Indian Journal Chemistry
Vol. 36B, August 1997, pp. 633 - 636

Rapid Communication

Solvent induced synthesis of spiro [Indole-pyran] system using condensation reactions†

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Received 23 June 1997 ; revised and accepted 18 August 1997

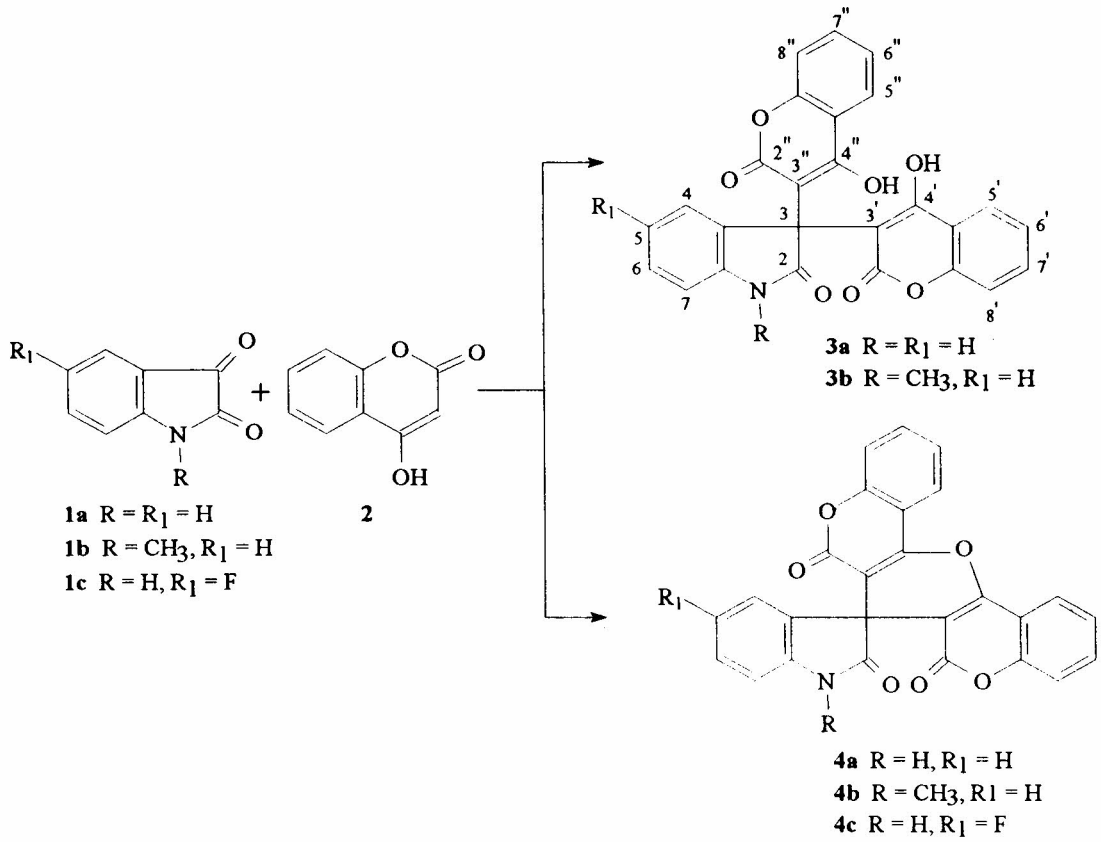
Reaction of indole-2,3-dione with 4-hydroxy-2*H*-1-benzopyran-2-one **2** has been studied under different media and a single one-step synthesis of a novel spiro[indole-pyran] system is achieved. Spiro[indole-3,7'-[6*H*,7*H*,8*H*]pyrano[3,2-*c*;5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione **4a**, its N-methyl **4b** and 5-fluoro **4c** analogues have been synthesised by the reaction of indole-2,3-dione **1a**, its N-methyl **1b** and 5-fluoro **1c** derivatives respectively with **2** under different reaction conditions. All the synthetic spiro compounds **4a-c** have been fully characterized on the basis of their IR, ^{1}H and ^{13}C NMR and mass spectral data.

