tracted with methylene chloride. The extracts were combined with the water insoluble layer, concentrated and fractionated through a Holzman column to give 36.1 g. of salicylaldehyde, b.p. 38–40°/0.55 mm., n_D^{25} 1.5701; and 16.8 g. of a yellow liquid, b.p. 88–90°/0.25 mm., n_D^{25} 1.5309, whose analyses corresponded to 2-acetoxybenzaldehyde.

Anal. Calcd. for $C_9H_8O_3$: C, 65.81; H, 4.91. Found: C, 65.91; H, 5.02.

The aqueous phase from the reaction mixture was made basic and extracted with methylene chloride for 12 hr. on a continuous extractor. Concentration of the methylene chloride solution left no residue.

N,N,N′,N′,N″-Pentaacetyldiethylenetriamine (IIb). To 4080 g. (40.0 moles) of acetic anhydride was added, dropwise, 515 g. (5.0 moles) of redistilled diethylenetriamine, keeping the temperature at 10–15° by external cooling. The solution was warmed to room temperature and then refluxed under a 20 plate Oldershaw column for 30 hr., during which time the theoretical amount of acetic acid was collected. The residue was concentrated *in vacuo*, leaving a viscous dark brown oil which solidified. The product was recrystallized from 3 l. of 2-propanol to give 823 g. (52.7%) of light yellow crystals, m.p. 106–108°. A second recrystallization gave a white solid; m.p. 109–110°.

The nitrolysis of N,N,N′,N′,N″-pentaacetyldiethylenetriamine. A. *With nitric acid and trifluoroacetic anhydride.* To 80 ml. (0.58 mole) of trifluoroacetic anhydride was added dropwise 16.8 ml. (0.4 mole) of 98–99% technical nitric acid, keeping the temperature at −10 to −20°. Then 31.3 g. (0.1 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine was added. The solid dissolved and the solution was allowed to stand in an ice-bath for 65 hr. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in methylene chloride, washed with saturated sodium carbonate solution, dried, and concentrated, leaving 28.8 g. (91.0%) of white solid, m.p. 120–122°. Recrystallization from ethanol raised the melting point to 122–123°.

B. *With nitrogen pentoxide in trifluoroacetic acid.* The Inorganic Synthesis preparation of nitrogen pentoxide[7] gives a yield of 50% and the procedure is only applicable for small-scale runs. This process was modified to give improved yields on a larger scale. In a 2-l. glass resin pot fitted with a sealed stainless steel horseshoe-shaped stirrer driven by an air motor, solid addition flask, and drying tube, was placed 336 ml. (8.0 moles) of 98–99% technical nitric acid. The acid was cooled to −20 to −10° and 426 g. (3.0 moles) of phosphorus pentoxide was added portionwise from the solid addition flask, keeping the temperature about −10° by external cooling. After the addition was complete, the reaction mixture was allowed to warm to room temperature. The addition flask was replaced with a distillation head and receiver which was connected through a drying tube to the water aspirator. The reaction mixture was then stirred under vacuum at ambient temperature for 4 hr. The nitrogen pentoxide which was collected in the receiver was light yellow to white needles, the yield was 333 g. (77%).

A mixture of 6.26 g. (0.02 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine, 12.0 g. (0.11 mole) of nitrogen pentoxide, and 10 ml. (0.16 mole) of trifluoroacetic acid was allowed to stand in an ice-bath for 43 hr., and then concentrated *in vacuo*. Working up in the same manner as described in A., above, there was obtained 5.1 g. (80.8%) yield of product, m.p. 121–122°.

C. *With nitrogen pentoxide in sulfur dioxide.* The procedure was the same as in B., above, except that a glass pressure bottle was used for the reaction vessel.

D. *With nitrogen pentoxide in dichloroacetic acid.* A mixture of 6.26 g. (0.02 mole) of *N,N,N′,N′,N″*-pentaacetyldiethylenetriamine, 10.8 g. (0.1 mole) of nitrogen pentoxide, and 38.7 g. (0.3 mole) of dichloroacetic acid was allowed to stand in an ice-bath for 24 hr. The reaction mixture was poured on ice and a saturated sodium carbonate solution was added until the resulting *p*H of the solution was 10. The product was collected and recrystallized from ethanol to give 4.52 g. (71.4%) of white crystals, m.p. 118–120°.

3-Nitraza-1,5-pentanediamine dihydrochloride (IId). A mixture of 31.6 g. (0.1 mole) of *N,N,N′,N′*-tetraacetyl-*N″*-nitrodiethylenetriamine and 50 ml. of 37% hydrochloric acid was refluxed for 4 hr. The reaction mixture was cooled and diluted with 50 ml. of methanol. The product was collected and dried to give 19.7 g. (89.1%) of white crystals, m.p. 259–263° dec. Recrystallization from 78% ethanol raised the melting point to 261–263° dec.

Acknowledgment. We are indebted to the Bureau of Ordnance for the financial support of this work and to Mr. E. R. Wilson for aid in the experimental work.

