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Mendeleev Commun., 1992, **2(4)**, 151–153
Mendeleev Communications

Reactions of *N*-Aminoquinolones with Ketones: A New Approach to the Synthesis of Tricyclic 6-Fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic Acids

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Reactions of 7-(X)-substituted ethyl 1-amino-4-oxo-1,4-dihydroquinoline-3-carboxylates (**1a–c**; X = F, Cl and 4-methylpiperazin-1-yl) with mono- and di-ketones have been studied. Treatment of **1a**; X = F with cyclohexanone and cyclopentanone in acetic acid resulted in the corresponding azomethynes; α-dicarbonyl compounds such as glyoxal, glyoxylic acid or ethyl pyruvate caused desamination of **1a** into ethyl, 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate, while reactions of **1a–c** with acetoacetone resulted in tricyclic 7-fluoro-4-oxopyrazolo[1,5-*a*]quinoline-4-carboxylic acids.

A new class of totally synthetic antibiotics, the so-called 'fluoroquinolones', has attracted the attention of chemists during the last decade.[1–8] Norfloxacin, perfloxacin, ciprofloxacin and other derivatives of 6-fluoro-7-piperazino-4-oxo-1,4-dihydroquinoline-3-carboxylic acid have already found applications in medicine and veterinary work as highly effective antibacterials. Nevertheless, great efforts are still being made by researchers to modify the structure of fluoroquinolones in order to achieve a lower toxicity and better pharmacokinetic profiles.[1–8]

We report here a new structural modification of fluoroquinolones based on the reactions of 1-amino-substituted 6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids **1** with ketones.

Treatment of ethyl 1-amino-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **1a** with cyclohexanone and cyclopentanone in acetic acid resulted in the corresponding azomethynes **2** and **2'** in good yields (Scheme 1, Table 1).

In reactions with α-dicarbonyl compounds such as glyoxal, glyoxylic acid or ethyl pyruvate, desamination of **1a** into ethyl 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **3** was found to occur. It is worth noting that the conditions used are rather mild since desamination of *N*-aminoheterocycles usually takes place at much higher temperature (180–230 °C).[9]

As far as β-diketones are concerned, compounds **1a–c** reacted smoothly with acetoacetone on heating in acetic acid, giving tricyclic pyrazolo[1,5-a]quinolines **4a–c** in 60–65% yields (Table 1). Some starting *N*-amino compound **1a** was also found to undergo desamination into **3**, but yields of the by-product **3** were relatively small (5–7%) (Scheme 1, Table 1).

Evidence for the structure of pyrazolo[1,5-a]quinolines

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Table 1 Reactions of 7-substituted ethyl 1-amino-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylates with ketones in refluxing acetic acid in the presence of air bubbling through the reaction mixture

Starting materials						
Aminoquinolone **1**						
Compound	X	Ketone	Reaction time/h	Product	Yield (%)	M.p/°C
1a	F	Cyclopentanone	2	**2**	35	136–137
1a	F	Cyclohexanone	2	**2'**	35	148–150
1a	F	Glyoxylic acid	0.25	**3**	70	207–208
1a	F	Ethyl pyruvate	0.25	**3**	70	207–208
1a	F	Acetoacetone	2	**4a**	60	168–170
				3	5	207–208
1a[a]	F	Acetoacetone	2	**4a**	4	168–170
1b	Cl	Acetoacetone	2	**4b**	50	172–174
1c	4-methyl piperazin-1-yl	Acetoacetone	2	**4c**	45	174–176

