SYNTHESIS OF POLYSUBSTITUTED 2,4-DIMETHYLQUINOLINES AS POTENTIAL ANTIMALARIAL DRUGS

Stoyan PARUSHEV[a], Yoncho VLAHOV[a], Radoslav VLAHOV[a], Peter NICKEL[b] and Günther SNATZKE[c]

[a] *Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria*
[b] *Pharmaceutical Institute, University of Bonn, D-5300, F.R.G.*
[c] *Ruhr University Bochum, D-4630 Bochum, F.R.G.*

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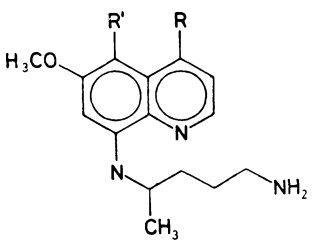
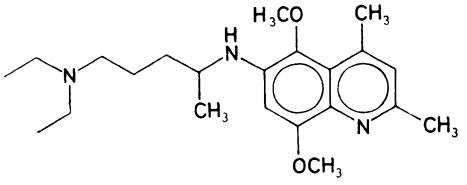
A synthetic way for obtaining 6-amino-2,4-dimethylquinoline derivatives from 2,5-dichloraniline by successive ring closure, nitration, aromatic substitution at so activated quinoline ring, followed by reduction of the nitro group to amino group and alkylation of the last is described.

Malaria infections are still a problem due to the adaptation of the disease-causing parasites to existing preparations[1,2]. Several 8-aminoquinoline compounds, for instance Primaquine (*I*), have been applied as chemotherapeutics for treatment of malaria diseases[1,3]. Introduction of a methyl group in 4-position and a trifluoromethylphenoxy group in 5-position in Primaquine modifies its biological activity[4,5].



