Absolute Configuration of 1-Phenylethyl *p*-Tolyl Sulphoxides and the Stereochemistry in the Oxidation of 1-Phenylethyl *p*-Tolyl Sulphide †

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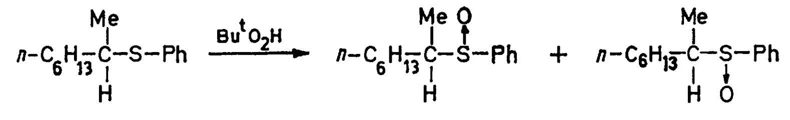
The absolute configurations of diastereoisomeric 1-phenylethyl *p*-tolyl sulphoxides have been established by o.r.d. and c.d. observations and these are in agreement with those obtained from chemical correlations. The stereochemistry of the oxidation of 1-phenylethyl *p*-tolyl sulphide to the sulphoxides is discussed in the light of the observed isomer distributions.

ASYMMETRIC induction occurs in the oxidation of sulphides to sulphoxides if the starting sulphide has a diastereotopic sulphur atom. Thus Cram and Pine[1] applied the principles of steric control of asymmetric induction[2] to the oxidation of (*R*)-2-octyl phenyl sulphide (I) and assigned the (*RR*) configuration to the high-melting sulphoxide rather than the low-melting one [equation (1)]. This assignment was made on the reasonable assumption that the oxidizing agent attacks the electron pair on sulphur which is in the least sterically hindered position in the most stable conformer (which has *trans*-coplanar phenyl and n-hexyl groups) and was supported by consideration of some thermodynamic data.[1] Mislow and his co-workers, however, pointed out that this assignment was incorrect in view of their o.r.d. results[3,4] which were confirmed by the *X*-ray analysis of menthyl *p*-iodobenzenesulphinate.[5]



$$n\text{-}C_6H_{13}\text{-}\overset{\text{Me}}{\underset{\text{H}}{C}}\text{-S-Ph} \xrightarrow{\text{Bu}^t\text{O}_2\text{H}} n\text{-}C_6H_{13}\text{-}\overset{\text{Me}}{\underset{\text{H}}{C}}\text{-}\overset{\text{O}}{S}\text{-Ph} + n\text{-}C_6H_{13}\text{-}\overset{\text{Me}}{\underset{\text{H}}{C}}\text{-}\underset{\text{O}}{S}\text{-Ph} \qquad (1)$$

(*R*)-(I) (*RR*)-(II) (*RS*)-(II)

We recently examined the configurational assignment of the diastereoisomeric 1-phenylethyl *p*-substituted phenyl sulphoxides (IV) produced in differing amounts by peracetic acid oxidation of the corresponding sulphide (III) [equation (2)], and tentatively concluded, on the basis of the n.m.r. solvent and substituent effects on the chemical shift of the methine proton, that the

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† Presented in part at the 5th Symposium on Organosulphur Chemistry, Japan, 1971, Abstracts, p. 40.

[1] D. J. Cram and S. H. Pine, *J. Amer. Chem. Soc.*, 1963, **85**, 1096.

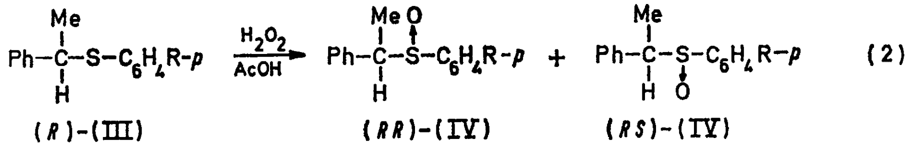
[2] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, 1952, **74**, 5828.

[3] K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1958.

[4] M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4835.

[5] E. B. Fleischer, M. Axelrod, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 1964, **86**, 3395.

high-melting major products have the (*RR*/*SS*) configuration and the low-melting minor products the (*RS*/*SR*) one.[6] Table 1 summarizes the n.m.r. data of sulphoxides (IV).


