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STEREOSPECIFIC SYNTHESIS OF A QUINUCLIDINYL ANALOGUE OF MEFLOQUINE-IV.

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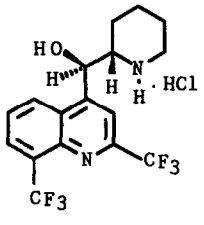
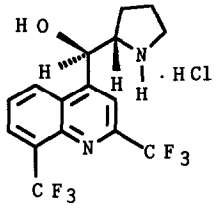
Summary: The quinuclidinyl analogue 1 related to the potent antimalarial agent mefloquine has been synthesised in a stereospecific way resting on the E geometry of the key step olefin 9 obtained via the Heck's palladium-catalysed vinylic substitution reaction.

Introduction

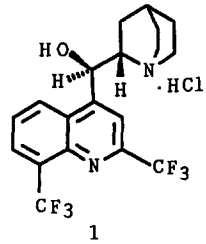
We have shown that the E geometry of the olefins obtained via the Heck's reaction[1] allows the generation of the erythro relationship between the amino and hydroxyl centers of mefloquine[2] and of nor-mefloquine[3] in a selective manner. At this point it seemed likely that the quinuclidinyl analogue 1 of mefloquine could be prepared along the same lines.



mefloquine



nor-mefloquine



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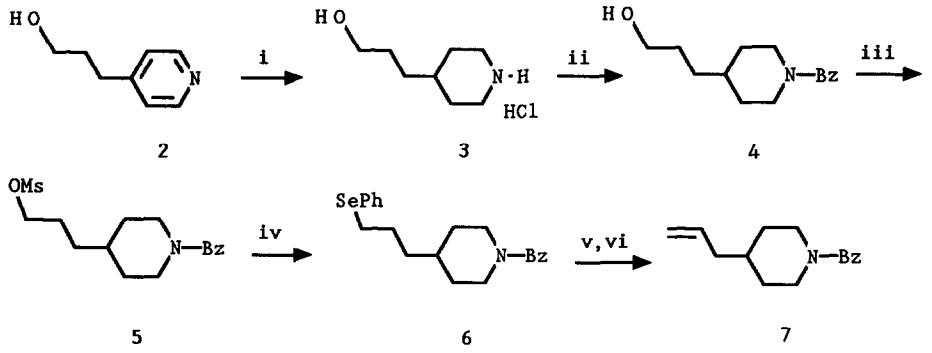
Results and discussion

The reaction sequence followed for the synthesis of the requisite piperidine olefin 7 starting from the readily available[4] 4-pyridinepropanol (2) is depicted in Scheme 1. Thus, catalytic hydrogenation of 2 over Pt/C in the presence of HCl proceeded smoothly and the hydro-

chloride 3 was obtained in 85% yield as colourless crystals. The clean benzoylation of 3 under Schotten-Baumann conditions with benzoyl chloride in ethyl ether, afforded pure 4 as an oil in 90% yield after usual work up of the reaction mixture; crude 4 could be processed into the next step without further purification.

