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A Versatile Synthesis of Tricyclic Analogues of Quinolone Antibacterial Agents: Use of a Novel Reformatsky Reaction

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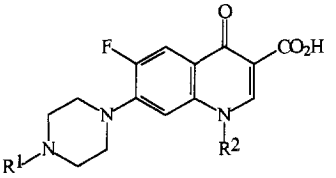
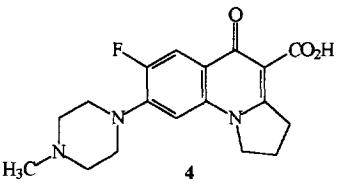
Abstract: A simple synthesis of tricyclic analogues of the quinolone antibiotics bearing a diverse range of substituents on the aromatic ring is described. The key steps involve unprecedented Reformatsky reaction between diethyl bromomalonate and N-arylpyrrolidine-2-thiones **8**, followed by cyclisation of the resulting enaminone intermediates **9** in polyphosphoric acid. Copyright © 1996 Elsevier Science Ltd

The fortuitous discovery of nalidixic acid, reported in 1962,[1] introduced to the world a new class of potent antibiotics that proved to be particularly effective against infections caused by Gram-negative bacteria.[2] The quinolone antibacterials, as they came to be called, inhibit the synthesis of bacterial DNA by targetting DNA gyrase, the enzyme responsible for DNA supercoiling.[3] The current generation of fluorinated quinolones includes compounds such as ciprofloxacin (**1**), norfloxacin (**2**) and pefloxacin (**3**), which are amongst the most effective broad-spectrum agents developed to date.[2] They are now frequently the drugs of choice for treating infections of the urinary and genital tracts, gastrointestinal infections, and, occasionally, infections of the lower respiratory tract. Their popularity is due at least in part to their relative lack of toxicity, ease of administration (often oral), good absorption, and effective penetration of tissue. However, of the thousands of quinolones that have been synthesised for testing, fewer than ten are commercially available for clinical use. Thus the search for improved quinolone antibacterials is by no means over; drug discovery in this field continues to be driven by the need for enhanced performance, efficacy against a broader spectrum of microorganisms, and the growing problem of bacterial resistance.

Structure-activity relationships for the quinolone antibacterials, summarised in a classic review by Albrecht,[4] and updated recently,[5] have pointed to the need for a small hydrophobic substituent on nitrogen (N1) of about the same size as an ethyl group. While substituents at C2 invariably render the compounds inactive, a bridge between N1 and C2 seldom destroys activity. The bridges in such active tricyclic quinolones usually contain three atoms, and may include nitrogen, sulfur or oxygen, as in the recently reported 5-oxothiazolo[3,2-*a*]quinoline-4-carboxylic acids[6] and 5-oxopyrazolo[1,5-*a*]quinoline-4-carboxylic acids.[7] The all-carbon bridged pyrrolo[1,2-*a*]quinolinone **4** – in effect a pefloxacin analogue – has a minimal inhibitory concentration (MIC) of 0.78 μg ml^{-1} against *Staphylococcus aureus* CMX686B, and 1.56 μg ml^{-1} against *Escherichia coli*.[8] The tricyclic nucleus of **4** was prepared by a variation of the Bayer route,[9] and involved cyclisation of intermediate **5** by treatment with sodium hydride in THF at 75°C.



1 $R^1 = H$, $R^2 =$ cyclopropyl
2 $R^1 = H$, $R^2 = CH_2CH_3$
3 $R^1 = CH_3$, $R^2 = CH_2CH_3$



