

Note

Nucleophilic substitutions on 3-chloro-4-fluoronitrobenzene

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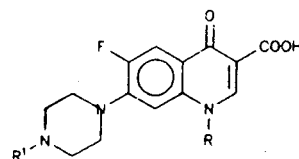
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Nucleophilic substitutions on 3-chloro-4-fluoronitrobenzene **5** with piperazines occur on the fluorine rather than on the chlorine atom as reported, to yield 3-chloro-4-piperazinylnitrobenzenes **8** and **9**.

Our interest in antibacterial 6-fluoro-7-piperazinylquinolones like ciprofloxacin **1** and pefloxacin **2**¹ led us to consider 4-fluoro-3-(substituted)-piperazinyl nitrobenzenes **3** and **4** as starting materials in one route. A recently published Indian Patent² reported the formation of **3** in 90% yield from 3-chloro-4-fluoronitrobenzene **5** by reaction with N-acetyl piperazine **6** in pyridine at 120-125° for 4 hr. The patent further describes the conversion of **3** into ciprofloxacin **1** via several obvious steps. *A priori* the substitution of chlorine *meta* to nitro group in **5** in preference to the intrinsically more reactive fluorine at position - 4 which is further activated by a *para*-placed nitro group seemed unlikely, but the patent claim had to be tested since **1** had been reportedly obtained from **3**.

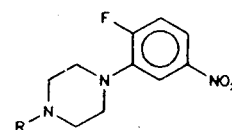
In the event, the reaction of **5** with **6** in pyridine at 120-125° for 4 hr gave a yellow product. m.p. 91-92° (from MeOH) in poor yield (lit². m.p. claimed for **3**, 48-51°). The reaction of **5** and **6** went better when heated neat at 60° for 2 hr to afford the same product in 53% yield. Physical data however established the identity of the product beyond doubt as **8**, arising from **5** by displacement of fluorine as expected and not chlorine. Analysis. Found: C, 50.72; H, 4.94; N,



1. R= cyclopropyl

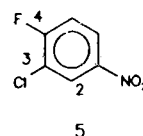
R¹= H

2. R= C₂H₅; R¹= CH₃

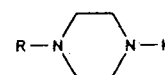


3. R= COCH₃

4. R= CH₃

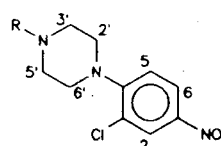


5



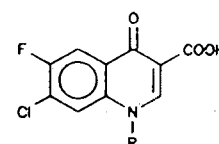
6. R= COCH₃

7. R= CH₃



8. R= COCH₃

9. R= CH₃



10

14.83; M⁺ 283, 285. Calcd for C₁₂H₁₄ClN₃O₃: C, 50.81; H, 4.97; N, 14.82%; M⁺, 283.72; ¹H NMR (60 MHz, CDCl₃): δ 8.27 (C₂-H, d, J = 2.5 Hz), 8.13 (C₆-H, dd, J = 8.2, 2.5 Hz), 7.03 (C₅-H, d, J = 8 Hz), 3.73 (4H at C-3' and C-5', unresolved m), 3.23 (4H at C-2' and C-6', unresolved m), 2.15 (COCH₃, s).

Condensation of **5** with N-methylpiperazine **7** should have given **4** according to the patent which would lead to pefloxacin **2** by the reaction sequence outlined therein. However, the reaction of **5** and **7** in pyridine at 120-125° for 4 hr gave only **9** in 59% yield [m.p. 94-95° (from MeOH)] and not **4**. Analysis. Found: C, 51.82; H, 5.65; N, 16.32; M⁺ 255, 257. Calcd for C₁₁H₁₄ClN₃O₂: C, 51.67; H, 5.52; N, 16.47%; M⁺ 255.71; ¹H NMR (60 MHz, CDCl₃): δ 8.18 (C₂-H, d, J = 2.5 Hz), 8.03 (C₆-H, dd, J = 8, 2.5 Hz), 7.03 (C₅-H, d, J = 8 Hz), 3.20 (4H at C-2' and

C-6', m), 2.57 (4H at C-3' and C-5', m), 2.32 (CH₃, s).

The regrettable conclusion that **3** and **4** which could well serve as starting materials for **1** and **2** respectively cannot be obtained from **5** by nucleophilic substitution thus becomes inevitable. We wish to point out that the conventional synthesis of **1**, **2** and similar compounds depends upon a preferential nucleophilic substitution of chlorine in **10** with piperazines in the final step but now the chlorine is activated by a *para*-placed carbonyl group while the fluorine does not enjoy such activation.

Acknowledgement

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References

- 1 Dirlam J P, Jaynes B H & Jefson M R, *Ann Rep Med Chem*, 30, 1995, 104.
- 2 *Indian Pat* 170657 (to Ranbaxy Laboratories Ltd); May 2, 1992; *Chem Abstr*, 120, 1994, P. 30783 W.