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Nitriles in Heterocyclic Synthesis: the Reaction of Ethyl 2-Oxoindoliden-3-ylidene Cyanoacetate and of 3-Dicyanoethylideneindoliden-2-one with Phenols and Amines

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ABSTRACT

*The reactions of ethyl 2-oxoindoliden-3-ylidene cyanoacetate (**2a**) and of 3-dicyanoethylideneindoliden-2-one (**2b**) with phenols and amines have been reported. © 1996 John Wiley & Sons, Inc.*

α,β-Unsaturated nitriles are highly reactive reagents and have been extensively utilized in heterocyclic synthesis [1]. Reactions of nucleophiles with these reagents normally take place at the β-carbon [2,3]. Moreover, when C-β carries other electron-attracting functional groups, reactions at the α carbon also occur [4,5]. Thus, whereas ethyl 2-oxoindoliden-3-ylidene cyanoacetate (**2a**) and 3-dicyanoethylideneindoliden-2-one (**2b**) have been reported to react with pyrazolones and with active methylene ketones [2] to yield spiropyranopyrazoles, phenols and amines have recently been reported to react with 4-(dicyanomethylene)-3-methyl-1-phenyl-2-pyrazolin-5-one (**3**) to yield products resulting from addition at C-α and subsequent hydrogen cyanide elimination [4]. It seemed to us that the behavior of **2** toward the same reagents should be investigated.

Thus, it has been found that **2a** reacts with β naphthol in ethanol for a 2 hour period in the presence of a catalytic amount of triethylamine to yield a 1:1 adduct. The IR spectrum of this adduct revealed the absence of a CN band and the appearance of a band for an NH_2 function. Thus, two structures were considered (cf. structures **4** and **5**). Compound **4** may be assumed to be formed by addition of C-1 of the β naphthol to the β-carbon atom in **2a** with subsequent cyclization, yielding the spiropyran derivative **4a**. Alternatively, **5** may result by attack of the phenolic (OH) ring opening and recyclization. Structure **4a** was established for the reaction product based on ^{13}C NMR spectroscopy, which revealed the presence of a signal at $\delta = 50$ for an sp^3 carbon atom. This signal was assigned to the indolidin C-3. Another high field carbon at $\delta = 109$ also appeared, and this was assigned to the enamine carbon of the pyran moiety in **4a**. If the reaction product were **5**, it would be difficult to assign these signals. Similarly, **2b** reacted with β naphthol to yield **4b**. Compounds **2a,b** reacted also with 8-hydroxyquinoline, yielding

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6a,b. Structure **6** was inferred from its ^{13}C NMR spectrum, which also revealed an *sp*^{3} carbon at δ = 50 and an enamine carbon at δ = 110. The reaction of resorcinol with the ylidenemalononitriles had been shown earlier to yield 1:1 adducts. These were formulated by Elagamy et al. [6] as the benzopyrans **7**. However Abdel-Latif [7], ignoring the existence of this report, has assigned the structure **8** for the same reaction products. Now, in our hands, resorcinol also reacted with **2a,b** to yield 1:1 adducts which, by similarity to the literature, may be assigned either structure **9** or the isomeric structure **10**. Structure **9** could be established for these reaction products based on its nonidentity with a sample of **10b**, prepared by refluxing **2b** for a 15 hour period with cyclohexan-1,3-dione (**11**) in dioxane in the presence of sulfur and piperidine, and subsequent oxidation of the resulting adduct (**12**).

Unexpectedly, an attempt to effect condensation of *o*-hydroxyacetophenone with **2a** resulted in the formation of a product of molecular formula $C_{16}H_{11}NO_3$ (M^+ = 266 *m/e*). This can thus be formulated as either **13**, resulting from addition at C-β and elimination of ethyl cyanoacetate, or the isomer **14**, which may result by ring opening of **13** and recyclization. This latter structure was preferred for the reaction product based on its IR spectra, which revealed only one carbonyl signal. Moreover, the reaction product showed the existence of a carboxylic acid group. The formation of this product may thus be considered as an extension of the Friedländer quinoline synthesis [8].

In contrast to the behavior of **2a**, compound **2b** reacted with *o*-hydroxyacetophenone to yield the product of condensation with water elimination (M^+ = 313 *m/e*). The IR spectrum of this product revealed the presence of only one cyano band at 2200 cm^{-1} and one conjugated carbonyl signal at 1670 cm^{-1}. This product was thus assigned structure **15**. Compound **15** is assumed to be formed by attack of the methyl function in *o*-hydroxyacetophenone at the indolidine C=O in **2b** to yield the diketone **16**. This then cyclizes to **17**, then to **15**. To our knowledge, this is the first reported ring enlargement of indolidinemalononitriles into quinolines, since the previously reported [9] ring enlargement by action of pyrazolones proved later to be incorrect [2].

