91. *Aryloxy-derivatives of Pyrimidines, Quinoxalines, and Quinolines.*

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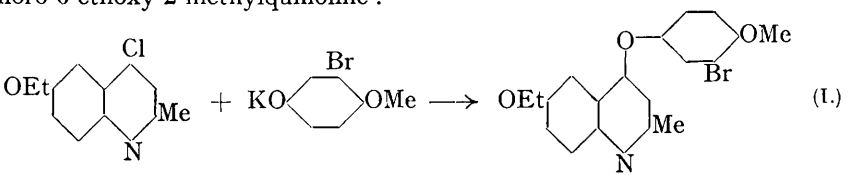
It is frequently assumed that one of the important constitutional factors conferring anti-malarial activity on quinine and its analogues is the presence of two discrete basic centres in the molecule. We have prepared, for examination by the Chemotherapy Committee of the Medical Research Council, a number of aryloxy-compounds. The readily accessible 2 : 4 : 6-trichloropyrimidine has been found to react smoothly with potassium phenoxides, and in this way 2 : 4 : 6-*triphenoxy*-, 2 : 4 : 6-*tri*-p-*anisoxy*-, 2 : 4 : 6-*tri*-p-*tolyloxy*- and 2 : 4 : 6-*tri*-p-*chlorophenoxy-pyrimidine* have been obtained. Similar replacement of reactive halogen was effected in the quinoxaline series, and from 2 : 3-dichloroquinoxaline four 2 : 3-diaryloxyquinoxalines have been made. In addition, 2 : 3-*dianilino*-, 2 : 3-*di*-m-*toluidino*- and 2 : 3-*di*-p-*toluidino-quinoxaline* have been prepared.

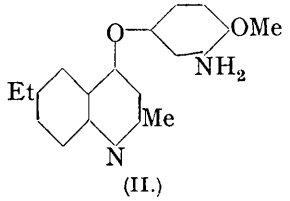
In the quinoline series, the starting material chosen was 4-*chloro*-6-*ethoxy*-2-*methyl-quinoline*, which is readily obtainable from the corresponding, known, 4-hydroxy-compound. The chlorine atom was found to react with potassium phenoxides, and has been successfully replaced by the phenoxy-, *p*-tolyloxy-, *p*-anisoxy-, and *p*-chlorophenoxy-groups. The anisoxy-compound seemed to be of greatest interest, since mononitration, followed by reduction, should lead to 4-m-*amino*-p-*methoxyphenoxy*-6-*ethoxy*-2-*methyl*-

quinoline (II), a substance possessing not only the right kind of disposition of basic centres but also the alkoxy-groups. The above nitration did actually take place in the sense mentioned, for replacement of the amino-group in (II) gave a *bromo*-compound (I), identical with that obtained by condensing potassium 3-bromo-4-methoxyphenoxide with 4-chloro-6-ethoxy-2-methylquinoline :

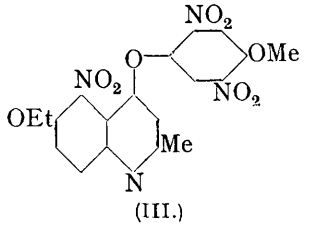


(I.)

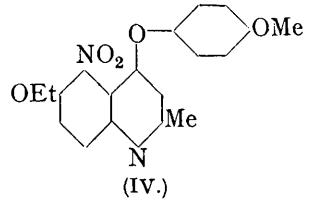
Further nitration of the mononitro-compound or of the parent anisoxy-compound could not be caused to stop when only one more nitro-group had been introduced, but the trinitro-compound, which we regard as (III), was readily obtained.



(II.)



(III.)



(IV.)

4-Chloro-6-ethoxy-2-methylquinoline is nitrated to give a compound which, by well-established analogies, must be *4-chloro-5-nitro-6-ethoxy-2-methylquinoline*, and the latter reacts with potassium *p*-methoxyphenoxide to give (IV). This compound resembled its isomeride in that it refused to undergo simple mononitration.

Experimental.

2 : 4 : 6-*Triphenoxypyrimidine*.—Potassium hydroxide (7·5 g.; 5·25 mols.) was treated with 2 drops of water and then heated until it just fused. Phenol (22 g.; 9 mols.) was added, and then gradually 5 g. (1 mol.) of 2 : 4 : 6-trichloropyrimidine. Interaction was vigorous and was completed by heating the mixture for 20 minutes at 210—220°. The whole was cooled and shaken with excess of alkali. The 2 : 4 : 6-*triphenoxypyrimidine* left undissolved crystallised from alcohol–acetone in slender needles, m. p. 156° (Found : C, 73·6; H, 4·4. $C_{22}H_{16}O_3N_2$ requires C, 74·2; H, 4·5%). Yield, almost theoretical.

