[CONTRIBUTION FROM THE AYERST RESEARCH LABORATORIES]

New Psychotropic Agents. Derivatives of Dibenzo[*a*,*d*]-1,4-cycloheptadiene

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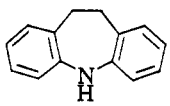
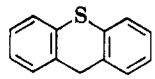
A series of 5-dialkylaminoalkyl-5-hydroxydibenzo[*a*,*d*]-1,4-cycloheptadienes was prepared by alkylating dibenzo[*a*,*d*]-1,4-cycloheptadien-5-ones with basically substituted Grignard reagents. The corresponding 5-dialkylaminoalkyl- and 5-dialkylaminoalkylidenedibenzo[*a*,*d*]-1,4-cycloheptadienes were also synthesized. Other alkylation procedures were adopted in instances where the Grignard method was unsuitable. Many of the compounds possess pharmacological activities characteristic of psychotropic agents. Some of the relationships between structure and activity are briefly mentioned.

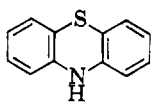
The discovery of the tranquilizing properties of certain phenothiazine derivatives[1] has led medicinal chemists to investigate related tricyclic ring systems. These have included homophenothiazine,[2] phenoxazine,[3,4] phenoselenazine,[3] and the azaphenothiazines.[5] Recently derivatives of dibenzo[*b*,*f*]-azepine (I)[6] and thiaxanthene (II)[7] have proved to be useful psychotropic agents. After consideration of the structural relationships between the latter two ring systems and phenothiazine (III), it appeared that an investigation of derivatives of dibenzo[*a*,*d*][1,4]cycloheptadiene (IV) might lead to compounds with useful pharmacological properties.[8]



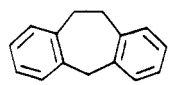
I



II



III



IV

The preparation of dibenzo[*a*,*d*][1,4]cycloheptadien-5-one has been described by several workers.[9] A combination of the various reported methods was used to prepare the substituted dibenzo[*a*,*d*]-[1,4]-cycloheptadien-5-ones. Contrary to one report,[9a] catalytic hydrogenation of benzalphthalide did give the desired 2-(phenethyl)benzoic acid and in satisfactory yields. This procedure was preferred to that in the literature requiring hydriodic acid and was in fact the only method available for the reduction of 3,4-dimethoxybenzalphthalide. The cyclodehydrations of the 2-(phenethyl)benzoic acid were effected in good yields by heating in a polyphosphoric acid medium. Bromination followed by dehydrobromination gave the desired dibenzo[*a*,*e*]-[1,3,5]cycloheptatrien-5-ones in each case. Heating the intermediate bromo compounds at 200° caused a smooth evolution of hydrogen bromide and allowed the introduction of the double bond at the 10,11 position of the ring. Heating with triethylamine was found to be equally satisfactory.

The use of basically substituted Grignard reagents was first developed by Marxer[10] who investigated the alkylation of many aldehydes and ketones with various dialkylaminoalkylmagnesium chlorides. This method was reinvestigated only recently and extended to include cyclic ketones.[11] The dibenzo[*a*,*d*][1,4]cycloheptadien-5-ones and the corresponding trienes were alkylated in this manner with various dialkylaminoalkylmagnesium chlorides and heterocyclic aminoalkylmagnesium chlorides. The tertiary carbinols thus produced are listed in Tables I, II, and III and represented by formula *A*. Although ether, benzene, toluene, and xylene could be employed as reaction solvents, tetrahydrofuran was found to be superior as the Grignard complex did not precipitate. Consequently, the reaction proceeded more rapidly and with better yields. From some of the Grignard reactions investigated a by-product, 5-hydroxydibenzo[*a*,*d*][1,4]cycloheptadiene, was isolated in varying amounts. This reflected the reducing capabilities of the particular Grignard reagents which have been reported to assume greater importance when cyclic ketones are involved.[12] In all the successful Grignard reactions, the basic nitrogen atom and the halide atom were separated by three carbon atoms.

(1) J. Delay, P. Deniker, and J. M. Harl, *Annales Médico-Psychologiques*, **110**, 112 (1952).

(2) R. Jacques, A. Rossi, E. Urech, H. J. Bein, and K. Hoffman, *Helv. Chim. Acta*, **42**, 1265 (1959).

(3) M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, **26**, 190 (1961).

(4) H. Linde, *Arch. Pharm.*, **294**, 45 (1961).

(5) A. R. Gennaro, *J. Org. Chem.*, **24**, 1156 (1959).

(6) P. E. Feldman, *Am. J. Psychiatry*, **115**, 1117 (1959).

(7) W. Kruse, *Am. J. Psychiatry*, **116**, 849 (1960).

(8) After our work had been completed, some of these compounds were disclosed in Belgian Patents **577,057** and **578,122**; Derwent Belgian Patent Reports *58A* and *61B* (1960). Compound *1B*, Table 1, is now marketed as "Elavil"® by Merck & Co. Inc.

(9) (a) W. Treibs and H. J. Klinkhammer, *Chem. Ber.*, **84**, 671 (1951). (b) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951). (c) V. Mychajlyszyn and M. Protiva, *Coll. Czech. Chem. Comm.*, **24**, 3955 (1959).

(10) A. Marxer, *Helv. Chim. Acta*, **24**, 209 (1941).

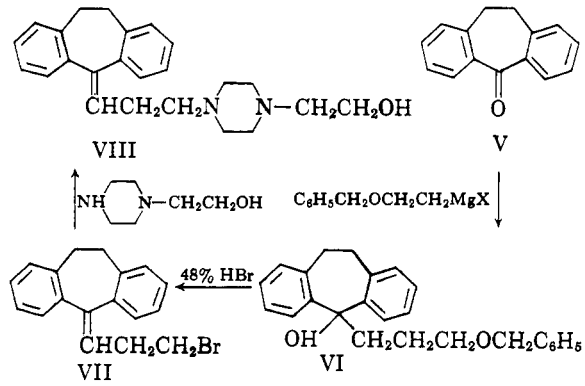
(11) G. E. Bonvicino and R. A. Hardy, U. S. Patent **2,940,969**; June 14, 1960.

(12) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, New York, 1954, p. 149.

Dehydration of the tertiary carbinols gave the 5-dialkylaminoalkylidene derivatives in good yields. These are listed in Tables I, II, and III and represented by formula *B*. The majority of the dehydrations were effected by heating in acetic anhydride. Acetyl chloride in chloroform and ethanolic hydrogen chloride were also used, the latter method being the most convenient. The dehydration of compounds containing one or more substituents in one of the benzene rings could yield isomeric olefins of the classical *cis* and *trans* type. As geometric isomers can differ greatly in their pharmacological properties, efforts were made to isolate the isomers in each case where their existence was indicated. These efforts were successful with compounds *24B* and *27B* but not with *23B*, *25B*, *28B*, and *29B*. (See Tables II and III.) The isomers were arbitrarily designated as α- and β-forms.

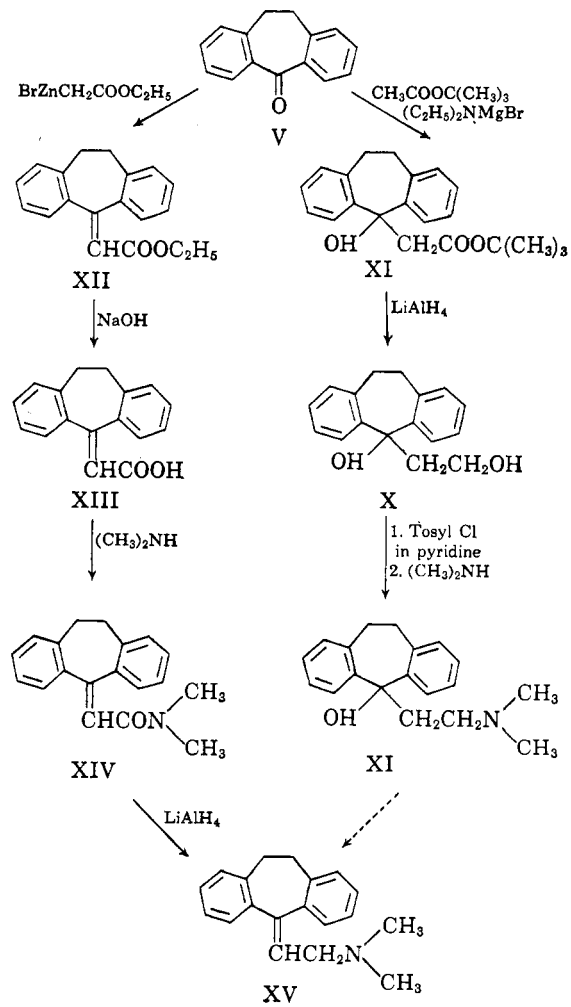
The 5-dialkylaminoalkyldibenzo[*a*,*d*][1,4]cycloheptadienes, represented by formula *C* in Tables I and II, were prepared by reduction of the tertiary carbinols with hydriodic acid and red phosphorus. Catalytic hydrogenation of the olefins proceeded only very slowly and was considered impractical as a preparative method. A direct alkylation of dibenzo[*a*,*d*][1,4]cycloheptadiene at the 5-methylene carbon atom with a dialkylaminoalkyl halide and a suitable alkaline condensing agent offered an alternative route to these compounds. Such alkylations have been successfully performed with related tricyclic ring systems.[13] An attempt to carry out this reaction with dimethylaminopropyl chloride and sodium hydride resulted in complete recovery of the starting material. This lack of reactivity may be explained by the nonplanarity of the dibenzo[*a*,*d*][1,4]cycloheptadiene ring, which does not permit the necessary resonance stabilization of the carbanion. The classical example of this phenomenon is to be found in the unreactivity of the cage-like compound "Triptycene" when compared with triphenylmethane.[14]

