Anticonvulsants. I. Dibenzo[a,d]cycloheptadiene-5-carboxamide and Related Compounds

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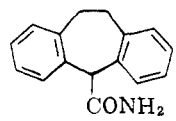
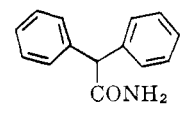
A series of dibenzo[a,d]cycloheptadiene- and dibenzo[a,e]cycloheptatriene-5-carboxamides has been prepared and evaluated as anticonvulsant agents. Other tricyclic carboxamides derived from the introduction of a methylene, isopropylidene, trimethylene, sulfur, or oxygen bridge between the *o,o'*-positions of the phenyl rings in diphenylacetamide were also evaluated. The effect on activity caused by the introduction of an ethylene bridge into certain other benzhydryl containing anticonvulsants to give their dibenzo[a,d]cycloheptadiene analogs was studied. The title compound and its cycloheptatriene analog were found to possess good anticonvulsant activities in mice with low orders of toxicity and neurotoxicity.

During the course of an investigation into new psychotropic agents it was necessary to prepare dibenzo[a,d]cycloheptadiene-5-carboxylic acid.[1] Hydrolysis of the corresponding 5-cyano compound by aqueous sulfuric acid gave the carboxylic acid together with minor amounts of dibenzo[a,d]cycloheptadiene-5-carboxamide (I). The latter was found to possess a high order of anticonvulsant activity and was more potent orally than diphenylacetamide (II),[2] the open-ring analog.



I



II

A series of tricyclic carboxamides was prepared in order to study the effect on activity caused by the introduction of substituents on the ring and on the amide nitrogen atom as well as the effect of changing the juxtaposition of the benzene rings by altering the bridging groups. Carboxamide derivatives of dibenzo[a,d]-cycloheptadienes, dibenzo[a,e]cycloheptatrienes, 9,10-dihydroanthracenes, dibenzo[a,d]cyclooctadiene, and thioxanthene were prepared (see Table I). Several known tricyclic carboxamides were also prepared for comparison and are listed in Table II. Many of the carboxamides were synthesized *via* the corresponding nitriles which in turn were obtained by treating the appropriate chloro compound with silver cyanide in dry benzene.[1] The 5-cyanodibenzo[a,e]cycloheptatrienes were conveniently prepared by adding a dilute solution of the halide very slowly to the silver cyanide in order to suppress the formation of side products. 5-Cyanodibenzo[a,e]cycloheptatriene itself could also be prepared by treatment of the corresponding diene with bromine followed by distillation, or with N-bromosuccinimide and subsequent heating with triethylamine. In both cases, however, the product was obtained in low yield and was difficult to purify. Treatment of 5-cyanodibenzo[a,d]cycloheptadiene with sodamide and dimethyl sulfate gave the corresponding 5-methyl derivative.

The attempted controlled hydrolyses[3] of 5-cyanodibenzo[a,d]cycloheptadiene to the carboxamide using concentrated sulfuric acid at 25°, boiling hydrochloric acid, hot polyphosphoric acid, or hydrogen peroxide in aqueous sodium hydroxide were unsuccessful. The amide was obtained in 41% yield by heating the nitrile with a mixture of equal parts of sulfuric acid, acetic acid, and water and in 70% yield using potassium hydroxide in boiling ethanol for 18 hr. Heating diphenylacetonitrile with the latter reagent for 2 hr. gave a 68% yield of diphenylacetamide[4a] while 9-cyanoxanthene gave the corresponding carboxamide in 60% yield after heating for 20 min. with aqueous, alcoholic potassium hydroxide.[4b] An additional method, suitable for the preparation of the dibenzo[a,d]cycloheptadiene-5-carboxamides, involved saturating a suspension of the appropriate nitrile in aqueous acetic acid with boron trifluoride.[3] Application of this procedure to 5-cyanodibenzo[a,e]cycloheptatriene however, gave only tarry products. In this case the nitrile was first hydrolyzed to the carboxylic acid with boiling, aqueous sulfuric acid, and the amide was prepared *via* the acid chloride. It could also be obtained by direct hydrolysis of the nitrile with alcoholic potassium hydroxide.

Several alternative routes to dibenzo[a,e]cycloheptatriene-5-carboxylic acid were investigated. Dibenzo[a,e]cycloheptatriene was metalated with either butyllithium[5] or potassium amide[6] and the metal derivative was carbonated to give low yields of the carboxylic acid. The required hydrocarbon was readily obtained by a modification of the procedure of Tardieu.[7] Treatment of 5-chlorodibenzo[a,e]cycloheptatriene with lithium in tetrahydrofuran[8] followed by carbonation

(1) M. A. Davis, S. O. Winthrop, J. Stewart, F. A. Smahara, and F. Herr, *J. Med. Chem.*, **6**, 251 (1963).

(2) W. J. Close and M. A. Spielman in "Medicinal Chemistry," V. V. W. H. Hartung, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 159.

(3) C. R. Hauser and D. S. Hoffenberg, *J. Org. Chem.*, **20**, 1448 (1955).

(4) (a) R. Anschütz and R. Romig, *Ann.*, **233**, 347 (1886); (b) E. Kasztreiner and L. Vargha, *Acta Chim. Acad. Sci. Hung.*, **32**, 473 (1962).

(5) C. L. Dubl, A. E. Drukker, and J. H. Biel, U. S. Patent 2,985,660 (1961).

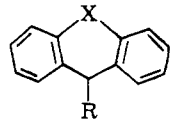
(6) F. J. Villani, C. A. Ellis, C. Teicholman, and C. Bigos, *J. Med. Pharm. Chem.*, **5**, 373 (1962).

(7) P. Tardieu, *Ann. Chim.* (Paris), **6**, 1445 (1961).

