11H-Isoindolo[2,1-*a*]indol-11-ones: Novel Rearrangement Products from the Attempted Preparation of 2-(2-Diethylaminomethylphenyl)isatogens

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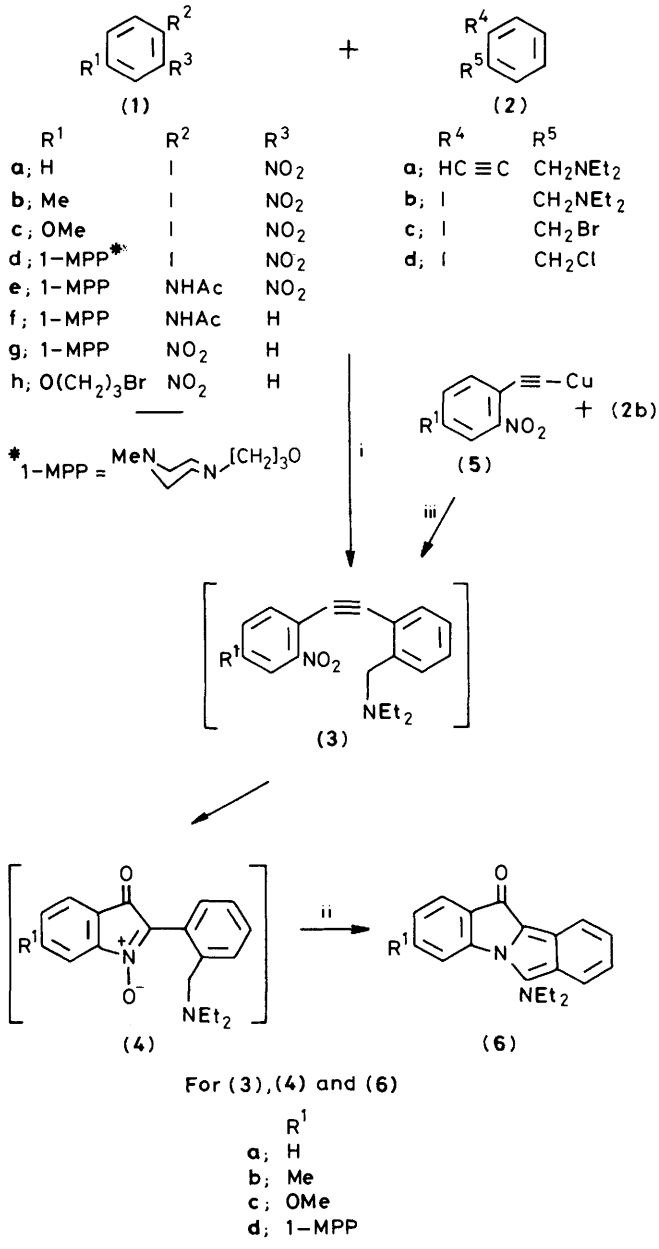
The attempted synthesis of 2-(2-diethylaminomethylphenyl)isatogens, from appropriately substituted phenylacetylenes and aromatic iodo compounds by two different routes gave novel substituted 11*H*-isoindolo[2,1-*a*]indol-11-ones (**6a—d**) as the only identifiable products. Their structures were established from spectroscopic and chemical studies. A mechanism, involving the rearrangement of the expected isatogens to isoindoloindoles, is proposed.

