Amitriptyline Metabolites. Synthesis of (*R*,*S*)-(*Z*)- and (*R*,*S*)-(*E*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine

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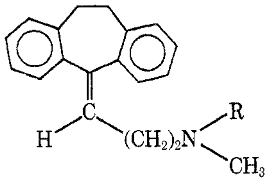
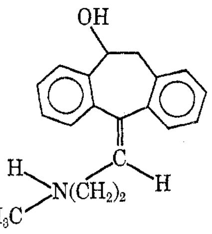
The synthesis of (*R*,*S*)-(*Z*)- and (*R*,*S*)-(*E*)-*N*-methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, 2 and 3, respectively, metabolites of the antidepressant drug amitriptyline, is described. Configurational assignments of 2 and 3 are based on an nmr study of (*E*)-*N*-methyl(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (8) using tris(dipivalomethanato)europium as a shift reagent.

Amitriptyline (**1a**) and nortriptyline (**1b**) are drugs that are widely used in the treatment of depressive illness. The *Z* and *E* geometrical isomers of *N*-methyl-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, **2** and **3**, respectively, are major metabolites of both drugs.[1-3]



1a, R = CH_3
b, R = H



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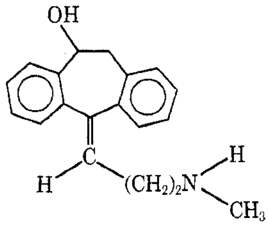

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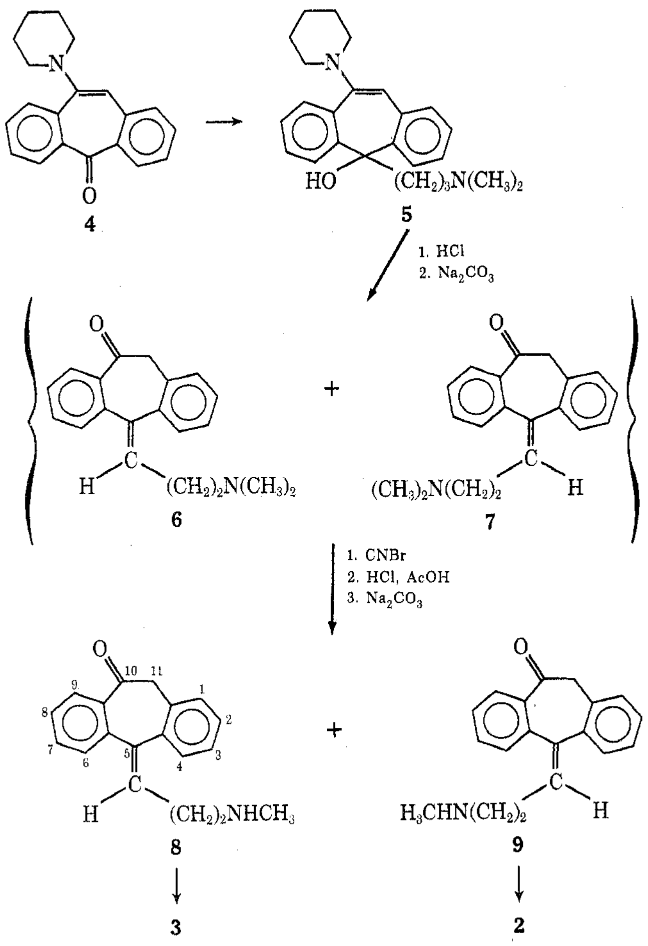
In previous reports on the metabolism of **1a** and **1b**, the isolation and spectral characterization of **2** and **3** have been described. However, no assignment of geometrical configuration of these compounds has been made. The recent introduction of the nmr shift reagent, tris(dipivalomethanato)europium,[4] has now made possible the assignment of geometrical configuration of synthetically prepared samples of the racemates of **2** and **3**.

Addition of dimethylaminopropylmagnesium chloride to the known enamine-ketone **4**[5] afforded the crystalline alcohol **5** in 82% yield. Prolonged acid hydrolysis of **5** in 6 *N* hydrochloric acid resulted in hydrolysis of the enamine moiety to a carbonyl function and simultaneous dehydration of the alcohol moiety to give a quantitative yield of the mixed geometric isomers **6** and **7** (Scheme I). In a number of preparations, glpc product analysis showed an average ratio of these geometric isomers to be 81:19. The isomer ratios of these products were also measured by nmr spectroscopy using the relative areas of the *N*-methyl proton peaks of **6** and **7**.[6] In a typical experiment, an isomer ratio of 75:25 was found for the mixture.

