(5 ml), concentrated HCl (5 ml) was added. After refluxing for 12 hr, the solution was evaporated *in vacuo*, taken up in H_2O, neutralized ($NaHCO_3$), and extracted three times with $CHCl_3$. The $CHCl_3$ solution was evaporated, and the oil obtained was taken up in a minimum amount of EtOH. The yield of XVIII was 37 mg (28%): mp 238–242°; nmr of the hydrochloride (DMSO-d_6), 2-CH_3 −162, 5-CH_2 −257, −272, −275, −290 (AB quadruplet), α^4-H −388, phenyl −441, C_6-H −490. *Anal.* ($C_{14}H_{13}NO_2$) C, H, N.

Acknowledgments.—This study was supported in part by a research grant (CA-08793) from the National Cancer Institute, U. S. Public Health Service. We wish to express our thanks to Dr. Charles A. Nichol for his continued interest in this program, and to Mr. George Fricke and Mr. Norman Angelino for capable technical assistance. We are also grateful to Dr. Harry B. Wood and Dr. Robert E. Engle of the Cancer Chemotherapy National Service Center for making avai able to us a quantity of 3,α^5-*O*-dibenzylpyridoxol.

Antidepressants. II.[1] Bridged Ring Ether Derivatives in the Dibenzocycloheptene Series[2]

MARCIA E. CHRISTY, CAROLE C. BOLAND, JUNE G. WILLIAMS, AND EDWARD L. ENGELHARDT

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., West Point, Pennsylvania

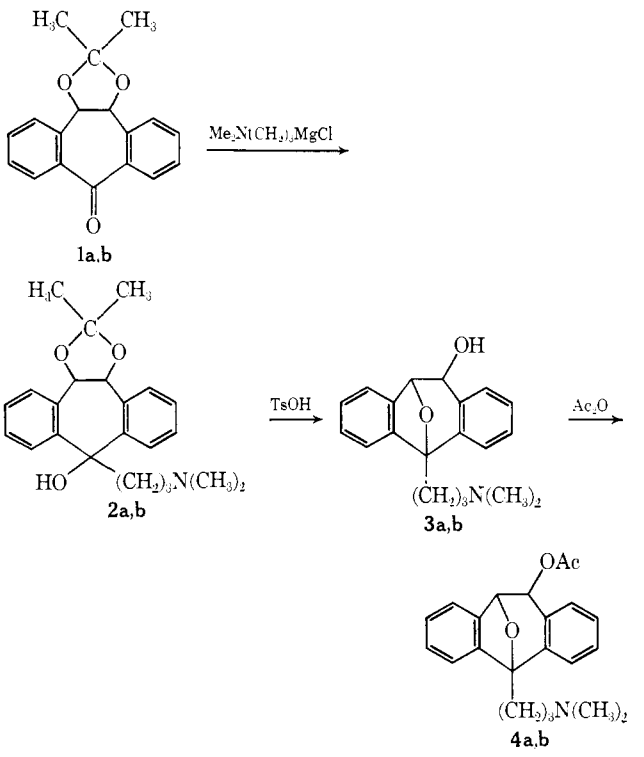
Received October 31, 1969

The synthesis and proof of structure of novel 11-substituted 5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine derivatives is reported. These compounds exhibit potent tetrabenzazine-antagonizing activity.

5H-Dibenzo[*a*,*d*]cycloheptene-5-propylamine derivatives related to amitriptyline and protriptyline have been the subject of a synthetic program in our laboratories.[1] In an extension of this investigation to 10- and 11-substituted dibenzocycloheptenes, novel bridged ring ether derivatives that have shown significant antidepressant activity were synthesized and are described in this paper.

The carbinol **2a** was obtained by the Grignard reaction of the known acetonide of *cis*-10,11-dihydro-10,-11-dihydroxy-5H-dibenzo[*a*,*d*]cyclohepten-5-one[3] (**1a**) with 3-dimethylaminopropylmagnesium chloride. When **2a** was subjected to *p*-toluenesulfonic acid catalyzed hydrolysis in refluxing MeOH, the product was a crystalline base that was not the expected 5,10,11-triol **10**. The empirical formula, $C_{20}H_{23}NO_2$, corresponded with the loss of one molecule of H_2O from this structure. The uv spectrum of the product showed no strong maximum in the 230–240-mμ region characteristic of unsaturation at the 5,α-positions[4] and the ir spectrum, showing strong C–O stretching bands at 1020 and 1080 cm^{-1}, was consistent with an ether linkage in addition to OH. The product afforded a monoacetyl derivative upon treatment with Ac_2O, but failed to react with LAH, $NaOCH_3$ in refluxing MeOH, or KOH in ethylene glycol. This behavior eliminated 10,11-dihydroxy-5,α-unsaturated and 10,11-epoxide structures from consideration and seemed consistent only with the 5,10-bridged ether **3a**. A similar sequence starting from the *trans* acetonide **1b** afforded the isomeric *trans* ether **3b** (Scheme I).