Isatogens (3*H*-indol-3-one 1-oxides) exhibit a wide range of biological activities. They have significant antimicrobial activity against a wide range of bacteria,[1a,b] mycobacteria,[1c] and fungi.[1d] Recently a novel range of isatogens have been patented as plant antifungals.[1e] In mammalian systems isatogens are inhibitors of the synthesis of adenosine triphosphate (ATP) by mitochondrial preparations[1a] and antagonise the inhibitory (relaxant) effects of exogenous ATP on the smooth muscle of the *taenia caeci* of the guinea pig. We have published two structure–activity studies on the biochemistry and pharmacology of isatogens. These indicate that two important molecular features of biologically active isatogens are (i) the presence of a 2-(2-substituted phenyl) or 2-pyridyl ring[2], and/or (ii) a 6-substituent which has electron-releasing properties.[3] Since a major requirement for many *in vitro* biological investigations is the availability of water-soluble compounds we set out to prepare isatogens with a suitable salt-forming aliphatic amino group present in the molecule. Isatogens are known to react with primary and secondary amines *via* nucleophilic addition and subsequent rearrangement.[1a] We therefore attempted the preparation of a series of isatogens (**4a—d**) possessing a tertiary aliphatic amino group. It was thought desirable to introduce this group at the 2-position of the phenyl ring since this position is associated with maximal biological activity. The synthetic pathway (Scheme 1) was adopted because it has proved of the greatest general utility.

The nitro compounds (**1a—c**) were readily available. The propyl ether (**1d**) was prepared from the corresponding nitro anilide (**1e**) by acid hydrolysis and subsequent iodination *via* a Sandmeyer reaction. The nitro anilide was, in turn, obtained by nitration of the anilide (**1f**) which was prepared by the reduction and acetylation of the corresponding nitro compound (**1g**). The latter was synthesized by the reaction of 1-methylpiperazine with the known bromo ether (**1h**).[4]

The acetylene (**2a**) was prepared by King's method[5] from 2-diethylaminomethyliodobenzene (**2b**). In our hands this reaction was often sluggish and gave variable and frequently low yields despite careful purification of the reagents and control of the reaction conditions. The addition of a catalytic amount of copper(I) iodide increased both the speed of the reaction and product yields (50—65%). The iodo compound (**2b**) was prepared from the known bromomethyl[6] (**2c**) or the commercially available chloromethyl (**2d**) compounds.

2-Nitroiodobenzenes couple with arylacetylenes in triethylamine at room temperature using bis(triphenylphosphine)-palladium(II) dichloride and copper(I) iodide as catalysts[7] to give 2-aryl-1-(2-nitrophenyl)acetylenes. These are usually formed in high yields and isolated as brown oils which require further treatment such as heating under reflux with nitrosobenzene in chloroform to cyclise to isatogens.[1a] However, if the



Scheme 1. *Reagents:* i, $[Pd(PPh_3)_2Cl_2]$–CuI–Et_3N; ii, heat, $CHCl_3$; iii, heat, pyridine.

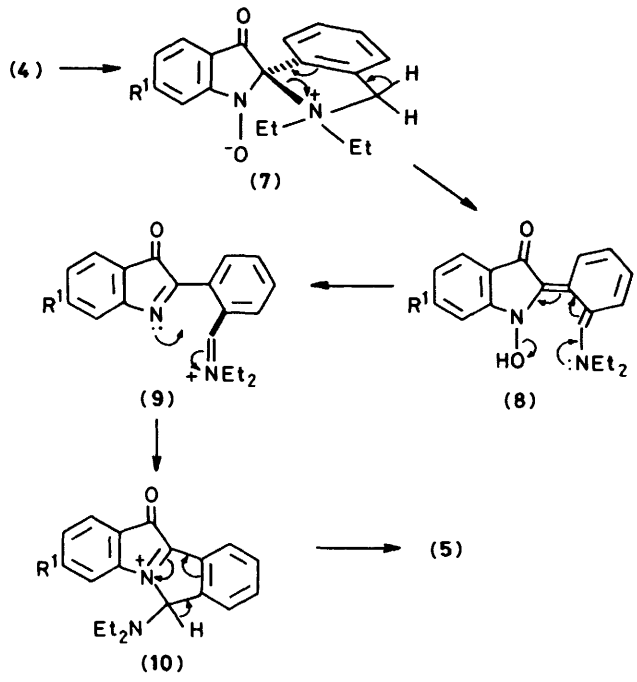
temperature of the reaction or subsequent work-up rises above *ca.* 40 °C cyclisation to the isatogens takes place spontaneously but is rarely complete.[8] The reactions of the iodo compounds (**1a—d**) with the acetylene (**2a**), where the temperature was kept below 40 °C, gave the expected brown oils in good yields. The oils showed a single yellow spot on thin layer chromatography, and i.r. spectroscopy showed the presence of an acetylenic (C≡C) stretching vibration at *ca.* 2 210 cm^{-1}. The absence of any acetylenic (C–H) absorption at 3 300 cm^{-1} and isatogen carbonyl absorption at *ca.* 1 710 cm^{-1} indicated that all the starting acetylene had reacted and that no significant cyclisation to the corresponding isatogen had occurred. However the oils were unstable and quickly darkened on standing or heating. Thin layer chromatography of the darkened oils showed both purple and orange compounds to be present and a carbonyl band was present in the i.r. region at 1 705—1 710 cm^{-1}. 2-(2-Substituted phenyl)isatogens are orange and never intensely coloured since the phenyl and isatogen rings are no longer co-planar.[9] This evidence is consistent with the formation of the diarylacetylenes (**3a—d**) and isatogens (**4a—d**) as transient intermediates in the formation of the purple compound. It was not possible to isolate the pure diarylacetylenes or isatogens.