(*R*)-(III) (*RR*)-(IV) (*RS*)-(IV) (2)

R = Me,H,Cl or NO_2

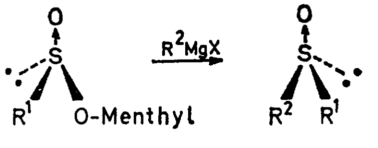
This conclusion is in line with that drawn from a conformational analysis along the lines used by Cram and Pine.[1] However, since we felt from other results [1,3,7] that this assignment might not be valid, we re-examined the absolute configuration of the diastereoisomeric 1-phenylethyl *p*-tolyl sulphoxides (IV; R = Me) by chemical correlations and found that the earlier conclusion [6] was in error.[8] This is a surprising result since to explain the evidence in Table 1 on the basis of the revised assignent we must conclude either that the conformer having *trans*-oriented phenyl groups is not important, or that the consideration of n.m.r. solvent effects which is based on reliable evidence [9] is not valid in the present case.

TABLE 1

Solvent and substituent effects on the methine chemical shifts of 1-phenylethyl *p*-substituted phenyl sulphoxides (IV)

	$\tau(CF_3CO_2H) - \tau(CCl_4)$				$\tau(C_6H_6) - \tau(CCl_4)$			
R	Me	H	Cl	NO_2	Me	H	Cl	NO_2
Major	−0·84	−0·76	−0·72	−0·61	+0·09	+0·14	+0·22	+0·37
Minor	−0·64	−0·59	−0·51	−0·50	+0·21	+0·25	+0·35	+0·57

It is important to establish the absolute configuration of (IV) beyond any shadow of doubt, since this constitutes the key link in deducing the stereochemistry of the α-sulphinyl carbanion.[10] To remove the remote possibility that the reaction of menthyl sulphinate with phenylethylmagnesium chloride may proceed with retention of the configuration in this particular case {though there are precedents [3,4,11] that the general reaction [equation (3)] is stereospecific and proceeds with inversion at sulphur} we examined the o.r.d. and c.d. spectra of optically active sulphoxides prepared by two independent routes. The results allow comment on the stereochemistry of the diastereoisomeric transition states in the oxidation of sulphides to sulphoxides.



(3)

EXPERIMENTAL

N.m.r. spectra were determined for deuteriochloroform solutions on a JEOL JNM-4H-100 100 MHz instrument. O.r.d. and c.d. spectra were measured with a JELCO UV-5 automatic recording spectrophotometer.

Treatment of Menthyl Toluene-p-*sulphinate with* 1-*Phenylethylmagnesium Chloride*.—To a solution in ether of optically pure (*S*)-menthyl toluene-*p*-sulphinate (0·025 mol), $[\alpha]_D$ −200° (*c* 5, acetone), was added 1-phenylethylmagnesium chloride (0·05 mol) during 30 min. After addition was complete, the mixture was refluxed for 8 h, and then treated with saturated ammonium chloride. The ether was removed to give an oil which was dissolved in light petroleum (100 ml) and left at 0° for 12 h. The crystalline precipitate was filtered and washed with light petroleum giving a mixture of diastereoisomeric sulphoxides (2·7 g), $[\alpha]_D$ +67° (acetone). This was recrystallized from ethanol and twice from ligroin giving pure sulphoxide (IVa) as needles, $[\alpha]_D$ −11° (*c* 19, acetone), m.p. 122°, τ 8·33 (d, α-Me) and 6·23 (q, CH). The mother liquor was chromatographed on 100—200 mesh silica gel with light petroleum–ether (2 : 1) as eluant, and gave pure sulphoxide (IVb), $[\alpha]_D$ +183° (*c* 4, acetone), m.p. 91°, τ 8·46 (α-Me) and 5·98 (CH).

