spontaneously rose to about 80°; this temperature was maintained for 10 min by application of heat. The resulting solution was poured onto crushed ice (1 kg) and neutralized with NH_4OH. The product was separated by filtration, dried, and recrystallized; the yield was 14.2 g.

3. 3-Aminopyrazinecarbonitriles (IV). Method A. 3-Amino-6-chloropyrazinecarbonitrile (IVd).—A solution of IIId (4.0 g, 0.02 mole) in 2.5% HCl (100 ml) was stirred and heated on a steam bath for 10 min. The product began separating during the heating; after cooling, the mixture was filtered, dried, and recrystallized.

Method B. 3-Amino-5-dimethylamino-6-chloropyrazinecarbonitrile (IVj).—A solution of IVa (10.0 g, 0.05 mole) in DMSO (50 ml) was stirred and treated with 25% aqueous Me_2NH (20 ml). The mixture was heated at 65° for 15 min and poured into H_2O (150 ml). The precipitate which separated was removed by filtration, washed with H_2O, dried, and recrystallized.

For the synthesis of related compounds, the pure liquid or gaseous amines were used.

4. N-Amidinopyrazinecarboxamidines (VII). Method A. N-Amidino-3-aminopyrazinecarboxamidine (VIIa).—3-Aminopyrazinecarbonitrile[6] (2.2 g, 0.018 mole) was added to HCl (10 g) in EtOH (100 ml), and the mixture was allowed to stand overnight. The imino ether hydrochloride (V) which separated was removed by filtration and dried, mp 205° dec; it was used in the following reaction without purification or characterization.

A solution of guanidine in MeOH was prepared by dissolving Na (0.92 g, 0.04 g-atom) in MeOH (50 ml), adding guanidine hydrochloride (4.0 g, 0.04 mole), and stirring for 15 min. Compound V was added, and within a few minutes a solid began to separate. After 2 hr, the solid was collected on a filter, suspended in H_2O, and dissolved by adding dilute HCl. Precipitation of the product with dilute NaOH gave VIIa.

Method B. N-(2-Imidazolin-2-yl)-2-amino-6-chloropyrazinecarboxamidine (VIIc). Step 1. Methyl 3-amino-6-chloropyrazinethiocarboximidate (VI).—CH_3SH (2.5 g, 0.053 mole) was admitted below the surface of EtOH (100 ml) containing 5% NaOH (2 drops). The solution was stirred, IVd (5.0 g, 0.032 mole) was added, and the mixture was heated to effect solution. After stirring at room temperature for 15 min, H_2O (100 ml) was added. The precipitated VI was isolated (6.2 g, 95%) and twice recrystallized from EtOH to give pure VI, mp 192–194° dec. *Anal.* ($C_6H_7ClN_4S$) C, H, N.

Step 2. VIIc.—Na (0.46 g, 0.02 g-atom) was dissolved in MeOH (50 ml); 2-amino-2-imidazoline·HCl (2.44 g, 0.02 mole) was added, and the solution refluxed for 15 min. The NaCl was removed by filtration, the filtrate was treated with VI (2.0 g, 0.01 mole), and the mixture was refluxed for 30 min. After cooling, the product that separated was removed by filtration, washed with water, dried, and purified by reprecipitation.

Method C. N-Amidino-3-amino-5-dimethylamino-6-chloropyrazinecarboxamidine (VIIb).—Na (460 mg, 0.02 g-atom) was dissolved in *i*-PrOH (50 ml), guanidine·HCl (1.91 g, 0.02 mole) was added, and the mixture was refluxed for 30 min. After cooling, IVj (3.95 g, 0.02 mole) was added, and the solution was evaporated *in vacuo* to a volume of 10 ml. After standing at 25° for 2 hr, H_2O (100 ml) was added; the precipitate that formed was removed by filtration and purified by reprecipitation.

5. 2,4-Diaminopteridines (VIII). 2,4-Diamino-6-chloropteridine (VIIIc).—Na (920 mg, 0.04 g-atom) was dissolved in MeOH (50 ml), guanidine·HCl (4.0 g, 0.043 mole) was added, and the mixture was refluxed for 30 min. After filtration, the filtrate was cooled and treated with IVd (2.0 g, 0.013 mole); the mixture was refluxed for 30 min. Upon chilling, VIIIc (1.9 g, 75%) separated. The product was removed by filtration and purified by reprecipitation.

6. Other Syntheses. 3-Amino-6-chloropyrazinethiocarboxamide (X).—A suspension of VI (2.0 g, 0.01 mole) in pyridine (20 ml) was stirred, and a steam of H_2S gas was admitted below the surface of the solvent for 2 hr. The solvent was evaporated *in vacuo* and the residual yellow solid was recrystallized from C_6H_6; yield 1.8 g (98%), mp 193–195°. *Anal.* ($C_5H_5ClN_4S$) C, H, N.

3-Amino-6-chloropyrazinecarboximidic Acid Hydrazone (IX).—To a solution of NH_2NH_2 (1.34 g, 0.042 mole) in EtOH (65 ml) was added IVd (6.5 g, 0.042 mole), and the solution was refluxed for 1.5 hr. After cooling, the precipitate was separated by filtration; yield 5.4 g (69%), mp 168–170°. Recrystallization from EtOH gave material melting at 169–171°. *Anal.* ($C_5H_7ClN_6$) C, H, N.

Antidepressants. Tetrabenazine-Antagonizing Activity in a Series of 5H-Dibenzo[*a*,*d*]cycloheptene-5-propylamines

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A series of 5H-dibenzo[*a*,*d*]cycloheptene-5-propylamine derivatives has been synthesized and studied for tetrabenazine-antagonizing activity. In both the nortriptyline (Ia) and protriptyline (II) series, activity was maximal in compounds with a 10,11 double bond. Nuclear substituents reduced potency in both series. A striking difference in activity between geometric isomers was observed in the two pairs studied. In one pair, demethylation of the tertiary amine that is the more active in blocking conditioned avoidance gives rise to the more potent tetrabenazine antagonist. The primary amine congeners of nortriptyline and protriptyline have reduced activity, relative to the parent compounds.

Demethylation to desipramine is one of the transformations occurring in the metabolism of imipramine.[2,3] Studies in these laboratories[4,5] demonstrated that N-demethylation is involved in the metabolism of amitriptyline.

Sulser, Watts, and Brodie[6] found desipramine to be a potent antagonist of the central effects of reserpine and 2-ethyl-1,3,4,6,7,11b-hexahydro-3-isobutyl-9,10-dimethoxy-2H-benzo[*a*]quinolizin-2-ol. Nortriptyline (Ia) was found to retain the antibenzoquinolizine action of amitriptyline (Ib).[6,7]

(1) To whom inquires should be addressed.

(2) B. Herrmann, W. Schindler, and R. Pulver, *Med. Exp.*, **1**, 381 (1959).

(3) B. Herrmann and R. Pulver, *Arch. Int. Pharmacodynam. Ther.*, **126**, 454 (1960).

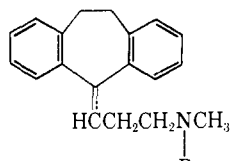
(4) H. B. Hucker and C. C. Porter, *Fed. Proc.*, **20**, 172 (1961).

(5) H. B. Hucker, *Pharmacologist*, **4**, 171 (1962).

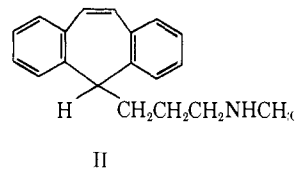
(6) F. Sulser, J. Watts, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **96**, 279 (1962).

(7) V. G. Vernier, F. R. Alleva, H. M. Hanson, and C. A. Stone, *Fed. Proc.*, **21**, 419 (1962).

