hydrochloric acid normality of 1.0 or 1.2. At this normality the vast majority of the 4-aminoazobenzene dyes show slight changes in the C_ϵ/A_ϵ ratio with a change in normality. For more basic compounds (such as 4'-amino DAB) this ideal plateau would be found at a lower normality. The ideal situation would be to obtain C_ϵ/A_ϵ values at the lowest normality at which a 100% of the monocationic salt was present. It is felt that the determination of the C_ϵ/A_ϵ ratio at a normality of 1.0 to 1.2 in most cases is close to the ideal situation and, although less accurate, is a much simpler procedure. Consequently it would be of greater value for the determination of the structure of an unknown azo dye.

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[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

Ultraviolet-Visible Absorption Spectra of Quinoxaline Derivatives[1]

EUGENE SAWICKI,[2] BARBARA CHASTAIN, HAZEL BRYANT, AND ALBERT CARR

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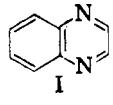
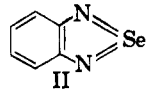
Over forty ultraviolet-visible absorption spectra of fifteen quinoxaline derivatives have been determined in alcoholic and acidic solutions. The spectra and the structure of the cations are discussed. Several new quinoxaline derivatives have been prepared.

In a previous paper[3] a number of 2,1,3-benzoselenadiazoles or piaselenoles, were prepared as possible purine antagonists. The spectra of the piaselenole derivatives were also investigated in the hope of shedding more light on the spectral properties of biologically important heterocyclic ring systems. For this reason it was decided to investigate the spectral properties of the quinoxalines, which are potential folic acid antagonists.

If one considers the tetravalent organoselenium atom, =Se=, as being somewhat similar to the =CH—CH= group, then a striking resemblance is evident between quinoxaline, I, and the tetravalent selenium structure of piaselenole, II. Like the



I



II

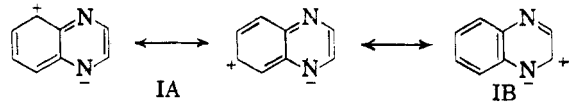
piaselenoles, quinoxaline derivatives form monocationic and dicationic salts. The dicationic salts usually absorb at the longest wave length and the bases at the shortest wave length.

In 2,3-dimethyl- or 2,3-diphenyl-quinoxaline substitution of an electron-donor group in the 6-position causes an increasing bathochromic shift in the order H < OCH_3 < C_6H_5 < SCH_3 < NH_2 for the base and monocationic forms and, except for the more strongly basic amino compound, for the dicationic compounds, Table I. The same order has been found for the analogously substituted 2,1,3-benzoselenadiazole derivatives[3] and in *para* substituted triphenylmethane dyes.[9] The fused benzene ring in 2,3-diphenyl-1,4-diazaanthracene is approximately equivalent in electron-donor properties to the 6-methoxy group as shown by the spectral data, Table I.

The sequence of proton addition in the 6-substituted quinoxalines (in the absence of an amino group) is shown in the spectra of 6-methylthio-2,3-diphenylquinoxaline, Fig. 1. In the important zwitterionic resonance structures of this compound, the 4-nitrogen is the electron-attracting resonance terminal and consequently has the greatest electron density and thus attracts the first proton.

In 2,3-symmetrically disubstituted quinoxalines the bathochromic shift increases in the series H < CH_3 < C_6H_5 < $C_6H_4OCH_3$ < $C_6H_3O_2CH_2$ < CH = CH — C_6H_5 < $(CH = CH)_2C_6H_5$[10] < $(CH = CH)_3C_6H_5$.[10]

Some of the zwitterionic resonance forms which are strong contributors to the excited state are



IA IB

Thus substitution of an electron-donor group in the 2,3,5,6,7 or 8 positions should cause the excited state structure to be of lower energy than IA or IB because the substituent(s) would accept the positive charge much more readily than would the unsubstituted position and consequently the compound(s) would absorb at longer wavelength.