I R = R' = H
II R = Me ; R' = O CF3

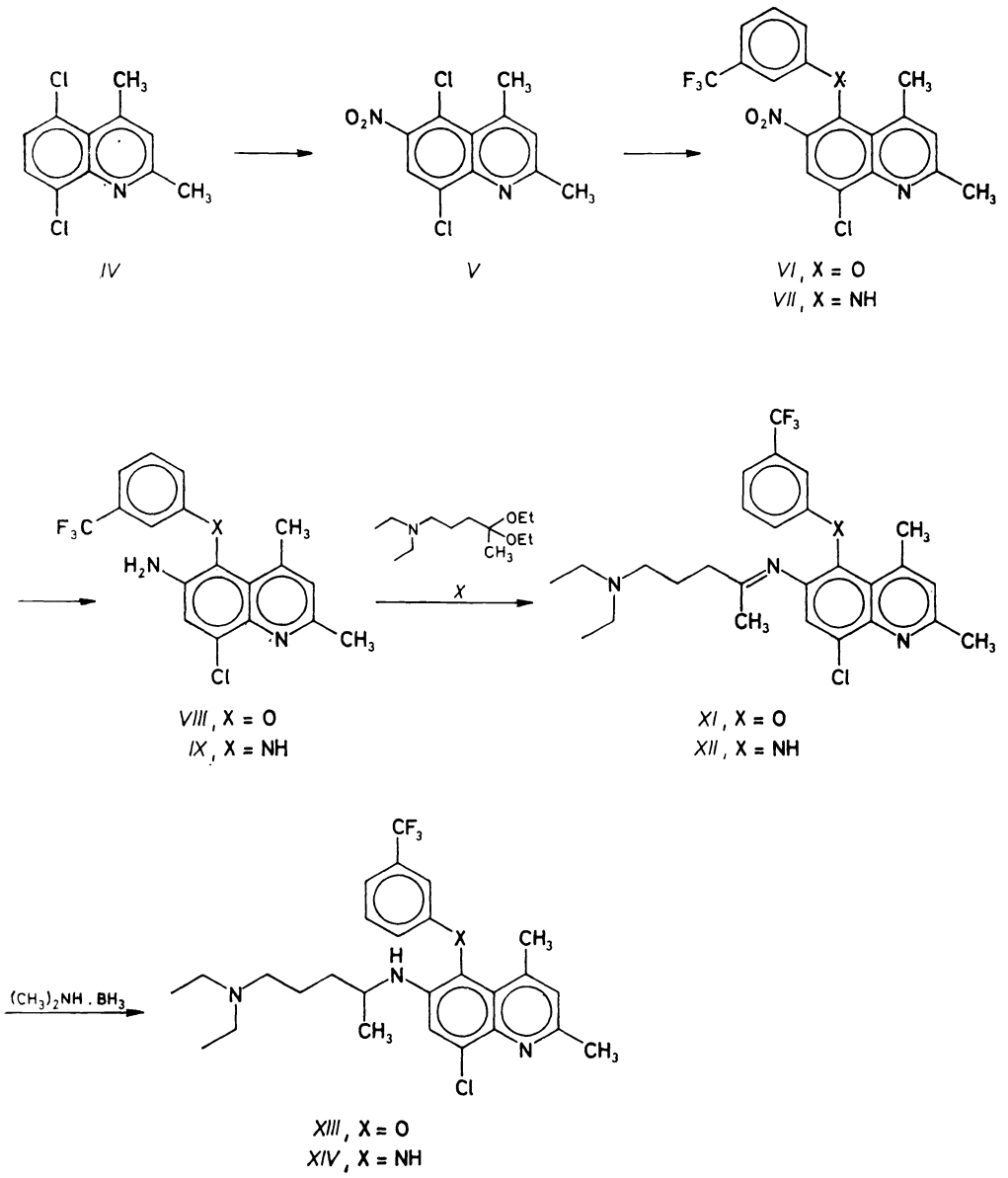


III

It is well known that the antimalarial activity of 6-aminoquinoline compounds is similar to that of 8-aminoquinolines. Thus compound *III* has a broad spectrum activity. Unfortunately it is too highly toxic to be used in human medicine[6,7]. Thus,

effects of replacement of the methoxy groups in *III* by a trifluoromethylphenoxy substituent and a halogen are of interest in the study of its biological activity.

In this paper we describe the first synthesis of 8-chloro-6-(4-diethylamino-1-methyl--butylamino)-2,4-dimethyl-5-(3-trifluoromethylphenoxy)-quinoline (*XIII*) and 8-chlo-



SCHEME 1

ro-6-(4-diethylamino-1-methyl-butylamino)-2,4-dimethyl-5-(3-trifluoromethylphenylamino)-quinoline (*XIV*), which are compounds of potential antimalarial activity.

A method for obtaining 2,4-dimethylquinoline products was developed by Combes[8,9]. Unfortunately the yield is very low when 2,5-dichloroaniline is used as a starting material. Thus we followed a method first described by Reed[10] and known as "Beyer's condensation"[11,12] and 5,8-dichloro-2,4-dimethylquinoline (*IV*) could be isolated in good yield.

The nitration of *IV* at 5°C with fuming nitric acid and sulfuric acid leads, after treatment with ammonia, to 5,8-dichloro-2,4-dimethyl-6-nitroquinoline (*V*) in quantitative yield[12]. The activated quinoline ring reacts with a number of nucleophils; in our hands it reacts with potassium 3-trifluoromethylphenolate and with lithium 3-trifluoromethylanilide to *VI* and *VII*, respectively, in excellent yield (Scheme 1).

The nitro group of compound *VI* was reduced to an amino group with the help of sodium dithionite[13], while in *VII* it was reduced by Raney-Ni in acetone medium[14]. The reaction of the aromatic amine *VIII* or *IX* with 1-diethylamino-4,4-diethoxypentane (*X*) (ref.[15]) in the presence of NH_4Cl results in the respective imines (Schiff bases) *XI* and *XII*, respectively. These imines were reduced by dimethylaminoborane in the presence of glacial acetic acid to compounds *XIII* and *XIV* (ref.[16]).