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

TABLE I

TRICYCLIC CARBOXAMIDES AND RELATED COMPOUNDS



No.	X	Ring substituent	R	M.p., °C.	Recrystn. solv.	Yield, %	Formula	Anal., calcd. over found C	H	N
1	CH_2CH_2		$CONH_2$	193–194	[a]	85[j]	$C_{16}H_{15}NO$	80.98	6.37	5.90
								80.94	6.60	6.10
2	CH_2CH_2		$CONHCH_3$	201–202	[b,c]	54[k]	$C_{17}H_{17}NO$	81.24	6.82	5.57
								80.98	6.81	5.56
3	CH_2CH_2		$CONHCH_2C_6H_5$	110–111	[c,d]	75[k]	$C_{23}H_{21}NO$	84.37	6.47	4.28
								84.12	6.47	4.21
4	CH_2CH_2	3-Cl	$CONH_2$	175–177	[c,e]	59[j]	$C_{16}H_{14}ClNO$	70.73	5.19	13.05[n]
								70.46	5.39	12.78
5	CH_2CH_2	2,4-$(CH_3)_2$	$CONH_2$	194–196	[a]	83[j]	$C_{18}H_{19}NO$	81.47	7.22	5.28
								81.21	7.20	5.23
6	CH_2CH_2	5-CH_3	$CONH_2$	210–211	[c,f]	72[j]	$C_{17}H_{17}NO$	81.24	6.82	5.57
								80.85	6.68	5.88
7	CH_2CH_2	5-NH_2	$CONH_2$	281–282 dec.	[b,c]	28[k]	$C_{16}H_{16}N_2O$	76.16	6.39	11.10
								76.78	7.11	10.74
8	CH=CH		$CONH_2$	217–219	[b,c]	75[k,l]	$C_{16}H_{13}NO$	81.68	5.57	5.95
								81.41	5.50	5.99
9	CH=CH	3-Cl	$CONH_2$	196–197	[g]	80[k,m]	$C_{16}H_{12}ClNO$	71.23	4.48	13.15[n]
								70.94	4.61	13.17
10	CH_2		$CONH_2$	151–152	[b,c]	68[k]	$C_{15}H_{13}NO$	80.69	5.87	6.27
								80.35	5.85	6.28
11	$C(CH_3)_2$		$CONH_2$	164–165	[c,f]	59[k]	$C_{17}H_{17}NO$	81.24	6.82	5.57
								81.53	6.92	5.73
12	$(CH_2)_3$		$CONH_2$	170–171	[c,d]	62[k]	$C_{17}H_{17}NO$	81.24	6.82	5.57
								81.39	7.03	5.46
13	S		$CONH_2$	222–223	[b,c]	24[k]	$C_{14}H_{11}NOS$	69.70	4.59	5.80
								69.44	4.78	6.03
14	CH_2CH_2		=NOH	167–170	[b]	83	$C_{15}H_{13}NO$	80.70	5.87	6.27
								80.97	5.95	6.23
15	CH_2CH_2		$NHCOCH_3$	280–282	[h]	39	$C_{17}H_{17}NO$	81.24	6.82	5.57
								81.39	6.98	5.53
16	CH_2CH_2		$NHCONH_2$	282–283 dec.	[b,i]	56	$C_{16}H_{16}N_2O$	76.16	6.39	11.10
								76.52	6.48	10.75
17	CH_2CH_2		$NHCONHCOCH_3$	203–204	[b]	44	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52
								73.24	6.31	9.50

[a] Acetonitrile. [b] Ethanol. [c] Hexane. [d] 2-Propanol. [e] Ethyl acetate. [f] Benzene. [g] Isopropyl acetate. [h] Dioxane. [i] Ethylene dichloride. [j] From the corresponding nitrile and BF_3. [k] From the corresponding carboxylic acid chloride. [l] Also prepared in 55% yield by heating the nitrile with KOH in boiling ethanol for 12 hr. [m] Both the corresponding acid and acid chloride were not characterized due to difficulties incurred in purifications. [n] Chlorine.

gave the carboxylic acid in 35% yield. 5-Chlorodibenzo[a,d]cyclooctadiene when treated in this manner gave only the dimeric hydrocarbon, bis-(5-dibenzo[a,d]cyclooctadienyl). Dibenzo[a,d]cycloheptadiene-5-carboxylic acid has been prepared in 39% yield from 5-methoxydibenzo[a,d]cycloheptadiene by treatment with sodium–potassium alloy followed by carbon dioxide.[9] Application of this method to 5-methoxydibenzo[a,e]cycloheptatriene gave a very low yield of the desired acid.

Metalation of 9,10-dihydroanthracene with butyllithium with subsequent carbonation following a published procedure[10] gave the 9-carboxylic acid which was contaminated with the 9,10-dicarboxylic acid.[11] A purer product was obtained by reducing the quantity of the metalating agent. 9,9-Dimethyl-9,10-dihydroanthracene-10-carboxylic acid was obtained in a similar manner from the corresponding hydrocarbon (IV) which was prepared by the acid-catalyzed cyclization of 2-benzyl-α,α-dimethylbenzyl alcohol (III). This alcohol was prepared from methyl 2-benzylbenzoate and methyllithium. Similar attempted cyclizations of the homologous 2-benzyl-α,α-diethyl- and 2-benzyl-α,α-diisopropylbenzyl alcohols were unsuccessful.[12] Heating III with hydrogen chloride in acetic acid gave significant amounts of the styrene derivative (V) whose presence was indicated by the characteristic absorption in the near infrared region. The use of 70% aqueous sulfuric acid minimized the formation of V giving 9,9-dimethyl-9,10-dihydroanthracene (IV) and a little 9-methylanthracene. The hydrocarbon IV was characterized by its conversion to 10,10-dimethylanthrone (VII) on treatment with chromium trioxide. The small amount of 10-hydroxy-10-methylanthrone (VIII) which was also formed was best removed by converting it to anthraquinone through further oxidation of the mixture.

(9) C. van der Stelt, *Belgian Patent* 616,907 (1962); *Derwent Reports*, **93A**, 7 (1962).

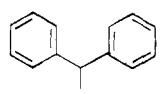
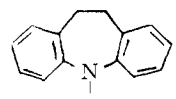
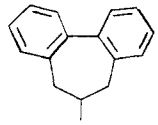
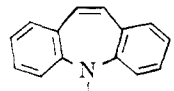
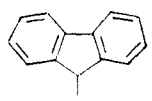
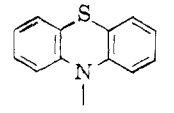
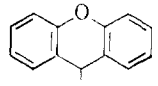
(10) R. B. Burtner and J. W. Cusic, *J. Am. Chem. Soc.*, **65**, 1582 (1943).

(11) B. M. Mikhailov and A. N. Blokhina, *Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 279 (1949); *Chem. Abstr.*, **44**, 2963 (1950).

(12) E. de B. Barnett, J. W. Cook, and I. G. Nixon, *J. Chem. Soc.*, 504 (1927).

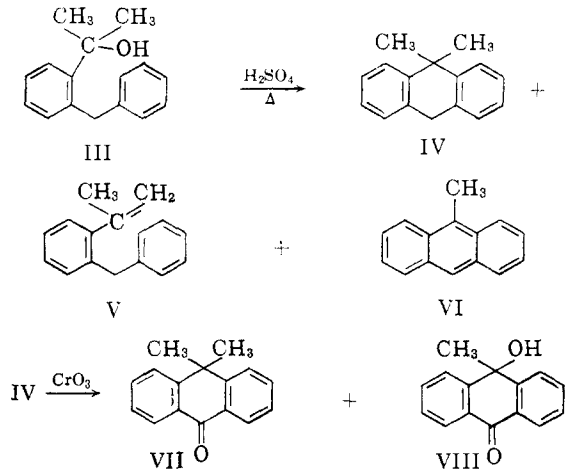
TABLE II

KNOWN COMPOUNDS $RCONH_2$

No.	R		No.	R	
18		*a*	22		*f*
19		*b, c*	23		*g*
20		*d*	24		*h*
21		*e*			

[a] See ref. 2. [b] J. Kenner, *J. Chem. Soc.*, 613 (1913). [c] The intermediate 2,2-bis-(hydroxymethyl)- and 2,2,-bis-(bromomethyl)-diphenyl were prepared as described by D. M. Hall, M. S. Lesslie, and E. E. Turner, *ibid.*, 711 (1950). [d] R. Stollé and P. Wolf, *Ber.*, **46**, 2248 (1913). [e] See ref. 4b. [f] C. J. Morel and P. Hafliger, U. S. Patent 2,762,796 (1956). [g] W. Schindler, U. S. Patent 2,948,718 (1960). [h] S. Paschkowezky, *Ber.*, **24**, 2905 (1891).