Oxidation of (S)-1-*Phenylethyl* p-*Tolyl Sulphide to Diastereoisomeric Sulphoxides*.—(*R*)-(+)-1-Phenylethyl chloride [8] (1·6 g), $[\alpha]_D$ +80·5°, was treated in ethanol with sodium toluene-*p*-thiolate, prepared from *p*-thiocresol (1·7 g) in ethanol with sodium (0·32 g), to give (*S*)-(−)-1-phenylethyl *p*-tolyl sulphide (2·3 g), $[\alpha]_D$ −130° (neat, 10 cm). This was treated in AcOH (10 ml) at 0° with 30% hydrogen peroxide (1·1 ml) and then left for 5 h at room temperature. Dilution of the mixture with water gave an oily precipitate which solidified slowly. This was filtered and washed thoroughly with water giving crude sulphoxides (1·7 g). This material was a 2·5 : 1 mixture of diastereoisomeric sulphoxides (by n.m.r.). Two recrystallizations from

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[6] M. Nishio, *Chem. Comm.*, 1969, 51.

[7] (*a*) F. G. Bordwell, D. D. Phillips, and J. M. Williams, *J. Amer. Chem. Soc.*, 1968, **90**, 426; (*b*) C. Y. Meyers and A. M. Malte, *ibid.*, 1969, **91**, 2123.

[8] M. Nishio and K. Nishihata, *Chem. Comm.*, 1970, 1485.

[9] P. Laszlo, *Progr. N.M.R. Spectroscopy*, 1966, **3**, 348.

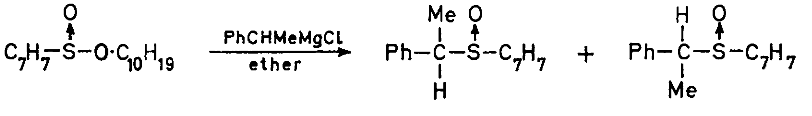
[10] (*a*) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, 1965, **87**, 5489; (*b*) M. Nishio, *Chem. Comm.*, 1968, 562; (*c*) R. M. Carlson and P. M. Helquist, *J. Org. Chem.*, 1968, **33**, 2596; (*d*) R. R. Fraser and F. J. Schuber, *Chem. Comm.*, 1969, 397; (*e*) A. Rauk and S. Wolfe, *Canad. J. Chem.*, 1969, **47**, 113; (*f*) M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1969, 607; (*g*) S. Iriuchijima and G. Tsuchihashi, *Tetrahedron Letters*, 1969, 5259; (*h*) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Amer. Chem. Soc.*, 1969, **91**, 3839; (*i*) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148; (*j*) K. Nishihata and M. Nishio, *Chem. Comm.*, 1971, 958; (*k*) T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **92**, 3077; (*l*) R. Lett, S. Bory, B. Moreau, and A. Marquet, *Tetrahedron Letters*, 1971, 3255; (*m*) K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 1972, 1730; (*n*) *Tetrahedron Letters*, 1972, 4839.

[11] (*a*) C. J. M. Stirling, *J. Chem. Soc.*, 1963, 5741; (*b*) K. K. Andersen, *J. Org. Chem.* 1964, **29**, 1953; (*c*) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 1964, **86**, 5637; (*d*) D. N. Jones and M. J. Green, *J. Chem. Soc.* (*C*), 1967, 532.

ligroin gave pure sulphoxide (IVd), the major product, $[\alpha]_D$ −8° (*c* 15, acetone), m.p. 122°, n.m.r. spectrum identical with that of (IVa). The mother liquor was twice chromatagraphed on silica gel with light petroleum–ether (3 : 1) as eluant, giving the pure sulphoxide (IVc), $[\alpha]_D$ −171° (*c* 1, acetone), m.p. 86—88°. N.m.r. spectrum identical to that of (IVb).

Equilibrations.—Racemic (*RS*/*SR*)-(IV) (0·5 g) was dissolved in sodium methoxide (0·01 mol) in methanol (20 ml) and refluxed for 5 h. N.m.r. analysis of the resulting mixture revealed that it consisted of 2 : 1 (*RS*/*SR*)-(IV) : (*RR*/*SS*)-(IV).

