New Psychotropic Agents. V. Derivatives of 5-Cyano- and 5-Carboxamidodibenzo[a,d]cycloheptadiene

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A series of 5-dialkylaminoalkyl-5-cyano and -5-carboxamidodibenzo[a,d]cycloheptadienes has been prepared. The nitriles were derived by alkylation of 5-cyanodibenzo[a,d]cycloheptadiene; hydrolysis of some of them by sulfuric acid furnished the corresponding carboxamides. A tertiary carboxamide was prepared from pyrrolidine *via* dibenzo[a,d]cycloheptadiene-5-carboxylic acid and its acid chloride; this was then alkylated in the usual manner. Various routes to the carboxylic acid were investigated. Certain of the compounds possessed moderate spasmolytic activity while the 5-(3-aminopropyl)-5-carbonitriles had actions on the central nervous system characteristic of the antidepressant agent amitriptyline.

In our continuing search for new structures with useful psychotropic activities[1] it was considered of interest to introduce additional groupings into the 5-position of certain 5-dialkylaminoalkyldibenzo[a,d]cycloheptadienes.[2] The cyano and carboxamido groups were chosen because of their ease of introduction. Closely related benzhydryl compounds, *i.e.*, basically substituted diphenylacetonitriles, and the corresponding amides, have been studied extensively as pharmacodynamic agents, particularly as spasmolytics and analgesics.[3] Other workers[4,5] have reported investigations on 5-dialkylaminoalkoxydibenzo[a,d]cycloheptadienes. These may be regarded as ring analogs of the corresponding benzhydryl ethers in which the phenyl groups are linked by an *o,o'*-ethylene bridge.

The nitriles, listed in Table I, could be prepared conveniently by alkylation of 5-cyanodibenzo[a,d]cycloheptadiene (II) in toluene with the appropriate aminoalkyl chloride, using sodium hydride as the condensing agent. An exception was the preparation of VI; here the nitrile was first alkylated with 1,2-dibromoethane employing conditions similar to those used with diphenylacetonitrile,[6] and the partially purified 5-(2-bromoethyl)-5-carbonitrile (III) was then treated with 4-carbethoxy-4-phenylpiperidine.

The preparation of II could be effected in good yield from the interaction of the 5-chloro compound (I) with silver cyanide in anhydrous acetonitrile or, more conveniently, benzene. Attempted preparations with cuprous cyanide in either pyridine[7] or dimethylsulfoxide[8] gave little or none of the desired product. Attempted displacement of the *p*-toluenesulfonate ester of dibenzo[a,d]cycloheptadiene-5-ol with potassium cyanide or heating the free alcohol with a mixture of sodium cyanide, glacial acetic acid, and sulfuric acid[9] was also unsuccessful.

The cyano group in compound V could be readily removed by treating with sodium amide in boiling xylene[10] to furnish IX. This provides an alternative route to the 2-aminoethyl compounds which cannot be prepared *via* a Grignard reaction.[2]

Hydrolysis of certain of the basic nitriles to the corresponding carboxamides (Table II) was effected by heating with 90% sulfuric acid at about 100°. In this manner V was converted to VIII. This procedure, used for the preparation of the related diphenylacetamides,[11] gave compounds from which it was somewhat difficult to obtain pure salts. Compound VII was obtained from the pyrrolidide, 2-morpholinoethyl chloride and sodium hydride in toluene in 38% yield. Similar alkylations of tertiary diphenylacetamides have been reported[11,12] to give only fair yields of products. The intermediate pyrrolidide was obtained from pyrrolidine and dibenzo[a,d]cycloheptadiene-5-carboxylic acid (IV) *via* the acid chloride.

The carboxylic acid could be prepared by the acid hydrolysis of the nitrile (II) or, more simply, by the interaction of the chloride (I) with lithium in tetrahydrofuran with subsequent carbonation following a procedure developed for the synthesis of diphenylacetic acid from benzhydryl chloride.[13] The dimeric hydrocarbon 5,5'-bisdibenzo[a,d]cycloheptadiene[5] was, however, not cleaved to the 5-lithio compound when treated with lithium in tetrahydrofuran under a variety of conditions. *sym*-Tetraphenylethane is known to give diphenylmethyllithium under mild conditions.[13] Metalation of dibenzo[a,d]cycloheptadiene by potassium amide in liquid ammonia and by sodium-naphthalene in tetrahydrofuran followed by carbonation gave the acid in yields of 32 and 10%, respectively. Similar metalations of diphenylmethane gave diphenylacetic acid in yields of 90%[14] and 70%,[15] respectively. The low acidity of this hydrocarbon was further demon-

(1) Part IV: S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Chem.*, **6**, 130 (1963).

