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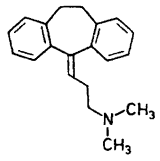
Rigid Analogues of Amitriptyline. Preparation of 5-(3-Dimethylaminocyclohexylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and *cis*- and *trans*- 5-(3-Dimethylaminocyclohexyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene

TOMAS DE PAULIS

Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden

The synthesis and characterisation of three novel analogues of amitriptyline, *2*, *6* and *7*, are described, in which the flexible dimethylaminopropyl chain is incorporated in a cyclohexane ring. The *cis*- and *trans*-isomers were separated by column chromatography and the structure elucidation was performed by NMR. The stereochemical assignments suggest that the reported structures of the corresponding 4-substituted analogues *9* and *10* should be reversed.

In the search for new psychotropic agents, compounds with a rigid structure have sometimes been employed.[1] Rigid analogues of the tricyclic antidepressant agents have been reported from this laboratory [2] and others.[3,4] The synthesis and spectral characteristics of three new compounds, *2*, *6* and *7*, are now described, in which the structural elements of amitriptyline *1*, are preserved, but where the positional freedom of the amino nitrogen atom has been limited. The pharmacological activities of these compounds have been reported recently.[5]



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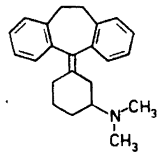

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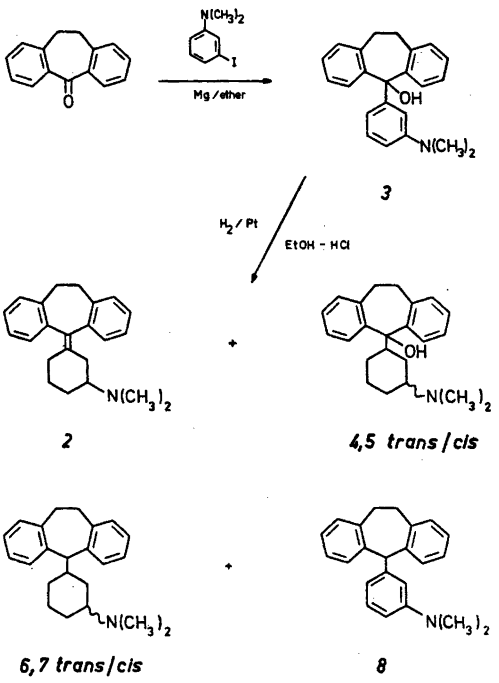
The title compounds were synthesized by the method of Villani *et al.*[3] A Grignard reaction of dibenzosuberone with *N*,*N*-dimethyl-3-iodo-aniline gave 5-(3-dimethylaminophenyl)-5-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, *3*. Catalytic hydrogenation in ethanol with platinum as catalyst gave a product of varying composition depending on the amount of hydrochloric acid used in the reaction. An equimolar addition produced a mixture of the *trans* and *cis* isomers of 5-(3-dimethylaminocyclohexyl)-5-hydroxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene *4* and *5* together with some starting material and the aniline derivative *8*. The desired 5-(3-dimethylaminocyclohexylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, *2*, was formed in ca. 14 % yield according to the GLC-analysis. When the hydrogenation was carried out with a five-fold excess of hydrochloric acid, no starting material was observed and the yield of *2* had increased to 23 %. These conditions also favoured the production of the *trans* and *cis* isomers of 5-(3-dimethylaminocyclohexyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene, *6* and *7*. *4* was quantitatively dehydrated to give the corresponding unsaturated compound *2* by treatment with a mixture of concentrated hydrochloric acid and acetic acid.

The products were separated and isolated by column chromatography and thin-layer chromatography. Spectral characteristics of the new compounds are given in the experimental part.

The structural assignments of the amines *4*, *5*, *6* and *7* are based on their NMR spectra. Assuming a chair conformation of the cyclo-



hexane ring, in which the bond connecting the tricyclic nucleus occupies an equatorial position,[6] the dimethylamino group in the 3-position is either equatorial (*cis*) or axial (*trans*) depending on the configuration. In the isomer *6*, the signals from the methylene protons of the cyclohexane ring are confined between δ 1.1 and 1.7. In the isomeric amine *7* the signals for the cyclohexane protons exhibit a broad multiplet ranging from δ 0.7 to 2.2, which clearly distinguishes it from *6*. In isomer *6* a doublet (partly hidden) at δ 2.3, with a separation of 7 Hz, was observed.* These spectral characteristics are also seen in the corresponding 5-hydroxy derivatives *4* and *5*. Aliphatic signal between δ 1.0 and 1.6 in isomer *4* and between δ 0.9 and 2.0 in *5*.

