Bioorganic & Medicinal Chemistry Letters, Vol.2, No.1, pp. 53-58, 1992
Printed in Great Britain

0960-894X/92 $3.00 + .00
Pergamon Press plc

NOR-MEFLOQUINE: STEREOSPECIFIC SYNTHESIS AND BIOLOGICAL PROPERTIES

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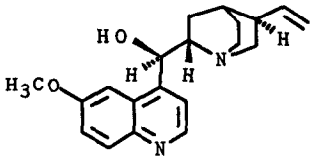
(*Received* 23 *October* 1991)

Summary: Nor-mefloquine, the pyrrolidinyl analog 1 related to mefloquine has been synthesised in a stereospecific way resting on the E geometry of the key-step olefin 4 obtained via the Heck's palladium-catalysed vinylic substitution reaction. Against P. berghei in vivo (mice), 1 was as active as mefloquine.

Introduction

Although a vaccine remains the likeliest way of preventing entire populations from having a severe attack of malaria, it is now clear that genetic engineering will not deliver any quick or universal remedy for this pleague. Furthermore, the emergence and spread of drug resistance, in particular chloroquine resistance, demands new drugs for the treatment of the "most devastating parasite disease in the tropics".[1]

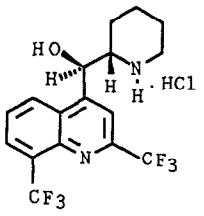
The available literature on the "antimalarial methanols" related to quinine shows that particular emphasis has been put on the structur-



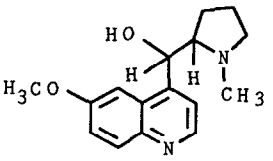
quinine

al variability of the aromatic residue and its substituents and less on the quinuclidine moiety.[2,3] Nevertheless, replacement of the quinuclidinyl for a simpler piperidyl rest with the concomitant

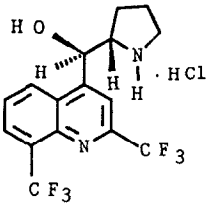
introduction of two trifluoromethyl groups on the quinoline moiety culminated with the potent antimalarial drug mefloquine.[4] So far, to the best of our knowledge, in the field of aryl and heteroaryl antimalarial methanols a pyrrolidinyl unit as cyclic side chain has never been introduced since the pioniering work of Ruzicka who prepared the specimen **A** which turned out to be inactive.[5]



mefloquine



A



1

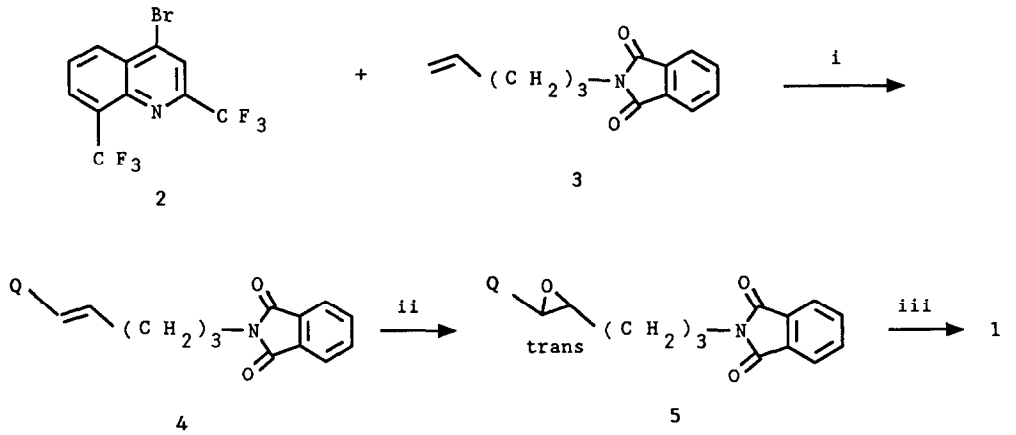
In this paper we report the synthesis and biological activities of nor-mefloquine, the erythro isomer (±)2,8-bis(trifluoromethyl)-α-(2-pyrrolidinyl)-4-quinolinemethanol (1) related to the potent antimalarial drug mefloquine, erythro (±)2,8-bis(trifluoromethyl)-α-(2-piperidyl)-4-quinolinemethanol. The nor denomination was given because compound 1 contains one CH_2 less, in the cyclic side chain, than mefloquine