It was of interest to extend this investigation to include the dibenzo[a,d]cycloheptadiene analogs of other benzhydryl derived anticonvulsants. Benzilamide[13] has been prepared by the interaction of methyl benzilate and ammonium hydroxide in the presence of ammonium chloride[14] or by heating benzilic acid and ammonium carbonate in acetic acid.[15] Application of these methods to the analogous methyl 5-hydroxydibenzo-[a,d]cycloheptadiene-5-carboxylate and to the free acid[16] failed to give recognizable amounts of the desired 5-hydroxydibenzo[a,d]cycloheptadiene-5-carboxamide. By a modification of the method described for the preparation of α-aminodiphenylacetamide,[17] the action of ammonia on 5-chlorodibenzo[a,d]cycloheptadiene-5-carbonyl chloride[16] gave 5-aminodibenzo[a,d]-cycloheptadiene-5-carboxmide in 28% yield. The dibenzo[a,d]cycloheptadiene analogs of N-benzhydrylacetamide,[2] 1-benzhydrylurea[18] and 1-acetyl-3-benzhydryl urea,[19] were also prepared. Prolonged heating of dibenzo[a,d]cycloheptadiene-5-one with hydroxylamine hydrochloride in aqueous pyridine gave the 5-oxime which was reduced catalytically to the 5-amino compound.[20] The crude product from the hydrogenation was acetylated directly to furnish 5-acetamidodibenzo-[a,d]cycloheptadiene. The two dibenzo[a,d]cycloheptadienyl ureas were prepared by methods similar to those used for the corresponding benzhydryl compounds.[21-23] Thus 5-chlorodibenzo[a,d]cycloheptadiene and silver cyanate in boiling acetonitrile gave the 5-isocyanate which, on treatment with ammonium hydroxide, furnished the urea. Acetylation of this with acetyl chloride then gave 1-(5-dibenzo[a,d]cycloheptadienyl)-3-acetylurea.



Biological Activity.—The novel tricyclic compounds listed in Table I together with several known tricyclic carboxamides (Table II) were tested in mice for their acute toxicity, anticonvulsant activity, and neurotoxic effect. All materials were injected in the form of suspensions which were made up with 4 to 5 drops of Tween 80 in 10 ml. of water. In most cases the approximate LD_{50} values were determined using 20 mice per compound, in other cases the LD_{50} was calculated by the method of Litchfield and Wilcoxon,[24] injecting 4 to 5 doses to groups of 10 animals each. In these latter cases the standard errors of the LD_{50} are shown in Table III.

The protective effect of the compounds against the tonic phase of maximal electroshock seizure (MES) was tested in a similar way as described by Swinyard, *et al.*[25] Groups of 10 animals were pretreated with increasing doses of the compounds and 60 min. later an electrical shock (30 mA; 0.2 sec.) was applied through corneal electrodes. The ED_{50} values were calculated from the number of protected animals.[24] The effect on MES was investigated after i.p. and oral application of the drugs. The antipentylenetetrazole effect was measured by oral administration. Four to 5 groups of 10 mice were used to determine the ED_{50} values[24] which protected against the tonic phase of the pentylenetetrazole convulsion. The drugs were given 60 min. before an i.p. dose of 100 mg./kg. of the convulsant.

The ataxia produced by the compounds was measured in mice by means of the rotating bar test.[26] Groups of 10 mice received increasing doses of the compounds orally and 60 min. later they were placed on a rotating bar. They were considered ataxic if they fell off the bar twice in 1 min. The affected mice were placed back on the bar immediately after the first fall. The data were evaluated in all-or-none terms and the ED_{50} values were calculated.[24]

(13) H. H. Merritt and T. J. Putnam, *Epilepsia*, [2] **3**, 51 (1945).
(14) A. Rahman and M. O. Farooq, *Naturwissenschaften*, **41**, 15 (1954).
(15) C. H. Kao and S.-Y. Ma, *Science Rept. Natl. Tsing Hua Univ., Ser. A*, **1**, 17 (1931); *Chem. Abstr.*, **26**, 1592 (1932).
(16) M. A. Davis, F. A. Sunohara, F. Herr, and R. Gaudry, *J. Med. Chem.*, **6**, 513 (1963).
(17) J. H. Billman and P. H. Hidy, *J. Am. Chem. Soc.*, **65**, 760 (1943).
(18) See ref. 2, p. 139.
(19) See ref. 2, p. 42.
(20) Preparation of this compound by a different procedure has been reported by J. Bernstein and K. A. Losee, U. S. Patent 3,052,721 (1962).
(21) J. J. Donleavy and J. English, Jr., *J. Am. Chem. Soc.*, **62**, 218 (1940).
(22) I. A. Kaye, I. C. Kogon, and C. L. Parris, *ibid.*, **74**, 403 (1952).
(23) R. Duschinsky, U. S. Patent 2,560,522 (1951).
(24) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
(25) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *ibid.*, **106**, 319 (1952).
(26) N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1946).

