SEARCH FOR PHYSIOLOGICALLY ACTIVE COMPOUNDS

Part XII. Synthesis and Fungistatic Activity of 5: 6- and 5 : 8-Quinoline Quinone

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Abstract

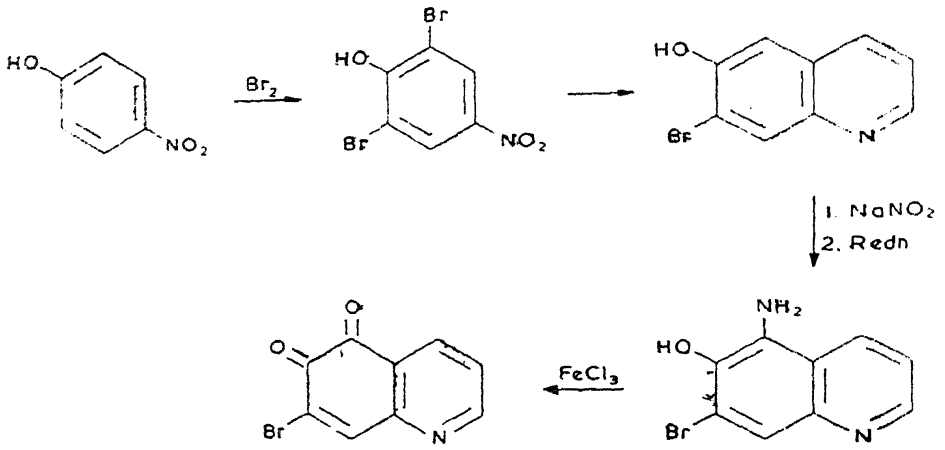
A few 5 : 6- and 5 : 8-quinoline quinones have been synthesised by oxidising the corresponding aminohydroxy and diaminoquinolines. The required aminohydroxy quinolines could be prepared by nitrosation of hydroxy quinolines and subsequent reduction. Coupling the mono-amino quinolines with diazotised sulphanilic acid and reduction afforded the diamino quinolines. 6 : 7-Dichloro- and 6 : 7-dibromo-5 : 8-quinoline quinones exhibited fungistatic activity nearly equal to that of 2 : 3-dichloro-1 : 4-naphthoquinone.

The quinoline quinones (dihydroquinoline diones) are of biological interest because of the physiological activity of both quinolines and quinones.[1] The quinoline quinones possess diverse physiological activity. Substituted 5 : 8-quinoline quinones are useful fungicides[2,3] and bactericides[4,5] whereas some of the polynuclear quinones[6,7] built on the dihalo quinoline quinones are useful tuberculostatic and cytostatic substances. A number of alkylene-imino quinones have been prepared which are capable of inhibiting the growth of tumor nuclei.[8] Some of the hydroxy and amino 5 : 8-quinoline quinones possess marked amoebicidal activity of which 6-hydroxy-7-undecyl-5 : 8-quinone was reported to be the best.[9]

Since most of the previously reported physiologically active quinoline quinones have a substituent in 6- or 7-position the present work has been undertaken to synthesise a few substituted 5 : 6- and 5 : 8-quinoline quinones and evaluate their fungistatic and bacteriostatic activity. With a view to study the structure-physiological activity relationship, a few previously reported quinoline quinones have also been synthesised following the standard procedures.

The general methods of synthesis of substituted quinoline quinones include the oxidation of amino hydroxy quinolines, of diamino or dihydroxy

quinolines and by the introduction of suitable substituent in the quinoline quinone directly. In the present investigation, 7-bromo-5:6-quinoline quinone (I) has been synthesised by the ferric chloride oxidation of 5-amino-6-hydroxy-7-bromo quinoline. This intermediate amino hydroxy quinoline is obtained from 4-nitrophenol by brominating the latter to 2:6-dibromo-4-nitrophenol,[10] which on modified Skraup synthesis gave 6-hydroxy-7-bromo quinoline.[11,12] This hydroxy quinoline on nitrosation and reduction by the usual procedure gave the 5-amino-6-hydroxy-7-bromoquinoline.

