# Nitriles in Heterocyclic Synthesis. A Novel Synthesis of Spiropyran-4-Ylindolidene Derivatives



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The structure of the products of reaction of 2-oxo-3-dicyanomethylidene-2,3-dihydroindole (**1a**) and 2-oxo-3-cyanoethoxycarbonylmethylidene-2,3-dihydroindole (**1b**) with the pyrazolin-5-one derivatives **2a,b** could be established via $^{13}$C nmr and high resolution $^1$H nmr to be the spiropyranylindolone derivatives **5a-d**.

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$\alpha,\beta$-Unsaturated nitriles are highly reactive reagents and their utility in heterocyclic synthesis has received considerable recent interest [1,2]. As a part of our program directed for development of new approaches for the synthesis of azoles [3] and azines [4] utilizing readily obtainable polyfunctional nitriles as starting materials, we have previously reported [5] that 2-oxo-3-dicyanomethylidene-2,3-dihydroindole (**1a**) and 2-oxo-3-cyanoethoxycarbonyl methylidene-2,3-dihydroindole (**1b**) reacted with the 2-pyrazolin-5-one derivatives **2a,b** and with 2-ethoxycarbonylmethyl-2-thiazolin-5-one (**3**) to yield the 4-azoloylquinoline derivatives **4** *via* ring opening and recyclization (*cf.* chart 1). Recently, the same results were republished by another group [6] who, perhaps, were unaware of our work. The quinoline structure **4** was assigned for the reaction products, in both papers, based on the presence of a signal at δ 8.5 ppm which was attributed for the quinoline H-5 and H-8. However, during inspection of the $^{13}$C nmr and the high resolution $^1$H nmr spectra of the reaction

