STEREOCHEMICAL STUDIES. LXII.*

THE HOFMANN-SAYTZEFF AND THE *syn-anti* ELIMINATION DICHOTOMY: A RELATIONSHIP BETWEEN THE TWO PHENOMENA**

†J.SICHER***, M.SVOBODA, M.PÁNKOVÁ and J.ZÁVADA

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 6

Received December 4th, 1970

The steric course of bimolecular eliminations of *erythro*- and *threo*-5-methyl-6-decyltrimethylammonium chlorides (*I*, X = $\overset{(+)}{N}(CH_3)_3$), *cis*- and *trans*-2-methylcyclododecyltrimethylammonium chlorides (*II*, X = $\overset{(+)}{N}(CH_3)_3$) and of the corresponding *p*-toluenesulphonates (*I* and *II*, X = OTs) has been studied using five different base–solvent combinations. Quantitative data have been obtained on the contribution of *syn*- and *anti*-elimination to the formation of the trialkylated olefins *III* and *V* indicating that both the processes may play an important role in dependence on the conditions used. The discovery that the two mechanisms operate in the eliminations leading to the dialkylated ("Hofmann") as well as trialkylated ("Saytzeff") olefins necessitated a reconsideration of the significance of the Hofmann - Saytzeff (H/S) ratios. For the 'onium compounds *I* and *II* (X = $\overset{(+)}{N}(CH_3)_3$), the "overall" H/S ratios have been approximately dissected into the corresponding *syn*- and *anti*-components. Two opposing trends have been found: while the *syn*-elimination shows a very strong preference for Hofmann olefin formation, *anti*-elimination shows a strong (yet less pronounced) preference for Saytzeff olefin formation. It is suggested that the opposing trends follow from different electronic characteristics of the two processes.

Recent work[1–11] has demonstrated that base induced eliminations in compounds of the type R.CH(X).CH_2.R′ to give the olefin *cis*- and *trans*-R.CH = CH.R′ do not – as had formerly been believed[12–15] – invariably proceed by *anti*-elimination. In some common E2 reactions – notably when X is an 'onium group – there is a tendency for the *trans*-olefin to be formed by *syn*-elimination, and the *cis*-olefin by *anti*-elimination. In cases where this tendency for a dual reaction mode is strongly pronounced we speak of a *syn-anti* elimination dichotomy. This discovery poses the

* Part LXI: This Journal *36*, 3140 (1971).

** This is the twenty first of a series of papers dealing with the mechanism of elimination reactions; for previous paper see ref.[1].

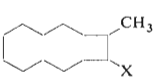
*** Deceased September 8th, 1970.

question whether *syn*-elimination is also a possible reaction mode in the formation of trialkyl substituted olefins, $R.R'C{=}CH.R''$, from substrates of the type $R.R'CH.CH(X).R''$. This question is not only interesting in its own right, but is also important in conjunction with the problem of orientation (Saytzeff *vs* Hofmann) in olefin forming elimination[13,16]. We have now investigated the base induced elimination of the

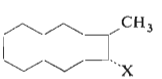
$$C_4H_9.\underset{\displaystyle CH_3}{\underset{|}{CH}}{-}\underset{\displaystyle X}{\underset{|}{CH}}.C_4H_9$$

erythro- and *threo-I*

threo- and *erythro*-pairs *I* ($X = \overset{(+)}{N}(CH_3)_3$ and OTs); since derivatives of the twelve-membered ring had earlier proved to be very useful in elimination studies[11], we also carried out a parallel investigation on the *cis-* and *trans*-pairs *II* ($X = \overset{(+)}{N}(CH_3)_3$ and OTs).



cis-II



trans-II

Five base–solvent combinations were employed for the elimination of the 'onium and three for the elimination of the corresponding tosylates (Table I).

Synthesis

The diastereoisomeric tosylates *I* (X = OTs) and the quaternary bases *I* ($X = \overset{(+)}{N}(CH_3)_3$ were synthesised starting from *cis-* and *trans*-5,6-epoxydecane which, by reaction with dimethylmagnesium[18], afforded respectively the alcohols *threo-I* and *erythro-I* (X = OH). Conversion of the alcohols to the corresponding (inverted) quaternary amines *I* ($X = \overset{(+)}{N}(CH_3)_3$ was brought about *via* the tosylates *I* (X = OTs) by reaction with sodium azide, followed by hydride reduction and quaternization. Both the alcohols and the amines were uniform by gas chromatography; moreover, since the stereochemistry of the reactions employed is known, the configuration of the tosylates and quaternary amines may be regarded as established. The configurations of the disubstituted olefins (*cis-* and *trans-IV*) follow from their infrared spectra. The trisubstituted olefins (*cis-* and *trans III*) were assigned configuration on the basis of the outcome of the elimination of the diastereoisomeric dimethylamine oxides *I* ($X = N(CH_3)_2O$). This reaction is known to be a *syn*-elimination[19]; it follows that the

TABLE I

Conditions of Elimination Reactions of 'Onium Compounds and Tosylates *I* and *II*

X[a]	Base[b]/solvent	Base, M	Volume, ml	°C	Time, h
$\overset{(+)}{N}(CH_3)_3$	CH_3OK/CH_3OH	2·0	2·0	130	30
$\overset{(+)}{N}(CH_3)_3$	$t\text{-}C_4H_9OK/t\text{-}C_4H_9OH$	1·0	2·5	110	8
$\overset{(+)}{N}(CH_3)_3$	$t\text{-}C_4H_9OK/(CH_3)_2SO$	0·5	2·5	25	2
$\overset{(+)}{N}(CH_3)_3$	$t\text{-}C_4H_9OK/C_6H_6$	0·5	3·0	130	30
OTs	$t\text{-}C_4H_9OK/HCON(CH_3)_2$	1·0	10	50	4
OTs	$t\text{-}C_4H_9OK/t\text{-}C_4H_9OK$	2·0	2·0	100	9
OTs	$t\text{-}C_4H_9OK/C_6H_6$	0·5	3·0	130	25

[a] The quaternary chlorides (100 mg) and tosylates (100 mg) were dried for several hours on the oil pump before the experiment; [b] potassium tert-butoxide was purified by sublimation at 220°C and 12 Torr.

trisubstituted olefin formed in predominant amount from the *threo*-base is the *cis*-isomer,* while that formed from the *erythro*-base must be the *trans*-isomer.** These assignments are supported by NMR evidence.

trans-2-Methylcyclododecanol (*II*, X = OH, m.p. 61 – 62°C) and *cis*-2-methylcyclododecanol (*II*, X = OH, m.p. 71 – 72°C) were obtained by oxidative hydroboration of *cis*- and *trans*-1-methylcyclododecene, respectively. An alternative synthesis consisted in reduction (catalytically or by hydride) of the readily available 2-methylcyclododecanone[20], followed by gas chromatographic separation of the *cis*- and *trans*-isomers. The conversion of the alcohols into the quaternary 'onium salts (*trans*- and *cis*-*II*, X = $\overset{(+)}{N}(CH_3)_3$) was performed by the same procedure as in the case of the open-chain compounds.

