assigned a score of 6. Analgetic activity was evaluated employing a hot wire analgetic apparatus at 50°.[32] Antagonism of pentylenetetrazole (iv infusion of 0.5% solution) induced minimal (clonic) and maximal (tonic) seizures was utilized as a test for anticonvulsant activity.[33] Neuromuscular blocking activity was tested using an inclined wire mesh screen at a 60° angle.[34]

Antihistaminic, anticholinergic, and nonselective antispasmodic activities in vitro were determined utilizing the guinea pig ileum, suspended in Krebs' solution at 37 ± 0.5° and bubbled with 95% O_2–5% CO_2.[2b,35] The LD_{50} and ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[36] Statistical comparisons of test compounds vs. vehicle-treated control animals were carried out employing an analysis of variance followed by a t test or a Mann–Whitney U test.[37] Values are expressed as the mean (95% confidence limits) or mean ± SEM.

References and Notes

(1) The authors gratefully acknowledge support of this work through U.S. Public Health Service Grants NS-10203 from the National Institute of Neurological Diseases and Stroke and MH-22570 from the National Institute of Mental Health. A preliminary account of this work was presented to the Division of Medicinal Chemistry, 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975, MEDI 61.
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Novel Analogs of Tricyclic Psychopharmacological Agents†

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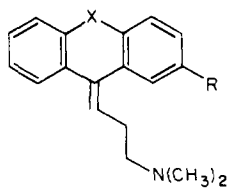
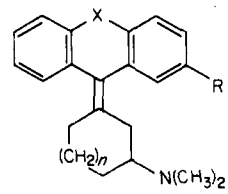
The synthesis of several novel analogs of amitriptyline and chlorprothixene, in a number of which the position of the side-chain nitrogen atom is rigidly fixed with respect to the tricyclic nucleus, is described. The compounds were evaluated for antidepressant-like activity in the Dopa and serotonin interaction tests and for potential antipsychotic activity in the methamphetamine interaction test. 5-(3-Dimethylaminocyclohex-1-enyl)-5*H*-dibenzo[*a*,*d*]cycloheptene (**12**) was about equipotent with imipramine in the Dopa and methamphetamine tests, and 3-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-spiro-6'-3'-methyl-3'-azabicyclo[3.1.0]hexane (**23**) also displayed marked activity in the same tests. Prototype compounds for other ring systems, 3-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylidene)tropane (**16**) and 5-(3-dimethylaminocycloheptylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (**18**), were less active.

A number of theories[1-4] have been proposed to explain the relationship between chemical structure and activity within the class of tricyclic psychopharmacological agents. The observation[5,6] that the antipsychotic activity of chlorprothixene [(*Z*)-**1**] is fifty times greater than that of (*E*)-**1** implies that such activity is critically dependent on the stereochemical relationship between an aromatic ring and the side-chain amino group. Since chlorprothixene and the antidepressant drug amitriptyline (**2**) retain considerable side-chain flexibility, it was of interest to synthesize analogs of these agents, represented by structure

† This paper is dedicated to the memory of Professor Edward E. Smissman.



1, X = S; R = Cl
2, X = $-CH_2CH_2-$; R = H

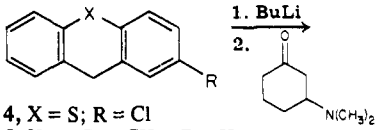


3
X = S, $-CH_2CH_2-$, -CH=CH-
R = H, Cl
n = 1, 2

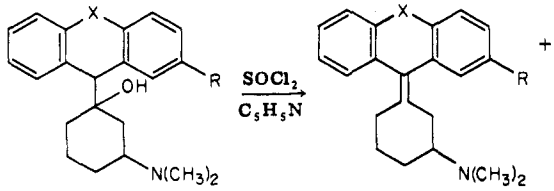
3, in which the spatial relationship between the tricyclic nucleus and the side-chain amino group is more rigidly fixed. Although in one instance the desired chlorprothixene analog 9 could not be separated from its double-bond isomers 11 and 13, and in another case only the endocyclic olefin 12 was isolated, it was considered worthwhile to test these compounds for psychopharmacological activity. In addition, this report describes the synthesis and preliminary pharmacological screening of compounds 16, 18, and the novel spirocyclopropyl derivative 23, prepared as rigid side-chain analogs of amitriptyline.

