ture with stirring for three hours during which time the color of the mixture changed through brown and green to an intense blue. After cooling, the precipitated chloride was separated by filtration and washed with ethanol, giving 160 g. (64%) of glistening green crystalline material. This was recrystallized from acetic acid in which the product is sparingly soluble.

A sample of the free base was prepared by treatment of a slurry of the chloride in ethanol with a slight excess of aqueous ammonium hydroxide solution. The base was obtained as a red-brown solid showing a reddish color in ethanol solution. However, since the solid base tended to decompose on storage, this derivative and other similar ones were retained as the chlorides.

Method B.—To 90 ml. of ethanol was added 7 g. (0.025 mole) of 2-amino-5-di-*n*-propylaminophenol dihydrochloride and 6.5 g. (0.025 mole) of 4-benzylamino-1,2-naphthoquinone.[17] The mixture was heated to the reflux temperature with stirring for five hours, during which time it acquired an intense blue color. The glistening green product which precipitated on cooling was removed by filtration, giving 7.3 g. (62%) of the chloride. This product was identical with that prepared above under Method A.

9-Amino-5-benzylaminobenzo[a]phenoxazonium Chloride.—The procedure is based on the method of Kehrmann[9] for the preparation of the corresponding 5,9-diamino derivative.

To a solution of 30 g. (0.114 mole) of 4-benzylamino-1,2-naphthoquinone[17] in 500 ml. of ethanol was added 30 g. (excess) of 2,5-diaminophenol dihydrochloride.[18] After stirring at the reflux temperature for a 3-hour period, the mixture was allowed to cool and the precipitated green product was removed by filtration and washed with ethanol and ether.

(17) L. F. Fieser and M. Fieser, THIS JOURNAL, **57**, 494 (1935).

(18) F. Kehrmann and G. Betsch, *Ber.*, **30**, 2098 (1897).

After extraction of the crude green product with a total of 800 ml. of acetic acid, there remained a black insoluble residue which was discarded. Upon cooling the extract, 25 g. (57%) of product was obtained in the form of dark olive-green crystalline material which was recrystallized from butanol. This material was insoluble in ether but moderately soluble in ethanol, forming an intensely colored solution which appeared blood-red by reflected light and blue by transmitted light through a thin layer. Addition of a trace of ammonia solution releases the base from the chloride, forming a red-brown solution. The analytical data for this compound are recorded in Table II.

5-Amino-9-(mono or di)-alkylaminobenzo[a]phenoxazonium Salts.—These compounds were prepared by described methods[6] using aqueous acetic acid as the vehicle for the condensation of the nitrosophenols with the 1-naphthylamine derivatives. Purification was effected by recrystallization from acetic acid in which these derivatives are only sparingly soluble.

Spectrophotometric Determinations.—These were carried out on ethanol solutions of the dyes in 1-cm. glass cells using a General Electric type of automatic recording spectrophotometer.

Acknowledgments.—We are grateful to Dr. M. E. Hultquist and Dr. R. J. Turner for their coöperation on this project and we wish to thank Mr. H. L. Komarowski for his assistance in the preparation of some of these compounds. We are indebted to Mr. O. E. Sundberg and associates for the microanalyses and to Mrs. R. Kaselis and Miss M. R. O'Rourke for the spectrophotometric determinations.

BOUND BROOK, N. J. RECEIVED JULY 26, 1951

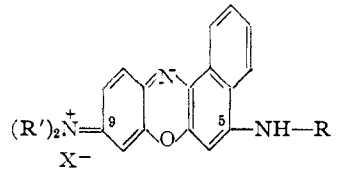
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Chemotherapeutic Dyes. II. 5-Arylamino-9-dialkylaminobenzo[a]phenoxazines[1]

BY MOSES L. CROSSLEY, RICHARD J. TURNER, CORRIS M. HOFMANN, PAUL F. DREISBACH AND ROBERT P. PARKER

Because of the tumor growth-retarding and antituberculous actions of various 5-aralkylamino-9-dialkylaminobenzo[a]-phenoxazines, a series of related 5-arylamino-9-(mono- and di)-alkylaminobenzo[a]phenoxazines was prepared for study. The preferred method of preparation involved amination of 9-dialkylaminobenzo[a]phenoxazines with aromatic amines although some members of the series were synthesized by reaction of 5-(N-mono- and N,N-di-)-alkylamino-2-nitrosophenols with 1-(N-aryl)-naphthylamines. In this series of compounds, the alkyl radicals on the 9-amino group were varied from methyl through *n*-hexyl. Maximum antituberculous activity resulted when two propyl radicals were present on the 9-amino group. Twenty-six of the compounds of this series when administered orally to mice possessed activity equivalent to or greater than that of streptomycin administered subcutaneously at optimum dosage.

In a previous communication,[2] a series of 5-benzylamino-9-dialkylaminobenzo[a]phenoxazonium salts has been described (I, where R is benzyl and R′ is lower alkyl) which, administered orally, retard the growth of transplanted tumor tissue in mice and greatly increase the survival time of mice previously infected with a bovine strain of tubercle bacillus.



I

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting in Cleveland, Ohio, April 8th to 12th, 1951.

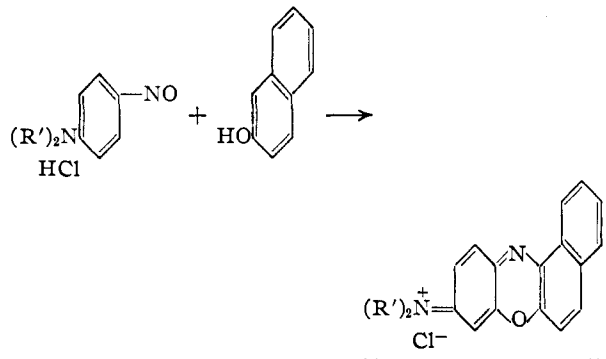
(2) M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, THIS JOURNAL, **74**, 573 (1952).

The high activities exhibited by certain of the dyes of type I led us to investigate further the effect of structural modifications upon the antituberculous and tumor growth-retarding activities. The present paper describes a series of benzo[a]-phenoxazines containing aryl- and substituted aryl-amino groups in the 5-position (I, R is aryl and R′ is alkyl). A few compounds are reported which are 9-monoalkylamino derivatives (*i.e.*, I, one R′ is H).