Compounds in which the basic side-chain contained a functional group incompatible with the Grignard reagent could not be prepared by the usual method. For such cases, an indirect synthetic route was devised. This is illustrated in the preparation of 5-{3-[4-(2-hydroxyethyl)piperazino]propylidene}dibenzo[*a*,*d*][1,4]cycloheptadiene (VIII). The alkylation of ketone V with 3-benzyloxypropylmagnesium bromide or chloride gave the tertiary carbinol (VI) as well as some 5-hydroxydibenzo[*a*,*d*][1,4]cycloheptadiene, derived from the reduction of the ketone. The tertiary carbinol (VI) was not characterized as such, but was treated with 48% hydrobromic acid to give the 5-(3′-bromopropylidene) compound (VII). This could be used as a



common intermediate with which to alkylate various amines—*e.g.* 1-(2′-hydroxyethyl)piperazine—giving the desired 1-(2′-hydroxyethyl) basic alkylidene derivative (VIII). Compounds *5B*, *6B*, *7B*, *10B*, and *11B* were prepared by this route. (See Table I.) Attempts to alkylate ketone V with the Grignard reagent prepared from either 3-(tetrahydropyran-2-yloxy)propyl chloride or bromide were unsuccessful.

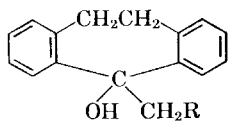
As the dialkylaminoethyl chlorides do not form Grignard reagents,[10] it was necessary to employ other procedures in order to secure compounds



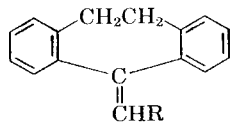
(13) J. A. King, R. I. Meltzer, and J. Doczi, *J. Am. Chem. Soc.*, **77**, 2217 (1955).

(14) R. Noller, *Chemistry of Organic Compounds*, W. B. Saunders Co., Philadelphia, 1957, p. 573.

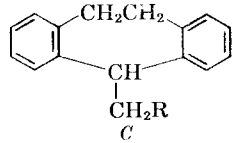
TABLE I. DIBENZO[*a,d*][1,4]CYCLOHEPTADIENES



A



B



C

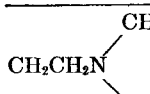
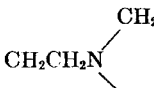
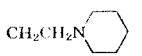
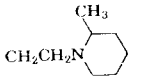
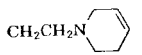
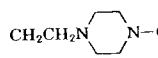
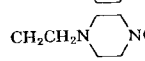
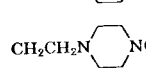
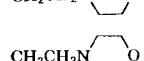
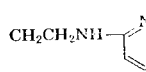
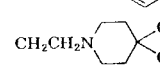
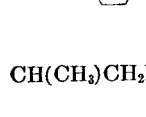
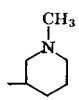
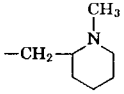
R	Cpd. No.	Salt	M.P.	Recryst. Sol.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
	*1A*	Base	118–120	*a*	60	$C_{20}H_{25}NO$	81.30	81.19	8.53	8.43	4.74	4.77		
	1A	HCl	209–210	*a*	—	$C_{20}H_{26}ClNO$					4.22	4.13	10.69	10.48
	1A	CH_3Br	233 dec.	*gc*	83	$C_{21}H_{28}BrNO$							20.50[m]	20.42
	1B	HCl	197–199	*f*	70	$C_{20}H_{24}NCl$	76.54	76.30	7.71	7.71	4.46	4.23	11.36	11.20
	1C	HCl	185–186	*ad*	53	$C_{20}H_{26}NCl$	76.06	76.28	8.29	8.19			11.28	11.35
	*2A*	Base	92–94	*a*	48	$C_{22}H_{29}NO$	81.71	82.37	9.04	8.88	4.33	4.24		
	2B	HCl	171–173	*f*	63	$C_{22}H_{28}ClN$	77.30	76.85	8.25	8.05	4.10	4.03	10.37	10.35
	2C	HCl	136–138	*ad*	65	$C_{22}H_{30}ClN$					4.07	4.06	10.31	10.38
	*3A*	Base	171–173	*ki*	57	$C_{23}H_{29}NO$	82.34	82.79	8.71	8.46	4.18	4.03		
	3A	HCl	219	*acd*	—	$C_{23}H_{30}ClNO$					3.76	3.86	9.51	9.61
	3B	HCl	225–226	*bd*	81	$C_{23}H_{28}ClN$	78.05	77.80	7.97	7.55	3.96	3.88	10.02	10.07
	3C	HCl	223–224	*bd*	83	$C_{23}H_{30}ClN$	77.62	77.94	8.50	8.15			9.96	10.06
	*4A*	Base	116–118	*aj*	25[n]	$C_{24}H_{32}NO$	82.47	83.12	8.94	8.71	4.01	4.06		
	4B	HCl	229	*bd*	73	$C_{24}H_{30}ClN$	78.34	78.57	8.22	8.05	3.81	3.79	9.64	9.88
	*5B*	HCl	198–200	*ad*	59	$C_{23}H_{26}ClN$	78.50	78.21	7.45	7.24	3.98	4.04	10.08	10.02
	*6B*	2HCl	248–249	*cd*	54	$C_{23}H_{30}Cl_2N_2$	68.16	67.66	7.46	7.38	6.91	6.78	17.50	17.72
	*7B*	2HCl	261–262 dec.	*c*	61	$C_{24}H_{32}Cl_2N_2O$	66.21	66.12	7.41	7.43	6.44	6.43	16.29	16.30
	*8B*	Dimaleate	184–186 dec.	*fl*	74	$C_{34}H_{40}N_2O_{10}$	64.14	64.37	6.33	6.24	4.40	4.30		
	8B	2HCl	242 dec.	*aed*	—	$C_{26}H_{34}Cl_2N_2O_2$	65.39	65.34	7.18	7.19			14.85	14.79
	*9A*	Base	154–156	*h*	50	$C_{22}H_{27}NO_2$	78.30	78.30	8.07	7.80	4.15	4.13		
	9A	HCl	209–210 dec.	*acd*	—	$C_{22}H_{28}ClNO_2$					3.75	3.68	9.48	9.76
	9B	HCl	232–234	*bd*	77	$C_{22}H_{26}ClNO$	74.25	74.08	7.36	7.44	3.94	3.76	9.96	9.98
	*10B*	Malcate	146–147 dec.	*bd*	30	$C_{27}H_{26}N_2O_4$	73.28	72.98	5.92	5.84	6.33	6.25		
	*11B*	HCl	205–206 dec.	*fe*	47	$C_{32}H_{36}ClNO_2$	76.54	76.14	7.23	7.23			7.06	7.55
	*12A*	Base	148–150	*h*	92	$C_{21}H_{27}NO$	81.51	82.17	8.80	8.47	4.53	4.68		
	12A	HCl	203 dec.	*acd*	—	$C_{21}H_{28}ClNO$					4.05	4.01	10.25	10.50
	12B	HCl	211–212	*ad*	81	$C_{21}H_{26}ClN$	76.93	76.93	8.00	7.84	4.27	4.22	10.81	10.83
	12C	HCl	188–190 dec.	*ad*	92	$C_{21}H_{28}ClN$	76.45	76.65	8.56	8.49			10.75	10.75

TABLE I (*continued*)