2 : 4 : 6-*Tri*-p-*tolyloxypyrimidine*, obtained similarly in almost theoretical yield, formed silky needles, m. p. 118°, from alcohol (Found : C, 75·0; H, 5·2. $C_{25}H_{22}O_3N_2$ requires C, 75·4; H, 5·5%).

2 : 4 : 6-*Tri*-p-*anisoxypyrimidine*, obtained from potassium *p*-methoxyphenoxide in 80% yield, separated from alcohol in needles, m. p. 120° (Found : C, 67·1; H, 5·0. $C_{25}H_{22}O_6N_2$ requires C, 67·3; H, 4·9%).

2 : 4 : 6-*Tri*-p-*chlorophenoxypyrimidine*, obtained in 75% yield, formed clusters of stout needles, m. p. 107°, from alcohol (Found : N, 6·0; Cl, 22·8. $C_{22}H_{13}O_3N_2Cl_3$ requires N, 6·1; Cl, 23·2%).

2 : 3-*Diphenoxyquinoxaline* was prepared in a similar manner, 1 mol. of 2 : 3-dichloroquinoxaline, 3·5 mols. of potassium hydroxide and 6 mols. of phenol being used, and the main reaction completed by heating at 100—120° for 20 minutes. The diphenoxy-compound crystallised from acetone in star-shaped clusters of needles, m. p. 160° (yield, 75%) (Found : N, 9·0. $C_{20}H_{14}O_2N_2$ requires N, 8·75%). It did not combine with methyl iodide when it was heated under pressure with excess of the latter for 8 hours at 100°.

2 : 3-*Di*-p-*tolyloxyquinoxaline*, obtained in 65% yield, formed needles, m. p. 145—146°, from alcohol (Found : N, 8·2. $C_{22}H_{18}O_2N_2$ requires N, 8·2%).

2 : 3-*Di*-p-*anisoxyquinoxaline* (yield, 54%) crystallised from glacial acetic acid in minute needles, m. p. 193—194° (Found : N, 7·5. $C_{22}H_{18}O_4N_2$ requires N, 7·5%).

2 : 3-*Di*-p-*chlorophenoxyquinoxaline* (yield, 73%), when crystallised from alcohol, had m. p. 153° (Found : N, 7·1. $C_{20}H_{12}O_2N_2Cl_2$ requires N, 7·3%).

A number of attempts to replace only one of the chlorine atoms in 2 : 3-dichloroquinoxaline by phenoxyl were unsuccessful. Nitration of 2 : 3-diphenoxyquinoxaline under various conditions led to mixtures from which no individuals were isolated.

2 : 3-*Dianilinoquinoxaline* was obtained by heating dichloroquinoxaline (1 mol.) with 5 mols. of aniline under reflux for a few minutes. When the vigorous reaction was complete, excess of aniline was removed by steam-distillation after addition of alkali; the residual dianilino-derivative crystallised from glacial acetic acid in clusters of deep yellow needles, m. p. 223° (Found : N, 17·8. $C_{20}H_{16}N_4$ requires N, 17·8%).

2 : 3-*Di*-m-*toluidinoquinoxaline*, obtained similarly, separated from glacial acetic acid in pale yellow plates, m. p. 225° (Found : N, 16·1. $C_{22}H_{20}N_4$ requires N, 16·5%).

2 : 3-*Di*-p-*toluidinoquinoxaline* formed yellow needles, m. p. 254°, from glacial acetic acid (Found : N, 16·5%).

4-*Chloro*-6-*ethoxy*-2-*methylquinoline*.—4-Hydroxy-6-ethoxy-2-methylquinoline (1 mol.), prepared by usual methods from ethyl acetoacetate and *p*-phenetidine, was heated with 1·5 mols. of phosphorus pentachloride and a little phosphoryl chloride at 145° for 1 hour. The mixture was then poured on ice and steam-distilled. The *chloro*-compound distilled in 80—85% yield and crystallised from light petroleum (b. p. 60—80°) in clusters of prismatic needles, m. p. 65° (Found : Cl, 16·15. $C_{12}H_{12}ONCl$ requires Cl, 16·05%).

4-*Chloro*-5-*nitro*-6-*ethoxy*-2-*methylquinoline*.—The last-mentioned chloro-compound (10 g.) was gradually added to 35 c.c. of nitric acid (*d* 1·5) kept at 0°. The solution obtained was poured on ice, and the whole made neutral. The precipitate formed was dried, and then crystallised from light petroleum in hexagonal prisms, m. p. 125° (yield, 90%) (Found : N, 10·8; Cl, 12·8. $C_{12}H_{11}O_3N_2Cl$ requires N, 10·5; Cl, 13·3%).