SCHEME I



a = *cis* isomer
b = *trans* isomer

The significant nmr characteristics of the carbinols **3a** and **3b** and the corresponding acetates **4a** and **4b** are summarized in Table I and are in accord with the chemical nonequivalence of the 10 and 11 protons, the position of the secondary alcohol substituent, and the 5,10-epoxy linkage in the bridged ring ether structure. The lack of spin coupling between the 10 and 11 protons in the *cis* isomers **3a** and **4a** as compared to their *trans* counterparts is also shown by the precursor acetonide **2a** and apparently is attributable to the H–C_{10}–C_{11}–H bond angles.[5] The downfield position of the OH signal

(1) Previous paper: E. L. Engelhardt, M. E. Christy, C. D. Colton, M. B. Freedman, C. C. Boland, L. M. Halpern, V. G. Vernier, and C. A. Stone, *J. Med. Chem.*, **11**, 325 (1968).

(2) Presented in part at the 10th National Medicinal Chemistry Symposium of the American Chemical Society, Bloomington, Ind., June 27, 1966.

(3) G. L. Buchanan and D. B. Jhaveri, *J. Org. Chem.*, **26**, 4295 (1961).

(4) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *ibid.*, **27**, 230 (1962).

(5) Examination of Dreiding models reveals that the dihedral angle at the intersection of the planes formed by $HC_{10}C_{11}$ and $C_{10}C_{11}H$ is approximately 75° in the *cis* isomer **3a** and 25° in the *trans* isomer **3b**. From the Karplus equation, J would be expected to approach zero as the dihedral angle approaches 90° and to have its largest value as the dihedral angle approaches 0°.

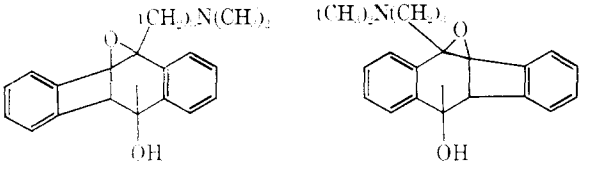
in the *cis*-alcohol **3a** relative to the *trans* isomer **3b** probably reflects the deshielding effect of the more proximal ether O in the *cis* isomer.

TABLE I
NMR CHARACTERISTICS OF BRIDGED RING ETHER DERIVATIVES[a]

Compound	11-Substituent	δ, J, Hz for Proton 10	11	OH
3a	*cis*-OH	5.45 s	4.33 s	3.58 s
3b	*trans*-OH	5.37 d (6)	5.07 d (6)	2.72 s
4a	*cis*-OAc	5.63 s	5.48 s	
4b	*trans*-OAc	5.69 d (6)	6.33 d (6)	
14	=O	5.53 s		
19	*trans*-NH_2	5.37 d (6)	4.45 d (6)	
20	*trans*-$NHCOCH_3$	5.58 d (6)	5.70 d (6)	

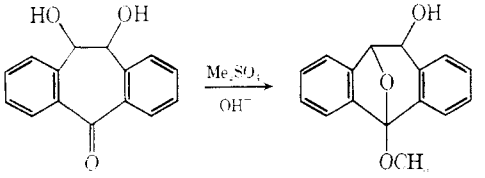
[a] Nmr spectra were determined in $CDCl_3$ on a Varian A-60A spectrometer. Chemical shifts (δ) are reported relative to TMS (δ 0.00) internal standard. Signals are designated as s, singlet and d, doublet.

Resolution of the *trans* racemate **3b** into the enantiomorphs **5** and **6** *via* its salts with (+)- and (−)-tartaric acids was carried out primarily to obtain the optical isomers for biological evaluation; however, it also provided further confirmation of the bridged ether structure.



5 6

The formation of oxygen-bridged dibenzocycloheptene derivatives has been reported previously by Buchanan and Jhaveri[3] who obtained the bridged ketals **8a** and **b** from the isomeric diols **7a** and **b**.

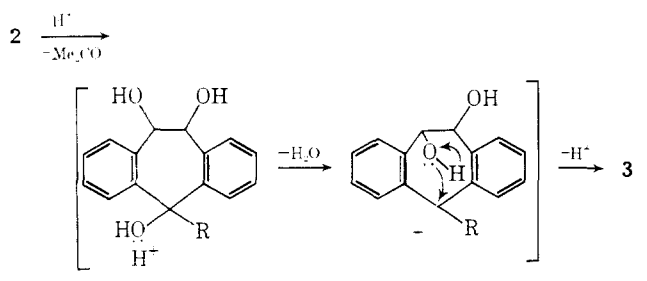


7a,b 8a,b

a = *cis* isomer
b = *trans* isomer

Other transannular reactions of dibenzocycloheptene derivatives have been reported recently.[6]

It seems probable that the 5,10,11-triol is an intermediate in the formation of the 5,10-epoxy derivative.

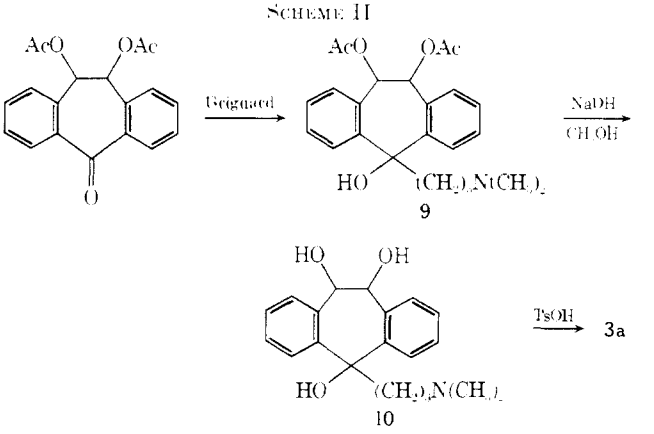


R = $(CH_2)_3N(CH_3)_2$

yielding a carbonium ion at the 5 position that undergoes intramolecular attack by the 10-OH.