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[CONTRIBUTION FROM THE REGA INSTITUTE, UNIVERSITY OF LOUVAIN]

Phenoxazines. I. Ring-Substituted Derivatives

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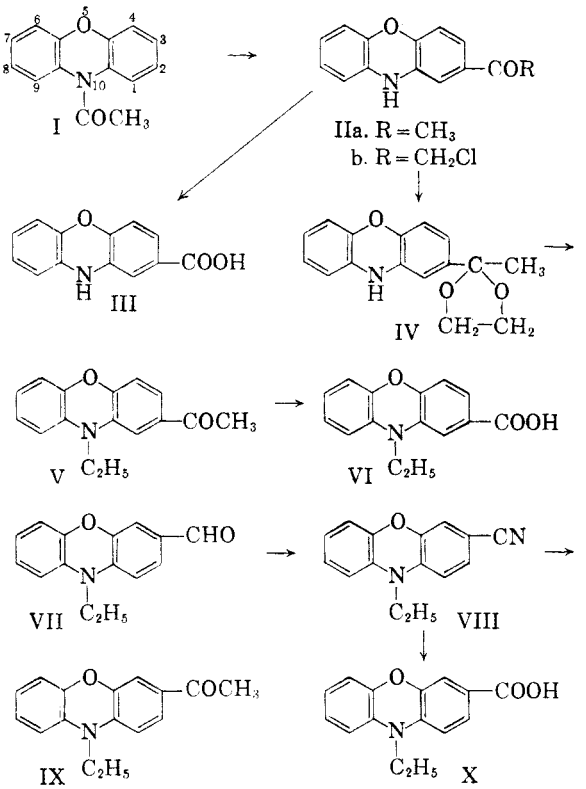
Several 2-acylphenoxazines have been prepared by a Friedel-Crafts reaction. The structure of these products is based on the examination of the infrared and ultraviolet spectra of 2- and 3-acetyl-10-ethylphenoxazine. Other 2-substituted phenoxazines also were synthesized.

Several C-monoacylphenoxazines were prepared by a Friedel-Crafts reaction with 10-acetylphenoxazine (I). Because no method is known for the transformation of phenoxazines into substances of known structure, the formulation of our reaction products is based on the infrared bands typical for substituted benzene derivatives and supported by a comparison of their ultraviolet spectra with those previously reported for phenothiazine.

Unsymmetrical trisubstituted benzene structures show a characteristic band in the 12.0–12.5 μ region, while vicinal trisubstituted derivatives have a band in the 12.5–13.15 μ region.[1,2,3] It has been shown that these bands are present in phenothi-

azines having a trifluoromethyl-[4,5,6,7] a fluoro-[5] or a methylmercapto- substituent.[8] These characteristic bands were also observed in the monomethylcarbazoles.[9]

The bands typical for 1,2,4-trisubstituted benzene derivatives were present in our acylphenoxazines. But, as both 2- or 3- substituted phenoxazines have this configuration, it was necessary to prepare compounds with these structures.



The direct ethylation of 2-acetylphenoxazine by heating with ethyl iodide, a method used for the preparation of 2-acetyl-10-ethylphenothiazine,[10] gave only starting material. It has already been observed that some phenoxazines are not acidic enough for ethylation under these conditions.[11]

It has been shown that alkylation of 2-acetylphenothiazine in the presence of sodamide gives poor yields, but that the same reaction could be effected after protection of the ketone group as a ketal.[12] The ethylenedioxy derivative of 2-acetylphenoxazine (IV) was prepared according to the method of Salmi[13] by azeotropic distillation of the ketone and ethyleneglycol in an inert solvent (benzene, toluene) in the presence of *p*-toluenesulfonic acid. The ketal was also prepared, in better yield, by acid catalysed exchange dioxolanation with 2-methyl-2-ethyl-1,3-dioxolane (butanone cycloethylene ketal).[14] From this ketal (IV), 2-acetyl-10-ethylphenoxazine (V) was prepared by ethylation in the presence of sodamide, followed by acid hydrolysis. 2-Acetyl-10-ethylphenoxazine was oxidized with sodium hypobromite to the corresponding acid (VI).

By analogy with observations in the carbazole[15] and phenothiazine series[16,17] the Vilsmeier-Haack reaction was expected to yield 3-formyl-10-ethylphenoxazine (VII). Its oxime was dehydrated to the nitrile (VIII). This product gave, by reaction with methylmagnesiumiodide, the corresponding acetyl derivative (IX). The nitrile was also hydrolysed to 3-carboxy-10-ethylphenoxazine (X), which had the melting point of the same product prepared by another method.[11b]

We had also hoped to prepare 3-acetyl-10-ethylphenoxazine by Friedel-Crafts acetylation of 10-ethylphenoxazine; but the product we obtained corresponded to analysis for a diacetyl derivative (formulated as 3,7-diacetyl-10-ethylphenoxazine). This structure is also supported by the infrared spectrum (Fig. 1, Curve D). The bands typical for a 1,2,4-trisubstituted benzene derivative (12.16 and 12.38 μ) are present, but the strong band in the 13.0–13.6 μ region, typical for an *o*-disubstituted benzene structure[3] is absent. The carbonyl band at 5.98 μ is also double. This result is in agreement with the work of Cauquil and Casadevall,[18] who proved that a Friedel-Crafts reaction with 10-methylphenothiazine gave 3,7-diacetyl-10-methylphenothiazine, and not 3-acetyl-10-methylphenothiazine, as has been stated.[19]

