Oximes were prepared as illustrated by the following general example.

Spiro[5.5]undecane-3-ketoxime.—A mixture of 50 g. of hydroxylamine hydrochloride and 60 g. of sodium acetate was dissolved in the least amount of water to give a clear solution at 40°. Spiro[5.5]undecan-3-one (55 g.) was added with stirring and the mixture was vigorously shaken for 1 hr. The precipitated product was filtered, washed with water, and dried. After drying, the product (60 g.) melted at 109–110°. Recrystallization from methanol and water yielded the pure material, m.p. 110–111°.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.93. Found: C, 72.97; H, 10.53, N, 7.64.

The spiroamines were all prepared by the following general method.

3-Aminospiro[5.5]undecane.—The above oxime (50 g.) was dissolved in anhydrous ether and was slowly added to a solution of 25 g. of $LiAlH_4$ in 1 l. of anhydrous ether. After stirring 3 hr., the mixture was decomposed with water in the usual manner and filtered. The ethereal solution was dried, and the ether was stripped off. Vacuum distillation of the residue gave the product (38 g., 82%), b.p. 110–112° (12 mm.). Conversion in the usual manner with alcoholic HCl and ether gave the hydrochloride, m.p. 298–300°.

Anal. Calcd. for $C_{11}H_{22}ClN$: C, 64.84; H, 10.88; Cl, 17.40; N, 6.87. Found: C, 64.72; H, 10.94; Cl, 17.20; N, 6.73.

The **picrate** was prepared in the usual manner using methanol as a solvent and adding water until precipitation started; m.p. 231–232°.

Anal. Calcd. for $C_{17}H_{24}N_4O_7$: N, 14.13. Found: N, 14.26.

The **phenylthiourea** was prepared in hexane and after recrystallization from methanol melted at 156–157°.

Anal. Calcd. for $C_{18}H_{26}N_2S$: C, 71.47; H, 8.66; N, 9.26. Found: C, 71.74; H, 8.87; N, 9.03.

N-Formyl-3-aminospiro[5.5]undecane.—To a solution of 8.3 g. of 3-aminospiro[5.5]undecane in 25 ml. of alcohol was added 4.7 g. of formic acid. The resultant mixture was heated at reflux and the excess formic acid was stripped off. The residue on distillation yielded 7 g. of product, b.p. 183–184° (5 mm.).

Anal. Calcd. for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.63; H, 10.75; N, 7.04.

N-Methyl-3-aminospiro[5.5]undecane.—Reduction of the above formyl derivative in the usual manner with $LiAlH_4$ gave the product, b.p. 112–114° (9 mm.), which was converted to the hydrochloride, m.p. 172–173°.

Anal. Calcd. for $C_{12}H_{24}ClN$: C, 66.49; H, 10.69; Cl, 16.28; N, 6.46. Found: C, 66.71; H, 10.90; Cl, 16.10; N, 6.38.

N,N-Dimethyl-3-aminospiro[5.5]undecane.—To 8.3 g. of 3-aminospiro[5.5]undecane was added 12.8 g. of formic acid in portions with intermediate cooling. After standing for 10 min., 12 ml. of 37% formaldehyde was added with stirring. The mixture was refluxed for 4 hr., allowed to cool, and stripped. The residue was dissolved in 10% HCl, and the solution was filtered, cooled, neutralized with NaOH, and extracted with ether. After drying (Na_2SO_4) the ether was removed and the residue was distilled, b.p. 122–124° (9 mm.), yield 6.3 g. The oil was converted directly into the **hydrochloride**, m.p. 283°, yield 6.3 g.

Anal. Calcd. for $C_{13}H_{26}ClN$: C, 67.35; H, 11.31; Cl, 15.30; N, 6.04. Found: C, 67.22; H, 11.39; Cl, 15.13; N, 6.16.

N-Benzoyl-3-aminospiro[5.5]undecane.—The usual procedure of the Schotten–Baumann reaction was employed and 8 g. of product was obtained from 5 g. of the amine. Recrystallization from methanol gave the pure material, m.p. 139–140°.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.65; H, 9.29; N, 5.16. Found: C, 79.63; H, 9.38; N, 5.02.

N-Benzyl-3-aminospiro[5.5]undecane.—The preceeding amide on reduction with $LiAlH_4$ in the usual manner yielded the product which was converted directly to the **hydrochloride**, m.p. 241–242° (from water).

Anal. Calcd. for $C_{18}H_{28}ClN$: C, 73.56; H, 9.60; Cl, 12.07; N, 4.77. Found: C, 73.35; H, 9.80; Cl, 11.98; N, 4.92.

Structure–Activity Relationships in the Cyproheptadine Series

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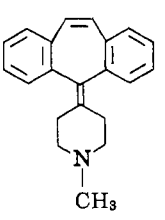
A series of compounds related to cyproheptadine has been prepared and the antihistaminic and antiserotonin properties were studied. The structural variations include: replacement of the methyl on nitrogen by other groups, introduction of halogen substituents in the aromatic nucleus, saturation of the 5,α or the 10,11 double bond, and replacement of the dibenzocycloheptene nucleus by xanthene, thioxanthene, or fluorene systems. The antihistaminic and antiserotonin actions of the thioxanthene congener closely approximate those of cyproheptadine. All other compounds, with the exception of the N-ethyl analog of cyproheptadine, were less active.

Cyproheptadine (I) was prepared in the course of synthesis of a series of dialkylaminopropylidenedibenzocycloheptenes for study as tranquilizing agents.[1] It proved to be without notable action on the central nervous system; however, the antihistamine and antiserotonin activities that are rather widely distributed throughout the series were found to be exceptionally prominent in this compound.[2] These properties led to the introduction of cyproheptadine as an antipruritic drug.[3]



I

In order to elucidate structure–activity relationships, twenty-one related compounds were synthesized and

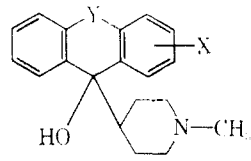
(1) E. L. Engelhardt, M. E. Christy, H. C. Zell, C. M. Dylion, M. B. Freedman, and J. M. Sprague, Abstracts of Papers, 141st National Meeting of the American Chemical Society, Washington, D. C., March 1962, p. 4N.

(2) C. A. Stone, H. C. Wenger, C. T. Ludden, J. M. Stavorski, and C. A. Ross, *J. Pharmacol. Exptl. Therap.*, **131**, 73 (1961).

(3) Periactin®.

