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Synthesis and NMR Studies of Z- and E-Isomers of 10-Oxo and 10-Hydroxy Derivatives of Amitriptyline and Nortriptyline

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The *N,N*-dimethyl and *N*-methyl derivatives of (*Z*)- and (*E*)-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine have been synthesized from the 10-oxo isomers of the *N,N*-dimethyl derivatives with conservation of the geometrical configuration. Structural assignments were based upon chemical shift displacement of the aromatic protons by addition of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium. The presence of solvent dependent equilibria of intramolecular hydrogen bonded and non-hydrogen bonded conformations of the *Z*-hydroxy isomers were demonstrated by ^{1}H and ^{13}C NMR spectra.

The 10-hydroxy derivatives of the antidepressant drugs amitriptyline and nortriptyline have considerable interest as metabolites of these drugs with a pharmacological activity of their own.[1-4] The synthesis of these compounds and the corresponding 10-oxo compounds, the separation of *Z*- and *E*-isomers, the assignments of the geometrical configuration to the isomers and some NMR data have been reported by Remy *et al.*,[5] and some additional data are given in Refs. 6–8, but the *Z*-10-oxo and the *Z*-10-hydroxy derivatives have not been properly described in these reports. The reason is that their method of synthesis results in mixtures of isomers with a low content of *Z*-isomers.

We describe here another synthetic approach which gives the pure isomers in high yield. The structure of the isomers are assigned by analysis of their ^{1}H and ^{13}C NMR spectra and their IR spectra.

Chemistry. The route we have used for the synthesis is shown in Scheme 1.

Compound *1* is obtained as a 1:1 mixture of isomers and this proportion is conserved in *2* and *3*.[6] Compound *3* is separated into isomeric fractions giving a total yield of 40 % *3E* and 35 % *3Z* isolated as pure isomers. The following steps are performed with the pure isomers under conditions that give very little isomerization. In this way we get two series of compounds from *3* and *7*, each series consisting of compounds with the same configuration. The assignments of structure by spectral analysis are in accordance with this, so that the *E*-isomers are found in one of the series and the *Z*-isomers in the other.

The route used by Remy *et al.*[5] is shown in Scheme 2.

Two of the steps, from *8* to *3* and from *9* to *6* require prolonged heating in strong acid solution and give rearrangement to mixtures of isomers predominantly containing *E*-isomers. The isomers of the oxo compounds are separated and reduced to the hydroxy compounds with $NaBH_4$. The reported melting points and NMR spectra of *E*-isomers are in accordance with our results, while both the physical data and the NMR spectra reported for the *Z*-isomers are inconsistent with our data.

Surprisingly the acid hydrolysis of the enamine *8* to *3* is slow whereas the corresponding hydrolysis of *2* and *3* (Scheme 1) is more rapid. The reason for this is probably that *8* first is converted to the epoxy compound *8a* and that *3* is formed very slowly from this *endo*-bridged compound.

