3. *The Preparation and Therapeutic Properties of Certain Acridine Derivatives. Part III. 5-Styrylacridines and their Quaternary Salts.*

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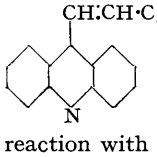
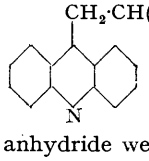
This paper deals chiefly with those 5-styrylacridines containing an amino- or dimethylamino-group in the styryl portion of the molecule, the remainder of the acridine portion being unsubstituted, and their quaternary salts. In some respects the compounds described differ from those given in the literature, as do also some of the reactions. The results of the therapeutic tests will be reported later. The work is being continued.

In Part II (J., 1938, 654) derivatives of *s*-(6-amino-2-quinolyl)-5-acridylethene and their quaternary salts were investigated. We have now prepared 5-styrylacridines of the type (I, R = NR'R'') and their quaternary salts; their therapeutic properties have been investigated.

By heating 5-methylacridine with *o*-nitrobenzaldehyde there was obtained, instead of the styryl derivative expected, the substance α-(o-*nitrophenyl*)-β-(5-*acridyl*)*ethanol* (II). Attempts to prepare the styryl derivative

(I.)  (II.) 

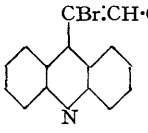
by carrying out the reaction with zinc chloride or acetic anhydride were unsuccessful, nor could the ethanol be dehydrated by acetic anhydride.

Porai-Koschitz, Solodowinkoff, and Troitzki (*Z. Farb.-Ind.*, 1907, **6**, 291) claimed the preparation of 5-m-*nitrostyrylacridine* (I, R = NO_2) by heating 5-methylacridine and *m*-nitrobenzaldehyde with anhydrous zinc chloride. They did not characterise it but converted it into the corresponding amino-compound. Friedländer (*Ber.*, 1905, **38**, 2840), who prepared it by heating the reactants alone, described it as a yellow solid, m. p. 206—208°. On repeating the former experiments, slightly modified, we obtained the nitrostyryl derivative as bright yellow crystals, m. p. 210°. Friedländer's experiment was also repeated, and we obtained the nitrostyryl derivative in small amount as a cream-coloured solid, m. p. 207°, together with a larger amount of α-(m-*nitrophenyl*)-β-(5-*acridyl*)*ethanol* (as II), a pale yellow crystalline solid, m. p. 145°, not described by Friedländer. These two 5-*m*-nitrostyrylacridines, m. p.'s 210° and 207°, gave a depression of m. p. on admixture; the difference may be due to stereoisomerism of the *cis-trans* type. The ethanol could not be dehydrated by heat to give a styryl derivative. For the purposes of this work, we used our preparation of m. p. 210°; on reduction it gave 5-*m*-aminostyrylacridine (I, R = NH_2) with properties as described by Porai-Koschitz *et al.* The *acetyl* derivative (I, R = NHAc), yellow crystals, was converted into 5-m-*aminostyrylacridine methochloride*.

By heating 5-methylacridine and *p*-nitrobenzaldehyde with zinc chloride, Porai-Koschitz *et al.* (*loc. cit.*) obtained 5-*p*-nitrostyrylacridine (I, R = NO_2) as a yellow crystalline monohydrate, becoming anhydrous at 110° and then melting at 212°, analysing both forms. We condensed the two reactants under various conditions