Spiro indoles are known for their broad spectrum of biological activities[1]. Of the various spiro indoles, spiro[indole-pyran] system attracted our attention due to its pharmacological properties[2,3] and also because of the scanty information available on its synthesis[4]. In view of this, we have investigated the reaction of indole-2,3-dione **1a** with 4-hydroxy-2*H*-1-benzopyran-2-one **2**, both possessing individual biological activities[5,6], under different reaction conditions and explored the possibilities for the formation of a novel spiro [indole-pyran] system in one-pot reaction.

The reaction of **1a** with **2** in 1:2 ratio in glacial acetic acid, exclusively yielded a single colourless product, the mass spectrum of which showed the molecular ion peak at *m/z* 453, corresponding to the molecular formula $C_{26}H_{15}NO_7$, thus indicating that two coumarin moieties are probably coupled with indole nucleus. Its IR spectrum showed characteristic absorption bands at 3400 (-OH), 3132(>NH) and 1710 and 1655 cm^{-1}(lactam carbonyls). The ^{1}H NMR spectrum showed a multiplet at δ 7.14 (H-6', H-6", H-7', and H-7") and two *ortho*- and *meta*- coupled double doublets at δ 8.32 (H-5' and H-5") and 7.88 (H-8' and H-8") thus accounting for all the protons of both the coumarin nuclei. Further, it displayed two multiplets at δ 7.68 (H-4 and H-7) and 7.50 (H-5 and H-6) corresponding to the protons of indole nucleus. Since ^{1}H NMR did not provide any evidence for the characteristic signal of the proton at C-3 position in the coumarin nucleus, it appeared that the proton at C-3 position in both the coumarin nuclei had taken part in the condensation reaction with the free carbonyl at C-3 position of indole nucleus. Further, the presence of hydroxyl group was confirmed by ^{13}C NMR spectrum as carbon carrying OH group appeared at δ 162.06. EIMS also showed the presence of a prominent peak at *m/z* 435 due to loss of H_2O from the molecule and another at *m/z* 407 due to loss of a carbonyl group. These data support the structure for this compound as 3,3-bis-(2-oxo-4-hydroxy-2*H*-1-benzopyran-3-yl)indole-2-(1*H*)-one **3a**.

However, when the above reaction was carried out in absolute ethanol it resulted in the formation of a new compound that was found to be different from **3a**. It showed M^+ peak at *m/z* 435, corresponding to the molecular formula $C_{26}H_{13}NO_6$ indicating again the presence of two coumarin moieties along with an indole nucleus. Its IR spectrum showed absorptions at 3140 (>NH), 1735 and 1660(lactam carbonyls), 1603(>C=C<) and 1200 cm^{-1} (pyran ether linkage). The ^{1}H NMR spectrum showed a multiplet at δ 7.14 (H-6', H-6", H-7' and H-7") and two *ortho* coupled doublets at δ 8.40 (H-5' and H-5") and 7.92 (H-8' and H-8") corresponding to the protons of both the coumarin nuclei. Besides these, multiplets at δ 7.72(H-4 and H-7) and 7.56 (H-5 and H-6) for protons of the indole nucleus were also observed. Further, its ^{13}C

† Part of the results have been presented at the International Symposium on '*Perspectives in Bioorganic Chemistry*' held in New Delhi, India during 8-9 December 1994 and included in *Pure & Appl Chem*, 68, **1996**, 739



NMR spectrum displayed a characteristic signal at δ 100.83 for the presence of a C-3 spiro carbon atom of indole along with signals for carbonyls at δ 178.42, 160.00 and 157.83. EIMS showed a prominent peak at *m/z* 379 due to the loss of two carbonyl groups from the molecule. Considering the above spectral data and their comparison with those of compound **3a**, this compound was characterized as spiro[indole-3,7'-[6*H*,7*H*,8*H*]pyrano[3,2-*c* ; 5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione (**4a**). The spiro compound **4a** was also obtained from **3a** by refluxing the latter in absolute ethanol, thereby confirming its assigned constitution.

