Novel Synthesis of Furo[2,3-*b*]indole Derivatives

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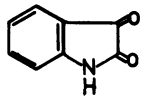
Isatin reacted with diethyl 3-amino-2-cyano-2-pentenedioate in ethanol and in presence of Et_3N to give 3-(1-amino-2-cyano-2-ethoxycarbonylethenyl-2*H*-furo[2,3-*b*]indol-2-one. The reaction of (2-oxo-3-indolinylidene)-malononitrile (**3a**) with the diethyl ester gave a mixture of diethyl 3-amino-4-(2-amino-3-cyano-4-quinolyl-carbonyl)-2-cyano-2-pentenedioate (80%) and diethyl 3-amino-4-(2-amino-3-cyano-3a*H*-furo[2,3-*b*]indol-3a-yl)-2-cyano-2-pentanedioate (20%). Treatment of **3a** and 3-[cyano(ethoxycarbonyl)]methylene-2-indolinone (**3b**) with 2-(ethoxycarbonylmethyl)-2-thiazolin-4-one gave the corresponding two pyrano[4′,5′-*c*] and furo[2″,3″-*b*]indole compounds, respectively. When **3a** and **3b** also reacted, with 3-methyl-2-pyrazolin-5-one or 3-methyl-1-phenyl-2-pyrazolin-5-one, the corresponding four spiro indoline-3,4′-(1′*H*)-pyrano[2, 3-*c*]pyrazol products were obtained. The reaction of **3b** with benzoylacetonitrile gave ethyl 2-amino-3a-[benzoyl(cyano)methyl]-3a*H*-furo[2,3-*b*]indole-3-carboxylate.

It is well known that indole itself and some of its derivatives are known to induce leuckaemia in rodents.[1] Polynuclear indoles are used as potential carcinogenic and/or leuckaemogenic.[2]

The present paper constitutes a study on a novel synthesis of these compounds involving condensation of nucleophiles with isatin or its ylidene derivatives. Treatment of isatin (**1**) with diethyl 3-amino-2-cyano-2-pentenedioate in the presence of triethylamine (Et_3N) as basic catalyst gave the corresponding 3-(1-amino-2-cyano-2-ethoxycarbonylethenyl)-2*H*-furo[2,3-*b*]indol-2-one (**2**) (through Knoevenagel condensation followed by cyclization).



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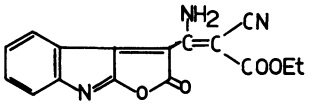
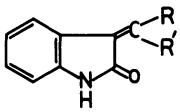
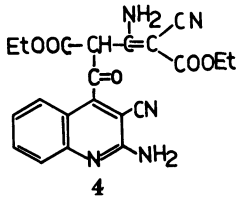


The structure of compound **2** has been confirmed by its IR absorption spectrum which showed broad band extending at 3300—3150 cm^{-1} (NH_2), at 2205 cm^{-1} (C≡N), at 1710, 1750 cm^{-1} (C=O of the ester and ring) and broad band extending at 3020—2900 cm^{-1} (CH_2, CH_3 stretches). The ^{1}H-NMR spectrum revealed the following signals: multiplet extending at δ 7.6—8.3 (m, 4H; aromatic protons), triplet at δ 2.2 (t, 3H, ester CH_3), quartet at δ 4.1 (q, 2H, ester CH_2), and singlet at δ 3.7 (s, 2H, NH_2). Similarly, treatment of (2-oxo-3-indolinylidene)malononitrile[3] (**3a**) with the diethyl ester in the presence of Et_3N produced a mixture of diethyl 3-amino-4-(2-amino-3-cyano-4-quinolylcarbonyl)-2-cyano-2-pentenedioate (**4**) (yield 80%) and diethyl 3-amino-4-(2-amino-3-cyano-3a*H*-furo[2,3-*b*]indol-3a-yl)-2-cyano-2-pentenedioate (**5**) (20% yield), respectively.



