## 323. *The Preparation and Therapeutic Properties of Certain Acridine Derivatives. Part I. Anil and Styryl Derivatives of* 2 : 8-*Diaminoacridine and Acridine-5-aldehyde respectively.*

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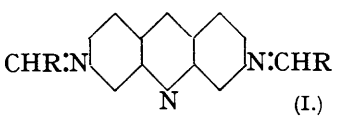
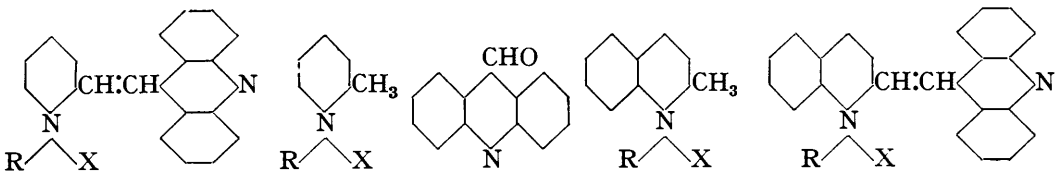
It has been shown by Browning, Cohen, Gulbransen, and others (*Proc. Roy. Soc.*, 1926, *B*, **100**, 293; 1929, **105**, 99; 1931, **108**, 119; **109**, 51; 1932, **110**, 249; 1933, **113**, 293, 300; 1934, **115**, 1; *J. Path. Bact.*, 1931, **34**, 592) that basic derivatives of various anil and styryl quinoline and benzthiazole compounds exhibit parasiticidal action. The anils in general are antiseptic *in vitro* (in serum as well as in aqueous medium) towards ordinary bacteria such as *Staphylococcus* and *B. coli*, and some of them have a therapeutic action on experimental *streptococcus* infection in mice. Certain of the styryl derivatives are effective chemotherapeutic agents in the treatment of experimental trypanosome infections.

With a view to further investigation on the relation between chemical constitution and antiseptic or trypanocidal properties, we have chosen certain types of acridine derivatives for examination. Acridine itself is known to have germicidal properties, and the 2 : 8-diamino-derivative, "Proflavine," is well known therapeutically. It seemed profitable, therefore, to examine derivatives of this substance with regard to both the effect of position of substituent groups and the type of linking of the group introduced. The preparation and properties of compounds named in the title are now described.

Anils of the general type (I) were prepared by heating 2 : 8-diaminoacridine with the requisite aldehyde in a solvent with addition of a little piperidine, which was found to be the most suitable catalyst. These anils were, however, too sparingly soluble in water, and their salts too readily hydrolysed, for biological tests. The following styryl compounds were prepared by condensing acridine-5-aldehyde with α-picolinealkiodide, type (II), or quinaldinealkiodide, type (III), with piperidine as catalyst: (1) s-(2-*pyridyl methiodide*)-




(I.)




(II.) (III.)

5-*acridylethene* (II, RX = MeI) and its *hydrochloride* (1*a*); (2) s-2-*pyridyl*-5-*acridylethene dimethiodide* (as II, RX = MeI); (3) s-(2-*pyridyl ethiodide*)-5-*acridylethene* (II, RX = EtI); (4) s-(2-*pyridyl ethiodide*)-(5-*acridyl methiodide*)*ethene*, (as II, RX = EtI); (5) s-(2-*quinolyl*

*methiodide*)-5-*acridylethene* (III, RX = MeI) and its *hydrochloride*; (6) s-2-*quinolyl*-5-*acridylethene dimethosulphate* (as III, RX = $Me_2SO_4$); (7) s-2-*quinolyl*-5-*acridylethene dimethochloride* (as III, RX = MeCl) and *dimethiodide*; (8) s-(2-*quinolyl ethiodide*)-(5-*acridyl methiodide*)*ethene* (as III, RX = EtI). In general, those styryls containing a quaternary ammonium group in both nuclei are orange or red, crystalline, and readily soluble in water.

We intend to investigate quaternary compounds of anils of type (I), also anils derived from acridine-5-aldehyde and amino-compounds of styryls derived from acridine.

