TABLE I

Extraction solvent	Plant used	Crude alkaloid	Alkali-soluble	Alkali-insoluble	Haplophytine	Cimicidine
Water	6.8 kg.	5.8 g.	3.6 g.		0.2 g.	
		100 γ/g. (80%)	100 γ/g. (95%)	200 γ/g. (5%)	25 γ/g. (75%)	....
Chloroform	7.7 kg. mature	39.3 g. 300 γ/g. (50%)	.....	.....	0.6 g. 18 γ/g. (50%)	....
Chloroform	8.1 kg. immature	.....	.....	.....	2.2 g. 18 γ/g. (50%)	0.2 g. 75 γ/g. (63%)

of cimicidine, the mother liquors from the first crystallization were treated with a 1:1 mixture of acetone and absolute ethanol and allowed to evaporate slowly over a period of two months, with occasional addition of fresh solvent. A crystalline material separated, which proved to be pure haplophytine. One recrystallization from ethanol–acetone gave clusters of needles (0.39 g.), m.p. 280–285° (dec.); $[\alpha]^{25}D$ +109° (1%, chloroform). The identity of this material with haplophytine was confirmed by identical infrared spectra. When the mixed solvent was removed from the mother liquors and replaced by pure acetone, cimicidine again crystallized, contaminated by only minute amounts of haplophytine. Only a small portion of very impure haplophytine has been isolated from a variety of further fractionations of the haplophytine and cimicidine mother liquors.

Insecticidal Data.—These data are summarized in Table I. In this table, the upper value represents the yield of material, and the lower values are the levels of treatment (contact) followed by the per cent. mortality. The crude alkaloid is a heterogeneous mixture, completely insoluble in petroleum ether and almost completely insoluble in water; it is somewhat soluble in dry acetone or absolute alcohol and much more soluble if 10% water is present.

Acknowledgments.—Mr. B. A. Krukoff of Merck & Co., Inc., assisted in the procurement and identification of the plant material used in this study. Earlier entomological investigations were conducted in the laboratories of Merck & Co., Inc., and at the New Jersey State Agricultural Experiment Station and Rutgers University, New Brunswick, N. J., under the direction of Dr. R. E. Heal. Later insecticidal assays were conducted by Professor C. W. Kearns of the Entomology Department, University of Illinois. Infrared spectra were determined by Miss Elizabeth Petersen, using a Perkin–Elmer spectrophotometer. Ultraviolet spectra were determined by Miss Ella Richards, using a Carr Recording Spectrophotometer. Analytical data were determined by Misses Rachel Kopel and Emily Davis, and Mrs. Jean Fortney, University of Illinois, in the analytical laboratories of Merck & Co., Inc. and by the Clark Microanalytical Laboratories, Urbana, Illinois. Marie Fischer assisted in the preparation of the manuscript. The authors gratefully acknowledge the assistance rendered.

RAHWAY, NEW JERSEY
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RECEIVED JULY 5, 1951

[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Chemotherapeutic Dyes. IV. Phenoxazines and Benzo[a]phenoxazines[1]

BY RICHARD C. CLAPP, JOE H. CLARK, JACKSON P. ENGLISH, CATHERINE E. FELLOWS, RUTH E. GROTZ AND ROBERT G. SHEPHERD

Four variations of the structure of 5-arylimino-9-dialkylaminobenzo[a]phenoxazines, compounds active against mouse tuberculosis, have been made. These were: (a) the introduction of a 6-methyl, (b) the introduction of a 10-chloro, (c) the preparation of 5- and 9-monoarylimino and of 5-arylimino-9-arylamino derivatives and (d) removal of the benzo group to give analogously substituted phenoxazines. None of the compounds was as active as the unmodified model.

Certain benzo[a]phenoxazine dyes of the Nile Blue type have been found to have interesting tumor-staining[2] and antituberculous activity when administered orally to infected mice.[3] The effect of variations in structure on such activity has been studied in the three series, 9-dialkylamino-5-aralkyliminobenzo[a]phenoxazines,[4] 9-di-alkylamino-5-aryliminobenzo[a]phenoxazines[5] and 9-dialkylamino-5-heterocyclic-iminobenzo[a]phenoxazines.[6] Compounds of the second series were of the greatest interest, although those of the first series possessed activity, while those of the third series were without significant activity.

The present investigation was undertaken cooperatively with the above investigators to study still other variations in the structure of these dyes. This paper reports the preparation of compounds embodying four variations of the structure of the most active of the benzo[a]phenoxazines, namely, the 5-arylimino-9-dialkylaminobenzo[a]phenoxazines (I).