Results and Discussion

Making use of the chemistry developed for one of our synthesis of mefloquine[6], the target molecule 1 was prepared in three steps as shown in the scheme. The starting monosubstituted olefin 3 was obtained quantitatively from potassium phthalimide and 5-bromo-1-pentene[7] in N,N dimethylacetamide at room temperature. The Heck's palladium-catalysed vinylic substitution reaction[8] of 3 with the 4-bromoquinoline 2 provided us , as in the case of mefloquine, with the *trans*-olefin 4 , which was isolated as colourless crystals in 58% yield , after flash chromatography. The reaction was catalysed with palladiumacetate [$Pd(OAc)_2$], o-tolyltriphenylphosphine in the presence of tributylamine (NBu_3). Hexamethylphosphoric triamide (HMPT) was found to be the most appropriate solvent for this reaction. Treatment of 4 with an excess of m-chloroperbenzoic acid (m-CPBA) in chloroform furnished, as one might anticipate from the

geometry of the key-step olefin 4, stereoselectively the trans epoxide 5. Although the epoxidation rate was slow, 5 was isolated in 77% yield as colourless crystals. Surprisingly, in THF the epoxidation of 4 never went to completion, we have no clear explanation for such a result. Subsequent hydrazinolysis of 5 in refluxing ethanol was accompanied by the spontaneous intramolecular epoxide opening with the free amino group, leading stereoselectively to the erythro compound 1. The overall yield of 1 from 2 was 36%.

Scheme



Reagents: i) $Pd(OAc)_2$, o-tolyltriphenylphosphine, NBu_3, HMPA, 100°C, 70 h
ii) m-CPBA, $CHCl_3$, 60°C, 48 h, iii) NH_2-NH_2, EtOH, reflux

Biological Activities

Antimalarial activity was determined in vivo against *Plasmodium berghei* in mice: after oral administration, the pyrrolidinyl analog of mefloquine showed an ED_{50} of 1.8 mg/kg which was the same ED_{50} exhibited by mefloquine.[9]

In Conscious Spontaneously Hypertensive rats nor-mefloquine 1 was also found to lower the blood pressure by 15% of the basal value with a dose of 100 mg.[10]

Conclusion

We have found[6] and developed a general method for generating the erythro relationship between the amino and hydroxyl centers of

mefloquine and the pyrrolidinyl analog 1 which is as potent as mefloquine against *Plasmodium berghei*. A quinuclidinyl analog of mefloquine has also been synthesised stereospecifically along this lines and will be the subject of a forthcoming publication.
In view of the biological results obtained with nor-mefloquine it would be interesting to introduce the pyrrolidinyl moiety on other classes of "antimalarial methanols" (e.i. Phenanthrene methanols).

Experimental

The methods were the same as described[11] unless otherwise quoted. The starting 4-bromoquinoline 2 was prepared following the procedure described in reference 4b.

5-Phthalimido-1-pentene (3)
A solution of potassium phthalimide (39 g, 0.21 mol) in 200 ml N,N-dimethylacetamide was treated dropwise under stirring at room temp. with 25 ml (0.21 mol) of 5-bromo-1-pentene. After 4h the reaction was finished (tlc) but for convenience, was let stir overnight and was worked up on next day. The mixture was poured on ice and extracted with ethyl ether. The organic extracts were backwashed with water (6x), brine, dried, filtered and evaporated to dryness under reduced pressure to give 3 as a colourless oil (42.7 g, 0.198 mol, 94%) which crystallised on standing and was used in the next step without further purification. - ^{1}H NMR (90 MHz, $CDCl_3$) δ ~1.5-2.4 (m, $-CH_2-CH_2-$), ~3.5-3.9 (m, $N-CH_2-$), ~ 4.8-5.3 (m, $CH_2=$), ~5.5-6.2 (m, -CH=), ~7.6-8 (m, heteroaryl H) ppm.