and in no case could this substance be obtained; instead, there resulted the anhydrous nitrostyryl derivative as yellow crystals, m. p. 293°, and showing similar solubility to the substance described by them. Heating the reactants together without zinc chloride gave, in addition to a small amount of the nitrostyryl derivative, m. p. 293°, α-(p-*nitrophenyl*)-β-(5-*acridyl*)*ethanol* (as II) as a pale yellow crystalline powder, m. p. 174°. This ethanol gave, of course, the same analysis as the monohydrated nitrostyryl derivative described by Porai-Koschitz *et al.* but was quite different—it did not lose water on heating at 110° but underwent dehydration on heating with acetic anhydride, yielding our nitrostyryl derivative, m. p. 293°. According to Porai-Koschitz, his nitrostyryl derivative gave on reduction 5-*p*-aminostyrylacridine, m. p. 209°. Our nitrostyryl derivative, m. p. 293°, however, yielded on reduction 5-p-*aminostyrylacridine* (I, R = NH_2) as a yellow crystalline powder, m. p. 242°; again, the difference in these results may be due to stereoisomerism of the *cis-trans* type. This acridine was acetylated, and through the metho-*p*-toluenesulphonate and subsequent hydrolysis with hydrochloric acid was converted into its *methochloride hydrochloride*.

5-*p*-Dimethylaminostyrylacridine (I, R = NMe_2), best prepared by the method of Porai-Koschitz, was converted through the metho-*p*-toluenesulphonate and the methiodide into the *methochloride*.



(III.)

Addition of bromine in chloroform to 5-*p*-nitrostyrylacridine in chloroform precipitated an orange-red *product* considered to be (III), substitution, not addition, having occurred (cf. Loew, *Ber.*, 1903, **36**, 1670, for a similar case).

5-*p*-Aminostyrylacridine dyed wool violet and showed a series of colour changes depending on the pH value of the solution, varying from deep violet to yellow with decreasing pH. *p*-Dimethylaminostyrylacridine also showed a similar series of colour changes from deep blue to yellow, as noted by Porai-Koschitz. Such colour phenomena, which were not shown by 5-*m*-amino- or by 5-*p*-acetamido-styrylacridine, possibly involve a tautomeric quinonoid change of the nature indicated by Porai-Koschitz *et al.* (*loc. cit.*; *Z. Farb.-Ind.*, 1906, **5**, 317). 5-*p*-Aminostyrylacridine methochloride hydrochloride, a reddish-brown crystalline powder, gave a reddish-brown aqueous solution, becoming violet-red on dilution and yellow with a drop of dilute hydrochloric acid; the dilute violet-red solution with ammonia became more violet, and with more ammonia a greenish precipitate slowly formed. The effect of sodium hydroxide was similar; in this respect the methochloride differed from the free amine, which in acid solution on addition of excess alkali gave a yellow precipitate of the free base.

The substances now described have been tested therapeutically; the results, together with others, will be discussed in a subsequent communication. 5-*p*-Aminostyrylacridine methochloride hydrochloride is moderately antiseptic and possesses slight trypanocidal action; the 5-*p*-dimethylamino-analogue is strongly antiseptic but highly toxic. We hope later to report on styrylacridines and their quaternary salts containing substituents in the acridine nucleus.

Experimental.

5-Methylacridine, prepared by Bernthsen's method (*Annalen*, 1884, **224**, 35), was purified through the tartrate (Koenigs, *Ber.*, 1899, **32**, 3607). The *metho*-p-*toluenesulphonate* resulted from heating molecular quantities of the reactants for 2 hours at 145° with occasional stirring. The cold powdered melt could be recrystallised from alcohol with considerable loss and then from alcohol with addition of ether (Found: N, 3·7; S, 8·5. $C_{22}H_{21}O_3NS$ requires N, 3·7; S, 8·5%). The compound, a pale yellow crystalline powder, melted at 204° and was fairly soluble in alcohol, and readily soluble in water to a greenish-yellow solution with intense greenish fluorescence. Addition of ammonia or sodium hydroxide to the solution gave a white precipitate of, presumably, the acridinium base.