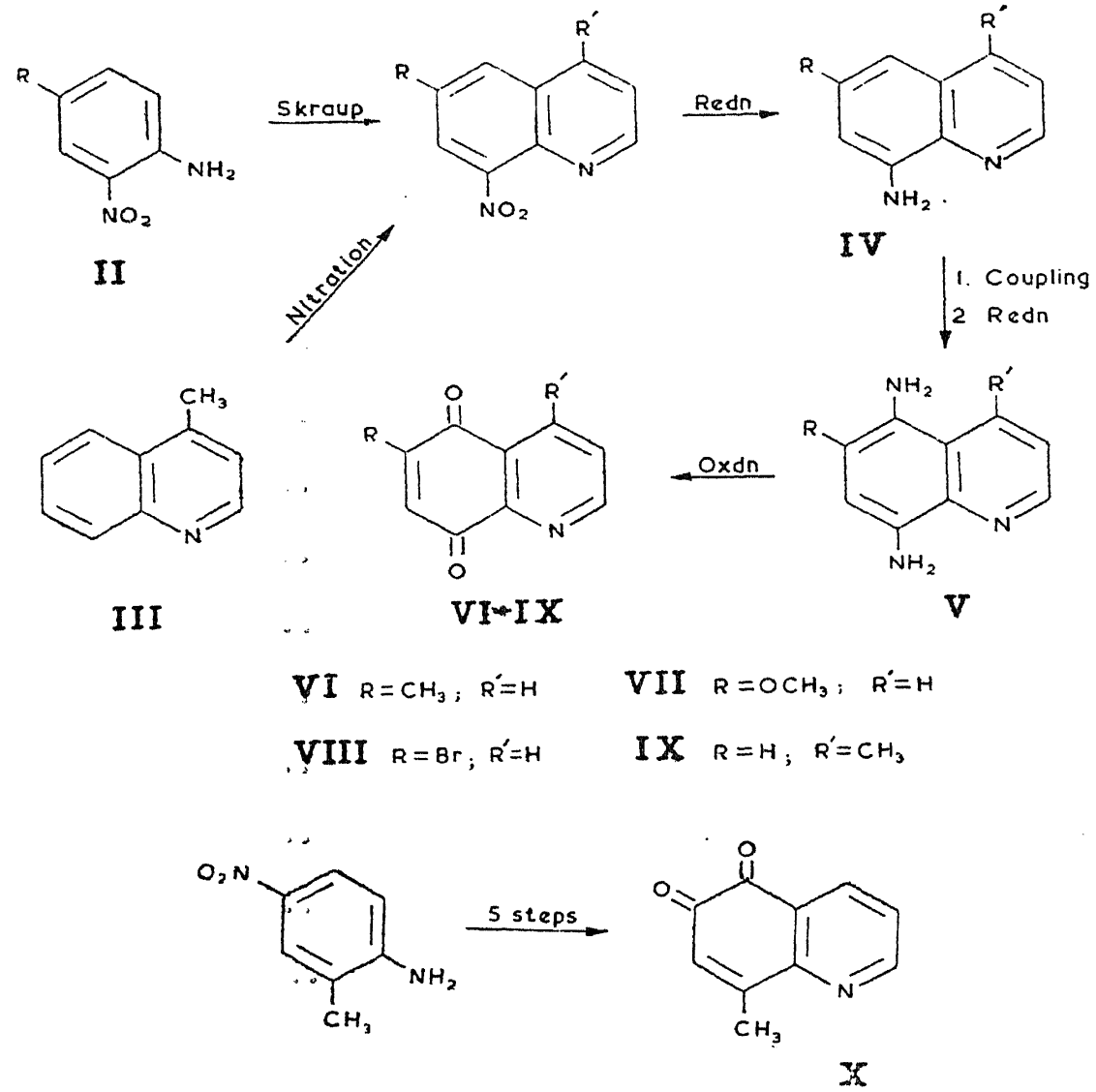


I

The other route followed for the synthesis of quinoline quinones is the oxidation of diamino quinolines. The substituted amino quinolines required for the oxidation have been prepared by Skraup synthesis from the corresponding nitroanilines (II)[13]. 4-Methyl-8-amino quinoline has, however, been made by nitrating lepidine (III) and subsequent reduction to the amine (IV). The second amino group has been introduced into the amino quinoline by coupling with diazotised sulphanilic acid and subsequent reduction of the dye to the diamine (V). 6-Methyl-(VI)[14] and 6-methoxy (VII)[1]-5:8-quinoline quinones are synthesised according to the standard methods for the purpose of comparison of their physiological activity. 6-Bromo (VIII) and 4-methyl (IX)-5:8-quinoline quinones have been prepared by oxidation of the corresponding 5:8-diamino quinolines, the oxidation being accomplished by potassium dichromate in sulphuric acid.

8-Methyl-5:6-quinoline quinone (X) has been prepared by a similar sequence of reactions starting from 2-methyl-4-nitroaniline.

Unsubstituted 5:8-quinoline quinone[15] and 6:7-dichloro- and 6:7-dibromo-5:8-quinoline quinones[16] have been synthesised according to the



methods reported in the literature for purpose of testing. All the quinoline quinones prepared have been tested for their fungistatic activity and the results obtained are recorded in Table I. The fungistatic activity has been determined by radial growth measurements of *Aspergillus niger* on treated synthetic medium. Of all the compounds listed, 6:7-dichloro- and 6:7-dibromo-5:8-quinoline quinones exhibited fungistatic activity equal to that of 2:3-dichloro-1:4-naphthoquinone.

