THE SYNTHESIS OF HETEROCYCLES FROM INDOLIN-2-ONE DERIVATIVES AND ACTIVE METHYLENE REAGENTS*

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Indole and some of its derivatives have been reported to possess interesting biological activities (e.g. ref.[1]). In continuation to our research[2 – 5] it was interesting to investigate the synthesis of multifunctionalized heterocyclic spiro derivatives via the reaction of isatin, ethyl cyanoacetate and an other active methylene compound. The synthesis is realized as a one-pot reaction.

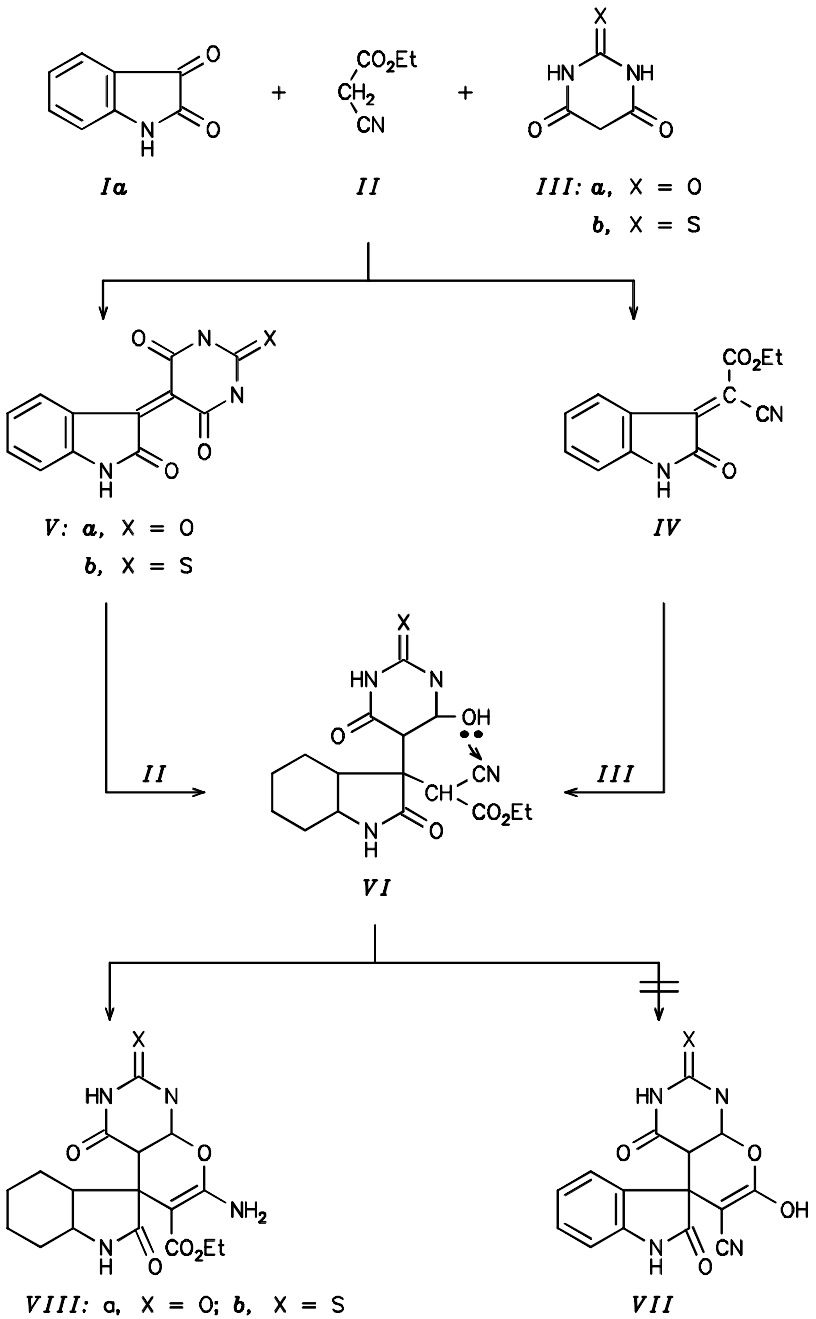
It has been found that refluxing of an ethanolic piperidine solution of equimolar ratios of isatin (*Ia*), ethyl cyanoacetate (*II*) and barbituric acid (*IIIa*) or thiobarbituric acid (*IIIb*) afforded a solid product whose structure was assumed, in accordance with elemental analysis and IR and ^{1}H NMR spectra, to be *VIIIa* and *VIIIb* (Scheme 1).