5-*Methylacridine and* o-*Nitrobenzaldehyde.*—α-(o-*Nitrophenyl*)-β-(5-*acridyl*)*ethanol* (II) was obtained in 81% yield by heating molecular quantities of 5-methylacridine and *o*-nitrobenzaldehyde at 100° for 6 hours, and was recrystallised twice from benzene, forming a pale yellow, crystalline powder, m. p. 177° (Found: C, 73·2; H, 4·7; N, 8·2. $C_{21}H_{16}O_3N_2$ requires C, 73·2; H, 4·7; N, 8·1%); it was sparingly soluble in the usual solvents except pyridine and glacial acetic acid. On attempted reduction with stannous chloride and hydrochloric acid it decomposed into 5-methylacridine. Heating alone at 110° or with acetic anhydride failed to effect dehydration to the styryl derivative, which also was not produced on carrying out the reaction in presence of zinc chloride or acetic anhydride.

5-*Methylacridine and* m-*Nitrobenzaldehyde.*—Since the original method of Porai-Koschitz *et al.* gave much tar, the temperature was reduced from 140—150° to 130°. 5 G. of 5-methylacridine and 3·92 g. of *m*-nitrobenzaldehyde were heated with 3·56 g. of anhydrous zinc chloride at 130° for 3 hours. The cold melt, after being powdered, washed with water, and allowed to dry, was recrystallised from pyridine and then alcohol, from which bright yellow crystals of 5-m-*nitrostyrylacridine* (I, R = NO_2), m. p. 210°, separated (Found: C, 77·0; H, 4·4; N, 8·6. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; N, 8·6%); yield 64%. It was insoluble in water and light petroleum, sparingly soluble in hydrochloric acid, ether, acetone, and alcohol. The yellow solution in chloroform gave an orange-red precipitate of a bromo-compound on addition of bromine in this solvent. On carrying out the reaction with acetic anhydride instead of zinc chloride, the same compound resulted in very poor yield.

In absence of a condensing agent, the reaction took a different course. The same amounts of reactants as before were heated at 100° for 7 hours; the brown melt began to solidify after 30 mins. and was quite solid after 45 mins. The powdered product, washed with a little warm alcohol, dried, and then recrystallised three times from benzene, gave a pale yellow crystalline powder of α-(m-*nitrophenyl*)-β-(5-*acridyl*)*ethanol* (II), m. p. 145°; yield 6·76 g. (76%) (Found: C, 73·5; H, 4·8; N, 8·1. $C_{21}H_{16}O_3N_2$ requires C, 73·2; H, 4·7; N, 8·1%). It was sparingly soluble in the common solvents except pyridine and glacial acetic acid. Heating at 110° did not effect elimination of water. The substance decomposed, giving 5-methylacridine, on attempted reduction with stannous chloride and hydrochloric acid.

Evaporation of the benzene mother-liquors from the above experiment left a resinous brown solid, which, after being washed with a little pyridine and then alcohol (washed product = 0·1 g.), was recrystallised from alcohol, from which pale cream crystals of the second form of 5-m-*nitrostyrylacridine* separated (Found: C, 77·8; H, 4·1; N, 8·6%), m. p. 207°. In general solubility it resembled the isomer of m. p. 210°; the mixed m. p. showed a strong depression. The almost colourless chloroform solution gave a reddish precipitate of a bromo-derivative on addition of bromine in this solvent.

5-*m*-Aminostyrylacridine, obtained by reduction of (I, R = NO_2) by the method of Porai-Koschitz (*loc. cit.*) in 91% yield, melted at 234° (lit. 232—234°) and possessed the properties described in the literature. The hydrochloride was

obtained as described by Porai-Koschitz. The *acetyl* derivative crystallised from aqueous alcohol (carbon) in yellow crystals, m. p. 252°; yield 83% (Found: C, 82·0; H, 5·2; N, 8·2. $C_{23}H_{18}ON_2$ requires 81·6; H, 5·3; N, 8·3%); it was insoluble in water, sparingly soluble in ether, benzene, and light petroleum, and soluble in alcohol and chloroform. It resembled the *p*-isomer in turning red with cold dilute hydrochloric acid, in which it was sparingly soluble, but differed from it in giving an orange-yellow solution in glacial acetic acid.