Since, in general, fluoro- and N-alkyl-indole derivatives are known to be more soluble and possess increased bioactivity[7], we were tempted to carry out the above condensation reaction taking 1-methylindole-2,3-dione **1b** and 5-fluoroindole-2,3-dione **1c** in place of **1a**. Indole-2,3-dione **1b** when refluxed with **2** in absolute ethanol afforded two compounds **4b** and **3b**, which were characterised as 1-methylspiro[indole-3,7'-[6*H*,7*H*,8*H*]pyrano[3,2-*c* ; 5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione **4b** and 3,3-bis-(2-oxo-4-hydroxy-2*H*-1-benzopyran-3-yl)-1-methylindole-2(1*H*)-one **3b**, respectively, on the basis of their detailed spectral studies and similarity in spectral behaviour with compounds **4a** and **3a** respectively. As the yield of the spiro compound **4b**, obtained above in a mixture, was poor we repeated the above reaction in glacial acetic acid and obtained surprisingly the desired compound **4b** in 80% yield.

We also carried out the reaction of 5-fluoroindole-2,3-dione **1c** with **2** in three different media (neutral, acidic and alkaline) under refluxing conditions and obtained the desired spiro compound **4c**, characterized as 5-fluorospiro[indole-3,7'-[6*H*,7*H*,8*H*]pyrano[3,2-*c* ; 5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione **4c** in 85% yield only in alkaline medium. However, no traces of **4c** was observed when the reaction was performed in either neutral or acidic medium as in the case of **1a** and **1b**.

Experimental Section

General. All melting points are uncorrected and were determined in a sulphuric acid-bath. IR data

were recorded on a Shimadzu model IR-435 spectrophotometer. ^{1}H NMR spectra were recorded either on a Bruker AC 250 MHz or on a Perkin-Elmer R-32 model (90 MHz)spectrometer. ^{13}C NMR spectra were recorded on a Bruker AC 62.89 MHz instrument (chemical shifts were quoted in δ, ppm relative to internal standard tetramethylsilane). Mass spectra were recorded on a Varian MAT 311A or a Jeol-JMS-DX 303 mass spectrophotometer. 1-Methyl-indole-2,3-dione[8] and 5-fluoro-indole-2,3-dione[9] were prepared by literature methods.

Reaction of indole-2,3-dione 1a with 4-hydroxy-2*H*-1-benzopyran-2-one 2 in glacial acetic acid. A mixture of **1a** (1.47 g, 10 mmoles) and **2** (3.24 g, 20 mmoles) in glacial acetic acid (50 mL) was refluxed in an oil-bath. The progress of the reaction was monitored by TLC. After 24 hr a light yellow solid separated out which was filtered, dried and crystallised from glacial acetic acid to give **3a** as white solid, yield 3.4g, m.p. 270° (dec); IR (KBr): 3400, 3132, 1710, 1655, 1573, 1500, 1495, 1454, 1380, 1286, 1116, 997, 760 cm^{-1}, ^{1}H NMR (TFA-*d*), : 7.14 (m, 4H, H-6', H-6", H-7' and H-7"), 7.50(m, 2H, H-5 and H-6), 7.68 (m, 2H, H-4 and H-7), 7.88 (dd, J=9.0 and 2.5Hz, H-8' and H-8"), 8.32(dd, 2H, H-5' and H-5"), 10.42 (s, lH, >NH); ^{13}C NMR (TFA-*d*): 181.03, 162.06, 160.68, 157.11, 152.11, 151.90, 140.16, 134.44, 126.56, 125.55, 124.17, 123.00, 122.16, 121.94, 110.73; EIMS *m/z* (%) : 453(M^+, 18), 435(M^+-H_2O, 12), 407(M^+-H_2O-CO, 16), 391(20), 369(5), 329(7), 307(100), 292(22), 154(80), 136(80), 120(15), 107(39).

