

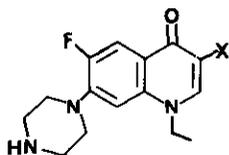
NOVEL SYNTHESIS OF QUINOLONE-3-SULFONIC ACID DERIVATIVES

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Abstract - The synthesis of 1-ethyl-6-fluoro-7-(1-piperazinyl)-1,4-dihydro-4-oxoquinoline-3-sulfonic acid is described. The use of a 2-bromophenyl sulfonate as a protected sulfonic acid is readily hydrolyzed under basic conditions is described.

The discovery of the quinolone family of highly potent antibacterial agents, exemplified by norfloxacin (1)¹, has prompted research in a number of laboratories directed towards the synthesis of analogs with optimized pharmacological properties.² As part of a program to obtain highly water soluble quinolone antibiotics, we became interested in synthesizing the analog, 2, of norfloxacin in which a sulfonate group replaces the carboxyl group.



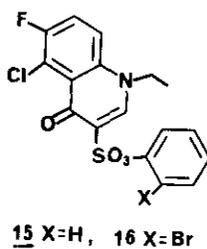
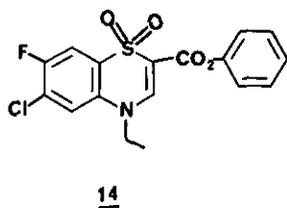
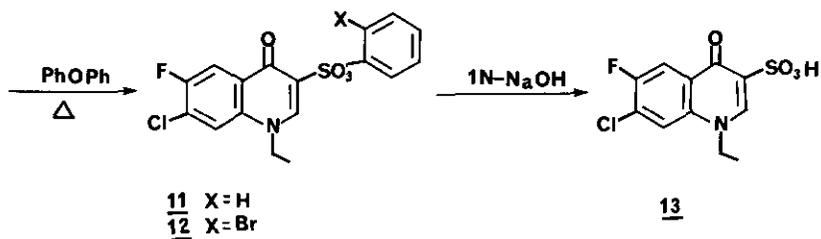
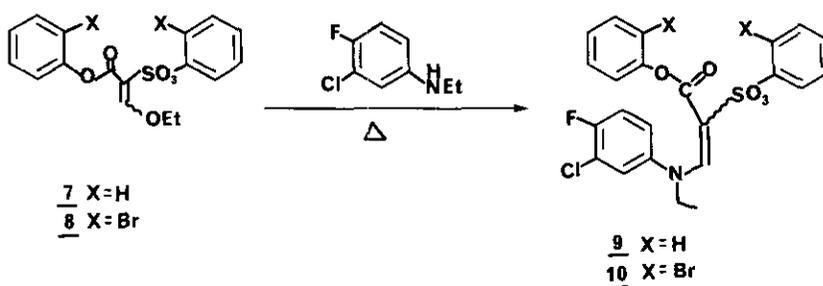
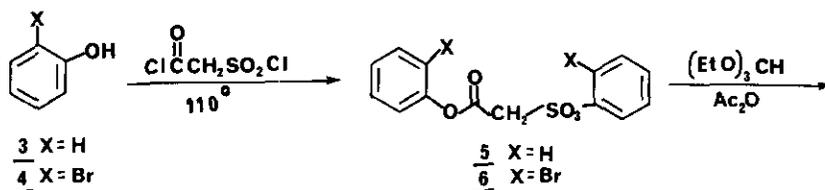
1 X = CO₂H
2 X = SO₃H

In the synthesis of 2, a critical problem is the protection of the sulfonic acid functionality. Our strategy for sulfonic acid protection involved the preparation of aryl sulfonate intermediates which would allow us to recover the sulfonic acid after the quinolone ring formation. Reaction of phenol with chlorosulfonylacetyl chloride at 110°C for 12 h afforded the bisaryl ester 5³ (92%) which, upon heating (120°C) with triethyl orthoformate in acetic anhydride, produced the enol ether 7 (85%) as a 1:1 E/Z mixture. The isomeric 7 thus obtained underwent coupling with 3-chloro-1-ethylamino-4-fluorobenzene in dichloroethane (reflux, 4 h) to yield 9 (1:1 E/Z, 82%) which, upon heating at 230°C in diphenyl ether,⁴ gave the quinolone sulfonate