(2) (a) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. A. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962). This ring system may be named 10,11-dihydro-5H-dibenzo[a,d]cycloheptene. "The Ring Index," American Chemical Society, 2nd Ed., 1960, p. 483. (b) Since the completion of this work, the preparation of several 5-basically substituted 5-cyanodibenzo[a,d]cycloheptadienes has been reported by C. van der Stelt in Belgian Patent 616,980 (1962); Derwent Report 93A, 1962, Section 3, p. 9.

(3) A comprehensive review of these and related compounds has been published: P. A. J. Janssen, "Synthetic Analgesics. Part I. Diphenylpropylamines," Pergamon Press, Inc., New York, N. Y., 1960.

(4) C. van der Stelt, A. F. Harms, and W. Th. Nauta, *J. Med. Pharm. Chem.*, **4**, 335 (1961).

(5) V. Mychajlyszyn and M. Protiva, *Collection Czech. Chem. Commun.*, **24**, 3955 (1959).

(6) D. J. Dupré, J. Elks, B. A. Hems, K. N. Speyer, and R. M. Evans, *J. Chem. Soc.*, 500 (1949).

(7) R. C. Fuson and A. J. Rachlin, *J. Am. Chem. Soc.*, **64**, 1567 (1942).

(8) M. S. Newman and H. Boden, *J. Org. Chem.*, **26**, 2525 (1961).

(9) R. Baltzly and E. Lorz, U.S. Patent 2,956,063 (1960).

(10) A. W. Ruddy, *J. Am. Chem. Soc.*, **73**, 4096 (1951).

(11) L. C. Cheney, W. B. Wheatley, M. E. Speeter, W. M. Byrd, W. E. Fitzgibbon, W. F. Minor, and S. B. Binkley, *J. Org. Chem.*, **17**, 770 (1952).

(12) Reference 3, p. 141.

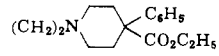
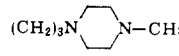
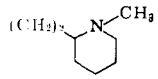
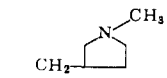
(13) C. Tamborski, G. J. Moore, and E. J. Skolski, *Chem. Ind.* (London), 696 (1962).

(14) R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 2325 (1947).

(15) H. Normant and B. Angelo, *Bull. Soc. Chim.*, 354 (1960).

Table I

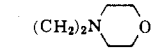
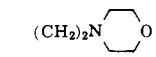
Dibenzo[a,d]cycloheptadiene-5-carbonitriles

R	No.	Salt	M.p., °C.	Recryst. solv.	Yield, %	Formula	Analyses: Calcd. over found C	H	N	Cl
$(CH_2)_2N(C_2H_5)_2$	1A	HCl	185–186 dec.	[a]	79	$C_{22}H_{27}ClN_2$			7.90	9.99
									7.95	10.07
$(CH_2)_2N(C_2H_5)_2$	1B	CH_3I	229–230 dec.	[d]		$C_{23}H_{29}N_2I$			6.09	27.57[j]
									5.98	27.60
$(CH_2)_2N[CH(CH_3)_2]_2$	2A	HCl	179–180 dec.	[c,e]	73	$C_{24}H_{31}ClN_2$	75.27	8.16		9.26
							75.18	8.15		9.39
$(CH_2)_2N[CH(CH_3)_2]_2$	2B	CH_3I	195–196 dec.	[e]		$C_{25}H_{33}IN_2$			5.74	26.00[j]
									5.73	25.90
	3A	Base	127–128 dec.	[f]		$C_{32}H_{34}N_2O_2$	80.30	7.16	5.85	
							79.86	7.23	5.79	
	3B	HCl	160–161 dec.	[d,g]	31	$C_{32}H_{35}ClN_2O_2$			5.44	6.88
									5.69	6.80
	3C	H_3PO_4	195	[c]		$C_{32}H_{37}N_2O_6P$	66.64	6.47	4.86	
							66.77	6.57	4.86	
$(CH_2)_3N(CH_3)_2$	4	HCl	232–233 dec.	[c,d]	69	$C_{21}H_{25}ClN_2$			8.22	10.40
									8.03	10.59
$CH_2CH(CH_3)CH_2N(CH_3)_2$	5	Fumarate	215–216 dec.	[b,d,e]	36	$C_{26}H_{30}N_2O_4$	71.86	6.96	6.45	
							71.80	7.17	6.33	
	6	Base	[a]		51	$C_{24}H_{28}N_2$	80.18	8.13	11.69	
							80.19	8.03	11.66	
	7	Benzilate	118–119 dec.	[c,f]	36	$C_{38}H_{40}N_2O_3$	79.69	7.04	4.89	
							79.79	7.22	5.03	
	8	HCl	213–215 dec.	[f]	39	$C_{22}H_{25}ClN_2$	74.88	7.14		10.05
							74.93	7.24		9.92

