SYNTHESIS AND PROPERTIES OF 2-(2-OXOINDOLIN-3-YLIDENE)-2-CYANOACETIC ACID PIPERIDIDES AND MORPHOLIDES

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The reaction of isatins with cyanoacetic acid piperidide or morpholide gives the corresponding derivatives of 2-(2-oxoindolin-3-ylidene)-2-cyanoacetic acid, which may be reduced to give amides of 2-(2-oxoindolin-3-yl)-2-cyanoacetic acid and react with ethanolic alkali to give quinoline derivatives.

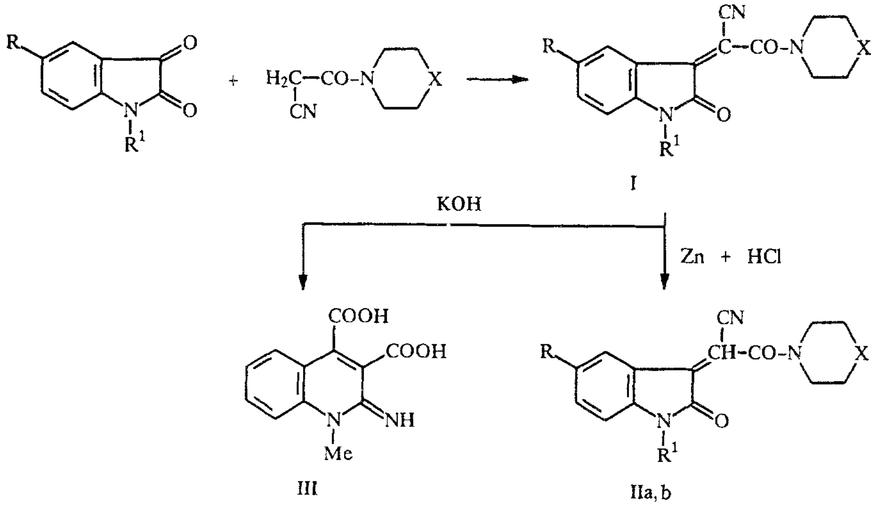
Isatin condenses with ethyl cyanoacetate to give ethyl 2-(2-oxoindolin-3-ylidene)-2-cyanoacetate [1].

Fahmy and Badr [2] have recently proposed a new method for the synthesis of derivatives of quinoline using the reaction of the latter with β-dicarbonyl compounds [2]. The reaction of substituted amides of cyanoacetic acid with isatin has not yet been studied.

In order to expand the scope of the reactions of isatin with cyanoacetic acid derivatives and study the properties of the resultant products, we investigated the reaction of the piperidide and morpholide of this acid with isatin and its 1- and 5-substituted analogs.

This reaction proceeds upon heating ethanolic solutions of the starting reagents in the presence of catalytic amounts of piperidine to give 2-(2-oxoindolin-3-ylidene)-2-cyanoacetic acid piperidides and morpholides (Ia-Ij, Table 1).

The IR spectra of these products have bands at 1620-1660 (amide CO), 1690-1720 (oxoindoline CO), and 2220 cm^{-1} (CN). The IR spectra of Ia-Ih also have a band at 3430 cm^{-1} (NH).



I

III

IIa,b

Ia,e R = R^1 = H; b,f R = Br, R^1 = H; c,g R = Cl, R^1 = H; d,h R = NO$_2$, R^1 = H; i,j R = H, R^1 = Me;
IIa R = R^1 = H; IIb R = H, R^1 = Me; Ia—d, i IIa X = CH$_2$; I e–h, j, IIb X = O

Perm Pharmaceutical Institute, 614600 Perm. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1611-1613, December, 1992. Original article submitted March 14, 1991.