Naegele and Wendisch have described the 220 MHz ^{1}H-NMR spectra of the *cis* and *trans* isomers of 3- and 4-alkyl substituted cyclohexylamines.[8] In *trans*-N-acetyl-3-methylcyclohexylamine (axial nitrogen) five protons are centered at δ 1.6 while in the equatorial amine only three protons are resonating in this region. This difference in the chemical shift is even more pronounced in the 4-*tert*-butylcyclohexylamines, in the spectra of which the *cis* isomer, bearing an axial nitrogen atom, has six protons displayed at δ 1.4 – 1.7, while in the *trans* form five of the axial protons, with the exception of the α-proton, are resonating around δ 1.1 and the signal of the four equatorial protons are centered around δ 1.7.

In accordance with these structural correlations, the compounds *4* and *6* are assigned a *trans*-configuration and the compounds *5* and *7* a *cis*-configuration. Villani *et al.* have characterized the stereoisomers of 5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptene by 60 MHz ^{1}H NMR.[3] They have used the appearances of the α-proton as a basis for the interpretation. One of the isomers, A, showed a complex multiplet centered at δ 2.68 and the other isomer, B, showed a doublet at δ 2.63. On this evidence the isomer A was considered to be the *trans* form and B the *cis* form.

It was found, however, that spectra of authentic samples of these compounds, prepared by the same method, differ very little in respect to the signal of the α-protons, as they are partly obscured by the methylamino singlets. Therefore, they offer a poor basis for an unambiguous assignment of the configurations. The spectra, however, exhibit the same features in the aliphatic region, as do the spectra of the corresponding 3-substituted analogues. In *9* (A) the signal of the cyclohexane protons ranges from δ 1.1 to 2.1, while in *10* (B) it ranges from δ 0.7 to 2.3. They differ also in respect to the position of the benzylic proton in the 5-position in the seven-membered ring, the doublets for which were found at δ 3.7 and 3.3 in isomer *9* and *10*, respectively. According to the reasoning above the assignments by Villani *et al.* might have to be reversed. Isomer A, *9*, should have the *cis* configuration with an axial dimethylamino group. Isomer B, *10*, should have the *trans* configuration. (See Fig. 1). In order to establish the structural assignments, carbon-13 spectra of these compounds were studied. The spectrum of *5* is included for comparison. The shifts and tentative line assignments are given in Table 1. They are based on signal multiplicities from off resonance experiments and comparison with the reported spectra of

* In primary aminocyclohexanes, the α-protons are often sufficiently deshielded to serve as a convenient tool for assignment of axial and equatorial protons.[7]

axial and equatorial 4-substituted dimethylaminocyclohexanes.[9] The compound bearing an axial dimethylamino group is expected to have the resonance of the α-carbon shifted upfield 4–5 ppm compared to that of the equatorial isomer.[9] The lines at δ 59.3 and 63.8 have been assigned to the α-carbons of isomer A and B, respectively, giving a shielding effect of 4.5 ppm from the axial amine. Thus, in accordance with the proposed structures, A (*9*) has a *cis* and B (*10*) has a *trans* configuration.

The structures of the stereoisomers of 5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene *9* and *10*, thus established, and the previously assigned structures of the corresponding 3-substituted analogues *6* and *7* are in accordance with their spectra. It is interesting to note that all the compounds with an axial dimethylamino group have shorter retention times on GLC than the corresponding equatorial stereoisomers.[10] This indicates that all these cyclohexylamines must exist in chair conformations. The drawings of compounds *6*, *7*, *9* and *10* in the figure are shown in the conformations of lowest energy. It has recently been shown that substituents in 5-position of 5*H*-dibenzo[*a*,*d*]cycloheptene prefer a pseudo-axial conformation.[11] It seems reasonable to assume that this also applies to the 10,11-dihydro series.