Chemistry. The most convenient approach to the synthesis of chlorprothixene and amitriptyline analogs such as 9 and 10 involves the addition of cycloalkyl organometallic reagents to appropriate tricyclic ketones to produce benzhydrylic alcohols, which may then be dehydrated to the desired compounds. In the present instance, this method was beset by numerous difficulties, of which the preparation of suitable cyclohexyl organometallics (the required dimethylaminocyclohexyl halide precursors for which were extremely unstable) and the unreactive nature of the ketones were the most important. The alternative route shown in Scheme I, in which cycloalkanols 7 and 8 are the key intermediates, was therefore employed. It was recognized at the outset that such alcohols could undergo dehydration to produce isomeric olefins and that in all likelihood the endocyclic olefins would predominate at the expense of the desired cycloalkylidene isomer. It was hoped, however, that under conditions of kinetic product control substantial amounts of the latter would be formed and that separation would be feasible. Compounds 7 and 8 were produced as shown, utilizing the very unstable amino ketone 6, for which a greatly improved synthetic procedure was developed. A wide variety of reagents and experimental conditions was employed in attempts to dehydrate 7 to afford a maximal yield of cycloalkylidene isomer 9 (see the Experimental Section). The conditions shown in Scheme I gave a product for which NMR analysis indicated a content of 33% of each of the isomeric olefins 9, 11, and 13. The use of thin-layer and column chromatographic techniques, employing a variety of stationary and mobile phases, failed to separate the mixture. Based on the work of Marshall[7] and Kropp,[8] who described the photochemical isomerization of 1-methylcyclohexene to methylenecyclohexane, the mixture of isomers was irradiated in 2-propanol. Unfortunately, extensive decomposition occurred under all experimental conditions tried and recovery of compound 9 was not possible. The mixture of isomers was therefore tested for psychopharmacological activity.

Scheme I

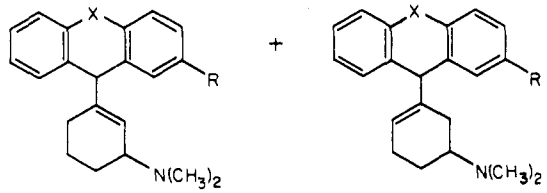


4, X = S; R = Cl
5, X = -CH=CH-; R = H



7, X = S; R = Cl
8, X = -CH=CH-; R = H

9, X = S; R = Cl (+E isomer)
10, X = -CH=CH-; R = H



11, X = S; R = Cl
12, X = -CH=CH-; R = H

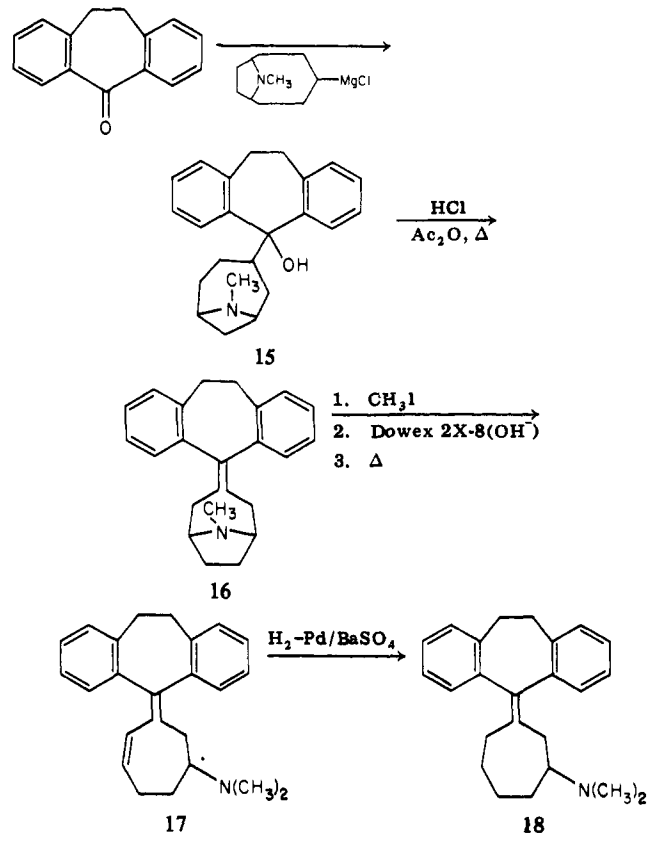
13, X = S; R = Cl
14, X = -CH=CH-; R = H

