A NOVEL SYNTHESIS OF CARBON-LABELLED QUINOLONE-3-CARBOXYLIC ACID ANTIBACTERIALS

Richard M. Carr and Derek R. Sutherland

Isotope Chemistry Group, Chemical Development Division, Glaxo Research & Development Limited, Greenford, Middlesex UB6 OHE, UK.

Summary

3-Iodoquinolones were prepared from the corresponding quinolone-3-carboxylic acids by Hunsdiecker-type iododecarboxylation reactions with lead tetraacetate and iodine. Cyanation of the iodo compounds with mixtures of potassium [^{13}C]cyanide and copper (I) iodide, gave [3-^{13}C]cyanoquinolones which on acidic hydrolysis afforded quinolone-[3-^{13}C]carboxylic acids. In this way, nalidixic acid, an immediate precursor of norfloxacin, and quinolone WIN57273 were labelled with carbon-13 in the metabolically stable carboxylic acid fragment.

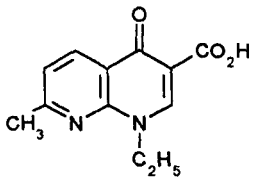
Key words: antibacterial, carbon-13, cyanation, Hunsdiecker, *iododecarboxylation, quinolone carboxylic acid*

Introduction

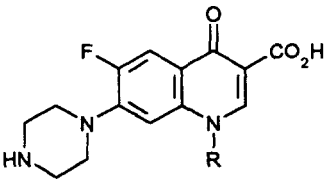
The first quinolone-type antibacterial to be marketed was the 8-azaquinolone-3-carboxylic acid nalidixic acid (1a) (Scheme 1) (1). This orally absorbed compound has a narrow spectrum of antibacterial activity, being active against gram negative organisms but with little activity against gram positive and *pseudomonas* bacteria. Moreover, adverse reactions to the drug were fairly common and resistance sometimes developed quickly in pathogens. More potent 6-fluoroquinolone-3-carboxylic acid antibacterials were developed in the early 1980's, and these have a much broader spectrum of activity then nalidixic acid, are better tolerated, and have more favourable pharmacokinetics. Examples of marketed drugs are norfloxacin (2a) (2), ciprofloxacin (3) (3) and ofloxacin (4a) (4) (Scheme 1). A large number of other quinolone antibacterials have been described (5,6).

CCC 0362–4803/94/100961–11

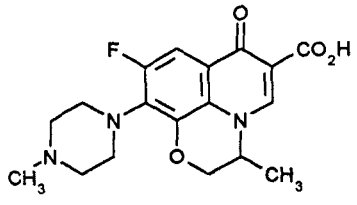
Received 6 May, 1994
Revised 10 May, 1994



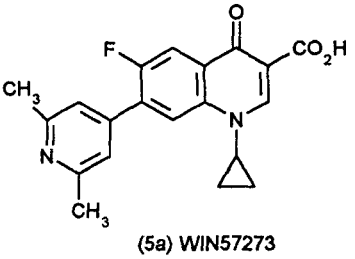
(1a) Nalidixic acid



(2a) Norfloxacin, R = ethyl
(3) Ciprofloxacin, R = cyclopropyl



(4a) Ofloxacin



(5a) WIN57273

Scheme 1

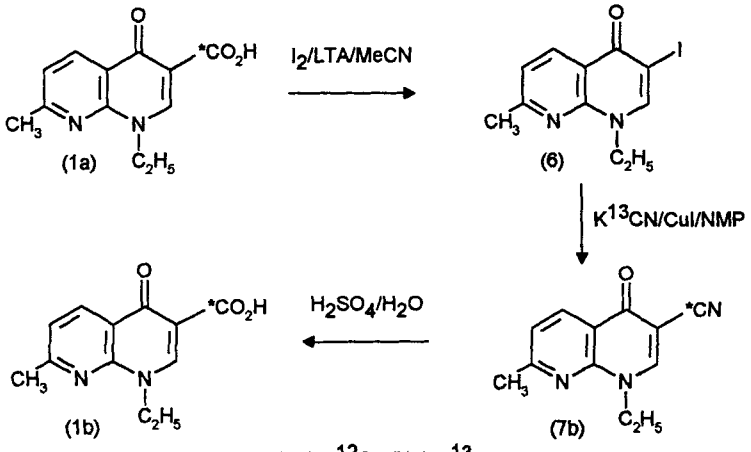
Carbon-labelled quinolone-3-carboxylic acids have normally been prepared *via* multi-step syntheses using labelled versions of reagents in the standard synthetic route to give ring-labelled products (7-9). Development of a short, general route to labelled quinolones, using the unlabelled drug substance as starting material, was desirable. There is no evidence (10-16) to suggest that the carboxylic acid substituent of quinolone antibacterials is metabolically unstable, and therefore it is a suitable position for a carbon label.

