112. *The Preparation and Therapeutic Properties of Certain 4-Substituted Quinoline Derivatives.*

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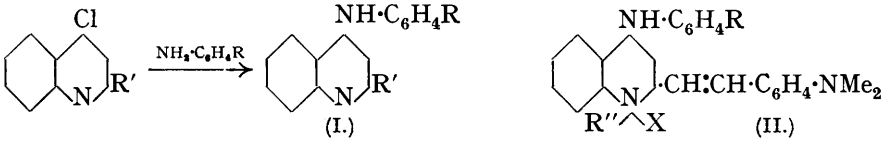
With a note on Antiseptic Properties and Trypanocidal Action by C. H. BROWNING, P. BROWNING, and J. V. M. ROBB.*

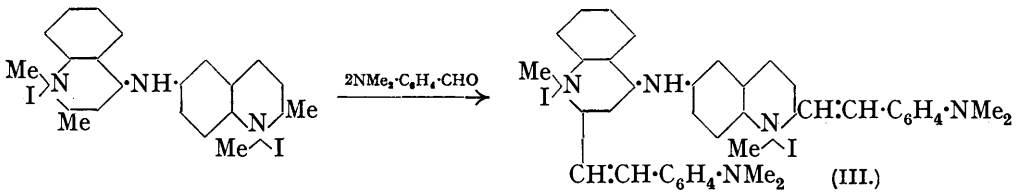
Certain quinoline derivatives with a substituted amino-group in position 4 and a methyl, styryl, or anilomethyl group in position 2, together with quaternary salts, have been prepared. These compounds have been examined as regards their antiseptic and trypanocidal properties.

IN continuation of previous work (J., 1938, 654), substituted 4-aminoquinoline derivatives have been prepared and examined.

A number of such substances were prepared by heating 4-chloro-2-methylquinoline with an appropriate amino-compound, followed by conversion, if necessary, into a quaternary salt [examples (1), (2), and (6)]. A compound of type (I, R′ = Me) as quaternary salt was



then condensed, piperidine being used as catalyst, with an aldehyde, giving an ethene such as (II) [examples (3) and (4)]. A diethene derivative (6) was obtained as quaternary salt (III) by condensing the dimethiodide of (5) with *p*-dimethylaminobenzaldehyde, thus :



The following substances were prepared by these general methods :

(1) 4-*Phenylamino*-2-*methylquinoline methochloride* (as from I; R = H, R′ = Me); (2) 4-p-*acetamidophenylamino*-2-*methylquinoline* (R = NHAc, R′ = Me) and the methosulphate, *methiodide*, and *methochloride*; (3) 4-*phenylamino*-2-p-*dimethylaminostyrylquin-*

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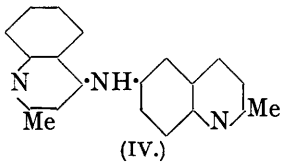
oline methiodide (R = H, R′ = CH:CH·C_6H_4·NMe_2) and the corresponding *methochloride*; (4) 4-p-*acetamidophenylamino*-2-p-*dimethylaminostyrylquinoline methiodide* and the corresponding *methochloride* (R = NHAc, R′ = CH:CH·C_6H_4·NMe_2); (5) 2 : 2′-*dimethyl*-4 : 6′-*diquinolylamine* (IV) and its *dimethiodide*; (6) 2 : 2′-*bis*-p-*dimethylaminostyryl*-4 : 6′-*diquinolylamine dimethiodide* (III) and the corresponding dimethochloride. (7) 4-p-*Acetamidophenylamino*-2-p-*dimethylaminoanilomethylquinoline methiodide* (as from I; R = NHAc, R′ = CH:N·C_6H_4·NMe_2) was prepared from the methiodide of (1) and *p*-nitrosodimethylaniline with piperidine as catalyst.



(IV.)

Antiseptic Properties and Trypanocidal Action.—The above compounds were examined for antiseptic properties *in vitro* and trypanocidal action *in vivo*. The results are in the table.