N-[(E)-5-[2,8-bis(trifluoromethyl)-4-quinolinyl]-4-pentenyl]phthalimide (4)
To a stirred solution of 2 (30.96 g, 90 mmol), 3 (19.35 g, 90 mmol) and NBu_3 (25.7 ml, 108 mmol) in 180 ml HMPT under argon was added o-tolyltriphenylphophine (2.19 g, 7.2 mmol) and $Pd(OAc)_2$ (0.8 g, 3.6 mmol). The reaction mixture was stirred for 70 h at 100°. The cooled dark reaction mixture was then poured onto ice-water and extracted with ethyl acetate. The organic extracts were thoroughfully backwashed with water (6x), brine, dried, filtered and evaporated to dryness under reduced pressure. The crude residue was purified by flash chromatography on silica gel (C_6H_{12}-EtOAc, 7-3) followed by recrystallisation from isopropyl ether to give 4 as colourless crystals, in 58% yield (24.9 g, 52 mmol). m.p. 97-98°C. - ^{1}H NMR δ ~1.93-2.25 ($-CH_2-$), ~2.35-2.75 (m, $-CH_2-=$), ~3.73-3.96 (m, $N-CH_2-$), ~6.56 (ddd, J_{trans}= 16 Hz, J_{gem}= 13 Hz, -CH=), ~7.2 (d, J_{trans}= 16 Hz, ϕ-CH=), ~7.5-8.4 (m, heteroaryl H) ppm. - MS, m/e, 478 (M), 459 (M-F), 331 (M-phthalimide).

N-[trans-5-[2,8-bis(trifluoromethyl)-4-quinolinyl]-4,5-epoxypentyl] phthalimide (5)
A stirred solution of 4 (14.34 g, 30 mmol) in 150 ml $CHCl_3$ was treated portionwise with m-CPBA (11.5 g, 60 mmol) at room temp.. The reaction mixture was then heated at 60° for 48h. After cooling, the

excess of peracid was destroyed as usual with a 10% aqueous solution of sodium sulfite and the solvent was evaporated under reduced pressure. Ethyl ether was then added, the organic phase was extracted with a 3% cold aqueous solution of $NaHCO_3$, washed with water, dried, filtered and evaporated to dryness under reduced pressure to give a colourless crystalline residue which was recrystallised from ethyl ether-isopropyl ether furnishing 11.4 g of 5 (23 mmol, 77%). m.p. 112-114°C. - ^1H NMR δ ~1.85-2.2 (m, $-CH_2-CH_2-$), ~2.9-3.2 (m, -CH-O-), ~3.7-4.0 (m, $N-CH_2-$), 4.38 (d, J_{trans} 2Hz, ϕ-CH-O-), ~7.6-8.4 (m, heteroaryl H) ppm. - MS, m/e, 494 (M), 475 (M-F).

erythro rac α-(2-Pyrrolidinyl)-2,8-bis(trifluoromethyl)-4-quinolinyl methanol hydrochloride (1).
A stirred solution of 5 (11.4 g, 23 mmol) in 50 ml EtOH was treated dropwise with NH_2-NH_2hydrate (1.12 ml, 22 mmol). The reaction mixture was then heated at reflux, after a few min , the phthalhydrazide began to crystallise out. At the end of the reaction (tlc), the solvent was concentrated under reduced pressure to a volume of approximately 10 ml and the reaction mixture was filtered. The filtrate was then treated with 3.75 ml of a 8N solution of HCl in EtOH (30 mmol). The solvent was removed in vacuo and the colourless crystalline residue was recrystallised from MeOH-Et_2O to give 7.5 g of 1 (18.7 mmol, 81%), m.p. 218°-220°C.- ^1H NMR ($DMSOd_6$) δ ~ 1.4-2.2 (m, $-CH_2-CH_2-$), ~ 3-3.5 (m, $N-CH_2-$), ~ 3.7-4.2 (m, N-CH-), 6.1 (d, J=3 Hz, -CH-O), 6.8 (OH), ~ 7.8-9 (m, heteroaryl H), 9.12 and 10.12 (broad s, NH_2^+) ppm. - MA calculated: C 47.95, H 3.77, N 6.99; found: C 47.83, H 3.81, N 7.05.

Acknowledgments - Our thanks are due to our colleagues of the Central Research Department for spectral data and elemental analyses.

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