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ELIMINATION OF THE ALKYLAMINO GROUP FROM DIASTEREOISOMERIC 2-BENZENESULPHONYL-3-DIMETHYLAMINOBUTANES

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Abstract—The synthesis of the title compounds is described. When these are heated in aqueous media, the alkylamino residue is quantitatively eliminated. An intramolecular elimination process with partial carbanionic character is found for both compounds. Whereas the *threo* compound undergoes a stereospecific *syn*-elimination in agreement with the proposed mechanism, the *erythro* isomer gives a mixture of products, probably as a result of partial inversion of the carbanionic intermediate.

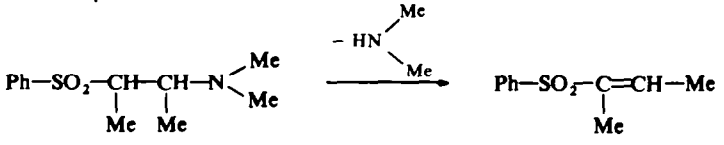
INVESTIGATIONS WERE carried out earlier[1] on the reactivity of β-activated alkylene-X-amine systems with thiophenols in aqueous organic media:

$$Ar{-}X{-}CH_2{-}CH_2{-}NR_2 + HS{-}Ar' \rightarrow Ar{-}X{-}CH_2{-}CH_2{-}S{-}Ar' + HNR_2$$

$$X = \rangle C{=}O,\ \rangle SO_2$$

It was found that the reaction proceeds by elimination of the alkylamino residue followed by addition of the thiol to the resulting double bond: an intramolecular elimination mechanism was proposed for the first stage.

To extend the above investigations and to verify the stereochemistry of the reaction mechanism, the elimination of the alkylamino residue from the diastereoisomeric 2-benzenesulphonyl-3-dimethylaminobutanes (Ia and Ib) has now been investigated:



Ia, Ib IIa, IIb

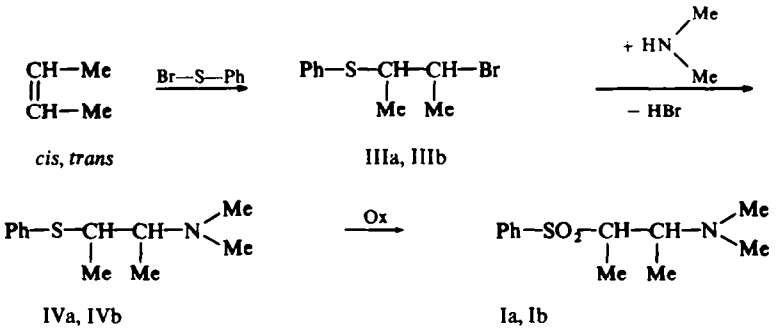
This reaction takes place when solutions of Ia and Ib are heated, and leads quantitatively to the vinyl sulphones IIa and IIb.

RESULTS

Products studies

Ia and Ib were synthesized by a series of steps of known stereochemical course starting with the commercially available isomeric 2-butenes.

Addition of the sulphenyl halide to the double bond is a *trans* addition.[2] The subsequent aminolysis proceeds with retention of configuration, as has also been



SCHEME A

found for acetolysis[3] and for substitution with thiol reagents[4] on analogous β-halothioesters. The *threo* β-amino sulphide (IVa) is thus obtained from *cis*-2-butene, and the *erythro* derivative (IVb) from the *trans*-alkene.

Subsequent oxidation of the sulphides to sulphones was carried out by one of the usual methods. The ^{1}H-NMR spectra of the diastereoisomers synthesized were recorded; the chemical shifts and coupling constants are given in the experimental section (Table 4).

The *erythro* derivatives of the series of compounds have higher coupling constants for the vicinal hydrogens than the *threo* isomers, as was also found by other authors[5] for various pairs of diastereoisomers. However, there are cases in which this tendency is not followed.[6]

On deuteration of the β-amino sulphones Ia and Ib, the two diastereoisomers were found to differ in their behaviour. On treatment with n-BuLi in anhydrous ether and then with D_2O, these compounds both gave the same compound deuterated α to the sulphonyl group (Va) in quantitative yield. The *threo* configuration is assigned to this product on the basis of comparison with the ^{1}H-NMR spectra of Ia and Ib (experimental).

In MeOD/NaOMe,[7] on the other hand, *erythro* isomer (Ib) gives the deuterated compound (Vb) (*erythro*) together with a small percentage of Va.