Meduna, Abood, and Biel[8] first reported desipramine to be an antidepressant in man. Desipramine and nortriptyline were subsequently introduced into clinical use. Definitive comparative clinical studies are lacking, but these secondary amines appear to be essentially equivalent to their tertiary congeners as antidepressants, although there may be differences with respect to side effects.[9-11]



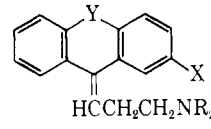
Ia, R = H
b, R = CH_3

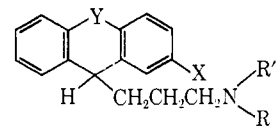


II

Following the early studies on nortriptyline, related compounds were synthesized and studied in the tetrabenazine-antagonism test.[12] This work culminated in the selection of protriptyline (II)[13] for clinical trial. In animal studies, protriptyline was found to be a more potent tetrabenazine antagonist than amitriptyline and to be considerably freer from tranquilizing activity. Studies in man have confirmed predictions that protriptyline would be a potent antidepressant with less sedative properties.[14] The present communication reports the synthesis and structure–activity relationships of compounds in the protriptyline series.

Chemistry.—Demethylation of the tertiary amines III and IV[15] was effected readily by converting them to the cyanamide *via* the von Braun cyanogen bromide reaction,[16] followed by hydrolysis. This method also was used successfully to remove the methyl group from nitrogen in V.





IIIa, Y = CH=CH; R = CH_3; X = Cl
b, Y = CH=CBr; R = CH_3; X = H
c, Y = CH=CH; R = H; X = H
d, Y = CH_2CH_2; R = H; X = H

IVa, Y = CH=CH; R = CH_3; R′ = CH_3; X = H
b, Y = CH=CH; R = CH_3; R′ = CH_3; X = $SO_2N(CH_3)_2$
c, Y = CH=CH; R = H; R′ = H; X = H
d, Y = CH=CH; R = H; R′ = CH_3; X = SO_2CH_3

(8) L. J. Meduna, L. G. Abood, and J. H. Biel, *J. Neuropsychiat.*, **2**, 232 (1961).

(9) H. G. Lafave, B. W. March, A. K. Kargas, and S. Y. Shaffler, *Am. J. Psychiat.*, **122**, 698 (1965).

(10) J. T. Rose, M. R. Leahy, I. C. A. Martin, and T. T. Westhead, *Brit. J. Psychiat.*, **111**, 1101 (1965).

(11) G. L. Klerman and J. O. Cole, *Pharmacol. Rev.*, **17**, 101 (1965).

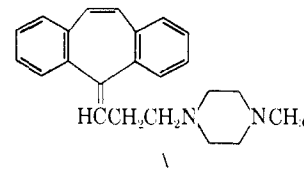
(12) V. G. Vernier, H. M. Hanson, and C. A. Stone in "Psychosomatic Medicine," J. H. Nodine and J. H. Moyer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, p 683.

(13) Vivactil®.

(14) E. A. Daneman, *Psychosomatics*, **6**, 342 (1965).

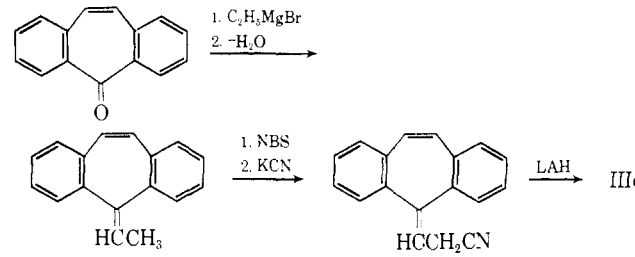
(15) (a) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman, and J. M. Sprague, Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, Abstract 4N; Merck & Co., Inc., Belgian Patents 578,122 (1959), 584,061 (1960); (b) M. Protiva, V. Hnevsova-Seidlova, Z. J. Vejdelek, I. Jirkovsky, Z. Votava, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (c) F. J. Villani, C. A. Ellis, C. Teichmann, and C. Bigos, *ibid.*, **5**, 373 (1962); (d) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

(16) H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).



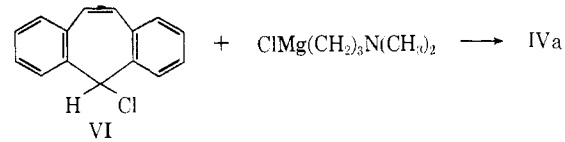
In the case of the 3-chloro derivative IIIa, though the demethylation sequence was carried out on the pure *cis* form, isomerization took place in the course of the hydrolysis step and separation of the geometric isomers was performed on the resulting mixture of secondary amines. The configurations of the secondary amines were established by converting the *trans* isomer to the same cyanamide that was obtained from the *trans* isomer of the tertiary amine pair. There is no evidence of isomerization in the cyanogen bromide reaction. The mixture of geometric isomers of the 10-bromo derivative IIIb was subjected to the demethylation sequence and the geometric isomers of the monomethylamines were separated. The primary amine IIIc was prepared by Scheme I. The primary amine IIId has

SCHEME I



been reported in another communication from these laboratories.[17]

The following route to tertiary amines such as IVa has been found highly satisfactory.[15a]



VI

The synthesis of 3-dimethylsulfamoyl-5H-dibenzo[*a*,*d*]cycloheptene-5-one (VII), the starting material for IVb, was carried out following Scheme II. The tertiary amines of structure IV that were employed as intermediates are shown in Table I.

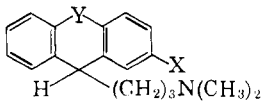
The synthesis of the primary amine IVc was carried out according to Scheme III and the synthesis of the methylsulfonyl compound IVd was carried out following Scheme IV.

The compounds of structures III and IV together with physical properties and analytical data are shown in Tables II and III.

Pharmacology. Test Method.—The potential antidepressant activity of the test compounds was assessed by their ability to antagonize the depressant actions of tetrabenazine in mice. Groups of Carworth CF-1 female albino mice ranging from 18 to 22 g were treated orally with the agent to be tested. Doses were determined using the base weight of the compound; volumes of injection were maintained at 0.01 ml/g of body weight. Drugs were coded and tested blind. Pro-

(17) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 1134 (1962).

TABLE I
INTERMEDIATE TERTIARY AMINES



Y	X	Yield, %	Mp or bp (mm), °C	Formula[d]
CH=CH	H	59	191–193	$C_{20}H_{24}ClN$[a]
CH=CH	Cl	...	153–155	$C_{24}H_{26}ClNO_4$[b]
CH=CH	SCH_3	88[c]	205–215 (0.3)	$C_{21}H_{25}NS$
CH=CH	$SO_2N(CH_3)_2$	54[c]	244–245 dec	$C_{26}H_{31}N_5O_7S$[e,f]

[a] Hydrochloride. [b] Hydrogen maleate. [c] Yield of undistilled base. [d] All compounds were analyzed for C, H, N. [e] Diliturate. [f] C: calcd, 56.00; found, 55.08.

triptyline- and control vehicle treated mice were studied simultaneously for positive and negative controls. Twenty animals were used at each dose level. The appropriate vehicle is indicated in the tables. After 30 min, 2-oxo-3-isobutyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11bH-benzo[*a*]quinolizine (tetrabenazine) was administered (32 mg/kg ip). One hour following injection of test compound, or 30 min following administration of tetrabenazine, the mice were examined for depression of exploratory behavior and for the presence or absence of ptosis. The time of observation following tetrabenazine was found earlier to correspond to the period of maximal depression after tetrabenazine in unprotected mice.[12]