No. of substance as in text.	Antiseptic action. *Staphylococcus aureus.* P.	*Staphylococcus aureus.* S.	Antiseptic action. *B. coli.* P.	*B. coli.* S.	Precipitation. P.	Precipitation. S.	Trypanocidal action. Dose in mg.	Trypanocidal action. Result.
1	4	2	4	2	—	—	0·4 *	No action
2	1	4	<1	20	—	—	3·3 *	,,
3	40	10	<1	1	20	—	1 †	,,
4	2	40	10	4	100	10	1·7 †	,,
5	2	20	1	40 ‡	—	—	0·7 *	Trace
6 Dimethochloride (dimethiodide similar) ...	200	200	10	200	40	—	5—1 *	Cure
							0·4	Relapse
7	4	4	1	2	10	2	2 †	No action

P = medium consisting of 0·7% neutral peptone water. S = ox serum previously heated at 56°.

Antiseptic action. The numbers are the reciprocals ÷ 1000, of the concentrations which suffice to produce inhibition of growth in 48 hours at 37°, so that the medium remains unclouded or shows at most very faint turbidity. In the former case subculture may yield no growth, or, as in the latter case, may show very slight growth.

Precipitation. The numbers are the reciprocals ÷ 1000, of the lowest concentrations which show precipitation in the media.

Trypanocidal action, as tested on *T. brucei*. The doses are reckoned per 20 g. body-weight of the mouse, injected subcutaneously 24 hours after inoculation, when scanty parasites were present in the blood.

* The doses shown approximate to the largest amounts borne by uninfected animals without producing obvious toxic effects, *e.g.*, loss of weight.

† The doses shown are limited by the solubility of the compounds.

‡ Results irregular.

Antiseptic Properties.—*Staphylococcus aureus* and *B. coli* were used as the test organisms and the procedure was that previously described. Nos. 1 and 2 are not highly antiseptic towards either organism. In the case of No. 2, especially with *B. coli*, the effect in serum is greater than in aqueous medium. The styryl compound of No. 1 (No. 3) shows enhanced action on *Staphylococcus*, but it is only weakly antiseptic towards *B. coli*. A similar observation to the last was made when corresponding analogues substituted in the 4- and the 6-position were compared, the latter being powerfully antiseptic (Ashley *et al.*, *Proc. Roy. Soc.*, 1933, *B*, **113**, 293). The effect of the acetamido-derivative (No. 4) in aqueous medium is not accurately ascertainable owing to its very low solubility, but in serum its action does not differ very greatly from that of No. 3. Compound No. 6 contains two styryl groups and is both a 4- and a 6-derivative. It shows markedly enhanced action as compared with the fragment of the molecule (No. 5) and is the most powerfully antiseptic member of the series, being extremely active against both organisms in serum. The corresponding dimethiodide is similar in potency.

Trypanocidal Action.—In order to detect trypanocidal action, mice infected experimentally with *T. brucei* were treated according to the method described by Browning *et al.* (*Proc. Roy. Soc.*, 1929, *B*, **105**, 99). With the exception of No. 6, all the compounds are without trypanocidal action even in considerable doses, the course of the infection being

practically uninfluenced. This agrees with the lack of trypanocidal properties shown by other 4-substituted derivatives where the corresponding 6-substituted analogue was active (Ashley *et al.*, *loc. cit.*). No. 6 has produced cure, but the range of effective dosage is not great.

Experimental.

