# ELIMINATION OF 2-t-BUTYL-4-DIMETHYLAMINO-1-PHENYLBUTAN-2-OL; MAGNETIC NON-EQUIVALENCE OF A TERTIARY BUTYL GROUP

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Abstract—Acid-catalysed elimination of 2-t-butyl-4-dimethylamino-1-phenylbutan-2-ol and its o-chloro analogue yield ternary mixtures of 2-t-butyl-4-dimethylamino-1-arylbutenes (one but-1- and two but-2enes). In each case the t-butyl PMR signal of one of the but-2-enes forms a sharp 9 proton singlet while that of the other isomer displays a sharp 6 plus a broad 3 proton singlet. These and other PMR differences are interpreted in terms of probable conformations and allow tentative configurational assignments to be made.

DURING the course of a study of structure-activity relationships among aminobutenes with antihistaminic properties<sup>1,3</sup> the acid-catalysed elimination of 2-t-butyl-4dimethylamino-1-phenylbutan-2-ol I (obtained from the Mannich base II) was investigated. The PMR spectrum of the total basic product derived from I after a four hour reflux period with an acetic-hydrochloric acid mixture indicated that only three of the four possible butenes (*cis* and *trans* IIIa and IVa) had been formed. Thus

$$\begin{array}{cccc} OH & O \\ | & || \\ PhCH_2C(CH_2)_2NMe_2 & t-BuC(CH_2)_2NMe_2 \\ | \\ t-Bu & & \\ I & II \\ ArCH=C(t-Bu) (CH_2)_2NMe_2 & ArCH_2C(t-Bu)=CHCH_2NMe_2 \\ III & IV \\ Ar = (a) Ph, (b) o C_6H_4VI & IV \end{array}$$

three vinylic signals, consisting of one singlet (characteristic of III) and two triplets (characteristic of IV) were present together with three distinct singlets in the N-Me resonance region. The individual components were separated as hydrochloride salts by fractional crystallization from ethanol-ether. Tentative configurational assignments, based on PMR (Table 1) and UV spectroscopic evidence are described below.

(1) The trans (t-Bu/Ph) but-1-ene IIIa, m.p.  $176-177^{\circ}$ . Catalin models demonstrate that conformers of *cis* and *trans* III in which the double bond and 1-Ph group are coplanar both entail serious non-bonded interactions although these are clearly of a much higher order when the t-Bu and Ph substituents are *cis*. From these considerations the sole but-1-ene formed is assigned a *trans* configuration since it doubtlessly represents the more stable form, the elimination procedure being one which allows equilibration. In further emphasis of relative *cis-trans* stabilities,

Compound (HCl)	Configuration	PMR Signals				
		vinylic	<u>CH</u> 2Ar <sup>3</sup>	<u>CH</u> <sub>2</sub> N <sup>c</sup>	NMe <sub>2</sub>	t-Bu <sup>∌</sup>
IIIa-1-ene	trans (Ar/t-Bu)	392*			1 <b>46</b> '	69.5
IIIb-1-ene (HBr)	trans (Ar/t-Bu)	387·5 <sup>6</sup>	_		148 <sup>b</sup>	72-5
IVa-2-ene	cis (t-Bu/H)	315 <sup>d</sup>	161-5	218	155 <sup>6</sup>	66·5 (6 protons) 111·5 (3 protons)
IVa-2-ene	trans (t-Bu/H)	3524	215	209	157·5 <sup>6</sup>	66.5
IVb-2-ene	cis (t- <b>B</b> u/H)	3214	172	220	1 <b>62</b> *	68 (6 protons) 113 (3 protons)
IVb-2-ene	trans (t- <b>B</b> u/H)	3624	215	204	1 <b>62</b> <sup>6</sup>	68

TABLE 1. PMR CHARACTERISTICS OF SOME 2-t-BUTYL-4-DIMETHYLAMINO-1-ARYLBUTENE HYDROCHLORIDES

" Chemical shifts in Hz from TMS (60 MHz), coupling constants in Hz; solvent CDCl<sub>3</sub>.

<sup>b</sup> Singlet(s).

