

TRANSANNULAR REACTIONS IN MEDIUM-SIZED RINGS

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1. Introduction

CHEMISTS have been intrigued by cyclic molecules throughout the development of the facts and theories of organic chemistry, but only in recent years have cyclic compounds containing from eight to eleven atoms in the ring been the subject of systematic research. When the obstacle of synthetic inaccessibility was removed it quickly became evident that the physical and chemical properties of medium rings (eight- to eleven-membered) do not fall between those of common rings (five- to seven-membered) and large rings (twelve-membered or larger).

The origin of the special properties of medium-ring compounds is largely steric in nature. X-Ray studies^{1,2} show that cyclic compounds with eight, nine, and ten carbon atoms have valence angles larger than tetrahedral and groups in 1,2-vicinal positions partially eclipsed. Although it is not yet possible to discuss the conformations of medium rings with the same degree of confidence permissible when dealing with the familiar chair and boat forms of cyclohexane it is encouraging to note the way in which such diverse methods as spectroscopy, dipole moment measurements, rates of isomerisation, heats of hydrogenation, and X-ray studies are contributing to this problem.^{3,4}

One feature of the geometry of medium-sized rings is the existence of steric interference between non-adjacent atoms. This energetically unfavourable property of medium-sized rings, termed *I*-strain by Brown,⁵ serves as an explanation for many of the chemical characteristics of these compounds. Substitution of a trigonal (sp^2) carbon atom for a tetrahedral (sp^3) carbon atom relieves *I*-strain by removing some non-bonded interaction and spreading one of the C-C-C bond angles. Consequently, reactions that proceed from a species consisting entirely of sp^3 carbon atoms to one in which an sp^2 carbon atom is present occur readily in medium-ring compounds. The solvolysis of cycloalkyl bromides and tosylates, the dissociation of cycloalkanone cyanhydrins, and the dissociation of aza-cycloalkane conjugate acids provide examples.⁶

Another unique feature of medium-ring geometry is the existence of

¹ J. D. Dunitz and V. Prelog, *Angew. Chem.*, 1960, **72**, 896.

² R. F. Bryan and J. D. Dunitz, *Helv. Chim. Acta*, 1960, **43**, 3.

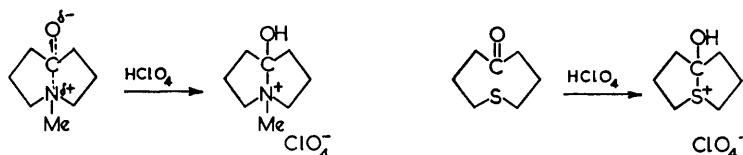
³ J. Sicher, *Progr. Stereochem.*, 1962, **3**, 202.

⁴ N. J. Leonard, *Chimia (Switz.)*, 1960, **14**, 231; see also J. B. Hendrickson, *J. Amer. Chem. Soc.*, 1964, **86**, 4854.

⁵ H. C. Brown, *J. Chem. Soc.*, 1956, 1248.

⁶ These and the corresponding reverse reactions ($sp^2 \rightarrow sp^3$) are discussed by J. Sicher, Ref. 3.

certain conformations in which opposite sides of the ring come into close proximity to each other. *X*-Ray analysis does not provide a direct proof of transannular strain since the exact positions of the hydrogen atoms cannot be determined, but calculations based on reasonable assumptions show that certain hydrogen atoms on carbon atoms in the 1,3-, 1,4-, and 1,5-positions must be very close to each other in nine- and ten-membered rings, thus indicating strong transannular interactions and strain.¹ This proximity effect is of considerable chemical significance and is responsible for the chemical behaviour described in this review. Leonard has used spectral evidence to demonstrate interactions in 1-methyl-1-azacyclo-octan-5-one⁷ and 1-thiacyclo-octan-5-one⁸ between the free electrons of the nitrogen and sulphur atoms with the carbon atom of the carbonyl group. Thus the eight-membered amino-ketone exhibits strong interaction in the ground state (by the infrared absorption of a carbon tetrachloride solution, for example) and in acid solution the electron shift indicated goes to completion forming a full bond. With the thia-ketone there is infrared evidence of both interacted and non-interacted forms, varying in



proportion with solvent. Interactions of a related kind exist between the carbonyl group and the double bond in *trans*-cyclodec-5-en-1-one, the ultraviolet spectrum of which shows differences from summation of the separate *trans*-cyclodecene and cyclodecanone curves.^{9,10} The infrared spectrum is normal, indicating that interaction is an excited-state phenomenon. These transannular interactions signify potential orbital overlap in the ground state or in the electronically excited state. By contrast, transannular reactions are chemical transformations which involve the formation of a full bond between atoms on opposite sides of the ring, or reactions which occur on an atom activated only by the proximity in space of a functional group located across the ring. Thus, the proximity effect is



found to give rise to electronic interactions and chemical reactions unique to medium-ring compounds and, as would be predicted, to facilitate

⁷ N. J. Leonard, *Rec. Chem. Progr.*, 1956, **17**, 243.

⁸ N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Amer. Chem. Soc.*, 1960, **82**, 4075.

⁹ N. J. Leonard and F. H. Owens, *J. Amer. Chem. Soc.*, 1958, **80**, 6039.

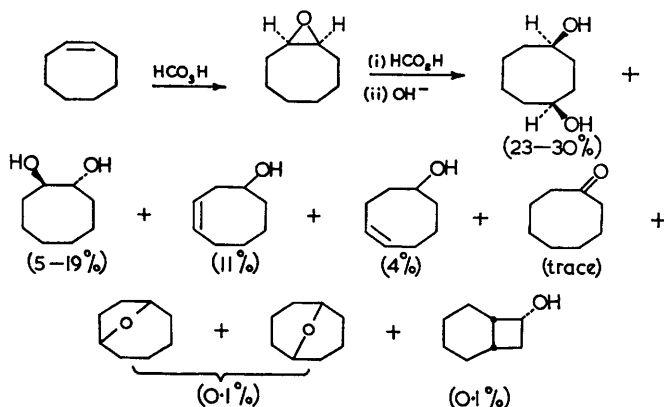
¹⁰ E. M. Kosower, W. D. Closson, H. L. Goering, and J. C. Gross, *J. Amer. Chem. Soc.*, 1961, **83**, 2013.

known ring-closure reactions. In this Review, transannular reactions have been arranged according to the electronic nature of the intermediate or transition state through which they proceed.*

2. Reactions Proceeding Through Carbonium Ions

Some of the most interesting examples of the proximity effect concern the behaviour of carbonium ions in medium-sized rings. It is not surprising that transannular reactions are most frequently observed under conditions which favour carbonium ion formation, since these are also the conditions under which rearrangements are most often encountered in other systems. Solvolytic and nucleophilic substitution reactions provide most of the examples.

(a) **Solvolytic reactions.**—The earliest systematic study of transannular reactions dealt with the formolysis of the cycloalkene oxides. Cope, Fenton, and Spencer¹¹ found that hydroxylation of *cis*-cyclo-octene with performic acid, followed by saponification of the intermediate formates, gives rise to considerable quantities of cyclo-octane-1,4-diol, subsequently identified as the *cis*-isomer,^{12,13} in addition to the expected *trans*-cyclo-



* Many examples of transannular reactions in highly unsaturated systems can be found in the chemistry of the terpenes and alkaloids. *cf.* J. F. King and P. de Mayo in "Molecular Rearrangements", vol. 2, ed. P. de Mayo, Interscience Publishers, New York, 1963, p. 771; E. W. Warnhoff, *ibid.*, p. 841. For an excellent review of terpenic compounds containing medium-sized rings, see F. Sorm, *Pure Appl. Chem.*, 1961, 2, 533. The valence tautomerism of unsaturated medium-sized rings has been reviewed recently, *cf.* E. Vogel, *Angew. Chem., Internat. Edn.*, 1963, 2, 7; R. Huisgen and co-workers, *Chem. Soc. Special Publ.* No 19, 1965, 3. This review has therefore been limited to a few of the more important classes of transannular reactions which occur in simple medium-sized ring compounds.

¹¹ A. C. Cope, S. W. Fenton, and C. F. Spencer, *J. Amer. Chem. Soc.*, 1952, 74, 5884.

¹² A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, and G. W. Wood, *J. Amer. Chem. Soc.*, 1957, 79, 3900.

¹³ A. C. Cope and B. C. Anderson, *J. Amer. Chem. Soc.*, 1957, 79, 3892.

octane-1,2-diol. The transannular elimination products, cyclo-oct-3- and -4-en-1-ol, are also formed. Minor products include cyclo-octanone, 1,4- and 1,5-epoxycyclo-octane¹⁴ and *endo-cis*-bicyclo[4,2,0]octan-7-ol.¹⁵

The protonated form of *cis*-cyclo-octene oxide (1) is most likely the first intermediate; transannular reaction to give the *cis*-1,4-glycol can then proceed by Paths A, B, or C as shown in Figure 1. Path A represents a completely concerted process in which a solvent molecule attacks at C-5 (or C-3) at the same time that a hydride ion from either C-5 or C-3 migrates across the ring and attacks the epoxide from the rear. This path, shown in more detail in Figure 2, would account for the observed *cis*-configuration of the transannular glycol. Path B represents an S_N1

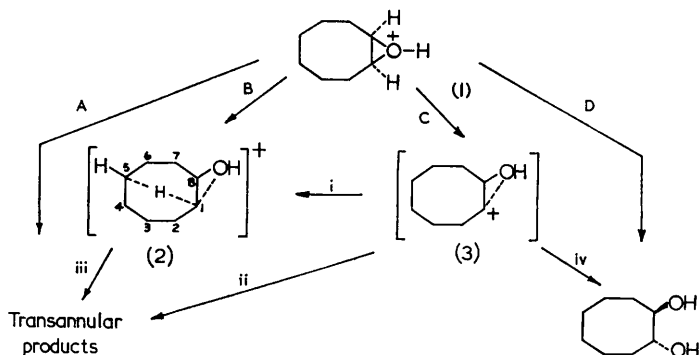


FIGURE 1

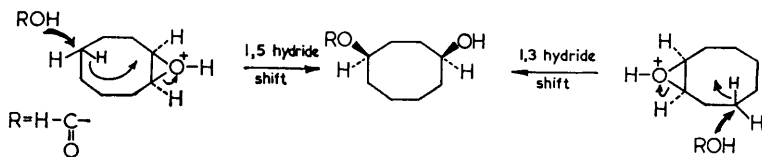


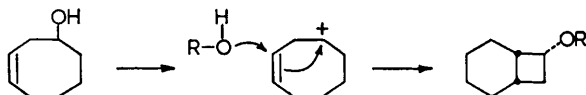
FIGURE 2

mechanism in which the slow step is the formation of the non-classical ion (2). Attack of solvent at C-1 would give the *trans*-1,2-glycol, at C-3 or C-5 the *cis*-1,4-glycol. Elimination of a proton from C-4 or C-6 would result in cyclo-oct-4- or -3-en-1-ol. Path C represents the slow formation of the classical ion (3), which must preserve some tetrahedral character by partial bonding to the adjacent hydroxyl group as shown, to account for the stereospecific formation of the *trans*-1,2- and *cis*-1,4-glycols. Formation of (3) can then be followed by fast steps (i), giving the non-classical ion (2) which can lead to transannular products, by (ii), giving the 1,4-glycol

¹⁴ A. C. Cope and A. Fournier, *J. Amer. Chem. Soc.*, 1957, **79**, 3896.

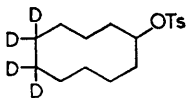
¹⁵ A. C. Cope and R. W. Gleason, *J. Amer. Chem. Soc.*, 1962, **84**, 1928.

directly, or by (iv) giving the normal product. Path D, leading to normal product, is a direct displacement on the protonated epoxide. A 1,2-hydride shift followed by loss of a proton from (3) would account for the presence of trace amounts of cyclo-octanone. The formation of *endo-cis*-bicyclo[4,2,0]octan-7-ol in the formic acid solvolysis of *cis*-cyclo-octene oxide can be explained by the sequence:



Trans-addition of formic acid ($R = \text{HCO}$) or water ($R = \text{H}$) and of the positive centre in the cyclo-oct-3-en-1-yl carbonium ion to the *cis*-double bond would give *endo-cis*-bicyclo[4,2,0]octan-7-ol as the bridged product. Since cyclo-oct-3-en-1-ol is a major product of the solvolysis reaction, it is reasonable to assume that it is an intermediate.

