

Synthesis of some new quinoline derivatives – potential antimalarial drugs

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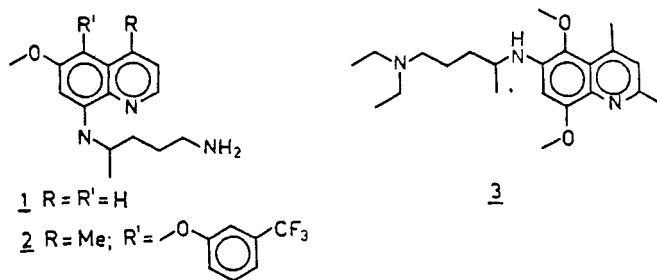
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Abstract - A synthetic way for obtaining some 6-amino-2,4-dimethylquinoline compounds with various substituents at C-5 and C-8 is described. These particular compounds are supposed to have a potential antimalarial activity.

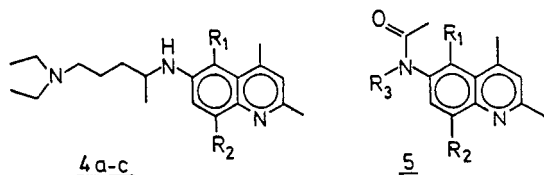
INTRODUCTION

Malaria infections are still a problem due to the adaption of the disease-causing parasites to existing preparations (ref. 1, 2). Several 8-aminoquinoline compounds, for instance Primaquine **1**, have been applied as chemotherapeutics for treatment of malaria diseases (ref.1,3). Introduction of methyl group in 4-position and trifluoromethylphenoxy group in 5-position in Primaquine modifies its biological activity (ref. 4, 5). It is well known that the antimalarial activity of 6-aminoquinoline compounds is similar to that of 8-aminoquinolines. Thus, compound **3** has a broad spectrum activity. Unfortunately, it is too highly toxic to be used in human medicine (ref. 6, 7). Thus, effects of replacement of both methoxy groups in **3** by a trifluoromethylphenoxy substituent are of interest in the study of their biological activities.

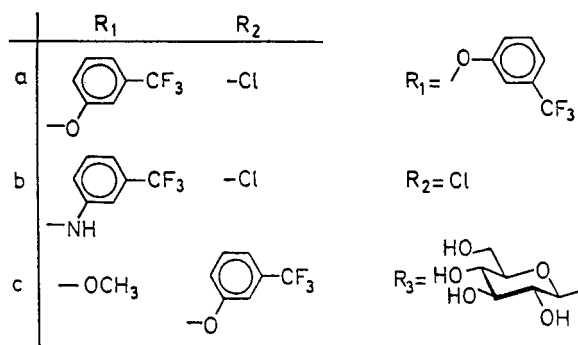
We suppose that the introduction of carbohydrate unit instead of the hydrocarbon chain into the amino group at 6-position would increase the biological activity.



In this article we present for the first time the synthesis in this field of four new compounds supposed to have antimalarial activity.



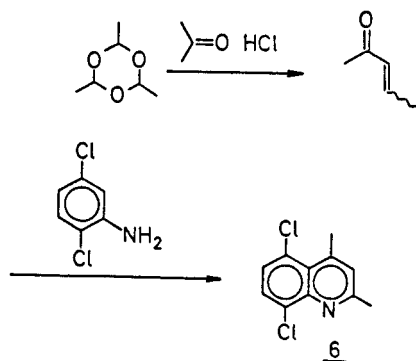
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SYNTHESIS OF 5,8-DICHLORO-2,4-DIMETHYLQUINOLINE (6)

A method for obtaining 2,4-dimethylquinoline products is developed by Combes (ref. 8, 9). Unfortunately, it runs with a very low yield when 2,5-dichloroaniline is used as a starting material. Thus, we followed a method first described by Reed (ref. 10) and known as "Beier's condensation" (ref. 11, 12), in the following way:

A mixture of paraaldehyde and acetone was saturated with dry hydrogen chloride and stirred for two days. After heating of this mixture with 2,5-dichloroaniline in the presence of nitrobenzene, the desired 5,8-dichloro-2,4-dimethylquinoline (6) was obtained in a good yield.