TABLE III
PHARMACOLOGICAL INVESTIGATIONS

Compound	LD_{50}, mg./kg., i.p.	MES ED_{50} mg./kg., i.p./oral	Antipentylenetetrazole ED_{50}, mg./kg., oral	Ataxia ED_{50}, mg./kg., oral
1	630 ± 31[a]	25 ± 1		
		33 ± 3.5	14.5 ± 3	400 ± 44
2	550	72 ± 5		
		280 ± 30	84 ± 6	>400
3	>1200	>400		
			>400	>400
4	550	47 ± 4		
		69 ± 4	49 ± 6	465 ± 41
5	>1400	125 ± 10		
		166 ± 10	158 ± 5	>800
6	850	62 ± 5		
		64 ± 6	30 ± 4	430 ± 31
7	>700	>200		
8	582 ± 33	16.5 ± 1		
		22.5 ± 2	13 ± 2	165 ± 20
9	650	11.8 ± 1		
		35 ± 1	8 ± 1	310 ± 14
10	380	25 ± 1		
		42 ± 7	15 ± 2	175 ± 20
11	250	>75		
		>100	46.5 ± 4	70 ± 5
12	520	37.5 ± 5		
		68 ± 6	29 ± 3	205 ± 36
13	>800	34 ± 2.7		
		66 ± 6.8		
14	350	49 ± 3		
			61 ± 5	>160
15	>1000	>300		
		>400	34.5 ± 6	>600
16	>1200	>400		
			53 ± 20	>400
17	1300	132 ± 11		
		299 ± 6	265 ± 8	>1400
18	1150 ± 61	26 ± 4		
		56 ± 2.3	30.5 ± 5	470 ± 18
19	750	100 ± 9		
		410 ± 37	45 ± 10	340 ± 12
20	>1200	36 ± 2		
		62 ± 5.4	22.5 ± 6	400–600
21	>1200	54 ± 3		
		53 ± 3	45 ± 6	>600
22	750	19 ± 1		
		20.5 ± 1.3	21.5 ± 1.8	176 ± 22
23	350	11.7 ± 1		
		18.8 ± 1.6	11.5 ± 2	66 ± 5.7
24	1300	31 ± 2		
		34.5 ± 4	20 ± 3	>300
Phenobarbital sodium	249 ± 12	11.6 ± 1.4		
		17.8 ± 2.6	3.6 ± 0.6	76 ± 3.6
Diphenylhydantoin	170 ± 13	9.6 ± 1.6		
		8.9 ± 0.8	7 ± 0.5	84 ± 9
Primidone	290 ± 21	17 ± 3		
		16 ± 3	2 ± 0.6	>250

[a] Standard error.

The results of the pharmacological investigation are given in Table III.

The anticonvulsant activity (MES, i.p.) of diphenylacetamide (18)[2] was maintained or increased by the introduction of an ethylene, ethylidene, or methylene bridge between the *o,o'*-positions of the phenyl rings (1, 8, 10). The oral activities of these compounds were significantly greater than that of diphenylacetamide. On the other hand, the bridging of the phenyl rings by a trimethylene, sulfur, or oxygen function (12, 13, 21) somewhat decreased the activity. The isopropylidene bridge gave a compound (11) which was inactive against MES even at ataxic doses.

In general the doses required to protect against the tonic seizures caused by pentylenetetrazole were smaller than those required for anti-MES effect. An exception was compound 19 (a position isomer of 1) which had a negligible anti-MES effect orally but had significant antipentylenetetrazole activity.

Within the series of dibenzo[a,d]cycloheptadiene-5-carboxamides, substitution either on the ring or on the carboxamido function invariably decreased the activity (2–7). The dibenzo[b,f]azepine-5-carboxamides (22, 23)[27] had good anticonvulsant activities but were considerably more neurotoxic (ataxia) than their corresponding carbocyclic analogs. The dibenzo[a,d]cycloheptadiene analogs of the known benzhydryl anticonvulsants (15–17) were found to be practically inactive against MES but 15 and 16 had some antipentylenetetrazole effects.

The ratios of the toxicity, neurotoxicity, and anticonvulsant effects of compounds 1, 8, and 9 compare favorably with those of leading antiepileptic drugs. Further investigations with these compounds are in progress.

Experimental

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

Dibenzo[a,e]cycloheptatriene.—A solution of the *p*-toluenesulfonate ester of 9-hydroxymethyl-9,10-dihydroanthracene[7] (28.7 g.) in anhydrous formic acid (200 ml.) was heated under reflux for 6 hr. and then chilled. The solid was filtered, washed with water, and dried. There was obtained 14.0 g. (93%) of product, m.p. 131–132° (raised to 132–133° on one recrystallization from 2-propanol) λ_{max}^{EtOH} 285 mμ (ε 14,300); lit.[7] m.p. 131–132°, λ_{max}^{EtOH} 285 mμ (ε 13,800).

2-Benzyl-α,α-dimethylbenzyl Alcohol (III).—Methyl 2-benzylbenzoate[12] [b.p. 109–112° (0.1 mm.)] was prepared from the corresponding acid.[28] A solution of the ester (22.6 g., 0.1 mole) in dry ether (100 ml.) was added dropwise to methyllithium derived from methyl iodide (71.0 g., 0.5 mole) and lithium (6.9 g., 1.0 g. atom) in ether (500 ml.). The mixture was heated under reflux for 3 hr., cooled, and poured onto ice and ammonium chloride. The organic solution was combined with the ethereal extracts of the aqueous layer, dried, and evaporated. There was obtained 21.6 g. of an oil which gradually solidified. Recrystallization from pentane gave a sample of product, m.p. 66–67°.

Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.63; H, 8.00.

9,9-Dimethyl-9,10-dihydroanthracene (IV).[29]—A well stirred mixture of alcohol III (12.4 g.) and 70% aqueous sulfuric acid (w./w., 25 ml.) was heated on the steam bath for 1.5 hr. The mixture was diluted with water, the product taken into benzene, and the organic layer was washed with sodium bicarbonate solution and dried. Evaporation left an oil which contained a small amount of an anthracene derivative. Distillation gave a fraction b.p. 109–116° (0.3–0.4 mm.), $n^{25}D$ 1.5937 – 1.5940 (8.4 g.) consisting of IV together with a trace of the isomeric styrene derivative (V) (weak band for terminal methylene at 1.5–1.6 μ). Thick layer chromatography on silica gel from hexane afforded a purified sample of IV as an oil which developed a blue fluorescence on standing; $n^{25}D$ 1.5916; λ_{max}^{EtOH} 255, 262, 269 mμ (ε 744, 895, 864).

Anal. Calcd. for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 91.89; H, 7.88.

From a similar reaction using a sample of the alcohol which had not been purified there was obtained, in addition to the expected product, a 5% yield of 9-methylanthracene, m.p. 79–80° (from hexane), λ_{max}^{EtOH} 257 mμ (ε 189,000); lit.[30] m.p. 79–80°, λ_{max} 256 mμ (ε 182,000).[31]

Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found: C, 93.39; H, 6.41.

Oxidation of 9,9-Dimethyl-9,10-dihydroanthracene.—A solution of IV (2.0 g., 0.01 mole) in glacial acetic acid (20 ml.) was kept at 50° and treated dropwise with chromium trioxide (1.4 g., 0.014 mole) dissolved in acetic acid (50 ml.) and water (50 ml.); little or no reaction took place below 50°. The bulk of the acetic acid was evaporated, the residue was stirred with water, and then

(27) W. Theobald and H. A. Kunz, *Arzneimittel-Forsch.*, **13**, 122 (1963).
(28) J. Rigaudy and L. Nedelec, *Bull. Soc. Chim. France*, 638 (1959).
(29) The preparation of this compound has been disclosed but no details or physical properties are given: Geigy S. A., Belgian Patent 601,168 (1961).
(30) F. Krollpfeiffer and F. Branshied, *Ber.*, **56**, 1817 (1923).
(31) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

taken into benzene. The solution was extracted with water and sodium bicarbonate, then dried, and evaporated to give 2.3 g. of residue, m.p. 77–94°. Repeated recrystallizations from hexane gave a small quantity of 10-hydroxy-10-methylanthrone (VIII), m.p. 154–155°, identified by comparison with an authentic specimen prepared from anthraquinone and methylmagnesium bromide.[32]

