ride. The excess phosphorus oxychloride was distilled by heating the sample on a water bath under reduced pressure. Heating was continued until the solution became a thick sirup. If heating was continued for a longer period of time the sulfonyl chloride decomposed to a crystalline material and the desired product was not obtained. The thick sirup was added to 400 ml. of ammonia. Evaporation of the ammonia left a tan solid which was decolorized with animal charcoal and crystallized from water yielding 9.7 g. (59% yield) of long white needles, m.p. 195–197°. Further crystallization from water increased the m.p. to 198–199°. Analytical data are given in Table I.

4,6-Diamino-5-pyrimdinesulfonamide (19).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2.5 g.) was dissolved in 50 ml. water to which 5 g. of Raney nickel[18] was added. This reaction mixture was refluxed for 3 hr. with vigorous stirring. Longer refluxing also will remove the sulfonamide group while a shorter reflux time leaves too much starting material. A 31% yield (0.63 g.) of **19** was obtained upon evaporation of the filtrate and crystallization of the residue from a small amount of water, m.p. 215–216.5°. Further crystallization from water gave an analytical sample, m.p. 221–222°. Analytical data are given in Table I.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide.—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2 g.) was added to 50 ml. water and cooled to 0° in an ice bath. Chlorine was slowly bubbled through this suspension until all of the solid went into solution and the solution was light yellow in color. (This takes a few minutes depending on how rapidly the chlorine is bubbled through the suspension. A large excess of chlorine should be avoided or the yield will be reduced greatly.) The product begins to separate shortly after the solid goes into solution. After standing in an ice bath for 0.5 hr. the mixture was filtered and after one crystallization from water yielded 1.6 g. (70% yield), m.p. 235–237°, with evolution of a gas. Further crystallization from water gave a sample that turns yellow at 235°, m.p. 249–250° dec.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide also was prepared by dissolving **18** (0.9 g.) in 10 ml. of acetic acid and 10 ml. of acetic anhydride. To this solution was added 1 ml. of 30% hydrogen peroxide. After a short time the reaction mixture became hot and the product separated from the solution. A 79% yield (0.81 g.) of crude product was obtained upon filtration. Two crystallizations from water gave material that was identical with that from the oxidation with chlorine. Analytical data are given in Table I.

8-Amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (20) and 8-Amino-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (21).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 2 hr. at 120–130° in 20 ml. of triethyl orthoformate. Upon cooling the thiadiazine **20** was obtained in an 86% yield (0.9 g.), m.p. 315–317°. An analytical sample was obtained by two crystallizations from N,N-dimethylformamide and water, m.p. 321–322° dec.; ν_{max} 1204, 1136, and 1079 cm.$^{-1}$; λ_{max} 249 mμ (ϵ 26,700).

Anal. Calcd. for $C_6H_7N_5O_2S_2$: C, 29.34; H, 2.86; N, 28.39; S, 26.15. Found: C, 29.16; H, 3.06; N, 28.24; S, 26.17.

Cyclization of sulfonamide **18** also was effected with refluxing trimethyl orthoformate yielding **20** in a 62% yield.

To 4,6-diamino-5-pyrimidinesulfonamide (**19**) (1.8 g.) was added 50 ml. of triethyl orthoformate and treated in a manner similar to **18**. Thiadiazine **21** was obtained in a 97% yield (1.76 g.). Two crystallizations from N,N-dimethylformamide and water gave an analytical sample, m.p. 308–309°; ν_{max} 1219, 1159, 1078, 1020, and 1002 cm.$^{-1}$; λ_{max} 244 mμ (ϵ 11,200) and 223 mμ (ϵ 22,000).

Anal. Calcd. for $C_5H_5N_5O_2S$: C, 30.15; H, 2.53; N, 35.16; S, 16.10. Found: C, 29.88; H, 2.71; N, 35.02; S, 16.30.