Chloroform solutions of the oils, without the presence of nitrosobenzene, rapidly turned purple on gently warming and t.l.c. showed the presence of only a single purple compound. Removal of the solvent and flash chromotography gave rather unstable purple oils, which finally crystallised in the reactions involving the iodo compounds (**1b, c**) (see Table 1).

In an alternative single-step syntheis of isatogens[10] we treated the iodo compound (**2b**) with copper(I) 2-nitrophenylacetylide (**5**) in refluxing pyridine. This reaction gave as the sole product, in quantitative yield, a purple compound identical with that obtained from the reaction of (**1a**) with (**2a**). The isolation of these deep purple products was entirely unexpected. Their i.r. spectra showed the absence of acetylenic groups and the presence of an isatogen-like carbonyl group at 1 710 cm^{-1}. Their mass spectra indicated that the molecular weights were 18 mass units (H_2O) less than the expected isatogens. No $M^+ - 17$ peak characteristic of isatogens[1a] was present, instead the sequential loss of mass units of 29, 28, 28 occurred. In compounds (**6a—d**) their n.m.r. spectra indicated only the presence of aromatic protons and two ethyl groups in addition to the signals expected for the methyl, methoxy and 3-(4-methylpiperazinyloxy)propoxy substituents. Isatogens readily lose the *N*-oxide oxygen atom, thereby serving as oxidising agents.[1a] We therefore postulated the *ortho*-quinonoidal isoindolo[2,1-*a*]indole structures (**6a—d**) for these purple compounds. Such molecules would be expected to be deeply coloured and have spectroscopic properties similar to those we had observed. However, direct intramolecular oxidation of the methylene group is unlikely since only methylene groups with adjacent strongly electron-withdrawing groups are known to react with isatogens.[1a] A possible mechanism consistent with the known chemistry of isatogens and indolones[1a] is outlined in Scheme 2.

Intramolecular nucleophilic attack by the tertiary amine at the 2-position of the isatogen ring first gives a zwitterionic spiro compound (**7**). The positive charge on the diethylamino nitrogen atom facilitates loss of one of the benzylic protons and subsequent formation of the 1-hydroxyindolone (**8**). This enamine is able to lose the *N*-hydroxy group by a mesomeric shift which generates the reactive iminium compound (**9**). Intramolecular attack by the weakly basic indolone ring nitrogen atom[11] leads to the isoindoloindolinium structure (**10**) which by loss of a proton and a further mesomeric shift gives the postulated structure (**6a—d**).