Dehydration of cycloalkanol 8 (Scheme I) also afforded a 2:1 mixture of endo- and exocyclic olefins, with isomers 12 and 14 predominating. In this case, a single isomer was separated from the mixture by fractional crystallization of the maleate. Comparison of the NMR spectrum of this base with that of N,N-dimethylamino-2-cyclohexene, prepared by the method of Willstatter and Hatt,[9] permitted its structural assignment as endocyclic olefin 12.

All attempts to produce the 10,11-dihydro analog of 8 failed, apparently because the benzylic protons at C-10 and C-11 in the dihydro analog of 5 are sufficiently acidic to interfere with successful completion of the addition reaction with amino ketone 6. Attempts to reduce the 10,11 double bond in compounds 8 and 12 were also unsuccessful.

Synthesis of 18 was accomplished as shown in Scheme II. Grignard addition and subsequent dehydration were patterned after the method of Engelhardt[10] and the

Scheme II



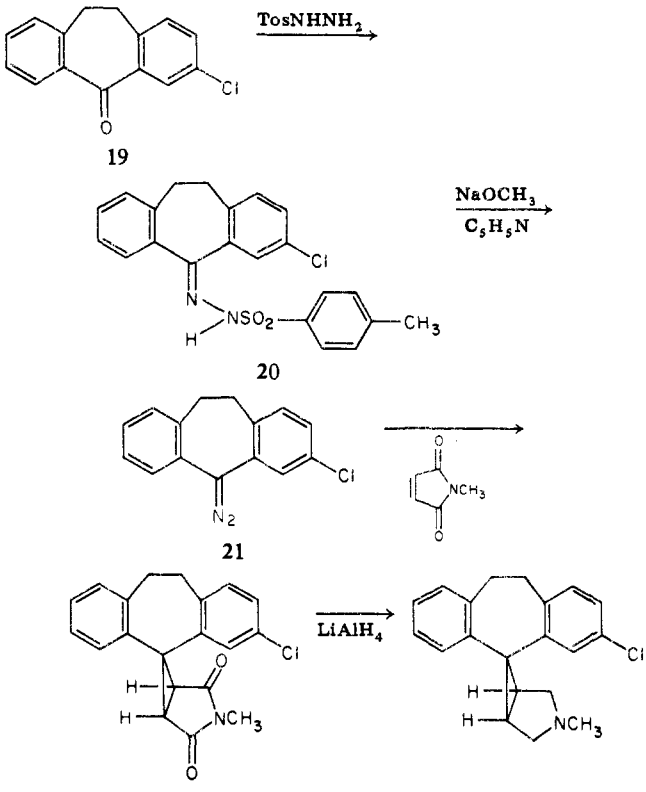
15

16

17

18

Scheme III



Hofmann elimination utilized the basic method of Humber.[11] As tetrasubstituted olefins are not normally reduced under atmospheric pressure in the presence of 5% palladium on a carrier, whereas disubstituted olefins are,[12] selective reduction of 17 to 18 presented no difficulty.

