Journal of Medicinal Chemistry

Volume 18, Number 1 January 1975

Benzopyranopyridine Derivatives. 1. Aminoalkyl Derivatives of the Azaxanthenes as Bronchodilating Agents†

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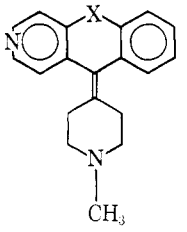
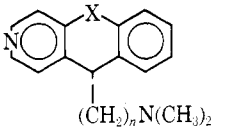
The preparation of the four isomeric azaxanthones 3 and a number of their aromatic ring substituted derivatives is described. These ketones were converted into the title compounds which were examined for their biological properties. The most interesting compound in this series, the 1-methyl-4-piperidylidene derivative of 1-azaxanthene (**12a**), shows the profile of an orally effective potent bronchodilating agent as well as a moderate antihistamine. Biological properties of this compound were compared to a number of antihistamines as well as known bronchodilating agents. Structure-activity relationships are also discussed.

Compounds of formula **1a** and **2a** have shown very potent antihistaminic and/or anaphylactic activity in laboratory animals[1] and one compound in this series has been proven highly effective in clinical trials in man.‡ This work was extended to include a study of the syntheses and pharmacological properties of the corresponding aminoalkyl derivatives of the isosteric azaxanthenes (**1b** and **2b**).

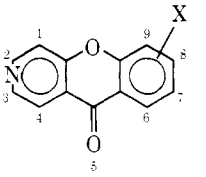


1a, X = CH_2CH_2
b, X = O



2a, X = CH_2CH_2
b, X = O

The ketones **3**§ required for this work were prepared by the intramolecular cyclization of the corresponding phenoxypyridine acids or nitriles. In those cases wherein X is hydrogen or when a para-substituted phenoxypyridine acid was used, PPA is the reagent of choice for the cyclization and gave excellent yields of the azaxanthones.& However, in the meta-substituted phenoxypyridine acid series, this reagent gave a mixture of 6- and 8-substituted azaxanthones. The use of $AlCl_3$ on the meta-substituted phenoxypyridine acid chloride in CS_2 sterically directed the orientation so that only the 8-substituted azaxanthone was isolated.[4] Under these latter conditions, 2-(*m*-trifluoromethylphenoxy)nicotinoyl chloride was converted into 8-trichloromethyl-1-azaxanthone in approximately 50% yield.** Fusion of the latter compound with antimony trifluoride[6] gave the desired trifluoromethyl derivative in low yield.



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The cyclization of 2-(*p*-carboxyphenoxy)nicotinic acid could not be achieved with PPA. However, using 30–35% fuming H_2SO_4,[7] the cyclization was effected in about 30% yield.

Nitration of 1-azaxanthone gave the 7-nitro derivative which was reduced to the 7-amino compound. Diazotization and replacement (Cu_2Cl_2) gave the 7-chloro ketone identical with the compound obtained from 2-(*p*-chloro-

†Presented in part at the American Chemical Society Symposium on Contemporary Approaches to Antiallergy Therapy, Los Angeles, Calif., April 1974.

‡Azatadine Schering, 6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine dimaleate.

§For convenience throughout this series we prefer to designate these compounds as derivatives of azaxanthone and indicate the position of the nitrogen and other substituents on the ring by the standardized numbering system shown in **3**. However, the Chemical Abstracts names for the 1-, 2-, 3-, and 4-azaxanthones are 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one, 5*H*-[1]benzopyrano[2,3-*c*]pyridin-5-one, 10*H*-[1]benzopyrano[3,2-*c*]pyridin-10-one, and 10*H*-[1]benzopyrano[3,2[*b*]pyridin-10-one, respectively.

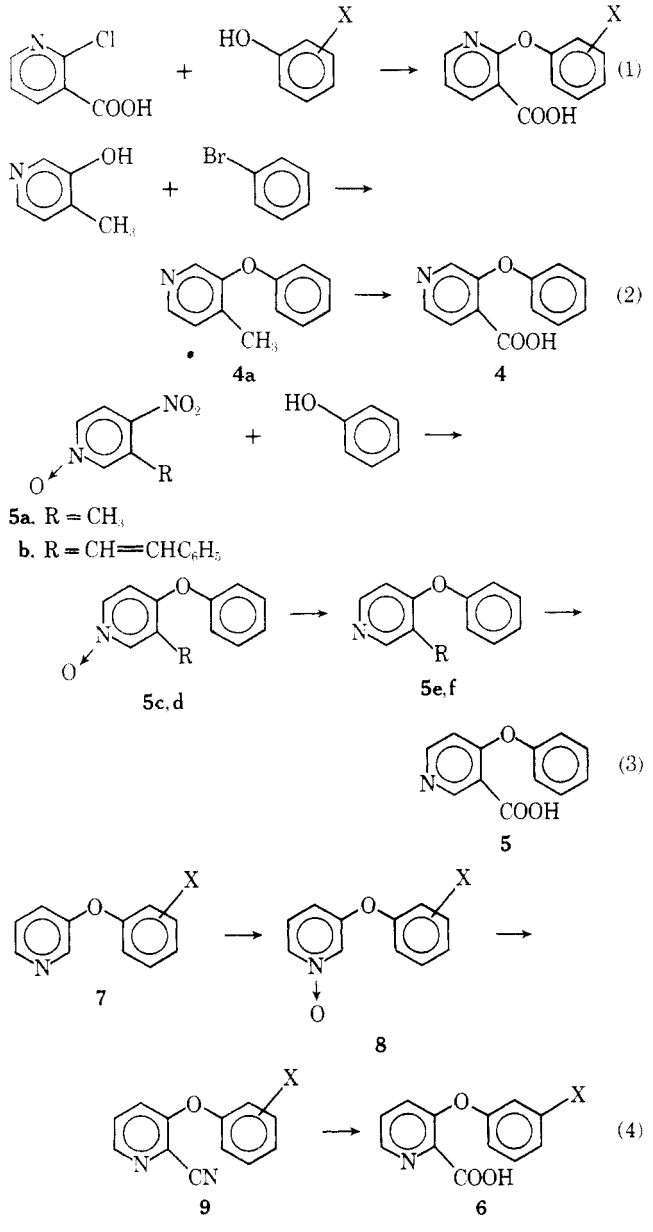
&The 1-aza- and 3-azaxanthones reported herein have been previously prepared in low yields (see ref 2 and 3).

**This interesting replacement of the trifluoromethyl group by $AlCl_3$ has been previously reported. See ref 5.

phenoxy)nicotinic acid by cyclization. This same series of reactions was used to prepare the corresponding derivatives in the 4-azaxanthone series.

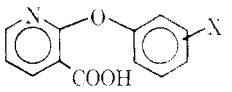
The phenoxypyridinecarboxylic acids were prepared by the methods shown in Scheme I. 2-Chloronicotinic acid was condensed with sodium phenoxide using an excess of the phenol as reaction solvent (method A). When the phenol was not readily available the condensation was modified using equimolecular quantities of the acid and the sodium phenolate in DMF (method B). Table I lists the properties of the compounds prepared by these methods.

Scheme I



3-Phenoxyisonicotinic acid **4** required for the synthesis of 2-azaxanthone was prepared by the oxidation of 3-phenoxy-4-picoline (**4a**), the latter obtained by the Ullmann condensation of 3-hydroxy-4-picoline and bromobenzene (eq 2, Scheme I).

4-Phenoxynicotinic acid (**5**), was prepared as shown in eq 3 of Scheme I. Displacement of the nitro group in **5a** or **5b** by phenoxide in the presence of K_2CO_3 gave the phenyl ethers **5c** and **5d** which were N-deoxygenated (PCl_3 and $CHCl_3$) to the pyridyl ethers **5e** and **5f**, respectively. Oxidation (aqueous $KMnO_4$) gave the desired acid **5**.