Aniline reacted with **2a,b** to yield the same reaction product. This was formulated as **18** and is assumed to be formed by addition of the amino function at C-α and subsequent loss of hydrogen cyanide or the ethyl formate moiety. This is similar to the behavior of **3** toward the same reagents. In contrast to this, more basic amines, such as *p*-anisidine and *p*-hydroxyaniline, react with **2a** to yield the Keteimines **19a,b**. These are assumed to be formed by addition of the nucleophilic amino function at C-β and subsequent loss of ethyl cyanoacetate.

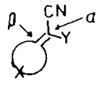
It may thus be concluded that reaction of **2a,b** with nucleophiles may involve both C-α, C-β and the indolidine C=O. It seems that a delicate balance between the three possible reaction routes exists. Thus, the nature of the reaction product is highly dependent on the applied reaction conditions.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer. ^{13}C NMR spectra were measured in DMSO[d_6] on a Bruker spectrometer (250) MHz, and chemical shifts are expressed as δ. ^1H NMR spectra were measured in DMSO[d_6] with a Varian EM-390 (90 MHz) spectrometer, and chemical shifts are reported in δ. Mass spectra were recorded on a mass spectrometer MS 9(AEI) at 70 eV. Microanalytical data (C,H,N) were obtained from the Microanalytical Data Unit at Cairo University.

The Reaction of 2-Oxo-2,3-dihydroindole Derivatives **2a,b** *with Phenols and Amines*

General Procedure. A suspension of equimolecular amounts (0.01 mole) of **2a** or **2b** with the appropriate phenol or amine was heated under reflux in absolute ethanol (50 mL) in the presence of a catalytic amount of triethylamine (3 drops) for 1–2 hours (monitored by TLC). The reaction mixture was then evaporated under reduced pressure and the remaining solid was collected by filtration and crystallized from the proper solvent.



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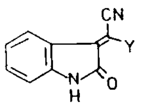

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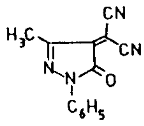

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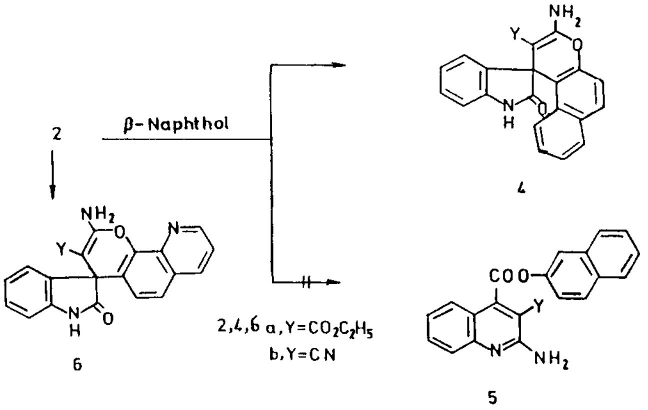
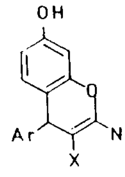


Compound **4a** formed colorless crystals from ethanol. Yield 80%, m.p. 290°C. IR: ν = 3450,3300(NH_2), 1710(ester CO), and 1670 cm^{-1} (indolidin CO). ^1H NMR: δ = 1.85(s,3H,CH_3), 4.0(q,2H,CH_2), 6.9–7.6(m,10H, aromatic protons), and 7.9(s,br,2H,NH_2). ^{13}C NMR: δ = 180.6(indole C-

2), 167.8(ester CO), 159.8(pyran C-6), 146.9(pyran C-2), 143.1(indole C-7a), 130.9(indole C-3a), 109.3(pyran C-3), 59.0(ester CH$_2$), 50.4(spiro carbon), 13.4(ester CH$_3$), and 146–114(aromatic carbons). Found: C, 71.23; H, 4.48; N, 7.33%. Calcd. for C$_{23}$H$_{18}$N$_2$O$_4$ C, 71.49; H, 4.69; N, 7.25%.

Compound **4b** formed colorless crystals from dioxane. Yield 72%. m.p. 230°C. IR: ν = 3300,3200(NH$_2$), 2200(CN), 1670(CO), and 1640 cm^{-1} (NH$_2$). ^{1}H NMR: δ = 6.49(s,2H,NH$_2$) and 6.9–7.8(m,10H, aromatic protons). Found: C, 74.56; H, 3.87; N, 12.27%. Calcd. for C$_{21}$H$_{13}$N$_3$O$_2$ C, 74.32; H, 3.86; N, 12.38%.