The preparation of compounds of type I in which R is aryl and R′ is alkyl has been accomplished preferably by two methods, A and B outlined below, which are described in the literature.[3]

(3) Method A: (a) R. Meldola, *Ber.*, **12**, 2065 (1879); (b) R. Hirsch and F. Kalckhoff, *ibid.*, **23**, 2992 (1890); (c) C. C. Schlarb, *Chem. Zeit.*, **15**, 1281 (1891); (d) German Patent 56,722, *Frdl.*, **3**, 374 (1890-1894); and others. Method B: (e) German Patent 45,268, *Frdl.*, **2**, 173 (1887-1890); (f) R. Möhlau and K. Uhlmann, *Ann.*, **289**, 115 (1896).

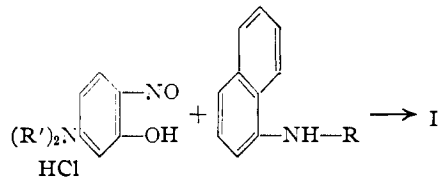
METHOD A



II (A Meldola Type Blue*)

II + Arylamine ⟶ I

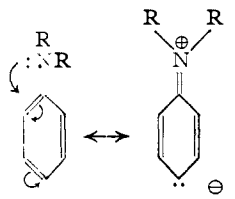
METHOD B



A third method[4] which was used satisfactorily for the preparation of 5-phenylamino-9-diethylaminobenzo[a]phenoxazine, involves the reaction of a 4-arylamino-1,2-naphthoquinone with a 2,5-diaminophenol such as 2-amino-5-diethylaminophenol.

Preferably, method A was used, for from one Meldola Type Blue compound, many different 5-arylamino-9-dialkylaminobenzo[a]phenoxazines are accessible by amination with various readily available arylamines. Method B requires the separate synthesis of a 1-(N-aryl)-naphthylamine for each compound of type I.

The syntheses of the required intermediates followed established procedures. The preparation of N-mono- and N,N-dialkylanilines was accomplished by a modification of the procedure of Hickenbottom.[5] Nitrosation of the N-alkylated anilines proceeded normally except in the case of N,N-diisopropylaniline. It appears that steric hindrance prevents the two isopropyl groups from entering the same plane with the benzene ring, a process which must occur if the nitrogen atom is to donate an electron pair and activate the *p*-position. Hickenbottom reports an unsuccessful attempt to nitrosate

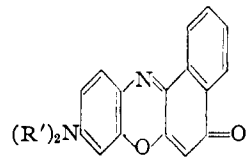


N-methyl-N-*t*-butylaniline.[6] Apparently a similar steric effect is found in the present case.

The condensations of N,N-dialkyl-4-nitrosoanilines with 2-naphthol, and 5-dialkylamino-2-nitrosophenols with 1-(N-aryl)-naphthylamines were carried out in boiling ethanol. In the first case, zinc chloride was used as a condensing agent and the resultant Meldola Type Blue, isolated as a chloride–zinc chloride double salt, was converted to the zinc-free nitrate salt. Without zinc chloride, indefinite products were obtained which have been identified as mixtures containing some 5-(4-dialkylaminophenylamino)-9-dialkylaminobenzo[a]phenoxazines.[3b]

A one to one mole ratio of 2-naphthol and the N,N-dialkyl-4-nitrosoaniline in this reaction gave products of satisfactory quality, although the use of an extra one-half mole of nitroso intermediate to act as a hydrogen acceptor is sometimes recommended.

Amination of the Meldola Type Blue nitrate salts with aryl amines was generally carried out at room temperature in ethanol solution although heat was sometimes employed to effect complete solution of the reactants initially. Higher temperatures generally caused formation of excessive amounts of tarry products. It was found in some instances that aeration of the reaction mixture assisted the oxidation in this type of reaction and caused an increase in yield as well as a decrease in the reaction time. Amination was accomplished successfully with both aromatic primary and secondary amines of approximate pK_a range[7] of 4 to 7. Stronger bases, such as aliphatic amines with a pK_a greater than 7, led to a mixture of products, the main component of which was identified as the oxazone, III.



III

This oxazone is generally formed as the main product by the direct oxidation of Meldola Type Blues.[8]

Schlarb reported the preparation of 5-dialkylamino-9-dialkylaminobenzo[a]phenoxazines by the treatment of Meldola Blue with dimethylamine and diethylamine.[3c] However, we have been unable to obtain satisfactory products when Meldola Type Blues were treated with aliphatic amines under Schlarb's conditions.

Amination of a Meldola Type Blue in the 5-position by treatment with an aromatic amine may be compared with the well known reaction of aniline with 1,4-naphthoquinone to give the 2-anilino derivative or with 1,2-naphthoquinone to give the 4-anilino derivative. Treatment of other heterocyclic compounds such as phenoxazine or phenothiazine with amines has also been described to result in amination with the formation of ring-substituted amino derivatives.[9]

Although a detailed study of the mechanism of the amination was not undertaken, it is possible

(*) When R′ is methyl, compound II is Meldola Blue. Throughout this paper, compounds of type II are termed Meldola Type Blues.

(4) F. Kehrmann, E. Grillet and P. Borgeaud, *Helv. Chim. Acta*, **9**, 866 (1926).

(5) W. J. Hickenbottom, *J. Chem. Soc.*, 992 (1930).

(6) W. J. Hickenbottom, *ibid.*, 946 (1933).

(7) N. F. Hall, THIS JOURNAL, **52**, 5115 (1930); N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3469 (1932); R. P. Bell and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1288 (1949).

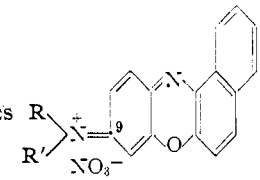
(8) J. F. Thorpe, *ibid.*, 324 (1907).

(9) F. Kehrmann, *Ber.*, **31**, 977 (1898); *ibid.*, **34**, 1625, 4173 (1901); *ibid.*, **49**, 54 (1916); F. Kehrmann and W. Schaposchnikoff, *ibid.*, **33**, 3291 (1900); F. Kehrmann, *Ann.*, **322**, 1 (1902).

that the benzo[a]phenoxazine in the form of a carbonium ion reacts with a nucleophilic anion, $ArNH^-$, liberated from the weakly basic aromatic amines to introduce the 5-arylamino grouping, or with a hydroxyl ion, formed in the presence of strong bases, to form the 5-oxazone.