[a] B.p. 206–210° (1–2 mm.). [b] Acetonitrile. [c] Ether. [d] Ethanol. [e] 2-Propanol. [f] Petroleum ether (b.p. 100–120°). [g] Water. [h] Methanol. [i] Acetone. [j] Iodine.

Table II

Dibenzo[a,d]cycloheptadiene-5-carboxamides

Z	R	No.	Salt	M.p., °C.	Recryst. solv.	Yield, %	Formula	Analyses: Calcd. over found C	H	N	Cl
NH_2	$(CH_2)_2N(C_2H_5)_2$	9	Oxalate	161–162 dec.	[a,b]	69	$C_{24}H_{30}N_2O_5$	67.58	7.09	6.57	
							67.35	7.17	6.59	
NH_2	$(CH_2)_2N[CH(CH_3)_2]_2$	10A	Base	112–113 dec.	[c]	55	$C_{24}H_{32}N_2O$	79.08	8.85	7.69	
							78.91	8.55	7.28	
NH_2	$(CH_2)_2N[CH(CH_3)_2]_2$	10B	CH_3I	158–163 dec.	[b,d]		$C_{25}H_{35}IN_2O$		5.53	24.48[e]
									5.11	24.41
		11A	Base	148–149	[c]	38	$C_{28}H_{32}N_2O_2$	77.19	7.97	6.93	
							77.03	7.45	6.87	
		11B	HCl	244–246 dec.	[b]		$C_{26}H_{33}ClN_2O_2$	70.81	7.54	6.35	8.04
							70.75	7.72	6.69	8.05
NH_2	$(CH_2)_3N(CH_3)_2$	12	Oxalate	176–177 dec.	[a,b]	67	$C_{23}H_{28}N_2O_5$	66.97	6.84	6.79	
							66.39	6.91	6.61	

[a] Ethanol. [b] Ether. [c] Petroleum ether (b.p. 80–100°). [d] Acetone. [e] 2-Propanol. [f] Iodine.

strated by its inability to be metalated by sodium hydride,[2] phenylsodium or butyllithium.[16] In contrast, dibenzo[a,e]cycloheptatriene may be easily metalated.[17,18]

(16) The action of propyllithium on diphenylmethane gives diphenylmethyllithium in good yields: H. Gilman, and B. J. Gaj, *J. Am. Chem. Soc.*, **82**, 6326 (1960).

(17) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigos, *J. Med. Pharm. Chem.*, **5**, 373 (1962).

(18) C. I. Judd, A. E. Dunkker, and J. H. Biel, U.S. Patent 2,985,660 (1961).

