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STUDIES OF THE ELIMINATION OF 4-ARYL-3-METHYL-4-PIPERIDINOLS—V[1]

SOME FACTORS AFFECTING THE DIRECTION OF ELIMINATION

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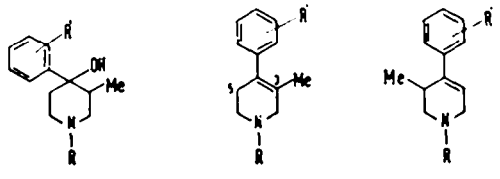
Abstract—The isomeric compositions of binary mixtures of alkenes resulting from the acid-catalysed elimination of 4-aryl-3-methyl-4-piperidinols are considered in the light of the relative stabilities of 3- and 5-methyl-4-aryl-1,2,5,6-tetrahydropyridines (the former are shown to be the more stable under acid conditions), the probable stereochemistry of the reaction (evidence for a preferred *trans* mechanism is described) and the influence of protonated nitrogen upon the rates of equilibration of the isomeric alkenes.

IN PART I of this series[2] it was shown that mixtures of 3- and 5-methyl-1,2,5,6-tetrahydropyridines result when *trans* (aryl/methyl) 4-aryl-3-methyl-4-piperidinols (I) are treated with a mixture of acetic and hydrochloric acids at the reflux temperature. In mixtures derived from 4-phenyl-, *o*- and *m*-tolyl- and *p*-dimethylaminophenyl-piperidinols the ratio of the 3-(II) to the 5-methyltetrahydropyridine (III) was, in most cases, approximately 1:2 (after a 12 hr heating period), whereas in those derived from 4-*p*-tolyl- and *p*-methoxyphenyl- piperidinols, the ratio was approximately 4:1. In this paper, some factors influencing the relative proportions of isomeric tetrahydropiperidines formed in these reactions, are considered.



I II III

R = [a] CH_2Ph; [b] Et; [c] Me; [d] H

Relative stabilities of the 3- *and* 5-*methyltetrahydropyridines* (II *and* III). Isomer stabilities were investigated by heating a pure isomer in a mixture of acetic and hydrochloric acids and assessing isomer proportions in the product from the PMR integrals of the vinylic and sec-methyl (characteristic of the 5-methylalkene) and t-methyl (characteristic of the 3-methylalkene) signals (Table 1). The extent of isomerization of the 5-methyltetrahydropyridine (IIIa, R′ = H) increased with time, the 3-Me:5-Me ratio being approximately 6:1 after 96 hr treatment (Table 1, Nos. 1–4).

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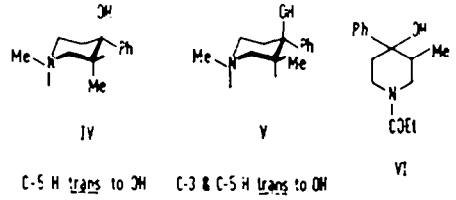
[1] Part IV. A. F. Casy, A. H. Beckett and M. A. Iorio, *Tetrahedron* **22**, 2751 (1966).
[2] A. F. Casy, A. H. Beckett, M. A. Iorio and H. Z. Youssef, *Tetrahedron* **21**, 3387 (1965).

A mixture of similar composition was obtained from the 3-methyl isomer (IIa, R′ = H) after a 6 hr heating period. Further heating had no significant effect upon this ratio (Table 1, Nos. 6–8) which is therefore assumed to represent the equilibrium value. In the case of the N-ethyl analogues, the extent of isomerization of the 5-methyl (IIIb, R′ = H) was more than twice that of the 3-methyl isomer (IIb, R′ = H) after a 6 hr treatment (Table 1, Nos. 9 and 10).

These results establish the 3-methyl (II) to be more stable than the 5-methyltetrahydropyridines (III) under these conditions. Thus, the generally observed greater stability of tetra- compared with tri-substituted alkenes is followed in the present examples in spite of the fact that resonance interactions between the 4-aryl group and the double bond are greater in 5-methyl isomers (non-bonded interactions are more pronounced in planar conformations of 3-methyl- than in 5-methyl-4-aryltetrahydropyridines).[3]

The 5-methylalkene (IIIa, R′ = H) was unchanged after 24 hr in boiling toluene. This result, together with the finding that rates of isomerization were greater in aqueous hydrochloric acid than in an acetic–hydrochloric acid mixture (Table 1, Nos. 2 and 5; 12 and 14), show that these alkene equilibrations probably proceed via addition products (such as the original t-alcohol or a 4-chloro derivative) which subsequently eliminate by the E1 mechanism, and require a polar solvent,

Stereochemistry. Evidence for the stereochemistry of the acid-catalysed elimination of 4-aryl-3-methyl-4-piperidinols was derived from a study of the elimination of isomeric pairs of piperidinols, the probable conformations of which are known.[4] A preferred *trans* stereochemical course for these reactions is supported by the following facts.