The first variation involves the substitution of a methyl group in the 6-position of the nucleus in order to study the effect of its possible interaction with substituents in the arylimino group. The

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Cleveland, Ohio, April, 1951. Paper III in this series, M. L. Crossley, C. M. Hofmann and P. F. Dreisbach, THIS JOURNAL, 74, 584 (1952).

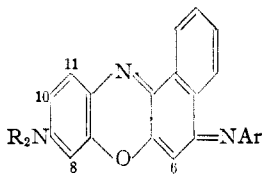
(2) See M. L. Crossley, P. F. Dreisbach, C. M. Hofmann and R. P. Parker, *ibid.*, 74, 573 (1952), ref. 2.

(3) H. J. White, M. E. Schlosser and M. B. DiCenzo, paper presented at Meeting of Society of American Bacteriologists, Chicago, Ill., May, 1951.

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

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

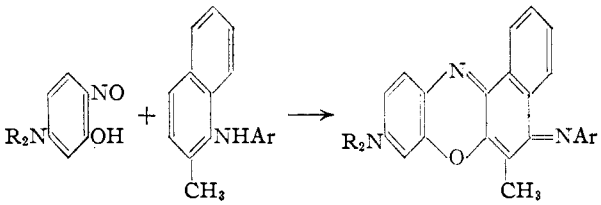
(6) M. L. Crossley, C. M. Hofmann and P. F. Dreisbach, *ibid.*, 74, 584 (1952).



I

second is the introduction of a chlorine atom into the 10-position of the nucleus. The third is the preparation of 5- or 9-monoarylimino- and 5-arylimino-9-arylaminobenzo[a]phenoxazines. The fourth is the preparation of analogously substituted phenoxazines—in effect, the elimination of the benzo ring.

Three benzo[a]phenoxazines with a 6-methyl substituent were prepared from N-(*o*- or *p*-tolyl)-2-methyl-1-naphthylamine and 2-nitroso-5-(diethyl- or di-*n*-propylamino)-phenol.

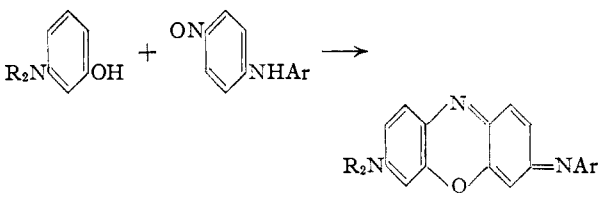


The yields of the dyes themselves were low, 17–25%, and the materials were extremely tedious to purify. It was found best to handle and characterize the compounds as the free bases, in which form they were amenable to chromatography and crystallization.

The 10-chloro derivatives were prepared in 25–30% yields by the reaction of 2-amino-4-chloro-5-(di-*n*-propylamino)-phenol and 4-anilino- or *p*-toluidino-1,2-naphthoquinone rather than by the above method for which the required nitrosophenol could not be obtained.

The compounds of the third variation were prepared by three methods. 9-Phenyliminobenzo[a]-phenoxazine was obtained in about 20% yield by the reaction of 4-nitrosodiphenylamine and 2-naphthol. 5-(*p*-Tolylimino)-9-(*p*-toluidino)benzo-[a]phenoxazine was prepared from 1-(*p*-tolylamino)-naphthalene and 2-nitroso-5-(*p*-toluidino)-phenol. It was found that the preparation of 5-phenyliminobenzo[a]phenoxazine from *o*-aminophenol and 4-anilino-1,2-naphthoquinone, reported by Goldstein and Ludwig-Semelitch,[7] was improved from a 10% yield to a 70% yield by the use of the free base of the phenol rather than the hydrochloride.

Two 3-arylimino-7-dialkylaminophenoxazines were prepared by the reaction



This is the method of Möhlau, Klimmer and Kahl[8] for a homolog. In the case of 7-diethylamino-3-phenyliminophenoxazine the yield was 80% but this dropped to 25% in the case of 7-dipropylamino-3-(*p*-tolylimino)-phenoxazine. Other reactions were attempted for this type of preparation but none was as satisfactory as the above. The reaction of *p*-nitrosodiethylaniline and *m*-anilinophenol, the nitroso and hydroxy groups of the above reactants being interchanged, appeared to give 3-diethylamino-5-phenyl-7-phenazone in acetic acid.

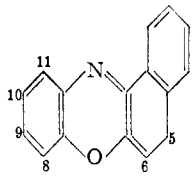
The compounds were tested orally by the drug-diet method in tuberculosis of mice by Dr. H. J. White and his collaborators in this Laboratory by a method which has been described.[9] These results are reported in Table I as activity ratios (reproducible within twofold limits) of the compound in question in terms of 5-phenylimino-9-diethylaminobenzo[a]phenoxazine. This compound[5] and 5-(*p*-tolylimino)-9-dipropylaminobenzo[a]phenoxazine[5] are included for comparison purposes. The activity ratio is the ratio of the diet concentration of the standard to the diet concentration of the compound under test required to give an equivalent effect.