Confirmation of the structures *VIIIa* and *VIIIb* follows from their preparation from compound *IV*, synthesized separately, and barbituric acids *IIIa* and *IIIb* in 1 : 1 molar ratio under the same reaction conditions.

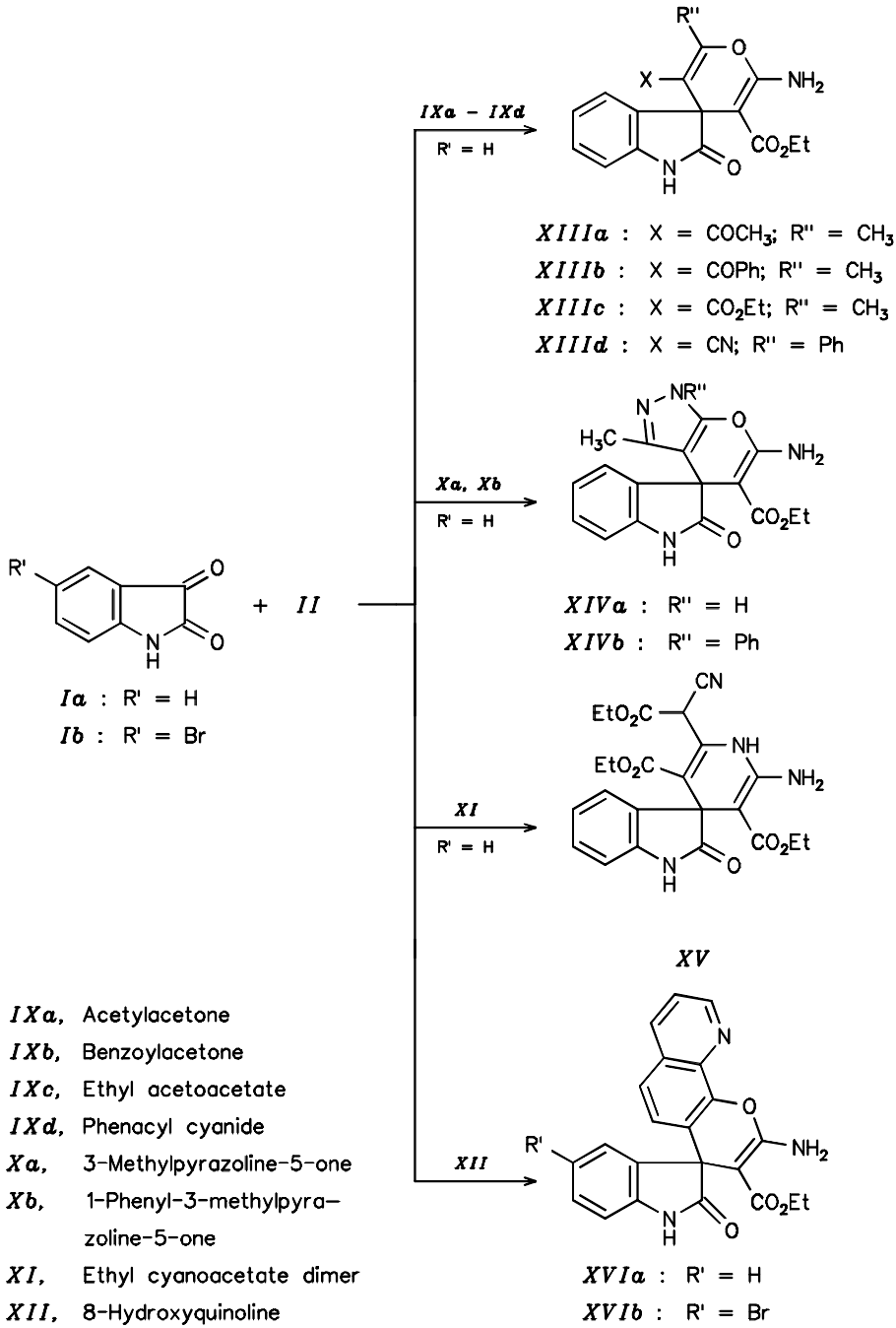
Further condensation reactions were carried out under the same experimental conditions (Scheme 2). Isatin (*Ia*), ethyl cyanoacetate (*II*) and active methylene compounds *IX – XI* afforded spiropyran-4-yl indolidene derivatives *XIII*; spiro[indoline-3,4′(1*H*)-pyrano[2,3-*c*]pyrazol]-2-one derivatives *XIVa* and spiropyridin-4-yl indolidene derivative *XV*. Structures *XIII – XV* were proven by an independent synthesis by reaction of the compound *IV* with the appropriate active methylene compound *IX – XII* under the same reaction conditions.