On the basis of the above spectral data compound **3a** was characterized as 3,3-bis-(2-oxo-4-hydroxy-2*H*-1-benzopyran-3-yl)-indol-2-(l*H*)-one.

Reaction of 1a with 2 in absolute ethanol. A mixture of **1a** (1.47g, 10 mmoles) and **2** (3.24g, 20 mmoles) in absolute ethanol (50 mL) was refluxed for 22 hr. A yellow solid that separated out was filtered, dried and crystallised from glacial acetic acid to give **4a** as a light yellow solid, yield 2.8 g, m.p. 280° (dec); IR (KBr): 3140, 3050, 1735, 1660, 1603, 1573, 1200 cm^{-1}: ^{1}H NMR (TFA-*d*): 7.14 (m, 4H, H-6', H-6", H-7' and H-7"), 7.56 (m, 2H, H-5 and H-6), 7.72(m, 2H, H-4 and H-7), 7.92(d, 2H, H-8' and H-8"), 8.40(d, 2H, H-5' and H-5"), 10.46(s, 1H, >NH); ^{13}C NMR(TFA-*d*): 178.42, 160.00, 157.83, 140.00, 134.16, 129.59, 125.83, 100.83; EIMS m/z (%) : 435(M^+, 40), 379(M^+-2×CO, 28), 368(95), 334(31), 317(28), 308(32), 293(12), 284(31), 265(48), 257(100), 255(78), 251(68), 180(25), 163(95), 147(92).

On the basis of the above spectral data compound **4a** was characterized as spiro[indole-3,7'-[6*H*,7*H*,8*H*]pyrano[3,2-*c*;5,6-*c'*]di[1]benzo-pyran]-2(3*H*),6',8'-trione.

Synthesis of spiro[indole-3,7'-[6*H*,7*H*,8H]-pyrano-[3,2-*c* ; 5,6-*c'*]di[1]benzopyran]-2(3*H*), 6', 8'-trione 4a. A suspension of 3,3-bis-(2-oxo-4-hydroxy- 2*H* -1- benzopyran-3-yl)-indole-2-(1*H*)-one **3a** (1.5g) in absolute ethanol (50 mL) was refluxed for 6 hr. A clear yellow solution was obtained. The progress of the reaction was monitored by TLC. On cooling the reaction mixture, a yellow solid separated out which was filtered, dried and crystallized from glacial acetic acid to give a light yellow solid, yield 1.2g. It was comparable with compound **4a** in all respects (Co-TLC, Co-IR and m.m.p).

Reaction of 1-methyl-indole-2,3-dione[8] 1b with 2 in absolute ethanol. A mixture of **1b** (1.61 g, 10 mmoles), and 4-hydroxy-2*H*-1-benzopyran-2-one **2** (3.24 g, 20.0 mmoles) in absolute ethanol (50 mL) was refluxed for 70 hr. The solid that separated out was filtered, dried and crystallized from glacial acetic acid to give 1-methyl spiro[indole-3,7'-[6*H*,7*H*,8H] pyrano [3,2-*c*;5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione **4b** as a light yellow solid, yield 1.15 g, m.p. 270°; IR (KBr) : 2872, 1709, 1654, 1600, 1480, 1452, 1360, 1332, 1244, 1212, 1192, 1140, 1080 cm^{-1}; ^{1}H NMR(TFA *d*) : 3.50(3H, >N-CH_3), 7.05-8.40(m, 12H, Ar-H); EIMS m/z (%) : 449(M^+, 64), 421(M^+-CO, 18), 392(M^+-CO-NCH_3, 11), 376(15), 336(32), 279(14), 262(39), 260(11), 252(12), 233(11), 215(12), 196(13), 162(10), 149(44).