Pharmacological Activity.—Six compounds (4–8, 12) were screened for their effects in a series of tests for antidepressant and certain other central actions. The tests included were: the determination of acute toxicity (LD_{50}), potentiation of a sub-narcotic dose of ethanol, protection against maximal electroshock seizures (MES) mydriatic action, ataxic effect, and influence on a conditioned response (runway test). A detailed description of these methods has been reported pre-

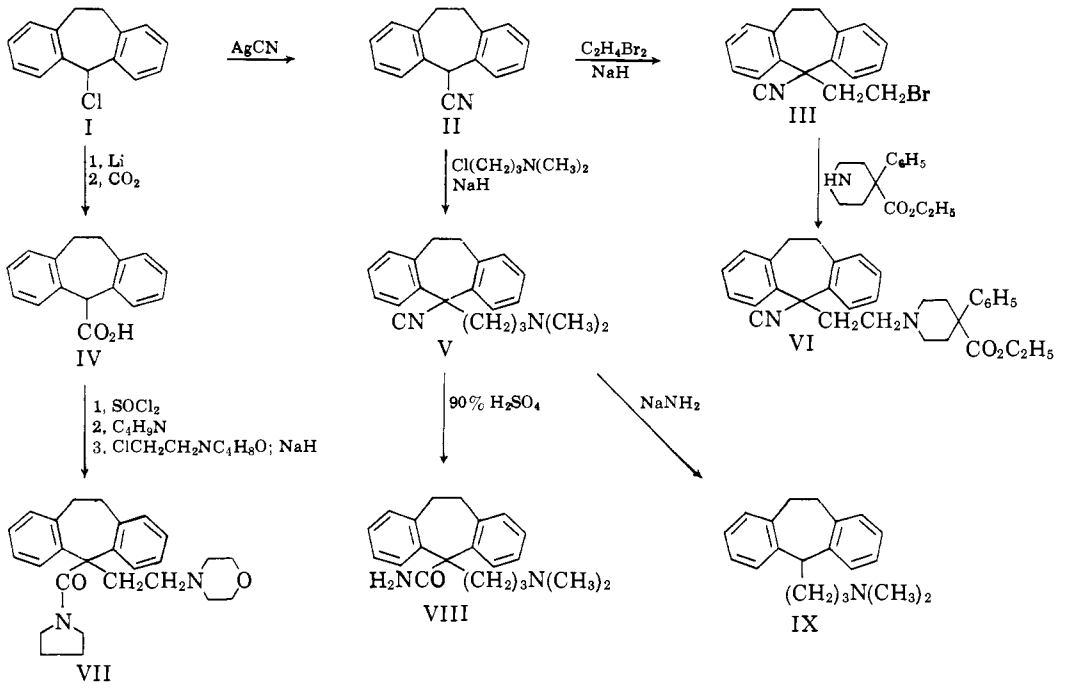


TABLE III

PHARMACOLOGICAL ACTIVITY *in vivo*

Compound no.	LD_{50} approx., mg./kg.[a]	Narcosis potentiation ED_{50} ± S.E., mg./kg.[a]	MES, mg./kg.[a]	Mydriasis[c] caused by 1/4 LD_{50}[a]	Ataxia ED_{50} approx., mg./kg.[b]	Runway ED_{50} approx., mg./kg.[b]
4	120	32 ± 5	38 ± 1	7.6	>67	9
5	240	24 ± 2	21 ± 1	10	90	22
6	90	8 ± 1	>20	1.9	>70	20
7	135	13 ± 2	>36	7.8	>105	21
8	110	8 ± 1	>27	26.6	49	8
12	150	40 ± 4	>40	4.6	..	30
Amitriptyline	83	7.9 ± 0.8	10 ± 0.8	19	53	8

[a] Mice, i.p. [b] Rats, i.p. [c] The numbers represent unit increases over control pupil diameter; 40 is approximately the maximal dilation. > means that the compound was inactive up to the dose indicated in the table.

viously.[19] The results are presented and compared to those of amitriptyline in Table III. In all cases the doses are expressed in terms of the free base.

The profile of activity of these compounds was similar to that of amitriptyline, and, therefore, they might be expected to possess antidepressant properties. In general, however, the compounds were less potent and less toxic. In the runway test, compounds 4 and 8 compare favorably to amitriptyline, whereas the others are much less active. It is interesting to note that compound 12, in which the carbonitrile group of compound 4 is replaced by a carboxamido group, was the least effective. While there were some compounds which were as potent as amitriptyline in other tests, *e.g.*, narcosis potentiation, all of the compounds were inferior to it against MES.

