

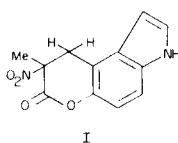
Misbahul Ain Khan and Maria Lúcia de Brito Morley (1)

Seção de Química, Instituto Militar de Engenharia, Urca, 22290 Rio de Janeiro, RJ, Brasil
Received February 23, 1979

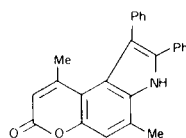
The hydrazones derived from coumarin-6-ylhydrazine and ethyl 6-hydrazinochromone-2-carboxylate undergo facile indolization to give 3*H*,7*H*-pyrano[3,2-*e*]indol-7-ones (IIIb-IIIg) and ethyl 9-oxo-3*H*,9*H*-pyrano[3,2-*e*]indole-7-carboxylates (IVb-IVd), respectively, in good yields. Compounds IVb-IVd are derivatives of a new ring system.

J. Heterocyclic Chem., **16**, 997 (1979).

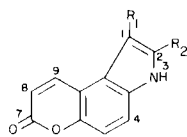
We have recently reported the synthesis of a ring system where a pyrrole ring was fused to the pyrone ring of coumarin (2). The fusion of a pyrrole ring to the benzene ring of a coumarin or a chromone could also lead to various interesting ring systems. A literature search revealed the existence of only two derivatives (I (3) and II (4)) of the 3*H*,7*H*-pyrano[3,2-*e*]indol-7-one system (IIIa) but not mention of the 3*H*,9*H*-pyrano[3,2-*e*]indol-9-one ring system (IVa) or its derivatives is made. As such we undertook the investigation of these systems beginning with the synthesis of some derivatives which we would now like to report.



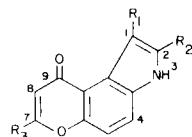
I



II



III

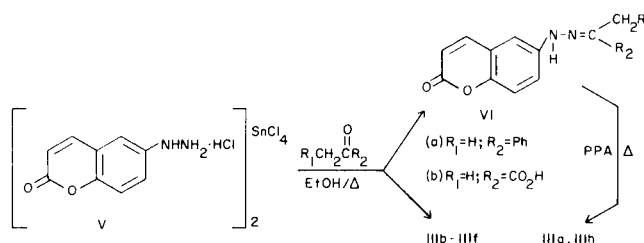


IV

(a) $R_1 = R_2 = H$ (b) $R_1 = R_2 = Me$ (c) $R_1 = Me; R_2 = H$ (d) $R_1, R_2 = -(CH_2)_4-$ (e) $R_1 = Ph; R_2 = Me$ (f) $R_1 = Me; R_2 = Ph$ (g) $R_1 = H; R_2 = Ph$ (h) $R_1 = H; R_2 = CO_2H$ (a) $R_1 = R_2 = R_3 = H$ (b) $R_1 = R_2 = Me; R_3 = CO_2Et$ (c) $R_1, R_2 = -(CH_2)_4-; R_3 = CO_2Et$ (d) $R_1 = Ph; R_2 = Me; R_3 = CO_2Et$ (e) $R_1 = Ph; R_2 = Me; R_3 = CO_2H$

Of the alternatives available for the synthesis of these ring systems, we chose the use of Fischer's indolization in view of its versatility as well as the availability of starting materials which could easily be prepared. The syntheses of III is presented in Scheme 1. Coumarin-6-ylhydrazine (V) was prepared according to Morgan and Micklethwait (5); it

was, without isolation, condensed with appropriate carbonyl compounds in ethanol under reflux leading to the direct formation of the desired III (Method A). In the case of condensations with acetophenone or with pyruvic acid the respective hydrazones were isolated from these reactions. The hydrazone (VIa) was cyclized to IIIg by heating with polyphosphoric acid (Method B). The overall yields of III were in the range of 62-87%.



The synthesis of 3*H*,9*H*-pyrano[3,2-*e*]indol-9-ones (IVb-IVd) essentially followed Scheme 1. Starting from ethyl 6-aminochromone-2-carboxylate (6) followed by successive diazotization, reduction of the diazonium salt with stannous chloride and heating the hydrazine thus formed with carbonyl compounds, IVb-IVd were obtained in yields of over 60%.