TABLE I

SUBSTITUTED 9-AMINOBENZO[a]PHENOXAZONIUM NITRATES

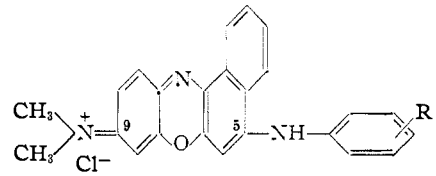


R	R'	Yield, %	Abs. max., mμ Base	Salt	Empirical formula	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found
H	*i*-C_3H_7	51	471	552	$(C_{19}H_{17}ClN_2O)_2ZnCl_2$[a]	58.1	58.0	4.36	4.43	7.13	6.95
CH_3	*n*-C_3H_7	46	435	576	$C_{20}H_{19}N_3O_4$	65.7	65.7	5.24	5.48	11.5	11.3
C_2H_5	C_2H_5	50	435	572	$C_{20}H_{19}N_3O_4$	65.7	65.7	5.24	5.29	11.5	11.4
C_2H_5	*n*-C_3H_7	30	430	576	$C_{21}H_{21}N_3O_4 \cdot H_2O$	63.5	63.3	5.83	5.36	10.6	11.0
n-C_3H_7	*n*-C_3H_7	29	438	579	$C_{22}H_{23}N_3O_4 \cdot {}^1/_2H_2O$	65.7	65.3	6.01	6.15	10.4	10.1
n-C_4H_7	*n*-C_4H_9	39	438	579	$C_{23}H_{25}N_3O_4 \cdot 1{}^1/_2H_2O$	63.6	63.8	6.50	6.05	9.67	9.69
n-C_4H_9	*n*-C_4H_9	31	440	581	$C_{24}H_{27}N_3O_4 \cdot H_2O$	65.6	65.1	6.65	6.59	9.56	9.41

[a] *Anal.* Calcd.: Cl, 18.0. Found: Cl, 17.9

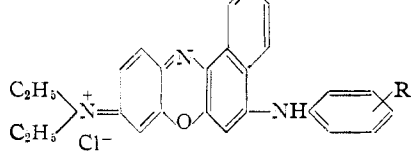
TABLE II

SUBSTITUTED 5,9-DIAMINOBENZO[a]PHENOXAZONIUM SALTS[a]:



A.

R	Yield, %	Abs. max., mμ Base	Salt	Empirical formula	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found	Chlorine Calcd.	Found	Anti-Tb activity
H	23	524	648	$C_{24}H_{20}ClN_3O$	71.7	71.8	5.02	5.24	10.4	10.6	8.82	8.78	+
2-CH_3	23	518	645	$C_{25}H_{22}ClN_3O \cdot H_2O$	69.2	69.4	5.57	5.74	9.69	9.55	8.17	8.30	−
3-CH_3	36	522	654	$C_{25}H_{22}ClN_3O$	72.2	72.2	5.33	5.21	10.1	10.1	8.54	8.16	±
4-CH_3	28	522	655	$C_{25}H_{22}ClN_3O \cdot {}^1/_2H_2O$	70.7	70.6	5.46	5.20	9.89	9.85	8.34	8.40	++
2-Cl	24	519	638	$C_{24}H_{19}ClN_4O_4$[b]	62.3	62.4	4.14	4.31	12.1	12.0	7.66	7.72	+
3-Cl	39	526	657	$C_{24}H_{19}Cl_2N_3O \cdot 1{}^1/_2H_2O$	62.4	61.8	4.58	4.68	9.09	9.13	15.3	15.0	−
4-Cl	60	526	659	$C_{24}H_{19}Cl_2N_3O$	66.1	66.4	4.39	4.39	9.63	9.65	16.3	16.1	±
2,5-DiCl	30	526	639	$C_{24}H_{18}Cl_2N_4O_4 \cdot {}^1/_2H_2O$[b]	56.9	56.7	3.78	4.11	11.1	10.9	14.0	13.9	−
2-OCH_3	36	518	649	$C_{26}H_{22}ClN_3O_2 \cdot H_2O$	66.7	66.4	5.38	5.54	9.34	9.10	7.88	8.02	−
4-OCH_3	11	526	652	$C_{26}H_{22}ClN_3O_2 \cdot 1{}^1/_2H_2O$	65.4	65.0	5.49	5.23	9.16	8.86	7.73	7.77	+
3-OH	43	516	650	$C_{24}H_{20}ClN_3O_2 \cdot 2H_2O$	63.5	63.5	5.33	4.53	9.26	9.47	7.81	7.83	− ?
4-COOH	96[c]	525	660	$C_{25}H_{20}ClN_3O_2 \cdot 2H_2O$	62.3	62.7	5.02	4.98	8.72	8.26	7.36	7.79	− ?
3-OH, 4-COOH	95[c]	520	661	$C_{25}H_{20}ClN_3O_4 \cdot {}^1/_2H_2O$	63.8	63.8	4.50	4.29	8.92	8.94	7.53	7.31	−
4-SO_2NH-(2-Pyrimidyl)	44[d]	531	665	$C_{28}H_{23}ClN_6O_4S \cdot H_2O$[e]	58.3	58.4	4.37	4.24	14.6	14.5	6.14	6.25	−

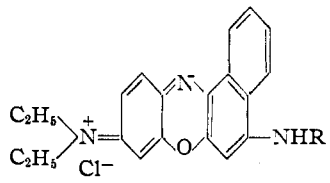


B.