It may be noted that one of the compounds, 11B, which is a ring-analog of a compound reported to have analgesic action in the range of meperidine,[20,21] did not have any analgesic effect in doses up to 80 mg./kg., s.c., when tested by the radiant heat method in mice.

The water-soluble compounds were also tested against acetylcholine- and histamine-induced contraction in isolated guina pig by the method of Magnus. The per cent inhibition was calculated from contractions obtained before (control) and after the ileum had been in contact with the test compound for 2 min. The average value from a minimum of 3 strips of each of 3 or more concentrations was plotted and the median effective concentration (EC_{50}) was calculated. The EC_{50} values are expressed in terms of the free base. The results are found in Table IV.

In our series the tertiary amines had antiacetylcholine activity which was less than 4% of that of atropine. These compounds are less active than the

TABLE IV

ANTISPASMODIC ACTIVITY IN ISOLATED GUINEA PIG ILEUM

	Antiacetylcholine activity		—Antihistamine activity—	
Compound no.	EC_{50} (μg./ml.)	Relative potency Atropine = 100	EC_{50} (μg./ml.)	Relative potency Promethazine = 100
1A	0.1	4.0	0.4	1.0
1B	.01	40.0	.36	1.1
2A	.23	1.7	.35	1.2
2B	.02	20.0	.12	3.3
4	.13	3.1	.11	3.6
6	1.2	0.33	.45	0.9
8	0.31	1.3	.77	.52
9	4.3	.93	8.0	.05
10B	0.9	.44	>20	> .02
11B	10.0	.04	0.9	.45
12	9.3	.04	5.0	.08
Amitriptyline	0.038	9.5	0.005	80
Atropine	.004	100		
Promethazine			.004	100

(19) F. Herr, J. Stewart, and M. P. Charest, *Arch. Intern. Pharmacodyn.*, **134**, 328 (1961).

(20) P. A. J. Janssen and A. H. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957).

(21) E. G. van Proosdij-Hartzema and D. K. de Jongh, *Acta Physiol. Pharmacol. Neer.*, **5**, 398 (1957); cited from ref. 3, p. 75.

analogous benzhydryl compounds described by de Jongh.[22] Replacement of the carbonitrile group in compounds 1A and 4 by the carboxamido group to give compounds 9 and 12 decreased both antiacetylcholine and antihistamine activity, whereas a similar replacement in de Jongh's series increased the antiacetylcholine activity. Quaternarization of the amines to give compounds 1B and 2B increased the antiacetylcholine activity, a result in agreement with de Jongh's findings.

When the peripheral activities of our compounds are compared to those of amitriptyline it is seen that only two compounds (1B and 2B) are more active against acetylcholine, whereas they all have markedly diminished antihistamine activity (less than 4% of promethazine compared to 80% for amitriptyline).

Experimental[23]

5-Cyanodibenzo[a,d]cycloheptadiene (II).—A solution of 5-chlorodibenzo[a,d]cycloheptadiene (I)[4] (315 g., 1.4 mole) in dry benzene (800 ml.) was added to a stirred suspension of silver cyanide (254 g., 1.9 mole) in benzene (800 ml.) and the mixture was heated under reflux for 12 hr. The inorganic material was filtered off, washed with fresh solvent, and the combined solutions were treated with charcoal and evaporated. Recrystallization from 95% ethanol or carbon tetrachloride–hexane gave 267 g. (89% yield) of the nitrile as white needles, m.p. 91–92°.

Anal. Calcd. for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.34; H, 5.92; N, 6.48.

Dibenzo[a,d]cycloheptadiene.—A mixture of dibenzo[a,d]-cycloheptadiene-5-one (99.0 g., 0.47 mole), absolute ethanol (50 ml.) and Raney nickel (no. 28; 1 teaspoonful) was hydrogenated at 102 kg./cm.^{2} at 150° until the theoretical amount of hydrogen was consumed (5 hr.). The mixture was diluted with ethyl acetate, filtered, evaporated, and distilled to give 61.9 g. (67% yield) of the hydrocarbon, b.p. 122–128° (0.4–0.5 mm.), m.p. 75–76° (lit.[5] m.p. 75°).