The results presented in Table I show that substitution in the 6- or 10-position has a profound effect in lowering the activity of the parent compounds. The removal of the benzo ring or of the 9-dialkylamino substituent also lowers activity. It is apparent that some activity is present in the compounds having aryl substituents in the 5- and 9-positions. Whether these effects are an expression of

TABLE I

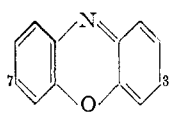
ANTITUBERCULOUS ACTIVITY IN MICE

BENZO[a]PHENOXAZINES



5	6	9	10	Activity ratio
$C_6H_5N=$	H	$(C_2H_5)_2N-$	H	1 (standard)
4-$CH_3C_6H_4N=$	H	$(n\text{-}C_3H_7)_2N-$	H	4+
4-$CH_3C_6H_4N=$	CH_3	$(n\text{-}C_3H_7)_2N-$	H	0.12
2-$CH_3C_6H_4N=$	CH_3	$(n\text{-}C_3H_7)_2N-$	H	.06
2-$CH_3C_6H_4N=$	CH_3	$(C_2H_5)_2N-$	H	.25
$C_6H_5N=$	H	$(n\text{-}C_3H_7)_2N-$	Cl	.12
4-$CH_3C_6H_4N=$	H	$(n\text{-}C_3H_7)_2N-$	Cl	.12
$C_6H_5N=$	H	H	H	.12
H	H	C_6H_5N-	H	.03
4-$CH_3C_6H_4N=$	H	4-$CH_3C_6H_4NH-$	H	.06

PHENOXAZINES



3	7	Activity ratio
$C_6H_5N=$	$(C_2H_5)_2N-$	0.01
4-$CH_3C_6H_4N=$	$(n\text{-}C_3H_7)_2N-$	.03

(7) H. Goldstein and Z. Ludwig-Semelitch, *Helv. Chim. Acta*, **2**, 655 (1919).

(8) R. Möhlau, K. Klimmer and E. Kahl, *Z. Farben- u. Textilchemie* **1**, 354 (1902); *Chem. Zentr.*, **73**, 458 (1902).

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

the changed absorption and excretion of these compounds or of their inherent antituberculous activity is not known.

Experimental[10]

2-Methyl-N-(*o*-tolyl)-1-naphthylamine. A.—A mixture of 9.1 g. (0.032 mole) of 2-methyl-1-naphthylamine hydriodide,[11] 19 g. (0.12 mole) of 2-methyl-1-naphthylamine[12] and 25 g. (0.23 mole) of *o*-toluidine was refluxed for 88 hours. By this time the liquid temperature had risen from 217 to 250°, the evolution of ammonia having begun immediately. The cooled reaction mixture was treated with ether and an excess of dilute hydrochloric acid. The ether was separated from the aqueous slurry, clarified with Darco, evaporated and the residue distilled; 4 g. distilled at 70–80° (1 mm.) and had a freezing point of 22° (this may have been crude 2-methylnaphthalene, m.p. 35–36°.) A second fraction distilled at 165–185° (1 mm.) and solidified readily upon treatment with hexane. This gave 12 g. of m.p. 93–107°, a crude yield of 33%. The compound was purified by crystallization from ethanol and heptane to give 4 g. of m.p. 114–117°, and 3 g. of m.p. 112–115°.

Anal. Calcd. for $C_{18}H_{17}N$: N, 5.7. Found: N, 5.6.

In another run a reaction time of 70 hours gave a crude yield of 52%.[13]

B.—A mixture of 50.8 g. (0.23 mole) of 1-bromo-2-methylnaphthalene,[14] 98 g. (0.92 mole) of *o*-toluidine and 7 g. (0.05 mole) of cuprous oxide[15] (J. T. Baker & Co.) was refluxed for about 16 hours with little rise in temperature (193 to 195°). The product was cooled, dissolved in 500 cc. of benzene and extracted with 1 liter of 1:4 hydrochloric acid to remove unchanged toluidine. The benzene was then concentrated and diluted with petroleum ether to obtain a crop of crude tolylmethylnaphthylamine. The filtrate was treated with gaseous hydrogen chloride. The resulting solid was filtered and the filtrate evaporated to recover 27 g. of crude 1-bromo-2-methylnaphthalene.

