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p-QUINONE METHIDES AS GEOMETRIC ANALOGUES OF QUINOLONE CARBOXYLATE ANTIBACTERIALS

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Abstract: In an attempt to examine the role of the N(1)-alkyl or -aryl moiety of the quinolone antibacterials, several quinone methides such as perinaphthindenone carboxylates (6) were synthesized as 1-carba(sp^2) analogues of the quinolone structure, and found to have no antibacterial activity. These results together with literature information are interpreted as the necessity of at least one nitrogen atom at the position of 1, 3, 4a, 6 or 8 in the quinolone-like skeleton for the antibacterial activities.

Since the initial serendipitous discovery more than thirty years ago that nalidixic acid possessed antibacterial activity against Gram-negatives, the 6-fluoro and 7-amino substituted quinolone carboxylates (1) such as ciprofloxacin and ofloxacin constitute a major class of antibacterial agents with both Gram-negative and Gram-positive activities. A number of quinolone antibacterials are in the market and at least a dozen in the developmental stages.[1] The antibacterial activity of quinolones was initially shown to result from selective inhibition of bacterial DNA synthesis in the presence of competent RNA and protein syntheses. Subsequently it was found that DNA gyrase, an enzyme essential for DNA replication, was the target of the antibacterial action. [2]

Several molecular mechanisms have been proposed for the inhibition of DNA gyrase by quinolones. One possibility is that the ternary complex formed by DNA, gyrase and quinolone is immobilized by covalent interactions presumably by the Michael addition of a bionucleophile present either on DNA or the enzyme to the quinolone molecule with or without the help of divalent metal ions.[3] However, recent model studies have shown that the Michael reactivity of quinolones toward a number of common nucleophiles is very low, indicating that such covalent interactions on an intact quinolone molecules are unlikely.[4a] The other possibility is that the quinolone molecules uncouple the enzymatic DNA breakage and the reunion reaction chain by forming a stable ternary intermediate complex with gyrase and double-stranded DNA.[5-7] Shen et al. have proposed a cooperative quinolone-DNA binding model for the inhibition of DNA gyrase.[5] The Shen's model invokes three important molecular interactions: 1) the hydrogen bonding between DNA bases and the β-keto carboxylate moiety of quinolone, 2) the π–π stacking interactions between two planar quinolone rings, and 3) hydrophobic interactions between the N(1)-alkyl or aryl tails of two quinolone molecules.

Mitscher et al. have studied coumarins and chromones (2),[3a] and 1-carba analogue **3**[3b] as geometric models for oxolinic acid, and found them to be without any activity. Based on the Shen's model, the inactivity of the chromones and coumarins may be attributed to the lack of the N(1) substituent that is necessary for the hydrophobic interactions. Furthermore, the inactivity of the dimethyl-1-carba analogue (**3**) can be explained by the fact that the *gem*-dimethyl groups of **3** appears to occupy the forbidden spatial

zone present above or below the ring plane as the inactive quinolone derivative (4) does.[4b]

We have reasoned that the role of the N(1) atom and its substituent of quinolones can be adequately evaluated only by the availability of the 1-deaza analogues of quinolone in which the proper geometry requirements are satisfied. On the basis of our modeling studies,[4b,c] a number of quinone methides are expected to meet such geometric requirements, and thus considered as possible 1-deaza analogues of the quinolone carboxylates. However, our previous studies have shown that the quinone methide (5), the simplest 1-carba analogue of quinolone carboxylate, although readily generated under various conditions, displays very high reactivities toward nucleophilic species resulting in the formation of the addition products.[8] Therefore, we thought that quinone methides which are either sterically hindered or stabilized by an extended conjugation might be more viable 1-carba analogues. In the present work we describe the synthetic studies of such quinone methides (6).

