guanazole. The 2-methyl group obliterates not only the effects based upon tautomerism in the 1-phenylguanazole but, presumably, also that of some of the ionic contributions. As a consequence, the original pattern is really lost, and a faint memory is apparent only at the inflection points.

The 1-aryl-3,5-diimino-1,2,4-triazolidine structure (*i.e.*, I) for the 1-arylguanazoles has been preferred by Pellizzari.[14] This diimino formula does not readily explain the loss of only one nitrogen atom when 1-phenylguanazole is treated with caustic[15] and the behavior on acetylation.[15] The formation of monohydrochlorides and picrates[14,15] by the 1-arylguanazoles may not necessarily be considered in this matter, for it is well known that the mutual proximity of potentially basic groups may prevent the full showing of the basic properties. As examples of this behavior, one may cite certain polynitrogen heterocycles which form only monosalts.[16–18] Mann and Watson[19] have discussed salt formation in polyamine types, and they comment, *inter alia*, "it is suggested that the positive pole created by the initial salt formation exerts a strong electronic attraction, and this attraction, relayed by the inductive or mesomeric effect, may virtually immobilize the lone pair of electrons on a neighboring nitrogen atom and so deactivate this atom." Evidence here presented renders it desirable that the 1-substituted guanazoles should be considered to have the amino-imino structures indicated as III or IV rather than as diimino compounds as I. It does not appear to be possible to exclude the possibility of structure V, use of which has been made in the formulation of the products obtained from 1-phenylguanazole and isothiocyanates.[20]

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TABLE III
SPECTRAL CHARACTERISTICS OF SOME GUANAZOLE DERIVATIVES

Guanazole derivatives	Maxima[a]; λ in mμ, ε × 10³ — Ethanol λ	ε	0.01 *N* HCl λ	ε	0.01 *N* NaOH λ	ε
1-Phenyl	266	10.6	250	8.4	254	8.9
	(238	4.0)	(237	6.6)	(232	5.1)
2-Methyl-1-phenyl	216	30.0	224	19.7	220	22.1[b]
	245	7.0[b]	(218	18.1)	260	6.1[b]

[a] Values for minima given in parentheses. [b] Inflection point.

Experimental

1-Arylguanazoles.—All guanazoles were prepared as described in another publication.[2]

Absorption Spectra.—The spectrophotometric studies were all carried out with a Beckman quartz spectrophotometer, model DU, serial no. D-377. The method and solvents used have been described in other contributions from these laboratories.[5,6]

Acknowledgments.—To Dr. E. J. Lawson we owe much for his helpful counsel and patience in discussions concerning the potential ionic configurations in 1-arylguanazoles. A considerable portion of the spectrophotometric studies have been due to the efforts of Mrs. M. Becker and Mr. M. Priznar.

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RENSSELAER, N. Y.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Some 9-Amino-3-nitroacridine Derivatives

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A series of 9-amino-3-nitroacridine types bearing hydroxylated side-chains was prepared for investigation as potential chemotherapeutic agents. In most cases, the 6,7-positions of the acridine nucleus were substituted, as by dimethoxy, methylenedioxy and ethylenedioxy groups; two derivatives of 9-amino-7-butoxy-3-nitroacridine also were made.

It appears that the investigation of 9-amino-3-nitroacridine derivatives has been largely neglected because little antimalarial activity has been found in this type[2]; the most interesting property in the group lies in their activity against microörganisms, which is even exhibited by 9-amino-3-nitroacridine itself.[3–6a] 9-(3-Diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine (I), also known as Nitroakridine 3582 (Hoeschst) and 3043B for Entozon (Entozon is a mixture of I with 6,9-diamino-2-ethoxyacridine, Rivanol, and urea), and its salts have been the most carefully studied of the 9-amino-3-nitroacridines.[1,6–11] It has been claimed that this compound, and certain salts and combinations containing it, possess activity against

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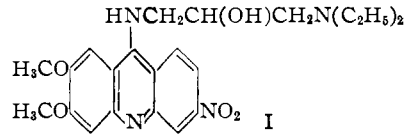
(11) K. Streitwolf and H. Oesterlin, German Patents, 613,349; 618,567.