Cyanation of a variety of iodoaromatic compounds has recently been achieved with mixtures of potassium [^{13}C]cyanide and copper (I) iodide (17), thereby obviating synthesis of the classical cyanation reagent, copper (I) cyanide. Consequently, it was decided to examine the preparations of 3-iodoquinolones by Hunsdiecker-type iododecarboxylation of quinolone-3-carboxylic acids, followed by application of the novel cyanation mixture (*vide supra*). Hydrolysis of the resulting nitrile would give the corresponding quinolone [^{13}C]carboxylic acid.

Results and Discussion

Nalidixic acid (1a) was readily available as a convenient model compound. Iododecarboxylation of (1a) with lead tetraaccetate (LTA) and iodine in carbon tetrachloride (18) or acetonitrile at reflux, irradiated with a tungsten lamp (100 watt), gave 3-iodoquinolone (6) in 62 or 51% yield, respectively (Scheme 2). An alternative iododecarboxylation of (1a) with iodosobenzene diacetate afforded (6) in 47% yield.

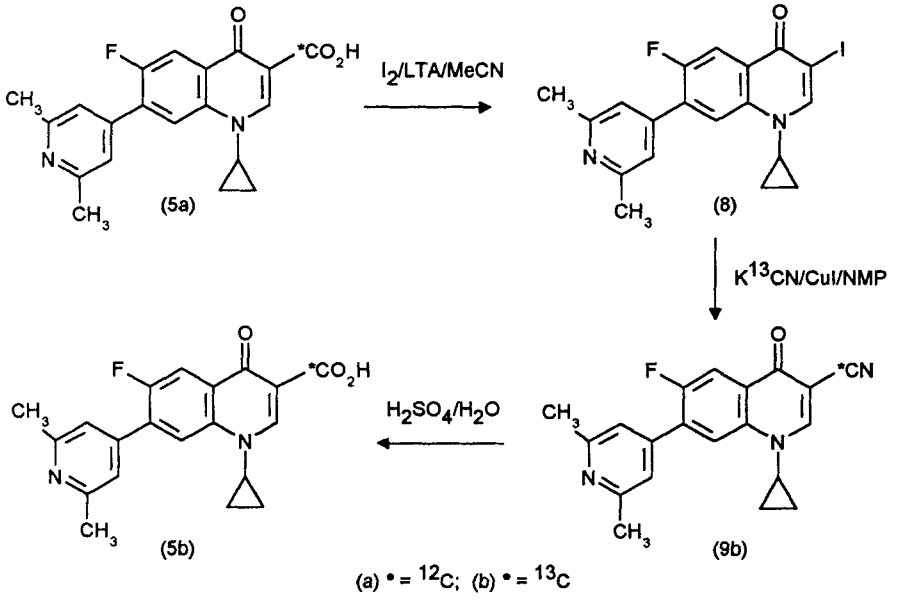
Cyanation of substrate (6) with one molar equivalent of potassium [^{13}C]cyanide and 0.5 molar equivalents of copper (I) iodide in N-methyl-2-pyrrolidinone (NMP) at reflux gave labelled nitrile (7b) in 67% yield. Finally, hydrolysis of (7b) with 9M sulphuric acid, gave carbon-13-labelled nalidixic acid (1b) in 86% yield (Scheme 2).