We have isolated *8a* as a dihydrochloride after

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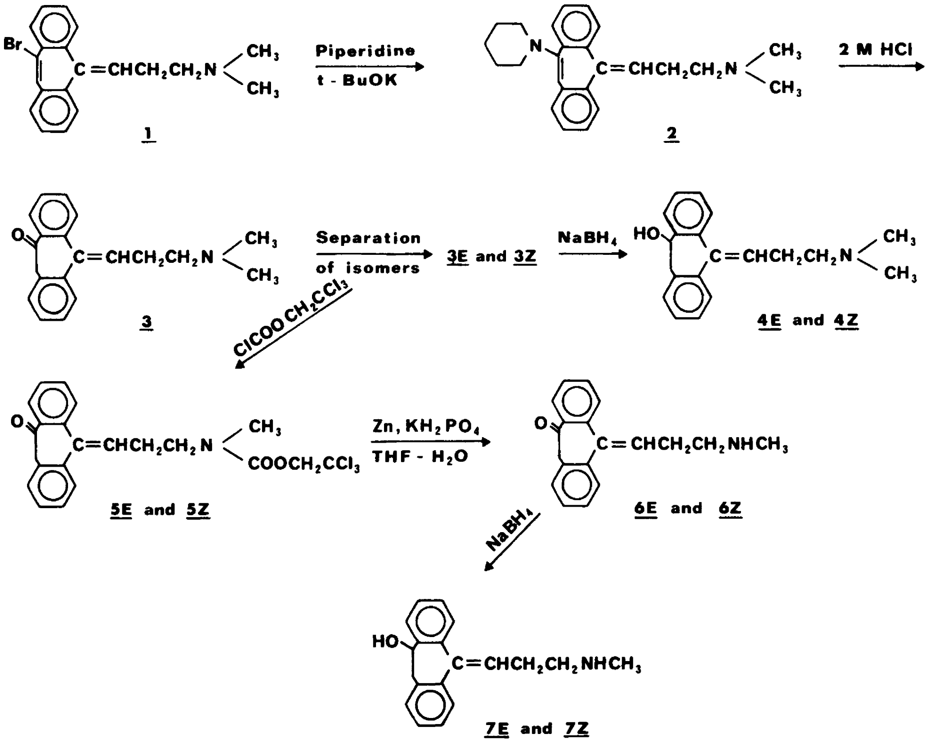
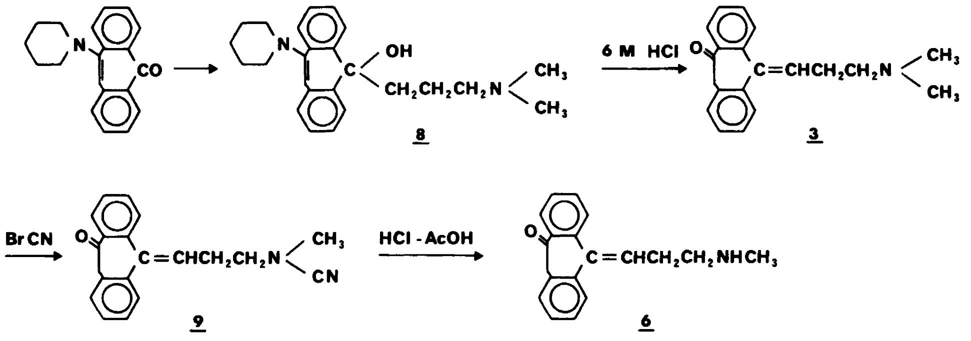


Scheme 1.

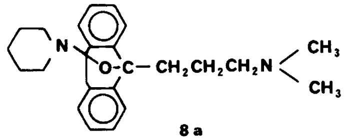
short-term treatment of *8* with acid. The structure was confirmed by the NMR spectrum of the free base.

NMR studies. The use of ^1H NMR to the assignment of *E*- or *Z*-structure to tricyclic aromatics containing an amine function in a double bonded side chain, by addition of chemical shift reagents, has been demonstrated in several cases.[5,8,10] It has been found that only the chemical shifts of protons in the aromatic nucleus on the same side of the double bond as the complexing amine function are affected by the shift reagent.

We have found that tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium in relatively low concentration is a very useful reagent for elucidation of the structure of the isomers of the monomethyl keto derivative *6*.



Scheme 2.



8a

The signals from the four protons in the ring out of conjugation to the carbonyl group appear in the aromatic envelope within a rather narrow range (δ ~7.15 ppm, marked with an arrow in Fig. 1). By addition of 40 mg of shift reagent to 50 mg of sample in $CDCl_3$ solution these signals are split and the absorptions are displaced downfield for the *6E* compound, while under the same experimental conditions the corresponding signals from the *6Z* compound remain almost uneffected (Fig. 1). Remy *et al.* reported the fluorinated shift reagent to be unsatisfactory for the assignment as they suggest a strong complexing capability to the keto group.[5]

We did not observe this type of complex formation to any significant extent as the proton ortho to the carbonyl group was only slightly displaced downfield ($\Delta\delta_{ortho}$ ~0.15 ppm), which is similar to the displacement found with the tris(dipivalo-methanato)europium reagent.[5] However, with the dimethylamino compounds *3* the complexing ability of the amine function under the same experimental conditions was found to be much less and complex formation with the keto group was recognized by significant downfield chemical shift displacements of the protons ortho to the keto groups ($\Delta\delta_{ortho}$ (*3E*): 0.69 ppm; $\Delta\delta_{ortho}$ (*3Z*): 0.60 ppm). Unfortunately, Remy *et al.* did not report the effect of chemical shifts reagent upon their claimed *Z*-isomer (*6Z*).[5] However, in our synthesis the *3E* and *3Z* isomers are uniquely related to the *6E* and *6Z* isomers as the intermediate synthetic steps are performed with conservation of the isomer configuration.

