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QUINOLONE ANTIBIOTICS: STUDY OF REACTIVITY AND IMPURITY PROFILE OF PIPERAZINE WITH CHLORO-FLUORO-QUINOLONE CARBOXYLIC ACID IN AQUEOUS MEDIUM.

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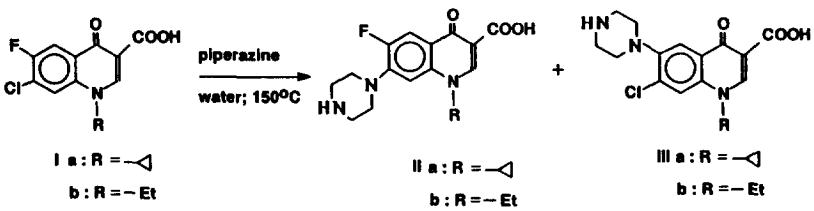
ABSTRACT: The reaction of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acid with piperazine in water was studied. The product ciprofloxacin was isolated and the impurity formed in the reaction was isolated and characterized as 1-cyclopropyl-7-chloro-6-piperazinyl-4-oxo-1,2-dihydroquinoline-3-carboxylic acid. Similarly norfloxacin was also synthesised. Copyright © 1996 Published by Elsevier Science Ltd

Ciprofloxacin (**IIa**) and norfloxacin (**IIb**) are widely used antibiotics in bulk quantities. **IIa** is the most widely used as third generation quinolone antibiotic in the world and is superior to chloroamphenicol, aminoglycosides and cephalosporin; and commonly used for curing enteric fever, septicaemia, bronchopneumonia oesteromyelitis, prostatis and non-genococeal urethritis.

Ciprofloxacin is conventionally prepared by the condensation of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acid (**Ia**) with piperazine in the presence of pyridine[1] or triethylamine[2] as the solvents. This was also prepared by making borate or fluoroborate complex of quinolone carboxylic acid and then condensation with piperazine or piperazine derivative in dimethylsulfoxide, dimethylformamide or dimethylacetamide as the solvent to yield piperazino-quinolone carboxylic acid borate or fluoroborate complex which on further hydrolysis yielded ciprofloxacin[3-7].



With the current global awareness in developing environmentally friendly technologies and our philosophy in developing such technologies, it was decided to carry out the reaction in non-hazardous solvent. Performing a reaction in water is the ultimate dream of an organic chemist. This communication describes our effort towards this.

In order to study the reactivity of piperazine with chloro-fluoro-quinolone carboxylic acid **Ia** and avoid the excess of piperazine and solvents which are normally employed (DMF, DMSO, or DMAC) in known processes, the condensation of piperazine with 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acid (**Ia**) in water was studied. A variety of conditions varying time, temp.

& concentration were studied. Under optimised conditions it was observed that piperazine reacts at both position C-6 (replacement of fluorine) and C-7 (replacement of chlorine).

In a typical experiment a mixture of 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,2-dihydroquinoline-3-carboxylic acid (**Ia**, 0.18 mole) , piperazine (0.36 mole) in 100 ml water was heated at 150°C for 4-5 hrs. Then reaction mixture was cooled and filtered. The solid thus obtained was purified by trituration with 10% acetic acid to furnish ciprofloxacin[8] (**IIa**) in 65% yield and the impurity (**IIIa**) corresponding to attack of piperazine at C-6 position in 8-10%.

The impurity (**III**) was purified by crystallization in pure form and identified as 1-cyclopropyl-7-chloro-6-piperazinyl-4-oxo-1,2-dihydroquinoline-3-carboxylic acid by its spectral analysis (^{1}HNMR, ^{13}C NMR, Mass spectra).[9]

In order to study the generality of the above reaction for other quinolone antibiotics, **Ib** was treated with piperazine under identical condition to furnish norfloxacin (**IIb**) in 50 % yield.

In conclusion, we have demonstrated that the water serves as an excellent medium for the condensation of chloro-fuoro quinolone carboxylic acids with piperazine for the synthesis of ciprofloxacin & norfloxacin. Considering the importance of quinolone antibiotics by virtue of their broad spectrum activity, we believe this method would be of interest for the synthesis of quinolone antibiotics.

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8. **IIa**:^{1}HNMR 200 MHz, CD_3COOD) δ : 1.24 (m, 2H), 1.50 (m, 2H), 3.65 (s, 4H), 3.75 (s,5H), 7.65 (d, J = 7 Hz,1H, H-8), 7.92 (d, J = 13 Hz, 2H, H-5), 8.75(s, 1H, H-2).^{13}CNMR (50 MHz): (CD_3 COOD) : 8.3 (t), 36.77 (d), 44.3 (t), 47.27 (t), 107.3 (d), 112.2 (d), 120.1 (s), 120.3 (s), 140.0 (s), 145.4 (s), 145.6 (s), 149 (d), 169.2 (s), 177.3 (s). Mass Spectrum: (M^+): 331 (31%), 287 (82%),245 (100%).
9. **IIIa**: ^{1}HNMR: (200 MHz, CD_3COOD) : 1.25 (m, 2H), 1.48 (m, 2H), 3.45(s, 4H), 3.55 (s, 4H), 3.82 (m, 1H), 8.08 (s,1H), 8.40 (s, 1H), 8.93 (s,1H).^{13}CNMR: (50 MHz): (CD_3 COOD) : 8.3 (t), 36.8 (d), 44.88 (t), 48.95 (t), 108.2 (s), 117.2 (d), 127.3 (d), 125.8 (s), 157.8 (s), 139.5 (s), 147.7 (s), 149.5 (d), 169.5 (s), 178.4 (s). Mass Spectrum: M^+: 347 (7%), 69 (25%), 60, 56 (100%).

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