Table I. Compounds of Formula 

No.	X	Method	Yield, %	Mp, °C	Formula[a]
1	H	A	85	179–181[b]	
2	*m*-Cl	A	98	168–169[c]	$C_{12}H_8ClNO_3$
3	*p*-Cl	A	55	155–157[c]	$C_{12}H_8ClNO_3$
4	*m*-OCH_3	A	54	153–154[d]	$C_{13}H_{11}NO_4$
5	*m*-F	B	41	145–147[c]	$C_{12}H_8FNO_3$
6	*p*-F	B	67	181–183[c]	$C_{12}H_8FNO_3$
7	*m*-CF_3	B	32	144–146[e]	$C_{13}H_8F_3NO_3$
8	*m*-CH_3	A	69	147–148[d]	$C_{13}H_{11}NO_3$
9	*p*-CH_3	A	70	164–165[c]	$C_{13}H_{11}NO_3$
10	*p*-COOH	*f*	43	222–224[g]	$C_{13}H_9NO_5$
11	*m*-$COCH_3$	B	24	153–155[e]	$C_{14}H_{11}NO_4$
12	*p*-$COCH_3$	B	9	190–191[g]	$C_{14}H_{11}NO_4$
13	*p*-*t*-Bu	A	82	179–181[h]	$C_{16}H_{17}NO_3$

[a] All compounds were analyzed for C, H, and N and the results were within 0.4% of theory. [b] Lit.[2] mp 179–180°. [c] From *i*-PrOH. [d] From EtOAc. [e] From C_6H_6–petroleum ether. [f] Oxidation of compound **9** with alkaline $KMnO_4$. [g] From EtOH after washing with $(CH_3)_2CO$ to remove starting material. [h] From dilute EtOH.

Compound **5** was not obtained analytically pure as it was contaminated by a small amount of 4-ketodihydronicotinic acid (nmr analysis about 10–15%) but was of sufficient purity for ring closure to the 3-azaxanthone.

Equation 4 in Scheme I summarizes the preparation of the phenoxypicolinic acids **6** required for the synthesis of the 4-azaxanthones. The 1-oxides **8** were converted into the 2-cyano derivatives by methods previously reported.[8] Direct ring closure of **9a** (X = H, method G) produced 4-azaxanthone in excellent yield. The 8-substituted derivatives were prepared from the acids **6** by the $AlCl_3$ method indicated above. The ketones prepared by these methods are listed in Table II.

The carbinol intermediates (Table III) were obtained in the usual manner from the ketones (experimental methods K and L) and were subjected to a dehydration procedure to yield the unsaturated derivatives (Table IV). In the majority of cases, PPA at 100–120° was the dehydrating agent of choice. However, in certain cases, especially with the dialkylaminoalkylcarbinols, concentrated HCl in the Ac_2O was very effective. The dehydration of the 8-methoxycarbinol (Table III, **47**) was carried out with $SOCl_2$ in anhydrous pyridine, thereby preventing the facile hydrolysis of the methoxy group by PPA or strong mineral acids.

Interestingly, if the dehydration of carbinol **42** (Table III) is carried in PPA at 100–120°, excellent yields of **12a** are obtained. If, however, the reaction is carried out at 180–200°, the endocyclic structure **12b** is obtained exclusively. The structure of these isomers was established by the usual spectral analyses. Of particular importance was the uv spectra of **12a** and **12b** showing ϵ_{245} 13,200, ϵ_{280}

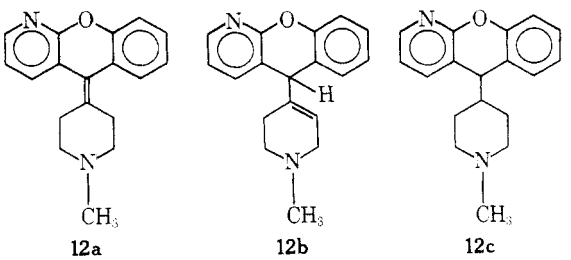
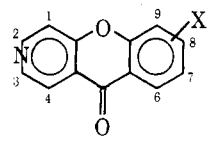


Table II. Compounds of Formula 

No.	Position of N	X	Method	Yield, %	Mp, °C	Formula[a]
14	1	H	C	98	178–182[b]	
15	1	8-Cl	D	80	189–190[c]	$C_{12}H_6ClNO_2$
16	1	7-Cl[d]	C	64	198–200[c]	$C_{12}H_6ClNO_2$
17	1	8-OCH_3	*e*	52	179–180[c]	$C_{13}H_9NO_3$
18	1	8-OH	*f*	59	329–330[g]	$C_{12}H_7NO_3$
19	1	8-$O(CH_2)_2N(Me)_2$	*h*	38	53–55[i]	$C_{18}H_{20}N_2O_3$
20	1	8-F	D	62	193–195[c]	$C_{12}H_6FNO_2$
21	1	7-F	C	88	179–181[i]	$C_{12}H_6FNO_2$
22	1	8-CF_3	*e*		170–172[i]	$C_{13}H_6F_3NO_2$
23	1	8-CCl_3	D[e]	49	122–123[i]	$C_{13}H_6Cl_3NO_2$
24	1	7-NO_2	H	76	237–239[c]	$C_{12}H_6N_2O_4$
25	1	7-NH_2	I	91	246–248[g]	$C_{12}H_8N_2O_2$
26	1	8-CH_3	D	69	151–152[c]	$C_{13}H_9NO_2$
27	1	7-CH_3	C	67	166–168[j]	$C_{13}H_9NO_2$
28	1	7-COOH	*e*	31	300–304[g]	$C_{13}H_7NO_4$
29	1	7-*t*-Bu	C	78	98–100[j]	$C_{16}H_{15}NO_2$
30	2	H	C	91	157–158[i]	$C_{12}H_7NO_2$
31	3	H	C	83	183–185[k]	$C_{12}H_7NO_2$
32	4	H	G	84	204–205[l]	$C_{12}H_7NO_2$
33	4	8-Cl	D	59	213–214[c]	$C_{12}H_6ClNO_2$
34	4	7-NO_2	H	60	283–285[i]	$C_{12}H_6N_2O_4$
35	4	7-NH_2	I	86	290–292[g]	$C_{12}H_8N_2O_2$
36	4	7-Cl	J	46	210–213[m]	$C_{12}H_6ClNO_2$
37	4	7-CH_3	G	64	192–193[j]	$C_{13}H_9NO_2$
38	4	8-CH_3	D	49	157–159[j]	$C_{13}H_9NO_2$
39	4	7-F	G	83	223–224[j]	$C_{12}H_6FNO_2$

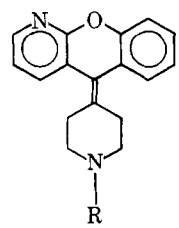
[a]All compounds were analyzed for C, H, and N, and the results were within 0.4% of theory. [b]This compound was previously prepared in poor yield (ref 2) by cyclization of compound 1 (see Table I) using $POCl_3$. Mp (reported) 182–183°. [c]From EtOAc. [d]See experimental method J for alternate synthesis. [e]See Experimental Section for details. [f]Pyridine hydrochloride demethylation of compound **16**. [g]From EtOH. [h]Alkylation of compound 17 using $Cl(CH_2)_2N(CH_3)_2$ and NaOEt: see F. J. Villani, C. A. Ellis, R. F. Tavares, M. Steinberg, and S. Tolksdorf, *J. Med. Chem.*, **13**, 359 (1970). [i]From CH_3CN. [j]From C_6H_6–petroleum ether. [k]Reference 3 reported a 10% yield of this compound having mp 184.5°. [l]From C_6H_6. [m]From *i*-PrOAc.