The mother liquors from the above recrystallizations deposited on standing a product in the form of white flakes which was constant-melting at 103–104°, carbonyl at 1667 cm.$^{-1}$, λ_{max}^{EtOH} 268 mμ (ε 18,350); lit.[33,34] m.p. 104.5–105.5° and 99.5–100.5°. Thin-layer chromatography indicated that a small quantity of VIII was still present. Other workers[34] have also reported difficulties in separating a mixture of these two compounds. An analytically pure sample was obtained in the following manner. A sample of the crude material (0.9 g.) was dissolved in acetic acid. The solution was held between 60–70° while chromium trioxide (0.12 g.) dissolved in acetic acid containing a little water was added dropwise while stirring. No further reaction occurred on the addition of more oxidant. The mixture was processed as above to give an insoluble fraction (0.05 g.), m.p. 284–285° (from benzene), undepressed on admixture with anthraquinone. The remaining material was 10,10-dimethylanthrone (VII), white flakes from hexane, m.p. 101–102° (0.4 g.)

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.20; H, 6.32.

3-Chlorodibenzo[a,e]cycloheptatriene-5-ol.—A solution of 3-chlorodibenzo[a,e]cycloheptatriene-5-one[35] (30.1 g., 0.13 mole) in dry tetrahydrofuran (300 ml.) was added dropwise while stirring to a suspension of lithium aluminum hydride (5.2 g., 0.14 mole) in dry ether (250 ml.). The reaction mixture was heated under reflux for 2 hr., cooled, and treated successively with water (5 ml.), 20% sodium hydroxide (4 ml.), and water (18 ml.). The solid was filtered, washed with warm ethyl acetate, and the combined filtrates were evaporated *in vacuo*. Recrystallization from 2-propanol–hexane gave 26.6 g. (88%) of product, m.p. 142–143°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57; Cl, 14.61. Found: C, 74.78; H, 5.19; Cl, 14.40.

3,5-Dichlorodibenzo[a,d]cycloheptadiene.—A solution of 3-chlorodibenzo[a,d]cycloheptadiene-5-ol[36] (21.5 g.) in benzene (250 ml.) was saturated with gaseous hydrogen chloride. The upper layer was separated, dried over calcium chloride, and evaporated. Recrystallization of the residue from petroleum ether (b.p. 80–100°) gave 20.8 g. (89%) of product, m.p. 112–114°. An analytical sample had m.p. 114–115°.

Anal. Calcd. for $C_{15}H_{12}Cl_2$: C, 68.44; H, 4.60; Cl, 26.93. Found: C, 68.29; H, 4.70; Cl, 27.10.

3,5-Dichlorodibenzo[a,e]cycloheptatriene.—The preceding procedure was applied to 3-chlorodibenzo[a,e]cycloheptatriene-5-ol. The product, obtained in a yield of 72%, was recrystallized from carbon tetrachloride–hexane mixture, m.p. 157–158°.

Anal. Calcd. for $C_{15}H_{10}Cl_2$: C, 69.00; H, 3.86; Cl, 27.16. Found: C, 69.02; H, 3.87; Cl, 26.93.

5-Chloro-2,4-dimethyldibenzo[a,d]cycloheptadiene.—Treatment of 2,4-dimethyldibenzo[a,d]cycloheptadiene-5-ol[36] with hydrogen chloride gave the product in 83% yield, m.p. 111–112° (from cyclohexane).

Anal. Calcd. for $C_{17}H_{17}Cl$: C, 79.54; H, 6.63; Cl, 13.84. Found: C, 79.75; H, 6.88; Cl, 13.75.

5-Chlorodibenzo[a,d]cyclooctadiene.—Treatment of dibenzo[a,d]cyclooctadiene-5-ol[37] with hydrogen chloride gave an 88% yield of product, m.p. 122–123° (from carbon tetrachloride–hexane).

Anal. Calcd. for $C_{16}H_{15}Cl$: C, 79.20; H, 6.23; Cl, 14.61. Found: C, 79.45; H, 6.36; Cl, 14.52.

5-Cyanodibenzo[a,e]cycloheptatriene. (a)—Silver cyanide (32.4 g., 0.24 mole) was suspended in dry benzene (250 ml.) and a little of the solvent was distilled in order to secure anhydrous conditions. The mixture was kept at about 35°, covered with a dark cloth, and a solution of 5-chlorodibenzo[a,e]cycloheptatriene[38] (27.4 g., 0.12 mole) in benzene (250 ml.) was added dropwise over 3 hr., efficient stirring being maintained throughout. The mixture was heated under reflux for 7 hr., the solid filtered, and the solution evaporated *in vacuo*. One recrystallization of the residue from hexane gave 20.6 g. (79%) of product, m.p. 98.5–99°. An analytical sample had m.p. 99–100°, λ_{max}^{EtOH} 288 mμ (ε 13,500).

Anal. Calcd. for $C_{16}H_{11}N$: C, 88.45; H, 5.10; N, 6.45. Found: C, 88.16; H, 5.19; N, 6.46.

From another reaction which was carried out in somewhat less solvent and in which the halide was added more rapidly there was also isolated a *hydrocarbon* (0.7 g.), small rectangular prisms from isopropyl acetate, m.p. 213–215°.

Anal. Found: C, 94.09; H, 5.93.

(b).—Bromine (4.0 g., 0.025 mole) was added slowly to 5-cyanodibenzo[a,d]cycloheptadiene[7] (5.5 g., 0.025 mole) which was maintained at 130°; copious fumes were evolved. The mixture was then kept at 220° until the reaction was complete and the dark, tarry material was distilled, b.p. 178–182° (0.1 mm.). Repeated recrystallization from ethanol gave 0.5 g. of the product, m.p. 99–100°, λ_{max}^{EtOH} 286 mμ (ε 12,090).

(c).—A mixture of 5-cyanodibenzo[a,d]cycloheptadiene (5.5 g., 0.025 mole) and N-bromosuccinimide (4.9 g., 0.0275 mole) in dry carbon tetrachloride (100 ml.) was stirred over a heating lamp for 48 hr. After the first 2 hr. a brown color developed, coincident with the formation of a white, granular precipitate and thereafter the internal temperature was constant at 75°. The mixture was filtered while warm and the filtrate was chilled. There was obtained 1.2 g. of 10-bromo-5-cyanodibenzo[a,d]cycloheptadiene, m.p. 138–139° dec.

Anal. Calcd. for $C_{16}H_{10}BrN$: Br, 26.80. Found: Br, 27.05.

