115. *The Preparation and Therapeutic Properties of Certain Acridine Derivatives. Part II. Derivatives of* s-(6-*Amino*-2-*quinolyl*)-5-*acridylethenes.*

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With a Note on Trypanocidal Action by C. H. Browning, P. Browning, R. Gulbransen, and J. V. M. Robb.*

For reasons discussed in the theoretical part of this paper, it was decided to introduce into the quinolylacridylethenes described in Part I amino-, acetamido-, and dimethylamino-groups in position 6 of the quinoline part of the molecule. A series of such compounds was prepared in the form of quaternary salts and examined for trypanocidal action in mice infected experimentally with *T. brucei*. In general, the compounds showed trypanocidal action, which is discussed, the results being marked with s-(6-*amino*-2-*quinolyl methochloride*)-5-*acridylethene hydrochloride*, s-(6-*acetamido*-2-*quinolyl methosulphate*)-5-(*acridyl methosulphate*)*ethene*, and s-(6-*acetamido*-2-*quinolyl methochloride*)-5-(*acridyl methochloride*)*ethene*.

In Part I (J., 1936, 1484) the quinolylacridylethene series was investigated and we next considered the introduction of substituents into the molecule.

It had been found by Browning, Cohen, and their co-workers that, while quinolyl styryl compounds tended to show therapeutic action in animals experimentally infected with trypanosomes, this property was especially marked when there were present simultaneously a free amino-group, either in the benzene or the quinoline nucleus, and an acylamido-group in the other nucleus (*Proc. Roy. Soc.*, 1929, *B*, **105**, 99; 1933, *B*, **113**, 293). Accordingly, we decided in the first place to incorporate one such group. The orientation of the substituent groups in the quinoline nucleus had also been shown to be of great importance; *e.g.*, s-(6-acetamido-2-quinolyl methosulphate)-*p*-dimethylaminophenylethene or the corresponding methochloride is a powerful trypanocide, whereas the 7-acetamido-isomer is less active and the 4-isomer (methochloride) has no action in similar doses.

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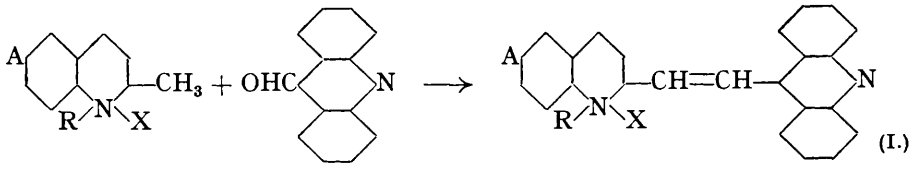
Accordingly, a series of quinolylacridylethene derivatives containing amino-, acetamido-, and dimethylamino-groups in position 6 of the quinoline portion of the molecule was prepared and examined.

The following compounds were prepared by condensing the appropriate quinaldine alkiodide with acridine-5-aldehyde in a solvent with piperidine as catalyst :



(I.)

(1) s-(6-*Acetamido-2-quinolyl methiodide*)-5-*acridylethene* (I; A = NHAc, RX = MeI) which was converted into the corresponding (2) *methochloride* by means of silver chloride and then by deacetylation with boiling hydrochloric acid into the *hydrochloride* of (3) s-(6-*amino-2-quinolyl methochloride*)-5-*acridylethene* (I; A = NH_2, RX = MeCl); treatment of (1) with excess of methyl sulphate gave (4) s-(6-*acetamido-2-quinolyl methosulphate*)-5-(*acridyl methosulphate*)*ethene* (as I; A = NHAc, RX = Me_2SO_4), which with sodium chloride gave (5) the corresponding *dimethochloride*; (6) s-(6-*acetamido-2-quinolyl ethiodide*)-5-*acridylethene* (I; A = NHAc, RX = EtI), from which by means of silver chloride the corresponding (7) *ethochloride* was prepared and thence by deacetylation with boiling hydrochloric acid the *hydrochloride* of (8) s-(6-*amino-2-quinolyl ethochloride*)-5-*acridylethene* (I; A = NH_2, RX = EtCl); (9) s-(6-*acetamido-2-quinolyl metho-p-toluenesulphonate*)-5-*acridylethene* (I; A = NHAc, RX = $C_6H_4Me{\cdot}SO_3Me$) and then converted into the (10) 5-(*acridyl methosulphate*)*ethene*; (11) s-(6-*dimethylamino-2-quinolyl methiodide*)-5-*acridylethene* (I; A = NMe_2, RX = MeI) and from this the corresponding (12) *methochloride* and its *hydrochloride*.

