53. *The Reaction of Ring-substituted* cyclo*Hexylamines with Nitrous Acid. An Interpretation based on Conformational Analysis.*

By J. A. Mills

Deamination of *cyclo*hexylamines with simple alkyl substituents in the ring is conformationally specific: equatorial amino-groups afford alcohols of the same configuration; polar amino-groups react by elimination plus inversion. The retention of configuration in the deamination of equatorial amino-groups is a true stereospecific process, and a pyramidal transition state is postulated to explain this. The principles of conformational analysis are used to assign configurations to *cis*-decalyl derivatives.

SIMPLE acyclic primary amines not containing reactive neighbouring groups undergo deamination through intermediate formation of a diazonium ion which decomposes by a S_N1 process and affords an alcohol of largely inverted configuration, *e.g.*:

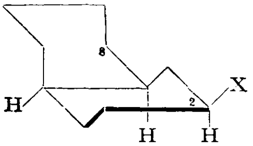
$$\text{L-R·NH}_2 + \text{HNO}_2 \longrightarrow \text{R·N}_2^+ \longrightarrow \text{R}^+ \longrightarrow \text{D-R·OH} + \text{DL-R·OH}$$

(Brewster, Hiron, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 179). Kinetic studies have not been made on simple cyclic primary amines, but Hückel's summary of his own work and that of others (*Annalen*, 1938, **533**, 1) and a recent publication by Cornubert (*Bull. Soc. chim.*, 1951, C 23) show that the deamination of primary *cyclo*hexylamines with simple alkyl substituents in the ring does not follow the simple pattern of the acyclic amines. Of an epimeric pair of amines, it is usual for one epimer (*e.g.*, menthylamine, carvomenthylamine, *iso*menthylamine) to give on deamination a good yield of alcohol of predominantly the same configuration as the amine used, whereas the other (*neo*menthylamine, *neo*carvomenthylamine, etc.) undergoes much elimination, but may afford some alcohol of largely inverted configuration. This also holds for epimeric amino-*trans*-decalins (Hückel, *loc. cit.*), but, following recent configurational assignments by Dauben and Hoerger (*J. Amer. Chem. Soc.*, 1951, **73**, 1504), it is probable that *all four* possible 1- and 2-amino-*cis*-decalins are deaminated with retention of configuration. In the *cyclo*pentane series, both the epimeric 2-*cyclo*pentyl*cyclo*pentylamines are deaminated with elimination plus inversion (Hückel, Gross, and Doll, *Rec. Trav. chim.*, 1938, **57**, 555).

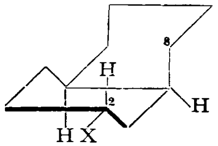
Only in the *cyclo*hexane series has the peculiar difference between epimers been observed, and to understand the cause it is necessary to apply modern ideas on the stereochemistry of *cyclo*hexane derivatives. All of the *cyclo*hexylamines named may exist with the ring in its more stable, " chair " conformation, and the amino-groups will then occupy either " equatorial " (*e*) or " polar " (*p*) positions. The factors deciding the most stable conformation of a particular substance have been discussed by Hassel and Ottar (*Acta Chem. Scand.*, 1947, **1**, 929), Beckett, Pitzer, and Spitzer (*J. Amer. Chem. Soc.*, 1947, **69**, 2488), Barton (*Experientia*, 1950, **6**, 316), Johnson (*ibid.*, 1951, **7**, 315), and Barton and Rosenfelder (*J.*, 1951, 1048).

First, it may be deduced that the course of deamination of *cyclo*hexylamines is conformationally specific; if the amino-group is equatorial in the most stable conformation of the molecule, deamination affords an alcohol of the same configuration; if it is polar, elimination and inversion occur. For the monocyclic amines this is easily demonstrated; Barton (*loc. cit.*) has assigned conformations to some of them, and the same principles apply to the others. Barton has also discussed general relations between conformation, reactivity, stability, and mode of formation, and when these are applied to the data collected by Hückel configurations and conformations are readily derived for *trans*-decalin derivatives; the 1- and the 2-amino-*trans*-decalin with equatorial amino-groups afford on deamination *trans*-decalols of the same configuration, whereas their epimers with polar amino-groups react by elimination plus inversion.

