Heterocycles [*c*]-Fused onto Indoloquinoxaline. Synthesis of Novel Pyrano[2',3':4,5]indolo[2,3-*b*]quinoxalin-2-ones

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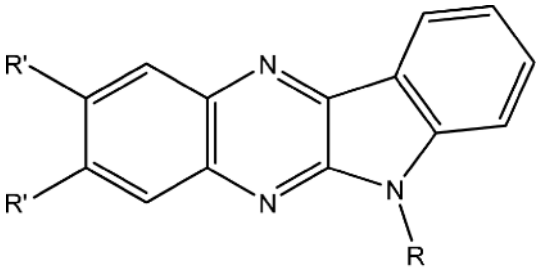
A synthesis of 4-methylpyrano[2,3-*e*]indole-2,8,9-trione (**5**) is achieved from 7-amino-4-methylcoumarin by adopting the classical Sandmeyer methodology. The cyclocondensation reaction of pyrano-isatin **5** with the appropriately substituted *o*-phenylenediamines **6** in polyphosphoric acid proceeded regioselectively to furnish the respective pyrano[2',3':4,5]indolo[2,3-*b*]quinoxalines **7a** – **c**. Structural assignments of the new compounds are based on microanalytical and spectral (IR, MS and NMR) data.

Key words: 7-Aminocoumarin, Regioselective Cyclization, Pyrano[2,3-*e*]indole-2,8,9-trione, *o*-Phenylenediamines, Cyclocondensation

Introduction

The parent 6*H*-indolo[2,3-*b*]quinoxaline system **1** (Fig. 1), an analog of the cytotoxic agent ellipticine, had been first synthesized in 1895 [1] *via* cyclocondensation of isatin with *o*-phenylenediamine. Following this versatile route, several derivatives of **1** were prepared and intensely studied [2 – 16]. Derivatives of this tetracyclic heteroaromatic system are important DNA interchelators [5 – 8], some of which display antitumor activity [5 – 7], while others are useful agents for the treatment of autoimmune disease [9] and multiple sclerosis [10]. Certain derivatives with basic appendages at the *N*(6)-position, such as **2** [8] (Fig. 1), exhibit potent antiviral activity [11 – 14] against *e. g.*, *herpes simplex* virus type 1 (HSV-1), *cytomegalo* virus (CMV) and *vericella-zoster* virus (VZV). Compound **2** (referred to as B-220) and its congeners are believed to act *via* inhibition of the decapsidation process of the virus [11 – 16].

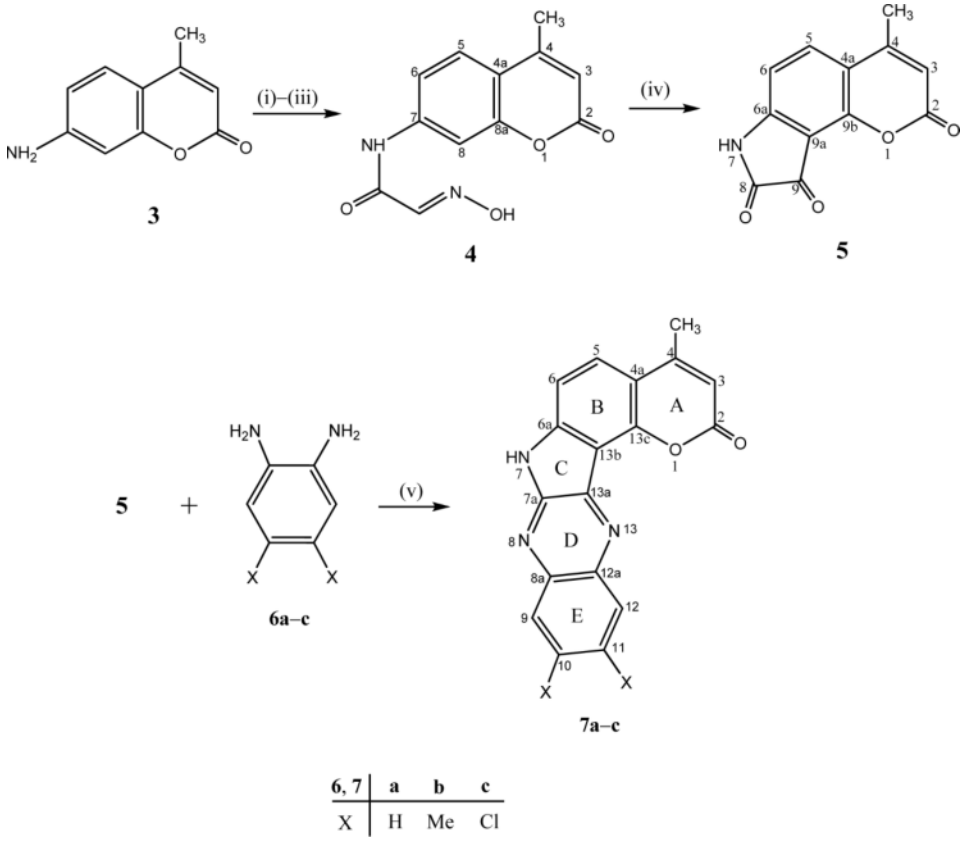
In the present study, we wish to report on the synthesis of indolo[2,3-*b*]quinoxalines condensed with 2-pyranone, exemplified by **7a** – **c** as shown in Scheme 1.