Chart 1

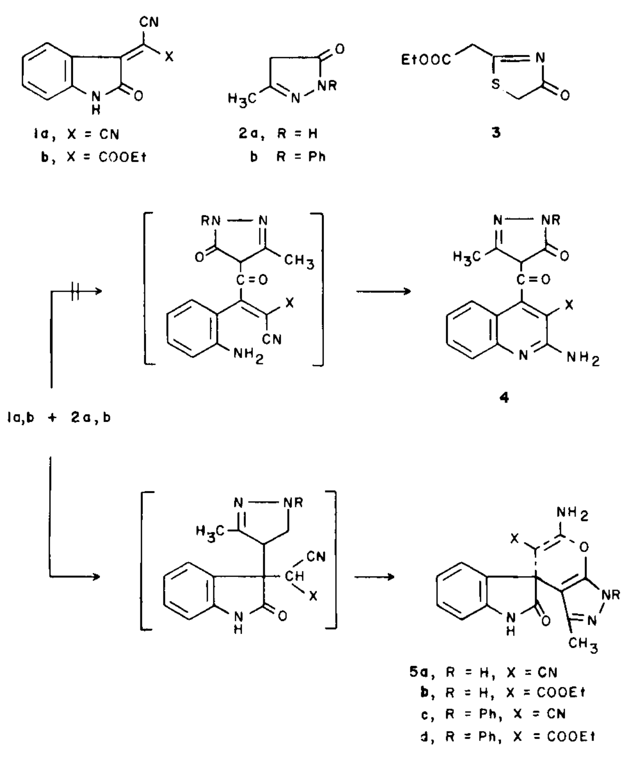


Chart 2

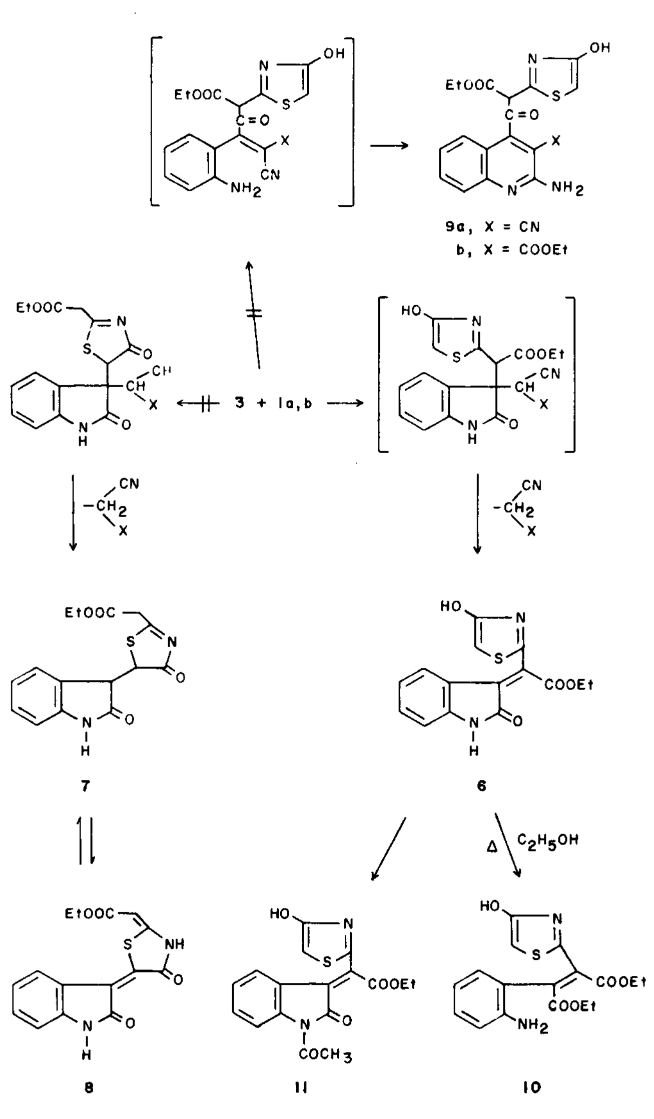

Table 1

Analytical Data of Compounds **5**, **6**, **10**, and **11**

| Compound colour | Crystallisation solvent | Mp. °C | Yield % | Molecular Formula Molecular Weight | Analysis (%) Found/required C | H | H |
|---|---|---|---|---|---|---|---|
| **5a** white | ethanol | 285-286 | 54 | $C_{15}H_{11}N_5O_2$ (293.13) | 61.3<br>61.4 | 4.1<br>3.7 | 23.9<br>23.8 |
| **5b** white | ethanol | 281-282 | 61 | $C_{17}H_{16}N_4O_4$ (340.13) | 59.9<br>60.0 | 4.3<br>4.7 | 16.3<br>16.4 |
| **5c** pale yellow | acetic acid | 219 | 59 | $C_{21}H_{15}N_5O_2$ (369.19) | 68.1<br>68.3 | 3.8<br>4.0 | 18.5<br>18.9 |
| **5d** yellowish white | ethanol | 235 | 65 | $C_{23}H_{20}N_4O_4$ (414.19) | 66.4<br>66.6 | 4.8<br>4.8 | 13.6<br>13.4 |
| **6** red | dioxan | 253-254 | 62 | $C_{15}H_{12}N_2O_4S$ (316.17) | 57.0<br>56.9 | 3.7<br>3.8 | 8.7<br>8.9 |
| **10** red | ethanol | 260-261 | 54 | $C_{17}H_{18}N_2O_5S$ (362.18) | 55.6<br>56.3 | 4.4<br>4.9 | 7.6<br>7.7 |
| **11** red | acetic acid | 276-277 | 55 | $C_{17}H_{14}N_2O_5S$ (358.18) | 56.4<br>56.9 | 3.8<br>3.9 | 7.6<br>7.8 |

products, which believed to be **4**, we discovered that this structure assignment was incorrect. In the present paper, we present data that establish new structures for the reactions products of **1a,b** with **2a,b** and with **3**.

The $^{13}C$ nmr of the products of reaction of **1a,b** with **2a,b** revealed a signal at $\delta$ 47.3 ppm for one $sp^3$ carbon that is not linked to any protons. The quinoline structure **4** does not have such a carbon atom. In addition, $^1H$ nmr revealed that the two protons signal at $\delta$ 8.5 ppm disappears on long stand with deuteriumoxide indicating that the two protons are not linked to the carbon atom. Moreover, the high resolution $^1H$ nmr spectra of the reaction products revealed that this signal is for two magnetically equivalent and non coupled protons, consequently, we excluded completely structure **4** as a possibility. Several other isomeric structures were thus considered. However, the spectral data seemed to be only intelligably interpretable for the spiropyranylindolone structure **5** (*cf.* experimental). It is of value to report here that the signals for the ester group of compounds **5b,d** appeared as triplet and quartet at $\delta$ 0.7 and $\delta$ 3.8 respectively, higher by about $\delta$ 0.4 ppm than the usual ester group signals. This shielding effect of the ester protons is due to the benzene ring pi-electrons over which the $OCH_2CH_3$ moiety is located in the most stable conformation.