The reason why all 1- and 2-amino-*cis*-decalins are deaminated with retention of configuration is that a single substituent at positions other than ring junctions in *cis*-decalin tends to occupy an equatorial position. This gives the maximum number of *e* substituents, and is possible because of the flexibility of the accepted conformation of *cis*-decalin (Bastiansen and Hassel, *Nature*, 1946, **157**, 765) which may exist in two equivalent forms, interconvertible by transforming all *e* bonds into *p* and *vice versa.* (I) and (II) show the more stable conformations of an epimeric pair of *cis*-2-decalyl derivatives, each with the substituent X equatorial. This flexibility of *cis*-decalin is reduced if more than one substituent is present.



(I)



(II)

Secondly, it may be deduced that the retention of configuration observed in deamination of equatorial amino-groups is due to a stereospecific process. For monocyclic amines such as menthylamine, one epimer of which has an *e* and the other a *p* amino-group, the retention of configuration during deamination of the *e* epimer may be due to a stereospecific process, or may merely follow from hydroxylation of some intermediate by a mechanism which gives an alcohol with the most stable conformation. The almost complete retention of configuration proved by Dauben and Hoerger (*loc. cit.*) to occur during deamination of both epimeric 2-amino-*cis*-decalins is decisive : configuration must be retained at every stage during deamination of equatorial amino-groups.

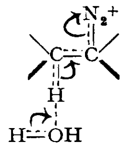
This evidence excludes a true carbonium ion as intermediate, because the distinction between the epimeric amines would disappear at that stage, and each would give rise to the same mixture of the two possible equatorial alcohols if maximum stability were the only requirement for the hydroxylation process. In any case, a mechanism involving carbonium ions would have been unlikely in deaminations with retention of configuration, because with, *e.g.*, menthylamine those molecular rearrangements which should result from the presence of a positive charge adjacent to a methine group (Wallis, in Gilman's " Organic Chemistry," Wiley, New York, 2nd edn., 1943, vol. I, pp. 1004—1009; Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173) seem to be absent.

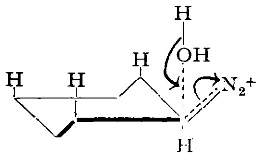
There is no reason to doubt the formation of a diazonium ion as an intermediate in all deaminations; it is in the mode of its decomposition that the *cyclo*hexylamines differ from saturated acyclic amines. All published deaminations have been carried out in acid solution, and must involve attack on the diazonium ion by a water molecule, not a hydroxyl ion. The only requirement is that the acidity should not be so high as to prevent the formation of the diazonium ion (Kornblum and Iffland, *J. Amer. Chem. Soc.*, 1949, **71**, 2137). Successful deaminations are possible in very weakly acidic solutions, *e.g.*, Wallach (*Annalen*, 1907, **353**, 318) noted that a few drops of acetic acid suffice for the decomposition of aqueous solutions of menthylamine nitrite. In the following discussion will be found suggestions that both elimination and displacement with retention are bimolecular processes, but as usually carried out they will have first-order kinetics. It seems impossible to apply the decisive test of carrying out the decomposition of the diazonium ion in the presence of base, because of the great speed of the second stage of the reaction, and the necessity for acidic conditions in the first stage.

Barton and Rosenfelder (*loc. cit.*) have shown that steroid vicinal dibromides suffer easy elimination in the presence of iodide ion only if the atoms eliminated are *trans* and both polar, so that four atomic centres are coplanar (cf. Winstein, Pressman, and Young, *J. Amer. Chem. Soc.*, 1939, **61**, 1645). They pointed out that a similar geometric specificity seems to hold for other elimination reactions of *cyclo*hexane derivatives, including that resulting from the action of nitrous acid on *cyclo*hexylamines. If the regular occurrence of elimination with amines containing polar amino-groups is due to the presence of an adjoining polar (*trans*) hydrogen atom, the reaction may proceed by the path shown in (III).