<sup>c</sup> Doublet J5 (NH<u>Me</u><sub>2</sub>) or J 7-7.5 (<u>CH</u><sub>2</sub>N).

<sup>4</sup> Triplet J7.

equilibration of the pure but-1-ene in a hot acetic-hydrochloric acid mixture failed to yield the second but-1-ene component (no vinylic signals other than that of the starting material were detected in the PMR spectrum of the equilibrated product). UV characteristics of the but-1-ene ( $\lambda_{max}$  238 mµ,  $\varepsilon$  8600) are indicative of, at least, a partially effective phenyl-double bond chromophore, and support the *trans* configurational assignment.

(2) The two but-2-enes IVa, m.ps 243° and 183–184°. From integrals of the two vinylic PMR signals, the former preponderated slightly in the total elimination mixture. The PMR spectra of the isomers differed in several respects, most notably in regard to the t-Bu signal; this was a sharp 9 proton singlet in one isomer, and a sharp 6 plus a broad 3 proton singlet (W<sub>H</sub> 2·5 Hz) in the other (Fig. 1). The latter, originally noted in the spectra of mixtures was first attributed to an impurity but its persistence in the spectrum of an analytical sample showed it to represent one of the three t-Bu/Me proton groups. A unique environment for one of these Me groups is to be anticipated if the  $\frac{PhCH_2}{t-Bu} C = \text{fragment of the molecule adopts the preferred conformation shown in Fig. 2, provided restricted rotation about the t-butyl-alkene$ 

link may be assumed. In this conformation two of the t-Bu Me groups have essentially equivalent environments (allowing for some degree of rotational freedom about the  $CH_2$ -phenyl linkage) while the third group lies in the plane of the double bond. According to current views of the anisotropies of the C—C double bond<sup>4</sup> the latter Me group falls in a deshielding cone and this fact accounts for its low field resonance



FIG. 1 t-Butyl PMR Signals (100 MHz) of 2-t-butyl-4-dimethylamino-1-phenylbut-2-ene, m.p. 183-184° in DMSO-d<sub>6</sub>. A: both signals at room temperature. B: 3-proton (lower field) signal at 100°. C: 3-proton signal at 100° when sample irradiated at the frequency of the vinylic signal (sweep width 1000 Hz for A, 100 Hz for B and C).



FIG. 2



position relative to that of the other two Me groups. The alternative coplanar conformation V may be rejected because this arrangement requires Me to be shielded. The magnetic influence of Ph upon Me in the double bond plane (Fig. 2) is difficult to assess from models but is likely to augment deshielding due to the double bond. The conformation of Fig. 2 would be expected to arise as a result of the aromatic ring being forced towards the t-Bu substituent through non-bonded interactions with the R substituent which is *cis* to benzyl. Hence, evidence of configuration is



provided since it follows, from these arguments, that the but-2-ene showing Me nonequivalence within the t-Bu group must be the cis H/t-Bu isomer with R the bulky dimethylaminomethyl function. In the *trans* isomer a partial conformation as in Fig. 3 is more probable; this will allow the aromatic group to be deflected away from the t-Bu group and towards the vinylic substituent (R in Fig. 2), more easily achieved in this case because R is hydrogen in the *trans* isomer. In a conformation of this type (Fig. 3), rotation of the t-Bu group about the alkene link is free with the result that the group produces a sharp 9 proton PMR singlet.



Double resonance experiments at 100 MHz reveal that the vinylic (and benzylic) protons are weakly spin-spin coupled (J = 0.6 Hz) to the isolated 3-proton t-butyl-methyl signal (Fig. 1) (the 6-proton signal remained a sharp singlet at the higher frequency). This observation further supports a coplanar Me-double bond conformation because such an arrangement allows the coupled groups to be linked by near-planar zig-zag paths (shown in VI for Me and vinyl protons), an established requirement for long-range coupling.<sup>5</sup>

The rest of the PMR differences between the but-2-ene isomers may now be interpreted in terms of the conformations shown in Figs 2 and 3.

