vent. The residue was treated with 50 ml. of *N* hydrochloric acid and the aqueous solution was extracted with ether. The ether layer was discarded. The aqueous layer was made alkaline by the addition of 15 ml. of 5 *N* sodium hydroxide and the organic base was extracted into ether. The ether layer was washed with water, dried over magnesium sulfate and distilled. A low-boiling forerun was discarded and (−)V was collected at 144–148° (0.08 mm.). The yield was 4.6 g. (57%), $n^{25}D$ 1.562, $[\alpha]^{25}D$ −13.3°.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.5; H, 9.0; N, 10.4. Found: C, 80.1; H, 8.9; N, 10.7.

(+)-N²-Methyl-N¹-phenethyl-N¹-phenyl-1,2-propanediamine (V).—A mixture of 25.4 g. (0.1 mole) of (+)I, 200 ml. of 90% ethanol and 1.5 g. of 10% palladium-on-carbon catalyst was reduced and treated with 12 g. of phenylacetaldehyde as described for the (−)-enantiomer (V). The yield of product, b.p. 148–152° (0.05 mm.), $n^{25}D$ 1.564, $[\alpha]^{25}D$ +13.8°, was 60%.

Anal. Calcd. for $C_{18}H_{24}N_2$: C, 80.5; H, 9.0; N, 10.4. Found: C, 80.5; H, 9.3; N, 10.5.

(−)-N²-Methyl-N¹-phenyl-1,2-propanediamine (IV).—The forerun from the distillation of the above reaction product was redistilled and the portion which distilled at 88–92° (0.1 mm.) was collected, $n^{25}D$ 1.543, $[\alpha]^{25}D$ −29.8°.

Anal. Calcd. for $C_{10}H_{18}N_2$: C, 73.1; H, 9.8; N, 17.1. Found: C, 72.8; H, 10.2; N, 17.0.

(+)-N-[2-(Methylphenethylamino)propyl]propionanilide (III).—A mixture of 1.8 g. of (−)-N²-methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine and 5 ml. of propionic anhydride was heated on the steam bath for 2 hr. and distilled. (+)III was collected at 160–165° (0.1 mm.), $n^{25}D$ 1.544, $[\alpha]^{25}D$ +25.2.°

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 76.9; H, 8.6; N, 8.7.

(−)-N-[2-(Methylphenethylamino)propyl]propionanilide (III). Method A.—(+)-N²-Methyl-N²-phenethyl-N¹-phenyl-1,2-propanediamine was treated with propionic anhydride as described for (+)III. (−)III was collected at 162–166° (0.05 mm.), $n^{25}D$ 1.545, $[\alpha]^{25}D$ −25.9°.

Anal. Calcd. for $C_{21}H_{28}N_2O$: C, 77.7; H, 8.7; N, 8.6. Found: C, 76.7; H, 8.8; N, 8.5; H_2O, 1.2.

Method B.—A mixture of 3.0 g. of (+)-N-[2-(benzylmethylamino)propyl]-propionanilide hydrochloride and 10 ml. of *N* sodium hydroxide was shaken and the organic base was extracted into ether. The ether layer was dried over magnesium sulfate and concentrated to remove the solvent. The residue was mixed with 80 ml. of 90% ethanol and 0.5 g. of 10% palladium-on-carbon catalyst and reduced in a Parr hydrogenator under about 3.099 kg./cm.² of hydrogen. The reaction flask was opened, 1.08 g. of phenylacetaldehyde and 0.5 g. of catalyst was added and the reduction was continued for 20 hr. The catalyst was filtered off and the mother liquor was concentrated to remove solvents. The residue was dissolved in 20 ml. of *N* hydrochloric acid, extracted with ether and the ether layer was discarded. The aqueous layer was made alkaline by addition of 8 ml. of 5 *N* sodium hydroxide and the organic base was extracted into ether. The ether layer was distilled and 1.4 g. (50%) of (−)III, $n^{25}D$ 1.543, $[\alpha]^{25}D$ −25.2°, was collected at 160–165° (0.1 mm.).