This representation of the reaction as an $E2$ process, rather than as the $E1$ elimination observed for acyclic amines, encounters some difficulties. From the data of Hückel, Tappe, and Legutke (*Annalen*, 1940, **543**, 191) it is seen that, when alternative paths for *trans*-elimination are available, elimination towards a methine group is always prominent, and may predominate, whereas Dhar, Hughes, Ingold, Mandour, Maw, and Woolf (*J.*, 1948, 2093) have shown that base-induced $E2$ elimination from other 'onium ions follows the Hofmann rule of preferential elimination away from a methine group if possible. However, the extent of elimination towards a methine group during deamination of polar amino-groups is not as great as that during solvolysis ($E1$) reactions of related halides and toluene-*p*-sulphonates. Although the observed elimination of polar amino-groups may not yet be fully explicable, the postulate of the transition state shown in (III) seems to provide a valid criterion for studies on configuration. Carbonium ions evidently play some part in the reaction, as *neo*menthylamine affords some menthan-4-ol and traces of menthol (Hückel, Tappe, and Legutke, *loc. cit.*); the menthol may arise by the mechanism which holds for the deamination of acylic amines.

(III)





(IV)

For the deamination of *cyclo*hexylamines with equatorial amino-groups, the simplest mechanism which accommodates the facts is shown in (IV). A broadside displacement of the diazonium group by a water molecule, proceeding through a pyramidal transition state, will be a stereospecific process resulting in retention of configuration. The geometry of the chair ring is favourable to this type of displacement when the group to be displaced is equatorial, and at the same time unfavourable to either displacement with inversion or *trans*-elimination.

There are certain theoretical objections to a pyramidal transition state in displacement reactions (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252), and more decisive evidence is needed; as stated above, the kinetic approach is likely to be difficult. It may be noted that one example of deamination of a primary amine to an alcohol with retention of configuration, under conditions where intermediate formation of a carbonium ion is improbable, is provided by 1-amino*apo*camphane (Bartlett and Knox, *J. Amer. Chem. Soc.*, 1939, **61**, 3184); in this, the environment of the bridge-head amino-group is in some respects comparable to that of an equatorial amino-group in simple *cyclo*hexylamines.

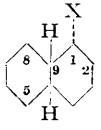
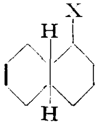
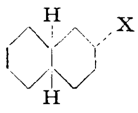
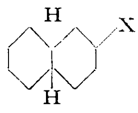
The deamination of *cyclo*hexylamines containing reactive neighbouring groups is not considered here; the dependence of the course of deamination on geometric factors has been discussed for the 2-hydroxy*cyclo*hexylamines by McCasland (*ibid.*, 1951, **73**, 2293).

In our opinion, it may be assumed as a working hypothesis that the deamination of a purely equatorial amino-group would occur with complete retention of configuration and without elimination, and that the existence of partial polar character in the amino-group is indicated if some elimination and partial inversion occur. The concept of a purely equatorial amino-group cannot at present be illustrated by examples, but the hypothesis is in harmony with published data. Menthylamine, the 1-amino-*trans*-decalin with an acetyl derivative of m. p. 141°, and the 2-amino-*trans*-decalin with an acetyl derivative of m. p. 88°, which appear to show complete retention and no elimination on deamination (Hückel, *loc. cit.*), have a strong tendency to exist in conformations with *e*-amino-groups because all substituents will then be *e*. The extent of elimination appears to increase in the order, carvomenthylamine, *iso*menthylamine, *iso*carvomenthylamine (cf. Hückel, *loc. cit.*, and refs. cited there), which conformational analysis indicates to be the order of increasingly polar character in the amino-group, although on balance this group still will be equatorial.