The absorption of the vinylic protons from the *E*- and *Z*-isomers are distinctly different in our spectra ($\delta_{CH=}$(*3Z* and *6Z*) ~5.9 ppm (t) J=7 Hz, $\delta_{CH=}$(*3E* and *6E*) ~6.2 ppm (t) J=7 Hz), while Remy *et al.* reported vinylic shifts ~6.2 ppm for both *E* and *Z* compounds.

In a previous patent [7] it was suggested that the hydroxy group and the amine side chain were linked together by an intramolecular hydrogen bond in compound *4Z*, while the corresponding *E*-isomer (*4E*) was observed to be non-hydrogen bonded. In the *E*-isomers (*4E* and *7E*) intramolecular hydrogen bonding was confirmed to be absent as we observed sharp singlet signals from the methyl groups with chemical shifts independent of solvent ($CDCl_3$ or DMSO-d_6) (Table 1).

However, when the spectra of *Z*-isomers (*4Z* and *7Z*) were obtained in $CDCl_3$, two relatively broad peaks appeared from the methyl groups

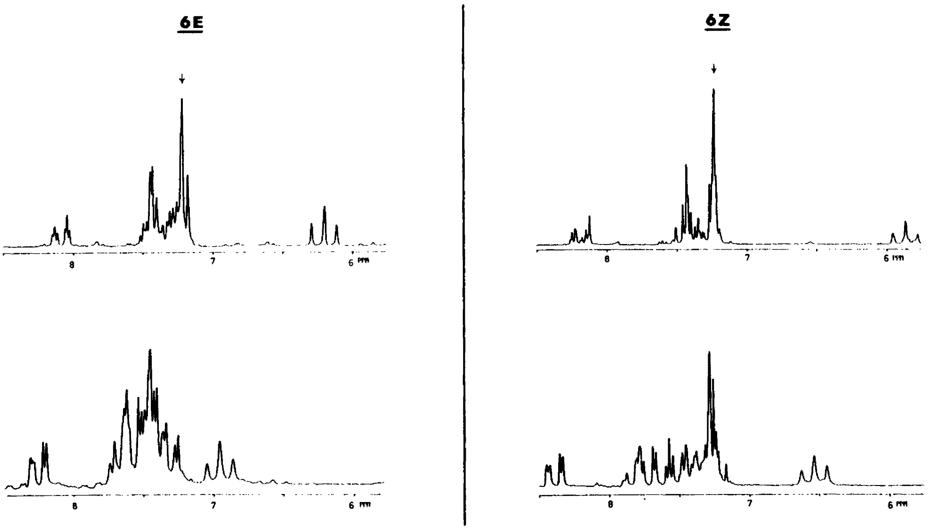


Fig. 1. Aromatic part of ^1H NMR spectra of compounds *6E* and *6Z* before (upper spectra) and after (lower spectra) addition of tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium.

Table 1. ^{1}H NMR chemical shifts of *N*-methyl groups at 30 °C.

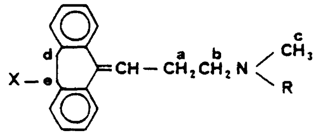
Compound	Solvent	δ (CH_3)/ppm
4E	$CDCl_3$	2.05 (6H)
	DMSO-d_6	2.00 (6H)
7E	$CDCl_3$	2.24 (3H)
	DMSO-d_6	2.18 (3H)
4Z	$CDCl_3$	1.73 (3.8H); 2.08 (2.2H)
	DMSO-d_6	2.03 (6H)
7Z	$CDCl_3$	2.05 (~1.5H); 2.30 (~1.5H) [a]
	DMSO-d_6	2.18 (3H)

[a] At 45 °C these signals collpase to a broad singlet at δ=2.20 ppm.

(Table 1). On heating, these peaks collapse to a broad singlet signal. These findings suggest the *Z*-hydroxy compounds exist in an equilibrium of intramolecular hydrogen bonded and a non-hydrogen bonded conformation. In the hydrogen bonded conformation the amine side chain must be folded with the hydroxy group in a pseudo-axial position, while the distance in the conformation with the hydroxy group in a pseudo-equatorial position obviously is too large for an internal hydrogen bond. In a polar aprotic solvent (DMSO-d_6) the methyl signals appear as sharp singlets (Table 1) indicating that the intramolecular hydrogen bonds are broken and stronger hydrogen bonds established to the solvent. IR spectra recorded in $CHCl_3$ solution also indicate a higher proportion of free OH in *4E* and *7E* than in the corresponding *4Z* and *7Z* isomers as measured by higher peak intensities at ν_{OH} ~3560 cm^{-1}. The OH stretching bond for hydrogen bonded OH groups at ν_{OH} ~3300 cm^{-1} was strong and broad for all four hydroxy compounds.