(1) *cis* (Ph/Me) 1,3-Dimethyl-4-phenyl-4-piperidinol (IV, preferred conformation) gave the 5-methyltetrahydropyridine (IIIc, R′ = H) as sole elimination product in 80% yield, when heated at 50–52° with 16–17% aqueous hydrochloric acid for 24 hr (Table 1, No. 11); if elimination were *cis* or unselective, an alkene mixture should result. The complete absence of the 3-methyl isomer shows the 5-methyl derivative to be stable under these conditions and hence interpretation of the result is uncomplicated by isomerizations. Under the same conditions the *trans* (Ph/Me) piperidinol (V, preferred conformation) was not eliminated (see below).

(2) Using the above elimination conditions, the *cis* (aryl/methyl) 4-*p*-tolylpiperidinol (Ib, R′ = *p*-Me) gave the 3- and 5-methylalkenes (II and IIIb, R′ = *p*-Me) in the ratio of 1 to 2·5 (together with a trace of starting material), while the corresponding *trans* piperidinol gave equal amounts of the two alkenes plus 45% of unchanged substrate (Table 1, Nos. 16 and 17). In these cases, a significant interconversion of the 5-methyl- (III) into the 3-methyl-alkene (II) probably occurs [the equilibration rate of

[3] A. H. Beckett, A. F. Casy and M. A. Iorio, *Tetrahedron* **22**, 2745 (1966).
[4] A. F. Casy, *Tetrahedron* **22**, 2711 (1966).

the 4-*p*-tolyl- is faster than that of the 4-phenyltetrahydropyridine (IIIa) (Table 1, Nos. 1 and 18]. However, allowing for this, the fact that more of the 5-methyltetrahydropyridine (IIIb, R′ = *p*-Me) is produced from the *cis*-piperidinol, indicates a preference for *trans* elimination; the approximately equal amounts of the 3- and 5-methyl isomers formed from the *trans* piperidinol (Ib, R′ = *p*-Me) is consistent with the same stereochemistry, because *trans* hydrogen atoms are available at both the 3- and 5- positions in this isomer. The relative proportion of the 5-methyl isomer (IIIb, R′ = *p*-Me) was also greater in the *cis* (Ib, R′ = *p*-Me)-derived mixture after a 12 hr reflux period in acetic–hydrochloric acid (Table 1, Nos. 19 and 21).

Trans elimination mechanisms, well known in E2 reactions, have also been recognized in certain El processes (notably in menthyl and neomenthyl derivatives)[5] and the presently described reactions (acid-catalysed dehydration of t-benzylic alcohols), which almost certainly proceed by an El mechanism, provide further examples of El substrates which eliminate most readily when the ionising group and the β-hydrogen atom are *trans* diaxial. The elimination of the 4-piperidinols (I) by a hot mixture of acetic and hydrochloric acids probably proceeds via an intermediate chloro derivative or ester (Cl or protonated OCOMe as ionising group), and the greater reactivity of the *cis* piperidinols (Ib, R′ = *p*-Me and Ic, R′ = H) compared with corresponding *trans* isomers is possibly a result of such intermediates being formed with greater ease in the former isomers because they lack the gauche (3 Me/OH) interactions of the *trans* forms. In the case of alkene equilibrations, the formation of diastereoisomeric mixtures of adducts is more likely than that of a pure *cis* or *trans* (Me/Ph) intermediate;* hence the occurrence of 3-methyltetrahydropyridines in alkene mixtures obtained from *cis* (Me/Ar) piperidinols (I) (as in Table 1, Nos. 16 and 19) is still consistent with a *trans* elimination mechanism since, although this alkene cannot be so-derived from the original *cis* substrate, it can be produced from a *trans* (Me/Ar) equilibration intermediate.

Influence of positively charged nitrogen. Protonated nitrogen appears to be unfavourable to the elimination of the 4-phenylpiperidinols (I) in general and to the formation of the 3-methyltetrahydropyridines (II) in particular, on the following grounds.

(1) While the elimination of 2-methyl-1-phenylcyclohexanol† [the non-basic analogue of the piperidinols (I)], was virtually complete after a 30 min reflux period in an acetic–hydrochloric acid mixture, the same treatment of the *trans*-piperidinol (Ic, R′ = H) resulted in an 80% recovery of starting material (Table 1, Nos 24 and 13).