The alkylamino residue was eliminated from the derivatives Ia and Ib by refluxing in water-dioxane (1 : 1 v/v) buffered at pH 11.

When the *threo* isomer (Ia) is used, only 2-benzenesulphonyl-2-butene (IIa) is obtained; the *erythro* isomer (Ib), gives a mixture of the two isomeric alkenes, from which isomer IIb (30%) can be separated. Tests were carried out to check that the starting isomers (Ia, Ib) and individual alkenes (IIa, IIb) do not isomerise under the reaction conditions.

Examination of the ^{1}H-NMR spectra of the two isomeric alkenes and comparison with the literature data[8] for angelic and tiglic acids and their esters shows that the *cis*-Me structure may be assigned to the alkene IIa and the *trans*-Me structure to the isomer IIb (see Scheme B).

Elimination carried out under various experimental conditions on the diastereoisomeric 2-benzenesulphonyl-3-bromobutanes (VIa; *threo* and VIb; *erythro*) led stereospecifically to the alkenes IIb and IIa respectively, as had already been observed by other authors[9, 10] for similar compounds.

Rates studies

The quantitative investigations of the elimination of the alkylamino residue from the β-amino sulphones Ia and Ib was carried out at 88° in buffered aqueous solution, the reagents and products being soluble in water at the concentrations and at the temperature used. The reaction rate was measured by following the disappearance of compounds Ia and Ib spectrophotometrically (experimental).

The reaction was found to be first order with respect to the β-amino sulphones for at least two half-lives. The rate constants increased rapidly with increasing pH of the buffer up to pH values close to the pK_a value of the bases, and then remained constant (Table 1).

In the pH range examined, the values of the rate constants for the compound Ia are roughly double those for the isomer Ib.

The reaction constants were determined in the temperature range 50 to 88°; the activation parameters found are shown in Table 2.

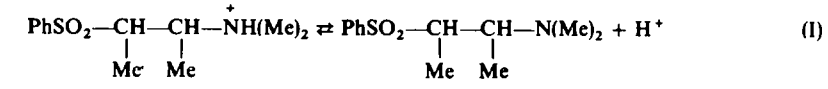
For all the pH values and temperatures used, while Ia gave only the *cis*-alkene (IIa), Ib gave a mixture of the two isomers. The ratio, as determined by gas chromatography, was found to be independent of the pH, reaction time, and reaction temperature.

By investigation of the reactivities of the two diastereoisomers Va and Vb, it was possible to determine the isotope effect for the reactions investigated, which was found to be equal for the two isomers (k_H/k_D = 3·2 at 88°). Compounds Va and Vb also give the same distribution of the elimination products as Ia and Ib.

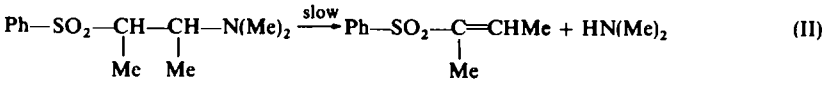
When the reaction was carried out on the two isomers (Ia and Ib) at pH 11 in D_2O, no appreciable isotope exchange was observed in the products remaining after 50% reaction.

DISCUSSION

On the basis of these results and by analogy with the findings in the earlier investigations,[1] the elimination can, in buffered solutions, be represented for the two diastereoisomers as follows:



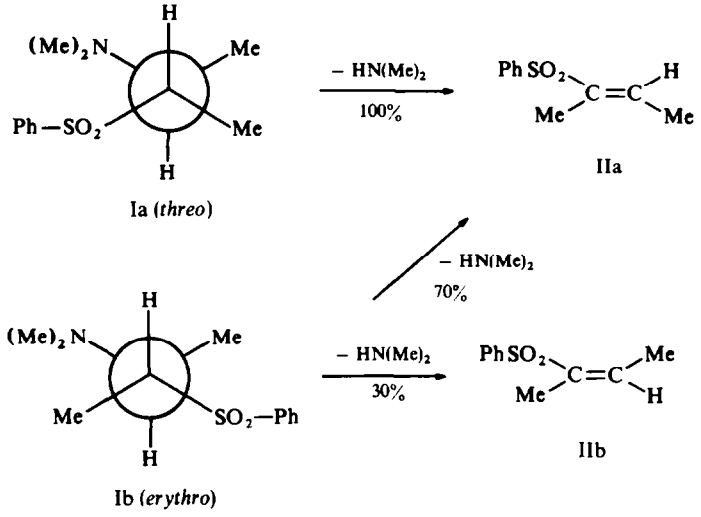
(I)



(II)

Step I is an acid-base equilibrium, in which the relative concentrations of the acid and of the conjugate base are fixed by the pH of the buffer. In step II, i.e. the elimination of the alkylamino residue, the reactive species is the free base. When the base is completely available (pH of buffer > pK_a of the base), no further increase in the rate constants is found when the pH is increased.