In an effort to determine whether a transannular hydride ion is participating in the rate-determining dissociation of a medium-ring compound, that is, whether the non-classical ion (2) or the classical ion (3) is initially produced, a study was made of the kinetics of the solvolysis of cyclodecyl tosylate, deuterated at C-5 and C-6; hydride ions are known to migrate from these positions accounting for 10% of the overall solvolysis reaction. If C-H bond breaking is involved in the rate-determining step, the reaction rate should be reduced when deuterium is substituted for hydrogen. Prelog and Borčić¹⁸ observed an isotope effect $k_{\text{H}}/k_{\text{D}} = 1.08$. However, if this effect were really due to transannular participation in the rate-determining step there should also be a significant change in the ratio of normal to



transannular products. Degradation of the *trans*-cyclodecene formed showed that the deuterated tosylate gives the same amount of transannular reaction as the undeuterated tosylate; therefore the slower rate for the deuterium compound does not arise from the difference in rate of C-H and C-D bond breaking and thus it seems unlikely that a bridged non-classical ion is formed. Prelog suggests that this isotope effect may be due to a decrease in ground state transannular strain in the deuterated tosylate because of the smaller van der Waals radius of deuterium. Accordingly the solvolysis of *cis*-cyclo-octene oxide is interpreted in terms of a mechanism (Path C, Figure 1) in which no hydride shift occurs in the slow step, although the mechanism of this reaction does not necessarily parallel the mechanism of cyclodecyl tosylate solvolysis.

¹⁸ Unpublished results of V. Prelog and S. Borčić quoted by V. Prelog and J. G. Traynham in "Molecular Rearrangements", vol. 1, ed. P. de Mayo, Interscience Publishers, New York, 1963, p. 593.

The extent to which transannular reaction occurs on solvolysis of *cis*-cyclo-octene oxide can be correlated with the acid strength of the solvent. Thus trifluoroacetic acid forms products exclusively from transannular reaction whereas the product from acetic acid containing sodium acetate contains 76% of the normal product and only 24% of transannular products (Table 1).¹⁷

TABLE 1. *Solvolysis of cis-Cyclo-octene Oxide with Various Acids*

Acid used (undiluted)	Normal reaction %	Transannular reaction %
Trifluoroacetic acid	0	100
Trichloroacetic acid	6	94
Formic acid	13	87
Acetic acid	46	54
Acetic acid containing sodium acetate	76	24
Trimethylacetic acid	no reaction	

These results can be related to medium effects in neighbouring group participation;¹⁸ as the solvent becomes relatively less nucleophilic (trifluoroacetic acid less nucleophilic than acetic acid) the contribution of the migrating transannular hydride ion becomes more important. The differences between acetic acid and formic acid suggest that the ionising power of the solvent may also be important.

Figure 2 shows that the formation of transannular products can result from a 1,3- or a 1,5-hydride shift. The problem of determining which hydrogen atom shifts as hydride ion in the reaction leading to *cis*-cyclo-octane-1,4-diol has been solved by studying the solvolysis with formic acid of *cis*-cyclo-octene oxide labelled with deuterium at C-5 and C-6.¹⁹ The *cis*-1,4-glycol formed was oxidised to adipic acid, which was esterified with diazomethane. The α -deuterium atoms in the ester were then removed by equilibration with sodium methoxide in methanol. A similar degradation was performed with a second transannular product, cyclo-oct-3-en-1-ol. The equations in Figure 3 show that only a 1,3-hydride shift results in dimethyl adipate labelled in the β -position after equilibration, so that the mole percent of monodeuterated ester after equilibration is a direct measure of the amount of 1,3-shift. The dimethyl adipate formed from the labelled *cis*-cyclo-octane-1,4-diol contained 0.39 atom of deuterium per molecule after equilibration; therefore it can be concluded that it was formed to the extent of 39% by a 1,3-hydride shift and 61% by a 1,5-hydride shift. Before equilibration the ester contained 1.65 atoms of deuterium per molecule. Since loss of deuterium during oxidation was shown to be unlikely, the analysis of the unequilibrated dimethyl adipate indicates that

¹⁷ A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 1640.

¹⁸ A. Streitwieser, *Chem. Rev.*, 1956, **56**, 571, and references given there.

¹⁹ A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Amer. Chem. Soc.*, 1960, **82**, 6366.

the two deuterated *cis*-1,4- glycols formed by 1,5- hydride shifts were present in about equal amounts.

The dimethyl adipate from the cyclo-oct-3-en-1-ol contained 1.55 atoms of deuterium per molecule before equilibration and 0.06 atom of deuterium per molecule after equilibration. Thus, cyclo-oct-3-en-1-ol is formed to the extent of 6% by a 1,3-hydride shift and 94% by a 1,5-hydride shift. Analysis of the unequilibrated dimethyl adipate indicates that the cyclo-oct-3-en-1-ol formed by 1,5-hydride shifts contains approximately equal amounts of the two monohydric alcohols shown in Figure 3. This difference in the relative amounts of 1,3- and 1,5-hydride shifts in the formation of *cis*-cyclo-octane-1,4-diol and cyclo-oct-3-en-1-ol establishes that cyclo-oct-3-en-1-ol is not formed by dehydration of the glycol, and supports the view that there are no free carbonium ions in the

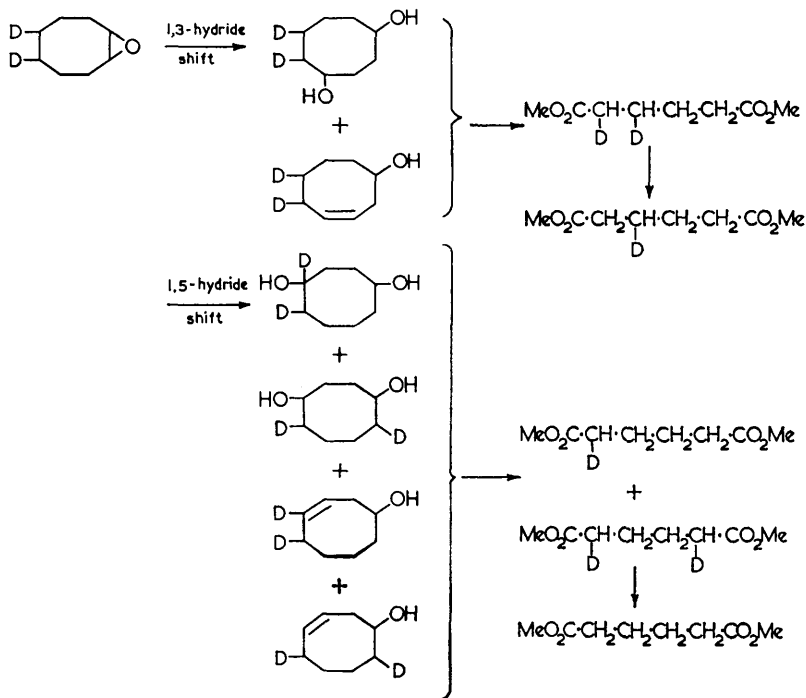
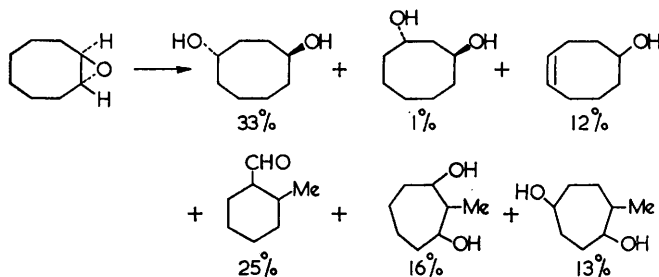


FIGURE 3

reaction. The formation of *cis*-cyclo-octane-1,4-diol to the extent of 61% by a 1,5-hydride shift and 39% by a 1,3-hydride shift is not surprising since Dreiding models indicate that either shift might occur, the 1,5-shift appearing to be somewhat more favourable. Since there appears to be no hindrance to attack by solvent at the carbon atoms from which either of the migrat-

ing hydrogen atoms originate, the amounts of hydride shifts are apparently controlled by the relative ease of hydride ion migration from each position. Cyclo-oct-3-en-1-ol formation, however, requires that the ring adopt a conformation with a planar configuration involving the two carbon atoms of the double bond being formed, the hydride ion shifting and the hydrogen ion being eliminated. Examination of Dreiding models indicates that such a conformation is much more favourable in the 1,5-hydride shift than in the 1,3-hydride shift.

The formolysis of *trans*-cyclo-octene oxide has been found to give products formed by a transannular hydride shift of the kind observed in the formolysis of the *cis*-oxide.²⁰ In addition, three compounds formed by ring contraction were isolated.²¹



The occurrence of transannular reactions in the hydroxylation of other medium-ring cycloalkenes has been observed. Neither *cis*- nor *trans*-cyclononene gave any 1,2-diol, but each gave a mixture of the stereoisomeric 1,5-diols.²² With cyclodecene, the *cis*-olefin gave exclusively one of the stereoisomers of the 1,6-diol, and the *trans*-olefin, the other.²³ *cis*- and *trans*-Cycloundecene gave diols which were different from either of the known 1,2-diols.²⁴ Only the normal 1,2-diols are formed from reaction of *cis*- and *trans*-cyclododecene with peroxyformic acid.²⁵ From the hydrolysis of *cis*-cycloheptene oxide only 2.4% of *cis*-cycloheptane-1,4-diol is obtained,²⁶ and from the reaction of cyclohexene with peroxyformic acid only a trace (0.03%) of *trans*-cyclohexane-1,4-diol.²⁷ These findings demonstrate that the proximity effect leading to 1,3-, 1,4-, 1,5-, or 1,6-hydride shifts on the opening of 1,2-epoxide rings under acid conditions is a phenomenon peculiar to medium ring systems of eight to eleven

²⁰ A. C. Cope, A. Fournier, and H. E. Simmons, *J. Amer. Chem. Soc.*, 1957, **79**, 3905.

²¹ A. C. Cope, P. Scheiner, and M. J. Youngquist, *J. Org. Chem.*, 1963, **28**, 518.

²² V. Prelog, K. Schenker, and W. Küng, *Helv. Chim. Acta*, 1953, **36**, 471.

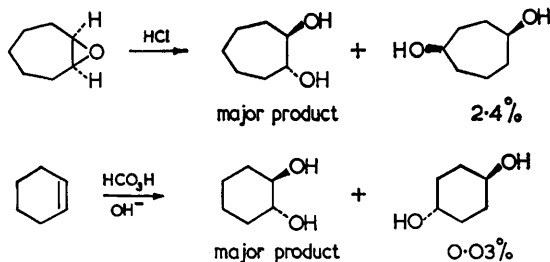
²³ V. Prelog and K. Schenker, *Helv. Chim. Acta*, 1952, **35**, 2044.

²⁴ V. Prelog and V. Boarland, *Helv. Chim. Acta*, 1955, **38**, 1776.

²⁵ V. Prelog and M. Speck, *Helv. Chim. Acta*, 1955, **38**, 1786.

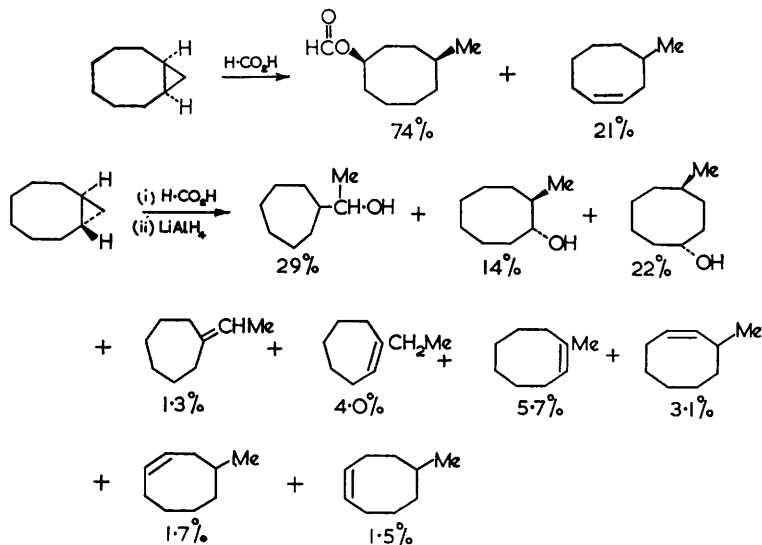
²⁶ A. C. Cope, T. A. Liss, and G. W. Wood, *J. Amer. Chem. Soc.*, 1957, **79**, 6287; *Chem. and Ind.*, 1956, 823.

