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NOVEL, SIMPLE METHOD FOR THE PREPARATION OF 7-HYDROXY-4-PHENYLQUINOLINE-2-CARBOXYLIC ACID

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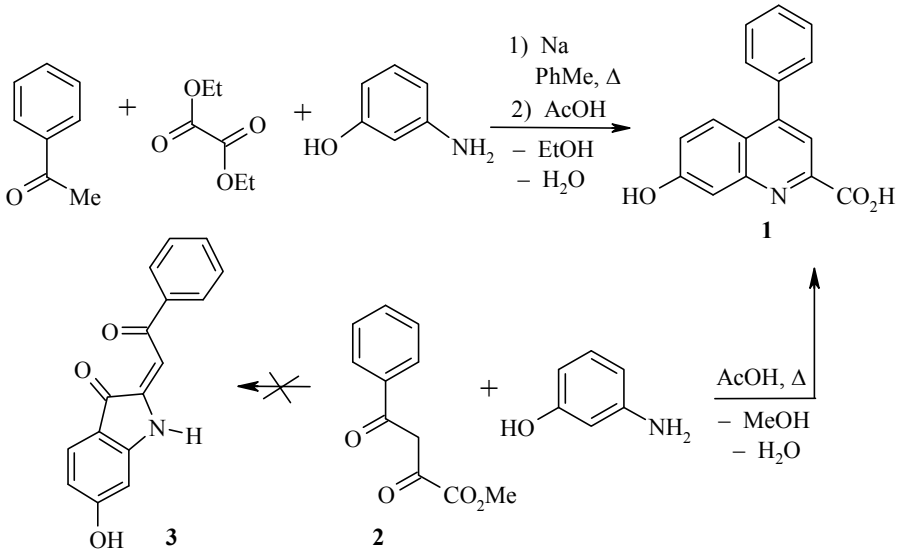
Derivatives of quinoline-2-carboxylic (quinaldic) acid [1] are used as model structures of natural antibiotics [2] and biologically active protein molecules [3] and appear in the composition of triostin [4] and saframycin A [5]. The quinaldic acid structural unit is found in *Ephedra sp.* alkaloids [6]. Quinoline-2-carboxylic acids substituted at C-7 remain unavailable up to this time with the exception of the known 7-R-4-oxo derivatives.



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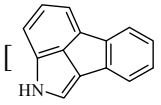
We have developed a very simple, novel method for preparation of 7-hydroxy-4-phenylquinoline-2-carboxylic acid (**1**) through a triple-component heterocyclization of acetophenone with diethyl oxalate and *m*-aminophenol. According to preliminary data this reaction may be used as a simple and convenient method for the synthesis of a wide series of 7-hydroxy- and 7-amino-substituted 4-(het)aryl- and 4-alkylquinaldic acids [7].

It should be noted that the reaction of methyl 2,4-dioxo-4-phenylbutanoic (benzoylpyruvic) acid (**2**) and *m*-aminophenol also gives compound **1** which was previously mistakenly assigned the structure 6-hydroxy-2-(2-phenylethylidene-2-oxo)-1,2-dihydro-3H-indol-3-one (**3**) [8].

Acid **1** shows bacteriostatic activity towards *Staphylococcus aureus* strains.

IR spectra were recorded on an Infralum FT-02 spectrometer as a thin vaseline oil film. The ^{1}H NMR spectrum of acid **1** was recorded on a Bruker DRX-500 instrument (500 MHz) using DMSO-d_6 and with TMS as internal standard. The mass spectrum of compound **1** was taken on a Finnigan MAT Incos-50 instrument using electron impact with direct introduction.

7-Hydroxy-4-phenylquinoline-2-carboxylic acid (1). Small fragments of sodium (0.58 g, 25 mmol) were introduced with stirring into a mixture of acetophenone (2.9 ml, 25 mmol) and diethyl oxalate (3.4 ml, 25 mmol) in toluene (100 ml) and refluxed for 1 h. AcOH (20 ml) and *m*-aminophenol (2.73 g, 25 mmol) were then introduced and the mixture was again refluxed for 2 h. The precipitate formed was filtered off, washed with cold water (100 ml), dried, washed with hot EtOH, and recrystallized from AcOH. Yield 3.0 g (45%); decomp. temperature 328-329ºC. IR spectrum, ν, cm^{-1}: 3180 (C(7)OH), 1648 (COOH), 1620 (C=C, C=N), 1598, 1530, 1410 (CH in plane), 1323, 1313, 1255, 1242, 1212, 1167, 1137, 997, 973, 876, 849, 827 (CH out of plane), 777, 753, 697, 656, 575, 537. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.26 (1H, d, *J* = 10.0, C(6)H); 7.38 (1H, s, C(8)H); 7.51-7.55, 8.21 (1H, s, C(3)H); 8.23-8.25 (5H, m, C_6H_5); 8.51 (1H, d, *J* = 11.0, C(5)H); 10.35 (1H, br. s, C(7)OH). Mass spectrum (70 eV), *m/z* (I_{rel}, % peaks with I_{rel} > 3% are reported): 266 $[M+1]^+$ (19), 265 $[M]^+$ (100), 264 $[M-H]^+$ (8), 248 $[M-OH]^+$ (3), 247 $[M-H_2O]^+$ (4), 236 $[M-CO-H]^+$ (4), 222 (9), 221 $[M-CO_2]^+$ (54), 220 $[M-CO_2-H]^+$ (60), 219 $[M-CO_2-2H]^+$ (6), 204 $[M-CO_2-H]^+$ or $[C_{15}H_{10}N]^+$ (7), 191 []$^+$ or $[C_{14}H_9N]^+$ (10), 190 $[C_{14}H_8N]^+$ (9), 165 (7), 110 (6), 95 (8), 91 (6), 89 (12), 88 (5), 77 $[C_6H_5]^+$ (13), 76 (6), 75 (5), 63 (22), 62 (10), 53 (5), 51 (12), 50 (7), 45 (15), 43 (7), 39 (12). Found, %: C 72.69; H 4.32; N 5.11. $C_{16}H_{11}NO_3$. Calculated, %: C 72.45; H 4.18; N 5.28.

Condensation of Methyl 2,4-Dioxo-4-phenylbutanoate (2) with *m*-Aminophenol. A mixture of compound **2** (1.0 g, 5 mmol) and *m*-aminophenol (0.55 g, 5 mmol) in AcOH (30 ml) was refluxed for 1 h. The precipitate formed was filtered off and recrystallized from AcOH to give compound **1** (0.65 g, 49%).

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