(a) Vinylic signals. The vinylic proton is close to the aromatic ring in the Fig. 3 conformation and removed from it in that of Fig. 2, hence, the aromatic influence

upon the vinylic resonance should be greater in the *trans* H/t-Bu isomer. In fact, the *trans* signal (352 Hz) is significantly lower field than that of the corresponding *cis* proton (315 Hz) and the *trans* value corresponds closely with the vinylic chemical shift (358 Hz) observed for the 1,2 diphenylbut-2-ene VII where vinylic hydrogen has a similar environment to that of the same proton in the Fig. 3 conformation.<sup>2</sup> It is difficult to predict the magnetic influence of the aryl group upon the vinylic proton in *trans* IV (Fig. 3) because of the numerous rotational possibilities about bonds linking benzyl carbon to the aryl and alkene functions. However, inspection of models shows that a deshielding effect may reasonably be expected and this conclusion is supported by the even lower field position (362 Hz) of the vinylic signal in the analogue IVb (described later) where the electronegativity of the aryl function is enhanced by the inclusion of an *o*-Cl atom.



(b) Benzyl methylene signals. From the modified Schoolery rules<sup>6</sup> the expected chemical shift for Ph <u>CH<sub>2</sub></u> in IV is 198 Hz at 60 MHz;\* thus the cis signal (161.5 Hz) has an unusually high field, and the trans (215 Hz) a low field position. These differences are attributed chiefly to anisotropic influence of the C—C double bond which, on the basis of the shielding zone diagram of ApSimon and others<sup>4</sup> would be expected to be screening for the methylene protons of the Fig. 2 conformation and deshielding for the Fig. 3 arrangement. Deviations from the calculated chemical shift value are therefore consistent with the assigned configurations.

(c) Methylene amino and dimethylamino signals. The similar resonance positions of the isomeric  $\underline{CH}_2N$  and  $\underline{NMe}_2$  signals show that the *cis* and *trans* dimethylaminomethyl substituents differ little in their environments. This is only likely to be the case if the aromatic group is removed from the aminomethyl function in the *cis*  $CH_2N/CH_2Ph$  isomer (as it must be in the *trans* form). An arrangement of this type is an essential feature of the proposed *cis* conformation (Fig. 2) which therefore receives further support.

Entirely comparable results followed the elimination of the o-chlorophenyl analogue of the butanol I, PMR characteristics to the three butenes isolated closely resembling corresponding members of the original series (Table 1). The spectrum of one of these butenes again displayed a two component t-Bu signal and the observed separation was equal to that seen in the phenylbutene example. Observation of non-equivalent signals in the two examples cited must be associated with large barriers to rotation of the t-Bu group about its link to the double bond which may reasonably be expected on account of the highly crowded nature of the *cis* molecule IV and its o-chlorophenyl congener. This conclusion is supported by temperature studies upon *cis* IVa in DMSO-d<sub>6</sub> at 100 MHz, the 3- and 6-proton signals moving together as the temperature is raised (separations are 80-4 Hz at room temperature, 75-6 Hz at 100°, 73-4 Hz at 150° and 71.8 at 180°), although the extent of movement noted is

\* 
$$\tau_{CH_2} = 8.75 - \Sigma 0.75$$
 () + 1.3 (Ph) = 6.7 (198 Hz).

unusually small for a hindered rotation situation. This point is being further investigated.

To the best of our knowledge, the present examples are the first cases of magnetic non-equivalence within a t-Bu group to be reported.

#### EXPERIMENTAL

1-t-Butyl-3-dimethylaminopropan-1-one (II). Pinacolone (49.5 g), paraformaldehyde (20 g) and dimethylammonium chloride (53 g) were heated under reflux in EtOH (40 ml) containing concentrated HCl (1 ml) for 6 hr. The cooled mixture was diluted with acetone (250 ml) and stored at 5° when the Mannich ketone II hydrochloride (82.2 g 88%) separated, m.p. 173–174° from EtOH-Et<sub>2</sub>O. (Found: C, 55.8; H, 10-2; N, 7.2. C<sub>9</sub>H<sub>20</sub>ClNO requires: C, 55.8; H, 9.9; N, 7.2%).

