crystallized from ethanol to give 63 g. (83%) of crude product. Recrystallization from acetone and from ethanol gave material m.p. 150–151° (diacetyl derivative m.p. 181–182°).

Breakdown of N,N′-Diaryltrimethylenediamines.—Decomposition of the diamines (0.1–0.2 mole) was carried out in a simple Claisen distillation apparatus at *ca.* 250° and 20 mm. The catalyst was added as 48% hydrobromic acid. Heating was continued until little further material distilled. The distillate (86–90% of original weight except for the *o*-tolyl- and 2-naphthyldiamines for which it was *ca.* 80%) was fractionated and the final separation of intermediate fractions was achieved by chemical methods. With these mixtures, Hickinbottom's method[7] of separating primary amines as their zinc chloride complexes proved far less satisfactory than the Hinsberg method.

The tetrahydroquinolines obtained from the phenyl-, *o*-tolyl-, *p*-tolyl-, and naphthyldiamines were fully characterized by physical constants, infrared spectra, preparation of derivatives, and dehydrogenation to the corresponding quinolines. The tetrahydroquinoline fraction from the breakdown of N,N′-di-*m*-tolyltrimethylenediamine had b.p. 144–150° at 17 mm.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.6; H, 8.85; N, 9.5. Found: C, 81.8; H, 8.45; N, 9.3.

It was separated into components using a Beckman "Megachrom" gas chromatograph, with columns packed with 35% w./w. Apiezon J on C22 firebrick and with a column temperature at 180°. The first fraction (60% of total) was 7-methyltetrahydroquinoline; its benzoyl derivative had m.p. 77–78° and its hydrochloride had m.p. 205–206° (literature values are 70–72° and 175°, respectively). The second fraction (40% of total) was 5-methyltetrahydroquinoline; benzoyl derivative m.p. 125–126°, hydrochloride m.p. 239–240° (literature values are 121° and 238–240°, respectively).

The julolidines obtained in the decomposition were:

Julolidine, b.p. 130–140° at 7 mm., m.p. 37° (from acetone). Analytical figures were good and the compound gave a picrate of m.p. 173°, a methiodide of m.p. 218° and a hydrochloride of m.p. 211° (literature figures are 171, 186, and 218°, respectively).

9-Methyljulolidine[8] (from N,N′-di-*p*-tolyltrimethylenediamine), b.p. 158–160° at 10 mm.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.15; H, 9.05; N, 7.95.

This compound gave a picrate of m.p. 167°, a methiodide of m.p. 230° and a hydrochloride of m.p. 230°.

8-Methyljulolidine[9] (from N,N′-di-*m*-tolyltrimethylenediamine), b.p. 172–180° at 17 mm.

Anal. Calcd. for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.3; H, 9.3; N, 7.6.

This compound gave a picrate of m. p. 158° and a methiodide of m.p. 209–210°.

Breakdown of N,N′-diphenyltetramethylenediamine was carried out in a similar manner. The diamine (15.1 g.) gave 14.1 g. of distillate which on fractionation gave 4.6 g. of aniline and 8.0 g. of N-phenylpyrrolidine, b.p. 142–145° at 27 mm. (picrate m.p. 115.5°, not depressed by addition of an authentic sample).

Breakdown of N,N′-diarylethylenediamines was carried out as above except that the residue in the decomposition flask was examined for involatile products. Thus in the breakdown of 61 g. of N,N′-diphenylethylenediamine, with 2.25 ml. of hydrobromic acid (s.g. 1.46), at 250° and 100 mm., the distillate (28.7 g.) was shown to consist mainly of aniline with lesser amounts of N,N′-diphenylpiperazine and unchanged diamine. Using the gas chromatograph, no evidence was obtained for the presence of indoline in the intermediate fractions. The residue (34.7 g.) was neutralized and distilled to give a fraction b.p. 195 to 200° at 1 mm. which was fractionally recrystallized to give mainly N,N′-diphenylpiperazine and some unchanged diamine. No further compounds could be isolated from the residue (*ca.* 7 g.).

The two N,N′-dinaphthylethylenediamines were decomposed at 280–290° and 18 mm. The distillate in each case consisted of the almost pure naphthylamine; a trace of impurity in the 2-naphthylamine proved to be N-(2-naphthyl)piperazine when isolated as its benzenesulphonyl derivative, m.p. 193.5–194.5°.

Anal. Calcd. for $C_{20}H_{20}N_2O_2S$: C, 68.2; H, 5.7; N, 8.0; mol. wt., 352. Found: C, 67.8; H, 5.6; N, 8.2; mol. wt. (Signer's method), 349.

The distillation residues were neutralized and fractionally recrystallized from chloroform to give the N,N′-dinaphthylpiperazines. Evaporation of the mother liquors deposited intractable tars, of b.p. greater than 300° at 1 mm., and these defied further separation.

Acknowledgment.—The authors are indebted to the New Zealand Universities Research Committee for financial assistance.

(7) W. J. Hickinbottom, *J. Chem. Soc.*, 992 (1930).

(8) Only literature reference, Pinkus, *Ber.*, **25**, 2804 (1892), gives no analysis or constants.