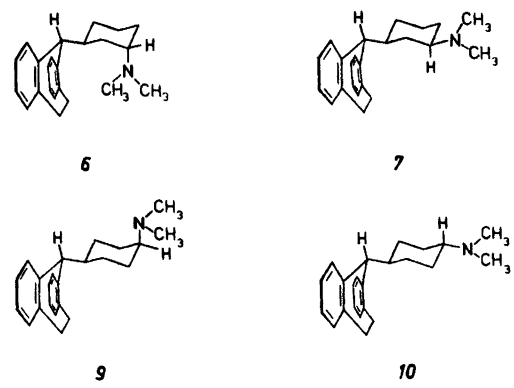
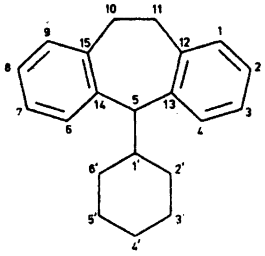


Fig. 1. Structures of the isomeric 5-(dimethylaminocyclohexyl)-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cycloheptenes *6*, *7*, *9* and *10* in the preferred conformations.

Table 1. Tentative assignments of carbon-13 shifts in *5*, *9* and *10*.



Carbon No.	*5*	*9*	*10*
CH_3	41.4	43.1	41.6
1′	45.6	40.7	42.5
2′	33.9	26.6	32.0
3′	63.5	32.8	32.9
4′	29.7	59.3	63.8
5′	24.6	32.8	32.9
6′	26.9	26.6	32.0
1	127.0	130.5	130.5
2	125.8	125.4	125.4
3	126.8	126.4	126.6
4	130.8	131.6	131.6
5	80.4	61.8	62.2
10	27.3	27.5	28.7
12	137.5	138.7	138.8
13	144.5	141.0	140.9

EXPERIMENTAL

Melting points were determined on a microscope hot stage (Leitz) and are uncorrected. Mass spectra (MS) were recorded at 70 eV on an LKB 9000 spectrometer. ^{1}H NMR spectra of the free amines were obtained on a Varian A-60 A instrument operating at 37 °C and ^{13}C NMR spectra were obtained on a Varian CFT-20 instrument at 35 °C with deuteriochloroform as solvent. Chemical shifts are expressed as δ-values (ppm from tetramethylsilane). Elemental analyses were performed by Professor A. Kirsten, Ultuna, Sweden and are within ±0.4 % of the calculated values if not otherwise stated. Thin-layer chromatography (TLC) was performed on precoated Merck Silica Gel F_{254} plates. Gas chromatography (GLC) was performed on a Perkin Elmer 3920 instrument with a 200 × 0.3 cm column of 3 % OV-17 on Chromosorb.

*5-(3-Dimethylaminophenyl)-5-hydroxy-10,11-dihydro-5*H*-dibenzo*[a,d]*cycloheptene 3.* *N,N*-Dimethyl-3-iodoaniline[12] (25 g, 0.10 mol) was dissolved in 50 ml of dry tetrahydrofuran (THF) and the solution was slowly added at 40 °C to a mixture of 10 ml of THF and 3 g (0.12 mol) of magnesium turnings which had been activated by 0.5 g of iodine. When the addition was completed 140 ml of THF was added and the reaction mixture was stirred for 1 h at 40 °C. Then a solution of 10 g (0.09 mol) of 10,11-

dihydro-5*H*-dibenzo[*a,d*]-cycloheptene-5-one [13] in 50 ml of THF was added at 25 °C. The deep violet solution was heated under reflux for 2 h. After cooling it was poured into a stirred solution of 50 g of NH_4Cl in 400 ml of water. Extraction of the reaction products with chloroform, drying and evaporation of the solvent gave 37.6 g of an oily residue. Crystallization from 250 ml of ethanol gave 26.2 g (83 %). M.p. 136–137 °C. MS: *m/e* 329 M^+ (100 %). Anal. ($C_{23}H_{23}NO$) C, H, N, O.