2-t-Butyl-4-dimethylamino-1-phenylbutan-2-ol (I). 1-t-Butyl-3-dimethylaminopropan-1-one (27.8 g) in Et<sub>2</sub>O (50 ml) was added to a soln of benzylmagnesium chloride prepared from benzyl chloride (45 g) and Mg (9.7 g) in Et<sub>2</sub>O (400 ml), the mixture heated under reflux for 2 hr and decomposed with crushed ice and NH<sub>4</sub>Cl. The organic phase was dried (MgSO<sub>4</sub>), concentrated, and the residue acidified with EtOH-HCl; on cooling the hydrochloride I (32.8 g), m.p. 193° from EtOH-Et<sub>2</sub>O, separated. (Found : C, 67.4; H, 9.9; N, 4.7. C<sub>16</sub>H<sub>28</sub>ClNO requires : C, 67.2; H, 9.5; N, 4.9%). The o-chlorophenyl analogue of I obtained by treating II with o-chlorobenzyl magnesium chloride, formed a hydrochloride, m.p. 174° (Found : C, 60.2; H, 8.7; N, 4.2. C<sub>16</sub>H<sub>27</sub>Cl<sub>2</sub>NO requires : C, 60.0; H, 8.5; N, 4.4%).

Acid catalysed elimination of 2-t-butyl-4-dimethylamino-1-phenylbutan-2-ol. The hydrochloride 1 (15 g) was heated under reflux with a mixture of AcOH (100 ml) and conc HCl (50 ml) for 4 hr; the mixture of butenes, isolated as previously reported,<sup>1</sup> had a PMR spectrum in CDCl<sub>3</sub> which displayed three vinylic signals [singlet 381, triplets (J = 7 Hz) 337 and 305 Hz from TMS] and three N-Me signals (singlets 130, 127 and 123 Hz from TMS). The mixture (9.5 g) was acidified with EtOH-HCl and fractionally crystallized from EtOH-Et<sub>2</sub>O to give the following hydrochlorides: (a) the trans (H/t-Bu) but-2-ene IVa (1.08 g), m.p. 243°. (Found: C, 71.4; H, 9.4; N, 4.9. C<sub>16</sub>H<sub>26</sub>ClN requires: C, 71.7; H, 9.75; N, 5.2%); (b) the cis (H/t-Bu) but-2-ene IIIa (0.36 g), m.p. 183-184°. (Found: C, 71.5; H, 9.7; N, 5.0%); (c) the trans (t-Bu/Ph) but-1-ene IIIa (0.36 g), m.p. 176-177°. (Found: C, 71.5; H, 9.7; N, 5.4%);  $\lambda_{max}$  238 mµ (a 8600 in H<sub>2</sub>O). The following hydrochlorides were isolated from the o-chlorophenyl analogue of I: (a) the trans (H/t-Bu) but-2-ene IVb (0.78 g), m.p. 233-234°. (Found: C, 63.8; H, 8.5; N, 4.4. C<sub>16</sub>H<sub>25</sub>Cl<sub>2</sub>N requires: C, 63.6; H, 8.3; N, 4.6%). (b) the cis (H/t-Bu) but-2-ene IVb (0.60 g), m.p. 195-196°. (Found: C, 63.8; H, 8.6; N, 4.4).

The hydrobromide of the trans (t-Bu/Ph) but-1-ene IIIb (1.83 g) was collected, m.p. 175°. (Found: C, 55·3; H, 7·4; N, 4·2;  $C_{16}H_{25}BrClN$  requires: C, 55·4; H, 7·3; N, 4·0%); UV absorption spectrum in water showed end-absorption only.

The PMR spectra were obtained with Varian A-60 (CDCl<sub>3</sub> as solvent with TMS as internal standard) and HA-100 (DMSO-d<sub>6</sub> as solvent) instruments.

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#### Note added in Proof.

"An earlier example of magnetic non-equivalence within a t-butyl group, namely that of the adduct formed between tetrafluorobenzyne and t-butylbenzene, has now been noted [J. P. N. Brewer, H. Heaney and B. A. Marples, *Chem. Commun.* 1, 27 (1967)].