The triol **10** has been prepared in the *cis* series from the corresponding diacetate **9**. Treatment of **10** with a catalytic amount of *p*-toluenesulfonic acid in refluxing MeOH yielded the bridged ether **3a** (Scheme II).

SCHEME II



Conversions of the parent 11-OH bridged ring ether **3b** to several related compounds are shown in Scheme III. Both the *cis* and *trans* carbinols **3a** and **b** undergo ring opening and pinacol rearrangement on heating with mineral acid, yielding the anthracene-9-carboxaldehyde derivative **11**. Demethylation of the side-chain tertiary amino group to the corresponding secondary amine **13** was accomplished by conversion into the urethan **12** that was hydrolyzed in base. The *cis* isomer **3a** was demethylated similarly. The *trans* 11-carbinol **3b** afforded the 11-ketone **14** on Oppenauer oxidation. The *cis* 11-carbinol **3a** failed to undergo oxidation under strenuous Oppenauer conditions. Reduction of the ketone **14** with KBH_4 gave **3b** stereospecifically. The ketone **14** proved to be a versatile intermediate to other 11-substituted derivatives, affording the tertiary carbinol **15** from the Grignard reaction, the 11-unsubstituted derivative **17** *via* the thioketal **16** and desulfurization, and the 11-amino derivative **19** *via* reduction of the oxime **18**. By either LAH or Na and EtOH reduction, the amine **19** was obtained as a single isomer. It was shown to be *trans* by its nmr spectrum that exhibited the spin coupling between the 10 and 11 protons characteristic of *trans* isomers in the series and the downfield shift of the 11-proton upon acetylation of the amine to the amide **20** (Table I).

Biological Results.—The bridged ring ethers have shown exceptionally potent tetrabenazine-antagonizing activity in mice.[7] Data for representative compounds and three standard drugs are recorded in Table II. The compounds have shown no depressant activity in conditioned avoidance protocols. Generally, the *trans* isomers have exhibited greater potency than the corresponding *cis* isomers and the secondary amines have shown no marked differences in activity from the tertiary amines in the series. The optical isomers of **3b** both showed equivalent activity of approximately the same order as the racemate.

(6) T. A. Dobson, M. A. Davis, A. M. Hartung, and J. M. Manson, *Can. J. Chem.*, **46**, 2843 (1968); T. A. Dobson, M. A. Davis, and A. M. Hartung, *ibid.*, **46**, 3391 (1968).

(7) For a description of the testing protocol, see ref 1.

SCHEME III

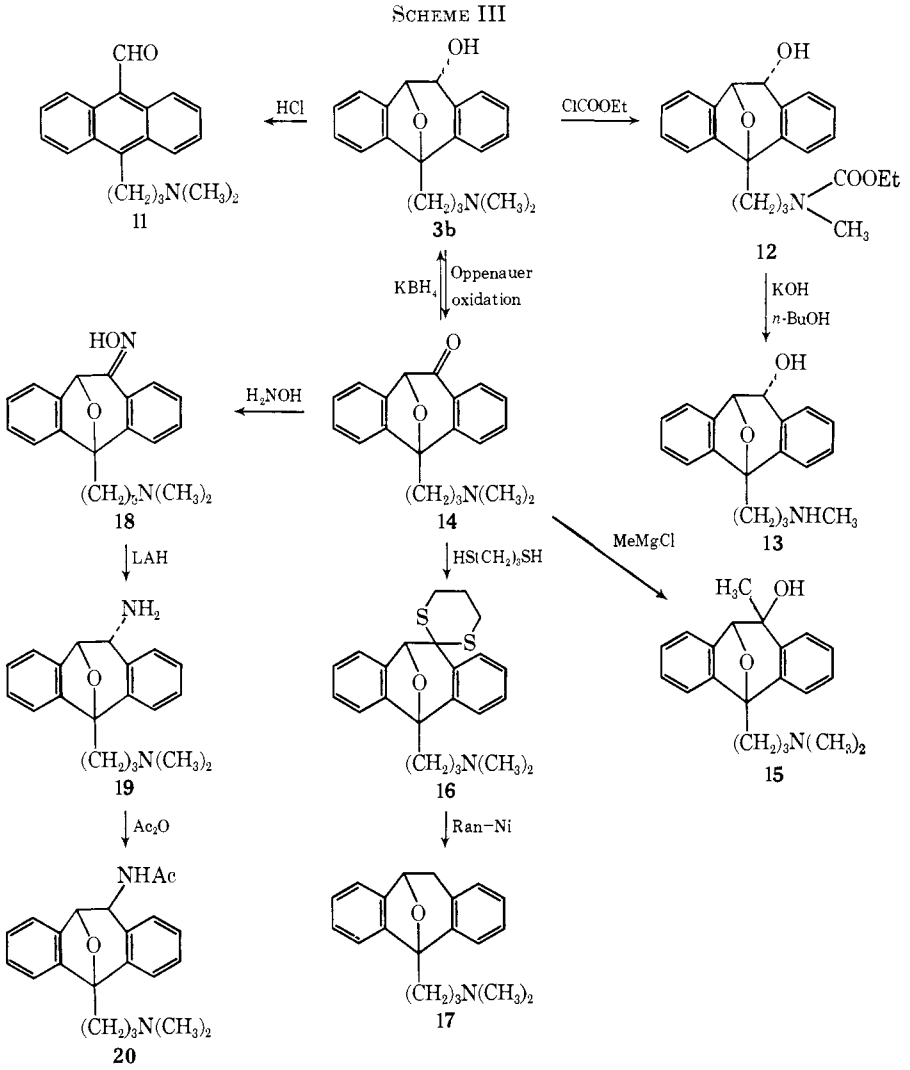
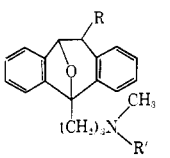