TABLE I

CARBINOLS



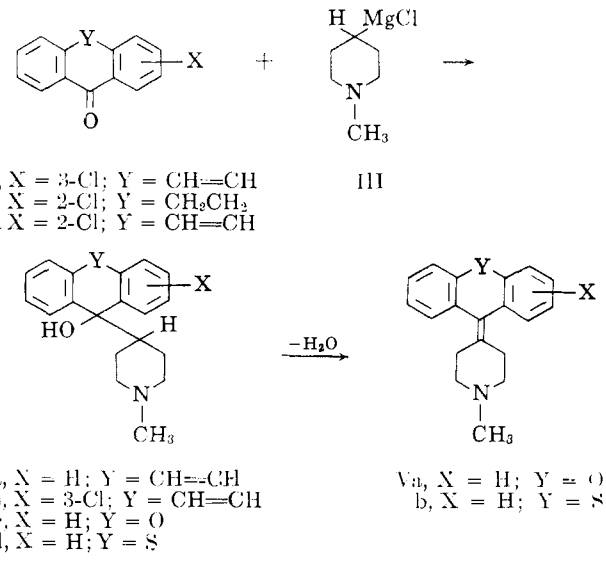
Y	X	Method	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH=CH	H	A-1	50	166.7–167.7	$C_{21}H_{23}NO$	82.59	82.39	7.59	7.67	4.59	4.58
CH=CH	1-Cl	A-2	23	186–188	$C_{21}H_{22}ClNO$	74.20	73.96	6.53	6.67	4.12	3.72
CH=CH	2-Cl	A-3	23	158–159	$C_{21}H_{22}ClNO$	74.20	73.90	6.53	6.59	4.12	3.73
CH=CH	3-Cl	A-1	32	199–200	$C_{21}H_{22}ClNO$	74.20	73.90	6.53	6.39	4.12	4.01
CH=CH	3-Br	A-2	38	212.6–213.6	$C_{21}H_{22}BrNO$	65.63	65.86	5.77	6.04	3.65	3.44
CH_2CH_2	H	A-1	59	180–181	$C_{21}H_{25}NO$	82.04	81.79	8.20	7.93	4.56	4.64
CH_2CH_2	2-Cl	A-3	22	174–176	$C_{21}H_{24}ClNO$	73.76	73.52	7.08	7.30	4.10	3.81
...[a]	H	A-1	43	217–218	$C_{19}H_{21}NO$	81.68	81.38	7.58	7.70	5.02	5.18
O	H	A-1	45	200–201	$C_{19}H_{21}NO_2$	77.26	77.23	7.17	7.31	4.74	4.92
S	H	A-2	39	191.6–192.4	$C_{19}H_{21}NOS$	73.26	73.19	6.80	7.10		
S	2-Cl[b]	A-1	39	221.8–222.8	$C_{19}H_{20}ClNOS$[c]	65.97	66.01	5.83	5.84	4.05	4.00

[a] Fluorene compound. [b] Thioxanthene numbering. [c] *Anal.* Calcd.: Cl, 10.25. Found: Cl, 10.13.

studied pharmacologically. The series includes the following systematic variations in structure I: (1) replacement of the methyl group by other alkyl and substituted alkyl groups, (2) introduction of halogen at various positions in the tricyclic nucleus, (3) saturation of the 5,α or the 10,11 double bond, and (4) replacement of the 10,11-vinylene bridge by oxygen, sulfur, or joining the benzene rings together directly in a fluorene system.

Chemistry.—Scheme I was employed for the synthesis of compounds with variations in the tricyclic ring system. The substituted 5H-dibenzo[*a*,*d*]cyclohepten-5-ones (II) were prepared by modifications of published methods.[4,5] Since our conditions are somewhat different, representative procedures are described in the Experimental Section.

SCHEME I



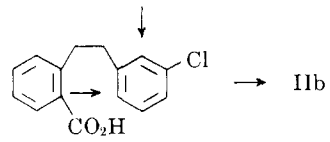
IIa, X = 3-Cl; Y = CH=CH
b, X = 2-Cl; Y = CH_2CH_2
c, X = 2-Cl; Y = CH=CH

III

IVa, X = H; Y = CH=CH
b, X = 3-Cl; Y = CH=CH
c, X = H; Y = O
d, X = H; Y = S

Va, X = H; Y = O
b, X = H; Y = S

The synthesis of IIb involved an ambiguous ring closure of the acid VI. The product melted over a range of 4° and was found to contain 4% of a second component by gas chromatography. Zone refining afforded pure material with a melting point in agreement with that reported by Winthrop, *et al.*[5c] The position of the chlorine was confirmed by n.m.r. studies on IIc.



VI

Dialkylaminopropyl Grignard reagents, first prepared by Marxer,[6] have been employed extensively in recent years.[5,7] 1-Methyl-4-chloropiperidine readily formed a Grignard reagent (III) under the conditions used in our earlier studies. Condensation of III with the appropriate ketone afforded the carbinols IV. Yields were substantially lower than those obtained previously from dimethylaminopropylmagnesium chloride. In the preparation of IVa and its 2-chloro derivative, the corresponding 5H-dibenzo[*a*,*d*]cyclohepten-5-ol was isolated as a by-product, paralleling the observation of Winthrop, *et al.*,[5c] that reduction of the ketone is sometimes a side reaction. The carbinols prepared are listed in Table I. Representative procedures are described in the Experimental Section (methods A-1, A-2, and A-3).

Dehydration of the carbinol IVa was accomplished by heating the hydrochloride with acetic anhydride in acetic acid solution (method B-1). The 3-chloro derivative (IVb) failed to undergo dehydration under these conditions, but was dehydrated readily by fusing

(4) (a) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951); (b) W. Treibs and H. J. Klinkhammer, *Chem. Ber.*, **84**, 671 (1951); (c) T. W. Campbell, R. Ginsig, and H. Schmid, *Helv. Chim. Acta*, **36**, 1489 (1953).

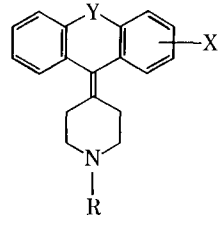
(5) (a) M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdělek, I. Jirkovský, Z. Votava, and J. Metyšová, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (b) F. J. Villani, C. A. Ellis, C. Teichmann, and C. Bigos, *ibid.*, **5**, 373 (1962); (c) S. O. Winthrop, M. A. Davis, G. S. Myers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).