The quinoxaline derivatives formed monocationic salts in 50% alcoholic 6*N* hydrochloric acid with the exception of the amino derivatives which

(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

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(3) E. Sawicki and A. Carr, *J. Org. Chem.*, **22**, 503 (1957).

(4) R. Bost and E. Towell, *J. Am. Chem. Soc.*, **70**, 903 (1948).

(5) H. Goldstein and M. Streuli, *Helv. Chim. Acta*, **20**, 650 (1937).

(6) F. Bell and J. Kenyon, *J. Chem. Soc.*, 2708 (1926).

(7) H. Gilman and H. Broadbent, *J. Am. Chem. Soc.*, **70**, 2619 (1948).

(8) G. Bennett and G. Willis, *J. Chem. Soc.*, 1960 (1928).

(9) N. Deno, J. Jaruzelski, and A. Schriesheim, *J. Org. Chem.*, **19**, 155 (1954).

(10) F. Bohlmann, *Chem. Ber.*, **84**, 860 (1951).

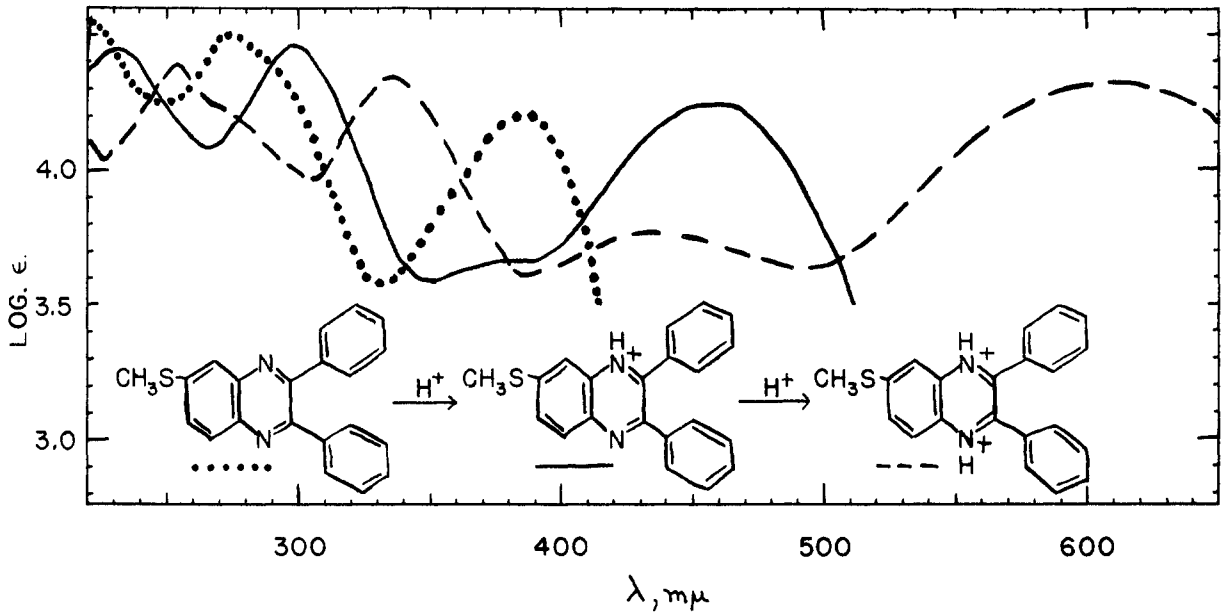
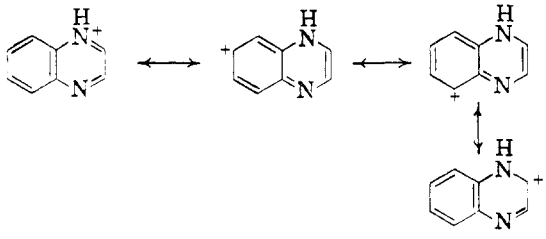


Fig. 1. Ultraviolet-visible Absorption Spectra of 2,3-Diphenyl-6-methylmercaptoquinoxaline in 95% Ethanol (.....); 50% Alcoholic 6*N* Hydrochloric Acid (— · — ·) and 95% Sulfuric Acid (– – – –).