R	Cpd. No.	Salt	M.P.	Recryst. Sol.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$\overset{*}{C}H(CH_3)CH_2N(CH_3)_2$	*13A*	Base	140–141[o]	[h]	77[v]	$C_{21}H_{27}NO$	81.51	81.34	8.80	8.68	4.53	4.46		
	13A	− Tartrate	155–156[p]	[b]	—	$C_{25}H_{33}NO_7$	65.34	65.61	7.24	7.21				
	13A	+ Tartrate	182–183[q]	[b]	—	$C_{25}H_{33}NO_7$	65.35	65.16	7.24	7.24				
	13C	HCl	194–195[r]	[a]	68	$C_{21}H_{28}ClN$							10.75	10.80
$\overset{*}{C}H(CH_3)CH_2N(CH_3)_2$	*14A*	Base	140–141[s]	[h]	27[z]	$C_{21}H_{27}NO$	81.51	81.83	8.80	8.71	4.53	4.49		
	14A	+ Tartrate	156–157[t]	[b]	—	$C_{25}H_{33}NO_7$	65.34	65.73	7.24	7.14				
	14A	− Tartrate	184–185[u]	[b]	—	$C_{25}H_{33}NO_7$	65.34	65.18	7.24	7.22	3.05	3.03		
	14C	HCl	194–195[v]	[a]	75	$C_{21}H_{28}ClN$	76.45	76.58	8.56	8.41			10.75	10.74
$C(CH_3)_2CH_2N(CH_3)_2$	*15A*	Base	101–103	[i,j]	48	$C_{22}H_{29}NO$	81.69	81.96	9.04	8.96	4.33	4.27		
	15B	HCl	236–239 dec.	[af]	87	$C_{22}H_{28}ClN$	77.29	77.45	8.25	7.95			10.37	10.38
	15C	HCl	169–171	[bd]	82	$C_{22}H_{30}ClN$	76.83	76.79	8.79	8.71			10.31	10.34
$CH_2N(CH_3)_2$	*16A*	HCl	225–227 dec.	[ced]	61	$C_{19}H_{24}ClNO$	71.89	72.14	7.61	7.32			11.17	11.17
	16B	HCl	213–215	[ad]	49	$C_{19}H_{22}ClN$					4.67	4.53	11.82	12.02
	16C	HCl	199–200	[ed]	82	$C_{19}H_{24}ClN$	75.58	75.97	8.00	7.77			11.74	11.72
$CH_2N\langle\rangle N-CH_3$	*17A*	Base	161–163	[h]	62	$C_{22}H_{28}N_2O$	78.53	79.09	8.39	8.22	8.33	8.68		
	17B	Base	106–108	[h]	—	$C_{22}H_{26}N_2$	82.97	83.13	8.23	8.04	8.80	8.47		
	17C	2HCl	310–313 dec.	[ce]	50	$C_{22}H_{30}Cl_2N_2$	67.19	66.94	7.69	7.44			18.03	18.17
	*18A*	Base	163–164	[b]	78	$C_{22}H_{27}NO$	82.80	82.31	8.47	8.27	4.36	4.37		
	18B	H_2SO_4	261–262 dec.	[ced]	80	$C_{22}H_{27}NO_4S$	65.82	66.04	6.78	6.69	3.49	3.19	7.97[w]	7.94
	18B	$HCl \cdot H_2O$	142–144 dec.	[ad]	—	$C_{22}H_{28}ClNO$	73.82	73.24	7.88	7.59			9.91	9.89
	*19A*	Base	135–136 dec.	[l]	72	$C_{21}H_{25}NO$	82.04	82.57	8.20	8.31	4.56	4.33		
	19A	HCl	221 dec.	[bd]	—	$C_{21}H_{26}ClNO$	73.33	73.52	7.62	7.41	4.07	3.72	10.31	10.55
	19B	Oxalate	191–193 dec.	[ced]	63	$C_{23}H_{25}NO_4$	72.80	72.71	6.64	6.54	3.69	3.58		
	19C	Oxalate	168–169 dec.	[cd]	79	$C_{23}H_{27}NO_4$	72.42	72.49	7.13	6.91	3.67	3.48		
	*20A*	HCl	239 dec.	[cd]	37[x]	$C_{23}H_{30}ClNO$	74.29	74.16	8.13	7.89	3.77	3.59	9.54	9.52
	20A	Base	117–118	[ai]	—	$C_{23}H_{29}NO$	82.34	82.49	8.71	8.65	4.18	4.19		
	20B	H_2SO_4	169–170	[ad]	61	$C_{23}H_{29}NO_4S$	66.49	66.58	7.04	6.75	3.37	3.12	7.70[w]	7.50
	20C	HCl	206–208 dec.	[f]	65	$C_{23}H_{30}ClN$	77.62	77.56	8.50	8.42	3.94	3.86	9.96	9.85
	*21A*	Base	114–115	[h]	55	$C_{21}H_{19}NO$	83.69	84.10	6.35	5.99				
	21A	HCl	178–179	[cd]	—	$C_{21}H_{20}ClNO$	74.69	75.15	5.97	5.95			10.49	10.83
	21C	Base	92–94	[j]	89	$C_{21}H_{19}N$	88.38	88.98	6.71	6.10	4.91	4.98		
	21C	HCl	257–259 dec.	[bd]	—	$C_{21}H_{20}ClN$	78.39	78.03	6.26	6.08			11.02	11.14
	*22C*	· HCl	221–223 dec.	[ad]	24	$C_{21}H_{26}ClN$	76.93	76.90	8.00	8.00	4.27	4.28	10.81	10.94

[a] Isopropyl alcohol. [b] Ethanol. [c] Methanol. [d] Ether. [e] Nitromethane. [f] Acetonitrile. [g] Acetone. [h] Ethyl acetate. [i] Benzene. [j] Hexane. [k] Butanone. [l] Isopropyl acetate. [m] Bromine. [n] A 41% yield of 5-hydroxydibenzo[a,d][1,4]cycloheptadiene was also obtained. [o] $[\alpha]_D$ +246.0° (chloroform). *Note:* All rotations done as 1% solutions. [p] $[\alpha]_D$ +63.5° (methanol). [q] $[\alpha]_D$ +89.0° (methanol). [r] $[\alpha]_D$ −21.4° (water). [s] $[\alpha]_D$ −246.2° (chloroform). [t] $[\alpha]_D$ −65.7° (methanol). [u] $[\alpha]_D$ −90.9° (chloroform). [v] $[\alpha]_D$ −20.8° (water). [w] Sulfur. [x] Reacton product isolated as the hydrochloride. A 9% yield of 5-hydroxydibenzo[a,d][1,4]cycloheptadiene was also obtained. [y] *Via* reaction of optically active Grignard reagent on ketone. [z] *Via* resolution of *12A*.

TABLE II. CHLORINATED DIBENZO[*a,d*][1,4]CYCLOHEPTADIENES

R	Chlorine Position	Cpd. No.	Salt	M.P.	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3 CH_2CH_2N CH_3	2	*23A*	Base	127–128[a]	61	$C_{20}H_{24}NOCl$	72.82	73.28	7.33	7.33	4.25	4.65		
		23B	HCl	195–196[a]	90[b]	$C_{20}H_{22}NCl_3$					4.02	3.76	20.36	20.43
CH_3 CH_2CH_2N CH_3		*24A*	Base	127–128[a]	61	$C_{19}H_{24}NOCl$	72.82	73.28	7.33	7.33	4.25	4.65		
		24B(α)	HCl	235–236[a]	17	$C_{20}H_{23}NCl_2$	68.96	68.47	6.66	6.41			20.36	20.19
		24B(β)	HCl	228–230[c]	15[d]	$C_{20}H_{23}NCl_2$	68.96	68.75	6.66	6.56			20.36	20.53
CH_3 CH_2CH_2N CH_3		*24C*	HCl	186–187[a]	80	$C_{20}H_{23}NCl_2$					4.00	3.78	20.24	20.35
CH_2CH_2N–CH_3	3	*25B*[f]	2HCl	251–253[g]	34	$C_{23}H_{27}N_2Cl_3$					6.37	6.16	24.22	23.99

[a] From isopropyl alcohol. [b] Only one compound was isolated although two geometric isomers are theoretically possible. [c] Purified as an oxalate salt from ethanol. [d] The two possible geometric isomers were isolated and designated α and β. The yield before separation of the mixture was 82%. [e] From isopropyl alcohol–ether. [f] The intermediate alcohol was not purified as it had already partially dehydrated. [g] From ethanol–ether.

containing two carbon atoms between the amino function and the dibenzo[*a,d*][1,4]cycloheptadiene ring. Two different routes were devised to prepare compounds of this type. These are illustrated below in the preparation of 5-(2′-dimethylaminoethylidene)dibenzo[*a,d*][1,4]cycloheptadiene (XV) and 5-(2′-dimethylaminoethyl)-5-hydroxydibenzo[*a,d*][1,4]cycloheptadiene (XI).