(9) Only literature reference, *Chem. Abstr.*, **50**, 717 (1956), lists only b.p. 179–180° at 19 mm.

Photosensitive Quinoxaline Pseudo Bases[1a]

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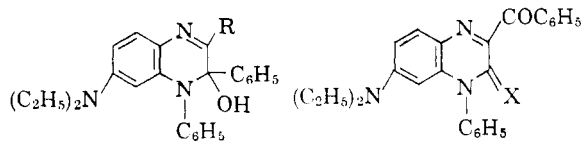
Two photosensitive quinoxaline pseudo bases, similar to one described previously, were prepared and their photoreactions studied. The previously reported pseudo base was found to give a photosensitive intermediate in its photoreaction. No analogous intermediates were observed in the case of the two new pseudo bases. Base-catalyzed dark reactions of the pseudo bases gave the same products, except one, as the photoreactions. A mechanism for the photoreactions is suggested.

The photoreaction of the pseudo base, I, to give the quinoxalone, IV, has been reported.[1b] It has been found that II and III undergo analogous photoreactions when irradiated within their long wave length absorption bands. The pseudo base, II, gives IV, identical with the photoproduct from I, while III gives V and VI.

The structure assigned to V is supported by its formation from VI in a base-catalyzed, ring-closing reaction of known type,[2] by its slow, acid hydroly-

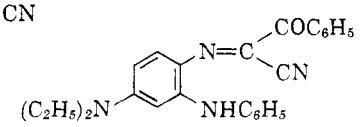
(1) (a) Contribution No. 2283 from the Kodak Research Laboratories; (b) P. M. Mader, *J. Org. Chem.*, **27**, 2217 (1962).

(2) A. A. Morton, "The Chemistry of Heterocyclic Compounds," McGraw-Hill Book Co., Inc., New York, N.Y., 1946, pp. 267, 270.



I. R = $-CO_2C_2H_5$
II. R = $-CON(CH_3)_2$
III. R = $-CN$

IV. X = O
V. X = NH



VI

sis to give IV (again a reaction of known type),[3] by its infrared spectrum, which shows nitrile to be absent, and by its avid protonation, consistent with the amidine-type structure. The assignment of the structure to VI is based primarily on its alternative synthesis by the oxidative coupling of 3 - anilino - N^1,N^1 - diethyl - *p* - phenylenediamine and benzoylacetonitrile. The structure is also supported by physical and chemical properties.

There was very little conversion of VI to V under the conditions of the photochemical experiments. Therefore, VI could not have been an intermediate in the formation of V in the photoreaction of III.

In the photolysis of III at room temperature, total yields of V plus VI were generally about 95%. Addition of proton donors to the reaction solvent favored the formation of VI at the expense of V. In acetone–water mixtures, for example, the yield of VI rose from 2%, leveling off at 64% as the water content was raised from near zero to ten molar. Likewise, the addition of small amounts of alcohols to benzene solutions of III increased the yield of VI to values higher than that (3%) obtained in their absence. In solutions containing proton donors, a decrease in temperature favored formation of VI.

The quantum efficiency for the photolysis of III in air-saturated acetonitrile at room temperature when irradiated within the range of 418–428 mμ was 0.3 ± 0.1. The quantum efficiencies for I and II are estimated to have been lower than this value by factors of about two and five, respectively. The quantum efficiency for I was influenced by the viscosity of the solution: the photolysis rate had only about one-half the value in Nujol that it had in *n*-heptane. Furthermore, none of the pseudo bases showed any appreciable photosensitivity when irradiated as crystalline or glassy solids. Removing most of the oxygen from benzene solutions of the pseudo bases increased the quantum efficiency of photolysis and decreased the yields of the major products.

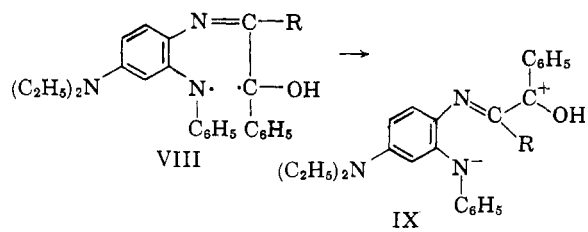
As reported previously,[1b] the yield of IV from I increased as the intensity of irradiation was decreased. This effect has been found to be due to the accumulation during irradiation of a photosensitive intermediate, VII, of unknown structure, having an absorption peak at about 480 mμ in benzene. In its photoreaction, VII gave unidentified products and no IV. In its dark reaction, it gave IV in a monomolecular reaction having a half-reaction time in benzene of 14 sec. at 25°. Both acid and base catalysis of this reaction were observed. In the dark, neither acid nor base affected the yield of IV from the intermediate, VII. During low-intensity irradiation, however, the presence of base increased the yield. An increase in temperature, which increased the rate of the dark reaction of VII, had the same effect. In each case, the increase in yield was due to a more favorable competition of the dark reaction of VII with its photolysis.