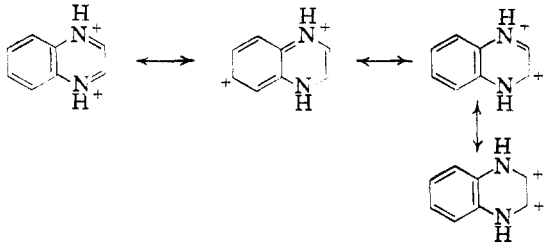
will be subsequently discussed. In the monocationic compounds the cationic resonating structures contributing to the overall structure are



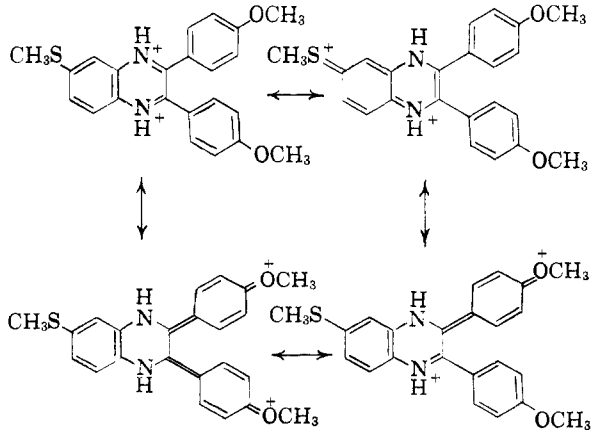
Because of a lack of separation of charge, there is a bathochromic shift as compared to the analogous base.

The quinoxaline derivatives formed dicationic salts in 95% sulfuric acid except for the amino compounds which formed tricationic salts. Bennett and Willis[11] have reported the color in sulfuric acid of some 28 2-styryl- and 2,3-distyryl quinoxaline derivatives substituted in the styryl benzene ring. The effect of increasing the length of conjugation by a CH=CH group in the dicationic symmetric salts is to push the long wave length band approximately 60–100 mμ into the visible.

In the dicationic compounds some of the dicationic resonating structures contributing to the overall structure are



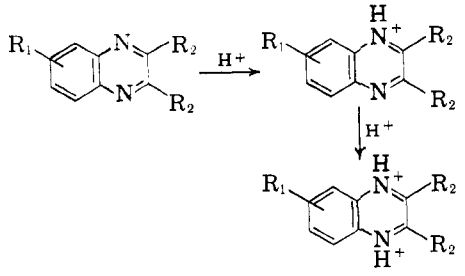
The bathochromic shift in these salts is apparently due to the greater amount of resonance in the excited state compared to the analogous monocationic salts. Substitution of electron-donor groups in both the aromatic and heterocyclic rings causes a much greater bathochromic shift than the presence of similar electron-donor groups in only the aromatic or heterocyclic rings, Table I. In this respect 2,3-bis-4′-methoxyphenyl-6-methylthioquinoxaline absorbs at the longest wave length in strong acid solution, Table I. Some of the dicationic resonating structures which account for the long wave length absorption of this compound in 95% sulfuric acid are shown below.



The spectra of the aminoquinoxalines in strong acid solution are exceptional because of the greater basicity of the amino group as compared to the phenyl, methoxy, or methylthio groups. The spectrum of 6-amino-2,3-diphenylquinoxaline, III, in alcohol contains a long wavelength band at 407 mμ which shifts to 492 mμ in 50% alcoholic 1.2*N* hydrochloric acid, Fig. 2 and Table I. In the same

(11) G. Bennett and G. Willis, *J. Chem. Soc.*, 256 (1929).