²⁷ A. C. Cope, H. E. Johnson, and J. S. Stephenson, *J. Amer. Chem. Soc.*, 1956, **78**, 5599.



members and is an occurrence of very small magnitude in common and large ring systems. Evidence for the fact that these hydride shifts are intramolecular is provided by the observation that a single stereoisomer of the transannular glycol is obtained from the C_7 , C_8 , and C_{10} cyclic olefins. Any kind of intermolecular process would be expected to give a mixture of stereoisomers. The difference in stereospecificity of the transannular reaction may be accounted for by assuming that the intermediate carbonium ions have different conformational stability. Thus, formation of both stereoisomeric glycols from the nine- and eleven-membered cyclic olefins may involve carbonium ions in which conformation is neither completely retained nor inverted.

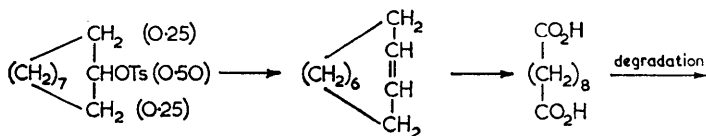
The acid-promoted opening of a cyclopropane ring fused to a medium-sized ring shows some similarities to epoxide solvolysis. Thus almost complete transannular reaction was observed in the formolysis of *cis*-bicyclo[6,1,0]nonane.²⁸ In addition to several transannular products,



²⁸ A. C. Cope and G. L. Woo, *J. Amer. Chem. Soc.*, 1963, **85**, 3601.

trans-bicyclo[6,1,0]nonane gave products of ring contraction.²⁹ The tendency toward transannular hydride shift in the bicyclo[*n*,1,0]alkanes (*n* = 4, 5, and 6) parallels that in the solvolysis of medium-ring cycloalkene oxides. Bicyclo[5,1,0]octane gives 12% 4-methylcycloheptyl acetate together with the normal products.³⁰ This amount is significantly greater than the slight amount (2.4%) observed in the opening of cycloheptene oxide. A trace of *trans*-4-methylcyclohexanol has been obtained from bicyclo[4,1,0]heptane.³¹

Amongst other reactions which may involve carbonium ions as intermediates are the solvolytic reactions of cycloalkyl tosylates. These differ notably from the epoxide reactions in that the position of the final substituent with respect to the initial one is not apparent unless a particular group in the ring is labelled. Heck and Prelog³² found that the acetolysis of cyclodecyl tosylate is first order and proceeds about 500 times faster than the acetolysis of cyclohexyl tosylate at 50° to give a mixture of *cis*- and *trans*-cyclodecene. The existence of transannular rearrangements during the reaction was demonstrated by using ¹⁴C-labelled cyclodecyl tosylate and, through an elegant degradative scheme, Prelog and Urech³³ succeeded in establishing the amount of labelled carbon at every ring position of the cyclodecene formed. The cyclodecene was converted to sebacic acid by



hydroxylation with osmium tetroxide followed by cleavage of the diol with lead tetra-acetate. The sebacic acid was then degraded stepwise to establish the positions of the radioactive carbon atoms. In the absence of hydride shifts all the labelled carbon should be found in the α - and β -positions. It is immediately obvious from the results in Table 2 that a great deal of rearrangement has occurred. What is most significant about the experimental findings is the minimum of radioactivity at the γ - and δ -positions. Comparison of the distribution data with the distributions calculated for the various types of hydride shifts reveals that 1,5- and 1,6-shifts have occurred, for only then can a minimum of ¹⁴C in the third (γ) pair of carbon atoms be achieved. No combination of reaction paths involving either no hydride shifts or 1,2-, 1,3-, and 1,4-shifts can give rise to such a minimum. In another labelling experiment cyclodecyl tosylate, deuterated at C-1, was solvolysed and the cyclodecene formed was converted into sebacic acid.³⁴ Subse-

²⁹ A. C. Cope and J. K. Hecht, *J. Amer. Chem. Soc.*, 1963, **85**, 1780.

³⁰ R. T. LaLonde and L. S. Forney, *J. Org. Chem.*, 1964, **29**, 2911.

³¹ R. T. LaLonde and L. S. Forney, *J. Amer. Chem. Soc.*, 1963, **85**, 3767.

³² R. Heck and V. Prelog, *Helv. Chim. Acta*, 1955, **38**, 1541.

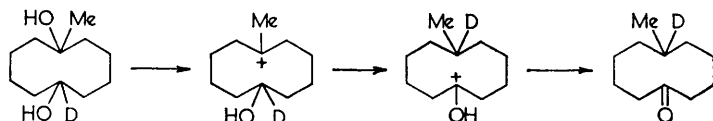
³³ H. J. Urech and V. Prelog, *Helv. Chim. Acta*, 1957, **40**, 477; V. Prelog, W. Kűng and T. Tomljenović, *Helv. Chim. Acta*, 1962, **45**, 1352.

³⁴ V. Prelog and S. Borčić, *Helv. Chim. Acta*, 1958, **41**, 199.

TABLE 2.³³ *Distribution of Radioactivity in Product of Solvolysis of ¹⁴C Labelled Cyclodecyl Tosylate. (Radioactivity of Reactants = 100).*

Pair of carbon atoms		<i>cis</i> -Cyclodecene	<i>trans</i> -Cyclodecene
COOH	COOH (α)	52	62
CH ₂	CH ₂ (β)	19	26
CH ₂	CH ₂ (γ)	0	1.5
CH ₂	CH ₂ (δ)	29	4
CH ₂ —	CH ₂ (ϵ)		6.5
Total beyond β -carbon atoms		29	12

quent degradation showed 81% of the deuterium in the α - and β -positions of the sebacic acid, no deuterium in the γ -position, and a total of 16% in the δ - and ϵ -positions. This provides further evidence that 1,5- and 1,6-hydride shifts are the predominant ones in the ten-membered ring. The occurrence of a 1,6-hydride shift to the exclusion of all others has been demonstrated in the reaction of 1-methylcyclodecane-1,6-diol, deuterated at C-6, with concentrated phosphoric acid.³⁵ 6-Methylcyclodecanone containing one deuterium atom per molecule was obtained. The alternative reaction path by way of a 1,5-hydride shift would be followed by



loss of deuterium to give the enol form of the ketone. [1,2,2,8,8-²H₅]Cyclodecyl brosylate has been solvolysed and the deuterium distribution in the substitution and elimination products determined by mass spectrometry.³⁶ The extents of rearrangement observed were about 53% for the acetolysis, 60% for the formolysis, and >62% for the trifluoroacetolysis. In the first two cases rearrangement proceeded almost exclusively by a transannular 1,5-hydride shift; the extent of 1,3-hydride shift was not appreciable. With ¹⁴C-labelled cyclononyl and cycloundecyl tosylates substantial amounts of radioactivity were found beyond the first two stages in the degradation.^{37,38} Only in the case of cyclododecyl tosylate was the distribution of radioactivity in the products that predicted by a classical reaction path.³⁹ Cycloheptyl tosylate showed a small but significant deviation (5%) from the classical prediction,⁴⁰ a finding which is

³⁵ V. Prelog and W. Küng, *Helv. Chim. Acta*, 1956, **39**, 1394.

³⁶ A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.*, 1963, **85**, 3747.

³⁷ V. Prelog, H. Kagi, and E. H. White, *Helv. Chim. Acta*, 1962, **45**, 1658.

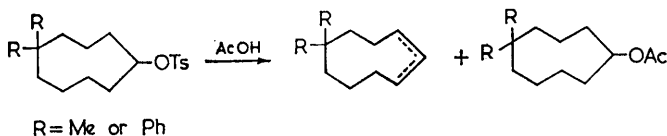
³⁸ L. O. Moore, unpublished results, see Ref. 16.

³⁹ W. Küng and V. Prelog, *Croat. Chem. Acta*, 1957, **29**, 357.

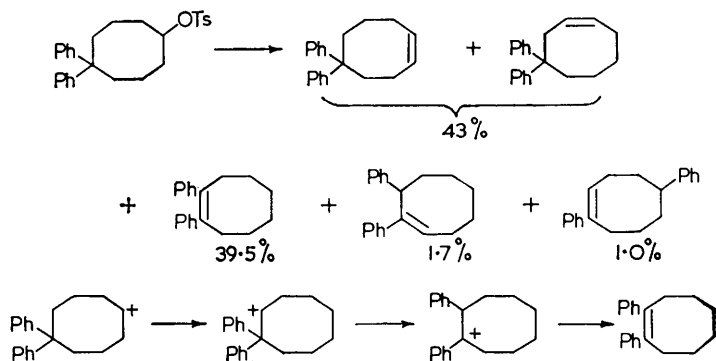
⁴⁰ S. J. Rhoads, unpublished results, see Ref. 16.

consistent with the observation that the hydrolysis of *cis*-cycloheptene oxide gives 2.4% of *cis*-cycloheptane-1,4-diol. Recent results of Reutov indicate that transannular hydride shifts are important in the solvolysis of cyclohexyl tosylate.⁴¹ Thus formation of cyclohexyl acetate in the acetolysis of [2,2,6,6-²H₄]cyclohexyl tosylate proceeded to the extent of 26% by way of 1,3-hydride shifts. This contrasts with the observation that the solvolysis of cyclohexene oxide gives only a trace of *trans*-cyclohexane-1,4-diol.

Although transannular hydride migration is now a well established phenomenon in medium-ring compounds, there have been no examples of similar transannular aryl or alkyl migrations until recently. Attempts have been made to induce both phenyl and methyl migration in nine- and ten-membered rings without success. It is noteworthy that in addition to the apparent absence of methyl or phenyl migration in the solvolysis of 5,5-diphenyl- and 5,5-dimethyl-cyclononyl tosylates in acetic acid, transannular hydride shifts were not observed.^{42,43} This suggests that



gem-di-alkyl or -aryl groups cause the nine-membered ring to adopt a conformation which is not favourable for transannular reaction. The presence of 1% of 1,5-diphenylcyclo-octene in the mixture of olefins obtained from solvolysis of 5,5-diphenylcyclo-octyl tosylate in trifluoroacetic acid constitutes the first known example of transannular phenyl migration.⁴⁴ *cis*-1,2-Diphenylcyclo-octene may be obtained from the initially formed carbonium ion by a 1,4-hydride shift followed by 1,2-



⁴¹ O. A. Reutov, *Pure Appl. Chem.*, 1963, 7, 203.

⁴² A. T. Blomquist and Y. C. Meinwald, *J. Amer. Chem. Soc.*, 1958, 80, 630.

⁴³ A. T. Blomquist and B. F. Hallam, *J. Amer. Chem. Soc.*, 1959, 81, 676.

⁴⁴ A. C. Cope, P. E. Burton, and M. L. Caspar, *J. Amer. Chem. Soc.*, 1962, 84, 4855.

phenyl migration and loss of a proton. Although it is known that in the unsubstituted cyclo-octyl series 1,3- and 1,5-hydride shifts occur to the exclusion of 1,4-hydride shifts, it may be that *gem*-diphenyl substitution alters the conformation of the ring so that 1,4-hydride migration can occur in the solvolysis of 5,5-diphenylcyclo-octyl tosylate. It is also possible that in this case a 1,4-hydride shift is favoured due to the additional stabilisation that may result from a synchronous 1,2-phenyl shift. The available evidence does not allow a choice between this process and an alternative multistep process.