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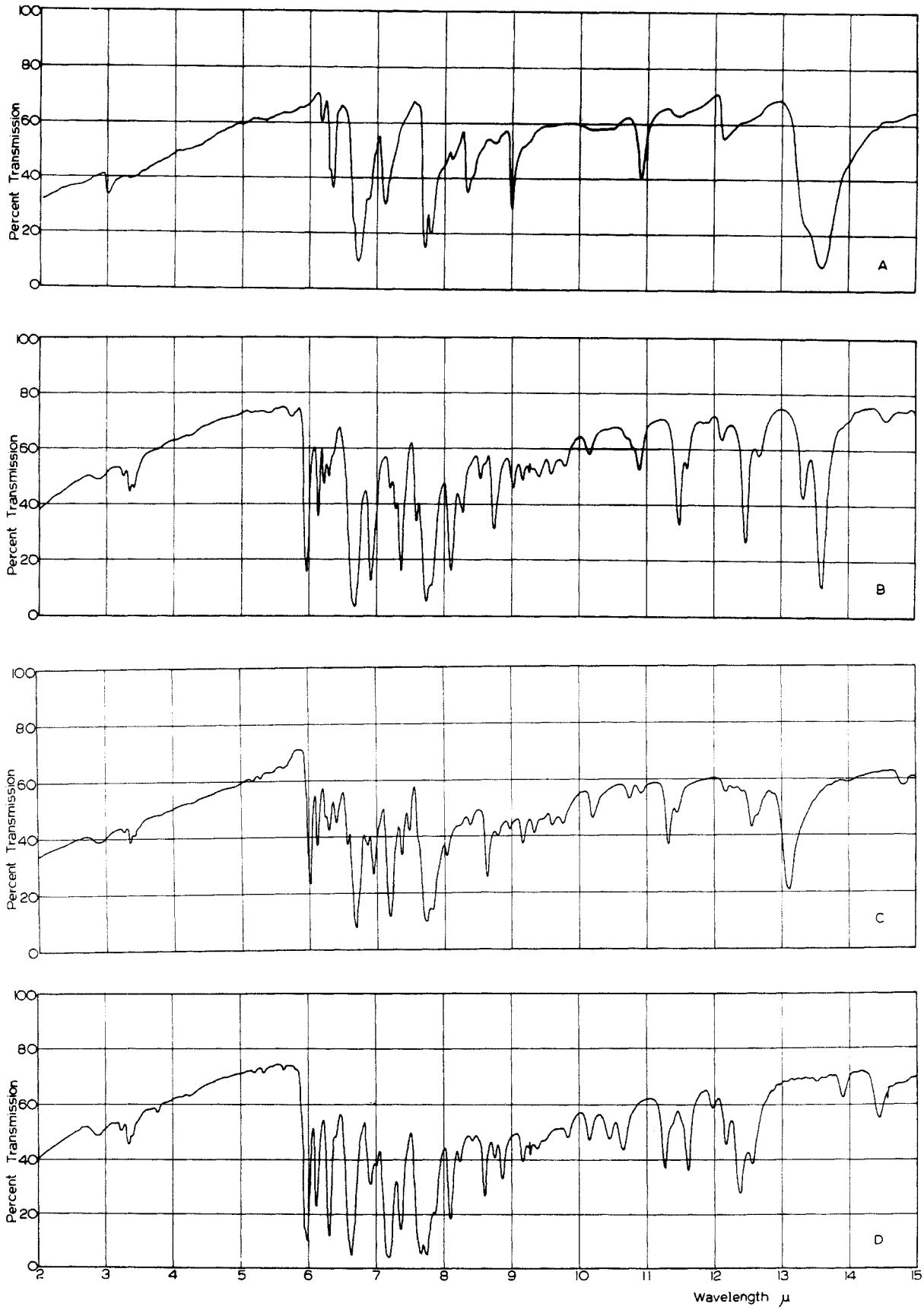


Fig. 1. Infrared spectra: curve A, phenoxazine; curve B, 2-acetyl-10-ethylphenoxazine (V); curve C, 3-acetyl-10-ethylphenoxazine (IX); curve D, 3,7-diacetyl-10-ethylphenoxazine. Concentration 0.5% in potassium bromide disks (approx. 0.5 mm. thick)

TABLE I

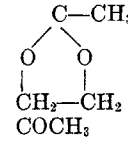
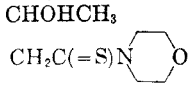
ULTRAVIOLET SPECTRA[a] OF ACETYLPHENOTHIAZINES AND -PHENOXAZINES

Phenothiazine	λmax. mμ (log ε)				
1 2-$COCH_3$	244.5 (4.42)		281.5 (4.44)		
2 2-$COCH_3$-10-C_2H_5	244.5 (4.35)		282.5 (4.33)		
3 3-$COCH_3$-10-CH_3	235 (4.24)	269 (4.33)	[285 (4.25)]		374 (3.74)
4 3,7-di($COCH_3$)-10-C_2H_5			289 (4.59)		400 (3.90)
Phenoxazine					
5 2-$COCH_3$	224 (4.32)		271 (4.49)	323 (3.84)	
6 2-$COCH_3$-10-C_2H_5	227 (4.30)	[260 (4.39)]	273 (4.48)	328 (3.95)	
7 3-$COCH_2$-10-C_2H_5		261 (4.38)	[274 (4.25)]		395 (4.11)
8 3,7-di($COCH_3$)-10-C_2H_5			273 (4.65)	334 (3.84)	418 (4.23)
9 2-$COCH_3$-10-$COCH_3$			244 (4.40)	279 (3.98)	

[a] Ultraviolet maxima were determined in ethanol solution. The figures between square brackets indicate a shoulder. The values for compounds 2-4 are taken from ref. 18.