The isoindolo[2,1-*a*]indole ring system is known, principally in the 6*H* form.[12a–c] The structure of an unusual rearrangement

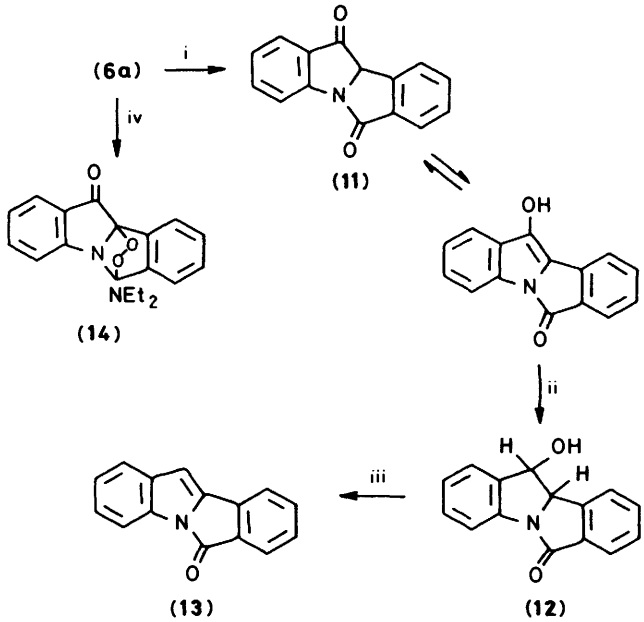


Scheme 2.

product of the alkaloid borreverine has been found by *X*-ray crystallography to be a tetrahydro-6*H*-isoindolo[2,1-*a*]indole derivative.[13] We report here the first examples of 11*H*-isoindolo[2,1-*a*]indol-11-ones.

The postulated structure of (**6b**) has now been confirmed by *X*-ray crystallography; as expected it is a planar molecule with only one of the *N*-ethyl groups out of the plane of the ring. It does not intercalate with deoxyribonucleic acids.[14]

Prior to the *X*-ray study we had carried out a number of chemical degradations of the purple compound (**6a**) which are summarised in Scheme 3. When concentrated hydrochloric acid was added dropwise to a stirred cold methanolic solution of the



Scheme 3. *Reagents:* i, H^+; ii, $NaBH_4$; iii, P_2O_5–benzene; iv, air.

purple compound the solution rapidly turned yellow. After concentration to low volume and cooling pale yellow crystals were deposited. These had i.r. absorption bands at 3 215, 1 720, and 1 680 cm^{-1}. The 220 MHz n.m.r. spectrum indicated the presence of aromatic protons and also showed a singlet at δ 11.96 which underwent deuterium exchange. The mass spectrum indicated loss of the diethylamino group and the presence of an additional oxygen atom. This data is consistent with the hydrolysis of the enamino group followed by aromatisation of the *ortho*-quinonoidal ring to give the tautomeric indolinone (**11**). This compound was reduced with sodium borohydride in methanol or lithium aluminium hydride in tetrahydrofuran to the pale yellow indolinol (**12**).[15] Dehydration of the indolinol required vigorous refluxing with phosphorus pentaoxide in benzene and afforded 6*H*-isoindolo[2,1-*a*]indol-6-one (**13**)[12b,c] which gave a mass spectrum identical with that of a sample kindly provided by Carruthers.[12c] The isoindoloindoles (**6a**—**c**) are fixed tautomers of, the more reactive, *ortho*-quinonoidal form of the isoindole ring system which reacts with atmospheric oxygen to form unstable peroxides (**14**).[16] The purple spots formed by the isoindoloindoles (**6a**—**d**) faded quite quickly when exposed to air and light, consistent with peroxide formation. Extraction of the colourless material from the t.l.c. plate gave a compound with a molecular ion corresponding to the peroxide. However solutions of these compounds in organic solvents only faded slowly when air was passed through them and no pure material could be obtained from these preliminary reactions.