8-Amino-3-methyl-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (22).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 1 hr. at 120–130° with stirring in 15 ml. of triethyl orthoacetate. Upon cooling the thiadiazine **22** was obtained in a 54% yield, m.p. 314–315°; ν_{max} 1149, 1099, 1050, and 1020 cm.$^{-1}$; λ_{max} 247 mμ (ϵ 28,300).

Anal. Calcd. for $C_7H_9N_5O_2S_2$: C, 32.42; H, 3.50; N, 27.01; S, 24.73. Found: C, 32.27; H, 3.61; N, 27.29; S, 24.90.

8-Amino-3,4-dihydro-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (23).—8-Amino-6-methylthio-1,2,4-pyrimido [4,5-*e*]thiadiazine 1,1-dioxide (**20**) (0.5 g.) was added slowly to 0.1 g. of sodium borohydride in 5 ml. of water. After standing for 3 hr. the reaction mixture was filtered to obtain the dihydro product **23** in an 81% yield (0.41 g.). One crystallization from water gave an analytical sample, m.p. 261–262°; ν_{max} 1202 and 1148 cm.$^{-1}$; λ_{max} 230 mμ (ϵ 26,600) and 255 mμ (sh).

Anal. Calcd. for $C_6H_9N_5O_2S_2$: C, 29.14; H, 3.67; N, 28.32; S, 25.93. Found: C, 29.11; H, 3.69; N, 28.41; S, 25.81.

Acknowledgment.—The authors wish to thank F. C. Chang of the University of Tennessee, Medical Units, for the infrared spectra.

(18) X. A. Dominquez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, **26**, 1625 (1961).

9-Aminoacridines and 4-Aminoquinolines. Steric Effects of N,N-Disubstitution[1]

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N,N-Disubstitution was found to labilize the aromatic amino bond of 9-aminoacridine to permit a previously unreported type of reaction with alcohols, yielding 9-acridinyl ethers. An analogous reaction in similarly N,N-disubstituted 4-aminoquinolines was not found; however, a pronounced effect on base strength and ultraviolet spectra upon increasing the bulk of the substituents was noted.

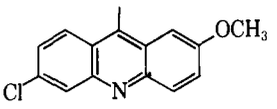
N,N-Disubstitution of 9-aminoacridine and 4-aminoquinoline derivatives was initially attempted to reduce intramolecular reactivity to other groups which were to be introduced at the end of an alkyl side chain; these objectives were abandoned in the quinoline series due to an unexpected rearrangement[2] and now in the acridine series due to inherent instability of the compounds to the conditions of subsequent reactions. In an attempt at synthesis of compound III, the reaction was carried out in refluxing Methyl Cellosolve, a procedure often found useful in moderating the sometimes destructively exothermic nature of such reactions,[3] and a compound subsequently identified as IV was isolated. Compound III was then synthesized in the absence of Methyl Cellosolve and its reactivity to or the alcohols near the boiling point of Methyl Cellosolve was investigated with a series of simple glycols, with ethylene chlorohydrin, and with diethylene glycol. The reactions all occurred rapidly near 115° and apparently were uncomplicated by side reactions, except in the case of ethylene chlorohydrin, where too long a reaction time led to alkylation of the nucleus. No attempt was made, however, to obtain optimum yields. Table I lists the products which are stable in the absence of active hydro-

(1) Supported in part by research grant CA-02975 from the National Cancer Institute, U. S. Public Health Service.

(2) R. M. Peck, *J. Org. Chem.*, **27**, 2677 (1962).

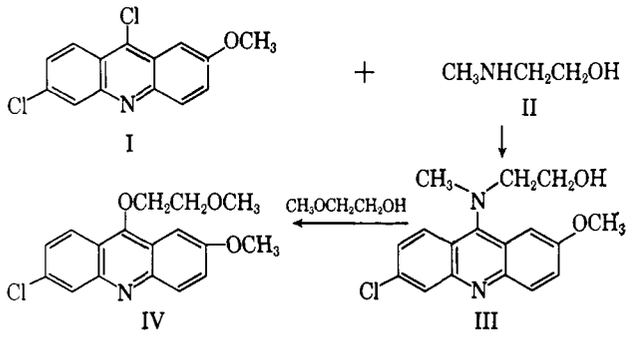
(3) R. M. Peck, R. K. Preston, and H. J. Creech, *ibid.*, **26**, 3409 (1961).