The elemental analyses and the proton magnetic resonance spectra established the identity of the compounds IIIb-IIIg and IVb-IVd. The protons at C-4 and C-5 appear as a pair of doublets with coupling constants of 9 Hz. The downfield doublet between δ 7.40 and 7.95 in the pmr spectra of III is tentatively assigned to the proton at C-4 in analogy with the shifts of the proton at C-7 of indoles (7). Like the coumarins the proton at C-8 and the proton at C-9 also constitute a pair of doublets with a coupling constant of 10 Hz. The proton at C-8 was found to be further upfield (between δ 6.10 and 6.42) as compared to the other protons of the system (8). The broad signal for the NH proton appeared between δ 11 and 12. In the case of IIIe, however, the signal for the proton at C-9 was found to be at a relatively higher field (δ 7.70) as compared to the other products (δ 8.20-8.50). This shift

towards higher field could be ascribed as due to the anisotropic shielding effect of the phenyl group situated at C-1 of IIIe. The solvent effects could easily be ruled out since all the spectra were taken in the same solvent, *viz.*, hexadeuterated dimethyl sulfoxide.

Similarly, the pmr of IVb-IVd exhibit two doublets with coupling constants of 9 Hz, the downfield doublet being assigned to the proton at C-4. The signal for the proton at C-8 was observed as a singlet between δ 6.70 and 6.85 and for the NH proton a broad signal between δ 11.35 and 11.82.

The infrared spectra of IIIb-IIIg show a strong absorption between 3260 and 3230 cm^{-1} due to an NH, and between 1695 and 1680 cm^{-1} for the intermolecular hydrogen bonded carbonyl group of the pyrone ring. In a similar manner the infrared spectra of IVb-IVe also show strong absorption at 3250 cm^{-1} due to the NH of the pyrrole and other absorptions at 1645-1640 cm^{-1} due to the intermolecular hydrogen bonded pyrone carbonyl group (9). In addition absorption bands between 1730-1750 cm^{-1} were also observed for the ester and the acid functions at the 7 position.

EXPERIMENTAL

All melting points are uncorrected. Pmr spectra were taken on a 60 MHz Hitachi Perkin-Elmer R-20B using tetramethylsilane as an internal standard. Ir absorption spectra were measured on a Perkin-Elmer model 180 and the elemental analyses on Perkin-Elmer 240.

Most of the starting material and the carbonyl compounds used in this work were either commercial products or were prepared by the literature methods as indicated.

General Procedure.

A solution of 0.01 mole of 6-aminocoumarin (5) or ethyl 6-aminochromone-2-carboxylate (6) in 5 ml. of hydrochloric acid was diazotized at -5 to 0° with sodium nitrite solution (0.8 g. dissolved in 3 ml. of water). After keeping at this temperature for 30 minutes the resulting diazonium salt was reduced by adding into a cold (-10 - -5°) solution of 5 g. of stannous chloride dissolved in 5 ml. of hydrochloric acid. The mixture was left in the refrigerator for a minimum period of two hours. The resulting mixture of coumarin-6-ylhydrazine hydrochloride and stannic chloride in hydrochloric acid or ethyl 6-hydrazinochromone-2-carboxylate hydrochloride and stannic chloride in hydrochloric acid (henceforth referred to as "coumarin-6-ylhydrazine" and "ethyl 6-hydrazinochromone-2-carboxylate", respectively) was directly reacted with the appropriate compound according to one of two methods.

Method A.

The mixture of the "hydrazine" and 0.01 mole of the carbonyl compound was heated under reflux for an hour in ethanol (20 ml.) or acetic acid (10 ml.). After cooling the reaction mixture was inverted over 100 g. of crushed ice. The product was filtered and purified.

Method B.

The hydrazone isolated in Method A together with 10 g. of polyphosphoric acid were heated on a water bath for an hour. After cooling, the reaction mixture was inverted over 100 g. of crushed ice, filtered and purified. The yields are based on the starting aminocoumarin or ethyl 6-aminochromone-2-carboxylate.

3*H*,7*H*-Pyrano[3,2-*e*]indol-7-ones.

1,2-Dimethyl-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIb).

