrO_3–pyridine complex (1:10 w/v) was allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with ether and washed with 10% AcOH and 5% $NaHCO_3$ and dried over anhydrous Na_2SO_4. Purification of the crystalline product by preparative tlc using cyclohexane–AcOEt (3:1) as developing solvent gave 46 mg (92%) of III, mp 146–147° (from MeOH). The ir spectrum was identical with that of authentic sample obtained by method A.

Desilylation of III. A. With Acetic Acid.—A solution of 61 mg of III in 5.5 ml of a AcOH–H_2O–THF mixture (3:1:1.5) was allowed to stand at 50° for 4 hr. The reaction mixture was diluted with AcOEt and washed with 5% $NaHCO_3$ and H_2O and dried over anhydrous Na_2SO_4. Upon usual work-up, the crystalline product was purified by preparative tlc to give 44 mg (100%) of dehydroisoandrosterone (IV), mp 146–147° (from acetone–hexane).

B. With Tetra-*n*-butylammonium Fluoride.—To a solution of 61 mg of III in 1 ml of THF was added tetra-*n*-butylammonium fluoride (160 mg) and the solution was allowed to stand at room temperature for 3.5 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, and dried over anhydrous Na_2SO_4. After work-up, the crystalline product was purified by preparative tlc to give 44 mg (100%) of dehydroisoandrosterone (IV), mp 141–142° (from acetone–hexane).

(4) Melting points are uncorrected. Ir spectra were measured on a Beckman IR-9 infrared spectrophotometer. Nmr spectra were obtained on a Varian EM-360 nmr spectrometer. Radioactive counting was done on a Nuclear-Chicago Unilux liquid scintillation counter.

Conversion of Androst-5-ene-3β,17β-diol to Dehydroisoandrosterone on a Microgram Scale.—To 612 μg of [4-^{14}C] androst-5-ene-3β,17β-diol (47,000 cpm) was added 0.10 ml of dimethyl-*tert*-butylsilyl chloride solution which was prepared from 60 mg of dimethyl-*tert*-butylsilyl chloride and 70 mg of imidazole in 1.5 ml of DMF under cooling. The mixture was stored at 0° with occasional shaking. After 1 hr the reaction mixture was diluted with ether, washed with H_2O, and dried over anhydrous Na_2SO_4. The 3-monosilyl ether purified by preparative tlc was oxidized with 0.2 ml of CrO_3–pyridine complex in 0.2 ml of pyridine at room temperature for 16 hr. Following usual work-up the oxidation product was treated without purification with 0.5 ml of a AcOH–H_2O–THF (3:1:1.5) solution at 55° for 3.5 hr. Ethanol was added and the solvent was evaporated under reduced pressure. The residue was submitted to tlc. The thin layer plate was scanned for radioactivity and the dehydroisoandrosterone area eluted was diluted with 20.2 mg of cold material and recrystallized to a constant specific activity of 335 cpm/μ*M* from acetone–hexane. Total counts were 23,800 cpm. This material was acetylated with Ac_2O and pyridine and the dehydroisoandrosterone acetate obtained was recrystallized to a constant specific activity of 334 cpm/μ*M* from aqueous acetone.

Acknowledgment.—This work was supported by Grant CA 07304 from the National Cancer Institute of Health.

Registry No.—I, 521-17-5; IIa, 42151-21-3; IIb, 42151-22-4; III, 42151-23-5; IV, 53-43-0; acetic acid, 64-19-7; tetra-*n*-butylammonium fluoride, 429-41-4; dimethyl-*tert*-butylsilyl chloride, 18162-48-6.

Heterocyclic Derivatives of Cholestane

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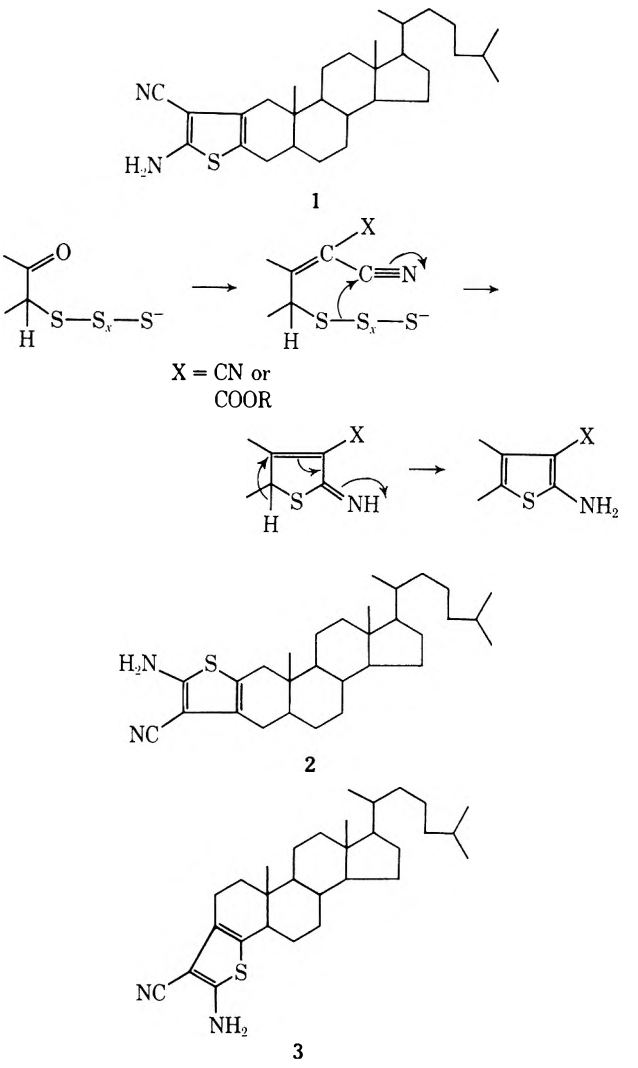
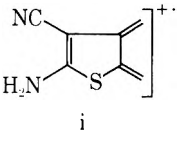
The reaction of cholestanone was reported[1] to give the 2′-aminocholest-2-eno[3,2-*b*]thiophene-4′-carbonitrile (**1**) under Gewalds'[2] conditions using sulfur and malononitrile. However, considering the proposed mechanism[2] (Scheme I) of the reaction, the assigned structure (**1**) seemed improbable. Since the initial step of the reaction requires enolization of the ketone followed by reaction with sulfur at the α position, the reaction product should have structure **2** as 3-keto steroids with 5α configuration are known[3] to enolize from the C_2 position to give the Δ^2 enol. However, the formation of the 4,3-*b* isomer (**3**) as a minor product of the reaction cannot be ruled out in view of the formation[4] of both the positional isomers of the steroidal indole derivatives from cholestanone by the Fischer indole synthesis. An unambiguous synthesis of **2** was achieved from cholestan-3-one-2α-thiol[5] following a known procedure.[6] The thiophene derivative (**2**) thus prepared was identical with the material prepared in our laboratory from cholestanone with sulfur and malononitrile.

Identical mass spectra of the samples of **2** from both

SCHEME I



the procedures indicate that the compound **2** obtained from cholestanone is free from the angular isomer **3**. The mass spectra of the compound **2** shows the peak for the molecular ion (*m/e* 466) besides a peak (*m/e* 150) for the retro-Diels–Alder fragment (i), which is the base



i

peak, with the metastable ion at *m/e* 48.5 (calcd, 48.3). Such a fragmentation is a characteristic mass spectral feature[7] of the steroidal heterocycles in which the heterocyclic ring is fused at the C_2 and C_3 positions of a Δ^2 steroid.

The melting point of the product **2**, prepared by both the procedures, is much higher than that reported[1,8] for the product obtained from cholestanone under Gewald's condition.