TABLE II

SUBSTITUTED PHENOXAZINES

	Substituent				Yield,		Nitrogen	
	Y	X	Method[a]	M.P.°	%	Formula	Calcd.	Found
IIa	$COCH_3$	H	A	211–213	89	$C_{14}H_{11}NO_2$	6.63	6.70
	$C(=NOH)CH_3$	H	A	217–220 dec.		$C_{14}H_{12}N_2O_2$	11.66	11.63
	$COCH_3$	$COCH_3$	A	106–108		$C_{16}H_{13}NO_3$	5.24	5.50
IV		H	E	127–129	39	$C_{16}H_{15}NO_3$	5.20	5.50
					60			
V	$COCH_3$	C_2H_5	E	77–79	56	$C_{16}H_{15}NO_2$	5.53	5.75
	$C(=NOH)CH_3$	C_2H_5	A	153–156		$C_{16}H_{16}N_2O_2$	10.44	10.16
	$COCH_2CH_3$	H	A	215–216	92[b]	$C_{15}H_{13}NO_2$	5.85	5.95
	$CO(CH_2)_2CH_3$	H	A	197–198	90[c]	$C_{16}H_{15}NO_2$	5.53	5.72
	COC_6H_5	H	A	197–201	38	$C_{19}H_{13}NO_2$	4.87	5.08
IIb	$COCH_2Cl$	H	A	218–219	96	$C_{14}H_{10}ClNO_2$	5.37	5.50
	$COCH_2Cl$	$COCH_3$	A	158–159	90[d]	$C_{16}H_{12}ClNO_3$	4.62	4.98
III	COOH	H	E	252–254	88	$C_{13}H_9NO_3$	6.17	6.21
VI	COOH	C_2H_5	E	218–220	28	$C_{15}H_{13}NO_3$	5.48	5.21
	$COOC_2H_5$	H	E	200–202	95	$C_{15}H_{13}NO_3$	5.48	5.58
	C_2H_5	H	E	110–112	83	$C_{14}H_{13}NO$	6.63	6.70
	C_2H_5	$COCH_3$	E	45–48		$C_{16}H_{15}NO_2$	5.53	5.70
	$CHOHCH_3$	H	E	132–134		$C_{14}H_{13}NO_2$	6.16	5.89
		H	E	187–189 dec.	54	$C_{18}H_{18}N_2O_2S$	8.58	8.41
	CH_2COOH	H	E	192–193 dec.	83	$C_{14}H_{11}NO_3$	5.81	5.92

[a] A: prepared by the method (a) described for 2-acetylphenoxazine. E: see Experimental. [b] When an equimolecular amount of propionyl chloride was used, the yield was 56%. It was also prepared from 10-propionylphenoxazine (m.p. 99–101°). [c] An equimolecular amount of butyrylchloride gave 75%. [d] Was also prepared by refluxing (2 hr.) 2-chloroacetylphenoxazine in acetic anhydride.

The infrared spectra of 2- and 3-acetyl-10-ethylphenoxazine (Fig. 1 Curves B and C) show the maxima of 1,2,4-trisubstituted (12.48 and 11.28, 12.56, and 11.32 μ) and of 1,2-disubstituted benzene derivatives (13.60 and 13.10 μ). The bands of asymmetrically substituted benzene structures are also present in the spectra of the acids VI and X but are weak (*cf.* ref. 11b).

The assignment of structure is also supported by the ultraviolet spectra (Table I). Cauquil and Casadevall[18] have found that 3-acetylphenothiazines absorb at a much higher wave length than the corresponding 2-acetyl derivatives. The same is true for the phenoxazines. *N*-alkylation has practically no influence on the maxima (compounds 1–2 and 5–6). Similarly, phenothiazine (254 and 318 mμ[20]) and 10-ethylphenothiazine (256 and 310 mμ[21]) have practically the same maxima. *N*-acetylation brings about a shift of the maxima to a shorter wave length (compounds 5–9). The same phenomenon was also observed with 10-acetylphenothiazine (229 and 260 mμ).[21]

Our results show that, when the amino group of phenoxazine is deactived by acylation, substitution during the Friedel-Crafts reaction occurs in one benzene ring at the carbon atom in the position *para*

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to the oxide bridge. Substitution occurs also in position 2 with *N*-acetylcarbazole,[22,23] -phenothiazine,[10,24-27] and -9,10-dihydroacridine.[28] 2,8-Diacetylphenothiazine could only be obtained by using a large excess of aluminum chloride and acetyl chloride.[29]

Friedel-Crafts reaction with *N*-alkyl carbazole,[30] -phenothiazine,[18] and also -phenoxazine gives a diacetyl derivative, with the substituents in the position *para* to the imino group.