The base was freed from the hydrochloride with ammonium hydroxide, combined with the crop previously obtained and recrystallized from heptane using Norit A; yield 8.2 g. (14%); m.p. 110–114°. Allowing for the recovered bromomethylnaphthalene, the yield is 33%. This material on further crystallization from heptane gave a product of m.p. 113–114.5° which did not depress the melting point of material prepared by Method A.

An attempt to prepare the compound using copper powder instead of cuprous oxide gave no reaction after 16 hours.

9-Diethylamino-6-methyl-5-(*o*-tolylimino)-benzo[a]phenoxazine.—Five grams (0.02 mole) of 2-methyl-N-(*o*-tolyl)-1-naphthylamine, 5.8 g. (0.03 mole) of 5-diethylamino-2-nitrosophenol,[16] 105 cc. of absolute alcohol and 5 cc. (0.05 mole) of concentrated hydrochloric acid were mixed and refluxed for 9 hours. The color changed from the original brown through green to a strong blue. Paper strip chromatography gave evidence of the presence of five dyes. The reaction mixture was concentrated, treated with sodium hydroxide and extracted with chloroform. The extract was evaporated to dryness and the residue was extracted with heptane. This extract was concentrated to saturation and passed three times with heptane through 3 × 20 inch columns of α-cellulose, collecting the first red fractions and discarding the residues. It was then concentrated and passed through cellulose in heptane containing 50 cc. of acetic acid per liter. The desired product remained on the column as a blue component and was thereby separated from a red impurity. The product was eluted from the column with alcoholic ammonia. This eluate was concentrated and crystallized from heptane; yield 175 mg., m.p. 179°.

Anal. Calcd. for $C_{28}H_{27}N_3O$: C, 79.8; H, 6.5; N, 10.0. Found: C, 79.5; H, 6.7; N, 9.9.

The spectrum in acid alcohol showed a peak of absorption at 665 mμ.

9-Di-*n*-propylamino-6-methyl-5-(*o*-tolylimino)-benzo[a]-phenoxazine.—A mixture of 7.4 g. (0.03 mole) of 2-methyl-N-(*o*-tolyl)-naphthylamine, 11.5 g. (0.045 mole) of 2-nitroso-5-di-*n*-propylaminophenol hydrochloride[4] and 75 cc. of absolute alcohol was refluxed for 4 hours. The reaction mixture was concentrated, neutralized with alcoholic potassium hydroxide, and passed through a 1.5 × 18 inch column of activated alumina (Eimer and Amend, 80–200 mesh) that had been wet with benzene, developing with this solvent. Only the first red component was collected. The eluate containing this was evaporated to dryness and the residue was again chromatographed on alumina in benzene, collecting the product in 600 cc. of eluate, in ten fractions. All fractions showed a single component when run on paper strips, developing with heptane–dibutylamine, and had identical visible spectra in both alcoholic hydrochloric acid and alcoholic potassium hydroxide. From the effluent immediately preceding the colored solutions and from the first fractions of this, crystals of the starting material, 2-methyl-N-(*o*-tolyl)-1-naphthylamine, were obtained and identified by mixed melting point. This impurity was left in benzene when the benzene solution was extracted with an equal volume (in 2 portions) of a 7:2:1 mixture of methanol, water and concentrated hydrochloric acid. The dye was recovered from the extracts by neutralization with ammonia, dilution with an equal volume of water and extraction into benzene. The benzene extract was concentrated to dryness and the gummy residue was crystallized by digestion with alcohol. There was thus obtained 3.45 g., a yield of 25%. It was further purified by solution in benzene, filtration, concentration and the addition of alcohol. The m.p. was 153–154°. The visible spectrum did not differ from other similarly substituted compounds.

Anal. Calcd. for $C_{30}H_{31}N_3O$: C, 80.1; H, 6.9; N, 9.3. Found: C, 80.2; H, 7.0; N, 9.3.

2-Methyl-N-(*p*-tolyl)-1-naphthylamine.—A mixture of 39 g. (0.24 mole) of 2-methyl-1-naphthylamine, 2.1 g. (0.0074 mole) of 2-methyl-1-naphthylamine hydriodide, and 38 g. (0.35 mole) of *p*-toluidine was refluxed for 19 hours by which time the temperature of the liquid had risen from 216 to 262°. After cooling, the reaction mixture was poured into dilute hydrochloric acid and the solution was extracted with ether. No material remained undissolved and the aqueous phase was extracted again with ether. The ether extracts were combined, washed with water, dried over sodium sulfate and the ether distilled. When the residue was distilled, 52.5 g. of a light yellow viscous liquid was collected at 161–169° (1 mm.). The distillate was crystallized from 150 cc. of hexane to give 44.9 g. (73%) of light yellow needles of m.p. 63–65°.

Anal. Calcd. for $C_{18}H_{17}N$: N, 5.7. Found: N, 5.8.