In this case, unlike earlier observations,[1] step II is not complicated by the addition of the amine to the alkene, which has a very low reactivity, as can also be deduced from observations made by Stirling.[11]



SCHEME B

The variation of the rate constants with the pH rules out base catalysis, and suggests an intramolecular mechanism in which the extraction of the proton α to the sulphonyl group is effected by the amine nitrogen. The value of the isotope effect (k_H/k_D = 3·2) for the two isomers also indicates a process having a partial carbanionic character[12] in the rate-determining step of the reaction.

The values of ΔS^{**} are negative and indicate a higher degree of order in the transition state than in the ground state, in agreement with the proposed mechanism.

The difference between the rate constants found for the two isomer ($k_{threo} \simeq 2k_{erythro}$) may be due to the greater steric hindrance produced when the $C_6H_5SO_2$ and Me groups are brought into the same plane, as is necessary for the *erythro* isomer Ib (cf. Scheme B). A course of this type has already been observed by other authors[9] for a similar case.

TABLE 1. RATE CONSTANTS FOR THE REACTION OF IA AND IB AT VARIOUS pH AT 88°

	Ia	Ib
pK_a^a	7·2	7·9
pH		$k \times 10^6$ sec^{-1}
5[b]	29	13
6·1[b]	229	98
7·1[b]	577	261
8[b]	941	373
9[c]	922	540
10[c]	953	547
11[c]	945	578

[a] at 25°; [b] phosphate buffer; [c] borate buffer

TABLE 2. RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE REACTION OF IA AND IB AT PH 11

Ia			
temp	$k \times 10^6$ sec^{-1}	ΔH^{**} (kcal mole^{-1})	ΔS^{**} (e.u.)
88	945	20 ± 0·5	− 18 ± 2
78	442		
65	132		
50	34		
Ib			
temp.	$k \times 10^6$ sec^{-1}	ΔH^{**} (kcal mole^{-1})	ΔS^{**} (e.u.)
88	578	22 ± 0·5	− 11 ± 2[a]
78	283		
65	78		
50	21		

[a] Without datum at 50°

The recent literature contains numerous results from the investigation of the *syn-anti* elimination dichotomy in acyclic systems,[13] and the various factors that could influence this have been analysed.[14]

In the case of the 2-arylsulphonyl-3X-butanes (X = Bs, I), it was found[9,10] that these compounds react by a stereospecific *trans*-elimination under various experimental conditions. This was confirmed by us for the compounds VIa and VIb (X = Br).

The kinetic data reported above for the compounds Ia and Ib show that the elimination is intramolecular. The extracting base, the alkylamino group, and the hydrogen α to the SO_2 come to lie on the same side, and this leads to a transition state (probably cyclic, involving a molecule of water), which is conformationally related to a syn-elimination.

This is confirmed by the stereochemical course found for the *threo* isomer (Ia), which gives the alkene IIa as only product (Scheme B).

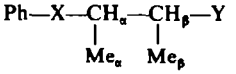
The *erythro* isomer (Ib), gives a mixture of the two alkenes (Scheme B). The parallelism found in the kinetic behaviour of the two isomers leads to the assumption of the same mechanism for both reactions.[15] It is probable that a carbanionic intermediate

TABLE 3. ELIMINATION REACTION OF IA AT PH 8 AND 88°

Time sec.	Optical density, D at 266 mμ
150	0·690
300	0·600
590	0·470
850	0·350
1200	0·260
1550	0·190
1800	0·140
2150	0·100

k from slope 950 × 10^{-6} sec^{-1}
k from least squares 941 × 10^{-6} sec^{-1} (r = 0·999)

TABLE 4. DATA OBTAINED FROM THE ANALYSIS OF THE ^1H NMR SPECTRA AT 60 MHz[a]