Evaporation of the carbon tetrachloride filtrate gave an additional 3.6 g. of the bromo compound which was combined with the preceding sample and heated under reflux for 18 hr. with triethylamine (50 ml.). The mixture was filtered while hot, the filtrate evaporated, the residue taken up in ether, and washed with dilute hydrochloric acid and water. Removal of the solvent and trituration of the residue with a little hexane gave a sample of triene, m.p. 87–88°, λ_{max}^{EtOH} 288 mμ (ε 10,400) which could not be purified by distillation.

5-Cyano-3-chlorodibenzo[a,d]cycloheptadiene.—Interaction of 3,5-dichlorodibenzo[a,d]cycloheptadiene (19.9 g., 0.076 mole) and silver cyanide (20.4 g., 0.15 mole) in benzene (550 ml.) gave 7.7 g. (40%) of product, m.p. 133–134° (from carbon tetrachloride–hexane).

Anal. Calcd. for $C_{16}H_{10}ClN$: Cl, 13.92; N, 5.50. Found: Cl, 13.98; N, 5.33.

5-Cyano-3-chlorodibenzo[a,e]cycloheptatriene.—3,5-Dichloro-[a,e]cycloheptatriene (26.1 g., 0.1 mole) and silver cyanide (26.8 g., 0.2 mole) in benzene (900 ml.) gave 19.2 g. (76%) of the nitrile, m.p. 137–138° (from carbon tetrachloride–hexane).

Anal. Calcd. for $C_{16}H_{10}ClN$: C, 76.35; H, 4.01; Cl, 14.09; N, 5.57. Found: C, 76.35; H, 4.02; Cl, 14.01; N, 5.51.

5-Cyano-2,4-dimethyldibenzo[a,d]cycloheptadiene.—Treatment of 5-chloro-2,4-dimethyldibenzo[a,d]cycloheptadiene (24.3 g., 0.095 mole) with silver cyanide (20.0 g., 0.15 mole) in benzene (500 ml.) gave 21.5 g. (92%) of the nitrile, m.p. 138–139° (carbon tetrachloride–hexane).

Anal. Calcd. for $C_{18}H_{17}N$: C, 87.41; H, 6.93; N, 5.66. Found: C, 87.12; H, 7.01; N, 5.61.

5-Cyano-5-methyldibenzo[a,d]cycloheptadiene.—A mixture of 5-cyanodibenzo[a,d]cycloheptadiene (11.0 g., 0.05 mole) and sodamide (2.15 g., 0.055 mole) in dry toluene (80 ml.) was stirred and heated under reflux for 1.5 hr. It was cooled to room temperature, treated dropwise with a solution of dimethyl sulfate (8.8 g., 0.07 mole) in toluene (20 ml.), and heated on the steam bath for 1 hr. The precipitate was filtered and the toluene solution was washed with water and evaporated. Distillation of the residue afforded 8.1 g. of an oil, b.p. 152–158° (0.3–0.4 mm.) which solidified, m.p. 55–62°. Recrystallization from ethanol gave 4.0 g. (34%) of product, m.p. 75–76°.

Anal. Calcd. for $C_{17}H_{15}N$: N, 6.00. Found: N, 5.98.

The use of sodium ethoxide in ethanol as condensing agent gave only unchanged starting material.

Dibenzo[a,e]cycloheptatriene-5-carboxylic Acid. (a)—A well stirred mixture of 5-cyanodibenzo[a,e]cycloheptatriene (7.0 g.) and 57% sulfuric acid (w./w., 70 ml.) was heated under reflux for 2.5 hr. The cooled mixture was diluted with water, the solid

(32) P. L. Julian, W. Cole, and G. Diemer, *J. Am. Chem. Soc.*, **67**, 1721 (1945).

(33) D. Y. Curtin and W. H. Richardson, *ibid.*, **81**, 4719 (1959).

(34) H. Heyman and L. Trawbridge, *ibid.*, **72**, 84 (1950).

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

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

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

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

filtered, and stirred with dilute sodium hydroxide solution. A little insoluble material was removed and acidification of the filtrate gave 6.6 g. (86% yield) of product, m.p. 239-240°. Recrystallization of a sample from chloroform–hexane gave m.p. 241–242°, λ_{max}^{EtOH} 288 mμ (ε 14,300); lit.[39] m.p. 234-237°.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.27; H, 4.82.

(**b**).—A solution of 5-chlorodibenzo[a,e]cycloheptatriene (5.0 g., 0.022 mole) in dry tetrahydrofuran (25 ml.) was added dropwise while stirring (nitrogen atmosphere) to a suspension of finely-cut lithium wire (0.61 g., 0.088 g. atom.) in the same solvent (15 ml.). A precipitate soon formed and the mixture developed a deep red color after being stirred at room temperature overnight. It was poured onto an excess of crushed Dry Ice, the mixture hydrolyzed by the addition of dilute hydrochloric acid, and the product was taken up in chloroform. The organic layer was extracted with dilute alkali and the aqueous layer was separated and acidified. One recrystallization of the product from chloroform–hexane gave a sample (1.8 g., 35%); m.p. 238–240° after sintering at 233°; λ_{max}^{EtOH} 285 mμ (ε 11,940).

The neutral product from the reaction appeared to be bis-(5-dibenzo[a,e]cycloheptatrienyl). Recrystallization from toluene gave a sample (0.4 g.), m.p. 315–316°, $\lambda_{max}^{CHCl_3}$ 296 mμ (ε 20,400).

Anal. Calcd. for $C_{30}H_{22}$: C, 94.20; H, 5.80. Found: C, 93.71; H, 5.57.

(**c**).—A 15.1% solution of *n*-butyllithium in hexane (Foote Chemical Co., 0.030 mole) was added dropwise under a nitrogen atmosphere to a solution of dibenzo[a,e]cycloheptatriene (5.3 g., 0.028 mole) in dry tetrahydrofuran (60 ml.). The reaction was slightly exothermic and a deep brown color developed. The mixture was stirred for 3.5 hr. at room temperature, poured onto crushed Dry Ice, and processed in the usual manner. The product, after one recrystallization from ethanol–hexane, had m.p. 240–241° (2.0 g., 31%). Carrying out the reaction in dry ether in place of tetrahydrofuran gave only a 5% yield of acid together with a 54% recovery of starting material.

(**d**).—A solution of the dibenzo[a,e]cycloheptatriene (5.3 g., 0.028 mole) in dry ether (200 ml.) was added to potassium amide derived from potassium (1.2 g., 0.031 g.-atom.) in liquid ammonia (200 ml.). The ammonia was allowed to evaporate and the mixture was carbonated and processed as previously described to give 1.2 g. (20%) of product, m.p. 241–242°.

(**e**).—A mixture of dibenzo[a,e]cycloheptatriene-5-ol (6.2 g., 0.03 mole) and sodamide (1.3 g., 0.033 mole) in dry benzene (70 ml.) was warmed gently for 1.5 hr., cooled, and treated with methyl iodide (8.5 g., 0.06 mole) in benzene (20 ml.). The mixture was heated under reflux for 1.5 hr., filtered, and the solution was washed with water, dried, and evaporated. The residual oil (6.4 g., ether at 1087 and 1120 cm.$^{-1}$; λ_{max} 264–282 mμ, (ε 12,500) was distilled to give a fraction (4.0 g.) of b.p. 142–144° (0.5 mm.), $n^{25}D$ 1.6408-1.6430.

