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STUDIES OF THE ELIMINATION OF 1,2-DIARYL-4-DIMETHYLAMINOBUTAN-2-OLS—II[1]

THE ELIMINATION OF 1,2-DIPHENYL-4-DIMETHYLAMINOBUTAN-2-OL AND RELATED COMPOUNDS

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Abstract—The acid-catalysed dehydration of 1,2-diphenyl-4-dimethylaminobutan-2-ol is shown to yield all four possible elimination products. Pure samples of *cis* and *trans* 4-dimethylamino-1,2-diphenylbut-1-ene and the corresponding *trans* (H/Ph) but-2-ene have been isolated and their configurations assigned by PMR and UV spectroscopy. Similar butene mixtures resulted when the related 1-*p*-tolyl- and 1-(2-pyridyl)-2-phenylbutanols were dehydrated.

THE elimination products of 1,2-diaryl-4-dimethylaminobutan-2-ols (I) using potassium hydrogen sulphate, orthophosphoric acid and phosphorus pentoxide in benzene as dehydrating agents,[2] were considered to be but-2-enes (II) on the grounds that the butene from the 1,2-diphenylbutanol (Ia) gave desoxybenzoin on oxidative cleavage with potassium permanganate and possessed antihistaminic activity which differed markedly from that of the isomeric but-1-ene (IIIa), obtained by an unambiguous route. As the acid-catalysed elimination of 1,2-diaryl-3-methyl-4-dimethylaminobutan-2-ols (using a mixture of acetic and hydrochloric acids) resulted in the exclusive formation of corresponding but-1-enes,[1] the elimination of the nor-analogues (I) under the same reaction conditions, has now been investigated.

$$\underset{\text{I}}{NMe_2(CH_2)_2C(OH)Ph{\cdot}CH_2Ar}$$

$$\underset{\text{II}}{NMe_2{\cdot}CH_2{\cdot}CH{:}CPh{\cdot}CH_2Ar} \qquad \underset{\text{III}}{NMe_2(CH_2)_2CPh{:}CHAr}$$

$$Ar = \text{(a) Ph,} \quad \text{(b) } p\text{-}C_6H_4Me, \quad \text{(c) 2-pyridyl}$$

The PMR spectrum of the total basic product derived from the butanol Ia, after a 3 hr reflux period with an acetic–hydrochloric acid mixture indicated it to be a mixture of all four possible butenes (*cis* and *trans*- IIa and IIIa). The vinylic signals consisted of two singlets and two triplets, characteristic of the but-1- and but-2-enes respectively; in addition, four closely placed singlets were found in the dimethylamino resonance region of the spectrum (Table, 1). The proportion of the but-1- to the but-2-enes, derived from the integrals of the vinylic PMR signals, was approximately 1·5 to 1 (within each pair, integrals of the lower field signals were the larger). Isomeric separations were attempted by fractional crystallization of the butene mixture after its acidification with ethanolic hydrogen chloride and much difficulty was experienced in obtaining fractions which melted over a narrow range. In one experiment, an

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[1] Part I. A. F. Casy, J. L. Myers and P. Pocha, *Tetrahedron* **22**, 1001 (1966).

[2] W. G. Stoll, Ch. J. Morel and Ch. Frey, *Helv. Chim. Acta* 33, 1194 (1950).

initial crop (m.p. 150–152°) was found to be a three component-mixture, consisting of the two but-1-enes (IIIa) and the but-2-ene (IIa) which had the lower field vinylic PMR signal (triplet) (Table, 2 and 3). The composition of this mixture was unchanged on further recrystallization. The following three pure hydrochlorides were eventually isolated from the mother liquors:

(1) the *cis* but-1-ene (IIIa)*, m.p. 193–194°. This was identical with the but-1-ene obtained from desoxybenzoin by an unambiguous route[3] and corresponded with the minor but-1-ene component of the ternary mixture of hydrochlorides, m.p. 150–152° (as seen from the identity of vinylic chemical shifts, Table, 2 and 4, 3 and 5). The environments of the bimethylene protons of this isomer are almost equivalent since their PMR signal was a broad singlet.

(2) the *trans* but-1-ene (IIIa), m.p. 152–167° (despite its wide m.p. range, this compound was pure, as judged by its PMR spectrum). Its vinylic chemical shift was the same as that of the lower field vinylic signal in the spectrum of the ternary hydrochloride and hence this isomer is the major but-1-ene component of the mixture (Table, 2 and 6). The bimethylene resonance signal of the *trans* but-1-ene (IIIa), in contrast with that of the *cis* isomer, formed a usual A_2B_2 pattern.

(3) the *trans* (H/Ph) but-2-ene (IIa), m.p. 112°. The vinylic chemical shift of this compound (as free base) characterized it as the minor but-2-ene component of the total elimination mixture which is absent from the ternary hydrochloride (Table, 1, 2, 7 and 8).