Unexpectedly, it was found that the product of reaction of **3** with **1a** is identical with the reaction product of **3** with **1b** (both products melted at 253-254° and crystallized from dioxan) and the same product could be obtained on treatment of **3** with isatin under the same experimental conditions utilized to effect the reaction of **3** with **1a,b**. It was thus believed that the reaction product was formed *via* addition of **3** to the activated double bond in **1a,b** to form

Table 2

Spectroscopic Data of Compounds **5**, **6**, **10** and **11**

| Compound | IR [$cm^{-1}$] (selected bands) | $^1H$ NMR [ppm] |
|---|---|---|
| **5a** | 3350, 3145 (NH and $NH_2$), 2190 (CN), 1715, 1645 (CO and $\delta$ $NH_2$) | 1.8 (s, 3H, $CH_3$), 6.49 (s, 2H, $NH_2$), 7.0-7.2 (m, 4H, $C_6H_4$), 10.45 (s, br, 1H, pyrazole NH) |
| **5b** | 3400, 3295, 3100 (NH and $NH_2$), 3020, 2195 ($CH_3$), 1715 (ester CO), 1690, 1665, 1625 (CO) | 0.75 (t, 3H, $CH_3$), 1.65 (s, 3H, $CH_3$)$_3$, 3.8 (q, 2H, $CH_2$), 6.9-7.16 (m, 4H, $C_6H_4$), 7.9 (s, br, 2H, 2 $NH_2$), 10.6 (s, 1H, pyrazole NH) |
| **5c** | 3480, 3320, 3190 ($NH_2$), 3090 (arom CH), 2920 ($CH_3$), 2200 (CN), 1710, 1660 (CO) | 1.75 (s, 3H, $CH_3$), 3.15 (s, br, 2H, $NH_2$), 7.0-7.9 (m, br, 9H, arom CH) |
| **5d** | 3365, 3250 ($NH_2$), 3050 (arom CH), 2990 ($CH_3$), 1700 (ester CO), 1640 (CO), 1620 ($\delta$ $NH_2$) | 0.9 (t, 3H, $CH_3$), 1.85 (s, 3H, $CH_3$), 4.0 (q, 2H, $CH_2$), 7.3-7.95 (m, 9H, $C_6H_5$, $C_6H_4$), 8.3 (s, 2H, $NH_2$) |
| **6** | 3300, 3200, 3090 (OH and NH), 3000, 2900 (CH and $CH_3$), 1695 (ester CO), 1670 (CO), 1610 (C=C) | insoluble in commonly used $^1H$ nmr solvents |
| **10** | 3650, 3200 (OH and $NH_2$), 3055 arom CH, 2980 ($CH_3$), 1690 (ester CO) 1610 ($\delta$ $NH_2$) | 1.2 (m, 6H, 2 $CH_3$), 3.5 (s, br, 2H, $NH_2$ and $H_2O$), 4.15 (m, 4H, 2 $CH_2$), 5.7 (s, 1H, thiazole H-5), 6.8-7.5 (m, br, 4H, $C_6H_4$), 8.8 (s, 1H, OH) |
| **11** | 3190, 3080 (OH), 2970 ($CH_3$), 1690 (ester CO) and 1610 (C=C and C=N) | insoluble in commonly used $^1H$ nmr solvents |

Table 3

$^{13}$C NMR Data of Compounds **5** and **6**

| Compound | |
|---|---|
| **5a** | 178.0 (indole C-2), 162.5 (pyran C-2), 155.3 (pyran C-6), 141.4 (pyrazole C-3), 134.9 (indole C-7a), 132.6 (indole C-3a), 128.9 (indole C-4), 124.4 (indole C-5), 122.5 (indole C-6), 118.6 (cyano carbon), 109.7 (indole C-7), 95.4 (pyran C-5), 55.5 (pyran C-3), 47.3 (pyran C-4) and 8.9 (pyrazole $CH_3$ function) |
| **5b** | 179.7 (indole C-2), 168.2 (ester CO), 162.9 (pyran C-2), 154.4 (pyran C-6), 141.9 (pyrazole C-3), 136.6 (indole C-7a), 134.7 (indole C-3a), 127.2 (indole C-4), 122.6 (indole C-5), 121.6 (indole C-6), 108.7 (indole C-7), 97.1 (pyran C-5), 74.3 (pyran C-3), 58.6 (ester $CH_2$), 11.1 (ester $CH_3$) and 8.9 pyrazole $CH_3$ function) |
| **5c** | 177.5 (indole C-2), 161.1 (pyran C-2), 145.0 (pyran C-6), 144.0 (pyrazole C-3), 141.6 (indole C-7a), 137.3 (phenyl C-1), 132.1 (indole C-3a), 129.3 (indole C-4), 129.2 (phenyl C-3,5), 126.5 (phenyl C-4), 124.8 (phenyl C-2,6), 122.6 (indole C-5), 120.1 (indole C-6), 117.9 (cyano carbon), 109.8 (indole C-7), 96.4 (pyran C-5), 56.4 (Pyran C-3), 47.8 (pyran C-4) and 11.6 (pyrazole $CH_3$ function) |
| **5d** | 179.1 (indole C-2), 167.8 (ester CO), 161.2 (pyran C-2), 144.1 (pyran C-6), 143.8 (pyrazole C-3), 142.8 (indole C-7a), 137.3 (phenyl C-1), 135.7 (indole C-3a), 129.1 (phenyl C-3,5), 127.5 (phenyl C-4), 126.1 (phenyl C-2,6), 122.9 (indole C-4), 121.5 (indole C-5), 119.8 (indole C-6), 108.7 (C-7), 98.1 (pyran C-5), 74.6 (pyran C-3), 58.8 (ester $CH_2$), 47.4 (pyran C-3), 12.9 (pyrazole $CH_3$ function), and 11.5 (ester $CH_3$) |
| **6** | 168.7 (ester CO), 167.1 (indole C-2), 166.4 (thiazole C-4), 145.1 (thiazole C-2), 142.8 (indole C-7a), 134.5 (indole C-3), 131.1 (indole C-3a), 127.8 (indole C-5), 124.6 (indole C-6), 121.5 (indole C-4), 120.4 (ylidenic carbon), 110.0 (indole C-7), 91.9 (thiazole C-5), 59.5 (ester $CH_2$) and 14.2 (ester $CH_3$) |