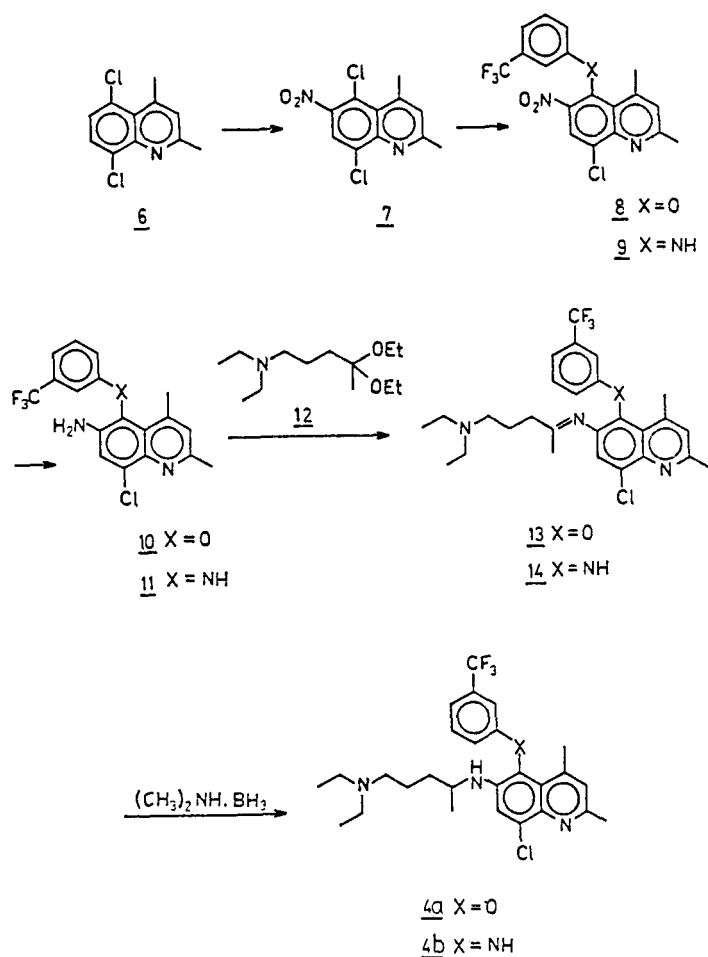


AROMATIC NUCLEOPHYLIC SUBSTITUTION IN OUR QUINOLINE RING

The nitration of 5,8-dichloro-2,4-dimethylquinoline at 5°C with fuming nitric acid and conc. H₂SO₄ gives, after treatment with ammonia, 5,8-dichloro-2,4-dimethyl-6-nitroquinoline (7) in a quantitative yield. So activated the quinoline ring reacts with a number of nucleophiles in our case it reacts with potassium-3-trifluoromethylphenolate and with lithium-3-trifluoromethylanilide to 8, respectively 9 in an excellent yield.

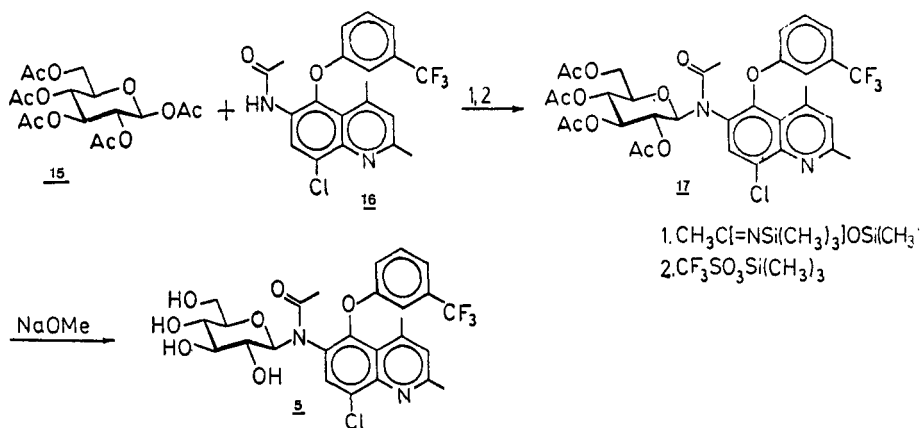
ALKYLATION OF THE AMINO GROUP AT C-6 IN SO FORMED QUINOLINE DERIVATIVES

The nitro group in compound 8 was reduced to an amino group with the help of sodium dithionite (ref. 13), while in 9 it was reduced by Raney-Ni in acetone medium (ref. 14). The reaction of the aromatic amine 10 or 11 with 1-diethylamino-4,4-diethoxypentane (12) (ref. 15) in the presence of NH₄Cl, results in obtaining the respective imines (Schiff base) 13 or 14. These imines were reduced by dimethylaminoborane in the presence of glacial acetic acid to compounds 4a or 4b (ref. 16).