5880, and ϵ_{309} 8020 nm compared to ϵ_{245} 5650, ϵ_{272} 4470, and ϵ_{289} 4830 nm, respectively. The benzyl proton (δ 4.75) as well as the vinyl proton (δ 5.79) in the nmr spectrum of **12b** was absent in the nmr spectrum of **12a**. Additional support for structure **12b** was the relative ease of catalytic hydrogenation to **12c**. The exo double bond of **12a** could also be isomerized to **12b** by heating with KOH in EtOH.

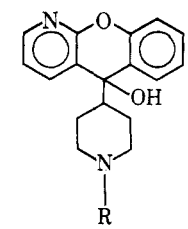
Early in the development of this project it was observed that maximum biological activity with minimal toxicity was found in the 1-aza series of compounds. To study the effects of structural modifications in this series, **12a** was treated with cyanogen bromide or ethyl chloroformate to give the expected derivatives (**13a,b**). Hydrolysis of these compounds under acidic or basic conditions produced carbinol **14a** as the major product along with a minor amount of the expected **13c**. Compound **14a** was identical in physical and spectral properties with the compound obtained by acid hydrolysis of the carbinol **14b**. Dehydration of **14a** under the usual PPA conditions gave **13c**, albeit in poor yield. Because of these difficulties and the inherent problems associated with the separation of **13c** from its N-alkylated derivatives, this approach to the synthesis of the latter compounds was abandoned in favor of the method whereby the substituted N-alkylated chloropiperidines were used to prepare the carbinols (Table III) which were then converted into the desired ylidenes (Table IV).

To gain some insight as to the nature of the receptor sites compounds **15** and **16**, lacking the conformational rigidity of the azaxanthenes, were prepared.

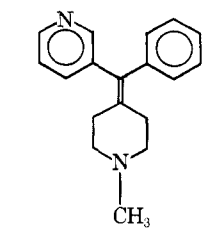
Biological Methods and Results. Unanesthetized guin-



13a, R = CN
b, R = COOEt
c, R = H



14a, R = H
b, R = CN



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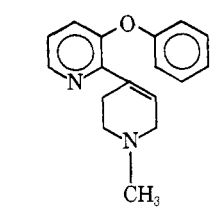

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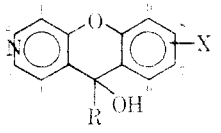
Table III. Compounds of Formula 

No.	Position of N	X	R	Method	Yield, %	Mp, °C	Formula[a]
40	1	H	$(CH_2)_2N(Me)_2$	K	61	126–128[b]	$C_{16}H_{18}N_2O$
41	1	H	$(CH_2)_3N(Me)_2$	L	65	116–118[c]	$C_{17}H_{20}N_2O$
42	1	H	4-$C_6H_{12}N$[d]	K	68	208–210[c]	$C_{18}H_{20}N_2O_2$
43	1	8-Cl	4-$C_6H_{12}N$	L	27	247–250[c]	$C_{18}H_{19}ClN_2O_2$
44	1	7-Cl	4-$C_6H_{12}N$	L	45	181–185[e]	$C_{18}H_{19}ClN_2O_2$[f]
45	1	8-F	4-$C_6H_{12}N$	L	56	210–212[c]	$C_{18}H_{19}FN_2O_2$
46	1	7-F	4-$C_6H_{12}N$	L	42	223–226[c]	$C_{18}H_{19}FN_2O_2$[g]
47	1	8-OCH_3	4-$C_6H_{12}N$	L	53	203–205[c]	$C_{19}H_{22}N_2O_3$
48	1	8-CH_3	4-$C_6H_{12}N$	K	76	225–226[c]	$C_{19}H_{22}N_2O_2$
49	1	7-CH_3	4-$C_6H_{12}N$	K	41	205–207[e]	$C_{19}H_{22}N_2O_2$
50	1	7-*t*-Bu	4-$C_6H_{12}N$	K	60	187–189[c]	$C_{22}H_{28}N_2O_2$
51	1	H	3-$C_7H_{14}N$[h]	K	50	166–168[i]	$C_{19}H_{22}N_2O_2$
52	1	H	3-$C_7H_{14}N$[j]	K	73	179–181[c]	$C_{19}H_{22}N_2O_2$
53	1	H	4-$C_7H_{14}N$[k]	K	51	195–197[e]	$C_{19}H_{22}N_2O_2$
54	1	H	4-$C_{12}H_{16}N$[l]	K[m]			
55	1	H	4-$C_8H_{14}N$[n]	K	47	159–161[c]	$C_{20}H_{22}N_2O_2$
56	2	H	4-$C_6H_{12}N$	K	61	155–157[e]	$C_{18}H_{20}N_2O_2$
57	3	H	4-$C_6H_{12}N$	K	80	170–171[c]	$C_{18}H_{20}N_2O_2$[o]
58	3	H	$(CH_2)_3N(Me)_2$	K	47	61–65[c]	$C_{17}H_{20}N_2O_2$
59	4	H	$(CH_2)_2N(Me)_2$	K	63	133–135[b]	$C_{16}H_{18}N_2O_2$
60	4	H	$(CH_2)_3N(Me)_2$	K	85	92–95[b]	$C_{17}H_{20}N_2O_2$
61	4	H	4-$C_6H_{12}N$	K	59	105–107[c]	$C_{18}H_{20}N_2O_2$
62	4	7-CH_3	4-$C_6H_{12}N$	K	66	116–117[c]	$C_{19}H_{22}N_2O_2$
63	4	7-F	4-$C_6H_{12}N$	K	80	122–123	$C_{18}H_{19}FN_2O_2$
64	4	H	4-$C_7H_{14}N$[k]	K	72	84–86	$C_{19}H_{22}N_2O_2$[p]
65	4	H	4-$C_{12}H_{16}N$[l]	K[q]			
66	4	H	4-$C_8H_{16}N$[r]	K[s]			

[a] All compounds were analyzed for C, H, and N. [b] From *i*-Pr_2O. [c] From CH_3CN. [d] 4-$C_6H_{12}N$ is 1-methyl-4-piperidyl. [e] From C_6H_6–petroleum ether. [f] H: calcd, 5.89; found, 6.37. [g] C: calcd, 68.77; found, 68.20. [h] 3-$C_7H_{14}N$ is 1-ethyl-3-piperidyl. [i] From $CHCl_3$–hexane. [j] 3-$C_7H_{14}N$ is 1-methyl-3-piperidylmethyl. [k] 4-$C_7H_{14}N$ is 1-ethyl-4-piperidyl. [l] 4-$C_{12}H_{16}N$ is 1-benzyl-4-piperidyl. [m] Isolated as maleic acid salt: mp 211–213°; yield 61%. *Anal.* ($C_{24}H_{24}N_2O_2 \cdot C_4H_4O_4$) C, H, N. [n] 4-$C_8H_{11}N$ is 1-allyl-4-piperidyl. 1-Allyl-4-chloropiperidine [*Anal.* ($C_8H_{14}ClN$) C, H, N], bp 77–78° (8 mm), was prepared from 1-allyl-4-piperidinol [*Anal.* ($C_8H_{15}NO$) C, H, N], bp 93–95° (4 mm), by the method of R. Fankhauser, C. A. Grob, and V. Krasnobejew, *Helv. Chim. Acta*, **49**, 690 (1966). [o] N: calcd, 9.45; found, 10.50. [p] C: calcd, 73.52; found, 72.96. The fumarate salt had mp 164–166°. *Anal.* ($C_{19}H_{22}N_2O_2 \cdot C_4H_4O_4$) C, H, N. [q] Isolated as maleic acid salt, mp 176–178°. *Anal.* ($C_{24}H_{24}N_2O_2 \cdot C_4H_4O_4$) C, H, N. [r] 4-$C_8H_{16}N$ is 1-isopropyl-4-piperidyl. [s] Isolated as fumarate salt, mp 186–187°, from EtOH–Et_2O. *Anal.* ($C_{20}H_{24}N_2O_2 \cdot C_4H_4O_4$) C, H, N.

ea pigs when subjected to an aerosol of a 0.1% solution of histamine dihydrochloride will develop dyspnea in 40–60 sec.[9] The dyspnea can be prevented by bronchodilating and/or antihistamine agents. The compounds were administered orally (30 mg/kg) to five fasted guinea pigs 1 hr before exposure to the histamine aerosol. If the test compound delayed the onset of dyspnea for 400–600 sec, it was assayed to determine the ED_{200} sec or that dose which would prevent the onset of dyspnea for 200 sec in 50% of 40 test animals. ED_{200} sec values for representative compounds in this series are given in Table V.