the corresponding intermediate Michael adducts which then losses either malononitdrile or ethyl cyanoacetate to yield the final isolable product. Similar phenomena has been previously reported by us in the reaction of cinnamonitriles with azolones which leads to the formation of ylidene azolones [7-10]. Two structures seemed to be possible for the reaction product (*cf.* structures **6-8**, chart 2). The $^{13}$C nmr spectrum revealed that the reaction product is **6** and not **7** or its tautomeric **8**, as it revealed the absence of signals for the exocyclic $CH_2$ or CH carbons as required by structures **7** or **8**.

Product **6** underwent ring opening when refluxed with ethanol to yield the product **10** of mp 260-261° which was previously incorrectly reported [5] to be **9a**. On the other hand, when compound **6** was refluxed with acetic acid the *N*-acetylindolone derivative **11** of mp 276-277° could be isolated, which was also previously reported incorrectly [5] to be **9b**.

## EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded (potassium bromide) on a Pye Unicam Sp-100 spectrophotometer. The $^{1}$H nmr and $^{13}$C nmr spectra were measured on a Varian EM-390 spectrometer with DMSO as the solvent and TMS as the internal reference and chemical shifts are expressed as ppm. Mass spectra were recorded on a Masspectrometer MS 30 and MS 9 (AEI) 70 eV. Microanalytical data (C,H,N) were obtained from the Microanalytical Data Unit at Cairo University.

Compounds **1a,b** were prepared following the literature procedure [11].

The Reaction of 2-Oxo-2,3-dihydroindole Derivatives **1a,b** with **2a,b**. General Procedure.

A suspension of equimolar amounts (20 mmoles) of **1** and the appropriate 3-methyl-2-pyrazolin-5-one derivatives **2a,b** were refluxed in absolute ethanol (50 ml) in the presence of catalytic amount of triethylamine (3 drops) for one hour. The reaction mixture was then evaporated under reduced pressure and the remaining solid, so formed, was collected by filteration and crystallized from the appropriate solvent (*cf.* Tables 1, 2, and 3).

The Reaction of **1a,b** with 2-Ethoxycarbonylmethyl-2-thiazolin-4-one (**3**).

2-Ethoxycarbonylmethyl-2-thiazolin-4-one (**3**) was prepared following the literature procedure [13].

A solution of each of **1a,b** (20 mmoles) in absolute ethanol (70 ml) was treated with 2-ethoxycarbonylmethyl-2-thiazolin-4-one (**3**) (20 mmoles, 3.7 g). The reaction mixture was refluxed for two hours then evaporated *in vacuo*. The remaining product was triturated with water and the resulting solid product was collected by filteration (*cf.* Tables 1, 2, and 3).

Reactions of **6**.

(a) With Ethanol.

Compound **6** (20 mmoles) was refluxed with absolute ethanol (70 ml) for 1 hour. Then the reaction mixture was evaporated *in vacuo*. The remaining product was triturated with water and the solid product, so formed, was collected. (*cf.* Tables 1 and 2).

(b) With Glacial Acetic Acid.

Compound **6** (20 mmoles) was refluxed with glacial acetic acid (100 ml) for 1.5 hour. Then the reaction mixture was evaporated under reduced pressure and the solid product, so formed, was collected by filteration (*cf.* Tables 1 and 2).

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