Oxidations.—Care was exercised to minimize oxidation to the sulphone and to avoid any loss in the extraction of products. The sulphoxides were repeatedly extracted from aqueous solutions with methylene chloride in the presence of saturated sodium chloride.



$$C_7H_7-\overset{O\uparrow}{S}-O\cdot C_{10}H_{19} \xrightarrow[\text{ether}]{\text{PhCHMeMgCl}} Ph-\underset{H}{\overset{Me}{C}}-\overset{O\uparrow}{S}-C_7H_7 + Ph-\underset{Me}{\overset{H}{C}}-\overset{O\uparrow}{S}-C_7H_7 \qquad (4)$$

(*RR*)-(+)-(IVb) (*SR*)-(−)-(IVa)

(a) *Hydrogen peroxide in acetone.* To an acetone (30 ml) solution of the sulphide (2·3 g) was added 30% hydrogen peroxide (1·1 ml). The solution was refluxed for 2 h and diluted with water. Acetone was removed before extraction.

(b) *Hydrogen peroxide in acetic acid.* To an acetic acid (10 ml) solution of the sulphide (2·3 g) was slowly added 30% hydrogen peroxide (1·1 ml) at 0°. The solution was stirred for 5 h at 0° and diluted with water. It was then neutralized with aqueous sodium carbonate prior to extraction.

(c) *Hydrogen peroxide in trifluoroacetic acid.* A similar procedure as that described above was used for this solvent.

TABLE 2

O.r.d. and c.d. spectra of 1-phenylethyl *p*-tolyl sulphoxides (in ethanol)

Compound	Conc. (g l^{-1})	λ/nm ([φ]) [a]					
(IVa) (*SR*)	0·153	350 (+1600)	300 (+4800)	279pk (+16,000)	259z	234tr (−115,000)	221z
(IVb) (*RR*)	0·141	350 (+3500)	300 (+15,500)	279pk (+46,000)	258z	233tr (−194,000)	221z
(IVc) (*SS*)	0·144	350 (−3100)	300 (−11,000)	278tr (−25,100)	256z	234pk (+158,000)	221z

	λ/nm ([θ])		
(IVa)	310 (0)	252max (+47,000)	224min (−112,000)
(IVb)	300 (0)	251max (+94,000)	223min (−144,000)
(IVc)	300 (0)	252min (−60,000)	223max (+82,000)

[a] pk = Peak, tr = trough, z = points at which the zero-rotation axis is crossed.

(d) *Sodium metaperiodate.* The sulphide (2·3 g) in ethanol (50 ml) was added to an aqueous solution of sodium metaperiodate (2·3 g) in water (50 ml) at 0°. The mixture was stirred for 12 h at 0° and filtered. Ethanol was removed prior to work-up.

(e) *t-Butyl hypochlorite.* To a methanol (100 ml) solution of the sulphide (2·5 g) was added t-butyl hypochlorite (1·1 g) at −78° and this was left for 1 h at −78°. Sodium carbonate was added to the solution prior to extraction. The resulting product contained *ca.* 50% unchanged sulphide.

(f) *Iodobenzene dichloride.* To an 80% aqueous pyridine (30 ml) solution of the sulphide (2·5 g) was added dropwise iodobenzene dichloride (2·7 g) in pyridine (30 ml) at 0°. This was stirred for 1 h at 0° and diluted with water prior to work-up. The product was contaminated with *ca.* 50% unchanged sulphide.