No intermediates analogous to VII were observed following flash photolysis of II and III. If such intermediates formed, they must have reacted to give the final products during the two seconds which elapsed between the flash and the first spectrophotometric measurements. Moreover, yields of the photoproducts were high even when high-intensity irradiation was used, showing that there was no appreciable accumulation of photosensitive intermediates during irradiation.

The formation of IV from I and II and of V from III was accomplished not only photochemically but also in base-catalyzed dark reactions. In another dark reaction, the photoproduct, VI, reverted slowly to the pseudo base, III. The unimolecular half-reaction time in acetonitrile was 160 hours at 23°. This reaction was catalyzed by acetic acid. In the acidic solution, the initially formed pseudo base was converted slowly to the magenta quinoxalinium ion by loss of hydroxyl ion. In the presence of a strong acid, the conversion of VI to the quinoxalinium ion was so fast that the pseudo base, if it formed as an intermediate, was not observed.

Discussion

The photochemical reactions described here may be explained as follows: Photoexcited pseudo base undergoes C—N bond rupture, giving the diradical, VIII. The dissociation energy of the



VIII IX

C—N bond of methylamine is 75 kcal./mole.[4] The energy required to break the C—N bond of

(3) E. C. Taylor, Jr., and C. K. Cain, *J. Am. Chem. Soc.*, **71**, 2282, 2538 (1949).

(4) M. Szwarc, *Chem. Rev.*, **47**, 75 (1950).

the pseudo bases should be lower than this value, owing to crowding of the groups attached to the carbon and the nitrogen. It is not unreasonable, then, to expect that absorption in the long wave length bands of the pseudo bases, corresponding to an energy increase of about 70 kcal./mole, could lead to breaking of this bond. In VIII, the radical centers are connected by a conjugated chain of atoms. As pointed out by Barton,[5] such a diradical can undergo a rapid, energetically favorable redistribution of the electrons, giving an ionic species. This redistribution and *cis-trans* isomerization around the azomethine linkage give IX. The negatively charged nitrogen can make a nucleophilic attack at R, leading to the formation of IV or V. The formation of VI results when the negative nitrogen of IX (R = CN) picks up a proton. The alternative mechanism, transfer of a hydrogen atom to the nitrogen of VIII, appears inconsistent with the effectiveness of *t*-butyl alcohol in increasing the yield of VI. This alcohol, lacking hydrogen on the α carbon, should be a relatively poor hydrogen-atom donor.[6]

Experimental

3-Benzoyl-7-diethylamino-1-phenyl-2(1)-quinoxalone (IV).—Syntheses of IV by oxidative condensation and by photolysis of I have been described.[1b] The compound has also been formed in the following reactions:

A. The Base-catalyzed Dark Reaction of I.—A solution of 4.9 mg. of I and 4×10^{-4} mole of tetramethylammonium hydroxide in 15 ml. of acetone and 0.4 ml. of water was allowed to stand 15 min. at 24°. The solution was diluted with benzene, washed with water, and dried over sodium sulfate. Chromatography on Florisil gave 3.7 mg. of product, which was crystallized from 85% ethanol. Physical properties were identical with those of IV prepared by other methods.[1b]

B. The Base-catalyzed Reaction of II.—The reaction is much slower than that of I. A reaction mixture similar to that in A. above was boiled for 15 min. The yield of IV was about 1%; much of the II remained unreacted.

C. Acid Hydrolysis of V.—A solution of 19.8 mg. of V in 15 g. of 50% sulfuric acid was heated at 95° for 10 days. Thirty-five per cent of the V was recovered, while 36% of the V was converted to IV (identified by its physical properties).

D. The Photolysis of II.—A solution of 50 mg. of II in 500 ml. of Eastman Grade benzene was irradiated in a 5-mm. layer 21 in. from a Conti-Glo Model 91 ultraviolet lamp (Continental Lithograph Corp., Cleveland, Ohio) for 10 hr. Evaporation of the solvent gave 50 mg. of brown, crystalline residue, which was crystallized from ethanol. The physical properties were identical with those of IV prepared by other methods.[1b]

6-Diethylamino-3,4-dihydro-3,4-diphenyl-3-hydroxy-2-N,N-dimethylquinoxalinecarboxamide (II).—A slurry of 3.0 g. (8.5×10^{-3} mole) of the sulfuric acid salt of 3-anilino-N^1,N^1-diethyl-*p*-phenylenediamine[7] in 40 ml. of water was added to a solution of 4 g. of potassium hydroxide and 4.2 g. (2.2×10^{-2} mole) of 2-benzoyl-N,N-dimethylacetamide[8] in 300 ml. of methanol. The mixture was stirred, and a solution of 13 g. of potassium ferricyanide in 40 ml. of water was added, dropwise, during 35 min. The mixture was stirred for 15 min. and filtered. The filtrate was acidified with 1.7 ml. of 12 *N* hydrochloric acid and diluted with 300 ml. of water. It was then neutralized with sodium hydroxide and washed eight times with benzene. Addition of 21 ml. of 2.4 *N* sodium hydroxide to the benzene-washed solution gave a precipitate of a mixture of II and its methyl ether, which was washed with dilute sodium hydroxide and dried. The dried material was dissolved in 25 ml. of benzene and the solution shaken with two 15-ml. portions of 0.24 *N* hydrochloric acid, whereupon the pseudo base, II, and its methyl ether went into the aqueous phase as the quinoxalinium salt. The aqueous solution was washed with benzene and then made alkaline with sodium hydroxide. The II which precipitated was rinsed with 0.1 *N* sodium hydroxide and dried over potassium hydroxide; wt.: 1.39 g. Five crystallizations from cyclohexane gave 0.22 g. of green-fluorescing II. When the crystals were dropped on a preheated stage (Kofler Heizbank), the lowest temperature at which rapid melting occurred was 142°. At lower temperatures, melting was slow and due to decomposition.