Scheme 2

The methodology used for the conversion of unlabelled nalidixic acid (1a) to [^{13}C]nalidixic acid (1b) was also successfully applied to the labelling of WIN57273 (5a). In this case, iododecarboxylation of (5a) with LTA and iodine in acetontrile afforded (8) in 65% yield. When carbon tetrachloride was used as solvent, the poor solubility of (5a) resulted in only a 19% yield being achieved (Scheme 3). The

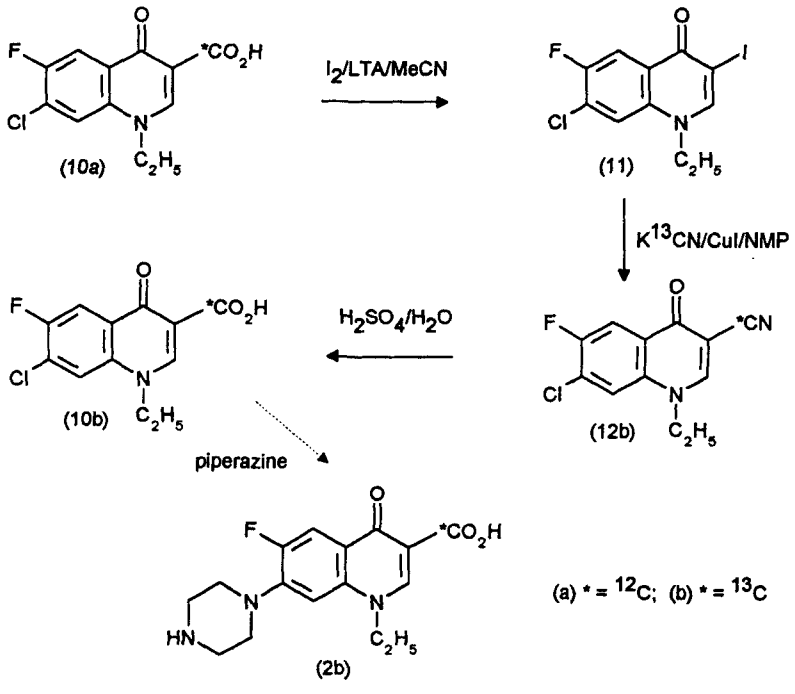
reaction was cleaner than that employing (1a), possibly because the 6-fluoro substituent in (5a) deactivates the aromatic ring with respect to electrophilic attack (iodination and/or acetoxylation). 3-Iodoquinolinone (8) was cyanated to give [^{13}C]nitrile (9b) in 62% yield. This underwent acidic hydrolysis to give [^{13}C]WIN57273 (5b) in 89% yield.



Scheme 3

Attempted iododecarboxylations of ciprofloxacin (3) using LTA, or iodosobenzene diacetate, and iodine, in acetonitrile at reflux as described above, gave only intractable mixtures, possibly as a result of electrophilic iodination or acetoxylation of the aromatic ring in (3). Interestingly, *N*-acetylciprofloxacin failed to react under the standard LTA/iodine conditions. In order to pursue a carbon labelling of 6-fluoro-7-piperidinoquinolones by the iododecarboxylation and cyanation strategy, the less activated precursor (10a) (19) of norfloxacin (2a) was employed. Iododecarboxylation of (10a) with LTA and iodine in acetonitrile, gave 3-iodoquinolone (11) in 69% yield (Scheme 4). Cyanation of (11) with potassium [^{13}C]cyanide and copper (I) iodide gave labelled [3-^{13}C]cyanoquinolone (12b) in 70% yield. Acidic hydrolysis of (12) afforded quinolone-3-carboxylic acid (10b) in

96% yield. The conversion of (10a) into (2a), by displacement of chlorine with piperazine has been described elsewhere (19).



Scheme 4

Syntheses of quinolone-[3-^{14}C]carboxylic acids, using potassium [^{14}C]cyanide, have not been performed. However, since the yields of the three quinolone-3-[^{13}C]carboxylic acids (1b), (5b) and (10b) from potassium [^{13}C]cyanide were in the range 56-67%, acceptable radiochemical yields in the same range can reasonably be anticipated. The methodology described for the preparation of (10b) from (10a), could undoubtedly be applied to the 1-cyclopropyl analogue of (10a) to give a carbon 13-labelled 7-chloroquinolone precursor of ciprofloxacin (3).

Conclusion

A novel route to quinolone antibacterials, carbon-labelled in the metabolically stable 3-carboxylic acid residue, has been demonstrated. Iododecarboxylation of the parent drug, or appropriate precursor, afforded 3-iodoquinolones, which readily underwent cyanation with potassium cyanide, in the presence of copper (1) iodide.

Subsequent acidic hydrolysis afforded carbon-labelled quinolones in good yield. The synthesis of other compounds by this simple iododecarboxylation/cyanation procedure will be the subject of future communications.