Scheme 1

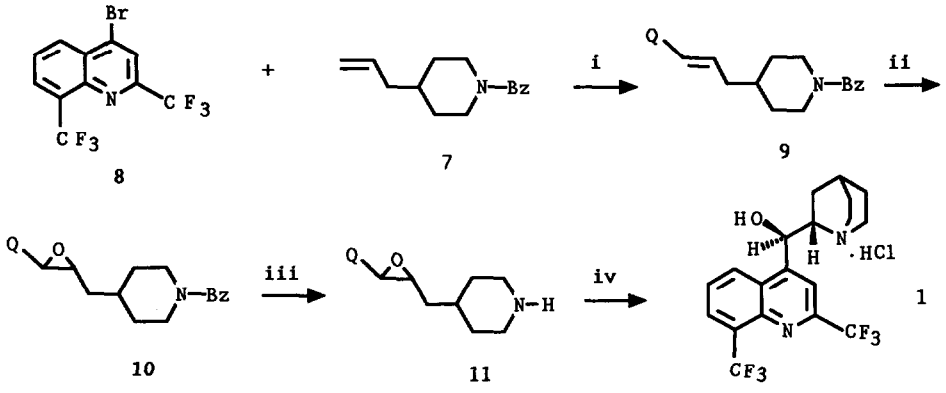


Reagents: i) H_2, Pt/C, H_2O, H^+ ii) PhCOCl, NaOH, Et_2O, 0°-5°C. iii) CH_3SO_2Cl, pyridine, Et_2O, 0°-5°C, rt. iv) PhSeNa, EtOH, rt, 2.5 h. v) m-CPBA, CH_2Cl_2, -5°C, rt 2 h vi) NEt_3, CCl_4, 80°C, 20 min

Though treatment of 4 with methanesulfonyl chloride in the presence of pyridine in ethyl ether at 5°C furnished the oily mesylate 5 in only 50% yield, we did not tried to improve the yield of this reaction because the quantity dealt with was sufficient for our purpose. Much to our surprise, mesylate 5 resisted direct conversion into the targeted olefin 7: nothing we did to this mesylate under basic conditions known to induce elimination met with success; the experiments led either to recovery of the starting material 5 or to intractable mixtures. Fortunately, there is ample evidence that selenium oxides[5] are synthetically equivalent to olefins, therefore our attention was directed to the synthesis of the phenylselenide 6 . To this end, diphenyldiselenide was treated with sodium borohydride ($NaBH_4$) in ethyl alcohol. The resulting phenylselenide anion was then treated with mesylate 5 at 20°C and the phenylselenide derivative 6 was isolated as an oil in over 95% yield after flash chromatography. Oxidation of 6 with m-chloroperbenzoic acid (m-CPBA) was followed by treatment with triethylamine in refluxing tetrachloromethane (CCl_4) to

induce the selen oxide elimination. We were delighted to discover that under these conditions, the targeted piperidyl olefin 7 could be obtained and was isolated as an oil in 43% yield after flash chromatography.

Scheme 2



Reagents:

i) $Pd(OAc)_2$, triphenyl-o-tolylphosphine, NBu_3, HMPA, 100°C, 20 h.
ii) m-CPBA, $(CH_2Cl)_2$, 80°C, 5 h. iii) DIBAL-H, -78°C, 6 h then rt.
iv) Toluene-EtOH (6-4), reflux, 48 h.

The piperidyl olefin 7 and the 4-bromo quinoline 8 were then submitted to the Heck's palladium vinylic substitution reaction under the conditions already described[2,3] (Scheme 2). The trans olefin 9 was isolated as crystals in 43% yield. The epoxidation of 9 with m-CPBA in 1,2-dichloroethane $(CH_2Cl)_2$ at reflux gave a single compound which turned out to be the trans epoxide as in the case of mefloquine[2] and nor-mefloquine[3]. So, in this case too, the epoxidation was stereoselective and 10 was isolated in 47% yield (considerable losses occurred during the chromatography, probably due to the lability of the epoxide). At this stage the last two steps relied on the beautiful work done towards the total synthesis of quinine[6]. Thus, mild reduction of the N-benzoyl protecting group of 10 with diisobutylaluminium hydride (DIBAL-H) in excess at -78°C furnished the amino epoxide 11 in 53% yield as yellowish crystals. At this stage, it must be stressed that our initial attempts at converting the aminoepoxide 11 into 1 were fairly disappointing; nevertheless, when 11 was heated at reflux in a mixture of toluene and ethanol (6:4) for 48 h, a complex mixture was

obtained from which 1 could be isolated in 54% yield after flash chromatography.