R	Yield, %	Abs. max., mμ Base	Salt	Empirical formula	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found	Chlorine Calcd.	Found	Anti-Tb activity
H	55[f]	532[g]	660	$C_{26}H_{21}ClN_3O \cdot H_2O$	69.7	69.5	5.85	5.85	9.38	9.36	7.92	7.95	+++
2-CH_3	24	528	653	$C_{27}H_{26}N_4O_4 \cdot {}^1/_2H_2O$[b]	67.6	67.7	5.68	5.96	11.7	11.5			+++
3-CH_3	25	528	660	$C_{27}H_{26}N_4O_4$[b]	69.0	69.1	5.58	5.61	11.9	11.8			+++
4-CH_3	27	533	660	$C_{27}H_{26}N_4O_4$[b]	69.0	69.0	5.58	5.30	11.9	11.7			++++
4-C_2H_5	28	533	659	$C_{28}H_{28}N_4O_4$[b]	69.4	69.3	5.82	5.94	11.6	11.6			+++
4-*i*-C_3H_7	22	528	655	$C_{29}H_{30}N_4O_4 \cdot H_2O$[b]	67.4	67.5	6.25	5.95	10.9	11.4			+++
4-*t*-C_5H_{11}	21	533	660	$C_{31}H_{34}N_4O_4$[b]	70.7	70.9	6.51	6.53	10.6	10.6			−
2-Cl	11	533	657	$C_{26}H_{23}Cl_2N_3O$	67.2	67.1	4.99	4.92	9.05	8.89	15.3	15.1	−
4-Cl	47	536	660	$C_{26}H_{23}Cl_2N_3O$	67.2	67.1	4.99	5.00	9.05	9.16	15.3	15.2	+++
2-OH	28	544	650	$C_{26}H_{24}ClN_3O_2 \cdot H_2O$	67.3	67.7	5.65	5.68	9.06	9.33	7.64	7.69	− ?
3-OH	13	532	659	$C_{26}H_{24}ClN_3O_2$	70.0	69.9	5.42	5.35	9.42	9.66	7.96	7.70	+
4-OH	17	535	660	$C_{26}H_{24}ClN_3O_2$	70.0	70.1	5.42	5.39	9.42	9.62	7.96	8.04	− ?
2-OCH_3	58	527	654	$C_{27}H_{26}ClN_3O_2 \cdot H_2O$	67.8	67.2	5.90	5.93	8.79	9.32	7.42	7.35	++
4-COOH	84[c]	536	667	$C_{27}H_{24}ClN_3O_3 \cdot {}^1/_2H_2O$	67.2	67.0	5.22	5.18	8.70	8.97	7.34	6.83	−
4-NO_2	46	400	579	$C_{26}H_{23}N_5O_6$[b]	62.3	62.1	4.62	4.62	14.0	13.9			−
2-OH, 5-Cl	44	537	658	$C_{26}H_{23}Cl_2N_3O_2 \cdot {}^1/_2H_2O$	63.8	63.7	4.94	5.15	8.59	8.48	14.5	14.3	− ?
4-$COCH_3$	37	543	670	$C_{28}H_{26}ClN_3O_2$	71.2	71.2	5.55	5.49	8.90	8.94	7.51	7.86	− ?
4-SO_2NH-(2-pyrimidyl)	57[d]	536	669	$C_{30}H_{27}ClN_6O_4S \cdot H_2O$[h]	59.5	59.4	4.83	4.77	13.9	14.1	5.86	5.78	− ?
2-C_6H_5	19	530	655	$C_{32}H_{28}ClN_3O \cdot {}^1/_2H_2O$	74.6	75.0	5.68	5.65	8.16	8.08	6.88	7.05	− ?
2-CH_3, 4-Cl, 5-NO_2	38	544	658	$C_{27}H_{23}ClN_4O_2$[b]	66.6	66.7	4.76	4.86	11.5	11.4	7.28	7.14	

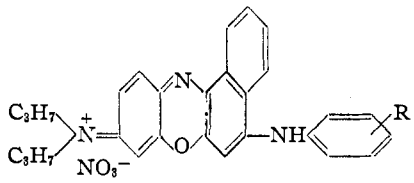
TABLE II (*Continued*)

C.



R	Yield, %	Abs. max., mμ Base	Salt	Empirical formula	Analyses, % Carbon Calcn.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found	Chlorine Calcd.	Found	Anti-Tb activity
1-Naphthyl	18	537	658	$C_{30}H_{26}ClN_3O\cdot 2H_2O$	69.8	69.5	5.86	5.89	8.13	7.96	6.88	7.23	– ?
2-Naphthyl	47	539	663	$C_{30}H_{26}ClN_3O\cdot{}^1/_2H_2O$	73.7	73.9	5.57	5.36	8.59	8.70	7.25	7.41	+

D.

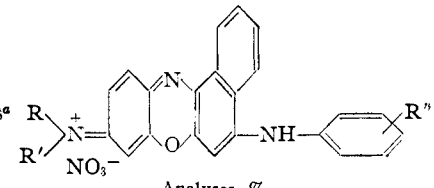


H	40[i]	531[k]	660	$C_{28}H_{28}N_4O_4\cdot H_2O$	66.9	67.2	6.02	5.61	11.2	11.3			++++
4-CH_3	47	531[l]	660	$C_{29}H_{30}N_4O_4\cdot{}^1/_2H_2O$[m,n]	68.6	68.6	6.16	6.21	11.0	11.3			++++
4-C_2H_5	21	532[o]	662	$C_{30}H_{32}N_4O_4\cdot{}^1/_2H_2O$[p]	69.0	69.0	6.38	6.26	10.7	10.8			+++
4-*i*-C_3H_7	32	527[q]	655	$C_{31}H_{34}N_4O_4$	70.7	70.7	6.51	6.46	10.6	10.4			+++
4-Cl	42	535	664	$C_{28}H_{27}ClN_4O_4$	64.8	64.7	5.24	5.40	10.8	10.7	6.83	7.02	++
4-$COOC_2H_5$	45	539	667	$C_{31}H_{32}N_4O_6$	66.9	66.7	5.80	5.81	10.0	10.0			– ?
2-CH_3	39	527[r]	665	$C_{29}H_{30}N_4O_4$	69.9	70.0	6.07	6.01	11.2	11.2			+++
3-CH_3	24	530	661	$C_{29}H_{30}N_4O_4$	69.9	69.8	6.07	6.09	11.2	11.3			+++
2,4-Di-CH_3	11	527	655	$C_{30}H_{32}N_4O_4$	70.2	70.2	6.29	6.19	10.9	10.9			+++

[a] Prepared by method A unless otherwise designated. [b] Nitrate. [c] Added 10 equivalents of sodium carbonate to reaction mixture. [d] Added 5 equivalents of sodium bicarbonate to reaction mixture. [e] *Anal.* Calcd.: S, 5.56. Found: S, 5.32. [f] By method B; 48% by method A: 48% by method of F. Kehrmann, *et al.* (ref. 4). [g] Base m.p. 178.5–179°. [h] *Anal.* Calcd.: S, 5.30. Found: S. 5.29. [i] Calcd. for base. [j] 48% by method B. [k] Base m.p. 151–152°. [l] Base m.p. 178–179°. [m] Bromide, *Anal.* Calcd. for $C_{29}H_{30}BrN_3O$: C. 67.5; H, 5.86; Br, 15.5; N, 8.14. Found: C. 67.6; H, 6.10; Br. 15.5; N, 8.20. [n] Sulfate, *Anal.* Calcd. for $C_{29}H_{31}N_3O_5S\cdot H_2O$: C. 63.1; H, 6.03; N. 7.61; S, 5.81. Found: C, 63.5; H, 6.08; N. 7.63; S, 6.14. [o] Base m.p. 171–172°. [p] Sulfate. *Anal.* Calcd. for $C_{30}H_{33}N_3O_5S\cdot H_2O$: C. 63.7; H. 6.24; N, 7.43; S. 5.67. Found: C, 63.3; H. 5.97; N. 7.17; S. 5.90. [q] Base m.p. 149–150°. [r] Base m.p. 147–148°.

