C, 120–135°, 8.9 g. The cooled residue crystallized and was identified as 1,3-di-*n*-hexylurea, m.p. 72–74°. Analyses shown in Table V are for cut B.

Other Trialkylureas.—The properties and analyses for trialkylureas that were similarly prepared are given in Table V. When dicyclohexylamine was treated with *n*-decylamine under similar conditions, only didecylurea, m.p. 94–95°, and cyclohexylamine were recovered from the mixture.

9-Substituted 3,6-Bis(dimethylamino)acridines

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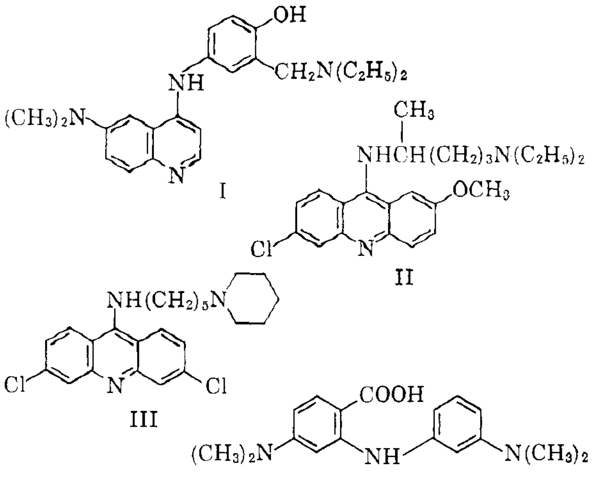
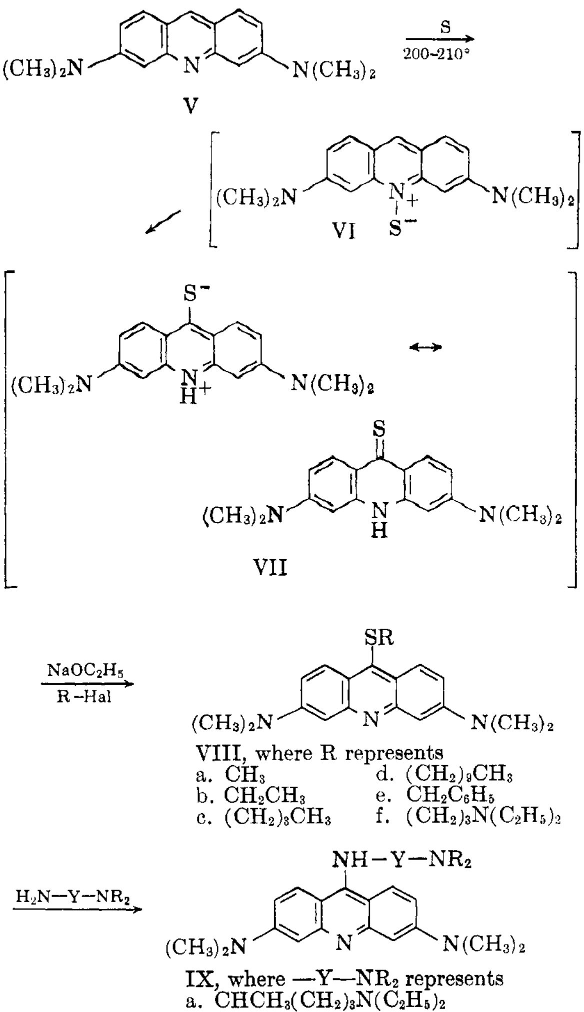
Fusion of 3,6-bis(dimethylamino)acridine and sulfur at 200–210° gave 3,6-bis(dimethylamino)-9(10H)-acridinethione. Alkylation of the sodium salt with the appropriate alkyl halide gave the corresponding 3,6-bis(dimethylamino)-9-(alkylmercapto)acridines. Condensation of 3,6-bis(dimethylamino)-9-(methylmercapto)acridine with various dialkylaminoalkylamines yielded the corresponding 3,6-bis(dimethylamino)-9-(dialkylaminoalkylamino)acridines.