Professor C. H. Browning, F.R.S., and Miss R. Gulbransen * report as follows on results of biological tests on the above compounds (1—8): "The compounds Nos. (1), (1*a*), (2), (3), (6) and (8) have been examined for antiseptic properties *in vitro* and for trypanocidal action in mice experimentally infected with *T. brucei* (the methods used were those described by us, *Brit. J. Exp. Path.*, 1921, **2**, 95; *Proc. Roy. Soc.*, 1929, *B*, **105**, 99). All these substances were moderately antiseptic towards *staphylococcus* in dilute peptone water (inhibition of growth at a concentration of 1 : 40,000 of the substances), except No. 8, which was distinctly more active. In serum, all suffered some diminution of action (inhibition of growth with concentrations of 1 : 10,000 to 1 : 20,000). For *B. coli*, the antiseptic action was much weaker than for *staphylococcus*, as was found also to be the rule generally with styryl quinoline compounds (Browning, Cohen, Ellingworth, and Gulbransen, *ibid.*, 1926, *B*, **100**, 293); but the action on *B. coli* was intensified somewhat in serum medium as compared with peptone water. All the substances were only moderately toxic for mice on subcutaneous injection, the tolerated dose ranging from 1 c.c. of a 1 : 200 dilution to 1 c.c. of a 1 : 600 dilution per 20 g. of body weight. They were all devoid of trypanocidal action. This inactivity is not surprising in view of the previous observations on related compounds, since all the substances are devoid of amino- or acylamino-groups."

## Experimental.

*Anils of* 2 : 8-*Diaminoacridine*.—The general method of preparing these compounds was to suspend 2—3 g. of diaminoacridine in 40—60 c.c. of absolute alcohol, and then add the aldehyde (about 2·5 mols.) with 6 drops of piperidine as catalyst, and heat under reflux on the water-bath. The resulting solution was allowed to cool, and if necessary concentrated, and the anil which separated was filtered off. All these anils were readily hydrolysed by acids into their components.

2 : 8-*Bisbenzylideneaminoacridine* (I, R = Ph) (1 hour's boiling) crystallised from alcohol in small, lemon-yellow, needle-shaped prisms, m. p. 220°; yield *ca.* 80% (Found: N, 10·9, 11·1. $C_{27}H_{19}N_3$ requires N, 10·9%). It is readily soluble in boiling pyridine and ethylene glycol monoethyl ether, very sparingly soluble in ether and water, and is slightly hydrolysed even by boiling water.

2 : 8-*Biscinnamylideneaminoacridine* (I, R = CHPh·CH) (½ hour's boiling) crystallised from pyridine or ethylene glycol monoethyl ether in microscopic golden-yellow needles, m. p. 252°; yield 75% (Found: N, 9·7, 9·7. $C_{31}H_{23}N_3$ requires N, 9·6%). It is readily soluble in these two solvents when hot, but very sparingly soluble in alcohol and ether.

2 : 8-*Bis*-p-*dimethylaminobenzylideneaminoacridine* (I, R = $NMe_2 \cdot C_6H_4$) (1 hour's boiling) was purified by refluxing with absolute alcohol; it formed microscopic orange-yellow, needle-shaped prisms, m. p. 230° (yield 75%), and its solubilities resembled those of the foregoing compound (Found: N, 14·9, 15·0. $C_{31}H_{29}N_5$ requires N, 14·9%). It oxidised readily, becoming brown.

2 : 8-*Bisanisylideneaminoacridine* (I, R = $C_6H_4 \cdot OMe$) (½ hour's boiling) crystallised from ethylene glycol monoethyl ether in small, lemon-yellow, needle-shaped prisms, m. p. 241—242° (Found: N, 9·6, 9·7. $C_{29}H_{23}O_2N_3$ requires N, 9·4%), readily soluble in hot alcohol, pyridine, and ethylene glycol monoethyl ether.