Experimental

M.p.s. are uncorrected. U.v. spectra were determined for ethanolic solutions with a Unicam SP-800 or Beckman DU-8 spectrophotometer. I.r. spectra were recorded with a Perkin Elmer 157G spectrophotometer. ^1H N.m.r. spectra were determined for $CDCl_3$ solutions with tetramethylsilane (TMS) as internal standard using either a Hitachi Perkin-Elmer R24B 60 MHz at Sunderland or a Varian 220 MHz instrument at the Physico-Chemical Measurement Unit (P.C.M.U.), Aldermaston. Mass spectra were determined using a Micromass VG-16F spectrometer (Sunderland) or a VG ZAG-IF spectrometer (P.C.M.U.). Merck 60PF silica gel was used for t.l.c. and preparative t.l.c., Merck 60 Kieselgel (230—400 mesh) was used for flash column chromatography. Solutions were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction of boiling range 40—60 °C.

The nitro compound (**1a**) was commercially available and compounds (**1b**, **c**) were prepared from the commercially available nitroanilines; (**1b**), 70%, m.p. 56—57 °C;[17] (**1c**), 67%, m.p. 61—62 °C.[18]

4-[3-(4-*Methylpiperazin*-1-*yl*)*propoxy*]*nitrobenzene* (**1g**). —A solution of 1-bromo-3-(4-nitrophenoxy)propane (**1h**) (10.0 g, 38.5 mmol) and 1-methylpiperazine (16.0 g, 0.16 mol) in dry tetrahydrofuran was heated under reflux in an atmosphere of nitrogen for 24 h. The solvent was removed under reduced pressure and the residue stirred with dilute hydrochloric acid (40 ml) for 10 min. The acid solution was washed with diethyl ether (2 × 25 ml) and then basified to pH 10—12 with 10% aqueous sodium hydroxide solution. The alkaline solution was extracted with diethyl ether (2 × 25 ml) and the combined extracts washed with water, dried and evaporated under reduced pressure to give the *nitrobenzene* (**1g**) as a yellow oil (7.2 g, 67%). A sample was recrystallised from ethanol, m.p. 42—43 °C (Found: C, 60.1; H, 7.5; N, 15.1. $C_{14}H_{21}N_3O_3$ requires C, 60.2; H, 7.6; N, 15.05%); $\nu_{max.}$ (thin film) 2 980, 2 800, 1 600, 1 520, and 1 340 cm^{-1} (NO_2); δ_H (60 MHz) 2.1 (2 H, m, CH_2), 2.35 (3 H, s, NMe), 2.5 (10 H, br s, CH_2N), 4.2 (2 H, t, *J* 6 Hz, OCH_2), 7.0 (2 H, d, *J* 10 Hz, 3,5-H), and 8.26 (2 H, d, *J* 10 Hz, 2,6-H); M^+, 279 (100%).

The nitro compound (**1g**) (6 g, 0.21 mol) dissolved in methanol (75 ml) was shaken in an atmosphere of hydrogen for 2 h with palladium–charcoal (10%; 100 mg) as a catalyst. After filtration and removal of the solvent 4-[3-(4-methylpiperazin-1-yl)propoxy]aniline was obtained as an unstable solid (5.2 g, 95%), which formed grey prisms from ethanol, m.p. 190—191 °C (decomp.) $\nu_{max.}$(KBr) 3 360 (NH_2), 2 940, 2 800, 1 625 (Ar) 1 510, 1 460, and 1 235 cm^{-1}; M^+, 249. The amine (5 g, 0.02 mol) was immediately acetylated by heating for 3 h with acetic anhydride (2.0 g, 0.02 mol) in dry benzene giving 4′-[3-(4-*methylpiperazin*-1-*yl*)*propoxy*]*acetanilide* (**1f**) (5.2 g, 89%), m.p. 122—123 °C (benzene) (Found: C, 65.85; H, 8.6; N, 14.4. $C_{16}H_{25}N_3O_2$ requires C, 65.9; H, 8.65; N, 14.4%); $\nu_{max.}$ (KBr) 3 290 (NH) 2 940, 2 800, 1 660 (amide I), 1 600 (Ar), 1 550 (amide II), and 1 510 cm^{-1}; δ_H (60 MHz) 1.93 (2 H, m, CH_2), 2.1 (3 H, s, COCMe), 2.3 (3 H, s, NMe) 2.5 (10 H, br s, NCH_2), 4.0 (2 H, t, *J* 8 Hz OCH_2), 6.86 (2 H, d, *J* 10 Hz, 3, 5-H), 6.9 (2 H, d, *J* 10 Hz, 3, 5-H), 7.4 (2 H, d, *J* 10 Hz, 2, 6-H), and 7.8 (1 H, br s, NH, exchangeable); M^+, 291 (42%).