This compound was isolated as a yellow solid from the reaction of "coumarin-6-ylhydrazine" and 2-butanone (Method A). Three crystallizations from ethanol (activated charcoal) gave IIIb, m.p. 271-272° as light yellow crystals in a yield of 67.2%; pmr (DMSO- d_6): δ 2.38 (s, CH_3), 6.35 (d, H-8), 7.00 (d, H-5), 7.40 (d, H-4), 8.45 (d, H-9), 11.15 (br., NH), $J_{4,5} = 9$ Hz, $J_{8,9} = 10$ Hz; ir (potassium bromide): 3260 (br., NH), 1680 (pyrone C=O), 1610, 1590, 1510, 1460, 1180, 1025, 800, 590 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.23; H, 5.09; N, 6.70.

1-Methyl-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIc).

The reaction of "coumarin-6-ylhydrazine" and propanal (Method A) gave a yellow solid which was filtered and washed with ether (3×10 ml.) and crystallized from ethanol (activated charcoal) giving IIIc as yellow crystals, m.p. 274-276°, yield 62.5%; pmr (DMSO- d_6): δ 2.50 (s, CH_3), 6.30 (d, H-8), 7.20 (s, H-2), 7.55 (d, H-4), 7.00 (d, H-5), 8.40 (d, H-9), 11.10 (br., NH), $J_{4,5} = 9$ Hz, $J_{8,9} = 10$ Hz; ir (potassium bromide): 3240 (br., NH), 1680 (pyrone C=O), 1610, 1590, 1510, 1400, 1180, 1025, 815 cm^{-1} .

Anal. Calcd. for $\text{C}_{12}\text{H}_9\text{NO}_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.50; H, 4.60; N, 6.96.

1,2-Tetramethylene-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIId).

The yellow solid obtained from the reaction of "coumarin-6-ylhydrazine" and cyclohexanone (Method A) was filtered and crystallized four times from ethanol (activated charcoal) giving IIIId as light yellow crystals, m.p. 277-279°, yield 73.4% pmr (DMSO- d_6): δ 1.10 (m, $-\text{CH}_2-$), 2.15 (m, $-\text{CH}_2-$), 6.30 (d, H-8), 6.90 (d, H-5), 7.45 (d, H-4), 8.25 (d, H-9), 11.00 (br., NH), $J_{4,5} = 9$ Hz, $J_{8,9} = 10$ Hz; ir (potassium bromide): 3250 (br., NH), 1685 (pyrone C=O), 2940, 1590, 1510, 1460, 1180, 805 cm^{-1} .

Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.01; H, 5.43; N, 5.79.

2-Methyl-1-phenyl-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIe).

The reaction of phenylacetone with "coumarin-6-ylhydrazine" (Method A) furnished a yellow precipitate which was filtered and crystallized from ethanol (activated charcoal) to give IIIe as yellow crystals, m.p. 240-242° in a yield of 87.5%; pmr (DMSO- d_6): δ 2.28 (s, CH_3), 6.10 (d, H-8), 7.00 (d, H-5), 7.37 (m, C_6H_5), 7.55 (d, H-4), 7.70 (d, H-9), 11.55 (br., NH), $J_{4,5} = 9$ Hz, $J_{8,9} = 10$ Hz; ir (potassium bromide): 3230 (br., NH), 1685 (pyrone C=O), 1610, 1595, 1490, 1460, 1235, 1220, 1150, 800, 760 cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.58; H, 4.71; N, 4.93.

1-Methyl-2-phenyl-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIIf).

The reaction product of "coumarin-6-ylhydrazine" and propiophenone (Method A), obtained as a yellow precipitate, was filtered, washed with ether (3×10 ml.) and crystallized from ethanol (activated charcoal) giving IIIIf, m.p. 238-239° as yellow crystals, yield 72.3%; pmr (DMSO- d_6): δ 2.30 (s, CH_3), 6.32 (d, H-8), 7.00 (d, H-5), 7.50 (m, C_6H_5), 7.95 (d, H-4), 8.50 (d, H-9), 11.45 (br., NH), $J_{4,5} = 9$ Hz, $J_{8,9} = 10$ Hz; ir (potassium bromide): 3250 (br., NH), 1695 (pyrone C=O), 1620, 1590, 1490, 1460, 1230, 1150, 1025, 800, 760 cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{13}\text{NO}_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.79; H, 4.84; N, 4.91.

2-Phenyl-3*H*,7*H*-pyrano[3,2-*e*]indol-7-one (IIIIf).