During the coöperative wartime antimalarial program it was observed that α-diethylamino-4-(6-dimethylamino-4-quinolylamino)-*o*-cresol (I) was more active than quinacrine (II) against blood-induced *Plasmodium gallinaceum* in the chick.[1] Further, certain 3,6-disubstituted 9-aminoacridines exhibit unexpectedly high antiparasitic activity. Thus, 3,6-dichloro-9-[5-(1-piperidino)amylamino]-acridine (III) has been reported to be four to eight times as effective as quinacrine against the tapeworm *Hymenolepis nana.*[2] It was therefore of interest to prepare certain 3,6-bis(dimethylamino)-9-aminoacridines (IX) for antiparasitic evaluation.



Rather than attempt the preparation of the desired 3,6-bis(dimethylamino)acridines by known methods[2] *via* the difficultly accessible 2-(*m*-dimethylaminoanilino)-4-dimethylaminobenzoic acid (IV), an alternative route was sought. 3,6-Bis(dimethylamino)acridine (V), a commercially available dye known as Acridine Orange,[3] appeared to be an unusually attractive starting material, especially in view of a report by Edinger and Arnold[4] that 9-(10H)-acridinethione is obtained in 85% yield by heating acridine with sulfur in a sealed tube at 190° for four hours. Utilizing a modification of this procedure, equimolar quantities of



VIII, where R represents

a. CH_3	d. $(CH_2)_9CH_3$
b. CH_2CH_3	e. $CH_2C_6H_5$
c. $(CH_2)_3CH_3$	f. $(CH_2)_3N(C_2H_5)_2$

IX, where —Y—NR_2 represents
a. $CHCH_3(CH_2)_3N(C_2H_5)_2$
b. $(CH_2)_3N[(CH_2)_2]_2O$
c. $(CH_2)_3N(CH_2CH_2OH)_2$

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[1] F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. T. Edwards, Ann Arbor, Mich., 1946, p. 1255.

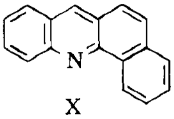
[2] F. H. Tendick, P. E. Thompson, and E. F. Elslager, U. S. Patent 3,012,036 (1961).

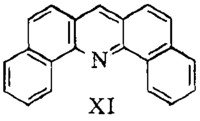
[3] Purchased from National Aniline Division, Allied Chemical Corp., New York 6, N. Y.

[4] A. Edinger and W. Arnold, *J. prakt. Chem.*, **64**, 182 (1901).

3,6-bis(dimethylamino)acridine (V) and resublimed sulfur were heated in an open flask at 200–210° for one-half hour. The mixture was cooled and the clinker-like residue was pulverized. Crystallization from pyridine or dimethylformamide gave 3,6 - bis(dimethylamino) - 9(10H) - acridinethione (VII) as shimmering reddish brown crystals with a purple luster, m.p. 360–361°. Alkylation of the sodium salt of VII with the appropriate alkyl halide gave the corresponding 3,6-bis(dimethylamino)-9-(alkylmercapto)acridines (VIIIa–f) (Table I) (methods I and II). Condensation of 3,6 - bis(dimethylamino) - 9 - (methylmercapto)-acridine (VIIIa) with the requisite dialkylaminoalkylamine afforded the corresponding 3,6-bis(dimethylamino) - 9 - (dialkylaminoalkylamino) - acridines (IXa–c).

The possibility that the high temperature reaction between 3,6-bis(dimethylamino)acridine and sulfur might be a free radical reaction was considered, but the probability was diminished by the observation that the yield of 3,6-bis(dimethylamino)-9(10H)-acridinethione was not affected when the reaction was carried out in the presence of 1% of free radical inhibitors such as hydroquinone and diphenylamine. Further, attempts to extend the reaction of Edinger and Arnold to certain acridine compounds containing a hindered nitrogen atom failed. Thus, only starting materials were isolated from the fusion of sulfur with benz[c]-acridine (X) or dibenz[c,h]acridine (XI) at 210–215°. Indeed, other workers[5–7] have observed similar steric effects during attempts to prepare N-oxides of various heterocyclic compounds having a hindered nitrogen atom. It therefore seems likely that sulfur initially attacks the acridine nitrogen atom to form the N-sulfide (VI), followed by a rearrangement of the N-sulfide to the acridinethione VII.