Experimental

General Methods: ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Bruker AC250, Varian XL200 and Varian Unity 400 spectrometers. ^{13}C NMR spectra were recorded on Bruker AC250 and Varian Unity 400 spectrometers. Infra Red (IR) spectra were recorded on a Nicolet 20SXB FT-IR spectrometer. Low and high resolution mass spectrometry (MS) was performed using Finnigan 4600 quadrupole and VG Autospec spectrometers respectively. Elemental analyses were carried out using Carlo Erba 1106 and Perkin-Elmer 240C microanalysers. Lead tetraacetate was recrystallised from acetic acid, containing a little acetic anhydride, washed with carbon tetrachloride, and dried *in vacuo* before use. Merck silica gel Kieselgel 60 (9385) was used throughout for flash column chromatography. Melting points are uncorrected.

***1-Ethyl-3-iodo-7-methyl-1H-[1,8]naphthyridin-4-one* (6)**

Method 1: A mixture of nalidixic acid (1a) (283mg, 1.22mmol), iodine (1.546g, 6.09mmol), and lead tetraacetate (2.701g, 6.09mmol) in carbon tetrachloride (70ml) was stirred at reflux under nitrogen whilst being irradiated with a 100 watt tungsten lamp. After 30min, the mixture was allowed to cool to 20°C, and saturated aqueous sodium hydrogen carbonate (50ml) added with stirring. The mixture was filtered through celite, and a few drops of 5% w/v aqueous sodium metabisulphite added to the filtrate to destroy any residual iodine. The organic phase was isolated and the aqueous phase re-extracted with carbon tetrachloride (30ml). The combined extracts were dried over anhydrous sodium sulphate and solvent removed by evaporation. The residue was purified by chromatography on silica (100g), eluted with dichloromethane-ethyl acetate (12:1). The product was triturated with diethyl ether (10ml) to give the *title compound* (237mg, 61.9%), m.p. 204-206°C; ν_{max} (nujol mull)/cm^{-1} 1603, 1429, 1378; δ_H (250MHz, $CDCl_3$) 8.60 (1H, d, 5-H), 8.20 (1H, s, 2-H), 7.25 (1H, d, 6-H), 4.45 (2H, q, CH_2CH_3), 2.65 (3H, s, 7-CH_3), 1.47 (3H, t,

$CH_2C\underline{H}_3$); m/z (Thermospray) 315 (MH^+ 100%); (Found: C, 41.9; H, 3.6; N, 8.8%. $C_{11}H_{11}IN_2O$ requires C, 42.1; H, 3.5; N, 8.9%).

Method 2: A mixture of nalidixic acid (1a) (315mg 1.36mmol), iodosobenzene diacetate (1.750g, 5.43mmol), and iodine (1.379g, 5.43mmol) in acetonitrile (50ml) was stirred at reflux under nitrogen whilst being irradiated with a 100 watt tungsten lamp. After 3h, the mixture was allowed to cool and the solvent removed by evaporation. The residue was re-dissolved in dichloromethane (50ml) and the resulting solution stirred with saturated aqueous sodium hydrogen carbonate (50ml) and a few drops of saturated aqueous sodium metabisulphite. The aqueous phase was re-extracted with dichloromethane (25ml), and the combined organic extracts dried over magnesium sulphate. Chromatography on silica (100g), eluted with dichloromethane-ethyl acetate (10:1) afforded iodoquinolone (6) (198mg, 46.5%), analytically identical with the compound prepared by method 1.

1-Cyclopropyl-7-(2,6-dimethyl-pyridin-4-yl)-6-fluoro-3-iodo-1H-quinolin-4-one (8)