9-Di-*n*-propylamino-5-(*p*-tolylimino)-6-methylbenzo[a]-phenoxazine.—Nineteen grams (0.077 mole) of 2-methyl-N-(*p*-tolyl)-1-naphthylamine and 29.7 g. (0.115 mole) of N,N-di-*n*-propyl-6-nitroso-3-aminophenol were dissolved in 200 cc. of absolute alcohol and refluxed for 3 hours. After cooling, the blue-green solution was made basic with aqueous ammonia and 600 cc. of water was added. The gum which precipitated was washed by decantation with water and dissolved in 250 cc. of boiling benzene. The cooled benzene solution was poured through a 2.5 × 12 inch column of activated alumina and the column was washed with benzene until essentially all of the red component had been removed, leaving behind a black band at the top of the column which was discarded. The red effluent showed only one component when spotted on a filter paper strip and run with heptane, whereas the original solution had shown several components. The benzene solution was concentrated to about 50 cc. and the addition of 700 cc. of alcohol threw down 6.4 g. of dark red-brown needles of m.p. 170–173°. This was dissolved in 100 cc. of warm benzene, filtered, concentrated to 50 cc., and treated with 600 cc. of alcohol; yield 5.9 g. (17%); m.p. 171–174°. Crystallization from 95% alcohol (850 cc./g.) did not change the melting point. The visible spectrum was not different from the compound without the 6-methyl group.

(10) Microanalyses reported represent the average of two values not differing by more than 0.3. They were carried out in these laboratories under the direction of Dr. J. A. Kuck. We are indebted to Mr. Paul Giesecke and co-workers for the spectra reported.

(11) Prepared in 79% yield from 2-methyl-1-naphthylamine by the addition of the amine to 1.5 molar proportions of 6% hydriodic acid, filtration, washing with water and drying at 65°.

(12) R. Adams and A. A. Albert, THIS JOURNAL, **64**, 1476 (1942).

(13) H. H. Hodgson and E. Marsden, *J. Soc. Chem. Ind.*, **58**, 156 (1939), have shown that even 2–3 hours' heating past the optimum 12 hours in the preparation of N-phenyl-1-naphthylamine by this method gives a marked reduction both of yield and quality of product.

(14) R. Adams and L. O. Binder, THIS JOURNAL, **63**, 2774 (1941).

(15) *Cf.* H. R. Slagh, U. S. Patent 2,391,848; *C. A.*, **40**, 1879 (1946).

(16) R. Möhlau, *Ber.*, **25**, 1060 (1892).

Anal. Calcd. for $C_{30}H_{31}N_3O$: C, 80.1; N, 9.3. Found: C, 79.5[17]; N, 9.4.

N,N-Di-*n*-propyl-2-chloroaniline.—This was prepared from tri-*n*-propyl phosphate[18] and 2-chloroaniline by the method of Thomas, Billman and Davis[19] for the lower homologs; b.p. 85–87° (1 mm.); $n^{24}D$ 1.5180; yield 39%; picrate, m.p. 136–139°.

Anal. Calcd. for $C_{12}H_{18}ClN$: N, 6.6. Found: N, 6.7.

N,N-Di-*n*-propyl-2-chloro-5-nitroaniline.—One hundred fifty-seven grams (0.74 mole) of N,N-di-*n*-propyl-2-chloroaniline was dissolved with cooling in 780 cc. of concentrated sulfuric acid and, while cooling in an ice-bath, a mixture of 50 g. of fuming nitric acid and 235 cc. of concentrated sulfuric acid was added. The ice-bath was then removed and the mixture was allowed to stand for 2 hours at room temperature, poured into ice and water, and made alkaline with aqueous ammonia. The separated oil was taken into ether, the ether washed with water, dried over sodium sulfate, and distilled. The fraction, 150 g. (79%), boiling at 131–138° (1 mm.) was collected; $n^{25}D$ 1.5495.

A picrate, m.p. 118–121°, was prepared for analysis.

Anal. Calcd. for $C_{18}H_{20}ClN_5O_9$: N, 14.4. Found: N, 14.6.

4-Chloro-3-di-*n*-propylaminoaniline.—Sixteen grams (0.062 mole) of N,N-di-*n*-propyl-2-chloro-5-nitroaniline was added dropwise to a solution of 64 g. of stannous chloride dihydrate in 130 cc. of concentrated hydrochloric acid. The compound was rapidly decolorized and there was considerable heat evolution. The reaction mixture was stirred for 10 minutes after the end of the addition, chilled in ice, and the separated solid was collected on sintered glass and washed on the filter with concentrated hydrochloric acid. The solid was dissolved in 300 cc. of water, and concentrated sodium hydroxide solution was added until all of the precipitated solid had redissolved. The oil that remained was taken into ether, the ether washed with water, dried with sodium sulfate and distilled. The residue was distilled to give 11.55 g. (82%) of product of b.p. 135–138° (2 mm.); $n^{25}D$ 1.5516.