Compound **6a** formed colorless crystals from ethanol. Yield 78%, m.p. 280°C. IR: ν = 3300,3100(NH$_2$), 1700(ester CO), 1670(indolidin CO), and 1600 cm^{-1} (δ NH$_2$). ^{13}C NMR: δ = 180.9(indole C-2), 161.1(ester CO), 150.5(pyran C-6), 142.8(pyran C-2), 142.1(indole C-7a), 136.0(indole C-3a), 109.4(pyran C-3), 58.9(ester CH$_2$), 50.7(spiro carbon), 13.2(ester CH$_3$), and 139–122(aromatic carbons). MS: *m/z* 388(M$^+$). Found: C, 68.20; H, 4.0; N, 10.63%. Calcd. for C$_{22}$H$_{17}$N$_3$O$_4$ C, 68.20; H, 4.42; N, 10.85%.



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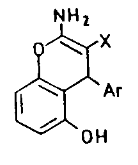

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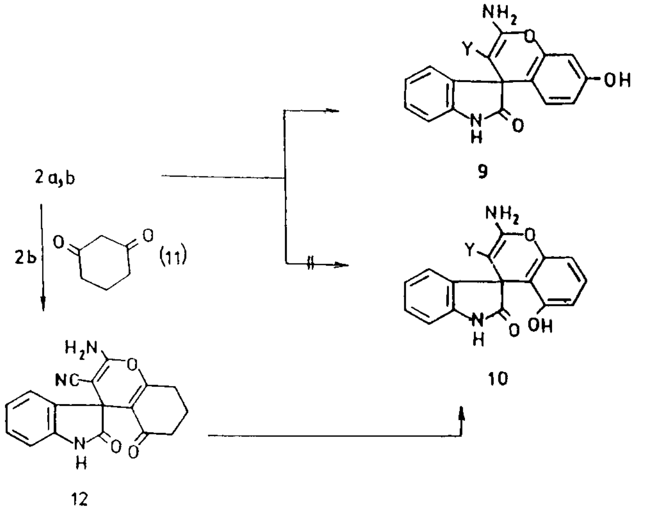
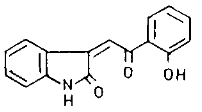


Compound **6b** formed yellow crystals from DMF. Yield 75%, m.p. >300°C. IR: ν = 3300,3150(NH$_2$), 2200(CN), 1670(CO), and 1640 cm^{-1} (NH$_2$). ^{13}C NMR: δ = 178.9(indole C-2), 150.7(pyran C-6), 141.3(pyran C-2), 141.9(indole C-7a), 134.8(indole C-3a), 118.6(CN), 110.2(pyran C-3), 51.2(spiro carbon), 137.5–122 (aromatic carbons). MS: *m/z* 341(M$^+$). Found: C, 70.49; H, 3.62; N, 16.44%. Calcd. for C$_{20}$H$_{12}$N$_4$O$_2$ C, 70.58; H, 3.55; N, 16.46%.

Compound **9a** formed yellow crystals from methanol. Yield 82%, m.p. 202°C. IR: ν = 3350–3150(br, OH and NH$_2$), 1720–1680 cm^{-1} (CO bands). ^{1}H NMR: δ = 1.3(t,3H,CH$_3$), 4.2(q,2H,CH$_2$), 6.7(s,br,2H,NH$_2$), and 6.8–7.9(m,8H, aromatic and OH protons). Found: C, 64.68; H, 4.62; N, 7.80%. Calcd. for C$_{19}$H$_{16}$N$_2$O$_5$ C, 64.77; H, 4.58; N, 7.95%.

Compound **9b** formed yellow crystals from ethanol. Yield 75%, m.p. 190°C. IR: ν = 3350–3100 (br,NH$_2$), 2200 (CN), 1670 cm^{-1} (CO). Found: C, 66.77; H, 3.52; N, 13.86%. Calcd. for C$_{17}$H$_{11}$N$_3$O$_3$ C, 66.88; H, 3.63; N, 13.76%.

Compound **12** formed colorless crystals from ethanol. Yield 55%, m.p. 240°C. IR: ν = 3420, 3320, 3180 (NH$_2$ and NH), 2220 cm^{-1} (CN). 1710–1690 (CO). Found: C, 66.38; H, 4.32; N, 14.0%. Calcd. for C$_{17}$H$_{13}$N$_3$O$_3$ C, 66.44; H, 4.26; N, 13.67%.