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

(7) (a) T. D. Perrine, *J. Org. Chem.*, **18**, 1356 (1953); (b) J. M. Sprague and E. L. Engelhardt, U. S. Patent 2,951,082 (1960); (c) G. E. Bonvicino, H. G. Arlt, Jr., K. M. Pearson, and R. A. Hardy, *J. Org. Chem.*, **26**, 2383 (1961); (d) J. M. Sprague, E. L. Engelhardt, and M. E. Christy, U. S. Patent 2,996,503 (1961).

TABLE II

UNSATURATED COMPOUNDS

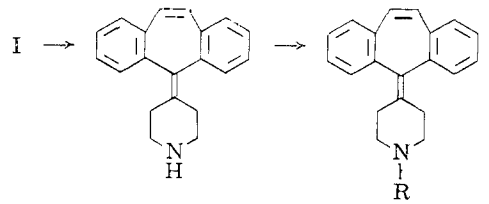


Y	X	R	Method	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Antiserotonin ED_{50}, mg./kg. s.c.[a,b]	Antihistaminic ED_{50}, mg./kg. i.p.[b]
CH=CH[c]	H	CH_3	B-1	..	214–216	$C_{21}H_{24}ClNO$[d]	73.76	73.69	7.08	7.31	4.10	4.19	0.03 (56)	0.04 (50)
CH=CH	H	H	*e*	91	290–292 dec.	$C_{20}H_{20}ClN$[f]	77.53	77.46	6.51	6.51	4.52	4.54	0.5 (4)	>12.5 (5)
CH=CH	H	C_2H_5	*e*	34	203.5–204.5	$C_{26}H_{27}NO_4$[g]	74.80	74.59	6.52	6.54	3.36	3.44	0.04 (8)	0.052 (10)
CH=CH	H	$CH_2CH=CH_2$	*e*	43	175–177	$C_{27}H_{27}NO_4$[g]	75.50	75.21	6.34	6.42	3.26	3.28	0.15 (8)	0.23 (10)
CH=CH	H	$CH_2CH_2CH_3$	*e*	63	214–216 (sintered 213)	$C_{27}H_{29}NO_4$[g]	75.15	75.34	6.77	6.86	3.25	3.23	0.5 (8)	0.11 (10)
CH=CH	H	CH_2CH_2OH	*e*	65	158–159	$C_{22}H_{23}NO$	83.24	83.00	7.30	7.29	4.41	4.38	0.1 (8)	0.18 (10)
CH=CH	H	$CH_2CH_2O_3SCH_3$	*e*	..	130.5–134 dec.	$C_{23}H_{26}ClNO_3S$[d,h]	63.95	64.47	6.07	6.22	3.24	3.24	>10 (4)	2.4 (5)
CH=CH	H	$CH_2CH_2N(CH_3)_2$	*e*	37	193–194.5	$C_{32}H_{36}N_2O_8$[i]	66.65	66.51	6.29	6.26	4.86	4.80	>10 (4)	>12.5 (5)
CH=CH	H	NO	*e*	75	179–180	$C_{20}H_{18}N_2O$	79.43	79.56	6.00	6.07	9.27	9.38	>10 (4)	>12.5 (5)
CH=CH	H	NH_2	*e*	..	143–144 dec. (sintered 142)	$C_{24}H_{24}N_2O_4$[g]	71.27	71.00	5.98	6.04	6.93	7.09	3.6 (4)	2.8 (5)
CH=CH	1-Cl	CH_3	B-2	62	85.3–88.3	$C_{21}H_{20}ClN$[j]	78.37	77.78	6.26	6.04			0.1 (4)	0.35 (5)
CH=CH	2-Cl	CH_3	B-2	84	119.5–121	$C_{21}H_{20}ClN$[k]	78.37	78.07	6.26	6.42			0.15 (4)	*Ca.* 0.3
CH=CH	3-Cl	CH_3	B-2[l]	65	197–198	$C_{25}H_{24}ClNO_4$[g]	68.57	68.39	5.52	5.47	3.20	3.27	0.08 (4)	1.1 (5)
CH=CH	3-Br	CH_3	B-2	85	200.6–203.1 dec.	$C_{25}H_{24}BrNO_4$[g,m]	62.23	62.30	5.01	5.39			0.24 (4)	1.0 (5)
CH_2—CH_2	H	CH_3	B-1	89	273–274 dec.	$C_{21}H_{24}ClN$[d]	77.40	77.23	7.42	7.46	4.29	4.45	0.1 (8)	0.04 (10)
CH_2—CH_2	2-Cl	CH_3	B-2	39	175.5–177.5	$C_{25}H_{26}ClNO_4$[g]	68.25	68.34	5.96	6.00	3.18	3.39	0.25 (4)	0.19 (10)
...[n]		CH_3	B-1	70	234.5–235.5	$C_{19}H_{20}ClN$[d]	76.62	76.87	6.77	6.98	4.70	4.66	>10 (4)	>12.5 (5)
O	H	CH_3	B-3	64	168.7–169.7	$C_{19}H_{23}ClNO_2$	68.77	68.71	6.68	7.15	4.22	4.24	0.25 (4)	3.0 (5)
S	H	CH_3	B-3	..	120.5–122.3	$C_{19}H_{19}NS$	77.76	77.76	6.53	6.79	4.77	4.56	0.03 (8)	0.04 (10)
S	2-Cl	CH_3	B-3	87	193.1–194.1	$C_{21}H_{22}ClNO_4S$[g]	62.22	61.92	4.99	5.22	3.16	3.10	0.04 (8)	0.05 (10)

[a] ED_{50} of chlorpheniramine = 0.05 (45). [b] The number in parentheses indicates the number of animals employed at each dose level (see text). [c] Cyproheptadine. [d] Hydrochloride monohydrate. [e] Preparation described in the Experimental Section. [f] Hydrochloride. [g] Hydrogen maleate. [h] *Anal.* Calcd.: Cl, 8.21; S, 7.42. Found: Cl, 8.02; S, 7.35. [i] Dihydrogen dimaleate. [j] *Anal.* Calcd.: Cl, 11.02. Found: Cl, 11.00. [k] *Anal.* Calcd.: Cl, 11.02. Found: Cl, 10.79. [l] Originally carried out by fusing the carbinol with *o*-sulfobenzoic anhydride at 135–140° for 1.5 hr. This carbinol was subsequently dehydrated by procedure B-2. [m] *Anal.* Calcd.: Br, 16.57. Found: Br, 16.38. [n] Fluorene derivative.

with *o*-sulfobenzoic anhydride. This reagent was employed in refluxing propionic acid for the dehydration of all of the halogen-substituted carbinols (method B-2). Subsequent studies showed that the carbinol IVb also underwent ready dehydration on refluxing with *p*-toluenesulfonic acid in propionic acid. The xanthene and thioxanthene compounds, IVc and IVd, were dehydrated in refluxing formic acid (method B-3). Carbinol IVa also underwent dehydration under these conditions. The thioxanthene Vb has been reported, subsequent to our work, in a patent.[8]

Demethylation of I to VII was effected by reaction with cyanogen bromide followed by hydrolysis of the resulting cyanamide. Alkylation of the secondary amine VII afforded a ready route to compounds with various groups in place of the 1-methyl in I.