Acknowledgment.—We wish to thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and associates for the determination of optical rotations.

New Psychotropic Agents.[1a] IV. Derivatives of Dibenzo[a,d][1,4]cycloöctadiene

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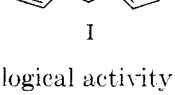
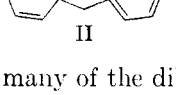
A series of 5-dialkylaminoalkyl-5-hydroxydibenzo[a,d][1,4]cycloöctadienes was prepared by treating dibenzo[a,d][1,4]cycloöctadien-5-one with basically substituted Grignard reagents. The corresponding 5-dialkylaminoalkyl- and 5-dialkylaminoalkylidenedibenzo[a,d][1,4]cycloöctadienes also were synthesized. Several of the compounds exhibited central and peripheral pharmacological activities similar to amitriptyline and other dibenzo[a,d][1,4]cycloheptadiene compounds. In general they were less potent centrally than amitriptyline and had less pronounced mydriatic effects.

A previous paper[2] in this series described the preparation of a number of compounds derived from dibenzo[a,d][1,4]cycloheptadiene (I). Other laboratories also have reported their investigations[3] on these and closely related compounds. Because of the pronounced pharmacological activity exhibited by many of the dibenzo[a,d][1,4]cycloheptadienes it became of interest to extend our investigations to the synthesis of related compounds derived from the homologous dibenzo[a,d][1,4]cycloöctadiene ring system (II).



I



II

Dibenzo[a,d][1,4]cycloöctadien-5-one (VI) has been reported[4] as an impure solid which was characterized only as its 2,4-dinitrophenylhydrazone. Since the reported synthesis is rather lengthy and the final product was obtained in low yield, an alternative method was developed which gave the desired ketone more readily. *o*-Phthalaldehydic acid (III) was treated with phenethylmagnesium bromide to form 3-(2-phenethyl)-phthalide (IV). Reduction with hydriodic acid and red phosphorus then produced 2-(3-phenylpropyl)benzoic acid (V) which underwent cyclodehydration with polyphosphoric acid to yield the ketone VI as a solid which easily was purified and characterized.

Attempts were made to synthesize 3-chlorodibenzo[a,d][1,4]cycloöctadien-5-one and dibenzo[a,d][1,4]-cyclononadien-5-one by a similar scheme to that described for VI. In both cases the syntheses failed at the cyclization step. Varying the reaction times and

(1) (a) Paper III in this series: S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm. Chem.*, **5**, 1207 (1962); (b) Department of Chemistry; (c) Department of Pharmacology.

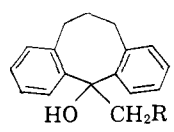
(2) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. A. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

(3) (a) M. Protiva, V. Hnevsova-Seidlova, Z. S. Vejdelek, J. Jirkovsky, Z. Votava, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (b) F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigo, *ibid.*, **5**, 373 (1962); (c) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dyhon, M. B. Freedman, and J. M. Sprague, American Chemical Society, 141st Natl. Meeting Abstracts, March 26, 1962.

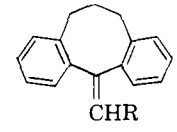
(4) C. D. Gutsche, E. F. Jason, R. S. Coffey, and H. E. Johnson, *J. Am. Chem. Soc.*, **80**, 5756 (1958).