TABLE II



No.		Tetrabenazine antagonism exploratory ED_{50} (mg/kg p.o.)
3a	R = *cis*-OH, R′ = CH_3	0.9
3b	R = *trans*-OH, R′ = CH_3	0.07
	R = *cis*-OH, R′ = H	1.6
13	R = *trans*-OH, R′ = H	0.016
14	R = =O, R′ = CH_3	0.25
18	R = NOH, R′ = CH_3	0.03
19	R = *trans*-NH_2, R′ = CH_3	0.058
	Protriptyline	0.3
	Amitriptyline	1.3
	Imipramine	2.37

Experimental Section[8]

***cis*-3a,12b-Dihydro-2,2-dimethyl-8-(3-dimethylaminopropyl)-8H-dibenzo[3,4:6,7]cyclohepta[1,2-*d*]-1,3-dioxol-8-ol. 2a.**—The Grignard reagent was prepared from 1.47 g (12 mmol) of 3-dimethylaminopropyl chloride and 290 mg (12 mg-at) of Mg in 12 ml of dry THF under N_2 and using 110 mg (1 mmol) of EtBr as initiator. A solution of 1.7 g (6.1 mmol) of *cis*-3a,12b-dihydro-2,2-dimethyl-8H-dibenzo[3,4:6,7]cyclohepta[1,2-*d*]-1,3-dioxol-8-one[3] in 13 ml of dry THF was added dropwise over 30 min to the stirred solution of the Grignard reagent cooled in ice. After 2 hr at room temperature, the bulk of the THF was evaporated, the residue dissolved in C_6H_6, and with ice-cooling, 6 ml of H_2O was added dropwise. The C_6H_6 layer was decanted from the gelatinous precipitate which then was extracted repeatedly with boiling C_6H_6. The combined C_6H_6 extracts were washed (H_2O), dried (Na_2SO_4), and evaporated. Crystallization of the residual solid from 95% EtOH gave 1.56 g (70%) of white needles, mp 181–188°. Recrystallizations from 95% EtOH and from *i*-PrOH afforded a purified sample, mp 189–190°: nmr ($CDCl_3$), δ 1.60 and 1.65 (s, 3 each, $C(CH_3)_2$), 2.15 (s, 6, $N(CH_3)_2$), 5.72 (s, 2, 10 and 11-H). *Anal.* ($C_{23}H_{29}NO_3$) C, H, N.

***trans* Isomer. 2b.**—The *trans* ketone **1b**[3] was reacted with an excess of $Me_2N(CH_2)_3MgCl$ as described for the *cis* isomer. The product was obtained as a viscous yellow oil in quantitative yield. A sample of the base was converted into the hydrogen oxalate that had constant mp 175.5–176.5° dec after repeated recrystallizations from *i*-PrOH–Et_2O; nmr ($CDCl_3$), δ 1.57 (s, 6, $C(CH_3)_2$), 2.20 (s, 6, $N(CH_3)_2$), 4.53 (d, J = 9 Hz, 1, 11-H), 5.37 (d, J = 9 Hz, 1, 10-H). *Anal.* ($C_{23}H_{29}NO_3 \cdot C_2H_2O_4$) C, H, N.

***cis*-10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cyclohepten-11-ol. 3a.**—*cis*-**2a** (2.95 g, 8 mmol) and 3.0 g (15.8 mmol) of *p*-toluenesulfonic acid hydrate in 300 ml of MeOH were heated to refluxing for 4 hr. After neutralization with 1 *M* KOH in MeOH, solvent was distilled and the residue was partitioned between C_6H_6 and H_2O. The C_6H_6 layer was washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. Crystallization of the residual solid from 50% EtOH gave 1.9 g (81%), mp 145–152°. Recrystallization from cyclohexane yielded 1.75 g, final mp 151–153°. *Anal.* ($C_{20}H_{23}NO_2$) C, H, N.