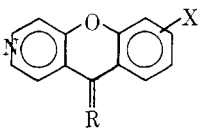
The antihistamine potencies *in vitro* (guinea pig ileum) were determined for the more active compounds by standard procedures.[10]

To differentiate between the true antihistamine and bronchodilating compounds, bronchodilation *in vitro* was determined by a modification of the isolated lung procedure of Bhattacharya and Delaunois.[11] Male guinea pigs were sensitized with an intraperitoneal injection of 1.0 ml and a subcutaneous injection of 0.5 ml of a 5% solution of egg albumen, 14 days before sacrifice, and the lungs were isolated. A challenge *in vitro* of 0.1 ml of the egg albumen will precipitate an antigen–antibody reaction in the perfused lung causing a severe bronchoconstriction. Bronchodilating drugs in contrast to the antihistamines are effective in relieving this bronchoconstriction. Doses ranging from 0.01 to 10 mg/lung were used.

Table V lists the biological profiles of some representative compounds in this series as well as a series of standard compounds for comparison. Included in these standards are the antihistamines, chlorpheniramine maleate (CTM),†† azatadine maleate,‡ and cyproheptadine.‡‡ These compounds, being potent antihistaminic agents, do not produce a bronchodilating effect on the guinea pig lung preparation. In contrast, isoproterenol and aminophylline, two known bronchodilating drugs, will dilate the isolated constricted lung.

Of considerable interest in the present series of compounds is the pharmacological activity of **12a** maleate (Table IV, **69** maleate). This compound shows the profile of a combined potent bronchodilator and moderate antihistaminic agent. The compound will relax the bronchospasm induced by anaphylaxis in the isolated perfused lung and will protect against histamine both *in vitro* and *in vivo*.

††Chlorpheniramine maleate (Schering Corp.).
‡‡Cyproheptadine (Merck Sharpe & Dohme).

Table IV. Compounds of Formula 

No.	Position of N	X	R	Yield, %	Mp or bp (mm), °C	Formula[a]
67	1	H	$CH(CH_2)_2N(Me)_2$	63	180–183 (0.04)	$C_{17}H_{18}N_2O$
68 HCl					210–215[b]	$C_{17}H_{18}N_2O \cdot HCl$
69	1	H	4-$C_6H_{11}N$[c]	83	125–127[d]	$C_{18}H_{18}N_2O$
69 maleate					206–208[e]	$C_{18}H_{18}N_2O \cdot C_4H_4O_4$
70	1	8-Cl	4-$C_6H_{11}N$	57	142–144[d]	$C_{18}H_{17}ClN_2O$
71	1	7-Cl	4-$C_6H_{11}N$	85	143–145[f]	$C_{18}H_{17}ClN_2O$
72	1	8-F	4-$C_6H_{11}N$	50	106–108[f]	$C_{18}H_{17}FN_2O$
73	1	7-F	4-$C_6H_{11}N$	57	168–170[f]	$C_{18}H_{17}FN_2O$
74	1	8-OCH_3	4-$C_6H_{11}N$[g]	49	137–138[f]	$C_{19}H_{20}N_2O_2$
75	1	8-CH_3	4-$C_6H_{11}N$	51	137–139[h]	$C_{19}H_{20}N_2O$
76 maleate	1	7-CH_3	4-$C_6H_{11}N$	31	217–218[i]	$C_{19}H_{20}N_2O \cdot C_4H_4O_4$
77	1	7-*t*-Bu	4-$C_6H_{11}N$	70	143–145[d]	$C_{22}H_{26}N_2O$
78	1	H	3-$C_7H_{13}N$[j]	37	118–120[k]	$C_{19}H_{20}N_2O$
79	1	H	3-$C_7H_{13}N$[l]	93	134–135[d]	$C_{19}H_{20}N_2O$
80	1	H	4-$C_7H_{13}N$[m]	75	116–117[k]	$C_{19}H_{20}N_2O$[n]
80 hemifumarate					215–217[b]	$C_{19}H_{20}N_2O \cdot 0.5C_4H_4O_4$
81	1	H	4-$C_8H_{13}N$[o]	83	143–144[d]	$C_{20}H_{20}N_2O$
82 fumarate	2	H	4-$C_6H_{11}N$	57	222–224[b]	$C_{18}H_{18}N_2O \cdot C_4H_4O_4$
83 hemifumarate	3	H	4-$C_6H_{11}N$	45	180–183[b]	$C_{18}H_{18}N_2O \cdot 0.5C_4H_4O_4$
84	3	H	$CH(CH_2)_2N(Me)_2$	65	163–167 (0.05)	$C_{17}H_{18}N_2O$
85 fumarate	4	H	4-$C_6H_{11}N$	71	180–182[b]	$C_{18}H_{18}N_2O \cdot C_4H_4O_4$
86	4	7-CH_3	4-$C_6H_{11}N$	43	124–125[d]	$C_{19}H_{20}N_2O$[p]
86 fumarate					190–191[b]	$C_{19}H_{20}N_2O \cdot C_4H_4O_4 \cdot 0.5H_2O$
87	4	7-F	4-$C_6H_{11}N$	61	117–118[d]	$C_{18}H_{17}FN_2O$
88 hemifumarate	4	H	4-$C_7H_{13}N$[m]	57	185–186[b]	$C_{19}H_{20}N_2O \cdot 0.5C_4H_4O_4$
89 fumarate	4	H	4-$C_8H_{15}N$[q]	62	173–175[b]	$C_{20}H_{22}N_2O \cdot C_4H_4O_4$
90	4	H	4-$C_{12}H_{15}N$[r]	47	148–150[f]	$C_{24}H_{22}N_2O$

[a] All compounds were analyzed for C, H, and N. [b] From absolute EtOH–ether. [c] 4-$C_6H_{11}N$ is 1-methyl-4-piperidylidene. [d] From *i*-Pr_2O. [e] From *i*-PrOH. [f] From CH_3CN. [g] See Experimental Section for details. [h] From $CHCl_3$–hexane. [i] From EtOH–EtOAc. [j] 3-$C_7H_{13}N$ is 1-ethyl-3-piperidylidene. [k] From hexane. [l] 3-$C_7H_{13}N$ is 1-methyl-3-piperidylmethylidene. [m] 4-$C_7H_{13}N$ is 1-ethyl-4-piperidylidene. [n] C: calcd, 78.05; found, 77.37. [o] 4-$C_8H_{13}N$ is 1-allyl-4-piperidylidene. [p] C: calcd, 78.05; found, 76.68. H: calcd, 6.90; found, 7.46. [q] 4-$C_8H_{15}N$ is 1-isopropyl-4-piperidylidene. [r] 4-$C_{12}H_{15}N$ is 1-benzyl-4-piperidylidene.

A comparison of the ED_{200} sec values from Table V shows that **12a** is approximately ten times more potent than aminophylline and about one-half as potent as isoproterenol on oral administration in guinea pigs.