Although it has been reported that certain ethyl arylidenecyanoacetate derivatives could not react with 8-hydroxyquinoline[6], we found that the condensation of the isatines *I*, ethyl cyanoacetate (*II*) and 8-hydroxyquinoline (*XII*) had afforded the corresponding spiro compounds *XVIa* and *XVIb* (Scheme 2).

* Part 7; Part 6 see ref.[4].



SCHEME 1


IXa – IXd
R' = H
XIIIa : X = COCH3; R'' = CH3
XIIIb : X = COPh; R'' = CH3
XIIIc : X = CO2Et; R'' = CH3
XIIId : X = CN; R'' = Ph
Xa, Xb
R' = H
XIVa : R'' = H
XIVb : R'' = Ph
+ II
Ia : R' = H
Ib : R' = Br
XI
R' = H
XV
XII
IXa, Acetylacetone
IXb, Benzoylacetone
IXc, Ethyl acetoacetate
IXd, Phenacyl cyanide
Xa, 3-Methylpyrazoline-5-one
Xb, 1-Phenyl-3-methylpyrazoline-5-one
XI, Ethyl cyanoacetate dimer
XII, 8-Hydroxyquinoline
XVIa : R' = H
XVIb : R' = Br

SCHEME 2

EXPERIMENTAL

All melting points are uncorrected. IR spectra (ν, cm^{-1}) were recorded in the KBr pellet on a Shimadzu-470 spectrophotometer. ^1H NMR spectra (δ, ppm) were measured on a Varian EM-390 spectrophotometer (90 MHz) in CD_3SOCD_3 solutions using tetramethylsilane as an internal standard. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University. Compound *IV* was prepared according to the described procedure[7], m.p. 215 °C (ethanol).

Sythesis of *VIIIa*, *VIIIb*, *XIIIa – XIIId*, *XIVa*, *XIVb*, *XV*, *XVIIa*, *XVIIb*. General Procedure

Method A. An equimolar (0.01 mol) mixture of each of isatin, ethyl cyanoacetate and active methylene compound *IIIa*, *IIIb*, *IXa – IXd*, *Xa*, *Xb*, *XI* or *XII* in ethanol (50 ml) was treated with piperidine (0.1 ml). The reaction mixture was heated for 3 – 5 h, the product separated or it was obtained after concentration and trituration with cold water. The products were collected by filtration, dried and recrystallized from an appropriate solvent.

Method B. An equimolar mixture of *IV* and active methylene compound *IIIa*, *IIIb*, *IXa – IXd*, *Xa*, *Xb*, *XI* or *XII* in ethanol (50 ml) was treated with piperidine (0.1 ml). The reaction mixture was heated for 3 – 6 h and worked up as described in method *A*.