The reaction of "coumarin-6-ylhydrazine" and acetophenone (Method A) gave acetophenone coumarin-6-ylhydrazone (VIa) isolated in 73.3% yield as yellow solid after three crystallizations from ethanol (activated charcoal), m.p. 168-169°; pmr (DMSO- d_6): δ 2.26 (s, CH_3), 6.40 (d, H-3), 7.50 (m, C_6H_5 and H-5, H-7, H-8), 8.20 (d, H-4), 9.40 (s, NH), $J_{3,4} = 10$ Hz; ir (potassium bromide): 3300 (br., NH), 1700 (pyrone C=O) cm^{-1} .

Anal. Calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.39; H, 4.84; N, 10.28.

The hydrazone (VIa) when treated with polyphosphoric acid (Method

B) gave dark brown solid which was extracted with ether (3 × 50 ml.). The ether extract after drying (anhydrous magnesium sulfate) was freed of the solvent to give a yellow solid which was crystallized from ethanol (activated charcoal) to furnish IIIg, m.p. 238-240° in 68% yield; pmr (DMSO-*d*₆): δ 6.42 (d, H-8), 7.10 (d, H-5), 7.30-7.90 (m, C₆H₅ and H-1), 7.60 (d, H-4), 8.40 (d, H-9), 11.92 (br., NH), J_{8,9} = 10 Hz; ir (potassium bromide): 3240 (br., NH), 1680 (pyrone C=O), 1610, 1595, 1490, 1460, 1230, 1220, 1150, 800, 760, 580 cm⁻¹.

Anal. Calcd. for C₁₇H₁₁NO₂: C, 78.16; H, 4.21; N, 5.36. Found: C, 78.03; H, 4.18; N, 5.45.

7-Oxo-3*H*,7*H*-pyrano[3,2-*e*]indole-2-carboxylic Acid (IIIh).

The reaction of "coumarin-6-ylhydrazine" and pyruvic acid (Method A) resulted in pyruvic acid coumarin-6-ylhydrazone (VIb) as yellow crystals, m.p. 237° (ethanol; activated charcoal), yield 85.1%; pmr (DMSO-*d*₆): δ 2.06 (s, CH₃), 6.40 (d, H-3), 7.42 (m, H-5, H-7 and H-8), 7.94 (d, H-4), 9.82 (s, NH), J_{3,4} = 10 Hz; ir (potassium bromide): 3300 (br., NH), 1710 (pyrone C=O), 1740 (acid C=O) cm⁻¹.

Anal. Calcd. for C₁₂H₁₀N₂O₄: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.66; H, 4.19; N, 11.15.

The treatment of the hydrazone (VIb) with polyphosphoric acid (Method B) gave a paste which was insoluble in most organic solvents and resisted all the efforts at its purification and hence isolation of IIIh.

3*H*,9*H*-Pyran[3,2-*e*]indol-9-ones.

Ethyl 1,2-Dimethyl-9-oxo-3*H*,9*H*-pyran[3,2-*e*]indole-7-carboxylate (IVb).

The reaction product from "ethyl 6-hydrazinochromone-2-carboxylate" and 2-butanone (Method A) was obtained as a yellow solid which on three crystallizations from ethanol (activated charcoal) gave IVb as yellow crystals, m.p. 253-254° in a yield of 63%; pmr (DMSO-*d*₆): δ 1.35 (t, CH₃), 4.38 (q, CH₂), J = 7.5 Hz, 2.40 (s, CH₃), 6.85 (s, H-8), 7.15 (d, H-5), 7.70 (d, H-4), 11.40 (br., NH), J_{4,5} = 9 Hz; ir (potassium bromide): 3250 (br., NH), 1640 (pyrone C=O), 1740 (ester C=O), 1610, 1590, 1510, 1460, 1230, 1180, 1150, 800 cm⁻¹.

Anal. Calcd. for C₁₈H₁₃NO₄: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.49; H, 5.52; N, 4.85.

Ethyl 9-Oxo-1,2-tetramethylene-3*H*,9*H*-pyran[3,2-*e*]indole-7-carboxylate (IVc).