SCHEME I



Although the hydrochloride salt of one of the isomers, **6** or **7**, crystallized readily and could be separated in a pure form, no attempt was made to separate and carry either pure isomer to a final product when it was observed that one of the isomers, and probably both, was isomerized on heating an acid. Thus, one of the

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(1) (a) H. B. Hucker and C. C. Porter, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **20**, 172 (1961); (b) H. B. Hucker, *Pharmacologist*, **4**, 171 (1962).

(2) R. E. McMahon, F. J. Marshall, H. W. Culp, and W. M. Miller, *Biochem. Pharmacol.*, **12**, 1207 (1963).

(3) L. Bertilsson and B. Alexanderson, *Eur. J. Clin. Pharmacol.*, **4**, 201 (1972).

(4) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) J. K. M. Saunders and D. H. Williams, *ibid.*, **93**, 641 (1971).

(5) W. Tochtermann, K. Oppenländer, and U. Walter, *Chem. Ber.*, **97**, 1318 (1964).

(6) D. C. Remy and W. A. Van Saun, Jr., *Tetrahedron Lett.*, **No. 27**, 2463 (1971).

TABLE I

CHEMICAL SHIFTS OF THE AROMATIC PROTONS IN (*E*)-*N*-METHYL-(10,11-DIHYDRO-10-OXO-5*H*-DIBENZO[*a,d*]CYCLOHEPTENE)-$\Delta^{5,\gamma}$-PROPYLAMINE (**8**)

Proton	δ ($CDCl_3$), free base	δ ($CDCl_3$), Eu(dpm)$_3$ complex	$\Delta\delta$
C_1H	7.2–7.5	7.85[a]	0.35–0.65[c]
C_2H	7.2–7.5	7.4–7.7	~0.2
C_3H	7.2–7.5	7.4–7.7	~0.2
C_4H	7.2–7.5	8.09[a]	0.59–0.89[c]
C_6H	7.2–7.5	7.4–7.7[a]	~0.2
C_7H	7.2–7.5	7.61 ± 0.03[b]	0.1–0.4[c]
C_8H	7.2–7.5	7.45 ± 0.03[b]	−0.05–0.25[c]
C_9H	8.15	8.31	0.16

[a] Preferred assignments. [b] Located by spin-decoupling experiments. [c] Represents minimum and maximum downfield displacement.

isomers, **6** or **7**, designated α, 98.9 mol % pure by differential scanning calorimetry, was converted into an equilibrium mixture (85:15 by glpc) on refluxing for 24 hr in 6 *N* hydrochloric acid.

N-Demethylation of the mixed tertiary amines **6** and **7** was effected *via* the von Braun cyanogen bromide method. The cyanamide derivatives were subjected to prolonged hydrolysis in an acetic acid–hydrochloric acid mixture. The isomer ratio of **8** to **9** in this reaction mixture was found to be 69:31 by expanded scale nmr examination of the *N*-methyl proton peaks. The geometric isomers **8** and **9** were successfully separated by crystallization.

Nuclear magnetic resonance spectroscopy has been used successfully in the assignment of configuration to geometric isomers in a series of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[*b,e*]oxepin[7] and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b,e*]thiepin[8] derivatives. In these sets of isomers, the presence of the oxygen or sulfur atom in the central seven-membered ring results in significant differences in the chemical shifts of the vinyl proton[7,8] and aromatic ring protons[8] of the *Z* and *E* isomers.