***trans* Isomer. 3b.**—Hydrolysis of the *trans*-acetonide **2b** as

(8) All melting points were determined with calibrated thermometers in a Thomas–Hoover capillary melting point apparatus. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements were within ±0.4% of the theoretical value. Unless noted otherwise, all concentrations were carried out in a rotary evaporator at reduced pressure.

above for the *cis* isomer yielded 81% of the *trans* isomer, mp 157–159°, after trituration of the crude solid with Et_2O. An analytical sample melted at 157–158° after recrystallization from C_6H_6 and sublimation at 140° (0.01 mm). *Anal.* ($C_{20}H_{23}NO_2$) C, H, N. A sample of this base was converted into the hydrogen maleate salt, mp 179–180° (EtOH–Et_2O). *Anal.* ($C_{20}H_{23}NO_2 \cdot C_4H_4O_4$) C, H, N.

***cis*-11-Acetoxy-10,11-dihydro-*N*,*N*-dimethyl-5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine (4a).**—*cis*-**3a** (500 mg, 1.62 mmol) in 10 ml of Ac_2O was refluxed for 4 hr. After evaporation to dryness, the residue was dissolved in H_2O and the cloudy solution was extracted with C_6H_6. The H_2O layer was cooled in ice and made basic with 40% aqueous NaOH, and the oily base was extracted into C_6H_6. Upon evaporation, the washed C_6H_6 extract yielded 450 mg of product as a light yellow oil. A sample of the base was converted into the hydrogen oxalate salt that was recrystallized twice from *i*-PrOH; mp 173–175° dec. *Anal.* ($C_{22}H_{23}NO_3 \cdot C_2H_2O_4$) C, H, N.

***trans* Isomer 4b.**—Acetylation of the *trans* carbinol **3b** as outlined above for the *cis* isomer yielded 80% of white crystalline product, mp 116.5–120°. Recrystallizations from petroleum ether (30–60°) gave the analytical sample, mp 125–126°. *Anal.* ($C_{22}H_{25}NO_3$) C, H, N.

Resolution of *trans*-3b.—The racemic *trans* carbinol **3b** (12.36 g, 0.04 mol) in 200 ml of hot EtOH was treated with a solution of 6 g (0.04 mol) of (−)-tartaric acid in 150 ml of hot EtOH. The solution was allowed to cool slowly and after 4 hr, a first crop of crystalline salt was collected. After chilling for 1.5 hr, a second crop was collected from the filtrate. Addition of 150 ml of Et_2O to the filtrate then precipitated a third crop: total solids, 14.0 g. The mother liquor was evaporated to dryness, the residual syrup dissolved in H_2O, and the base, liberated from the cold solution with 5% aqueous NaOH, was extracted into C_6H_6. Evaporation of the washed and dried extract and crystallization of the residual solid from C_6H_6–hexane yielded 1.35 g of the optically impure (−)-base, mp 154–157°. A solution of this base in 20 ml of hot EtOH treated with 1 equiv of (+)-tartaric acid in 10 ml of hot EtOH deposited 1.40 g of the tartrate, mp 237–239° dec. After three crystallizations from 95% EtOH, 800 mg of purified (−)-base·(+)-tartrate of constant rotation were obtained; mp 238–239° dec; $[\alpha]^{25}_{578}$ −271° (*c* 0.1, MeOH). *Anal.* ($C_{20}H_{23}NO_2 \cdot 0.5C_4H_6O_6$) C, H.

The (−)-base was regenerated from 700 mg of the (+)-tartrate by basifying an aqueous solution and extracting the base into C_6H_6. Evaporation of the washed and dried extract and crystallization of the residual solid from C_6H_6–hexane gave 476 mg, mp 156–158°: $[\alpha]^{25}_{578}$ −1100° (*c* 0.05, 0.01 *M* HCl in MeOH). *Anal.* ($C_{20}H_{23}NO_2$) C, H, N.

The *trans* racemate (12.36 g, 0.04 mol) in 200 ml of hot EtOH was treated with a solution of 6.0 g (0.04 mol) of (+)-tartaric acid in 150 ml of hot EtOH. After the addition of 50 ml of 95% EtOH, the solution was allowed to cool slowly, and after several days at room temperature, 13.5 g of a tartrate salt was collected. The mother liquor was evaporated to dryness, the residual syrup dissolved in H_2O, and the base, liberated from the cold solution with 20% aqueous NaOH, was extracted into C_6H_6. Evaporation of the washed and dried extract yielded 1.9 g of the optically impure (+)-base, mp 155–157°. A solution of this base in 20 ml of hot 95% EtOH treated with 1 equiv of (−)-tartaric acid in 5 ml of hot 95% EtOH deposited 850 mg of the tartrate, mp 238–239° dec. Dilution of the mother liquor with 15 ml of Et_2O gave a second crop of 800 mg, mp 234–235° dec. The once recrystallized (95% EtOH) second crop was combined with the first and after two recrystallizations from 95% EtOH, 1.05 g of purified (−)-base·(−)-tartrate of constant rotation was obtained; mp 238–239° dec; $[\alpha]^{25}_{578}$ +290° (*c* 0.1, MeOH). *Anal.* ($C_{20}H_{23}NO_2 \cdot 0.5C_4H_6O_6$) C, H.

The (+)-base was regenerated from 950 mg of the (−)-tartrate salt by the procedure described above for its enantiomer: 556 mg, mp 156–158°; $[\alpha]^{25}_{578}$ +1100° (*c* 0.05, 0.01 *M* HCl in MeOH). *Anal.* ($C_{20}H_{23}NO_2$) C, H, N.