Scheme III was employed for the synthesis of the spirocyclopropyl derivative 23. Preparation of diazo compound 21 was carried out in two steps according to the procedure of Moritani.[13] Addition of *N*-methylmaleimide afforded first the intermediate pyrazolone and then the imide 22 which, owing to its poor solubility in solvents suitable for $LiAlH_4$ reductions, was reduced using the Soxhlet extraction procedure of Blicke.[14]

Pharmacology. The activity of the compounds in this study as potential antidepressant or antipsychotic agents was evaluated by the methods described below.

a. Dopa Interaction Studies in Mice (Potential Antidepressant Activity). The test[15] consists of a potentiated motor response in mice pretreated with a low dose of a monoamine oxidase inhibitor (pargyline, 40 mg/kg, po) and a challenging dose of DL-Dopa (200 mg/kg). Mice treated with an antidepressant such as imipramine show a maximal reaction with motor activity, jumping, fighting, and squeaking (increased irritability). The responses observed were graded as slight (1), moderate (2), or marked (3). The results of these tests are shown in Table I.

b. Serotonin Interaction Studies in Mice (Potential Antidepressant Activity). Antidepressants such as imipramine potentiate the central effects of serotonin as well as those of dopamine.[16] Mice were pretreated with pargyline (40 mg/kg, po) followed by drug, and then challenged with 5-hydroxytryptophan (100 mg/kg, ip) 1 or 4 hr later. The behavioral effects observed were graded as slight (1), moderate (2), or marked (3) and included tremors, head movements, abducted limbs, and irritability. The results of these tests are shown in Table II.

c. Methamphetamine Interaction Test in Mice (Potential Antipsychotic Activity). The antagonism or potentiation of methamphetamine-induced hyperactivity in mice was evaluated in motor activity chambers equipped with photocells (Lehigh Valley Model No. 1497). Groups of mice were premedicated with the test compound and then administered methamphetamine (3 mg/kg, sc). Three mice were placed in each chamber and a total of nine mice were used per test dose. Changes in motor activity were recorded as counts from the photocells and compared to methamphetamine treated controls. The results of this study are presented in Table III.

These preliminary studies indicate that a number of the test compounds possess psychopharmacological activity. In particular, compound 12 is equipotent with imipramine in the Dopa interaction test designed to measure antidepressant activity. The spirocyclopropane derivative 23, the amitriptyline analog 18, and the mixture of isomers

Table I. Dopa Interaction Studies in Mice[a,b]

Compound	Dose, mg/kg, po	Rating[c]
12	5	1
	10	2
	20	3
	25	3
	100	3
15	25	2
	100	2
16[d]	25	1
	100	2
18	25	2
	100	3
23	25	2
	100	3
9, 11, 13[e]	25	2
	100	3
Imipramine (active std)	5	1
	10	2
	20	3
	25	3
	100	3

[a] Performed as described in the Pharmacology section. In all cases a 4-hr pretreatment time was employed. [b] For each dose four mice were used. [c] See Pharmacology section for definition of ratings. [d] Preliminary toxicological screening indicates approximate acute LD_{50} of 30–100 mg/kg ip and 100–300 mg/kg po. [e] Mixture of isomers.

Table II. Serotonin Interaction Test in Mice[a,b]

Compound	Dose, mg/kg, po	Rating[c] 1 hr	Rating[c] 4 hr
12	25	1	1
	50	2	2
	100	2	2
16	25	0	0
	50	1	1
	100	2	1
18	25	0	
	50	0	
	100	0	
23	25	0	2
	50	1	2
	100[d]	2	2
9, 11, 13[e]	25	0	
	50	0	
	100	1	
Chlorimipramine (active std)	25	3	2
	50	3	3
	100	3	3

[a] See footnote *a*, Table I. [b] For each dose three mice were used. [c] See footnote *c*, Table I. [d] Drug-induced 3+ tremors at 1 and 4 hr; see Pharmacology section. [e] See footnote *e*, Table I.