Carbazole itself gives a 3,6-diacetyl derivative.[30] Phenothiazine yields 10-acetyl- and 2,10-diacetylphenothiazine.[24] Substitution of phenoxazine occurs at the same place as with phenothiazine. The properties of our 2-acetylphenoxazine are identical with those described for a product obtained recently by the same method,[31] but it has been formulated, without proof, as 3-acetylphenoxazine.

2-Ethylphenoxazine was obtained by Wolff-Kishner reduction, and 1-(2-phenoxazinyl)ethanol by sodiumborohydride reduction of 2-acetylphenoxazine. (IIa).

2-Phenoxazinyl acetic acid was prepared by hydrolysis of the thiomorpholide, obtained by Willgerodt reaction with 2-acetylphenoxazine. The decarboxylation of this acid to 2-methylphenoxazine did not proceed satisfactorily.

2-Phenoxazine carboxylic acid (III) was prepared by alkaline hydrolysis of the pyridine addition product of 2-chloroacetyl-10-acetylphenoxazine (*cf.* ref. 25, 27, 32).

EXPERIMENTAL[33]

2-Acetylphenoxazine (IIa). (a). A suspension of 22.5 g. (0.10 mole) of 10-acetylphenoxazine in 400 ml. of carbon disulfide was added slowly and with stirring to 40 g. (0.3 mole) of powdered aluminum chloride. After refluxing for 1 hr., 11.7 g. (0.15 mol) of acetyl chloride was added at a rate sufficient to maintain boiling. The mixture was refluxed with stirring for another 2 hr. and, after cooling, the solvent was decanted. The gummy residue was decomposed with crushed ice and conc. hydrochloric acid. The precipitate was filtered, washed, and suspended in 200 ml. of glacial acetic acid and 50 ml. of 20% hydrochloric acid and refluxed for 10 min. The precipitate was filtered, washed with water, and dried, 22 g., m.p. 209–212°. By continuous extraction with 250 ml. of benzene, 20.2 g. (89%) of greenish yellow crystals were obtained, m.p. 211–213°.

When aluminum chloride was added to a suspension of equimolecular amounts of acetyl chloride and 10-acetylphenoxazine in carbon disulfide, the yield was only 55%.

In one experiment, *2,10-diacetylphenoxazine* was isolated before hydrolysis. Recrystallization in ethanol gave a white product with a melting point of 106–108°.

The *oxime* of 2-acetylphenoxazine was prepared by refluxing with hydroxylamine hydrochloride in pyridine-ethanol solution: m.p. 217–220° dec.

(b) A suspension of 2.6 g. of 2-chloroacetylphenoxazine and 3.2 g. zinc powder in 20 ml. of glacial acetic acid was heated with stirring at 90–95° during 2.5 hours. After refluxing for a short time, zinc was removed by filtration and washed with 10 ml. of hot acetic acid. After cooling, 1.7 g. (75%) of greenish-yellow crystals, m.p. 213–215°, were obtained.

(c) Aluminum chloride was added to a solution of phenoxazine and acetyl chloride in carbon disulfide, as described by Müller.[31] The portion boiling at 215–230°/17 mm. was recrystallized from ethanol and gave 5.5 g. of 10-acetylphenoxazine, m.p. 142–145°. The portion boiling at 255–280°/17 mm. gave upon recrystallization in ethanol, 5.5 g. of yellow crystals, m.p. 100–130°. This material was refluxed in 25 ml. acetic acid and 6 ml. of 20% hydrochloric acid for 10 min., and gave, upon cooling, 4.20 g. of a product melting at 212–214°. Recrystallization in ethanol yielded greenish-yellow crystals, m.p. 214–216°, undepressed upon admixture of 2-acetylphenoxazine prepared by method a.

Phenoxazine-2-carboxylic acid (III). A 54-g. sample (0.18 mole) of 2-chloroacetyl-10-acetylphenoxazine was dissolved by heating in 200 ml. of pyridine. The solution was kept at 90° for 10 min., cooled, and poured into 500 ml. dry ether. The precipitate was filtered, washed with 150 ml. of ether, and dissolved in 150 ml. of hot ethanol. The solution was made basic by adding 500 ml. of 10% sodium hydroxide solution, refluxed for 10 min., distilled under reduced pressure to remove most of the alcohol, and acidified with 20% hydrochloric acid, to yield 38 g. (88%) of a tan-colored product, m.p. 242–244°. Recrystallization in ethanol-water raised the melting point to 252–254°.

The acid was transformed into the *ethyl ester* by refluxing for 12 hr. in hydrochloric acid-absolute ethanol. The melting point of the dark green product was 200–202°.