Since the preparation of pure alkanone-2-thiols, which are required for the regiospecific synthesis of the cycloalkenothiophene derivatives of type **2**, from the

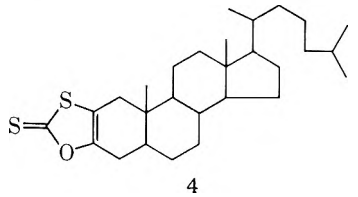
(1) M. S. Manhas, V. V. Rao, P. A. Seetharaman, D. Succardi, and J. Pazdera, *J. Chem. Soc. C*, 1937 (1969).
(2) K. Gewald, E. Schinke, and H. Bottcher, *Ber.*, **99**, 94 (1966).
(3) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, p 161.
(4) D. J. Harvey and S. T. Reid, *Tetrahedron*, **28**, 2489 (1972).
(5) D. A. Lightner and C. Djerassi, *Steroids*, **2**, 583 (1963).
(6) K. Gewald, *Ber.* **98**, 3571 (1965).
(7) H. E. Audier J. Bottin, M. Fetizon, and J. C. Gramain, *Bull. Soc. Chim. Fr.*, 4027 (1971); P. Jacquignon, M. Croisy-Delcey, and A. Croisy, *ibid.*, 4251 (1972); D. J. Harvey, W. A. Laurie, and R. I. Reed, *Org. Mass Spectrom.*, **5**, 1183 (1971).
(8) Professor Manhas has kindly informed the author that the actual melting point of **2** is 285° and that the reported melting point, 235°, is a typographical error.

α-xanthatoalkanones[5,9] free from disulfides is rather difficult, we looked for a simpler method for the regioselective preparation of compound 2. Alkyl xanthates are known to yield the alkylthiols upon reaction with amines.[10] This cleavage may proceed by direct attack of the amine on the xanthate or on the dithiocarbonate produced by thermal rearrangement of the xanthate.[11] Thus, when cholestan-3-one 2α-xanthate[12] was allowed to react with malononitrile in the presence of morpholine in boiling ethanol, compound **2** was produced. The reaction proceeds through the cholestan-3-one-2α-thiol produced by the direct cleavage of the cholestan-3-one 2α-xanthate since cholestan-3-one-2α-thiol is produced when the xanthate is refluxed in ethanol in the presence of morpholine. The xanthate remains unchanged in boiling ethanol in the absence of the amine or when heated neat at 150°.

During the preparation of the cholestan-3-one-2α-thiol by the known[5] procedure of acid-catalyzed decomposition of the cholestan-3-one 2α-xanthate it was observed that the nature of the solvent employed has a profound effect on the nature of the product formed. While in ether solution the thiol is formed, in benzene solution a new compound is produced in good yield as the only product. The product, $C_{28}H_{44}OS_2$, did not show any absorption above 1700 cm^{-1} in the ir spectrum attributable to a saturated ketone. The nmr spectrum did not have any signal for the vinylic proton. The mass spectrum showed a peak for the molecular ion (*m/e* 460) and a peak (*m/e* 316) due to the loss of fragment ii or iii. On the basis of these data, structure **4** or **5** could be envisaged for the product.

ii

iii



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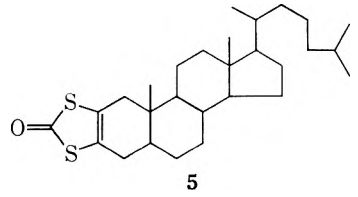
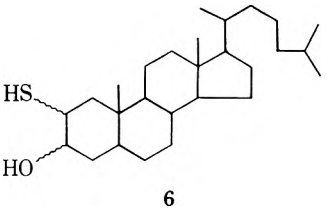


5

The ir spectrum of the compound did not have a strong band[13] for the C=O group of the S–CO–S moiety at 850–827 cm^{-1} and bands above 1650 cm^{-1} attributable to a cyclic dithiocarbonate present in structure **5**.[14] The presence of bands at 1635 and 890 cm^{-1}, on the other hand, suggested[15] that the compound should be represented by structure **4**. This was verified by chemical means. The compound showed positive reaction with iodine–sodium azide solution for the C=S group.[16] Reduction of the product with lithium aluminum hydride gave a small amount of a compound which was identified as the 3-hydroxycholestane-2-thiol (**6**).



6

The ir spectrum showed a band at 3400 cm^{-1} for the OH group. The mass spectrum had peaks at *m/e* 420 (M^+), 402 ($M^+ - H_2O$), and 386 ($M^+ - H_2S$).

Experimental Section[17]

2′-Aminocholest-2-eno[2,3-*b*]thiophene-4′-carbonitrile (**2**). **A.**—A thoroughly stirred mixture of cholestan-3-one (3.86 g), malonitrile (0.66 g), sulfur (0.32 g), and morpholine (2 ml) in dry ethanol was heated at 48° for 5 hr. The reaction mixture was cooled and the precipatate was filtered and washed with ethanol. The colorless solid, mp 270–278° dec, crystallized from THF–methanol as colorless needles: 2.5 g (54%); mp 279–281° dec (lit.[1,8] mp 235°); ir (KBr) 3480, 3220, 2200, 1645, 1600, 1530 cm^{-1}; uv max ($CHCl_3$) 242 nm (ε 5499), 290 (5326); mass spectrum *m/e* 466 (M^+), 353 ($M^+ - C_8H_{17}$), 150.

Anal. Calcd for $C_{30}H_{46}N_2S$: C, 77.19; H, 9.93; N, 6.0; S, 6.87. Found: C, 77.22; H, 9.93; H, 5.91; S, 6.69.

B.—Cholestan-3-one-2α-thiol (0.5 g) in ether (20 ml) solution was treated with dry ethanol (10 ml), morpholine (5 drops), and malonitrile (0.15 g) and the mixture was heated on the steam bath for 0.5 hr. The solid was filtered and washed successively with ether and ethanol, when a yellowish solid, mp 267–278° dec, was obtained which on recrystallization from THF–methanol gave colorless needles (0.23 g), mp 283–284° dec. This material was identical with the material prepared in A by mixture melting point and ir comparison.

C.—A mixture of cholestan-3-one 2α-ethyl xanthate (0.5 g), ethanol (25 ml), malononitrile (0.2 g), and morpholine (4 drops) was heated on a steam bath for 3 hr. The precipitate was filtered and washed with ethanol. The solid (0.3 g), mp 270–275° dec, was crystallized from THF–methanol and $CHCl_3$–methanol, when pale yellow needles (170 mg), mp 283–285° dec, found identical with the material prepared in B by mixture melting point and ir comparison, were obtained.

2′-Thiocholest-2-eno[2,3-*d*][1,3]oxathiolane (**4**).—To a solution of cholestan-3-one 2α-ethyl xanthate (3.5 g) in benzene (70 ml) cooled in an ice bath, HCl gas was bubbled in. The solution started to solidify in a few minutes, when the ice bath was removed and HCl was bubbled in for a further 40 min. The flask was tightly stoppered and left at room temperature for 48 hr. The benzene was removed on a steam bath by blowing in nitrogen. The residue was dissolved in benzene and the solution was filtered through silica (25 g) and eluted with benzene (300 ml), when a solid (3.2 g) was obtained which on crystallization from ether (charcoal) gave colorless needles (1.8 g), mp 135–136°. The residue from the mother liquor was chromatographed on silica (60 g) and eluted with benzene–petroleum ether (bp 30–60°) (1:1), when a solid was obtained which on crystallization from ether afforded colorless needles (0.7 g), mp 135–136°, identi-

(9) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 1, Chemical Publishing Co., New York, N. Y., 1958, p 29.