The amide (**1f**) (3.5 g, 0.12 mol) was stirred at room temperature with 25% nitric acid (30 ml) and the reaction was monitored by t.l.c. ($CHCl_3$–NEt_3 19:1 or $CHCl_3$–ethanol 9:1). When no starting material remained (*ca.* 2 h) crushed ice was added to the solution. The solution was basified and the product extracted with diethyl ether (2 × 30 ml). The combined extracts were washed and dried. Removal of the solvent gave a yellow-brown oil, which was hydrolysed by heating with dilute hydrochloric acid (20 ml) at 100 °C. When the reaction was complete (t.l.c.) the reaction mixture was cooled, filtered, basified, and extracted with diethyl ether (2 × 30 ml). Evaporation of the solvent gave 4-[3-(4-*methylpiperazin*-1-*yl*)*propoxy*]-2-*nitroaniline* as a red oil (2.8 g 80%) which slowly solidified and was crystallised from ethanol, m.p. 133—134 °C (Found: C, 57.1; H, 7.45; N, 18.8. $C_{14}H_{22}N_4O_3$ requires C, 57.1; H, 7.5; N, 19.0%); $\nu_{max.}$ (KBr) 3 500 (NH_2) 1 590, 1 530, 1 340 (NO_2), and 1 420 cm^{-1}; δ_H (60 MHz) 2.02 (2 H, m, CH_2), 2.32 (3 H, s, NMe), 2.55 (10 H, br s, NCH_2), 4.25 (2 H, t, *J* 6 Hz, OCH_2) 6.65 (1 H, d, *J* 10 Hz, 6-H), 7.06 (1 H, dd, *J* 2, 10 Hz, 5-H), and 7.45 (1 H, d, *J* 2 Hz, 3-H).

The above amine (2.5 g, 8.5 mmol) under classical Sandmeyer reaction conditions gave 4-[3-(4-*methylpiperazin*-1-*yl*)*propoxy*]-2-*nitroiodobenzene* (**1d**) (2.95 g, 85%), m.p. 98—99 °C (ethanol) (Found: C, 41.6; H, 5.0; N, 10.35; I, 31.15. $C_{14}H_{20}IN_3O_3$ requires C, 41.5; H, 5.0; I, 31.3; N, 10.35%); $\nu_{max.}$ 2 940, 2 500, 1 600 (Ar) 1 530, 1 360 (NO_2) 1 470, and 1 235 cm^{-1}; δ_H (60 MHz) 2.1 (2 H, m, CH_2), 2.31 (3 H, s, NMe) 2.58 (10 H, br s, NCH_2), 4.1 (2 H, t, *J* 6 Hz, OCH_2), 7.95 (1 H, d, *J* 10 Hz, 6-H), 6.9 (1 H, dd, *J* 2.5, 10 Hz 5-H), and 7.11 (1 H, d, *J* 2.5 Hz, 3-H); (Found: M^+, 405.0689. $C_{14}H_{20}IN_3O_3$ requires *M*, 405.0682).