Attempts to condense ethyl acetate with ketone V using sodium or lithium amide in liquid ammonia[15] gave mainly unchanged starting material. The condensation was carried out successfully, however, with *t*-butyl acetate and diethylaminomagnesium bromide[16] to give the hydroxy ester (IX), which was reduced by lithium aluminum hydride to the diol (X). A monotosylate was prepared but, because of its instability, it was not characterized. It was allowed to react as such with dimethylamine to furnish the desired amino alcohol (XI).

The ketone (V) was also successfully condensed with carbethoxymethylzinc bromide using a Reformatsky reaction to yield the carbethoxymethylidene derivative (XII). Saponification to the acid (XIII) followed by heating with dimethylamine to form the amide (XIV) with a subsequent reduction by lithium aluminum hydride gave the 5-(2′-dimethylaminoethylidene) derivative (XV). Dehydration of XI in the normal manner would also furnish XV.

As α,α-diphenyl-2-piperidinemethanol[17] and α,α-diphenyl-2-piperidinemethane[18] are active as central nervous system stimulants, it was of interest to investigate analogous compounds (XVII and XIX) derived from dibenzo[*a,d*][1,4]cycloheptadiene. The ketone (V) was alkylated with 2-pyridyllithium to give the 5-hydroxy-5-(2′-pyridyl) derivative (XVI). Attempted catalytic hydrogenation of the heterocyclic ring of XVI in the form of the free base or its hydrochloric or methobromide salts under a variety of conditions could not be accomplished. When, however, the hydroxyl group was removed from XVI in the usual manner by treatment with hydriodic acid and red phosphorous, the pyridine ring of the resulting compound (XVIII) could be reduced to the desired 5-(2′-piperidyl) derivative (XIX). The homologous 5-(2′-piperidylmethyl) compound (*22C*, Table I) was prepared in an analogous manner starting with 2-picolyllithium.

The resolution of a racemic mixture possessing useful pharmacological activity into its optical antipodes has, on occasion, produced compounds whose properties were superior to those of the

(15) W. R. Dunnevant and C. R. Hauser, *J. Org. Chem.*, **25**, 506, 1296, 1693 (1960).

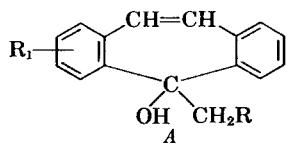
(16) K. Sisido, H. Nozaki, and O. Kurihara, *J. Am. Chem. Soc.*, **74**, 6254 (1952).

(17) F. G. McCarty, C. H. Tilford, and M. G. Van Campen, Jr., *J. Am. Chem. Soc.*, **79**, 472 (1957).

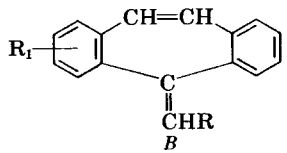
(18) J. Heer, E. Sury, and K. Hoffman, *Helv. Chim. Acta*, **38**, 134 (1955).

TABLE III

DIBENZO[*a,e*][1,3,5]CYCLOHEPTATRIENES



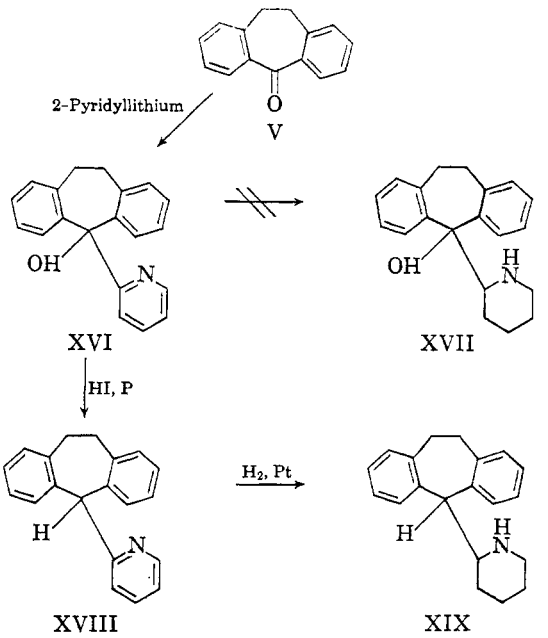
A



B

R	R_1	Cpd. No.	Salt	M.P.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
$CH_2CH_2N(CH_3)_2$	H	*26A*	Base	137–138[a]	62	$C_{20}H_{20}NO$	80.90	82.43	7.90	8.04	4.77	4.47		
		26B	HCl	216–217[a]	30	$C_{20}H_{22}NCl$	77.01	76.54	7.11	7.01			11.37	11.69
$CH_2CH_2N(CH_3)_2$	3-Chloro	*27A*	Base	138–140[a]	47	$C_{20}H_{22}NOCl$					4.27	4.20	10.88	10.87
		27A	H_3PO_4	140 dec.[b]	—	$C_{20}H_{25}NO_5ClP$			7.27	7.12[c]	3.28	2.77	8.32	8.13
		27B(α)	HCl	227–229[d]	34	$C_{20}H_{21}NCl_2$					4.04	3.88	20.47	20.80
		27B(β)	HCl	165–166[e]	9[f]	$C_{20}H_{21}NCl_2$					4.04	3.82	10.23[g]	10.39
$CH_2CH_2N(CH_3)_2$	2,3-Dimethoxy	*28A*	Base	220–222[h]	21	$C_{22}H_{27}NO_3$	74.75	74.69	7.69	7.44	3.96	3.91		
		28B	HCl	92–98[i]	75	$C_{22}H_{26}NO_2Cl$					3.76	3.55	9.53	9.32
$CH(CH_3)CH_2N(CH_3)_2$	3-Chloro	*29A*	Base	151–153[j]	85	$C_{21}H_{24}NOCl$	73.79	74.01	7.07	7.04	4.09	3.80		
		29B	HCl	195–197[k]	39	$C_{21}H_{23}NCl_2$					3.89	3.55	9.84[g]	10.28
CH_2CH_2N(N–CH_3)	3-Chloro	*30A*	Base	130–131[l]	66	$C_{23}H_{27}N_2OCl$					7.31	6.83	9.26	9.07

[a] From isopropyl alcohol. [b] From acetone-methanol. [c] Phosphorus. [d] From isopropyl alcohol–ether. [e] Purified as an oxalate salt from ethanol and as a hydrochloride from ethyl acetate. [f] The two possible geometric isomers were isolated and designated α and β. The yield before separation of the mixture was 85%. [g] Ionic chlorine. [h] From benzene-hexane. [i] Amorphous compound which was purified by several precipitations from methanol-ether. [j] From aqueous acetone. [k] From isopropyl alcohol–ether. [l] From acetone.



racemate. Attempts to resolve 5-(3′-dimethylamino - 2′ - methylpropyl)dibenzo[*a,d*][1,4]cycloheptadiene (*12C*) into its optical antipodes (*13C* and *14C*) by the usual procedures were unsuccessful. Each antipode was finally prepared in an indirect manner and by different routes. The ketone (V) was alkylated with a Grignard reagent derived from optically active (−)3-dimethylamino-2-methylpropyl chloride to give the (+)tertiary carbinol (*13A*). Treatment with hydriodic acid and red phosphorus gave one of the desired antipodes (*13C*). The (−)tertiary alcohol (*14A*) could be obtained by treating the racemic tertiary alcohol (*12A*) with (+)tartaric acid, recrystallizing the resulting salt from ethanol and finally reconverting it to the free base. Hydriodic acid and red phosphorus treatment then gave the antipode (*14C*).

Ultraviolet spectral data were found indispensable in following the course of certain reactions, particularly so when effecting dehydration of the tertiary alcohols which results in a large increase in resonance. Spectral data for some typical compounds are listed in Table IV.

TABLE IV

ULTRAVIOLET SPECTRAL DATA

Compound	Wave Length, Mμ	Molecular Ext. Coeff.
1A Base	264	504
1B HCl	240	16,650
1C HCl	264	655
26A Base	227 (S)	25,200
	295	15,600
26B HCl	226	52,300
	295	12,000

Pharmacological activity. All the compounds listed in Tables I, II, and III have been screened for their pharmacological actions on the central nervous system as well as for their peripheral effects. The detailed results will be reported elsewhere. Compound *1B*, in particular, has received an extensive investigation and has been compared with other psychotropic drugs.[19] In general, these compounds exhibited a spectrum of pharmacological activities characteristic of both tranquilizers and antidepressants. As such, they reduced spontaneous motility, potentiated narcosis, caused hypothermia, and were anticonvulsants. Most significantly, they influenced various conditioned responses in animals.