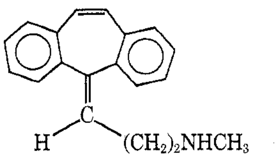
Examination of the nmr spectra of **8** and **9** showed that, whereas there was no significant difference in the chemical shifts of the vinyl protons, there were slight differences in the chemical shifts of the aromatic protons. In an attempt to enhance the difference in chemical shifts of the aromatic protons, the nmr spectra of these isomers (**8** and **9**) were reexamined in the presence of tris(dipivalomethanato)europium, Eu(dpm)$_3$.[4,9]

Analysis of the differential downfield shifts of the aromatic protons resulting from the addition of small amounts of Eu(dpm)$_3$ to a $CDCl_3$ solution of **8** strongly suggested the *E* configuration. The initial findings utilizing a fluorinated shift reagent[10] proved unsatisfactory in that the aromatic protons were not resolved. It seemed reasonable to attribute this failure to the greater complexing capability of the halogenated agent which would result in significant binding with the ketone as well as the nitrogen. Complexation at both sites could well obscure the trends which permitted the configurational assignments in the related 3-substituted *N,N*-dimethyl(5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine series.[6] Based on this supposition, the study was repeated with the weaker, and more selective, Eu(dpm)$_3$. Addition of approximately 0.3 mol of rare earth reagent/mol of substrate (**8**) resulted in the appearance of two aromatic protons displaced downfield from the aromatic envelope (7.85 and 8.09). The magnitude of the aromatic ring proton shifts (Table I, $\Delta\delta$) cannot be determined with any great degree of accuracy since the initial chemical shifts within the overlapping multiplets between δ 7.2 and 7.5 are indeterminate. This problem is further complicated by an overall deshielding of the aromatic envelope by roughly 0.2 ppm. There is no question, however, that the two newly resolved aromatic protons experienced larger than the average displacement as shown in Table I. Since both were doublets with unresolved fine structure, they are assigned to α protons. Together with the already resolved C_9H at δ 8.31 (C_9H is the hydrogen atom peri to the 10-keto group), this accounts for three out of a total of four such protons (*i.e.*, the C_1, C_4, C_6, and C_9H).

Previous studies with other unsymmetrically substituted cyclobenzaprine derivatives in the presence of Eu(dpm)$_3$ have shown that only the protons on the ring cis to the complexing site are shifted significantly downfield. As an example, the chemical shifts of the aromatic protons in (*E*)- and (*Z*)-3-chloro-*N,N*-dimethyl(5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine are given in Table II.

Since neither the C_9 proton nor the C_8 and C_7 protons (located within the aromatic envelope by spin decoupling) of **8** were deshielded appreciably, it follows that the doublets are reasonably assigned to the C_1 and C_4 protons and that the side chain in **8** is therefore located trans relative to the ketone.

Reduction of the ketone groups of **8** and **9** with sodium borohydride completed the syntheses of (*R,S*)-(*E*)- and (*R,S*)-(*Z*)-*N*-methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a,d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, **3** and **2**, respectively. Beside being isomerically pure by tlc and nmr, both **2** and **3** were free from traces of **10** which could arise from dehydration.[2,11] The 10,11-vinyl hydrogens of **10** show a sharp singlet at δ 6.83 ($CDCl_3$); this absorption was completely absent in the spectra of **2** and **3**.



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Experimental Section

Melting points were determined on a Thomas-Hoover "Unimelt" capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were determined on Varian A-60A and HA-100 spectrometers in $CDCl_3$, and all shifts are relative to tetramethylsilane as an internal standard. Where isomer ratios were measured by nmr using the relative areas of the *N*-methyl protons of each isomer, the *N*-methyl proton region of the nmr spectrum was examined using a 50-Hz sweep width. Relative areas were measured with a planimeter. Gas–liquid partition chromatography (glpc) was carried out with a

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(7) Chas. Pfizer & Co., British Patent 1,018,995 (1966).

(8) M. Rajšner, E. Srátek, J. Metyšova, and M. Protiva, *Collect. Czech. Chem. Commun.*, **34**, 1963 (1969).

(9) "Eu-Resolve," Ventron Corp.

(10) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(11) A. deLeenheer and A. Heyndrickx, *J. Pharm. Sci.*, **60**, 1403 (1971).