7′-Amino-6′-ethoxycarbonyl-4′-hydroxy-2′-oxospiro-
[indoline-3,5′(1*H*)-pyrano[2,3-*d*]pyrimidin]-2-one (*VIIIa*)

Yellow crystals from ethanol, yield 90%. M.p. 260 °C (dec.). IR spectrum: 3 300 – 3 100 (OH, NH, NH_2); 1 730 (ester CO). ^1H NMR spectrum: 1.68 t, 3 H (CH_3); 2.60 q, 2 H (CH_2); 6.94 – 7.97 m, 6 H (arom. + NH_2). For $C_{17}H_{14}N_4O_6$ (370.3) calculated: 55.13% C, 3.81% H, 15.13% N; found: 55.18% C, 3.76% H, 15.14% N.

7′-Amino-6′-ethoxycarbonyl-4′-hydroxy-2′-mercaptospiro-
[indoline-3,5′(1*H*)-pyrano[2,3-*d*]pyrimidin]-2-one (*VIIIb*)

Brown crystals from ethanol, yield 80%. M.p. > 300 °C. IR spectrum: 3 300 – 3 100 (OH, NH, NH_2); 1 730 (ester CO). For $C_{17}H_{14}N_4O_5S$ (386.4) calculated: 52.84% C, 3.65% H, 14.50% N; 8.30% S; found: 52.89% C, 3.60% H, 14.46% N, 8.34% S.

5′-Acetyl-2′-amino-3′-ethoxycarbonyl-6′-methylspiro-
[indoline-3,4′(1*H*)-pyran]-2-one (*XIIIa*)

Pale yellow crystals from ethanol, yield 72%. M.p. 232 °C. IR spectrum: 3 350, 3 150 (NH, NH_2); 1 730 (ester CO); 1 675 (acetyl CO). For $C_{18}H_{18}N_2O_5$ (342.3) calculated: 63.15% C, 5.30% H, 8.18% N, found: 63.20% C, 5.29% H, 8.15% N.

2′-Amino-5′-benzoyl-3′-ethoxycarbonyl-6′-methylspiro[indoline-3,4′(1*H*)-pyran]-2-one (*XIIIb*)

Colourless crystals from ethanol, yield 70%. M.p. 236 – 238 °C. IR spectrum: 3 300, 3 250, 3 200, 3 100 (NH, NH_2); 1 720 (ester CO); 1 680 (benzoyl CO). For $C_{23}H_{20}N_2O_5$ (404.4) calculated: 68.30% C, 4.99% H, 6.93% N; found: 68.27% C, 5.00% H, 6.88% N.

2′-Amino-3′,5′-diethoxycarbonyl-6′-methylspiro[indoline-3,4′(1*H*)-pyran]-2-one (*XIIIc*)

Pale yellow crystals from ethanol, yield 75%. M.p. 176 °C. IR spectrum: 3 350, 3 200 (NH, NH_2); 1 730 (ester CO). ^{1}H NMR spectrum: 0.57 – 0.97 tt, 6 H (2 CH_3); 2.06 s, 3 H (CH_3); 3.66 – 3.94 qq, 4 H (2 CH_2); 6.94 – 8.05 m, 6 H (arom. + NH_2). For $C_{19}H_{20}N_2O_6$ (372.4) calculated: 61.28% C, 5.41% H, 7.52% N; found: 61.24% C, 5.45% H, 7.57% N.

2′-Amino-5′-cyano-3′-ethoxycarbonyl-6′-phenylspiro[indoline-3,4′(1*H*)-pyran]-2-one (*XIIId*)

Pale buff crystals from ethanol, yield 70%. M.p. 205 – 207 °C. IR spectrum: 3 400, 3 300, 3 200 (NH, NH_2); 2 200 (CN); 1 730 (CO). For $C_{22}H_{17}N_3O_4$ (387.4) calculated: 68.21% C, 4.42% H, 10.85% N; found: 68.25% C, 4.38% H, 10.80% N.