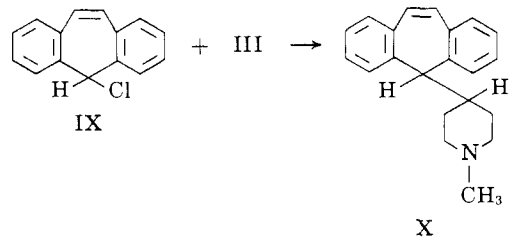


VII

VIIIa, R = CH_2CH_2OH
b, R = $CH_2CH_2O_3SCH$
c, R = NH_2

Condensation of VII with ethylene oxide gave the 2-hydroxyethyl derivative VIIIa. This compound was converted to the mesyl ester VIIIb by the action of methanesulfonic anhydride. The action of nitrous acid on VII yielded a nitroso derivative that afforded the hydrazine structure (VIIIc) on reduction with lithium aluminum hydride.

The 5,α-dihydro derivative (X) of cyproheptadine was prepared by condensation of 5-chloro-5H-dibenzo[*a*,*d*]cycloheptene (IX) with the Grignard reagent III.



IX X

The synthesis of X by condensation of 1-methyl-4-chloropiperidine with the lithium derivative of 5H-dibenzo[*a*,*d*]cycloheptene has been reported.[9]

With one exception (Va), the ultraviolet spectra of the carbinols (IV) and unsaturated compounds (V) are similar to the spectra of their dialkylaminopropyl and dialkylaminopropylidene congeners[5c,7c] and support the structures assigned.

Though the ultraviolet spectrum of the xanthene carbinol (IVc) is in reasonably good agreement with the data reported by Bonvicino, *et al.*,[7c] for 2-methoxy-9-(3-dimethylaminopropyl)xanthen-9-ol, there are dissimilarities in the spectra of the respective dehydration products. The infrared spectra are consistent with the structures. Spectral data for representative compounds are recorded in the Experimental Section.

(8) Sandoz, S. A., Belgian Patent 603,154 (1961).

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

Pharmacology. Test Methods.—The pharmacology of cyproheptadine has been described.[2] A brief summary of the tests employed to compare the antihistaminic and antiserotonin potencies in the series of analogs follows.

Antiserotonin activity was studied by the ability of the agents to antagonize the edema resulting from the local injection of serotonin in the hind paw of the rat. Briefly, the agents or control vehicle were administered subcutaneously 30 min. prior to the injection of 5 γ of serotonin (base) into one hind paw. The other hind paw was injected with the same volume of saline (0.05 ml.) and served as a baseline to determine the degree of swelling induced in serotonin-treated feet within each individual animal. Thirty minutes after serotonin, the animals were sacrificed and both hind feet were removed in a standard manner and weighed. The results are expressed as per cent inhibition of the weight gain due to serotonin as compared to that obtained in the control (vehicle treated) group. Three doses of each agent were employed with 4–8 rats/dose level. The dose required to inhibit the swelling by 50% was estimated graphically.

Antihistaminic activity was studied in guinea pigs by the histamine aerosol technique, in which death is induced by aerosolization of 0.5% histamine for a 3-min. period. The agents were administered intraperitoneally 30 min. before the aerosol; 5–10 animals were employed at each of four dose levels. Protection was considered present when the animals were observed to be alive 10 min. after the end of the aerosol exposure period. It is to be mentioned that, of the untreated controls run concurrently, only 4 guinea pigs of 130 survived the exposure to histamine. The dose required to protect 50% of the animals was estimated from a log-probit plot of the data.

Structure–Activity Relationships.—The most potent compounds with respect to both antihistaminic and antiserotonin activity are cyproheptadine (I) and its thioxanthene congener (Vb). The very close parallelism between the biological actions of these compounds constitutes an excellent example of bioisosterism between sulfur and vinylene in a condensed aromatic ring system.[10] The xanthene analog Va is much less potent. This reflects the greater divergence between the biological effects of thioethers and their oxygen isosteres.[11]

Saturating the 10,11 double bond of I lowered antiserotonin activity slightly, but did not affect antihistaminic potency. The fluorene analog of I was inactive.

The nature of the substituent on the piperidine nitrogen is important, methyl and ethyl giving the highest potency with respect to both antihistaminic and antiserotonin properties. Larger alkyl and substituted-alkyl groups lead to lessening of activities of both types. The two activities are roughly parallel except in the case of the secondary amine (VII) which retains some antiserotonin activity but little antihistaminic activity.

Halogen substituents in the benzene rings of the dibenzocycloheptene derivatives uniformly lead to re-

(10) V. B. Schatz, "Medicinal Chemistry," A. Burger, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 72.

(11) H. L. Friedman, First Symposium on Chemical-Biological Correlation, National Academy of Sciences–National Research Council, Washington, D. C., 1951, p. 303.

ductions in both activities. The effect of a chloro substituent in the 2-position of the thioxanthene nucleus was much less marked.

Experimental Section[12]

5H-Dibenzocycloheptene-5-ones. 3-Benzylidenephthalides.—Phthalic anhydride was condensed with the appropriate phenylacetic acid following the procedure of Weiss.[13] Melting points were in accord with those reported for the 3-chloro[5c] and 4-chloro[14,5b,c] derivatives.

3-(*o*-Chlorobenzylidene)phthalide was obtained in 77% yield, m.p. 169–169.5°, after recrystallization from absolute alcohol.[15]

Anal. Calcd. for $C_{15}H_9ClO_2$: C, 70.18; H, 3.53. Found: C, 69.91; H, 3.75.

3-(*p*-Bromobenzylidene)phthalide was obtained in 69% yield, m.p. 171.5–172.5°, from CCl_4.[16]

Anal. Calcd. for $C_{15}H_9BrO_2$: C, 59.82; H, 3.01. Found: C, 59.76; H, 3.44.