TABLE II

CHEMICAL SHIFTS OF THE AROMATIC PROTONS IN (*E*)- AND (*Z*)-3-CHLORO-*N*,*N*-DIMETHYL(5*H*-DIBENZO[*a*,*d*]CYCLOHEPTENE)-$\Delta^{5,\gamma}$-PROPYLAMINE

	E (trans) isomer			*Z* (cis) isomer		
Proton	δ (CCl$_4$), free base	δ (CCl$_4$), Eu(dpm)$_3$ complex[a]	$\Delta\delta$	δ (CCl$_4$), free base	δ (CCl$_4$), Eu(dpm)$_3$ complex	$\Delta\delta$
C_1H	7.07[b]	7.11	0.04	7.13–7.25	7.46	0.21–0.33
C_2H	7.12	7.11	−0.01	7.13–7.25	7.46	0.21–0.33
C_4H	7.23	7.11	−0.12	7.13–7.25	8.37	1.12–1.24
C_6H	7.15–7.25	7.72	0.47–0.57	7.13–7.25	7.31	0.12 ± 0.06
C_7H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1
C_8H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1
C_9H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1

[a] Approximately 0.2 mol Eu(dpm)$_3$/mol of substrate. [b] Parts per million relative to internal tetramethylsilane.

4 mm (i.d.) × 6 ft glass 5% QF-1 on acid-washed dimethylchlorosilane-treated Chromosorb G column, 100–120 mesh. Thin layer chromatography (tlc) was perhaps the most useful analytical method in studying purity of the final products **2** and **3**. Tlc's were performed on Analtech fluorescent silica gel G plates; spots were detected by uv, exposure to iodine, Dragendorff's reagent, and charring with sulfuric acid and heat (100° for 5–15 min). R_f^1 and R_f^2 values refer to the systems: CHCl$_3$–CH$_3$OH–concentrated NH$_4$OH (60:8:1, v/v/v) and cyclohexane–CH$_3$OH–diethylamine (7:2:1, v/v/v), respectively.[12]

The conversion of amine salts into the free base form, for nmr, ir, tlc, and glc analyses, was carried out in a standard manner. The salt was dissolved in water and treated with an excess of a saturated sodium carbonate solution. The precipitate was extracted into benzene or ether, washed with water, dried over magnesium sulfate, and filtered. The solvent was removed on a rotary evaporator at a final temperature of about 80°.

***N*,*N*-Dimethyl-3-(5-hydroxy-10-piperidino-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)propylamine (5).**—To a cooled, stirred solution of 10.0 g (0.0346 mol) of ketone **4**[5] in 150 ml of dry THF was added dropwise 40 ml of a 1.92 *M* solution of dimethylaminopropylmagnesium chloride in THF. The solution was stirred overnight at room temperature. The THF was removed and the residue was dissolved in benzene. Water was added slowly while stirring until a clear benzene phase and a gelatinous residue formed. The benzene was decanted, and the residue was extracted with hot benzene. The combined benzene extracts were evaporated leaving a white crystalline residue that was recrystallized from absolute ethanol to give 10.7 g (82%) of **5**, mp 169.5–171°.

Anal. Calcd for C$_{25}$H$_{32}$N$_2$O: C, 79.74; H, 8.57. Found: C, 79.49; H, 8.54.

Mixed Geometric Isomers of *N*,*N*-Dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (6 and 7).—A solution of 6.0 g of **5** in 100 ml of 6 *N* HCl was refluxed for 14 hr. The solution was evaporated to dryness, and the residue was converted into a mixture of the free bases, C=O band 1684 cm^{-1} (liquid film). Glpc separates the two geometric isomers, designated α and β; a ratio of 80:20 was found for this sample. Integration of the areas of the *N*-methyl protons observed in the nmr spectrum of this sample gave a ratio of 75:25 for the two isomers: nmr (CDCl$_3$) δ 2.12 (s, N(CH$_3$)$_2$), 2.16 (s, N(CH$_3$)$_2$) (combined N(CH$_3$)$_2$ = 6 H), 2.2–2.5 (m, -CH$_2$CH$_2$-, 4 H), 3.78 and 4.45 (double d, J_{gem} = 13 Hz -CH$_2$CO-, 2 H), 6.21 (t, J = 7 Hz, vinyl CH, 1 H), 7.15–7.52 and 8.0–8.2 (m, aromatic CH).

One of the hydrochloride salts of *N*,*N*-dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (designated the α form) crystallized readily from the mixture and was separated in pure form by recrystallization from ethanol-ether, mp 221–224° dec (reported[13] mp 222–226°). The free base of the α form was crystallized from hexane, mp 71–73°. Differential scanning calorimetry (dsc) indicated the sample to be 98.9 mol % pure: R_f^1 0.89, R_f^2 0.83.