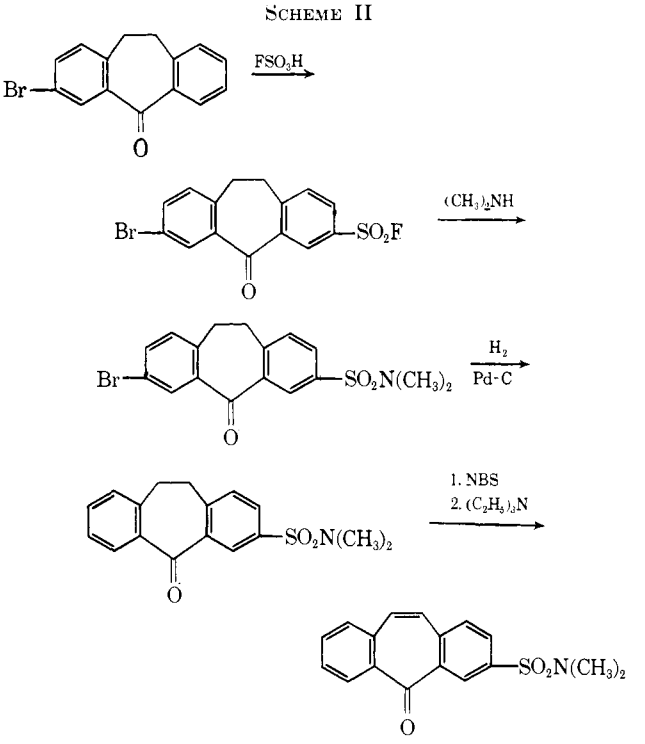
After being placed upon an elevated 20 × 30 cm stainless steel mesh, normal mice "explore" their new environment. The following criteria were adopted to measure this exploratory activity: (a) movement to the edge of mesh, (b) turning of head 45° to the left and right, and (c) walking in a half circle. The preceding phenomena occur within 10 sec of placement in normal mice. Presence of a, b, or c indicates exploratory behavior during the test procedure and is recorded as such. Tetrabenazine abolished this exploratory behavior and, in addition, caused distinct ptosis of the eyelids. Protection, by the test compounds, against these effects of tetrabenazine was adjudged to have resulted if the mouse exhibited any one of the three criteria of exploratory behavior and if the eyelids were not closed by more than one-third. The proportion of mice protected at each dose level was used to estimate ED_{50}'s by the method of Litchfield and Wilcoxon.[18] The data are recorded in Tables II and III.

Structure–Activity Relationships.—In the nortriptyline series (Table II), introduction of a 10,11-double bond increased potency. Nuclear substituents reduced potency. The difference in activity between geometric isomers is noteworthy. The *cis* isomer of the 3-chloro pair is only slightly less active than the unsubstituted compound, while the *trans* form is markedly less potent. This difference is interesting in view of the fact that antiavoidance activity is much stronger in the *cis* than in the *trans* isomer of the corresponding N,N-dimethyl compounds. This observation calls to mind the findings of Bickel, Sulser, and Brodie[19] that

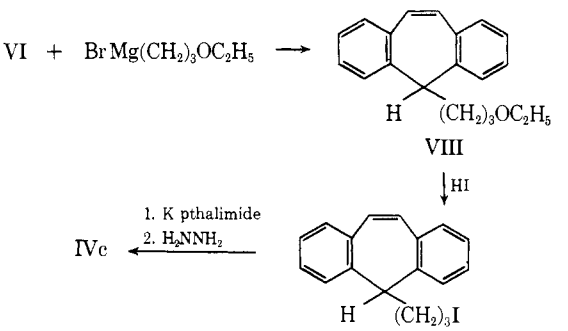
(18) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Therap.*, **96**, 99 (1949).

(19) M. H. Bickel, F. Sulser, and B. B. Brodie, *Life Sci.*, **4**, 247 (1963).

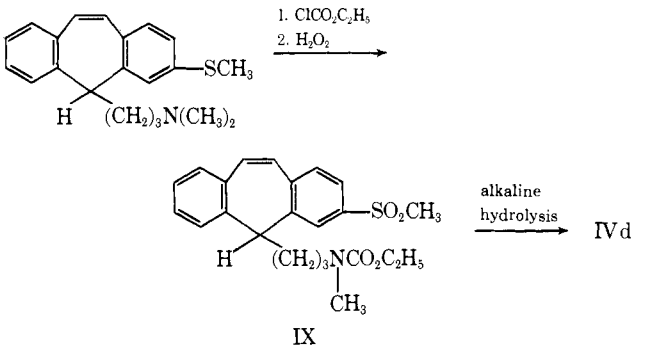
SCHEME II



SCHEME III



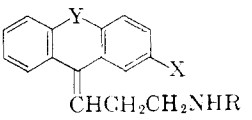
SCHEME IV



demethyltriflupromazine is a more potent antibenzoquinolizine than demethylpromazine. The marked difference in potency between the isomers with a 10-bromo substituent is also noteworthy. The configurations of these isomers are not known.

Protriptyline (II) is clearly the most potent tetrabenazine antagonist found in this study. In this series (Table III) as in the nortriptyline series, saturating the 10,11-double bond or introducing nuclear substituents lowers activity. The primary amine con-

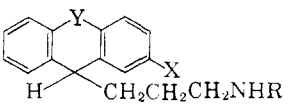
TABLE II



Y	X	R	Yield, %	Mp, °C	Formula[a]	Vehicle[f]	ED50, mg/kg (95% confidence limits)	Rel potency[g]
CH_2CH_2	H	CH_3	51	215.5–217	$C_{19}H_{22}ClN^b$	W	0.7 (0.35–1.4)	0.36
CH=CH	H	CH_3	40	202.5–203.5	$C_{21}H_{21}NO_4{}^c$	W	0.51 (0.37–0.70)	0.49
CH=CH								
α isomer	Cl	CH_3		263–265	$C_{19}H_{19}Cl_2N^b$	W	>32	...
β isomer	Cl	CH_3		165–166	$C_{23}H_{22}ClNO_4{}^d$	M	0.86 (0.52–1.42)	0.29
CH=CBr								
α isomer	H	CH_3		166–167.5	$C_{23}H_{22}BrNO_4{}^d$	W	3.35 (2.1–5.36)	0.075
β isomer	H	CH_3		219 dec	$C_{21}H_{20}BrNO_4{}^e$	M	0.75 (0.56–1.05)	0.33
CH=CH	H	H		177.5 dec	$C_{22}H_{21}NO_4{}^d$	M	3.25 (2.26–4.68)	0.08
CH=CH	H		55	165–166	$C_{30}H_{32}N_2O_8{}^c$	W	>32	...

[a] All compounds were analyzed for C, H, N. [b] Hydrochloride. [c] Hydrogen oxalate. [d] Hydrogen maleate. [e] Dihydrogen dimaleate. [f] W = H_2O, M = methocel. [g] Protriptyline = 1.

TABLE III



Y	X	R	Yield, %	Mp, °C	Formula[a]	Vehicle[e]	ED50, mg/kg (95% confidence limits)	Rel potency[f]
CH=CH	H	CH_3	67	169–170	$C_{19}H_{22}ClN^b$		0.25 (0.17–0.38)[c]	1.0
CH=CH	Cl	CH_3	66	193–195 dec	$C_{19}H_{21}Cl_2N^b$	M	3.0 (1.76–5.71)	0.08
CH=CH	$SO_2N(CH_3)_2$	CH_3	32	133.5–135.5 dec	$C_{20}H_{28}N_2O_6S^d$	W	0.42 (0.27–0.66)	0.6
CH=CH	SO_2CH_3	CH_3	88	114–115 dec	$C_{22}H_{25}NO_6S^d$	W	2.0	0.13
CH=CH	H	H		263–265 dec	$C_{18}H_{20}ClN^b$	W	0.84 (0.53–1.32)	0.3
CH_2CH_2	H	CH_3	77	175–176	$C_{19}H_{24}ClN^b$	W	1.90 (1.31–2.75)	0.13
CH_2CH_2	Cl	CH_3	48	192–193 dec	$C_{19}H_{23}Cl_2N^b$	W	2.35 (1.68–3.29)	0.11
$CH_2CH_2CH_2$	H	CH_3	75	178.5–179.5	$C_{20}H_{26}ClN^b$	W	1.10 (0.8–1.52)	0.23

[a] All compounds were analyzed for C, H, N. [b] Hydrochloride. [c] Values based on 16 studies. [d] Hydrogen oxalate. [e] W = H_2O, M = methocel. [f] Protriptyline = 1.

geners of protriptyline and nortriptyline are active but show diminished potency relative to the parent secondary amines.

