## 185. *The Nitration of Some Aryloxy-2- and -4-methylquinolines. Syntheses of Substances having Possible Antimalarial Action.*

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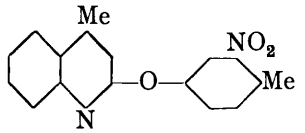
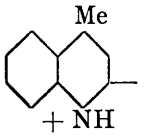
The antimalarial properties of the cinchona alkaloids and of such substances as " plasmochin " appear to be connected with the presence in the molecule of two discrete basic centres. We have therefore prepared, for examination by the Chemotherapy Committee of the Medical Research Council, some amino- and other derivatives of 2-phenoxy-4-methylquinoline and of 4-phenoxy-2-methylquinoline, and the investigation has been extended to obtain information as to the orienting effect of the corresponding methylquinolinoxyl radicals.

2-Chloro-4-methylquinoline reacts readily with potassium phenoxide to give 2-*phenoxy*-4-*methylquinoline*. The latter substance when mononitrated, gives, as the main product, 2-(4′-*nitrophenoxy*)-4-*methylquinoline*, the constitution of which follows from the fact that piperidine scission gives 2-hydroxy-4-methylquinoline and 4-nitrophenylpiperidine.

2-p-*Tolyloxy*-4-*methylquinoline* undergoes trinitration under conditions approximately similar to those which convert 2-phenyl-4-methylquinoline into the mononitro-compound. Mononitration of the tolyloxy-compound could only be effected by using potassium nitrate and excess of concentrated sulphuric acid, and gave 2-(3′-*nitro*-4′-*methylphenoxy*)-4-*methylquinoline* (I), as was shown by synthesis (*a*) of (I) from 2-chloro-4-methylquinoline and potassium 2-nitro-*p*-tolyloxide, and (*b*) of the isomeric 2-(2′-*nitro*-4′-*methylphenoxy*)-4-*methylquinoline*.




(I.)

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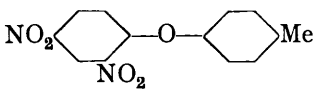


(III.)

This result is of some interest, for, although the effective deactivating influence is the group-ion (II), it must be remembered that 2 : 4-dinitro-4′-methyldiphenyl ether (III), in which powerful deactivating groups are present, undergoes not 3′- but 2′-nitration (Fox and Turner, J., 1930, 1853). It seems probable that the formation of (I) is not due simply to the depression of the electromeric activity of the ether oxygen atom. The result suggests that oxonium salt-formation may be the responsible factor.

Further nitration of (I) gives 2-(2′ : 5′-*dinitro*-4′-*methylphenoxy*)-4-*methylquinoline*, the constitution of which rests on three observations: (*a*) the dinitro-compound was produced from the mononitro-compound without the use of concentrated sulphuric acid; (*b*) the corresponding *diamino*-compound could be diazotised, suggesting a *p*- rather than an *o*-diamine; and (*c*) the dinitro-compound was very readily converted by piperidine into a dinitropiperidinotoluene. 2-(3′ : 5′-Dinitro-4′-methylphenoxy)-4-methylquinoline would be unaffected by piperidine, whilst in the corresponding 2′ : 3′-dinitro-compound decreased activating effect of the nitro-groups would be expected.

The trinitro-derivative of 2-*p*-tolyloxy-4-methylquinoline is probably the 2′ : 3′ : 5′-compound, since mononitration of the 2-*p*-tolyloxy-compound in nitric acid alone would be expected to give the 2′-nitro-compound. The trinitro-compound is unaffected by piperidine, even at high temperatures, and therefore cannot contain nitro-groups in both the 2′- and the 6′-position, although the non-reactivity in this sense would be compatible with the presence of three nitro-groups in positions 2′, 3′, and 5′. Thus, 4-bromo-2 : 2′ : 3′-trinitro-4′-methyldiphenyl ether reacts with piperidine to give 4-bromo-2-nitrophenylpiperidine and 2 : 3-dinitro-*p*-cresol, showing that activation produced by the isolated nitro-group is effective and that produced by the nitro-group which is di-ortho-substituted is ineffective.