Anal. Calcd. for $C_{27}H_{30}N_4O_2$: C, 73.3; H, 6.8; N, 12.7. Found: C, 73.5; H, 7.0; N, 12.8.

Spectra: In acetone, λ_{max} 380 mμ (log ϵ 4.28); in benzene, λ_{max} 387 mμ (log ϵ 4.28); in the infrared region (Nujol mull), there is a broad band in the hydroxyl region at 2.92 μ. There is no carbonyl band below 6.2 μ.

(2-Anilino-4-diethylaminophenylimino)benzoylacetonitrile (VI). A. By Oxidative Coupling.—To a mixture of 0.145 g. (10^{-3} mole) of benzoylacetonitrile (Eastman Grade), 0.353 g. (10^{-3} mole) of the sulfuric acid salt of 3-anilino-N^1,N^1-diethyl-*p*-phenylenediamine,[7] 15 ml. of benzene, and 15 ml. of 13% aqueous sodium carbonate solution was added, all at once, with agitation, a solution of 1.4 g. of potassium ferricyanide in 10 ml. of water. Agitation was continued for 1 min., and then the benzene phase was separated, washed once with water, once with 0.1 *N* hydrochloric acid, and three times with water. The washing operations were carried out quickly to minimize loss of VI through its slow conversion to the pseudo base, III. The solution was dried over sodium sulfate and freeze-dried at reduced pressure. The crude product was crystallized by dissolving it in 6 ml. of benzene and adding to the solution 16 ml. of cyclohexane in 10- and 6-ml. portions. The 0.2 g. of product was recrystallized in the same manner. The crystals melted very quickly on the Kofler stage at 170°. At lower temperatures, melting was slow and due to decomposition.

Anal. Calcd. for $C_{25}H_{24}N_4O$: C, 75.7; H, 6.1, N, 14.1. Found: C, 75.4; H, 6.0; N, 13.9.

Spectra: In acetonitrile, λ_{max} 275 mμ (log ϵ 4.26), $\lambda_{shoulder}$ 294 mμ (log ϵ 4.16), λ_{max} 515 mμ (log ϵ 4.63); in the infrared region (chloroform solution), there is a weak band at 3.03 μ, ascribed to N—H (diphenylamine at the same molar concentration gives a band of approximately equal intensity at 2.91 μ), a nitrile band at 4.53 μ, and a shoulder at 6.14 μ, the lowest wave length at which a band is found in the double-bond region.

B. By Photolysis of III.—A solution of 50 mg. of III in 200 ml. of acetone plus 50 ml. of water was irradiated in a 5-mm. layer 2.5 in. from two 15-watt fluorescent lamps (Westinghouse F15T8/D) for 50 min. To the solution were added 70 ml. of benzene and 150 ml. of water. The benzene phase was washed five times with water, dried over sodium sulfate, and chromatographed on Florisil. After the column had been washed with benzene, the VI was eluted with acetonitrile. The chromatography was carried out as

(5) D. H. R. Barton, *Helv. Chim. Acta*, **42**, 2604 (1959).

(6) C. F. Wells, *Trans. Faraday Soc.*, **57**, 1703, 1719 (1961).

(7) Prepared by R. Bent, of Kodak Research Laboratories, using the method of J. C. Arcos and J. A. Miller, *J. Am. Chem. Soc.*, **77**, 3128 (1955).

(8) Prepared by J. Figueras, of Kodak Research Laboratories, by the reaction of dimethylamine hydrochloride and ethyl benzoylacetate in dimethylformamide plus sodium acetate, m.p. 83.5–84.5°.

rapidly as possible to minimize loss of VI through its conversion to quinoxalinium ion on the Florisil. The residue from the eluate was crystallized from benzene–cyclohexane, giving 10 mg. of product having physical properties identical with those of the VI made by oxidative coupling.