NN-*Diethyl*-o-*iodobenzylamine* (**2b**).—2-Bromomethyliodobenzene (**2c**) was prepared from 2-iodotoluene in 60% yield, m.p. 52—53 °C (lit.,[7] m.p., 52—53 °C). The chloro- or bromomethyl compound (0.16 mol) was heated under reflux with diethylamine (4.35 g, 0.6 mol) in dry tetrahydrofuran in an atmosphere of nitrogen. When t.l.c. showed that all the starting material had disappeared the reaction mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in dilute HCl (2 M; 25 ml) and the solution washed with diethyl ether (2 × 15 ml) and then basified. Extraction with diethyl ether (3 × 30 ml) followed by washing, drying, and evaporation of the solvent gave a pale yellow oil (4.6 g, 95%), b.p. 106—107 °C/0.5 mmHg, which gave a single peak on g.l.c. (OV-17, 225/200 °C R_t 6.5 min); $\nu_{max.}$ (thin film) 2 980, 2 895, 1 570, 1 450, 1 200, and 1 150 cm^{-1}; δ_H (60 MHz) 1.08 (6 H, t, *J* 8

Table 1. Analytical data for isoindolo[2,1-*a*]indoles (**6a**—**d**)

Compound (Formula)	Yield (%)	Solvent	M.p. (°C)	Found(%) (Required) C	H	N
(**6a**) ($C_{19}H_{18}N_2O$)	70		Red oil	M^+	290.1422* (290.1419)	
(**6b**) ($C_{20}H_{20}N_2O$)	65	MeOH bright red crystals	135—136	78.8 (78.85	6.6 6.2	9.2 9.25)
(**6c**) ($C_{20}H_{20}N_2O_2$)	62	EtOH maroon needles	79—80	74.8 (74.95	6.2 6.3	8.7 8.8)
(**6d**) ($C_{27}H_{34}N_4O_2$)	35		purple-red oil	M^+	446.2664* (446.2674)	

* The oils were unstable at room temperature but could be stored for several days at −10 °C under nitrogen. T.l.c. provided proof of homogeneity, the freshly prepared compounds running as single spots in different systems; (**6a**) ethyl acetate–toluene (2:1), R_f 0.38; diethyl ether–light petroleum (b.p. 40—60 °C)(9:1), R_f 0.45 (**6d**) Chloroform–methanol–triethylamine (93:2:5) R_f 0.35; chloroform–methanol (8:2), R_f 0.44.

Table 2. Spectroscopic data for isoindolo[2,1-*a*]indoles (**6a**—**d**)

Compound	$\lambda_{max.}$(EtOH) nm	$\nu_{max.}$ (cm^{-1})	δ_H ($CDCl_3$)	*m/z*
(**6a**)	311, 254	(film) 2 970, 1 710 (CO), 1 650, 1 610	(60 MHz) 1.36 (6 H, t, *J* 8 Hz, NCH_2Me), 3.61 (4 H, q, *J* 8 Hz, NCH_2Me), 6.9—7.98 (8 H, m, ArH).	290 (M^+, 95%, 261 (98), 233 (100), 205 (15).
(**6b**)	378, 326, 292	(disc) 2 980, 1 710 (CO), 1 650 1 620, 1 540, 1 510	(60 MHz) 1.42 (6 H, t, *J* 8 Hz, NCH_2Me), 1.82 (3 H, s, Me), 3.68 (4 H, q, *J* 8 Hz, N-CH_2Me), 6.82—7.90 (7 H, m, ArH).	304 (M^+, 78%), 275 (100), 247 (90), 219 (17).
(**6c**)	322, 303, 275	(disc) 2 980, 2 800, 1 710 (CO), 1 650	(220 MHz) 1.16 (6 H, t, *J* 8 Hz, NCH_2Me), 3.46 (4 H, q, *J* 8 Hz, NCH_2Me), 3.96 (3 H, s, OMe), 6.68—7.68 (7 H, m, ArH).	320 (M^+, 92%), 291 (100), 263 (75), 235 (12).
(**6d**)	290, 256	(film) 2 940 2 800, 1 710 (CO), 1 650, 1 460, 1 350.	(60 MHz) 1.20 (6 H, t, *J* 8 Hz, NCH_2Me), 2.00 (2 H, m, CH_2), 2.30 (3 H, s, N-Me), 2.3 (3 H, s, NMe), 2.52 (10 H, br s, NCH_2), 4.2 (2 H, t, *J* 6 Hz, OCH_2), 6.5—7.9 (7 H, m, ArH).	446 (M^+, 100), 417 (35), 289 (20).