The yellow solid isolated from the reaction of "ethyl 6-hydrazinochromone-2-carboxylate" and cyclohexanone (Method A) was crystallized from aqueous *N,N*-dimethylformamide to give IVc, m.p. 284-285°, in a yield of 68%; pmr (DMSO-*d*₆): δ 1.35 (t, CH₃), 4.38 (q, CH₂), J = 7.5 Hz, 1.75 (m, -CH₂-), 2.75 (m, -CH₂-), 6.80 (s, H-8), 7.18 (d, H-5), 7.68 (d, H-4), 11.35 (br., NH), J_{4,5} = 9 Hz; ir (potassium bromide): 3250 (br., NH), 1645 (pyrone C=O), 1750 (ester C=O), 2945, 1620, 1590, 1500, 1460, 1220, 1180, 1100, 800 cm⁻¹.

Anal. Calcd. for C₁₈H₁₇NO₄: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.64; H, 5.54; N, 4.38.

Ethyl 2-Methyl-9-oxo-1-phenyl-3*H*,9*H*-pyran[3,2-*e*]indole-7-carboxylate (IVd).

The reaction of "ethyl 6-hydrazinochromone-2-carboxylate" and phenylacetone (Method A) furnished a yellow solid which when crystallized from *N,N*-dimethylformamide gave IVd as yellow crystals, m.p. 268°, yield 61.5%; pmr (DMSO-*d*₆): δ 1.35 (t, CH₃), 4.38 (q, CH₂), J = 7.5 Hz, 2.32 (s, CH₃), 6.70 (s, H-8), 7.20 (m, C₆H₅), 7.25 (d, H-5), 7.80 (d, H-4), 11.82 (br., NH), J_{4,5} = 9 Hz; ir (potassium bromide): 3250 (br., NH), 1640 (pyrone C=O), 1750 (ester C=O), 1610, 1590, 1510, 1460, 1230, 1180, 810, 760, 580 cm⁻¹.

Anal. Calcd. for C₂₁H₁₇NO₄: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.50; H, 4.96; N, 3.81.

2-Methyl-9-oxo-1-phenyl-3*H*,9*H*-pyran[3,2-*e*]indole-7-carboxylic Acid (IVe).

Compound IVd (1.2 g., 0.005 mole) was dissolved in a mixture of 10 ml. of acetic acid and 10 ml. of hydrochloric acid and heated on a water bath for an hour. After cooling, the reaction mixture was inverted over ice and the brown solid which precipitated was filtered and dried giving IVe as yellow crystals on crystallization from aqueous *N,N*-dimethylformamide, m.p. 289-290°, yield 60%; pmr (DMSO-*d*₆): δ 2.32 (s, CH₃), 6.75 (s, H-8), 7.20 (m, C₆H₅), 7.25 (d, H-5), 7.80 (d, H-4), J_{4,5} = 9 Hz; ir (potassium bromide): 3250 (br., NH), 1645 (pyrone C=O), 1730 (acid C=O), 1620, 1585, 1500, 1465, 1235, 1185, 1025, 800, 760 cm⁻¹.

Anal. Calcd. for C₁₉H₁₃NO₄: C, 70.35; H, 4.56; N, 4.23. Found: C, 70.26; H, 4.78; N, 4.27.

Acknowledgments.

We would like to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Financiadora de Estudos e Projetos (FINEP) for financial support.

REFERENCES AND NOTES

- (1) Abstracted in part from the Master's thesis of Maria Lúcia de Brito Morley, Instituto Militar de Engenharia, 1975.
- (2) M. A. Khan and M. L. de B. Morley, *J. Heterocyclic Chem.*, **15**, 1399 (1978).
- (3) F. Troxler, *Helv. Chim. Acta*, **51**, 1214 (1968).
- (4) H. Meyer, *Acta Chem. Scand., Ser. B*, **29**, 133 (1975).
- (5) G. T. Morgan and F. M. G. Micklethwait, *J. Chem. Soc.*, **85**, 1230 (1904).
- (6) G. Barker and G. P. Ellis, *J. Chem. Soc. C*, 2230 (1970).
- (7) S. P. Hiremath and R. S. Hosmane, *Adv. Heterocycl. Chem.*, **15**, 278 (1973).
- (8) R. F. M. White and H. Williams, in "Physical Methods in Heterocyclic Chemistry", Vol. 4, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1971, p. 232.
- (9) G. Barker and G. P. Ellis, *J. Chem. Soc. C*, 2609 (1970).