***cis*-10,11-Diacetoxy-10,11-dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[*a*,*d*]cycloheptene-5-ol (9).**—A solution of the Grignard reagent prepared from 24.3 g (0.2 mol) of $Me_2N(CH_2)_3Cl$ and 4.86 g (0.2 g-atom) of Mg in 75 ml of dry THF was added dropwise to a stirred suspension of 30 g (0.0925 mol) of *cis*-10,11-diacetoxy-10,11-dihydro-5H-dibenzo[*a*,*d*]cycloheptene-5-one[3] in 100 ml of dry THF cooled in ice. After 2 hr in the cold, the bulk of the THF was evaporated, the residue dissolved in C_6H_6, and with ice-cooling, 30 ml of H_2O was added dropwise. The C_6H_6 layer was decanted from the gelatinous precipitate which then was extracted repeatedly with boiling C_6H_6. The combined extracts were extracted with 0.5 *M* citric acid and the cooled acid extract was made basic with 40% aqueous NaOH. The oily base was extracted into C_6H_6 and the washed extract was evaporated. Crystallization of the residual yellow oil from cyclohexane and recrystallization of the product from hexane–Et_2O gave 20.5 g (54%) of white crystals, mp 133–136°. Recrystallization from hexane afforded the analytical sample, mp 134–135°. *Anal.* ($C_{24}H_{29}NO_5$) C, H, N.

***cis*-10,11-Dihydro-5-(3-dimethylaminopropyl)-5H-dibenzo[*a*,*d*]cycloheptene-5,10,11-triol (10).**—Compound **9** (400 mg, 0.97 mmol) and 320 mg (5.7 mmol) of KOH in 14 ml of MeOH were heated to refluxing for 15 min. After evaporation to dryness, the residual solid was triturated with H_2O, collected, and dried to yield 250 mg (79%) of product, mp 161–163°. Repeated recrystallizations from EtOH–H_2O gave purified material, mp 164.5–165.5°. *Anal.* ($C_{20}H_{23}NO_4$) C, H, N.

The triol **10** was converted in 52% yield into the *cis* bridged ring ether carbinol **3a** by refluxing with *p*-toluenesulfonic acid in MeOH as outlined for the preparation of **3a**. Identity of the product was established by comparison (mixture melting point, ir, nmr) with an authentic sample.

Pinacol Rearrangement of 3a. 10-(3-Dimethylaminopropyl)-anthracene-9-carboxaldehyde (11).—The *cis* carbinol **3a**, 1.0 g (3.24 mmol), was dissolved in 20 ml of 6 *N* HCl. The colorless solution slowly became yellow and was deep red after heating for 40 min on the steam bath. The cooled solution was made basic with 5% aqueous NaOH and the oily base was extracted into C_6H_6. Evaporation of the washed (H_2O) extract left 800 mg of dark yellow oil that was converted into the HCl salt by treating an EtOH solution with a slight excess of HCl in EtOH. Dilution with Et_2O precipitated 250 mg (24%) of yellow crystalline hydrochloride, mp 192–195° dec. Recrystallizations from *i*-PrOH and from EtOH–Et_2O gave an analytical sample: mp 204–206° dec; $\lambda_{max}^{(95\%)}$ 235.5, 264, 374 mμ (*e* 31,392, 66,125, 5876); nmr (DMSO-d_6), δ 2.77 (s, 6, $N(CH_3)_2$), 11.47 (s, 1, CHO). *Anal.* ($C_{20}H_{21}NO \cdot HCl$) C, H, N.

The *trans* isomer **3b** gave a deep orange solution in 6 *N* HCl after heating 1 hr on the steam bath, but was recovered essentially unchanged on work-up. After refluxing a solution of **3b** in concentrated HCl for 30 min, work-up of the dark red solution gave 22% of **11**. Identity of the product was established by comparison (mixture melting point, ir) with an authentic sample.

***trans*-11-Acetoxy-*N*-carbethoxy-10,11-dihydro-5,10-epoxy-*N*-methyl-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine.**—*trans*-**4b** (5.5 g, 15.7 mmol) was added in portions to 160 ml of ethyl chloroformate with stirring and cooling in ice. Stirring in the cold was continued for 1.5 hr and the mixture then was heated at reflux for 16 hr. The clear yellow solution was evaporated and the oily residue was partitioned between C_6H_6 and H_2O. The C_6H_6 extract was washed (H_2O), 0.5 *M* citric acid, H_2O), dried (Na_2SO_4), and evaporated to yield 5.2 g of viscous yellow oil. Crystallization from Et_2O petroleum ether (30–60°) gave a first crop of 2.4 g, mp 75–76°, and a second crop of 2.0 g, mp 72–73°; combined yield, 68%. Repeated recrystallizations from Et_2O–petroleum ether afforded the analytical sample, mp 81–82°. *Anal.* ($C_{24}H_{27}NO_5$) C, H.

***cis* Isomer.**—A solution of 600 mg (1.7 mmol) of the *cis*-acetate **4a** in 3 ml of dry C_6H_6 was added dropwise to a stirred solution of 0.7 ml of ethyl chloroformate in 2 ml of C_6H_6. A yellow gum separated, but dissolved on warming the mixture. After 1 hr at reflux, the solution was diluted with C_6H_6 and washed (2 *N* HCl, H_2O). Evaporation gave 650 mg (92%) of the urethane as a viscous oil. This product was suitable for further use and was characterized only by its ir spectrum.