Dibenzo[a,d]cycloheptadiene-5-carboxylic Acid (IV). A.—A well stirred suspension of the nitrile (II) (26.2 g., 0.12 mole) in 57% sulfuric acid (160 ml.) was heated under reflux for 5.5 hr. The mixture was cooled, diluted with water, the collected precipitate was stirred with dilute sodium hydroxide solution and the suspension was filtered. Acidification of the filtrate gave 20.1 g. (70% yield) of needles from ethylene dichloride, m.p. 220–221°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.17; H, 5.85.

From the alkali-insoluble material there was isolated 4.0 g. (14% yield) of dibenzo[a,d]cycloheptadiene-5-carboxamide, long needles from acetonitrile, m.p. 193–194°.

Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.94; H, 6.60; N, 6.10.

B.—Lithium (from a 40% dispersion in oil; 32.4 g., 1.86 g. atom) was suspended in dry tetrahydrofuran (500 ml.) and the mixture was stirred under nitrogen. About 30 ml. of a solution of I (100 g., 0.41 mole) in tetrahydrofuran (250 ml.) was added and the mixture was stirred and heated under reflux for 3 hr., during which time a deep red color developed. Heating was continued and the remainder of the solution was added dropwise over a period of 4 hr. The reaction was completed by heating for a further 2 hr., and keeping overnight at room temperature. The mixture was poured onto an excess of Dry Ice and when it had come to room temperature the unused lithium was destroyed by the addition of ethanol. It was then poured into dilute hydrochloric acid and the chloroform extract of the aqueous layer was extracted with 10% sodium hydroxide solution. The alkaline layer was washed with hexane and acidified to furnish 76.2 g. (73% yield) of the acid, m.p. 217°.

C.—Potassium (1.1 g., 0.028 g. atom) was added in small portions to liquid ammonia (150 ml.) containing a few crystals of ferric nitrate. When the blue color had been discharged, a solution of dibenzo[a,d]cycloheptadiene (4.9 g., 0.025 mole) in dry ether (100 ml.) was added dropwise. A characteristic red-yellow color developed at once. The mixture was stirred at room temperature until all of the ammonia had evaporated (*ca.* 2 hr.), fresh ether being added from time to time to maintain the original volume. A large excess of finely divided Dry Ice was added and the mixture was stirred overnight. The suspension was poured into cold water (100 ml.), the ether layer separated, washed with dilute sodium hydroxide solution and dried. Evaporation left 3.2 g. (65% recovery) of hydrocarbon, m.p. 75–77°. Acidification of the combined alkaline layers gave 1.9 g. (32% yield) of the acid, m.p. 221°.

D.—Sodium (0.6 g., 0.025 g. atom) was added to naphthalene (3.2 g., 0.025 mole) dissolved in dry tetrahydrofuran (20 ml.). The mixture was stirred at room temperature for 1 hr., and a solution of dibenzo[a,d]cycloheptadiene (4.9 g., 0.025 mole) in tetrahydrofuran (15 ml.) was added, causing a slightly exothermic reaction. It was stirred for a further 2 hr., carbonated with Dry Ice and processed in the usual manner to give 1.0 g. of acidic material, m.p. 190–210°. One recrystallization from acetic acid afforded 0.6 g. (10% yield) of the desired acid, m.p. 220–222°.

Dibenzo[a,d]cycloheptadiene-5-carbonyl Chloride.—A solution of thionyl chloride (31.0 g., 0.26 mole) in dry benzene (30 ml.) was added dropwise to a stirred suspension of the carboxylic acid (31.0 g., 0.13 mole) in benzene. The mixture was heated under reflux for 3 hr., cooled, and evaporated *in vacuo*. The residue was triturated with a little cold petroleum ether (b.p. below 40°) and dried to furnish 24.9 g. (75% yield) of the acid chloride, m.p. 67–69°. A purified sample, needles from hexane, had m.p. 71–72°.

Anal. Calcd. for $C_{16}H_{11}ClO$: C, 74.86; H, 5.10; Cl, 13.81. Found: C, 74.56; H, 5.02; Cl, 13.84.