* The isomer in which both the n-butyl groups are on the same side of the double bond is designated as *cis*.

** Since the starting amines are uniform by gas chromatography, it follows that the 0·2 and 0·7% of the "other" trisubstituted olefin obtained, respectively, from the *erythro*- and *threo*-amine oxides *I* (Table II) are a measure of the stereochemical homogeneity of this reaction.

EXPERIMENTAL

erythro-5-Methyl-6-decanol

A 0·5M solution of ethereal dimethylmagnesium[18] (300 ml) was treated with *trans*-5,6-epoxydecane (20 g, 0·23 mol) and refluxed for 8 h. Gas chromatographic analysis of a sample showed that only a small part of epoxide had reacted; dioxane (200 ml) was therefore added to the reaction mixture, the ether distilled off and the residue refluxed for 16 h.

It was then diluted with ether (200 ml) and carefully treated with acetone (50 ml) followed by 1M-HCl (500 ml) and the product taken up in ether. The combined extracts were washed with 1M-HCl, water and dried. The ether was removed and the residue distilled at 110—120°C/14 Torr to yield 20 g of the crude product which was purified by preparative vapour phase chromatography on a "Carbowax" column and subsequent distillation, b.p. 106°C/12 Torr. The yield was 15 g (67%). For $C_{11}H_{24}O$ (172·3) calculated: 76·67% C, 14·04% H; found: 76·60% C, 13·95% H.

threo-5-Methyl-6-decanol

A 0·5M ethereal solution of dimethylmagnesium (300 ml) was treated with *cis*-5,6-epoxydecane (20 g, 0·13 mol). The reaction was complete after 10 h reflux. The product was isolated as described above. Purification by preparative vapour phase chromatography afforded 11·6 g (53%) of the pure product, b.p. 108°C/14 Torr. For $C_{11}H_{24}O$ (172·3) calculated: 76·67% C, 14·04% H; found: 76·71% C, 14·11% H.

erythro-5-Methyl-6-decyl *p*-Toluenesulphonate

A solution of the *erythro*-alcohol (3·45 g) and *p*-toluenesulphonyl chloride (4·2 g, *i.e.* 10% excess) made up under cooling in pyridine (15 ml) was allowed to stand at 0°C for 40 h, diluted with water, the product taken up in pentane, the pentane extracts washed with 1% hydrochloric acid, followed by water to a neutral reaction. The pentane solution was dried and the pentane removed under reduced pressure. The residue (6·35 g) was an oil which could not be made to crystallise. threo-5-*Methyl-6-decyl* p-*toluenesulphonate* was prepared from the *threo*-alcohol as described above for the *erythro*-isomer. It is an oil.

erythro-5-Methyl-6-dimethylaminodecane

A solution of *threo*-5-methyl-6-decyl *p*-toluenesulphonate (6·4 g, 0·019 mol), sodium azide (8·5 g, 0·13 mol) and sodium hydrogen carbonate (2·6 g) in dimethyl sulphoxide (130 ml) was heated under stirring to 95°C for 5 h. The cooled reaction mixture was poured into ice-cold saline (500 ml) and the product taken up in pentane. The extracts were washed with water, dried and the pentane distilled off. The crude azide (2·98 g) thus obtained was an oil; it was taken up in ether (20 ml) and treated with a solution of lithium aluminium hydride (2·5 g; 0·07 mol) in ether (75 ml). The solution was refluxed for 3 h, cooled and decomposed by addition of water (12 ml). The precipitated inorganic material was filtered off and washed thoroughly with ether. The amine was taken in 5% hydrochloric acid, set free by conc. potassium hydroxide solution and taken up in ether. The ethereal solution was dried over potassium hydroxide pellets, the ether distilled off over a column and the residue (2·25 g) subjected to methylation with formic acid–formaldehyde using the standard procedure described in detail previously[21]. The dimethylamino derivative obtained is an oil, b.p. 98—100°C/14 Torr;the overall yield was 2·27 g (57%). For $C_{13}H_{29}N$ (199·4) calculated: 78·31% C, 14·66% H, 7·03% N; found: 78·53% C, 14·65% H, 7·03% N.

threo-5-Methyl-6-dimethylaminodecane

The *erythro*-5-methyl-6-decyl *p*-toluenesulphonate (6·4 g) by the same procedure afforded 2·52 g (63%) of the dimethylamino derivative, b.p. 98—100°C/14 Torr. For $C_{13}H_{29}N$ (199·4) calculated: 78·31% C, 14·66% H, 7·03% N; found: 78·41% C, 14·71% H, 6·98% N.

erythro-5-Methyl-6-decyltrimethylammonium Iodide

A solution of *erythro*-5-methyl-6-dimethylaminodecane (1·5 g; 0·0075 mol) and methyl iodide (1·6 g; 50% excess) in benzene was allowed to stand at ambient temperature for 2 days in the dark. The solidified reaction mixture was diluted with pentane, the crystals filtered off, washed with pentane and crystallised from acetone–ether. Yield 2·5 g (97%), m.p. 155—156°C. For $C_{14}H_{32}IN$ (341·3) calculated: 49·26% C, 9·45% H, 4·10% N; found: 49·18% C, 9·36% H, 4·03% N.

threo-5-Methyl-6-decyltrimethylammonium Iodide

This was obtained in 95% yield from the *threo*-dimethylamino derivative, using the procedure described above. M.p. 126—127°C (acetone–ether). For $C_{14}H_{32}IN$ (341·3) calculated: 49·26% C, 9·45% H, 4·10% N; found: 49·09% C, 9·24% H, 3·84% N.