N-GLYCOSILATION OF AMINOQUINOLINE DERIVATIVES

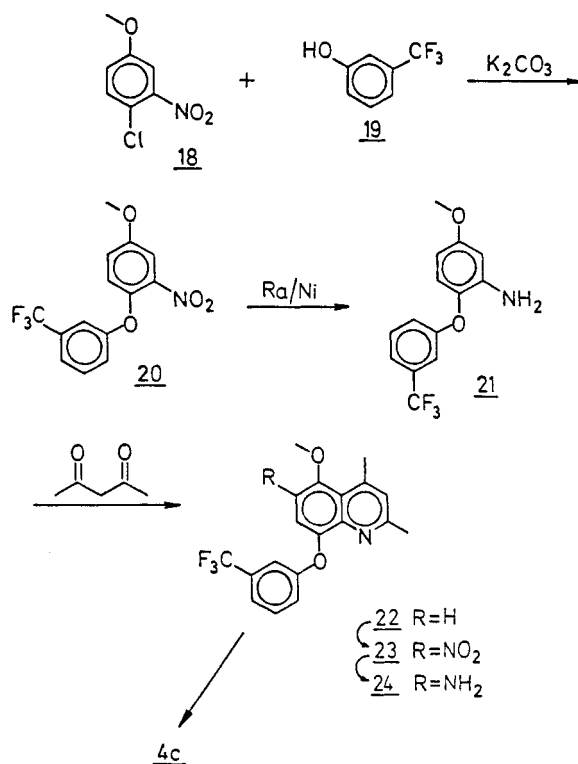
Then we suggested the carbohydrate residue to be built in by the nitrogen at C-6 in compound 10, instead of the hydrocarbon chain, i.e. to obtain the respective N-glycoside.



After acetylation of 6-aminoquinoline derivative 10 with acetic anhydride, the obtained amide 16 is silylated with N,O-Bis-(trimethylsilyl)-acetamide. Thus, a tautomeric mixture of N- and O-silylated forms is obtained. The O-silylic derivative has an increased nucleophilicity at the N-atom and in the presence of trimethylsilyltriflate it reacts with the intermediately obtained acyloxonium cation of paracylated carbohydrates 15 to derivative 17 (ref. 17). Then, in our case, the ester-acetyl groups are hydrolyzed with sodium methoxide in methanol to 5.

ALKYLATION OF SUBSTITUTED AT C-8 6-AMINOQUINOLINE

When obtaining the compound 4c, we use 4-chloro-3-nitroanisole (18) as a starting material and suggest the following reaction scheme for synthesis of the key intermediate of the type of 24.



The nitro compound 20 is catalytically reduced to amino compound with the help of Raney-Ni and H₂ at normal pressure in acetone medium (ref. 14). We applied the method of Combes (ref. 8, 9) and with the help of acetylacetone (ref. 20), we obtained the respective 2,4-dimethylquinoline derivative 22 with very good yield. The nitration at 6-position in the quinoline ring was carried out by means of 65% HNO₃ in acetic anhydride medium (ref. 18), followed by a catalytic reduction of the nitro group with the help of Raney-Ni and H₂. The alkylation of the amino group at C-6 in the compound 24 was carried out under the same reaction conditions as those used for obtaining 4a and 4b with the help of 1-diethylamino-4,4-diethoxy-pentane to compound 4c.

REFERENCES

- Peters W., *Chemotherapy and Drug Resistance in Malaria*, Academic Press London - New York (1970).
- Peters W., W. H. G. Richards, *Antimalarial Drugs*, Handb. Exp. Pharm. **68**, Springer Verlag, Berlin - Heidelberg - New York - Tokyo (1984).
- Carson P. E., in ref. 2, 83.
- Sweeney T. R., in ref. 2, 325.
- La Montagne M. P., P. Blumbers, *J. Med. Chem.*, **25**, 1094 (1982).
- Nickel P., *The Role of Quinoid Structures in Antimalarial Drugs*.
- Werburtun D., in ref. 2, 471.
- Combes A., *Bul. Soc. Chim. France*, **49**, 90 (1888).
- Combes A., *Compt. rend.*, **106**, 142 (1887).
- Reed J., *J. Pr. Chem.*, **32**, 630 (1885).
- Beyer, *ibid.*, **33**, 393 (1886).
- Roberts E. and E. Turner, *J. Chem. Soc.*, 1832 (1927).
- Houben-Weyl, Georg Thime Verlag - Stuttgart, vol. XI/1, p.437 (1958).
- Nickel P., L. Schrimpl, E. Fink and O. Dann, *Liebigs Ann. Chem.*, **744**, 119 (1971).
- Elderfield R., W. Vaughan, B. Millward and J. Ross, *J. Org. Chem.*, **23**, 1378 (1958).
- Nickel P., H. Barnickel, A. Wolff, E. Fink and O. Dann, *Arch. Pharm.*, **310**, 81 (1977).
- Snatzke G. and J. Vlahov, *Liebigs Ann. Chem.*, 439 (1985).
- Nickel P. and E. Fink, *ibid.*, 367 (1976).