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(17) Melting points were determined on a Mel-Temp apparatus and are uncorrected. Unless otherwise stated, ir and uv spectra were determined for chloroform and methanol solutions, respectively. Nmr spectra were determined for deuteriochloroform solutions with tetramethylsilane as internal reference and mass spectra were determined on a MS30 instrument at 70 eV. Silica for chromatography refers to Mallincrodt SilicAR CC-7.

cal with previous crop (mixture melting point, ir, tlc): ir 1635, 1500, 860, 890 cm^{-1}; uv 275 nm (ϵ 2930), 238 (2300); nmr no signal above δ 2.4 ppm; mass spectrum m/e 460 (M^+), 445 ($M^+ - CH_3$), 432 ($M^+ - CO$), 400 ($M^+ - COS$), 316 ($M^+ - 144$).

Anal. Calcd for $C_{28}H_{44}OS_2$: C, 72.98; H, 9.63; S, 13.92. Found: C, 72.61; H, 9.48; S, 13.64.

Lithium Aluminum Hydride Reduction of 3.—A solution of **3** (0.5 g) in ether (50 ml) was added to a suspension of lithium aluminum hydride (2 g) in ether (100 ml); the mixture was refluxed for 32 hr, cooled, and decomposed with a saturated solution of Na_2SO_4 and then treated with dilute hydrochloric acid (10%) till acidic. The ether layer was separated and the aqueous portion was extracted with ether (140 ml). The combined ether solution was washed with water, dried (Na_2SO_4), and evaporated, when a colored oil (0.31 g) was obtained which was found to be a complex mixture of products by tlc. This was chromatographed on silica (25 g). Elution with benzene–petroleum ether (2:1) gave a highly colored oil (a complex mixture by tlc) (0.15 g) which could not be purified and identified. Elution of the column with benzene gave a solid (60 mg), which on several crystallizations from ether–methanol gave a colorless solid: mp 173–177° (sintering at 171°); ir 3400, 800 cm^{-1}; nmr δ 3.3–4.1 ppm (broad, 2 H); mass spectrum m/e 420 (M^+), 405 ($M^+ - CH_3$), 402 ($M^+ - H_2O$), 387 ($M^+ - SH$), 386 ($M^+ - H_2S$).

Anal. Calcd for $C_{27}H_{48}OS$: C, 77.06; H, 11.60. Found: C, 77.20; H, 11.48.

Cholestan-3-one-2α-thiol.—A solution of cholestan-3-one 2α-ethyl xanthate (0.5 g) in dry ethanol (30 ml) containing morpholine (5 drops) was refluxed in a nitrogen atmosphere for 5 hr. The solvent was removed and the residue was chromatographed on silica (25 g) using benzene–petroleum ether (1:1) as eluent, when a solid (0.22 g) was obtained which upon crystallization from ether–methanol in a nitrogen atmosphere gave colorless needles (0.172 g), mp 154–158°. This was found to be the cholestan-3-one-2α-thiol by comparison of ir, nmr, and uv spectra with those of an authentic sample prepared by the known[5] procedure. However, when the reaction was carried out in the presence of air, the only identifiable product was the bischolestan-3-one 2,2′-disulfide[5] (identity established by mixture melting point, ir, and tlc comparison with an authentic sample).

Attempted Rearrangement of Cholestan-3-one 2α-Ethyl Xanthate. A.—The xanthate (50 mg) was heated at 150° for 0.5 hr The residue was found to be identical with starting material by tlc (single spot with R_f identical with that of the starting material) and ir comparison.

B.—A solution of the xanthate (0.2 g) in dry ethanol (25 ml) was refluxed for 6 hr. The solution was filtered from a small amount of insoluble residue and then concentrated. The oily residue was chromatographed on silica. Elution of the column with benzene–petroleum ether (1:2) gave an oil which on crystallization from methanol gave a solid (115 mg), mp 115–116°, identical with the starting material by mixture melting point and ir comparison.

Acknowledgment.—The author wishes to thank Dr. J. W. Ahlberg and his associates for analytical and spectral data and Dr. J. Hribar for mass spectral data and assistance in the interpretations.

Registry No.—**2**, 42086-95-3; **4**, 42086-96-4; cholestan-3-one, 15600-08-5; cholestan-3-one-2α-thiol, 42086-97-5; cholestan-3-one 2α-ethyl xanthate, 42086-98-6; malononitrile, 109-77-3.

Cyclopropylamine Rearrangement[1]

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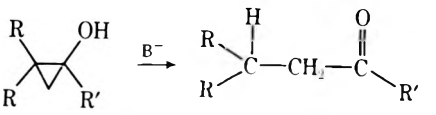
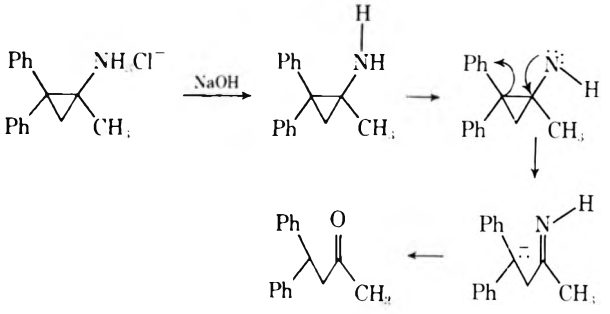
The cyclopropanol rearrangement was originally observed by Magrane and Cottle[2] and extensively explored by DePuy and coworkers.[3] The rearrangement involves the reaction of cyclopropanols with base to yield the corresponding aldehydes or ketones.



In a recent paper Kuehne and King[4] noted that cyclopropylamines were remarkably stable toward both acidic and basic conditions. The amines studied were all tertiary amines and therefore lacking amino hydrogens. We wish to report an example in which a facile rearrangement, comparable with the cyclopropanol rearrangement, occurs when a primary cyclopropylamine reacts with base. A similar rearrangement has been postulated for the hydride reduction of *N*-cyclopropylimines[5] and *N*-cyclopropylformamide[6] derivatives. However, it is not clear from these latter experiments whether the rearrangement occurs during hydride reduction as postulated by these workers or during the subsequent base work-up of the reduction product.

1-Methyl-2,2-diphenylcyclopropylamine was prepared by refluxing 1-methyl-2,2-diphenylcyclopropyl isocyanate[7] with hydrochloric acid. The amine is isolated as its stable hydrochloride salt. Treatment of the amine salt with aqueous or methanolic sodium hydroxide results not in the formation of the free cyclopropylamine but rather one obtains 4,4-diphenyl-2-butanone as the sole product. The propensity for this rearrangement is remarkable since one can achieve this reaction by treatment of the amine salt with aqueous sodium bicarbonate.



The scope, limitations, and stereochemistry of the cyclopropylamine rearrangement are currently under investigation.

Experimental Section

1-Methyl-2,2-diphenylcyclopropylamine Hydrochloride.—A solution of 7.2 g (0.29 mol) of 1-methyl-2,2-diphenylcyclopropyl isocyanate,[7] 45 ml of concentrated hydrochloric acid, and 90 ml of water was refluxed overnight. On cooling the amine hydrochloride precipitated out of solution and was removed by filtration,

(1) The support of this work by a Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.

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(3) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Amer. Chem. Soc.*, **88**, 3347 (1966), and earlier references cited therein. See also A. Nickon, J. L. Lambert, S. J., R. O. Williams, and N. H. Werstuik, *ibid.*, **88**, 3354 (1966).

(4) M. E. Kuehne and J. C. King, *J. Org. Chem.*, **38**, 304 (1973).

(5) C. L. Bumgardner, E. L. Lawton, and J. G. Carver, *J. Org. Chem.*, **37**, 407 (1972).

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(7) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).

washed with acetone, and recrystallized from ethanol to yield 7.5 g (0.29 mol): mp 112–120° dec after drying under vacuum at 80°; nmr (TFA) δ 1.64 (s, 3), 2.12 (d, 2, J = 3.5 Hz), 6.96 (s, br, 3), 7.27 (m, 10).