Anal. Calcd for C$_{20}$H$_{21}$NO: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.54; H, 7.35; N, 4.81.

A 2.0-g (0.00688 mol) sample of this free base, α form, mp 71–73°, was reduced with 1.30 g (0.0374 mol) of sodium borohydride dissolved in 40 ml of methanol. After refluxing for 1 hr, the methanol was removed and the residue was recrystallized from hexane to give one of the geometrically pure forms, designated α, of **(*R*,*S*)-*N*,*N*-dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine:** mp 95.5–97.5°; nmr (CDCl$_3$) δ 2.05 (s, N(CH$_3$)$_2$, 6 H), 2.2 to 3.5 (m, aliphatic CH, 7 H), 5.0 (broad s, OH, 1 H), 5.91 (t, J = 7 cps, vinyl CH, 1 H), 7.1–7.7 (m, aromatic CH); R_f^1 0.70.

Anal. Calcd for C$_{20}$H$_{23}$NO: C, 81.87; H, 4.77; N, 7.90. Found: C, 81.67; H, 4.67; N, 7.93.

Acid Isomerization of the α Form of *N*,*N*-Dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine.—A sample of the free base, α form, mp 71–73°, was dissolved in 6 *N* HCl. After refluxing for 24 hr, the solution was evaporated and the hydrochloride salt residue was converted into the free base. Glpc analysis of the mixture showed both isomers to be present and in a ratio of 85:15.

Mixed Geometric Isomers of *N*-Methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (8 and 9).—To a magnetically stirred solution of 2.5 g (0.0236 mol) of cyanogen bromide in 5 ml of benzene was added dropwise over 0.5 hr a solution of the mixed geometric isomers **6** and **7** (4.27 g, 0.0147 mol, 75:25 isomer ratio by nmr) dissolved in 15 ml of benzene. The solution was stirred overnight at room temperature. The benzene was decanted and a small amount of orange residue was washed with benzene. The combined benzene extracts were washed with two 100-ml portions of 3 *N* HCl and three 100-ml portions of water. After evaporation of the benzene, the residue was dissolved in a mixture of 75 ml glacial acetic acid, 20 ml of water, and 25 ml of concentrated HCl. This solution was stirred and refluxed for 16 hr. The solution was evaporated to dryness, and the residue was converted into a mixture of the free bases **8** and **9** with sodium carbonate solution, ir (liquid film) 3358 (NH) and 1690 cm^{-1} (C=O). Integration of the areas of the *N*-methyl protons observed in the nmr spectrum of this sample gave a ratio of 69:31 for the two isomers: nmr (CDCl$_3$) δ 1.21 (s, NH, 1 H), 2.2–2.9 (m, -CH$_2$CH$_2$-, with a singlet at 2.36 (NCH$_3$) having a shoulder at 2.30 (NCH$_3$), 7 H), 3.79 and 4.41 (double d, J_{gem} = 13 Hz, -CH$_2$CO-, 2 H), 6.23 (t, J = 7 Hz, vinyl CH, 1 H), and 7.2–7.6 and 8.0–8.2 (m, aromatic CH, 8 H).

Separation of the Geometric Isomers 8 and 9.—A mixture of the secondary amines **8** and **9** (1.57 g, isomer ratio 69:31 by nmr) was dissolved in 20 ml of benzene. Dry HCl gas was passed into the solution until no further precipitation occurred. The mixture was stirred to give a semisolid residue A and a clear benzene supernatant B. The benzene phase was decanted from the solid.

Residue A.—The semisolid residue crystallized on being triturated with benzene. Recrystallization of this material from isopropyl alcohol-ether gave ***N*-methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine hydrochloride,** α form, mp 219–224° dec, R_f^1 0.66, R_f^2 0.49 (free base).

Anal. Calcd for C$_{19}$H$_{19}$NO·HCl: C, 72.72; H, 6.42; N, 4.46; Cl, 11.30. Found: C, 72.09; H, 6.55; N, 4.27; Cl, 11.19.

After being converted into the free base, expanded scale nmr examination showed a single *N*-methyl proton absorption peak at δ 2.36. High-resolution nmr spectroscopy using the shift

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(12) E. C. Munksgaard, *Acta Pharmacol. Toxicol.*, **27**, 129 (1969).