TABLE I



R_1	R_2	M.P., °C.	λ_{max} (log ϵ) 95% EtOH	50% EtOH 6*N* HCl	95% H_2SO_4
H	CH_3	105–106[a]	237 (4.39)[b]	247 (4.42)	220 (3.96)
			315 (3.84)	340 (4.03)	255 (4.42)
					362 (4.17)
6-CH_3O	CH_3	99–100[a]	248 (4.28)	260 (4.27)	268 (4.29)
			340 (3.91)	340[c] 3.66)	370 (3.85)
				377 (3.91)	448 (3.90)
6-CH_3S	CH_3	76–78	262 (4.39)	225 (4.32)	237 (4.30)
			360 (3.86)	280 (4.30)	306 (4.31)
				340 (3.38)	380 (3.43)
				419 (3.87)	560 (3.95)
H	C_6H_5	124–125[a]	244 (4.53)[b]	255 (4.53)	225 (4.19)
			265 (4.36)	280 (4.08)	270 (4.50)
			345 (4.07)	390 (4.13)	*380* (3.72)
					470–475 (4.16)
H	C_6H_5, 4′-$C_6H_4NMe_2$	121–122[a]	235 (4.54)	245 (4.62)[d]	220 (4.18)
			310 (4.26)	265 (4.35)	270 (4.46)
			406–409 (4.06)	345 (4.07)	375 (3.73)
				410 (2.54)	460 (4.11)
				530–535 (2.21)	
6.7-$(CH)_4$	C_6H_5	187–189[e]	232 (4.59)	240 (4.58)	252 (4.44)
			275 (4.72)	295 (4.60)	325 (4.46)
			305 (4.52)	422 (4.28)	510 (4.36)
			388 (4.10)		
6-CH_3O	C_6H_5	155–156[a]	228 (4.43)	~224 (4.35)	254 (4.33)
			255 (4.52)	270 (4.43)	284 (4.32)
			275 (4.30)	420 (4.21)	300 (4.21)
			366 (4.15)		400 (3.69)
					516–520 (4.29)
6-C_6H_5	C_6H_5	148[f]	268 (4.62)	233 (4.33)	255 (4.26)
			365 (4.02)	288 (4.51)	287 (4.30)
				418 (4.24)	324 (4.28)
					546–554 (4.26)
6-CH_3S	C_6H_5	144–145	272 (4.50)	232 (4.45)	253 (4.39)
			385 (4.20)	297 (4.46)	270 (4.22)
				378 (3.65)	335 (4.35)
				458 (4.23)	435 (3.76)
					610 (4.31)
6-NH_2	C_6H_5	176–178[g]	245 (4.37)	242 (4.41)[h]	225 (4.29)
			265 (4.35)	294 (4.30)	270 (4.50)
			292 (4.41)	355 (3.84)	380 (3.75)
			407 (4.00)	492 (4.00)	480 (4.15)
5-NH_2-7-Cl[d]	C_6H_5	214–215	230 (4.37)	247 (4.47)[i]	230 (4.22)
			267 (4.27)	270 (4.25)	262 (4.31)
			305 (4.55)	290 (4.17)	282 (4.15)
			355 (3.64)	355 (4.03)	435–440 (4.07)
			402 (3.40)	520 (2.64)	520 (3.45)
H	4-CH_3O-C_6H_4	148–149[a]	250 (4.63)	222 (4.51)	545 (4.21)[i]
			282 (4.29)	265 (4.51)	
			370 (4.15)	300 (4.15)	
				435 (4.15)	

TABLE I (*Continued*)