RESULTS AND DISCUSSION

Treatment of (*S*)-(−)-menthyl toluene-*p*-sulphinate with 1-phenylethylmagnesium chloride gave a *ca.* 1 : 1 mixture of 1-phenylethyl *p*-tolyl sulphoxides [equation (4)]. Chromatography on silica gel afforded the pure diastereoisomers (IVa) and (IVb). The o.r.d. and c.d. characteristics for these sulphoxides are listed in Table 2. Both diastereoisomers exhibit o.r.d. curves with the mid-point of the Cotton effect at 249 nm, and c.d. curves with the maximum at 252 and 251 nm, and the minimum at 224 and 223 nm, respectively. This demonstrates that the isomers have the (*R*) configuration at sulphur, since it has been established by Mislow,[3] that in alkyl aryl sulphoxides, the Cotton effect corresponding to the u.v. primary band occurring at *ca.* 235—255 nm (which has been considered to arise from coupling between the forbidden benzene $\pi \longrightarrow \pi^*$ and the allowed sulphoxide $n \longrightarrow \pi^*$ transitions[3,12]) has a high molecular amplitude and the positive sign characterizes the absolute (*R*) configuration. The c.d. data correspond well with those of Stirling[11a] that (*R*)-(+)-benzyl

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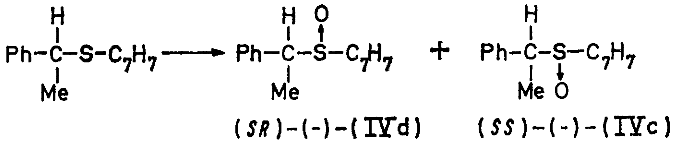
[12] G. Leandri, A. Mangini, and R. Passerini, *J. Chem. Soc.*, 1957, 1386.

p-tolyl sulphoxide has a positive and a negative extremum at 250 and 220 nm, with [θ] +86,000 and −125,000 respectively. This result demonstrates that the above reaction proceeded with inversion of the configuration and establishes that the earlier assignments by chemical correlation[8] are correct.

Treatment of (*S*)-(−)-1-phenylethyl *p*-tolyl sulphide[8] with peracetic acid at room temperature gave a *ca.* 2·5 : 1 mixture of the diastereoisomeric sulphoxides. Chromatography on silica gel afforded pure materials (IVc) and (IVd). The minor component (IVc) exhibited o.r.d. and c.d. spectra (see Table 2) which were essentially enantiomeric to those of (IVa) and (IVb) indicating that this isomer has the (*S*) configuration at sulphur. This also is in accord with the chemical correlation result which requires the minor component of the oxidation products to have the (*SS*) configuration [equation (5)].



$$\mathrm{Ph{-}\overset{H}{\underset{Me}{C}}{-}S{-}C_7H_7 \longrightarrow Ph{-}\overset{H}{\underset{Me}{C}}{-}\overset{O}{\overset{\uparrow}{S}}{-}C_7H_7 + Ph{-}\overset{H}{\underset{Me}{C}}{-}\underset{O}{\underset{\downarrow}{S}}{-}C_7H_7} \quad (5)$$

(*SR*)-(-)-(IVd) (*SS*)-(-)-(IVc)

Invalidation of the earlier n.m.r. method[6] calls into question the basis on which the earlier assignment was made and suggests that conformers with *trans*-phenyl groups, which were *a priori* considered to be most populated, are in fact not important in these cases. This is an unusual circumstance in view of the steric factors involved. In this connection, the origin of the erroneous conclusions on the configurational assignments of diastereoisomeric 2-octyl phenyl sulphoxides[1] and of (±)- and *meso*-bis-1-phenylethyl sulphones[7] should also be considered.

It is known that axially oriented oxygen on sulphur in thian 1-oxides is energetically preferred to the equatorial configuration.[13,14] Johnson has suggested that an attractive interaction between the oxygen and the ring accounts for this,[13] and this has been substantiated by a theoretical study.[15] An analogous argument applied to this conformationally mobile system, *i.e.*, possible creation of a favourable interaction between the oxygen atom and another part of the molecule, may provide some explanation of the present result. However, the evidence does not allow a clear conclusion to be drawn. In view of this, dipole moment studies are currently being undertaken.

