The *syn–anti* Elimination Dichotomy: A Common Feature in Hofmann Elimination

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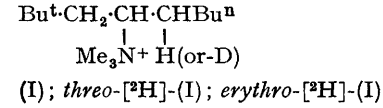
RECENTLY, we have shown[1] that in the reaction of cycloalkyltrimethylammonium salts with alkoxides in the corresponding alcohols the *cis*-cycloalkenes are formed by an *anti*-elimination but the *trans*-cycloalkenes by a *syn*-elimination. The important question arose whether this represents another manifestation of the exceptional behaviour of alicyclic, and particularly, medium-ring molecules,[2] or whether—contrary to currently held views[3]—such mechanistic dichotomy represents a more general phenomenon in the Hofmann elimination, and also operates in open-chain systems.

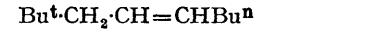
We have now examined the reaction (under conditions set out in the Table) of the quaternary ammonium base (I) and its β-deuterium-labelled derivatives *threo*-[^{2}H]-(I) and *erythro*-[^{2}H]-(I), leading to the *cis–trans* olefin pairs (II) and (III). This system was selected because it was expected that elimination would proceed preferentially away from the t-butyl group and thus lead to a relatively homogeneous product; it was hoped that this would simplify the analytical problems.

The β-deuterated derivatives *threo*-[^{2}H]-(I) and *erythro*-[^{2}H]-(I) were synthesised from *trans*-(II), obtained by sodium–liquid ammonia reduction of the corresponding acetylene. Oxidative deuteroboration[4] of *trans*-(II) gave two position isomeric alcohols from which the required isomer, *threo*-[^{2}H]-(IV), was isolated by preparative v.p.c. Similarly, reduction of the epoxide corresponding to *trans*-(II) with $LiAlD_4$–$AlCl_3$[5] gave *erythro*-[^{2}H]-(IV), together with a position isomer from which it was separated by v.p.c. The alcohols *erythro*-[^{2}H]-(IV) and *threo*-[^{2}H]-(IV) were converted into the quaternary salts, *threo*-[^{2}H]-(I) and *erythro*-[^{2}H]-(I), respectively, by reaction of their toluene-*p*-sulphonate esters with sodium azide followed by $LiAlH_4$ reduction and quaternisation. Of the four potential elimination products, one [*trans*-(II)] was available from the above synthesis, the other three were also prepared by unambiguous routes.*

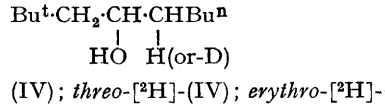
Formation of *trans*-(II) by *syn*-elimination and of *cis*-(II) by *anti*-elimination would involve loss of deuterium in the reaction of *threo*-[^{2}H]-(I) but retention of deuterium in the reaction of *erythro*-[^{2}H]-(I) (Scheme 1). Hence, if in this system, as in the cycloalkane series, *trans*-olefin arises by *syn*-elimination and *cis*-olefin by *anti*-elimination, then formation of both *trans*-(II) and *cis*-(II) from



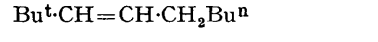
(I); *threo*-[^{2}H]-(I); *erythro*-[^{2}H]-(I)



cis- and *trans*-(II)



(IV); *threo*-[^{2}H]-(IV); *erythro*-[^{2}H]-(IV)



cis- and *trans*-(III)

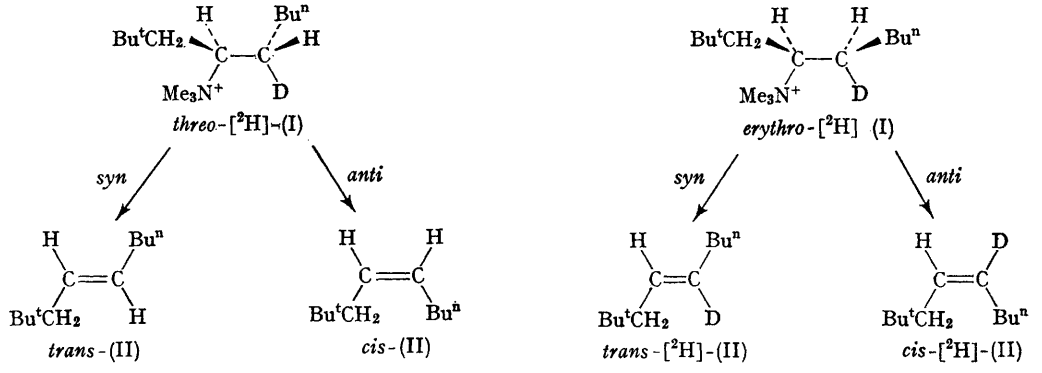
* All new compounds gave satisfactory elemental analyses, and their spectral properties were in accordance with the structures assigned.