2-(*o*-Chlorophenethyl)benzoic Acid.—Hydriodic acid (55–58%) (250 ml.) was heated to 100° in an atmosphere of CO_2 while hypophosphorous acid was added dropwise until the iodine color was discharged. 3-(*o*-Chlorobenzylidene)phthalide (45.1 g., 0.176 mole) and red phosphorus (34.7 g., 1.12 g.-atoms) were added, and the mixture was heated to refluxing with stirring for 23 hr. while maintaining an atmosphere of CO_2 in the apparatus.[17] The source of heat then was removed and water (200 ml.) was added gradually through the condenser while stirring vigorously and maintaining the CO_2 atmosphere.[17] After cooling, the solid was collected, washed with water, and ground with *ca.* 400 ml. of 2 *N* K_2CO_3 solution. The unreacted phosphorus was separated by filtration through a layer of diatomaceous earth and the product precipitated by addition of 3 *N* HCl. The yield of crude product, m.p. 137–138.5°, was 40.6 g., 89%. Recrystallization from benzene followed by recrystallization from absolute alcohol gave product, m.p. 139–140.5°.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.10; H, 5.02; neut. equiv., 260.7. Found: C, 69.33; H, 5.38; neut. equiv., 257.3.

2-(*m*-Chlorophenethyl)benzoic acid was obtained in 73% yield, m.p. 91–93.5°.[18]

2-(*p*-Bromophenethyl)benzoic acid was obtained in 79% yield, m.p. 127–128°.

Anal. Calcd. for $C_{15}H_{13}BrO_2$: C, 59.02; H, 4.29; Br, 26.17. Found: C, 58.61; H, 4.36; Br, 25.78.

3-Bromo-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one.[19]—Polyphosphoric acid (490 g.) was heated to 120° and stirred while 2-(*p*-bromophenethyl)benzoic acid (148.2 g., 0.486 mole) was added over a period of 30 min. The mixture was heated to 150° with stirring for 7 hr., then cooled and poured into ice–water. The product was extracted into ether and acidic material was removed by back-extraction with NaOH. After removal of the ether, the residue was distilled under reduced pressure. The yield of product, b.p. 159–161° (0.08 mm.), was 98 g. (70%). The product crystallized on cooling, m.p. 77.5–80.5°. An analytical sample melted at 82.5–83.3° after recrystallization from hexane.

Anal. Calcd. for $C_{15}H_{11}BrO$: C, 62.72; H, 3.86; Br, 27.83. Found: C, 62.77; H, 4.01; Br, 27.81.

1-Chloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one was obtained in 76% yield, m.p. 53.2–54.5°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.56. Found: C, 74.00; H, 4.86.

2-Chloro-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one was obtained in 67% yield, m.p. 71–75°.

Anal. Calcd. for $C_{15}H_{11}ClO$: C, 74.23; H, 4.57. Found: C, 73.88; H, 4.57.

A sample, m.p. 74.5–76.5°, was obtained by zone refining. Winthrop, *et al.*,[5c] report m.p. 76–78°. It seems probable that our material contains some of the 4-isomer.

3-Bromo-5H-dibenzo[*a*,*d*]cyclohepten-5-one.—A mixture of 3-bromo-10,11-dihydro-5H-dibenzo[*a*,*d*]cyclohepten-5-one (48.9 g., 0.17 mole), N-bromosuccinimide (30.3 g., 0.17 mole), and CCl_4 (270 ml.) was stirred while benzoyl peroxide (365 mg.) was added. The mixture then was cautiously heated to refluxing. Initiation of the reaction was evidenced by the appearance of an orange color and vigorous refluxing. The source of heat was removed until the reaction subsided.[20] The mixture then was heated to refluxing with stirring for 2 hr. A second reaction was carried out employing the same quantities and conditions, the combined reaction mixtures were filtered to remove solids, and the filtrate was extracted with 5% NaOH, then washed with water. The CCl_4 then was distilled under reduced pressure. The residual 3,10-dibromo-5H-dibenzo[*a*,*d*]cyclohepten-5-one was added gradually while warm to 700 ml. of triethylamine. A reaction took place almost immediately and a solid separated. The mixture was heated to refluxing with stirring for 10 hr. Water then was added to dissolve the solid, and the reaction mixture was extracted with benzene. The benzene extract was evaporated under reduced pressure to remove the bulk of the triethylamine, the residue was taken up in benzene, the solution was washed with dilute HCl followed by water, and the benzene was evaporated. The residue, a brown solid, m.p. 92.5–97°, weighed 96.6 g. Two recrystallizations from cyclohexane, after treatment with decolorizing carbon, gave 67.5 g. (70%) of product, m.p. 107–108°. An analytical sample from another experiment melted at 108–108.8° after recrystallization from hexane.

Anal. Calcd. for $C_{15}H_9BrO$: C, 63.17; H, 3.18; Br, 28.03. Found: C, 63.17; H, 3.35; Br, 27.89.

1-Chloro-5H-dibenzo[*a*,*d*]cyclohepten-5-one was obtained in 58% yield, m.p. 137.5–138.9°, from cyclohexane.

Anal. Calcd. for $C_{15}H_9ClO$: C, 74.85; H, 3.77; Cl, 14.73. Found: C, 74.72; H, 4.02; Cl, 14.57.

2-Chloro-5H-dibenzo[*a*,*d*]cyclohepten-5-one was obtained in 65% yield, m.p. 159–160°.[21,22]

Anal. Calcd. for $C_{15}H_9ClO$: C, 74.85; H, 3.77; Cl, 14.73. Found: C, 75.13; H, 3.91; Cl, 14.68.

Carbinols of General Structure IV. Method A-1. 5-(1-Methyl-4-piperidyl)-5H-dibenzo[*a*,*d*]cyclohepten-5-ol (IVa).—An atmosphere of dry nitrogen was maintained in the apparatus throughout the reaction. Magnesium turnings (5.45 g., 0.22 g.-atom) were covered with tetrahydrofuran[23] (20 ml.). A crystal of iodine was added followed by 1.2 g. of ethyl bromide. When the vigorous reaction had subsided, a solution of 4-chloro-1-methylpiperidine[24] (29.4 g., 0.22 mole) in tetrahydrofuran (volume of solution, 103 ml.)[25] was added dropwise at such a rate that gentle refluxing was maintained. When the addition was complete, the reaction mixture was heated to refluxing with stirring for 1 hr.[26] The reaction mixture was cooled to 5–10° and stirred while 5H-dibenzo[*a*,*d*]cyclohepten-5-one[4] (22.7 g., 0.11 mole) was added in portions. After stirring for 1 hr., during which the reaction mixture was allowed to warm up to room temperature, the bulk of the tetrahydrofuran was distilled at 40–50° under reduced pressure. Benzene, 150 ml., was added

(12) All melting points are corrected.