3a, R = R′ = CN
b, R = CN, R′ = COOEt



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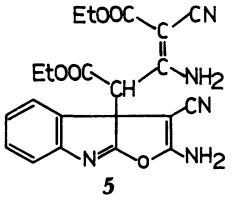

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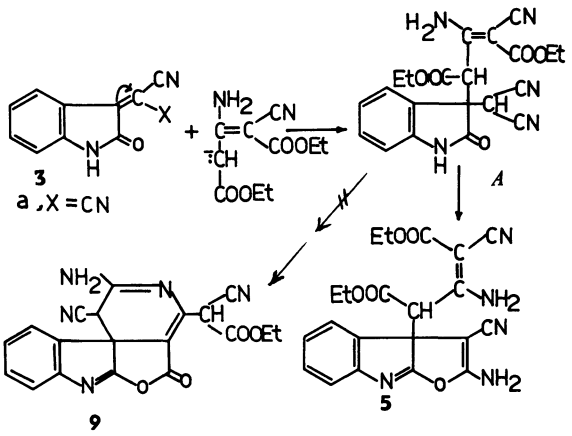
Formation of the quinoline derivative (**4**) may be rationalized in terms of a carbanion attack at the carbonyl carbon of (2-oxo-3-indolinylidene)malononitrile followed by ring opening and recyclization affording the structure **4** according to the mechanism discussed in a previous paper.[4] Compound **5** was suggested to be formed by the carbanion attack at the olefinic carbon of the ylidene followed by cyclization producing the final product (Scheme 1).

The assigned structure of compound **4** was based on its IR spectrum which showed broad band at 3300—3150 cm^{-1} (NH_2), 2250, 2200 cm^{-1} (C≡N), broad band extending at 1740—1700 cm^{-1} (C=O), and 3000—2950 cm^{-1} (CH_2, CH_3 stretches). Moreover, ^{1}H-NMR spectrum of compound **4** revealed singlet at δ 3.7 (s, 2H, NH_2), quartet at δ 4—4.4 (q, 4H for 2 ester CH_2), triplet at δ 1.2 (t, 3H ester CH_3); triplet at δ 1.5 (t, 3H, CH_3 of the other ester group), and multiplet extending at δ 6.9—7.5 (m, 5H, 4H aromatic protons and CH proton.[5] Further proof for the suggested structure was derived from its electronic spectrum which exhibits characteristic quinoline maxima at λ_{max}360 nm (log ε 4.88), 285 (5.32), and 235 (5.30),[6] although with some bathochromic shift due to substituent effects.

The assigned structure of compound **5** was inferred from its IR spectrum which showed broad band at 3300—3150 cm^{-1} for NH_2, at 2210 cm^{-1} for C≡N, a broad band at 1750—1710 cm^{-1} for C=O, and a broad band extending at 3010—2950 cm^{-1} for CH_2, CH_3 stretches. It may be suggested that the final separated product formed should be through the suggested intermediate structure **A** (Scheme 1). However, probable formation of **9** from **A** is excluded on bases of analytical data reported.



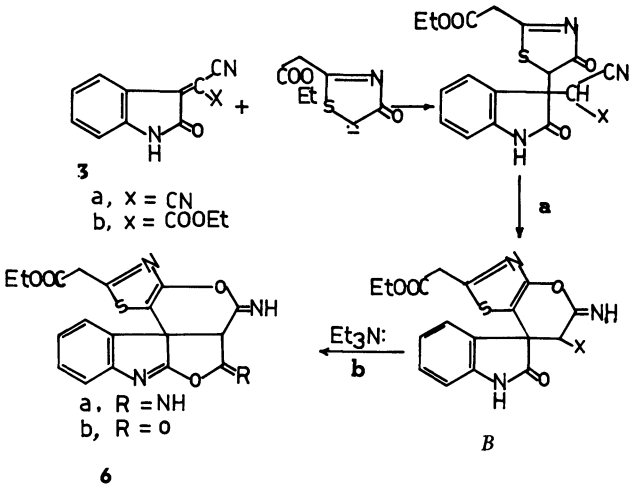
Scheme 1.