5-*Nitro*-4-p-*anisoxy*-6-*ethoxy*-2-*methylquinoline*.—The foregoing compound was condensed with potassium *p*-methoxyphenoxide by the usual method (above) and gave the 4-p-*anisoxy*-derivative as buff hexagonal prisms, m. p. 109°, from light petroleum (Found : N, 8·3. $C_{19}H_{18}O_5N_2$ requires N, 7·9%).

4-*Phenoxy*-2-*ethoxy*-2-*methylquinoline* was prepared by condensing 4-chloro-6-ethoxy-2-methylquinoline (1 mol.) with 2 mols. of phenol in presence of 1·33 mols. of potassium hydroxide by the above general method. The reaction was complete in an hour at 180—190° and the phenoxy-compound (yield, 83%) crystallised from light petroleum in star-like clusters of needles, m. p. 107—108° (Found : N, 5·05. $C_{18}H_{17}O_2N$ requires N, 5·0%). The *methiodide*, formed by heating the base with methyl iodide in a closed tube at 100° for 3 hours, separated from water in needles, m. p. 210° (Found : I, 30·1. $C_{17}H_{17}O_2NI$ requires I, 30·2%).

4-p-*Anisoxy*-6-*ethoxy*-2-*methylquinoline* forms hexagonal prisms, m. p. 115°, from light petroleum (Found : N, 4·7. $C_{19}H_{19}O_3N$ requires N, 4·6%). The *methiodide* crystallises from dilute alcohol in leaflets, m. p. 216° (Found : I, 27·9. $C_{20}H_{22}O_3NI$ requires I, 28·2%).

4-p-*Tolyloxy*-6-*ethoxy*-2-*methylquinoline*, minute cubes from light petroleum, has m. p. 134° (Found : N, 5·0. $C_{18}H_{19}O_2N$ requires N, 4·8%). The *methiodide* forms needles, m. p. 213°, from alcohol (Found : I, 30·1. $C_{19}H_{22}O_2NI$ requires I, 29·2%).

4-p-*Chlorophenoxy*-6-*ethoxy*-2-*methylquinoline* crystallises from light petroleum in rectangular prisms, m. p. 125° (Found : N, 4·8; Cl, 11·2. $C_{18}H_{16}O_2NCl$ requires N, 4·5; Cl, 11·3%). The *methiodide*, needles from dilute alcohol, has m. p. 213—214° (Found : I, 27·7. $C_{19}H_{19}O_2NCII$ requires I, 27·9%).

4-m-*Nitro*-p-*methoxyphenoxy*-6-*ethoxy*-2-*methylquinoline*.—4-*p*-Anisoxy-6-ethoxy-2-methylquinoline (10 g.) was added to a mixture of 150 c.c. of glacial acetic acid and 150 c.c. of nitric acid (*d* 1·5) at 0°. The solution was poured on ice and neutralised. The precipitate was crystallised from ethyl alcohol–light petroleum and the *nitro*-compound was thus obtained as cream needles, m. p. 183—184° (Found : N, 8·0. $C_{19}H_{18}O_5N_2$ requires N, 7·9%). The *methiodide*, needles from alcohol, melts at 224° (decomp.) (Found : I, 27·0. $C_{20}H_{21}O_5N_2I$ requires I, 27·2%). The nitro-compound could not be obtained by condensing 4-chloro-6-ethoxy-2-methylquinoline with the potassium derivative of 3-nitro-4-methoxyphenol.

4-m-*Amino*-p-*methoxyphenoxy*-6-*ethoxy*-2-*methylquinoline*, obtained from the preceding nitro-compound by reduction with stannous chloride in glacial acetic–hydrochloric acid solution, and extracted according to general practice, crystallised from alcohol in rectangular plates, m. p. 139° (Found : N, 8·6. $C_{19}H_{20}O_3N_2$ requires N, 8·6%).

4-m-*Bromo*-p-*methoxyphenoxy*-6-*ethoxy*-2-*methylquinoline*.—(*a*) The last-named amino-compound was diazotised in hydrochloric acid, and the solution added to one of cuprous bromide in hydrobromic acid. By usual procedure the *bromo*-compound was isolated, and was obtained in prismatic needles after several crystallisations from alcohol (charcoal). It melted at 193—

194° (Found: Br, 19·7. $C_{19}H_{18}O_3NBr$ requires Br, 20·6%). (*b*) 4-Chloro-6-ethoxy-2-methylquinoline was condensed with 3-bromo-4-methoxyphenol in presence of potassium hydroxide at 180—190°. The condensation mixture was treated with warm alkali. The tarry solid left was extracted with light petroleum (b. p. 60—80°) until it was free from unchanged chloro-compound, and then crystallised from dilute alcohol. The bromo-compound obtained melted at 193—194° alone or when mixed with the product from (*a*) (Found: Br, 20·2%).

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