Spiro[3*H*-pyrazole-3,3′-oxindoles] Derived from 1,2,3,4-Tetrahydroquinoline

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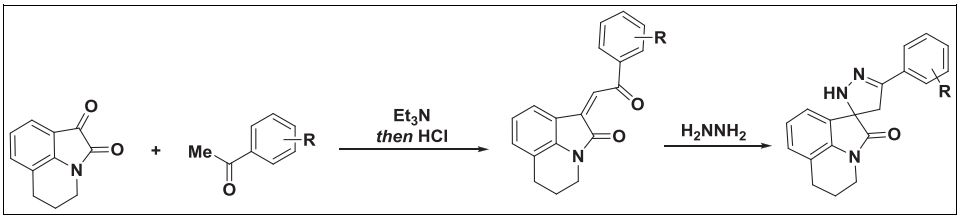

Aldol condensation of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione with aryl methyl ketones generates 3-(aroylmethylidene)oxindoles, which react with hydrazine to generate tricyclic spiro[3*H*-pyrazole-3,3′-oxindoles].

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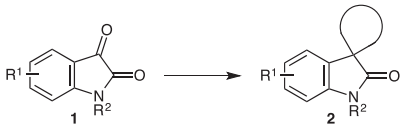
INTRODUCTION

Interest in spirooxindoles, that is, compounds **2** having an oxindole nucleus but with a spirocyclic ring fused at C-3, has been considerable, as one may judge from a 2014 comprehensive review [1] on "Recent Progress on Routes to Spirooxindole Systems Derived from Isatin" in this journal and a 2014 Tetrahedron Report [2] on "Recent Advances in the Synthesis of Biologically Active Spirooxindoles." This interest continues unabated – for example, we are aware of six reports already in 2015 that deal with the conversion of isatins (1*H*-indole-2,3-diones) into spirooxindoles [3–8].



Nearly all of the work concerned with the synthesis of spirooxindoles has utilized isatins **1** as the original starting materials, because these substances are relatively easy to prepare and possess two easily distinguished carbonyl groups – amide and ketone – each significantly more reactive than normal examples by virtue of the influence of the other adjacent carbonyl group. Most often, the isatin has been converted first into either a 3-methyleneoxindole (by aldol-type condensation) or a 3-imino-oxindole (by condensation with an amine), these then used for the formation of the spiro ring.

We were led to investigate the tricyclic isatin **3** and to assess whether its reactions would parallel those of the "normal" bicyclic isatins – we were aware that the extra strain imposed by the third ring might affect the typical isatin reactivity. No previous work had employed the tricyclic oxindole, 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**) until our investigation [9] that in fact showed "normal" behavior in conversions summarized in Scheme 1. We were intrigued to examine other processes involving **3** and here describe our results producing spiro[3*H*-pyrazole-3,3′-oxindoles] **7** (Scheme 2.)

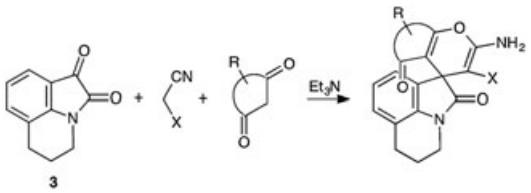
RESULTS AND DISCUSSION

5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**) was prepared following a literature procedure [10] in which 1,2,3,4-tetrahydroquinoline was reacted with oxalyl chloride and the resulting amide-acid chloride cyclized by treatment with aluminum chloride.

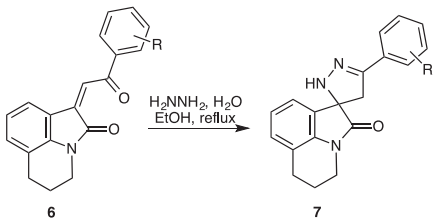
Reaction of amido-ketone **3** with several aryl methyl ketones **4a–g** proceeded easily at room temperature (RT) under the influence of triethylamine in ethanol to produce keto-alcohols **5a–g**. Dehydration of the alcohols to produce the conjugated ketones **6a–g** was achieved simply and efficiently by heating in acetic acid with catalytic hydrogen chloride. Each of the conjugated ketones reacted smoothly with hydrazine to produce spirocyclic oxindoles **7** (Scheme 3 and Table 1).

