SYNTHESIS OF AMIDES OF 2-OXOQUINOLINCARBOXYLIC ACIDS

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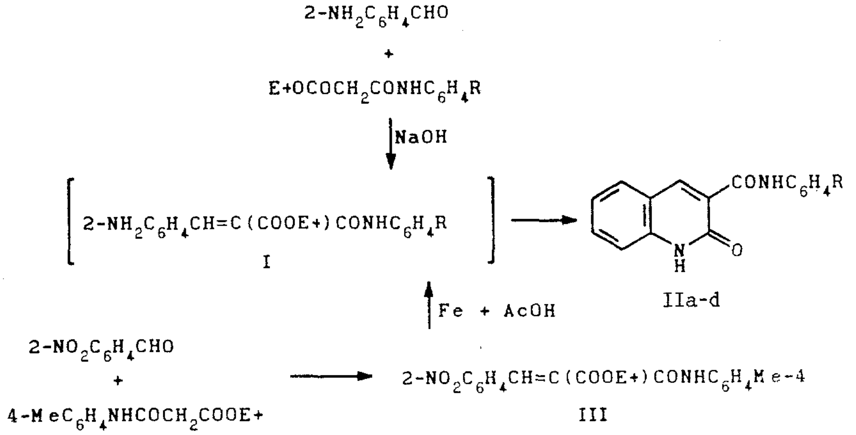
The reaction of aryl amides of monoethyl malonate with 2-aminobenzaldehyde in ethanol in the presence of catalytic amounts of base is found to give aryl amides of 2-oxoquinolin-3-carboxylic acid.

We described earlier the reactions of 2-aminobenzaldehyde and potassium isatinate with substituted amides of acetoacetic [1, 2] and cyanoacetic [3] acids and showed that substituted amides of 2-methyl- and 2-aminoquinolin-3-carboxylic acid and their derivatives could be obtained by these reactions.

In the present work we have studied the reaction of 2-aminobenzaldehyde with aryl amides of monoethyl malonate and established that on boiling for 2 h in ethanol in the presence of catalytic amounts of sodium hydroxide these reactants give good yields of the aryl amides of 2-oxoquinolin-3-carboxylic acid (IIa-d; see Table 1).



IIa R=H; b R=4-CH$_3$; c R=2-CH$_3$O; d R=4-CH$_3$O; III R=4-CH$_3$

Apparently, the aldehyde group of the 2-aminobenzaldehyde first reacts with the methylene group of the amides of ethyl malonate, leading to the formation of intermediate amides of 3-(2-aminophenyl)-2-carbethoxyacrylic acid (I) which cyclize to the quinoline ring through the reaction of the amino and carbethoxy groups. This hypothesis is confirmed by the formation of amide III on condensation of 2-nitrobenzaldehyde with the p-toluidine of ethyl malonate. Amide III is converted to compound IIb on reduction. In this case, it can be asserted unequivocally that a compound of type I is formed as an intermediate product.

Attempts to condense 2-aminobenzaldehyde with the di(p-toluidine) of malonic acid under the conditions of the synthesis of compounds IIa-d proved unsuccessful. When the reaction is carried out under more rigorous conditions, in boiling butanol in the presence of sodium butylate, the product formed is the p-toluidide of IIb instead of the expected di(p-toluidide) of (2-aminobenzylidine)malonic acid. Apparently, the latter is the intermediate product, but then cyclizes with the expulsion of p-toluidine.

In the case of compound IIc it was shown that the action of phosphorus oxychloride leads to the formation of the o-anisidide of 2-chloroquinolin-3-carboxylic acid (IV).

The structures of the compounds obtained were confirmed by IR and PMR spectroscopy.

EXPERIMENTAL

The IR spectra were taken in petroleum jelly on a UR-20 instrument. The PMR spectra were recorded on an RYa-2310 (60 MHz) instrument for 5% solutions of the compounds in DMSO-D$_6$, with HMDS as an internal standard.

The elementary analyses for C, H, Cl, and N correspond to the calculated values.