^{13}C NMR spectra were run of both the ketones *3* and *6* and the hydroxy compounds *4* and *7* to confirm the structural assignments and to study the conformational equilibria of the hydroxy compounds (Table 2). The assignments of saturated carbons were based upon off-resonance

Table 2. ^{13}C NMR spectra [δ (ppm) (intensity)].[a]



Compound	X	R	Temp. (°C)	Solvent	a	b	c	d	e
3E	=O	CH_3	45	$CDCl_3$	27.8 (1.2)	59.0 (1.0)	45.0 (2.3)	50.2 (1.1)	193.6 (0.4)
6E	=O	H	45	$CDCl_3$	29.6 (0.9)	51.2 (1.0)	35.7 (0.7)	50.3 (1.0)	193.7 (0.2)
3Z	=O	CH_3	45	$CDCl_3$	27.9 (1.0)	59.2 (1.0)	45.1 (2.2)	50.4 (1.0)	194.2 (0.2)
6Z	=O	H	45	$CDCl_3$	29.8 (1.0)	51.5 (1.0)	35.9 (0.8)	50.5 (0.9)	194.1 (0.3)
4E	–OH	CH_3	45	$CDCl_3$	27.6 (1.0)	59.2 (1.0)	44.9 (2.2)	40.0 (0.09) 42.0 (0.04)	68.5 (0.08) 72.0 (0.04)
			58		27.6 (1.0)	59.2 (1.0)	44.9 (2.5)	41.0 (0.23)	70.5 (0.17)
7E	–OH	H	45	$CDCl_3$	29.3 (1.0)	51.1 (1.0)	35.4 (1.1)	40.0 (0.14) 42.0 (0.05)	68.5 (0.15) 72.0 (0.05)
4Z	–OH	CH_3	45	$CDCl_3$	26.9 (0.1)	59.3 (1.0)	44.9 (1.2)	41.9 (0.2)	68.0 (0.06) 73.0 (0.06)
			58		26.9 (0.3)	59.3 (1.0)	44.9 (1.7)	41.9 (0.5)	70.0 (0.05)
			45	DMSO-d_6	27.2 (0.9)	58.7 (1.0)	44.7 (2.5)	42.7 (0.3)	67.5 (0.2)
7Z	–OH	H	45	$CDCl_3$	29.1 (0.1)	51.4 (1.0)	35.7 (0.3)	42.0 (0.4)	68.0 (0.11) 75.1 (0.07)

[a] Measured as relative peak heights (peak b chosen as unity).

decoupling and selective ^{1}H-heterodecoupling experiments. Both *E*- and *Z*-isomers of the hydroxy compounds clearly exist in two conformations in $CDCl_3$ solution at 45 °C as the C_e carbon and, to some extent, the C_d carbon atoms are split into two broad (low intensity) signals (Table 2). These signals gradually collapse to a single peak of higher intensity as a function of increasing temperatures. This conformational equilibrium is probably due to ring inversion with a relatively high energy barrier. In the *Z*-isomers (*4Z* and *7Z*) the intramolecular hydrogen bonding results in a broadening of the peaks from the carbon atoms in the side chain, especially peaks from C_a and C_c carbon atoms. By heating the samples further the lines sharpen. In DMSO-d_6 the intramolecular hydrogen bonds are broken and sharp peaks of approximately unit intensity are obtained.

EXPERIMENTAL

Melting points were determined on a Büchi SMP-20 and are corrected. IR spectra were recorded in $CHCl_3$ solution (10 % W/V) on a Perkin Elmer 377 instrument. ^{1}H NMR spectra were recorded at 80 MHz and ^{13}C NMR spectra were recorded at 20 MHz on a Bruker WP 80 DS spectrometer. TMS was used as internal reference standard. The samples were dissolved in $CDCl_3$ or DMSO-d_6 (10 % W/V in 5 mm tubes for ^{1}H NMR spectra and 20 % W/V in 10 mm tubes for ^{13}C NMR spectra).