The keto-alcohol **5a** showed doublets at δ 3.59 and 4.06 for the CH_2 with J 17.1 Hz, while the CH of the conjugated ketone **6a** appeared as a singlet at δ 7.86, and in the final pyrazole **7a**, the CH_2 was observed as two doublets at δ 3.41 and 3.71 with J 16.5 Hz. The signals for the pyrazole **7a** were accompanied by a broad singlet at δ 6.6 for the *N*-hydrogen. Infrared spectroscopy was also used to monitor the transformations. The keto-alcohol **5a** had absorptions at 1704 and 1684 cm^{-1} changing to 1707 and 1652 cm^{-1} in the spectrum of **6a**, and there was a single carbonyl

Scheme 1



Scheme 3



absorption at 1706 cm^{-1} for **7a**. Comparable spectroscopic data were obtained for each of the products **7b–g**.

CONCLUSIONS

It seems that the extra strain present in the tricyclic isatin **3** does not preclude its reacting in this dihydropyrazole-forming sequence, in a manner completely analogous to that of simpler, bicyclic isatins [11]. We intend to make further use of the reactivity inherent in this interesting keto-lactam in future studies.

EXPERIMENTAL

General. The chemicals used in this work were obtained from Fluka and Merck and were used without purification. Melting points were recorded on Electrothermal Engineering LTD 16218 (Bibby Scientific Limited, Staffordshire, UK). ^1H NMR and ^{13}C NMR spectra were recorded on an Avance AQS 300 MHz spectrometer (Brucker, Karlsruhe, Germany) at 300 and 75 MHz, respectively. Chemical shifts δ are in parts per million (ppm) measured in $CDCl_3$ or DMSO-d_6 as solvent and relative to TMS as the internal standard. IR spectra were obtained on a Nexus 670 FT-IR instrument (Thermonicolet, USA). Microanalyses were performed on a Leco Analyzer 932.

2-(1,2,3,4-Tetrahydroquinolin-1-yl)-2-oxoacetyl chloride. Oxalyl chloride (0.7 g, 5.5 mmol) was added dropwise to a solution of 1,2,3,4-tetrahydroquinoline (0.36 g, 2.7 mmol) in benzene (10 mL) at 5°C. The mixture was stirred for 2 h at RT; then the benzene was evaporated leaving the acid chloride as a solid. The crude product was used without further purification. IR ν_{max} (KBr): 3039, 2946, 1735, 1663, 1598, 1488, 1411 cm^{-1}.

5,6-Dihydro-4H-pyrrolo[3,2,1-ij]quinoline-1,2-dione (3). Sublimed $AlCl_3$ (0.4 g, 3.1 mmol) was added slowly to a solution of 2-(1,2,3,4-tetrahydroquinolin-1-yl)-2-oxoacetyl chloride (1.2 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight at RT; then aq HCl (2 M, 30 mL) was added. The organic layer was separated and washed with aq $KHCO_3$ (2 M, 20 mL) then H_2O (20 mL). Finally, the CH_2Cl_2 was evaporated using a rotary evaporator. The residue was recrystallized from ethanol to give a white solid (0.18 g, 85%), mp 197°C. IR ν_{max} (KBr): 3446, 3041, 2946, 2882, 1730, 1597, 1473, 1350, 1314, 1242, 1162, 1081, 1046 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.02–2.09 (m, 2H), 2.8 (t, 2H, J = 6 Hz), 3.77 (t, 2H, J = 6 Hz), 7.00 (t, 1H, J = 7.5 Hz), 7.34 (d, 1H, J = 7.5 Hz), 7.4 (d, 1H, J = 7.5 Hz).

General procedure for the synthesis of conjugated ketones (6a–g) via keto-alcohols (5a–g). 5,6-Dihydro-4*H*-pyrrolo [3,2,1-*ij*]quinoline-1,2-dione (**3**) (0.187 g, 1 mmol) and the substituted acetophenone (**4a–g**) (1.5 mmol) were dissolved in EtOH (5 mL), and Et_3N (5 drops) was then added. The reaction mixture was stirred for 2–3 h at RT, and a colorless solid was formed. The solid was filtered off; then glacial AcOH (10 mL) and 2–3 drops of conc HCl were added to the precipitate and the resulting mixture heated at reflux for 6–8 h, then cooled, and neutralized with aq KOH when a red solid formed, which was filtered off and recrystallized from EtOH to give the methylene-oxindole **6a–g**.