TABLE I



9-Acridinyl substituent	M.p., °C.	Anal.[a] Calcd. C	H	N	Cl	Found C	H	N	Cl
—OCH_2CH_2OH	216–217.5	63.30	4.65	4.62	11.69	63.51	4.67	4.68	12.34
—$O(CH_2)_3OH$	157.5–159.5	64.38	5.08	4.41		64.66	5.22	4.52	
—$O(CH_2)_4OH$	166–168.5	65.18	5.46	4.22		65.56	5.84	4.27	
—$O(CH_2)_6OH$	131.5–132	66.03	5.83	4.05		66.18	5.95	4.09	
—$OCH_2CH_2OCH_3$	113–115	64.30	5.08	4.41	11.17	64.12	5.05	4.72	11.59
—$OCH_2CH_2OCH_2CH_2OH$	131.5–134	62.19	5.22	4.02		62.71	5.29	4.11	
—OCH_2CH_2Cl	122–123.5	59.64	4.06	4.35	22.00	59.60	4.20	4.43	22.10

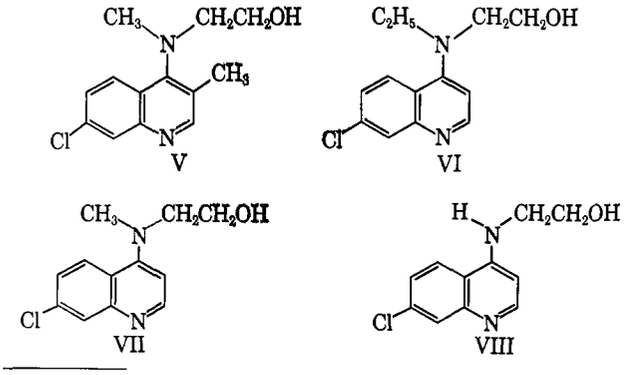
[a] Values are either single analyses or averages of checks.



gen compounds, but are quickly decomposed even by dilute acetic acid.[4]

To investigate whether other N,N-disubstituted 9-aminoacridines have the same property or whether the nature of the substituents is a factor, 6-chloro-2-methoxy-9-morpholinoacridine[5] was heated in the presence of ethylene glycol. It was found that no reaction occurred at 115°; reaction occurred, but did not go to completion, over a two-hour period at 140°. These results suggest that the degree of conjugation of the nitrogen at position 9 with the acridine nucleus is a function of the bulkiness of the nitrogen substituents which determine the ease with which that group is displaced by the alcohol.

To discover if a corresponding reaction was readily demonstrable in the quinoline series when a 3-substituent simulates the crowding effect of the second benzenoid ring of acridine, compounds V, VI, and VII were synthesized and compared with one another and with the reference compound VIII.[6]



(4) R. O. Clinton and C. M. Suter, *J. Am. Chem. Soc.*, **70**, 491 (1948).

(5) O. Yu. Magidson, A. M. Grigorovskii, and E. P. Hal'perin, *J. Gen. Chem. USSR*, **8**, 56 (1938).

(6) R. C. Elderfield, W. J. Gensler, O. Birstein, F. J. Kreysa, J. T. Maynard, and J. Galbreath, *J. Am. Chem. Soc.*, **68**, 1250 (1946).

None of these underwent a corresponding reaction with alcohols, even at elevated temperatures. With the most hindered compound, V, an hour's heating at 170° in ethylene glycol yielded only starting material and an approximately equal quantity of 7-chloro-3-methyl-4-quinolinol.

