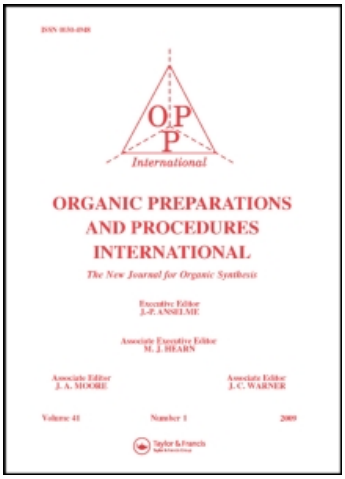

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SYNTHESIS OF 6-SUBSTITUTED-6H-INDENO[1,2-c]ISOQUINOLINE-5,11-DIONES

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SYNTHESIS OF 6-SUBSTITUTED-6H-INDENO[1,2-c]ISOQUINOLINE-5,11-DIONES

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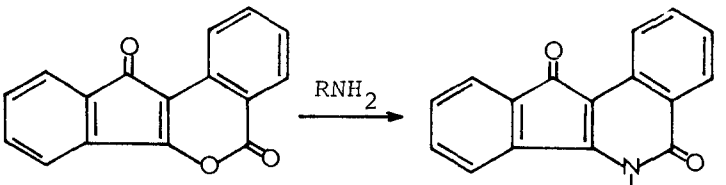
The reported anti-tumor activity in The National Cancer Institute 3P S31 test for 6-methyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (II, R=CH_3) suggested the synthesis of other 6-substituted derivatives of this system for testing. The 6-methyl derivative (II, R=CH_3) was originally prepared by the methylation of the unsubstituted compound (II, R=H) in alkaline solution.[1] The present compounds were prepared by heating 11-ketoindeno[1,2-c]isocoumarin (I) with a primary amine in a mixture of



I II

a) R = C_2H_5 b) R = n-C_3H_7 c) R = $(CH_3)_2CH$ d) R = n-C_4H_9 e) R = CH_2=$CHCH_2$
f) R = $CH_2C{\equiv}CH$ g) R = CH_2CH_2OH h) R = $PhCH_2$ i) R = 2-Furfuryl
j) R = Ph k) R = 3-Pyridyl

ethanol and benzene. The conditions parallel those reported earlier for the condensation of the isocoumarin (I) with o-phenylenediamine.[2]

The structure for these compounds was based on their IR and NMR spectra. The IR spectra showed absorptions at approximately 5.90 and 6.0 μ for the carbonyl and amide groups respectively. The NMR spectra for all the compounds were characterized by two doublets at approximately δ 8.30 and 8.65 for the 1-and 4-hydrogens respectively. These

assignments were based on a comparison of these spectra with that obtained for the isocoumarin (I) which showed the 1-and 4-hydrogens as a multiplet at δ 8.22-8.40. The amide structure in II would cause greater deshielding of the 4-hydrogen and a shift to the δ 8.55 region. Substitution of either a phenyl or 3-pyridyl group in the 6-position produced in addition a doublet at δ 5.46 and 5.52 respectively which is ascribed to the 7-hydrogen. This assignment is based solely on the shielding observed for this hydrogen in models of these compounds (IIj,k).

The condensation proceeded without the formation of any by-products for all of the amines tried with the exception of 3-aminopyridine and t-butylamine. The former gave in addition to the desired product a small amount of biphthalyl,[3] while t-butylamine gave the di-t-butylamine salt of o,o'-benzoindicarboxylic acid instead of the desired isoquinoline; the acid is a hydrolysis product of biphthalyl.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. NMR spectra were obtained with a JEOL FX 90Q spectrophotometer.

General Procedure for 6-Substituted-6H-indeno[1,2-c]isoquinoline-5,11-diones.- The isocoumarin I (0.75g, 0.003 mole) was heated at reflux with 0.004 mole of the amine in a mixture of absolute ethanol (25 ml) and benzene (25 ml) from 8 to 24 hours. The resulting solution upon cooling and concentrating gave the isoquinoline.

6-Ethyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIa) was obtained as a red solid in 96% yield, mp 191-192°, after one recrystallization from ethyl acetate. IR(Nujol): 5.92(CO), 6.04(CON) μ; NMR($DCCl_3$): δ 1.51 (t, 3H, CH_3, J=7 Hz, 4.51 (q, 2H, CH_2, J=7 Hz), 7.29-7.72 (m, 6H, aromatic Hs), 8.25 (d, 1H, 1-H, J=3.4 Hz), 8.58 (d, 1H, 4-H, J=8.1 Hz).