EXPERIMENTAL

Silica gel column chromatography: Merck Kieselgel 60 (70—230 μm). Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra (cm^{-1}): UR-20 (Zeiss, Jena). ^1H NMR spectra: Bruker WM-250 spectrometer at 250 MHz; δ values in ppm relative to internal TMS. MS: JEOL, JMS D3000 apparatus.

5,8-Dichloro-2,4-dimethylquinoline (*IV*)

Through a solution of 96 g (711 mmoles) paraldehyde in 160 ml of acetone, dry HCl was blown in the course of 3 h under vigorous stirring. The solution was then further stirred for 3 days at room temperature, then it was added to a suspension of 46 g (284 mmol) 2,5-dichloroaniline and 20 ml of nitrobenzene in 100 ml of conc. HCl. The mixture was heated to 100°C and thoroughly stirred for 10 h. The resulting black solution was cooled to room temperature and poured onto ice and water. The separated black oily layer was extracted 3 times with ether. The water phase was treated with 25% ammonia under stirring and cooling until pH 7·5 was obtained. The precipitate was filtered off, washed with water, and dried in vacuum. Yield: 18·6 g (29%). M.p.: 117—119°C (ethanol). IR: 3 015, 3 000, 2 980, 1 610, 1 560, 1 500, 1 470, 1 380, 1 365, 1 350, 1 330, 1 185, 1 125, 1 090, 1 040, 1 005, 980, 930, 875, 830, 705, 625 cm^{-1}. ^1H NMR: 2·7 (s, 3 H); 3·0 (s, 3 H); 7·15 (s, 1 H); 7·35, 7·65 (2 H, AB-system). MS: m/z = 225 (M^+, 100%), 190, 154, 148, 127, 113, 99, 94, 87, 77, 74.

5,8-Dichloro-2,4-dimethyl-6-nitroquinoline (*V*)

Compound *IV* (12 g, 54 mmol) was slowly added at 0°C to 60 g of a mixture of 1 portion of fuming HNO_3, and 2 portions of conc. H_2SO_4. The resulting orange suspension was stirred 3 h

at room temperature, then it was poured onto ice and water, thoroughly stirred, and treated with 25% NH_3, until pH 7·5 was reached. The obtained yellowish-white crystals were recrystallized from ethanol. Yield: 13·7 g (95%). M.p.: 154—156°C (ethanol). IR: 3 005, 2 980, 1 610, 1 550, 1 490, 1 465, 1 450, 1 380, 1 320, 1 240, 1 160, 1 110, 1 040, 985, 960, 900, 880, 855, 800 cm^{-1}. ^1H NMR: 2·8 (s, 3 H); 3·1 (s, 3 H); 7·3 (s, 3 H); 7·9 (s, 1 H). MS: m/z = 270 (M^+, 100%), 224, 212, 189, 154, 113, 99, 87, 77, 63.

8-Chloro-2,4-dimethyl-6-nitro-5-(3-trifluoromethylphenoxy)quinoline (*VI*)