TABLE III

SUBSTITUTED 5,9-DIAMINOBENZO[a]PHENOXAZONIUM NITRATES[a]



R	R	R″	Yield, %	Abs. max., mμ Base	Salt	Empirical formula	Analyses, % Carbon Calcd.	Found	Hydrogen Calcd.	Found	Nitrogen Calcd.	Found	Anti-Tb activity
H	C_2H_5	H	39[b]	521	642	$C_{24}H_{20}ClN_3O\cdot{}^1/_2H_2O$[c]	70.0	69.4	5.13	5.12	10.2	10.6	+
H	*i*-C_4H_7	H	21	519	645	$C_{28}H_{22}N_4O_4$	67.9	68.0	5.01	5.07	12.7	12.8	++
CH_3	*n*-C_3H_7	4-CH_3	34	527	657	$C_{27}H_{25}N_3O$[d,e]	79.6	79.7	6.18	6.13	10.3	10.2	+++
C_2H_5	*n*-C_3H_7	H	44	531	660	$C_{27}H_{26}N_4O_4$	68.9	68.9	5.57	5.52	11.9	11.9	+++
C_2H_5	*n*-C_3H_7	4-CH_3	38	532	660	$C_{28}H_{28}N_4O_4$	69.5	69.3	5.83	5.69	11.6	11.5	++++
C_2H_5	*n*-C_4H_7	4-C_2H_5	41	532	660	$C_{29}H_{29}N_3O$[d,f]	80.0	79.9	6.70	6.79	9.65	9.57	– ?
C_2H_5	*n*-C_3H_7	4-OCH_3	24	535	660	$C_{28}H_{27}N_3O_2$[d,g]	76.9	76.6	6.22	6.05	9.60	9.40	+++
n-C_3H_7	*i*-C_3H_7	4-CH_3	36	532	663	$C_{29}H_{30}N_4O_4\cdot{}^1/_2H_2O$	68.6	68.7	6.15	6.00	11.1	11.0	+++
n-C_3H_7	*n*-C_4H_9	H	50	536[h]	664	$C_{29}H_{30}N_4O_4$	69.9	70.1	6.06	6.16	11.2	11.1	+++
n-C_3H_7	*n*-C_4H_9	2-CH_3	44	531	655	$C_{30}H_{32}N_4O_4$	70.3	70.3	6.30	6.21	10.9	11.1	+++
n-C_3H_7	*n*-C_4H_9	4-CH_3	27	533	662	$C_{30}H_{32}N_4O_4$	70.3	70.2	6.30	6.35	10.9	10.8	+++
n-C_3H_7	*n*-C_4H_9	4-Cl	44	539	665	$C_{29}H_{29}ClN_4O_4$[i]	65.4	65.5	5.48	5.69	10.5	10.5	– ?
n-C_4H_9	*n*-C_4H_9	H	31[j]	532[k]	661	$C_{30}H_{32}N_4O_4\cdot{}^1/_2H_2O$	69.0	69.1	6.35	6.50	10.8	10.8	+
n-C_4H_9	*n*-C_4H_9	4-CH_3	30[l]	535	664	$C_{31}H_{34}N_4O_4$	70.6	70.5	6.50	6.63	10.7	10.6	+
n-C_5H_{11}	*n*-C_5H_{11}	H	89[b]	534	662	$C_{32}H_{38}N_3O$[d,m]	80.5	80.7	7.39	7.20	8.80	8.72	±
n-C_5H_{11}	*n*-C_5H_{11}	4-CH_3	49[b]	534	662	$C_{33}H_{37}N_3O$[d,n]	80.6	80.7	7.58	7.56	8.55	8.67	±
n-C_6H_{13}	*n*-C_6H_{13}	H	42[b,p]	534	663	$C_{34}H_{39}N_3O$[d,q]	80.8	80.8	7.77	7.43	8.31	8.15	–

[a] By Method A unless otherwise specified. [b] By Method B. [c] Chloride, *Anal.* Calcd.: Cl, 8.64. Found: Cl, 8.22. [d] Base. [e] M.p. 174–175°. [f] M.p. 170–170.5°. [g] M.p. 151.5–152°. [h] Base m.p. 137–138°. [i] *Anal.* Calcd.: Cl. 6.66. Found: Cl, 6.46. [j] 29% yield by Method B. [k] Base m.p. 153–154°. [l] Method B gives 78% yield of base. m.p. 151–153°. [m] M.p. 125.5–126°. [n] M.p. 114.5–116°. [p] Prepared by T. Rees. [q] M.p. 127.5–128°.

Several members of the series were prepared by both methods A and B and identical products resulted. For the 9-di-*n*-amylamino and the 9-di-*n*-hexylamino members of the series, method B only was used since the necessary nitrosophenols were more easily available than the nitrosoanilines.

The conditions employed in method B were similar to those described for method A in paper I of this series[2] for the preparation of 5-benzylamino derivatives.

Satisfactory melting or decomposition points of the benzo[a]phenoxazonium salts were not ob-

served. Normal melting points were exhibited by the base form in those cases where they were isolated. The wave lengths of maximum absorption in the visual range of both the salt and the base form were determined. Variation of the substituents on either 5- or 9-amino groups in this series of benzo[a]phenoxazines did not cause major changes in the absorption maxima. The magnitude of shift with structural change was similar to that observed with the benzyl derivatives described in paper I of this series.[2]

The benzo[a]phenoxazines are listed in the Tables I through III.

Pharmacological Activity

Staining and Tumor Growth-retarding Action.—Details of the tissue staining and retarding action of some of these compounds have been reported elsewhere by Dr. M. R. Lewis and co-workers[10] of the Wistar Institute of Anatomy and Biology. We are indebted to these investigators for information on such actions of these compounds.

Compared with the 5-benzylamino derivatives described in paper I of this series,[2] the 5-arylamino derivatives generally do not show as marked a tumor growth-retarding action by oral administration to tumor-bearing mice. Of the 5-arylamino derivatives which show definite retarding effects, the 9-diethylamino and 9-dipropylamino members show the most pronounced effect. With the exception of the 9-dimethylamino homologs, the present compounds generally exhibit an appreciable differential tumor staining effect, and, as well, a more pronounced differential fatty tissue staining effect when administered orally to mice than do the corresponding 5-benzylamino compounds. The presence of an acidic group such as hydroxy or carboxy on the phenyl ring destroys such action. The use of basic dyes of the Nile Blue type in fat staining work *in vitro* is well known.[8]

Antituberculous Action.—Many of these 5-arylamino-9-dialkylaminobenzo[a]phenoxazines exhibit strong antituberculous action upon oral administration to mice infected with a bovine strain of tubercle bacillus as shown by a marked increase in median survival time of infected mice when compared with that of infected untreated controls. The testing procedure has been described[11] and the details of the results of the activity determinations will be published elsewhere[12] by Dr. H. J. White and co-workers at the Stamford Laboratories of the American Cyanamid Co., to whom we are indebted for the information on the testing results.