H	3,4-CH_2O_2-C_6H_3	199–200[k]	224 (4.63) 247 (4.44) 265 (4.34) 295 (4.12) 375 (4.09)	230 (4.51) 255 (4.34) 290 (4.26) 447 (4.02)	555–570 (4.09)[j]
H	C_6H_5CH=CH	193–194[l]	304 (4.64)[b] 345 (4.38) 395 (4.26)	230 (4.29) 310 (4.48) 448 (4.29)	240 (4.17) 342 (4.30) 370 (4.20) 546–554 (4.33)
6-CH_3S	4-CH_3O-C_6H_4	144–145	220 (4.58) 225 (4.59) 240 (4.39) 275 (4.53) 285 (4.49) 396 (4.30)	226 (4.39) 265 (4.20) 296 (4.38) 396 (3.55) 480 (4.29)	245 (4.20) 290 (4.26) 320 (4.26) 348 (4.30) 480–490 (3.82) 650 (4.43)

[a] Reference 4. [b] In methanol—F. Bohlmann, *Chem. Ber.*, **84**, 860 (1951). [c] All underlined values are shoulders. [d] In 50% alcoholic 0.1*N* hydrochloric acid. In 50% alcoholic 1.2*N* hydrochloric acid λ_{max} (log ϵ) values are 255 (4.54); 280 (4.15); 384 (4.16). [e] Reference 5. [f] Reference 6. [g] Reference 7. [h] In 50% alcoholic 1.2*N* hydrochloric acid. In 50% sulfuric acid λ_{max} (log ϵ) values are 254 (4.44); 290 (3.99); 405 (4.03). [i] In 50% alcoholic 1.2*N* hydrochloric acid. In 50% sulfuric acid λ_{max} (log ϵ) values are 228 (4.35); 260 (4.46); 280 (4.20); 417 (4.17). [j] Unstable solution. Spectrum below 360 mμ not determined. [k] Reference 3. [l] Reference 8.

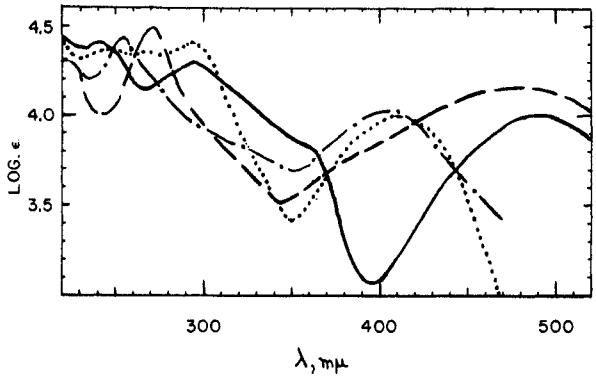
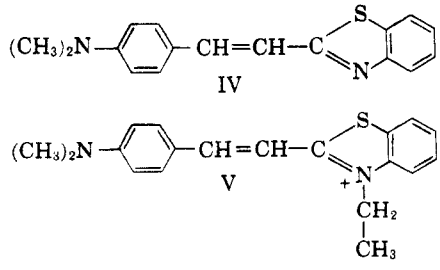
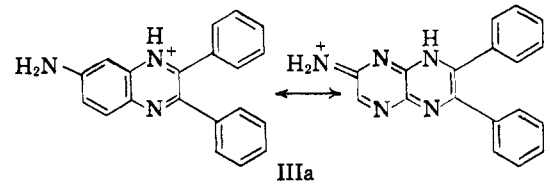


Fig. 2. Ultraviolet-visible Absorption Spectra of 2,3-Diphenyl-6-aminoquinoxaline in 95% ethanol (. . . . .); 50% alcoholic 1.2*N* hydrochloric acid (——); 50% sulfuric acid (— · — ·); and 95% sulfuric acid (– – – –).

manner the base 2-*p*-dimethylaminostyrylbenzothiazole, IV, λ_{max} 400 mμ, absorbs at a much shorter wave length than its ethiodide, V, λ_{max} 524 mμ, when compared in methyl alcoholic solution.[12]