It will be recalled that both 1,5- and 1,3-hydride shifts were demonstrated in the solvolysis of *cis*-cyclo-octene oxide; on the other hand, the solvolysis of cyclo-octyl brosylate indicated that in the absence of ring substituents, 1,5-hydride shifts constitute the major path of the reaction, and that the extent of 1,3-hydride shift is small. In an effort to elucidate some of the structural features which lead to transannular rearrangement of a medium-ring carbonium ion, several cyclo-octyl compounds were solvolysed in which dissociation and rearrangement lead to carbonium ions of different stabilities. The solvolysis of *cis*- and *trans*-5-phenylcyclo-



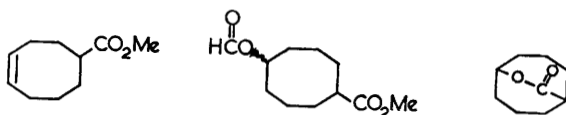
octyl tosylate illustrates the effect of placing a phenyl group in the 5-position of the cyclo-octane ring relative to the leaving group.⁴⁵ The stereochemistry of the *cis*-tosylate is such that the back side of C-1 is especially vulnerable to attack by a migrating hydride ion from the 5-position; subsequent formation of a tertiary carbonium ion at C-5 followed by loss of a proton makes the 1,5-shift favourable. Thus the *cis*-tosylate gives 1-phenylcyclo-octene (81.2%) (Table 3). In the reaction of the *trans*-tosylate such a path is not available and the main course of the reaction is the formation of the normal elimination and substitution products. The formation of 4-phenylcyclo-octanol in the solvolyses of both the *cis*-

TABLE 3.⁴⁵ *Products of Formolysis of cis- and trans-5-Phenylcyclo-octyl Tosylates.*

Products (%)						
<i>cis</i> -Tosylate	81.2	11.0	—	1.4	1.4	2.5
<i>trans</i> -Tosylate	19.0	47.5	2.6	8.1	2.3	18.8

⁴⁵ A. C. Cope and R. B. Kinnel, unpublished results.

and the *trans*-tosylates presumably arises by a 1,2-hydride shift followed by attack of solvent. A somewhat similar situation is found in the solvolysis of 5-methylcyclo-octyl tosylate⁴⁶ and 5-*t*-butylcyclo-octyl tosylate.⁴⁷ Thus the effect of the *cis*-5-methyl substituent is greatly to increase the proportion of 1,5-hydride shift (90%), and that of the *trans*-5-methyl substituent is to favour the formation of unrearranged products (90%). That neither the 5-methylcyclo-octyl tosylates nor the 5-*t*-butylcyclo-octyl tosylates gave rise to detectable amounts of 1,3-hydride shift may be explained in terms of relative carbonium ion stabilities or perhaps more likely as a conformational phenomenon. *cis*-Cyclo-octene oxide, a system that does give rise to 1,3-hydride shift, differs considerably in ring geometry from any reasonable cyclo-octane ring conformation. It may be that the occurrence of a 1,3-hydride shift during the formolysis of *cis*-cyclo-octene oxide is the exception rather than the rule for solvolysis of cyclo-octane derivatives.



In a continuation of these studies, the effect of a methoxycarbonyl group was investigated in the solvolysis of the tosylates of methyl *cis*- and *trans*-5-hydroxycyclo-octanecarboxylate.⁴⁸ Unlike a 5-methyl substituent, which stabilises the tertiary carbonium ion formed by a 1,5-hydride shift, the 5-methoxycarbonyl substituent would destabilise the incipient carbonium ion formed by 1,5-hydride migration; the solvolysis would therefore be expected to take a different course. The formation of methyl cyclo-oct-4-enecarboxylate as the main product from both the *cis*- and the *trans*-tosylates confirms this interpretation (Table 4). In addition to the expected effect of the 5-methoxycarbonyl group preventing a 1,5-hydride

TABLE 4. *Products of Formolysis of Tosylates of cis and trans-Methyl 5-hydroxycyclo-octanecarboxylates*

Products (%)	91	8.5	—
<i>cis</i> -Tosylate	91	8.5	—
<i>trans</i> -Tosylate	78	18	4.4

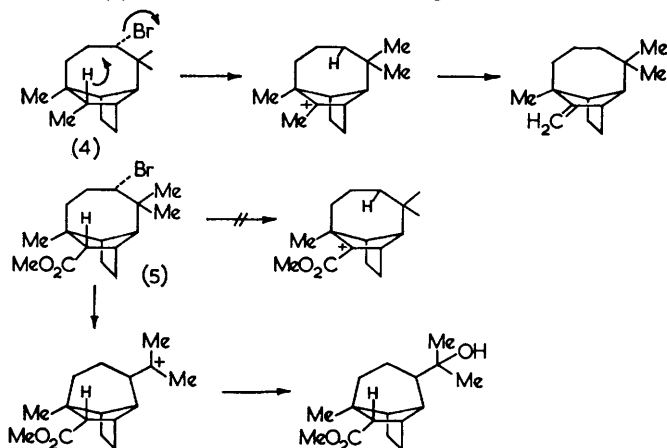
shift because of its electron-withdrawing properties, a transannular effect of the ester itself is indicated by formation of the 1,5-lactone from the *trans*-tosylate. The solvolysis of two longifolene derivatives provides further examples of the destabilising effect of a methoxycarbonyl substituent. The bromide (4) rearranges quantitatively to longifolene via a 1,5-hydride shift; replacement of the methyl substituent by a methoxy-

⁴⁶ A. C. Cope and D. M. Gale, *J. Amer. Chem. Soc.*, 1963, **85**, 3743.

⁴⁷ N. L. Allinger and S. Greenberg, *J. Amer. Chem. Soc.*, 1962, **84**, 2394.

⁴⁸ A. C. Cope and D. L. Nealy, *J. Amer. Chem. Soc.*, 1965, **87**, 3122.

carbonyl substituent (5) causes an alternative ring contraction to take place.⁴⁹



The acetolysis of *cis*- and *trans*-cyclo-octane-1,2-diol ditosylate and *cis*-cyclo-octane-1,4-diol ditosylate may also involve carbonium ions of different stabilities. The 1,2-ditosylates would lead initially to the carbonium ion (6) in which the positive charge is adjacent to the tosylate group, whereas the 1,4-ditosylate would lead to the carbonium ion (7) in which the positive charge is four carbon atoms removed from the tosylate group. Ion (6) can give rise to 2-acetoxycyclo-octyl tosylate (8) or cyclo-oct-2-en-1-yl tosylate (9), whereas ion (7) can lead to 4-acetoxycyclo-octyl tosylate (10), cyclo-oct-3-en-1-yl tosylate (11), or cyclo-oct-4-en-1-yl tosylate (12). The question to be resolved is the relationship between carbonium ions (6) and (7), that is, whether initially generated (6) rearranges to (7), or (7) to (6). It is obvious from the results (Table 5) that the mechanistic picture in Figure 5 is an over-simplification. Clearly, planar

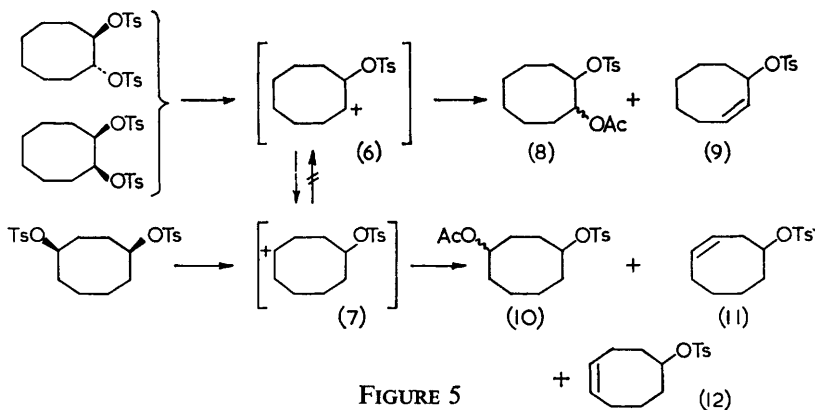


FIGURE 5

⁴⁹ G. Ourisson, *Proc. Chem. Soc.*, 1964, 274.

carbonium-ion intermediates are inadequate to explain the results, since the *cis*- and *trans*-1,2-ditosylates, which would give the same planar carbonium ion, give different product mixtures. The complete absence of any cyclo-octane-1,2-diol and cyclo-oct-2-en-1-ol from any of the product mixtures eliminates (8) and (9) as initial products in any of the solvolyses; all the products can be envisioned as arising from (10), (11), and (12) via carbonium ion (7). This means that carbonium ion (6) rearranges irreversibly to carbonium ion (7). The destabilisation of a carbonium ion by a neighbouring arennesulphonate group, through its electron-withdrawing effect, has been reported⁵¹ and is demonstrated in these studies by the

TABLE 5.⁵⁰ *Products of Acetolysis of cis- and trans-Cyclo-octane-1,2-diol Ditosylate and cis-Cyclo-octane-1,4-diol Ditosylate.*

	1	2	3	4	5	6	7	8	9
	2-9	1-8	2-9	2-1	20	—	—	13	40
	9-9	6-8	5-6	11-0	2-7	15	4	21	21
	12	1-0	4-2	4-5	3-6	5-3	4-4	5	42

much slower rate of solvolysis of *trans*-cyclo-octane-1,2-diol ditosylate compared with cyclo-octyl tosylate (rate factor of 720 at 73°). Thus the driving force for a transannular hydride shift is apparently the greater stability of the carbonium ion in which the positive charge is four carbon atoms removed from the tosylate group. The generalisation that a transannular hydride shift will occur in a medium-ring compound if such a rearrangement leads to a more stable carbonium ion will probably prove useful in predicting the course of other medium-ring reactions.

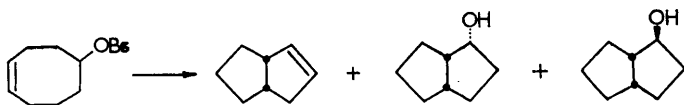
The products listed in Table 5 probably arise as follows: the three cyclo-octadienes (Columns 2, 3, and 4) can be formed by elimination from (11) and (12). Likewise, the two cyclo-octenols (Columns 8 and 9) can be derived directly from (11) and (12). The bicyclic products (Columns 1, 6, and 7) probably arise from (12). It has been shown that the corresponding brosylate, cyclo-oct-4-en-1-yl brosylate, gives *cis*-bicyclo[3,3,0]oct-2-ene, *endo-cis*-bicyclo[3,3,0]octan-2-ol, and *exo-cis*-bicyclo[3,3,0]octan-2-ol as major solvolysis products.^{52,53} Apparently (12) is a major intermediate in

⁵⁰ A. C. Cope, S. Moon, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 1650

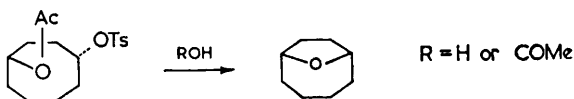
⁵¹ S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, 1948, **70**, 821.

⁵² A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, 1959, **81**, 1643.

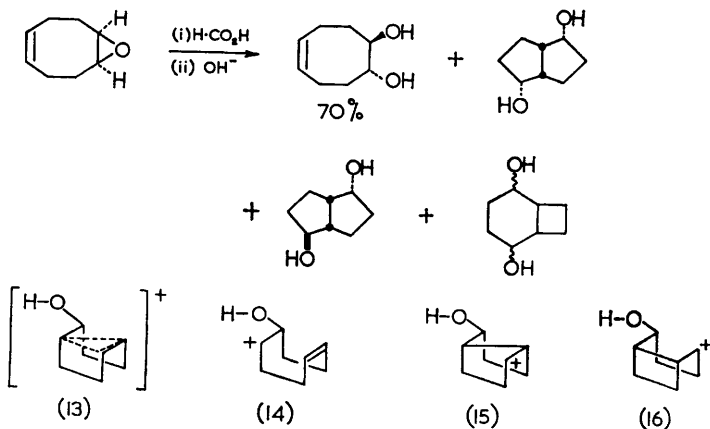
⁵³ A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1960, **82**, 4299.



the solvolysis of the *cis*-1,2-ditosylate but not of the *trans*-1,2-ditosylate, since in the later case the bicyclic alcohols are not formed. From the *trans*-compound it appears that *trans*-(10) is the most important intermediate; elimination can then give cyclo-oct-3- and -4-en-1-ol, both major products of the solvolysis. Furthermore, the stereochemistry is correct for intramolecular substitution, accounting for the formation of 1,4-epoxy-cyclo-octane (Column 5) as a major product.



In the solvolytic reactions discussed so far, the transannular reaction of interest has been a hydride or phenyl shift. Another type of transannular reaction is possible, namely the shift of a pair of electrons, resulting in the formation of a bicyclic compound. When *cis-cis*-cyclo-octa-1,5-diene mono-epoxide is solvolysed under conditions which lead to a transannular hydride shift in the corresponding saturated compound, the bicyclic products can all be explained by migration of the double bond, and no hydride shift need be assumed.⁵⁴ The products may arise from the non-classical ion (13), or from the classical ions (14), (15), and (16).