In Tables II and III, an arbitrary rating system has been used for comparing these compounds which simply indicates a graded activity based upon median survival time increase and similar to the one used in paper I in this series.[2] Streptomycin, by subcutaneous injection at the optimum dosage level, received a 2+ rating on this basis.

(10) M. R. Lewis, P. P. Goland and H. A. Sloviter, *Cancer Research*, **9**, 736 (1949).

(11) M. J. Baker, M. E. Schlosser and H. J. White, *Ann. N. Y. Acad. Sci.*, **52**, 678 (1949).

(12) H. J. White, M. E. Schlosser and M. J. DiCenza, to be published. Paper presented before the Society of American Bacteriologists, Detroit, Mich., April, 1951.

The antituberculous activity of these 5-arylamino-9-dialkylaminobenzo[a]phenoxazines differs markedly with structural changes. Activity greatly increases as the alkyl radical on the 9-amino group is progressively lengthened from methyl to propyl and then decreases sharply with alkyl groups of greater chain length. The presence of at least one propyl group maintains the increased activity, for both the 9-ethyl-*n*-propylamino and the 9-*n*-butyl-*n*-propyl derivatives received high ratings. Maximum activity was found for the 9-di-*n*-propyl members.

High activity is maintained or increased by substitution on the aryl ring in the 5-position of electropositive groups such as chloro or methyl, but the presence of larger alkyl radicals decreases activity. The position of the substituted methyl group is also important, para-substituted derivatives generally being more active than ortho derivatives which in turn are more active than meta derivatives. With an electronegative substituent, such as nitro, carboxy, carbethoxy or acetyl, a sharp decrease in activity is noted.

Experimental

N-Alkylanilines.—When not available, the necessary N-mono- and N,N-dialkylanilines were prepared by known methods involving the alkylation of aniline or an N-monoalkylaniline with an alkyl halide.

N-Isopropylaniline,[5] b.p. 89–90° (14 mm.), (ref. gives 206–208°).

N-Isopropyl-N-*n*-propylaniline[13] from N-isopropylaniline and *n*-propyl bromide.

N,N-Diisopropylaniline[14] from N-isopropylaniline and isopropyl iodide.

N-Methyl-N-*n*-propylaniline[15] from N-methylaniline and *n*-propyl bromide.

N-Ethyl-N-*n*-propylaniline[15] from N-ethylaniline and *n*-propyl bromide.

N-*n*-Butyl-N-*n*-propylaniline, b.p. 247–251°, was prepared in 63% yield from N-*n*-butylaniline and *n*-propyl bromide using a procedure based on the method of Stoermer and v. Lepel.[16]

Anal. Calcd. for $C_{13}H_{21}N$: C, 81.6; H. 11.0; N, 7.33. Found: C, 81.7; H, 10.8; N, 7.35.

N-Alkyl-4-nitrosoanilines.—For the nitrosation of the N,N-dialkylanilines, procedures based on known methods were used, involving treatment of a cooled (5°) hydrochloric acid solution of the aniline derivative with an aqueous solution of sodium nitrite. Where the hydrochloride did not precipitate directly from the reaction mixture due to excessive solubility, the solution was made alkaline with sodium carbonate or sodium hydroxide and the liberated nitroso base was obtained by filtration or extraction with ether. By treatment of an ether solution of the base with an alcoholic solution of hydrogen chloride, the yellow crystalline hydrochlorides were obtained. These were generally purified by recrystallization from ethanol. The purified compounds were generally stable on storage for short periods, but after several weeks standing, considerable decomposition often was observed. The procedure which follows is typical for the type of nitrosation where the hydrochloride did not precipitate directly.

N-Ethyl-N-*n*-propyl-4-nitrosoaniline Hydrochloride.—An aqueous solution of 8.3 g. (0.12 mole) of sodium nitrite in 15 ml. of water was added dropwise with stirring to a cold (5°) solution of 16.3 g. (0.10 mole) of N-ethyl-N-*n*-propylaniline, 30 ml. of concentrated hydrochloric acid and 40 ml. of water over a 15-minute period. After stirring one hour more at 5°, the reaction mixture was made alkaline with 5 *N* sodium hydroxide solution, causing the nitroso base to

(13) J. v. Braun, *Ber.*, **33**, 2728 (1900).

(14) A. Zander, *Ann.*, **214**, 138 (1882).

(15) (a) A. Claus and H. Hirzel, *Ber.*, **19**, 2785 (1886). (b) R. L. Bent, *et al.*, THIS JOURNAL, **73**, 3100 (1951).

(16) R. Stoermer and V. F. v. Lepel, *Ber.*, **29**, 2110 (1896).

separate as a green oil. The liberated base was taken up in approx. 200 ml. of ether and after drying the ether extract, the base in solution was converted to the hydrochloride by the addition of an excess of a saturated ethanol solution of hydrogen chloride. The hydrochloride which precipitated was removed by filtration, 16.6 g. (73%), and was purified from an ethanol–ether solution, giving a bright yellow solid, m.p. 130.5° dec. The preparation of this compound has been described previously but the solid was not characterized.[15b]

Anal. Calcd. for $C_{11}H_{16}N_{20}$·HCl: C, 57.8; H, 7.49; N, 12.3; Cl, 15.5. Found: C, 57.7; H, 7.77; N, 12.1; Cl, 15.3.

N,N-Diethyl-4-nitrosoaniline,[17] m.p. 81.5–83°, was converted to the hydrochloride, m.p. 128–129° dec.

N,N-Di-*n*-propyl-4-nitrosoaniline,[18] m.p. 42°, likewise was converted to the hydrochloride, m.p. 130–131° dec. (77%).

Anal. Calcd. for $C_{12}H_{18}N_2O$·HCl·H_2O: C, 55.3; H, 8.10; N, 10.8; Cl, 13.6. Found: C, 54.7; H, 8.04; N, 10.4; Cl, 13.8.

N,N-Di-*n*-butyl-4-nitrosaniline hydrochloride,[19] m.p. 103–103.5° dec. (83%).

Anal. Calcd. for $C_{14}H_{22}N_2O$·HCl·H_2O: C, 58.2; H, 8.73; N, 9.70; Cl, 12.3. Found: C, 58.1; H, 8.54; N, 9.65; Cl, 12.6.

N-Methyl-N-*n*-propyl-4-nitrosoaniline hydrochloride,[16] m.p. 104–105° dec. (85%).

Anal. Calcd. for $C_{10}H_{14}N_2O$·HCl·H_2O: C, 51.6; H, 7.37; N, 12.0; Cl, 15.2. Found: C, 51.2; H, 7.10; N, 11.9; Cl, 15.2.