2-Ethylphenoxazine. A mixture of 64.5 g. of 2-acetylphenoxazine and 53 ml. 80% hydrazine hydrate in 270 ml. of ethylene glycol was refluxed for 30 min. A solution of 48 g. of potassium hydroxide in 110 ml. of ethylene glycol was added and refluxed for another hour. Water and ethylene glycol were distilled until a boiling point of 190–195° was reached; refluxing was continued for 3 hr. The solution was cooled, and after adding 600 ml. of ethanol and 1200 ml. of water, the precipitate was collected. A small amount of product that had sublimed during distillation and refluxing was washed with dilute acid and filtered. The wet products were dissolved in benzene, the water layer was removed, and the organic solution was dried. After evaporation of the solvent, the product was distilled, 50 g. (83%) b.p. 170°/0.7 mm. m.p. 108–110°. After sublimation at 140° (bath temperature)/0.5 mm. the melting point of the white product was 110–112°.

2-Ethyl-10-acetylphenoxazine. 2-Ethylphenoxazine was refluxed (3 hr.) with acetic anhydride. The solution was decomposed with water, and after standing for several weeks, the product crystallized. After three recrystallizations in ethanol-water, the melting point was 45–48°.

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(33) All melting points are uncorrected. The microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany, and the infrared spectra were obtained by Dr. Z. Hainski, S.E.R.A.I. Laboratories, Brussels.

2,10-Diethylphenoxazine was a lightly colored oil, distilling at 160°/0.25 mm., that did not crystallize in the refrigerator. It was prepared by refluxing (3 hr.) equimolecular amounts of sodamide and 2-ethylphenoxazine in toluene with 1.6 moles of ethyl iodide. Ethylation in liquid ammonia gave a dark product, that decomposed upon distillation.

1-(2-Phenoxazinyl)ethanol. A 750-mg. sample of sodium borohydride dissolved in 20 ml. of isopropanol was added to a solution of 2.8 g. of 2-acetylphenoxazine in 80 ml. of dioxane. The mixture was stirred for 2 hr., then heated on the waterbath for an 1/2 hr.; after cooling, the excess hydride was decomposed with acid. After concentrating *in vacuo* and adding water, 2.25 g. of a product melting at 90–100° was obtained. After recrystallization in benzene-petroleum ether, and cyclohexane-benzene, the melting point of the light rose colored product was 132–134°.

Reduction with lithium aluminum hydride in ether gave only a very dark product. There was no uptake of hydrogen when a dioxane solution of 2-acetylphenoxazine was shaken in the presence of platinum (Adams) catalyst.

2-Acetylphenoxazine cycloethylene ketal (IV). (a) A mixture of 20 g. 2-acetylphenoxazine, 160 ml. ethylene glycol, 500 ml. toluene (distilled over sodium) and 600 mg. *p*-toluenesulfonic acid monohydrate was distilled during 7 hr. During the operation, the upper phase of the distillate was returned to the flask.

The contents of the flask were cooled, neutralized with a sodium bicarbonate solution, washed with water, and dried over sodium sulfate. The filtered solution was evaporated to dryness, under reduced pressure, and the residue was taken up with 200 ml. of benzene. The unchanged acetylphenoxazine (2 g.) was filtered and the filtrate was poured into a column of silica gel (2 cm. diameter, 18 cm. height). The ketal was eluted with benzene (500 ml.). After evaporation of the solvent 9.4 g. (39%) of greenish crystals, m.p. 118–126°, was obtained. After recrystallization in ethanol, the melting point was 127–129°.

(b) A mixture of 10 g. of 2-acetylphenoxazine, 100 ml. of 2-methyl-2-ethyl-1,3-dioxolane, and 500 mg. *p*-toluene sulfonic acid monohydrate was heated, and the liberated butanone, admixed with the reactant dioxolane, was distilled slowly through a short Vigreux column for a period of 5 hr. (15 ml. distillate). The contents of the reaction flask were diluted with 100 ml. of benzene, neutralized with sodium bicarbonate, and further worked up as described under a. Yield: 7.30 g. (60%), m.p. 120–126°.

2-Acetyl-10-ethylphenoxazine (V). To a solution of 10.8 g. (40 mmoles) of 2-acetylphenoxazine cyclo ethylene ketal in 15 ml. toluene were added 1.60 g. (40 mmoles) of sodamide, and the mixture was refluxed with stirring for 1/4 hr. A 10-g. sample (80 mmoles) of ethyl iodide was added and refluxing was continued for 2 hr. After washing with water and drying, the solvent was removed under reduced pressure and the residue was refluxed for 15 min. in 50 ml. ethanol and 10 ml. 3.5% hydrochloric acid solution. After diluting with water, the suspension was extracted with 500 ml. of benzene. The yellow insoluble product at the interphase was separated and identified as unchanged 2-acetylphenoxazine (0.64 g., m.p. 209–212°). The benzene solution, after washing and drying, was concentrated to a volume of 100 ml., and another 0.66 g. of 2-acetylphenoxazine, m.p. 208–216°, was filtered. The filtrate was poured onto a column of silica gel (diameter 2 cm., height 17 cm.), and the product was eluted with benzene. The solution was concentrated to a small volume and the product was precipitated by addition of petroleum ether, 5.7 g., m.p. 65–70°. After recrystallization in ethanol-water and in methanol, 4.0 g. of yellow crystals, m.p. 77–79°, was obtained.