Confirmation of these observations was noted in the ability of **12a** to lower pulmonary resistance and to increase pulmonary compliance[12-14] in anesthetized dogs at an intravenous dose of 0.025 mg/kg. The compound is not a β-adrenergic activator and will inhibit phosphodiesterase and the release of histamine from peritoneal mast calls.§§ The complete biological activity of this compound will be published in the appropriate pharmacological journals.

Structure–Activity Relationships. The tertiary carbinols (Table III) and the dimethylaminoalkylidene derivatives have shown little or no activity in these test procedures. Maximum activity is found in the 1-methyl-4-piperidylidene derivatives. Substitution of the 1-methyl group by ethyl does not effect the potency in the dyspnea screen but this compound shows only slight activity in the dog resistance and compliance preparation at iv doses of 1, 4, and 8 mg/kg. Substitution of the 1-methyl group by hydrogen, benzyl, or allyl results in a marked drop in activity. Moving the double bond from the exo position as in **12a** to the endo position as in **12b** results in a considerable loss in activity. However, saturation of the double bond (**12c**) produces a compound having only moderate activity. Aromatic ring substitution, with the possible exception of the 7-fluoro compound, does not enhance the activity.

The 1-ethyl-3-piperidylidene and the 1-methyl-3-piperidylmethylidene derivatives were inactive at the screening dose of 30 mg/kg orally. Compounds **15** and **16** were inactive in prolonging the onset of dyspnea for 340 and 90 sec, respectively, at an oral screening dose of 30 mg/kg.

§§Unpublished results from these laboratories.

Experimental Section[&&]

2-Phenoxynicotinic Acid (Method A). Commercial NaOMe (35 g, 0.65 mol) was dissolved in 150 ml of anhydrous MeOH and 140 g (1.5 mol) of phenol was added followed by 50 g (0.32 mol) of 2-chloronicotinic acid. The MeOH was removed by distillation

[&&] Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were performed by the Physical Analytical Department of the Schering Corp. Where the analysees are indicated only by the symbols of the elements, the analytical values were within 0.4% of the theoretical values. All new compounds were submitted for ir and nmr analyses and the spectra were in agreement with theoretical values. The authors acknowledge the assistance of Dr. Milton Yudis and Mr. James Morton in the interpretation of the nmr spectra and to Mr. James McGlotten for the mass spectral data. Unless otherwise noted, all ketones were 1-spot material on tlc using silica gel plates and a solvent mixture of $CHCl_3$, MeOH, and NH_4OH (90:9:1). In those cases where the possibility for cis and trans isomers at the double bond exists, the mixture was not separated into its components for preliminary pharmacological screening.

Table V. Biological Results

Compd no.	ED_{200} sec, mg/kg	*In vitro* antihistamine ED_{50}, mg/l.	Guinea pig lung[a]
68 HCl	30		
69 maleate (12a)	12.2	0.0009	+
70	5.7	0.002	+
71	>30	0.1	−
72	2.1		
73	2.5	0.014	+
74	>30		+
75	6.6	0.0024	
76 maleate	2.9	0.0025	
78	>30		+
79	>30		
80 hemifumarate	15.6	0.0016	+
82 fumarate	5.5	0.001	+
83 hemifumarate	3.4	0.002	+
85 fumarate	0.71	0.0003	±
12b	>30		
12c	7.1	0.15	+
CTM	0.25	0.002	−
Azatadine	0.01	0.001	−
Isoproterenol	5.2	0.028	+
Aminophylline	117.0	>100	+
Cyproheptadine	0.704	0.001	−

[a] + = relaxation; − = no effect.

and the residue was heated at 180° for 1 hr, cooled to 100°, and poured into ice. The solution was extracted several times with Et_2O and the aqueous layer was acidified with HOAc, cooled, and filtered. The solid was washed with H_2O, dried, and recrystallized.

2-(*m*-Fluorophenoxy)nicotinic Acid (Method B). To a solution of 10.8 g (0.2 mol) of NaOMe in 150 ml of MeOH was added a slurry of 11.1 g (0.1 mol) of *m*-fluorophenol and 15.8 g (0.1 mol) of 2-chloronicotinic acid in 100 ml of MeOH. The MeOH was completely removed by distillation, 100 ml of anhydrous DMF was added, and the mixture was heated with stirring under reflux for 2 hr. The excess solvent was removed and the residue was dissolved in H_2O and extracted (Et_2O). The aqueous solution was acidified (HOAc), cooled, filtered, washed with H_2O, dried, and recrystallized.

Ring Closure (Method C). A mixture of the phenoxypyridine acid and 50 times its weight of PPA was heated with stirring at 100–120° for 16 hr and poured into ice. The solution was basified (50% NaOH), cooled, and filtered. Alternatively, the ketone was extracted with $CHCl_3$ and washed (H_2O), the solvent removed, and the residue recrystallized.

Ring Closure (Method D). In a typical experiment, the meta-substituted phenoxypyridine acid (0.1 mol) was suspended in 200 ml of anhydrous C_6H_6 and 25 ml of $SOCl_2$ was added dropwise with stirring and at reflux. Heating was continued for 2 hr and the excess solvent was removed *in vacuo* on the steam bath. An additional 50 ml of dry C_6H_6 was added and the mixture taken to dryness. Carbon disulfide (750 ml) was added followed by the portionwise addition of $AlCl_3$ (0.25 mol) and the mixture was stirred at reflux for 6–8 hr. The solvent was removed and the residue was decomposed by addition of 10% HCl and ice. If the HCl salt precipitated it was filtered and suspended in H_2O, basified (NaOH) and extracted with $CHCl_3$, and washed (H_2O), the solvent was removed, and the residue was recrystallized. Alternatively, the acid solution was strongly basified (NaOH) and processed as described.

8-Methoxy-1-azaxanthone. The strongly basic solution from the above procedure was treated with 0.15 mol of $(Me)_2SO_4$ and stirred at room temperature for 6 hr. The yellow precipitated solid was filtered and extracted with refluxing EtOAc. Concentration of these extracts gave the title compound.

8-Trichloromethyl-1-azaxanthone. From 22.6 g (0.08 mol) of 2-(*m*-trifluoromethylphenoxy)nicotinic acid by method D there was obtained 12 g of the title compound. The mass spectrum shows a parent *m/e* of 313.

8-Trifluoromethyl-1-azaxanthone. The above trichloromethyl compound (9.7 g, 0.03 mol) was heated at 150° for 15 min with 10.7 g (0.06 mol) of SbF_3. After cooling, water and $CHCl_3$ were added and the $CHCl_3$ extracts were taken to dryness. This material was dissolved in $CHCl_3$ and chromatographed on a silica gel column using $CHCl_3$ as the eluent. The crude product after several recrystallizations from *i*-Pr_2O had mp 170–172°, yield 1.9 g.

4-Phenoxy-3-picoline 1-Oxide (5c). A mixture of 30.8 g (0.2 mol) of 4-nitro-3-picoline 1-oxide[15] (5a), 37.6 g (0.4 mol) of phenol, and 27.6 g (0.2 mol) of K_2CO_3 was heated on the steam bath for 4.5 hr, poured into H_2O, basified (NaOH), extracted ($CHCl_3$), and washed (H_2O), the solvent was removed and the residue crystallized from C_6H_6–petroleum ether: mp 113–116°. *Anal.* ($C_{12}H_{11}NO_2$) C, H, N.

4-Phenoxy-3-stilbazole 1-Oxide (5d). From 4-nitro-3-stilbazole 1-oxide,[16] (5b), using the above procedure, this compound was obtained in 46.5% yield: mp 126–128° (from C_6H_6–petroleum ether). *Anal.* ($C_{19}H_{15}NO_2$) C, H, N.