N,N-*Dimethyl-3-(10,11-dihydro-10-oxo-5*H-*dibenzo[*a,d*]cycloheptene)-*$\Delta^{5,\gamma}$*-propylamine* (*3*). 10-Bromo-5-(3-dimethylaminopropyl)-5*H*-dibenzo[*a,d*]cycloheptene-5-ol[11] (447 g, 1.2 mol) is dehydrated by refluxing for 1.5 h with a mixture of 2.4 l AcOH and 1.2 l conc. HCl, followed by distillation of 1.5 l of the mixture. The dehydrated base (*1*) is isolated and dried by evaporating with toluene. It is dissolved in a mixture of 1.5 l dry toluene and 0.5 l dry piperidine, and to the mixture is added *t*-BuOK (225 g, 2 mol) during 10 min (cooling, temp. <65 °C). The mixture is stirred for 2 h at 85 °C, cooled and washed with water. The toluene phase containing *2* is extracted with 3 M HCl (2 l), and the acid solution is heated for 2 h at 80 °C. The isomer mixture of *3* is converted to the free base, dissolved in light petroleum (0.7 l) and cooled. One of the isomers of *3* crystallizes from the solution and the other is obtained from the mother liquor after evaporation and crystallization as hydrochloride from EtOH. The mother liquor from the hydrochloride is converted to the free base, and the crystallization procedure is repeated giving a further crop of the two isomers. 140 g (40 %) of the crystalline base m.p. 65–67 °C is obtained. This is sufficiently pure for the following steps. Recrystallization raises the m.p. to 75–76 °C (lit.[5] 71–73 °C). Anal. ($C_{20}H_{21}NO$) C,H,N. The *E*-configuration is assigned to this isomer on the basis of its conversion without isomerization to *4E*, *6E* and *7E*.

^{1}H NMR ($CDCl_3$): δ 2.11 (s, 6H), 2.0–2.5 (m, 4H), 3.74 (d, 1H, J=13 Hz), 4.45 (d, 1H, J=13 Hz), 6.19 (broad t, 1H, J=7 Hz), 7.1–7.5 (m, 7H), 8.0–8.2 (m, 1H).

Of the other isomer of *3*, isolated as hydrochloride, 138 g (35 %) m.p. 250–255 °C is obtained, which is used without purification in the following steps. Recrystallization from EtOH raises the m.p. 262–265 °C (lit.[6] 251–253 °C). Anal. ($C_{20}H_{21}$ NO·HCl) C,H,N. The chemical conversion of this isomer to *4Z*, *6Z* and *7Z* has established that it has the *Z*-configuration. ^{1}H NMR ($CDCl_3$); δ 2.18 (s, 6H), 2.1–2.7 (m, 4H), ~3.8 (broad d, 1H, J~14 Hz), ~4.4 (broad d, 1H, J~14 Hz), 5.85 (broad t, 1H, J=7 Hz), 7.1–7.5 (m, 7H), 8.1–8.3 (m, 1H).

(E)-N-*Methyl-3-(10,11-dihydro-10-oxo-5*H-*dibenzo[*a,d*]cycloheptene)-*$\Delta^{5,\gamma}$*-propylamine* (6E). To a solution of *3E* (115 g, 0.395 mol) in 1 l dry toluene is added $ClCOOCH_2CCl_3$ (90 g, 0.425 mol) and the mixture is heated at 80–90 °C for 3 h. The mixture is cooled, washed with 0.5 M HCl, and the toluene phase is evaporated leaving 190 g of *5E* as a yellow oil. According to the procedure described by Just *et al.*[12] this is dissolved in 1.2 l THF and stirred with 1 M KH_2PO_4 (0.24 l) and Zn-powder (240 g) for 2 h. The temperature is kept below 30 °C. The mixture is filtrated and the THF is evaporated. The residue is dissolved in 10 % AcOH and the acid solution is washed with ether. The free base of *6E* is isolated and the hydrochloride is crystallized from 1-propanol yielding 75 g (60 %), m.p. 217–220 °C. Recrystallization from EtOH raises the m.p. to 226–228 °C (lit.[5] 219–224 °C). Anal. ($C_{19}H_{19}NO \cdot HCl$) C,H,N. ^{1}H NMR of the free base ($CDCl_3$): δ 2.38 (s, 3H), 2.2–2.8 (m, 4H), 1.48 (broad s, 1H), 3.78 (d, 1H, J=13 Hz), 4.41 (d, 1H, J=13 Hz), 6.20 (t, 1H, J=7 Hz), 7.1–7.5 (m, 7H), 8.0–8.2 (m, 1H). The *E*-configuration was assigned to this isomer on the basis of the ^{1}H NMR spectrum after addition of a chemical shift reagent (see text).