Catalytic hydrogenation of 5-(3-dimethylaminophenyl)-5-hydroxy-10,11-dihydro-5H-dibenzo-[a,d]*cycloheptene, 3.* A. *With an excess of HCl.* The dimethylaniline derivative (*3*) (3.0 g, 0.009 mol) was dissolved in 150 ml of abs. ethanol and 0.5 g of PtO_2 was added followed by 4 ml (0.05 mol) of concentrated HCl. The mixture was hydrogenated at 0.38 MPa and 55 °C for 20 h. The catalyst was filtered off and the filtrate was evaporated to give 3.2 g of a residue, which was dissolved in ether and extracted with 0.5 M HCl. The extract was made alkaline with concentrated NH_3 and extracted with ether. Drying (Na_2SO_4) and evaporation of the solvent gave 2.0 g oil. GLC analysis on OV-17 at 250 °C showed six peaks with the following relative areas and retention times: A (17 %, 6.0 min), B (13 %, 6.5 min), C (17 %, 11.0 min), D (14 %, 12.0 min), E (15 %, 12.8 min) and F (28 %, 18.0 min). The oil was placed on a column of 200 g Si-gel (0.063 mm) and eluted with a mixture of methanol-acetone 1:1. The compounds were obtained in the following order: From (30 ml) fractions 5–9 0.8 g of compound *8* (D), fractions 10–13 0.6 g of unreacted starting material (F), fractions 36–48 0.6 g of compound D and fraction 49–50 0.2 g of compound A, fractions 55–59 0.2 g of compound C, fractions 60–65 0.2 g of compound E and 0.5 g of compound B. Compound A was identified as 5-(3-dimethylaminocyclohexylidene)-10,11-dihydro-5*H*-dibenzo-[*a,d*]cycloheptene *2* and compound B was a mixture of the corresponding saturated analogues *6* and *7* by interpretation of their GLC-MS spectra.

B. *With equimolar amounts of HCl.* To a solution of 10.0 g (0.030 mol) of *3* in 250 ml of warm ethanol, 2.4 ml (0.028 mol) of conc. HCl was added followed by 0.5 g of PtO_2. The mixture was hydrogenated at 60 °C and 0.4. MPa in a Parr apparatus for 16 h. The catalyst was filtered off and the solvent was evaporated. The residue was dissolved in a mixture of 300 ml of water and 100 ml of 1 M HCl and shaken with 100 ml of ether. The aqueous layer was separated and made alkaline with conc. ammonia and extracted with 3 × 100 ml of chloroform. Drying and evaporation of the solvent gave 9.5 g of an oil. A sample was analyzed on GLC at 250 °C. The six major peaks were: compound *2* (14 %, 6.0 min), *6* (3 %, 6.2 min), *4* (6 %, 11.0 min), *8* (28 %, 12.0 min), *5* (20 %, 12.7 min), the starting material, *3* (24 %, 18.0 min) and 5 % unidentified material. The oil was dissolved in 0.1 M HCl and 2 M NH_3 was added to pH 5. Extraction with 100 ml of ether removed 2.0 g of *8*, from the aqueous layer, which was then made alkaline and extracted with $CHCl_3$. Evaporation of the solvent gave 7.5 g residue. Trituration with 400 ml of hot pentane gave upon cooling 2.5 g crystals. The GLC-analysis showed a mixture of *5* and the starting material (*3*). Separation on 30 g of Si-gel (0.063 mm) in methanol-acetone (1:1) as the eluent gave 1.3 g of *3*, m.p. 136–137 °C, and 0.8 g of cis-*5-(3-dimethylaminocyclohexyl)-5-hydroxy-10,11-dihydro-5H-dibenzo*[a,d]*cycloheptene 5*, m.p. 174–175 °C from EtOH. MS: *m/e* 335 (2 %) 209 (11 %), 131 (1 %), 127 (26 %), 126 (100 %), 85 (1 %), 84 (1 %), 71 (1 %), 58 (1 %), ^1H NMR: Broad multiplet at δ 0.9–2.0. Singlet (6H) at δ 2.2. ^{13}C NMR: δ 144.5 ds, 137.5 s, 130.8 d, 127.0 dd, 126.8 d, 125.8 dd, 80.5 s, 63.5 d, 45.6 d, 41.4 q, 33.9 t, 29.7 t, 27.3 t, 26.9 t, 24.6 t. The duplication of some lines are due to magnetic anisotropy from the cyclohexylamine moiety. The oxalate had m.p. 150–155 °C (EtOH–i-PrOH). Anal. ($C_{25}H_{31}NO_5$) C: calc. 70.6; found 71.4 %, H, N.