6-Diethylamino-3,4-dihydro-3,4-diphenyl-3-methoxy-2-quinoxalinecarbonitrile (X).—This material, the methyl ether of the pseudo base, III, was prepared as an intermediate in the synthesis of III. This was done because of the ease with which the ether could be purified by recrystallization. Crude VI, heavily contaminated with III, was prepared by the oxidative coupling of 5×10^{-3} mole each of benzoylacetonitrile and 3-anilino-N^1,N^1-diethyl-*p*-phenylenediamine. The crude product was converted completely to pseudo base III by dissolving it in 1 *N* hydrochloric acid (giving the quinoxalinium salt) and making the solution strongly basic with sodium hydroxide. The precipitated pseudo base was washed with 0.1 *N* sodium hydroxide and dried over potassium hydroxide; wt. 1.51 g. Without purification, most of the pseudo base was converted to the methyl ether, X, by dissolving it in 20 ml. of methanol containing 3 drops of 10% methanolic potassium hydroxide and boiling the solution for 45 sec. The ether crystallized as the solution cooled. It was recrystallized from 115 ml. of methanol containing 6 drops of 10% methanolic potassium hydroxide, giving 0.87 g. of bright yellow, green-fluorescing product, which was dried over potassium hydroxide. The crystals melted at 195° on the Kofler hot stage; at lower temperatures, melting was slow and due to decomposition. The ether, X, is not photosensitive.

Anal. Calcd. for $C_{26}H_{26}N_4O$: C, 76.1; H, 6.4; N, 13.7. Found: C, 75.7; H, 6.4; N, 14.0.

Spectra: In acetonitrile, λ_{max} 224 mμ (log ε 4.44), $\lambda_{shoulder}$ 260 mμ (log ε 3.92), λ_{max} 305 mμ (log ε 3.91), λ_{max} 426 mμ (log ε 4.55); the infrared spectrum (Nujol mull) has no band in the OH region. In potassium bromide pressing, a nitrile band is present at 4.50 μ; in the n.m.r. spectrum, a single peak, corresponding to three protons, is found in the field position where methoxy resonances normally occur. All resonance absorptions are consistent with the proposed structure, with no extra lines which could be due to hydroxyl group.[9]

6-Diethylamino-3,4-dihydro-3,4-diphenyl-3-hydroxy-2-quinoxalinecarbonitrile (III). A. From the Pseudo Base Methyl Ether, X.—To a slurry of 0.69 g. of X in 5 ml. of acetone was added 1.0 ml. of 3 *N* hydrochloric acid. The resulting deep magenta solution of the quinoxalinium salt was diluted with 10 ml. of water and poured into 32.5 ml. of a stirred 0.15 *N* sodium hydroxide solution. The pseudo base separated as lumps of tar and as emulsion. The emulsion was flocculated by diluting the mixture with 300 ml. of water and adding to it 10 ml. of saturated sodium sulfate solution. The lumps were broken up, and the product was filtered off, washed with 10^{-3} *N* sodium hydroxide, and dried over potassium hydroxide; wt. 0.64 g. One-half gram of the crude product was dissolved in 5 ml. of benzene, the solution filtered, and the filtrate diluted with 12 ml. of cyclohexane. The crystals of III, which formed on seeding, were separated and dried over potassium hydroxide; wt. 0.21 g.; color, yellow. Crystalline III is not fluorescent. The crystals melted instantly at 125° on the hot stage. At lower temperatures, melting was slow and due to decomposition.

Anal. Calcd. for $C_{25}H_{24}N_4O$: C, 75.7; H, 6.1; N, 14.1. Found: C, 76.0; H, 6.5; N, 14.3.

Spectra: In acetonitrile, λ_{max} 226 mμ (log ε 4.41), $\lambda_{shoulder}$ 260 mμ (log ε 3.96), λ_{max} 304 mμ (log ε 3.92), λ_{max} 422.5 mμ (log ε 4.52); in the infrared region (Nujol mull), there is a broad band in the OH region at about 3.05 μ. In potassium bromide, the nitrile band occurs at 4.51 μ. In the 6–9-μ region, the spectrum is very similar to that of the pseudo base ether X. Above 9 μ, there are several differences. For example, prominent bands at 9.51 and 10.76 μ in the ether are missing in the pseudo base.

B. From VI.—The absorption spectrum of a 3.5×10^{-5} *M* solution of VI in Eastman Spectro Grade acetonitrile slowly changed, approaching that of the pseudo base, III. The changes at 420 and 515 mμ were first order. When this change had gone to completion, the solution was exposed to light. The spectrum changed to that of V, confirming that the photosensitive pseudo base, III, had been formed in the solution from the VI. The half-reaction time was 160 hr. (*ca.* 23°). In the presence of 2.7×10^{-4} *M* and 2.7×10^{-3} *M* acetic acid, the half-reaction times at 25° were 103 and 10.9 min., respectively.

3-Benzoyl-7-diethylamino-1,2-dihydro-2-imino-1-phenylquinoxaline (V). A. By the Photolysis of III.—A solution of 0.10 g. of III in 200 ml. of Eastman Grade benzene was irradiated in a 4-mm. layer 4 in. from two 15-watt fluorescent lamps (Westinghouse F15T8/D) for 3 hr. Attempts to crystallize (from benzene–cyclohexane) the dark orange, resinous residue obtained on evaporation of the benzene gave unsatisfactory results. The material was dissolved in benzene and chromatographed on Florisil. After the column had been washed with acetonitrile to remove a small amount of VI, V was eluted using 90:10 acetone–triethylamine (100:2 acetone–28% ammonia can also be used.) It was found desirable to carry out the chromatography quickly to minimize loss of V through its slow hydrolysis to IV on the Florisil. The residue from the eluate was crystallized twice from 4:1 cyclohexane–benzene, giving 20 mg. of orange material melting at 147–150°. Further recrystallization or heating of this material just above its melting point converted it to a yellow polymorph melting at 173°. The lower melting point probably does not represent that of the pure low-melting polymorph, since the orange product was probably contaminated with some of the high-melting polymorph.