Trypanocidal Action.—The above compounds were examined for trypanocidal action in mice infected experimentally with *T. brucei*. The procedure followed was that described by Browning *et al.* (*loc. cit.*). The results are in the following table, those with 6-dimethylaminoquinaldine methochloride and *s*-(6-dimethylamino-2-quinolyl methochloride)phenylethene, from the paper cited, together with *s*-(2-quinolyl methosulphate)-5-(acridyl methosulphate)ethene and *s*-(2-quinolyl methochloride)-5-(acridyl methochloride)ethene, from Part I of this series, being added for comparison. Treatment was administered 24 hours after inoculation, when scanty trypanosomes were present in the blood; it consisted in a single subcutaneous injection of an aqueous solution of the substance. The dose of each substance, except when limited by solubility, approached the maximum tolerated without general toxic effects by uninfected animals.

Substance.	Dose, mg. per 20 g. mouse.	Therapeutic result.
(3) Hydrochloride	2·5 *	Marked
(4)	10	Marked
(5)	10	Marked
(8) Hydrochloride	1·7	Trace—slight
(10)	1·7 *	Trace—slight
(12) Hydrochloride	1·7	Trace—slight
6-Dimethylaminoquinaldine methochloride	0·18	0
s-(6-Dimethylamino-2-quinolyl methochloride)phenylethene	0·1	0
s-(2-Quinolyl methosulphate)-5-(acridyl methosulphate)ethene	3·3	0
s-(2-Quinolyl methochloride)-5-(acridyl methochloride)ethene	10	0

* Dose limited by solubility.
" Trace "—prolongation of life for several days beyond that of the untreated controls.
" Slight "—disappearance of parasites from the blood for several days to a week.
" Marked "—absence of parasites from the blood for 10 days or longer.
(Untreated control animals died in 3 or 4 days after inoculation.)

Conclusions.—In general, these compounds showed trypanocidal action. The insolubility of several of them (nos. 3, 5, and 10) prevented the administration of sufficiently large doses to obtain maximum effects. The results suggest that, with the quinolylacridylethenes prepared by us, the introduction of an amino- or an acetamido-group in position 6

of the quinoline nucleus produces trypanocidal activity. Further, the activity is due in part to the acridine portion of the molecule, since 6-dimethylaminoquinaldine methochloride and *s*-(6-dimethylamino-2-quinolyl methochloride)phenylethene (Browning *et al.*, *loc. cit.*), which both have a 6-amino-group, and the latter also the ethene linkage, are much more toxic for the mammalian host and do not exert trypanocidal action in doses approaching the maximum tolerated.

This work is being continued. It is hoped to publish shortly an account of investigations on compounds with an amino-group in position 4 of the quinoline nucleus.

Experimental.