(13) Hoffmann-La Roche and Co., Netherlands Patent Application 68,10177.

reagent tris(dipivalomethanato)europium has established that this α form has the *E* configuration (see text): nmr (100 MHz, $CDCl_3$) δ 2.37 (s, NCH_3, 3 H), ~2.40 (m, $CH_2C{=}$, 2 H), 2.71 (t, *J* = 7 Hz, NCH_2, 2 H), 3.78 (d, *J* = 13 Hz, 11 axial CH, 1 H), 4.42 (d, *J* = 13 Hz, 11 equatorial CH, 1 H), 6.22 (t, *J* = 7.5 Hz, vinylic CH, 1 H) 7.2–7.5 (m, aromatic CH, 7 H), 8.15 (d with fine structure, *J* = 8 Hz, C_9H, 1 H); nmr in presence of ~0.3 mol of $Eu(dpm)_3$ ($CDCl_3$) 4.13 (d, *J* = 13 Hz, 11 axial CH, 1 H), 4.42 (d, *J* = 13 Hz, 11 equatorial CH, 1 H), ~5.4 (broad, $CH_2C{=}$, 2 H), ~7.5 (broad, NCH_3, CH_2N, $HC{=}$, 6 H) 7.4–7.7 (m, aromatic H, 5 H), 7.85 (broadened d, *J* ≈ 8 Hz, C_1H, 1 H), 8.09 (broadened d, *J* ≈ 7–8 Hz, C_4H, 1 H), 8.31 (broadened d, *J* ≈ 8 Hz, C_9H, 1 H).

Supernatant B.—The supernatant benzene phase was concentrated to about 10 ml and allowed to stand. The solution was decanted from a small amount of oil that precipitated. This process was carefully repeated to give about 5 ml of a clear benzene solution. The benzene was evaporated to give 0.33 g of (*Z*)-*N*-methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-Δ$^{5,\gamma}$-propylamine hydrochloride as a viscous oil that could not be crystallized. After being converted into the free base, expanded scale nmr examination showed a single *N*-methyl proton absorption peak at δ 2.30; nmr ($CDCl_3$) δ 1.21 (s, NH, 1 H), 2.2–2.9 (m, $-CH_2CH_2-$, with a singlet at 2.30 (NCH_3), 7 H), 3.78 and 4.40 (double d, J_{gem} = 13 Hz, $-CH_2CO-$, 2 H), 6.21 (t, *J* = 7 Hz, vinyl CH, 1 H), and 7.2–7.6 and 8.0–8.2 (m, aromatic CH, 8 H).

(*R*,*S*)-(*E*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-Δ$^{5,\gamma}$-propylamine (3).—To a solution of 1.56 g of the E ketone **8** dissolved in 25 ml of absolute methanol was added a solution of 1.56 g of sodium borohydride dissolved in 3 ml of water. The solution was stirred and refluxed for 1.5 hr. The methanol was evaporated, and the residue was dissolved in benzene. The benzene solution was washed with water, dried, and filtered, and the solvent was evaporated to give 1.56 g of the (*R*,*S*)-*E* amino alcohol **3**: ir (KBr) 3400 (s, broad, OH), 3300 (m, broad, NH), 1555 (w), 675 (w), 560 (w), and 540 (w) cm^{-1}. A comparison of the infrared spectra of (*R*,*S*)-(*E*)-**3** and (*R*,*S*)-(*Z*)-**2** showed that the bands at 675, 560, and 540 cm^{-1} were stronger in the *E* spectrum: $R_f{}^1$ 0.57, $R_f{}^2$ 0.31; nmr ($CDCl_3$, 10% w/v) δ 1.26 (S, NH, 1 H), 2.0–2.52 (m, with peaks at 2.03 and 2.19 (NCH_3)), 2.74–3.68 (broad, $-CH_2CHOH-$, 2 H), 4.66–5.1 (broad, OH, 1 H), 5.85 (t, vinyl CH, 1 H, *J* = 7 Hz), and 7.0–7.4 (m, aromatic CH). The hydrogen maleate salt was prepared and crystallized from isopropyl alcohol, mp 156–157.5°.

Anal. Calcd for $C_{19}H_{21}NO \cdot C_4H_4O_4$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.70; H, 6.62; N, 3.60.