Table III. Methamphetamine Interaction Studies in Mice[a,b]

Compound	Dose, mg/kg, po	Photocell counts, mean ± SE	% change
Methamphetamine	3 (sc)	18,353 ± 631	
12	50	14,071 ± 1,304	23[c]
23	50	12,988 ± 181	29[c]
9, 11, 13[d]	50	17,941 ± 483	2
Methamphetamine	3 (sc)	20,878 ± 1,837	
15	50	18,601 ± 1,123	11
16	50	18,002 ± 1,649	14
18	50	18,478 ± 1,079	11
Imipramine (active std)[e]	10		19[c]
	20		32[c]

[a] See footnote a, Table I. [b] For each dose nine mice were used. [c] Significant at $p < 0.05$. [d] See footnote e, Table I. [e] Chlorpromazine as active standard had $ED_{50} = 5$ mg/kg; all the test compounds were inactive at this dose.

9, 11, and 13 also display moderate activity in this test. Compounds 12 and 23 are also active in the serotonin interaction test although, unlike chlorimipramine, neither elicits a full response over the dose range used. In the methamphetamine test for potential antipsychotic activity, 12 and 23 are about equipotent with imipramine but considerably less active than chlorpromazine.

Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Elemental analyses were performed on an F and M Model 185 C, H, N Analyzer, University of Kansas. Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Ir spectra were recorded on a Beckman IR-10 or Beckman IR-33 spectrophotometer. NMR spectra were recorded on a Varian T-60 analytical spectrometer using Me_4Si as internal standard and NMR data are reported as δ values (parts per million). Mass spectra were recorded on a Varian Associates CH5 mass spectrometer.

3-Dimethylaminocyclohexanone (6). Anhydrous Me_2NH (110.3 g, 2.46 mol) was condensed into a cooled flask and freshly distilled 2-cyclohexenone (59.1 g, 0.615 mol) was added dropwise to the stirred liquid at 0° over a period of 20 min. The mixture was stirred at 0° for a further 3 hr under an atmosphere of dry N_2. Excess Me_2NH was removed by passing a stream of dry N_2 over the solution at 25°. Last traces of Me_2NH were removed by evacuation of the reaction flask at 0.5 mm for 30 min to afford 86.3 g (quantitative yield) of 6 as a pale yellow, viscous liquid. Anal. ($C_8H_{15}NO$) C, H, N.

2-Chloro-9-(1-hydroxy-3-dimethylaminocyclohexyl)-thioxanthene (7). To a stirred solution of 2-chlorothioxanthene (4, Aldrich) (9.05 g, 0.039 mol) in 250 ml of Et_2O was added a 1.58 *M* solution of *n*-BuLi (25.3 ml, 0.04 mol). After 10 min, 6 (5.60 g, 0.04 mol) in 50 ml of Et_2O was added dropwise to the stirred reaction mixture. After stirring for 2 hr, H_2O was added and the Et_2O solution was separated and extracted with 5% HCl. The aqueous solution was basified with 20% NaOH and extracted with Et_2O. The Et_2O solution was dried (K_2CO_3), filtered, and concentrated in vacuo. Chromatography of the residue on a column of neutral alumina (activity grade III), using 10% Et_2O–hexane as the eluting solvent, afforded a yellow gum which, upon trituration with Et_2O, gave 4.32 g (29.7%) of 7, mp 125–128°. Anal. ($C_{21}H_{24}ClNOS$) C, H, N.