While most of the compounds possessed a high degree of antihistaminic, antiacetylcholine, and antiserotonin activities, the olefins (formula *B*) proved to be the more potent with respect to their central actions. This activity was qualitatively similar in compounds containing a three-carbon side chain with various basic groups. Branched-chain compounds (*12*, *15*, and *29*) retained the central activity; reducing the chain length to two carbons (*16* and *17*) caused a substantial decrease. Activity was increased by the 3-chloro substituent (*24* and *25*) and further increased by the introduction of a 10-,11-double bond (*27*, *29*, and *30*), while the most potent compounds resulted from a separation of the geometric isomers [*24B* (α and β), *27B* (α and β)]. In contrast, the optical antipodes (*13C* and *14C*) showed no significant superiority over the racemic mixture (*12C*).

EXPERIMENTAL

4-Chlorobenzalphthalide. 4-Chlorophenylacetic acid (51 g., 0.3 mole), phthalic anhydride (37.3 g., 0.25 mole), and sodium acetate (1 g.) were intimately mixed and heated for 3 hr. at 240°. The reaction mixture was then crystallized from ethanol to yield 52 g. of product, m.p. 151–153° (68% yield). One recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{15}H_9ClO_2$: C, 70.20; H, 3.53; Cl, 13.81. Found: C, 70,28; H, 3.56; Cl, 13.76.

3-Chlorobenzalphthalide. The interaction of 3-chlorophenylacetic acid (32.8 g., 0.19 mole), phthalic anhydride (27.7 g., 0.16 mole), and sodium acetate (0.6 g.) in the same manner as with the 4-chloro compound, gave 28 g. of product, m.p. 160–161°, unchanged on recrystallization from ethanol.

Anal. Calcd. for $C_{15}H_9ClO_2$: C, 70.20; H, 3.52; Cl, 13.81. Found: C, 70.01; H, 3.49; Cl, 14.16.

3,4-Dimethoxybenzalphthalide. As in the previous examples, 3,4-dimethoxyphenylacetic acid (58.5 g., 0.3 mole), phthalic anhydride (37 g., 0.25 mole), and sodium acetate (1 g.) gave 50 g. of product, m.p. 130–131° unchanged on recrystallization from ethanol.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.35; H, 4.96. Found: C, 71,85; H, 4.79.

2-[β-(4′-Chlorophenyl)ethyl]benzoic acid. 4-Chlorobenzalphthalide (49.5 g., 0.19 mole), 57% hydriodic acid (217 ml.), and red phosphorus (27 g.) were heated under reflux for 12 hr. After cooling, the reaction mixture was poured onto 250 g. of ice. The insoluble material was removed by filtration and heated under reflux for 20 min. with 125 ml. of

(19) F. Herr, J. Stewart, and M. P. Charest, *Arch. Int. Pharmacodyn, in press*, 1961.

concd. ammonium hydroxide. The mixture was then filtered and the filtrate acidified with dilute hydrochloric acid causing the product, 41.5 g., m.p. 127–128.5°, to precipitate. One recrystallization from ethanol raised the m.p. to 129–130°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02; Cl, 13.60. Found: C, 68.85; H, 4.82; Cl, 13.83.

2-[β-(3'-Chlorophenyl)ethyl]benzoic acid. As in the preceeding example, 3-chlorobenzalphthalide (28.4 g., 0.11 mole) was reduced with 57% hydriodic acid (125 ml.) and red phosphorus (15.5 g.) to give 16 g. of product, m.p. 88–89°. One recrystallization from aqueous isopropyl alcohol raised the melting point to 89–90°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02, Cl, 13.60. Found: C, 69.26; H, 4.90; Cl, 13.59.

2-[β-(3',4'-Dimethoxyphenyl)ethyl]benzoic acid. A mixture of 3,4-dimethoxybenzalphthalide (25 g.) in glacial acetic acid (100 ml.) and 2 g. of Raney nickel was subjected to hydrogenation at 1500 p.s.i. and 150° for 3 hr. The catalyst was removed by filtration and the solvent was evaporated. The residue was taken up in benzene and the benzene extracted with dilute sodium hydroxide. On acidification, the alkaline extracts deposited 12 g. of product, m.p. 128–132°. Three recrystallizations from aqueous ethanol raised the m.p. to 134–136°.

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.30; H, 6.28. Found: C, 71.03; H, 6.01.

3-Chlorodibenzo[a,d][1,4]cycloheptadien-5-one. 2-β-(4'-Chlorophenyl)ethylbenzoic acid (39.5 g., 0.15 mole) and polyphosphoric acid (200 g.) were heated together at 170° for 3 hr. The reaction mixture was then poured onto ice and extracted with ether. The extract was washed with a solution of 5% sodium carbonate, dried, and evaporated *in vacuo* to leave 28 g. of product as a viscous oil, b.p. 146–148° (0.08 mm.). Upon standing, the material solidified and was recrystallized from hexane to give an analytical sample with m.p. 65–66°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.24; H, 4.58; Cl, 14.61. Found: C, 74.64; H, 4.70; Cl, 14.73.

2-Chlorodibenzo[a,d][1,4]cycloheptadien-5-one. 2-[β-(3'-Chlorophenyl)ethyl]benzoic acid (16.2 g.) and 160 g. of polyphosphoric acid were heated together at 170° for 3 hr. The reaction was processed as before to yield 11 g. of product, b.p. 146–150° (0.05 mm.) which solidified on trituration with hexane, m.p. 76–78°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.55; Cl, 14.61. Found: C, 74.21; H, 4.29; Cl, 14.71.

2,3-Dimethoxydibenzo[a,d][1,4]cycloheptadien-5-one. 2-[β-(3',4' - Dimethoxyphenyl)ethyl]benzoic acid (136 g.) was added to polyphosphoric acid (650 g.) and the mixture was heated at 90° for 45 min. It was then processed in the usual manner to give 124 g. (94% yield) of product, m.p. 123–126°. Two recrystallizations from isopropyl alcohol gave an analytical sample, m.p. 127–128°.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 76.40 H, 5.79.

3-Chlorodibenzo[a,e][1,3,5]cycloheptatrien-5-one. 3-Chlorodibenzo[a,d][1,4]-cycloheptadien-5-one (20 g., 0.08 mole) was heated to 130° and bromine (12.8 g., 0.08 mole) was added dropwise. The addition took 1 hr. during which time the reaction with irradiated with ultraviolet light. After stirring the reaction mixture for an additional 30 min., the temperature was raised to 200° and held there until the evolution of hydrogen bromide had ceased. Distillation of the product with subsequent recrystallization from isopropyl alcohol gave 15.6 g. (79% yield) of material, m.p. 91–93°. When this compound was prepared by the triethylamine dehydrobromination procedure, a different crystal modification resulted, m.p. 109–111°. The two forms were interconvertible by suitable seeding.

Anal. Calcd. for $C_{15}H_9ClO$: C, 74.90; H, 3.77; Cl, 14.73. Found: C, 74.82; H, 3.60; Cl, 15.13.

2,3-Dimethoxydibenzo[a,e][1,3,5]cycloheptatrien-5-one. A solution of 2,3-dimethoxydibenzo[a,d][1,4]cycloheptadien-5-one (85.2 g., 0.318 mole), *N*-bromosuccinimide (62.1 g., 0.35 mole), and benzoyl peroxide (1.1 g.) in carbon tetrachloride (1200 ml.) was heated under reflux for 20 hr. The succinimide was separated by filtration and the filtrate washed with 5% sodium hydroxide solution followed by water. The residue obtained after removal of the carbon tetrachloride was added to triethylamine (1200 ml.) and heated under reflux for 16 hr. The reaction mixture was then filtered, evaporated *in vacuo*, and the residue triturated with dilute hydrochloric acid to yield 56 g. of product, m.p. 128–132°. Two recrystallizations from an acetone-methanol mixture gave a sample of m.p. 132–134°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.66; H, 5.29. Found: C, 76.60; H, 5.32.