Experimental Section[20]

Tertiary Amines III. Geometric Isomers of 3-Chloro-N,N-dimethyl-5H-dibenzo[a,d]cycloheptene-$\Delta^{5,\gamma}$-propylamine (IIIa).—In our hands the α-geometric isomer of IIIa formed a hydrochloride melting at 229.5–230.5°. The β isomer was obtained in the form of the base, mp 74–75°, and as the hydrogen maleate, mp 157–158°. Winthrop, *et al.*,[15d] report 227–229 and 165–166° as the melting points of the hydrochlorides of the α and β forms, respectively. It has been shown that the form we designate β has the *cis* configuration.[21]

10-Bromo-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cycloheptan-5-ol.—10-Bromo-5H-dibenzo[a,d]cyclohepten-5-one (20.0 g, 0.07 mole) dissolved in 40 ml of dry THF was added dropwise to a solution of 3-dimethylaminopropylmagnesium chloride that was prepared from 3-dimethylaminopropyl chloride (17.0 g, 0.14 mole) in 50 ml of THF.[22] The solution was cooled in an ice bath and an atmosphere of N_2 was maintained in the apparatus during the addition. After the addition was complete, the reaction was stirred 2 hr at room temperature and the solvent was distilled under reduced pressure from a bath maintained below 50°. The residue was taken up in C_6H_6 and the mixture was stirred and cooled in an ice bath while adding 25 ml of water dropwise to hydrolyze the excess Grignard reagent. The C_6H_6 layer was separated and the residue was extracted with two additional 50-ml portions of boiling C_6H_6. The combined benzene extracts were washed (H_2O) and the benzene was distilled. After removal of the last traces of solvent under reduced pressure the residue weighed 25.7 g. This product was dissolved in 350 ml of 0.5 *M* citric acid and the solution was extracted (C_6H_6). After rendering the solution alkaline with 10 *N* NaOH, the base was extracted with CH_2Cl_2. After distillation of the solvent the residue was crystallized from hexane to give 20 g (78.5%) of product, mp 118–119.5°. Further recrystallization raised the melting point to 118.5–120°. *Anal.* ($C_{20}H_{22}BrNO$) C, H, N.

10-Bromo-N,N-dimethyl-5H-dibenzo[a,d]cycloheptene-$\Delta^{5,\gamma}$-propylamine.—10-Bromo-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cyclohepten-5-ol (20.0 g, 0.0537 mole) was dissolved in 130 ml of F_3CCO_2H. Trifluoroacetic anhydride (65 ml) was added and the pale yellow solution was heated to refluxing with stirring for 1 hr. The bulk of the solvent then was distilled under reduced pressure, the residue was suspended in water, and the mixture was rendered alkaline with 10 *N* NaOH. The product was extracted with ether. After drying (Na_2SO_4), the ether was distilled and the residue was heated under reduced pressure to remove the last traces. The yellow oily product weighed 18.83 g (99%).

This product is a mixture of geometric isomers. A crystalline hydrogen oxalate was obtained from *i*-PrOH. After two recrystallizations from absolute EtOH–Et_2O, a third from *i*-PrOH,

(20) All melting points were determined with calibrated thermometers in a Thomas–Hoover capillary melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(21) Karst Hoogsteen, *Acta Cryst.*, **21**, A116 (1966).

(22) (a) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953); (b) J. M. Sprague and E. L. Engelhardt, U. S. Patent 2,951,082 (1960); (c) G. E. Bonvicino, H. G. Arlt, Jr., K. M. Pearson, and R. A. Hardy, *J. Org. Chem.*, **26**, 2383 (1961); (d) J. M. Sprague, E. L. Engelhardt, and M. E. Christy, U. S. Patent 2,996,503 (1961).

and another from absolute EtOH–EtOAc, a product, mp 159–164° (effervescence), was obtained. *Anal.* ($C_{22}H_{22}BrNO_4$) C, H, N.

5-[3-(4-Methyl-1-piperazinyl)propyl]-5H-dibenzo[a,d]cyclohepten-5-ol was obtained in 40% yield by condensing 4-methyl-1-piperazinylpropylmagnesium chloride with 5H-dibenzo[a,d]cyclohepten-5-one. The compound melted at 163.5–165.5° after recrystallization from *i*-PrOH. *Anal.* ($C_{23}H_{28}N_2O$) C, H, N.

1-(5H-Dibenzo[a,d]cyclohepten-5-ylidene)propyl-4-methylpiperazine (V).—5-[3-(4-Methyl-1-piperazinyl)propyl]-5H-dibenzo[a,d]cyclohepten-5-ol was dehydrated by the $(CF_3CO)_2O$–CF_3CO_2H procedure. The product, isolated as the dihydrogen dimaleate salt, melted at 187–188° after recrystallization from MeOH–Et_2O. *Anal.* ($C_{27}H_{30}N_2O_4$) C, H, N.

Tertiary Amines IV. N,N-Dimethyl-5H-dibenzo[a,d]cycloheptene-5-propylamine (IVa).—A solution of 5-chloro-5H-dibenzo[a,d]cycloheptene[23] (5.67 g, 0.025 mole), in 25 ml of THF, was added dropwise with stirring to 25 ml of 0.171 *M* 3-dimethylaminopropylmagnesium chloride in THF, while cooling in cold water. Stirring was continued for 2 hr at room temperature and for 15 min at reflux. Gilman's test for Grignard reagent was positive at the end of this time. The bulk of the solvent then was evaporated under reduced pressure below 50°. The residue was dissolved in C_6H_6 (50 ml) and the excess Grignard reagent was hydrolyzed by the dropwise addition of H_2O while cooling in ice. The benzene layer was separated by decantation, the gelatinous precipitate was extracted further with boiling C_6H_6 and the combined extracts were washed (H_2O). The benzene solution then was extracted with two 15-ml portions of 0.05 *M* citric acid, and the acid extract was cooled and rendered strongly alkaline with 10% NaOH. The oily base was extracted (C_6H_6) and the washed benzene extract was evaporated under reduced pressure, employing a film evaporator. The residual yellow oil weighed 5.5 g. The base was taken up in *i*-PrOH–Et_2O and 2.8 ml of 7.68 *N* HCl in absolute EtOH was added. The white crystalline hydrochloride separated, mp 184.5–187.5°, yield 5.35 g. Recrystallization from absolute EtOH–Et_2O gave 4.60 g (59%) of product, mp 187.5–189.5°. Analytical data are recorded in Table I.

Intermediates for Compounds in Table I. Cuprous Methylmercaptide.—Cuprous chloride (40.0 g, 0.4 mole) was added slowly with stirring to 300 ml of concentrated NH_4OH while cooling in ice under N_2. The salt dissolved, giving a dark blue solution which became green and slightly cloudy. EtOH (300 ml) was added and methylmercaptan was passed into the solution while stirring and cooling until the green color had disappeared and a bright yellow suspension resulted. After standing 15 hr the bulk of the mother liquor was siphoned off and the yellow solid was collected by centrifugation in four 250-ml centrifuge bottles. The precipitate was washed by centrifugation with four successive portions of 1:1 concentrated NH_4OH–H_2O and then with four portions of absolute EtOH and dried in a vacuum desiccator. The yield of finely divided yellow solid was 41.4 g (93%). It was used without further purification.