4-Phenoxy-3-picoline (5e). To a solution of 30 g (0.15 mol) of **5c** in 600 ml of anhydrous $CHCl_3$, a solution of 61.6 g of PCl_3 in 100 ml of $CHCl_3$ was added dropwise at 0–5° with stirring. The mixture was refluxed (stirring) for 2 hr, cooled, poured into H_2O, basified (NaOH), extracted ($CHCl_3$), and distilled: bp 104–107° (0.4 mm); yield 21.9 g (79%). *Anal.* ($C_{12}H_{11}NO$) C, H, N. The HCl salt had mp 220–222° (from EtOH–Et_2O). *Anal.* ($C_{12}H_{11}NO$·HCl) C, H, N.

4-Phenoxy-3-stilbazole (5f). This compound was obtained in 63% yield: bp 165–170° (0.5 mm). *Anal.* ($C_{19}H_{15}NO$) H, N; C: calcd, 83.49; found, 81.74. The HCl salt from EtOH–Et_2O melted at 229–230°. *Anal.* ($C_{19}H_{15}NO$·HCl) H, N; C: calcd, 73.66; found, 72.20.

4-Phenoxynicotinic Acid (5). To a suspension of 35 g (0.19 mol) of **5e** in 3.2 l. of H_2O, 90 g of $KMnO_4$ was added, at 70–75° in several small portions, over period of 1–1.5 hr and the mixture was heated overnight at 70–75°. After filtration, the aqueous solution was concentrated to a small volume *in vacuo* on the steam bath and acidified (HOAc). A saturated solution of $CuSO_4$ was added and the precipitated Cu salt was filtered and washed with H_2O. The Cu salt was suspended in 500 ml of H_2O and warmed on the steam bath, and a steady stream of H_2S gas was passed through the suspension (2–2.5 hr). The clear solution after filtration was concentrated to dryness *in vacuo* on the steam bath and the residue was recrystallized from EtOH: mp 170–178°. This product was contaminated with varying amounts of 4-ketodihydronicotinic acid (10–15%). Satisfactory analytical data could not be obtained but the product was of sufficient purity for the ring closure.

3-Phenoxy-4-picoline (4a, Method E). A mixture of 65.4 g (0.6 mol) of 4-methyl-3-pyridinol, 78.5 g (0.5 mol) of C_6H_5Br, 62.8 g of anhydrous K_2CO_3, and 6 g of Cu powder was heated at 230–250° for 3 hr. NaOH (100–150 ml of 50% solution) was added and the mixture was steam distilled. About 8 l. of distillate was collected, saturated with NaCl, extracted (Et_2O), dried, and distilled: bp 133–135° (10 mm); yield 66 g (70%). *Anal.* ($C_{12}H_{11}NO$) C, H, N.

Using a slight modification of method E, the following compounds were prepared.

3-Phenoxypyridine (7a): from 3-pyridinol and C_6H_5Br at 220–230°, yield 57%, bp 135–140° (15 mm) [lit.[17] bp 147–149° (17 mm)]. Alternatively, from 3-bromopyridine and C_6H_5OH at 230–240° for 3 hr, this compound was obtained in 59% yield.

3-(*m*-Chlorophenoxy)pyridine (7b): from 3-bromopyridine and *m*-chlorophenol for 4 hr at 180°, yield 79%, bp 122–124° (2 mm). *Anal.* ($C_{11}H_8ClNO$) C, H, N.

3-(*m*-Methylphenoxy)pyridine (7c, Method F). This method is a slight modification of method E and avoids the tedious steam distillation. A mixture of 94.8 g (0.6 mol) of 3-bromopyridine, 130 g (1.2 mol) of *m*-cresol, 156 g of anhydrous K_2CO_3, and 1 g of copper powder was heated at 200–210° for 4 hr, cooled slightly, and dissolved in H_2O. The solution was made strongly basic (NaOH) and extracted thoroughly with Et_2O (6–8 times). The combined Et_2O solution was extracted with dilute 10% HCl and the aqueous phase made basic with NaOH and extracted with Et_2O. After washing, the Et_2O solution was dried and concentrated and the residue was distilled: yield 86 g (78%); bp 124–127° (4 mm). *Anal.* ($C_{12}H_{11}NO$) C, H, N.

3-(*p*-Methylphenoxy)pyridine (7d). This compound was prepared in 73% yield by method F: bp 169–171° (13 mm). *Anal.* ($C_{12}H_{11}NO$) C, H, N.

3-(*p*-Fluorophenoxy)pyridine (7e). This compound was ob-

tained in 64% yield from *p*-fluorophenol using method F: bp 147–152° (9 mm). *Anal.* ($C_{11}H_8FNO$) C, H, N.

3-Phenoxyisonicotinic Acid (4). Oxidation ($KMnO_4$) of **4a** gave this acid in 25% yield: mp 235–237° (from EtOH). *Anal.* ($C_{12}H_9NO_3$) C, H, N.

3-Phenoxypyridine 1-Oxide (8a). To a solution of 37.8 g (0.1 mol + 10%) of *m*-chloroperbenzoic acid in 500 ml of $CHCl_3$ was added at room temperature with stirring a solution of 34.2 g (0.1 mol) of **7a** in an equal volume of $CHCl_3$ and the mixture was stirred overnight at room temperature. The mixture was washed successively with 10% KI, 20% $Na_2S_2O_7$, 10% NaOH, and H_2O and evaporated on steam bath. The residue was precipitated with petroleum ether, filtered, and recrystallized from C_6H_6–petroleum ether: mp 72–73°; yield 25.9 g (70%). *Anal.* ($C_{11}H_9NO_2$) C, H, N.

The following compounds were prepared by this procedure.

3-(*m*-Chlorophenoxy)pyridine 1-Oxide (8b): yield 67%; mp 68–69° (C_6H_6–petroleum ether). *Anal.* ($C_{11}H_8ClNO_2$) C, H, N.

3-(*m*-Methylphenoxy)pyridine 1-Oxide (8c): yield 56%; mp 52–53° (C_6H_6–hexane). *Anal.* ($C_{12}H_{11}NO_2$) C, H, N.

3-(*p*-Methylphenoxy)pyridine 1-Oxide (8d): yield 76%; mp 121–123° (C_6H_6–hexane). *Anal.* **($C_{12}H_{11}NO_2$) C, H, N.**

3-(*p*-Fluorophenoxy)pyridine 1-Oxide (8e): yield 70%; mp 128–130° (C_6H_6–hexane). *Anal.* ($C_{11}H_8FNO_2$) C, H, N.

2-Cyano-3-phenoxypyridine (9a). Compound **8a** (18.7 g, 0.1 mol) was warmed on the steam bath with stirring to 75–80°. Me_2SO_4 (12.6 g, 0.1 mol) was added dropwise maintaining the temperature at 80–85° during the addition, and the mixture was heated (2 hr) on the steam bath and dissolved in 30 ml of H_2O. Under N_2, this solution was added dropwise to a solution of 14.7 g of NaCN in 40 ml of H_2O keeping the temperature at 0–5° (very vigorous reaction!), and the mixture was stirred for 6 hr in an ice bath and allowed to warm to room temperature overnight. The product was extracted ($CHCl_3$) and washed and the solvent removed. The residue was recrystallized from petroleum ether: mp 74–75°; yield 10.5 g (53%). *Anal.* ($C_{12}H_8N_2O$) C, H, N.

2-Cyano-3-(*m*-chlorophenoxy)pyridine (9b): yield 73%; mp 92–93° ($CHCl_3$–hexane). *Anal.* ($C_{12}H_7ClN_2O$) C, H, N.

2-Cyano-3-(*m*-methylphenoxy)pyridine (9c): yield 57%; mp 93–94° (C_6H_6–hexane). *Anal.* ($C_{13}N_{10}N_2O$) C, H, N.