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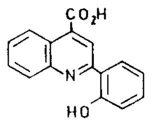

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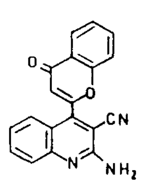

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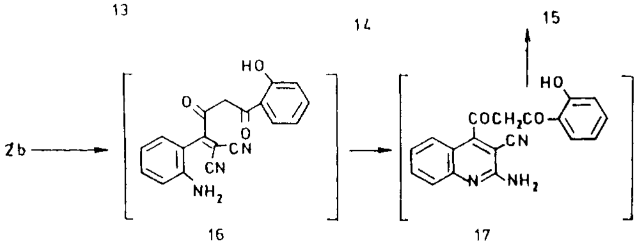

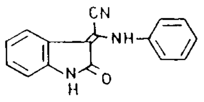

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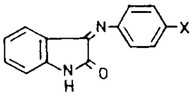

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	X
a	OCH$_3$
b	OH

Compound **14** formed yellow crystals from dioxan. Yield 75%, m.p. 245°C. IR: ν = 3400 (OH), 2290 (CH), 1690 cm^{-1} (CO), ^{1}H NMR: δ = 7.0–7.9 (m, 9H, aromatic and OH protons). MS: *m/z* 266(M$^+$). Found: C, 72.33; H, 4.32; N, 5.49%. Calcd. for C$_{16}$H$_{11}$NO$_3$ C, 72.45; H, 4.15; N, 5.28%.

Compound **15** formed orange crystals from ethanol. Yield 78%, m.p. 270°C. IR: ν = 3300 (NH$_2$), 2200 (CN), 1670 cm^{-1} (CO). MS: *m/z* 313 (M$^+$). Found: C, 72.74; H, 3.50; N, 13.49%. Calcd. for C$_{19}$H$_{11}$N$_3$O$_2$ C, 72.83; H, 3.54; N, 13.41%.

Compound **18** formed green crystals from DMF. Yield 82%, m.p. 280°C. IR: ν = 3300–3050 (br, NH groups), 2200 (CN), 1660 cm^{-1} (CO). Found: C, 73.69; H, 4.36; N, 16.20%. Calcd. for C$_{16}$H$_{11}$N$_3$O C, 73.55; H, 4.24; N, 16.08%.

Compound **19a** formed yellow crystals from ethanol. Yield 85%, m.p. 250°C. IR: ν = 3200 (NH), 1720 (CO), 1600 cm^{-1} (C=N). ^{1}H NMR: δ = 3.7 (s, 3H, OCH_3), 7.0–8.2 (m, 9H, aromatic and NH protons). ^{13}C NMR: δ = 163.7 (indole C-2), 157.2 (indole C-3), 146.9 (indole C-7a), 134.3 (indole C-3a), 55.3 (OCH_3), 154–111 (aromatic carbons). MS: *m/z* 253 (M$^+$). Found: C, 71.46; H, 5.06; N, 11.22%. Calcd. for $C_{15}H_{12}N_2O_2$ C, 71.42; H, 4.79; N, 11.10%.

Compound **19b** formed orange crystals from ethanol. Yield 82%, m.p. > 300°C. IR: ν = 3450–3250 (NH and OH), 1700 (CO), 1600 cm^{-1} (C=N). ^{13}C NMR: δ = 163.8 (indole C-2), 158.9 (indole C-3), 141.6 (indole C-7a), 134.0 (indole C-3a), 155–111 (aromatic carbons). MS: *m/z* 238 (M$^+$). Found: C, 70.34; H, 4.46; N, 11.75%. Calcd. for $C_{14}H_{10}N_2O_2$ C, 70.58; H, 4.23; N, 11.76%.

Synthesis of 10

A solution of **12** (2.0 g) in dioxane (20 mL) was treated with elemental sulfur (1.0 g) then with piperidine (0.5 mL). The reaction mixture was refluxed for 15 hours, then poured onto water. The solid product thus formed was collected by filtration and crystallized from dioxane.

Compound **10b** formed a brown powder. Yield 42%, m.p. > 300°C. IR: ν = 3500 (OH), 3430, 3380–3300 (NH_2 and NH), 2220 (CN), and 1700–1680 cm^{-1} (CO). Found: C, 66.88; H, 3.66; N, 13.52%. Calcd. for $C_{17}H_{11}N_3O_3$ C 66.88; H, 3.63; N, 13.76%.

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