Anal. Calcd. for $C_{25}H_{24}N_4O$: C, 75.7; H, 6.1; N, 14.1. Found: C, 75.8; H, 6.3; N, 14.1.

Spectra: In acetonitrile, the two crystalline forms give the same spectrum: λ_{max} 241 mμ (log ε 4.61), $\lambda_{shoulder}$ 295–317 mμ (log ε 3.77), λ_{max} 420 (log ε 4.14), λ_{max} 485 mμ (log ε 4.24); in the infrared region (KBr pressings), the two crystalline forms give spectra which are similar. Both give a band at 3.02 μ, which may be assigned to the NH. No nitrile band occurs in either. There are several bands which are considerably more prominent in one form than in the other. These bands occur at 5.98, 10.56, and 13.88 μ in the high-melting form and at 6.12 μ in the low-melting. It is suspected that the grinding operation involved in preparing the potassium bromide pressings may have resulted in some melting of the V, particularly in the case of the low-melting form, giving amorphous material. Consequently, the differences in the spectra may be due in part to different contents of amorphous V.

B. By the Base-catalyzed Reaction of VI.—A solution of 5 mg. of VI in 15 ml. of acetone plus two drops of 0.14 *N* aqueous tetramethylammonium hydroxide was allowed to stand 1 min. The solution was diluted with benzene and washed several times with water. After it had been dried over sodium sulfate, the solution was chromatographed on Florisil. The crude product was recrystallized from cyclohexane–benzene, giving tan-yellow crystals which melted at 172.5–173° (the high-melting polymorph). Spectra were identical with those of the photoproduct from III.

C. By the Base-catalyzed Reaction of III.—Two drops (0.065 ml.) of 0.14 *N* aqueous tetramethylammonium hydroxide was added to 10 ml. of 3×10^{-5} *M* III in acetonitrile. After the solution had been heated at 77° for 3 min., it was diluted with benzene, washed with water, dried over sodium sulfate, and chromatographed on Florisil. About 65% of the III was converted to V, identified by its absorption spectrum. When the reaction was carried out at 25°, rather than at 77°, the initial rate of increase in

(9) The n.m.r. measurements were obtained and interpreted by C. M. Combs, of Kodak Research Laboratories.

absorbance at 485 mμ indicated a monomolecular half-reaction time of about 180 min.

The pK_a of the Conjugate Acid of V.—The absorbances of 10-cm. thick layers at 503 mμ (λ_{max} of the conjugate acid of V) were measured at 25° for 1.5×10^{-6} *M* solutions of V in carbonate buffers having pH values in the range of 8.6–11.1 and an ionic strength of 0.1. These data and, in addition, an electrophoretic measurement indicated that the conjugate acid which forms in this pH range is a positively charged ion and results from the addition of a single proton to V. The average value for the pK_a of the conjugate acid was 10.1.

Photochemical Experiments.—Irradiation was carried out at 24–25°, unless noted otherwise. The following light sources were used: No. 1, Two Westinghouse F15T8/D fluorescent lamps in a white reflector; No. 2, Kodak Model 1 Signet 500 Projector having a double-convex lens (focal length: 6.8 cm.) in place of the projection lens; No. 3, Mecablitz 100 flashgun (Metz Co., Fürth, Germany); No. 4, Ascorlight Model A405 200-watt-sec. flashgun (American Speedlight Corp., Middle Village, New York).

Analyses were carried out as follows: Pseudo bases I and II in benzene were determined by shaking a 3.0-ml. sample with 5.0 ml. of 0.1 *N* hydrochloric acid and measuring the absorbance of the resulting quinoxalinium salt in the aqueous phase (530 mμ for I and 547 mμ for II). The photoproduct IV was isolated by chromatography on Florisil and determined spectrophotometrically in benzene at 415 mμ. Pseudo base III and its photoproducts V and VI were determined as follows: A 2.0-ml. sample of the irradiated solution was diluted with 10.0 ml. of ligroin (60–90°) and shaken for 15 sec. with 10.0 ml. of a solution of 0.1 g. of sodium dihydrogen phosphate in 250 ml. of distilled water. The amounts of III and VI were calculated from the absorbance of the ligroin phase at 410 and 510 mμ. The amount of V was obtained from the absorbance of the centrifuged aqueous phase at 500 mμ, after correction of this value for the absorbance due to the 4% of the III which entered the aqueous phase as the quinoxalinium ion. The analytical procedures were calibrated using solutions containing known amounts of the pseudo bases and photoproducts.