From the mother liquors 0.10 g of the corresponding *trans* isomer *4* was obtained. M.p. 151–152 °C from EtOH. ^1H NMR: δ 2.1 (m, *J* 12 Hz), 2.0 (s, 6 H), 1.0–1.6 (m, 8 H). Anal. ($C_{23}H_{29}NO$) C: Calc. 82.3; found 81.8 %, H, N, O.

The mother liquors from the pentane treatment were evaporated giving 4.1 g oil. This was subjected to column chromatography on 200 g of Si-gel (0.063 mm) with methanol–acetone (1:1) as the eluent. From 100 ml fractions there were obtained 1.0 g of *8*, m.p. 105–107 °C, 0.7 g of a mixture of compounds *2*, *3*, *6* and *7*, 1.0 g of *6* as an oil, 1.2 g of *2* and 0.3 g of a mixture of *7* and an unidentified material.

trans-*5-(3-Dimethylaminocyclohexyl)-10,11-dihydro-5*H-*dibenzo*[a,d]*cycloheptene, 6.* The material containing *6* (1.0 g) was treated with oxalic acid in acetonitrile and the oxalate was collected. Recrystallization from 20 ml acetonitrile gave 0.5 g, m.p. 101–103 °C. The analysis revealed the presence of one solvent molecule in the crystals. MS: *m/e* 319 (8 %), 193 (3 %), 127 (10 %), 126 (100 %) 124 (3 %), 84 (6 %), 71 (4 %), 58 (4 %) 44 (2 %). NMR: ($CDCl_3$) δ 7.1 (m, 8 H), 2.5–3.9 (m, 4 H), 3.6 (d, *J* 11 Hz), 1 H), 2.3 (d, *J* 7 Hz, 1 H), 2.1 (s, 6 H), 1.1–1.7 (m, 9 H). Anal. ($C_{27}H_{34}N_2O_4$): C, H, N, O.

cis-*5-(3-Dimethylaminocyclohexyl)-10,11-dihydro-5*H-*dibenzo*[a,d]*cycloheptene, 7.* From the fractions containing the amine *7* above the hydrochloride was prepared by treating an ether solution of the amine mixture (compound *6* and *7*) with 4 M HCl–ether. The crystals were washed with cold ethanol (5 ml). GLC showed a 90 % peak at 6.5 min (250 °C) corresponding to the amine *7* together with 5 % peaks of compound *2* (6.0 min) and *6* (6.2 min). NMR:

($CDCl_3$) δ 7.1 (m, 8H), 2.5–3.7 (m, 5H), 3.4 (d, J 10 Hz), 2.1 (s, 6H), 0.7–2.2 (m, 9H). MS: Identical with compound *6* (*vide supra*).

5-(3-Dimethylaminocyclohexylidene)-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene*, *2*. In a 25 ml open flask, 0.3 g (0.001 mol) of compound *4* was dissolved in a mixture of 2 ml of acetic and 2 ml of conc. HCl acid. It was heated on a water bath for 30 min. After cooling 25 ml of 2 M NaOH was added and the reaction mixture was extracted with 2 × 50 ml of ether. The combined ether layers were extracted with 2 × 50 ml of 1 M HCl, the extracts were made alkaline by addition of 2 M NaOH and extracted with 2 × 100 ml of ether. Drying and evaporation of the solvent gave 0.3 g of an oil. GLC-analysis showed one peak having a retention time identical to that of compound *2* (6.0 min). The hydrochloride was prepared from an ether solution. Recrystallization from 15 ml of butanone gave 0.2 g with m.p. 192–194 °C. NMR: ($CDCl_3$) δ 7.1 (narrow m, 8H), 2.4–3.7 (m, 4H), 2.5–3.0 (m, 1H), 2.2 (d, separation 6 Hz, 6H), 0.9–2.1 (m, 8H) MS: *m/e* (%), 317 (7), 274 (0.5), 272 (0.5), 126 (1.0), 124 (2.5), 85 (0.6) 84 (100), 71 (1.9), 58 (1.0). Anal.: ($C_{23}H_{28}ClN$) C, H, Cl, N.