6′-Amino-5′-ethoxycarbonyl-3′-methylspiro[indoline-3,4′(1*H*)-pyrano[2,3-*c*]pyrazol]-2-one (*XIVa*)

Buff crystals from ethanol, yield 85%. M.p. 284 – 286 °C (ref.[8] gives 285 – 286 °C). IR spectrum: 3 400, 3 150 (NH, NH_2); 1 730 (ester CO). ^{1}H NMR spectrum: 0.85 t, 3 H (ester CH_3); 1.23 s, 3 H (pyrazole CH_3); 3.83 q, 2 H (ester CH_2); 6.72 – 7.42 m, 6 H (arom. + NH_2); 11.53 s, 1 H (NH); 11.80 s, 1 H (NH). ^{13}C NMR spectrum: 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), 8.9 (pyrazole CH_3). For $C_{17}H_{16}N_4O_4$ (340.3) calculated: 59.99% C, 4.74% H, 16.46% N; found: 60.04% C, 4.70% H, 16.44% N.

6′-Amino-5′-ethoxycarbonyl-3′-methyl-1′-phenylspiro-[indoline-3,4′(1*H*)-pyrano[2,3-*c*]pyrazol]-2-one (*XIVb*)

Buff crystals from ethanol, yield 70%. M.p. 232 – 234 °C (dec.) (ref.[8] gives 235 °C). IR spectrum: 3 300, 3 200 (NH, NH_2); 1 730 (ester CO). ^{1}H NMR spectrum: 0.77 t, 3 H (ester CH_3); 1.6 s, 3 H (pyrazole CH_3); 3.73 q, 2 H (ester CH_2); 6.73 – 8.20 m, 11 H (arom. + NH_2); 11.4 s, 1 H (NH). ^{13}C NMR spectrum: 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 (indole C-7), 98.1 (pyran C-5), 74.6 (pyran C-3), 58.8 (ester CH_2), 47.4 (spiro carbon), 12.9 (pyrazole CH_3), 11.5 (ester CH_3). For $C_{23}H_{20}N_4O_4$ (416.4) calculated: 66.33% C, 4.84% H, 13.46% N; found: 66.30% C, 5.80% H, 13.42% N.

2′-Amino-3′,5′-diethoxycarbonyl-6′-cyano(ethoxycarbonyl)methylspiro-[indoline-3,4′(1*H*)-pyridin]-2-one (*XV*)

Orange crystals from ethanol, yield 90%. M.p. 196 – 197 °C. IR spectrum: 3 350 – 3 150 (NH, NH_2); 2 200 (CN); 1 740, 1 720 (esters, CO). ^{1}H NMR spectrum: 1.10 – 1.31 ttt, 9 H (3 CH_3); 3.97 – 4.26 qqq, 6 H (3 CH_2); 5.77 s, 1 H (CH); 7.14 – 7.86 m, 6 H (arom. + NH_2). For $C_{23}H_{24}N_4O_7$ (468.4) calculated: 58.97% C, 5.16% H, 11.96% N; found: 58.91% C, 5.20% H, 11.97% N.

9′-Amino-8′-ethoxycarbonylspiro[indoline-3,7′(1*H*)-pyrano[3,2-*h*]quinolin]-2-one (*XVIa*)

Colourless crystals from dimethylformamide–ethanol, yield 75%. M.p. 279 – 280 °C. IR spectrum: 3 400 – 3 200 (NH, NH_2); 1 730 (ester CO). ^{13}C NMR spectrum: 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), 129 – 122

(arom.), 109.4 (pyran C-3), 58.9 (ester CH_2), 50.7 (spiro carbon), 13.3 (CH_3). For $C_{22}H_{17}N_3O_4$ (387.4) calculated: 68.21% C, 4.42% H, 10.85% N; found: 68.25% C, 4.40% H, 10.81% N.

9′-Amino-5-bromo-8′-ethoxycarbonylspiro-
[indoline-3,7′(1H)-pyrano[3,2-*h*]quinolin]-2-one (*XVIb*)

Grey crystals from ethanol, yield 67%. M.p. 266 – 268 °C. IR spectrum: 3 300 – 3 200 (NH, NH_2); 1 730 (ester CO). For $C_{22}H_{16}N_3O_4Br$ (466.3) calculated: 56.67% C, 3.46% H, 9.01% N; found: 56.62% C, 3.50% H, 8.98% N.

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