An alloy was prepared from sodium (0.56 g.) and potassium (2.2 g.) in xylene. The xylene was replaced by dry ether and the preceding methyl ether (4.8 g.) was added. The mixture was stirred at room temperature for 1 hr. during which time the color turned through green to dark brown. It was heated under reflux for 4 hr. and carbonated. There was obtained 1.2 g. of crude carboxylic acid, m.p. 202–210°, λ_{max} 282 mμ (ε 8900). Recrystallization from chloroform–hexane afforded 0.2 g. of product, m.p. 235–236°.

2,4-Dimethyldibenzo[a,d]cycloheptadiene-5-carboxylic Acid.—A solution of 5-chloro-2,4-dimethyldibenzo[a,d]cycloheptadiene (5.1 g., 0.02 mole) in dry tetrahydrofuran (40 ml.) was added dropwise to a suspension of lithium (60% dispersion in oil; 0.5 g., 0.044 g. atom) in tetrahydrofuran (20 ml.) and the mixture was heated under gentle reflux for 3 hr. The lithio derivative thus formed was carbonated and processed in the manner described above to give 0.6 g. (10%) of the carboyxlic acid, m.p. 184–185° (from benzene–hexane).

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.36; H, 6.77.

9,10-Dihydroanthracene-9-carboxylic Acid.—A solution of *n*-butyllithium prepared[40] from *n*-butyl bromide (37.7 g., 0.27 mole) and lithium wire (4.8 g., 0.07 mole) in dry ether (150 ml.) was added dropwise under an atmosphere of dry nitrogen to a suspension of 9,10-dihydroanthracene (45.0 g., 0.25 mole) in ether (400 ml.). The dark solution was stirred at room temperature for 2 hr. and then heated under reflux for 45 min. It was poured onto an excess of crushed Dry Ice and processed in the usual manner to give 29.9 g. (53%) of acid, m.p. 206–208°.

9,9-Dimethyl-9,10-dihydroanthracene-10-carboxylic Acid.—The lithio compound derived from the interaction of 9,9-dimethyl-9,10-dihydroanthracene (8.4 g., 0.04 mole) and butyllithium (0.05 mole) in tetrahydrofuran (100 ml.) was carbonated and processed in the usual manner to give 5.3 g. (52%) of the carboxylic acid, m.p. 182–183° (from benzene); λ_{max}^{EtOH} 257 (i), 263, 271 mμ (ε 408, 526, 426). The isomeric 2-(α-methylvinyl)diphenylacetic acid, an *o*,α-disubstituted styrene, would be expected to have no ultraviolet absorption maxima.[41]

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.69; H, 6.29.

Dibenzo[a,d]cyclooctadiene-5-carboxylic Acid.—The impure nitrile (4.7 g.) obtained from the interaction of 5-chlorodibenzo-[a,d]cyclooctadiene with silver cyanide was heated under reflux for 12 hr. with 57% sulfuric acid (70 ml.). There was obtained 1.8 g. of acid, m.p. 182–183° (from chloroform–hexane).

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.74; H, 6.32.

Bis-(5-dibenzo[a,d]cyclooctadienyl).—A solution of 5-chlorodibenzo[a,d]cyclooctadiene (12.0 g., 0.05 mole) in dry tetrahydrofuran (55 ml.) was added dropwise to lithium (40% dispersion in oil, 3.5 g., 0.20 g.-atom) suspended in tetrahydrofuran (45 ml.). The mixture was heated under reflux for 42 hr. with occasional irradiation from a high intensity ultraviolet light; at no time was there any evidence of the formation of a lithio compound. The excess of lithium was destroyed by the cautious addition of a little ethanol followed by water. The product (10.4 g., 100%) was filtered and purified by sublimation *in vacuo;* m.p. 345–346°.

Anal. Calcd. for $C_{32}H_{30}$: C, 92.71; H, 7.29. Found: C, 92.43; H, 7.44.

Dibenzo[a,e]cycloheptatriene-5-carbonyl Chloride.—A suspension of dibenzo[a,e]cycloheptatriene-5-carboxylic acid (20.9 g., 0.09 mole) in dry benzene (200 ml.) was treated with thionyl chloride (30.0 g., 0.25 mole) dissolved in benzene (60 ml.). The reaction mixture was heated under reflux for 2.5 hr. and evaporated. One recrystallization of the residue from carbon tetrachloride–hexane gave 15.7 g. (69%) of product, m.p. 128–130°. An analytical sample had m.p. 129–130°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 75.45; H, 4.35; Cl, 13.92. Found: C 75.18; H, 4.31; Cl, 13.85.

Dibenzo[a,d]cycloheptadiene-5-carboxamide. (**a**)—A stream of boron trifluoride was passed over the surface of a stirred suspension of 5-cyanodibenzo[a,d]cycloheptadiene (11.0 g., 0.05 mole) in acetic acid (60 ml.) and water (11 ml.) until saturation was complete. The internal temperature rose spontaneously to 135°; in preparations involving larger quantities it was necessary to apply external heating in order to complete the reaction. The mixture was cooled, made alkaline by the gradual addition of 6 *N* sodium hydroxide, and the precipitate was collected, washed with water, and dried. The solid was then extracted with hot acetonitrile and ethyl acetate and the combined organic solutions were evaporated. One recrystallization of the residue from acetonitrile furnished 10.1 g. (85%) of the amide as long needles, m.p. 193–194°.

(**b**).—A stirred suspension of 5-cyanodibenzo[a,d]cycloheptadiene (0.9 g., 0.004 mole) in 1 ml. each of sulfuric acid, acetic acid, and water was heated under reflux for 1 hr. The mixture was cooled, diluted with water, and the precipitate was collected, washed with dilute sodium hydroxide, then with water, and dried. One recrystallization from acetonitrile gave 0.4 g. (41%) of amide, m.p. 193–194°.

(**c**).—A solution of 5-cyanodibenzo[a,d]cycloheptadiene (2.0 g.) and potassium hydroxide (6.0 g.) in ethanol (100 ml.) was heated under reflux for 18 hr. The solvent was removed *in vacuo*, water was added and the precipitate was collected and dried. It was slurried with a small quantity of ether, filtered, and recrystallized once from methanol giving 1.5 g. (70%) of amide, m.p. 191–193°. Acidification of the aqueous alkaline filtrate gave only a trace of the corresponding carboxylic acid.

Dibenzo[a,d]cycloheptadiene-5-N-methylcarboxamide.—A solution of dibenzo[a,d]cycloheptadiene-5-carbonyl chloride[1] (7.8 g., 0.033 mole) in dry acetone (30 ml.) was added dropwise to methylamine (25% aqueous solution; 60 ml). The mixture was

(39) S. J. Cristol and R. K. Bly, *J. Am. Chem. Soc.*, **82**, 6155 (1960).