A stirred mixture of (5a) (288mg, 0.817mmol), iodine (1.035g, 4.08mmol), and lead tetraacetate (1.809g, 4.08mmol) in acetonitrile (70ml) was heated at reflux under nitrogen whilst being irradiated with a 100 watt tungsten lamp. After 30min, the mixture was allowed to cool and the precipitate of lead diacetate removed by filtration. The solvent was removed by evaporation and the residue stirred with ethyl acetate (70ml), water (70ml), and saturated aqueous sodium hydrogen carbonate (30ml). A few drops of 5% w/v aqueous sodium metabisulphite were added to remove residual iodine, and the organic phase isolated. The aqueous phase was re-extracted with ethyl acetate (50ml and 30ml) and the combined extracts dried over anhydrous sodium sulphate. Solvent was removed by evaporation and the crude product purified by chromatography on silica (90g), eluted with ethyl acetate-methanol (20:1) to give the *title compound* (8) as a pale yellow, crystalline solid (229mg, 64.5%). This was dissolved in dichloromethane (10ml) and ethyl acetate (10ml) added. Dichloromethane was removed by evaporation causing the precipitation of crystalline (8) (186mg, 81.2% recovery), m.p. 268-270° (dec.); ν_{max} (nujol mull)/cm^{-1} 1611, 1560, 1377; δ_H (250MHz,

$CDCl_3$) 8.23 (1H, s, 2-H), 8.08 (1H, d, 5-H), 7.95 (1H, d, 6-H), 7.23 (2H, s, lutidine 3-H and 5-H), 3.54 (1H, m, cyclopropyl CH), 2.68 (6H, s, lutidine 2-CH_3 and 6-CH_3), 1.45-1.00 (4H, m, cyclopropyl CH_2); m/z (Thermospray) 435 (MH^+ 100%); (Found: C,52.5; H, 3.8; N, 6.4%. $C_{19}H_{16}FIN_2O$ requires C, 52.6; H, 3.7; N, 6.5%).

***7-Chloro-1-ethyl-6-fluoro-3-iodo-1H-quinolin-4-one* (11)**

Prepared according to the method used for the preparation of (8). Carboxylic acid (10a) (335mg, 1.24mmol) gave a crude product that was purified by chromatography on silica (130g), eluted with dichloromethane-ethyl acetate (6:1), to give the *title compound* as a white crystalline solid (301mg, 68.9%). This was recrystallised from minimum boiling toluene (20ml) giving *title compound* (11) (261mg, 86.7% recovery), m.p. 245°C; ν_{max} (nujol mull)/cm^{-1} 1585, 1540, 775, 738; δ_H (200MHz, DMSO-d_6) 8.66 (1H, s, 2-H), 8.12 (1H, d, 8-H), 7.98 (1H, d, 5-H), 4.37 (2H, q, CH_2CH_3), 1.33 (3H, t, CH_2CH_3); m/z (Thermospray) 352 (MH^+ 100%) (Found: C,37.3; H, 2.2; N, 4.0%. $C_{11}H_8ClFINO$ requires C, 37.6; H, 2.3; N, 4.0%).

***1-Ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-[3-^{13}C]-carbonitrile* (7b)**

A mixture of 3-iodoquinolone (6) (247mg, 0.787mmol), potassium [^{13}C]cyanide (52mg, 0.786mmol), and finely-ground cuprous iodide (75mg, 0.39mmol) in NMP (3ml) was heated at gentle reflux under nitrogen for 20h. The dark mixture was diluted with ethyl acetate (100ml) and the solution filtered through celite to remove a flocculent solid. The organic phase was isolated, and the aqueous phase re-extracted with ethyl acetate (50ml). The combined extracts were washed sequentially with water (2 x 50ml) and saturated brine (100ml), and dried over magnesium sulphate. The solvent was removed by evaporation and the residue purified by chromatography on silica (120g), eluted with dichloromethane-diethyl ether (10:1) to give the *title compound* (7b) (113mg, 67.1%), m.p. 225-226°C; ν_{max} (nujol mull)/cm^{-1} 2164 (C≡N), 1633, 1447; δ_H (250MHz, $CDCl_3$) 8.58 (1H, d, 5-H), 8.23 (1H, d, 2-H), 7.22 (1H, d, 6-H), 4.54 (2H, q, CH_2CH_3) 2.68 (3H, s, 7-CH_3), 1.52 (3H, t, CH_2CH_3); δ_C (63MHz, DMSO-d_6) 115.4 (^{13}CN enhanced); (Found: m/z [CI, CH_4 +ve] 215.101573 [MH^+]. $C_{11}{}^{13}CH_{12}N_3O$ requires 215.101392).