3-Chloro-5-hydroxy-5-(3'-dimethylaminopropyl)dibenzo[a,d][1,4]cycloheptadiene (24A). Magnesium turnings (3.6 g., 0.15 mole) were added to tetrahydrofuran (10 ml.) containing a few crystals of iodine. Ethyl bromide (0.5 ml.) was then added, followed by dimethylaminopropylchloride (18.3 g., 0.15 mole) dissolved in tetrahydrofuran (25 ml.) in a dropwise manner. The formation of the Grignard reagent started immediately; heat was evolved. 3-Chlorodibenzo-[a,d][1,4]cycloheptadien-5-one (18.6 g., 0.075 mole) dissolved in tetrahydrofuran (50 ml.) was then added dropwise at a rate sufficient to maintain gentle reflux, the addition being completed in 30 min. The reaction mixture was then heated under reflux for an additional 16 hr. The Grignard complex was decomposed by addition to a solution of ammonium chloride (25 g.) in water (1 l.) which caused the product to precipitate as a waxy solid. The crude product was crystallized from isopropyl alcohol furnishing 15.2 g., m.p. 125–127° (61% yield). One recrystallization from isopropyl alcohol raised the m.p. to 127–128° (see Table II).

3-Chloro-5-(3'-dimethylaminopropylidene)dibenzo[a,d][1,4]-cyclophetadienes (24B, α and β). The 3-chloro-5-hydroxy-5-(3'- dimethylaminopropyl)dibenzo[a,d][1,4]cycloheptadiene (14.2 g.) was dissolved in acetic anhydride (200 ml.) and heated under reflux for 4 hr. After removal of the acetic anhydride by distillation, the residue was triturated with aqueous sodium hydroxide and extracted with ether. The ether extract with dried and treated with gaseous hydrogen chloride causing the crude product hydrochloride (11.5 g.) to precipitate, m.p. 190–210°. It was a mixture of geometric isomers.

Higher melting, less soluble hydrochloride isomer (α). The crude product hydrochloride was recrystallized three times from isopropyl alcohol to give 2.3 g. of pure compound melting sharply at 235–236°. (See Table II.)

Lower melting, soluble hydrochloride isomer (β). The combined filtrates from the purification of the higher melting form were concentrated, yielding 5.8 g. of material melting at 192–201°. This was dissolved in water, the solution neutralized, the product taken up in ether and the ether dried and distilled leaving the free base as a viscous oil. An oxalate salt was prepared by the addition of ethanolic oxalic acid to an ethanol solution of the free base. The oxalate was purified by two recrystallizations from ethanol; m.p. 198–199°. It was then converted back to the hydrochloride in the usual manner to give 2 g. of a substantially pure hydrochloride, m.p. 228–230°. (See Table II.) The two isomeric hydrochlorides had a mixture m.p. of 205–220° and gave identical ultraviolet and infrared spectra. In an attempt to separate the isomers by fractional crystallizations of the hydrochlorides alone, a less pure β-isomer resulted, m.p. 192–196°. The α and β forms of compound *27B* were isolated in a similar manner.

5-(3'-Dimethylamino-2',2'-dimethylpropylidene)dibenzo-[a,d][1,4]cycloheptadiene (15B). A solution of the tertiary alcohol (*15A*) (5.4 g.) in absolute ethanol (100 ml.) was saturated with gaseous hydrogen chloride and heated under reflux for 3 hr. The ethanol was removed *in vacuo* and the residue crystallized from isopropyl alcohol to give 2.0 g. product hydrochloride, m.p. 236–239° dec. (See Table I).

5-[(N-Methyl-3'-piperidyl)methylidene]dibenzo[a,d][1,4]-cycloheptadiene (18B). A solution of the tertiary alcohol (*18A*) (6.0 g., 0.02 mole) and acetyl chloride (8.0 g., 0.1 mole) in dry chloroform (100 ml.) was heated under reflux for 4 hr. The reaction mixture was then washed with aqueous sodium carbonate followed by water and then dried. The chloroform was removed leaving 5.7 g. of an oil which was converted to a sulfate salt and recrystallized from methanol-nitromethane-ether to give the product, m.p. 261–262° dec. (See Table I.)

5-(3'-Dimethylaminopropyl)dibenzo[a,d][1,4]cycloheptadiene (1C). 5-(3'-Dimethylaminopropylidene)dibenzo[*a,d*]-[1,4]cycloheptadiene hydrochloride (22.8 g., 0.073 mole) dissolved in absolute ethanol (200 ml.) containing 0.4 g. of platinum oxide and a few drops of 70% perchloric acid was subjected to catalytic hydrogenation at room temperature and 50 p.s.i. After 30 hr., the catalyst was filtered, the ethanol evaporated, and the residue crystallized from isopropyl alcohol–ether to give 12 g., m.p. 175–180°. Two recrystallizations raised the m.p. to 185–186°. (See Table I.)

5-(3'-Diethylaminopropyl)dibenzo[a,d][1,4]cycloheptadiene (2C). 5 - (3' - Diethylaminopropylidene)dibenzo[*a,d*]-[1,4]cycloheptadiene hydrochloride (6 g. 0.018 mole) was added to acetic acid (120 ml.), 56% hydriodic acid (32 ml.) and red phosphorous (6 g.). The reaction mixture was heated under reflux for 12 hr. It was then filtered, evaporated, and the residue neutralized with aqueous sodium hydroxide and extracted with ether. Addition of hydrogen chloride to the dried ethereal extract caused the product hydrochloride (3.9 g.) to precipitate, m.p. 134–138°. Two recrystallizations from isopropyl alcohol-ether gave a sample of m.p. 136–138°. (See Table I.)

5-(3'-Benzyloxypropyl)-5-hydroxydibenzo[a,d][1,4]cycloheptadiene (VI). *Method a.* The Grignard reagent derived from 3-benzyloxypropyl chloride[20] (11.1 g., 0.06 mole) and magnesium (1.46 g., 0.06 mole) in tetrahydrofuran (50 ml.) was treated with ketone V (6.25 g., 0.03 mole) and the mixture was heated under reflux for 16 hr. After cooling, it was poured into ice water containing an excess of ammonium chloride. The oil was taken up in chloroform and the solution washed with water, dried, and evaporated. Distillation of the residual oil afforded a fraction b.p. 230–256° (0.13 mm.) n_D^{25} 1.6041–1.6035 (5.75 g.) which contained the desired carbinol (VI) together with some of its dehydration product. There was also obtained a fraction, b.p. 88–230° (0.13 mm.) 2.35 g.) which solidified. Recrystallization of the latter from ether-hexane gave a pure sample of 5-hydroxydibenzo[*a,d*][1,4]cycloheptadiene; m.p. 93°, undepressed on admixture with an authentic specimen.[9c]

Method b. 3-Benzyloxypropyl bromide[21] (119 g., 0.52 mole) and magnesium (12.6 g., 0.52 mole) in tetrahydrofuran (280 ml.) formed the Grignard reagent more readily than did the chloride. Treatment with V (91.5 g., 0.44 mole) as above gave a mixture (93.2 g.) of VI and its dehydration product. From an earlier fraction, b.p. 110–170° (1 mm.) (27 g.) there was obtained crystalline material (from isopropyl alcohol), m.p. 132–133°, in accord with the reported[9c] value for dibenzo[*a,e*][1,3,5]cycloheptatriene.

Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found: C, 93.65; H, 6.21.

The crude tertiary carbinol was used in the next step without further purification.

5-(3'-Bromopropylidene)dibenzo[a,d][1.4]cycloheptadiene (VII). A mixture of crude alcohol (VI) (91.5 g.) and 48% hydrobromic acid (600 ml.) was heated under reflux stirring for 16 hr. Water (two volumes) was added and the heavy dark oil was taken up in benzene. The organic layer was washed with water, dried and distilled to give benzyl bromide, b.p. 40–52° (0.5 mm.)(22.3 g.) and a fraction, b.p. 156–184° (0.20–0.35 mm.). Recrystallization of the latter from petroleum ether (b.p. below 40°) gave 42.9 g. (53% yield) of VII, m.p. 68–72°. Further recrystallization gave an analytical sample, m.p. 70–71°.

Anao. Calcd. for $C_{18}H_{17}Br$: C, 69.01; H, 5.43; Br, 25.55. Found: C, 69.34; H, 5.30; Br, 25.60.

The structure was confirmed by heating the compound with diethylamine; the product obtained was identical to *2B* which had been prepared by a different method.

5-{3-[4-(2-Hydroxyethyl)piperazinyl]propylidene}dibenzo-[a,d][1,4]cycloheptadiene (7B). A solution of VII (6.3 g., 0.02 mole) and 1-(2'-hydroxyethyl)piperazine (5.2 g., 0.04 mole) in dry benzene (70 ml.) was heated under reflux with stirring for 16 hr. The cooled mixture was filtered and the solution was extracted with a little water to remove any secondary amine, followed by dilute hydrochloric acid. The acidic layer was rendered alkaline and the product was taken up in benzene. Evaporation of the solvent left 6.0 g. of product, which, as the dihydrochloride, was recrystallized from methanol, m.p. 261–262° dec. (See Table I.) The other compounds prepared by this method were *5B*, *6B*, and *11B*.