N-Isopropyl-N-*n*-propyl-4-nitrosoaniline hydrochloride, m.p. 151° (61%).

Anal. Calcd. for $C_{12}H_{18}N_2O$·HCl: C, 59.4; H, 7.89; N, 11.5; Cl, 14.6. Found: C, 59.9; H, 7.90; N, 11.6; Cl, 14.7.

N-*n*-Butyl-N-*n*-propyl-4-nitrosoaniline hydrochloride, m. p. 127.5° dec. (63%).

Anal. Calcd. for $C_{13}H_{20}N_2O$·HCl·$^1/_2H_2O$: C, 58.7; H, 8.35; N, 10.5; Cl, 13.3. Found: C, 58.8; H, 8.37; N, 10.6; Cl, 13.6.

N-Isopropyl-4-nitrosoaniline Hydrochloride.—A solution of 142 g. (1.05 moles) of N-isopropylaniline, 300 ml. of concd. hydrochloric acid and 400 ml. of water was stirred and cooled to 5°. A solution of 86 g. (1.25 moles) of sodium nitrite in 150 ml. of water was added dropwise over a period of 90 minutes. After stirring one hour more, the dark red-orange mixture was extracted three times with small portions of ether and the combined ether extracts were dried over Drierite. After addition of 275 ml. of ethanol saturated with hydrogen chloride to the filtered ether solution to accomplish rearrangement,[20] it was allowed to stand at about 5° for four days. Filtration of the mixture gave 74 g. (37%) of N-isopropyl-4-nitrosoaniline hydrochloride as a yellow-orange solid. After purification from an alcohol–ether solution, 55 g. of pure product was obtained.

A crude sample melted at 141–144°. The purified analysis sample decomposed at about 200°, but this decomposition point was indefinite since it varied greatly with the rate of heating.

Anal. Calcd. for $C_9H_{12}N_2O$·HCl: C, 53.9; H, 6.53; N, 14.0; Cl, 17.7. Found: C, 54.0; H, 6.62; N, 13.9; Cl, 17.7.

A sample of **N-isopropyl-4-nitrosoaniline** base was prepared by treatment of an aqueous solution of the hydrochloride with a slight excess of sodium hydroxide solution. The base separated as a green solid, m.p. 53.3–53.7°, insoluble in water but easily soluble in ethanol to give a green solution.

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.8; H, 7.37; N, 17.1. Found: C, 65.7; H, 7.53; N, 16.8.

Benzo[a]phenoxazines. 9(Mono or di)-alkylaminobenzo[a]phenoxazonium Nitrates.—These were prepared by the condensation of 2-naphthol with a (mono or di)-alkyl-4-nitrosoaniline in methanol or ethanol in the presence of zinc chloride as a condensing agent. The method is illustrated by the preparation of the 9-diethylamino derivative described in detail below. In some cases the zinc chloride double salt precipitated as a gum and resisted crystallization. The method of conversion to the nitrate salt was the same for both crystalline and gummy zinc chloride double salts.

These salts are soluble in water and ethanol in which they form reddish-blue solutions. Addition of an alkaline reagent converts the salt to a base form which imparts a yellow color to the solution. The base forms were not studied further.

9-Diethylaminobenzo[a]phenoxazonium Nitrate.—To a boiling mixture of 123 g. (0.85 mole) of 2-naphthol and 65.4 g. (0.48 mole) of anhydrous zinc chloride in 680 ml. of ethanol was added 182 g. (0.85 mole) of N,N-diethyl-4-nitrosoaniline hydrochloride in small portions over a two-hour period. After the addition of the nitroso compound, the mixture was heated under reflux for two more hours. The dark green zinc chloride double salt which precipitated was filtered from the hot reaction mixture, giving 161 g. (47%) of product. Conversion of the zinc salt to the nitrate was accomplished by dissolving the former in hot water, 60 g. per 4 l., filtering to remove insoluble impurities, and adding 150 ml. of concd. nitric acid. The nitrate precipitated in the form of a brown amorphous solid. From 60 g. of the zinc chloride salt, 54 g. of the nitrate was obtained. The analytical data for this compound are recorded in Table I.

5-Arylamino-9-(mono or di)-alkylaminobenzo[a]phenoxazonium Nitrates.—The details of the procedure for each of two methods are illustrated below for the preparation of the 9-di-*n*-propylamino-5-phenylaminobenzo[a]phenoxazonium nitrate. In method A, the reaction is usually carried out by allowing the reactants to stand at room temperature. It is not always necessary to warm the initial reaction mixture to obtain complete solution. In some instances a stream of air was bubbled through the reaction solution for periods of about four hours to assist the oxidation, but this aeration did not appear to give consistent increases in the yields. The reaction appears to proceed to some extent with air excluded. In this case a portion of the Meldola Type Blue starting material may act as a hydrogen acceptor.

Although Method B was not generally applied, a number of derivatives were prepared using this procedure. The 9-di-*n*-amylamino and 9-di-*n*-hexylamino compounds were prepared using this method exclusively and the necessary 5-dialkylamino-2-nitrosophenol hydrochlorides were obtained as described in paper I of this series.[2] A number of the bases were isolated directly from the reaction mixture and purified as such without conversion to the salt.

Ethanol and acetic acid generally served satisfactorily as recrystallization media for the salts, giving the products as glistening green crystalline materials.

Addition of aqueous ammonia to an alcoholic slurry of the nitrate produced a free base which could be purified by recrystallization from an organic solvent such as butanol. The nitrates could easily be converted to the chlorides through the bases by treatment with hydrochloric acid, the chlorides then being purified by recrystallization from ethanol or acetic acid. The nitrates and chlorides are generally only slightly soluble in water and in contact with water tend to form deposits of the bases by hydrolytic action. In ethanol, they are sufficiently soluble to form intensely blue solutions. The sulfates of these compounds, several of which were prepared from the bases by treatment with sulfuric acid, are easily soluble in water. The bromides may also be prepared by treatment of the bases with hydrobromic acid.

9-Di-*n*-propylamino-5-phenylaminobenzo[a]phenoxazonium Nitrate. Method A.—A mixture of 19.7 g. (0.05 mole) of 9-di-*n*-propylaminobenzo[a]phenoxazonium nitrate, 14.0 g. (0.15 mole) of aniline and 150 ml. of ethanol was warmed gently until the reactants dissolved. The resultant solution was allowed to stand in an open beaker at room temperature for about 24 hours during which time the color of the solution changed from reddish-blue to greenish-blue. The precipitated product was removed by filtration, giving 10 g. (40%) of green crystalline solid. By recrystallization from ethanol in which it is sparingly soluble, the product was obtained as a glistening green crystalline material.