In the same manner, when **3a** and **3b** reacted with 2-(ethoxycarbonylmethyl)-2-thiazolin-4-one gave the corresponding compounds **6a** and **6b**, respectively. The formation of compounds **6a, b** was assumed to proceed via the attack of the carbanion nucleophile on the olefinic carbon of the ylidene, followed by the cycloaddition of highly acidic thiazole (OH) on the cyano group to form the suggested intermediate spiro compound (**B**) (Step a) followed by cycloaddition of the less acidic indole (OH) on the second cyano or the ester group to form the final isolated products, ethyl 5,6-diimino-thiazolo[4,5-*b*]pyrano[4′, 5′-*c*]furo[2″,3″-*b*]indole-2-acetate (**6a**) and ethyl 5-imino-thiazolo[4, 5-*b*]pyrano[4′,5′-*c*]furo[2″,3″-*b*]indole-6-one-2-acetate (**6b**), respectively (Step b) (Sheme 2). The suggested preliminary formation of intermediate spiro compound (**B**) although not separated in such mechanism had been proved through the separation of their analogues (**7a—d**) when cyclization proceeded in the absence of Et_3N which is discussed later.

The structure of compound **6a** agrees with its IR spectrum which showed broad band at 3200—3100 cm^{-1} NH), 3000—2900 cm^{-1} (CH_2, CH_3 stretches), 1700 cm^{-1} (C=O), and 1660 cm^{-1} (C=N-). Moreover, its ^{1}H-NMR spectrum in DMSO gives a clue for the assigned structure showing the following signals: triplet at δ 1.3 (t, 3H, ester CH_3), singlet at δ 2.8 (s, 2H, CH_2 group), quartet at δ 4—4.3 (q, 2H ester CH_2), singlet at δ 5.7 (s, 1H, CH proton), multiplet at δ 6.9—7.4 (m, 4H, aromatic protons), and two singlet at δ 8.1 and 9 (s, 2H, 2NH protons). The UV spectrum of **6a** in ethanol showed absorption bands at λ_{max} 425 nm (log ε 4.91), 270 (4.58), and 258 (3.76).

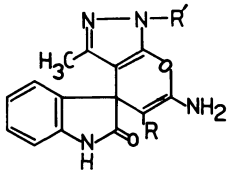
The IR spectrum of compound **6b** agrees well with the assigned structure which showed characteristic absorption bands at 3300, 3346 cm^{-1} (NH), 3000—2900 cm^{-1} (CH_2, CH_3 stretches), 1730, 1700 cm^{-1} (C=O ring and ester), and 1660 cm^{-1} (C=N). Its ^{1}H-NMR spectrum showed the following signals: triplet at δ 0.9 (t, 3H, ester CH_3), singlet at δ 2.7 (s, 2H, CH_2), quartet at δ 4.00 (q, 2H, ester CH_2), multiplet at δ 6.7—7.4 (m, 5H, CH proton and 4 aromatic protons), and singlet at δ 9.1 (s, 1H, NH proton). The UV spectrum of **6b** showed the following bands at λ_{max} 414nm (log ε 5.76), 279 (5.396), and 262 (5.98).

When **3a** or **3b** was treated with 3-methyl-2-pyrazolin-5-one or 3-methyl-1-phenyl-2-pyrazolin-5-one in ethanol or dioxane and in the absence of Et_3N, it gave the corresponding spiro products, namely, 6′-amino-5′-cyano-3′-methylspiro[indoline-3,4′(1′*H*)-pyrono[2,3-*c*]pyrazol]-2-one (**7a**); ethyl 6′-amino-3′-methyl-2-oxospiro[indoline-3, 4′(1′*H*)-pyrano[2,3-*c*]-pyrazole]-5′-carboxylate (**7b**), 6′-amino-5′-cyano-3′-methyl-1′-phenylspiro[indoline-3, 4′(1′*H*)-pyrano[2,3-*c*]-pyrazol]-2-one (**7c**), and ethyl 6′-amino-3′-methyl-2-oxo-1′-phenylspiro[indoline-3,4′(1′*H*)-pyrano[2,3-*c*]-pyrazole]-5′-carboxylate (**7d**) which is rationalized in terms of the addition of active methylene group on the olefinic double bond followed by cyclization on the same bases as in (Step a) of Scheme 2.



Scheme 2.