Both the bases, III and IV, contain a zwitterionic resonance system (associated with the long wave length band at about 400 mμ) involving a chain of 9 atoms with the electron-donor amino nitrogen and the electron attractor heterocyclic nitrogen (*e.g.*, the 4-nitrogen of III) as the main resonance terminals. On the other hand V, the monocationic form of IV, involves a lower energy cationic resonating system with the amino and heterocyclic nitrogens as resonance terminals. Unlike the salts there is an expenditure of energy necessary for the separation of charge in the excited state of the bases. Thus, in the salt there is a "closing up" of energy levels as compared to the base. This explains the absorption at longer wave length of the salts as compared to the bases. In the same way III in 1.2*N* hydrochloric acid must contain the monocationic salt, IIIa, with a resonance system fairly similar to V, *e.g.*, IIIa.



IIIa

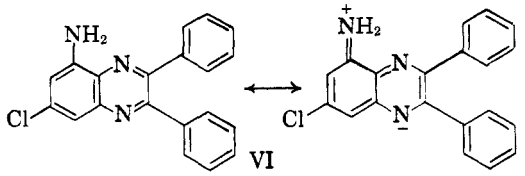
It is possible that in this same solution the tautomer involving proton addition to the amino nitrogen might be present to a smaller extent. This is implied by the presence of the strong shoulder at 355 mμ. The iso-*pi*-electronic 2,3-diphenylquinoxaline has its long wave length band at 345 mμ.

The spectrum of III in 50% sulfuric acid is closely similar to the spectrum of the monocationic salt of 2,3-diphenylquinoxaline in 50% alcoholic 6*N* hydrochloric acid, Table I. Consequently the second proton must add to the amino nitrogen of III. The spectrum of III in 95% sulfuric acid is closely similar to the spectrum of the dicationic salt of 2,3-diphenylquinoxaline in the same solvent. This means that in this strong acid solution a third proton must add to the remaining basic nitrogen of III.

In 2,3-diphenyl-5-amino-7-chloroquinoxaline, VI,

(12) L. Brooker and R. Sprague, *J. Am. Chem. Soc.*, **63**, 3203 (1941).

the zwitterionic resonance system associated with the long wavelength band contains an *o*-quinone ring system, *e.g.*



VI

The proton could be expected to add to the 1-nitrogen, but, just as in 2-aminoazobenzene as compared to 4-aminoazobenzene, and 4-aminopiaselenole as compared to 5-aminopiaselenole, the basicity of the electropositive amino nitrogen as compared to the electronegative nitrogen in the compounds containing an *o*-quinone zwitterionic resonance system is proportionally greater than the analogous basicities of the compounds containing the *p*-quinone zwitterionic resonance system. For example, the addition of the first proton to 4-aminopiaselenole goes to the amino nitrogen while in 5-aminopiaselenole it goes to the 3-nitrogen.[3] In 2-aminoazobenzene the first proton adds to the amino nitrogen while in 4-aminoazobenzene a mixture of monocationic tautomers is obtained consisting of two tautomers, one with the proton added to the amino nitrogen and the other with a proton attracted to the azo nitrogen furthest from the amino nitrogen.[13]

Fitting in with all these data the absorption spectrum of VI in 50% alcoholic 1.2*N* hydrochloric acid shows the presence of two tautomers, the minor one involving proton addition to the 1-nitrogen and containing bands at 520 and 300 mμ, and the other involving proton addition to the amino nitrogen with bands at 355 and 245 mμ and a shoulder at about 270 mμ. This latter tautomer would be expected to be closely similar spectrally to 2,3-diphenylquinoxaline which has bands at 345 and 244 mμ and a shoulder at 265 mμ (Table I). The spectrum of VI in 95% sulfuric acid has a strong band at 440 mμ which is due to the presence of a large amount of the dicationic salt and a weaker shoulder at about 520 mμ which is due to the tricationic salt. Except for the latter shoulder, the spectrum is closely similar to the spectra of the dicationic salt of VI and the monocationic salt of 2,3-diphenylquinoxaline. In the 4-amino compound the addition of the third proton is strongly repelled because of the resulting steric hindrance and neighboring positive charges.