TABLE I

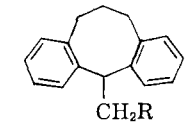
DIBENZO[a,d][1,4]CYCLOÖCTADIENES



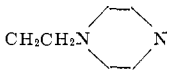
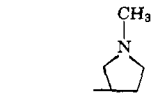
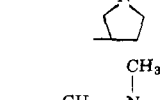
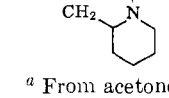
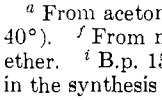
A



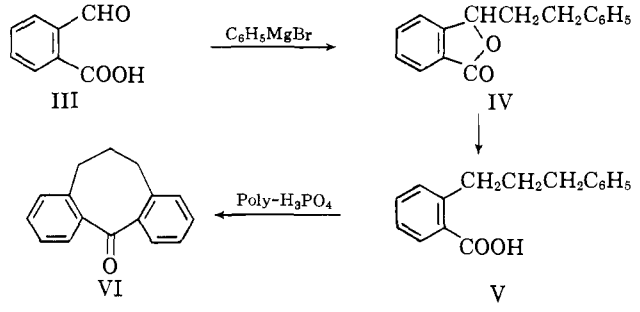
B



C

R	Cpd.	Salt	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
	1A	Base	129–131[a]	62	$C_{21}H_{27}NO$	81.51	82.37	8.80	8.82	4.53	4.56		
$CH_2CH_2N(CH_3)_2$	1B	HCl	175–177[b]	52	$C_{21}H_{28}ClN$					4.27	4.42	10.81	10.69
	1C	HCl	177–180[b]	29	$C_{21}H_{28}ClN$					4.24	4.08	10.75	10.54
	2A	Base	135–140[c]	81	$C_{22}H_{29}NO$	81.69	81.27	9.04	8.90	4.33	4.31		
$CH(CH_3)CH_2N(CH_3)_2$	2B	HCl	200–202[b]	84	$C_{22}H_{28}ClN$					4.10	3.80	10.37	10.17
	2C	HCl	231–232[c]	66	$C_{22}H_{30}ClN$					4.07	3.95	10.31	10.07
	3A	Base	162–163[d]	19[i]	$C_{22}H_{32}N_2O$	79.05	78.84	8.84	8.88	7.69	7.52		
	3B	2HCl	215–220 dec[b]	27[i]	$C_{24}H_{32}Cl_2N_2$					6.68	6.57	16.92	16.70
	3C	Base	89–90[e]	64	$C_{24}H_{32}N_2$	82.71	82.47	9.26	9.48	8.04	7.89		
	3C	2HCl	244–246[f]	..	$C_{24}H_{34}Cl_2N_2$					6.65	6.52	16.83	16.39
	4A	Base	134–136[c]	67	$C_{22}H_{27}NO$	82.20	81.55	8.47	8.56	4.36	4.25		
	4B	Base	[g]	32	$C_{22}H_{25}N$	87.14	86.42	8.24	8.56	4.62	4.55		
	4B	HCl	80–100[h]	..	$C_{22}H_{26}ClN$					4.12	4.03	10.44	10.09
	4C	Base	[i]	53	$C_{22}H_{27}N$	86.50	86.60	8.91	8.97	4.59	4.67		
	4C	HCl	222–224[b]	..	$C_{22}H_{28}ClN$					4.09	3.80	10.38	9.91
	5A	Base	154–156[j]	73	$C_{24}H_{31}NO$	82.47	82.43	8.94	8.85	4.01	4.03		
	5B	HCl	161–162[d]	51	$C_{24}H_{30}ClN$					3.91	3.86	9.92	9.91
	5C	Base	[k]	34	$C_{24}H_{31}N$	86.44	86.00	9.37	9.18	4.29	4.41		
	5C	HCl	200–202 dec[c]	..	$C_{24}H_{32}ClN$					3.79	3.39	9.57	9.55

[a] From acetone. [b] From isopropyl alcohol–ether. [c] From 2-propanol. [d] From ethyl acetate. [e] From petroleum ether (b.p. below 40°). [f] From methanol–ether. [g] B.p. 152–154° (0.13 mm.). [h] Amorphous; purified by repeated reprecipitations from methanol–ether. [i] B.p. 158–160° (0.13 mm.). [j] From methanol. [k] B.p. 166–170° (0.1 mm.). [l] The olefin was isolated as the major product in the synthesis of 3A.



temperatures did not give any of the desired ketones. Other methods of cyclodehydration such as the use of liquid hydrofluoric acid or the action of aluminum chloride on the corresponding acid chlorides employing the infinite dilution technique of Huisgen[5] were equally unsuccessful.