5-(3-Dimethylaminophenyl)-10,11-dihydro-5H-dibenzo[a,d]*cycloheptene*, *8*. Materials from the second hydrogenations containing compound 8 were combined and recrystallized from ethanol. M.p. 105–107 °C. GLC: Retention time 12.0 min (250 °C) TLC: R_F 0.82 (methanol-acetone, 1-1). MS: *m/e* (%), 313 (100), 122 (35). NMR: δ 7.2 (m, 8 H), 6.1–6.9 (m, 4 H), 5.2 (s, 1 H), 2.4–3.4 (m, 4 H), 2.7 (s, 6 H). Anal.: ($C_{23}H_{23}N$) C, H, N.

Preparation of cis- *and* trans-*5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5*H-*dibenzo*[a,d]-*cycloheptene*, *9 and 10*. A solution of 10.0 g (0.03 mol) of 5-(4-Dimethylaminophenyl)-10,11-dihydro-5-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene [3] in 250 ml of ethanol, containing 1 % conc. HCl and 0.5 g of PtO_2, was hydrogenated at 60 °C and 0.4 MPa for 15 h. The mixture was filtered and the solvent evaporated. The residue (12 g) was mixed with aqueous ammonia and extracted with 3 × 100 ml of chloroform. Drying and evaporation of the solvent gave 9.5 g of an amine mixture. GLC showed three components (1:10:10) with retention times 7.4 min, 7.7 min and 8.4 min (250 °C). Column chromatography separation on 400 g of aluminium oxide (activity II) with pentane–ether (10:1) as the eluent gave 0.3 g of the first compound. It was identified as *5-(4-dimethylaminocyclohexylidene)-10,11-dihydro-5*H-*dibenzo*[a,d]-*cycloheptene*. GLC: Retention time 7.4 min. MS: *m/e* (%), 317 (100), 272 (59), 124 (72). NMR: δ 7.1 (s, 8 H), 2.5–3.7 (m, 7 H), 2.3 (s, 3 H), 2.2 (s, 3 H), 1.0–2.2 (6 H).

The subsequent fractions gave 2.8 g of cis-*5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5*H-*dibenzo*[a,d]*cycloheptene*, *9*. The hydrochloride was recrystallized twice from 100 ml of i-PrOH. M.p. 270–272 °C. Lit.[3] m.p. 274–275 °C (A). TLC: R_F 0.11 in methanol–acetone (1:1). GLC: retention time 7.7 min at 250 °C. ^{1}H NMR: δ 7.1 (s, 8 H), 3.7 (d, J 11 Hz, 1 H), 2.6–3.8 (m, 4 H), 2.14 (s, 6 H), 1.1–2.1 (m, 9 H). ^{13}C NMR: (shifts and multiplicities from off resonance proton decoupling), δ 141.0 s, 138.7 s, 131.6 d, 130.5 d, 126.4 d, 125.4 d, 61.8 d, 59.3 d, 43.1 q, 40.7 d, 32.8 t, 27.5 t, 26.6 t. Anal.: ($C_{23}H_{30}ClN$) C, H, Cl, N.

From the last fractions there were obtained 2.2 g of trans-*5-(4-dimethylaminocyclohexyl)-10,11-dihydro-5*H-*dibenzo*[a,d]*cycloheptene*, *10*. M.p. 99–101 °C from pentane. Lit.[3] m.p. 100–101 °C (B). TLC: R_F 0.08 in methanol-acetone (1:1). GLC: Retention time 8.4 min. The hydrochloride (1.5 g) was crystallized from 50 ml of i-PrOH. M.p. 270–272 °C. ^{1}H NMR: δ 7.1 (s, 8 H), 2.5–3.7 (m, 4 H), 3.3 (d, J 10 Hz, 1H), 2.2 (s, 6 H), 0.7–2.3 (m, 10 H). ^{13}C NMR: δ 140.9 s, 138.8 s, 131.6 d, 130.5 d, 126.6 d, 125.4 d, 63.8 d, 62.2 d, 42.5 d, 41.6 q, 32.9 t, 32.0 t, 28.7 t. Anal.: ($C_{23}H_{30}ClN$) C, H, Cl, N.

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