Scheme 2

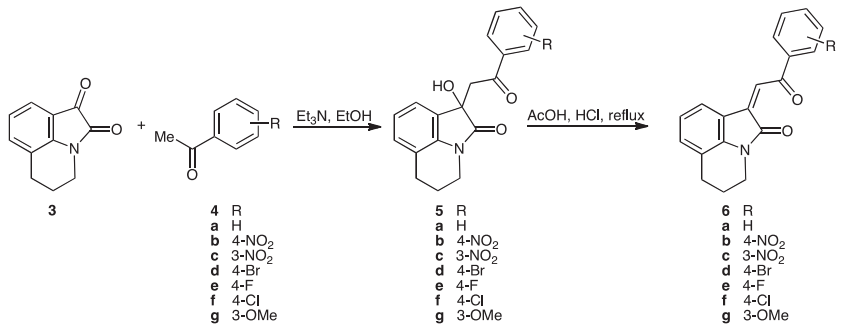


Table 1
Yields of products **5**, **6**, and **7**

R	Compound (%)	Compound (%)	Compound (%)
H	**5a** (79)	**6a** (71)	**7a** (64)
4-NO_2	**5b** (92)	**6b** (88)	**7b** (87)
3-NO_2	**5c** (91)	**6c** (85)	**7c** (87)
4-Br	**5d** (88)	**6d** (86)	**7d** (68)
4-F	**5e** (96)	**6e** (94)	**7e** (91)
4-Cl	**5f** (90)	**6f** (89)	**7f** (82)
3-OMe	**5g** (86)	**6g** (83)	**7g** (77)

1-Hydroxy-1-(2-oxo-2-phenylethyl)-5,6-dihydro-1H-pyrrolo [3,2,1-ij]quinolin-2(4H)-one (5a). White solid (90 mg, 79%) mp 195°C. ν_{max} (KBr): 3310, 2944, 1704, 1684, 1902, 1443 cm^{-1}; δ_H (300 Hz, DMSO-d_6): 1.89–1.94 (m, 2H), 2.72 (m, 2H), 3.59 (d, 1H, J = 17.1 Hz), 3.60 (t, 2H, J = 4.8 Hz), 4.06 (d, 1H, J = 17.1 Hz), 6.1 (1H, OH), 6.80 (t, 1H, Ar-H, J = 7.5 Hz), 7.00 (d, 1H, Ar-H, J = 7.5 Hz), 7.14 (d, 1H, Ar-H, J = 7.5 Hz), 7.32–7.65 (m, 3H, Ar-H), 7.86 (d, 1H, Ar-H, J = 8.1 Hz), 7.95 (d, 1H, Ar-H, J = 8.1 Hz); δ_C (75 MHz, DMSO-d_6): 197.1, 176.0, 140.5, 136.4, 134.7, 133.1, 130.3, 129.8, 128.1, 127.5, 123.5, 120.5, 74.6, 47.7, 27.0, 24.3, 21.0. Found: %C 74.19, %H 5.81, %N 4.49; $C_{19}H_{17}NO_3$ requires %C 74.25, %H 5.85, %N 4.56.

(Z)-1-(2-oxo-2-phenylethylidene)-5,6-dihydro-4H-pyrrolo[3,2,1-ij]quinolin-2(1H)-one (6a). Red crystals (60 mg, 71%) mp 192°C. ν_{max} (KBr): 3425, 2932, 1707, 1652, 1604, 1458 cm^{-1}, δ_H (300 MHz, $CDCl_3$): 2.02–2.12 (m, 2H), 2.80 (t, 2H, J = 6 Hz), 3.80 (t, 2H, J = 5.7 Hz) 6.97 (t, 1H, Ar-H, J = 7.8 Hz), 7.18 (d, 1H, Ar-H, J = 7.8 Hz), 7.29 (d, 1H, Ar-H, J = 7.8 Hz), 7.86 (s, 1H), 8.27 (d, 3H, Ar-H, J = 8.7 Hz), 8.39 (d, 2H, ArH, J = 8.4 Hz); δ_C (75 MHz, DMSO-d_6): 190.5, 166.0, 150.3, 137.6, 136.5, 133.5, 131.9, 131.5, 130.2, 126.6, 125.7, 125.1, 124.3, 121.2, 40.6, 24.2, 20.8. Found: %C 78.76, %H 5.19, %N 4.75; $C_{19}H_{15}NO_2$ requires %C 78.87, %H 5.23, %N 4.84.

Typical procedure for the preparation of compounds (7a–g). A mixture of compound **6a–g** (0.05 g, 0.172 mmol) and hydrazine hydrate 50% (0.6 mmol) in EtOH (5 mL) was stirred and heated at 70–80°C for 7–8 h then cooled slowly to 4°C. The solid that separated was filtered off and recrystallized from EtOH.