2-Cyano-3-(*p*-methylphenoxy)pyridine (9d): yield 35%; mp 72–73.5° (hexane). *Anal.* ($C_{13}H_{10}N_2O$) C, H, N.

2-Cyano-3-(*p*-fluorophenoxy)pyridine (9e): yield 43%; (C_6H_6–hexane). *Anal.* ($C_{12}H_7FN_2O$) C, H, N.

3-(*m*-Chlorophenoxy)picolinic Acid (6b). A solution of 45 g of **9b**, 45 g of KOH, and 600 ml of 70% EtOH was refluxed on steam bath for 5 hr and the excess solvent was removed *in vacuo*. The solution was acidified (HOAc) and the acid was converted into the Cu salt (mp 310° dec) and processed as described to give 26.6 g (53%) of acid having mp 135–137°. *Anal.* ($C_{12}H_8ClNO_3$) C, H, N.

3-(*m*-Methylphenoxy)picolinic Acid (6c). Using the above procedure 68 g of **9c** was converted to the title compound in a yield of 61%: mp 131–132° (from *i*-PrOH). *Anal.* ($C_{13}H_{11}NO_3$) C, H, N.

Ring Closure (Method G). A mixture of 0.1 mol of the 2-cyano-3-phenoxypyridine in 40 times its weight of PPA was heated with stirring at 195–200° for 6 hr. The cooled mixture was poured into ice H_2O, basified (NaOH), and extracted with $CHCl_3$. The organic solution was washed with H_2O and concentrated. The residue was triturated with hexane and processed as in Table II.

Method H. Nitration. Azaxanthone (0.2 mol) was added portionwise to 215 ml of concentrated H_2SO_4 keeping the temperature at 0–3°. Stirring was continued for 1.5–2 hr to allow complete solution. A solution of 25.8 g of KNO_3 in 70 ml of concentrated H_2SO_4 was added dropwise (−5 to 0°) and the mixture allowed to warm to room temperature and poured into 1 l. of ice H_2O. With cooling, the mixture was basified (NaOH), filtered, and washed thoroughly with H_2O and recrystallized.

Method I. Nitro compound (10 g) suspended in 300 ml of EtOH was reduced in a Parr hydrogenator at 60 psi in the presence of 0.5 g of 5% Pd/C. The reduction was completed in 2–2.5 hr, the catalyst filtered, the solvent removed, and the residue recrystallized. Alternatively, the same compound was obtained using $SnCl_2$ in HCl.

7-Chloro-1-azaxanthone (Method J). To a solution of 7.1 g (0.03 mol) of the NH_2 compound in 80 ml of concentrated HCl at 0–5° was added a solution of 2.3 g of $NaNO_2$ in 7 ml of H_2O. After 15 min the solution was poured into 4.1 g (0.04 mol) of Cu_2Cl_2 in 30 ml of concentrated HCl at 0° and mixture was stirred for 2 hr and allowed to stand overnight at room temperature. The mixture was cooled to 0° and carefully neutralized (NaOH), extracted (Et_2O), and washed and the solvent was removed. The residue was recrystallized: mp 199–200° (from EtOAc); yield 2.3 g (33%).

7-Carboxy-1-azaxanthone. 2-(*p*-Carboxyphenoxy)nicotinic acid (4 g, 0.025 mol) was added to 35 ml of fuming (30–35%) H_2SO_4 and the solution was heated on steam bath with stirring for 17 hr. The mixture was cooled to room temperature and poured into ice. The product was filtered, suspended in H_2O, and basified (NaOH). The clear solution was acidified (10% HCl) to pH 2; the product was filtered and recrystallized from EtOH.

5-Hydroxy-5-(1-methyl-4-piperidyl)-1-azaxanthene (Method K). Sodium metal (5 g, 0.22 g-atom) was dissolved in 250 ml of anhydrous liquid NH_3. After 20 min a suspension of 19.7 g (0.1 mol) of 1-azaxanthone in 150 ml of anhydrous THF was added and the mixture stirred for 0.5 hr. Freshly distilled 4-chloro-1-methylpiperidine (14.6 g, 0.1 mol + 10%) in an equal volume of THF waa added dropwise and the mixture stirred for 3–4 hr. Solid NH_4Cl (20 g) was added and the NH_3 allowed to evaporate. Water was cautiously added, the mixture separated and extracted ($CHCl_3$), the solvent removed, and the residue triturated with petroleum ether or hexane, filtered, and recrystallized.

5-Hydroxy-5-(1-methyl-4-piperidyl)-8-methoxy-1-azaxanthene (Method L). The Grignard reagent was prepared in the usual manner using 2.4 g (0.1 mol) of magnesium and 13.2 g (0.1 mol) of 4-chloro-1-methylpiperidine in 200 ml of anhydrous THE using I_2 and $C_2H_4Br_2$ as an initiator. Ketone (0.035 mol) in THF was added dropwise at 10° and the mixture was stirred at reflux for 3 hr and decomposed by addition of 20% NH_4Cl solution. The organic material was extracted ($CHCl_3$) and processed as usual.

General Dehydration Procedures. A mixture of the carbinol (Table III) and 50 times its weight of PPA was heated with stirring at 100–120° for 14–20 hr and the cooled mixture was poured into ice, basified (NaOH), extracted ($CHCl_3$), and washed (H_2O) and the solvent removed. The residue was processed as indicated in Table IV. Alternatively, 10 g of carbinol, 10 ml of concentrated HCl, and 80 ml of Ac_2O were warmed on the steam bath for 2 hr, poured into ice, made strongly basic (NaOH), and extracted ($CHCl_3$) and the product isolated.

5-(1-Methyl-4-piperidylidene)-8-methoxy-1-azaxanthene. A mixture of 4.8 g (0.015 mol) of the carbinol, 1.8 g (0.15 mol) of thionyl chloride, and 75 ml of dry pyridine was heated under reflux for 1 hr and cooled in an ice bath during the addition of 30 ml of 15% aqueous NaOH, and the solution was heated for 0.5 hr. The excess solvent was removed *in vacuo*, the residue was dissolved in water, extracted (Et_2O), and washed (H_2O), and the Et_2O was removed.

5-[1-Methyl-4-(1,2,5,6-tetrahydropyridyl)]-1-azaxanthene (12b). A mixture of 29.6 g (0.2 mol) of carbinol (Table III, **42**) and 1500 g of PPA was heated at 185–200° for 16 hr and poured into ice and processed as described above to give 22 g (41%) of this product having mp 135–138° (from *i*-Pr_2O). *Anal.* ($C_{18}H_{18}N_2O$) C, H, N.

5-(1-Methyl-4-piperidyl)-1-azaxanthene (12c). A solution of 13.4 g (0.045 mol) of **12b** in 250 ml of EtOH was reduced in Parr hydrogenator at 60 psi in the presence of 2.5 g of 5% Pd/C. After removal of the catalyst, the solution was concentrated to a residue, triturated with *i*-Pr_2O, and recrystallized from *i*-Pr_2O: yield 11.3 g (89%); mp 110–112°. *Anal.* ($C_{18}N_{20}N_2O$) C, H, N.

5-Dimethylaminoethyl-1-azaxanthene. To a solution of carbinol (Table III, **40**) (8.1 g, 0.03 mol) in 60 ml of concentrated HCl and 20 ml of HOAc was added 20 ml of 57% HI and the mixture was heated under reflux for 10 min. The cooled solution was poured into ice H_2O (50 ml) containing 8 g of $NaHSO_3$ and stirred in an ice bath for 20 min and washed with Et_2O. The aqueous layer was basified and extracted (Et_2O), washed, dried (Na_2SO_4), and distilled: bp 197–203° (1.6 mm); yield 5.2 g (68%). *Anal.* ($C_{16}H_{18}N_2O$) C, H, N.