Dehydration of 7.[17] A solution of $SOCl_2$ (1.78 ml, 0.025 mol) in 15 ml of CH_2Cl_2 was added dropwise during 15 min to a stirred solution of 7 (4.00 g, 0.011 mol) and pyridine (6.0 ml, 0.075 mol) in 50 ml of CH_2Cl_2 at 0°. The mixture was stirred at 0° for a further 2 hr. After washing with 50 ml of 3% HCl, followed by 50 ml of 2% NaOH, the CH_2Cl_2 solution was dried (K_2CO_3), filtered, and concentrated in vacuo to give 4.10 g of an amber gum: NMR ($CDCl_3$) δ 7.40–7.00 (m, 7, ArH), 5.00 (m, ~0.66, olefinic protons of 11 and 13), 4.48 (m, ~0.66, benzylic protons of 11 and 13), 3.01 [m, ~0.33, C*H*$N(CH_3)_2$ of 13], 2.45–0.75 (m, ~6.5, CH_2 of 9, 11, and 13), 2.15 and 2.11 [d, 6, $N(CH_3)_2$].[18] The maleate was prepared by mixing a solution of the crude product (1.43 g, 0.004 mol) in 3 ml of warm THF with maleic acid (0.47 g, 0.004 mol). The THF was removed and the residue was recrystallized (THF–Et_2O) to afford a white solid, mp 136.5–138°. Anal. ($C_{25}H_{26}ClNO_4S$) C, H, N. NMR integration indicated the product to contain the maleates (33% each) of the isomers 9, 11, and 13.

5*H*-Dibenzo[*a*,*d*]cycloheptene (5). A mixture of 5*H*-dibenzo[*a*,*d*]cycloheptenone (Aldrich) (7.0 g, 0.034 mol) and Al(*i*-PrO)$_3$ (20.0 g, 0.10 mol) was heated to 250°. Any liquid was allowed to distil and the residual solid was maintained at 250° for 10 min. The mixture was cooled to room temperature, treated with 28 ml of 12 *N* HCl in 60 ml of H_2O, and shaken for 1 hr and the remaining solid was collected and dried. Recrystallization (Me_2CO–EtOH) gave 3.5 g (54%) of 5, mp 130–133° (lit.[19] mp 123–128°).

5-(1-Hydroxy-3-dimethylaminocyclohexyl)-5*H*-dibenzo-[*a*,*d*]cycloheptene (8). To a stirred solution of 5 (32.6 g, 0.17 mol) in 400 ml of THF was added a 1.9 *M* solution of *n*-BuLi (89.5 ml, 0.17 mol). The solution was stirred for 10 min, then 6 (24.9 g, 0.17 mol) was added dropwise. After stirring for a further 10 min, the reaction mixture was treated with 10% NH_4Cl, the organic layer was separated, and the solvent was removed in vacuo. The residue was extracted with Et_2O and the resulting solution was worked up as described for 7. Crystallization of the crude product (EtOAc) yielded 13.87 g (24.5%) of 8, mp 147–148°. Anal. ($C_{23}H_{27}NO$) C, H, N.

5-(3-Dimethylaminocyclohex-1-enyl)-5*H*-dibenzo[*a*,*d*]-cycloheptene (12). This was prepared from 8 (2.0 g, 0.006 mol) using the procedure described for the dehydration of 7. The NMR spectrum ($CDCl_3$) of the crude product was similar to that obtained for the dehydration products of 7,[18] integration indicating a composition of ~33% of each of the isomers 10, 12, and 14. The maleate was prepared by adding a warm solution of the crude product (0.42 g, 0.0013 mol) in 3 ml of *i*-PrOH to a warm solution of maleic acid (0.155 g, 0.0013 mol) in 2 ml of *i*-PrOH. Upon cooling, 0.18 g of a pale-yellow crystalline solid separated. Recrystallization (*i*-PrOH) afforded 0.13 g of 12 maleate, mp 169.5–170°. Anal. ($C_{27}H_{29}NO_4$) C, H, N. The free base, 12, had NMR ($CDCl_3$) δ 7.22 (m, 8, ArH), 6.78 (s, 2, CH=CH), 4.69 (m, 1, C=CH), 4.58 (m, 1, Ar_2CH), 3.08 [m, 1, $CHN(CH_3)_2$], 2.11 [s, 6, $N(CH_3)_2$], 1.75–0.80 (m, 6, CH_2).