***trans*-10,11-Dihydro-5,10-epoxy-5-(3-methylaminopropyl)-5H-dibenzo[*a*,*d*]cyclohepten-11-ol (13).**—*trans*-11-Acetoxy-*N*-carbethoxy-10,11-dihydro-5,10-epoxy-*N*-methyl-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine (4.1 g, 10 mmol) and 20 g (0.35 mol) of KOH in 100 ml of *n*-BuOH were stirred and heated at reflux for 11 hr under N_2. Solvent was distilled and the residue was partitioned between C_6H_6 and H_2O. The washed C_6H_6 extract was extracted with several portions of 0.5 *M* citric acid. The ice-cold acid extract was made strongly basic with 40% aqueous NaOH and the base was extracted into C_6H_6. Evaporation of the washed and dried extract and crystallization of the oily residue from Et_2O–petroleum ether (30–60°) gave 1.5 g (51%) of product, mp 128–129°. A sample for analysis was obtained by sublimation at 115° (0.1 mm): mp 129–130°; nmr ($CDCl_3$), δ 2.22 (s,

3, CH_3), 5.15 (d, J = 6 Hz, 1, 11-H), 5.45 (d, J = 6 Hz, 1, 10-H). *Anal.* ($C_{19}H_{21}NO_2$) C, H, N.

This product (**13**) was obtained also in 35% yield by basic hydrolysis according to the above procedure for the oily urethan **12** prepared in 98% yield by refluxing the *trans*-carbinol **3b** in ethyl chloroformate for 30 hr. Identity of the product was established by comparison (mixture melting point, ir) of the hydrogen maleate salts prepared from samples of the base; mp 152–154° (*i*-PrOH–Et_2O). *Anal.* ($C_{19}H_{21}NO_2 \cdot C_4H_4O_4$) C, H, N.

***cis* Isomer.**—Basic hydrolysis of *cis*-11-acetoxy-*N*-carbethoxy-10,11-dihydro-5,10-epoxy-*N*-methyl-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine as described for the *trans* isomer gave 35% of the *cis* isomer of the secondary amine. The analytical sample, mp 138–139°, was obtained by repeated recrystallizations from Et_2O and sublimation at 130° (0.05 mm); nmr ($CDCl_3$), δ 2.28 (s, 3, CH_3), 4.31 (s, 1, 11-H), 5.45 (s, 1, 10-H). *Anal.* ($C_{19}H_{21}NO_2$) C, H, N.

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cyclohepten-11-one (**14**).—A solution of 49 g (0.158 mol) of *trans*-**3b** and 494 ml of freshly distilled cyclohexanone in 3 l. of dry PhMe was dried by distillation of about 600 ml of PhMe. Slow distillation was continued while a solution of 64 g (0.314 mol) of Al(*i*-OPr)$_3$ in 370 ml of dry PhMe was added dropwise over 1.5 hr and for an additional 45 min. After cooling, the mixture was hydrolyzed with 1 l. of saturated aqueous $NaKC_4H_4O_6$ and the aqueous phase was separated and reextracted with toluene. The combined organic layers were washed (H_2O) and extracted with three 350-ml portions of 0.5 *M* citric acid. The ice-cold acid extract was made strongly basic with 40% aqueous NaOH and the base was extracted into C_6H_6. Evaporation of the washed and dried extract and crystallization of the residual solid from hexane gave 33 g (68%) of analytically pure product, mp 76.5–78°. *Anal.* ($C_{20}H_{21}NO_2$) C, H, N.

The ketone **14** was reduced readily to the parent *trans*-carbinol **3b** by refluxing with excess KHB_4 in CH_3OH (67% yield).

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-11-methyl-5H-dibenzo[*a*,*d*]cyclohepten-11-ol (**15**).—A solution of the Grignard reagent prepared from 0.8 g (0.033 g-at) of Mg and excess MeCl in 125 ml of dry THF was added rapidly dropwise to a stirred solution of 5 g (0.0162 mol) of **14** in 75 ml of dry THF cooled in ice. After 1.5 hr at room temperature, the bulk of the THF was evaporated; the residue was dissolved in C_6H_6; and, with ice-cooling, 5 ml of H_2O was added dropwise. The C_6H_6 layer was decanted from the gelatinous precipitate which then was extracted repeatedly with boiling C_6H_6. The combined C_6H_6 layers were extracted with 0.5 *M* citric acid. The ice-cold acid extract was made basic with 40% aqueous NaOH and the base was extracted into C_6H_6. Upon evaporation, the washed and dried extract yielded a crystalline residue. Recrystallization from Et_2O–petroleum ether (30–60°) gave 4.2 g (80%), mp 125–127°. *Anal.* ($C_{21}H_{25}NO_2$) C, H.

A sample of this base was converted into the hydrogen maleate salt, mp 181–182° (EtOH). *Anal.* ($C_{21}H_{25}NO_2 \cdot C_4H_4O_4$) C, H, N.