11 (87%).⁵ There was no sign of the formation of the cyclic sulfone 14 or the regio isomer 15. It appears that the E/Z mixture 9 equilibrates under the thermal conditions and the carboxylic ester cyclizes preferentially over the sulfonate ester producing 11 exclusively. With 11 in hand, the saponification of the sulfonate ester was studied. To our initial surprise, the basic or acidic hydrolysis of 11 under a variety of conditions failed to produce the sulfonic acid 13.⁶ The highly stabilized vinylogous sulfonamide system in 11 might contribute to the difficult hydrolysis of 11. Thus, it appeared that an activated aryl sulfonate was required to permit the saponification. To this end, the 2-bromophenyl sulfonate 10 was prepared in a similar manner to that used for the synthesis of 9 (45% from 4).⁷ When 10 (1:1 E/Z mixture) was heated at 230°C in diphenyl ether (5 h), 12 and 16 were produced in a 2:1 ratio (38%). An explanation for the dramatic regioselective difference in the seemingly similar cyclization of 9 and 10 is not obvious.

Both 12 and 15 were cleanly separated by chromatography on silica gel and obtained as crystalline materials. The assignment of structure to these isomeric compounds is based upon the aromatic ¹H nmr of 13 and 17 (vide infra). Saponification of 12 (1N NaOH, rt, 2 h) gave the sulfonic acid 13 (85%) after C18 reverse phase column chromatography. Similarly, the isomeric sulfonic acid 17 was obtained (75%). Presumably, the smooth saponification of 12 compared to 11 is due to the inductive activation of the aryl sulfonate by the ortho bromine atom. In the ¹H nmr of 13, the C-5 and C-8 protons appeared as two doublets at δ 7.33 (J = 9.0 Hz) and δ 7.82 (J = 5.9 Hz). On the other hand, in the ¹H nmr of the isomer 17, the C-7 and C-8 protons appeared as two doublets of doublets at δ 7.56 (J = 9.4, 8.6 Hz) and δ 7.64 (J = 9.4, 4.4 Hz).

Finally, displacement of the C-6 chlorine atom of 13 with piperazine (1-methyl-2-pyrrolidinone, 170°C, 2 h) gave the norfloxacin C-3 sulfonic acid analog 2 (26%) after C18 reverse phase column chromatography. To our disappointment, the sulfonic acid 2 exhibited only weak activity against gram positive bacteria.



REFERENCES AND NOTES

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6. For example, treatment of 11 with 5N NaOH in EtOH-H₂O (reflux, 24 h) afforded ca 80% unchanged 11 and decomposed material.
7. All new compounds were fully characterized by the ir and ¹H nmr spectra, and gave satisfactory elementary analyses and/or high resolution mass spectra.

¹H nmr of the selected compounds are as follows:

13 (D₂O + 1 eq. NaHCO₃): δ 1.44 (t, J = 7.2 Hz, 3H), 4.30 (q, J = 7.2 Hz, 2H), 7.33 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 5.9 Hz, 1H), 8.59 (s, 1H).

17 (D₂O + 1 eq. NaHCO₃): δ 1.47 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H) 7.56 (dd, J = 9.4 & 8.6 Hz, 1H), 7.64 (dd, J = 9.4 & 4.4 Hz, 1H), 8.52 (s, 1H).

2 (D₂O): δ 1.75 (t, J = 7.2 Hz, 3H), 3.72 (broad s, 4H), 3.87 (broad s, 4H), 4.80 (q, J = 7.2 Hz, 2H), 7.34 (d, J = 6.8 Hz, 1H), 8.28 (d, J = 10.2 Hz, 1H), 9.38 (s, 1H).

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