Experimental

1. *7-Bromo-5:6-quinoline quinone*

(*a*) *5-Amino-6-hydroxy-7-bromo quinoline.*—To a suspension of 6-hydroxy-7-bromo quinoline (4 g.) in water (15 ml.), concentrated hydrochloric acid (5 ml.) and ice (15 g.) was added a solution of sodium nitrite (2 g.) in water (7 ml.) portionwise with stirring over a period of one hour at 0–4° C. The

TABLE I

Fungistatic activity of quinoline quinones

Quinone	% Inhibition at	
	100 p.p.m.	10 p.p.m.
5 : 8-Quinoline quinone	53	7
4-Methyl-5 : 8-quinoline-quinone	60	13
6-Methyl-5 : 8-quinoline-quinone	33	Nil
6-Methoxy-5 : 8-quinoline-quinone	Nil	Nil
6-Bromo-5 : 8-quinoline-quinone	96	27
6 : 7-Dibromo-5 : 8-quinoline-quinone	100	73
6 : 7-Dichloro-5 : 8-quinoline-quinone	100	67
7-Bromo-5 : 6-quinoline-quinone	47	Nil
8-Methyl-5 : 6-quinoline-quinone	7	Nil
2 : 3-Dichloro-1 : 4-naphthoquinone	100	100

mixture was allowed to stand overnight at 0° C., filtered off and washed with a little cold water, when 5-nitroso-6-hydroxy-7-bromo quinoline hydrochloride was obtained. Sodium dithionite (15 g.) was added gradually to the solution of 5-nitroso-6-hydroxy-7-bromoquinoline hydrochloride in aqueous sodium hydroxide (65 ml.; 3 N) at 40° C. Sulphuric acid (40 ml.; 12 N) was then added and stirred to remove any dissolved sulphur dioxide. The precipitated sulphate of 5-amino-6-hydroxy-7-bromo quinoline (3 g.) was filtered off after the mixture had been cooled in an ice bath.

(*b*) *7-Bromo-5: 6-quinoline quinone.*—5-Amino-6-hydroxy-7-bromo quinoline sulphate (3 g.) suspended in water (25 ml.) and chloroform (100 ml.) was shaken vigorously in a separating funnel with a solution of ferric chloride (9 g.) in water (15 ml.) and concentrated hydrochloric acid (3 ml.). The chloroform layer was quickly drawn off and the reaction mixture extracted with two more (100 ml.) portions of chloroform. The combined extracts were dried over anhydrous sodium sulphate, the solvent removed, petroleum ether (40–60° C.) added and the 7-bromo-5: 6-quinoline quinone allowed

to crystallise. Yellow needles, m.p. 124° C. (Found: C, 45·6, H, 1·9, N, 5·9; $C_9H_4BrNO_2$ required C, 45·4, H, 1·7, N, 5·9%).

2. *6-Bromo-5: 8-quinoline quinone.*—

6-Bromo-8-amino quinoline[13] (5 g.), prepared from 2-nitro-4-bromo-aniline[17] by Skraup synthesis and subsequent reduction of the nitro quinoline in the presence of palladium over carbon, was dissolved in dilute acetic acid (50 ml.). To a well-cooled and vigorously agitated solution the suspension of *p*-benzene diazonium sulphonate, prepared[18] from sulphanilic acid (5 g.), was immediately added. The dark coloured 5-(*p*-sulphophenylazo)-6-bromo-8-amino quinoline was filtered off and washed with water. The moist crude azo dye was suspended in sodium hydroxide (65 ml.; 5N) and treated with sodium dithionite (24 g.) at 40° C. The dark red solution was allowed to cool and slowly sulphuric acid (30 ml.; 12 N) was added. The solution was stirred until most of the dissolved gases were removed and oxidised directly without isolating the free diamine.

The diamine solution was vigorously agitated with a solution of potassium dichromate (10 g.) in water (100 ml.) and concentrated sulphuric acid (10 ml.). The resulting dark coloured solution was extracted repeatedly with chloroform. The combined chloroform extracts were washed with a saturated solution of sodium chloride and dried over anhydrous sodium sulphate. The solvent was removed and the addition of petroleum ether afforded brown needles of 6-bromo-5: 8-quinoline quinone, m.p. 125° C. (Found: C, 45·6, H, 2·0, N, 5·7; $C_9H_4BrNO_2$ required C, 45·4, H, 1·7, N, 5·9%).

3. *4-Methyl-5: 8-quinoline quinone*

Lepidine was nitrated[19] and reduced by iron filings in alcoholic hydrochloric acid to the corresponding 4-methyl-8-amino quinoline, m.p. 85° C. The amino quinoline was coupled with diazotised sulphanilic acid and reduced to the diamine as in the case of 6-bromo-5: 8-quinoline quinone and finally oxidised to the 4-methyl-5: 8-quinoline quinone, m.p. 126° C., pale yellow needles (Found: C, 69·3, H, 4·3, N, 8·1; $C_{10}H_7NO_2$ required C, 69·4, H, 4·1, N, 8·1%).

4. *8-Methyl-5: 6-quinoline quinone*

6-Nitro-8-methyl quinoline[20] was prepared and reduced to the amino by iron filings in alcoholic hydrochloric acid, m.p. 129° C. The amino quinoline on diazo coupling and reduction as described for 6-bromo-5: 8-quinoline quinone gave the diamine, which on oxidation with potassium

dichromate and sulphuric acid gave the 8-methyl-5:6-quinoline quinone, m.p. 136° C. (Found: C, 69·2, H, 4·4, N, 8·0; $C_{10}H_7NO_2$ required C, 69·4, H, 4·1, N, 8·1%).

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