X


XI

Absorption in the ultraviolet and low wave length visible range was used to assist in the characterization of the 9-substituted 3,6-bis(dimethylamino)acridines described. A comparison of the spectra of several representative compounds is shown in Fig. 1. The solid line represents 9-(10H)-acridinethione, the heavy broken line represents 3,6 - bis(dimethylamino) - 9(10H) - acridinethione, and the light broken line represents 3,6-bis(dimethylamino)-9-(methylmercapto)acridine. The spectrum of 9(10H)-acridinethione has features similar to those observed for acridone and for 9-imino-10-methylacridan,[8] which includes a very intense band at low wave length, a middle band of moderate intensity, and an intense highly resolved band at long wave length. Introduction of dimethylamino groups in the 3,6-positions produces a bathochromic shift of the intense band with some decrease in intensity, and a hypsochromic shift and increase in intensity of the band at long wave length. With the 9-methylmercapto compound, the intense band is shifted further to long wave length, while the long wave length band has moved well out into the visible.

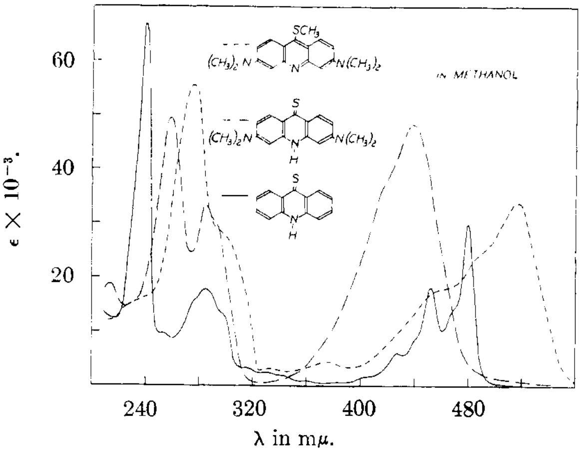


Fig. 1.—Absorption in methanol taken with a Cary-11 spectrophotometer.

Experimental[9]

3,6-Bis(dimethylamino)-9(10H)-acridinethione (VII).—A thoroughly pulverized mixture of 92 g. (0.347 mole) of 3,6-bis(dimethylamino)acridine (V) and 12 g. (0.375 mole) of resublimed sulfur was poured into a 1-l. round-bottom flask and the flask was placed in an oil or silicone bath that had been pre-heated to 190–200°. The bath temperature was subsequently maintained at 200–210° for 0.5 hr. during which time the mixture progressively melted to a black sirup, foamed, and resolidified. Hydrogen sulfide was evolved during the reaction. The flask was removed from the heating bath and allowed to cool. The coke-like residue was pulverized to give 101 g. (98%) of crude 3,6-bis(dimethylamino)-9(10H)-acridinethione as a reddish brown powder, m.p. <300°. Crystallization from boiling pyridine or dimethylformamide gave 85 g. (83%) of shimmering reddish brown crystals with a purple luster, m.p. 360–361°.

Anal. Calcd. for $C_{17}H_{19}N_3S$: C, 68.65; H, 6.44. Found: C, 68.39; H, 6.53.

Methods for Preparing 3,6-Bis(dimethylamino)-9-(alkylmercapto)acridines (VIIIa–f) (Table I). Method I.—To a solution of 3.0 g. (0.13 mole) of sodium in 300 ml. of absolute ethanol was added 32 g. (0.108 mole) of 3,6-bis(dimethylamino)-9(10H)-acridinethione (VII) and the mixture was boiled under reflux for 1 hr. The mixture was cooled to 50° and to it was added in small portions over a period of 0.5 hr. 17 g. (0.12 mole) of methyl iodide in 50 ml. of absolute

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[5] S. Maffei, *Gazz. chim. ital.*, **76**, 239 (1946).