Anal. Calcd for $C_{16}H_{18}NCl$: C, 73.82; H, 6.93; N, 5.41. Found: C, 73.62; H, 6.98; N, 5.26.

4,4-Diphenyl-2-butanone.—To a solution of 231 mg (0.84 mmol) of 1-methyl-2,2-diphenylcyclopropyl amine hydrochloride dissolved in 150 ml of water was added 100 ml of saturated sodium bicarbonate and the reaction mixture was allowed to stir for 24 hr at ambient temperatures. The mixture was extracted with ether and the ether extracted was washed with 5% hydrochloric acid [36 mg (0.13 mmol, 16%) of starting material was recovered]. The residue from the ether extract gave ir ($CHCl_3$) 1715 cm^{-1}; nmr ($CDCl_3$) δ 2.02 (s, 3, CH_3), 3.15 (d, 2, J = 7.5 Hz), 4.60 (t, 1, J = 7.0 Hz), 7.23 (s, 10). The residue was treated with 2,4-dinitrophenylhydrazine and 256 mg (0.64 mmol, 76%) of the hydrazone was isolated, mp 172–175° (lit.[8] mp 173–175°).

Using aqueous sodium hydroxide as the base instead of sodium bicarbonate yielded 63% of ketone and alcoholic sodium hydroxide gave a 69% yield.

Registry No.—1-Methyl-2,2-diphenylcyclopropylamine hydrochloride, 42253-75-8; 1-methyl-2,2-diphenylcyclopropyl isocyanate, 42253-76-9; 4,4-diphenyl-2-butanone, 5409-60-9.

(8) H. O. House, D. D. Traficanti, and R. A. Evans, *J. Org. Chem.*, **28**, 348 (1963).

Conformational Analysis of Hydroxyl by the Nuclear Magnetic Resonance Chemical Shift Method. Equivalence of Cyclohexanol and 4,4-Dimethylcyclohexanol as Mobile Systems

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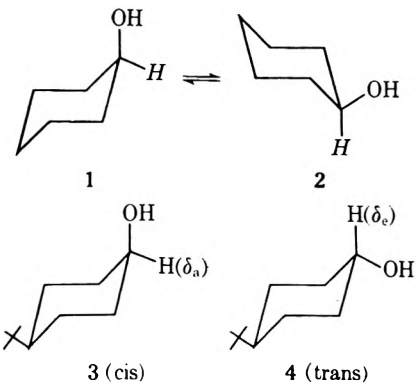
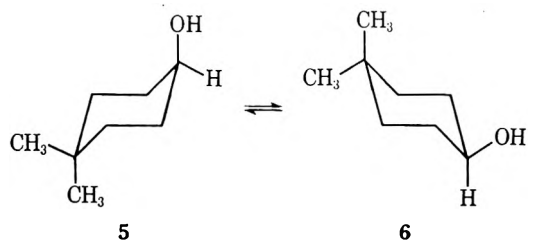
With a view to determining the change of conformational energy with solvent, we had in an earlier study[2] subjected the hydroxyl group to nmr chemical shift analysis[3,4] in a variety of solvents using 2,2,6,6-tetradeuterated cyclohexanol (1 ⇌ 2) as substrate and similarly deuterated *cis*- (3) and *trans*-4-*tert*-butylcyclohexanol (4) as conformationally rigid models.

The lack of correlation of free energy with solvent that was found at the time was attributed to possible ring distortion and anisotropy effects introduced by the *tert*-butyl holding group in the model systems.[5] It has recently been suggested, however, that substitution of 4,4-dimethylcyclohexyl systems in place of cyclohexyl would largely compensate for any disturbing factors imposed by the *tert*-butyl holding group and thus allow



for accurate free-energy determinations by nmr.[6] From this viewpoint, it seemed worthwhile to repeat our earlier work using tetradeuterated 4,4-dimethylcyclohexanol (5 ⇌ 6) as a hopefully more appropriate mobile system.



Use of the low-temperature nmr method is not practical for a solvent study of this type owing to potential solubility problems, complications from solute–solute association through hydrogen bonding (which would be very serious under these conditions especially in nonpolar solvents), and a lack of choice of a suitable solvent series due to freezing point problems.[7]

The results obtained in the course of this work are presented in Table I along with those of earlier work with deuterated cyclohexanols.[2] Some of the cyclohexanol data are revised values,[8] and, while the shifts in benzene, cyclohexane, and chloroform-*d* are in excellent

TABLE I

FREE ENERGY VALUES FOR THE HYDROXYL GROUP BY THE CHEMICAL SHIFT METHOD OF ELIEL

Solvent	Free energy values at 30°[a] Cyclohexyl	4,4-DMC[b]
Cyclohexane	0.61 ± 0.03[c]	0.60 ± 0.03
Acetone-d_6	0.76 ± 0.06[d]	0.72 ± 0.04
Chloroform-*d*	0.82 ± 0.05	0.88 ± 0.04
Benzene	0.89 ± 0.05[d]	0.85 ± 0.06
tert-Butyl alcohol	0.91 ± 0.07[e]	0.97 ± 0.06

[a] Total concentrations in all cases were 0.03 M or less in order to minimize complications from solute–solute hydrogen bonding. Error limits are standard deviations from the mean. [b] 4,4-Dimethylcyclohexyl. [c] Compared with value of 0.60 ± 0.02 obtained from Raney nickel equilibration of 4-*tert*-butyl cyclohexanones, ref 2b. [d] Revised value. [e] Compared with value of 0.95 ± 0.04 obtained from Raney nickel equilibration of 4-*tert*-butylcyclohexanones, ref 2b.

(1) Author to whom inquiries should be directed: John Stuart Research Laboratories, The Quaker Oats Company.

(2) (a) E. L. Eliel, D. C. Neilson, and E. C. Gilbert, *Chem. Commun.*, 360 (1968); (b) E. L. Eliel and E. C. Gilbert, *J. Amer. Chem. Soc.*, **91**, 5487 (1969).

(3) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 152–156; (b) E. L. Eliel, *Angew Chem.*, **77**, 784 (1965); *Angew. Chem., Int. Ed. Engl.*, **4**, 761 (1965).

(4) E. L. Eliel, *Chem. Ind. (London)*, 568 (1959).

(5) F. R. Jensen and B. H. Beck, *J. Amer. Chem. Soc.*, **90**, 3251 (1968); F. R. Jensen, C. H. Bushweller, and B. H. Beck, *ibid.*, **91**, 344 (1969); (b) F. R. Jensen and H. C. Bushweller, *Advan. Alicyclic Chem.*, **3**, 139 (1971).

(6) G. E. Hawkes and J. H. P. Utley, *Chem. Commun.*, 1033 (1969).

(7) C. H. Bushweller, J. A. Beach, J. W. O'Neil, and G. U. Rao, *J. Org. Chem.*, **35**, 2086 (1970).

(8) The present data were obtained by single scans on a Varian XL-100 instrument. The earlier results[2b] were derived from data obtained on a Varian A-60A instrument by repeated scanning and computer averaging with a CAT. Such scanning of dilute solutions may be affected by drift and by false triggering caused by impurity peaks.

agreement with the results previously obtained, the same is not true for acetone-d_6 and *tert*-butyl alcohol; for these solvents the new results are in much better agreement with those obtained by equilibration studies[2b,9] or expected on *a priori* considerations.

