CONVERSION OF 2-AMINO-3-PHENYL-4-QUINOLONE TO 1H-2,3-DIHYDRO-2,9-DIOXO-10-PHENYLIMIDAZO[1,2-a]QUINOLINE

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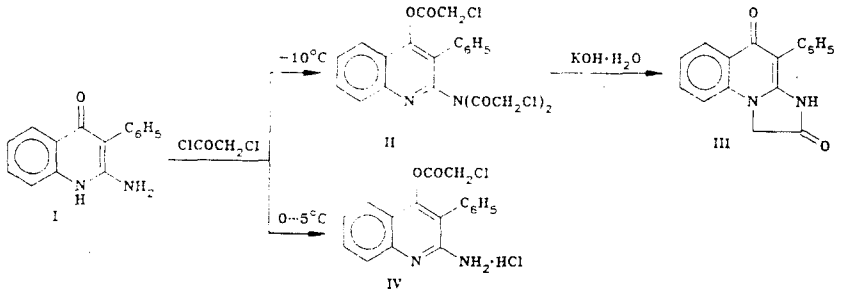
1H-2,3-Dihydro-2,9-dioxo-10-phenylimidazo[1,2-a]quinoline has been obtained from 2-amino-3-phenyl-4-quinolone by acylation with chloroacetyl chloride and cyclization of the intermediate 2-di(chloroacetyl)amino-3-phenyl-4-chloroacetoxyquinoline. The reaction of the latter with morpholine was studied.

Imidazo[1,2-a]quinolines are of interest in the search for biologically active substances [1-5]. Known methods of preparing these heterocycles are based on the cyclization reactions of 2-amino(hydroxy, chloro)quinoline and are intrinsically open to variation of the substituent in the pyridine ring [1, 3, 5]. In this work we use the preparation of imidazoquinolone III as an example of the synthesis of 1H-2,3-dihydro-2,9-dioxo-10-arylimidazo[1,2-a]quinolines from 2-amino-3-aryl-4-quinolones I. The latter have become available thanks to the method of preparing them from 2-arylmethylidene-3-indolinones [6].

Compound III is obtained by acylation of quinolone I by chloroacetyl chloride and cyclization of the intermediate trichloroacetyl derivative II. The yield of III based on quinolone I is 19%.



Compound II is prepared in 71% yield by treatment of quinolone I with chloroacetyl chloride in DMF at −10 to −15°C. At a higher temperature (0 to 5°C) the hydrochloride of the mono-O-acyl derivative IV is obtained in 69% yield.

By treatment with alcoholic base compound II is converted to the imidazoquinolone III and also hydrolyzed to the starting I.

The mass spectrum of the imidazoquinolone III shows a molecular ion peak with m/z in agreement with the molecular weight of III. In the IR spectrum absorption bands were seen for NH and C=O at 3500, 1750, and 1630 cm^{-1}, respectively. The PMR spectrum of III showed both aromatic proton signals and a singlet signal at 4.62 ppm corresponding to the methylene group of the imidazolinone ring.

The ester group of II and IV gave an absorption at 1790 cm^{-1} in the IR. Hydrochloride IV hydrolyzed readily upon dissolving in water to give the starting I. Upon treatment with morpholine compound II is converted in benzene to quinolone V in 90% yield or in DMF to quinolone VI in 48% yield.

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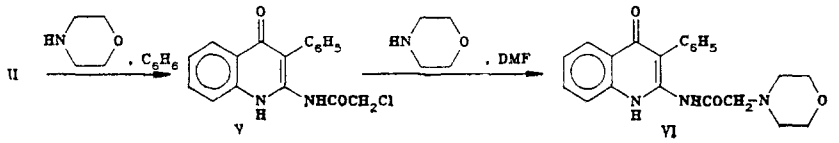

EXPERIMENTAL

IR Spectra were recorded in Vaseline mull using a Perkin-Elmer instrument. Mass spectra were taken on a Varian MAT-112 mass spectrometer at 70 eV with direct introduction of the sample into the ion source and an ionization chamber temperature of 180°C. PMR Spectra were recorded in DMSO-d_6 with TMS as reference standard using a Varian XL-200 instrument. The reaction course and compound purity were monitored by TLC on Silufol UV-254 plates using benzene–methanol (3:1) eluent and UV detection.