4-Chloro-2-methylquinoline was prepared from 4-hydroxy-2-methylquinoline (Conrad and Limpach, *Ber.*, 1887, **20**, 944) by slightly modifying the method of Fischer, Diepolder, and Wölfel (*J. pr. Chem.*, 1925, **109**, 59) to avoid local overheating; contamination of the chloro-compound with the troublesome violet impurity usually present was thus eliminated; yield, 90% as monohydrate. The compound is best purified through the tartrate and not by the steam distillation method employed by Conrad and Limpach and others; their method is slow, and the yield much decreased by hydrolysis of the chloroquinaldine. A hot alcoholic solution of the monohydrate was treated with alcoholic tartaric acid in excess. The tartrate, which separated on cooling, was collected, washed with alcohol and ether, and dissolved in hot water, and the base liberated by addition of the necessary quantity of sodium carbonate. 4-Chloro-2-methylquinoline separated as an oil, which solidified, on cooling, as the monohydrate.

4-*Phenylamino*-2-*methylquinoline Methochloride* (1).—2·7 G. of 4-phenylamino-2-methylquinoline (Fischer *et al.*, *loc. cit.*), recrystallised from methyl alcohol, was dissolved in 2 c.c. of nitrobenzene, and 1·6 g. of methyl sulphate added. The reaction was started at 50° and completed on the water-bath. The methosulphate separated overnight as a colourless crystalline substance. It was collected, dissolved in warm water, and transformed into the *methochloride* by addition of a saturated solution of sodium chloride. On recrystallisation successively from water and alcohol the substance was obtained in colourless crystals, m. p. 259—261°, readily soluble in water and alcohol and insoluble in ether (Found : N, 10·0. $C_{17}H_{17}N_2Cl$ requires N, 9·8%).

4-p-*Acetamidophenylamino*-2-*methylquinoline* (2) was prepared in almost theoretical yield by heating in an oil-bath an intimate mixture of 4-chloro-2-methylquinoline hydrate (20 g.) and *p*-aminoacetanilide (15 g.). A vigorous reaction commenced at 100°, the temperature rising spontaneously to 165°. The cold powdered hydrochloride was extracted with cold water, and the base liberated as a bulky yellow precipitate on the addition of sodium hydroxide. On recrystallisation from alcohol, in which it was sparingly soluble, it was obtained as a pale yellow, crystalline powder, m. p. 280—285° (Found : N, 14·3. $C_{18}H_{17}ON_3$ requires N, 14·4%). 14·6 G. of this substance and 7 g. of methyl sulphate in 100 c.c. of nitrobenzene were slowly heated to 120—130° till homogeneous, and the solution further heated for ½ hour on the water-bath. Addition of ether precipitated the methosulphate, which, after solidifying, was extracted with ether and dissolved in hot water. Addition of a saturated solution of potassium iodide precipitated the *methiodide*, which, after washing with water, alcohol, and ether, separated from aqueous alcohol in lemon-yellow crystals, m. p. 270—284° (decomp.), soluble in water and sparingly soluble in methyl and ethyl alcohols (Found : N, 9·9. $C_{19}H_{20}ON_3I$ requires N, 9·7%). The *methochloride*, prepared in a similar way with sodium chloride, was first recrystallised from water and finally from alcohol, in both of which it was very soluble; m. p. 278—285° (decomp.) (Found : N, 12·2. $C_{19}H_{20}ON_3Cl$ requires N, 12·3%).

4-*Phenylamino*-2-p-*dimethylaminostyrylquinoline Methiodide* (3).—4-Phenylamino-2-methylquinoline methiodide, previously prepared by Fischer and others (*loc. cit.*) by heating in a sealed tube, was obtained more expeditiously by heating 4-phenylamino-2-methylquinoline with methyl iodide in nitrobenzene under reflux for 1 hour; yield, 80%. A melt of 5 g. of this methiodide and 2·5 g. of *p*-dimethylaminobenzaldehyde with five drops of piperidine was heated at 140° (oil-bath) for 2 hours; the mass then became almost solid. The powdered product was freed from unchanged material by boiling first with ether and then with alcohol and was recrystallised from 50% aqueous alcohol. The *substance* formed red, felted, needle-shaped prisms, m. p. 250—260° (decomp.) after darkening at about 200°, moderately soluble in water and alcohol (Found : N, 8·6; I, 25·4. $C_{26}H_{26}N_3I$ requires N, 8·3; I, 25·1%). By means of silver chloride in aqueous methyl alcohol it was converted into the corresponding *methochloride*, which crystallised from nitrobenzene in red water-soluble prisms, m. p. 280—285° (decomp.) after darkening at 260° (Found : N, 10·2. $C_{26}H_{26}N_3Cl$ requires N, 10·1%).