1 (R = R' = H)
2 (R = $CH_2CH_2NMe_2$; R' = Me)

Fig. 1. Model indolo[2,3-*b*]quinoxalines.

These hybrid pentacyclic heterocycles might have potential bioactivity arising from the combination of bioactive entities of which the coumarin system (benzo[*b*]pyran-2-one/rings A, B) constitutes an integral part. It is noteworthy that coumarins are widely distributed in nature, found in various parts of plants and make up an important part of human diet [17 – 19]. Besides, coumarin derivatives exhibit good cell permeability, have been shown to be tolerated physiologi-



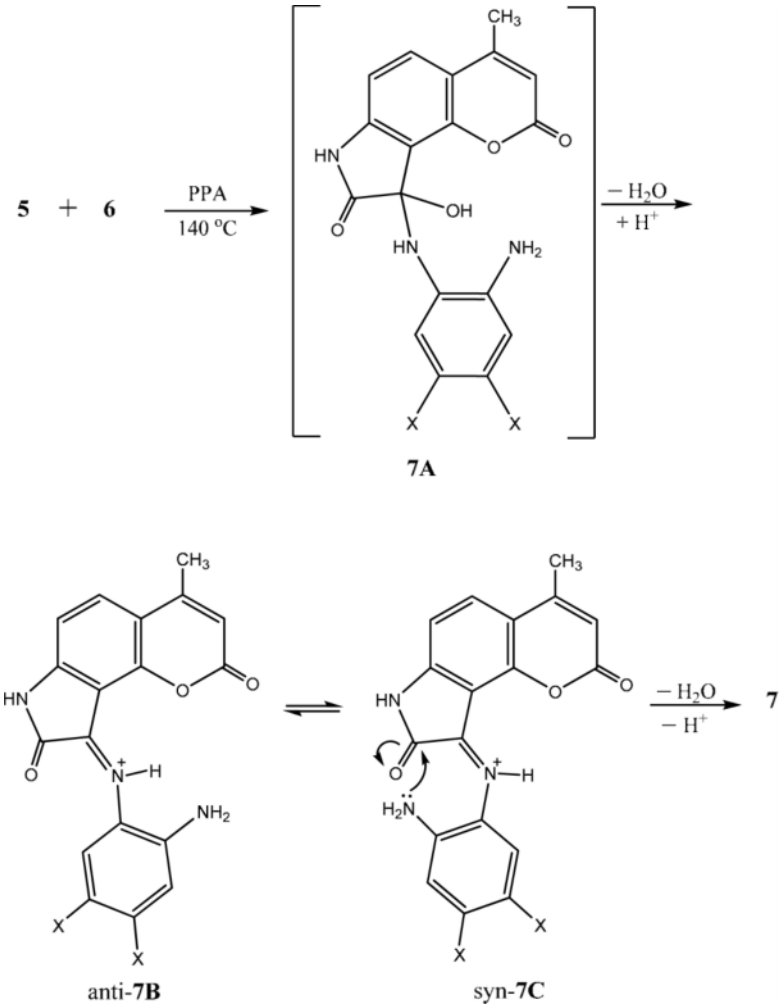
Scheme 1. (i) 4 % aq. HCl; (ii) $Cl_3CCH(OH)_2 \cdot H_2O/Na_2SO_4$; (iii) $NH_2OH \cdot HCl$; (iv) 95 % H_2SO_4, 90 °C, 2 h; (v) PPA (polyphosphoric acid), 140 °C, 2 h.