Elemental analytical data for C, H, Cl, and N agreed with those calculated.

2-Di(chloroacetyl)amino-3-phenyl-4-chloroacetoxyquinoline (II, $C_{21}H_{13}Cl_3N_2O_4$). A suspension of quinolone I (1.5 g, 6.4 mmole) in dry DMF (15 ml) and triethylamine (7.5 ml, 50 mmole) was prepared and cooled to −15°C. A solution of chloroacetyl chloride (3.75 ml, 50 mmole) in DMF (6 ml) was added dropwise with stirring keeping the temperature of the reaction mixture to −10 to −5°C. Stirring was continued for a further 30 min, the product poured onto ice, the precipitate filtered off, washed with water, refluxed with methanol, and again filtered. II (2.0 g, 71%) was obtained with mp 195°C (from DMF-ethanol 1:4). IR Spectrum: 1795, 1730 cm^{-1} (3 CO).

1H-2,3-Dihydro-2,9-dioxo-10-phenylimidazo[1,2-a]quinoline (III, $C_{17}H_{12}N_2O_2$). A solution of KOH (5%, 2.5 ml) was added to a suspension of the trichloroacetyl derivative II (0.23 g, 0.5 mmole) in ethanol (15 ml). The product was stirred at 20°C for 3 h, neutralized with HCl (1:10), the ethanol removed, and the residue treated with water. The precipitate was filtered off, washed with water and ethanol to give III (0.05 g, 27%) with mp 293-305°C (decomp., from methanol). IR Spectrum: 3500 (NH), 1750, 1630 cm^{-1} (CO). PMR spectrum: 4.62 (2H, s, CH_2); 11.3 (1H, s, NH); 7.30-8.14 ppm (9H, m, arom. protons). M^+ 276.

2-Amino-3-phenyl-4-chloroacetoxyquinoline hydrochloride (IV, $C_{17}H_{13}ClN_2O_2 \cdot HCl$). Chloroacetyl chloride (0.09 ml, 1 mmole) was added dropwise with stirring to a solution of the quinolone I (0.23 g, 1 mmole) in DMF (1.5 ml) which had been cooled to −5°C and the reaction mixture kept to 0-2°C. The precipitated solid was filtered off and washed with ether to give IV (0.24 g, 69%) with mp 220°C (from absolute ethanol). IR Spectrum: 3420, 3210, 3110 (NH_3), 1780 (CO), 1660 cm^{-1} (N=C–N).

2-Chloroacetylamino-3-phenyl-4-quinolone (V, $C_{17}H_{13}ClN_2O_2$). Morpholine (0.32 ml, 3.6 mmole) was added to a solution of the trichloroacetyl derivative II (0.23 g, 0.5 mmole) in benzene (20 ml) at 20°C. The mixture was stirred and left for 2 h and the precipitated solid was filtered off and washed with benzene and methanol to give V (0.14 g, 90%) with mp 187°C (from DMF-ethanol, 1:4). IR Spectrum: 3210, 3150 (NH), 1710, 1630 cm^{-1} (CO). PMR Spectrum: 4.17 (2H, s, $COCH_2Cl$); 10.03 (1H, s, $NHCOCH_2Cl$); 12.00 (1H, s, NH); 7.30-8.1 ppm (oH, m, arom. protons). M^+ 312.

2-Morpholinoacetylamino-3-phenyl-4-quinolone (VI, $C_{21}H_{21}N_3O_3$). Morpholine (0.52 g, 6 mmole) was added to the quinolone V (0.54 g, 1 mmole) in DMF (5 ml) and the product left for 12 h at 20°C. The solution was diluted with water and the precipitate filtered, washed with water and methanol to give VI (0.3 g, 48%) with mp 205-207°C (from methanol). IR Spectrum: 3440, 3200 (NH), 1690, 1630 cm^{-1} (CO). PMR Spectrum: 3.09 (2H, s, $COCH_2N(CH_2)_4$-O); 2.32 (4H, t, 2',6'-H morpholine); 3.22 (4H, t, 3',5'-H morpholine); 9.8 (1H, s, $NHCOCH_2$); 12.0 (1H, s, NH); 7.30-8.10 ppm (9H, m, arom. protons). M^+ 363.

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