TABLE 1. Indices of Compounds Synthesized

Compound	Chemical formula	Mp, °C	Yield, %
Ia	$C_{16}H_{15}N_3O_2$	213...215	83
Ib	$C_{16}H_{14}BrN_3O_2$	231...233	83
Ic	$C_{16}H_{14}ClN_3O_2$	235...237	30
Id	$C_{16}H_{14}N_4O_4$	274...275	62
Ie	$C_{15}H_{13}N_3O_3$	229...231	91
If	$C_{15}H_{12}BrN_3O_3$	237...239	85
Ig	$C_{15}H_{12}ClN_3O_3$	238...240	42
Ih	$C_{15}H_{12}N_4O_5$	271...272	69
Ii	$C_{17}H_{17}N_3O_2$	190...191	80
Ij	$C_{16}H_{15}N_3O_3$	208...210	77
IIa	$C_{16}H_{17}N_3O_2$	143...145	70
IIb	$C_{16}H_{17}N_3O_3$	115...117	55
III	$C_{12}H_{10}N_2O_4$	295...297	34

The PMR spectra of Ia-Ij have signals at 1.40-1.46 and 3.26-3.30 (piperidide or morpholide protons), multiplet at 7.16-7.33 (aromatic ring protons), and singlet at 10.70 ppm (NH).

Treatment of solutions of Ia and Ij with zinc dust in concentrated hydrochloric acid led to reduction of ylidene fragment and formation of the corresponding 2-(2-oxoindolin-3-yl)-2-cyanoacetamides IIa and IIb. The IR spectra of these amides have bands at 1660 (amide CO), 1700-1720 (oxoindoline CO), and 2240-2260 cm^{-1} (CN). The IR spectrum of IIa also has a band at 3370 cm^{-1} (NH). The PMR spectra of IIa and IIb have signals at 1.50 and 3.30 (piperidine or morpholine protons), doublets at 3.83 and 4.83 (CH groups), multiplet at 6.83-6.93 (aromatic ring protons), and singlet at 10.33 ppm (NH).

Treatment of 2-(1-methyl-2-oxoindolin-3-ylidene)-2-cyanoacetic acid (Ii) with 10% ethanolic potassium hydroxide led to recyclization with the formation of 2-imino-1-methylquinoline-3,4-dicarboxylic acid (III). No product was obtained with the reaction was carried with 10% and 20% aqueous potassium hydroxide. The IR spectrum of III has stretching bands at 1685, 1710 (CO), and 3410 cm^{-1} (NH) and its PMR spectrum has a singlet at 3.65 (CH_3), multiplet at 7.5 (aromatic protons and two carboxylic group protons), and broad signal at 11.33 ppm (NH).

EXPERIMENTAL

The IR spectra were taken for vaseline mulls on a UR-20 spectrometer. The PMR spectra were taken on an RYa-2310 spectrometer at 60 MHz for 5% solutions in DMSO-d_6 with HMDS as the internal standard. The indices of the compounds obtained are given in Table 1.

The elemental analysis data for C, H, Cl, Br, and N were in accord with the calculated values.

2-(2-Oxoindolin-3-ylidene)-2-cyanoacetic acid piperidides and morpholides (Ia)-(Ij). A mixture of 0.01 mole of the corresponding isatin, 0.01 mole cyanoacetic acid piperidide or morpholide, and five drops piperidine was heated at reflux in 25 ml 2-propanol for 13 h. The precipitate of Ia-Ij formed after cooling was separated, washed with ether, and crystallized from ethanol.

2-(2-Oxoindolin-3-yl)-2-cyanoacetic acid piperidide or morpholide (IIa), (IIb). A sample of 1 g Ia or Ij was dissolved in 30 ml ethyl acetate and 3 ml concentrated hydrochloric acid and 1 g zinc powder were added. The mixture was left at room temperature until colorless. The solvent was removed and the residue was washed with water until the washings were neutral. The product was crystallized from ethanol.

2-Imino-1-methylquinoline-3,4-dicarboxylic acid (III). A sample of 1 g (3 mmoles) Ii was added to 20 ml 10% ethanolic potassium hydroxide and stirred with moderate heating until the solution turned from red-violet to yellow-orange. The mixture was left for 12 h at room temperature. The precipitated potassium of III was filtered off, washed with acetone, dissolved in the minimum amount of water, and precipitated by the addition of hydrochloric acid. The precipitate was filtered off and crystallized from ethanol.

REFERENCES

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2. A. M. Fahmy and M. Z. A. Badr, J. Heterocycl. Chem., **21**, No. 4, 1233 (1984).