When the ultraviolet spectra and basicity of these compounds were determined, it was found that the presence of alkyl groups on the nitrogen and on the 3-position of the ring produced parallel and profound effects, additional substitution weakening the base strength and displacing the absorption maxima toward the visible (Fig. 1).

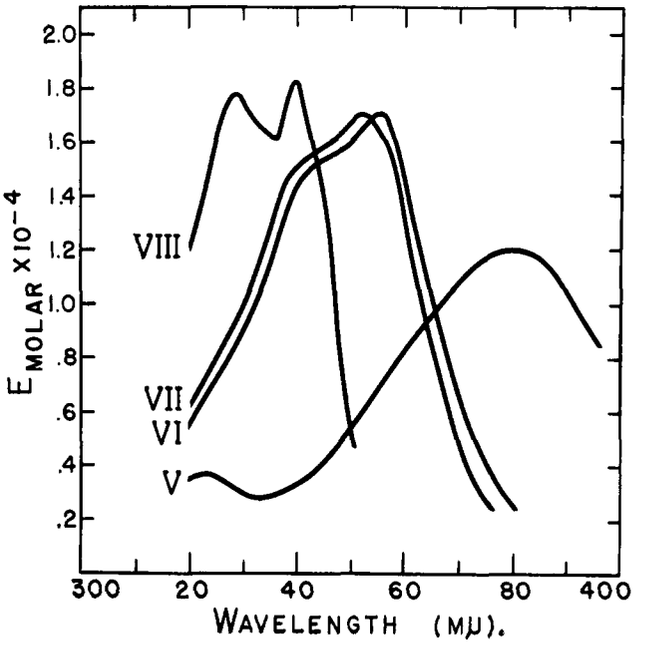


Fig. 1.—Roman numerals refer to designations in the text; the corresponding pK_a values (pH of one-half neutralization) were determined in 20% ethanol. VIII, pK_a 7.91; VII, pK_a 725; VI, pK_a 7.07; and V, pK_a 5.92. Spectra were determined in 0.01 *N* HCl.

In a pertinent comparison, Steck and Ewing[7] found that N,N-disubstitution *per se* produced no such shift in absorption spectrum where the substituents were small (methyl groups), and, in an even more interesting parallel with the present work, Irvin and Irvin[8] presented both absorption and base strength data on the antimalarial compounds SN-7618 and SN-6911 [7-

(7) E. A. Steck and G. W. Ewing, *ibid.*, **70**, 3397 (1948).

(8) J. L. Irvin and E. M. Irvin, *ibid.*, **69**, 1091 (1947).

TABLE II

DERIVATIVES OF 4-AMINOQUINOLINE

N,N-Substituents		Other substituents	Salt	M.p., °C.	Anal.[a] Calcd. C	H	N	Cl	Found C	H	N	Cl
CH_3	CH_2CH_2OH (VII)	7-Cl	HNO_3[b]	136–138	48.11	4.70	14.02		47.92	4.84	13.88	
CH_3	CH_2CH_2Cl	7-Cl	HCl	186–189	49.50	4.50	9.62	36.46	49.68	4.38	9.47	36.44
C_2H_5	CH_2CH_2OH (VI)	7-Cl	HNO_3[c]	137–139	49.85	5.14	13.40	11.30	49.97	5.28	13.46	11.59
C_2H_5	CH_2CH_2Cl	7-Cl	HCl	185–187	51.14	4.95	9.17	34.81	51.46	5.38	9.15	34.33
CH_3	CH_2CH_2OH (V)	7-Cl-3-CH_3	HNO_3[d]	133–138	49.85	5.14	13.40		50.27	5.19	13.24	
CH_3	CH_2CH_2Cl	7-Cl-3-CH_3	HCl	198–201	51.15	4.95	9.17	34.80	51.37	5.10	8.46	34.84