cis- and *trans*-5-Methyl-5-decene

A solution of triphenylphosphine (26·2 g, 0·1 mol) and n-pentyl bromide (15·1 g, 0·1 mol) in benzene (150 ml) was refluxed for 20 h. The solution was allowed to cool and the crystals of n-pentyltriphenylphosphonium bromide filtered off (28 g), dried on the oil pump and used directly in the subsequent operation. A solution of sodium hydride (1·15 g, 0·05 mol) in dry dimethyl sulphoxide (50 ml) was heated in an atmosphere of nitrogen under stirring to 75—80°C for 45 min, cooled in an ice-bath and treated with a solution of n-pentyltriphenylphosphonium bromide and then, after 10 min, with 2-hexanone (5 g, 0·05 mol), heated for 4 h to 40°C, and diluted with a ten-fold amount of water. The product was taken up in pentane, the pentane extracts washed with 1M-HCl, 1M-NaOH, water and dried. The greater part of the solvent was distilled off, the residue filtered through a column of alumina, the filtrate concentrated and the crude product distilled, b.p. 66°C/14 Torr. According to vapour phase chromatography it consists of a mixture of equal parts of the *cis*- and the *trans*-isomer. The separation of the mixture was carried out by elution chromatography using a column of silica gel (220 g) impregnated with 10% silver nitrate. Pentane was used as eluent and 30 ml fractions were collected. The *cis*-isomer was contained in fractions 120—145 (purity 97·1%), the *trans*-isomer in fractions 335—344 (purity 94%).

trans-5-Methyl-6-decene

erythro-5-Methyl-6-decyltrimethylammonium chloride (1·5 g, 0·006 mol) was added to a solution of sublimed potassium tert-butoxide (2·3 g; 0·02 mol) in dimethyl sulphoxide (40 ml). The solution was allowed to stand at 25°C for 2 h under nitrogen, poured into saturated sodium chloride solution and the product taken up in pentane. The usual work-up afforded 830 mg (89%) of an oil b.p. 65—67°C/15 Torr which according to vapour phase chromatography is 99% homogeneous. Infra-red spectrum: bands at 970 cm^{-1}, 1 670 cm^{-1} and 3015 cm^{-1}.

cis-5-Methyl-6-decene

The above *trans*-olefin was converted to the corresponding *cis*-isomer by the procedure described by Corey and Winter[17]. The olefin thus obtained was according to vapour phase chromatography 98% homogeneous. Infra-red spectrum: bands at 735 cm^{-1}, 1 653 cm^{-1} and 3005 cm^{-1}.

1-Methylcyclododecanol

Reaction of the Grignard reagent prepared from methyl iodide (14·2 g, 0·1 mol) with cyclododecanone (5·84 g, 0·03 mol) in ether under reflux for 6 h afforded, after the usual work-up, 5·8 g (91%) of 1-methylcyclododecanol, m.p. 91–92·5°C (light petroleum). For $C_{13}H_{26}O$ (198·4) calculated: 78·72% C, 13·21% H; found: 78·60% C, 13·01% H.

cis- and *trans*-1-Methylcyclododecene

1-Methylcyclododecanol (31·2 g) was added to 30% sulphuric acid and the mixture subjected to steam distillation. The distillate was taken up in ether, the extracts dried and taken down. The residue was found to consist of the required olefins, as well as unreacted starting alcohol. The latter was separated by crystallisation of the residue from light petroleum and subjected once more to the above reaction conditions: this operation was repeated four times. The mother liquors from the above crystallisations were combined and chromatographed in light petroleum on silicagel (200 g). The light petroleum fractions afforded 25·9 g of an olefine mixture, b.p. 119–121°C/15 Torr, consisting of *cis*-1-methylcyclododecene (45%), *trans*-1-methylcyclododecene (48·4%) and methylenecyclododecane (6·6%). Ether eluted 1 g of unreacted 1-methylcyclododecanol. The olefin mixture was separated into its components by repeated chromatography on silicagel containing 10% silver nitrate using pentane as eluent. This procedure afforded 6·6 g of *cis*-1-methylcyclododecene (as evidenced by NMR), b.p. 142–143°C/18 Torr. For $C_{13}H_{24}$ (180·3) calculated: 86·59% C, 13·41% H; found: 86·57% C, 13·32% H. Further, 4·0 g of *trans*-1-methylcyclododecene was obtained (as evidenced by NMR), b.p. 119–121°C/14 Torr. For $C_{13}H_{24}$ (180·3) calculated: 86·59% C, 13·41% H; found: 86·60% C, 13·41 H. In addition, a small amount of an olefin was obtained which was characterised as methylenecyclododecane, again on the basis of NMR evidence.

cis-1,2-Epoxycyclododecane

Prepared in the usual manner from *cis*-cyclododecene and monoperphthalic acid in ether in 86% yield, b.p. 129–131°C/14 Torr. For $C_{12}H_{22}O$ (182·3) calculated: 79·06% C, 12·16% H; found: 79·14% C, 12·22% H.

trans-1,2-Epoxycyclododecane

Prepared analogously from *trans*-cyclododecene in 85% yield, b.p. 130°C/14 Torr. For $C_{12}H_{22}O$ (182·3) calculated: 79·06% C, 12·16% H; found: 79·18% C, 12·10% H.

trans-2-Methylcyclododecanol

a) A solution of *cis*-1,2-epoxycyclododecane (4·55 g; 0·025 mol) and dimethylmagnesium (4·1 g 0·075 mol) in dioxane (50 ml) (made up by mixing etheral solutions of the components, adding dry dioxane and carefully distilling off the ether) was refluxed for 50 h. The cold solution was treated with hydrochloric acid (1 : 1) and the product taken up in ether. The ethereal extracts were washed with water, dried, taken down and the residue chromatographed on silica. The benzene eluates afforded 1·63 g (33%) of *trans*-2-methylcyclododecanol, m.p. 61–62°C (pentane). For $C_{13}H_{26}O$ (198·4) calculated: 78·72% C, 13·21% H; found: 78·81% C, 13·22% H. The remainder consisted largely of unreacted starting compound. *b*) A solution of *cis*-1-methylcyclododecene (1·8 g, 10 mmol) and sodium borohydride (0·168 g, 4·4 mmol) in diglyme (12 ml) was treated in the course of 30 min in a nitrogen atmosphere with boron trifluoride etherate (0·78 g, 5·5 mmol) in

diglyme (5 ml). The reaction mixture was stirred for 5 h at 0°C, treated with 3M-NaOH (3 ml) and 30% hydrogen peroxide (3 ml), allowed to stand overnight at room temperature, diluted with water, and the product taken up in ether. The crude product on chromatography on silicagel (100 g) in benzene afforded 1·2 g (61%) of *trans*-2-methylcyclododecanol, m.p. 61—62°C (pentane), identical in every respect with the sample obtained as described under *a*).