Dibenzo[a,d]cycloheptadiene-5-pyrrolidide.—A solution of the acid chloride (12.0 g., 0.047 mole) in dry benzene (50 ml.) was added dropwise and with stirring to pyrrolidine (7.8 g., 0.11 mole) dissolved in benzene (50 ml.) and the mixture was heated under reflux for 6 hr. The cooled solution was extracted with dilute hydrochloric acid, water and then dried and evaporated. Trituration of the residual oil with a little 2-propanol afforded the amide as a solid; prisms from 2-propanol–hexane, m.p. 115–117° (9.2 g., 67% yield).

Anal. Calcd. for $C_{20}H_{19}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.55; H, 7.41; N, 4.66.

5-Cyano-5-(2-diethylaminoethyl)dibenzo[a,d]cycloheptadiene.—Sodium hydride (53.8% dispersion in oil; 2.44 g., 0.055 mole) was added to dry toluene (50 ml.) followed by a solution of II (11.0 g., 0.05 mole) in toluene (50 ml.). The stirred suspension was warmed to the boiling point over a period of 0.5 hr., at which time a vigorous reaction set in with the development of a brown coloration. It was heated under reflux for 2.5 hr., cooled and treated dropwise with a solution of 2-diethylaminoethyl chloride (9.5 g., 0.07 mole) in toluene (20 ml.). Heating was continued for a further 5 hr., and the mixture was filtered and extracted with N hydrochloric acid. The acidic extracts were combined, washed with ether, and rendered alkaline with sodium hydroxide. The liberated oil was taken up in benzene, and the solution dried and evaporated *in vacuo* to constant weight. The product (14.2 g.) was converted to the hydrochloride salt which was recrystallized from acetonitrile–ether giving 14.0 g. (79% yield), m.p. 185–186° dec. (see Table I, no. 1A).

5-[2-(4-Carbethoxy-4-phenylpiperidino)ethyl]-5-cyanodibenzo[a,d]cycloheptadiene (VI).—To the sodium salt derived from the nitrile (11.0 g., 0.05 mole) and sodium hydride (53.8% dispersion in oil; 2.44 g., 0.055 mole) in dry toluene (100 ml.) was added dropwise and with stirring a solution of 1,2-dibromoethane (9.4 g., 0.10 mole) in toluene (10 ml.). The reaction mixture was then heated under reflux for 4 hr., filtered, and the solution concentrated *in vacuo*. Distillation gave a fraction b.p. 186° (0.3 mm.) (6.7 g.) as a yellow-colored oil containing 5-(2-bromoethyl)-5-cyanodibenzo[a,d]cycloheptadiene (III).

A solution of III (6.7 g., 0.02 mole), 4-carbethoxy-4-phenylpiperidine[24] (4.6 g., 0.02 mole) in dry xylene (75 ml.) was stirred and heated under reflux for 18 hr. The mixture was cooled, diluted with ether (200 ml.), and filtered. The solution was extracted with N hydrochloric acid (25 ml.) giving a salt (3.7 g.) which crystallized from the aqueous layer. This was collected, washed with a little water and ether, and recrystallized from aqueous ethanol to furnish 3.2 g. (31% yield) of the hydrochloride as white needles, m.p. 160–161° dec. (see Table I, no. 3B).

(22) D. K. de Jongh, E. C. van Proosdij-Hartzema, and P. Janssen, *Arch. Intern. Pharmacodyn.*, **103**, 100 (1955).

(23) Melting points were read on a Thomas–Hoover Uni-melt apparatus.

(24) R. H. Toeg and E. Walton, *J. Chem. Soc.*, 559 (1948).

5-(2-Diethylaminoethyl)dibenzo[a,d]cycloheptadiene-5-carboxamide.—A mixture of the carbonitrile (no. 1A) (15.0 g., 0.042 mole) and 90% sulfuric acid (30 ml.) was heated on the steam bath with stirring for 3 hr. It was cooled, poured into ice and water, and the mixture made alkaline with sodium hydroxide. The product was collected in chloroform and the organic layer was dried and evaporated. The residue was converted to the oxalate salt which was recrystallized from ethanol–ether, m.p. 161–162° dec. (12.2 g., 69% yield) (see Table II, no. 9).