The structure of compound **7a** was confirmed by its IR spectrum which showed absorption bands at 3400, 3150 cm^{-1} (NH and NH_2), 2205 cm^{-1} (C≡N), at 1720 cm^{-1} (C=O), and 1650 cm^{-1} (C=N). Moreover, its ^{1}H-NMR spectrum in DMSO gave further confirmation which showed the following signals: singlet at δ 1.6 (s, 3H, CH_3 group), multiplet at δ 6.9—7.5 (m, 6H, 4H aromatic protons and NH_2 protons) and two singlets at δ 10.6 and 12.2 (s, 2H, 2NH proton) (Table 1). Similarly, ^{1}H-NMR spectra of **7b—d**, Table 1 showed the corresponding characteristic signals confirming its assigned structures.



7 a, R = CN; R′ = H
b, R = COOEt; R′ = H
c, R = CN; R′ = Ph
d, R = COOEt; R′ = Ph

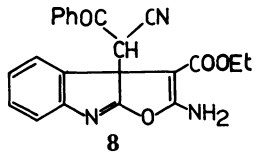
Table 1. UV, IR, and ^{1}H-NMR Spectral Measurements for the Compounds **7a—c**

Compound	UV spectra[a] λ_{max}/nm (log ε)	IR (KBr) ν/cm^{-1}	^{1}H-NMR (DMSO)[b,c] δ/ppm
7a	253 (4.18)	3400, 3150(NH, NH_2), 2205(C≡N), 1720(C=O), 1650(-C=N)	1.6(s, 3H, CH_3), 6.9—7.5(m, 6H, 4 aromatic protons, NH_2), 10.6, 12.2(s, 2H, 2NH)
7b	248.5(4.23)	3450, 3300(NH, NH_2), 1750, 1720 (C=O), 1630 (-C=N)	0.9(t, 3H, ester CH_3), 1.2(s, 3H, pyrazole CH_3), 4.0(q, 2H, ester CH_2), 6.9—7.8(m, 6H, 4 aromatic protons and NH_2), 10.8 (s, 2H, 2NH)
7c	246 (4.94)	3440, 3280, 3140(NH, NH_2), 2150 (C≡N), 1695(ring C=O), 1650(-C=N)	1.6(s, 3H, CH_3), 6.8—7.8(m, 11H aromatic and NH_2), 11(s, 1H, NH)
7d	248 (4.91)	3350, 3150(NH, NH_2), br 1720—1690 (ester and ring carbonyl)	1.1(t, 3H, ester CH_3), 1.6(s, 3H, CH_3), 4.1(q, 2H, CH_2), 6.9—7.8(m, 11H, aromatic and NH_2), 11(s, 1H, NH)

a) In absolute ethanol solvent. b) Dimethyl sulfoxide-d_6 solvent. c) s=Singlet, m=multiplet; q=quartet, t=triplet.

Treatment of **3b** with benzoylacetonitrile in ethanol and in the absence of Et_3N to give ethyl 2-amino-3a-[benzoyl(cyano)methyl]-3a*H*-furo[2,3-*b*]indole-3-carboxylate (**8**) (through an addition and cyclization mechanism on the same bases as that suggested in Scheme 1.

The structure of compound **8** was elucidated by its IR spectrum which showed broad band at 3500—3000 cm^{-1} for NH_2 group, 2205 cm^{-1} for CN, and 1740, 1710 cm^{-1} for C=O groups of ester and of ketone, respectively.



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The biological activity of the new compounds thus obtained is still under study and will be published elsewhere.

Experimental

Melting points are uncorrected. IR spectrum (KBr) were recorded on Shimadzu 408 Spectrophotometer. ^{1}H-NMR spectra were recorded on EM-390, 90 MHz and A-60, 60 MHz Spectrometer.

General Procedure. Isatin (0.1 mol) or its derivatives was treated under reflux in ethanol (40 ml) with 0.1 mol of the reagent in the presence of two drops of Et_3N/ and in the absence of Et_3N for 1 h, left to cool then filtered. The solid thus obtained was crystallized from the proper solvent.

3-(1-Amino-2-cyano-2-ethoxycarbonylethenyl)-2*H*-furo(2,3-*b*)-indol-2-one (2). It is obtained as red crystals from DMF, mp 270 °C; yield is ca. 60%. Found: C, 62.2; H, 3.5; N, 13.8%. Calcd for $C_{16}H_{11}N_3O_4$: C, 62.13; H, 3.55; N, 13.59%.