1-Cyclopropyl-7-(2,6-dimethyl-pyridin-4-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-[3-^{13}C] -carbonitrile (9b)

Prepared using the method decribed for (7b), from Iodo compound (8) (124mg, 0.286mmol), potassium [^{13}C]cyanide (19mg, 0.284mmol), and copper (I) iodide (27mg, 0.142mmol) (cyanation time 190min at 210^{o}C). The crude product was purified by chromatography on silica gel (100g), eluted with ethyl acetate-methanol (20:1), to give the *title compound* (60mg, 62.4%), m.p. 314-315^{o}C (dec.); ν_{max} (nujol mull)/cm^{-1} 2178 (C≡N), 1627, 1470; δ_H (400MHz, DMSO-d_6) 8.80 (1H, d, 2-H), 8.22 (1H, d, 8-H), 7.95 (1H, d, 5-H), 7.29, (2H, s, lutidine 3-H and 5-H), 3.76 (1H, m, cyclopropyl CH), 2.53 (6H, s, lutidine 2-CH_3 and 6-CH_3), 1.23 (4H, m, cyclopropyl CH_2); δ_C (100MHz, DMSO-d_6) 115.8 (^{13}CN enhanced); (Found: m/z [LSIMS +ve] 335.138762 [MH$^+$]. $C_{19}{}^{13}CH_{17}FN_3O$ requires 335.138920).

7-Chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-[^{13}C]-carbonitrile (12b)

Prepared using the method described for (7b), from Iodo compound (11) (199mg, 0.566mmol) potassium [^{13}C]cyanide (37mg, 0.560mmol), and copper (I) iodide (54mg, 0.283mmol) (cyanation time 360min at 210^{o}C). The crude product was purified by chromatography on silica gel (120g), eluted with dichloromethane-ethyl acetate (6:1 and 3:1) to give the *title compound* (12b) (98mg, 69.6%.), m.p. 275-276^{o}C; ν_{max} (nujol mull)/cm^{-1} 2216 (C≡N), 1629, 1603, 1489; δ_H (400MHz, DMSO-d_6) 8.83 (1H, d, 2-H), 8.22 (1H, d, 8-H), 7.99 (1H, d, 5-H), 4.38 (2H, q, CH_2CH_3), 1.38 (3H, t, CH_2CH_3); δ_C (100MHz, DMSO-d_6) 116.3 (^{13}CN enhanced); (Found: m/z [CI, CH_4 +ve] 252.042067 [MH$^+$]. $C_{11}{}^{13}CH_9ClFN_2O$ requires 252.042099).

1-Ethyl-7-methyl-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-[^{13}C]-carboxylic acid (1b)

A solution of (7b) (74mg, 0.35mmol) in 9M sulphuric acid (3ml) was heated at 130^{o}C for 2.5h. Water (1ml) was added and the solution adjusted from pH1.1 to pH6.9 by dropwise addition of 5M aqueous sodium hydroxide. The resulting crystalline precipitate was isolated by filtration, washed with water (10ml), and dried for 72h at 20^{o}C *in vacuo* to give the *title compound* (1b) (69mg, 85.6%), mp 226-230^{o}C; ν_{max} (nujol mull)/cm^{-1} 1690, 1618; ; δ_H (250MHz, $CDCl_3$) 13.50 (1H, s,

CO_2H), 8.91 (1H, d, 2-H), 8.68 (1H, d, 5-H), 7.40 (1H, d, 6-H), 4.63 (2H, q, CH_2CH_3), 2.73 (3H, s, 7-CH_3), 1.54 (3H, t, CH_2CH_3); δ_C (63MHz, $CDCl_3$) 166.8 ($^{13}CO_2H$ enhanced); (Found: m/z [CI, CH_4 +ve] 234.095903 [MH^+]. $C_{11}{}^{13}CH_{13}N_2O_3$ requires 234.095972).

***1-Cyclopropyl-7-(2,6-dimethyl-pyridin-4-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-[^{13}C]-carboxylic acid* (5b)**

Prepared using the method described for (1b). Nitrile (9b) (34mg, 0.102mmol) gave the *title compound* (5b) as a white crystalline solid (32mg, 89.1%), 305°C; ν_{max} (nujol mull)/cm^{-1} 1694, 1613, 898; δ_H (400MHz, $CDCl_3$) 14.43 (1H, s, CO_2H), 8.88 (1H, s, 2-H), 8.27 (1H, d, 5-H), 8.10 (1H, d, 8-H), 7.18 (2H, s, lutidine 3-H and 5-H), 3.64 (1H, m, cyclopropyl CH), 2.63 (6H, s, lutidine 2-CH_3 and 6-CH_3), 1.50-1.20 (4H, m, cyclopropyl CH_2); δ_C (100MHz, $CDCl_3$) 166.3 ($^{13}CO_2H$ enhanced); (Found: m/z (LSIMS +ve) 354.133582 [MH^+]. $C_{19}{}^{13}CH_{18}FN_2O_3$ requires 354.133501).