A picrate with a satisfactory melting point could not be obtained.

4-Chloro-3-di-*n*-propylaminophenol.—Thirty grams (0.13 mole) of the above amine was dissolved in 500 cc. of 2 *N* sulfuric acid, cooled in an ice-bath, and diazotized with a solution of 10.2 g. (0.15 mole) of sodium nitrite in 50 cc. of water in 15 minutes. After standing for an additional 15 minutes, it was added dropwise over 50 minutes to a stirred and boiling mixture of 6.5 g. of copper powder in 500 cc. of 2 *N* sulfuric acid. The mixture was boiled for 15 minutes after the completion of the addition, cooled, filtered and neutralized with sodium bicarbonate solution. The precipitated gum was taken into ether, the ether solution washed with water, and concentrated to about 250 cc. The ether solution was extracted a total of fifty times with 50-cc. portions of 2 *N* sodium hydroxide. This tedious step was essential to the purification, since distillation alone gave a much lower yield. The alkali extract was neutralized and the phenol was extracted with ether, the ether washed with water, dried over sodium sulfate, and distilled. The 27 g. of brown oil was distilled to give 15 g. (50%) of b.p. 120–134° (2 mm.); $n^{26}D$ 1.5427.

The picrate had m.p. 219° after crystallization from alcohol.

Anal. Calcd. for $C_{18}H_{21}ClN_4O_8$: N, 12.3. Found: N, 12.3.

4-Chloro-5-di-*n*-propylamino-2-nitrophenol.—Following the method of Van Duin[20] for the nitration of 2-chloro-N,N-dimethylaniline, 15 g. (0.066 mole) of 4-chloro-3-di-*n*-propylaminophenol was dissolved in 375 cc. of 10% nitric acid, the solution cooled in an ice-bath, and 0.3 g. of sodium nitrite was added. The solution became cloudy at once and an oil began to separate. This had completely solidified after standing 20 hours at room temperature. The resulting green solid was collected and washed with water; yield 14.8 g. (82%); m.p. 47–50°. The m.p. was raised to 48–51° by crystallization from hexane (cooling in Dry Ice–acetone).

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3$: N, 10.3. Found: N, 10.1.

4-Chloro-5-di-*n*-propylamino-2-aminophenol.—Twenty-seven and one-tenth grams (0.10 mole) of the nitrophenol above was added with stirring to a solution of 108 g. (0.48 mole) of stannous chloride dihydrate in 216 cc. of concentrated hydrochloric acid. The reduction was accompanied by heat and the precipitation of a light brown solid which was filtered and washed with concentrated hydrochloric acid after cooling. The precipitate was dried in a desiccator over sodium hydroxide, dissolved in 850 cc. of water, and the tin precipitated with hydrogen sulfide. The clarified solution (Hyflo) was neutralized with sodium bicarbonate and the product precipitated as bluish-white material which became light purple on drying; m.p. 117–122°; yield 15 g. (62%). It was not purified further for the subsequent reactions.

Catalytic reduction over platinum did not give as pure a product.

10-Chloro-9-di-*n*-propylamino-5-(*p*-tolylimino)-benzo[a]-phenoxazine.—A mixture of 6.8 g. (0.028 mole) of 4-chloro-5-di-*n*-propylamino-2-aminophenol, 7.4 g. (0.028 mole) of 4-*p*-toluidino-1,2-naphthoquinone, and 135 cc. of *n*-butanol was refluxed for 2.5 hours. After cooling, the precipitated red-brown needles were collected; yield 5.9 g.; m.p. 128–131°. This was dissolved in 1400 cc. of 95% alcohol, treated with 4 g. of Darco, and the filtrate concentrated to 700 cc. to give 4.1 g. of red-brown needles, m.p. 131–134°. Another similar treatment in 900 cc. of 95% alcohol with 1 g. of Darco gave 3.58 g. (27%); m.p. 134–136°. The Darco treatments removed a contaminant which appeared as a pink spot on filter paper when developed with heptane; the pure compound showed a single orange-red spot. The maximum of absorption in the visible spectrum in acidic alcohol is 630 mμ, some 45 mμ shorter than the 6-methyl compound.

Anal. Calcd. for $C_{29}H_{28}ClN_3O$: C, 74.1; H, 6.0; N, 8.9; Cl, 7.5. Found: C, 74.2; H, 6.1; N, 8.8; Cl, 7.4.

