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A NEW SYNTHETIC PATHWAY FOR 2-QUINOLONES

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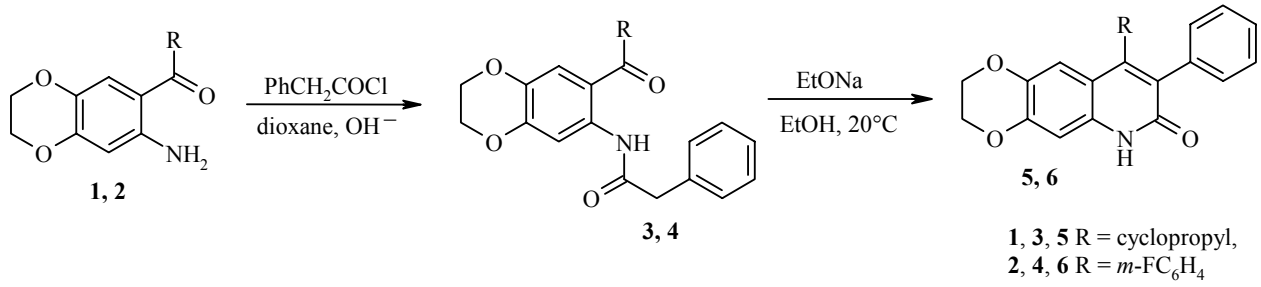
There has been recent interest in the synthesis and study of the biological properties of quinolones. This interest is largely due to the finding of 2-quinolones and 4-quinolones fragments in many alkaloids [1]. This has resulted in the synthesis of a large number of products containing the quinolone system and displaying antibacterial properties [2].

On the other hand, the search for drugs among quinolone derivatives has been hindered, in our view, by difficulties in synthesizing new compounds in this class. There is presently virtually only one quite efficient strategic pathway for the synthesis of quinolines, involving the condensation of anilines with β-keto esters and subsequent cyclization. Depending on the reaction conditions, either 4-quinolones (M. Konrad, L. Limpach [3-5]) or 2-quinolones are formed (L. Knorrr [6-8]).

We are the first to report an intramolecular variant of the Knoevenagel condensation providing the corresponding 2-quinolones in high yield using *ortho*-N-phenacyl derivatives **3** and **4**, which are readily obtained from anilines **1, 2** by acylation with phenylacetyl chloride.



1, 2 **3, 4** **5, 6**

1, **3**, **5** R = cyclopropyl,
2, **4**, **6** R = *m*-FC_6H_4

The synthetic scope of this reaction is now under investigation.

The IR spectra were taken on a UR-20 spectrometer for vaseline mulls. The ^{1}H NMR spectra were taken on an NMR spectrometer at 400 MHz. The solvent for **1-4** was $CDCl_3$; the residual protons of the deuterated solvent served as the internal standard. The solvent for **5** and **6** was DMSO-d_6 using TMS as the internal standard.

6-Amino-7-cyclopropylcarbonyl-1,4-benzodioxane (1) and 6-amino-7-(*m*-fluorobenzoyl)-1,4-benzodioxane (2) were obtained by the reduction of the corresponding nitro compounds as described in our earlier work [9].

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Benzodioxane 1 was obtained in 71% yield; mp 94-95°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 0.91 (2H, m); 1.16 (2H, m) and 2.48 (1H, m) cyclopropane protons; 4.22 (2H, m) and 4.31 (2H, m, OCH_2CH_2O); 5.89 (2H, br. s, NH_2); 6.12 (1H, s, H-5); 7.48 (1H, s, H-8). Found, %: C 65.55; H 5.81; N 6.19. $C_{12}H_{13}NO_3$. Calculated, %: C 65.74; H 5.96; N 6.39.

Benzodioxane 2 was obtained in 87% yield; mp 124-125°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 4.17 (2H, m) and 4.31 (2H, m, OCH_2CH_2O); 5.91 (2H, br. s, NH_2); 6.21 (1H, s, H-5); 6.91 (1H, s, H-8); 7.21 (1H, m); 7.32 (1H, m) and 7.41 (2H, m, ArH'). Found, %: C 65.64; H 4.26; N 4.93. $C_{15}H_{12}FNO_3$. Calculated, %: C 65.93; H 4.43; N 5.13.

6-N-Phenacylamino-7-cyclopropylcarbonyl-1,4-benzodioxane (3) was obtained from amine **1** as described in our previous work [10] in 84% yield; mp 137-138°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 0.98 (2H, m); 1.18 (2H, m) and 2.51 (1H, m) cyclopropane protons; 3.69 (2H, s, benzyl CH_2); 4.25 (2H, m) and 4.33 (2H, m, OCH_2CH_2O); 7.31 (1H, m) and 7.35 (4H, m, ArH'); 7.58 (1H, s, H-8); 8.31 (1H, s, H-5); 11.61 (1H, s, NH). Found, %: C 71.01; H 5.42; N 3.91. $C_{20}H_{19}NO_4$. Calculated, %: C 71.20; H 5.68; N 4.15.

6-N-Phenacylamino-7-(*m*-fluorobenzoyl)-1,4-benzodioxane (4) was obtained analogously from amine **2** in 91% yield; mp 157-158°C (ethanol). ^{1}H NMR spectrum, δ, ppm: 3.77 (2H, s, benzyl CH_2); 4.21 (2H, m) and 4.34 (2H, m, OCH_2CH_2O); 7.01 (1H, s, H-8); 7.21-7.45 (9H, m, ArH'); 8.26 (1H, s, H-5); 11.06 (1H, s, NH). Found, %: C 70.32; H 4.43; N 3.39. $C_{23}H_{18}FNO_4$. Calculated, %: C 70.58; H 4.63; N 3.58.

4-Cyclopropyl-6,7-ethylenedioxy-3-phenyl-2-quinolone (5). Compound **3** (0.67 g, 2 mmol) was added to a solution of sodium ethylate prepared from sodium (46 mg, 0.002 g-at) and ethanol (25 ml), stirred for 2 h at 20°C, poured into water (120 ml), and neutralized by adding 2 N hydrochloric acid. The precipitate formed was filtered off, washed with ethanol and ether, and dried in the air to give compound **5** (0.61 g, 91%); mp 301-302°C. IR spectrum, ν, cm^{-1}: 3000-2400 (N–H), 1640 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.02 (2H, m); 0.65 (2H, m) and 1.95 (1H, m) cyclopropane protons; 4.32 (4H, m, OCH_2CH_2O); 6.76 (1H, s, H-5); 7.35 (5H, m, ArH'); 7.57 (1H, s, H-8); 11.55 (1H, s, NH). Found, %: C 74.92; H 5.28; N 4.24. $C_{20}H_{17}NO_3$. Calculated, %: C 75.22; H 5.37; N 4.39.

6,7-Ethylenedioxy-3-phenyl-4-(*m*-fluorophenyl)-2-quinolone (6) was obtained in 91% yield (0.35 g) analogously from compound **4** (0.39 g) upon stirring the reaction mixture for 4 h, mp 354-355°C. IR spectrum, ν, cm^{-1}: 3000-2400 (N–H), 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.19 (2H, m) and 4.29 (2H, m, OCH_2CH_2O); 6.35 (1H, s, H-5); 6.88 (1H, s, H-8); 6.95 (2H, m); 7.06 (6H, m) and 7.31 (1H, m, ArH); 11.80 (1H, s, NH). Found, %: C 73.82; H 4.35; N 3.71. $C_{23}H_{16}FNO_3$. Calculated, %: C 73.98; H 4.32; N 3.75.

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