Conclusion

In conclusion we have shown that the Heck's palladium catalysed vinylic substitution reaction also allows the stereospecific synthesis of the quinuclidinyl analogue 1 of mefloquine though it must also be emphasised that no attempts were made to improve the yields of the reactions described herein. Nevertheless, the reaction sequence used in this work might be extended to the synthesis of more complex quinuclidinyl derivatives.

EXPERIMENTAL

The methods were the same as described[7] unless otherwise quoted. **4-Pyridinepropanol (2)** was prepared according to the literature[4].

4-Piperidinepropanol (3)
A stirred suspension of 4-pyridinepropanol (75.9 g, 0.55 mol) in water (330 ml) and aqueous concentrated HCl (76 ml ~ 0.91 mol, 12N in H_2O) and 5% Pt/C (18 g) was hydrogenated at 20°C for 11 h. The catalyst was removed by filtration and dioxane was added to the filtrate. The solvent was then removed under reduced pressure. The residue was recrystallised from MeOH and ethyl ether to give 84 g of the hydrochloride of 3 (0.47 mol, 85% yield), m.p. 150-155°C.

N-benzoyl-4-piperidinepropanol (4)
A 2N solution of aq NaOH (276 ml, 0.55 mmol) was added dropwise to a stirred solution of 3 (98.8 g, 0.55 mol) in H_2O (50 ml) at 5°C followed by the addition of ethyl ether (275 ml). The cooled reaction mixture was then treated dropwise for 30 min under vigorous stirring by the concomitant addition of a solution of benzoyl chloride (59.2 ml, 0.51 mol) in ethyl ether (275 ml) and NaOH (29.4 g, 0.62 mol) in water (275 ml). The reaction mixture was then stirred at 5°C for 75 min. Ethyl acetate was added and the organic extract was washed with water, brine, dried, filtered and evaporated to give 123.1 g (0.5 mol) of 4 as a colourless oil in 90% yield. - ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.48 (s, 5H, Ph), 4.8 and 3.9 (2xm, very broad, $2H_{eq}$, $-CH_2-N-$), 3.58 (m, 2H, $-CH_2O-$), ~ 3 (m, $2H_{ax}$, $-CH_2-N-$ and 1H, OH), ~ 1.9-0.9 (m, 9H, 4x$-CH_2-$, -CH-) ppm.

3-(1-Benzoyl-4-piperidyl)propyl methanesulfonate (5)
A solution of 4 (123.1 g, 0.5 mol) and pyridine (40.2 ml, 0.5 mol) in ethyl ether (500 ml) was treated dropwise for 30 min under stirring at 5°C with methanesulfonyl chloride (51.7 ml, 0.67 mol). After being stirred at room temperature for 3 days cold water was added, the organic phase was separated, extracted with cold saturated $NaHCO_3$, and water in sequence, dried, filtered and the solvent was removed under reduce pressure. The crude product was purified by flash chromatography (silica gel, ethyl acetate) to give pure 5 as an oil in 50% (80.9 g, 0.25 mol). - ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.4 (s-like m, 5H, Ph), ~ 4.5-3.9 (m, $2H_{eq}$, $-CH_2-N-$ and 2H, $-CH_2-OS$), 3.0 (s, 3H, CH_3-SO_2), 2.9 (m, $2H_{ax}$, $-CH_2-N-$), 2.0-0.9 (m, 9H, -CH-, 4x$-CH_2-$) ppm. - MS, m/e 325 (M), 246 (M-CH_3SO_2), 230 (M-OSO_2CH_3).