We have used the concepts developed above, with other established principles of conformational analysis, in attempts to check the assigned configurations of amines and alcohols of the *cis*-decalin series. The Table sets out the experimental data (Hückel, *loc. cit.*; Hückel, Tappe, and Legutke, *loc. cit.*; Hückel, *Ber.*, 1934, **67**, *A*, 129), and the suggested configurations. Dauben and Hoerger (*loc. cit.*) established the amine–alcohol relations for the 2-substituted compounds, and on the basis of catalytic hydrogenation data suggested the relative configurations (VII) and (VIII). The following argument strongly supports these assignments.

cis-*Decalylamines and* cis-*Decalols*

(Experimental data relate to the racemic substances corresponding to the active forms shown. The percentages are the approximate figures quoted by Hückel.)

	 (V)	 (VI)	 (VII)	 (VIII)
Alcohols (X = OH).				
M. p.	93°	55°	105°	18 or 31°
Amount of epimer present after equiln., %	*	*	80	20
Rate of hydrolysis (60°) of :				
hydrogen phthalate	0·0635	0·0209	—	—
hydrogen succinate	—	—	3·207	2·113
Amines (X = NH_2).				
M. p. of acetyl deriv.	181°	141°	88°	153
Elimn. during deamin., %	0	25	0	30
Retention during deamin., %	100	90	100	90

* Not measurable.

Complete inversion of the conformation (II) which we believe to be the most stable for a substance of configuration (VIII) brings the functional group into a polar position, and in effect converts a conformation with three *e* and two *p* into one with three *p* and two *e* groups; the difference in stability between the conformation (II) and the inverted conformation may not be very great, and the existence of a certain proportion of molecules with a polar amino-group is to be expected for (VIII; $X = NH_2$). For a substance with configuration (VII), inversion of the most probable conformation (I) causes the same alteration in the numbers of *e* and *p* groups, but when the functional group is *p* the $C_{(8)}$-group is also *p* and on the same side of the ring to which the two groups are attached; such an arrangement causes a marked overlapping of van der Waals barriers of individual atoms, and is likely to be associated with conformational instability (Hassel and Ottar, *loc. cit.*); therefore the structure (VII) should have much less tendency than (VIII) has to exist with the functional group polar. The greater reactivity and greater stability of the alcohol (VII; X = OH) relative to its epimer, and the more complete retention and absence of elimination during deamination of the amine (VII; $X = NH_2$), agree with the deduction that equatorial character should be more marked in the functional group of these substances than in their epimers. In these cases the examination of static models is misleading.

Similar reasoning supports the configurations (V) and (VI) for the *cis*-1-decalyl derivatives shown in the Table, which are the original assignments deduced by Hückel (*locc. cit.*) from the methods of preparation. In (V) the functional group is unlikely to take up the polar position because of the resulting interference from the $C_{(5)}$-group. In this series two items of supporting evidence are available. Barton (*J.*, 1949, 2174) has pointed out that, since in the Tschugaev elimination reaction the *cis*-decal-1-ol of m. p. 93° undergoes elimination preferentially towards $C_{(2)}$ (Hückel, Tappe, and Legutke, *loc. cit.*), the hydroxyl group in this alcohol must be *trans* to the $C_{(9)}$-H, because *cis*-elimination is the rule in the Tschugaev reaction (cf. also Alexander and Mudrak, *J. Amer. Chem. Soc.*, 1950, **72**, 1810) and occurs preferentially towards a methine group if possible. The hydrocarbon formed during deamination of the 1-amino-*cis*-decalin with the acetyl derivative of m. p. 141° is principally Δ^1-*cis*-octalin (Hückel, Tappe, and Legutke, *loc. cit.*), which is evidence for a *cis*-relation between the amino-group and the $C_{(9)}$-H, suppressing the otherwise preferred elimination towards the methine group.

If these configurational assignments are correct, the absence of elimination between the *trans*-amino-group and $C_{(9)}$-H in (V) is noteworthy; indeed, these *cis*-decalin derivatives provide some of the most striking examples of conformational influence on reactivity so far recognised.

It is possible that certain *cis*-decalin derivatives may have conformations different from the possible ones mentioned above, *e.g.*, one chair ring and one boat ring. In the absence of a stabilising factor, such as a bridge, all of these other conformations appear to be less probable than the two-chair types discussed, and in most cases would support the view that configuration (V) should have more equatorial character than (VI), and (VII) more than (VIII).

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