cally, and possess a broad range of pharmacological properties, including anti-coagulant, anti-tumor, and anti-inflammatory activities [20].

Results and Discussion

4-Methylpyrano[2,3-*e*]indole-2,8,9(7*H*)-trione (**5**), a pyrano-isatin which served as key intermediate, is prepared from 7-amino-4-methylcoumarin (**3**), using the classical Sandmeyer methodology [21 – 28] (Scheme 1). Thus, interaction of compound **3**, accessible from *m*-aminophenol [29, 30], with chloral hydrate and hydroxylamine hydrochloride produced the respective isonitroso derivative **4**. Subsequent regioselective intramolecular cyclization (at the C-8 locus) in conc. H_2SO_4 furnished the desired derivative **5** in 65 % overall yield. Recently, a pyrano[3,2-*e*]indole-1,2,7(3*H*)-trione has been prepared [31] from 6-aminocoumarin by a similar Sandmeyer methodology; the former pyranoindole, an unmethylated isomer of **5**, represents the first coumarin-based tricyclic condensed system with an isatin moiety. Cyclocondensation of the presently synthesized trione **5** with an appropriately substituted *o*-phenylenediamine **6** in polyphosphoric acid (PPA) at 140 °C afforded the corresponding target pyrano[2',3':4,5]indolo[2,3-*b*]quinoxalin-2-ones (**7a – c**) (Scheme 1). The production of compounds of type **7** is initiated by the formation of the intermediate carbinolamine **7A** (Scheme 2) which suffers dehydration to produce the corresponding pyrano-isatin-9-imine (*anti*-**7B**). This latter imine derivative is presumed to undergo facile *anti-syn* isomerization upon protonation; the cyclocondensation of the *syn*-isomer **7C**, involving the suitably located amino and lactam carbonyl groups, delivers the desired pentacyclic system **7**.

The IR, MS and NMR spectral data and microanalyses for the new compounds **4**, **5** and **7** are in



Scheme 2.

accordance with their assigned structures; details are given in the Experimental Section. Thus, the mass spectra display the correct molecular ion peaks for which the measured high-resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC, HMBC) experiments showed correlations that helped in the ^{1}H and ^{13}C signal assignments of most of the different carbons and their attached/neighboring hydrogens. Long-range correlations for compound **4** are observed between 5-H and each of C-7, C-8a and C-4, between 6-H and each of C-8 and C-4a, between 3-H and C-4a, as well as between the CH_3 protons and each of C-3 and C-4a. Long-range correlations for compound **5** are observed between 5-H and each of C-6a, C-9b and C-4, between 6-H and each of C-4a and C-9a, as well as between CH_3 protons and each of C-3 and C-4a. For compounds **7a**–**c**, long-range correlations are also observed between 3-H and C-4a, 5-H and C-4/C-13c, 6-H and C-4a/C-13b, 9-H and C-12a/C-11, as well as between 12-H and C-8a/C-10. However, the δ values for each of the carbon pairs 8a/12a, 9/12 and 10/11, and their attached protons 9/12 and 10-CH_3/11-CH_3 (belonging to the quinoxaline ring E in **7a**–**c**), could not be assigned with certainty and are given as interchangeable.