2 : 8-*Bis-salicylideneaminoacridine* (I, R = $C_6H_4 \cdot OH$) was prepared in a hot filtered solution of ethylene glycol monoethyl ether, being precipitated almost immediately. It was collected when cold, purified by refluxing with the same ether, washing with alcohol, and drying in a vacuum; yield 70%. It was a straw-coloured, microcrystalline powder, m. p. 282°, fairly soluble in hot pyridine, ethylene glycol monoethyl ether, nitrobenzene, and benzyl alcohol, very

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sparingly soluble in alcohol, insoluble in ether (Found : N, 10·3, 10·3. $C_{27}H_{19}O_2N_3$ requires N, 10·1%).

*Styryl Derivatives of Acridine.*—s-(2-*Pyridyl methiodide*)-5-*acridylethene* (1). To the deep brown solution of 35·3 g. of α-picoline methiodide and 31·0 g. of acridine-5-aldehyde (1 mol.) in 70 c.c. of absolute alcohol, 10 drops of piperidine were added, and the solution was boiled for 1½ hours, the whole mass becoming practically solid. It was collected hot, washed with a little absolute alcohol and ether, dried in a vacuum, and crystallised from aqueous alcohol, in which it was readily soluble; yield 50%. The substance was dimorphous, occurring in yellow leaflets or orange needles which were interconvertible by seeding a solution with the appropriate crystal; it became orange above 120°, darkened at about 215—220° and charred at about 220—225° with escape of gas (Found : N, 6·6, 6·9. $C_{21}H_{17}N_2I$ requires N, 6·6%). The *hydrochloride* (1*a*), prepared by dissolving the base in hot dilute hydrochloric acid and allowing it to cool, formed red, needle-shaped prisms, which were recrystallised from alcohol, washed with ether, and dried in a vacuum (Found : N, 6·1. $C_{21}H_{17}N_2I,HCl$ requires N, 6·1%).

s-2-*Pyridyl*-5-*acridylethene dimethiodide* (2). A suspension of 8·5 g. of (1) in 10 c.c. of ethylene glycol monoethyl ether containing 3·5 c.c. of methyl sulphate was warmed with shaking to 30—35°; reaction then commenced, the solid gradually dissolved, the temperature rose spontaneously to about 70°, and was maintained at 100° for 10—15 minutes. After cooling and standing for 24 hours, the orange-red methosulphate was collected and washed with a little absolute alcohol and much ether, a second crop being obtained by precipitation with ether. Addition of potassium iodide to a hot concentrated aqueous solution precipitated the *dimethiodide*; this crystallised from water in hydrated, red, needle-shaped prisms, which lost water on drying and became darker; addition of water restored the red colour (Found : N, 5·0, 5·2. $C_{22}H_{20}N_2I_2$ requires N, 5·0%).

s-(2-*Pyridyl ethiodide*)-5-*acridylethene* (3) was prepared in a similar way to (1) and was more soluble in water; yield 66%. It was recrystallised from water and then from alcohol and dried in a vacuum at 90°, forming orange platelets (Found : N, 6·5, 6·5. $C_{22}H_{19}N_2I$ requires N, 6·4%).

s-(2-*Pyridyl ethiodide*)-(5-*acridyl methiodide*)*ethene* (4). 6·6 G. of (3) were added gradually to 13 c.c. of methyl sulphate, and the temperature slowly raised. There was a vigorous reaction, the temperature was allowed to rise to 100° and maintained at that for 5—10 minutes. The orange-red methosulphate which separated on cooling was collected, washed with a little alcohol and much ether, and dissolved in a little hot water, and a saturated solution of potassium iodide added. The desired *substance* was immediately precipitated; it crystallised from water and then from alcohol in dark red, needle-shaped prisms, which were dried at 100° (Found : N, 4·9, 4·8. $C_{23}H_{22}N_2I_2$ requires N, 4·8%).