(13) R. Weiss, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 61.

(14) H. G. Krey, *Pharmazie*, **13**, 621 (1958).

(15) E. D. Bergmann [*J. Org. Chem.*, **21**, 462 (1956)] reports m.p. 163°.

(16) C. F. H. Allen and J. W. Gates, Jr. [*J. Am. Chem. Soc.*, **65**, 419 (1943)], report m.p. 154–155°; lit.[15] 162°.

(17) On some occasions when an inert atmosphere has not been maintained, sharp explosions have occurred in the condenser. A white solid, thought to be phosphonium iodide, sometimes collects in the condenser. It has been our practice to wash down the condenser with water thoroughly before admitting air to the system. No trouble has been encountered when this has been done. Some of the product sublimes into the lower portions of the condenser. This may not wash down easily.

(18) Lit.[5c] m.p. 89–90°.

(19) Campbell, *et al.*,[4c] employed polyphosphoric acid for the cyclization of 2-phenethylbenzoic acid in lieu of the Friedel–Crafts method used by earlier authors. Subsequent workers[5b,c] also have used this reagent under somewhat different conditions.

(20) Occasionally external cooling is necessary.

(21) Chloroform was used in place of benzene to redissolve the crude product prior to washing with acid. On concentrating this solution, the product crystallized in 65% yield. The melting point was 159–160°, unchanged by recrystallization from benzene–petroleum ether (b.p. 30–60°) or absolute alcohol.

(22) The position of the chlorine in this compound was confirmed by n.m.r. studies: private communication from N. R. Trenner.

(23) Tetrahydrofuran was dried and freed from peroxides by distillation from excess C_2H_5MgBr.

(24) S. M. McElvain and K. Rorig, *J. Am. Chem. Soc.*, **70**, 1828 (1948).

(25) This solution was dried (CaH_2) before use.

(26) A white solid, presumably the Grignard reagent, separated after about 20 min. at reflux. Additional solvent was employed in later experiments. A volume of 70 ml. of tetrahydrofuran/g. of Mg was found sufficient to prevent precipitation.

and the reaction mixture was cooled in an ice bath while the Grignard adduct was hydrolyzed by addition of 100 ml. of water. The benzene layer was separated and the gelatinous residue was extracted with three additional portions of boiling benzene. Distillation of the solvent from the combined benzene extracts gave 33.4 g. of a clear light brown resin. Crystallization from an alcohol–water mixture gave 19.5 g. (58%) of product, m.p. 156–157°. Recrystallization afforded 16.8 g. (50%) of product, m.p. 163–164° (sintered at 156°). An analytical sample prepared by a second recrystallization from alcohol–water followed by recrystallization from benzene–hexane gave material, m.p. 166.7–167.7°, λ_{max} 295–297 mμ (ε 14,157), in water containing sufficient HCl to dissolve.

Method A-2.—The procedure of method A-1 was carried out with the following modifications: (1) the ketone was added in tetrahydrofuran solution, (2) the Grignard adduct was hydrolyzed at 5–10° prior to distillation of the tetrahydrofuran, (3) $CHCl_3$ was used to extract the crude product if it was poorly soluble in benzene, (4) the crude product was converted to the hydrogen maleate in order to separate the product from nonbasic material, and (5) the base was isolated and recrystallized from hexane or a mixture of chloroform and hexane.

Method A-3.—The crude base, 2-chloro-5-(1-methyl-4-piperidyl)-5H-dibenzo[*a,d*]cyclohepten-5-ol (m.p. 137–150°, sintered at 130°) (11 g.), was isolated by extraction with chloroform and chromatographed on 300 g. of alumina (Brockmann, activity III). The crude product was applied to the column as the solid and elution was carried out with a series of solvents. After elution of a by-product with benzene, the product was eluted with benzene containing 25–35% ethyl ether and purified by recrystallization from a mixture of chloroform and hexane.

Isolation of a By-Product, 2-Chloro-5H-dibenzo[*a,d*]cyclohepten-5-ol.—The fraction eluted by benzene (7.3% yield) during isolation of 2-chloro-5-(1-methyl-4-piperidyl)-5H-dibenzo[*a,d*]cyclohepten-5-ol was recrystallized from hexane to give a product, m.p. 141.0–142.2°, $\lambda_{max}^{chloroform}$ 223 mμ (ε 33,000) and 283 mμ (ε 14,000).

Anal. Calcd. for $C_{15}H_{13}ClO$: C, 74.27; H, 4.57; Cl, 14.61. Found: C, 74.10; H, 4.89; Cl, 14.47.

Unsaturated Compounds of Structure V. Method B-1. 4-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine (I).—5-(1-Methyl-4-piperidyl)-5H-dibenzo[*a,d*]cyclohepten-5-ol (3.05 g., 0.01 mole) was dissolved in 15 ml. of glacial acetic acid. The solution was cooled in an ice bath while dry HCl was passed in. A white precipitate separated. After about 10 min., the flask was removed from the ice bath and acetic anhydride (3.07 g., 0.03 mole) was added. The mixture then was heated on the steam bath for 1 hr. The solid dissolved within the first 5 min. The reaction mixture then was poured into water. A finely divided white solid separated. The mixture was rendered strongly alkaline and the product was extracted into benzene. After washing with water, the benzene solution was concentrated to a volume of *ca.* 50 ml. and saturated with dry HCl. The white crystalline hydrochloride of the product was obtained in a yield of 2.5 g. (77%), m.p. 251.5–253.5°. Recrystallization from a mixture of absolute alcohol and absolute ether gave material, m.p. 252.5–253.5°. Prolonged drying at 110° *in vacuo* was required before satisfactory analyses were obtained; $\lambda_{max}^{H_2O}$ 223–224.5 mμ (ε 34,994), 237–242 (sh), and 284.5–286 (10,852).

Anal. Calcd. for $C_{21}H_{22}ClN$: C, 77.88; H, 6.85; N, 4.33. Found: C, 77.60; H, 6.80; N, 4.31.

The base was regenerated from the hydrochloride. It melted at 112.3–113.3° after recrystallization from an alcohol–water mixture.

Anal. Calcd. for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.88. Found: C, 87.77; H, 7.47; N, 4.85.