Anal. Calcd for $C_{18}H_{13}NO_2$: C, 78.55; H, 4.73; N, 5.09

Found: C, 78.44; H, 4.78; N, 4.87

6-n-Propyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIb) was obtained as an orange solid in quantitative yield, mp 169.5-170.5° after one recrystallization from ethyl acetate. IR(Nujol): 5.88(CO), 6.11(CON) μ; NMR($CDCl_3$): δ 1.12 (t, 3H, CH_3, J=7.2 Hz), 1.90 (sextet, 2H, CH_2), 4.41 (t, 2H, NCH_2, J=7.9 Hz), 7.23-7.70 (m, 6H, aromatic Hs), 8.24 (d, 1H, 1-H, J=8.8 Hz), 8.57 (d, 1H, 4-H, J=8.5 Hz).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.89; H, 5.19; N, 4.84

Found: C, 78.66; H, 5.03; N, 4.62

6-Isopropyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIc) was obtained as a red solid in 75% yield, mp 234-235° after one recrystallization from ethyl acetate. IR(Nujol): 5.88(CO), 5.99(CON) μ; NMR($CDCl_3$): δ 0.58 (d, 6H, $(CH_3)_2$, J=6.6 Hz), 4.56 (septet, 1H, NCH, J=6.6 Hz), 7.16-7.76 (m, 6H, aromatic Hs), 8.33 (d, 1H, 1-H, J=8.7 Hz), 8.79 (d, 1H, 4-H, J=8.3 Hz).

Anal. Calcd for $C_{19}H_{15}NO_2$: C, 78.89; H, 5.19; N, 4.84

Found: C, 78.99; H, 5.20; N, 4.68

6-n-Butyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IId) was obtained as a red solid in 72% yield, mp 157-158°, after two crystallizations from benzene. IR(Nujol): 5.93(CO), 6.08(CON) μ; NMR($DCCl_3$): δ 0.8-2.0 (m, 7H, $CH_3(CH_2)_2$), 4.36 (t, 2H, NCH_2, J=7.5 Hz), 7.09-7.8 (m, 6H, aromatic Hs), 8.25 (d, 1H, 1-H, J=8 Hz), 8.57 (d, 1H, 4-H, J=8.0 Hz).

Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.20; H, 5.61; N, 4.62

Found: C, 78.71; H, 5.37; N, 4.50

6-Allyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIe) was obtained as a red solid in quantitative yield, mp 165.6-167°, after one crystallization from ethyl acetate. IR(Nujol): 5.89(CO), 5.99(CON) μ; NMR($CDCl_3$):

5.08-5.15 (m, 4H, CH_2,=CH_2), 5.73-6.35 (m, 1H,=CH), 7.20-7.77 (m, 6H, aromatic Hs), 8.27 (d, 1H, 1-H, J=8.0 Hz), 8.61 (d, 1H, 4-H, J=8.7 Hz).

Anal. Calcd for $C_{19}H_{13}NO_2$: C, 79.44; H, 4.53; N, 4.88

Found: C, 79.31; H, 4.52; N, 4.70

6-Propargyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIf) was obtained as an orange solid in 82% yield, mp 235-237°, and needed no further purification. IR(Nujol): 5.86(CO), 6.02(CON) μ; NMR($CDCl_3$): δ 2.43 (t, 1H, ≡CH, J=2.6 Hz), 5.29 (d, 2H, CH_2, J=2.6 Hz), 7.20-7.74 (m, 6H, aromatic Hs), 8.31 (d, 1H, 1-H, J=7.9 Hz), 8.63 (d, 1H, 4-H, J=7.9 Hz).

Anal. Calcd for $C_{19}H_{11}NO_2$: C, 80.00; H, 3.86; N, 4.90

Found: C, 79.57; H, 3.82; N, 4.89

6-β-Hydroxyethyl-6H-indeno[1-2c]isoquinoline-5,11-dione (IIg) was obtained as orange needles in quantitative yield, mp 207-208°, after recrystallization from ethanol. IR(Nujol): 2.80(OH), 5.84(CO), 5.96(CON) μ; NMR($CDCl_3$): δ 2.44 (s, 1H, OH), 4.18 (t, 2H, CH_2O, J=5.7 Hz), 4.73 (t, 2H, CH_2N, J=5.5 Hz), 7.26-7.77 (m, 6H, aromatic Hs), 8.26 (d, 1H, 1-H, J=8.1 Hz), 8.61 (d, 1H, 4-H, J=8.2 Hz).