[6] F. Linsker and R. L. Evans, *J. Am. Chem. Soc.*, **68**, 874 (1946).

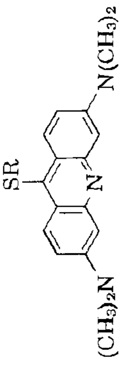
[7] I. J. Pachter and M. C. Kloetzel, *ibid.*, **73**, 4958 (1951).

[8] R. M. Acheson, "Acridines," Interscience Publishers, Inc., New York, N. Y., 1956, p. 289.

[9] Melting points are uncorrected.

TABLE I

3,6-BIS(DIMETHYLAMINO)-9-(ALKYLMERCAPTO)ACRIDINES[a]



Alkyl halide used	R	M.p., °C.	Yield purified, %	Procedure	Purification solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3I	CH_3	178–179	81	I	A	$C_{18}H_{21}N_3S$	69.42	69.09	6.80	6.79	13.49	13.37
CH_3CH_2Br	CH_2CH_3	186–187	33	I	C	$C_{19}H_{23}N_3S$	70.11	70.29	7.12	7.21	12.91	12.88
$CH_3(CH_2)_3Br$	$(CH_2)_3CH_3$	151–152	66	I	A	$C_{21}H_{27}N_3S$	71.34	71.08	7.70	7.32		
$CH_3(CH_2)_9Br$	$(CH_2)_9CH_3$	56–59	20	I	C	$C_{27}H_{39}N_3S$	74.09	74.17	8.98	9.39	9.60	9.89
$C_6H_5CH_2Cl$	$CH_2C_6H_5$	183–184	35	I	B	$C_{24}H_{25}N_3S$	74.38	74.36	6.50	6.59	10.84	10.77
$(C_2H_5)_2N(CH_2)_3Cl$	$(CH_2)_3N(C_2H_5)_2$	192–194	21	II	A	$C_{24}H_{34}N_4S.2C_7H_6O_3$	66.44	66.15	6.75	6.98	8.16	8.34

[a] The 3,6-bis(dimethylamino)-9-mercaptoacridines varied from orange to red in color. [b] A, ethanol–water; B, ethanol; C, acetone.

ethanol with mechanical stirring. Stirring was continued at room temperature for 16 hr. and the mixture was filtered leaving 3 g. of unchanged acridinethione. The dark reddish brown filtrate was heated to boiling, treated with decolorizing charcoal, and filtered. The filtrate was heated to boiling, hot water was added, and the mixture was cooled in an ice bath. The orange crystals were collected and dried *in vacuo;* weight, 27 g. (81%), m.p. 171–173°. The crude product was crystallized twice from ethanol (decolorizing charcoal) to give the desired 3,6-bis(dimethylamino)-9-(methylmercapto)acridine as feathery orange-red needles, m.p. 178–179° after drying *in vacuo* at 100° for 36 hr.

Method II.—To a solution of 1.5 g. (0.066 mole) of sodium in 150 ml. of absolute ethanol was added 18 g. (0.06 mole) of 3,6-bis(dimethylamino)-9(10H)-acridinethione and the mixture was boiled under reflux for 2 hr. To this boiling mixture was added in small portions over a period of 0.5 hr. 9.9 g. (0.066 mole) of 3-diethylaminopropyl chloride with mechanical stirring. Reflux was maintained for 15 hr. and the hot mixture was filtered and diluted with hot water. Upon cooling, the orange base was collected by filtration, suspended in excess 5 *N* sodium hydroxide solution, and extracted with ether. The dried ether extracts were treated with a solution of 25 g. of salicylic acid in 200 ml. of dry ether and the crude 3,6-bis(dimethylamino)-9-(3-diethylaminopropylmercapto)acridine disalicylate that precipitated was collected by filtration and crystallized from ethanol–water (decolorizing charcoal); yield, 8.6 g. (21%), m.p. 192–194°.