The hydrochloride monohydrate was prepared by dissolving the base (400 mg.) in 55 ml. of 1 *N* HCl at the boiling point and allowing the product to crystallize at room temperature. The product was dried for analysis ($CaCl_2$). The compound softened at 180° and melted at 214–216° when heated at a rate of 6°/min. from 180°. Analyses are recorded in Table II.

Method B-2. 4-(3-Bromo-5H-dibenzo[*a,d*]cyclohepten-5-ylidene)-1-methylpiperidine.—4-(3-Bromo-5-hydroxy-5H-dibenzo[*a,d*]cyclohepten-5-yl)-1-methylpiperidine (3.4 g., 0.00884 mole) and *o*-sulfobenzoic anhydride (3.26 g., 0.0177 mole) were dissolved in 75 ml. of propionic acid. After refluxing for 1.5 hr., the solution was cooled and poured into a mixture of ice and 40% NaOH solution. After adding more NaOH until the pH was 10, the mixture was extracted with chloroform, and the extract was washed with water and dried (Na_2SO_4). Distillation of the $CHCl_3$ under reduced pressure left 3.8 g. of a brown oily residue that became partially solid. The product was converted to the hydrogen maleate that was crystallized from a mixture of absolute alcohol and absolute ether in a yield of 3.60 g. (84.5%), m.p. 200.6–203.1° dec. Recrystallization gave product: m.p. 198.6–200.1°; $\lambda_{max}^{methanol}$ 219–220 mμ (ε 46,671), 243–245 (sh), 289–292 (13,259). Analyses are recorded in Table II.

Method B-3. 1-Methyl-4-(9-xanthylidene)piperidine (Va). 9-(1-Methyl-4-piperidyl)xanthen-9-ol (3.0 g., 0.0102 mole) was heated to refluxing in 40 ml. of formic acid (98–100%) for 2.5 hr. The bulk of the formic acid then was distilled on the steam bath under reduced pressure, the residue was dissolved in water, and the solution was made basic with NaOH. The product was extracted with benzene. After washing the extract with water, the benzene was distilled under reduced pressure leaving 2.61 g. of semisolid residue. The base was dissolved in 30 ml. of 1 *N* HCl, the solution was concentrated to *ca.* 20 ml., and the product was allowed to crystallize in the cold. The hydrochloride hydrate was obtained as a white crystalline solid in a yield of 0.88 g. (31%). It melted at 140–141° after drying ($CaCl_2$) at room temperature and at 168.7–169.7° after further drying at 60°; $\lambda_{max}^{chloroform}$ 240 mμ (ε 11,010), 278 (28701), 285 (infl), 305.5 (2911).[25,28] Analyses are recorded in Table II.

4-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-cyanopiperidine.—A solution of I (8.9 g., 0.031 mole) in 20 ml. of dry benzene was added dropwise to a stirred solution of BrCN (3.6 g., 0.034 mole) in 15 ml. of benzene at room temperature. When approximately half of the solution had been added, a white solid began to separate. When the addition was complete, benzene (15 ml.) was added to facilitate stirring, and the mixture was stirred for 75 min., then allowed to stand overnight. After the addition of 50 ml. of absolute ether, the product was collected and recrystallized from a mixture of acetone and absolute alcohol. The yield of product, m.p. 203–205°, was 6.18 g. (67%). An analytical sample, prepared by recrystallizing the product from a similar experiment from acetone and subsequently from ethyl acetate, melted at 203.5–204.5°.

Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.62; H, 6.30; N, 9.58.

4-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidene)piperidine (VII).—4-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-cyanopiperidine (6.18 g., 0.0206 mole) was added to a solution of glacial acetic acid (150 ml.), water (100 ml.), and concentrated HCl (15 ml.). The mixture was heated to refluxing for 16 hr. The solution was concentrated until solid began to separate (*ca.* 150 ml.) and diluted with water (100 ml.). The white crystalline hydrochloride, m.p. 290–292° dec., was obtained in a yield of 5.8 g. (91%). Analyses are recorded in Table II.

The hydrochloride was converted to the base that melted at 146.5–147.5° after recrystallization from a mixture of alcohol and water followed by recrystallization from a mixture of benzene and hexane.

Anal. Calcd. for $C_{20}H_{19}N$: C, 87.87; H, 7.01; N, 5.12. Found: C, 88.13; H, 7.05; N, 5.09.

4-(5H-Dibenzo[*a,d*]cyclohepten-5-ylidene)-1-ethylpiperidine.—Potassium *t*-butoxide (4.5 ml. of a 0.97 *M* solution) was added to a solution of VII (1.09 g., 0.004 mole) in 25 ml. of dry *t*-butyl alcohol. Ethyl iodide (0.624 g., 0.004 mole) was added and the solution was allowed to stand for 20 hr., then heated on the steam bath for 2 hr. In order to remove unreacted starting material, ethyl chloroformate (0.5 ml.) and pyridine (0.5 ml.) were added to the cooled solution which then was stirred 30 min. at room temperature and finally heated on the steam bath for 15 min. Water (10 ml.) and 1.25 *N* NaOH solution (10 ml.) were then added, and the mixture was shaken with benzene. The benzene layer was separated and washed with water, and the basic material was extracted into 200 ml. of 0.05 *M* citric acid solution. The acid extract then was made basic and the product was extracted into benzene. Distillation of the benzene on the steam bath under reduced pressure gave 0.48 g. of a viscous oily yellow base. The base was converted to the hydrogen maleate that was crystallized from a mixture of alcohol and ether. The yield of product, m.p. 202.5–203.5°, was 0.57 g. (34%). Further

(27) The xanthene carbinol (IVc) displayed the following ultraviolet maxima: $\lambda_{max}^{ethanol}$ 239 mμ (ε 11,910), 277.5–280.5 (sh), 284 (3012).