3-Methylmercapto-5H-dibenzo[a,d]cyclohepten-5-one.—3-Bromo-5H-dibenzo[a,d]cyclohepten-5-one (7.93 g, 0.028 mole), cuprous methylmercaptide (4.01 g, 0.036 mole), quinoline (44.8 ml), and pyridine (4.0 ml) were stirred and heated under reflux in a bath at 200° for 6 hr. The reaction mixture then was poured into a mixture of ice and 6 *N* HCl and extracted with five successive portions of C_6H_6, digesting each portion at boiling for about 15 min. The combined extracts were washed (3 *N* HCl, H_2O) and the solvent was evaporated under reduced pressure. The brown, oily residue weighed 7.41 g. Crystallization from MeOH after boiling with decolorizing carbon afforded 2.77 g of a yellow crystalline product, mp 66.5–67.5°. A brown oil that separated was subjected to evaporative distillation at 146° (0.1 mm) to give 2.65 g of crystalline product, mp 66.5–67.5° after recrystallization from MeOH. *Anal.* ($C_{16}H_{12}OS$) C, H, S.

3-Bromo-10,11-dihydro-7-fluorosulfonyl-5H-dibenzo[a,d]cyclohepten-5-one.—3-Bromo-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (17.0 g, 0.0593 mole) was added in portions with stirring to 100 ml of fluorosulfonic acid at room temperature under N_2.[24] The dark green solution was heated on a steam bath for 6.5 hr without stirring. After cooling, the solution was poured very *cautiously* and with stirring into 1.5 kg of finely crushed ice and the mixture was allowed to stand at room temperature overnight. The brown precipitate was collected, washed (H_2O), dried in a vacuum desiccator over NaOH, and extracted in a Sohxlet extractor with 700 ml of cyclohexane for 16 hr. On cooling, the cyclohexane extract deposited 11.65 g (53%) of dark yellow flakes, mp 148–151°. An analytical sample from another experiment, after repeated crystallizations from cyclohexane and treatment with decolorizing charcoal, was obtained as white flakes, mp 150–152°. *Anal.* ($C_{15}H_{10}BrFO_3S$) C, H, S.

3-Bromo-10,11-dihydro-7-dimethylsulfamoyl-5H-dibenzo[a,d]cyclohepten-5-one.—3-Bromo-10,11-dihydro-7-fluorosulfonyl-5H-dibenzo[a,d]cyclohepten-5-one (2.5 g, 0.00677 mole) was refluxed in a mixture of 30 ml of 25% dimethylamine in H_2O and 30 ml of *p*-dioxane for 3 hr. Solvents were distilled under reduced pressure and the residue was partitioned between C_6H_6 and H_2O. The washed and dried C_6H_6 extract was evaporated to dryness *in vacuo* leaving 2.1 g (76%) of product, mp 142–145°. An analytical sample was prepared by recrystallizations from benzene–hexane and from MeOH; mp 146–148°. *Anal.* ($C_{17}H_{16}BrNO_3S$) C, H, N.

10,11-Dihydro-3-dimethylsulfamoyl-5H-dibenzo[a,d]cyclohepten-5-one.—3-Bromo-10,11-dihydro-7-dimethylsulfamoyl-5H-dibenzo[a,d]cyclohepten-5-one (8.0 g, 0.0203 mole) dissolved in a mixture of 100 ml of absolute EtOH, 70 ml of DMF, and 5 ml of Et_3N was hydrogenated over 600 mg of 10% Pd-C at atmospheric pressure until the absorption of H_2 ceased. The catalyst was filtered off through a mat of diatomaceous earth and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with benzene and the insoluble triethylamine hydrobromide was separated by filtration. Evaporation of C_6H_6 and crystallization of the residual solid from absolute EtOH gave 6.1 g (97%) of product, mp 122–124°. An analytical sample from another experiment had the same melting point. *Anal.* ($C_{17}H_{17}NO_3S$) C, H, N.

3-Dimethylsulfamoyl-5H-dibenzo[a,d]cyclohepten-5-one.—A mixture of 10,11-dihydro-3-dimethylsulfamoyl-5H-dibenzo[a,d]-cyclohepten-5-one (5.6 g, 0.0178 mole), N-bromosuccinimide (3.35 g, 0.0188 mole), and benzoyl peroxide (50 mg) in 75 ml of CCl_4 was stirred and heated to refluxing for 1.5 hr. After cooling, the precipitate was collected, washed on the filter with CCl_4, suspended, thoroughly shaken in H_2O (50 ml), again collected, and dried *in vacuo* at 70°. The white solid 10-bromo derivative (4.1 g), mp 156–158° dec, was stirred and heated to refluxing in a mixture of 50 ml of C_6H_6 and 25 ml of Et_3N for 18 hr. The precipitate of triethylamine hydrobromide was removed by filtration and the filtrate was concentrated under reduced pressure until solid began to separate from the residue. After cooling, the product was collected and dried *in vacuo* at 70°, yield 2.95 g (53%), mp 135–138°. An analytical sample melted at 137–138° after recrystallization from 95% EtOH. *Anal.* ($C_{17}H_{15}NO_3S$) C, H, N.

3-Methylmercapto-5H-dibenzo[a,d]cyclohepten-5-ol.—To a stirred and refluxing solution of 3-methylmercapto-5H-dibenzo[a,d]cyclohepten-5-one (2.5 g, 0.01 mole) in 40 ml of MeOH, a solution of KBH_4 (1.35 g, 0.025 mole) in 10 ml of H_2O containing 2 drops of 40% NaOH was added dropwise. After stirring at reflux for 2 hr, the mixture was cooled in ice, and the product was collected, washed (EtOH), and dried; yield 2.1 g (83%), mp 120.5–122°. Dilution of the methanolic filtrate with H_2O precipitated a second crop of 0.375 g, mp 119–121°. An analytical sample was recrystallized from MeOH, mp 121–122°. *Anal.* ($C_{16}H_{14}OS$) C, H, S.

3-Chloro-5H-dibenzo[a,d]cyclohepten-5-ol was obtained in 87% yield, mp 142.5–143.5°, after recrystallization from absolute EtOH containing 5% of MeOH. *Anal.* ($C_{15}H_{11}ClO$) C, H, Cl.

3-Dimethylsulfamoyl-5H-dibenzo[a,d]cyclohepten-5-ol was obtained in 87% yield, mp 150–152° from EtOH. *Anal.* ($C_{17}H_{17}NO_3S$) C, H, N.

5-Chloro-3-methylmercapto-5H-dibenzo[a,d]cycloheptene.—Dry HCl was passed into a solution of 3-methylmercapto-5H-dibenzo[a,d]cyclohepten-5-ol (18 g, 0.071 mole) in 90 ml of dioxane at 5–10°. The product precipitated during this period and, after the addition of 150 ml of petroleum ether (bp 30–60°), was collected, washed with petroleum ether, and dried in a vacuum desiccator over KOH; yield 16 g (84%), mp 135–138°. Re-

(23) G. Berti, *Gazz. Chim. Ital.*, **87**, 293 (1957).

(24) The reaction vessel was a 300-ml three-necked round-bottom flask equipped with a Teflon-covered magnetic stirring bar and polyethylene inlet and outlet tubes, the latter attached to a polyethylene drying tube, half-filled with anhydrous NaF.

peated recrystallizations from cyclohexane gave a sample for analysis, mp 134–135°. *Anal.* ($C_{16}H_{12}ClS$) C, H.

3,5-Dichloro-5H-dibenzo[*a,d*]cycloheptene was obtained in a yield of 85%, mp 155–157°, from hexane. *Anal.* ($C_{15}H_{10}Cl_2$) C, H, Cl.

5-Chloro-3-dimethylsulfamoyl-5H-dibenzo[*a,d*]cycloheptene crystallized from the reaction mixture analytically pure, mp 139.5–143.5°. *Anal.* ($C_{17}H_{16}ClNO_2S$) C, H, N.