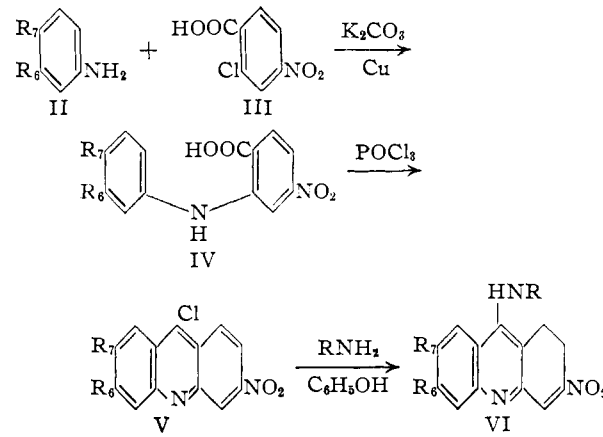
bacteria,[9-12] rickettsia,[5,13-15] viruses,[6,16-20] trichomonads[21] and babesiidae.[9] While certain antibiotics have ranges of activity which include those mentioned, this investigation was begun before such were well studied and was particularly concerned with those bearing an hydroxylated basic chain attached to position 9 of a 3-nitroacridine nucleus with at least one alkoxy group in position 6 or 7 or with a methylenedioxy- or ethylenedioxy group bridging positions 6 and 7.



I

The synthesis of the 9-chloro-3-nitroacridines required for reaction with the various amines was accomplished by the Ullmann reaction[22] as modified by Leśniański.[23,24] In this procedure, the intermediate N-arylanthranilic acids (*e.g.*, IV) prepared from an aniline (II) and a 2-halobenzoic acid (*e.g.*, III) undergo cyclization to the 9-chloroacridine (*e.g.*, V) by the action of phosphorus oxychloride. In the reactions of 2-chloro-4-nitrobenzoic acid with 3,4-dimethoxyaniline, 3,4-methylenedioxyaniline and 3,4-ethylenedioxyaniline, methanol or ethanol were satisfactory solvents, but with 4-butoxyaniline it was necessary to use pentanol (*cf.* refs. 25–27). The purified N-arylanthranilic acids were all cyclized without difficulty by use of phosphorus oxychloride in toluene.

The reaction of the 9-chloro-3-nitroacridines (V) with aliphatic amino compounds bearing hydroxyl groups, in phenol as a solvent (*cf.* refs. 27, 28), was exothermic but readily controlled; this produced the type VI of which I is an example. 7-Butoxy-9-chloro-3-nitroacridine, 9-chloro-6,7-methylenedioxy-3-nitroacridine and 9-chloro-6,7-ethylenedioxy-3-nitroacridine were caused to react with 3-diethylamino-2-hydroxypropylamine (VII) and N-(2-



hydroxyethyl) ethylenediamine (VIII). 9-Chloro-6,7-dimethoxy-3-nitroacridine was caused to react with these amines (in the case of VII, compound I being produced) and also N-(2-hydroxypropyl)-ethylenediamine (IX), N-(2-hydroxy-2-methylpropyl)-ethylenediamine (X), N-(2-hydroxyethyl)-1,3-propanediamine (XI), N-(2-hydroxy-2-methylpropyl)-1,3-propanediamine (XII) and N-(2-hydroxyethyl)-1,7-heptanediamine (XIII). The compounds produced by use of the amine VII were, ordinarily, the most difficult to purify. Since the hydrochlorides of the 9-amino-3-nitroacridines (Table I) lost hydrogen chloride readily upon drying at elevated temperatures, it was advisable to dry the products at room temperature. Several of the compounds thus obtained were hydrated. It was of interest that, while several of the intermediates did not give concordant values for nitrogen by the Dumas method,[29] most of the final products offered little difficulty.

The testing of the compounds herein described will be reported subsequently by other members of this Institute.

Experimental[30]

A. 9-Chloro-3-nitroacridines. I. 7-Butoxy-9-chloro-3-nitroacridine.—4-Butoxynitrobenzene was obtained in 68.5% yield by the action of butyl bromide upon potassium 4-nitrophenolate in butanol.[31] Use of butyl iodide gave yields of 54–58%.[32] The reduction of the nitro compound to 4-butoxyaniline in methanol with Raney nickel catalyst (25°, 80 atm.) gave a conversion of 92.5%; b.p. 95–98° (1 mm.).