10-Chloro-9-di-*n*-propylamino-5-phenyliminobenzo[a]-phenoxazine.—A mixture of 9.5 g. (0.039 mole) of 4-chloro-5-di-*n*-propylamino-2-aminophenol, 9.7 g. (0.039 mole) of 4-anilino-1,2-naphthoquinone and 180 cc. of *n*-butanol was refluxed for 2.5 hours, cooled and the precipitate collected. Two recrystallizations from 95% alcohol (3.5 cc./g.), using Darco as above, gave 4.5 g. (25%) of a product homogeneous by paper chromatography and melting at 123–125°.

Anal. Calcd. for $C_{28}H_{26}ClN_3O$: C, 73.7; H, 5.7; N, 9.2; Cl, 7.8. Found: C, 73.9; H, 5.7; N, 9.3; Cl, 7.8.

9-Phenyliminobenzo[a]phenoxazine.—A mixture of 4.32 g. (0.03 mole) of 2-naphthol, 180 cc. of glacial acetic acid, 4.8 cc. (0.3 mole) of 6 *N* hydrochloric acid and 18 cc. of water was heated to boiling and 9.0 g. (0.045 mole) of 4-nitrosodiphenylamine was added with shaking. The whole was boiled for 20 minutes with shaking and 1.8 cc. of concentrated aqueous ammonia and 720 cc. of water was added to make the mixture 3 *N* in acetic acid. The separated solid was filtered and the filtrate was poured into 300 cc. of concentrated aqueous ammonia and 700 g. of ice. The precipitate was collected, washed with water, and dried to give 8.5 g.; m.p. 110°. The initial precipitate was dissolved in 180 cc. of hot acetic acid and precipitated by addition of 720 cc. of water and the precipitate discarded. From the mother liquor, by the addition of 300 cc. of concentrated aqueous ammonia and 700 g. of ice, 2.7 g. was obtained. This was combined with the 8.5 g. of material and the whole recrystallized from 1900 cc. of heptane, filtering from 6 g. of insoluble material; 1.7 g. was obtained, and after several crystallizations from heptane (150 cc./g.), the melting point was constant at 153°.

Anal. Calcd. for $C_{22}H_{14}N_2O$: C, 82.0; H, 4.4; N, 8.7. Found: C, 81.8; H, 4.7; N, 8.6.

5-(*p*-Tolylimino)-9-(*p*-toluidino)-benzo[a]phenoxazine.—A solution of 10.5 g. (0.046 mole) of 2-nitroso-5-(*p*-toluidino)-phenol[21] and 10.2 g. (0.046 mole) of N-(*p*-tolyl)-1-naphthylamine in 110 cc. of 95% alcohol was treated with 5 cc. of concentrated hydrochloric acid, and the solution was re-

(17) Van Slyke analysis. Pregl carbon analyses were somewhat lower.

(18) *Organic Syntheses*, Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 109 (method for tributyl phosphate), b.p. 74–78° (1 mm.), yield 66%.

(19) *Cf.* D. G. Thomas, J. H. Billman and C. E. Davis, THIS JOURNAL, **68**, 895 (1946).

(20) C. F. Van Duin, *Rec. trav. chim.*, **51**, 878 (1932).

(21) R. Gnehm and L. Veillon, *J. prakt. Chem.*, [2] **65**, 66 (1902).

fluxed for 3.5 hours. On cooling the dark blue solution, 9.5 g. of brown hydrochloride was obtained. This material in 1 liter of 95% alcohol was treated with 200 cc. of concentrated ammonium hydroxide, and dilution with 3 l. of water yielded 7.95 g. of base. After several crystallizations of this material from benzene–hexane (Darco), 5.5 g. (27%) of green crystals, m.p. 213–217°, was obtained. When this product was chromatographed on paper with hexane, a single pink spot was observed.

Anal. Calcd. for $C_{30}H_{23}N_3O$: C, 81.6; H, 5.2; N, 9.5. Found: C, 81.6; H, 5.3; N, 9.5.

5-Phenyliminobenzo[a]phenoxazine.—A mixture of 1.15 g. (0.01 mole) of freshly recrystallized *o*-aminophenol, 2.4 g. (0.01 mole) of 4-anilino-1,2-naphthoquinone and 75 cc. of butanol was refluxed for 4.5 hours. Fifteen cc. of butanol was distilled and the distilland was chilled to give a crystalline mush. After washing the precipitate with butanol, 1 *N* sodium hydroxide, and water, there was 2.3 g. (70%) of material melting at 217–218°.[7] This was unchanged by crystallization from butanol (1 g./40 cc.). Less pure material was recovered from the mother liquors.

