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# SYNTHESIS OF SUBSTITUTED 2-AMINOQUINOLINE-3-CARBOXYLIC ACID AMIDES

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UDC 547.831.6.9.07:542.942.3

Substituted 3-(2-nitrophenyl)-2-cyanoacrylic acid amides were synthesized by the Knoevenagel reaction and were then reduced with iron in acetic acid to the corresponding 2-aminoquinoline-3-carboxylic acid amides.

Little study has been devoted to 2-aminoquinoline-3-carboxylic acid amides. The unsubstituted amide of this acid was obtained by the reaction of 2-aminobenzaldehyde with cyanoacetamide and was then used for the synthesis of biologically active pyrimido[4,5-b]quinolin-4-ones [1]. In order to synthesize substituted amides we used the reaction of 2-nitrobenzaldehyde with cyanoacetamides under the conditions of the Knoevenagel reaction to obtain 3-(2-nitrophenyl)-2-cyanoacrylic acid N-alkyl- and N-arylamides Ia-i (Table 1) in good yields; these products were used as the starting substances. The IR spectra of Ia-i contain bands at 1660-1690 (CO), 2230-2240 (CN), and 3340-3380 cm$^{-1}$ (NH).

Substituted 2-aminoquinoline-3-carboxylic acid amides IIa-f (Table 1) are formed in the reduction of amides Ia-f with iron in acetic acid. The IR spectra of IIa-f contain absorption bands at 1630-1660 (CO), 3140-3290 (NH), and 3360-3380 and 3425-3480 cm$^{-1}$ ($NH_2$). A multiplet centered at 7.5 ppm (9H, aromatic protons, and 2H, $NH_2$), a singlet at 8.33 ppm (1H, pyridine), and a singlet at 10.1 ppm (1H, NH) are observed in the PMR spectra of amide IIa.

Compounds IIa, b are identical to the substances described in [2], which were also synthesized by reduction of amides Ia, b and to which the 2-arylamino-3-cyanoquinoline structure was erroneously assigned.

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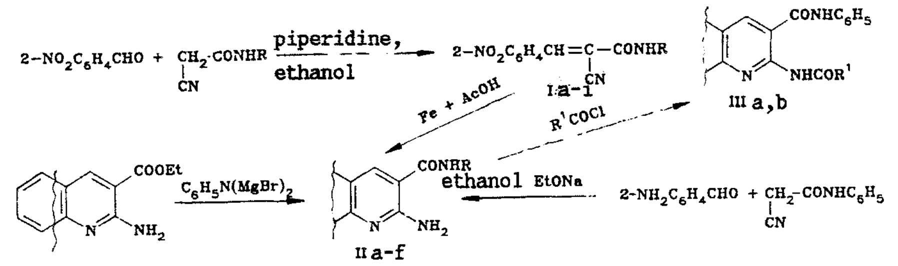
Perm State Pharmaceutical Institute, Perm 614000. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1515-1517, November, 1988. Original article submitted May 7, 1987; revision submitted November 24, 1987.

0009-3122/88/2411-1256$12.50



I, II a $R=C_6H_5$; b $R=p\text{-}CH_3C_6H_4$; c $R=p\text{-}CH_3OC_6H_4$; d $R=o\text{-}ClC_6H_4$; e $R=C_6H_{11}$; f $R==C_6H_5CH_2$; I g $R=p\text{-}BrC_6H_4$; h $R=CH_3$; i $R=CH_2=CH—CH_2$; III a $R=CH_3$; b $R=C_6H_5$

We undertook the alternative synthesis of amide IIa by the reaction of 2-aminobenzaldehyde with cyanoacetic acid anilide in the presence of sodium ethoxide. The substances obtained by the two methods were identical. Compound IIa was also synthesized by the reaction of ethyl 2-aminoquinoline-3-carboxylate with N,N-bis(bromomagnesium) aniline.

Acyl derivatives IIIa, b, the structures of which were confirmed by data from the IR and PMR spectra (see the experimental section), were also synthesized.

## EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra of 5% solutions of the compounds in $d_6$-DMSO were obtained with an RYa-2310 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard.

Substituted 3-(2-Nitrophenyl)-2-cyanoacrylic Acid Amides Ia-i. A solution of 3 g (20 mmoles) of 2-nitrobenzaldehyde, 20 mmoles of the substituted cyanoacetic acid amide, and five drops of piperidine in 30 ml of ethanol was refluxed for 1 h, after which the mixture was cooled, and the precipitate was removed by filtration and crystallized from ethanol.

Substituted 2-Aminoquinoline-3-carboxylic Acid Amides IIa-f. A 1.5-g sample of iron filings was added to a solution of 1 g (3 mmoles) of amide Ia-f in 20 ml of acetic acid, and the mixture was heated for 7 h on a water bath. It was then filtered, and the filtrate was diluted with water. The resulting precipitate was removed by filtration and crystallized from alcohol.

2-Aminoquinoline-3-carboxylic Acid Anilide (IIa). A) A solution of 1.35 g (6 mmoles) of ethyl 2-aminoquinoline-3-carboxylate [3] in 20 ml of ether was added to the dimagnesylamine obtained from 24 mmoles of ethylmagnesium bromide and 1.1 g (12 mmoles) of aniline in 20 ml of dry ether, and the mixture was refluxed for 1.5 h. It was then decomposed with a

TABLE 1. Characteristics of the Synthesized Compounds

| Compound | mp, °C | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|
| | | C | H | N | | C | H | N | |
| Ia | 210...212 [2] | 65,6 | 3,9 | 14,4 | $C_{16}H_{11}N_3O_3$ | 65,5 | 3,7 | 14,3 | 88 |
| Ib | 184...186 [2] | 66,7 | 4,3 | 13,7 | $C_{17}H_{13}N_3O_3$ | 66,5 | 4,2 | 13,7 | 82 |
| Ic | 213...214 | 63,3 | 4,2 | 13,3 | $C_{17}H_{13}N_3O_4$ | 63,1 | 4,0 | 13,0 | 60 |
| Id* | 172...174 | — | — | 13,0 | $C_{16}H_{10}ClN_3O_3$ | — | — | 12,8 | 60 |
| Ie | 116...118 | 64,6 | 5,7 | 14,1 | $C_{16}H_{16}N_3O_3$ | 64,4 | 5,4 | 14,1 | 44 |
| If | 111...112 | 66,6 | 4,5 | 13,9 | $C_{17}H_{18}N_3O_3$ | 66,4 | 4,2 | 13,7 | 58 |
| Ig† | 202...204 | — | — | 11,4 | $C_{16}H_{10}BrN_3O_3$ | — | — | 11,3 | 54 |
| Ih | 159...161 | 57,3 | 4,0 | 18,3 | $C_{11}H_9N_3O_3$ | 57,1 | 3,9 | 18,2 | 54 |
| Ii | 74...76 | 60,9 | 4,4 | 16,1 | $C_{13}H_{11}N_3O_3$ | 60,7 | 4,3 | 16,3 | 50 |
| IIa | 207...208 | 72,7 | 5,2 | 15,7 | $C_{16}H_{13}N_3O$ | 73,0 | 4,9 | 16,0 | 85 |
| IIb | 220...221 | 73,9 | 5,7 | 15,3 | $C_{17}H_{15}N_3O$ | 73,7 | 5,4 | 15,2 | 85 |
| IIc | 207...209 | 69,9 | 5,3 | 14,5 | $C_{17}H_{15}N_3O_2$ | 69,6 | 5,1 | 14,3 | 77 |
| IId‡ | 185...187 | — | — | 14,2 | $C_{16}H_{12}ClN_3O$ | — | — | 14,1 | 77 |
| IIe | 240...242 | 71,8 | 6,9 | 15,8 | $C_{16}H_{18}N_3O$ | 71,6 | 6,7 | 15,7 | 60 |
| IIf | 198...200 | 73,7 | 5,5 | 15,2 | $C_{17}H_{15}N_3O$ | 73,6 | 5,4 | 15,2 | 35 |
| IIIa | 177...179 | 70,8 | 4,9 | 13,8 | $C_{18}H_{15}N_3O_2$ | 71,1 | 5,2 | 13,6 | 50 |
| IIIb | 242...244 | 75,4 | 4,8 | 11,5 | $C_{23}H_{17}N_3O_2$ | 75,2 | 4,6 | 11,4 | 40 |

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*Cl found, %: 11.0; Cl calculated, %: 10.8.