Several other crops were isolated, all of which were mixtures of varying composition; a pure sample of the *cis* (H/Ph) but-2-ene (IIa) could not be obtained. The antihistaminic butene hydrochloride derived from the butanol Ia[3] (sample kindly supplied by Geigy Laboratories), and considered to be a pure but-2-ene, was examined by PMR spectroscopy and found to be virtually identical with the ternary mixture m.p. 150–152°.

The assignment of configurations to the butenes (II and IIIa) is based upon UV and PMR spectroscopic evidence. In the case of the but-1-enes, the overall planarity of the molecule is greater in the *trans* isomer (evidence of models). In consequence the absorption maximum of the phenyl double bond chromophore should be at longer wave lengths and more intense than that of the *cis* (less planar) isomer. Further, the vinylic proton of the *trans* isomer will be more deshielded by the aromatic groups than the corresponding *cis* proton (a proton suffers increasing deshielding due to a phenyl group the more it lies in the plane of the aromatic ring[4]). Hence the major (λ_{max} 263 mμ, ε 16800; vinylic chemical shift 406 c/s) is assigned the *trans*, and the minor but-1-ene (IIIa) (λ_{max} 255 mμ, ε 11,270; vinylic chemical shift 389 c/s) the *cis* configuration. In the case of the but-2-ene (IIa), the double bond and the 2-phenyl group may only be coplanar in the *cis* (H/Ph) isomer (in the *trans* isomer the same conformation is markedly unfavoured by ortho hydrogen-aminomethyl interactions). Hence the minor but-2-ene must have the *trans* (H/Ph) configuration because the chemical shift of its vinylic proton (337 c/s) is at higher field than that of the major isomer (367 c/s), while its UV spectrum does not display a styrenoid absorption band. Although the pure *cis* (H/Ph) isomer IIa could not be examined, indirect evidence for

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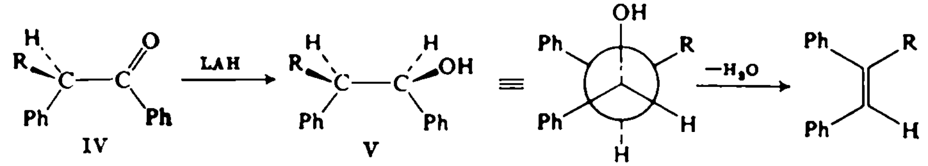
* Evidence for the configurations of the butenes is given later.

[3] W. G. Stoll, Ch. Frey and Ch. J. Morel, *Helv. Chim. Acta* **33**, 1208 (1950).

[4] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.* **29**, 1012 (1958).

its showing styrenoid absorption derives from the fact that the intensity and position of the styrenoid peak of the ternary hydrochloride mixture (λ_{max} 257 mμ, ε 13,100), which contains 30% of the *cis* but-2-ene and 70% of the but-1-enes, are intermediate between those of the pure *cis*- and *trans*-but-1-enes.

Formation of the *cis* but-1-ene (IIIa) by elimination of the sec-aminoalcohol (V) shows that formation of the latter [obtained by reducing the amino-ketone IV with aluminium isopropoxide[3] or LAH] proceeds according to Cram's rule of asymmetric induction.[5] By this rule, the *erythro* isomer (V) should predominate, a derivative which leads (by a *trans* elimination mechanism) to the *cis* but-1-ene (IIIa). Since none of the more stable *trans* but-1-ene is formed in this reaction, the elimination conditions (potassium hydrogen sulphate at 190–200°) do not promote equilibration. When the *cis* but-1-ene (IIIa) was treated with an acetic–hydrochloric acid mixture at the reflux temperature, a four-component-alkene mixture, very similar to that derived from the aminobutanol (Ia) by the same treatment, resulted. This mixture attained equilibrium after 3 hr or less, since its composition did not materially alter when longer heating periods were employed.



IV V

R = $Me_2N(CH_2)_2$

A four-component mixture of butenes (60% but-1- and 40% but-2-enes) was also obtained when the *p*-tolylamino-alcohol (Ib) was dehydrated by the acetic–hydrochloric acid procedure (Table, 9). Fractional crystallization of the base hydrochlorides gave mixtures [e.g. Table, 10, judged to be composed of the *cis* (H/Ar) but-2-ene and the *trans* but-1-ene by comparison of vinylic chemical shifts of the mixture with those of the 1,2-diphenyl analogues], no pure compounds being isolated. The 2-pyridylaminobutanol (Ic) was unaffected by hot acetic–hydrochloric acid, but was dehydrated when heated with phosphorus oxychloride and pyridine, the usual quaternary alkene mixture resulting (Table, 11). Fractional crystallization of the base hydrochlorides gave a pure but-1-ene which was assigned a *trans* configuration on the basis of its vinylic chemical shift and N-bimethylene PMR signal (Table, 12 and 13). Its UV spectrum showed absorption bands at 265 and 300 mμ (hydrochloride in ethanol).