An attempt to prepare 2-acetyl-10-ethylphenoxazine by heating 2-acetyl-phenoxazine with ethyl iodide in absolute ethanol at 120° gave only starting material.

10-Ethylphenoxazine-2-carboxylic acid (VI). A 2.37-g. sample (0.79 ml. = 15 mmoles) of bromine was dissolved in a cold (0°) solution of 1.60 g. (40 mmoles) of sodium hydroxide in 15 ml. water. A solution of 1.25 g. (5 mmoles) of 2-acetyl-10-ethylphenoxazine in 10 ml. dioxane was added, and the mixture was stirred at 0° for 30 min., and at room temperature for 60 min. The dioxane was distilled, under reduced pressure, at a bath temperature of maximum 50°, and the excess hypobromite was decomposed with a small amount of sulfite. The alkaline solution was extracted with ether; upon acidification of the aqueous solution, 400 mg. of a tan product, m.p. 215–217° dec., were obtained. Recrystallization in ethanol-water raised the melting point to 218–220°.

β-(2-Phenoxazinyl)thioacetomorpholide. A mixture of 11.2 g. (0.05 mole) of 2-acetylphenoxazine, 2.56 g. (0.08 mole) of sulfur, and 20 ml. freshly distilled morpholine was refluxed for 11 hr. After cooling overnight, 50 ml. of ethanol were added to the solid mass, which was filtered; 8.80 g. (54%) of a light tan product, m.p. 187–189° dec., were obtained. It was unchanged upon recrystallization in ethanol.

2-Phenoxazinyl acetic acid. A mixture of 8 g. β-(2-phenoxazinyl)thioacetomorpholide and 135 ml. of 10% alcoholic potassium hydroxide was refluxed for 14 hr. The solution was diluted with 270 ml. water and acidified with hydrochloric acid. The precipitate was filtered and crystallization from ethanol-water gave 5.2 g. (83%) of a tan product m.p. 185–189° dec. By recrystallization in ethanol the melting point was raised to 192–193°.

A 1-g. sample of the product was decarboxylated by heating at 195° in an oil bath. It was sublimed *in vacuo*, and the sublimate was taken up in benzene. The residue (140 mg.) obtained by evaporation of the solution, melted at 122–130°. It was resublimed *in vacuo*, and recrystallized, but the melting point remained undefinite (128–140°).

3-Formyl-10-ethylphenoxazine (VII). A mixture of 31 g. of 10-ethylphenoxazine, 21 g. of *N*-methylformanilide, 21 g. of phosphorus oxychloride, and 30 ml. *o*-dichlorobenzene was heated on the steambath for 4 hr. After addition of a solution of 90 g. of sodium acetate in 200 ml. water, the volatile products were removed by steam distillation. The residue was dissolved in a large volume of benzene. This solution, after drying, gave upon concentration, 11.3 g. of green crystals, m.p. 130–132°. A further crop was obtained by adding petroleum ether to the filtrate; 19 g., m.p. 110–115°. By recrystallization in an ethanol-benzene-petroleum ether mixture 6.0 g. of a product, m.p. 127–133°, were obtained. Total yield: 50%.

10-Ethylphenoxazine-3-aldoxime. A mixture of 12 g. (50 mmoles) of 3-formyl-10-ethylphenoxazine and 10.35 g. (150 mmoles) of hydroxylamine hydrochloride was warmed with 75 ml. of pyridine for 30 min. The mixture was poured into water and the green crystals were filtered, 12.5 g., m.p. 152–154°, unchanged upon recrystallization in ethanol-water.

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: N, 11.02. Found: N, 10.87.

3-Cyano-10-ethylphenoxazine (VIII). A 16.9-g. sample of 10-ethylphenoxazine-3-aldoxime was refluxed with 160 ml. acetic anhydride for 2 hr. The solution was poured into ice water and the product was extracted with ether. The solution was washed, dried, and evaporated, and the residue was distilled *in vacuo* (1.5 mm.) 10.5 g. (67%), m.p. 123–125°, unchanged upon recrystallization in ethanol-water.

Anal. Calcd. for $C_{15}H_{13}N_2O$: N, 11.81. Found: N, 11.95.

3-Carboxy-10-ethylphenoxazine (X). A solution of 1.78 g. of 3-cyano-10-ethylphenoxazine in 75 ml. of ethanol was refluxed with 18 ml. of 20% sodium hydroxide solution for 7 hr. The mixture was diluted with 18 ml. of water, the ethanol was distilled and the solution was acidified. The oily precipitate became solid after stirring with dilute hydrochloric acid. The product was filtered and gave upon crystallization in ethanol-water 1.30 g. (65%) of tan colored crystals, m.p. 200–202° dec. Further recrystallization in the same solvent mixture raised the melting point to 204–206°. Gilman and Moore[11b] give 207.5–210.5° for the same product prepared by a different method.

Anal. Calcd. for $C_{15}H_{13}NO_3$: N, 5.48. Found: N, 5.59.

The acid was transformed into the ethyl ester by refluxing for 20 hr. with hydrochloric acid-absolute ethanol. The melting point of the green crystals, after recrystallization in ethyl acetate–petroleum ether, was 86–89°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: N, 4.94. Found: N, 5.09.