1-Benzoyl-4-[3-(phenylselenyl)propyl]piperidine (6)
Under Ar, $NaBH_4$ (10 g, 0.26 mol) was added in portions at 20°C to a stirred suspension of diphenyldiselenide (31.2 g, 100 mmol) in ethanol (300 ml). The resulting solution was then treated dropwise with a solution of 5 (26 g, 80 mmol) in ethanol (100 ml) . The resulting light suspension was stirred for 2.5 h at the same temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between water and ethyl ether. The organic extracts were backwashed with water, dried and filtered. The solvent was removed under reduced pressure and the yellow oily residue was purified by flash chromatography [silica gel, CH_3CO_2Et-C_6H_{12} (6-4)] providing 6 as an oil in 95.5% yield (29.5 g, 76.5 mmol). - ^1H NMR δ ~ 7.65-7.1 (m, 10H, Ph), 4.17 (m, very broad $2H_{eq}$, $-CH_2-N-$), 3.2-2.5 (m, $2H_{ax}$, $-CH_2-N-$ + 2H, $-CH_2Se$), 2.0-0.7 (m, 4x$-CH_2-$, -CH-). - MS, m/e 386 (M), 230 (M-SePh).

4-Allyl-1-benzoylpiperidine (7)
Under Ar a solution of 6 (29.5 g, 76.5 mmol) in CH_2Cl_2 (100 ml) was treated dropwise under stirrring at -5°C with a solution of m-CPBA (31 g, 152.8 mmol) in CH_2Cl_2 (300 ml). The solution was then stirred 2 h at 20 °C. This m-CPBA oxidation product was added dropwise over 30 min to a refluxing solution of NEt_3 (21.3 ml, 152.8 mmol) in CCl_4 (1300 ml) and heating was continued for 20 min. After cooling the yellow solution was extracted with saturated $NaHCO_3$, washed with water and the organic extracts were dried and filtered. Concentration under reduced pressure gave an oil which was purified by flash chromatography [C_6H_{12}-ethyl acetate, (7-3); silica gel] to give 7 as a light beige-colored oil in 43% yield (7.5 g, 32.7 mmol). - ^1H NMR δ 6.93 (m, 5H, Ph), 5.8 (m, 1H, -CH=), 5.12 and 4.93 (2xm, CH_2=), 4.5 and 3.93 (2xm, $2H_{eq}$, $-CH_2N-$), 2.93 (m, $2H_{ax}$, $-CH_2N-$), 2.06 (m, 2H, $-CH_2-CH=$), ~ 1.87- 0.75 (m,3x$-CH_2-$ and -CH-) ppm. - MS, m/e 229 (M).

1-Benzoyl-4-[(E)-3-[2,8-bis(trifluoromethyl)-4-quinolinyl]allyl] piperidine (9)
Under argon a stirred solution of 7 (3.8 g, 16.7 mmol), 4-bromoquinoline 8 (5.7 g, 16.7 mmol) and NBu_3 (4.75 ml, 20.3 mmol) in HMPT (40 ml) was treated rapidly with $Pd(OAc)_2$ (0.149 g, 0.66 mmol), triphenyl-o-tolylphosphine (0.426 g, 1.4 mmol) and CuI (0.06 g, 0.3 mmol) at 20°C. The reaction mixture was then heated at 120°C for 20 h. After cooling at rt the dark reaction mixture was poured onto ice and extracted with ethyl acetate. The organic extracts were thoroughly washed with water, dried , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [CH_3CO_2Et-C_6H_{12}(6-4), silica gel] to give 9 as light beige coloured crystals in 42% yield (3.45 g, 7.0 mmol).
- ^1H NMR δ 7.18 (d, J=15.5 Hz, Q-C*H*=CH-), ~ 4.9-3.5 (m, very broad, $2H_{eq}$, $-CH_2N-$), 2.88 (m, $2H_{ax}$, $-CH_2N-$), 2.43 (m, 2H, =CH-CH_2-), ~ 2.1-1.5 (m, 5H, 2x$-CH_2-$ and -CH-) ppm.