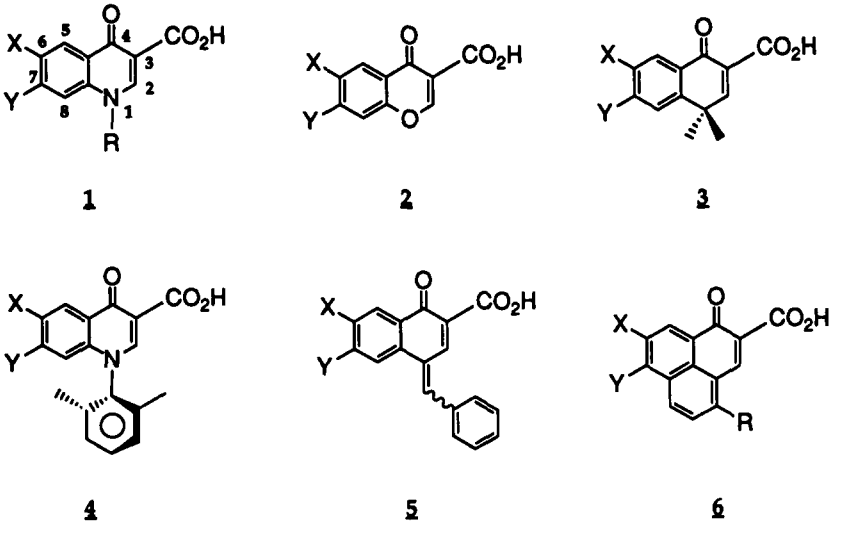
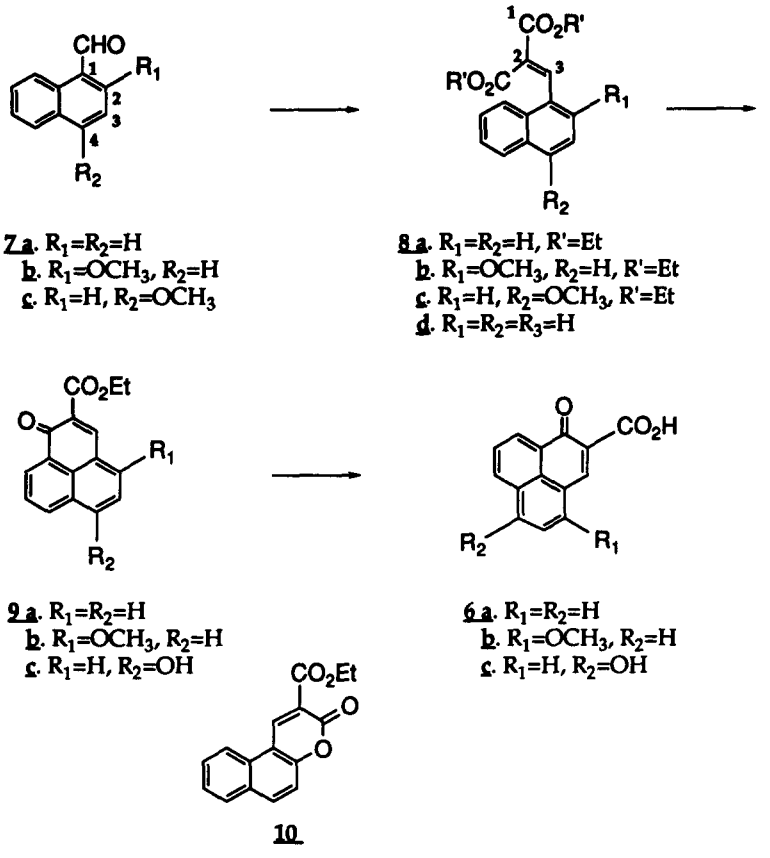


Figure 1. Quinolone and Geometric Analogues

The Knoevenagel condensation of naphthaldehyde (7a) with diethyl malonate and piperidine in benzene at reflux gave the oily product 8a in 85 % yield.[9] Treatment of 8a in polyphosphoric acid (PPA) at 110 °C for 1 hr[10] provided the tricyclic ketocarboxylate 9a in 51 % yield after chromatography (Scheme 1). Hydrolysis of 9a in THF and 30 % HCl at reflux yielded a yellow crystalline product 6a in 59 %. Alternatively, the Knoevenagel condensation of naphthaldehyde (7a) with malonic acid and piperidine in DMF in the presence of molecular sieve 4A at 40 °C provided a crystalline product 8d in 65 % yield. The dicarboxylate (8d) was successively treated with an excess amount of thionyl chloride at room temperature for 2 hr and then $AlCl_3$ in dichloromethane for 5 hr at the ambient temperature[11] to directly give 6a in 45 % yield after chromatography. Analogously, 2-methoxy- and 4-methoxy-naphthaldehyde (7b and 7c) were converted to the corresponding tricyclic ketocarboxylate 6b and 6c, respectively.[12]



Scheme 1. Synthesis of Perinaphthindenone carboxylates (6)

In principle, the cyclization of compounds **8** can lead to two different products, depending on the two distinct conformations available to the starting material, i.e. s-*cis* and s-*trans*, which appear to have similar strain energies (MM2 in MacroModel v. 3.5X). In the cyclizations of compounds **8a**, **8c** and **8d** under the stated conditions, the only observed products were compounds **9a**, **9c** and **6a**, respectively. However, in the case of **8b**, the PPA induced cyclization at 110 °C provided the desired product (**9b**) in 45 % together with an additional product (54 % yield), for which structure **10** was assigned on the basis of spectroscopic data.

Potential bioactivities of the quinone methides (**6**) have been examined against a panel of 20 bacterial strains including *S. aureus*, *S. pyonenes*, *E. coli*, *S. aeroginosa*, *Salmonella*, *Klebsiella*, and *Enterobacter*, and they were found to be completely devoid of any meaningful antibacterial activity. It has been reported that ABT-86719.1 and related 2-pyridones possess antibacterial activities similar to quinolone carboxylates.[13] Based on our results and the reported bioactivities of 2-pyridone carboxylate analogues, it may be suggested that in addition to the suitable geometric requirements as described above, at least one nitrogen atom may be required at the position of 1, 3, 4a, 6, or 8 in the quinolone-like ring skeleton for the antibacterial activities.

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