3-Acetyl-10-ethylphenoxazine (IX). A 0.72-g. sample (30 mmoles) of magnesium was treated in a nitrogen atmosphere, with 0.426 g. (20 mmoles) of methyl iodide in 15 ml. of anhydrous ether. A solution of 4.8 g. (20 mmoles) of 3-cyano-10-ethylphenoxazine in 50 ml. of benzene was added and refluxed with stirring for 2 hr. After cooling to 0°, 10 ml. of 6*N* hydrochloric acid was slowly added, and the mixture was refluxed, with stirring, for 6 hr. The benzene layer was removed, the brown precipitate was filtered and dissolved in ethanol. The solution was acidified with 10 ml. of 6*N* hydrochloric acid and refluxed for 6 hr. After diluting with water, the product was extracted with benzene. The combined benzene solutions were washed, dried, and evaporated. The residue was distilled *in vacuo* (250°/0.7 mm.). The product (2.43 g., m.p. 145–150°) was recrystallized from ethanol, and gave 1.8 g. (33%) of yellow crystals, m.p. 153–154°.

Anal. Calcd. for $C_{16}H_{15}NO_2$: N, 5.53. Found: N, 5.48.

The melting point of the *oxime* is 175–178°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: N, 10.44. Found: 10.66.

3,7-Diacetylphenoxazine. To a solution of 18 g. (0.085 mole) of 10-ethylphenoxazine and 6.89 g. (0.085 mole) of acetyl chloride in 300 ml. of carbon disulfide were added, slowly and with stirring, 34.5 g. (0.26 mole) of powdered aluminum chloride. After refluxing, with agitation, for 8 hr., the solvent was decanted and the residue was decomposed with crushed ice and conc. hydrochloric acid. The oily layer was extracted with ether; this solution gave, after evaporation and purification over a column of silica gel, 5 g. of unchanged 10-ethylphenoxazine. The ether insoluble residue (7.70 g., m.p. 160–165°) was extracted with benzene. The green insoluble product (2.2 g., m.p. 170–174°) gave upon recrystallization in ethanol 3,7-diacetyl-10-ethylphenoxazine, m.p. 178–180°. The benzene solution was filtered through a silica gel column and another 0.5 g. of unchanged 10-ethylphenoxazine was eluted with benzene. The 3,7-diacetyl-10-ethylphenoxazine was eluted with acetone. After evaporation and crystallization in ethanol, 2 g. of yellow green crystals, m.p. 178–180°, were obtained. The solutions of this product were strongly fluorescent.

Anal. Calcd. for $C_{18}H_{17}NO_3$: N, 4.76. Found: N, 5.26.

The *oxime* was prepared by reaction with hydroxylamine hydrochloride in pyridine-ethanol, and had melted at 236–237° dec.

Anal. Calcd. for $C_{18}H_{19}N_3O_3$: N, 12.96. Found: N, 12.28.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Preparation of Substituted 4,9-Naphth(2,3)imidazolediones

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A number of substituted 4,9-naphth(2,3)imidazolediones have been synthesized. Solubility in fatty oils has been increased by introducing substituents of high carbon and hydrogen content in the 2- position. Increased solubility in water was effected by introducing the hydroxyl or carboxyl group in the side chain in the 2- position and by introducing an amino group into the 5- position.

A number of 2-substituted-4,9-naphth(2,3)-imidazolediones have been prepared by Hoover and Day.[1] Certain of these compounds have a marked inhibiting effect on the growth of mutant microorganisms.[2]

In general, the 2-substituted-4,9-naphth(2,3)-imidazolediones are difficultly soluble and are not easy compounds to test. In this particular investigation it was decided to introduce substituents which would increase either solubility in fats or solubility in water. Long chain alkyl groups were introduced into the 2- position. 2-Dodecyl-, 2-hexadecyl-, and 2-chaulmoogryl-4,9-naphth(2,3)-imidazoledione were preparred by the general procedure described by Hoover and Day.[1] These compounds, compared with the 2-methyl derivative, are more soluble in fatty oils. 2-(2′-Phenylvinyl)-4,9-naphth-(2,3)imidazoledione, and 2-hydroxymethyl-4,9 naphth(2,3)imidazoledione were prepared by the same procedure. The last two were prepared as possible intermediates for making other compounds. It is interesting to note that the 2-hydroxymethyl compound is quite unreactive and it was impossible to make the corresponding chloromethyl or bromomethyl compound by the usual methods. The unreactivity of the 2-hydroxymethyl derivative in this series is similar to the unreactivity of 2-hydroxymethylnaphth(2,3)-imidazole noted by Brown.[3]

The preparation of these compounds may be outlined as follows:

2,3-dichloro-1,4-naphthoquinone $\xrightarrow[C_2H_5OH]{NH_3}$ 2-amino-3-chloro-1,4-naphthoquinone (I)

I + RCOCl ⟶ 2-acylamino-3-chloro-1,4-naphthoquinone (II)

II in $C_6H_5NO_2$ + NH_3 ⟶ 2-acylamino-3-amino-1,4-naphthoquinone (III)

III + NaOH ⟶ 2-substituted-4,9-naphth(2,3)imidazoledione

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