†Br found, %: 21.7; Br calculated, %: 21.5.

‡Cl found, %: 11.7; Cl calculated, %: 11.9.

saturated solution of ammonium chloride, and the ether layer was separated. The solvent and volatile impurities were removed by steam distillation, and the residue was crystallized from ethanol to give 0.52 g (32%) of a product with mp 205-207°C. No melting-point depression was observed for a mixture of this product with a sample of IIa obtained under the conditions of the preceding experiment.

B) A solution of 0.5 g (4 mmoles) of 2-aminobenzaldehyde and 0.6 g (4 mmoles) of cyanoacetic acid anilide in 5 ml of anhydrous ethanol was added to a solution of sodium ethoxide obtained from 0.3 g (4 mmoles) of sodium in 2 ml of anhydrous ethanol, and the mixture was refluxed for 1 h. It was then filtered, and the filtrate was diluted with water. The resulting precipitate was separated and crystallized from alcohol to give 0.58 g (54%) of a product with mp 205-206°C.

2-Acetamidoquinoline-3-carboxylic Acid Anilide (IIIa). A 3-ml sample of acetyl chloride was added dropwise to a solution of 1 g (2 mmoles) of IIa in 10 ml of anhydrous pyridine, and the mixture was heated for 30 min at 70°C. It was then poured into water, and the solidified residue was separated and crystallized from aqueous ethanol. IR spectrum: 1650, 1690 (CO), 3270, 3480 cm$^{-1}$ (NH). PMR spectrum: 1.36 and 2.36 (2s, 3H, $CH_3$), 7.5 (m, 9H, aromatic protons), 8.06 (s, 1H, pyridine), 9.06 and 10.0 ppm (2H, NH).

2-Benzamidoquinoline-3-carboxylic Acid Anilide (IIIb). A solution of 0.5 g (1 mmole) of amide IIa and 0.3 g (2 mmoles) of benzoyl chloride in 5 ml of pyridine was refluxed for 3 h, after which the mixture was cooled and poured into ice water. The resulting precipitate was removed by filtration and crystallized from methanol. PMR spectrum: 7.3 (14H, aromatic protons), 7.8 (s, 1H, pyridine), 8.8 and 9.01 ppm (2H, NH).

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# MASS-SPECTROMETRIC BEHAVIOR OF 9-HYDROXY-10-NITROSOPHENANTHRENE AND ITS DIAZA ANALOGS

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UDC 547.677'836:543.51

According to mass-spectral data, 9-hydroxy-10-nitrosophenanthrene in the gas phase exists primarily in this tautomeric form rather than in the 9-oxo-10-hydroxyimino tautomeric form, while passing to its 4,5-diaza and, particularly, its 1,8-diaza analogs shifts the equilibrium sharply to favor the o-quinoid form. The character of the fragmentation of the molecular ions of the polycyclic compounds differs markedly from the fragmentation of the acyclic rearrangement product — 2-carboxy-2'-cyanobiphenyl.

It is well known that o-hydroxynitrosoarenes are capable of undergoing cleavage with the formation of derivatives of o-cyanocinnamic acids [1-3]. This is associated with the fact that, according to spectral data, hydroxynitrosoarenes in solutions exist primarily in the o-quinone monooxime tautomeric form [4-6]. It was later established that a similar rearrangement can also be observed in a number of o-hydroxynitrosohetarenes of the indazole [7], benzotriazole [8], and indole [9, 10] series. It was recently found that some oximes are capable of undergoing the Beckman rearrangement also in the gas phase under electron

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0009-3122/88/2411-1258$12.50