(2) When 2-methyl-1-phenylcyclohexanol was heated in an acetic–hydrochloric acid mixture for 12 hr, 2-methyl-1-phenylcyclohexene (equivalent to the 3-methyltetrahydropyridines) rather than the 6-methyl isomer (equiv to the 5-methyltetrahydropyridines) preponderated in the resultant alkenic mixture (Table I, No. 22).

(3) When the amide VI was subjected to the above elimination process, the 3-methyltetrahydropyridine (IId, R′ = H) resulted, little, if any, of the 5-methyl isomer being detected in the total reaction product (Table 1, No. 25).

* In this respect, it is significant that the unchanged substrate remaining after acid treatment of *cis* Ic (R′ = H) (Table 1, No. 11) was a *cis-trans* mixture, as evident from the *sec.* methyl PMR signals (*cis* 45·5 c/s, *trans* 36 c/s).

† The PMR characteristics of this alcohol [in particular, the position of its s-methyl signal (37 c/s from TMS) and the broad nature of its aromatic signal (multiplet, main peaks 444, 440 c/s, W_H 12 c/s)][4] indicate it to be composed, largely, of the *trans* (Ph/Me) isomer.

Table 1. Integral data for mixtures of tetrahydropyridines II and III and related compounds[a]

No	Substrate	Heating period (hr)	PMR integrals			Ratio 3Me(II):5Me(III)[g]
			vinylic[b]	sec-Me[c]	t-Me[d]	
1	IIIa (R′ = H)	6	4	11	2·5	1:4·8
2		24	1·5	7	5	1:1·2
3		48	*f*	5·5	13·5	2·45:1
4		96	*f*	2·5	15	6:1
5		12[e]	not visible	2·5	20	8:1
6	IIa (R′ = H)	6	*f*	*f*	*h*	7:1
7		24	not visible	*f*	*h*	8:1
8		7 days	not visible	*f*	*h*	8:1
9	IIIb (R′ = H)	6	3	10	4	1:2·5
10	IIb (R′ = H)	6	*f*	2·5	17	6·5:1
11	*cis* Ic (R′ = H)	24[i]	5	17	—	5-Me sole elimination product
12	*trans* Ic (R′ = H)	12	6	16·5	16·5	1:1
13	*trans* Ic (R′ = H)	0·5	*f*	4[j]	4	1:1
14	*trans* Ic (R′ = H)	12[e]	*f*	7	16	2·3:1
15	*trans* Ic (R′ = H)	3[e]	2	7	12	1·7:1
16	*cis* Ib (R′ = *p*-Me)	24[i]	3	10	4	1:2·5
17	*trans* Ib (R′ = *p*-Me)	24[i]	*f*	5·5[j]	5	1:1
18	IIIa (R′ = *p*-Me)	6	2·5	8	13	1·6:1
19	*cis* Ib (R′ = *p*-Me)	12	3	6·5	11	1·7:1
20	*cis* Ib (R′ = *p*-Me)	2	3	11·5	10·5	1:1
21	*trans* Ib (R′ = *p*-Me)	12	not visible	4	20	5:1
22	2-methyl-1-phenylcyclohexanol	12	*f*	*k*	—	6·2(2Me):1(6Me)
23	2-methyl-1-phenylcyclohexanol	3	*f*	*k*	—	3:1
24	2-methyl-1-phenylcyclohexanol	0·5	*f*	*k*	—	2:1
25	VI	12	not visible	3	16	5·3:1

[a] Derived from t-alcohols or pure alkenes (bases or hydrochlorides) by the following general procedure: a mixture of the substrate (75 mg approx), conc HCl (0·3 ml) and glacial AcOH (0·6 ml) is heated under reflux for the stated period, made alkaline with aqueous ammonia and extracted with ether. The dried extract is evaporated and the residue examined by PMR spectroscopy in $CDCl_3$.

[b] Triplet, chemical shift near 360 c/s from TMS.

[c] Doublet, chemical shift near 60 c/s from TMS.

[d] Broad singlet, chemical shift near 96 c/s from TMS.

[g] Calculations for the 5 Me alkene (III) based upon both vinylic and s-Me integrals; results averaged if close, otherwise s-Me derived value taken. Integrals checked against that of the aryl signal.

[f] Signal visible but integral too small to be measured accurately.

[e] Solvent, conc HCl (4 ml) and water (4 ml), 80 mg substrate, reflux temp.

[h] Ratio obtained by comparing the 3-Me integral with the calculated 100% value (based upon the aromatic integral).

[i] Solvent, conc HCl (2 ml) and water (2 ml), 60 mg substrate, 50–52°.