5-Phenyl-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo [3,2,1-ij]quinolin]-2′-one (7a). White crystals (54 mg, 64%) mp 188°C; ν_{max} (KBr): 3271, 2937, 1706, 1613, 1477 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.03–2.07 (m, 2H), 2.80 (t, 2H, J = 5.7 Hz), 3.41 (d, 1H, J = 16.5 Hz) 3.71 (d, 1H, J = 16.5 Hz), 3.77 (t, 2H, J = 5.7 Hz), 6.6 (bs, 1H, NH), 6.94 (t, 1H, Ar-H, J = 7.5 Hz) 7.12 (d, 2H, Ar-H, J = 7.5 Hz), 7.39–7.41 (d, 3H, Ar-H, J = 6.3 Hz), 7.69 (m, 2H, Ar-H); δ_C (75 MHz, $CDCl_3$): 175.8, 150.8, 148.5, 138.4, 132.1, 130.3, 129.2, 128.6, 127.6, 126.4, 123.0, 120.7, 70.8, 44.2, 39.2, 24.4, 21.0. Found: %C 75.19, %H 5.59, %N 13.80. $C_{19}H_{17}N_3O$ requires %C 75.23, %H 5.65, %N 13.85.

5-(4-Nitrophenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7b). Yellow crystals (81 mg, 87%) mp 239°C; ν_{max} (KBr): 3263, 1695, 1629, 1599, 1506, 1481, 1339 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.04–2.08 (m, 2H), 2.82 (t, 2H, J = 5.7 Hz), 3.42 (d, 1H, J = 16.5 Hz), 3.72 (d, 1H, J = 16.5 Hz), 3.77 (t, 2H, J = 6.0 Hz), 6.31 (s, 1H, NH), 6.97 (dd, 1H, Ar-H, J_1 = 7.5 Hz, J_2 = 9 Hz), 7.14 (t, 2H, Ar-H, J = 9 Hz), 7.81 (d, 2H, Ar-H, J = 8.7 Hz), 8.26 (d, 2H, Ar-H, J = 8.7 Hz); δ_C (75 MHz, $CDCl_3$): 175.2, 147.9, 147.6, 138.2, 133.1, 129.4, 129.0, 126.7, 124.0, 123.1, 120.9, 120.8, 71.2, 43.5, 39.2, 24.4, 20.9. Found: %C 65.39, %H 4.58, %N 16.01. $C_{19}H_{16}N_4O_3$ requires %C 65.51, %H 4.63, %N 16.08.

5-(3-Nitrophenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7c). Yellow crystals (71 mg, 87%) mp 236°C. ν_{max} (KBr): 3271, 1695, 1629, 1602, 1527, 1480, 1350 cm^{-1}, δ_H (300 MHz, $CDCl_3$): 2.04–2.06 (m, 2H), 2.81 (t, 2H, J = 5.6 Hz), 3.44 (d, 1H, J = 16.5 Hz), 3.73 (d, 1H, J = 16.8 Hz), 3.75 (t, 2H, J = 5.8 Hz), 6.23 (s, 1H, NH), 6.96–6.98 (m, 1H, Ar-H), 7.10–7.16 (m, 2H, Ar-H), 7.59 (dd, 1H, Ar-H, J_1 = 7.2 Hz, J_2 = 6.9 Hz), 8.05 (d, 1H, Ar-H, J = 7.2 Hz), 8.20 (d, 1H, Ar-H, J = 6.9 Hz), 8.45 (s, 1H, Ar-H); δ_C (75 MHz, $CDCl_3$): 175.4, 148.5, 148.1, 138.6, 133.9, 131.7, 129.6, 129.5, 128.9, 123.4, 123.1, 121.0, 120.9, 120.8, 71.1, 43.7, 39.2, 24.4, 20.9. Found: %C 65.43, %H 4.56, %N 15.99. $C_{19}H_{16}N_4O_3$ requires %C 65.51, %H 4.63, %N 16.08.