s-(2-*Quinolyl methiodide*)-5-*acridylethene* (5). To the dark brown solution of 16·5 g. of quinaldine methiodide and 10 g. of acridine-5-aldehyde in 75 c.c. of absolute alcohol, 8 drops of piperidine were added and the whole was boiled for 5 hours; solid soon began to separate and the solution finally became greenish-blue. The precipitate was collected hot, washed with hot alcohol, and then refluxed with 70 c.c. of absolute alcohol for 1 hour to remove a green impurity; yield 85%. It was insoluble or sparingly soluble in all the usual solvents, and separated from 50% aqueous ethylene glycol monoethyl ether as a dark brown, crystalline powder, m. p. *ca.* 220—225° (decomp.) (Found : N, 6·1, 6·2. $C_{25}H_{19}N_2I$ requires N, 5·9%). It dissolved in acids, giving a red solution which generally deposited salts (*e.g.*, sulphate or nitrate) on cooling. The *hydrochloride*, prepared by cooling a solution in hot dilute hydrochloric acid, crystallised from water in hydrated, bright red, needle-shaped prisms, which became anhydrous on drying in a vacuum (Found : N, 5·5. $C_{25}H_{19}N_2I,HCl$ requires N, 5·5%). The aqueous solution was bright red and faintly acid to litmus.

s-2-*Quinolyl*-5-*acridylethene dimethosulphate* (6) was prepared by dissolving 20 g. of (5) in 20—30 c.c. of methyl sulphate with gentle heating. At 140° a vigorous reaction took place, and after 10—15 minutes at this temperature the mixture was set aside over-night. The practically solid mass was collected, washed with ether, and recrystallised from water, in which it was extremely soluble and from which it was deposited in orange-red crystals; these, after being washed with ether and dried in a vacuum, became more orange in colour, owing possibly to loss of water. As shown by analysis, the substance was the *dimethosulphate*, the iodine having been replaced [Found : N, 4·9, 5·0; $SO_4$ (pptn. as $BaSO_4$), 33·0, 32·4. $C_{28}H_{28}O_8N_2S_2$ requires N, 4·8; $SO_4$, 32·9%]; yield 65—70%. The m. p. was indefinite; darkening began at *ca.* 230°.

The *dimethochloride* (7), obtained as an orange precipitate by addition of saturated sodium chloride solution to a hot concentrated aqueous solution of the preceding compound and cooling,

crystallised from water in small orange prisms, and was easily soluble in alcohol, more readily in water [Found : N, 6·7, 6·8; Cl (pptn. as AgCl), 15·9, 15·9. $C_{26}H_{22}N_2Cl_2$ requires N, 6·5; Cl, 16·4%]. The corresponding *dimethiodide*, prepared in a similar way with potassium iodide, crystallised from water in dark red, needle-shaped prisms (Found : N, 4·6. $C_{26}H_{22}N_2I_2$ requires N, 4·5%).

s-(2-*Quinolyl ethiodide*)-(5-*acridyl methiodide*)*ethene* (8). A solution of 17·2 g. of quinaldine ethiodide, 10·3 g. of acridine-5-aldehyde, and 10 drops of piperidine in 60 c.c. of alcohol and 10 c.c. of water was refluxed for 3 hours. The reddish-brown product was collected hot, washed with alcohol and ether, and extracted twice (2 × 20 c.c.) with boiling absolute alcohol; yield 50%; it was insoluble in the usual solvents. A suspension of this compound in 20 c.c. (large excess) of methyl sulphate was heated to 70°; a violent reaction occurred, and a red solution resulted. The temperature was kept at 100—110° for 10—15 minutes. After standing overnight, the orange-red methosulphate, which was extremely soluble in water, was collected, washed with ether, and dissolved in a little hot water. Addition of solid potassium iodide produced a bulky, bright red precipitate of the desired *compound*; this crystallised from water, aqueous alcohol, or aqueous ethylene glycol monoethyl ether in red, hydrated, needle-shaped prisms, which lost solvent in the air and became darker. The substance was dried in a vacuum at 100° (Found : N, 4·7, 4·5. $C_{27}H_{24}N_2I_2$ requires N, 4·4%). The methochloride, yellow needle-shaped prisms very soluble in water, and the methobromide, orange prisms easily soluble in water, were prepared in a similar way by using sodium chloride and potassium bromide.

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