This acetyl derivative was heated with methyl *p*-toluenesulphonate (1 mol.) at 145° for 1 hour with occasional stirring; the powdered product (1 g.) was dissolved in 2 c.c. of water and boiled for 1 hour with an equal volume of concentrated hydrochloric acid. Since no crystals separated on cooling, the solution was evaporated on the water-bath, and the filtered aqueous solution of the yellowish-brown residue was exactly neutralised with potassium carbonate solution. Addition with shaking of solid potassium iodide (1·5 g.) caused immediate precipitation of yellowish-brown 5-*m*-aminostyrylacridine methiodide, which was dissolved in methyl alcohol–water (1 : 1) and boiled for 8 hours with excess of freshly precipitated and washed silver chloride. The solution, after separating and washing residual silver salts with hot aqueous methyl alcohol, left, on evaporation, a yellowish-brown crystalline residue of 5-m-*aminostyrylacridine methochloride*, which was recrystallised from absolute alcohol–ether (Found: N, 8·0; Cl, 10·1. $C_{22}H_{19}N_2Cl$ requires N, 8·1; Cl, 10·3%). It did not melt, but sintered and decomposed above 200° and was slightly hygroscopic; yield 0·3 g. The deep yellow aqueous solution gave no immediate precipitate with a drop of ammonia.

5-*Methylacridine and* p-*Nitrobenzaldehyde*.—The method of Porai-Koschitz *et al.* (*loc. cit.*) gave only a poor yield of 5-p-*nitrostyrylacridine*, m. p. 293° (cf. p. 6). An improved method was devised, exactly the same conditions being used as for the corresponding *m*-compound; yield 90% (Found: C, 77·6; H, 4·4; N, 8·6. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; N, 8·6%). It formed bright yellow crystals, m. p. 293°, and was not hydrated. In general solubility it agreed with the hydrate of m. p. 212° described by the authors quoted. It developed an orange-red colour with concentrated hydrochloric acid or glacial acetic acid, and an ethereal solution showed a slight greenish-yellow fluorescence. A chloroform solution on addition of bromine in the same solvent gave an orange-red precipitate, which was washed with chloroform and dried. This *product* (III) (Found: Br, 20·2. $C_{21}H_{13}O_2N_2Br$ requires Br, 19·8%) was almost insoluble in the common solvents except pyridine and hot glacial acetic acid; it remained unmelted at 360°.

In absence of zinc chloride the above condensation took a different course. 5 G. of 5-methylacridine and 3·92 g. of *p*-nitrobenzaldehyde were heated at 100° for 6 hours; after 10 mins. a pale yellow solid separated from the brown melt, which then solidified. The powdered product was washed with a little warm alcohol and crystallised twice from benzene; yield 81%. The *α*-(p-*nitrophenyl*)-*β*-(5-*acridyl*)*ethanol* (Found: C, 73·1; H, 4·8; N, 8·1. $C_{21}H_{16}O_3N_2$ requires C, 73·2; H, 4·7; N, 8·1%) was a pale yellow, crystalline powder, m. p. 174°, unchanged by recrystallisation from other solvents or by purification in other ways. It was sparingly soluble in the usual solvents except pyridine and glacial acetic acid, and did not lose water on heating at 110°, in contrast to the hydrate described by Porai-Koschitz, but on heating at 130° with acetic anhydride for 3 hours it yielded the *p*-nitrostyryl derivative of m. p. 293° by elimination of water. On attempted reduction with stannous chloride and hydrochloric acid the compound partly decomposed into 5-methylacridine, isolated as the tartrate, and *p*-nitrobenzaldehyde: even warming with hydrochloric acid brought about this decomposition. In addition to the ethanol, a small amount of the *p*-nitrostyryl derivative was formed as a by-product.

In presence of acetic anhydride, the reaction gave the *p*-nitrostyryl derivative, in alcoholic solution with piperidine the ethanol resulted, but in pyridine solution with piperidine the product was the *p*-nitrostyryl derivative.