Thirty-three grams (0.2 mole) of 4-butoxyaniline, 35.3 g. (0.26 mole) of powdered, anhydrous potassium carbonate, 36.3 g. (0.18 mole) of 2-chloro-4-nitrobenzoic acid[33] and 0.5 g. of copper powder in 150 cc. of pentanol were stirred and refluxed for 5 hr. The excess amine and solvent were steam distilled, the residues diluted to 500 cc. with water, boiled with Darco G-60 and filtered. Acidification of the cooled filtrates gave 56.0 g. (85% yield) of crude greenish product, m.p. 170–174°. To obtain pure N-(4′-butoxyphenyl)-4-nitroanthranilic acid from the crude, it was necessary to crystallize from 85% ethanol, dissolve the greenish solid in

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(29) Satisfactory nitro nitrogen values were obtained in such cases by use of the method described by S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," John Wiley and Sons, Inc., New York 16, N. Y., 1949, p. 82.

(30) All melting points recorded were corrected, whereas boiling points were not.

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(32) G. O. Gutekunst and H. LeB. Gray, THIS JOURNAL, **44**, 1742 (1922).

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caustic and re-precipitate after treatment with Darco. The product crystallized from 80% ethanol as orange blades, m.p. 197.3–197.8°, yield 64.5%.

Anal. Calcd. for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.81; H, 5.60; N, 8.27.

Cyclization of N-(4′-butoxyphenyl)-4-nitroanthranilic acid to 7-butoxy-9-chloro-3-nitroacridine was accomplished by use of phosphorus oxychloride in toluene as described below for the 6,7-dimethoxy type. The pure compound was obtained in 69% yield after three crystallizations from heptane; long, golden-brown needles, m.p. 159–160°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.51; Cl, 10.72; N, 8.47. Found: C, 61.60; H, 4.51; Cl, 10.79; N, 8.52.

II. **9-Chloro-6,7-dimethoxy-3-nitroacridine.**[34]—4-Nitroveratrole was prepared in 75% pure yield from veratrole.[35] A suspension of 450 g. (2.46 mole) of 4-nitroveratrole in 1.4 l. of ethanol was reduced at 25° and 50 atm. with 10% palladium–charcoal catalyst. The reduction mixture containing 4-aminoveratrole was filtered and kept under nitrogen. A mixture of 337 g. (2.44 moles) of anhydrous potassium carbonate, 492 g. (2.66 moles) of 2-chloro-4-nitrobenzoic acid and 0.5 l. of water at 60° was prepared, then the solution of 4-aminoveratrole, 25 g. of copper powder and 25 g. of Filter-cel were added. The mixture was stirred vigorously and the alcohol removed until the still temperature reached 92°, then refluxed for 5 hr. The solids which were collected were extracted with 2 l. of boiling water after mixing with 25 g. of Darco G-60 and 50 g. of Filter-cel; the filter-cake was re-extracted with the boiling liquors, then chilled. The potassium salt of N-(3,4-dimethoxyphenyl)-4-nitroanthranilic acid was collected from the extracts (357 g.) and the liquors concentrated. A total yield of 392 g. (45%) of the salt was obtained; acid isolated from the salt melted at 221–223.5°.

A mixture of 356.3 g. (1.0 mole) of potassium N-(3,4-dimethoxyphenyl)-4-nitroanthranilate and 3.5 l. of toluene was stirred while *ca.* 0.5 l. of distillate was collected to ensure anhydrous conditions before the addition of 220 cc. (368 g., 2.4 moles) of phosphorus oxychloride during 15 minutes. The well-stirred mixture was refluxed for 3 hr. and then 0.5 l. of distillate removed *in vacuo*. Cooling of the residue gave the phosphorus salt of 9-chloro-6,7-dimethoxy-3-nitroacridine, which was collected, then washed with toluene and ether. The complex was decomposed by gradually adding it to a well-stirred mixture of 310 cc. of 35% sodium hydroxide solution, 1300 cc. of water and 1300 g. of ice and stirring for 2 or 3 hr. at 0°. A brownish product resulted; this was washed free of alkali, air-dried and washed with benzene. The 9-chloro-6,7-dimethoxy-3-nitroacridine was boiled with 4 l. of ethylene dichloride for 2 hr., cooled and the light yellow product dried. A yield of 230 g. (72%) resulted, m.p. 246–248° dec.

