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Note

Nucleophilic substitutions on 3-chloro-4- fluoronitrobenzene

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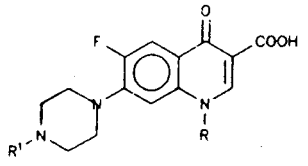
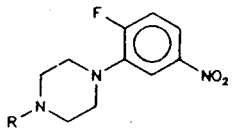
Nucleophilic substitutions on 3-chloro-4- fluoronitrobenzene **5** with piperazines occur on the fluorine rather than on the chlorine atom as reported, to yield 3-chloro-4-piperazinylnitrobenzenes **8** and **9**.

Our interest in antibacterial 6-fluoro-7-piperazinylquinolones like ciprofloxacin **1** and pefloxacin **2**[1] led us to consider 4-fluoro-3-(substituted)-piperazinylnitrobenzenes **3** and **4** as starting materials in one route. A recently published Indian Patent[2] reported the formation of **3** in 90% yield from 3-chloro-4-fluoronitrobenzene **5** by reaction with N-acetylpiperazine **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**.

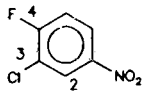
In the event, the reaction of **5** with **6** in pyridine at 120- 125° for 4 hr gave a yellow product. m.p. 91-92° (from MeOH) in poor yield (lit[2]. m.p. claimed for **3**, 48-51°). The reaction of **5** and **6** went better when heated neat at 60° for 2 hr to afford the same product in 53% yield. 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, 14.83; M^+ 283, 285. Calcd for $C_{12}H_{14}ClN_3O_3$: C, 50.81; H, 4.97; N, 14.82%; M^+, 283.72; ^1H NMR (60 MHz, $CDCl_3$): δ8.27 (C_2-H, d, J =2.5Hz), 8.13 (C_6-H, dd, J =8.2, 2.5 Hz), 7.03 (C_5- H, d, J =8Hz), 3.73 (4H at C- 3′ and C- 5′, unresolved m), 3.23 (4H at C- 2′ and C-6′, unresolved m), 2.15 ($COCH_3$, s).



1. R= cyclopropyl
   R¹= H
2. R= C_2H_5; R¹= CH_3



3. R= $COCH_3$
4. R= CH_3



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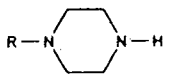
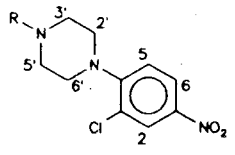
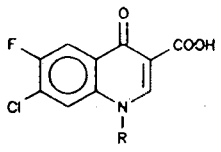


6. R= $COCH_3$
7. R= CH_3



8. R= $COCH_3$
9. R= CH_3



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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 $C_{11}H_{14}ClN_3O_2$: C, 51.67; H, 5.52; N, 16.47%; M^+ 255.71; ^1H NMR (60 MHz, $CDCl_3$: δ 8.18 (C_2-H, d, J =2.5 Hz), 8.03 (C_6-H, dd, J =8, 2.5 Hz), 7.03 (C_5-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 (CH_3, 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.