5-p-*Aminostyrylacridine* was obtained by reduction of the nitrostyryl derivative by Porai-Koschitz's method, but differed from his product. The stannichloride gave a brown solution in water which became violet on dilution; addition of excess of sodium hydroxide solution to this salt in water gave a yellow-brown precipitate. This precipitate, after being washed with water and allowed to dry, yielded 5-*p*-aminostyrylacridine; recrystallisation from pyridine–alcohol and then washing with alcohol afforded a yellow crystalline powder (Found: C, 85·5; H, 5·5; N, 9·4. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4; N, 9·5%); yield 90%. It melted at 242° (Porai-Koschitz, 209°) and was sparingly soluble in alcohol, ether, benzene, and light petroleum, in which solvents Porai-Koschitz's compound is stated to be readily soluble, but was more soluble in pyridine and chloroform. The hydrochloride was obtained in brown crystals by cooling a hot solution of the base in hydrochloric acid. On admixture with bromine, both dissolved in chloroform, a beautiful violet colour developed which on further addition of bromine disappeared with separation of a brown precipitate. The *acetyl* derivative, purified as for the corresponding *m*-compound, was a yellow crystalline powder (yield 82%), m. p. 236° (Found: C, 81·1; H, 5·5; N, 8·3. $C_{23}H_{18}ON_2$ requires C, 81·6; H, 5·3; N, 8·3%), insoluble in water, sparingly soluble in dilute hydrochloric acid (turning red), ether, benzene, and light petroleum, soluble in alcohol, chloroform, acetone, and glacial acetic acid, giving a deep red solution in the last (cf. the free amino-compound, which gave a deep violet). Boiling concentrated hydrochloric acid soon hydrolysed it into the amine. Heating with methyl *p*-toluenesulphonate (1 mol.) at 145° for 1 hour produced the metho-*p*-toluenesulphonate, which when cold was without purification dissolved in water (1 g. per 3 c.c.) and boiled for 1 hour with an equal volume of concentrated hydrochloric acid. After standing overnight, the small, dark reddish-brown crystals of 5-p-*aminostyrylacridine methochloride hydrochloride* (0·5 g.) were collected and washed with a little 15% hydrochloric acid (Found: N, 7·4; Cl, 18·5. $C_{22}H_{19}N_2Cl,HCl$ requires N, 7·3; Cl, 18·5%); further quantities were obtained from the mother-liquors by evaporation, the residue being washed and crystallised from a little alcohol. The salt, a reddish-brown crystalline powder, decomposed with sintering at about 250° and dissolved easily in water to a reddish-brown solution (see p. 6).

5-*p*-Dimethylaminostyrylacridine, prepared in 75% yield by the method of Porai-Koschitz, had properties agreeing with those described in the literature. The hydrochloride, obtained by solution in dilute hydrochloric acid and evaporation on the water-bath, formed dark blue crystals after drying at 100° and gave an intense blue-black solution in water, becoming violet on dilution. The deep red solution of the base in chloroform gave on addition of bromine in this solvent at first a deep violet colour and then a reddish-brown precipitate. The base was heated with methyl *p*-toluenesulphonate (2 mols.) at 145° for 1 hour, and the cooled powdered melt of the crude metho-*p*-toluenesulphonate in a little water was boiled for 1 hour with concentrated hydrochloric acid. On cooling and standing no crystals separated, so the solution was evaporated to dryness on the water-bath, the residue was converted by potassium iodide in the usual way into 5-*p*-dimethylaminostyrylacridine methiodide (yellow-brown, slightly soluble in water, easily soluble in methyl alcohol), and then by means of silver chloride into 5-p-*dimethylaminostyrylacridine methochloride*, which separated in greenish-brown hygroscopic crystals from absolute alcohol–ether (Found: N, 7·5; Cl, 9·5. $C_{24}H_{23}N_2Cl$ requires N, 7·5; Cl, 9·5%). It did not melt but darkened and decomposed above 200° and was easily soluble in water to a deep green solution, which gave no immediate precipitate with a drop of ammonia; yield, 0·45 g. from 1 g. of 5-*p*-dimethylaminostyrylacridine.

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