(40) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

(41) Y. Hirschberg, *ibid.*, **71**, 3241 (1949).

then heated briefly, diluted with water, and the precipitate was recrystallized from ethanol–hexane to give 4.5 g. (54%) of product, m.p. 201–202°.

5-Aminodibenzo[a,d]cycloheptadiene-5-carboxamide.—A mixture of 5-chlorodibenzo[a,d]cycloheptadiene-5-carbonyl chloride[6] (3.0 g., 0.01 moles) and liquid ammonia (25 ml.) was stirred overnight in a pressure bottle. The ammonia was evaporated and the residue was slurried with a little water. The chlorine-free, insoluble material was recrystallized from ethanol–hexane giving 0.7 g. (28%) of amide, m.p. 281–282° dec.

5-Oximinodibenzo[a,d]cycloheptadiene.—Dibenzo[a,d]cycloheptadiene-5-one (100 g., 0.48 mole) and hydroxylamine hydrochloride (84.5 g., 1.2 moles) were heated under reflux for 96 hr. with a 1–1 mixture of aqueous pyridine (610 ml.). The solution was evaporated *in vacuo* and the residue taken up in chloroform. The solution was washed with water, dried, and the solvent removed giving 89 g. (83%) of the oxime m.p. 161–167°. A purified sample had m.p. 167–170° (from ethanol).

5-Acetamidodibenzo[a,d]cycloheptadiene.—A solution of the preceding oxime (12.0 g., 0.054 mole) in ethanol (250 ml.) was saturated with ammonia and hydrogenated at 3.5 kg./cm. and ambient temperature in the presence of 10% palladium-on-charcoal. The theoretical quantity of hydrogen was consumed after 14 hr. The catalyst was filtered, the solution evaporated *in vacuo*, and the residue was warmed on the steam bath for 20 min. with acetic anhydride (100 ml.). Water (500 ml.) was added and the mixture was heated to boiling. The aqueous layer was decanted and the solid material was triturated with a little methanol and recrystallized once from dioxane to give 5.3 g. (39%), m.p. 280–282°.

5-Dibenzo[a,d]cycloheptadienyl Isocyanate.—Silver cyanate (22.5 g., 0.15 mole) was added to a solution of 5-chlorodibenzo[a,d]cycloheptadiene[36] (22.9 g., 0.10 mole) in anhydrous acetonitrile (140 ml.). The mixture was slowly heated to the boiling point and then kept under reflux for 12 hr. in the dark. Filtration, followed by evaporation of the solvent, left a solid residue from which the product was isolated by trituration with hot hexane. Removal of the hexane left 17.4 g. (74%) of the isocyanate, m.p. 62–63°, unchanged on recrystallization from pentane.

Anal. Calcd. for $C_{16}H_{11}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.49; H, 5.74; N, 5.82.

5-Dibenzo[a,d]cycloheptadienylurea.—A solution of the isocyanate (6.3 g., 0.027 mole) in dry acetone (40 ml.) was added dropwise while stirring to concentrated ammonium hydroxide (30 ml.). The reaction mixture was heated under reflux for 0.5 hr., cooled, diluted with water, and the precipitate was collected. Recrystallization from a 1:1 ethanol–ethylene dichloride mixture gave 3.8 g. (56%) of the urea as fine needles, m.p. 282–283° dec.

1-(5-Dibenzo[a,d]cycloheptadienyl)-3-acetylurea.—Acetyl chloride (12 ml.) was added dropwise to a stirred suspension of the preceding compound (2.8 g., 0.11 mole) in dry pyridine (65 ml.), the internal temperature being kept below 20° by means of external cooling. The mixture was then heated on the steam bath for 1 hr., cooled, and treated with ethanol (25 ml.) followed by water (300 ml.). The precipitate was collected, washed with water, and a little cold ethanol. Recrystallization from ethanol (charcoal) gave 1.4 g. (44%), m.p. 203–204°.

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The Anticonvulsant Activity of 3-Acylindoles Compared with Phenobarbital

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The anticonvulsant activity of various 3-acylindoles was determined and the structure-activity relationship studied. The optimum compound tested was 3-isobutyryl-1-methylindole.

Numerous workers have implicated serotonin[1a] as having some important role in central nervous system function. For a summary of the uncertain state of affairs regarding the possible function of this amine in the CNS one should consult the concluding remarks of Erspamer's review.[1b]

Bonnycastle[2] has shown in the rat that elevation of brain serotonin is a consequence of the administration of various central nervous system depressants. On the other hand, many simple indole derivatives show predominately excitatory actions.[3] During the course of routine screening, it was noted that a considerable number of 3-acylindoles had anticonvulsant action. The present report describes the study of a series of 3-acylindoles as anticonvulsants and the correlations between structure and activity are noted.

Pharmacological Methods.—All compounds were injected intraperitoneally in freshly prepared solutions or suspensions using 0.25% aqueous methyl cellulose. Injection volume was 0.01 ml./g. body weight. A Hans Tech electroshock apparatus delivering current of variable intensity for 0.2 sec. through ear clip electrodes was utilized.

Mice.—Groups of 15 Carworth Farms male mice weighing 18–22 g. were injected with test compound at 100 mg./kg. Similar groups were injected with phenobarbital sodium (10 and 20 mg./kg.) and vehicle in each experiment. Thirty min. after administration (separate experiments at 30, 60, and 90 min. after administration had shown that peak effect occurred in representative compounds at 30 min.) the animals were subjected to electroshock. Current strength in milliamperes was varied in 0.05 log units. The "up-down" procedure described by Kimball[4] was utilized to estimate the log of the current strength causing tonic extensor seizures in 50% of the animals and its 95% confidence interval.

Rats.—The procedure described for mice was utilized with the following changes: (1) rats (Upjohn-Sprague-Dawley ancestry) weighing 80 to 150 g. were utilized (within an experiment the weight range was ±10 g. of the mean); (2) phenobarbital sodium controls received 9 and 18 mg./kg.; (3) test compounds were injected at 25 mg./kg. Test compounds were evaluated relative to the control groups in each experiment. Compounds were reported as active if the current strength 50 (test compound) was greater than the upper 95% confidence interval of untreated controls. The activity of test compound relative to phenobarbital was based upon the effect of test compound relative to

(1) (a) For a recent review on serotonin see V. Erspamer in "Progress in Drug Research," Vol. 3, E. Jucker, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 151; (b) p. 329.

(2) D. D. Bonnycastle, M. F. Bonnycastle, and E. G. Anderson, *J. Pharmacol. Exptl. Therap.*, **135**, 17 (1962).

(3) H. H. Keasling, unpublished observations from this Laboratory.

(4) A. W. Kimball, W. T. Burnett, and D. G. Doherty, *Radiation Res.*, **1** 1 (1954).