3-Trifluoromethylphenol (8 g, 0·05 mol), 5·8 g of 50% KOH and 35 ml of benzene were mixed, stirred and boiled for 3 h in a round-bottom flask equipped with a water separator. Then the benzene was distilled off in vacuum, the precipitate was treated 3 times with benzene (20 ml), and the solvent was evaporated in vacuum after every treatment. 1·1 g (0·006 mol) of the isolated potassium phenolate was mixed with 1·35 g (0·005 mol) of 5,8-dichloro-2,4-dimethyl-6-nitroquinoline (*V*) and 5 ml dry DMF, then the mixture was heated to 120—130°C for 3 h. After cooling to room temperature it was slowly added dropwise to icewater under thorough stirring. The crude product was recrystallized from ethanol. Yield: 1·99 g (90%). M.p.: 206—207°C (ethanol). IR: 1 600, 1 575, 1 540, 1 495, 1 460, 1 445, 1 370, 1 330, 1 290, 1 230, 1 180, 1 135, 1 100, 1 070, 920, 860, 815, 700 cm^{-1}. ^1H NMR: 2·71 (s, 3 H); 2·83 (s, 3 H); 6·87 (d, 1 H); 7·05 (s, 1 H); 7·28 (s, 1 H); 7·35 (d, 1 H); 7·41 (t, 1 H); 8·38 (s, 1 H). MS: m/z = 396 (M^+), 377, 349, 315, 281, 235 (100%), 190, 177, 143, 115, 95, 77, 63.

8-Chloro-2,4-dimethyl-6-nitro-5-(3-trifluoromethylphenylamino)quinoline (*VII*)

Solution (1·9 ml, 2 mmol) of butyllithium (1·6 molar solution in hexane) was added dropwise under argon at −78°C to 490 mg (3 mmol) of 3-amino-benzotrifluoride, dissolved in 5 ml of dry THF. After 20 min 800 mg (2·96 mmol) of 5·8-dichloro-2,4-dimethyl-6-nitroquinoline (*V*), dissolved in 5 ml of THF, were added to the above mixture, and the reaction mixture was stirred under argon for 12 h. Thereafter it was added slowly dropwise and under thorough stirring to ice and water. The crude product was filtered off and chromatographically purified (benzene). Yield: 713 mg (60%). M.p.: 165—167°C (benzene). IR: 3 360, 3 010, 1 595, 1 570, 1 540, 1 490, 1 465, 1 440, 1 370, 1 340, 1 310, 1 240, 1 180, 1 140, 1 110, 1 080, 915, 890, 855, 700 cm^{-1}. ^1H NMR: 2·5 (s, 3 H); 2·8 (s, 3 H); 6·63 (d, 1 H); 6·86 (s, 1 H); 7·10—7·28 (m, 3 H); 8·50 (s, 1 H); 9·30 (s, 1 H). MS: m/z = 395 (M^+, 100%), 378, 361, 348, 314, 271, 243, 216, 203, 185, 163, 140, 119, 95, 91, 77.

6-Amino-8-chloro-2,4-dimethyl-5-(3-trifluoromethylphenoxy)quinoline (*VIII*)

A mixture of 3·96 g (10 mmol) of 8-chloro-2,4-dimethyl-6-nitro-5-(3-trifluoromethylphenoxy)-quinoline (*VI*), 7·00 g (40 mmol) of sodium dithionite, 25 ml ethylene glycol monomethyl ether, and 25 ml water was heated under reflux for 1·5 h. Further 25 ml of water and 25 ml of HCl were added dropwise to the still warm solution. The reaction mixture was then boiled for 15 min under intensive stirring. After cooling to room temperature it was poured onto 150 ml of ice and water. The resulting green-brown solution was brought to pH 7·5 with 25% ammonia. Yield 3·12 g (85%). M.p. 191—193°C (ethanol). IR: 3 480, 3 390, 2 970, 1 615, 1 590, 1 440, 1 380, 1 365, 1 320, 1 275, 1 160, 1 124, 1 085, 1 060, 950, 880 cm^{-1}. ^1H NMR: 2·57 (s, 3 H); 2·68 (s, 3 H); 3·86 (s, 2 H); 6·90 (d, 1 H); 7·03 (s, 1 H); 7·13 (s, 1 H); 7·28—7·47 (m, 3 H). MS: m/z = 366 (M^+), 347, 256, 221 (100%), 193, 160, 128, 103, 95, 74.