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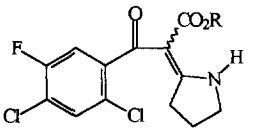
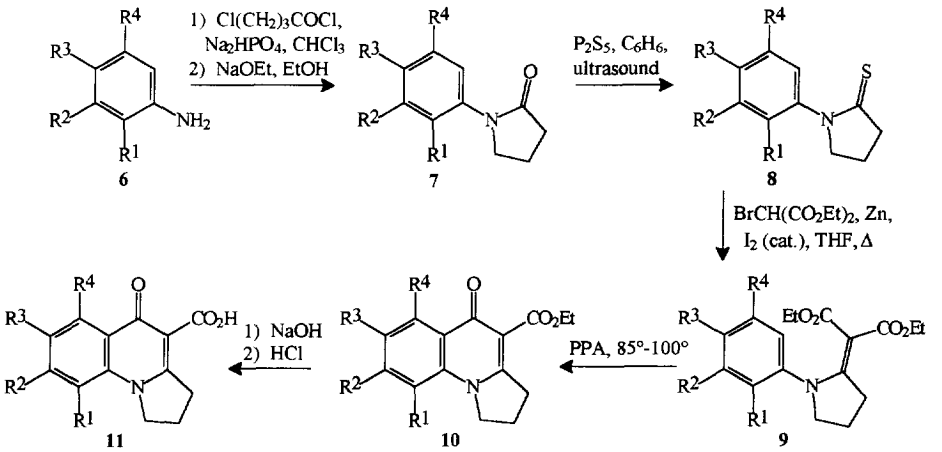


5

Our ongoing research into the use of enaminones as precursors for alkaloids and other nitrogen-containing heterocycles[10] has led us to devise a new synthetic route to potentially useful 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acids that not only provides access to the active compound **4** but also allows for flexibility in the nature, number and position of substituents on ring A (Scheme, below). This versatility comes about because our initial starting materials are anilines, which are readily available, or easily prepared, with an almost limitless variety of substituents. Conversion of the anilines **6** into *N*-arylpyrrolidin-2-ones **7** was achieved by acylation with 4-chlorobutyryl chloride followed by cyclisation of the resulting amides with sodium ethoxide in ethanol (73-97% yields; see Table). Thionation of lactams **7** with phosphorus pentasulfide in benzene was promoted by sonicating the heterogeneous reaction mixture in an ultrasonic cleaning bath[11] to give *N*-arylpyrrolidine-2-thiones (62-92% yields).



Our plan at this stage was to convert the pyrrolidine-2-thiones **8** into vinylogous urethanes **9** by Eschenmoser sulfide contraction[12] with diethyl bromomalonate, after which we intended to prepare the quinolone ring by the standard Gould-Jacobs cyclisation[13] under thermal or acid-induced conditions. In the event, sulfide contraction gave unexpectedly variable results, necessitating a change of strategy. We have previously prepared a vinylogous urethane in a unique Reformatsky reaction between *N*-phenylpyrrolidine-2-thione, ethyl bromoacetate and zinc-copper couple[14] – an exceptional transformation in the light of the failure of other workers to achieve similar reactions with

thiocarbonyl compounds other than thiocarbonates, dithioesters and thioketones.[15] When we attempted a zinc-mediated condensation of diethyl bromomalonate with pyrrolidine-2-thiones **8**, we observed smooth conversion into the desired products **9** provided that four equivalents each of zinc and the bromomalonate were used, and that iodine (0.2 eq.) was used as an activator. While the products were easily isolated (aqueous work-up and chromatography on silica) and characterised by spectroscopic methods, they could never be obtained entirely free of a malonate-derived impurity (*ca* 10%). The slightly contaminated vinylogous urethanes (*ca* 65-100% yields) were cyclised without further purification by heating in polyphosphoric acid at *ca.* 100°C to give the pyrrolo[1,2-*a*]quinolones **10** in overall yields of 46-69% based on the thiolactams **8**. In the case of the *m*-tolyl substrate **8c**, Gould-Jacobs cyclisation occurred both *ortho* and *para* to the methyl group to yield product **10c** (20%) and its regioisomer **10j** (44%); in two other cases in which isomers could possibly be formed (**8g**, **8i**), cyclisation was regiospecific.