III. **9-Chloro-6,7-methylenedioxy-3-nitroacridine.**—A portion of the required 3,4-methylenedioxyaniline was obtained in 88% yield, b.p. 85–86° (1 mm.) (m.p. 44.5–45.5°), from the reduction of 3,4-methylenedioxynitrobenzene in methanol with Adams catalyst at 3 atm. hydrogen pressure. The nitro compound was a by-product from the preparation of 6-nitropiperonal[36] or made from 1,2-methylenedioxybenzene[37] by nitration.[38] Some had been prepared earlier by a Hofmann degradation of piperonylamide.[39]

The reaction of 3,4-methylenedioxyaniline, 2-chloro-4-nitrobenzoic acid and potassium carbonate in the presence of copper powder and Filter-cel was carried out after the method described for 4-aminoveratrole. A 91% yield of crude N-(3,4-methylenedioxyphenyl)-4-nitroanthranilic acid (m.p. *ca.* 210°) was collected; two crystallizations from 60% methanol (charcoal) gave a 60% yield of pure compound. The beautiful garnet plates melted at 246–247°.

Anal. Calcd. for $C_{14}H_{10}N_2O_6$: C, 55.63; H, 3.34; N, 9.27. Found: C, 55.52; H, 3.36; N, 9.40.

Conversion of the above acid to 9-chloro-6,7-methylenedioxy-3-nitroacridine followed the same pattern as the related types. The crude material was crystallized from chlorobenzene to give the desired compound as fluffy yellow needles, m.p. >300°, in a purified yield of 63%.

Anal. Calcd. for $C_{14}H_7ClN_2O_4$: C, 55.55; H, 2.33; Cl, 11.71; N,[29] 4.63. Found: C, 55.51; H, 2.33; Cl, 11.82; N,[29] 4.57.

IV. **9-Chloro-6,7-ethylenedioxy-3-nitroacridine.**—1,4-Benzodioxane (1,2-ethylenedioxybenzene) was made by the method of Ghosh.[40] The nitration according to the directions of Vorländer[41] was not particularly satisfactory, but the modification of Heertjes, *et al.*,[42] readily gave 80% yields of pure 4-nitro-1,2-ethylenedioxybenzene even with large batches.

The reduction of pure 4-nitro-1,2-ethylenedioxybenzene with Adams catalyst at 40° and 3 atm. was run in methanol. The filtered reduction liquors were employed in the same manner as described above for the 3,4-dimethoxyaniline; N-(3,4-ethylenedioxyphenyl)-4-nitroanthranilic acid was isolated in 69% yield (after one crystallization from dilute ethanol with use of Darco G-60; m.p. *ca.* 235°). Further crystallization gave the pure compound in the form of golden needles, m.p. 249–250.5°.

Anal. Calcd. for $C_{15}H_{12}N_2O_6$: C, 56.96; H, 3.83; N,[29] 4.43. Found: C, 57.23; H, 3.53; N,[29] 4.32.

Interaction of the anthranilic acid type with phosphorus oxychloride in toluene was accomplished in the usual manner. The 9-chloro-6,7-ethylenedioxy-3-nitroacridine isolated after one crystallization from xylene melted *ca.* 285° (86.5% yield). Further crystallization from chlorobenzene (followed by extraction with boiling ether to remove the adhering solvent) produced the pure compound; orange microcrystals, m.p. 298.7–299.5° (76% yield from the acid).

Anal. Calcd. for $C_{15}H_9ClN_2O_4$: C, 56.88; H, 2.87; Cl, 11.19; N,[29] 4.43. Found: C, 56.96; H, 2.92; Cl, 11.23; N,[29] 4.23.

B. **Side-Chains. 3-Diethylamino-2-hydroxypropylamine (VII) and N-(2-hydroxyethyl)-ethylenediamine (VIII)** were redistilled commercial products.

N-(2-Hydroxypropyl)-ethylenediamine (IX), b.p. 88–91° (3 mm.), $n^{25}D$ 1.4744, was obtained in 48% yield from ethylenediamine and propylene oxide.[43] The by-product, N,N′-bis-(2-hydroxypropyl)-ethylenediamine, was isolated in 21.5% yield; shimmering white platelets from ethanol, m.p. 147–147.5°.

Anal. Calcd. for $C_8H_{20}N_2O_2$: C, 54.51; H, 11.44; N, 15.90. Found: C, 54.80; H, 11.41; N, 15.88.

N-(2-Hydroxy-2-methylpropyl)-ethylenediamine (X), b.p. 89–93° (2 mm.), $n^{25}D$ 1.4670, was prepared (58.5% yield) from ethylenediamine and isobutylene oxide.[43] N,N′-Bis-(2-hydroxy-2-methylpropyl)-ethylenediamine was also formed (22.5% yield); it crystallized from hexane as white blades, m.p. 69.5–70°.

Anal. Calcd. for $C_{10}H_{24}N_2O_2$: C, 58.79; H, 11.84; N, 13.72. Found: C, 58.74; H, 11.12; N, 13.60.