5-(2-Morpholinoethyl)dibenzo[a,d]cycloheptadiene-5-pyrrolidide (VII).—A solution of the pyrrolidide (8.3 g., 0.028 mole) in dry toluene (50 ml.) was added to sodium hydride (53.8% dispersion; 1.45 g., 0.032 mole) suspended in toluene (50 ml.). The mixture was stirred and heated under reflux for 4 hr., during which time a precipitate formed and an orange color developed. A solution of 2-chloroethylmorpholine (6.7 g., 0.045 mole) in toluene (50 ml.) was added dropwise and heating was continued for an additional 1 hr. The mixture was filtered while hot and the solution was extracted with dilute hydrochloric acid. The aqueous layer was extracted with ether, made alkaline and the oil was taken up in benzene. Evaporation of the solvent left the product as a solid; needles from petroleum ether (b.p. 80–100°) or ethyl acetate–hexane, m.p. 148–149° (4.4 g., 38% yield) (see Table II, no. 11A).

Removal of the Cyano Group.—A suspension of sodium amide (2.3 g., 0.06 mole) in xylene (100 ml.) was treated with the free base V (5.1 g., 0.015 mole) and the mixture was stirred and heated under reflux for 16 hr. It was cooled, treated with water, and the organic layer was extracted with dilute hydrochloric acid. The acidic layer was made alkaline and the product was collected in benzene. Evaporation of the solvent gave 4.1 g. (87% yield) of IX; the hydrochloride, m.p. 185–187°, was identical with an authentic sample.[2]

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Some Analogs of Imipramine

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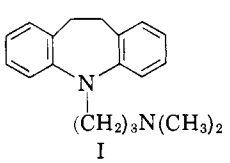
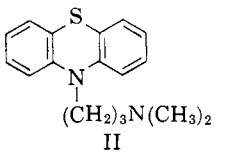
As part of a search for compounds possessing antidepressant properties, some dialkylaminoalkyl derivatives of 5,6,11,12-tetrahydrodibenz[b,f]azocine, 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine have been synthesized. A summary of the pharmacological results is given. In various tests for autonomic activity and for antagonism of reserpine effects the N-(3-dimethylaminopropyl) derivatives of the first two ring systems possessed negligible activity, whereas 5-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]diazepine showed activity comparable to that of imipramine.

In 1957 it was shown[1] in the Swiss clinics that 5-(3-dimethylaminopropyl)-10,11-dihydrodibenz[b,f]azepine (imipramine) (I) was a useful drug in the treatment of depressive syndromes, and it has since achieved an established position in therapy. It was synthesized[2] initially as an antihistamine, and was tested for tranquillizing properties in view of its close chemical similarity to the phenothiazines. The structural resemblance between imipramine and 10-(3-dimethylaminopropyl)-phenothiazine (promazine) (II), contrasted with their remarkable pharmacological and clinical differences, stimulated speculation on the changes in activity that might be encountered by further changes in the ring system. Häfliger has pointed out[3] that both molecules have similar volume and shape, but that



I



II

whereas promazine is a symmetrical molecule, the ring structure of imipramine is asymmetrical, the two aromatic rings being markedly twisted relative to each other. Moreover, with promazine the sulfur atom enables the conjugation of the benzene rings to extend over this bridge, whereas the two-carbon bridge of imipramine acts as a barrier to conjugation.

With physicochemical points such as these in mind, and with the aim of discovering agents which show modified pharmacological properties compared to imipramine, we have synthesized various derivatives of 5,6,11,12-tetrahydrodibenz[b,f]azocine (V), 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI), and 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine (XXI). Recently, other groups of workers with presumably the same approach in mind, have described several similar tricyclic systems carrying dialkylaminoalkyl side chains, which are variations of the imipramine and promazine structures. Examples of such compounds are the drug 5-(3-dimethylaminopropylidene)-10,11-dihydrodibenzo[a,d]cycloheptene (amitriptyline),[4] and N-(ω-dialkylaminoalkyl) derivatives of 5,6 dihydro-11H-dibenz[b,e]azepine,[5] 5,10,11,12-tetrahydrodibenz[b,g]azocine,[6] 6,11-dihydrodibenzo[b,e][1,4]thiazepine,[7] and 10,11-dihydrodibenzo[b,f][1,4]thiazepine.[8]

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