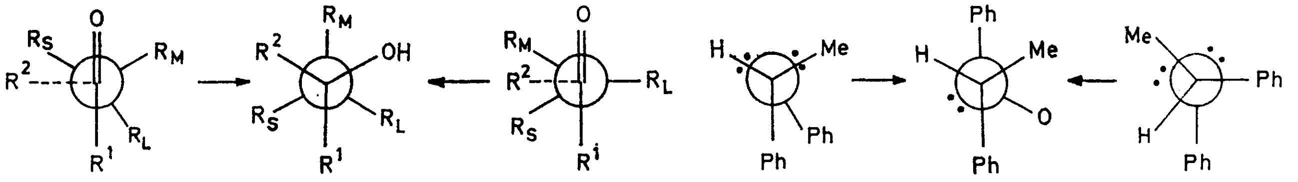


FIGURE (a) Cram's open-chain model, (b) Felkin's model. (c) and (d) represent models corresponding to (a) and (b) respectively. The conformation of the products depicted are not necessarily the most stable.

The result also raises the problem of the topology of the diastereoisomeric transition states in the oxidation of sulphides. In order to establish whether the nature of the oxidant or the solvent determines the stereochemistry of the product for acyclic sulphides as they do for cyclic sulphides, we examined the effect of reagent on the product ratio of the diastereoisomeric sulphoxides. Product analyses were made by integration of the n.m.r. spectra of total crude materials (Table 3).

The results, although the number of oxidizing agents is rather limited, show that the proportion of the diastereoisomeric sulphoxides is not significantly affected by change in the oxidant in this case. Oxidation with peroxides, periodate, hypochlorite, and iodobenzene dichloride result in a preponderance of (*RS*/*SR*)-(IV) which, as it happens, is the thermodynamically more stable isomer. That this is not a result of thermodynamic control is apparent by the fact that the oxidation with hypochlorite was conducted at −78° and

TABLE 3

Oxidation of 1-phenylethyl *p*-tolyl sulphide

Condition	(°C)	(*RS*/*SR*)-(IV) : (*RR*/*SS*)-(IV)
Hydrogen peroxide in acetone	57	2·9 : 1
Hydrogen peroxide in AcOH	0	2·5 : 1
Hydrogen peroxide in CF_3CO_2H	0	1·7 : 1
Sodium metaperiodate in aqueous EtOH	0	2·5 : 1
t-Butyl hypochlorite in MeOH	−78	1·6 : 1
Iodobenzene dichloride in pyridine–H_2O	0	1·6 : 1

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[13] (*a*) C. R. Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 1020; (*b*) C. R. Johnson and D. McCants, jun., *ibid.*, 1965, **87**, 1109.

[14] J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936; (*b*) J. B. Lambert, R. C. Keske, and D. K. Weary, *ibid.*, 1967, **89**, 5921.

[15] N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminsky, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

is suggested by Johnson's finding that the less stable *trans*-sulphoxide preponderates in the oxidation mixture of 4-t-butylthians with peroxy-reagents.[13]

The predominant formation of the (*RS*/*SR*)-isomer cannot be expected from a transition state with a *trans*-coplanar arrangement of the phenyl groups. This is a possible mechanism based principally on the open-chain model of Cram's rule [2,16] since the present result is formally ascribed to it. More attractive is a mechanism analogous to Felkin's model,[17] where the importance of the steric interaction between the entering group (R^2) and the achiral group (R^1) has been stressed. The present result may also be formally ascribed to this (see Figure). An increase in the selectivity with increasing steric bulk in R^1 is expected from Felkin's model. Our preliminary observation on the peracid oxidation of 1-phenylethyl t-butyl sulphide gives a result * suggestive of this mechanism.

[2/1319 *Received*, 12*th June*, 1972]

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* Almost exclusive formation of (*RR*/*SS*)-1-phenylethyl t-butyl sulphoxide occurs which corresponds to (*SR*/*RS*)-(IV). A systematic study on the effect of variation of the bulk of the achiral group will form the subject of a future paper.

[16] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.*, 1959, **81**, 2748. See also D. J. Cram and D. R. Wilson, *ibid.*, 1963, **85**, 1245; G. J. Karabatsos, *ibid.*, 1967, **89**, 1367.

[17] M. Cherest, H. Felkin, and N. Prudent, *Tetrahedron Letters*, 1968, 2199.