Spiro[10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene]-11,2′-*m*-dithiane (**16**).—Compound **14** (900 mg, 3 mmol) and 1 ml of 1,3-propanedithiol in 20 ml of glacial HOAc were stirred with 2 ml of BF_3 etherate for 1.5 hr and then allowed to stand overnight at room temperature. The solution was poured into 300 ml of ice-cold 5% aqueous NaOH. The precipitate of the product was collected, washed thoroughly with H_2O, air-dried, and dissolved in 150 ml of Et_2O. Evaporation of the filtered solution left 1.1 g (92%), mp 122–126°. A sample for analysis melted at 130.5–132° after recrystallizations from EtOH–H_2O and *i*-PrOH; nmr ($CDCl_3$), δ 2.20 (s, 6, $N(CH_3)_2$), 5.92 (s, 1, 10-H). *Anal.* ($C_{23}H_{27}NOS_2$) C, H, N.

10,11-Dihydro-*N*,*N*-dimethyl-5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine (**17**).—A solution of 600 mg (1.5 mmol) of **16** in 75 ml of EtOH was stirred at reflux with *ca.* 7 g of W-2 Raney Ni for 24 hr. The mixture was filtered and the filtrate evaporated, leaving the colorless oily base that was converted into the hydrogen maleate salt in EtOH–Et_2O; 280 mg (45%), mp 135–138°. Recrystallizations from *i*-PrOH–Et_2O and EtOH–Et_2O gave purified material: mp 141.5–143.5°; nmr ($CDCl_3$), δ 2.21 (s, 6, $N(CH_3)_2$), 3.45 and 3.71 (d, J = 6 Hz, 1 each, 11-CH_2), 5.57 (d, J = 6 Hz, 1, 10-H). *Anal.* ($C_{20}H_{23}NO \cdot C_4H_4O_4$) C, H, N.

10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene-11-one Oxime (**18**).—A solution of 5.5 g (18 mmol) of **14**, 1.4 g (20 mmol) of $H_2NOH \cdot HCl$, and 2.7 g (20 mmol) of $NaOAc \cdot 3H_2O$ in 160 ml of MeOH–20 ml of H_2O was heated under reflux for 2.5 hr. Solvent was distilled and the residual syrup was dissolved in 300 ml of H_2O. The solution was made strongly basic with 40% aqueous NaOH and the precipitate was collected, washed (H_2O), partially dried in a vacuum oven at 70°, and recrystallized from 95% EtOH to yield 4.7 g (81%), mp 206–210°.[9] The analytical sample from a previous experiment had the same melting point range after repeated recrystallizations from 95% EtOH; nmr (DMSO-d_6), 2.23 (s, 6, $N(CH_3)_2$), 6.55 (s, 1, 10-H), 7.80 (m, 1, OH). *Anal.* ($C_{20}H_{22}N_2O_2$) C, H, N. A sample of this base was converted into the hydrogen maleate salt, mp 184–186° dec (EtOH). *Anal.* ($C_{20}H_{22}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

***trans*-10,11-Dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cyclohepten-11-amine** (**19**).—Under N_2, a solution of 4.15 g (12.9 mmol) of **18** in 200 ml of dry THF was added dropwise over 1 hr to a stirred suspension of 800 mg (21 mmol) of LAH in 50 ml of THF. After 22 hr of stirring at room temperature, the mixture was cooled in ice and hydrolyzed by the successive dropwise addition of 0.8 ml of H_2O, 0.8 ml of 15% aqueous NaOH, and 2.4 ml of H_2O. The precipitate was filtered and washed with 75 ml of boiling C_6H_6. Evaporation of the combined filtrate and washings left 3.9 g of the oily base that was converted into the dihydrogen dimaleate salt in EtOH–Et_2O, yielding 4.1 g (58%), mp 162–165° dec. Repeated recrystallizations from *i*-PrOH–Et_2O gave purified material, mp 171–172° dec. *Anal.* ($C_{20}H_{24}N_2O \cdot 2C_4H_4O_4$) C, H, N.

***trans*-11-Acetamido-10,11-dihydro-5-(3-dimethylaminopropyl)-5,10-epoxy-5H-dibenzo[*a*,*d*]cycloheptene** (**20**).—*trans*-**19** (2.0 g, 6.5 mmol) was dissolved in 10 ml of Ac_2O at room temperature. In a mildly exothermic reaction, a white precipitate separated. After several hours, the mixture was evaporated to dryness and the residue dissolved in H_2O. The H_2O solution was cooled in ice and made basic with 5% aqueous NaOH, and the solid base was extracted into C_6H_6. Upon evaporation, the washed C_6H_6 extract yielded 2.2 g (96%) of white crystals, mp 177–180°. The analytical sample from a previous experiment melted at 179–181° after repeated recrystallizations from MeCN. *Anal.* ($C_{22}H_{21}N_2O_2$) C, H.

Acknowledgment.—The authors wish to thank K. B. Streeter, Y. C. Lee, and their staff for the microanalytical data, W. R. McGaughran, and E. L. Cresson for the spectroscopic measurements, and Dr. N. R. Trenner for his help in the interpretation of the nmr spectra. We are also indebted to Dr. L. M. Halpern for the pharmacological data.

(9) Tlc of the oxime showed a major component of R_f 0.50 and a trace minor component of R_f 0.45 (fluorescent silica gel, $CHCl_3$–MeOH–concentrated NH_4OH, 60:8:1); its stereochemical identity was not determined.