cis-2-Methylcyclododecanol

a) The reaction of *trans*-1,2-epoxycyclododecane with dimethylmagnesium, under the conditions reported for the corresponding *cis*-epoxide, gave none of the required alcohol. A compound, m.p. 67—71°C (pentane), analysing for $C_{12}H_{22}O$, was isolated; it is presumably a product of transannular epoxide ring opening. *b*) Oxidative hydroboration of *trans*-1-methylcyclododecene (1·8 g), by the same procedure as described for the *cis*-isomer, afforded 1·45 g (73%) of the title compound, m.p. 71—72°C (pentane). For $C_{13}H_{26}O$ (198·4) calculated: 78·72% C, 13·21% H; found: 78·69% C 13·19% H. *c*) 2-Methylcyclododecanone[20] on reduction with lithium aluminium hydride in ether afforded a mixture of *cis*- and *trans*-2-methylcyclododecanol in a 2 : 1 ratio. The alcohols were separated by preparative vapour phase chromatography on a Carbowax 2000 column (1 m × 35 mm) at 190°C. Recrystallisation of the "*cis*-fraction" from pentane gave the *cis*-isomer, m.p. 70—72°C, which contained 0·5% of the *trans*-isomer.

cis-2-Methylcyclododecyl *p*-Toluenesulphonate

Prepared by the standard procedure, in pyridine. M.p. 63—65°C (pentane, —70°C). For $C_{20}H_{32}O_3S$ (352·5) calculated: 68·14% C; 9·15% H; found: 68·35% C. 8·79% H.

trans-2-Methylcyclododecyl *p*-Toluenesulphonate

Prepared from the corresponding alcohol by the standard procedure, m.p. 75—77°C (pentane, —70°C). For $C_{20}H_{32}O_3S$ (352·5) calculated: 68·14% C, 9·15% H; found: 68·42% C, 9·24% H.

cis-2-Methylcyclododecyldimethylamine

a) A solution of *trans*-2-methylcyclododecyl *p*-toluenesulphonate (650 mg) and sodium azide (1·2 g) in N-methylpyrrolidone (10 ml) was heated under stirring for 6 h to 160°C. The cold reaction mixture was diluted with water, the product taken up in pentane, the extracts washed with water, dried and taken down. The crude azide (370 mg) was heated with lithium aluminium hydride (320 mg) in ether (30 ml) for 3 h, 1 ml of water was added, the inorganic material filtered off and the crude amine (250 mg) which was isolated in usual manner, subjected to methylation with formic acid–formaldehyde as described previously[21] to give 210 mg (50%) of the title compound, b.p. 153—154°C/16 Torr. For $C_{15}H_{31}N$ (225·4) calculated: 79·92% C, 13·86% H, 6·21% N; found: 79·92% C, 13·87% H, 6·37% N. *b*) Solutions of 2-methylcyclododecanone[19] (1·96 g) in ethanol (15 ml), hydroxylamine hydrochloride (1·4 g) in water (2·5 ml) and sodium acetate (2·75 g) in water (2·5 ml) were mixed, refluxed for 15 min and diluted with water. The oxime was filtered off and recrystallised from light petroleum, m.p. 105—107°C, yield 1 g. For $C_{13}H_{25}NO$ (211·4) calculated: 73·88% C, 11·92% H, 6·63% N; found: 74·06% C 12·06% H, 6·63% N. A solution of the oxime (14·5 g) in ethanol (200 ml) was subjected to hydrogenation in the presence of Raney nickel catalyst (1·5 g) at 100 atmospheres at room temperature. The usual isolation procedure afforded 12 g of a mixture of *cis*-

and *trans*-2-methylcyclododecylamines (b.p. 160—162°C/14 Torr). This was then methylated by the Clarke-Eschweiler procedure to give 11·4 g of a mixture of *cis*- and *trans*-2-methylcyclododecyldimethylamine, b.p. 140—142°C/10 Torr, containing 93% *cis*- and 7% *trans*-isomer. The *cis*-isomer was isolated from this mixture by preparative gas chromatography (Apiezon on Chromosorbe impregnated with potassium hydroxide at 150°C).

trans-2-Methylcyclododecyldimethylamine

Prepared, in 45% yield, from *cis*-2-methylcyclododecyl *p*-toluenesulphonate as described under *a*) above. B.p. 150—152°C/16 mm. For $C_{15}H_{31}N$ (225·4) calculated: 79·92% C, 13·86% H, 6·21% N; found: 79·62% C, 14·01% H, 6·33% N.

cis-2-Methylcyclododecyltrimethylammonium Iodide

Reaction of *cis*-2-methylcyclododecyldimethylamine (3·19 g) with methyl iodide (3·1 g) in benzene (7 ml) at room temperature for 12 h afforded 4·22 g (81%) of the quaternary iodide, m.p. 203 to 205°C, raised to 212—213°C on recrystallisation from water. For $C_{16}H_{34}IN$ (367·4) calculated: 52·31% C, 9·33% H, 3·81% N; found: 52·03% C, 9·44% H, 3·77% N.

trans-2-Methylcyclododecyltrimethylammonium Iodide

Prepared as the above *cis*-isomer. M.p. 169—170°C (water). For $C_{16}H_{34}IN$ (367·4) calculated: 52·31% C, 9·33% H, 3·81% N; found: 52·39% C, 9·50% H, 3·88% N.

Quaternary Chlorides

The title compounds were prepared from the corresponding iodides by treatment with silver chloride under standard conditions[5]. They were dried on the oil pump for several hours at 100°C previous to the elimination reaction.