Compounds					Chemical shift (τ) ppm[b]					Coupling constants H_2		
	X	Y	Isomer	Solv.	α-H d.q.	β-H d.q.	α-CH_3 d.	β-CH_3 d.	$N(Me)_2$ s.	H_α-H_β	H_α-CH_α	H_β-CH_β
IIIa	S	Br	*threo*	CS_2	6·35	5·75	8·60	8·32	—	3·15	7·05	6·90
IIIb	S	Br	*erythro*	CS_2	6·80	5·90	8·60	8·25	—	6·35	6·75	6·75
VIa	SO_2	Br	*threo*	CS_2	6·52	5·21	8·65	8·25	—	2·55	7·05	7·05
VIb	SO_2	Br	*erythro*	CS_2	6·93	5·48	8·70	8·25	—	3·90	6·90	6·90
IVa	S	$N(Me)_2$	*threo*	CS_2	6·68	7·57	8·85	9·00	7·80	6·35	6·75	6·60
IVb	S	$N(Me)_2$	*erythro*	CS_2	6·98	7·60	8·73	8·92	7·81	8·70	6·70	6·70
	S	$N(Me)_2 \cdot HCl$	*threo*	$CDCl_3$	6·05	6·73	8·45	8·55	7·21	3·00	6·90	6·90
	S	$N(Me)_2 \cdot HCl$	*erythro*	$CDCl_3$	6·02	6·33	8·49	8·55	7·02	3·15	7·05	7·05
Ia	SO_2	$N(Me)_2$	*threo*	$CDCl_3$	6·70	6·85	8·68	8·98	8·05	5·25	6·75	6·75
Ib	SO_2	$N(Me)_2$	*erythro*	$CDCl_3$	6·90[c]		8·75[c]		7·83	—	—	—

[a] Solution 20% w/v; [b] s., singlet; d., doublet; d.q., double-quartet; [c] multiplet not analyzed

occurs in a fast and irreversible step of the reactions and that it can undergo inversion,[16] in the case of the *erythro* isomer, at a rate comparable with the rate of the elimination, with the result that a mixture of the alkenes is formed. This inversion is understandable since the deuteration experiments showed that the carbanion of the *erythro* isomer is less stable than that of the *threo* isomer.

EXPERIMENTAL

M.ps and b.ps are uncorrected. ^{1}H-NMR spectra were recorded with a Jeolco C-60 H L spectrometer, TMS as internal reference. The chemical shifts are in ppm (τ) (±0·01) and coupling constants (*J*) in Hz (±0·05). IR spectra were recorded with a Beckman 5 IR spectrometer and UV spectra with a Beckman DU instrument. The pH measurements were carried out with a glass electrode connected to a Beckman Zeromatic pH meter, a calomel electrode being used as the standard. Microanalyses were carried out with an F and M 185 CHN Analyser. The gas–chromatographic determinations were carried out with a Carlo Erba Fractovap GV with a 2 m column packed with silicone SE 30 (5%) on Chromosorb W (60–80 mesh) at 180°, N_2 as carrier gas.

threo-2-*Phenylthio*-3-*bromobutane* (IIIa). A current of *cis*-butene (Fluka) was bubbled into a solution of sulphenyl bromide in $CHCl_3$ until the solution was decolorized, the temperature being kept below 0°. The solvent was evaporated under vacuum, and the residue distilled. B.p. 88–91°/0·4 mm. Yield 90% (Found: C, 48·82; H, 5·40. $C_{10}H_{13}BrS$ requires: C, 48·98; H, 5·34%).

erythro-2-*Phenylthio*-3-*bromobutane* (IIIb). The same procedure was used for the preparation of the *erythro* derivative, starting with *trans*-butene (Fluka). B.p. 87–89°/0·3 mm. Yield 92% (Found: C, 48·89; H, 5·36. $C_{10}H_{13}BrS$ requires C, 48·98; H, 5·34%).

threo-2-*Benzenesulphonyl*-3-*bromobutane* (VIa). Compound IIIa was oxidised in $CHCl_3$ with the stoichiometric quantity of *m*-chloroperbenzoic acid. B.p. 141°/0·1 mm (Found: C, 43·65; H, 5·01. $C_{10}H_{13}BrO_2S$ requires: C, 43·33; H, 4·72%).

erythro-2-*Benzenesulphonyl*-3-*bromobutane* (VIb). The product was obtained as described above with isomer IIIb as the starting material. It had m.p. 59–61°/EtOH). (Found: C, 43·71; H, 4·58. $C_{10}H_{13}BrO_2S$ requires: C, 43·33; H, 4·72%).

threo-2-*Phenylthio*-3-*dimethylaminobutane* (IVa). A solution of IIIa in benzene or EtOH was introduced into an autoclave with excess Me_2NH and heated to 65° for 8 hr. After cooling, the mixture was washed with 10% NaOH and dried (Na_2SO_4). Yield 96%: b.p. 97–99°/0·7 mm (Found: C, 68·88; H, 8·93; N, 6·67. $C_{12}H_{19}NS$ requires: C, 68·86; H, 9·15; N, 6·69%).