2-(4′-*Methoxyphenoxy*)- and 2-(4′-*ethoxyphenoxy*)-4-*methylquinoline* undergo 3′-mono-

nitration, as is shown by the fact that the products are converted by aqueous-alcoholic ammonia at 175° into 2-(3′-*nitro*-4′-*aminophenoxy*)-4-*methylquinoline*.

The deactivating influence of the 4-methyl-2-quinoliniumoxyl ion-group is also shown by the observation that, although the 3′-*amino*-derivatives of the above tolyloxy-, anisyloxy-, and phenetyloxy-bases condense normally with acetylacetone, none of the anils formed undergoes the Combes ring-closure in the presence of concentrated sulphuric acid. These cyclisations are, of course, also hindered by the 4′-substituents (Me, OMe, OEt). The anil obtained from 2-(3′-*aminophenoxy*)-4-*methylquinoline* and acetylacetone passes readily into 5 or 7-(4′-*methyl*-2′-*quinolinoxy*)-2 : 4-*dimethylquinoline* under standard conditions, as would be anticipated.

4-p-*Tolyloxy*-2-*methylquinoline*, formed from 4-chloro-2-methylquinoline and potassium *p*-tolyloxide, like its 2-4-analogue, is mononitrated in position 3′ under similar conditions, showing that the proximity in space of the ring nitrogen and the ether oxygen is not responsible for the 3′-nitration. The 4-(3′-*nitro*-4′-*methylphenoxy*)- and 4-(2′-*nitro*-4′-*methylphenoxy*)-2-*methylquinolines* required for proving the constitution of the above nitration product were more readily prepared from the appropriate nitrocresol (and 4-chloroquinaldine) than were the analogous compounds in the lepidine series.

Nitration of 4-(4′-*methoxyphenoxy*)-2-*methylquinoline* gave the 3′-nitro-compound.

As in the lepidine series, attempted preparation of diquinolyl ethers by the Combes reaction with the amines obtained by reducing the mononitration products of 4-*phenoxy*-, 4-(4′-*methoxyphenoxy*)-, and 4-(p-*tolyloxy*)-2-*methylquinoline* failed, but 4-(3′-*aminophenoxy*)-2-*methylquinoline* readily gave 5 or 7-(2′-*methyl*-4′-*quinolinoxy*)-2 : 4-*dimethylquinoline*.

## Experimental.

2-*Phenoxy*-4-*methylquinoline*.—Potassium hydroxide (85% KOH) (11 g.) was fused in presence of a few drops of water, 28 g. of phenol added as soon as the cooling alkali began to crystallise, and then 18 g. of 2-chloro-4-methylquinoline. The mixture was heated for 2 hours in a bath at 190°, excess of dilute sodium hydroxide solution added, and the whole shaken and cooled until a crystalline meal separated. This, recrystallised from alcohol or light petroleum (b. p. 40—60°), gave white leaflets, m. p. 51° (17 g.; 76% yield) (Found : N, 6·05. $C_{16}H_{13}ON$ requires N, 5·9%). A similar procedure was adopted for the preparation of the other simple aryl quinolyl ethers described below. The phenoxymethylquinoline was recovered unchanged after being heated at 195° with excess of piperidine for 6 hours.

The *methiodide*, obtained by heating the components in a sealed tube at 100° for an hour, crystallised from methyl alcohol in scarlet prisms, m. p. 200—210°. Recrystallisation from water gave sulphur-yellow prisms, m. p. 220° (decomp.) (Found : I, 34·7. $C_{17}H_{16}ONI$ requires I, 35·1%).

2-(4′-*Nitrophenoxy*)-4-*methylquinoline*.—Phenoxymethylquinoline (1 g.) was added to a mixture (at 20°) of 20 c.c. of nitric acid (*d* 1·5) and 50 c.c. of glacial acetic acid. After 5 minutes the solution was heated at 50° for 5 minutes, cooled, and poured into much water. The precipitate cystallised from alcohol in pale yellow needles, m. p. 140—141° (corr.). Recrystallisation from benzene–light petroleum (b. p. 40—60) gave colourless needles, m. p. 141—142° (corr.), which became pale yellow on keeping (yield, 85%) (Found : N, 10·2. $C_{16}H_{12}O_3N_2$ requires N, 10·0%). Attempted nitration of phenoxylepidine in concentrated sulphuric acid solution led to sulphonation.