TABLE

Elimination reactions of $Bu^t\cdot CH_2\cdot CH(\overset{+}{N}Me_3)\cdot CH_2Bu^n$ (I) *and of* $Bu^t\cdot CH_2\cdot CH(\overset{+}{N}Me_3)\cdot CHDBu^n$ {erythro-[^{2}H]-(I) *and* threo-[^{2}H]-(I)}: *Olefin composition, values of* k_H/k_D *and* [^{2}H]*-content in olefinic product*

Reaction conditions	Substrate[a]	Product[b,c] *trans*-(II) (%)	k_H/k_D[d]	*cis*-(II) (%)	k_H/k_D[d]	*trans*-(III) (%)	(%) [^{2}H]-Species Calc.[e]	Found
MeOK–MeOH (135°)	(I)	43·4	—	51·4	—	5·2	—	—
	erythro-[^{2}H]-(I)	40·4	1·0	54·5	0·9	5·1	—	—
	threo-[^{2}H]-(I)	47·7	2·3	39·1	3·3	13·2	—	—
Bu^tOK–Bu^tOH (110°)	(I)	93·9	—	3·0	—	3·1	—	—
	erythro-[^{2}H]-(I)	92·2	1·2	4·0	0·9	3·8	91·0	91·5
	threo-[^{2}H]-(I)	89·5	2·9	1·8	4·7	8·7	8·5	11·5
Bu^tOK–Me_2SO (40°)	(I)	95·4	—	1·7	—	2·9	—	—
	erythro-[^{2}H]-(I)	95·1	1·1	1·7	1·1	3·2	91·0	91·5
	threo-[^{2}H]-(I)	86·8	4·2	2·0	3·3	11·2	10·5	12·0
Pyrolysis	(I)	83·1	—	5·8	—	11·1	—	—
	erythro-[^{2}H]-(I)	79·0	1·1	9·1	0·7	11·9	91·0	91·0
	threo-[^{2}H]-(I)	70·8	2·6	4·2	3·1	25·0	24·0	26·5

[a] The deuterium content (as determined on the intermediate alkanols *threo*-[^{2}H]-(IV) and *erythro*-[^{2}H]-(IV) by mass spectrometry) is 91 ± 2% for *erythro*-[^{2}H]-(I) and 96 ± 2% for *threo*-[^{2}H]-(I). [b] Less than 1% of *cis*-(III) was present and this was disregarded in the calculation of the product composition. [c] Determined by v.p.c. on a 50 m. glass capillary coated with squalene at 40°; all four isomers were cleanly separated. [d] The average error in k_H/k_D is ±0·3 for the reactions of *erythro*-[^{2}H]-(I), and ±0·8 for the reactions of *threo*-[^{2}H]-(I). [e] Calculated for exclusive *syn* → *trans* and *anti* → *cis* routes, taking a correction for incomplete deuterium labelling in the substrate.



SCHEME

threo-[^{2}H]-(I) should be subject to a distinct isotope effect, k_H/k_D, whereas the formation of the corresponding olefins from *erythro*-[^{2}H]-I by the same reaction paths should show an isotope effect equal or close to unity As has been pointed out previously,[1,6] the values of k_H/k_D can be estimated from the composition of the olefin isomer mixture obtained in the reactions of the deuterated and non-deuterated compounds.

The results (Table) show clearly that, under all the four (greatly differing) sets of reaction conditions, formation of both *trans*-(II) and *cis*-(II) from *threo*-[^{2}H]-(I) is subject to a notable isotope effect (k_H/k_D 2·3—4·7) whereas the isotope effects in the same reactions of *erythro*-[^{2}H]-(I) are invariably close to unity (k_H/k_D 0·9—1·2). The results are thus in agreement with the view that *cis*-(II) arises by *anti*-elimination and *trans*-(II) by *syn*-elimination either largely or exclusively.

Supporting evidence in favour of this conclusion was obtained from a comparison of the (total) deuterium content in the olefin mixture in each run with the amount calculated on the assumption of the dual mechanism defined above. The Table

shows reasonably good agreement between the experimental and the thus calculated values.†

In 1962 Ingold[7] gave a penetrating analysis of *E*2 reaction mechanisms, leading to the important conclusion that "if proton transfer were extensive enough in the *E*2 transition state, the electrophilic substitution (at C-β), as well as the nucleophilic substitution (at C-α) coupled with it, might involve inversion. This would produce *syn*-planar stereospecificity (*syn*-elimination)". This prediction has now found experimental verification;‡ our findings suggest, indeed, that *syn*-elimination is a common reaction mode in Hofmann elimination, under a wide range of reaction conditions. However, there is the important proviso that in an elimination leading to a *cis–trans* olefin pair, *syn*-elimination operates in *trans*-olefin formation but not, or only to a small extent, in *cis*-olefin formation.

These findings shed new light on many important aspects of bimolecular elimination mechanisms: we propose to deal with some of these in papers to be published shortly.

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† In view of the very small amount of material available the deuterium content in the olefin mixtures had to be determined by mass spectrometry, even though this involves some uncertainty because the four olefin isomers do not afford the molecular ion with the same yield. However, even large differences in the yields would not seriously affect the results since one isomer, *trans*-(II), predominates in the mixtures in all the three cases examined.

‡ A *syn*-elimination involving an ylid intermediate ($\alpha'\beta$-mechanism) [G. Wittig and T. F. Burger, *Annalen*, 1960, **632**, 85; A. C. Cope and A. S. Mehta, *J. Amer. Chem. Soc.*, 1963, **85**, 1949] is excluded by the absence of deuterium in the trimethylamine formed in the reaction of *threo*-[^{2}H]-(I).

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