(17) A. Kopp, *Ber.*, **8**, 621 (1875).
(18) A. Mandl, *Monatsh.*, **7**, 99 (1886).
(19) J. Reilly and W. J. Hickenbottom, *J. Chem. Soc.*, 99 (1918).
(20) O. Fischer, *Ann.*, **286**, 156 (1895).

After drying for several hours at 100°, this analyzed as the monohydrate. The analytical data for this compound are recorded in Table II D.

Method B.—To a solution of 219 g. (1.0 mole) of 1-(N-phenyl)-naphthylamine in 2000 ml. of ethanol was added 388 g. (1.5 moles) of 5-di-*n*-propylamino-2-nitrosophenol hydrochloride[2] and several drops of concd. hydrochloric acid. The mixture was heated to the reflux temperature with stirring for seven hours and then cooled to room temperature. After diluting with an equal volume of ethanol, the solution was treated with an excess of concd. aqueous ammonium hydroxide which caused precipitation of the base as a slightly tacky material which congealed to a dark green solid after standing for a short time. This was suspended in just sufficient ethanol to completely cover the material and a small excess of concd. nitric acid was added slowly with agitation, causing the formation of the solid nitrate. After removal by filtration, the product was recrystallized from ethanol, giving 260 g. (57%) of glistening green nitrate. This was identical with the product obtained above by Method A.

9-(*n*-Butyl-*n*-propylamino)-5-(N-methyl-N-4-methylphenylamino)-benzo[a]phenoxazonium Nitrate.—A mixture of 22.2 g. (0.05 mole) of 9-(*n*-butyl-*n*-propylamino)-benzo[a]-phenoxazonium nitrate, 18.2 g. (0.15 mole) of N-methyl-4-toluidine and 125 ml. of ethanol was warmed gently to give a clear solution. A fine stream of air was bubbled through the solution for 18 hours during which time a green crystalline product separated. Filtration gave 6.3 g. (25%) of green crystals which were recrystallized from 250 ml. of ethanol. The wave length of maximum absorption of the nitrate in ethanol solution was 664 mμ. A solution of the base in ethanol showed maximum absorption at 534 mμ.

Anal. Calcd. for $C_{31}H_{34}N_4O_4 \cdot H_2O$: C, 68.4; H, 6.66; N, 10.3. Found: C, 68.1; H, 6.35; N, 10.5.

9-Di-*n*-propylamino-5-(N-ethyl-N-phenylamino)-benzo[a]-phenoxazonium Nitrate.—A mixture of 19.7 g. (0.05 mole) of 9-di-*n*-propylaminobenzo[a]phenoxazonium nitrate, 18.2 g. (0.15 mole) of N-ethylaniline and 125 ml. of ethanol was warmed gently until the reactants dissolved. A fine stream of air was bubbled through the solution for four hours and the solution was then allowed to stand in an open beaker at room temperature for several days. The color of the solution gradually changed from reddish-blue to a greenish-blue. Addition of water caused precipitation of an oil which upon stirring repeatedly with diethyl ether congealed to a dark solid, 14.8 g. (58%). Addition of ammonium hydroxide to an ethanol solution of the crude nitrate caused precipitation of a brown base which was reconverted to the purified nitrate by rubbing up with dilute nitric acid. The absorption maxima of the salt and the base in ethanol solution were found to be at 659 and 531 mμ, respectively. This product was given an antituberculous rating of 2+.

Anal. Calcd. for $C_{30}H_{32}N_4O_4$: C, 70.3; H, 6.29: N, 10.9. Found: C, 70.4; H, 6.17; N, 10.8.

Spectrophotometric Determinations.—These were carried out in ethanol solution as described in paper I of this series.[2]

Acknowledgments.—We are grateful to Dr. M. E. Hultquist and Dr. J. J. Denton for their interest and coöperation on this project and we acknowledge the assistance of Mr. H. L. Komarowski in preparing some of these compounds. We are indebted to Mr. O. E. Sundberg and associates for the microanalyses and to Mr. F. C. Dexter and Miss M. R. O'Rourke for the spectrophotometric determinations.

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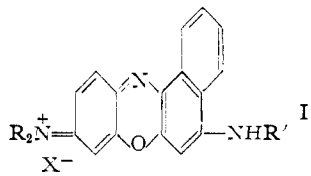
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT OF THE CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Chemotherapeutic Dyes. III. 5-Heterocyclicamino-9-dialkylaminobenzo[a]phenoxazines[1]

BY MOSES L. CROSSLEY, CORRIS M. HOFMANN AND PAUL F. DREISBACH

In order to study the effect on tumor growth-retardation and antituberculous action caused by introduction of a heterocyclicamino group in the benzo[a]phenoxazines, a series of 9-dialkylamino-5-heterocyclicaminobenzo[a]phenoxazines was prepared. The method of preparation involved amination of 9-dialkylaminobenzo[a]phenoxazines with various amino-heterocycles. None of the compounds of this series possessed significant activity.

In the two preceding papers in this series,[2,3] there are described the preparation and properties of a number of benzo[a]phenoxazine dyes of the general formula, I, in which R designates alkyl, R′



I

aralkyl or aryl and X the anion of a salt. Some of these compounds exhibited strong antituberculous activity in mice and showed differential staining and growth-retarding effects on transplanted tumor tissue in mice.

In view of the marked changes in activity that were noted when various arylamino and aralkylamino groups were substituted in the 5-position of the benzo[a]phenoxazine nucleus, it was considered important to investigate other structural modifications. The introduction of a heterocyclic group in many systems has been shown to modify the pharmacological activity of the parent compound, a striking example of this being in the sulfanilamide series.

Therefore, a series of 9-dialkylaminobenzo[a]-phenoxazines was prepared which contained a 5-heterocyclicamino group. These compounds were obtained by a procedure similar to that described in paper II of this series[3] for the preparation of the related 5-arylamino derivatives. The procedure involved reaction of a 9-dialkylaminobenzo[a]phenoxazonium nitrate with an excess of the aminoheterocycle in ethanol solution. The pK_a values of the aminoheterocycles used in this series fall in the range of 3 to 7, which is the range of pK_a values of the aromatic amines used successfully in the preparation of similar aryl derivatives. When more basic heterocyclic amines such as piperidine were

(1) Presented before the Division of Medicinal Chemistry at the American Chemical Society Meeting in Cleveland, Ohio, April 8th to 11th, 1951.

(2) M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, THIS JOURNAL, **74**, 573 (1952).

(3) M. L. Crossley, R. J. Turner, C. M. Hofmann, P. F. Dreisbach and R. P. Parker, *ibid.*, **74**, 578 (1952).