The effect of light intensity on the yield of IV from I was determined by irradiating a 4.3×10^{-5} *M* solution in benzene in a 14-mm. test tube at various distances from Source No. 1. The time of irradiation was adjusted so that 80–83% of the I reacted. For intensity values of 1000, 520, 280, and 47 footcandles, the respective yields (based on I consumed) of IV were 57, 69, 75, and 89%. In another intensity series, a 3.7×10^{-5} *M* solution of I in benzene in a Beckman 1-cm. silica cell was given single-flash irradiation at distances of 4, 6, 9, 12, and 25 in. from Source No. 4. The respective percentages of I that reacted were 98, 94, 35, and 8, and the corresponding yields (based on I consumed) of IV were 7, 19, 53, 69, and 78%. In a temperature series, a 4.65×10^{-5} *M* solution of I in benzene in a 14-mm. test tube was irradiated using Source No. 1 at 450 foot-candles for 110 sec. At 2, 25, and 52°, the respective percentages of I that reacted were 74, 84, and 87, and the corresponding yields (based on I consumed) of IV were 52, 66, and 78%.

Observations of the fugitive intermediate, VII, were made following flash photolysis of solutions of I by Source No. 3 or Source No. 4. By using the Cary spectrophotometer and an attachment which allowed flashing the sample in the cell compartment, recording of absorbance could be started within 1–2 sec. following the flash. In this way, the λ_{max} for VII was estimated and the rate of the dark reaction measured. When the Beckman DU instrument was used, about 5 sec. elapsed between flashing and reading. It was possible to observe the catalysis of the dark reaction of VII (giving IV) when a drop of 2×10^{-4} *M* ethanolic potassium hydroxide was added to 2.5 ml. of 5×10^{-5} *M* solution of I in benzene either before or after flashing. (There was no appreciable effect of ethanol itself, and the concentration of base used did not noticeably promote the dark reaction of I to give IV.) When a drop of 5×10^{-3} *M* hydrochloric acid (in acetonitrile) was added to 2.5 ml. of 4×10^{-5} *M* I in acetonitrile immediately after flashing, the rate of increase in absorbance at 420 mμ (due to formation of IV from VII) was increased. Catalysis of the reaction by acetic acid in benzene was also observed.

The presence of 0.01 ml. of 1.3×10^{-3} *M* ethanolic potassium hydroxide in 3 ml. of a 4.4×10^{-5} *M* benzene solution of I increased the yield of IV from 30 to 78% when the solution was photolyzed (to completion) in a 14-mm. test tube for 2 min. at 1.25 in. from Source No. 1. When flash photolysis was used, the presence of the ethanolic potassium hydroxide had no effect on either the extent of photolysis (55%) or the yield of IV (54%) based on I consumed. Likewise, there was no difference in the yields of IV obtained when 0.04 ml. of 12 *N* aqueous hydrochloric acid was added either 3 sec or 3 min. following flash photolysis of 3 ml. of 3×10^{-5} *M* I in acetonitrile. That is, the yield was the same whether the dark reaction of VII took place in the absence or the presence of acid.

The effect of intensity on the yield of IV in the flash photolysis of pseudo base II was determined using a 3.37×10^{-5} *M* solution in benzene in a 1-cm. Beckman silica cell and Source No. 4. For source-to-sample distances of 0.5, 2.5, and 5 in., the respective percentages of reaction of the II were 50, 36, and 24, and the corresponding yields were 89, 88, and 92%.

In the determination of the effect of the concentration of water in acetone on the yields of V and VI from photolyzed III, the pseudo base concentration was 4.75×10^{-5} *M*, and nearly complete photolysis was achieved by a 7-min. exposure of the solutions in a 1-cm. Beckman silica cell 2.25 in. from Source No. 1. The effect of temperature was determined using an acetone solution containing III and water at concentrations of 4.76×10^{-5} *M* and 14.3 *M*, respectively. Samples in a 12-mm. test tube were irradiated for 1 min. at 6.5 in. from Source No. 2 (*ca.* 2.5×10^4 footcandles), giving complete photolysis. For temperatures of −13, 1, 24, and 60°, the respective yields of V were 11, 16, 28, and 54%, and the corresponding yields of VI were 69, 72, 66, and 38%. The effects of alcohols in benzene on the yield of VI from III were determined using reagent-grade benzene which had been stored for 3 days over calcium hydride. The alcohols (except benzyl alcohol) were dried for 3 days over Drierite. Concentrations of III and alcohol were 8.2×10^{-5} *M* and 0.2 *M*, respectively, and 1-min. irradiation of solutions in a 14-mm. test tube located 6.5 in. from Source No. 2 was used. For the alcohols methanol, ethanol, isopropyl alcohol, *n*-butyl alcohol, *t*-butyl alcohol, and benzyl alcohol, the respective yields of VI were 24, 24, 20, 25, 8, and 10%. Total yields of V plus VI were 94–96%, based on the III used.