7-Diethylamino-3-phenyliminophenoxazine.—A solution of 8.25 g. (0.05 mole) of *m*-diethylaminophenol in 100 cc. of glacial acetic acid, 4 cc. of concentrated hydrochloric acid and 6 cc. of water was brought to the boiling point and 15 g. (0.075 mole) of 4-nitrosodiphenylamine was added over a period of 5 minutes. The solution was boiled for 45 minutes longer and 454 cc. of water was added. The precipitate was discarded. The filtrate was added to sufficient concentrated aqueous ammonia to give a basic reaction. The separated solid was collected and dissolved in hot benzene, the benzene evaporated to one-half volume, and one-half volume of petroleum ether was added to precipitate a solid which was discarded. The mother liquor was evaporated and the residue was dissolved in acetic acid and precipitated with ammonia; yield 13.5 g. (79%); m.p. 105° (variable with traces of solvent). Absorption maxima (visible): in 4% alcoholic potassium hydroxide, 557 mμ; in 10% sulfuric acid, 452 mμ (very weak), 645 mμ; in 30% sulfuric acid, 652 mμ.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.9; H, 6.2; N, 12.2. Found: C, 76.6; H, 6.4; N, 12.3.

5-Phenyl-7-diethylamino-3-phenazone.—A solution of 1.33 g. (0.0075 mole) of 4-nitrosodiethylaniline and 0.92 g. (0.005 mole) of 3-anilinophenol in 3.5 cc. of 80% acetic acid was prepared by warming, and a vigorous reaction took place spontaneously. When the vigorous boiling stopped the reaction mixture was allowed to stand overnight, diluted with 10 cc. of acetic acid and 5 cc. of ethanol and poured into ammonia and ice to precipitate the base. The precipitate was collected and dried. The solid was treated with 20% methanol in ether (250 cc./g.) and filtered to remove the insolubles. The filtrate was chromatographed on a 27 × 270 mm. alumina column, developing with the same solvent. The fast yellow band was discarded and the following red band was collected. The residues on the column were discarded. The effluent containing the red band was concentrated to dryness, the residue was dissolved in benzene and chromatographed on alumina. All of the color was absorbed on the top of the column from benzene and the column was developed with 10% methanol in ether, which gave rise to a fast yellow band (discarded) and a following red band which was collected. The slower material was discarded.

The solution of the red band was evaporated and the residue was crystallized from benzene; yield 80 mg. (5%); m.p. 261–264°.

Anal. Calcd. for $C_{22}H_{21}N_3O$: C, 76.9; H, 6.2; N, 12.2. Found: C, 76.4; H, 6.4; N, 12.2.

The compound is red in alkali, purple in 1–30% sulfuric acid, and blue in 50–95% sulfuric acid.

7-Dipropylamino-3-(*p*-tolylimino)-phenoxazine.—A solution of 10.2 g. (0.053 mole) of *m*-di-*n*-propylaminophenol[5] in 132 cc. of glacial acetic acid and 12 cc. of water was heated to boiling and 20 g. (0.08 mole) of 4-nitroso-4′-methyldiphenylamine[22] was added over 5 minutes. The color changed immediately from yellow to green to blue. The refluxing was stopped after 45 minutes and sufficient water to make the mixture 1 *N* in acetic acid was added. The resulting precipitate was filtered and discarded. The filtrate was poured into excess ammonia, the gummy precipitate separated, and the mother liquor extracted with benzene. The gummy precipitate was dissolved in the extract and the benzene solution was dried with potassium carbonate. The dried benzene solution was heated to boiling and treated with 5 volumes of petroleum ether to precipitate 5.9 g. Evaporation of the mother liquor left a 7.6-g. residue. The 5.9 g. was dissolved in benzene and chromatographed on alumina, developing with 0.5% methanol in benzene to give 4.8 g. in the main fraction. This was combined with the 7.6 g. above, the whole dissolved in glacial acetic acid and precipitated by pouring into excess aqueous ammonia. The precipitate was further purified by solution in benzene, precipitation of impurities with 1 volume of petroleum ether, conversion of the soluble portion to its hydrochloride in methanol, and reconversion to the free base by solution of the hydrochloride in acetic acid and pouring into ammonia; yield 5 g. (25%); m.p. 126–131°. The visible spectrum is entirely similar to that of 7-diethylamino-3-phenyliminophenoxazine.

Anal. Calcd. for $C_{25}H_{27}N_3O$: C, 77.9; H, 7.1; N, 10.9. Found: C, 77.3; H, 7.4; N, 10.1.

STAMFORD, CONNECTICUT RECEIVED SEPTEMBER 26, 1951

(22) A. Reichold, *Ann.*, **255**, 163 (1889).