5-Tropyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (15). A Grignard reagent was prepared by the addition of a solution of 3-chlorotropane[20] (8.7 g, 0.05 mol) in 50 ml of dry (CaH_2) THF to Mg turnings (5.0 g, 0.205 g-atom), previously activated in 50 ml of dry THF by the addition of EtBr (1.46 g, 0.01 mol) and $BrCH_2CH_2Br$ (3.76 g, 0.02 mol) in the presence of an I_2 crystal. The reaction mixture was refluxed for 5 hr and then cooled to 5–10°. With continuous stirring, a solution of 10,-11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (Aldrich) (6.0 g, 0.029 mol) in 50 ml of dry THF was slowly added. The mixture was stirred for a further 3 hr at 5–10°. The Et_2O solution was decanted and the solvent was removed in vacuo to yield 11.5 g of crude product. This material was treated with H_2O (20 ml), extracted with PhH (3 × 100 ml), concentrated, and chromatographed on a column of neutral alumina (270 g, activity grade III). Elution with 50% PhH–$CHCl_3$ afforded 5.1 g (53%) of 15: mp 183–185°; NMR ($CDCl_3$) δ 2.70 (s, 1, OH); mass spectrum, *m*/*e* 333 (M^+), 315 ($M - H_2O$). Anal. ($C_{23}H_{27}NO$) H, N; C: calcd, 83.1; found, 84.0.

3-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)tropane (16). Dry HCl gas was bubbled for 10 min through a solution of 15 (3.0 g, 0.009 mol) in 15 ml of AcOH. Ac_2O (3.0 g, 0.04 mol) was added and the mixture was heated at 90° for 1.5 hr. After cooling, the mixture was basified with saturated K_2CO_3 solution and extracted with PhH. The combined PhH extracts were dried ($MgSO_4$) and the solvent was removed in vacuo. Crystallization of the residue (EtOAc) gave 16, mp 130–132°. Anal. ($C_{23}H_{25}N$) C, H, N.

The methiodide was prepared by reaction of 16 with excess MeI for 12 hr in refluxing MeOH and was obtained as white spars, mp 279–282°. Anal. ($C_{24}H_{28}NI$) C, H, N.

5-(3-Dimethylaminocyclohept-6-enylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (17). A solution of 16 methiodide (1.25 g, 0.0027 mol) in MeOH–H_2O (35:25) was passed through a column of Dowex-2X-8 ion exchange resin (5.0 g) which had been treated previously with 1 *N* NaOH (75 ml), followed

by washing to pH 7 with H_2O–MeOH (2:1). The eluent was distilled at 95° under reduced pressure and the residual brown oil was chromatographed on a column of neutral alumina (100 g, activity grade III). Elution with 20% $CHCl_3$–hexane afforded **17**, mp 71–72°. Anal. ($C_{24}H_{27}N$) C, H, N.

5-(3-Dimethylaminocycloheptylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (18). A solution of **17** (0.4 g, 0.0012 mol) in 60 ml of EtOH was shaken over 5% $Pd/BaSO_4$ (0.3 g) at 25° and under 1 atm of H_2 pressure. The catalyst was removed by filtration and the solvent was distilled in vacuo to afford **18** as a pale-brown oil.

A solution of **18** (0.54 g, 0.0016 mol) in 10 ml of warm EtOH was added to a solution of maleic acid (0.19 g, 0.0016 mol) in 10 ml of warm EtOH. After chilling, the separated solid was collected to give **18** maleate, mp 139–140°. Anal. ($C_{28}H_{33}NO_4$) C, H, N.

3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (19). *o*-[2-(4'-Chlorophenyl)ethyl]benzoic acid (Aldrich) (50.5 g, 0.19 mol) was slowly added to PPA (250 g) at 90°. The temperature of the reaction mixture was raised to 170° over a period of 2 hr and maintained at this temperature for a further 3 hr. The warm mixture was poured over 1 l. of crushed ice and the resulting oil was extracted with Et_2O. The combined Et_2O extracts were washed with 10% Na_2CO_3 and then with H_2O and dried ($MgSO_4$). The residual oil obtained after removal of the solvent was distilled under vacuum to afford **19**, bp 166° (1.0 mm). The oil solidified on standing: mp 61–62° (lit.[21] mp 62–64°).