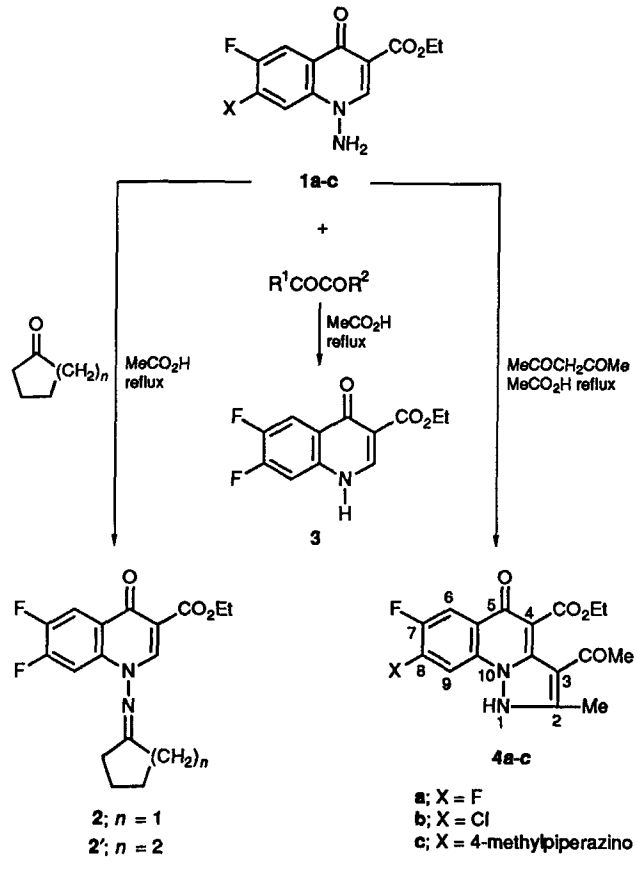
[a] Without bubbling air through the reaction mixture.

4a–c is provided by their ^{1}H, ^{13}C and ^{19}F NMR and mass spectroscopic data.†

In the ^{1}H NMR spectrum of **4a** the H-6 and H-9 resonances appear as double doublets with characteristic $^3J(^1H—^{19}F)$ and $^4J(^1H—^{19}F)$ coupling constants, which show that no structural changes have occurred in the benzene ring of the starting *N*-aminoquinoline **1a**. From the absence of H-2 in the pyridine ring and NH_2 resonances and appearance of the Me and COMe signals, it is clear that the $C_2—N—NH_2$ fragment of **1a** participates in the cyclization with acetoacetone. The ^{13}C NMR spectroscopic data for **4a** are also in full agreement with the proposed structure.†

Two alternative pathways for the formation of pyrazoloquinolines **4a–c** can be advanced. The first one involves condensation of the *N*-amino compounds **1a–c** with acetoacetone, resulting in the formation of hydrazones **5a–c** followed by intramolecular nucleophilic attack at C-2. The formation of hydrazones **5** seems to be very likely because of a very similar reaction, between **1a** and monoketones (see compounds **2** and **2'** in Scheme 1). As far as the intramolecular nucleophilic substitution of hydrogen (S_NH)[10] at C-2 in compounds **5a–c** is concerned, it has been shown that this step, like other S_NH processes, requires an external oxidant (*e.g.* air bubbling through the reaction mixture) in order to achieve good yields of the final products **4a–c** *via* oxidation of the intermediate adducts **6a–c** (Scheme 2). Although a few examples of the S_NH reactions at C-2 of the pyridine ring in the quinolone series have been reported in the literature,[11,12] the reaction discovered appears to be a new synthetic route to tricyclic fluoroquinolones.

Another reaction pathway suggests that the cationic species **7** formed on O-protonation of *N*-aminoquinolones **1** by acetic acid can be regarded as a 1,3-dipole. The latter participates in a 1,3-dipolar cycloaddition reaction with the enol form of acetoacetone to give the final pyrazolo[1,5-a]quinolines **4** through