***7-Chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-[^{13}C]-carboxylic acid* (10b)**

Prepared using the method described for (1b). Nitrile (12b) (63mg, 0.250mmol) gave the *title compound* (10b) as a white crystalline solid (65mg, 96.3%), mp 292-295°C; ν_{max} (nujol mull)/cm^{-1} 1690, 1607, 808; δ_H (400MHz, DMSO-d_6) 9.03 (1H, d, 2-H), 8.41 (1H, d, 8-H), 8.19 (1H, d, 5-H), 4.61 (2H, q, CH_2CH_3), 1.38 (3H, t, CH_2CH_3); δ_C (100MHz, DMSO-d_6) 165.9 ($^{13}CO_2H$ enhanced); (Found: m/z [CI, CH_4 +ve] 271.037523 [MH^+]. $C_{11}{}^{13}CH_{10}ClFNO_3$ requires 271.037326).

Acknowledgements

The authors thank Keith Brinded for MS data, Dr Bob Lancaster for NMR and IR data, and Miss Pat McDonough for microanalyses.

References

1. Lesher G.Y., Froelich E.J., Gruett M.D., Bailey J.H. and Brundage R.P.- J. Med. Pharm. Chem. 5: 1063 (1962)
2. Wolfson J.S.and Hooper D.C.- Ann. Internal Med. 108: 238 (1988)

3. Campoli-Richards D.M., Monk J.P., Price A., Benfield P., Todd P.A. and Ward A .- Drugs 35: 373 (1988)
4. Todd P.A. and Faulds D.- Drugs 42: 825 (1991)
5. Radl S.and Bouzard D.- Heterocycles 34: 2143 (1992)
6. Bouzard D., Recent Progress in the Chemical Synthesis of Antibiotics, ed. Lukacs G. and Ohno M., Springer-Verlag, Berlin Heidelberg, p249, 1990
7. Kagemoto A., Negoro T., Nakao M., Ochi T., Chiba K., Kataoka M. and Sekine Y.- Arzneim.-Forsch. 41: 744 (1991)
8. Seifert H.M., Maruhn D., Maul W., Förster D. and Ritter W.- Arzneim.-Forsch. 36: 1496 (1986)
9. Okazaki O., Kurata T. and Tachizawa H.- Xenobiotica 19: 419 (1989)
10. Edelson J., Davison C. and Benziger D.P.- Drug Metab. Rev. 6: 105 (1977)
11. Gau W., Kurz J., Petersen U., Ploschke H.J. and Wuensche C.- Arzneim.-Forsch., 36: 1545 (1986)
12. Wise R., J. Antimicrob. Chemother.- 13: Suppl. B., 59 (1984)
13. Matsunaga Y., Miyazaki H., Oh-e Y., Nambu K., Furukawa H., Yoshida K. and Hashimoto M.- Arzneim.-Forsch. 41: 747 (1991)
14. Matsunaga Y., Miyazaki H., Nomura N. and Hashimoto M.- Arzneim.-Forsch. 41: 760 (1991)
15. Wong F.A and Flor S.C., Drug Metab. Dispos.- 18: 1103 (1990)
16. Okazaki O., Kurata T., Hashimoto K., Sudo K., Tsumura M. and Tachizawa H., Chemotherapy- 32: Suppl.1., 1202 (1984)
17. Carr R.M., Cable KM, Wells G.N., and Sutherland D.R., J. Labelled Compd. Radiopharm.- submitted for publication
18. Barton D.H.R., Faro H.P. Serebryakov E.P. and Woolsey N.F.- J. Chem. Soc 2438 (1965)
19. Koga H., Itoh A., Murayama S., Suzue S. and Irikura T.- J. Med. Chem. 23: 1358 (1980)
20. Mitscher L.A., Sharma P.N., Chu D.T.W., Shen L.L. and Pernet A.G., J. Med. Chem.- 30: 2283 (1987)