N-(2-Hydroxyethyl)-1,3-propanediamine (XI) resulted when 2-(2-hydroxyethyl)-propionitrile was catalytically reduced in ammoniacal ethanol[44,45]; b.p. 105–107° (1 mm.), $n^{25}D$ 1.4837.

N-(2-Hydroxy-2-methylpropyl)-1,3-propanediamine (XII) was obtained by catalytic reduction of the related propionitrile in ammoniacal ethanol[46]; b.p. 102–106° (4 mm.), $n^{25}D$ 1.4672.

(34) This procedure was devised by Dr. B. F. Tullar of the Development Laboratories of this Institute during 1945. It was partly based upon experiments of Drs. C. E. Kwartler, W. Boehme and E. A. Steck. The over-all yield obtained from veratrole and 2-chloro-4-nitrobenzoic acid was uniformly about 24%, while the procedure of Miller and Wagner[7] would produce 9-chloro-6,7-dimethoxy-3-nitroacridine in *ca.* 13% yield.

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TABLE I

9-AMINO-3-NITROACRIDINE HYDROCHLORIDES

R_6	R_7	R_9[a]	Yield, %	Appearance[b]	M.p., °C.[c]	Analyses, % Calcd. N	Calcd. Cl	Found N	Found Cl
H	O(*n*-C_4H_9)	VII	58.5	Scarlet microcrystals	182–184[d]	10.72	13.57	10.58[e]	13.30[e]
		VIII	76	Orange platelets	290–292	11.89	15.04	11.86[f]	15.00[f]
OCH_3	OCH_3	VIII	71	Scarlet needles	240–243	11.96	15.14	11.74[g,h]	15.22[g,h]
		IX	78.5	Orange microcrystals	250–251	11.84	14.98	11.99	14.80
		X	70	Orange needlets	253–257	11.29	14.29	11.19[i]	14.39[i]
		XI	68	Brick red microcrystals	228–228.5	11.00	13.92	11.00[j]	13.88[j]
		XII	73	Brick red needlets	235–235.5	11.17	14.14	11.01	14.19
		XIII	65.5	Scarlet microcrystals	238–239	10.58	13.39	10.48	13.46
$-OCH_2O-$		VII	62	Bright orange prisms	251–251.5	11.54	14.61	11.32[k,l]	14.62[k]
		VIII	72.5	Orange microcrystals	>300[m]	12.38	15.67	12.42[n]	15.38[n]
$-OCH_2CH_2O-$		VIII	50	Garnet needlets	236–238	12.25	15.51	12.24	15.45
		VII	74	Russet microcrystals	198–199	10.83	13.70	10.68[o]	13.87[o]

[a] Code as given in text. [b] Method of purification as detailed for compound I except in cases of those bearing side-chain (VII), which have been noted in the Experimental. [c] Melting with decomposition unless otherwise stated. It was advisable to immerse the sample in bath at a temperature *ca.* 20° below the m.p. and heat rapidly to obtain reproducible values. [d] No decomposition. This compound was investigated as a trypanocide by R. Schnitzer and W. Silberstein [*Z. Hyg. Infektionskrankh.*, **109**, 519 (1929)], but no constants were given. [e] Hemihydrate. *Anal.* Calcd. for $C_{24}H_{32}N_4O_4 \cdot 2HCl \cdot 0.5 H_2O$: H_2O, 1.72. Found: H_2O, 1.57. [f] Dry basis; sample contained 0.61% water. [g] Hemihydrate. *Anal.* Calcd. for $C_{19}H_{22}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.92. Found: H_2O, 2.04. [h] Anhydrous material was obtained by prolonged drying at 100° (0.5 mm.) and replacing lost HCl by action of an absolute ether solution of hydrogen chloride. The product was washed with 5:1 ether–ethanol and dried; scarlet microcrystals resulted, m.p. 260–263°. *Anal.* Calcd. for $C_{19}H_{22}N_4O_5 \cdot 2$ HCl: N, 12.20; Cl, 15.44. Found: N, 12.43; Cl, 15.42. [i] Hemihydrate. *Anal.* Calcd. for $C_{21}H_{26}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.81. Found: H_2O, 1.82. [j] Dihydrate. *Anal.* Calcd. for $C_{20}H_{24}N_4O_4 \cdot 2HCl \cdot 2H_2O$: H_2O, 7.07. Found: H_2O, 6.90. [k] Dry basis; sample contained 1.23% water. [l] Dumas determination made with use of copper(II) acetate after method of D. F. Hayman and S. Adler, *Ind. Eng. Chem., Anal. Ed.*, **9**, 197 (1937). [m] Chars at *ca.* 250°. [n] Hemihydrate. *Anal.* Calcd for $C_{18}H_{18}N_4O_5 \cdot 2HCl \cdot 0.5H_2O$: H_2O, 1.99. Found: H_2O, 1.89. [o] Monohydrate. *Anal.* Calcd. for $C_{22}H_{26}N_4O_6 \cdot 2HCl \cdot H_2O$: H_2O, 3.48. Found: H_2O, 3.15.