The filtrate was concentrated under reduced pressure to dryness. TLC examination of the solid residue, thus left, indicated the presence of another component which was different from the starting

materials and compound **4b** and hence labelled as **3b**. Compound **3b** was purified by column chromatography. Elution with ethyl acetate-benzene (20:80) gave 3,3-bis-[2-oxo-4-hydroxy-2*H*-1-benzopyran-3-yl]-1-methylindole-2-(1*H*)-one as colourless crystal, yield 1.35 g, m.p. 145° ; IR(KBr) : 3348, 3000, 1703, 1652, 1615, 1603, 1560, 1480, 1458, 1372, 1312, 1292, 1212, 1080 cm^{-1}. ^1H NMR (DMSO-d_6) : 3.18(s, 3H, >N-CH_3), 6.94(m, 2H, H-5 and H-6), 7.10(m, 4H, H-6', H-6", H-7' and H-7"), 7.27(dd, 2H, H-4 and H-7), 7.41(dd, 2H, H-8' and H-8"), 7.89(dd, 2H, H-5' and H-5"), 9.68(s, 2H, 2×OH); ^{13}C NMR (DMSO-d_6) : 178.10, 159.74, 155.09, 152.18, 149.37, 132.78, 131.84, 131.57, 130.35, 127.94, 127.56, 124.51, 121.59, 118.66, 116.47; EIMS *m/z* (%) : 440(M^++1-28, 32), 422(100), 379(10), 365(12), 320(92), 305(60), 279(38), 234(90), 186(29), 162(25), 146(42).

Reaction of 1-methylindole-2,3-dione 1b with 2 in glacial acetic acid. A mixture of **1b** (1.61g, 10.0 mmoles) and 4-hydroxy-2*H*-1-benzopyran-2-one **2** (3.24g, 20.0 mmoles) in glacial acetic acid (50 mL) was refluxed in an oil-bath for 70 hr. The solid that separated out was filtered, dried and crystallised from glacial acetic acid to give the spiro compound **4b,** yield 3.5 g.

Reaction of 5-fluoroindole-2,3-dione 1c with 2 in absolute ethanol in the presence of diethyl amine. A mixture of **1c** (1.65g, 10.0 mmoles), **2** (3.24, 20.0 mmoles) and diethylamine (0.5 mL) in absolute ethanol (50 mL) was refluxed in an oil-bath for 72 hr. A pink solid that separated out was filtered, dried and crystallised from hot glacial acetic acid to give 5-fluorospiro[indole-3,7'-[6*H*,7*H*,8*H*] pyrano [3,2-*c*;5,6-*c'*]di[1]benzopyran]-2(3*H*),6',8'-trione **4c** as a light pink solid, yield 3.85 g, m.p. 270°; IR (KBr) : 3160, 1732, 1655, 1600, 1572, 1338, 1280, 1252, 1203, 1176, 1146, 1092, 1032, 878 cm^{-1}; ^1H NMR (DMSO-d_6) : 7.03(d, 1H, H-6), 7.30(d, 1H, H-7), 7.54(m, 4H, H-6', H-6", H-7' and H-7"), 7.61(d, 1H, H-4), 7.83(d, 2H, H-8' and H-8"), 8.46(d, 2H, H-5' and H-5"), 10.88(bs, 1H, >NH); ^{13}C NMR(DMSO-d_6) : 178.20, 168.28, 154.92, 152.07, 134.10, 131.00, 128.82, 125.26, 123.82, 112.54, 115.52, 101.4; EIMS m/z (%) : 453(M^+, 15), 452(10), 422(20), 396(10), 368(18), 316(5), 262(18), 234(18), 173(8), 105(12).

Acknowledgement

The authors express their sincere gratitude to Danish International Development Agency (DANIDA), Denmark and CSIR, New Delhi for financial assistance.

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