6-Aminoquinaldine and its derivatives were prepared by the methods described by Hamer (J., 1921, **119**, 1432) and Browning, Cohen, Ellingworth, and Gulbransen (*Proc. Roy. Soc.*, 1924, *B*, **96**, 325). The 6-nitroquinaldine, previously thoroughly washed, was purified through the nitrate (charcoal), the minimum amount of dilute nitric acid being used to avoid formation of tar as much as possible; the free base (pale yellow) was precipitated by aqueous ammonia, added till the solution was alkaline to Congo-paper but acid to litmus to avoid contamination by a red impurity. 6-Aminoquinaldine can be conveniently purified through the tartrate (yellow needle-shaped prisms from water), precipitated by mixing alcoholic solutions of the base and tartaric acid, 6-nitroquinaldine giving no precipitate. The yield of 6-acetamidoquinaldine methiodide is slightly improved by using 25% excess of methyl iodide and heating for 2 hours on the water-bath. *6-Acetamidoquinaldine ethiodide*, prepared by refluxing 10 g. of 6-acetamidoquinaldine and 5 c.c. of ethyl iodide in 50 c.c. of nitrobenzene for 2 hours on the water-bath and then cooling, crystallised from aqueous alcohol in yellow prisms, m. p. 265—270° (decomp.), after darkening at about 250° (Found: N, 8·1. $C_{14}H_{17}ON_2I$ requires N, 7·9%).

s-(6-*Acetamido*-2-*quinolyl methiodide*)-5-*acridylethene* (1), prepared by refluxing on the water-bath for 2 hours a filtered solution of 10·7 g. of 6-acetamidoquinaldine methiodide and 8 g. of acridine-5-aldehyde in 80 c.c. of alcohol and 30 c.c. of water with 5 drops of piperidine, was collected hot and purified by repeated extraction with hot alcohol; yield, 80%. It was a red crystalline powder, m. p. 233—240° (decomp.) after darkening at about 140°, insoluble or almost insoluble in the usual solvents, including water, moderately soluble in nitrobenzene, from which it separated crystalline (Found: N, 8·1; 8·1. $C_{27}H_{22}ON_3I$ requires N, 7·9%). It was converted into the corresponding *methochloride* (2) by repeated boiling for several hours with a suspension of freshly precipitated silver chloride in aqueous methyl alcohol; the filtrate was concentrated, and the orange powder recrystallised from methyl alcohol. The substance darkened at 190° and melted at 220—228° (decomp.) (Found: N, 9·5. $C_{27}H_{22}ON_3Cl$ requires N, 9·6%).

s-(6-*Amino*-2-*quinolyl methochloride*)-5-*acridylethene hydrochloride* (3), prepared by boiling (2) with concentrated hydrochloric acid and a little water for 3—4 hours and treating the cold solution with dilute aqueous sodium carbonate to reduce the acidity somewhat, crystallised from methyl alcohol containing a little water in dark red prisms, m. p. 205—210° (decomp.), after darkening at about 180°. It dissolved readily in water or ethyl alcohol and after diazotisation yielded a dye with β-naphthol (Found: N, 9·6. $C_{25}H_{20}N_3Cl,HCl$ requires N, 9·7%).

s-(6-*Acetamido*-2-*quinolyl methosulphate*)-5-(*acridyl methosulphate*)*ethene* (4) was prepared by heating at 120°, and then at 130—140° for 25 minutes, 9 g. of (1) in 30 c.c. of nitrobenzene with 7 c.c. (large excess) of methyl sulphate. After standing overnight, the orange-red powder was recrystallised twice from alcohol containing a little water; it darkened at 200° and melted at 225—235° (decomp.), contained no halogen, and dissolved readily in water or alcohol (Found: N, 6·4. $C_{30}H_{31}O_9N_3S_2$ requires N, 6·5%). The corresponding *dimethochloride* (5), prepared in the usual way by adding a saturated sodium chloride solution to a hot aqueous solution of the substance and allowing it to cool, formed an orange precipitate, which was recrystallised first from water and then from aqueous alcohol, in which solvents it dissolved readily (Found: N, 8·5. $C_{28}H_{25}ON_3Cl_2$ requires N, 8·6%). The dimethonitrate (orange) and dimethiodide (dark red) can be prepared similarly.