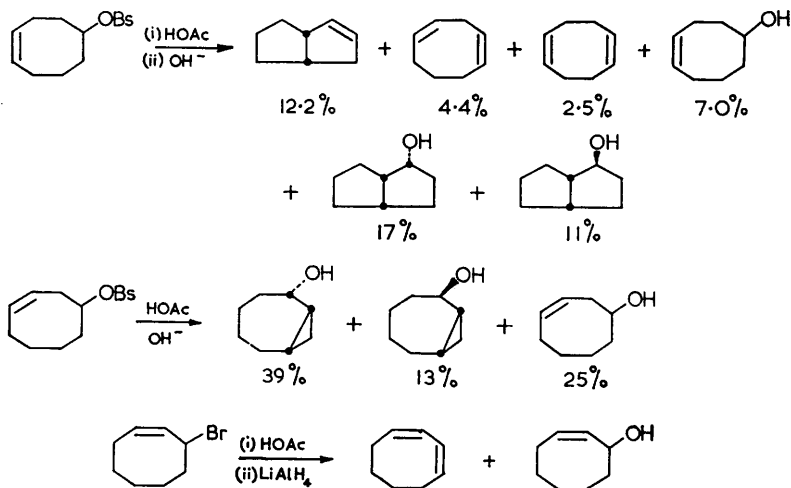


The study of proximity effects in cyclo-octene derivatives has been extended to the solvolysis of cyclo-oct-4-en-1-yl brosylate, cyclo-oct-3-en-1-yl brosylate, and 3-bromocyclo-octene.^{52,55} The formation of large

⁵⁴ A. C. Cope and B. Fisher, unpublished results.

⁵⁵ A. C. Cope, S. Moon, and P. E. Peterson, *J. Amer. Chem. Soc.*, 1962, **84**, 1935.

amounts of bicyclic products certainly establishes that transannular migration of the double bond has occurred; whether it occurs during or subsequent to the rate-determining step is more difficult to establish. Rate measurements (Table 6) were made in order to determine whether such



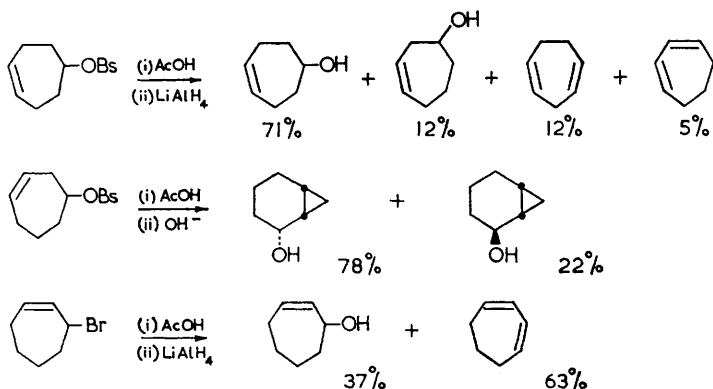
participation by the double bond would give rise to a pronounced enhancement of the solvolysis rate as has been observed in various homoallylic systems. In fact, cyclo-oct-4-en-1-yl brosylate solvolyses at a rate 0.017 times as fast as cyclo-octyl brosylate. This result becomes meaningful only when allowance is made for the fact that the solvolysis rate of cyclo-octyl brosylate is itself strongly enhanced over that of cyclohexyl brosylate; that this enhancement is due to relief of steric strain in the transition state for formation of a planar carbonium ion provides a good basis for explaining these results. Thus it appears that introduction of only one double bond into a cyclo-octane derivative is sufficient to relieve much of the strain in the molecule. Accordingly, the solvolysis rate of cyclo-oct-4-en-1-yl brosylate would be similar to the rate for cyclohexyl brosylate in the absence of rate enhancement due to double-bond participation. The observed relative rate of 2.9, together with the relative lack of stereoselectivity of the reaction indicates little, if any, double-bond participation. Cyclo-oct-3-en-1-yl brosylate solvolyses 130 times more rapidly than cyclo-oct-4-en-1-yl brosylate and 370 times as fast as cyclohexyl brosylate. Since the double bond at the 3,4-position would be expected to relieve the same amount of *I*-strain as the double bond at the 4,5-position, cyclo-oct-3-en-1-yl brosylate would be expected to solvolyse at the same rate as cyclo-oct-4-en-1-yl brosylate in the absence of double-bond participation. The amount of double-bond participation is then indicated by the rate enhancement by a factor of 370 compared to cyclohexyl brosylate. The

TABLE 6. *Relative Rates of Acetolysis of Cyclo-octyl, Cyclo-oct-4-en-1-yl, Cyclo-oct-3-en-1-yl, and Cyclohexyl Brosylates*

Brosylate	k/k cyclo-octyl	k/k cyclohexyl
Cyclo-octyl	1.000	185
Cyclo-oct-4-en-1-yl	0.017	2.9
Cyclo-oct-3-en-1-yl	2.1	370

predominant formation of *endo*-bicyclo[5,1,0]octan-2-ol is consistent with a concerted process in the solvolysis of cyclo-oct-3-en-1-yl brosylate. Since this discussion of rates is based on the assumption that an eight-membered ring containing one double bond has much of its medium-sized ring strain relieved, it should be stated that other chemical evidence also favours such a hypothesis. Thus addition of hydrogen bromide to cyclo-octa-1,5-diene⁵⁶ gives 5-bromocyclo-octene in good yield, indicating that the addition of a second mole of hydrogen bromide to 5-bromocyclo-octene is somewhat slower, presumably because of the strain attending the formation of the completely saturated compound.

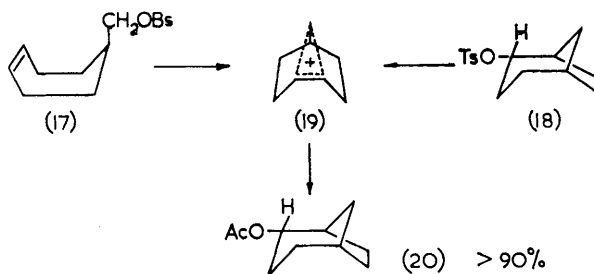
Cycloheptenyl derivatives have been solvolysed and the products compared with those obtained in the solvolysis of cyclo-octenyl derivatives.⁵⁷ Solvolysis of cyclohept-4-en-1-yl brosylate in either acetic acid or trifluoroacetic acid gave cyclohept-4-en-1-ol, cyclohept-3-en-1-ol, and cyclohepta-1,3- and -1,4-dienes in contrast to cyclo-oct-4-en-1-yl brosylate which gave bicyclic products in addition to the normal products. Acetolysis of cyclohept-3-en-1-yl brosylate produced *endo*- and *exo*-bicyclo[4,1,0]heptan-2-ol. Cyclohept-2-en-1-yl bromide gave the expected cyclohept-2-en-1-ol and cyclohepta-1,3-diene.



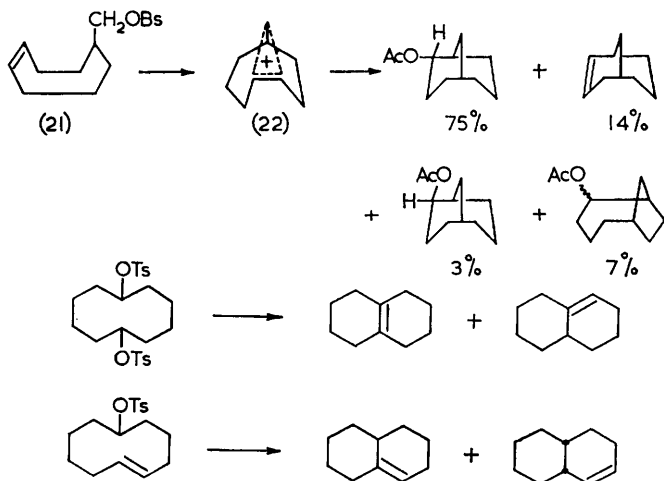
These studies have been extended to cycloheptenyl and cyclo-octenyl derivatives in which the aren Sulphonate group is not directly attached to the medium-sized ring. The acetolysis of cyclohept-4-ene-1-methyl

⁵⁶ K. Ziegler and H. Wilms, *Annalen*, 1950, 567, 1.

⁵⁷ A. C. Cope, C. H. Park, and P. Scheiner, *J. Amer. Chem. Soc.*, 1962, 84, 4862.



brosylate (17)⁵⁸ and of *endo*-bicyclo[3,2,1]oct-2-yl tosylate(18)⁵⁹ have been reported to produce almost exclusively *endo*-bicyclo[3,2,1]oct-2-yl acetate(20) *via* the symmetrical bridged ion (19).⁶⁰ The solvolysis of a homologue of (17), cyclo-oct-4-ene-1-methyl brosylate(21)⁶¹ is of interest for two reasons. First, (17) may give rise to the symmetrical ion (19), whereas the analogous bridged ion from (21) is unsymmetrical and can lead to derivatives of either bicyclo[3,3,1]nonane or bicyclo[4,2,1]nonane. Second, homologous cyclo-octene and cycloheptene derivatives show markedly different behaviour in solvolysis. The acetolysis of (21) was found to give *endo*-bicyclo[3,3,1]non-2-yl acetate (75%), bicyclo[3,3,1]non-2-ene (14%), *exo*-bicyclo[3,3,1]non-2-yl acetate (3%), and a fourth compound tentatively identified as bicyclo[4,2,1]non-2-yl acetate (7%). The exclusive formation of bicyclic products and the stereochemistry of the major product may indicate the intervention of the non-classical ion (22).



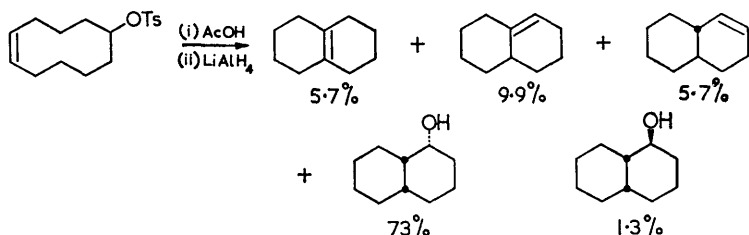
⁵⁸ G. LeNy, *Compt. rend.*, 1960, **251**, 1526.

⁵⁹ H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, 1961, **83**, 1397.

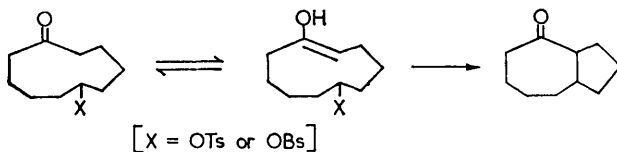
⁶⁰ S. Winstein and P. Carter, *J. Amer. Chem. Soc.*, 1961, **83**, 4485.

⁶¹ A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Amer. Chem. Soc.*, 1965, **87**, 3130; see also M. Hanack and W. Kaiser, *Angew. Chem.*, 1964, **76**, 572.

After it was found that both stereoisomeric cyclodecane-1,6-diol ditosylates decompose to mixtures of 1,9- and 9,10-octalin on heating with diethylaniline,⁶² an investigation of the decomposition of *trans*-cyclodec-5-en-1-yl tosylate, a likely intermediate in the decomposition of the ditosylate, was undertaken.⁶³ The isolation of a mixture of 1,9- and *cis*-1,2-octalin, and the fact that the mixture contained little if any 9,10-octalin shows the *trans*-cyclodec-5-en-1-yl tosylate cannot be the sole intermediate in the reaction of the ditosylates with diethylaniline in which 9,10-octalin is one of the products. The acetolysis of *cis*-cyclodec-5-en-1-yl tosylate is highly stereoselective, giving predominantly *endo-cis*-bicyclo[4,4,0]decan-2-ol.⁶⁴ A concerted process, involving simultaneous dissociation of the tosylate group, migration of the double bond, and attack by solvent would explain the high degree of stereoselectivity, whereas formation of the *cis*-1-decalyl carbonium ion would be expected to give a mixture of *endo-cis*- and *exo-cis*-bicyclo[4,4,0]decan-2-ol. It is interesting to note that the



lithium aluminium hydride reduction of *cis*-cyclodec-5-en-1-yl tosylate proceeds predominantly *via* a transannular path.⁶⁴ Goering⁶⁵ has attempted to ascertain whether the double bond of *cis*-cyclodec-5-en-1-yl tosylate participates during the rate-determining step of solvolysis. It was observed initially that 6-oxocyclodecyl tosylate and brosylate undergo ethanolysis at much faster rates than the cyclodecyl derivatives, presumably because of participation of the carbonyl group in the enol form. The rate for the *cis*-cyclodec-5-en-1-yl tosylate was found to be 10 and 7 times faster in ethanolysis and acetolysis, respectively, than cyclodecyl tosylate.⁶⁶



⁶² A. C. Cope and G. Holzman, *J. Amer. Chem. Soc.*, 1950, **72**, 3062.