In contrast with results obtained when the amino-butanols (Ia–c) were used as elimination substrates, no but-2-enes resulted when related 3-methyl-analogues were dehydrated under the same equilibration conditions.[1] This is probably due to the fact that stability differences between the positional isomers are more pronounced in the 3-methylbutenes as a result of planar conformations of the but-2-enes being additionally unfavoured by interactions involving the 3-methyl substituent.

EXPERIMENTAL

Acid-catalysed elimination of 4-dimethylamino-1,2-diphenylbutan-2-ol and the 1-p-tolylanalogue (Ib). The 1,2-diphenylaminobutanol[6] (Ia; 1 g) was treated with a mixture of acetic (25 ml) and conc. HCl (10 ml) and by the previously described method,[1] the free base (total product of the Table, 1) was

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[5] D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.* **74**, 5828 (1952).

[6] A. Pohland and H. R. Sullivan, *J. Amer. Chem. Soc.* **75**, 4458 (1953).

TABLE. PMR CHARACTERISTICS OF SOME 1,2-DIARYL-4-DIMETHYLAMINO-BUT-1 AND BUT-2-ENES[a]

No.	Elimination substrate	Elimination sample	Vinylic proton		NMe_2[b]	Miscellaneous
			C-1[b]	C-3[c]		
1.	Ia (1,2-diphenyl)	total base	406 389[d]	367 338	135, 131, 129, 127	234[d] ($N\underline{CH}_2\underline{CH}_2$) 219[d] ($\underline{CH}_2Ph$)
2.		hydrochloride[e] m.p. 150–152°	416 401[d]	375	166, 160	237, 229[d] ($\underline{CH}_2Ph$) 199, 185[f] ($N\underline{CH}_2\underline{CH}_2$)
3.		base from above hydrochloride	406 389[d]	367	135, 131, 128	233[d] ($N\underline{CH}_2\underline{CH}_2$) 187[g] J7 ($N\underline{CH}_2CH{:}$)
4.		*cis* but-1-ene (IIIa) hydrochloride m.p. 193–194°	401	..	168	188[d] ($N\underline{CH}_2\underline{CH}_2$)
5.		base from above hydrochloride	390		132	234[d] ($N\underline{CH}_2\underline{CH}_2$)
6.		*trans* but-1-ene (IIIa) hydrochloride m.p. 152-167°	416	-	162	192, 186[f] ($N\underline{CH}_2\underline{CH}_2$)
7.		*trans* (H/Ph) but-2-ene (IIa) hydrochloride, m.p. 112°	—	358	160	225[d] ($\underline{CH}_2Ph$) 213·5[g] J7 ($N\underline{CH}_2CH{:}$)
8.		base from above hydrochloride	..	337	129	221[d] $\underline{CH}_2Ph$) 172[g] J7 ($N\underline{CH}_2CH{:}$)
9.	Ib (1-*p*-tolyl 2-phenyl)	total base	406 388[d]	366 340[h]	137, 133, 128·5	141·5[b] (Ar-Me) 232[d] ($N\underline{CH}_2\underline{CH}_2$) 217[d] ($\underline{CH}_2Ar$)
10.		hydrochloride[e] m.p. 164–194°	414	374[h]	173, 163	142[b] (Ar-Me) 219[d] ($\underline{CH}_2Ar$) 193, 187[f] ($N\underline{CH}_2\underline{CH}_2$)
11.	Ic[1-(2-pyridyl) 2-phenyl]	total base	406 403	372 (J6·5) 335 (J6·5)	137, 136, 134, 130	249[b], 244[d] ($\underline{CH}_2Ar$) 211, 204, 200, 196 158, 153, 148[f] ($N\underline{CH}_2\underline{CH}_2$)
12.		*trans* but-1-ene (IIIc) hydrochloride[i]	422	..	173	198[d] ($N\ \underline{CH}_2\underline{CH}_2$)
13.		base from above hydrochloride	406	-	139	213, 206, 201, 197 161, 156, 151, 144[f] ($N\ \underline{CH}_2\underline{CH}_2$)

[a] in $CDCl_3$ except for No. 12; chemical shifts in c/s from TMS (60 Mc), coupling constants in c/s [b] singlet. [c] triplet (J7). [d] broad singlet. [e] mixture. [f] broad signals of A_2B_2 pattern (better resolved in Nos. 11 and 13.) [g] doublet. [h] centre of poorly resolved triplet. [i] in D_2O (DSS as internal standard).