Experimental Section

The following chemicals, used in this study, were purchased from Acros and were used as received: Chloral hy-

drate, 3-aminophenol, methoxycarbonyl chloride, hydroxylamine hydrochloride, polyphosphoric acid [84 % phosphorus (as P_2O_5)]. IR spectra were recorded from KBr discs on a Nicolet Impact-400 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III). Chemical shifts are expressed in ppm (δ units), with TMS as internal standard; J values for ^{1}H-^{1}H coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were acquired (in positive or negative mode) using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker Apex-4 (7-Tesla) instrument. The samples were dissolved in acetonitrile, diluted in spray solution (methanol-water 1 : 1 v/v + 0.1 % formic acid) and infused using a syringe pump with a flow rate of 2 μL. min^{-1}. External calibration was conducted using arginine cluster in a mass range m/z =175 – 871. Elemental analyses were performed on a Euro Vector elemental analyzer, model EA 3000.

*7-Amino-4-methylcoumarin (**3**)*

This compound, required in the present study, was prepared according to a literature procedure [29, 30] which involves interaction of *m*-aminophenol with methoxycarbonyl chloride as the initial step; the resulting *N*-protected *m*-aminophenol underwent cyclocondensation upon reaction with ethyl acetoacetate and conc. sulfuric acid, followed by removal of the *N*-protecting group (*via* treatment with sodium hydroxide) to deliver the title compound; m. p. 225 – 226 °C (lit. [29, 30]: m. p. 226 – 227 °C).

*2-(Hydroxyimino)-N-(4-methyl-2-oxo-2H-chromen-7-yl) acetamide (**4**)*

Crystalline sodium sulfate (36 g), a hot solution of 7-amino-4-methylcoumarin (**3**) (3.5 g, 20 mmol) in 4 % aqueous hydrochloric acid (25 mL), and a solution of hydroxylamine hydrochloride (4.6 g, 66 mmol) in water (10 mL) were added successively to a solution of chloral hydrate (3.3 g, 20 mmol) in water (10 mL). Thereafter, the reaction mixture was refluxed with continuous stirring for 4 h, and the resulting solution was filtered while hot. The precipitated product was collected by suction filtration, washed with cold water and dried. Yield: 4.5 g (92 %); m. p. 216 – 218 °C. – IR (KBr): ν = 3286, 3179, 3136, 3109, 2928, 1690, 1621, 1589, 1535, 1395, 1357, 1229, 1149, 1072, 1007, 922, 846 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.43 (s, 3H, 4-C*H*$_3$), 6.28 (s, 1H, 3-H), 7.66 (dd, J = 8.7, 2 Hz, 1H, 6-H), 7.69 (s, 1H, N=C*H*), 7.73 (d, J = 8.7 Hz, 1H, 5-H), 7.84 (d, J = 2 Hz, 1H, 8-H), 10.62 (s, 1H, N-H/exchangeable with D$_2$O), 12.32 (s, 1H, O-H/exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 18.4 (4-CH$_3$), 106.8 (C-6), 113.0 (C-3), 115.9 (C-4a), 116.3 (C-8), 126.3 (C-5), 142.2 (C-7), 144.3 (-C=N), 153.5 (C-8a), 154.0 (C-4), 160.4 (C-2), 161.3 (O=C-NH). – $C_{12}H_{10}N_2O_4$ (246.22): calcd. C 58.54, H 4.09, N 11.38; found C 58.39, H 4.03, N 11.26. – HRMS ((−)-ESI): m/z = 245.05676 (calcd. 245.05623 for $C_{12}H_9N_2O_4$, [M–H]$^-$).