Hydrochloride m.p. 117–8° (from acetone). (Found: C, 58·91; H, 8·34; N, 5·79. $C_{12}H_{20}ClNS$ requires: C, 58·63; H, 8·20; N, 5·69%).

erythro-2-*Phenylthio*-3-*dimethylaminobutane* (IVb). The *erythro* compound was prepared in the same manner, with IIIb as the starting material. Yield 98% b.p. 96–98°/0·3 mm (Found: C, 68·65; H, 9·11; N, 6·68. $C_{12}H_{19}NS$ requires: C, 68·86; H, 9·15; N, 6·69%). Hydrochloride m.p. 121° (from EtOAc) (Found: C, 58·19; H, 8·73; N, 5·82. $C_{12}H_{20}ClNS$ requires: C, 58·63; H, 8·20; N, 5·69%).

threo-2-*Benzenesulphonyl*-3-*dimethylaminobutane* (Ia). This product was prepared by oxidation of IVa with aqueous $KMnO_4$ acidified with H_2SO_4.

The mixture was made alkaline and extracted with ether. The ether solution was dried (Na_2SO_4) and evaporated. Yield 80%. Hydrochloride m.p. 169–70° (from acetone) (Found: C, 52·19; H, 7·42; N, 5·20. $C_{12}H_{20}ClNO_2S$ requires: C, 51·88; H, 7·25; N, 5·04%) pK_a 7·2 in water at 25°. UV (HCl 10^{-3} N) λ_{max} 260 mμ (log ε = 3·00); λ_{max} 266 mμ (log ε = 3·14); λ_{max} 274 mμ (log ε = 3·08).

erythro-2-*Benzenesulphonyl*-3-*dimethylaminobutane* (Ib). The *erythro* (Ib) was obtained by a procedure similar to that described above. Yield 82%. M.p. 60–62° (from petroleum ether) (Found: C, 59·99; H, 8·01; N, 5·76. $C_{12}H_{19}NO_2S$ requires: C, 59·71; H, 7·93; N, 5·80). UV (HCl 10^{-3} N) same as *threo* isomer.

threo-2-*Benzenesulphonyl*-2-D-3-*dimethylaminobutane* (Va). An equimolar quantity of n-BuLi in ether was slowly added to a well stirred solution of Ia in dry ether at − 20° under N_2. The mixture was allowed to stand for one hr, then a small excess of D_2O added. The organic phase was dried and evaporated. Yield 95%. Hydrochloride m.p. 168–170° (from acetone). The ^{1}H-NMR spectrum in solution ($CDCl_3$; 10%) showed complete isotope exchange τ 2·31 (5H, m., aromatic); 6·68 (1H, q., H_α); 8·05 (6H, s., N/Me_2 8·68 (3H, s., Me_α) 8·94 (3H, d., Me_β) (*cf.* Table 4).

When Ib was subjected to the same treatment, it gave the above product (Va), as shown by IR and ^{1}H-NMR spectra and m.p. of hydrochloride.

erythro-2-*Benzenesulphonyl*-2-D-3-*dimethylaminobutane* (Vb). A solution of Ib in MeOD was treated with an equimolar solution of NaOMe in MeOD. The mixture was allowed to stand for 15 days at room temperature. After evaporation of solvent, the residue was crystallised from petroleum ether. The free base has m.p. 59–60°. Yield 60%. The ^{1}H-NMR spectrum in solution ($CDCl_3$; 10%) showed 90% isotope exchange. τ 2·31 (5H, m., aromatic): 6·90 (1H, q, H_β); 7·80 (6H, s., NMe_2): 8·75 (3H, s., Me_α); 8·75 (3H, d., Me_β). (*c.f.* Table 4).

(cis-*methyl*)2-*Benzenesulphonyl*-2-*butene* (IIa). (a) *From* Ia *hydrochloride*. A solution of Ia hydrochloride in aqueous dioxane (1:1) buffered at pH 11 was heated under reflux for 7 hr. Solvent was evaporated and the residue found (by GLC) to consist of a single product. M.p. 49° (EtOH). (lit[10] m.p. 51°). The ^{1}H-NMR spectrum (CCl_4; 20%): τ 2·35 (5H, m., aromatic); 3·13 (1H, q.q., vinylic H); 8·15 (3 H, d.q., Me_α); 8·21 (3H, d.q., Me_β): J_H Me_β = 6·30 Hz; $J_{Me_\alpha Me_\beta}$ = 1·05 Hz J_{Me_α} H = 1·50 Hz.