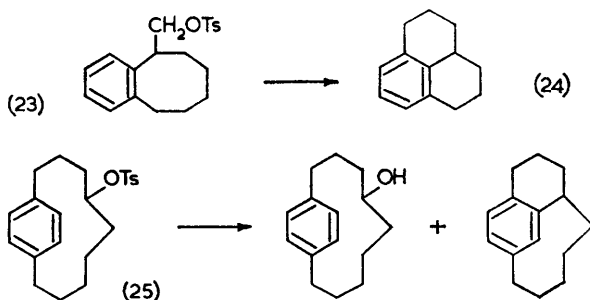
⁶³ A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Amer. Chem. Soc.*, 1955, **77**, 3594.

⁶⁴ A. C. Cope and P. Jenkins, unpublished results.

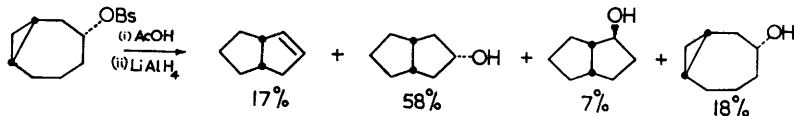
⁶⁵ H. L. Goering, A. C. Olson, and H. H. Espy, *J. Amer. Chem. Soc.*, 1956, **78**, 5371.

⁶⁶ H. L. Goering, H. H. Espy, and W. D. Closson, *J. Amer. Chem. Soc.*, 1959, **81**, 329.

Although these results may be due to conformation factors, double-bond participation seems a more likely explanation in view of the more pronounced effect during ethanolysis than acetolysis, since participation would be expected to lead to greater enhancement in the poorer ionising solvent. Furthermore, solvolysis of the saturated compound should be accelerated by *I*-strain, which would be reduced by the presence of a double bond. Huisgen and Seidl⁶⁷ have shown that even when the double bond is part of a benzene ring system, transannular participation can take place. Thus tosylate (23) gives tetrahydropiperinaph-thane (24) on solvolysis. A similar effect has been observed in the solvolysis of (25).⁶⁸



The various bicyclo[5,1,0]octanols possess cyclopropane rings that are held in proximity to the hydroxyl group. Suitable derivatives of these alcohols have been solvolysed in order to determine the influence of the cyclopropane ring on the initially formed carbonium ion.^{55,69} The pre-



dominant formation of the bicyclo[3,3,0]octane system on solvolysis of *endo*-bicyclo[5,1,0]oct-3-yl brosylate clearly indicates extensive participation by the cyclopropane ring. Similar results have been obtained with *exo*-bicyclo[5,1,0]oct-3-yl brosylate and also with *exo*- and *endo*-bicyclo[5,1,0]oct-4-yl brosylates.

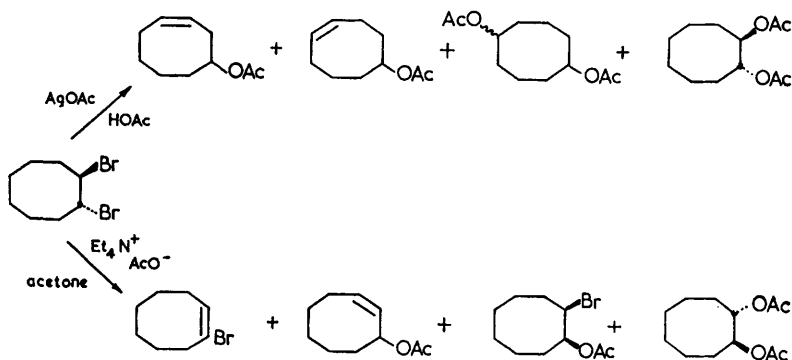
(b) **Other carbonium ion reactions.**—A comparison of the products from S_N1 and S_N2 reactions shows that in the eight-membered ring transannular products are formed only under S_N1 conditions and confirms the earlier conclusion that transannular hydride shifts are favoured by the transitory formation of carbonium ions. The reaction of *trans*-1,2-dibromocyclooctane with silver acetate in acetic acid (typical S_N1 conditions) gives

⁶⁷ R. Huisgen and G. Seidl, *Angew. Chem.*, 1957, **69**, 390.

⁶⁸ D. J. Cram and M. Goldstein, *J. Amer. Chem. Soc.*, 1963, **85**, 1063.

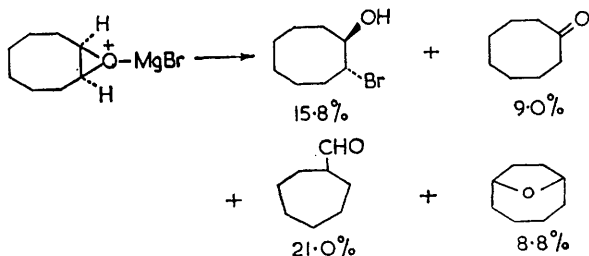
⁶⁹ A. C. Cope, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, 1962, **84**, 4850.

transannular products almost exclusively;⁷⁰ reaction of the same dibromide with tetraethylammonium acetate in acetone (typical S_N2 conditions) yields only the normal elimination and substitution products.⁷¹ The seven-membered ring dibromide reacts according to the classical course even under S_N1 conditions,⁷² further emphasising the importance of ring size in directing the path of the reaction. The cyclic bromonium ion intermediates postulated in the addition of bromine to olefins are formally analogous to the oxonium-ion intermediates involved in the acid-catalysed opening of epoxides, and the possibility that bromine addition to medium-ring olefins might proceed by a transannular path has been considered.⁷⁰



Zavada and Sicher have shown that addition of bromine to *cis*- and *trans*-cyclodecene gives rise, in a stereospecific reaction, to *cis*- and *trans*-1,6-dibromocyclodecane, respectively.⁷³ More recently, the addition of bromine to 1-chlorocyclo-octene has been shown to give some transannular reaction.⁷⁴

The deamination of ¹⁴C-labelled cyclodecylamine gives some trans-



⁷⁰ A. C. Cope and G. W. Wood, *J. Amer. Chem. Soc.*, 1957, **79**, 3885.

⁷¹ A. C. Cope and H. E. Johnson, *J. Amer. Chem. Soc.*, 1957, **79**, 3889.

⁷² A. C. Cope, E. M. Acton, H. E. Johnson, and G. W. Wood, *J. Amer. Chem. Soc.*, 1957, **79**, 6292.

⁷³ J. Zavada and J. Sicher, *Proc. Chem. Soc.*, 1961, 199.

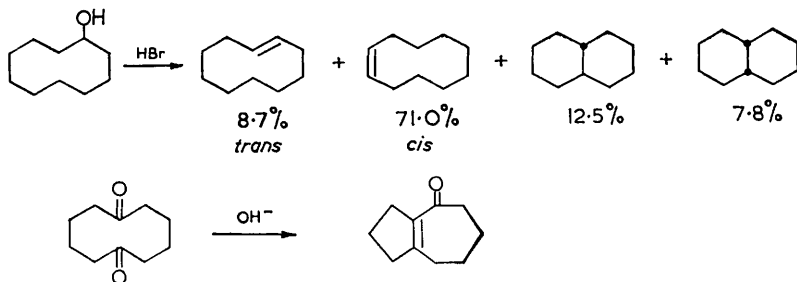
⁷⁴ J. Wolinsky and K. Erickson, *Chem. and Ind.*, 1964, 1953.

annular hydride shift, although the extent appears to be less than that observed in the solvolysis of labelled cyclodecyl tosylate.⁷⁵ An important difference between the deamination and solvolysis is that the olefin obtained from cyclodecyl tosylate is largely *trans*-cyclodecene, while that from cyclodecylamine is *cis*-cyclodecene. Lewis acid-catalysed ring opening of *cis*- and *trans*-cyclo-octene oxide has been shown to afford a variety of products from transannular reactions.⁷⁶

In several instances the formation of bridged compounds has been observed from completely saturated compounds in reactions proceeding through carbonium ions. One of the isomeric *trans*-1-decalols was isolated from the formolysis of cyclodecene oxide.²³ Similar bridged products were detected in the hydrocarbon fraction from the reaction between cyclodecanol and hydrobromic acid.⁷⁷

3. Reactions Proceeding Through Carbanions and Carbenes

Even before the systematic study of the cationic transannular rearrangements of medium-ring compounds described in the previous section was undertaken, there existed in the literature several examples of base catalysed intramolecular alkylations. In 1933, Hückel and Schnitzspahn⁷⁸ reported the intramolecular condensation of cyclodecane-1,6-dione. Although the occurrence of such a condensation may depend to some extent upon the operation of a proximity effect, such reactions are not unique to medium-ring chemistry; the formation of a five-, six-, or seven-membered ring by the base-catalysed condensation of a compound containing an active methylene group is a standard technique of organic chemistry. In the intramolecular condensation formulated above, the hydrogen atoms adjacent to the carbonyl group are activated, independent of any transannular reaction. Prelog has suggested that such reactions be termed "trivial" transannular reactions to contrast them with reactions which are unique to medium-sized rings.



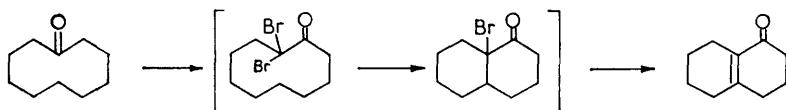
⁷⁵ V. Prelog, H. J. Urech, A. A. Bothner-By, and J. Wursch, *Helv. Chim. Acta*, 1955, **38**, 1095.

⁷⁶ A. C. Cope and J. K. Hecht, *J. Amer. Chem. Soc.*, 1962, **84**, 4872.

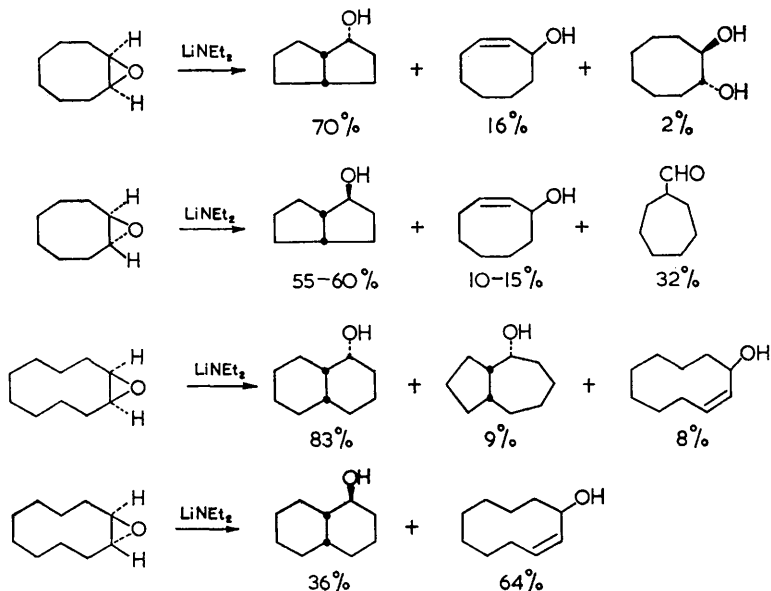
⁷⁷ A. C. Cope, M. Brown, and G. L. Woo, *J. Amer. Chem. Soc.*, 1965, **87**, 3107.

⁷⁸ W. Hückel and L. Schnitzspahn, *Annalen*, 1933, **505**, 274.

However, transannular eliminations have been observed in which the labile hydrogen atom is activated only by a functional group on the opposite side of the ring. The formation of bicyclic unsaturated ketones from the base treatment of the products of the bromination of cyclononane and cyclodecanone with two moles of *N*-bromosuccinimide has been reported.⁷⁹ In these reactions a ring closure occurs, in which the labile hydrogen atom is six carbon atoms removed from the bromine atom and five carbon atoms removed from the carbonyl group.



The reaction of *cis*-cyclo-octene oxide with the strong base lithium diethylamide results in the formation of an intramolecular alkylation product, *endo-cis*-bicyclo[3,3,0]octan-2-ol. *trans*-Cyclo-octene oxide gives *exo-cis*-bicyclo[3,3,0]octan-2-ol and cycloheptancarboxyaldehyde as the major products.⁸⁰ similar reactions have been observed with *cis*- and *trans*-cyclodecene oxides.⁸¹ Two mechanisms can be postulated to explain the formation of these bicyclic products. In the case of *cis*-cyclodecene oxide, for example, the base could remove a proton from a carbon atom



⁷⁹ K. Schenker and V. Prelog, *Helv. Chim. Acta*, **36**, 896.

⁸⁰ A. C. Cope, H. H. Lee, and H. E. Petree, *J. Amer. Chem. Soc.*, **1958**, **80**, 2849.