3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one *p*-Toluenesulfonylhydrazone (20). A solution of **19** (19.4 g, 0.08 mol), *p*-toluenesulfonyl hydrazide (18.6 g, 0.10 mol), and 12 *N* HCl in 100 ml of EtOH was refluxed for 8 hr. The reaction mixture was cooled and the precipitated white solid (22.8 g) was removed by filtration. Recrystallization (Me_2CO) of the crude product yielded 20.2 g (61.7%) of **20**, mp 185–190°. Anal. ($C_{22}H_{19}ClN_2O_2S$) C, H, N.

3-Chloro-5-diazo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (21). To a solution of **20** (19.0 g, 0.046 mol) in 180 ml of dry pyridine was added NaOMe (2.7 g, 0.05 mol). The solution was heated at 70° with stirring for 2 hr, cooled, poured into 300 ml of cold H_2O, and extracted with hexane. The hexane solution was thoroughly washed with H_2O, dried (K_2CO_3), and filtered. The filtrate was concentrated to ca. 25 ml and chilled. The precipitated solid was collected to afford 6.0 g (51.3%) of **21** as deep-purple crystals: mp 64–66°; ir 2050 cm^{-1} (N≡N stretching). Anal. ($C_{15}H_{11}Cl_2$) C, H, N.

3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-spiro-6'-3'-methyl-3'-azabicyclo[3.1.0]hexane-2',4'-dione (22). A solution of **21** (2.54 g, 0.01 mol) and *N*-methylmaleimide[22] (1.22 g, 0.01 mol) in 50 ml of PhH was refluxed until evolution of N_2 ceased (ca. 30 hr). The solvent was removed in vacuo and the residue was crystallized (EtOAc) to give 2.55 g (75.7%) of **22**, mp 231.5–232.5°. Anal. ($C_{20}H_{16}ClNO_2$) C, H, N.

3-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-spiro-6'-3'-methyl-3'-azabicyclo[3.1.0]hexane (23). A suspension of $LiAlH_4$ (0.5 g, 0.013 mol) in 25 ml of Et_2O was placed in a flask fitted with a Soxhlet extractor and **22** (0.91 g, 0.003 mol) was placed in the extractor thimble. The Et_2O solution was refluxed for 40 hr. Excess $LiAlH_4$ was decomposed by dropwise addition of 10% NaOH and the Et_2O solution was decanted from the granular aluminum salts. The solid was washed with Et_2O and the combined Et_2O solutions were dried (K_2CO_3) and filtered. Removal of the solvent afforded 0.67 g (80%) of **23** as a pale-yellow gum which was converted to the maleate. Recrystallization (*i*-PrOH) gave **23** maleate: mp 185.5–186.5°; mass spectrum *m/e* 309 (M^+ of free amine); NMR ($CDCl_3$) δ 7.45–6.83 (m, 7, ArH), 4.40–2.45 (m, 10, CH_2 and CH), 2.37 (s, 3, NCH_3). Anal. ($C_{24}H_{24}ClNO_4$) C, N; H: calcd, 5.68; found, 6.34.

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(17) The following reagents and conditions were also used in attempts to dehydrate **7** to afford a maximal yield of **9**: HCl–PhH, 25°, 2 hr; HCl–dioxane, 25°, 4 days; *p*-TosCl–pyridine, 25°, 20 hr; Me_2SO, 180°, 14 hr; $POCl_3$–pyridine, 25°, 28 hr; KOH–MeOH, reflux, 2 min; $SOCl_2$–pyridine, −15°, 3 hr; PhCOCl–pyridine, reflux, 24 hr.
(18) These assignments were based on comparison of the NMR spectrum of the crude product with that of *N,N*-dimethylamino-2-cyclohexene:[9] NMR (neat) δ 5.62 (s, 2, −CH=CH−), 3.05 [m, 1, C*H*$N(CH_3)_2$], 2.20 [s, 6, $N(CH_3)_2$], 2.10–1.40 (m, 6, CH_2).
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