The treatment of ketone VI with basically substituted Grignard reagents gave the desired tertiary carbinols in good yields (A, Table I). Treatment of the tertiary carbinols with ethanolic hydrogen chloride gave the corresponding olefins (B, Table I) while reduction of the carbinols with hydriodic acid and red phosphorus yielded the desired 5-dialkylaminoalkyldibenzo[a,d]-[1,4]cycloöctadienes (C, Table I). The ketone VI was also reduced to 5-hydroxydibenzo[a,d] [1,4]cycloöctadiene by treatment with lithium aluminum hydride in tetrahydrofuran. The use of sodium borohydride in methanol gave the 5-hydroxy compound but in this case it could not be purified satisfactorily by repeated recrystallizations. Since this manuscript was submitted some of the compounds described above were reported by K. Stach and H. Spingler, *Monatsh.*, **93**. 896 (1962).

Pharmacological Activity.—The compounds were studied in the series of pharmacological tests used in these laboratories to screen for antidepressant and other central nervous system and peripheral activities. The tests included were: determination of acute toxicity (LD_{50}), potentiation of a sub-hypnotic dose of ethanol, protection against maximal electroshock seizures (MES), mydriatic action, depression of orientational hypermotility, ataxic effect and influence on a conditioned response (runway test). A detailed description of these methods has been reported previously.[6] The compounds were tested further for their ability to inhibit contractions induced by acetylcholine and histamine in isolated guinea pig ileum. The results are presented in Table II. For comparative purposes the data obtained for amitriptyline are also included. The doses for the *in vivo* tests and the concentrations for the *in vitro* tests are expressed in terms of the base in all cases.

No single test result is sufficient to indicate specific psychotropic activity; rather, one must consider the profile of test results and the relative potency of a compound on different tests.[6] Because no one structural modification resulted in a regular increase in the potency of a compound in all tests it was not possible to draw any clear structure–activity relationships. Several of the compounds did have central and peripheral effects similar to those of amitriptyline and other dibenzo[a,d][1,4]cycloheptadiene and cycloheptatriene compounds studied in these laboratories.[2] In general, it can be said that on the basis of an absolute dose, the compounds in the present series have less potent central effects and, with the exception of 5B and 5C, less pronounced mydriatic effects than amitriptyline. Compounds of this general structure having potent central effects (on conditioned responses, potentiation of narcosis) accompanied by high ratios of the ataxic doses to those eliciting these effects as well as low

(5) R. Huisgen and G. Horeld, *Ann. Chem.*, **562**, 137 (1949).