9-(4-Diethylamino-1-methylbutylamino)-3,6-bis(dimethylamino)acridine Disalicylate (IXa).—A mixture of 16 g. (0.0515 mole) of 3,6-bis(dimethylamino)-9-(methylmercapto)acridine (VIIIa) and 25 g. (0.158 mole) of N^1,N^1-diethyl-1,4-pentanediamine was stirred and heated at 140° for 5 hr. Methyl mercaptan was evolved during the reaction and the solid dissolved. Upon cooling, the mixture was slowly poured into 300 ml. of water with vigorous mechanical stirring. Stirring was continued for 1 hr. and the sticky orange precipitate was collected by filtration. The crude product was suspended in a solution of 20 g. of sodium hydroxide in 150 ml. of water, and the base was extracted with several 200 ml. portions of ether in which it was difficultly soluble. The combined ether extracts were dried over anhydrous potassium carbonate, the drying agent was collected, and the orange-red filtrate was treated with a solution of 16 g. of salicylic acid in 100 ml. of anhydrous ether. A red oil separated, the ether was decanted, and the residue was washed with anhydrous ether. Crystallization from an acetone–ether mixture gave 18.3 g. (51%) of bright orange-yellow crystals. The compound softened at 127–130°, resolidified and melted again at 168–172°.

Anal. Calcd. for $C_{26}H_{39}N_6 \cdot 2C_7H_6O_3 \cdot H_2O$: C, 67.11; H, 7.46; N, 9.78; H_2O, 2.52. Found: C, 67.13; H, 7.45; N, 9.94; H_2O (Karl Fischer), 2.68.

3,6-Bis(dimethylamino)-9-[3-(4-morpholinyl)propylamino]acridine Trihydrochloride (IXb).—A mixture of 4.0 g. (0.013 mole) of 3,6-bis(dimethylamino)-9-(methylmercapto)acridine (VIIIa) and 15 g. of phenol was stirred and heated on the steam bath for 15 min. Subsequently, 2.1 g. (0.0145 mole) of 1-(3-aminopropyl)morpholine was added and the mixture was stirred and heated on the steam bath for 3 hr. Upon cooling, the mixture was slowly poured into a solution of 8 ml. of concentrated hydrochloric acid in 75 ml. of acetone with vigorous stirring. The orange-yellow solid that separated was collected by filtration and was crystallized twice from an ethanol–acetone mixture. The product was dried *in vacuo* at 60° and allowed to equilibrate in the air; yield, 5.5 g. (72%), m.p. 178–180° dec.

Anal. Calcd. for $C_{24}H_{33}N_5O \cdot 3HCl \cdot 4H_2O$: C, 48.94; H, 7.53; N, 11.89; Cl^-, 18.06. Found: C, 48.68; H, 7.21; N, 12.13; Cl^-, 18.20.

2,2′-{3-[3,6-Bis(dimethylamino)-9-acridinylamino]propylimino}diethanol Trihydrochloride (IXc).—Utilizing the procedure described under IXb above, 6.2 g. (0.02 mole) of 3,6-bis(dimethylamino)-9-(methylmercapto)acridine and 3.5 g. (0.02 mole) of 2,2′-(3-aminopropylimino)diethanol afforded 6.1 g. (54%) of orange crystals from ethanol-acetone, m.p. 154° dec.

Anal. Calcd. for $C_{24}H_{35}N_5O_2 \cdot 3HCl \cdot 2H_2O$: C, 50.48; H, 7.42; N, 12.27; Cl^-, 18.63; H_2O, 6.31. Found: C, 50.63; H, 7.29; N, 12.19; Cl^-, 18.27; H_2O (Karl Fischer), 6.05.