Elimination Procedures

Eliminations in homogeneous media: The reactions were carried out under nitrogen in sealed tubes (for conditions see Table I). After heating for the time indicated, the tubes were cooled to 0°C and the contents acidified using 0·5M-HCl. The olefins were taken up in pentane and analysed by v. p. c. *Pyrolysis of the quaternary hydroxides*: The quaternary iodides were converted to the hydroxides by passing their aqueous solutions through an Amberlit IR-400 ion exchange column. The solutions were taken to dryness on a rotatory evaporator, the residue transferred to a Hickmann flask fitted with a dry ice trap. The residual water was distilled off at 40°C on the oil pump (2 h) and the decomposition carried out on aspirator raising the temperature gradually up to 170°C. The distillate was taken up in pentane (5 ml), extracted with 0·5M-HCl, washed with water to neutrality and analysed by v. p. c. *Pyrolysis of the amine oxides*: The amine oxides were prepared from the corresponding dimethylamino derivatives by reaction with hydrogen peroxide in the usual manner[19] and dried on the pump for 2 h previous to the reaction. The pyrolysis was carried out exactly as described above for the quaternary hydroxides. *Vapour phase chromatography:* The analyses were performed on a Carlo Erba Fractovap GT chromatograph using an Apiezon capillary (50 m) at 80—120°C.

RESULTS

The elimination in the systems *I* and *II* can each give rise to four olefins, the *cis*- and *trans*-5-methyl-5-decenes (*III*) (Saytzeff olefins) and the *cis*- and *trans*-5-methyl-6-decenes (*IV*) (Hofmann olefins) from the open chain system *I*; and the *cis*- and *trans*-1-methylcyclododecenes (*V*) (Saytzeff olefins) and the *cis*- and *trans*-2-methylcyclododecenes (*VI*) (Hofmann olefins) from the cyclic system *II*, respectively. The olefin composition obtained in the eliminations of *I* and *II* is reproduced in Tables II

TABLE II

Elimination Reactions of *erythro*- and *threo*-5-Methyl-6-decyl Derivatives *I* ($X = \overset{(+)}{N}(CH_3)_3$, $N(CH_3)_2O$, OTs) under Different Conditions: Olefin Composition

Configuration	Reaction conditions	5-Methyl-5-decene (Saytzeff)			5-Methyl-6-decene (Hofmann)	
		% *cis*	% *trans*	% *syn*	*cis* %	% *trans*
		'Onium compounds				
erythro	CH_3OK/CH_3OH	42·1[a]	2·2[s]	5·0	6·4	49·3
threo		0·2[s]	53·3[a]	0·4	8·2	38·3
erythro	$t\text{-}C_4H_9OK/t\text{-}C_4H_9OH$	1·8[a]	1·2[s]	40·0	1·0	96·0
threo		0·2[s]	4·4[a]	4·4	1·5	93·9
erythro	$t\text{-}C_4H_9OK/(CH_3)_2SO$	0·7[a]	0·4[s]	36·0	0·3	98·6
threo		0·2[s]	2·3[a]	8·0	≪0·1	97·5
erythro	$t\text{-}C_4H_9OK/C_6H_6$	0·2[a]	4·5[s]	96·0	≪0·1	95·3
threo		3·2[s]	0·4[a]	89·0	~0·1	96·3
erythro	pyrolysis	5·0[a]	0·9[s]	15·0	1·9	92·2
threo		0·4[s]	15·7[a]	2·5	1·6	82·3
		Amine oxides				
erythro	pyrolysis	0·2[a]	51·9[s]	99·6	≪0·1	47·9
threo		32·8[s]	0·7[a]	98·0	1·5	65·0
		Tosylates				
erythro	$t\text{-}C_4H_9OK/HCON(CH_3)_2$	38·3[a]	0·2[s]	~0·5	2·3	59·2
threo		0·2[s]	41·6[a]	~0·5	1·0	57·2
erythro	$t\text{-}C_4H_9OK/t\text{-}C_4H_9OH$	51·3[a]	2·4[s]	4·5	14·2	32·1
threo		3·7[s]	35·5[a]	9·5	21·5	39·3
erythro	$t\text{-}C_4H_9OK/C_6H_6$	35·0[a]	2·0[s]	5·4	5·1	57·9
threo		0·8[s]	17·6[a]	4·8	9·8	71·8

[a] Produced by *anti*-elimination; [s] produced by *syn*-elimination.

and III. A cursory inspection of the Tables reveals a very strong dependence of the olefin composition obtained not only on the nature of the base, the solvent and the leaving group but also on the configuration of the reactant; not unexpectedly, this is particularly strongly evident in the case of the cyclic reactant. A discussion of the trends observed will be possible if we take into account the steric course of the reactions under discussion.

Steric Course of the Elimination Leading to the Trialkyl Substituted Olefins

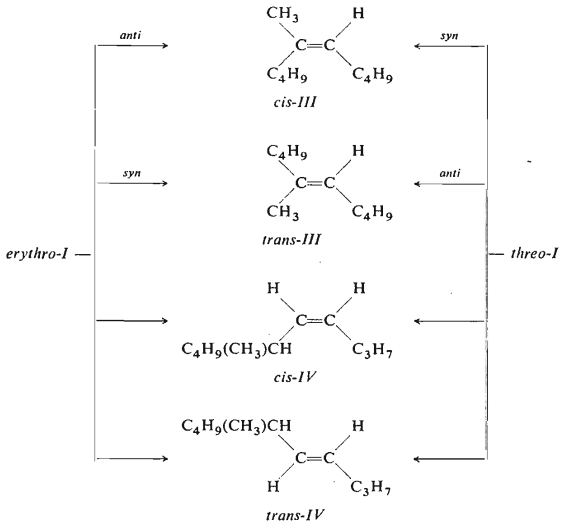
Information concerning the steric course of the formation of the Saytzeff olefins *cis-III* and *V* and *trans-III* and *V* follows directly from a configurational correlation between reactant and product (Schemes 1 and 2). Tables II and III show that in the

Table III

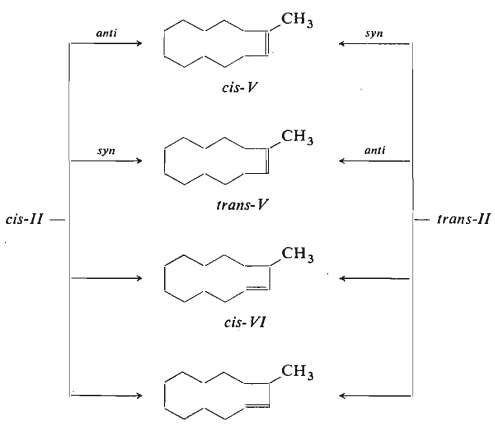
Elimination Reactions of *cis*- and *trans*-2-Methylcyclododecyl Derivatives (*II*; $X = \overset{(+)}{N}(CH_3)_3$, OTs): Cyclododecene Composition