The nitro-compound is not rapidly attacked by piperidine, from which it may readily be crystallised. Scission was effected by heating 2 g. of the nitro-compound with 5 c.c. of piperidine for 3 hours at 170—180° in a sealed tube. On cooling, 2-hydroxy-4-methylquinoline separated (m. p. and mixed m. p. 220°). The mother-liquor was poured into dilute acetic acid, and the precipitate collected and crystallised from alcohol. The *p*-nitrophenylpiperidine had m. p. and mixed m. p. 105°.

2-(4′-*Aminophenoxy*)-4-*methylquinoline*, obtained by reducing the nitro-compound with iron filings, alcohol, and a trace of hydrochloric acid, separated from alcohol in pale brown prisms, m. p. 135° (73% yield) (Found : N, 11·3. $C_{16}H_{14}ON_2$ requires N, 11·2%). The other amino-bases described below were obtained by a similar process, unless it is stated to the contrary. The base condensed with acetylacetone during 2 hours' boiling; the *anil* crystallised from light petroleum (b. p. 80—100°) in yellow plates, m. p. 109° (yield, 70%) (Found : N, 8·9.

$C_{21}H_{20}O_2N_2$ requires N, 8·7%). When a solution of the anil in concentrated sulphuric acid was heated at 100° for 2 hours, hydrolysis, not ring closure, took place (amino-compound isolated, m. p. 135°).

2-(3′-*Nitrophenoxy*)-4-*methylquinoline*.—Potassium hydroxide (85% KOH) (7 g.) was fused in the presence of a larger quantity of water, *viz.*, 5 c.c., than was used in the preparation of the nitro-free ethers. *m*-Nitrophenol (18 g.) and water (in all 15 c.c.) were added in small portions, and then 18 g. of 2-chlorolepidine. The mixture was heated for 5 hours at 170—180°, treated with dilute alkali solution, cooled, and filtered. The solid, freed from chlorolepidine by steam distillation from excess of alkali, crystallised from alcohol in needles (10 g.), m. p. 152° (Found : C, 68·5; H, 4·6. $C_{16}H_{12}O_3N_2$ requires C, 68·5; H, 4·6%).

2-(3′-*Aminophenoxy*)-4-*methylquinoline* formed buff prisms from alcohol, m. p. 170—171° (Found : C, 76·6; H, 5·9. $C_{16}H_{14}ON_2$ requires C, 76·7; H, 5·6%).

The anil formed by heating the base with acetylacetone crystallised from light petroleum (b. p. 80—100°) in small needles, m. p. 81° (Found : N, 8·8. Calc. : N, 8·7%).

5 *or* 7-(4′-*Methyl*-2′-*quinolinoxy*)-2 : 4-*dimethylquinoline*.—A solution of the anil in 12 parts of cold concentrated sulphuric acid was heated at 100° for 40 minutes and then poured into water. Addition of ammonia and warming gave a solid precipitate, which crystallised from alcohol in hexagonal plates, m. p. 173° (Found : C, 80·2; H, 5·95. $C_{21}H_{18}ON_2$ requires C, 80·3; H, 5·9%).

2-(p-*Tolyloxy*)-4-*methylquinoline*, obtained from 2-chlorolepidine and potassium *p*-tolyloxide, crystallised from methyl or ethyl alcohol or from light petroleum (b. p. 40—60°) in needles, m. p. 60° (Found : N, 5·8. $C_{17}H_{15}ON$ requires N, 5·6%). The *methiodide*, crystallised from alcohol and then from water, formed pale yellow prisms, m. p. 197—198° (decomp.) (Found : I, 32·0. $C_{18}H_{18}ONI$ requires I, 32·5%).

2-(3′-*Nitro*-4′-*methylphenoxy*)-4-*methylquinoline*.—(*a*) 2-(*p*-Tolyloxy)lepidine (10 g.) was dissolved in 50 g. of concentrated sulphuric acid and cooled to − 5°, and a solution of 4 g. of potassium nitrate in 50 g. of concentrated sulphuric acid added with stirring, the temperature being kept below − 5°. The solution was poured on ice and after some time the resulting solid was collected; it crystallised from alcohol in pale yellow needles, m. p. 121° (Found : N, 9·5. $C_{17}H_{14}O_3N_2$ requires N, 9·5%).