From the data in Table I, it is seen that both systems yield the same results within the experimental error of the method; substitution of 4,4-dimethylcyclohexanol for cyclohexanol has very little effect on $\Delta G°_{OH}$ obtained by the chemical shift method of Eliel. These data, moreover, point out again the difficulty involved when one makes a solvent study of a potentially interacting X group using the *tert*-butyl systems as standards. While the results in cyclohexane, acetone-d_6, and *tert*-butyl alcohol are in accord with the expected values (based on other techniques for measuring conformational equilibria using the *tert*-butyl substituted models), the free energies obtained in chloroform-*d* and especially benzene are not.[2,9,10] It is generally accepted that chloroform is a significantly weaker hydrogen donor and benzene a much weaker hydrogen acceptor than the data indicate.

An inequality in shielding of the axial and equatorial carbinyl protons in the mobile cyclohexanols compared with the *tert*-butyl analogs probably accounts for the anomalously high apparent free-energy values observed in these solvents. The 4-*tert*-butyl compounds fail as even approximate models when differential solvent–solute interactions of this type come into play. This inequality may be ascribed to differential dipole[11] and/or buttressing effects[12] in the *tert*-butyl models (as compared with the mobile systems), both of which could affect the relative shielding of the carbinyl protons and hence the free energy.

Based on the data obtained from this work, we conclude that the 4,4-dimethylcyclohexyl system is generally not a better model than cyclohexyl for use in the Eliel nmr equation, but is in fact essentially equal to it. This conclusion agrees with that earlier reached by Reisse[7,8] with respect to halocyclohexanes. We further conclude, as have others before us,[6,13,14] that the chemical-shift method of Eliel generally yields reasonable *approximate* values of $\Delta G°$ in inert solvents, and may still be useful as a semiquantitative tool for conformational studies when the low-temperature method is inapplicable because of potential complications (strong solute–solute interactions, solubility problems, freezing of solvent, etc.).

(9) See E. L. Eliel and S. H. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965), for a comprehensive study of the dependence of the free energy of the hydroxyl group on solvent.

(10) As one proceeds from inert to polar solvents, $-\Delta G°_{OH}$ (ax $\rightleftharpoons$ eq) becomes larger, because the polar solvent associates more strongly with the equatorial than with the axial group, thus stabilizing the former.

(11) H. R. Nace and R. H. Nealey, *J. Amer. Chem. Soc.*, **88**, 65 (1966).

(12) R. Cornubert, *Bull Soc. Chim. Fr.*, 996 (1956).

(13) J. Reisse, *Conform. Anal, Pap. Int. Symp.* **1969**, 219 (1971).

(14) G. Ransbotyn, R. Ottinger, J. Reisse, and G. Chiurdoglu, *Tetrahedron Lett.*, 2535 (1968).

Experimental Section

Cyclohexanol-*2,2,6,6-d*$_4$ as well as *cis*- and *trans*-**4-*tert*-butylcyclohexanol-*2,2,6,6-d*$_4$** were all available from our previous study.[2b]

4,4-Dimethylcyclohex-2-enone was prepared *via* the method of Bordwell and Wellman.[15]

4,4-Dimethylcyclohexanone was prepared by hydrogenation of 4,4-dimethylcyclohex-2-enone over 10% palladium in acetic acid.[15]

4,4-Dimethylcyclohexanone-*2,2,6,6-d*$_4$ was synthesized by deuteration of 4 4-dimethylcyclohexanone using the method of Streitwieser, *et al.*[16]

The procedure is entirely analogous to that used for preparation of the deuterated ketone intermediate leading to cyclohexanol-*2,2,6,6-d*$_4$.[2b] Nmr showed the ketone (mp 38–40°, >99% pure by glpc analysis) to be over 95% deuterated in the α positions.

4,4-Dimethylcyclohexanol-*2,2,6,6-d*$_4$ was obtained by mixed hydride ($LiAlH_4$–$AlCl_3$) reduction of 4,4-dimethylcyclohexanone-*2,2,6,6-d*$_4$.[2b,17] From 8 g (0.062 mol) of the ketone was obtained 7 g (0.053 mol) of product which was distilled (76–77°, 10 mm) to give 4.5 g of pure alcohol (99.9% by glpc analysis). Integration of the nmr spectrum showed the material to be >96% deuterated in the α positions.

Nmr Determination of Equilibrium Constants.—The instrument used was a Varian XL-100 spectrometer. The probe temperature was 30° in all cases. In order to avoid having to measure absolute shifts, a modification of the Eliel equation was used for analysis (eq 1).

$$K_{eq} = \frac{(\delta_a - \delta)/(\delta_a - \delta_e)}{1 - [(\delta_a - \delta)/(\delta_a - \delta_e)]} \quad (1)$$

Two alcohol mixtures were prepared for each solvent studied, one containing deuterated 4,4-dimethylcyclohexanol and deuterated *cis*-4-*tert*-butylcyclohexanol which yielded $\delta_a - \delta$, the other containing both deuterated *cis*- and *trans*-4-*tert*-butylcyclohexanol which yielded $\delta_a - \delta_e$. In order to minimize solute–solute hydrogen bonding, each alcohol of the pair was present in a concentration of 0.015 *M* or less. Shift differences were measured between the centers of the carbinyl hydrogen peaks. Analyses using deuterated cyclohexanol were carried out in analogous fashion.

Acknowledgment.—The authors gratefully acknowledge the help and encouragement of Professor E. L. Eliel of the University of North Carolina at Chapel Hill.

Registry No.—Cyclohexanol, 108-93-0; 4,4-dimethylcyclohexanol, 932-01-4.

(15) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 1347 (1963).

(16) A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(17) E. L. Eliel, F. J. L. Martin, and D. Nasipuri, *Org. Syn.*, **47**, 16 (1967).

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972)

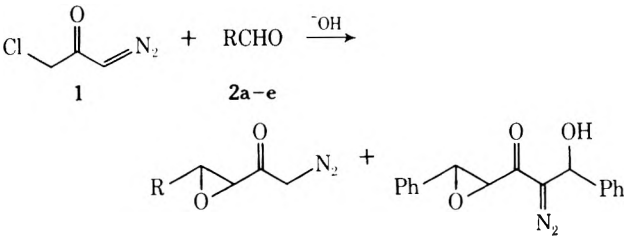
Darzens Condensation of 1-Chloro-3-diazopropanone

Summary: 1-Chloro-3-diazopropanone underwent Darzens condensation with various aldehydes leading to the synthesis of epoxy diazo ketones.

Sir: The ability of diazomethyl ketones to undergo various base-catalyzed condensation reactions similar to ordinary ketones is now well established. These include intramolecular aldol and Dieckman-type condensation[1] and intermolecular aldol condensation,[2,3] as well as an intramolecular alkylation reaction.[4] We now report the first example of Darzens condensation of a diazo ketone.

Treatment, in stoichiometric amounts, of a cold methanolic solution (20 ml) of 1-chloro-3-diazopropanone (**1**, 0.2 *M*) and benzaldehyde (0.2 *M*) with aqueous sodium hydroxide solution (4 ml, 1 *M*), followed by addition of water (30 ml) to the reaction mixture after 30 min, precipitated 1-diazo-3,4-epoxy-4-phenyl-2-butanone (**3a**) in 69% yield as a yellow solid (recrystallized from methanol–water): mp 95–96°; *m/e* 188 (M^+); nmr ($CDCl_3$) δ 7.33 (s, 5 H, Ph), 5.58 (s, 1 H, CHN_2), 3.91 (d, 1 H, J = 1.5 Hz, epoxymethine), 3.48 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); ir ($CHCl_3$) 4.76 (s, CHN_2), 6.13 μ (s, CO). *Anal.* Calcd for $C_{10}H_8O_2N_2$: C, 63.83; H, 4.25; N, 14.87. Found: C, 63.77; H, 4.52; N, 14.85. The diazomethyl ketone nature of the product was further verified by treating a deuteriochloroform solution of **3a** with 1 drop of deuterium oxide containing a catalytic amount of sodium carbonate upon which the azomethine peak at δ 5.58 was completely removed from the nmr spectrum.[2] The formation of a single isomer and the magnitude of the coupling constant of the epoxymethine protons of **3a** implies stereoselective control of the reaction leading to the formation of the epoxide ring with trans stereochemistry. Darzens condensation of chloroacetone with benzaldehyde is known to proceed in a similar stereoselective manner.[5]