Scheme 1

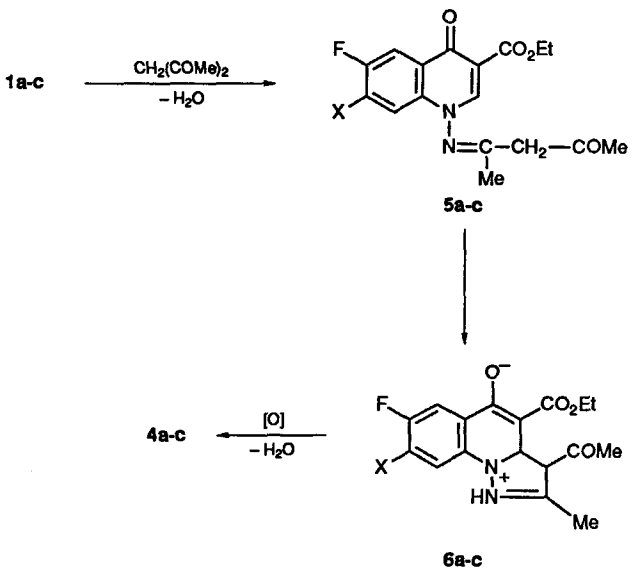
† *General procedure and selected spectroscopic data* for 3-acetyl-7,8-difluoro-4-ethoxycarbonyl-2-methyl-5-oxo-1,5-dihydropyrazolo[1,5-a] quinoline **4a** are given below.

A mixture of 0.134 g (0.5 mmol) ethyl 1-amino-6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **1a** and 0.5 g (5.0 mmol) of acetoacetone were refluxed in acetic acid for 2 h. The reaction was then treated with water (1:1), cooled to room temperature and the precipitate obtained was filtered off. The solid was extracted with chloroform followed by vacuum evaporation, which gave 0.95 g (65%) of **4a** as a white crystalline product with m.p. 170–172°C. A second product (0.07 g, 5%), insoluble in $CHCl_3$, was identified as 6,7-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate **3** with m.p. 207–208°C.

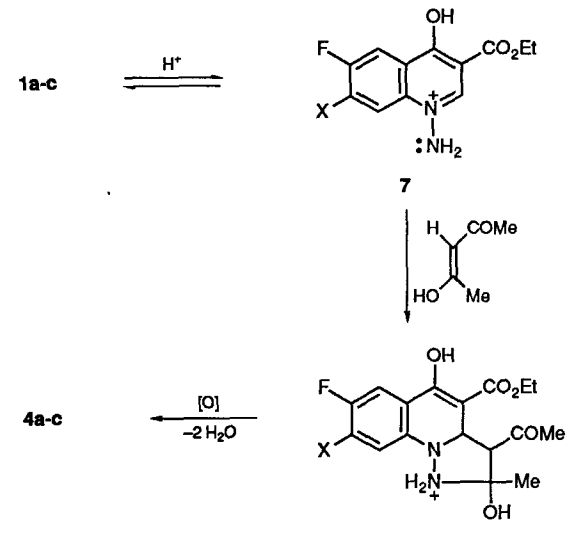
In the ^{1}H and ^{13}C NMR spectra of **4a**, unequivocal assignments of proton and carbon resonances were achieved on the basis of chemical shifts and coupling constants and also by means of selective decoupling experiments.

^{1}H NMR ($CDCl_3$): 1.38 (t, 3H, OCH_2CH_3, ^3J 7.3 Hz), 2.41 (s, 3H, $COCH_3$), 2.52 (s, 3H, $C_2—CH_3$), 4.44 (q, 2H, OCH_2CH_3, ^3J 7.3 Hz), 8.04 [dd, H-9, ^3J(H-9, F-8) 10.3 Hz, ^4J(H-9, F-7) 8.1 Hz], 8.26 [dd, H-6, ^3J(H-6, F-7) 10.7 Hz, ^4J(H-6, F-8) 7.0 Hz], 12.48 (br s, 1H, NH).