(b) *From* VIb. A solution of VIb in benzene was treated with Me_3N. The precipitate was filtered off, and the solvent evaporated. Investigation by GLC showed the presence of only one product in the residue. M.p. 49° (EtOH). The IR and ^{1}H-NMR spectra of the products obtained by the two methods are identical.

(trans- *methyl*) 2-*Benzenesulphonyl*-2-*butene* (IIb). (a) *From* Ib, Ib, when treated as described above (a for Ia), gave a mixture of alkenes, found by GLC to contain 70% of IIa.

Chromatography on an Al_2O_3 column (eluent: ligroin) gave IIa and its isomer IIb, m.p. 33° (from petroleum ether). (Found: C, 60·70; H, 6·16. $C_{10}H_{12}O_2S$ requires: C, 61·19; H, 6·16%).

The ^{1}H-NMR spectrum (CCl_4; 20%). τ 2·35 (5H, m., aromatics); 3·93 (H, q.q., vinylic); 7·90 (3H, d.q., Me_β); 8·12 (3H, d.q., Me_α): J_{H,Me_β} = 7·5 Hz; J_{H,Me_α,Me_β} = J_{H,Me_α} = 1·50 Hz.

(b) *From* VIa. Treatment of a solution of VIa in benzene with Me_3N led quantitatively to IIb.

Kinetic studies

A buffered 10^{-2} M aqueous solution of the β-amino sulphone (Ia or Ib) was allowed to react in a thermostat. Samples were taken from time to time, and the components of the acidified reaction mixture separated with CH_2Cl_2. The reaction rate was measured by following the variation of the optical density of the β-amino sulphone in the suitably diluted aqueous phase at λ = 266 mμ.

The products were determined in the dry organic phase by gas chromatography.

An example of the decrease in the optical density with time is shown in Table 4.

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REFERENCES

1. A. S. Angeloni, P. De Maria, A. Fini and G. Salvadori, *Tetrahedron* **26**, 5601 (1970)
2. N. Kharasch and A. J. Havlik, *J. Am. Chem. Soc.* **75**, 3734 (1953)
3. A. J. Havlik and N. Kharasch, *Ibid.* **78**, 1207 (1956)
4. L. Benati, M. Tiecco and A. Tundo, *Boll. Sci. Fac. Chim. Ind. Bo.* XXI, 161 (1963); *Gazz. Chim. Ital.* **95**, 1189 (1965)
5. J. W. Emsley, J. Feney and L. H. Sutcliffe, *High Resolution NMR Spectroscopy* p. 690, Pergamon Press Ltd. London (1966); C. A. Kingsbury and W. B. Thornton. *J. Org. Chem.* **31**. 1000 (1966); C. A. Kingsbury and C. D. Best, *Ibid.* **32**, 6 (1967); H. G. Barlow, G. L. Fleming, R. N. Haszeldine and A. E. Tipping, *J. Chem. Soc.* (C). 2744 (1971)
6. G. H. Schmid, *Can. J. Chem.* **46**, 3415 (1968)
7. G. H. Roitman and D. J. Cram, *J. Am. Chem. Soc.* **93**, 2225, (1971)
8. R. R. Fraser, *Can. J. Chem.* **38**, 549 (1960)
9. F. G. Bordwell and P. S. Landis, *J. Am. Chem. Soc.* **79**, 1593 (1957)
10. P. S. Skell and J. H. McNamara, *Ibid.* **79**, 85 (1957)
11. S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc.* (B), 351 (1967)
12. J. F. Bunnet, *Angew. Chem.* (Int. Ed.) I, 225 (1962)
13. J. Sicher and J. Zavada, *Coll. Czech. Chem. Comm.* **33**, 1278 (1968)
14. D. S. Bailey and W. H. Saunders Jr., *J. Am. Chem. Soc.* **92**, 6904 (1970); D. S. Bailey, F. C. Montgomery, G. W. Chodak and W. H. Saunders Jr., *Ibid.* **92**, 6911 (1970)
15. W. F. Bayne and E. I. Snyder, *Tetrahedron Letters* 571 (1971)
16. D. J. Cram, *Fundamental of Carbanion Chemistry*, p. 105. Academic Press. (1965)
17. H. Lecker, *Ber. Dtsch. chem. Ges.* **58**, 412 (1925)