(*b*) A mixture, prepared normally, of 8 g. of 2-chlorolepidine, 8 g. of 2-nitro-*p*-cresol, 3·5 g. of 85% potassium hydroxide, and 10 c.c. of water was heated at 140° for 2 hours. The nitro-compound obtained melted, alone or mixed with the product from (*a*), at 121°. The 3′-nitro-compound was unaffected by prolonged heating with piperidine at 160°.

2-(2′-*Nitro*-4′-*methylphenoxy*)-4-*methylquinoline*, prepared similarly to (*b*), crystallised from alcohol in pale yellow, hexagonal plates, m. p. 148°. A mixture with the product from (*a*) above melted at 100—115° (Found : C, 69·8; H, 4·8; N, 9·9. $C_{17}H_{14}O_3N_2$ requires C, 69·8; H, 4·2; N, 9·6%).

The 2′-nitro-compound was unaffected by a short heating with piperidine, whilst at 160° a gum was formed from which no definite substance could be isolated.

2-(2′ : 5′-*Dinitro*-4′-*methylphenoxy*)-4-*methylquinoline*.—A solution of 2-(3′-nitro-4′-methylphenoxy)-4-methylquinoline in 30 parts of nitric acid (*d* 1·5) at 20° was heated at 60—70° for 20 minutes and poured into water, and ammonia added. The precipitate crystallised from alcohol in pale yellow needles, m. p. 186° (Found : N, 12·6. $C_{17}H_{13}O_5N_3$ requires N, 12·4%).

A solution of the dinitro-compound in piperidine was boiled for a short time. Yellow needles separated on cooling. Hot dilute alkali solution was added to dissolve 2-hydroxylepidine, and the solid was crystallised from alcohol, yellow needles of 2 : 5-*dinitro*-4-*methylphenylpiperidine*, m. p. 166—167°, being obtained (Found : N, 15·7. $C_{12}H_{15}O_4N_3$ requires N, 15·7%).

2-(2′ : 5′-*Diamino*-4′-*methylphenoxy*)-4-*methylquinoline*, obtained from the dinitro-compound, separated from alcohol as a brownish powder, m. p. 204° (Found : N, 15·1. $C_{17}H_{17}ON_3$ requires N, 15·1%).

2-(3′-*Amino*-4′-*methylphenoxy*)-4-*methylquinoline*, obtained by reducing the 3′-nitro-compound, crystallised from alcohol in small stout prisms, m. p. 174° (Found : N, 10·7. $C_{17}H_{16}ON_2$ requires N, 10·6%).

The base condensed readily with boiling acetylacetone; the *anil* formed small needles, m. p. 139—140°, from alcohol or light petroleum (b. p. 80—100°) (Found : N, 8·7. $C_{22}H_{22}O_2N_2$ requires N, 8·6%). Concentrated sulphuric acid converted the anil into the parent amino-compound.

2-(2′ : 3′ : 5′ ?-*Trinitro*-4′-*methylphenoxy*)-4-*methylquinoline*.—When 2-*p*-tolyloxy-4-methylquinoline was dissolved in a mixture of 10 parts of nitric acid (*d* 1·5) and 10 parts of glacial

acetic acid, the product formed depended largely on the temperature. From — 5° to 15°, the nitrate of the base was sometimes formed, and in addition dinitrocresols and 2-hydroxylepidine. When the temperature was allowed to rise to 50° for a few minutes, and the solution poured into water, the *trinitro*-compound separated. After crystallisation from alcohol, it had m. p. 315° (Found : N, 14·7. $C_{17}H_{12}O_7N_4$ requires N, 14·6%). The trinitro-compound was also the main product when the base was added to 3—5 parts of nitric acid (*d* 1·5) at — 10° or at 0°.

No variation of the conditions of nitration led to a mono- or a dinitro-compound.

2-(4′-*Methoxyphenoxy*)-4-*methylquinoline*, obtained from quinol methyl ether (yield 94%), crystallised from alcohol in prisms, m. p. 103° (corr.) (Found : N, 5·3. $C_{17}H_{15}O_2N$ requires N, 5·3%). The *methiodide* crystallised from alcohol in golden rhombs, m. p. 182° (corr. : decomp.) (Found : I, 31·2. $C_{18}H_{18}O_2NI$ requires I, 31·2%).