Demethylation of Tertiary Amines. N-Methyl-5H-dibenzo[*a,d*]cyclohepten-5-propylcyanamide.—A solution of N,N-dimethyl-5H-dibenzo[*a,d*]cycloheptene-5-propylamine (3.90 g, 0.0141 mole) in 20 ml of dry C_6H_6 was added dropwise to a stirred solution of BrCN (1.7 g, 0.016 mole) in 15 ml of dry C_6H_6.[25] A yellow second phase separated. After standing overnight, the solvent was evaporated on the steam bath on a film evaporator under reduced pressure, the residue dissolved in 50 ml of CH_2Cl_2. The solution was washed (H_2O, 20 ml of 0.1 *M* citric acid, H_2O). After drying (Na_2SO_4) the solvent was evaporated and the residue was dried on the steam bath under reduced pressure (film evaporator). The yellow oily cyanamide was obtained in a yield of 3.65 g (90%).

In most cases the cyanamide was hydrolyzed without additional purification.

10,11-Dihydro-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylcyanamide was prepared following the foregoing procedure and was obtained in a yield of 85%, mp 70.5–73°. Recrystallization from hexane gave product, mp 73–75°, λ_{max}^{MeOH} 239 mμ (ε 14,419). *Anal.* ($C_{20}H_{20}N_2$) C, H, N. The ir spectrum (KBr) showed a strong maximum at 4.53 μ (cyanamide).

N-Methyl-5H-dibenzo[*a,d*]cycloheptene-5-propylamine (II).—A solution of N-methyl-5H-dibenzo[*a,d*]cycloheptene-5-propylcyanamide (3.65 g, 0.126 mole) in a mixture of AcOH (45 ml), H_2O (30 ml), and concentrated HCl (6 ml) was heated to refluxing for 64 hr. The solution was evaporated to near dryness under reduced pressure, the residue was dissolved in H_2O, and the solution was rendered alkaline with NaOH. The base was extracted (C_6H_6), the extract was washed (H_2O), and C_6H_6 was removed on a film evaporator under reduced pressure. The yellow oily base weighed 3.04 g. It was taken up in *i*-PrOH, a small excess of a solution of dry HCl in absolute EtOH was added, and the solution was diluted with absolute Et_2O. The yield of the white crystalline II·HCl was 2.8 g (74%). Recrystallization from *i*-PrOH–Et_2O furnished material with the properties recorded in Table III.

***cis*- and *trans*-3-Chloro-N-methyl-5H-dibenzo[*a,d*]cyclohepten-$\Delta^{5,7}$-propylamine.**—*cis*-3-chloro-N,N-dimethyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine (2.5 g, 0.00807 mole) was converted to the cyanamide. The product was obtained as a colorless crystalline solid, mp 116–118.5°, yield 77%. An analytical sample melted at 117.5–118.5° after recrystallization from cyclohexane. *Anal.* ($C_{20}H_{17}ClN_2$) C, H, N.

A solution of the cyanamide (2.0 g, 0.00623 mole) in a mixture of AcOH (40 ml), H_2O (26 ml), and concentrated HCl (4 ml) was heated to refluxing with stirring for 18 hr. The solution was evaporated to dryness under reduced pressure, the residue was dissolved in 150 ml of H_2O, and the solution was extracted with three 35-ml portions of C_6H_6. A colorless solid separated and was collected by filtration. This product, mp 181–185°, was recrystallized from absolute EtOH–Et_2O and from *i*-PrOH–Et_2O to give material, mp 183–185° (sintered 179°). This product was converted to the base and then to the hydrogen maleate, yield of 650 mg, mp 160–162°, from absolute EtOH–Et_2O. Further recrystallizations from *i*-PrOH–Et_2O and EtOH–Et_2O gave *cis* 3-chloro-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine hydrogen *maleate*, mp 165–166°.

A mixture of the cyanamide (1.5 g, 0.00467 mole), 16.7 g of KOH, and 25 ml of MeOH was heated to refluxing with stirring for 48 hr. The mixture was diluted (H_2O) and extracted (C_6H_6). After washing (H_2O), the benzene was evaporated under reduced pressure and the residue was taken up in ether. Some insoluble material was removed and the ether was evaporated, leaving 1.19 g of a clear yellow oil. This product was taken up in 12 ml of absolute EtOH, and 1.07 ml of 4.13 *N* dry HCl in EtOH was added. On diluting with Et_2O a crystalline product separated. This material, mp 230–243° dec, weighed 600 mg. Three recrystallizations from absolute EtOH–Et_2O gave 214 mg of *trans* 3-chloro-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine hydrochloride, mp 263–265°.

Proof of Configuration of the Geometric Isomers of 3-Chloro-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine. *trans*-3-Chloro-N-cyano-N-methyl-5H-dibenzo[*a,d*]cyclohepten-$\Delta^{5,7}$-propylamine.—A solution of 379 mg (1.22 mmoles) of *trans*-3-chloro-N,N-dimethyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine in 5 ml of dry C_6H_6 was added to 155 mg (1.46 mmoles) of BrCN in 5 ml of dry C_6H_6. The reaction mixture was stirred overnight at room temperature. After washing (H_2O, dilute citric acid, H_2O), the benzene was dried and evaporated under reduced pressure to give 355 mg of white solid, mp 72–75°, yield 97%. Recrystallization from ether–petroleum ether gave purified material, mp 74–75°. *Anal.* ($C_{20}H_{17}ClN_2$) C, H, N.

Similarly, a solution of 177 mg (0.6 mmole) of *trans*-3-chloro-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine in 3 ml of dry C_6H_6 was added to 40 mg of BrCN (0.38 mmole) in 2 ml of C_6H_6. After stirring overnight, the precipititate of the amine hydrobromide was removed by filtration and the benzene filtrate was worked up. The product consisted of 95 mg of white solid, mp 68–73°. This material proved to be identical with the cyanamide prepared from the *trans* isomer of the tertiary amine as shown by their superimposable ir spectra and mixture melting point which gave no depression.

α and β Isomers[26] of 10-Bromo-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine.—A mixture of 10-bromo-N-methyl-5H-dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylcyanamide (23.3 g, 0.0639 mole), 400 ml of AcOH, 45 ml of concentrated HCl, and 300 ml of H_2O was heated to refluxing for 12 hr. The bulk of the solvent was distilled, the residue was taken up in H_2O (550 ml), and the solution was extracted (C_6H_6). The aqueous layer was made strongly alkaline with NaOH and the base was extracted (C_6H_6). The mixture of geometric isomers was obtained in a yield of 19.2 g (88.5%). This product was dissolved in 100 ml of hot absolute EtOH. A solution of 6.90 g (0.0595 mole) of maleic acid in 40 ml of warm absolute EtOH was added and diluted with 200 ml of absolute Et_2O. The crystalline product that separated was collected and dried. This product, mp 157.5–158.5°, weighed 9.34 g. Three recrystallizations from MeOH–Et_2O afforded a product with a constant melting point of 166–167.5°. This is designated the "α" geometric isomer.

The mother liquors from the first crystallization afforded a second crop of maleate, weighing 1.72 g, mp 152–156°. The mother liquors were evaporated to dryness, the residue was taken up in H_2O, and the solution was rendered strongly alkaline with 10 *N* NaOH. The base was extracted (C_6H_6), the extract was washed (H_2O), and the solvent was evaporated to give 9.7 g of the oily base. This material was combined with a similar product from another experiment, total weight 10.80 g, and dissolved in C_6H_6 (20 ml). The solution was divided into two equal parts, and each portion was applied to a column containing 60 g of alumina (Merck, reagent) in a 2-cm diameter polyethylene tube. The columns had been filled under CCl_4, activated with 75 ml of Me_2CO, and washed with 75 ml of C_6H_6 before applying the material. Each column was eluted with 100 ml of $CHCl_3$, then slit lengthwise, and a strip of filter paper moistened with MeOH was inserted. After drying, the paper strips were examined under uv light and sprayed with Dragendorff's reagent to locate components. The $CHCl_3$ eluate contained 7.51 g of material. There was a zone of Dragendorff-positive material with high fluorescence about one-third of the way down the column. The section below the fluorescent zone was cut out from both columns and eluted with boiling MeOH. Evaporation of the MeOH afforded 1.66 g of a yellow oil. This material showed a single component of R_f 0.2 when subjected to tlc on alumina developed with CH_2Cl_2 containing 5% of *i*-PrOH. A portion was converted to the hydrogen oxalate salt that was crystallized to constant melting point from absolute EtOH. The hydrogen oxalate salt of the β form melted at 219–220° dec.