*4-Methylpyrano[2,3-e]indole-2,8,9(7H)-trione (**5**)*

Compound **4** (2.46 g, 10 mmol) was added portion-wise to 95 % sulfuric acid (25 mL) at ~55 °C with stirring. Thereafter, the temperature of the reaction mixture was raised to 90 °C and maintained there for 2 h. The resulting solution was then cooled to r. t., treated with crushed ice (200 g), and allowed to stand overnight. The precipitated brown product was filtered, washed successively with hot water (4 × 30 mL), cold methanol (10 mL), and dried. Yield: 0.8 g (35 %); m. p. 325 – 328 °C. – IR (KBr): ν = 3464, 3191, 3088, 3054, 2989, 1765, 1719, 1629, 1586, 1388, 1326, 1270, 1221, 1163, 1083, 892, 862 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.39 (s, 3H, 4-C*H*$_3$), 6.30 (s, 1H, 3-H), 6.86 (d, J = 8.3 Hz, 1H, 6-H), 7.97 (d, J = 8.3 Hz, 1H, 5-H), 11.43 (s, 1H, N-H/exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 18.8 (4-CH$_3$), 105.1 (C-9a), 108.8 (C-6), 112.2 (C-3), 115.7 (C-4a), 136.4 (C-5), 150.4 (C-6a), 154.0 (C-4), 154.1 (C-9b), 159.1 (C-2), 159.8 (C-8), 180.0 (C-9). – $C_{12}H_7NO_4$ (229.19): calcd. C 62.89, H 3.08, N 6.11; found C 62.67, H 3.03, N 6.02. – HRMS ((+)-ESI): m/z = 252. 02673 (calcd. 252.02728 for $C_{12}H_7NO_4Na$, [M+Na]$^+$).

*7H-4-Methylpyrano[2',3':4,5]indolo[2,3-b]quinoxalin-2(2H)-one (**7a**)*

A stirred suspension of *o*-phenylenediamine (**6a**) (1.1 g, 1 mmol) and **5** (2.3 g, 1 mmol) in PPA (20 g) was heated at 135 – 140 °C (oil bath) for 2 h. After cooling to room temperature, the reaction mixture was poured, with stirring, onto crushed ice (60 g). The resulting brown precipitate was collected under suction, washed successively with water, ethanol and diethyl ether, and dried. Yield: 1.9 g (63 %); m. p. > 360 °C. – IR (KBr): ν = 3426, 3276, 3114, 2976, 1710, 1605, 1466, 1384, 1309, 1211, 1129, 1078, 1046, 907, 843 cm^{-1}. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 2.50 (s, 3H, 4-C*H*$_3$), 6.37 (s, 1H, 3-H), 7.55 (d, J = 8.3 Hz, 1H, 6-H), 7.79 (dd, J = 7.7, 8.0 Hz, 1H, 10-H or 11-H), 7.85 (dd, J = 8.0, 7.7 Hz, 1H, 11-H or 10-H), 8.05 (d, J = 8.3 Hz, 1H, 5-H), 8.11 (d, J = 8.3 Hz, 1H, 12-H or 9-H), 8.35 (d, J = 7.7 Hz, 1H, 9-H or 12-H), 12.55 (s, 1H, N-H/exchangeable with D$_2$O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): δ = 19.3 (4-CH$_3$), 107.3 (C-13b), 109.7 (C-6), 112.3 (C-3), 113.9 (C-4a), 127.8 (C-10 or C-11), 128.8 (C-12 or C-9), 129.5 (C-5), 130.5 (C-11 or C-10), 130.5 (C-9 or C-12), 138.8 (C-13a), 139.4 (C-8a or C-12a), 140.5 (C-12a or C-8a), 146.8 (C-7a), 148.0 (C-6a), 151.7 (C-13c), 155.7 (C-4), 161.2 (C-2). – $C_{18}H_{11}N_3O_2$ (301.30): calcd. C

71.75, H 3.68, N 13.95; found C 71.84, H 3.62, N 13.78. – HRMS ((+)-ESI): $m/z = 302.09240$ (calcd. 302.09295 for $C_{18}H_{12}N_3O_2$, $[M+H]^+$).