⁸¹ A. C. Cope, M. Brown, and H. H. Lee, *J. Amer. Chem. Soc.*, **1958**, **80**, 2855.

(C-6 or C-7) located across the ring from the epoxide ring with concerted opening of the epoxide by the carbanion so formed (Path 1, Figure 6) to give *cis-cis*-1-decalol. Attack by the carbanion on the other carbon atom of the epoxide ring would produce *endo-cis*-bicyclo[5,3,0]decan-2-ol. In the second possible mechanism (Path 2, Figure 6), the base removes a proton from one of the carbon atoms of the epoxide ring, followed by breaking of the bond between the oxygen atom and the carbon atom which has lost a proton to form a carbene intermediate, which can then form a hydride ion from the same carbon atom to the electron-deficient carbon atom. Similar attack on C-7 would produce *endo-cis*-bicyclo[5,3,0]decan-2-ol. The mechanisms are represented as concerted since the products are single stereoisomers. Paths 1 and 2 have been distinguished by deuterium tracer studies with the deuterated epoxide (26).⁸² If the reaction of (26) with lithium diethylamide proceeded according to Path 1 (Figure 7) the

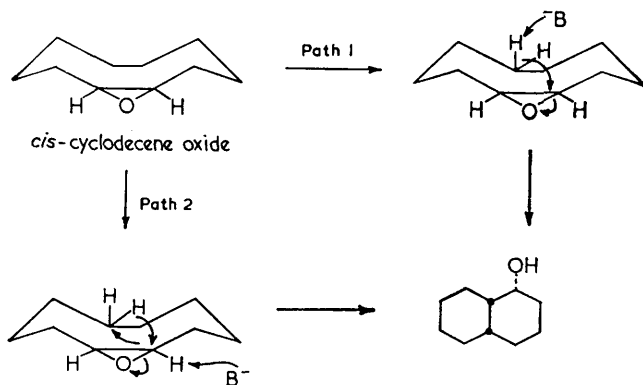
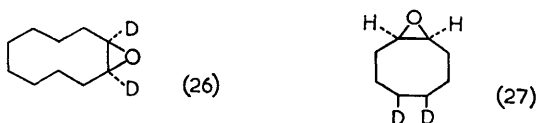


FIGURE 6

bicyclic products (Figure 7) should retain all the deuterium atoms that were present in the original epoxide. Conversely, if the reaction proceeded



according to Path 2, 0.8 to 1.0 atom of deuterium per molecule would be lost and the bicyclic products would have the deuterium distribution indicated by the structures in Figure 7. The reaction of (26) with lithium diethylamide gave *cis-cis*-1-decalol and *endo-cis*-bicyclo[5,3,0]decan-2-ol containing 0.96 and 0.93 atom of deuterium per molecule, respectively. This corresponds to a loss of 0.82 and 0.85 atom of deuterium per mole-

⁸² A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *J. Amer. Chem. Soc.*, 1960, **82**, 6370.

cule. Thus, the concerted carbene mechanism (Path 2) appears to be the route by which these bicyclic alcohols are formed. Further support for a concerted carbene intermediate was obtained from the reaction of (27)

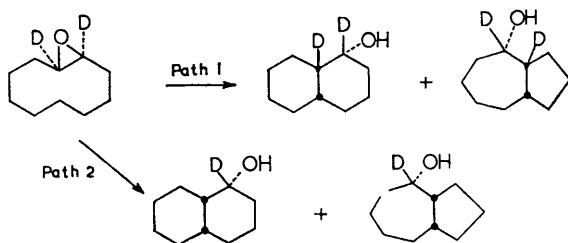
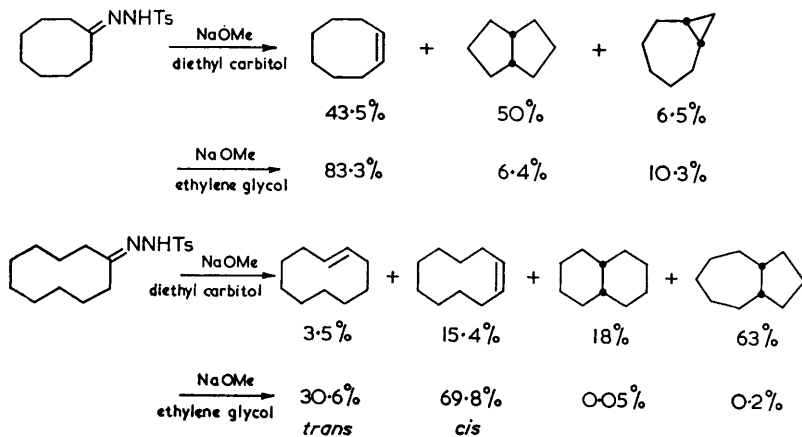


FIGURE 7

with lithium diethylamide.⁸² The *endo-cis*-bicyclo[3,3,0]octan-2-ol formed was found to contain 1.97 atoms of deuterium per molecule, showing that no deuterium atoms are removed from C-5 or C-6 of the epoxide during the reaction.

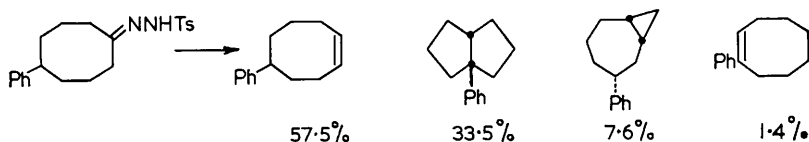
Another transannular reaction which may proceed *via* a carbene intermediate is the base-catalysed decomposition of tosylhydrazones of medium-ring ketones. The hydrocarbon mixtures isolated from the decomposition of cyclo-octyl and cyclodecyl tosylhydrazones in diethyl carbitol were found to contain more bicyclic products than olefins.^{83,77} The bicyclic hydrocarbons formed in these reactions all possess the *cis*-configuration, regardless of thermodynamic stability relative to the *trans*-isomers. This high degree of stereospecificity can be explained by a carbene mechanism involving a 1,3-, 1,5-, or 1,6-transannular hydrogen migration and intramolecular insertion. The formation of olefin is explained by a 1,2-hydride shift. Decomposition of cyclo-octyl and cyclodecyl tosyl-



⁸³ L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, 1961, 83, 3159.

hydrazones in ethylene glycol also gives bicyclic hydrocarbons but in much smaller total amounts than did the decompositions in diethyl carbitol. The decomposition in ethylene glycol probably proceeds by the cationic path, proposed by Friedman and Shechter,⁸⁴ involving elimination of a β -proton to give olefins or of a transannular proton to give bicyclic products.

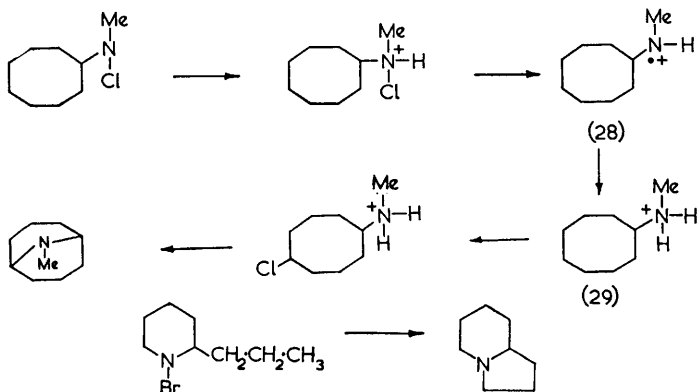
The formation of bicyclic compounds has also been observed in the base-catalysed decomposition of 5-phenylcyclo-octyl tosylhydrazone.⁸⁵ On the other hand, the hydrocarbon fraction from the decomposition of 5,5-diphenylcyclo-octyl tosylhydrazone consisted mostly of 5,5-diphenylcyclo-octene.⁸⁶



Experiments designed to generate the C_8 and C_{10} carbenes have also been carried out by irradiating the hydrazones of cyclo-octanone and cyclo-decanone, and by oxidising these hydrazones with mercuric chloride in methanol containing potassium hydroxide.⁸⁷ Bicyclic hydrocarbons were formed in substantial amounts, although the *cis*-cyclic olefins were the principal products.

4. Reactions Proceeding Through Free Radicals

The first example of a transannular radical rearrangement in a medium-sized ring was reported by Wawzonek and Thelen⁸⁸ who obtained *N*-methylgranatanine by irradiating a strongly acid solution of *N*-chloro-*N*-



⁸⁴ L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, 1959, **81**, 5512.

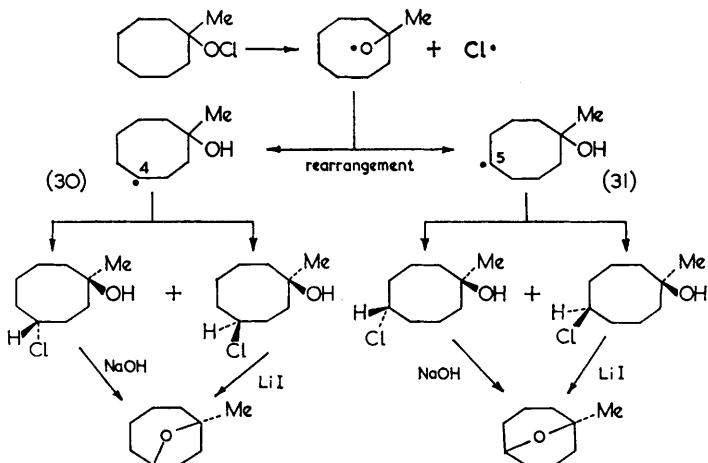
⁸⁵ A. C. Cope and R. B. Kinnel, unpublished results.

⁸⁶ A. C. Cope and N. Jensen, unpublished results.

⁸⁷ A. C. Cope and R. Clarkson, unpublished results.

⁸⁸ S. Wawzonek and P. J. Thelen, *J. Amer. Chem. Soc.*, 1950, **72**, 2118.

methylcyclo-octylamine. However, this reaction is not unique to medium-ring compounds; it is an example of the well established route to *N*-substituted pyrrolidines, originally discovered by Hofmann who obtained δ -coneceine from the reaction of *N*-bromoconiine with sulphuric acid. Later mechanistic studies of the Hofmann-Löffler reaction⁸⁹ indicate that the radical ion (28) is an intermediate, and that it rearranges to (29) by abstraction of a hydrogen atom from the 5-position of the cyclo-octane ring. As this requires a seven-membered transition state (not ordinarily encountered in this type of reaction) and no products of attack at the 4-position were reported, a proximity effect must have operated. It has been reported that the alkoxy-radical rearrangement of cyclo-octyl nitrite gives a product (characterised as cyclo-octane-1,4-dione) resulting from attack on a hydrogen atom in the 4-position.⁹⁰ In neither of these cases was it possible to determine the stereochemistry of the primary products. A pronounced proximity effect has been observed in the photochemically induced rearrangement of 1-methylcyclo-octyl hypochlorite at 0°.⁹¹ The mixture of primary products consisted of *trans*-4-, *trans*-5-, *cis*-4-, and *cis*-5-chloro-1-methylcyclo-octanol in yields of 28%, 21%, 7%, and 3%, respectively. Thus a total of 59% of the decomposition of 1-methylcyclo-octyl hypochlorite proceeds *via* transannular radical re-



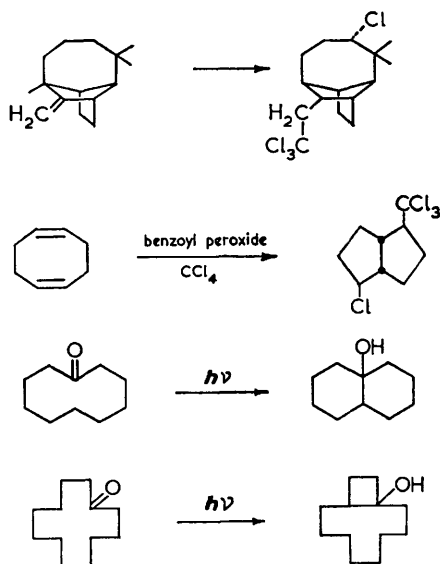
arrangements involving both the 4-position (35%) and the 5-position (24%) of the cyclo-octane ring. The hydrogen atoms at the single 5-position are therefore about 1.4 times as reactive as those at the two 4-positions in spite of the requirement of a seven-membered transition state for hydrogen abstraction. Models indicate that when the cyclo-octane ring is in the

⁸⁹ E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, 1960, **82**, 1657.