Anal. Calcd for $C_{18}H_{13}NO_3$: C, 74.23; H, 4.47; N, 4.81

Found: C, 74.23; H, 4.98; N, 4.61

6-Benzyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIh) was obtained as orange needles in 94% yield, mp 202-205°, after one crystallization from benzene. IR(Nujol): 5.92(CO), 6.05(CON) μ; NMR($CDCl_3$): δ 5.78 (s, 2H, CH_2), 7.25-7.83 (m, 11H, aromatic), 8.35 (d, 1H, 1-H, J=8.0 Hz), 8.74 (d, 1H, 4-H, J=7.72 Hz).

Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.90; H, 4.45; N, 4.15

Found: C, 81.54; H, 4.29; N, 3.77

6-[2-Furfuryl]-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIi) was obtained as orange needles in quantitative yield, mp 249-251°, after one

crystallization from ethyl acetate. IR(Nujol): 5.88(CO), 6.03(CON) μ; NMR($CDCl_3$): δ 5.71 (s, 2H, CH_2), 6.36 (broad s, 2H, 2 β-Hs(furan)), 6.90-7.70 (m, 7H, aromatic hydrogen and α-H in furan), 8.32 (d, 1H, 1-H, J=7 Hz), 8.69 (d, 1H, 4-H, J=8.1 Hz).

Anal. Calcd for $C_{21}H_{13}NO_3$: C, 77.06; H, 3.98; N, 4.28

Found: C, 76.63; H, 3.77; N, 3.98

6-Phenyl-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIj) was obtained as a red solid in 74% yield, mp 241-243°, after two crystallizations from benzene. IR(Nujol): 5.91(CO), 6.01(CON) μ; NMR($CDCl_3$): δ 5.46 (d, 1H, 7-H, J=7.3 Hz), 6.80-7.80 (m, 10H, aromatic Hs), 8.30 (d, 1H, 1-H, J=8.0 Hz), 8.65 (d, 1H, 4-H, J=8.0 Hz).

Anal. Calcd for $C_{22}H_{13}NO_2$: C, 81.73; H, 4.02; N, 4.37

Found: C, 81.46; H, 3.95; N, 4.16

6-[3-Pyridyl]-6H-indeno[1,2-c]isoquinoline-5,11-dione (IIk).- The reaction gave an 82% yield of an orange solid containing a white impurity; mp 240-270°. Fractional crystallization or separation by column chromatography on silica using chloroform removed the white solid. The resulting red compound melted at 274-279° after one recrystallization from ethyl acetate. IR(Nujol): 5.89(CO), 5.99(CON) μ; NMR($CDCl_3$): δ 5.52 (d, 1H, 7-H, J=7.0 Hz), 7.00-7.90 (m, 8H, aromatic Hs), 8.32 (d, 1H, 1-H, J=8.8 Hz), 8.70 (d, 2H, 4-H, 6-H (pyridine), J=8.1 Hz), 8.88 (d, 1H, 1-H (pyridine), J=5.52).

Anal. Calcd for $C_{21}H_{21}N_2O_2$: C, 77.78; H, 3.7; N, 8.64

Found: C, 77.36; H, 3.29; N, 8.45

The white solid isolated in a 2.5% yield melted at 344-351° after one recrystallization from ethanol. The melting point and infrared spectrum (1780 cm^{-1}) were in agreement with the values 352-354° and 1780 cm^{-1} for biphthalyl in the literature;[3] m/e 264.

Anal. Calcd for $C_{16}H_8O_4$: C, 72.73; H, 3.03

Found: C, 72.74; H, 2.82

Reaction of Isocoumarin (I) with t-Butylamine.- The isocoumarin (I) (0.75g) was heated with t-butylamine (1 ml) in a mixture of ethanol (25 ml) and benzene (25 ml) for 72 hrs. Removal of the solvent followed by the addition of benzene gave a pale yellow solid (0.53g) melting at 193-195° with gas evolution. Purification by dissolving in ethanol and precipitation with ethyl acetate gave a white solid melting at 196-199°d. The elemental analysis and treatment with alkali indicated that this compound was the di-t-butylamine salt of o,o'-benzoindicarboxylic acid.

Anal. Calcd for $C_{24}H_{34}N_2O_6$: C, 64.57; H, 7.72; N, 6.27

Found: C, 64.77; H, 7.32; N, 6.05

The salt (0.095g) was dissolved in dilute sodium hydroxide and the resulting solution was acidified. The resulting white solid (0.053g) melted at 263-268° with decomposition. IR(Nujol): 3.04(OH), 5.75(CO).

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.00

Found: C, 63.90; H, 3.56

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