Coupled ^{13}C NMR Spectrum of **4a** ($CDCl_3$): 13.56 (q, $C_2—CH_3$, ^1J 128.8 Hz), 13.83 (qt, OCH_2CH_3, ^1J 127.6 Hz, ^2J 2.4 Hz), 31.70 (q, $COCH_3$, ^1J 127.6 Hz), 62.51 (tq, OCH_2CH_3, ^1J 148.9 Hz, ^2J 4.3 Hz), 97.25 [d, C_4, ^5J(C-4, F-7) 1.8 Hz], 105.12 [dd C_9, ^1J 172.4 Hz, ^2J(C-9, F-8) 23.3 Hz], 112.54 [dd, C_{5a}, ^3J(C-5a, F-7) 6.7 Hz, ^4J(C-5a, F-8) 2.4 Hz], 112.82 [ddd, C_6, ^1J 169.7 Hz, ^2J(C-6, F-7) 20.1 Hz, ^3J(C-6, F-8) 2.4 Hz], 116.64 (br m, C_3), 133.30 [d, C_{9a}, ^3J(C-9a, F-8) 11.6 Hz], 134.50 (s, C_{3a}), 148.43 [dddd, C_8, ^1J(C-8, F-8) 249.9 Hz, ^2J(C-8, F-7) 14.3 Hz, ^2J(C-8, H-9)~^3J(C-8, H-6) 6.1 Hz], 154.17 [dddd, C_7, ^1J(C-7, F-7) 258.8 Hz, ^2J(C-7, F-8) 15.0 Hz, ^2J(C-7, H-6)~^3J(C-7, H-9) 6.1 Hz], 151.18 [q, C_2, ^2J(C-2, H—CH_3) 6.7 Hz], 160.40 [ddm, C_5, ^4J(C-5, F-7) 3.1 Hz, ^5J(C-5, F-8) 1.8 Hz], 169.15 (t, $CO_2CH_2CH_3$, ^3J 3.0 Hz), 196.35 (q, $COCH_3$, ^2J 3.0 Hz).



Scheme 2



Scheme 3

oxidation of the intermediate cycloadducts **8**. Scheme 3 has also to be considered as a plausible one since cycloaddition reactions of *N*-aminoquinolinium salts with 1-acetyl-2-methoxyethene and cyclopentadienones leading to derivatives of the same ring system have been reported in the literature.[13,14]

References

1 D. Bouzard, in *Recent Progress in the Chemical Synthesis of Antibiotics*, Springer-Verlag, Berlin, Heidelberg, 1990, pp. 249–283.
2 *The Quinolones*, ed. V. T. Andriole, Academic Press, New York, 1988.
3 *The Quinolones*, ed. P. B. Fernandes, J. R. Prous, Barcelona, 1986.
4 R. Albrecht, *Prog. Drug Res.*, 1987, **21**, 9.
5 D. C. Leysen, A. Haemers and S. R. Pattyn, *Antimicrob. Agents Chemother.*, 1989, **33**, 1.
6 H. C. New, *Int. J. Antimicrob. Agents*, 1991, **1**, 47.
7 D. T. W. Chu and P. B. Fernandes, *Antimicrob. Agents Chemother.*, 1989, **33**, 131.
8 G. A. Mokrushina, S. G. Alexeev, V. N. Charushin and O. N. Chupakhin, *Zh. Vses. Khim. O-va im. D. I. Mendeleeva*, 1991, **34**, 447.
9 M. A. Badawy, S. A. Abdel-Hady, A. H. Mahmoud and Y. A. Ibrahim, *J. Org. Chem.*, 1990, **55**, 344.
10 Since the specific nature of the leaving group is formally that of a hydrine ion, the use of the symbol S_NH was suggested for this type of reaction. For a review of the S_NH reactions, see O. N. Chupakhin, V. N. Charushin and H. C. van der Plas, *Tetrahedron*, 1988, **44**, 1.
11 M. C. Schroeder and J. C. Kiely, *J. Heterocycl. Chem.*, 1988, **25**, 1769.
12 L. E. Lesheski, *J. Heterocycl. Chem.*, 1989, **26**, 1675.
13 Y. Yamashita and M. Masumura, *Tetrahedron Lett.*, 1979, 1765.
14 Y. Tominaga, Y. Ichihara, T. Mori, C. Kamino and A. Hosomi, *J. Heterocycl. Chem.*, 1990, **27**, 263.

Received: Moscow, 17th March 1992
Cambridge, 12th May 1992; Com. 2/01529C