Configuration	Reaction conditions	1-Methyl (*V*) (Saytzeff)			2-Methyl (*VI*) (Hofmann)	
		% *cis*	% *trans*	% *syn*	% *cis*	% *trans*
		'Onium compounds				
cis	CH_3OK/CH_3OH	18·0[a]	0·5[s]	2·7	0·9	80·6
trans		1·3[s]	35·8[a]	3·5	53·1	9·8
cis	t-C_4H_9OK/t-C_4H_9OH	0·8[a]	0·2[s]	20·0	≪0·1	99·0
trans		3·1[s]	11·4[a]	21	10·3	75·2
cis	t-$C_4H_9OK/(CH_3)_2SO$	~0·1[a]	~0·1[s]	~50	≪0·1	99·8
trans		2·4[s]	17·5[a]	12	7·3	72·8
cis	t-C_4H_9OK/C_6H_6	0·3[a]	0·9[s]	75	≪0·1	98·8
trans		13·9[s]	4·9[a]	74	4·2	77·0
cis	pyrolysis	1·6[a]	0·5[s]	24	≪0·1	97·9
trans		3·0[s]	60·6[a]	4·7	7·5	28·9
		Tosylates				
cis	t-$C_4H_9OK/HCON(CH_3)_2$	33·2[a]	3·0[s]	8·3	9·1	54·7
trans		≪0·1[s]	9·0[a]	≪1·0	30·2	60·8
cis	t-C_4H_9OK/t-C_4H_9OH	18·8[a]	7·0[s]	27	15·8	58·4
trans		2·8[s]	2·8[a]	50	41·7	52·7
cis	t-C_4H_9OK/C_6H_6	4·2[a]	2·9[s]	41	2·1	90·8
trans		1·6[s]	0·5[a]	76	9·5	88·4

[a] Produced by *anti*-elimination; [s] produced by *syn*-elimination.



SCHEME 1



SCHEME 2

reactions of the 'onium compounds *I* and *II* ($X = \overset{(+)}{N}(CH_3)_3$) with tert-butoxide in benzene *syn*-elimination is responsible for 74–96% of the Saytzeff olefins formed; in tert-butanol or in dimethyl sulphoxide, or under pyrolytic conditions, the contribution of *syn*-elimination to Saytzeff olefin formation is small to appreciable, depending very strongly on the configuration of the quaternary base;* in methoxide–methanol the proportion of *syn*-elimination is very small (0·4–5%) in every case. In the reaction of the open-chain tosylates (*I*, X = OTs) the contribution of *syn*-elimination towards Saytzeff olefin formation is only 0·5–10%, under any of the reaction conditions investigated. For the cyclic tosylates, the contribution of *syn*-elimination to Saytzeff olefin formation is significantly greater than in the open-chain system.** The effect of base and solvent on the proportion of *syn*-elimination in Sayetzeff olefin formation, by and large, follows the trend noted[1,3,7,10,11,23] for other systems. Thus, in the case of the reaction of the tosylates with tert-butoxide, the percentage of *syn*-elimination in Saytzeff olefin formation increases on going from the solvent dimethylformamide, to tert-butanol and benzene. For the 'onium bases, the two extreme situations are observed for methoxide–methanol on the one hand and tert-butoxide–benzene on the other: the former strongly favours the *anti*-elimination mechanism, the latter the *syn*. The other three systems examined represent intermediate situations. As regards the way in which steric course depends on the nature of the leaving group we can see from the data given in Tables II and III that the tendency towards *syn*-elimination is greater in the reaction of the 'onium compounds than of the corresponding tosylates. *syn*-Elimination is thus indeed a possible reaction mode in the formation of trialkylated olefins. Moreover, the results listed in Tables II and III show that the dependence of the steric course (*syn* or *anti*) in the formation of the trialkylated olefins on the nature of the base–solvent system as well as on the nature of leaving group follow much the same pattern as has been found for the corresponding eliminations leading to the dialkyl substituted olefins[1].

The Hofmann - Saytzeff and the *syn-anti* Dichotomy

The problem of orientation (Hofmann or Saytzeff) in bimolecular eliminations has frequently been discussed in the past[13,16,24–32]. The discovery that two mechanisms

* The contribution of *syn*-elimination to the formation of *III* is substantially higher in the reaction *erythro-I* $\xrightarrow{syn}$ *trans-III* than in *threo-I* $\xrightarrow{syn}$ *cis-III*; this may reflect smaller eclipsing interactions in the transition state leading to the *trans*-isomer. However, a corresponding trend is not found in the formation of the olefins from the tosylates *I* (X = OTs), the contribution of *syn*-elimination from the two diastereoisomers here being similar.

** In an experiment, expressly labelled by the authors as preliminary, Brown and Klimisch[22] have found that *trans*-2-methylcycloöctyl tosylate on reaction with tert-butoxide in tert-butanol affords, in equal amounts, two peaks, believed to correspond to the Hofmann and the Saytzeff olefin. If this is correct, it would imply that the proportion of Saytzeff elimination (probably *syn*) in the cycloöctyl system is very much larger than in the case of *II*.

(*anti* and *syn*) may operate in eliminations leading to the dialkylated as well as the trialkylated olefins necessitates a reconsideration of the significance of the Hofmann - Saytzeff (H/S) ratios. Clearly, a more meaningful interpretation should be possible if the "overall" ratios H/S could be separated into the corresponding *syn*- and *anti*-components, *i.e.* $(H/S)_{syn}$ and $(H/S)_{anti}$.

From the present study we have quantitative data on the contribution of *syn*- and *anti*-elimination to the formation of the trialkylated (*i.e.* Saytzeff) olefins. We have no corresponding direct information concerning the steric course of formation of the dialkylated (*i.e.* Hofmann) olefins in the present reactions. However, on the basis of analogy with earlier findings[1-3,8] on related, deuterium labelled, substrates, it appears safe to suggest that in the reaction of the 'onium compounds *I* and *II* ($X = \overset{(+)}{N}(CH_3)_3$) with tert-butoxide in the three solvents examined, and on pyrolysis (but not necessarily in the reaction with methoxide in methanol) the Hofmann olefins arise according to the *syn-anti* elimination pattern, the *trans*-olefin being formed mainly by *syn*- and the *cis*-isomer mainly by *anti*-elimination.*

For the reactions of the 'onium bases *I* and *II* we have therefore equated the percentage of the *trans*-isomer in the *cis-trans* Hofmann olefin mixture to the percentage of *syn*-elimination in Hofmann olefin formation (H_{syn}); and, analogously, the percentage of the *cis*-isomer in the Hofmann olefin mixture to the percentage of *anti*-elimination in Hofmann olefin formation** (H_{anti}). Using these figures, and the contribution of *syn*- and *anti*-elimination to Saytzeff olefin formation directly determined from the olefin mixture analysis (*cf.* Tables II and III and Schemes 1 and 2), we have calculated the ratios $(H/S)_{syn}$ and $(H/S)_{anti}$ (Tables IV and V).