⁹⁰ P. Kabasakalian and E. R. Townley, *J. Org. Chem.*, 1962, **27**, 2918.

⁹¹ A. C. Cope, R. S. Bly, M. M. Martin, and R. C. Petterson, *J. Amer. Chem. Soc.*, 1965, **87**, 3111.

favoured skewed crown conformation the oxygen atom can approach a hydrogen atom on C-5 easily, but cannot come close to one at C-4. Some less favoured conformation is evidently necessary for a shift from C-4. The resulting radicals (30) and (31) apparently do not retain their original configuration because the *trans*-chlorohydrins are the predominant primary products. The stereochemistry of products may be governed by the steric requirement of the bulky incoming 1-methylcyclo-octyl hypochlorite molecule which furnishes the chlorine atom. A similar transannular free-radical reaction, initiated by light or a peroxide, has been observed with longifolene. Thus, addition of carbon tetrachloride or bromotrichloromethane gives products of transannular hydrogen transfer.⁴⁹ When the eight-membered ring contains a double bond, free-radical intramolecular alkylation can occur.⁹² A related transannular reaction



is the formation of bicyclic alcohols on irradiation of cyclodecanone⁹³ and cyclododecanone.⁹⁴ However, this reaction is general for ketones having a γ -hydrogen atom and it is not unique to medium ring ketones.

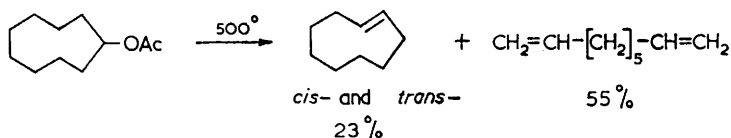
5. Other Transannular Reactions

There are many transannular reactions which cannot be placed in any of the above categories with any degree of certainty, because of the incomplete state of present knowledge of their mechanisms. Several pyrolytic reactions

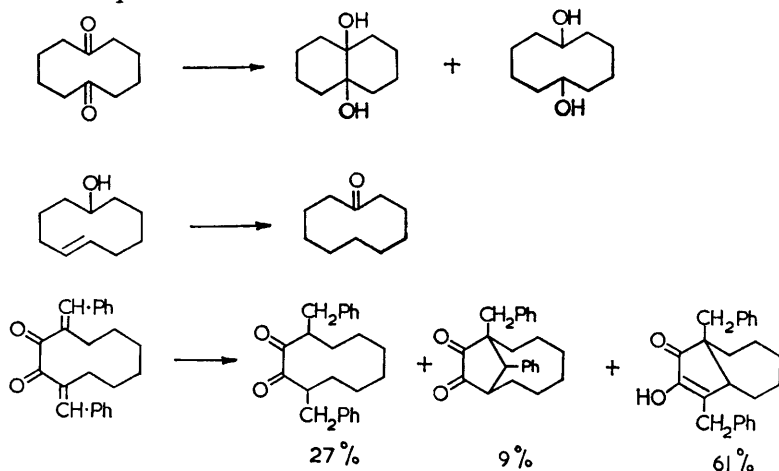
⁹² R. Dowbenko, *Tetrahedron*, 1964, 20, 1843.

⁹³ M. Barnard and N. C. Yang, *Proc. Chem. Soc.*, 1958, 302.

⁹⁴ B. Camerino and B. Patelli, *Experientia*, 1964, 20, 260.



of medium-ring compounds have been observed to proceed anomalously and have been interpreted in terms of transannular reactions.^{95,96,97} The pyrolysis of cyclononyl acetate or *S*-methylxanthate gives predominantly nona-1,8-diene, instead of the expected cyclononene. The benzoates and acetates of cyclo-octanol and cyclodecanol also give $\alpha\omega$ -dienes and the expected olefins. The diene may be formed directly from the cyclic acetate by a transannular elimination of acetic acid, or it may be formed by pyrolysis of the initially produced cyclic olefin. *trans*-Cyclononene does, indeed, give a high yield of nona-1,8-diene under the conditions of the pyrolysis. The pyrolysis of the hydrogen phthalates of cyclo-octanol and cyclodecanol gives small amounts of bicyclic compounds and ring contraction products.



Plattner and Hulstkamp⁹⁸ were the first to observe that the nickel-catalysed reduction of cyclodecane-1,6-dione gave some decalin-9,10-diol. Similar transannular reactions have been observed in the sodium in pentyl alcohol reduction of cyclodecane-1,6-dione dioxime^{99,100} and of 6-hydroxycyclodecanone oxime.¹⁰¹ Another interesting transannular

⁹⁵ A. T. Blomquist and P. R. Taussig, *J. Amer. Chem. Soc.*, 1955, **77**, 6399.

⁹⁶ A. T. Blomquist and P. R. Taussig, *J. Amer. Chem. Soc.*, 1957, **79**, 3505.

⁹⁷ A. C. Cope and M. J. Youngquist, *J. Amer. Chem. Soc.*, 1962, **84**, 2411.

⁹⁸ P. A. Plattner and J. Hulstkamp, *Helv. Chim. Acta*, 1944, **27**, 211.

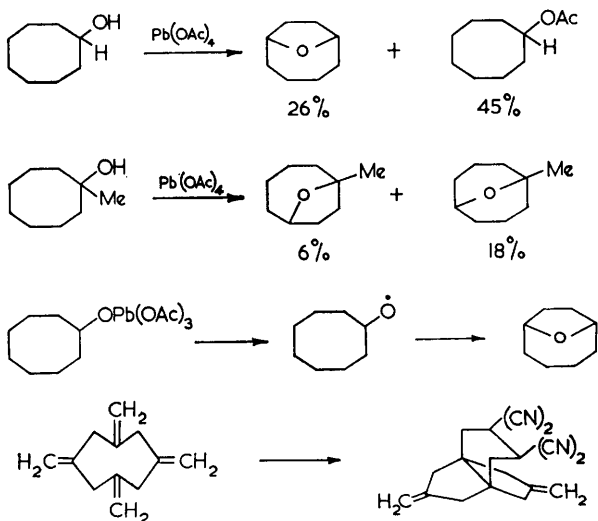
⁹⁹ P. A. Plattner and J. Hulstkamp, *Helv. Chim. Acta*, 1944, **27**, 220.

¹⁰⁰ P. A. Plattner, *Helv. Chim. Acta*, 1944, **27**, 801.

¹⁰¹ A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Amer. Chem. Soc.*, 1955, **77**, 3590; 3594.

reaction is the isomerisation of *cis*-cyclodec-5-en-1-ol to cyclodecanone in the presence of palladium and ethanol.¹⁰¹ The reaction of 3,10-dibenzylidenecyclodecane-1,2-dione at 300° with palladium on charcoal leads to two transannular reaction products.¹⁰²

A recent report¹⁰³ of the formation of a five-membered cyclic ether on treatment of a steroidal alcohol with lead tetra-acetate suggested that a similar reaction with a medium-ring alcohol might lead to transannular products. Reaction of lead tetra-acetate with cyclo-octanol gave 1,4-epoxycyclo-octane among other products; cycloheptanol gave 1,4-epoxycycloheptane. 1-Methylcyclo-octanol gave a mixture of 1,4- and 1,5-epoxy-1-methylcyclo-octane.¹⁰⁴ Cyclo-octene and cycloheptene also gave products formed by transannular reaction. A free-radical mechanism^{105,106} has been postulated for the formation of cyclic ethers in this reaction. The first intermediate may be the lead ester which decomposes homolytically. The intermediate radical can then attack the hydrogen atom in the 4-position to give 1,4-epoxycyclo-octane.



Williams and Benson¹⁰⁷ have observed that 1,3,5,7-tetramethylenecyclo-octane undergoes a transannular Diels-Alder reaction with tetracyanoethylene. The intermediacy of a nitrenium ion has been postulated

¹⁰² N. J. Leonard and J. C. Little, *J. Amer. Chem. Soc.*, 1958, **80**, 4111.

¹⁰³ G. Cainelli, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1959, **42**, 1124.

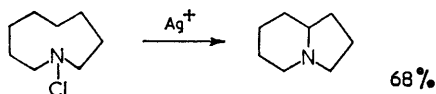
¹⁰⁴ A. C. Cope, M. Gordon, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, 1965, **87**, 3119.

¹⁰⁵ G. Cainelli, B. Kamber, J. Keller, M. Lj. Mihailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, 1961, **44**, 518.

¹⁰⁶ J. Kalvoda and K. Heusler, *Chem. and Ind.*, 1963, 1431.

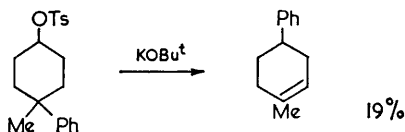
¹⁰⁷ J. K. Williams and R. E. Benson, *J. Amer. Chem. Soc.*, 1962, **84**, 1257.

to explain the formation of indolizidine on treatment of *N*-chloroazacyclononane with silver ions.¹⁰⁸



6. Conclusion

Transannular reactions in the chemistry of medium-ring compounds are now well established, and there is little doubt that many more examples will be uncovered. These reactions have been related to a proximity effect, that is, the spatial proximity of the opposite sides of a medium-sized ring. Although this Review has dealt primarily with transannular reactions in medium-sized rings, there is no apparent reason why other ring systems and acyclic molecules cannot be influenced in such a way as to allow the occurrence of similar phenomena. For example, a 1,4-phenyl shift has



recently been demonstrated in the six-membered ring.¹⁰⁹ There is a growing body of evidence to support the view that proximity effects may influence the chemical behaviour of open-chain molecules. Thus reaction of oct-1-ene oxide with trifluoroacetic acid yields small amounts of abnormal products, octane-1,3-, -1,4-, -1,5-, -1,6-, and -1,7-diols, in addition to the normal product, octane-1,2-diol.¹¹⁰ Hill and Carlson have recently demonstrated a simple example of a 1,5-hydride migration to an acyclic carbonium ion in the acid-catalysed isomerisation of 2-deuterio-6-methylhept-5-en-2-ol to 6-deuterio-6-methylheptan-2-one.¹¹¹

The extension of the principles underlying the chemistry reviewed here to macromolecular and biological systems may prove to be of great significance. Cohen and Witkop¹¹² have reported that some medium-ring keto-amides exhibit unusual reactivity and undergo an interesting transannular reaction. A similar transformation has been observed in the peptide portion of an ergot alkaloid.¹¹³

A proximity effect may also operate in the biosynthesis of oleic acid

¹⁰⁸ D. E. Edwards, D. Vocelle, J. W. ApSimon, and F. Haque, *J. Amer. Chem. Soc.*, 1965, **87**, 678.

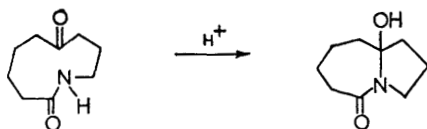
¹⁰⁹ A. R. Abdun-Nur and F. G. Bordwell, *J. Amer. Chem. Soc.*, 1964, **86**, 5695.

¹¹⁰ A. C. Cope, L. J. Fleckenstein, S. Moon, and H. E. Petree, *J. Amer. Chem. Soc.*, 1963, **85**, 3752.

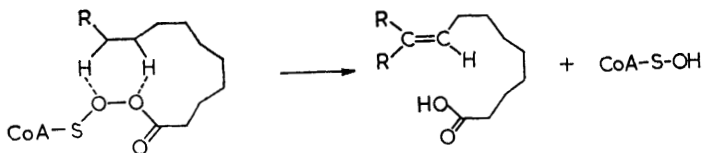
¹¹¹ R. K. Hill and R. M. Carlson, *J. Amer. Chem. Soc.*, 1965, **87**, 2772.

¹¹² L. A. Cohen and B. Witkop, *J. Amer. Chem. Soc.*, 1955, **77**, 6595.

¹¹³ A. Stoll, *Fortschr. Chem. org. Naturstoffe*, 1952, **9**, 134.



from stearic acid. Bloch¹¹⁴ has shown that this process requires nicotinamide adenine dinucleotide phosphate and the coenzyme A derivative of the saturated fatty acid as well as molecular oxygen. This behaviour may be rationalised by the suggestion that oxygen reacts with the acetyl coenzyme A to form a species which may then undergo an intramolecular dehydrogenation to the *cis*-olefin *via* a mechanism such as that shown.¹¹⁵



¹¹⁴ D. K. Bloomfield and K. Bloch, *J. Biol. Chem.*, 1960, **235**, 337.

¹¹⁵ J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins", Benjamin, New York, 1964, p. 135.