Treatment of a cold methanolic solution (20 ml) of diazo ketone **1** (0.2 *M*) containing an excess of benzaldehyde (2 ml) with an excess of aqueous sodium hydroxide (8 ml, 1 *M*) solution for 30 min, addition of water (30 ml), extraction with methylene chloride, and chromatography of the concentrate on Florisil (60 g, activity II) afforded 44% epoxy diazo ketone **3a**



a, R = Ph
b, R = *p*-$NO_2C_6H_4$
c, R = *p*-$CH_3OC_6H_4$
d, R = *t*-PhCH=CH
e, R = 2-thienyl

(eluted with CCl_4) and 41% a diastereomeric mixture of 2-diazo-1,5-diphenyl-4,5-epoxy-1-hydroxy-3-pentanone (**4**) (eluted with 9:1 benzene–ether). These products form as a result of Darzens and aldol condensations at the methylene and diazo carbons, respectively. The diastereomeric mixture had mp 77–106°;[6] *m/e* 266 ($M^+ - 28$); nmr ($CDCl_3$) δ 7.35 (d, 10 H, 2 Ph), 6.12 (d, 1 H, CHOH), 4.25 (d, 1 H), CHOH), 4.10 (d, J = 1.5 Hz, epoxymethine, isomer A), 4.02 (d, sum of A + B = 1 H, J = 1.5 Hz, epoxymethine, isomer B), 3.70 ppm (d, 1 H, J = 1.5 Hz, epoxymethine); nmr ($CDCl_3$–D_2O) same as above except for δ 6.12 (s, 1 H, CHOD), and lacking the 4.25-ppm peak; ir ($CHCl_3$) 2.95 (w, OH), 4.77 (s, CHN_2), 6.19 μ (s, CO). *Anal.* Calcd for $C_{17}H_{14}O_3N_2$: C, 69.41; H, 4.76; N, 9.52. Found: C, 69.17; H, 4.78; N, 9.40. The diastereomeric mixture of Darzens aldol product **4** dissolved in methanol was cleaved cleanly into epoxy diazo ketone **3a** and benzaldehyde by aqueous sodium hydroxide solution confirming the structure assigned to it.[3]

Reaction of chloro diazo ketone **1** to give an epoxy diazomethyl ketone was found to be of general applicability as exemplified by reaction with representative aldehydes **2a–e** to give epoxy diazomethyl ketones **3a–e** in 46–88% yields.[7] The chemistry of epoxy diazomethyl ketones is currently under investigation.

Acknowledgment.—We thank the University of North Dakota for support of this research. One of us (M. H. K.) is indebted to Sigma Xi for a Research Award.

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(1) T. L. Burkoth, *Tetrahedron Lett.*, 5049 (1969).
(2) N. F. Woolsey and M. H. Khalil, *J. Org. Chem.*, **37**, 2405 (1972).
(3) E. Wenkert and C. A. McPherson, *J. Amer. Chem. Soc.*, **94**, 8084 (1972).
(4) N. F. Woolsey and D. D. Hammargren, *Tetrahedron Lett.*, 2087 (1970).
(5) H. Kwart and L. G. Kirk, *J. Org. Chem.*, **22**, 116 (1957).

(6) From this diastereomeric mixture, isomer A, mp 110.5–111.5°, and isomer B, mp 78.5–80°, have been isolated. Isomer A and the diastereomeric mixture both are cleaved by base to **3a** in high yield.
(7) No attempt was made to prepare and isolate the diadducts similar to **4** from aldehydes **2b–e**.

Additions and Corrections

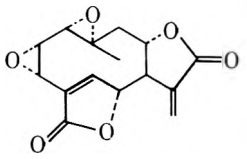
Vol. 35, 1970

F. R. Stermitz and F. A. Norris: Oxidative Acylation. A New Reaction of Primary Nitro Compounds.

Page 527. It has come to our attention that T. Urbanski and W. Guzynaska, *Roczniki Chem.*, **25**, 213 (1951), reported the isolation in 12% yield of an unknown compound by treating nitropropane with ketene and NaOAc at 100°. The unknown was thought to be either $CH_3CH(N{=}O)OAc$ or *N,O*-diacetyl-*N*-propionylhydroxylamine. We reported the latter as a new compound (structure IIa) in the above paper. It is apparent from the method of preparation that Urbanski's unknown compound was indeed *N,O*-diactyl-*N*-propionylhydroxylamine and that he had achieved the first oxidative acylation, albeit in a less practical sense (compare our 70% yield of IIa from nitropropane by warming with acetic anhydride).

W. Herz, P. S. Subramaniam, P. S. Santhanam, K. Aota, and A. L. Hall: Structure Elucidation of Sesquiterpene Lactones from *Mikania scandens* (L.) Willd.

Page 1454. Column 1, first structure. Formula 1 should be



Samuel P. McManus, John T. Carroll, and Charles U. Pittman, Jr.: Acid-Catalyzed Cyclization Reactions. IX. The Formation of Oxazolinium and Thiazolinium Cations from *N*-Allyl- and Substituted *N*-Allylamides, -urethanes, -ureas, and -thioureas.

Page 3770. The chemical shifts of the ring protons in thiazolinium ions **2p** and **2q** were incorrectly assigned. In Table II, the correct values for cation **2p** are δ 4.30 (m) and 4.70 (m, C-4 protons) and 4.70 (m, C-5 protons). For cation **2q**, the correct values are δ 4.19 (m) and 4.60 (m, C-4 protons) and 4.60 (m, C-5 protons). All peaks are broad and, in each case, one C-4 and one C-5 proton are not resolved.

Vol. 36, 1971

D. E. Dorman, M. Jautelat and J. D. Roberts*: Carbon-13 Nuclear Magnetic Resonance Spectroscopy. Quantitative Correlations of the Carbon Chemical Shifts of Acyclic Alkenes.

We are indebted to Dr. V. D. Mochel for pointing out inconsistencies in the parameters reported for the calculation of ^{13}C chemical shifts of alkenes which have turned out to be proofreading errors.

Page 2761. In Table III, footnote *b*, the value of $(\alpha + \alpha')$ should be -2.61 ± 0.12 ppm.

Page 2761. In Table IV, the correction parameter for cis in the first column should be 0.55 ± 0.02 ppm. A line was omitted from this table which follows directly after the cis parameter as follows.

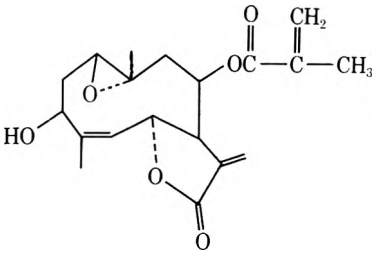
Corr β	2.82 ± 0.08	1.832 ± 0.019	2.686 ± 0.012

Page 2763. The last two sentences of the first paragraph of section B were actually inoperative for the resonances considered in Table VII.

Vol. 37, 1972

W. Herz* and S. V. Bhat: Woodhousin, a New Germacranolide from *Bahia woodhousei* (Gray) Gray.

Page 910. Column 1, formula **15**. Formula **15** should be



M. J. Tremelling and J. M. McBride*: Solvent Steric Effects. V. Azobis-2-methyl-3-phenyl-2-butane. The Absolute Configuration of Some Derivatives of 2-Methyl-3-phenylbutane.