The maleate salt was recrystallized from EtOH–EtOAc and had mp 146–147°. *Anal.* ($C_{16}H_{18}N_2O \cdot C_4H_4O_4$) C, H, N.

5-Dimethylaminoethyl-4-azaxanthene. From carbinol (Table III, **59**) by the same procedure this compound was obtained in 61% yield: bp 127–130° (0.1 mm). *Anal.* ($C_{16}H_{18}N_2O$) C, H, N.

Phenyl-3-pyridyl(1-methyl-4-piperidyl)carbinol. Using method K this compound was prepared from 25.6 g of 3-benzoylpyridine (0.15 mol), 20 g (0.15 mol) of 1-methyl-4-chloropiperidine (0.15 mol), and 7.6 g of sodium metal: mp 133–135° (from EtOAc). *Anal.* ($C_{18}H_{22}N_2O$) C, H, N.

(1-Methyl-4-piperidylidene)phenyl-3-pyridylmethane (15). The above carbinol (14 g) was added portionwise to 600 ml of 85% H_2SO_4 at room temperature and stirred overnight. The mixture was poured into ice, basified (NaOH), and extracted with Et_2O.

The solvent was removed and the residue was triturated with hexane and recrystallized from hexane: yield 6.2 g (46%); mp 67–68°. *Anal.* ($C_{18}H_{20}N_2$) C, H, N.

3-Phenoxy-2-pyridone. A mixture of 93.5 g (0.5 mol) of 3-phenoxypyridine 1-oxide in 390 ml of Ac_2O was heated under reflux for 3 hr and the excess Ac_2O removed *in vacuo*. The solid residue was heated under reflux for 16 hr with 200 ml of concentrated HCl, poured into ice H_2O, and extracted with $CHCl_3$; the extracts were washed (H_2O), concentrated, and recrystallized several times from EtOAc: mp 159–160°; yield 51 g (54%). *Anal.* ($C_{11}H_9NO_2$) C, H, N.

2-Bromo-3-phenoxypyridine. 3-Phenoxy-2-pyridone (40 g, 0.21 mol) and 90 g (0.21 mol) of triphenylphosphine dibromide were heated under nitrogen until the mixture melted and then heated at 140° for 0.5 hr. The temperature was increased to 180° and so maintained for 20 min and the mixture was poured into ice H_2O, made strongly basic (50% NaOH), and steam distilled. The distillate was extracted with $CHCl_3$, washed, concentrated, and distilled: bp 178–183° (9 mm); yield 31 g (59%). *Anal.* ($C_{11}H_8BrNO$) C, H, N.

4-Hydroxy-1-methyl-4-(3-phenoxy-2-pyridyl)piperidine. To a freshly prepared solution of *n*-BuLi (from 18.7 g of *n*-butyl bromide and 2 g of lithium metal in 50 ml of Et_2O) under N_2 was added with stirring at −40° a solution of 2-bromo-3-phenoxypyridine (31 g, 0.12 mol) in 50 ml of Et_2O. After 15 min a solution of 9.3 g (0.08 mol) of freshly distilled 1-methyl-4-piperidone in 100 ml of Et_2O was added and the mixture was stirred at −40° for 2 hr, allowed to warm to room temperature overnight, decomposed with H_2O, extracted (Et_2O), washed, and dried (Na_2SO_4), and the Et_2O was removed. The residue was recrystallized from acetonitrile: mp 106–107°; yield 7 g (31%). *Anal.* ($C_{17}H_{20}N_2O_2$) C, H, N.

1,2,5,6-Tetrahydro-1-methyl-4-(3-phenoxy-2-pyridyl)pyridine (16). A stirred mixture of 2.8 g (0.01 mol) of the above carbinol and 100 g of PPA was heated at 140° for 4 hr and poured into ice, basified, extracted ($CHCl_3$), and distilled: bp 140–143° (0.1 mm); yield 1.7 g (64%); *m/e* 266, one vinyl porton appears as a broad triplet centered at δ 6.5. *Anal.* ($C_{17}H_{18}N_2O$) H, N; C: calcd, 76.69; found, 75.45. The maleate salt after recrystallization from EtOH–Et_2O melted at 173–175°. *Anal.* ($C_{17}H_{18}N_2O \cdot C_4H_4O_4$) C, H, N.

5-(1-Cyano-4-piperidylidene)-1-azaxanthene (13a). A solution of 12.5 g (0.045 mol) of **12a** in 150 ml of C_6H_6 was added dropwise with stirring at room temperature to a solution of 5.3 g (0.05 mol) of cyanogen bromide in 100 ml of C_6H_6. The mixture was stirred for 4 hr and filtered. The C_6H_6 solution was concentrated to half volume and an equal volume of petroleum ether was added: mp 181–183°; yield 10.6 g (82%) (from C_6H_6–petroleum ether). *Anal.* ($C_{18}H_{15}N_3O$) C, H, N.

5-(1-Cyano-4-piperidyl)-5-hydroxy-1-azaxanthene (14b). This compound was obtained in 54% yield by CNBr reaction on carbinol **42** (Table III): mp 228–230° (from EtOAc). *Anal.* ($C_{18}H_{17}N_3O_2$) C, H, N.

5-(4-Piperidyl-5-hydroxy)-1-azaxanthene Hemihydrate (14a). A solution of 2.4 g of **14b** in 50 ml of HOAc, 5 ml of HCl, and 30 ml of H_2O was heated under reflux for 16 hr and the solvents were removed *in vacuo*. The residue was dissolved in H_2O and basified (NaOH), extracted ($CHCl_3$), washed, and concentrated. This compound was recrystallized from $CHCl_3$–hexane: mp 233–235°; yield 1.8 g. *Anal.* ($C_{17}H_{18}N_2O_2 \cdot 0.5H_2O$) C, H, N. This same compound was obtained from **13a** by this procedure. Tlc (silica gel plates using 50% acetone, $CHCl_3$) of the mother liquors shows a spot corresponding to **13c**.

5-(Piperidylidene)-1-azaxanthene (13c). A mixture of 11.6 g (0.04 mol) of **14a** and 600 g of PPA was heated with stirring for 14 hr at 115–120° and poured into H_2O. The solution was basified (NaOH) and extracted ($CHCl_3$), washed and concentrated to a residue, and extracted with hot CH_3CN and treated with charcoal. The solvent was removed and the residue was converted to the maleic acid salt in EtOAc: mp 209–211°; yield 5.5 g (37%) (from EtOH–Et_2O). *Anal.* ($C_{17}H_{16}N_2O \cdot C_4H_4O_4$) C, H, N. The maleate salt was dissolved in H_2O, basified (Na_2CO_3), and extracted ($CHCl_3$), and product after removal of solvent was recrystallized several times from CH_3CN: mp 144–145°. *Anal.* ($C_{17}H_{16}N_2O$) C, H, N.

5-(1-Carbethoxy-4-piperidylidene)-1-azaxanthene (13b). Compound **12a** (5.6 g, 0.02 mol) dissolved in 20 ml of C_6H_6 was added dropwise with stirring to 6.4 g (0.06 mol) of ethyl chloroformate in 100 ml of C_6H_6 and the mixture was heated under reflux overnight. The solvent was removed *in vacuo* and the residue was dissolved in C_6H_6 and precipitated with an equal volume of hexane. The first crop of crystals was discarded (ir and tlc showed only starting material). The second crop, mp 126–132°, 3.4 g, was recrystallized several times from EtOAc–*i*-Pr_2O to give 3.0 g (46%) of product having mp 132–133°. *Anal.* ($C_{20}H_{20}N_2O_3$) C, H, N.

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