Arylamides of 2-Oxoquinolin-3-carboxylic Acid (IIa, d). A solution of 1.2 g (10 mmoles) of 2-aminobenzaldehyde, 10 mmoles of the substituted amide of monoethyl malonate, and 3-5 drops of 10% solution of sodium hydroxide in 15 ml of ethanol is boiled for 2 h. The precipitate that forms is filtered off and crystallized from DMF.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Molecular formula	T_{mp}, °C	IR spectrum cm^{-1}		PMR spectrum, δ, ppm	Yield, %
			C=O	NH		
IIa	$C_{16}H_{12}N_2O_2$	330...331	1635, 1660	3130...3180	7,26...8,19 (9H, m, H_{arom}); 8,97 (1H, s, 4-H); 12,21 (1H, br.s, NH); 12,76 (1H, br.s, NH)	85
IIb	$C_{17}H_{14}N_2O_2$	341...343	1630, 1675	3180; 3320	2,21 (3H, s CH_3); 7,03...8,03 (8H, m. H_{arom});8,87 (1H,s, 4-H); 11,94 (1H, br.s., NH); 12,45 (1H,br.s., NH)	72
IIc	$C_{17}H_{14}N_2O_3$	288...290	1625, 1675	3130...3180	3,85 (3H s, CH_3O); 6,82...8,53 (8H, m, H_{arom});8,88 (1H,s, 4-H) 12,21 (1H, br.s, NH); 12,42 (1H, br.s, NH)	68
IId	$C_{17}H_{14}N_2O_3$	310...311	1625, 1665	3130...3180	3,75 (3H,s, CH_3O); 6,82...8,15 (8H, m H_{arom});8,97 (1H,s, 4-H); 12,08 (1H, s NH); 12,76 (1H,br.s, NH)	64
III	$C_{19}H_{18}N_2O_5$	128...130	1625; 1700	3220	1,19 (3H, t. CH_3); 2,15 (3H,s, CH_3); 4,30 (2H, d, CH_2); 6,92...8,19 (8H, m, Harom.);7,95 (1H,s, H-C=C-); 10,37 (1H s NH)	40 (A) 50(B)
IV	$C_{17}H_{13}ClN_2O_2$	168...170	1660	3340	3,80 (3H, s, CH_3O); 6,89...8,19 (8H, m, Harom.);8,50 (1H, s, 4-H); 9,80 (1H, br.s NH)	87

p-Toluidide of 3-(2-Nitrophenyl)-2-carbethoxyacrylic Acid (III). A. A solution of 1.5 g (10 mmoles) of 2-nitrobenzaldehyde, 2.2 g (10 mmoles) of p-monoethyl malonate, and 5 drops of piperidine in 10 ml of ethanol is boiled for 8 h. The solvent is distilled off, and the solidified residue crystallized from a 1:1 benzene:hexane mixture.

B. A solution of 1.5 g (10 mmoles) of 2-nitrobenzaldehyde and 2.2 g (10 mmoles) of the p-toluidide of monoethyl malonate in 5 ml of glacial acetic acid is heated on a water bath for 8 h, cooled, and diluted with water. The precipitate that forms is filtered off, washed with water, dried, and crystallized from benzene.

Reduction of the p-Toluidide of 3-(2-Nitrophenyl)-2-carbethoxyacrylic Acid. A mixture of 0.8 g (2 mmoles) of compound III and 1 g of iron filings in 10 ml of glacial acetic acid is heated on a water bath for 6 h, cooled, filtered, and diluted with water. The precipitate that forms is filtered off and crystallized from DMF to obtain 0.35 g (56%) of compound IIb. Mp 341-343°C. The melting point of a mixture with a sample of compound IIb obtained in one of the previous experiments was not depressed.

Condensation of 2-Aminobenzaldehyde with the Di(p-toluidide) of Malonic Acid. Sodium butylate, prepared from 0.23 g (10 mmoles) of sodium and 5 ml of butanol, is added to a solution of 1.2 g (10 mmoles) of 2-aminobenzaldehyde and 2.8 g (10 mmoles) of the di(p-toluidide) of malonic acid in 90 ml of butanol. The mixture is boiled for 3-4 h, cooled, treated with hydrochloric acid, and the precipitate that forms is filtered off and crystallized from DMF to obtain 1 g (40%) of compound IIb. Mp 341-343°C. The melting point of a mixture with a sample of compound IIb obtained by the condensation of 2-aminobenzaldehyde with the p-toluidide of monoethyl malonate was not depressed.

o-Anisidide of 2-Chloroquinolin-3-carboxylic Acid (IV). A mixture of 1.5 g (5 mmoles) of the o-anisidide of 2-oxoquinolin-3-carboxylic acid Id, 2 g of phosphorus pentachloride, and 10 ml of phosphorus oxychloride is heated at 120-130°C (the temperature of a metal bath) for 2 h, diluted with water, and the precipitate that forms is filtered off and crystallized from ethanol.

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