N-(2-Hydroxyethyl)-1,7-heptanediamine (XIII).—Pimelonitrile[47] was reduced in 10% ammoniacal ethanol with Raney nickel catalyst at 60 atm. and 90°. An 88% yield of 1,7-heptanediamine was collected at 52–54° (1 mm.); this compound was prepared[48] earlier by sodium–ethanol reduction of pimelonitrile.

A solution of 33.3 g. (0.26 mole) of 1,7-heptanediamine in 100 cc. 90% methanol was stirred at 0° in a flask equipped with condenser through which brine was circulated at −10°. To this there was added 12 cc. (10.6 g., 0.24 mole) of liquefied ethylene oxide contained in a jacketed dropping funnel having brine circulated through the jacket. When addition had been completed (*ca.* 0.5 hour), the reaction mixture was allowed to warm to room temperature, and reaction caused the temperature to rise to 40°. The mixture was stirred for 3 hr., then refluxed for 1 hr. before fractionation. A yield of 20.9 g. (47%) of N-(2-hydroxyethyl)-1,7-heptanediamine (XIII) was collected at 164–168° (1 mm.), $n^{25}D$ 1.4751.

Anal. Calcd. for $C_9H_{22}N_2O$: N, 16.08. Found: N, 16.10.

C. 9-Amino-3-nitroacridines.—The 9-amino-3-nitroacridine derivatives which were prepared by the reaction of the appropriate 9-chloro-3-nitroacridine and amine in phenol melt have been presented with pertinent data in Table I. Indication of the procedure employed is given in the preparation of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine, for this is somewhat different in certain respects from those published.[7,8]

I. 9-(3-Diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine Dihydrochloride.—A melt comprised of 440 g. of phenol and 220 g. (0.69 mole) of 8-chloro-6,7-dimethoxy-3-nitroacridine was stirred under reflux at 70°. The heat was removed and 123 g. (0.84 mole) of 3-diethylamino-2-hydroxypropylamine was added at such a rate that the temperature did not exceed 95°. At the end of the addition, heating was resumed for 1 hr.; the mixture was cooled to 40° and poured into a well-stirred solution of 120 cc. of concd. hydrochloric acid in 4 l. of acetone at 20°, then stirred for an hour or two. A brick-red hydrochloride resulted and was leached well with acetone to remove phenol. The crude product was dissolved in 1 l. of water at 70–75° and charcoaled. The filtrates were at 40–45° when 350 cc. of concd. hydrochloric acid was added and thereafter cooled very slowly, then collected, slurried the product with acetone, washed with acetone and ether. This scarlet dihydrochloride was dried *in vacuo* below 50° to avoid loss of HCl; m.p. 223–225° dec. The product weighed up to 250 g. and contained some 5–9.5% moisture; the yield, on the dry basis, was 56–65%. Miller and Wagner[7] have reported a product containing 6.8% water; Hurst[19] employed a sample containing *ca.* 8% moisture.[49]

In the case of most compounds listed in Table I, the method detailed for the preparation and purification of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-dimethoxy-3-nitroacridine dihydrochloride was that followed. However, in the case of the types bearing the 3-diethylamino-2-hydroxypropylamine chain (VII), variations were desirable. In most cases the phenol melt was quenched in acetone–40% ethanolic hydrogen chloride mixture, and the crude products crystallized from ethanol–ether. A pure sample of 9-(3-diethylamino-2-hydroxypropylamino)-6,7-methylenedioxy-3-nitroacridine dihydrochloride was most readily obtained by merely extracting the crude with boiling ethanol and drying the residue. The products were, ordinarily, dried *in vacuo* over phosphoric anhydride, sodium hydroxide pellets and wax. Use of high temperatures for drying led to considerable loss of hydrogen chloride, which was sometimes difficult to replace. All determinations of water content were done by the Karl Fischer method.

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