The approximate quantum yield for the photolysis of III was determined using a solution of 1.87×10^{-7} mole of III in 3 ml. of acetonitrile, which was irradiated in a 1-cm. Beckman cell in the beam of a calibrated monochromatic photographic sensitometer.[10] The total irradiation corresponded to the absorption by the III of about 4.9×10^{-8} quantum at 423 mμ, and, from the increase in absorbance at 485 mμ, it was estimated that 1.4×10^{-8} mole of V was

TABLE I

EFFECT OF AIR ON THE PHOTOREACTIONS IN BENZENE

Pseudo base	Extent of reaction, %		Product yield,[a] %	
	Air-satd.	Air-free	Air-satd.	Air-free
I	51	69	84 (IV)	65
II	25	43	86 (IV)	67
III	40	47	98 (V + VI)	84

[a] Based on pseudo base which underwent reaction.

(10) Constructed and calibrated by J. S. Hayward of Kodak Research Laboratories.

formed. Under the conditions used, V was the major product; only a few per cent of VI was formed.

The effect on the photoreactions of removing the air from the solutions was determined using benzene solutions of I, II, and III having concentrations of 4.6×10^{-5} *M*, 4.3×10^{-5} *M*, and 8.8×10^{-5} *M*, respectively. The solutions, in 14-mm. test tubes, were swept with benzene-saturated nitrogen (Linde, 99.9%) for 5 min. prior to and during irradiation. Source No. 1 was used as follows: for I, 1.5 min. at 9.75 in.; for II, 7 min. at 6 in.; for III, 5 min. at 16 in. For comparison, duplicate experiments were run using air in place of nitrogen. Results are given in Table I.

The Synthesis of Derivatives of α-Mercaptoamidines[1,2]

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General syntheses of α-amidinium thiosulfates (Bunte salts) and N,N′-diaryl-α-(acetylmercapto)acetamidines as potential antiradiation drugs are described.

With the discovery by Patt[3] in 1950 that mice could be protected by cysteine against otherwise lethal doses of radiation by X-rays, a new field of investigation was opened. In 1951, Bacq[4] showed that both 2-mercaptoethylamine and 3-mercaptopropylamine are more effective radioprotective agents than cysteine. A large number of analogs and functional derivatives of the above amino thiols have since been tested[5] for this activity. In the most promising compounds, the salient features appeared to be a basic functional group separated from a thiol, or potential thiol group, by two or three carbon atoms. It had been shown that when the thiol group in these amino thiols was replaced by a thiosulfate (Bunte salt) or an isothiuronium group, the activity equalled that of the parent, but these derivatives were much less toxic.

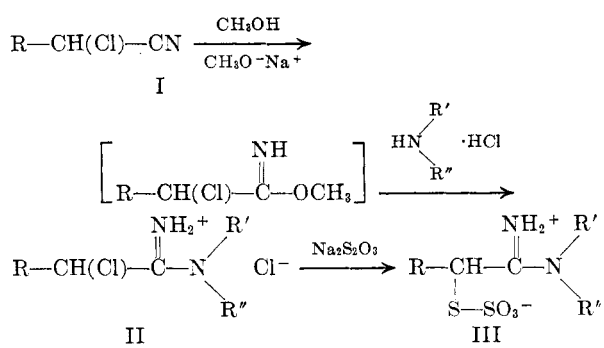
In designing potential antiradiation drugs which adhered to the above criteria, we turned our attention to the synthesis of α-mercaptoamidines and functional derivatives thereof. In these molecules the amidine is the basic group located in the vicinity of a group capable of releasing a thiol group. Three sulfur-containing groups which we considered for incorporation in the molecules were those which are hydrolyzed readily to thiols, such as the thiosulfate (Bunte salt), thiol ester, and isothiuronium groups.

Thus, this paper describes the synthesis of α-amidinium thiosulfates, III (always presented as the zwitterion), α-(acetylmercapto)acetamidines, VI, and that of an α-isothiuronium amidinium salt, VII.

In exploring synthetic routes to these amidines, it was planned to introduce the sulfur-bearing functional group as the last step. The ideal intermediates for the synthesis of all of these compounds was found to be the α-haloamidines.

The reaction scheme which proved most versatile was that leading to α-amidinium thiosulfates (Bunte salts) III. The starting materials for their synthesis were α-chloronitriles, I. When these nitriles were treated with methanol and sodium methoxide, the methyl α-chloroimidate[6] was formed but not isolated and reacted immediately with ammonium chloride or an amine hydrochloride to furnish the α-chloroamidine hydrochloride, II.

These salts were, in general, crystalline, water-soluble solids but proved to be potent vesicants which were difficult to purify. However, it was found that the impure salts were satisfactory for use in the next step.



The reaction of II with sodium thiosulfate provided highly crystalline Bunte salts, III, which were readily purified. Although contact with the latter produced most objectionable skin-rashes, they could be handled much more easily than the chloroamidines. This reaction scheme lent itself to the preparation of α-thiosulfate derivatives of acet-, propion-, and phenylacetamidines, III. Ammonia and aliphatic primary and second-

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(2) From a thesis submitted by Thomas L. Welsh to the Graduate College of the University of Illinois in partial fulfillment of the requirements of the degree of Doctor of Philosophy. The preliminary findings were presented before the Anti-Radiation Drug Symposium sponsored by the Medicinal Section of the American Chemical Society in Washington, D. C., on March 29, 1962.

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