Page 1073. Professor Luciano Lardicci (University of Pisa) has called to our attention that the original assignment of the *S* absolute configuration to (−)-2-methyl-3-phenylbutane (II) by Červinka and Hub is incorrect [*cf.* O. Červinka, V. Dudek, and L. Hub, *Z. Chem.*, 9, 267 (1969); L. Lardicci and R. Menicagli, *Chim. Ind.* (*Milan*), **51**, 1387 (1969); and D. E. Clark and H. S. Mosher, *J. Org. Chem.*, **35**, 1114 (1970)]. Since all our configurational assignments are based on correlation with II, each one should be reversed

L. A. Hulshof, Aafje Vos,* and Hans Wynberg: The Crystal and Molecular Structure and Absolute Configuration of *d*-Spiro[3.3]heptane-2,6-dicarboxylic Acid at −160°.

Page 1767. We reported that the dextrorotatory Fecht acid or *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (see Figure 1, page 1768) has the *R* configuration. The assignment was based on (a) application of Lowe's rule to the spiro[3.3]heptane system, (b) special solvent effects of *d*-Fecht acid, (c) use of Klyne's sector rule for carboxylic acids and esters, and (d) X-ray diffraction with anomalous scattering. Although the last-named method, *viz.*, the anomalous X-ray scattering studies, could in principle give definitive information, this was not the case with Fecht acid because of the very small differences in anomalous scattering between the carbon and oxygen atoms. Thus, as stated in our previous paper, only eight Bijvoet pairs (five with Cr Kα radiation and three with Cu Kα radiation) had intensity differences of sufficient magnitude to be considered and only a 75% correspondence between observed and calculated intensity order for *hkl* and $h\bar{k}l$ reflections was obtained. The X-ray work was therefore repeated using the dextrorotatory barium salt of *d*-Fecht acid with the composition $C_9H_{12}O_4 \cdot C_{18}H_{22}O_8Ba \cdot H_2O$. The anomalous scattering effect of the barium atom was, as expected, sufficiently large to allow an unambiguous assignment of the absolute configuration of Fecht acid. So, in contrast to the assignment suggested previously we now find that *d*-Fecht acid has the *S* instead of the *R* configuration (see the correct absolute configuration of *d*-Fecht acid in the Figure 1′). A full account of the work will be given (B. van Dijk, L. A. Hulshof, H. Wynberg, and J. L. de Boer, manuscript to be submitted to *J. Amer. Chem. Soc.*) and an attempt will be made to explain the failure of the methods previously used for the determination of the absolute configuration of *d*-Fecht acid. Preliminary studies suggest that the nonplanarity of the four-membered ring is a major factor causing the discrepancies between theory and experiment.

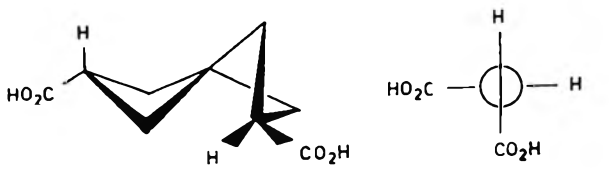


Figure 1′.—*S*-(+)-Spiro[3.3]heptane-2,6-dicarboxylic acid with the notation of R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); *Angew. Chem.*, **78**, 417 (1966).

Rae Victor, Raphael Ben-Shoshan, and Shalom Sarel*: Photoinduced Formation of Vinylcyclohexatriene–Iron Carbonyl Complexes from Substituted Vinylbenzenes. Localization of Electrons in Aromatic Substrates *via* π Coordination to Metal.

Page 1934. Footnote *b*, legend of Table III. The footnote should read "*J* taken for all compounds (Hz): $H_{2'a}H_{2'b}$ = 2.2–2.7; $H_{2'a}H_{1'}$ = 7.8–9.0; $H_{2'b}H_{1'}$ = 6.7–7.2; H_2H_3 = 5.0–5.7; H_2H_6 = 1.5–1.9; H_3H_4 = 6.0–6.3; H_3H_5 = 1.5–2.7; H_4H_5 = 4.5; H_5H_6 = 6.0–6.9."

W. Herz,* S. V. Bhat, and A. Srinivasan: Berlandin and Subacaulin, Two New Guianolides from *Berlanderia subacaulis*.

Page 2532. Abstract. The last sentence of the abstract should read "Berlandin is either **1b** or differs from acetylsubacaulin (**2b**) in configuration of the epoxide ring."

H. W. Heine,* P. G. Williard, and T. R. Hoye: The Synthesis and Reactions of Some 1-(Nitroaryl)diaziridines.

Page 2982. Column 2. In line 25, "**22**" should read 2-isopropyl-6-nitrobenzotriazole 1-oxide; in lines 34 and 35, "**23**" should read 2-cyclohexyl-6-nitrobenzotriazole 1-oxide; in line 58, "**24**" should read 1-(2,4-dinitrophenyl)-2-isopropylhydrazine; in lines 66 and 67, "**25**" should read 1-(2,4-dinitrophenyl)-2-cyclohexylhydrazine; in line 76, "**Preparation of 22 from 25**" should read **Preparation of 2-Isopropyl-6-nitrobenzotriazole 1-Oxide from 1-(2,4-Dinitrophenyl)-2-isopropylhydrazine.**"

Page 2983. Column 1. In line 1, "**Synthesis of 23 from 25**" should read "**Synthesis of 2-Cyclohexyl-6-nitrobenzotriazole 1-Oxide from 1-(2,4-Dinitrophenyl)-2-cyclohexylhydrazine.**

David J. Pokorny and William W. Paudler*: Naphthyridine Chemistry. XIV. The Meisenheimer Reaction of the 1,X-Naphthyridine 1-Oxides.

Page 3105. Column 1, lines 15 and 63. Reference to E. M. Hawes and D. G. Wibberley [*J. Chem. Soc. C*, 1564 (1967)] reporting their syntheses and pmr spectra of 2-chloro- and 2-methoxy-1,8-naphthyridines was inadvertently left out. We wish to thank Dr. Hawes for bringing this to our attention.

R. A. Abramovitch,* G. Grins, R. B. Rogers, J. L. Atwood, M. D. Williams, and S. Crider: A Novel β-Alkylation of Pyridine and Quinoline 1-Oxides.

Page 3383. Column 1. In lines 23 and 24, "$J_{5,6}$ = 3 Hz" should read $J_{5,6}$ = 6 Hz; in lines 24 and 25, "$J_{4,5}$ = 4, $J_{5,6}$ = 3 Hz" should read $J_{4,5}$ = 8.9, $J_{5,6}$ = 6 Hz.

Louis A. Carpino* and Grace Y. Han: The 9-Fluorenylmethoxycarbonyl Amino-Protecting Group.

Page 3404. We have been informed of difficulties in the synthesis of 9-fluorenylmethanol. For most of the work described we applied the reproducible, although tedious, formylation of fluorene by means of potassium ethoxide in ether (86%) followed by cross-Cannizzaro reduction of the 9-formylfluorene (65%) [W. Wislicenus and M. Waldmuller, *Ber.*, **42**, 785 (1909); W. G. Brown and B. A. Bluestein, *J. Amer. Chem. Soc.*, **65**, 1082 (1943)]. More recently we have greatly simplified the method for the synthesis of this key alcohol by substituting sodium hydride for potassium metal and dispensing with the isolation of the intermediate aldehyde. The overall yield from fluorene is about the same as in the two-step procedure. The yield may be further increased by using a larger excess of both sodium hydride and ethyl formate. On a large scale it is advantageous to recover unreacted fluorene by evaporation of the original ether extract.