Attempts to analyze this salt by differential thermal analysis (dta), differential scanning calorimetry (dsc), and phase solubility analysis were unsuccessful.

A crystalline neutral naphthalene-1,5-disulfonate salt was prepared and recrystallized from methanol, mp 242°.

Anal. Calcd for $(C_{19}H_{21}NO)_2 \cdot C_{10}H_8O_6S_2$: C, 68.06; H, 5.95; N, 3.31; S, 7.57. Found: C, 67.67; H, 5.97; N, 3.22; S, 7.50.

On attempted analysis by dta, this salt showed a sharp endotherm at 242° (in air) (234° *in vacuo*), followed by a very sharp exotherm of crystallization to give presumably norcyclobenzaprine naphthalene-1,5-disulfonate which then melted at 309°.

Phase solubility analysis of the (*R*,*S*)-(*E*)-naphthalene-1,5-disulfonate salt showed it to be 99.8% pure.

(*R*,*S*)-(*Z*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo-[*a*,*d*]cycloheptene)-Δ$^{5,\gamma}$-propylamine (2).—In a manner similar to that described for reduction of the *E* isomer **8**, the *Z* isomer **9** (0.33 g) was reduced to **2** using 0.10 g of sodium borohydride: ir (KBr) 3400 (s, broad, OH), 3300 (m, broad, NH), 675 (m), 560 (w), and 540 (w) cm^{-1}. A comparison of the infrared spectra of (*R*,*S*)-(*E*)-**3** and (*R*,*S*)-(*Z*)-**2** showed that the OH stretching band at 3400 was stronger in the *Z* spectrum. The band at 1555 cm^{-1}, seen in the spectrum of **3**, is not present in the spectrum of **2**: $R_f{}^1$ 0.52, $R_f{}^2$ 0.24; nmr ($CDCl_3$, 10% w/v) δ 1.26 (s, NH, 1 H), 2.0–2.6 (m, with peaks at 2.21 (NCH_3) and 2.39), 2.82–3.7 (broad, $-CH_2CHOH-$, 2 H), 4.66–5.1 (broad, OH, 1 H), 5.85 (t, vinyl CH, 1 H, *J* = 7 Hz), and 7.0–7.4 (m, aromatic). The (*R*,*S*)-*Z* isomer **2** did not form a crystalline hydrogen maleate salt on long standing. The hydrogen oxalate salt was prepared and recrystallized from absolute ethanol, mp 135–137° (foaming).

Anal. Calcd for $C_{19}H_{21}NO \cdot C_2H_2O_4$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.93; H, 6.50; N, 3.52.

Attempts to analyze this salt by dta and dsc were unsuccessful.

Registry No.—**2**, 37439-87-5; **2** hydrogen maleate, 37439-88-6; **3**, 37439-89-7; **3** hydrogen maleate, 37439-90-0; **3** naphthalene-1,5-disulfonate salt, 37439-91-1; **4**, 37439-92-2; **5**, 37439-93-3; **6**, 37439-94-4; **7**, 37440-21-4; **8**, 37508-15-9; **8** HCl, 37440-24-7; **9**, 37440-22-5; (*R*,*S*)-*N*,*N*-dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-Δ$^{5,\gamma}$-propylamine, 37440-23-6.

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N-Hydroxypteridines Structurally Analogous to Oncogenic *N*-Hydroxypurines. Covalent Hydration of 1-Hydroxy-2-oxo-1,2-dihydropteridine[1]

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1-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine has been synthesized and its properties compared with the analogous 3-hydroxypurine derivative. A technique was devised for the catalytic reduction of 5-nitrocytosine 3-oxide to the requisite 5-aminocytosine 3-oxide necessary for the synthesis of the 1-hydroxy-2-oxo-1,2-dihydropteridine. The latter undergoes facile covalent hydration, including addition of methanol and ethanol.

The biological importance of pteridines and the existence of oncogenic[2] purine *N*-oxides suggested that consideration should be given to the possible chemical and biological properties of structurally analogous pteridine *N*-oxide derivatives. Few pteridine *N*-oxides are known[3,4] and the only one structurally analogous to the oncogenic 3-hydroxyxanthine (**1**, R = H) is 1-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-6,7-dimethylpteridine[3] (6,7-dimethyl **2**, R = H).

The desired 1-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-

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