2-4′-Dimethylaminophenyl-3-phenylquinoxaline in 50% alcoholic 0.1*N* hydrochloric acid has an ultraviolet spectrum closely similar to the spectrum of 2,3-diphenylquinoxaline in alcohol, Table I. This means that the first proton adds to the amino nitrogen. The two weak bands in the visible are due either to impurities or possibly to a very small amount of the tautomer involving proton addition to the 1-nitrogen. In 50% alcoholic 1.2*N* hydrochloric acid a second proton adds to give a dicationic salt (with a proton on the amino nitrogen and a proton possibly on the 4-nitrogen) closely similar spectrally to the monocationic salt of 2,3-diphenylquinoxaline. In 95% sulfuric acid a tricationic salt is formed iso-*pi*-electronic and spectrally similar to the dicationic salt of 2,3-diphenylquinoxaline, Table I.

(13) E. Sawicki, *J. Org. Chem.*, **21**, 605 (1956).

EXPERIMENTAL[14]

2,3-Diphenyl-5-amino-7-chloroquinoxaline. A fine suspension of 18.8 g. of 1,2-diamino-3-nitro-5-chlorobenzene was added to a solution of 90 g. of stannous chloride dihydrate in 100 ml. of concentrated hydrochloric acid. The solution was evaporated to one-half volume, cooled, and filtered. The crystals were washed with concentrated hydrochloric acid, methanol, and then ether. Twenty-one grams of 1,2,3-triamino-5-chlorobenzene dihydrochloride was obtained.

Equivalent amounts of the dihydrochloride and benzil were allowed to react in aqueous methanol. Two crystallizations from ethanol gave a 75% yield of bright yellow crystals of the quinoxaline, m.p. 214–215°. The compound had a green fluorescence in acetone.

Anal. Calcd. for $C_{20}H_{14}ClN_3$: N, 12.7. Found: N, 12.5.

2,3-Dimethyl-6-methylthioquinoxaline. 1,2-Diamino-4-methylthiobenzene hydrochloride and 2,3-butanedione were reacted in aqueous methanol. Crystallization from hexane gave an 80–85% yield of yellow crystals, m.p. 76–78°.

Anal. Calcd. for $C_{11}H_{12}N_2S$: N, 13.7. Found: N, 13.8.

2,3-Diphenyl-6-methylthioquinoxaline. 1,2-Diamino-4-methylthiobenzene hydrochloride and benzil were allowed to react in aqueous methanol. Crystallization from heptane gave a 90% yield of bulky yellow crystals, m.p. 144–145°.

Anal. Calcd. for $C_{21}H_{16}N_2S$: C, 76.8; H, 4.88; N, 8.54. Found: C, 76.5; H, 4.81; N, 8.50.

2,3-Di-4′-methoxyphenyl-6-methylthioquinoxaline. Equivalent amounts of 1,2-diamino-4-methylthiobenzene hydrochloride and *p*-anisil were refluxed in acetic acid for 30 min. Addition of excess water and fractional crystallization of the precipitated solid from heptane gave 40–50% yield of yellow needles, m.p. 144–145°.

Anal. Calcd. for $C_{23}H_{20}N_2O_2S$: N, 7.22. Found: N, 7.15.

Absorption spectral data. The spectra of all compounds were measured with a Beckman Model DU spectrophotometer. The 50% alcoholic 6*N* hydrochloric acid solution consisted of 50 ml. of concentrated hydrochloric acid diluted to 100 ml. with 95% ethanol; 50% sulfuric acid consisted of 50 ml. of concentrated sulfuric acid diluted to 100 ml. with 95% ethanol; 95% sulfuric acid consisted of 5 ml. of 95% ethanol diluted to 100 ml. with concentrated sulfuric acid.

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(14) Melting points are uncorrected. Analyses are by the Peninsular ChemResearch, Inc., Gainesville, Fla.