isolated, acidified with ethanolic HCl and fractionally crystallized.[*] The following *hydrochlorides* were obtained: the *cis* but-1-ene (IIIa), m.p. and mixed m.p. 193–194° (reported[8] m.p. 194–195° for material prepared by a different route), λ_{max} 255 mμ (ε 11,270 in H_2O) . (Found: C, 75·1; H, 7·7. Calc. for $C_{18}H_{22}ClN$: C, 75·1; H, 7·65%.); the *trans but-l-ene* (IIIa), m.p. 152–167°, λ_{max} 263 mμ (ε 16,800 in H_2O) (Found: C, 75·55; H, 7·9%); the *trans* (H/Ph) *but-2-ene* (IIa), m.p. 112–112·5°. (Found: C, 70·8; H, 7·9. $C_{18}H_{22}ClN{\cdot}H_2O$ requires: C, 70·7; H, 7·9%), ν_{max} 3500 cm^{-1} (H_2O)—its UV absorption spectrum in water showed end-absorption only; a ternary mixture (II and IIIa), m.p. 150–152°, λ_{max} 257 mμ (ε 13,100 in H_2O). (Found: C, 75·4; H, 7·7; N, 4·6. Calc. for $C_{18}H_{22}ClN$: C, 75·1; H, 7·65; N, 4·9%.) The PMR spectrum of this mixture was identical with that of the "but-2-ene" hydrochloride,[3] m.p. 135–138°. The *cis* but-l-ene (IIIa) was also obtained from desoxybenzoin by reported methods.[1,8] The intermediate IV was characterized as a *hydrochloride*, m.p. 248–250° from EtOH. (Found: C, 70·8; H, 7·15; N, 4·3. $C_{18}H_{22}ClNO$ requires: C, 71·2; H, 7·25; N, 4·6%.) Acid-catalysed elimination of Ib, *hydrochloride*, m.p. 162° from EtOH-ether. (Found: C, 71·0; H, 8·5; N, 4·1. $C_{19}H_{24}ClNO$ requires: C, 71·4; H, 8·15; N, 4.4%.), gave 3 crops of butenes of wide m.p. ranges. Recrystallization of the first crop gave a mixture of the *trans* IIIb and the *cis* (H/Ph) IIb, m.p. 180–193°, λ_{max} 261·3 mμ (ε 16,300 in H_2O). (Found: C, 71·3; H, 7·95; N, 4·4. $C_{19}H_{24}ClN{\cdot}H_2O$ requires: C, 71·4; H, 8·1; N, 4·4%.), ν_{max} 3450 cm^{-1} (H_2O).

*4-Dimethylamino-2-phenyl-*1*-(2-pyridyl)butan-2-ol and its elimination.* β-Dimethylaminopropiophenone (30 g) in ether (30 ml) was added to lithium 2-picolyl, prepared from 2-picoline (46 g), bromobenzene (67·5 g) and Li (9 g) in ether (350 ml), the mixture stirred overnight and then decomposed with crushed ice. The ethereal phase was dried (Na_2SO_4), concentrated, and the residue (49 g) distilled to give Ic (32 g), b.p. 190–200°/0·4–0·5 mm, characterized as a *dipicrate*, m.p. 183–184° from EtOH. (Found: C, 48·3; H, 4·15; N, 15·8. $C_{29}H_{28}N_8O_{15}$ requires: C, 47·8; H, 3·85; N, 15·4%.) A mixture of Ic (3 g), pyridine (50 ml) and $POCl_3$ (2·5 ml) was heated in an oil-bath at 100° for 30 min. Most of the solvents were removed by distillation under red press and the free base, isolated as usual, acidified with ethanolic HCl. Crystallization of the product from EtOH–ether, gave the *trans but-*1*-ene* (IIIc) *dihydrochloride*, m.p. 168–170°, λ_{max} 293 mμ (ε 14,500), 260·5 (ε 11,980 in H_2O); 300 (ε 19,120), 265 (ε 13,800 in EtOH); free base λ_{max} 295 (ε 15,810), 270 (ε 14,380 in EtOH). (Found: C, 61·0; H, 6·7; N, 8·6. $C_{17}H_{22}Cl_2N_2\delta$ 0·5 H_2O requires: C, 61·1; H, 6·9; N, 8·4%), ν_{max} 3400 cm^{-1} (H_2O).

The PMR spectra were obtained on a 60 M.c. Varian A-60 and a Perkin-Elmer R-10 instrument with TMS as internal standard ($CDCl_3$ as solvent unless otherwise stated). We thank Miss J. Lovenack (School of Pharmacy, University of London), and Mr. G. McDonough for measuring the spectra. The UV spectra were recorded on a Beckman DK-2 and a Unicam SP800 instrument.

[*] No uniformity in the order of crystallization of products was observed, the reaction being carried out several times. The chief product was the mixture, m.p. 150–152°, (1 g approx. from 3 g butanol) while only small yields (0·3–0·4 g) of the pure isomers were obtained.