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

TABLE II

PHARMACOLOGICAL INVESTIGATIONS

	LD_{50} (approx.) mg./kg. mice i.p.	Potentiation of narcosis ED_{50} mg./kg. mice i.p.	MES ED_{50} mg./kg. mice i.p.	Mydriasis caused by 0.25 LD_{50} mice i.p.[a]	% Difference in motility 0.25 LD_{50} rats i.p.	Ataxia (approx.) ED_{50} mg./kg. rats i.p.	Runway (approx.) ED_{50} mg./kg. rats i.p.	Antiacetylcholine EC_{50} μg./ml.[b]	Antihistamine EC_{50} μg./ml.[b]
1A	200–250	11.2 ± 4	26.5 ± 1.4	+8.1	−75	110	50		
1B	133–160	12.5 ± 2.9	25.8 ± 1.5	+7.9	−75	69	18	0.18 ± 0.045	0.036 ± 0.006
1C	78–89	>22[c]	>33[c]	+4.0	−32	89	13	0.08 ± 0.018	0.069 ± 0.005
2B	70–90	13.6 ± 2.0	31 ± 5.6	0	−26	53	18	0.16 ± 0.045	0.045 ± 0.004
2C	110 ± 4.5	18 ± 3	39 ± 1.1	+2.6	−50	89	13	0.08 ± 0.018	0.038 ± 0.003
3C	104–125	25.2 ± 4	>33[c]	0	−57	>88[c]	12.5	0.174 ± 0.033	0.09 ± 0.025
4B	67–77	11 ± 3.5	>18[c]	+3.8	−5	40	13	0.013 ± 0.001	0.0085 ± 0.003
4C	58–64	26.5 ± 3.5	>14[c]	+2.7	−15	>53[c]	27	0.023 ± 0.003	0.028 ± 0.006
5B	90–110	12.6 ± 2.3	31 ± 1.8	+17	−37	58	13	0.011 ± 0.003	0.012 ± 0.003
5C	72–81	26 ± 2.7	>18[c]	+23	−26	>50[c]	6.7	0.09 ± 0.027	0.26 ± 0.03
Amitriptyline	83 ± 2.5	7.9 ± 0.8	10 ± 0.8	+19	−37	53	8	0.038 ± 0.003	0.004 ± 0.000

[a] The numbers represent unit increases over control pupil diameter. +40 is the approximate maximal dilation. [b] EC_{50} is the concentration which inhibited the normal response to 0.1 μg./ml. of either acetylcholine or histamine by 50%. [c] > means that the compound was inactive up to the dose indicated.

mydriatic actions are being investigated further as psychotropic drugs of the antidepressant type.

Experimental

Melting points are uncorrected.

3-(3-Phenylpropyl)phthalide.—This compound was prepared by the procedure described in the literature[7] for its lower homolog, 3-phenethylphthalide. 3-Phenylpropyl bromide (200 g., 1 mole) and magnesium (24 g., 1 mole) in 800 ml. of ether were allowed to form the Grignard reagent. *o*-Phthaldehydic acid (60 g., 0.4 mole) was then added portionwise and the reaction carried through in the usual manner to yield 83 g. (83%) of product, m.p. 66–70°. Two recrystallizations from hexane–ethanol mixture gave an analytical sample, m.p. 70–71°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.39; H, 6.40.

3-(2-*p*-Chlorophenethyl)phthalide.—In the same manner as described for the preceding compound, 2-(*p*-chlorophenethyl) chloride (22.6 g., 0.13 mole), magnesium (3.15 g., 0.13 mole) and *o*-phthalaldehydic acid (8.3 g., 0.055 mole) gave 10.6 g. (70%) of product, m.p. 103–105°. Two recrystallizations from isopropyl alcohol gave an analytical sample, m.p. 103–104°.

Anal. Calcd. for $C_{16}H_{13}ClO_2$: C, 70.46; H, 4.80. Found: C, 70.66; H, 5.07.

2-(4-Phenylbutyl)benzoic Acid.—This compound was prepared by the procedure of Cope and Fenton[8] for the reduction of 3-benzalphthalide. 3-(3-Phenylpropyl)phthalide (61.5 g., 0.24 mole), 280 ml. of 57% hydriodic acid and 35 g. of red phosphorus gave 33 g. (54%) of product, m.p. 68–72°. Two recrystallizations from 70% ethanol gave an analytical sample, m.p. 70–72°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.30; H, 7.13. Found: C, 80.23; H, 7.14.

2-(3-*p*-Chlorophenylpropyl)benzoic Acid.—In a manner similar to that described for the preceding compound, 3-(*p*-chlorophenethyl)phthalide (10 g., 0.037 mole), 40 ml. of 57% hydriodic acid and 5 g. of red phosphorus gave 6 g. of product (60% yield), m.p. 86–88°. Two recrystallizations from 70% ethanol gave an analytical sample, m.p. 90–91°.

Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 69.94; H, 5.50; Cl, 12.90. Found: C, 70.03; H, 5.65; Cl, 13.05.

Dibenzo[a,d][1,4]cycloöctadien-5-one (VI).—2-(3-Phenylpropyl)benzoic acid (70 g., 0.28 mole) and 700 g. of polyphosphoric acid were heated together at 170° for 2.5 hr. The reaction mixture then was poured onto ice and the aqueous mixture extracted with ether. The ether extract was washed with a solution of 5% sodium carbonate, dried and evaporated *in vacuo* leaving 40 g. of crude material which crystallized from benzene–hexane mixture to give 35 g. (54%) of product, m.p. 147–149°. One recrystallization gave an analytical sample, m.p. 148–149°; λ_{max} (ethanol), 264; ε 18,700.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.34. Found: C, 86.46; H, 6.47.

5-Hydroxydibenzo[a,d][1,4]cycloöctadiene.—A solution of VI (9.3 g., 0.042 mole) in dry tetrahydrofuran (100 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (6.4 g., 0.17 mole) in tetrahydrofuran. The reaction mixture was heated under reflux for 4 hr., cooled and hydrolyzed by the successive addition of water (6.4 g.), 20% sodium hydroxide solution (4.8 ml.) and water (22 ml.). The precipitate was filtered off and washed with benzene. The combined filtrates were dried and evaporated and the residue was recrystallized from 2-propanol–hexane to give 6.0 g. (64%) of product, m.p. 117–118°.

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.46; H, 7.07.

5-Hydroxy-5-(3-dimethylaminopropyl)dibenzo[a,d][1,4]cycloöctadiene.—Magnesium turnings (3.6 g., 0.15 mole) were covered with 20 ml. of tetrahydrofuran. A crystal of iodine and a few drops of ethyl bromide were added to initiate the formation of the Grignard reagent. Dimethylaminopropyl chloride (18.1 g., 0.15 mole) dissolved in 30 ml. of tetrahydrofuran then was added dropwise while heating under reflux. After a few min. the exothermic reaction commenced. The addition was completed in 20 min. and heating was continued for an additional hr. Dibenzo[a,d][1,4]cycloöctadien-5-one (16.6 g., 0.075 mole) then was added dropwise over 20 min. or at a rate sufficient to maintain refluxing. The reaction mixture then was heated under reflux for an additional 16 hr. The Grignard complex was decomposed by adding the reaction mixture to 500 ml. of an ice and ammonium chloride mixture with stirring. The product precipitated as an oil and was taken up in chloroform. On evaporating the chloroform extract, 14 g. of solid product resulted with m.p. 110–115°. Two recrystallizations from acetone gave an analytical sample, m.p. 129–131° (see Table I).

5-(3-Dimethylaminopropylidene)dibenzo[a,d][1,4]cycloöctadiene.—5-Hydroxy-5(3-dimethylaminopropyl)dibenzo[a,d][1,4]-cycloöctadiene (8 g.) was dissolved in 150 ml. of absolute ethanol which then was saturated with hydrogen chloride. The solution was heated under reflux for 4 hr. The ethanol was then evaporated *in vacuo* and the residue crystallized from isopropyl alcohol–ether mixture to yield 4.3 g., m.p. 175–177° of product as the hydrochloride salt. A second recrystallization did not change the melting point (see Table I); λ_{max} (ethanol) 246; ε 8360.

5-(3-Dimethylaminopropyl)dibenzo[a,d][1,4]cycloöctadiene.—The appropriate alcohol (9 g.) was reduced in the usual manner with 45 ml. of hydriodic acid (57%) and 9 g. of red phosphorus in 180 ml. of acetic acid to yield 4.8 g. of crude product as an oil. This was converted to a hydrochloride salt, (2.7 g.) m.p. 172–177°. Three recrystallizations from isopropyl alcohol–ether mixture gave an analytical sample, m.p. 177–180° (see Table I).

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