*7H-4,10,11-Trimethylpyrano[2',3':4,5]indolo[2,3-b]quinoxalin-2(2H)-one (**7b**)*

This compound was prepared from 4,5-dimethyl-1,2-phenylenediamine (**6b**) (1.4 g, 1 mmol) and **5** (2.3 g, 1 mmol) by following the procedure and experimental conditions as described above for **7a**. Yield: 2.2 g (67%); m. p. $> 360\,^{\circ}C$. – IR (KBr): $\nu = 3422$, 3196, 3108, 2976, 1732, 1600, 1464, 1382, 1319, 1217, 1165, 1078, 1055, 918, 866 cm^{-1}. – ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta = 2.53$ (s, 3H, 4-CH_3), 2.61 (s, 3H, 10-CH_3 or 11-CH_3), 2.64 (s, 3H, 11-CH_3 or 10-CH_3), 6.36 (s, 1H, 3-H), 7.49 (d, $J = 8.5$ Hz, 1H, 6-H), 7.84 (s, 1H, 12-H or 9-H), 7.99 (d, $J = 8.5$ Hz, 1H, 5-H), 8.10 (s, 1H, 9-H or 12-H), 12.55 (s, 1H, N-H/exchangeable with D_2O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 19.4$ (4-CH_3), 20.3 (11-CH_3 or 10-CH_3), 20.5 (10-CH_3 or 11-CH_3), 106.7 (C-13b), 108.9 (C-6), 111.5 (C-3), 113.0 (C-4a), 127.1 (C-12 or C-9), 128.1 (C-5), 128.7 (C-9 or C-12), 136.9 (C-11 or C-10), 137.4 (C-10 or C-11), 138.7 (C-8a or C-12a), 138.9 (C-12a or C-8a), 140.0 (C-13a), 145.6 (C-7a), 146.5 (C-6a), 150.6 (C-13c), 154.7 (C-4), 160.3 (C-2). – $C_{20}H_{15}N_3O_2$ (329.35): calcd. C 72.94, H 4.59, N 12.76; found C 72.75, H 4.52, N 12.66. – HRMS ((+)-ESI): $m/z = 330.12370$ (calcd. 330.12425 for $C_{20}H_{16}N_3O_2$, $[M+H]^+$).

*7H-10,11-Dichloro-4-methylpyrano[2',3':4,5]indolo[2,3-b]quinoxalin-2(2H)-one (**7c**)*

This compound was prepared from 4,5-dichloro-1,2-phenylenediamine (**6c**) (1.8 g, 1 mmol) and **5** (2.3 g, 1 mmol) by following the procedure and experimental conditions as described above for **7a**. Yield: 2.4 g (65%); m. p. $> 360\,^{\circ}C$. – IR (KBr): $\nu = 3423$, 3213, 3130, 3049, 2976, 1703, 1602, 1440, 1382, 1317, 1240, 1185, 1082, 1052, 980, 918, 866 cm^{-1}. – ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta = 2.54$ (s, 3H, 4-CH_3), 6.39 (s, 1H, 3-H), 7.52 (d, $J =$ 8.4 Hz, 1H, 6-H), 8.06 (d, $J = 1.7$ Hz, 1H, 5-H), 8.32 (s, 1H, 12-H or 9-H), 8.56 (s, 1H, 9-H or 12-H), 12.73 (s, 1H, N-H/exchangeable with D_2O). – ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 19.2$ (4-CH_3), 106.7 (C-13b), 109.1 (C-6), 111.9 (C-3), 113.5 (C-4a), 128.7 (C-12 or C-9), 129.3 (C-5), 130.3 (C-11 or C-10), 132.0 (C-10 or C-11), 129.6 (C-9 or C-12), 138.4 (C-8a or C-12a), 139.1 (C-12a or C-8a), 139.8 (C-13a), 146.3 (C-7a), 147.5 (C-6a), 150.9 (C-13c), 154.4 (C-4), 160.0 (C-2). – $C_{18}H_9Cl_2N_3O_2$ (370.19): calcd. C 58.40, H 2.45, N 11.35; found C 58.24, H 2.40, N 11.22. – HRMS ((+)-ESI): $m/z = 370.01446$ (calcd. 370.01501 for $C_{18}H_{10}Cl_2N_3O_2$, $[M+H]^+$).

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