5-{3-[4-(2-Acetoxyethyl)piperazinyl]propylidene}dibenzo-[a,d][1,4]-cycloheptadiene (8B). Acetyl chloride (2.3 g.. 0.03 mole) was added to *7B* (5.4 g., 0.015 mole) dissolved in dry chloroform (60 ml.) and the solution was heated under reflux for 2 hr. The dark solution was then shaken out with cold aqueous sodium bicarbonate and the chloroform layer was washed with water. Drying and evaporation left the product as an oil which, as the dimaleate salt, formed hard rosettes from acetonitrile-dimethylformamide mixture, m.p. 184–186° dec. (See Table I.)

5-[3'-(2"-Pyridylamino)propylidene]dibenzo[a,d][1,4]cycloheptadiene (10B). A solution of 2-aminopyridine (5.65 g., 0.06 mole) in dry xylene (25 ml.) was added gradually to a suspension of sodium hydride (2.68 g. of a 53.8% oil dispersion; 0.06 mole) in xylene (25 ml.) and the mixture was heated under reflux with stirring for 2.5 hr. Compound VII (9.4 g., 0.03 mole) dissolved in xylene (25 ml.) was then added and the heating was continued for 20 hr. The mixture was shaken out with water and the dark aqueous phase discarded. Extraction of the organic layer with dilute hydrochloric acid gave a dark gum which was triturated with a litte water and ether. Conversion to the free base gave a product (4.1 g., 42% yield) which was essentially free of aminopyridine. The maleate, pale yellow needles from ethanol-ether (Nuchar), had m.p. 146–147° dec. (See Table I.)

5-Hydroxy-5-(carbo-tert-butoxymethyl)dibenzo[a,d][1,4]cycloheptadiene (IX). The Grignard reagent was prepared from ethyl bromide (132 g., 1.2 mole) and magnesium (29.2 g., 1.2 mole) in ether (500 ml.). The solution was cooled in ice while diethylamine (87.6 g., 1.2 mole) in ether (150 ml.) was added dropwise. The mixture was then heated under reflux for 0.5 hr., cooled again to −5° and an ethereal solution of V (125 g., 0.6 mole) and *tert*-butyl acetate (69.6 g. 0.6 mole) was added dropwise. The mixture was heated gradually to the reflux temperature and held there for 2 hr. After cooling, it was poured into an ice-water mixture containing an excess of ammonium chloride. The product was taken up in benzene (troublesome emulsions occurred), the benzene solution was washed with water, and dried. Evaporation of the solvent and crystallization of the residue from aqueous isopropyl alcohol gave the product as white needles, m.p. 98–100° (151 g., 78% yield). An analytical sample had m.p. 100–103°.

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 78.11; H, 7.47.

5-Hydroxy-5-(2'-hydroxyethyl)dibenzo[a,d][1,4]cycloheptadiene (X). To a mixture of lithium aluminum hydride (2.3 g., 0.06 mole) and tetrahydrofuran (75 ml.) was added a solution of IX (13.3 g., 0.041 mole) in tetrahydrofuran (75 ml.) over a period of 20 min. (A transient blue color was produced indicating possible enolization of the ester.) The mixture was heated under reflux for 4 hr. and then hydro-

(20) R. E. Lyle, E. J. De Witt, and I. G. Pattison, *J. Org. Chem.*, **21**, 61 (1956).

(21) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

lyzed by the gradual addition of 20% sodium hydroxide (6 ml.). Filtration and evaporation of the solvent with subsequent recrystallization of the residue from isopropyl acetate gave 8.1 g. (78% yield) of product, m.p. 124–125°. An analytical sample had m.p. 125–127°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.79; H, 7.14.

5-Hydroxy-5-(2'-dimethylaminoethyl)dibenzo[a,d][1,4]cycloheptadiene (16A). Tosylation of the primary hydroxyl group of X was accomplished by using conditions described in the literature[22] for related compounds. The diol (X) (43.2 g., 0.17 mole) was dissolved in a mixture of dry pyridine (60 ml.) and benzene (60 ml.). The solution was cooled to 2° while freshly recrystallized *p*-toluenesulfonyl chloride (34.0 g., 0.178 mole) in benzene (60 ml.) was added over a period of 15 min. The mixture was stirred at room temperature for 6 hr. and was washed with water, cold dilute hydrochloric acid, sodium bicarbonate, and finally with water. Evaporation of the solvent and crystallization of the residue from benzene-hexane mixture gave a product, assumed to be the 2'-*p*-toluenesulfonate ester of X, as white crystals, m.p. 91–100° (57.3 g., 59% yield). Attempted recrystallization gave material which rapidly decomposed on drying; accordingly it was used directly for the next step.

A mixture of the tosylate (8 g., 0.02 mole) and anhydrous dimethylamine (7 ml.) in methanol (40 ml.) was heated in a pressure bottle between 50–55° for 18 hr. The solvent was removed, the residue treated with sodium carbonate solution, and the product was taken up in benzene. The organic layer was washed with carbonate, then with water, and dried. Evaporation left 4.7 g. of product as an oil which appeared to contain a small amount of the corresponding olefin (*16B*). It was converted to the hydrochloride which, on recrystallization from methanol-nitromethane-ether gave a pure sample of *16A*, m.p. 225–227° dec. (3.9 g., 61% yield). (See Table I.) Compound *17A* was also prepared by this method.

5-Carboxymethylidenedibenzo[a,d][1,4]cycloheptadiene (XIII). Zinc granules (19.5 g., 0.3 mole) were covered with 1 l. of an ether-benzene solution (1:1). A crystal of iodine and ethyl bromide (1 ml.) was added to activate the zinc surface. The solution was heated under reflux while a mixture of 41.6 g. (0.2 mole) of dibenzo[a,d][1,4]cycloheptadien-5-one and 55 g. (0.33 mole) of ethyl bromoacetate in ether (200 ml.) was added dropwise over a period of 12 hr. The reaction mixture was heated under reflux for an additional 12 hr. The zinc bromide adduct was then hydrolyzed by the addition of 20% sulfuric acid (500 ml.). The organic layer was separated and the aqueous layer further extracted with benzene. The combined organic layers were washed with dilute sulfuric acid, sodium carbonate solution, and finally with water. After drying with sodium sulfate, the solvents were removed by distillation *in vacuo*. The residual oil distilled at 0.25 mm. with a boiling range of 146 to 162° to yield 35 g. of crude 5-carbethoxymethylidenedibenzo[a,d]-[1,4]cycloheptadiene contaminated with unchanged ketone. It was not further purified at this stage.

The crude ester was hydrolyzed by heating it under reflux in a solution of sodium hydroxide (22 g.), water (200 ml.), and ethanol (300 ml.) for 2 hr. After removal of the ethanol by distillation, the remaining aqueous mixture was extracted with chloroform and then neutralized with dilute hydrochloric acid, causing the product to precipitate as a white solid (14.6 g), m.p. 165–169°. Two recrystallizations from isopropyl alcohol gave an analytical sample, m.p. 172–173°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.57; H, 5.63. Found: C, 81.79; H, 5.42.

5-(N,N-Dimethylcarboxyamidomethylidene)dibenzo[a,d]-[1,4]cycloheptadiene (XIV). 5-Carboxymethylidenedibenzo[a,d][1,4]cycloheptadiene (12.8 g.) was dissolved in ether (300 ml.) and treated with an excess of an ethereal dimethylamine solution. The solid dimethylammonium salt was filtered, dried, and heated at 170° under a nitrogen atmosphere for 10 hr. After cooling, the fused mass was extracted with chloroform and the chloroform was extracted with dilute sodium hydroxide solution. Neutralization of the alkaline extract gave 7 g. of recovered starting material. The chloroform extract was dried and evaporated to yield 3.2 g of product, m.p. 131–133°. One crystallization from aqueous methanol gave an analytical sample, m.p. 133–134°.

Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.00; H, 6.86; N, 5.03. Found: C, 82.15; H, 6.78; N, 5.06.

5-(2'-Dimethylaminoethylidene)dibenzo[a,d][1,4]cycloheptadiene (16B). Amide XIV (3.1 g., 0.011 mole) was dissolved in tetrahydrofuran (75 ml.), which was added dropwise to lithium aluminum hydride (0.83 g., 0.022 mole) in tetrahydrofuran (50 ml.). After the addition was complete (15 min.) the reaction mixture was heated under reflux for 3 hr. On cooling, water (3 ml.) was cautiously added and the aluminum hydroxide filtered off. The filtrate was dried and evaporated to yield 2 g. of the free base, as a light brown, viscous oil.