5-(4-Bromophenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7d). White crystals (63 mg, 68%) mp 221°C. ν_{max} (KBr): 3272, 1695, 1627, 1598, 1482 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.03–2.06 (m, 2H), 2.80 (t, 2H, J = 5.7 Hz), 3.36 (d, 1H, J = 16.5 Hz) 3.67 (d, 1H, J = 16.8 Hz), 3.75 (t, 2H, J = 5.7 Hz), 6.08 (bs, 1H, NH), 6.95 (t, 1H, Ar-H, J = 7.5 Hz), 7.12 (dd, 2H, Ar-H, J_1 = 7.8, J_2 = 7.2 Hz), 7.53 (bs, 4H, Ar-H); δ_C (75 MHz, $CDCl_3$) 175.6, 150.8, 149.7, 138.5, 131.8, 131.1, 130.0, 128.7, 127.8, 123.3, 123.0, 120.8, 70.9, 43.9, 39.2, 24.4, 20.9. Found: %C 59.58, %H 4.17, %N 10.91. $C_{19}H_{16}BrN_3O$ requires %C 59.70, % H 4.22, %N 10.99.

5-(4-Fluorophenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7e). White crystals (69 mg, 92%) mp 206°C. ν_{max} (KBr): 3276, 1701, 1629, 1512, 1481 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.03–2.06 (m, 2H), 2.80 (t, 2H, J = 5.7 Hz), 3.37 (d, 1H, J = 16.5 Hz), 3.68 (d, 1H, J = 16.5 Hz), 3.75 (t, 2H, J = 5.7 Hz), 6.05 (s, 1H, NH), 6.95 (t, 1H, Ar-H, J = 7.8 Hz), 7.0–7.2 (m, 4H, Ar-H), 7.66 (dd, 2H, Ar-H, J_1 = 8.1 Hz, J_2 = 5.7 Hz); δ_C (75 MHz, $CDCl_3$): 175.8, 164.9, 161.6, 149.8, 138.6, 130.1, 128.6, 128.4, 128.2, 123.0, 120.7, 115.8, 70.8, 44.2, 39.2, 24.4, 20.9. Found: %C, 70.02, %H, 4.96, %N, 13.03. $C_{19}H_{16}FN_3O$ requires %C 71.01, %H 5.02, %N 13.08.

5-(4-Chlorophenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7f). White crystals

(68 mg, 82%) mp 217°C. ν_{max} (KBr): 3263, 1706, 1609, 1589, 1481 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.04–2.06 (m, 2H), 2.80 (t, 2H, $J = 5.4$ Hz), 3.36 (d, 1H, $J = 16.5$ Hz), 3.67 (d, 1H, $J = 16.8$ Hz), 3.75 (t, 2H, $J = 5.7$ Hz), 6.80 (bs, 1H, NH), 6.95 (t, 1H, Ar-H, $J = 6.9$ Hz), 7.12 (dd, 2H, Ar-H, $J_1 = 7.8$ Hz, $J_2 = 7.2$ Hz), 7.37 (d, 2H, Ar-H, $J = 8.1$ Hz), 7.61 (d, 2H, Ar-H, $J = 7.8$ Hz); δ_C (75 MHz, $CDCl_3$): 175.7, 159.8, 149.6, 138.5, 135.0, 130.6, 130.0, 128.8, 128.7, 127.5, 123.0, 120.7, 70.9, 44.0, 39.2, 24.4, 20.9. Found: %C 67.41, %H 4.72, % N 12.39. $C_{19}H_{16}ClN_3O$ requires %C 67.56, %H 4.77, %N 12.44.

5-(3-Methoxyphenyl)-2,4,5′,6′-tetrahydro-2′H,4′H-spiro[pyrazole-3,1′-pyrrolo[3,2,1-ij]quinolin]-2′-one (7g). White crystals (56 mg, 77%) mp 219°C. ν_{max} (KBr): 3254, 1704, 1652, 1599, 1572, 1477, 1348 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 2.03–2.05 (m, 2H), 2.79 (t, 2H, $J = 5.1$ Hz), 3.39 (d, 1H, $J = 16.8$ Hz) 3.70 (d, 1H, $J = 16.8$ Hz), 3.75 (t, 2H, $J = 5.4$ Hz), 3.85 (s, 3H, OCH_3), 6.05 (bs, 1H, NH), 6.94 (dd, 2H, Ar-H, $J_1 = 7.2$ Hz, $J_2 = 7.5$ Hz), 7.08–7.21 (m, 3H, Ar-H), 7.27–7.31 (m, 2H, Ar-H); δ_C (75 MHz, $CDCl_3$): 175.7, 159.7, 150.7, 138.5, 133.3, 130.7, 129.6, 128.6, 127.5, 123.0, 120.7, 119.1, 115.6, 110.8, 70.4, 55.3, 44.3, 39.1, 24.4, 20.9. Found: %C, 71.86, %H, 5.71, %N, 12.56. $C_{20}H_{19}N_3O_2$ requires %C 72.05, %H 5.74, %N 12.60.

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