2-(3′-*Nitro*-4′-*methoxyphenoxy*)-4-*methylquinoline*.—The anisyloxy-base (5 g.) was gradually added to a mixture of 50 c.c. each of glacial acetic acid and nitric acid (*d* 1·5). The solution was heated at 50° for 10 minutes and poured into much water. The precipitate obtained crystallised from alcohol in pale yellow needles, m. p. 112—113° (corr.) (yield, 99%) (Found : N, 9·2. $C_{17}H_{14}O_4N_2$ requires N, 9·0%).

2-(3′-*Nitro*-4′-*aminophenoxy*)-4-*methylquinoline*.—The last-named nitro-compound (2·3 g.) was heated in a sealed tube at 170—180° for 3 hours with 6 c.c. each of aqueous ammonia (*d* 0·880) and absolute alcohol. The cooled tube contained a brown solid, which was dissolved in dilute hydrochloric acid. The filtered solution was treated with dilute aqueous ammonia, and the solid crystallised three times from alcohol, orange needles, m. p. 156° (softening at 154°), being obtained (Found : N, 14·0. $C_{16}H_{13}O_3N_3$ requires N, 14·2%).

2-(3′-*Amino*-4′-*methoxyphenoxy*)-4-*methylquinoline* formed stout prisms, m. p. 138—139° (corr.), from alcohol (Found : N, 10·1. $C_{17}H_{16}O_2N_2$ requires N, 10·0%). The *salicylidene* derivative formed orange prisms, m. p. 127—128°, from methyl alcohol (Found : N, 7·3. $C_{24}H_{20}O_3N_2$ requires N, 7·3%).

The amino-compound and acetylacetone gave the *anil*, which separated from light petroleum (b. p. 80—100°) in brownish prisms, m. p. 115—116° (Found : N, 7·95. $C_{22}H_{22}O_3N_2$ requires N, 7·7%). Concentrated sulphuric acid converted the anil into the parent amino-compound.

2-(4′-*Ethoxyphenoxy*)-4-*methylquinoline* was obtained in 75% yield from quinol ethyl ether; it crystallised from alcohol or from light petroleum (b. p. 40—60°) in long prisms, m. p. 90—91° (Found : N, 5·1. $C_{18}H_{17}O_2N$ requires N, 5·05%). The *methiodide* formed yellow needles from alcohol or water, softening at 181°, m. p. 185—186° (decomp.) (Found : I, 29·6. $C_{19}H_{20}O_2NI$ requires I, 30·1%).

2-(3′-*Nitro*-4′-*ethoxyphenoxy*)-4-*methylquinoline*.—A solution of the phenetoxy-base (1 g.) in a mixture of 20 c.c. each of nitric acid (*d* 1·5) and glacial acetic acid was warmed at 50° for 5 minutes, cooled, and poured into water. The precipitate (yield, 80%) crystallised from alcohol in aggregates of needles or in hexagonal prisms, m. p. 120—121°. Recrystallisation from light petroleum (b. p. 80—100°) gave twinned hexagonal plates, m. p. 121° (Found : N, 8·7. $C_{18}H_{16}O_4N_2$ requires N, 8·6%).

Alcoholic ammonia in a sealed tube at 170—180° converted the nitro-compound into 2-(3′-nitro-4′-aminophenoxy)-4-methylquinoline, m. p. 156°, a mixture with the nitroamine compound obtained from the anisoxy-compound melting at 156°.

2-(3′-*Amino*-4′-*ethoxyphenoxy*)-4-*methylquinoline* formed brownish plates, m. p. 130—131°, from alcohol (Found : N, 9·7. $C_{18}H_{18}O_2N_2$ requires N, 9·5%).

4-*Phenoxy*-2-*methylquinoline*, prisms from light petroleum (b. p. 40—60°), melted at 73° (Found : N, 5·85%). The *methiodide*, orange-red needles from alcohol or water, had m. p. 210° (decomp.) (Found : I, 33·3%).