[a] Values are either single analyses or averages of checks. [b] Free base, m.p. 95–97°. [c] Free base, m.p. 85–87°. [d] Free base, m.p. 120–121°.

chloro-4-(4-diethylamino-1-methylbutylamino) - quinoline and 7-chloro-3-methyl-4-(4-diethylamino-1-methylbutylamino)quinoline, respectively], among others, which showed the effect of a 3-methyl substituent on these two parameters. Presence of a 3-methyl group lowered the base strength of the aromatic moiety by about 0.8 unit and displaced the absorption peak in acid solution to longer wave lengths by about 10 mμ. In the present work the parallel pair, V and VII, show significantly greater shifts, namely, 1.3 units and 30 mμ. This is consistent with ascribing the cause of these effects to steric hindrance which becomes more critical as crowding increases. The steric factor in this case arises from interference with molecular planarity of one of the resonance forms of the salt cation.[9]

Table II lists the constants and analyses for these compounds and their chloro derivatives which have been prepared in a project on the synthesis of antitumor agents.[3]

Experimental

6-Chloro-2-methoxy-9-[(2-hydroxyethyl)methylamino]acridine (III).—A mixture of 5.0 g. of 6,9-dichloro-2-methoxyacridine and 10.0 g. of redistilled methylaminoethanol was stirred in a heating bath maintained at 110–112°. An exothermic reaction was noted and the internal temperature rose a degree above the external while the solid dissolved (0.75 hr.). After an additional 0.25 hr. the product crystallized; after a further 0.5 hr., the mixture was cooled, diluted with 50 ml. of ethanol, filtered, washed, and dried. The yield was 4.4 g. (69%), m.p. 173–180°. An analytical sample melted at 185–186° on rapid heating; on slower heating, an intramolecular reaction apparently occurred and a high-melting product was formed.

(9) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 170.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2$: C, 64.38; H, 5.41; N, 8.83; Cl, 11.17. Found: C, 64.59; H, 5.51; N, 8.63; Cl, 11.22.

(6-Chloro-2-methoxy-9-acridinyl)-2-hydroxyethyl Ether.—A mixture of 1.0 g. of the 9-amino compound and 10 ml. of ethylene glycol was stirred and heated in a bath held at 115 ± 2° for 15 min. The product precipitated from the solution, was removed by filtration and washed. It weighed 0.8 g. (83%), m.p. 212–217°. Recrystallization from ethanol gave the analytical sample reported in Table I.

The compounds in Table II were synthesized by well known methods of amination and chlorination.[3] An example of the former is included.

7-Chloro-4-(2-hydroxyethyl)methylaminoquinoline (VII).—A mixture of 20 g. (0.1 mole) of 4,7-dichloroquinoline and 15 g. of methylaminoethanol was stirred and heated. At 115° the reaction became exothermic and proceeded at 115–120° without further heating, and was complete after an hour's heating at 120°. The mixture was taken up in dilute acetic acid, filtered, and the nitric acid salt precipitated by addition of a large excess of saturated sodium nitrate (alternatively the base was precipitated with alkali and recrystallized). The crude material weighed 26 g.; recrystallization from water gave 16.5 g., m.p. 132–135° (55%).

Physical Measurements.—Ultraviolet spectra were determined on a Beckman Model DU spectrophotometer, the pH determinations on a Beckman pH meter with glass electrode. In the latter, an accurately weighed sample of 1 mmole of base was dissolved in a small amount of ethanol, 0.5 meq. of standardized 0.1 *N* hydrochloric acid was added, and the mixture made up immediately to 500 ml. containing in all 100 ml. of ethanol. The pH was measured immediately. As a check, a solution of 1 meq. of the nitric acid salt half-neutralized with standard sodium hydroxide was diluted to the same concentration and the pH measured immediately.

Acknowledgment.—The technical assistance in the determination of physical constants by Miss Evelyn R. Breuninger, Mr. Richard H. Creech, and Mrs. Ann J. Miller is gratefully acknowledged.