s-(6-*Acetamido*-2-*quinolyl ethiodide*)-5-*acridylethene* (6) was prepared from 6-acetamidoquinaldine ethiodide as with (1), the heating being from 3—3½ hours; it was purified by extraction with hot alcohol (yield, 70%). The dried substance was reddish-orange, but on exposure to air or on moistening with alcohol it became yellowish-brown, presumably owing to solvation. It darkened at about 235° and melted at about 238° (decomp.) and in solubility resembled (1)

(Found : N, 7·8. $C_{28}H_{24}ON_3I$ requires N, 7·7%). It was converted by silver chloride in the usual way into the corresponding ethochloride (7), an orange mass, which was converted into s-(*6-amino-2-quinolyl ethochloride*)-*5-acridylethene hydrochloride* (8) as with (3). This substance crystallised from 50% aqueous alcohol in dark red, needle-shaped prisms, m. p. 280—300° (decomp.), readily soluble in water and alcohol (Found : N, 9·5. $C_{26}H_{22}N_3Cl,HCl$ requires N, 9·4%).

s-(*6-Acetamido-2-quinolyl metho*-p-*toluenesulphonate*)-*5-acridylethene* (9) was prepared by refluxing on the water-bath for 3 hours 9·3 g. of 6-acetamidoquinaldine metho-*p*-toluenesulphonate * and 6·1 g. of acridine-5-aldehyde in 75 c.c. of alcohol with 8 drops of piperidine. The product was collected hot, extracted with hot alcohol, and recrystallised from aqueous alcohol (yield, 5·6 g.). The yellow crystalline powder, darkening at about 240° and melting at about 250° (decomp.), was moderately easily soluble in hot water and sparingly soluble in alcohol (Found : N, 7·4. $C_{34}H_{29}O_4N_3S$ requires N, 7·3%). The corresponding methochloride (orange-yellow) and methiodide (dark red) were obtained by precipitating aqueous solutions with sodium chloride and potassium iodide.

s-(*6-Acetamido-2-quinolyl metho*-p-*toluenesulphonate*)-*5-(acridyl methosulphate)ethene* (10) was prepared by heating first at 100° and then at 120—130° for ½ hour 3·7 g. of (9) with 0·8 c.c. of methyl sulphate in 23 c.c. of nitrobenzene. The product, collected after standing overnight, was washed with alcohol and ether and recrystallised from aqueous alcohol, from which it separated in small orange-yellow needles, m. p. 245—248° (decomp.), after darkening at about 240° (Found : C, 62·0; H, 5·3; S, 8·8. $C_{36}H_{35}O_8N_3S_2$ requires C, 61·6; H, 5·0; S, 9·1%). It was moderately easily soluble in alcohol, and soluble in water, from which solution the dimethochloride (orange) and the dimethiodide (orange-red) could be precipitated in the usual way.

s-(*6-Dimethylamino-2-quinolyl methiodide*)-*5-acridylethene* (11) was prepared by boiling for 4 hours a solution of 2 g. of 6-dimethylaminoquinaldine methiodide and 1·5 g. of acridine-5-aldehyde in 30 c.c. of alcohol with 4 drops of piperidine. The product (yield, 60%), collected hot and extracted with hot alcohol, was a dark red, crystalline powder moderately easily soluble in methyl and ethyl alcohols, sparingly soluble in hot water (Found : I, 25·0. $C_{27}H_{24}N_3I$ requires I, 24·5%). It was converted in the usual way by silver chloride in methyl alcohol into the corresponding *methochloride* (12), a red crystalline substance, m. p. 200—210° (decomp.) after darkening at about 150°, moderately easily soluble in hot water (Found : N, 10·0. $C_{27}H_{24}N_3Cl$ requires N, 9·9%). This methochloride was converted, by solution in a little dilute hydrochloric acid, followed by cooling, into the hydrochloride, which crystallised from methyl alcohol as a very dark purple powder, decomposing at about 220° but not completely melted at 300°, and readily soluble in water or alcohol.

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