Diethyl 3-Amino-4-(2-amino-3-cyano-4-quinolylcarbonyl)-2-cyano-2-pentenedioate (4). It is formed as yellow crystals from acetone mp 258 °C; yield is ca; 80%. Found: C, 59.9; H, 4.4; N, 16.5%. Calcd for $C_{21}H_{19}N_5O_5$: C, 59.8; H, 4.5; N, 16.6%.

Diethyl 3-Amino-4-(2-amino-3-cyano-3a*H*-furo[2,3-*b*]indol-3a-yl)-2-cyano-2-pentenedioate (5). It is obtained by evaporation of the acetone mother liquor of the product **4** crystallization, then poured onto water to give a solid product which crystallized from dilute ethanol as brown crystals, mp 160 °C; yield is ca. 20%. Found: C, 59.80; H, 4.5; N, 16.4%. Calcd for $C_{21}H_{19}N_5O_5$: C, 59.85; H, 4.51; N, 16.6%.

Ethyl 5,6-Diimino-thiazolo[4,5-*b*]pyrano[4′,5′-*c*]furo[2″,3″-*b*]indole-2-acetate (6a). It is isolated as red crystals from DMF-H_2O, mp 300 °C, yield is ca. 80%. Found: C, 56.29; H, 3.5; N, 14.5%. Calcd for $C_{18}H_{14}N_4O_4S$: C, 56.51; H, 3.66; N, 14.65%.

Ethyl 5-Imino-thiazolo[4,5-*b*]pyrano[4′,5′-*c*]furo[2″,3″-*b*]indole-6-one-2-acetate (6b). It is formed as red crystals of mp 280 °C from DMF-H_2O, yield is ca. 70%. Found: C, 56.5; H, 3.5; N, 10.8%. Calcd for $C_{18}H_{13}N_3O_5S$: C, 56.39; H, 3.39; N, 10.96%.

6′-Amino-5′-cyano-3′-methylspiro[indoline-3,4′(1′*H*)-pyrano-[2,3-*c*]pyrazol]-2-one (7a). It is formed as colorless crystals from acetone, mp 275 °C; yield is ca. 70%. Found: C, 61.8; H, 4.0; N, 23.85%. Calcd for $C_{15}H_{11}N_5O_2$: C, 61.6; H, 3.75; N, 23.89%.

Ethyl 6′-Amino-3′-methyl-2-oxospiro[indoline-3,4′(1′*H*)-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (7b). It is obtained from acetone as colorless crystals of mp 212 °C; yield is ca. 72%. Found: C, 60.3; H, 4.6; N, 16.7%. Calcd for $C_{17}H_{16}N_4O_4$: C, 60.0; H, 4.7; N, 16.5%.

6′-Amino-5′-cyano-3′-methyl-1′-phenylspiro[indoline-3,4′(1′*H*)-pyrano[2,3-*c*]pyrazole]-2-one (7c). Obtained as colorless crystals from acetone, mp 220 °C, yield 70%. Found: C, 68.1; H, 3.9; N, 18.88%. Calcd for $C_{21}H_{15}N_5O_2$: C, 68.29; H, 4.06; N, 18.96%.

Ethyl 6′-Amino-3′-methyl-2-oxo-1′-phenylspiro[indoline-3,4′-(1′*H*)-pyrano[2,3-*c*]pyrazole]-5′-carboxylate (7d). It is isolated as pale yellow crystals from acetone, mp 205 °C; yield is ca. 83%. Found: C, 66.6; H, 5.0; N, 13.4%. Calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.8; N, 13.46%.

Ethyl 2-Amino-3a[benzoyl(cyano)methyl]-3a*H*-furo[2,3-*b*]indole-3-carboxylate (8). It is obtained as brown crystals from acetone, mp 218 °C, yield is 67%. Found: C, 68.6; H, 4.3; N, 10.69%. Calcd for $C_{22}H_{17}N_3O_4$: C, 68.2; H, 4.3; N, 10.8%.

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