4-p-*Acetamidophenylamino*-2-p-*dimethylaminostyrylquinoline methiodide* (4) was prepared by melting a mixture of 4·3 g. of the methiodide of (2) and 5 g. of *p*-dimethylaminobenzaldehyde, adding five drops of piperidine, and heating for 9 hours at 130—140° (oil-bath). The product was treated with ether to remove unchanged aldehyde, and the residue crystallised from nitrobenzene. It formed dark red prisms, m. p. 270—275° (decomp.) (Found : N, 10·0. $C_{28}H_{29}ON_4I$

requires N, 9·9%). By means of silver chloride it was converted in the usual way into the corresponding *methochloride*, which crystallised from nitrobenzene in orange-red prisms, darkening at about 280° and unmelted at 310° and moderately soluble in alcohol and water (Found : N, 11·7. $C_{28}H_{29}ON_4Cl$ requires N, 11·9%).

2 : 2′-*Dimethyl*-4 : 6′-*diquinolylamine*. (5).—An intimate mixture of 7·9 g. of 6-amino-2-methylquinoline and 9·8 g. of 4-chloro-2-methylquinoline hydrate was gradually heated with stirring to 170—180° ; reaction then commenced, the temperature rising spontaneously to 270°. The crude powdered hydrochloride was extracted with hot water, and the solution filtered and boiled with charcoal. On addition of sodium carbonate to the aqueous solution the *base* was precipitated. After several recrystallisations from alcohol it was obtained as a colourless powder, m. p. *ca.* 110°, readily soluble in absolute alcohol but insoluble in water (Found : N, 14·1. $C_{20}H_{17}N_3$ requires N, 14·1%). The *dimethiodide*, obtained by heating 3 g. of the substance with 5 c.c. of methyl iodide in 10 c.c. of nitrobenzene for 2 hours, was recrystallised first from water and finally from aqueous alcohol. It formed yellow prisms, m. p. 230—275° (decomp.) (Found : N, 7·3. $C_{22}H_{23}N_3I_2$ requires N, 7·2%).

2 : 2′-*Bis*-p-*dimethylaminostyryl*-4 : 6′-*diquinolylamine dimethiodide* (6) was prepared from the preceding compound (4·1 g.) by melting it with 8·5 g. of *p*-dimethylaminobenzaldehyde, adding five drops of piperidine, and heating the mixture at 130—140° for 9 hours. The cold product was repeatedly extracted with boiling ether, hot water and hot alcohol, and the residue purified from aqueous methyl alcohol. It was obtained as an amorphous purple powder, m. p. 230—255° (decomp.), moderately soluble in water and alcohol (Found : N, 8·5. $C_{40}H_{41}N_5I_2$ requires N, 8·3%). It was converted in the usual way into the corresponding dimethochloride, a purple amorphous powder, which was not further purified owing to its great solubility in water and organic solvents.

p-*Acetamidophenylamino*-2-p-*dimethylaminoanilomelhylquinoline Methiodide* (7).—A suspension of 4·3 g. of the methiodide of (2) and 1·9 g. of *p*-nitrosodimethylaniline in 40 c.c. of alcohol containing a little water and five drops of piperidine was boiled for 10 hours. The *product* separated on standing overnight and was freed from any unchanged nitrosodimethylaniline by boiling with ether. It crystallised from nitrobenzene in dark red prisms of indefinite m. p. and was readily soluble in alcohol (Found : N, 12·6. $C_{27}H_{28}ON_5I$ requires N, 12·4%).

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