6-Amino-8-chloro-2,4-dimethyl-5-(3-trifluoromethylphenylamino)quinoline (*IX*)

Compound *VII* (2 g, 5 mmol), acetone (40 ml), and Raney-Ni (20 g) were stirred at room temperature for 6 h. The Raney-Ni was filtered off and the reaction mixture was washed several times with acetone. The acetone was evaporated under vacuum and the crude product was chromatographically purified (benzene). Yield: 1·85 g (70%). M.p.: 189—190°C (benzene). IR: 3 480, 3 380, 2 920, 1 615, 1 590, 1 480, 1 380, 1 330, 1 250, 1 215, 1 160, 1 125, 1 090, 1 060, 950, 880, 869 cm^{-1}. ^1H NMR: 2·65 (m, 3 H); 2·73 (s, 3 H); 4·14 (broadened s, 2 H); 5·39 (broadened s, 1 H); 6·63 (d, 1 H); 6·81 (s, 1 H); 7·19—7·27 (m, 3 H). MS m/z = 365 (M^+), 351 (100%), 281, 206, 179, 141.

8-Chloro-6-(4-diethylamino-1-methylbutylamino)-2,4-dimethyl-5-(3-trifluoromethylphenoxy)quinoline (*XIII*)

Compound *VIII* (370 mg, 1 mmol), 0·5 ml (2 mmol) of 4,4-diethoxy-1-diethylaminopentane (*X*) and 10 mg of NH_4Cl were mixed in a small flask and placed in a metal-bath preheated to 220°C. The reaction mixture was heated to the same temperature for about 10 min, then it was cooled to room temperature. A solution of 230 mg (4 mmol) of boranedimethylamine in 2 ml of glacial acetic acid was added and the reaction mixture was heated to 40°C. The colour of the mixture changed from dark to reddish. It was stirred for 15 min and evaporated to dryness. The residue was treated with 3 ml 6M HCl and 10 ml methanol, and stirred for 10 min. The solvent was evaporated and the methanol treatment was repeated two more times. Water (3 ml) was added to the red-brown precipitate, then it was stirred for 10 min and filtered. The orange filtrate was treated with 3 ml of 10M NaOH and extracted with toluene (4 × 10 ml). The organic phase was dried with anhydrous Na_2SO_4 and the solvent was evaporated in vacuum. The resulting red-brown oil was chromatographed on Silicagel (cyclohexane). Yield· 200 mg (62%). M.p.: 73—74°C (cyclohexane). IR: 3 420, 2 960, 2 925, 2 800, 1 610, 1 480, 1 440, 1 380, 1 370, 1 320, 1 275, 1 165, 1 125, 1 085, 1 055, 880, 750 cm^{-1}. ^1H NMR: 1·00 (t, 6 H); 1·12 (d, 3 H); 2·30—2·50 (m, 4 H); 2·38—2·53 (m, 3 H); 2·60 (s, 3 H); 2·70 (s, 3 H); 4·80 (d, 1 H); 6·90—7·54 (m, 6 H). MS: m/z = = 507 (M^+), 492, 478, 435, 366, 346.

8-Chloro-6-(4-diethylamino-1-methylbutylamino)-2,4-dimethyl-5-(3-trifluoromethylphenylamino)quinoline (*XIV*)

The reaction conditions were the same as for the synthesis of *XIII*. Yield: 180 mg (41%, oil). IR: 3 420, 2 920, 1 610, 1 480, 1 380, 1 370, 1 330, 1 250, 1 160, 1 125, 1 090, 1 060, 880 cm^{-1}. ^1H NMR: 1·00 (t, 6 H); 1·21 (d, 3 H); 2·31—2·53 (m, 4 H); 2·41 (m, 2 H); 2·49 (d, 3 H); 2·58 (m, 3 H); 2·69 (s, 3 H); 3·62 (broadened m, 1 H); 4·35 (broadened s, 1 H); 5·85 (s, 1 H); 6·62 to 7·78 (m, 6 H). MS: m/z = 506 (M^+), 491, 477, 434, 365, 345.

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