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The Mesylation of Kojic Acid and Other 3-(or 5)-Hydroxy-4H-pyran-4-ones. Displacement of a Mesyloxy Group under Acidic Conditions[1,2]

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With methanesulfonyl chloride in pyridine in a short term reaction, kojic acid gave the dimethanesulfonate. A long term reaction led to an oily product, which with hydrochloric acid yielded 2-chloromethyl-5-mesyloxy-1,4-pyrone. Pyridinium salts from kojic acid dimethanesulfonate and several 2-halomethyl-1,4-pyrone derivatives are described. The mesyloxy group of kojic acid dimethanesulfonate is displaced in hydrobromic and hydrochloric acids to afford the 2-halomethyl derivative.

Kojic acid (I), available from the action of a variety of microörganisms on several carbohydrates, is potentially an important synthetic precursor of many 1,4-pyrone (4H-pyran-4-one) derivatives.[3] The present paper describes the preparation of kojic acid dimethanesulfonate from I and excess methanesulfonyl chloride, as well as mesyl derivatives of related 3-(or 5)-hydroxy-1,4-pyrones.[4] The initial aim of the present study, to block selectively the enolic hydroxyl group of I by interaction of I with one mole of methanesulfonyl chloride, did not prove feasible. There is reported the isolation of 2-chloromethyl-5-mesyloxy-1,4-pyrone from the action of hydrochloric acid on an unidentified long-term mesylation product of I. The reaction of kojic acid dimethanesulfonate with hydrohalogen acids is included, as well as certain interconversions of 2-halomethyl-1,4-pyrone derivatives.

Reaction of kojic acid (I) with methanesulfonyl chloride in pyridine, over a relatively long term of forty-eight hours, did not lead to a water-insoluble product. By extraction procedures, an oily product was obtained, which upon treatment with hydrochloric acid gave 2-chloromethyl-5-mesyloxy-1,4-pyrone (II) in low yield. The identity of II was confirmed by its independent preparation through mesylation of chlorokojic acid (III), and by reduction of II to give allomaltol methanesulfonate (V). Independent synthesis of V was achieved by direct mesylation of allomaltol (IV), which was prepared from III by a modification (sequel) of Yabuta's reduction procedure.[5] These reactions are summarized in Chart I.

In view of the well known tendency of reactive sulfonic esters to undergo quaternization in pyridine,[6] a short term mesylation of I was investigated to avoid this potential side reaction. The colorless, crystalline, water-insoluble kojic acid dimethanesulfonate (VI) was obtained in yields up to 70% with a large excess of mesyl chloride in pyridine at 0° by carefully controlling the reaction period. From Fig. 1, it is evident that satisfactory yields of VI can be obtained only in a narrow time interval in the vicinity of fifteen minutes. With mesyl chloride in pyridine, the 3-(or 5)-hydroxy-1,4-pyrones allomaltol (IV), maltol (VII), and pyromeconic acid (VIII) gave the methanesulfonic esters V, IX, and X, respectively. The duration of the reaction appeared less critical in the mesylation of IV, VII, and VIII.

I. $R = H$
VI. $R = CH_3SO_2$
VII. $X = R = H; Y = CH_3$
VIII. $X = Y = R = H$
IX. $X = H; R = CH_3SO_2; Y = CH_3$
X. $X = Y = H; R = CH_3SO_2$

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[1] This investigation was supported in part by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service, and in part by a grant from the University of Nebraska Research Council.

[2] A preliminary account of this work was presented before the Organic Chemistry Division, 125th National Meeting of the American Chemical Society, Kansas City, March, 1954, Abstracts, p. 9-N.

[3] A review of the extensive literature on kojic acid is given by A. Beelik, "Advances in Carbohydrate Chemistry," Vol. 11, M. L. Wolfrom, ed., Academic Press, New York, N. Y., 1956, pp. 145–183.

[4] Properties, but not experimental procedures for preparation, of several of these derivatives are included in ref. 3.

[5] T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).