(28) The n.m.r. spectrum of Va confirmed the structure assigned, although the presence of a "moderately small amount of an unidentified impurity" was observed: private communication from N. B. Tremner.

recrystallizations from alcohol–ether mixtures gave product, m.p. 203.5–204.5°. Analyses are recorded in Table II.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-propylpiperidine.—A solution of VII (5.47 g., 0.02 mole) in toluene (50 ml.) was refluxed with sodamide (0.78 g., 0.02 mole) for 15 hr. After cooling to room temperature, *n*-propyl iodide (3.40 g., 0.02 mole) was added and the mixture was stirred 1 hr. during which time a light brown precipitate separated. The mixture then was heated on the steam bath for 1 hr. and finally at reflux for 30 min. After cooling, water (50 ml.) and hexane (200 ml.) were added, and the mixture was agitated. The organic layer was separated and washed with additional portions of water. After standing for 10 days, some prismatic crystals had separated that were removed by filtration, and the solution was concentrated to *ca.* 25 ml. In order to remove unreacted starting material, maleic anhydride (4.70 g., 0.05 mole) in 35 ml. of benzene was added, and the solution was refluxed 20 min. Methanol, 5 ml., then was added and the solution was concentrated to *ca.* 25 ml. Hexane (200 ml.), water (200 ml.), and triethanolamine (14.9 g., 0.1 mole) were added, and the mixture was shaken. The clear yellow organic layer was separated and washed with water. Evaporation of the solvent afforded 4.42 g. of the base as a clear light brown residue. The base was converted to the hydrogen maleate that was recrystallized from *n*-propyl alcohol: m.p. 214–216° (sintered at 213°); λ_{max} 219–220 mμ (ε 44,030), 236–243 (sh), 283–286 (10,887).

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-allylpiperidine was prepared by the procedure employed for the propyl compound.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-(2-dimethylaminoethyl)piperidine was prepared by substantially the same procedure employed for the propyl compound with the following modifications. Compound VII was refluxed 3 hr. with 2.1 equiv. of sodamide. 2-Diethylaminoethyl chloride hydrochloride (1.1 equiv.) was then added to the warm solution. Stirring and refluxing were continued for 12 hr. Sodium hydroxide solution was employed in place of the triethanolamine for removal of acidic material following the maleic anhydride step.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-(2-hydroxyethyl)piperidine (VIIIa).—A solution of VII (5.47 g., 0.02 mole) in 109 ml. of alcohol was cooled to 0° and ethylene oxide was passed in until the gain in weight was 1.76 g. The container was closed and heated to 65–70° in an autoclave for 1 hr. The solvent then was distilled and the last traces were removed by azeotropic distillation with benzene. The crystalline residue was extracted with boiling hexane, then recrystallized from a mixture of benzene and hexane. Further recrystallizations from mixtures of alcohol and water gave product, m.p. 158–159°.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-(2-mesyloxyethyl)piperidine (VIIIb).—A solution of methanesulfonic anhydride (1.22 g., 0.007 mole) in 4 ml. of acetonitrile was added to a solution of 2.10 g. (0.00662 mole) of VIIIa in 100 ml. of acetonitrile. After 48 hr. at room temperature, some crystals that had been deposited were separated by decantation and approximately 50 ml. of the solvent was distilled at 35–45° under reduced pressure. After 3 days in the refrigerator, the solid that had separated was removed by filtration, and the solvent was distilled at 25–30° under reduced pressure. The syrupy methanesulfonate salt of VIIIb was dissolved in absolute alcohol (13 ml.), 0.84 ml. of an 8.9 *N* solution of dry HCl in absolute alcohol was added, and the hydrochloride of VIIIb was precipitated by adding absolute ether portionwise. The product was recrystallized by dissolving in methanol and keeping the temperature below 30° while absolute ether was added gradually to incipient turbidity.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-nitrosopiperidine.—To a suspension of VII (9.78 g., 0.0358 mole) in 200 ml. of water was added 36 ml. of 1 *N* HCl with stirring, followed by 835 ml. of water. The mixture was heated to 75–80° on a steam bath. A cloudy solution resulted. A solution of 3.06 g. (0.043 mole) of $NaNO_2$ in the minimum quantity of water then was added and stirring was continued while the temperature was maintained for 2 hr. Shortly after addition of the nitrite, the pH rose and was adjusted to 6.4–6.8 by addition of 6 ml. of 1 *N* HCl. The pH then remained constant. At the end of the heating period, the mixture was cooled to 10° and the white precipitate was collected. The yield of product, m.p. 176–178°, was 8.11 g., 75%. Recrystallization from isopropyl alcohol raised the melting point to 179–180°.

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-ylidene)-1-aminopiperidine (VIIIc).—The nitroso compound (4.83 g., 0.016 mole) was dissolved in 25 ml. of tetrahydrofuran. Gradual addition of 17 ml. of a 1.03 *M* solution of $LiAlH_4$ in tetrahydrofuran was planned, but because of apparatus failure, approximately half of this solution was added rapidly. A pink color developed, hydrogen was evolved, and the mixture became warm. In spite of external cooling, the reaction became violent and a large proportion of the reaction mixture was lost by foaming out of the condenser. The remaining hydride solution was added after the reaction mixture had been cooled to room temperature. Evolution of hydrogen continued but stopped before the final portion was added. After stirring for an additional hour at room temperature, a solution of water in tetrahydrofuran was added to decompose the excess hydride. Ether was added and the mixture was filtered. After washing the filter cake with ether, the combined filtrate and washings were dried (Na_2SO_4). Distillation of the solvent in a nitrogen atmosphere left 1.62 g. of a pale yellow oil. The hydrogen maleate of VIIIc was obtained in a yield of 0.97 g. of product, m.p. 143–145° (sintered at 142°). A second crop of product, 0.27 g., m.p. 135–137° (sintered at 134°), was obtained from the mother liquors. After three recrystallizations from mixtures of absolute alcohol and ether, the product melted at 143–144° dec. (sintered at 142°).

4-(5H-Dibenzo[*a*,*d*]cyclohepten-5-yl)-1-methylpiperidine (X).—The Grignard reagent was prepared from 1-methyl-4-chloropiperidine (13.36 g., 0.1 mole) and Mg (2.43 g., 0.1 g.-atom) in tetrahydrofuran. The volume of the reaction mixture was *ca.* 100 ml. The solution was cooled to room temperature and stirred while a solution of 5-chloro-5H-dibenzo[*a*,*d*]cycloheptene[29] (17.0 g., 0.075 mole) in tetrahydrofuran (100 ml.) was added dropwise. The reaction mixture was cooled during the addition. After stirring at room temperature for 2 hr., the mixture was heated to reflux for 15 min. Isolation of the product was carried out by substantially the procedure employed for I. The crude base was obtained in a yield of 18.1 g. The base was converted to the hydrochloride, but one attempt to recrystallize this salt yielded amorphous material. The base was regenerated and converted to the hydrogen maleate that melted at 190–191° after recrystallization from alcohol–ether[30] mixtures, followed by recrystallization from *n*-propyl alcohol and finally from absolute ethanol.

Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.46. Found: C, 73.88; H, 6.64; N, 3.54.

(29) G. Berti, *Gazz. chim. ital.*, **87**, 293 (1957).

(30) Lit.[9] m.p. 189–192°.