4-[(trans)-3-(1-Benzoyl-4-piperidyl)-1,2-epoxypropyl]-2,8-bis-(trifluoromethyl)quinoline (10)
A stirred solution of 9 (2.4 g, 4.9 mmol) in $(CH_2)_2Cl_2$ (100 ml) was treated under stirring at 20°C with m-CPBA (2.8 g, 14.7 mmol). The reaction mixture was heated under reflux for 5h. Under stirring and ice-cooling a 10% solution of sodium sulfite was added dropwise to destroy the excess of m-CPBA. The organic phase was quickly washed with cold water, 3% $NaHCO_3$ aq solution and water, dried, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography [silica gel,CH_3CO_2Et- C_6H_{12}(4-6)] to give 1.2 g of 10

as colourless foam (2.3 mmol, 47%). - ^{1}H NMR δ 8.47-8.12 (m, 2H), 7.96-7.66 (m, 2H), 7.44 (s, 5H), ~ 4.86-3.62 (m, very broad, $2H_{eq}$, $-CH_2N-$), 4.33 (d, 1H, J_{trans}=2Hz, Q-C*H*OCH), ~ 3.28-2.68 (m, 1H, Q-CHOC*H* and $2H_{ax}$,$-CH_2N-$), ~ 2.18-1.05 (m, 7H, 3x$-CH_2-$, -CH-) ppm - MS, m/e 508 (M).

4-[(trans)-1,2-Epoxy-3-(4-piperidyl)propyl]2,8-bis(trifluoromethyl)quinoline (11)

Under argon and stirring a solution of 10 (1.14 g, 2.24 mmol) in toluene (36 ml) and THF (4 ml) was treated dropwise at -78°C for 5 min with a solution of DIBAL-H in toluene (3.9 ml, 4.5 mmol). The reaction mixture was stirred at room temperature for 4h then cooled to 0°C and cautiously quenched with water (15 ml). Ethyl acetate was added and the pH was adjusted to pH ≈ 3 with a solution of citric acid (10% in water). The organic phase was separated washed with water, dried, filtered and concentrated under vacuum. The orange residue was treated with 2.3 ml 1N HCl in MeOH and the solvent was removed under reduced pressure to give an oil which crystallised from CH_2Cl_2-Et_2O furnishing 0.48g of light orange crystals (1.18 mmol, 53%). - ^{1}H NMR δ ~ 9.62-9.0 (broad,2H, NH_2^+), 8.79 (d, J=8.5Hz, 1H), 8.46 (d, J=7Hz, 1H), 8.05 (dd, 1H), 7.79 (s, 1H), 4.86 (quite a d, 1H, J≈1.5Hz, Q-C*H*OCH-), ~ 3.68-2.62 (m, 5H,-CH-O, 2x$-NCH_2-$), ~ 2.22-1.25 (m, 7H, -CH-, 3x$-CH_2-$) ppm. - Ms, m/e 404 (M).

(rac-erythro-)-α-[(SR)-1-Azabicyclo[2.2.2]oct-1-yl]-2,8-bis(trifluoromethyl)quinoline-4-methanol (1)

Under argon a solution of 11 (0.2g, 0.5 mmol) in toluene (6 ml) and MeOH (4 ml) was heated under reflux for 48h. The dark solution was concentrated under reduced pressure and the residue was purified by flash chromatography [silica gel, benzene-MeOH-NH_4OH (136-60-4)] to give 0.11g of 1 as orange crystals (0.27 mmol, 54%). - ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.3 (d, 1H, J=9Hz), 8.19 (s, 1H), 7.98 (d, 1H, J=7.5Hz), 7.41 (dd, 1H), 6.36 (s, 1H, -CH-O), ~ 6 (very broad s, -OH), 4.22-4.02 (m, 1H, -NCH-), 3.27-3.05 (m, 2H, $-NCH_2-$), 3.04-2.86 and 2.86-2.67 (2xm, 2H, $-NCH_2-$), 2.16-1.1 (m, 7H, 3x$-CH_2-$, -CH-) ppm. Ms m/e 404 (M), 387 (M-OH).

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