9-Fluorenylmethanol.—A mixture of 8.3 g of fluorene, 8.5 ml of dry ethyl formate, 100 ml of anhydrous ether, and 6.5 g of NaH (57% dispersion in mineral oil) was refluxed with stirring for 3 hr and the resulting slurry was poured onto a mixture of ice and water such that the final aqueous volume was ~200 ml. An additional 75 ml of ether was added, the mixture was shaken in a separatory funnel, and the ether layer separated and was discarded. The aqueous layer was extracted once with 75 ml of ligroin (bp 60–70°), the ligroin was discarded, and the aqueous layer was stirred at room temperature for 1 hr after the addition of 22 ml of 35–40% aqueous formaldehyde solution. The off-white solid was filtered, washed twice with water, dried in air, and recrystallized from ligroin (bp 88–98°) to give 5.25 g (54.3%) of the alcohol as tiny papery needles: mp 100–101°; nmr ($CDCl_3$) δ 2.0 (s, 1, OH), 3.8–4.0 (m, 3, $CHCH_2$), 7.1–7.8 (m, 8, aryl). On the 0.05 *M* scale given above the yield can be raised to 60% by the use of 15 ml of ethyl formate and 10 g of sodium hydride dispersion.

R. K. Hill,* R. Soman, and S. Sawada: Asymmetric Induction in the Thermal Reactions of Allylic Alcohols with *N,N*-Dimethylacetamide Dimethyl Acetal and Triethyl Orthoacetate.

Page 3738. Column 2, line 6. The rotation of amide V is +15.7°, not −15.7°. Column 2, lines 23, 24, and 32. The configurations are *S*, not *R*. We thank Professor R. M. Magid, University of Tennessee, for calling our attention to these errors.

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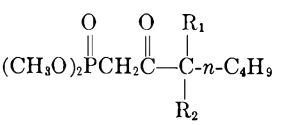
R. A. Abramovitch* and B. W. Cue, Jr.: *N*-Hydroxypyrroles and Related Compounds.

Page 173. Column 1. In the summary, in line 3, "2-cyanopyrroles" should read *N*-hydroxy-2-cyanopyrroles. In line 4, "1-hydroxy-2-pyrrolones" should read 3-substituted 2,3-dihydro-2-pyrrolones.

M. Hayashi,* H. Miyake, T. Tanouchi, S. Iguchi, Y. Iguchi, and F. Tanouchi: The Synthesis of 16(*R*)- or 16(*S*)-Methylprostaglandins.

Page 1250. Column 2. Structure **2a, 2b** should be



"**4c**" should read **4a**. For **2b–13b**, "16(*R*)-methyl series" should read 16(*S*)-methyl series.

Page 1251. Column 1, line 19. "**7a**" should read **7b**.

B. Goričnik, Z. Majerski, S. Borčić,* and D. E. Sunko: Secondary Deuterium Isotope Effects in the Solvolysis of Cyclobutyl and Cyclopropylcarbinyl Methanesulfonates.

Page 1885. Column 2, Acknowledgment. The acknowledgment is incomplete and should read as follows. This work has been supported in part by a grant from the Research Council of the Republic of Croatia and in part by PL 480 Grant administered by the National Institutes of Health, Bethesda, Md., Agreement No. 02-001-1.

DMF ACETALS

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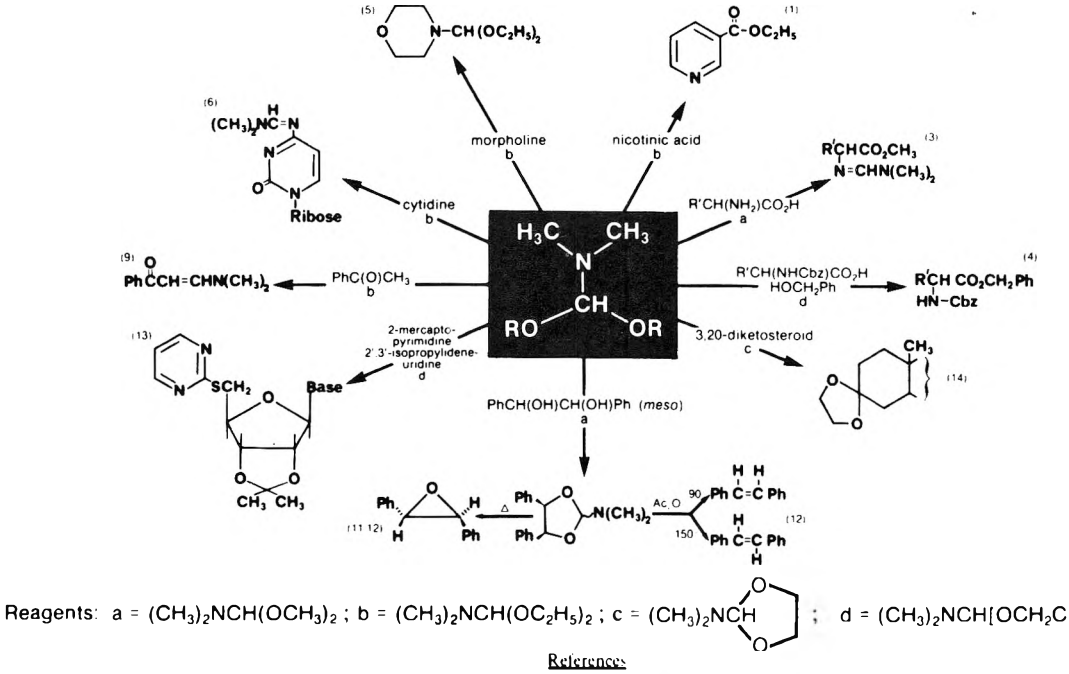
DMF acetals constitute a class of versatile synthetic and analytical reagents. With these acetals, carboxylic acids at room temperature give directly the corresponding esters;[1,2,3] amino acids form *N*-dimethylaminomethylene esters, suitable for glc analysis.[3] With **DMF dineopentyl acetal**, which is itself unreactive toward carboxylic acids but acts as a mediator, *N*-protected amino acids can be esterified with a wide variety of alcohols.[2,4] **DMF acetals** react with primary amino functions to yield *N*-dimethylaminomethylene derivatives.[5,6,7] The N^6-dimethylaminomethylene derivative of 9-β-D-arabinofuranosyladenine has anti-viral properties.[8] **DMF acetals** react with active methylene compounds such as acetophenone, ethyl cyanoacetate, 2-methylquinoline methiodide, etc.[5,9,10] Vicinal diols, *e.g.*, racemic and *meso*-diphenylethane-1,2-diol, cyclohexane-1,2-diol and 5α, 6β-dihydroxycholestane, are converted to epoxides and olefins.[11,12] The conversion of a nucleoside primary alcohol to a sulfide using **DMF dineopentyl acetal** has been reported. Raney nickel desulfurization gave the 5′-deoxy derivative.[13]

Many other reactions of **DMF acetals** are documented in our technical information bulletin which is available on request.



Reagents: a = $(CH_3)_2NCH(OCH_3)_2$; b = $(CH_3)_2NCH(OC_2H_5)_2$; c = $(CH_3)_2NCH$ (cyclic ketal) ; d = $(CH_3)_2NCH[OCH_2C(CH_3)_3]_2$

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14,278-6	*N,N*-Dimethylformamide dicyclohexyl acetal	10g $9.00; 50g $30.00
14,277-8	*N,N*-Dimethylformamide diethyl acetal	10g $11.90; 50g $49.90
17,853-5	*N,N*-Dimethylformamide diisopropyl acetal	5g $6.00; 25g $20.00
14,073-2	*N,N*-Dimethylformamide dimethyl acetal	12g † $7.50; 25g $11.15; 100g $36.60
14,024-4	*N,N*-Dimethylformamide dineopentyl acetal	10g $10.80; 50g $36.00
17,852-7	*N,N*-Dimethylformamide dipropyl acetal	5g $6.00; 25g $20.00

† Denotes tenth-molar unit

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