The free base was dissolved in ether and treated with ethereal hydrogen chloride giving the hydrochloride salt (1.6 g.), m.p. 211–213°. One recrystallization from isopropyl alcohol-ether gave an analytical sample melting at 213–215°. (See Table I.)

5-Hydroxy-5-(2'-pyridyl)dibenzo[a,d][1,4]cycloheptadiene (XVI). *n*-Butyl bromide (52 g., 0.38 mole) dissolved in dry ether (100 ml.) was added dropwise to a stirred and cooled (−10°) suspension of finely cut lithium wire (5.17 g., 0.75 mole) in ether (300 ml.). The mixture was stirred until dissolution of the metal was completed and it was then held between −60 and −40° while a solution of 2-bromopyridine (52 g., 0.33 mole) in ether (50 ml.) was added over 15 min. A solution of ketone V (62.5 g., 0.30 mole) in ether (150 ml.) was then added and the mixture was stirred for an additional 2 hr. at about −40°. It was allowed to warm to room temperature overnight and was hydrolyzed by the addition of ammonium chloride solution. The buff-colored precipitate was filtered and dried, giving 82 g. (86% yield) of product, m.p. 201–204°. Recrystallization of a portion from methanol furnished an analytical sample, m.p. 203–205°.

Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.88; H, 6.06, N, 4.51.

The hydrochloride was prepared by treating a methanolic suspension of the base with hydrogen chloride. Ether was added to the solution and the precipitate was recrystallized from methanol-ether, m.p. 194–195° dec.

Anal. Calcd. for $C_{20}H_{18}ClNO$: C, 74.18; H, 5.60; Cl, 10.95. Found: C, 74.32; H, 5.34; Cl, 10.99.

The *methobromide* was prepared by heating a methanolic suspension of the base with an excess of methyl bromide in a a pressure bottle at 65° for 50 hr. followed by keeping the mixture at room temperature for 3 days. Evaporation of the solvent and recrystallization of the product from an ethanol-methanol mixture gave prisms, m.p. 217–218° dec.

Anal. Calcd. for $C_{21}H_{20}BrNO$: C, 65.98; H, 5.27; Br, 20.90. Found: C, 65.97; H, 5.11; Br, 21.10.

Compound *21A* was made in an analogous manner from 2-picolyllithium.

5-(2'-Pyridyl)dibenzo[a,d][1,4]cycloheptadiene (XVIII). A mixture of XVI (21 g.), red phosphorus (21 g.), hydriodic acid (56%, 105 ml.), and glacial acetic acid (385 ml.) containing hypophosphorous acid (0.5 ml.) was heated under reflux with stirring for 3 hr. The product was isolated in the manner described for compound *2C* giving 18.5 g. (98% yield) of material, m.p. 145–147°. Recrystallization from isopropyl acetate gave an analytical sample, m.p. 148–150°.

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.52; H, 6.32, N, 5.16. Found: C, 88.92; H, 6.34; N, 5.15.

(22) M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, **78**, 1060 (1956).

The hydrochloride was recrystallized from ethanol-ether, m.p. 218–220° dec.

Anal. Calcd. for $C_{20}H_{18}ClN$: C, 78.05; H, 5.89; Cl, 11.52; N, 4.55. Found: C, 78.29; H, 6.00; Cl, 11.36; N, 4.59.

In a similar manner, hydriodic acid reduction of *21A* gave *21C*.

5-(2'-Piperidyl)dibenzo[a,d][1,4]cycloheptadiene (XIX). A mixture of XVIII hydrochloride (4.3 g.) and platinium oxide (0.15 g.) in dioxane (100 ml.) and water (50 ml.) was hydrogenated at 50 p.s.i. and at 70° for 46 hr.; about 76% of the theoretical quantity of hydrogen was consumed. The catalyst was removed and the solution evaporated; the residue was dissolved in isopropyl alcohol and on scratching the solution deposited crystals (0.8 g.), m.p. 329–330° dec. The isopropyl alcohol filtrate was evaporated and the residue was converted to the free base giving on trituration with a little ether an insoluble fraction (1.1 g.), m.p. 143–144°, undepressed on admixture wtih starting material. The ether-soluble portion was converted to the hydrochloride, combined with the original high-melting fraction, and recrystallized from ethanol-methanol-ether mixture. There was obtained the product (0.5 g.) in the form of short needles, m.p. 331° dec.

Anal. Calcd. for $C_{20}H_{24}ClN$: C, 76.54; H, 7.71; Cl, 11.30. Found: C, 76.78; H, 7.49; Cl, 11.52.

Hydrogenation of the analogous pyridylmethyl compound (*21C*) under similar conditions proceeded more readily to give *22C* in 24% yield.

Resolution studies. (+) *5-Hydroxy-5-(3'-dimethylamino-2'-methylpropyl)dibenzo[a,d][1,4]cycloheptadiene (13A).* (+) Camphorsulfonic acid was added to a large excess of 3-dimethylamino-2-methylpropyl chloride and the resulting salt was recrystallized; $[\alpha]_D$ +4.6° (c = 2; water). It was converted to the free base, the hydrochloride of which had m.p. 172–174° and $[\alpha]_D$ −19.0° (c = 2; water).

The Grignard reagent derived from this base halide (10.4 g., 0.077 mole) and magnesium (1.82 g., 0.075 mole) in tetrahydrofuran (75 ml.) was treated with ketone V (10.4 g., 0.05 mole). The reaction mixture was heated under reflux for 3 hr. and processed in the usual manner. Crystallization of the resulting product from ethyl acetate gave 11.9 g. (77% yield) of material m.p. 137–141°; $[\alpha]_D$ +231° (c = 1-chloroform). Purification was effected by treating an ethanolic solution with a small excess of (−) tartaric acid; recrystallization of the salt from ethanol and regeneration of the base. Treatment with (+) tartaric acid in a similar manner gave the diastereoisomeric salt. (See Table I.)

This basic alcohol could also be obtained in less satisfactory yield by resolution of the racemic form (*12A*) with (−) tartaric acid. There was obtained in addition to the desired (+) base·(−) tartrate salt, the diastereoisomeric (−) base· (−) tartrate which, however, could be separated by recrystallization. Treatment of these salts with aqueous sodium carbonate gave purified samples of the isomeric bases. (See Table I.)

(−)*5-Hydroxy-5-(3'-dimethylamino-2'-methylpropyl)dibenzo[a,d][1,4]-cycloheptadiene (14A).* A suspension of the racemic alcohol *12A* (77.3 g., 0.25 mole) in hot ethanol (600 ml.) was treated with a solution of (+) tartaric acid (39.2 g., 0.26 mole) in the same solvent (150 ml.) and the mixture was agitated for a short time to complete dissolution of the base. The bulk of the solvent was removed *in vacuo* and acetone (150 ml.) was added followed by a little ether to the turbidity point. The precipitate obtained after the mixture had been refrigerated for several days was recrystallized from ethanol giving the (−) base·(+) tartrate, m.p. 156–157° (17.0 g., 30% yield). Conversion of this salt to the base gave a pure sample of *14A*. (See Table I.)

The filtrate from the original precipitate was concentrated and the product was converted to the free base giving 52 g. of material, m.p. 134–140°. One recrystallization from ethyl acetate raised the m.p. to 148–150°; the material, $[\alpha]_D$ +7.7° (c = 1; chloroform) being slightly enriched with the (+) base. Treatment with (−) tartaric acid gave, as described in the case of the racemic alcohol, the (−) tartrates both the (+) and the (−) bases. (See Table I.)

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[CONTRIBUTION FROM THE DIVISION OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF WISCONSIN]

Esters of *N*-Methyl-3-hydroxypiperidine Having Psychotomimetic Activity. II[1,2]

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A series of esters of *N*-methyl-3-hydroxypiperidine has been prepared as a part of a study of the structure-activity relationship of certain compounds having hallucinogenic activity.

Esters of *N*-methyl-3-hydroxypiperidine (I) have been shown to be capable of eliciting striking psychic effects in humans as well as marked behavioral changes in animals.[5,6] The psychotomimetic or hallucinogenic episodes which these esters precipitated occurred most readily when R_1 was hydroxyl, R_2 was phenyl, and R_3 was phenyl or cyclohexyl or cyclopentyl.[6] In 1960, Cannon[2] synthesized a num-

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(2) J. G. Cannon, *J. Org. Chem.*, **25**, 959 (1960), should be considered as Part I of the series.

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