Table. Percentage yields for the sequence of conversions **6** → **7** → **8** → **10** → **11**[16]

Entry	R^1 - R^4	Lactam 7	Thiolactam **8**	Tricyclic ester **10** (over two steps)	Tricyclic acid **11**
a	$R^1 = R^2 = R^3 = R^4 = H$	80	69	61	91
b	R^1 = Me, $R^2 = R^3 = R^4 = H$	84	76	65	96
c	$R^1 = R^3 = R^4 = H$, R^2 = Me	77	62	20 (**10c**) + 44 (**10j**)[a]	89 (**11c**); 87 (**11j**)[a]
d	$R^1 = R^2 = R^4 = H$, R^3 = Me	94	73	64	92
e	$R^1 = R^2 = R^4 = H$, R^3 = OMe	73	66	63	81
f	$R^1 = R^4$ = OMe, $R^2 = R^3 = H$	97	84	49	85
g	$R^1 = R^4 = H$, R^2–R^3 = OCH_2O	81	79	59	69
h	R^1 = Br, $R^2 = R^3 = R^4 = H$	92	92	46	100
i	$R^1 = R^4 = H$, $R^2 = R^3$ = F	88	83	69	91

[a] **10j**, **11j**: $R^1 = R^2 = R^3 = H$, R^4 = Me

The syntheses of the tricyclic quinolonecarboxylic acids **11** were completed by hydrolysis of esters **10** with hot aqueous sodium hydroxide solution, followed by precipitation of the free acids with concentrated hydrochloric acid. 7,8-Difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**11i**) was itself transformed into the hydrochloride salt of the biologically active pefloxacin analogue **4** by heating with excess *N*-methylpiperazine (65°C, 48 h), followed by treatment with hydrochloric acid (27% yield). Compound **11i** is thus a potentially valuable precursor for other amine-substituted pyrrolo[1,2-*a*]quinolinone analogues of clinically useful quinolone antibiotics.

The simple, versatile and relatively economical methodology we have disclosed in this *Letter* is applicable in principle not only to the synthesis of a wide range of pyrrolo[1,2-*a*]quinolinones, but also to related compounds in which other carbocycles or heterocycles may bridge N1-C2 in the quinoline ring. Furthermore, the chemistry of the intrinsically interesting new condensation of thiolactams with a Reformatsky reagent requires further exploration.

Typical procedure for zinc-mediated condensation 8 → 9 followed by cyclisation to 10

A solution of diethyl bromomalonate[17] (4 eq.) in dry THF (5-10 ml) was added in portions over 30 min to a mixture of Zn powder (4 eq., activated beforehand by heating at 150°C) and I_2 (*ca* 0.2 eq.) in boiling THF (5-10ml) under an atmosphere of dry N_2 gas. The appropriate *N*-arylpyrrolidine-2-thione **8** (1-7 mmol scale) was added as a solid in one portion; a small volume of THF (5-10 ml) was used to ensure quantitative transfer. The mixture was heated under reflux for 1-1.5 h. After cooling, aqueous K_2CO_3 solution (50%, 20-40 ml) was added, and stirring was maintained for up to 2 h. The aqueous phase was extracted with diethyl ether, and the ether extracts were copiously washed with aqueous KI solution (10%). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo*. The crude residue was purified by chromatography on silica gel using CH_2Cl_2 as eluant followed by hexane - ethyl acetate mixtures. The products **9**, contaminated with an inseparable malonate-derived impurity, were dissolved in diethyl ether (3-4 ml) and added to polyphosphoric acid (*ca* 10 g per g of crude **9**). The stirred mixture was heated at 85-100°C for 1-1.5 h, after which ice-water (*ca* 30 ml) was added. Stirring was maintained for 0.75 h before the solution was extracted with CH_2Cl_2 (4 x 40 ml). The dried ($MgSO_4$) extracts were evaporated *in vacuo*, and the crude residue was purified by elution from a column of silica gel with hexane - ethyl acetate mixtures to yield the pyrrolo[1,2-*a*]quinolinones **10**.

Acknowledgements

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