5H-Dibenzo[*a,d*]cycloheptene-$\Delta^{5,7}$-propylamine (IIIc). 5-Ethyl-5H-dibenzo[*a,d*]cyclohepten-5-ol.—Ethylmagnesium bromide was prepared from 3.64 g (0.15 g-atom) of Mg and 16.4 g

(25) In some experiments a current of nitrogen was swept through the apparatus with the objective of removing methyl bromide in order to avoid formation of the quaternary salt.

(26) These isomers are designated α and β in order of isolation. The configurations are unknown.

(0.15 mole) of EtBr in 175 ml of Et_2O. 5H-Dibenzo[a,d]cyclohepten-5-one (15.5 g, 0.075 mole) was added in portions over 45 min. During this time another 175 ml of ether was added. The mixture was stirred 1 hr at room temperature after the addition was complete, then heated to refluxing for 15 min. The excess Grignard reagent and the Grignard adduct then were hydrolyzed with 500 ml of saturated NH_4Cl. The ether layer was separated, washed (H_2O), and dried (Na_2SO_4). Distillation of the ether left 16.78 g (95%) of a pale yellow oil that crystallized, mp 63–65°. Two recrystallizations from *i*-PrOH–H_2O did not change the melting point. *Anal.* ($C_{17}H_{16}O$) C, H.

5-Ethylidene-5H-dibenzo[a,d]cycloheptene.—5-Ethyl-5H-dibenzo[a,d]cyclohepten-5-ol (13.7 g, 0.058 mole) was added portionwise to 80 ml of AcCl. The solution was heated to refluxing for 1.5 hr. The AcCl then was evaporated under reduced pressure on a film evaporator and the residue was dissolved in C_6H_6. After washing (2 *N* K_2CO_3, H_2O) and drying (Na_2SO_4), the benzene was distilled. The residue was distilled under reduced pressure and the fraction, bp 130–135° (0.02 mm), was collected. The product crystallized to give 7.99 g of an oily solid. Recrystallization from 95% EtOH gave a product, mp 52.8–57.5°. *Anal.* ($C_{17}H_{14}$): C, 93.53; H, 6.47. Found: C, 93.01; H, 6.82.

5-(2-Bromoethylidene)-5H-dibenzo[a,d]cycloheptene.—A mixture of 5-ethylidene-5H-dibenzo[a,d]cycloheptene (10.9 g, 0.05 mole), N-bromosuccinimide (8.9 g, 0.05 mole), benzoyl peroxide (15 mg), and 150 ml of CCl_4 was stirred and heated to refluxing on the steam bath for 4 hr. After cooling, succinimide was filtered off and washed with CCl_4. The combined filtrate and washings were evaporated to dryness under reduced pressure. Crystallization of the residual solid from petroleum ether gave 10.65 g (72%) of product, mp 87.5–89.5°. An analytical sample, after recrystallization from petroleum ether, melted at 89–90°. *Anal.* ($C_{17}H_{13}Br$) C, H, Br.

5-(2-Cyanoethylidene)-5H-dibenzo[a,d]cycloheptene.—A solution of 5-(2-bromoethylidene)-5H-dibenzo[a,d]cycloheptene (7.5 g, 0.025 mole) in Me_2CO (75 ml) was treated with a solution of KCN (5.0 g, 0.077 mole) in 15 ml of H_2O and the mixture was heated to refluxing for 12 hr. The solution was evaporated to dryness under reduced pressure and the residue was partitioned (Et_2O–H_2O). The ethereal layer was separated, washed (H_2O), and dried (Na_2SO_4). Evaporation of the ether under reduced pressure gave an oily solid residue. Trituration with a mixture of petroleum ether–Et_2O (3:1, 40 ml) afforded white crystals, mp 95–101°, yield 4.9 g (81%). Repeated recrystallizations from *i*-PrOH–H_2O and from hexane gave an analytical sample, mp 103–105°. *Anal.* ($C_{18}H_{13}N$) C, H, N.

5H-Dibenzo[a,d]cycloheptene-$\Delta^{5,\gamma}$-propylamine.—Under N_2, $LiAlH_4$ (380 mg, 0.01 mole) was suspended in 15 ml of dry, peroxide-free THF. The mixture was stirred and heated to reflux for 4 hr. After cooling in an ice bath, the mixture was stirred while a solution of 5-(2-cyanoethylidene)-5H-dibenzo[a,d]-cycloheptene (1.21 g, 0.005 mole) in 20 ml of THF was added dropwise over 20 min. The deep red solution was stirred for 1 hr in the cold and then hydrolyzed by the successive dropwise addition of H_2O (0.4 ml), 20% NaOH (0.4 ml), and H_2O (1.0 ml). The granular precipitate was filtered and washed (absolute Et_2O). The combined filtrate and washings were evaporated to dryness under reduced pressure. The residual yellow oily base was dissolved in absolute EtOH and treated with maleic acid in absolute EtOH. Dilution with ether precipitated the hydrogen maleate as white crystals, mp 171–173° dec, yield 0.45 g (25%). Repeated crystallizations from absolute EtOH–Et_2O gave an analytical sample melting at 176.5–177.5° dec. *Anal.* ($C_{22}H_{21}NO_4$) C, H, N.

5H-Dibenzo[a,d]cycloheptene-5-propylamine (IVc). 5-(3-Ethoxypropyl)-5H-dibenzo[a,d]cycloheptene (VIII).—To a stirred solution of the Grignard reagent prepared from 3-ethoxypropyl bromide (6.44 g, 0.0386 mole) and Mg turnings (940 mg, 0.0386 g-atom) in 50 ml of absolute Et_2O, a solution of 5-chloro-5H-dibenzo[a,d]cycloheptene (5.67 g, 0.025 mole) in 50 ml of absolute Et_2O–15 ml of THF was added dropwise over 40 min. A deep yellow color developed, the mixture was warmed to refluxing, and a white gum separated. After stirring for 1 hr at room temperature, the mixture was poured into 300 ml of saturated NH_4Cl and the ether layer was separated. After reextraction of the aqueous layer (Et_2O), the combined organic extracts were washed (H_2O), dried (Na_2SO_4), and evaporated under reduced pressure. Distillation of the residue gave 4.14 g of cloudy yellow oil, bp 140–150° (0.1 mm). The product was dissolved in petroleum ether and refrigerated overnight. After filtration from a trace of white solid, the solvent was evaporated and the residue was redistilled to yield 3.10 g (45%) of clear yellow oil, bp 145–148° (0.1 mm), $n^{25}D$ 1.6086. *Anal.* ($C_{20}H_{22}O$) C, H.

5-(3-Iodopropyl)-5H-dibenzo[a,d]cycloheptene.—With a stream of N_2 passing through the stirred solution, 5-(3-ethoxypropyl)-5H-dibenzo[a,d]cycloheptene (1.6 g, 0.00575 mole) in 9 ml of Ac_2O was heated to 65°. HI (55–58%) (4 ml) was added in 0.5-ml portions keeping the temperature below 80°. When the addition was completed, the mixture was held at 78° for 45 min. After cooling to room temperature, the mixture was poured into 75 ml of ice water and the oily product was extracted (C_6H_6). The benzene extract was washed (H_2O, saturated $Na_2S_2O_3$, H_2O, saturated $NaHCO_3$, H_2O). Distillation of the benzene under reduced pressure left 1.76 g of yellow oil. This material gave a positive test for I^- with alcoholic $AgNO_3$, but the ir spectrum indicated contamination with acetate. The crude product was suitable for subsequent use and no attempt was made to obtain a pure sample.