The values show clearly two opposing trends: while the *syn*-elimination reaction shows a very strong preference for Hofmann olefin formation, *anti*-elimination shows a strong (yet less pronounced) preference for Saytzeff olefin formation; *i.e.* $(H/S)_{syn}$ is large, $(H/S)_{anti}$ is small.

Elimination of 'onium bases is, in the minds of organic chemists, associated with Hofmann orientation (Hofmann rule!). A few "violations" of this rule have been reported; they refer to elimination in 'onium bases derived from *cis*-2-methylcyclohexylamine[30] (*VII*), neo-menthylamine[29] (*VIII*) and the 4-β- and 6-β-aminocholestanes[31,32] (*IX* and *X*) which all give very high proportions of the Saytzeff olefins. This "abnormal" behaviour has been ascribed[29] to steric features, *i.e.* the large

* It is not possible to draw analogous conclusions for the reaction of the corresponding tosylates and this aspect will hence not be discussed here.

** The *cis*/*trans* 5-decene ratios in the *anti*-component of the elimination of 5-decyltrimethylammonium bases have been found[1] under analogous reaction conditions invariably higher than unity. Moreover, this situation persists, though less pronouncedly, even in the elimination of the sterically very demanding 2,2-dimethylnonyl-3-trimethylammonium base[35]. Therefore, it seems justified for the present purposes to neglect the *anti* → *trans* contribution to the Hofmann olefin formation, in spite of the very high overall *trans*/*cis* ratio.

gauche and/or *syn*-axial interactions to which the extremely bulky trimethylammonium group is exposed; these interactions are visualised as leading to a ground state stretching of the $C\overset{(+)}{\text{—}}N$ bond which induces a shift of the mechanism towards the E1 side of the spectrum of transition states and thus takes it out of the sphere of influence of the Hofmann rule.

TABLE IV

"Hofmann" to "Saytzeff" Ratios (H/S) in the *syn*- and *anti*-Components of the Elimination of *erythro*- and *threo*-5-Methyldecyl-6-trimethylammonium Chlorides under Different Conditions

Configuration	Conditions	H/S Ratio		
		overall	*syn*-route	*anti*-route
erythro	pyrolysis	16	102	0·38
threo		5·3	206	0·10
erythro	CH_3OK/CH_3OH	1·25	22·4	0·15
threo		0·87	192	0·15
erythro	$t\text{-}C_4H_9OK/C_4H_9OH$	32	80	0·55
threo		21	470	0·34
erythro	$t\text{-}C_4H_9OK/C_6H_6$	20	21·2	$\ll$0·5
threo		26	30·1	$\sim$0·25
erythro	$t\text{-}C_4H_9OK/(CH_3)_2SO$	90	247	0·43
threo		39	487	$\ll$0·5

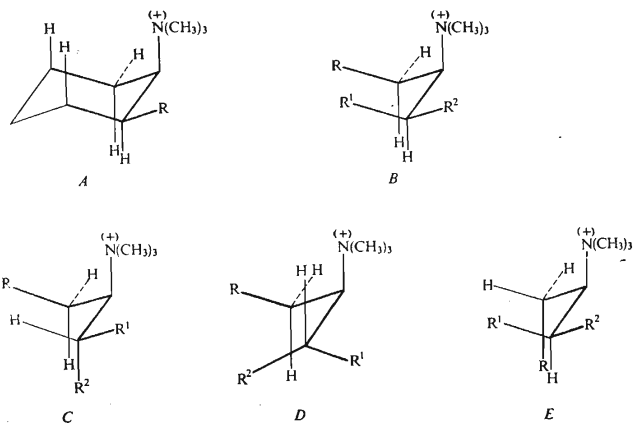
TABLE V

"Hofmann" to "Saytzeff" Ratios (H/S) in the *syn*- and *anti*-Components of the Elimination of *cis*- and *trans*-2-Methylcyclododecyltrimethylammonium Chlorides under Different Conditions

Configuration	Conditions	H/S Ratio		
		overall	*syn*-route	*anti*-route
cis	pyrolysis	47	196	$\ll$0·06
trans		0·57	9·6	0·12
cis	CH_3OK/CH_3OH	4·4	161	0·05
trans		1·7	7·5	1·5
cis	$t\text{-}C_4H_9OK/t\text{-}C_4H_9OH$	99	495	$\ll$0·12
trans		4·7	24·2	0·90
cis	$t\text{-}C_4H_9OK/C_6H_6$	82	110	$\ll$0·33
trans		4·3	5·5	0·86
cis	$t\text{-}C_4H_9OK/(CH_3)_2SO$	$\sim$500	$\sim$1 000	$\ll$1·0
trans		4·0	30·3	0·42

Our present findings lead us to suggest that in 'onium compounds *anti*-elimination will much more frequently show strong preference for Saytzeff orientation than it has been anticipated. In the cyclohexyl systems *VII*–*X* both the Hofmann as well as the Saytzeff olefins presumably arise by *anti*-elimination, *syn*-elimination being practically precluded by the geometry of the systems; the preferred formation of the Saytzeff olefins in these systems must hence be considered "normal" rather than "exceptional". Unlike in the above cyclohexyl derivatives, the situation in corresponding open-chain or many-membered ring systems is no longer simplified by a homogeneous reactions course and the preference of *anti*-elimination for Saytzeff orientation is hence not evident in the overall result of the reaction. The *anti*-elimination component is submerged by the more important *syn*-component; the salient features of the former mechanism thus become apparent only after dissection into the *syn*- and *anti*-elimination contributions.