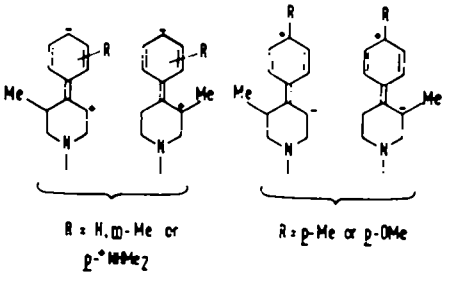
[j] s-Me (40 c/s) integral 9 (≡45% unchanged piperidinol).

[k] t-Me signal not resolvable; ratio calculated from observed and calculated s-Me integral.

[l] s-Me (38 c/s) integral 24 (≡80% unchanged piperidinol).

In the light of these factors, consideration may now be given to the isomeric compositions of products derived from the piperidinols (I) after a 12 hr reaction period. The relative proportion of the tri-to the tetra-substituted alkene is greater in the initial products than in products isolated after a prolonged heating period, as is evident from the results of experiments in which substrates were heated for differing periods of time (Table 1, Nos 14 and 15, 19 and 20). Hence 5-methyltetrahydropyridine formation from *trans* 4-phenyl(etc)-3-methylpiperidinols is even more favoured than is indicated from the composition of products isolated after a 12 hr reaction period, and most of the 3-methyltetrahydropyridine content must therefore be derived from the 5-methyl isomer as a result of equilibration. In *trans* substrates, loss of either a C-3, or an axial C-5 proton is consistent with a *trans* elimination process and the preferred loss of the latter proton may be associated with its greater acidity (the acidity of the C-3 proton is reduced by the inductive influence of the C-3 methyl substituent).

The factors of stereochemistry and β-proton acidity are equally applicable to the elimination of 2-methyl-1-phenylcyclohexanol and there is evidence that substantial amounts of tri-substituted alkene are also produced initially when this compound is heated with acid (the proportion of 6-methyl-1-phenylcyclohexene in the alkene mixture rises as the reflux period is reduced from 12 hr to 30 min (Table 1, Nos 22–24)*. On this account, therefore, it is considered that the different isomeric ratios of tri- to tetra-substituted alkenes obtained from the 4-aryl-3-methylpiperidinols (I, R′ = H, *o*- and *m*-Me, and *p*-NMe_2) on the one hand and 2-methyl-1-phenylcyclohexanol and the 4-aryl-3-methyl-piperidinols (I, R′ = *p*-Me and *p*-OMe) on the other, stem largely from the influence of protonated nitrogen upon the rates of equilibration of the isomeric alkenes. The evidence that protonated nitrogen retards the elimination process is also applicable to the influence of $\overset{+}{N}H$ upon equilibration because transition states for the two processes are probably similar. This influence may be interpreted in terms of positively charged nitrogen destabilizing carbonium ion intermediates that have reduced electron densities at the C-3 or C-5 positions. The more probable resonance contributors (VII) of the alkenes (II and III) are known from UV studies,[8] and if it is assumed that their electronic characteristics at C-3 and C-5 reflect those of corresponding elimination intermediates, it follows that positively charged nitrogen



VII

* The observation that 2-methyl-1-phenylcyclohexanol treated with 2·5% H_2SO_4 in AcOH for 20 min at room temp gives 77% of 6-methyl- and 20% of 2-methyl-1-phenylcyclohexane,[7] provides further evidence in this respect.

[6] D. V. Banthorpe, *Elimination Reactions* pp. 117 and 152. Elsevier, London (1963).

[8] R. B. Carlin and H. P. Landerl, *J. Am. Chem. Soc.* **75**, 3969 (1953).

[7] E. W. Garbisch, Jr., *J. Org. Chem.* **27**, 4247 (1962).

will destabilize the intermediates leading to the alkenes (II and III, R' = H, *m*-Me and *p*-MNe_2) to a greater extent than those from which the alkenes (II and III, R' = *p*-Me and *p*-OMe) are derived.

EXPERIMENTAL

Compounds I, II and III have been previously reported.[3,4] 2-Methyl-1-phenylcyclohexanol, b.p. 40°/0·6 mm, n_D^{26} 1·5369 (lit.[4] b.p. 105–106°/1 mm, n_D^{26} 1·5359) was prepared from 2-methylcyclohexanone and lithium phenyl. The mixture of alkenes derived from this alcohol after treatment with acid (Table, footnote *a*) distilled at 70–80°/0·8 mm, n_D^{26} 1·5460 (lit.[4] b.p. 78°/1 mm, n_D^{25} 1·5460). The PMR spectra were obtained on a Perkin Elmer R-10 instrument in $CDCl_3$ with TMS as internal standard. Thanks are due to Mr. G. McDonough for recording the spectra.

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