N-(5H-Dibenzo[a,d]cycloheptene-5-propyl)phthalimide.—A solution of crude 5-(3-iodopropyl)-5H-dibenzo[a,d]cycloheptene (1.76 g, 0.0049 mole) in 10 ml of DMF was stirred with potassium phthalimide (925 mg, 0.005 mole) at 90° for 45 min. The cooled mixture was diluted with 25 ml of $CHCl_3$ and poured into 50 ml of H_2O. The aqueous layer was separated and extracted with two 25-ml portions of $CHCl_3$, and the combined $CHCl_3$ extracts were washed (H_2O, 1% NaOH, H_2O) and dried (Na_2SO_4). Evaporation of the $CHCl_3$ under reduced pressure left an oily solid which was freed from oil by trituration with 15 ml of 1:1 ether–petroleum ether. The yield of white solid, mp 123–126°, was 900 mg (48%). An analytical sample from another experiment melted at 125.5–131.5° after recrystallization from *i*-PrOH; λ_{max}^{EtOH} 292 mμ (ε 6002). *Anal.* ($C_{26}H_{21}NO_2$) C, H, N. The ir spectrum (KBr) showed strong maxima at 5.62 and 5.85 μ (CO).

5H-Dibenzo[a,d]cycloheptene-5-propylamine.—A solution of N-(5H-dibenzo[a,d]cycloheptene-5-propyl)phthalimide (2.15 g, 0.0054 mole) in 50 ml of boiling 95% EtOH was treated with 0.6 ml of 100% hydrazine hydrate and refluxing was continued for 2 hr. The solution was cooled in an ice bath and acidified to pH 2 with concentrated HCl. The voluminous precipitate of phthalhydrazide was separated by filtration and washed with two 4-ml portions of cold 95% EtOH. The filtrate was concentrated under reduced pressure to a volume of approximately 5 ml, diluted with 40 ml of H_2O, filtered from a small amount of solid, and concentrated under reduced pressure until solid started to separate. After cooling, the precipitate of the amine hydrochloride was collected to yield 1.35 g (87.5%), mp 254–257° dec. Repeated recrystallizations from *i*-PrOH gave material melting at 263–265° dec, $\lambda_{max}^{H_2O}$ 290 mμ (ε 12,724). The ir spectrum (KBr) showed maxima at 3.4, 6.25, 6.7, 6.95, 7.2, 8.6, 12.45, and 13.15 μ.

N-Methyl-3-methylsulfonyl-5H-dibenzo[a,d]cycloheptene-5-propylamine (IVd).—A solution of N,N-dimethyl-3-methylmercapto-5H-dibenzo[a,d]cycloheptene-5-propylamine (2.05 g, 0.0063 mole) in 12 ml of dry C_6H_6 was added dropwise to a stirred solution of ethyl chloroformate (2.0 ml) in 8 ml of C_6H_6 at room temperature. A viscous yellow oil separated but redissolved when the mixture was heated to refluxing for 3 hr. The cooled solution was diluted with additional benzene and washed (H_2O, 3 *N* HCl, H_2O). Distillation of the benzene under reduced pressure left 2.0 g (83%) of a yellow viscous oil. A solution of this product in 20 ml of AcOH was stirred and cooled to 12°. H_2O_2 (30%, 2 ml) was added dropwise with continued cooling in an ice bath, and the reaction mixture then was stirred for 40 hr at room temperature. After dilution to a volume of *ca.* 100 ml with H_2O, the mixture was extracted (C_6H_6). Evaporation of the washed and dried benzene extract under reduced pressure left 2.15 g (97%) of a yellow viscous oil. This product, the urethan IX, was hydrolyzed to the secondary amine.

Solid KOH (1.6 g, 0.026 mole) was added to a solution of the urethan (2.4 g, 0.00567 mole) in 24 ml of *n*-BuOH. The red-brown mixture was heated to refluxing with stirring under N_2 for 12 hr. H_2O was added to dissolve the insoluble material and the mixture was evaporated to dryness on a film evaporator. The residue was partitioned between C_6H_6 and H_2O, the benzene layer was separated, and the aqueous layer was extracted further (C_6H_6). The combined benzene extracts were extracted with 35 ml of 0.5 *M* citric acid in two portions. The acid extract was cooled in ice and made basic with 40% NaOH. The product was extracted (C_6H_6), the extract was washed (H_2O), and C_6H_6 was

evaporated under reduced pressure on a film evaporator. The residual yellow oily base weighed 1.2 g (64%). The base (1.1 g) was converted to the hydrogen oxalate salt that crystallized from absolute EtOH–absolute Et_2O (15 ml each) in a yield of 1.4 g, mp 114–119° dec. Further recrystallization from EtOH–Et_2O gave an analytical sample, mp 114–115° dec.

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Synthesis and Central Nervous System Depressant Activity of New Piperazine Derivatives. I

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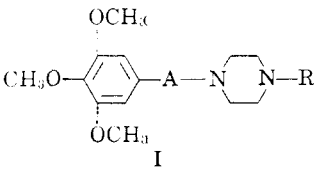
Fifty-two N^1,N^4-disubstituted piperazine derivatives, in which the N^1 substituents are 3,4,5-trimethoxybenzoyl or 3,4,5-trimethoxybenzoylalkyl and the N^4 substituents are methyl, 2-(2′-hydroxyethoxy)ethyl, cyclohexyl, benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, 2-phenethyl, phenyl, chloro- or methoxyphenyl, tolyl, 2,6-xylyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl groups, have been synthesized and screened for CNS activity. The majority of the compounds produced CNS depressant effects as shown by gross observation of intact animals and confirmed by motor activity studies and in some cases by conditioned-avoidance behavior.

In the search for better CNS drugs, the synthesis and screening of compounds having a 3,4,5-trimethoxyphenyl group as an essential moiety have given encouraging results.[2-4] A considerable amount of literature has established the CNS activity of compounds containing a piperazine moiety.[5] A number of 3,4,5-trimethoxybenzamides,[6] and 3,4,5-trimethoxyacetophenone[7] have been reported to possess CNS depressant or tranquillizing activity. Recently, Mannich bases of 1-aryl-4-acetyl-5-methylpyrazoles[8] and different acetophenones[9] with N-substituted piperazines have been reported to have good sedative–tranquillizing activity. The butyrophenone derivatives of the general formula N^1-(aroylalkyl)-N^4-(substituted)piperazines[10] have also been studied, one of which, N^1-[γ-(*p*-fluorobenzoyl)propyl]-N^4-(*o*-methoxyphenyl)piperazine (haloanisone),[11] is at present undergoing clinical trials. Accordingly, the synthesis of the compounds having general formula I was undertaken.



I

A = CO, $COCH_2$, $COCH_2CH_2$, $CH(OH)CH_2CH_2$, $COCH_2CH_2CH_2$, or $CH(OH)CH_2CH_2CH_2$

R = CH_3, 2-(2′-hydroxyethoxy)ethyl, cyclohexyl, benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, phenethyl, C_6H_5, *o*- or *p*-chlorophenyl, *o*-, *m*-, or *p*-methoxyphenyl, *o*-, *m*-, or *p*-tolyl, 2,6-xylyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl

Chemistry.—The requisite N-monosubstituted piperazines were prepared according to literature methods.[12] N-Alkyl-, N-cycloalkyl-, N-aralkyl-, and N-hetero-

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