The steric explanation offered for preferred Saytzeff orientation in the reaction of the cyclohexyl derivatives *VII*–*X* (Scheme 3*A*) may, as can be seen from Scheme 3*B*, be extended to our case of preferred Saytzeff orientation in the *anti*-elimination component of the system *I* ($X = \overset{(+)}{N}(CH_3)_3$). However, unlike in the cyclohexyl derivatives in question, the open-chain system *I* has available to it conformations (Scheme 3*C*, *D*) which are suitably set up for *anti* → *cis* elimination in the Hofmann direction



SCHEME 3

but in which the 'onium group is not embedded in a milieu of alkyl residues.* Yet, as our results suggest, the molecule makes only sparing use of this opportunity. One is therefore tempted to draw from this the conclusion that the preferred formation of the Saytzeff olefin in *anti*-elimination even in 'onium base eliminations follows from the electronic characteristics of this reaction. Since the transition state in *anti*-elimination possesses (unlike its *syn* counterpart) considerable double bond character, it derives stabilisation through successive alkyl substitution.

Obviously, other factors can alter the rather delicate balance profoundly. The steric factors may either further reinforce (as in the systems *VII–X*), or, contrariwise, completely suppress the Saytzeff orientation by shielding the base approach[31]. Similarly, the inductive effects may control the orientation in the systems lacking the sufficient ability of hyperconjugative stabilisation (*e.g.* unbranched open-chain compounds) of the transition state.

Consider next the orientation in the *syn*-elimination component, where we find a very strong preference for Hofmann orientation. Both steric and polar interpretations for this observation may be considered, and some arguments are available to distinguish between the two. Thus, the amine oxide elimination (*syn*-elimination) is known to be largely insensitive towards polar effects[33]: the outcome of this reaction might hence afford information on the operation of steric factors. Now, *threo-I* ($X = N(CH_3)_2O$) as well as *erythro-I* ($X = N(CH_3)_2O$) have been found to give the Hofmann and Saytzeff olefins in equal amount, or a mild excess of the former, respectively. It follows that the principal feature responsible for the very high preference for Hofmann orientation found for the *syn*-elimination component of the reaction of the quaternary ammonium bases is probably not of steric origin. A polar factor is hence responsible and this could well be the higher acidity of the hydrogen on the secondary carbon[16,27]. The circumstance that this property is of such importance agrees with previous suggestions[1,5–7,34] that in the *syn*-E2 reaction the transition state is E1cb-like, thus contrasting with the *anti*-E2 reaction for which all the available evidence points to a more synchronous mechanism[7].

REFERENCES

1. Sicher J., Závada J., Pánková M.: This Journal *36*, 3140 (1971).
2. Pánková M., Sicher J., Závada J.: Chem. Commun. *1967*, 394.
3. Bailey D. S., Saunders W. S.: Chem. Commun. *1968*, 1598.
4. Závada J., Svoboda M., Sicher J.: Tetrahedron Letters *1966*, 1627.
5. Sicher J., Závada J.: This Journal *32*, 2122 (1967).
6. Závada J., Sicher J.: This Journal *32*, 3701 (1967).

* Alternative steric explanations might be suggested for the preferred Saytzeff orientation, *e.g.* in terms of steric hindrance to the base approach[3]. However, the steric situation seems to be similar in the present case both for the formation of the Hofmann (Scheme 3*C*, *D*) and the Saytzeff (Scheme 3*E*) olefin.

7. Sicher J., Závada J.: This Journal *33*, 1278 (1968).
8. Závada J., Svoboda M., Sicher J.: This Journal *33*, 4027 (1968).
9. Závada J., Krupička J., Sicher J.: Chem. Commun. *1967*, 66.
10. Závada J., Krupička J., Sicher J.: This Journal *33*, 1393 (1968).
11. Svoboda M., Závada J., Sicher J.: This Journal *33*, 1415 (1968).
12. Saunders W. S.: *The Chemistry of Alkenes* (S. Patai, Ed.). Interscience, New York 1964.
13. Banthorpe D. V.: *Elimination Reactions*. Elsevier, New York 1963.
14. Banthorpe D. V. in: *Studies in Chemical Structure and Reactivity* (J. H. Ridd, Ed.). Methuen, London 1966.
15. Bunnet J. F.: Angew. Chem. *74*, 731 (1962).
16. Ingold C. K.: *Structure and Mechanism in Organic Chemistry*. Cornell University Press, Ithaca, New York 1953.
17. Corey E. J., Winter R. A. E.: J. Am. Chem. Soc. *85*, 2677 (1963).
18. Christensen B. G., Strachen R. G., Trenner N. R., Arison B. H., Hirchmann R., Chemerda J. M.: J. Am. Chem. Soc. *82*, 3995 (1960).
19. Cope A. C., Trumbull E. R.: *Organic Reactions*, Vol. 11, p. 317. Wiley, New York 1960.
20. Spencer T. A., Britton R. W., Watt D. S.: J. Am. Chem. Soc. *89*, 5727 (1967).
21. Závada J., Krupička J., Sicher J.: This Journal *31*, 4273 (1966).
22. Brown H. C., Klimisch R. L.: J. Am. Chem. Soc. *88*, 1430 (1966).
23. Sicher J., Pánková M., Závada J., Kniežo L., Orahovats A.: This Journal *36*, 3128 (1971).
24. Brown H. C., Wheeler O. H.: J. Am. Chem. Soc. *78*, 2199 (1956).
25. Brown H. C., Moritani J.: J. Am. Chem. Soc. *78*, 2203 (1956).
26. Brown H. C., Klimisch R. L.: J. Am. Chem. Soc. *88*, 1425 (1966).
27. Banthorpe D. V., Hughes E. D., Ingold C.: J. Chem. Soc. *1960*, 4054.
28. Saunders W. H., Fahrenholtz S. R., Caress E. A., Löwe J. P., Schreiber M.: J. Am. Chem. Soc. *87*, 3401 (1965).
29. Hughes E. D., Wilby J.: J. Chem. Soc. *1960*, 4094.
30. Brownlee T. H., Saunders W. H.: Proc. Chem. Soc. *1961*, 314.
31. Ledger R., Smith A. J., McKenna J.: Tetrahedron *20*, 2413 (1964).
32. Wall E. N., McKenna J.: J. Chem. Soc. (B) *1970*, 318.
33. Sahyun M. R. V., Cram D. J.: J. Am. Chem. Soc. *85*, 1263 (1963).
34. Brown K. C., Saunders W. H.: J. Am. Chem. Soc. *92*, 4292 (1970).
35. Závada J., Pánková M., Sicher J.: This Journal, in press.

Translated by the authors.