4-(4′-*Nitrophenoxy*)-2-*methylquinoline*.—A solution of phenoxyquinaldine (5 g.) in a mixture of 100 c.c. of nitric acid (*d* 1·5) and 50 c.c. of glacial acetic acid was heated at 50° for 15 minutes and poured into water. A pale yellow nitrate which separated was decomposed with aqueous ammonia. The nitro-compound crystallised from alcohol in long yellow prisms, m. p. 177° (Found : N, 10·0%). Heated with piperidine for 3 hours in a sealed tube at 170—180°, it yielded 4-nitrophenylpiperidine, m. p. and mixed m. p. 105°.

4-(4′-*Aminophenoxy*)-2-*methylquinoline*, a brown crystalline powder from alcohol, had m. p. 168° (Found : N, 10·6%).

4-(3′-*Nitrophenoxy*)-2-*methylquinoline* was obtained in 65% yield from 4-chloroquinaldine, potassium hydroxide, and *m*-nitrophenol; it separated from alcohol in pale yellow prisms, m. p. 135—136° (Found : N, 10·5%).

4-(3′-*Aminophenoxy*)-2-*methylquinoline*, brownish prisms, m. p. 101—102°, from alcohol (Found : N, 10·9%), reacted normally with acetylacetone. The crude anil was converted by concentrated sulphuric acid into 5 or 7-(2′-*methyl*-4′-*quinolinoxy*)-2 : 4-*dimethylquinoline*, which formed thin hexagonal plates, m. p. 194—195°, from alcohol (Found : N, 8·8%).

4-(4′-*Methylphenoxy*)-2-*methylquinoline*, obtained in 55% yield from *p*-cresol, crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 89—90° (Found : N, 5·6%). The *methiodide*, bronze prisms from water, softened at 204° and melted at 207—208° (decomp.) (Found : I, 32·7%).

4-(3′-*Nitro*-4′-*methylphenoxy*)-2-*methylquinoline*.—(*a*) The tolyloxyquinaldine (5 g.) was dissolved in 25 g. of concentrated sulphuric acid and slowly treated (below — 5° with stirring) with a solution of 2 g. of potassium nitrate in 25 g. of concentrated sulphuric acid. After 20 minutes the solution was poured on ice. The sulphate precipitated was decomposed with aqueous ammonia; the nitro-base crystallised from alcohol in pale yellow needles, m. p. 163° (Found : N, 9·7%).

(*b*) 4-Chloro-2-methylquinoline was condensed with 2-nitro-*p*-cresol in the presence of potassium hydroxide solution. The product had m. p. 161°; a mixture with the product from (*a*) melted at 160—162°.

4-(2′-*Nitro*-4′-*methylphenoxy*)-2-*methylquinoline*, from 3-nitro-*p*-cresol, crystallised from alcohol in pale yellow needles, m. p. 134—135° (Found : N, 9·6%). A mixture with the 3′-nitro-compound (*a*) melted at 116—122°.

4-(3′-*Amino*-4′-*methylphenoxy*)-2-*methylquinoline* formed prisms, m. p. 98—99°, from alcohol (Found : N, 10·9%).

4-(4′-*Methoxyphenoxy*)-2-*methylquinoline*, from quinol methyl ether, crystallised from alcohol in prisms, m. p. 168° (Found : N, 5·3%). The *methiodide* crystallised from water in prisms, m. p. 225—226° (decomp.; softening at 223°) (Found : I, 31·6%).

4-(3′-*Nitro*-4′-*methoxyphenoxy*)-2-*methylquinoline*.—The anisoxy-base (5 g.) was dissolved in a mixture of 50 c.c. each of nitric acid (*d* 1·5) and glacial acetic acid at 20°. The temperature rose to 28° and was caused to rise to 50° during 15 minutes. The solution was poured into water, the separated nitrate decomposed with aqueous ammonia, and the nitro-base crystallised from alcohol, forming pale yellow needles, m. p. 205—206° (Found : N, 9·0%). When the nitro-compound was heated with alcoholic ammonia at 170°, a nitroamine was obtained. The presence of the amino-group was shown by diazotisation, but the base could not be obtained pure.

4-(3′-*Amino*-4′-*methoxyphenoxy*)-2-*methylquinoline*, small plates from alcohol, melted at 171—172° (Found : N, 10·2%).

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