(Z)-N-*Methyl-3-(10,11-dihydro-10-oxo-5*H-*dibenzo[*a,d*]cycloheptene)-*$\Delta^{5,\gamma}$*-propylamine* (6Z). This is prepared as above from *3Z*. The free base of *6Z* is isolated as an oil (yield 85 %), which is used without purification in the last step. A hydrochloride can be crystallized from EtOH, m.p. after recrystallization 210–212 °C. Anal. ($C_{19}H_{19}NO \cdot HCl$) C,H,N. ^1H NMR of the free base ($CDCl_3$): δ 1.93 (broad s, 1H), 2.38 (s, 3H), 2.3–2.9 (m, 4H), ~3.8 (broad d, 1H, J~14 Hz), ~4.4 (broad d, 1H, J~14 Hz), 5.86 (t, 1H, J=7 Hz), 7.1–7.6 (m, 7H), 8.1–8.3 (m, 1H).

The oxo compounds *3E, 3Z, 6E* and *6Z* are reduced to hydroxy compounds with $NaBH_4$ in MeOH. Typically, the oxo compound as free base (50 g, 0.18 mol) is refluxed for 1.5 h with $NaBH_4$ (25 g, 0.66 mol) in 1.5 l MeOH. All the hydroxy compounds are crystallized as free bases from diethyl ether or isopropyl ether. The yields of recrystallized bases are 50–70 %.

*(*E*)-*N,N*-Dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (*4E*).* M.p. 102–104 °C (lit.[7] 96 °C). Anal. ($C_{20}H_{23}NO$) C,H,N. IR ($CHCl_3$): 3560 (m, free OH), 3340 (s,broad, hydrogen bonded OH) cm^{-1}. ^1H NMR ($CDCl_3$); δ 2.05 (s, 6H), 2.2–2.4 (m, 4H), 2.8–3.8 (m, 3H), 4.6–5.2 (m, 1H), 5.88 (broad t, 1H, J=7), 7.1–7.5 (m, 8H).

*(*Z*)-*N,N*-Dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (*4Z*).* M.p. 133–135 °C (lit.[7] 135–136 °C). Anal. ($C_{20}H_{23}NO$) C,H,N. IR ($CHCl_3$): 3550 (w, free OH), ~3300 (s, broad, hydrogen bonded OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.73 (broad s, 3.8H), 2.08 (broad s, 2.2H), 1.9–2.7 (m, 5H), 2.9–3.8 (m, 2H), 4.9–5.5 (m, 1H), 5.89 (broad t, 1H, J=7 Hz), 7.0–7.6 (m, 8H).

*(*E*)-*N*-Methyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (*7E*).* M.p. 113–114 °C. Anal. ($C_{19}H_{21}NO$) C,H,N. IR ($CHCl_3$): 3560 (m, free OH), 3310 (s, broad, hydrogen bonded OH) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.85 (broad s, 1H), 2.24 (s, 3H), 2.1–2.7 (m, 4H), 2.9–3.7 (m, 3H), 4.6–5.1 (m, 1H), 5.88 (t, 1H, J=7 Hz), 7.1–7.5 (m, 8H).

*(*Z*)-*N*-Methyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (*7Z*).* M.p. 108–110 °C. Anal. ($C_{19}H_{21}NO$) C,H,N. IR ($CHCl_3$): 3560 (w, free OH), 3310 (s, broad, hydrogen bonded OH) cm^{-1}. ^1H NMR ($CHCl_3$): δ 2.05 (broad s, 1.5 H), 2.30 (broad s, 1.5 H), 2.0–2.8 (m, 5H), 2.9–3.6 (m, 3H), 4.9–5.4 (m, 1H), 5.85 (t, 1H, J=7 Hz), 7.0–7.6 (m, 8H).

*1-(10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5*H*-dibenzo[*a,d*]cyclohepten-10-yl)-piperidine (*8a*).* 5-(3-Dimethylaminopropyl)-10-piperidino-5*H*-dibenzo[*a,d*]cyclohepten-5-ol (*8*)[7] is heated at 80–90 °C with 2 M HCl for 2 h, converted to the free base and the dihydrochloride is crystallized from Me_2CO as a monohydrate. The same product is obtained from *8* by short-term heating in $CHCl_3$ with excess of HCl, evaporating and crystallizing from Me_2CO. M.p. 215–216 °C. Anal. ($C_{25}H_{32}N_2O \cdot 2HCl \cdot H_2O$) C,H,N. ^1H NMR ($CDCl_3$) (of the free base): δ 1.2–3.2 (m, 17H), 2.24 (s, 6H), 3.87 (d, 1H, J=17 Hz), 6.9–7.3 (m, 8H).

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