Hz, 2 × $MeCH_2$), 2.62 (4 H, q, *J* 8 Hz, 2 × NCH_2Me), 3.5 (2 H, s, NCH_2Ph) 6.73—7.9 (4 H, m, ArH); (Found, M^+, 289.0394. $C_{11}H_{16}IN$ requires *M*, 289.0392).

N,N-*Diethyl*-o-*ethynylbenzylamine* (**2a**).—The preparation of this compound following King's[6] method was monitored by g.l.c. (OV 17 225/200 °C, R_t 4.2 min). However despite very careful control of the reagents [lithium acetylide–ethylenediamine complex, Aldrich Chemical Co., freshly fused anhydrous zinc chloride and tetrakis-(triphenylphosphine)palladium] and the conditions and time of the reaction, the yields of the product were extremely variable and usually low to very low. The addition of copper(I) iodide (10 mg) along with the tetrakis-(triphenylphosphine)palladium (1.15 g) led to consistently shorter reaction times and higher yields, *ca.* 70%. Attempts to distil the product led to decomposition even under reduced pressure; $\nu_{max.}$ 3 259 (acetylenic CH), 2 800, 2 100 (C≡C), and 1 580 cm^{-1}; δ_H, 1.01 (6 H, t, *J* 8 Hz, 2 × NCH_2Me), 2.65 (4 H, q, *J* 8 Hz, 2 × NCH_2 Me), 2.8 (1 H, s, C≡CH), 3.65 (2 H, s, NCH_2), 6.68—7.7 (4 H, m, ArH); (Found, M^+, 187.1353. $C_{13}H_{17}N$ requires *M*, 187.1357).

Synthesis of Isoindolo[2,1-a]*indoles* (**6a**—**d**).—*Method 1.* The iodobenzenes (**1a**—**1d**) (5 mmol) and the benzylamine (**2a**) (4.5 mmol) were dissolved in triethylamine and bis(triphenylphosphine)palladium(II) dichloride (15 mg) and copper(I) iodide (20 mg) were added. The reaction mixture was stirred overnight in an atmosphere of nitrogen. The solvent was removed below 40 °C to give a brown oil which was dissolved in chloroform. The chloroform solution was washed and dried and the solvent was removed <40 °C. The resulting brown oils (**3a**), 92%, (**3b**), 90%, (**3c**), 90%, and (**3d**), 85% gave single spots on t.l.c. and showed an acetylenic stretching vibration at *ca.* 2 210 cm^{-1}. With time or when heated above 40 °C the oil darkened and showed a major deep purple spot and a faint orange spot on t.l.c. The acetylenic i.r. band was absent and a carbonyl band appeared at 1 710 cm^{-1}.

The unstable oils, without further purification, were dissolved in chloroform (50 ml) and the solution heated under reflux for 1 h. T.l.c. indicated the presence of a single purple compound. The solvent was removed and the product purified by flash chromatography, (**6a**—**c**) with chloroform–methanol (98:2 as eluant) (**6d**) with chloroform–methanol–triethylamine (94:4:4) as eluant (Table 1).

Method 2. A solution of copper(I) 2-nitrophenylacetylide (**5**)[10] (1.02 g, 4.88 mmol) and the benzylamine (**2b**) (1.38 g, 4.77 mmol) in dry pyridine (60 ml) was heated under reflux in an atmosphere of nitrogen for 1 h. The solution rapidly turned purple and t.l.c. showed the presence of only a purple compound. After cooling, the solution was filtered (Celite) and the solvent was removed under reduced pressure and the crude product purified by the above flash chromatographic procedures to give (**6a**) (1.6 g, 100%). (Table 1)

11-*Hydroxy*-6H-*isoindolo*[2,1-a]*indol*-11-*one* (**11**).—Concentrated hydrochloric acid (0.75 ml) was added very slowly to a stirred solution of the isoindoloindole (**6a**) (1.4 g, 4.8 mmol) in methanol (30 ml) under nitrogen. When the addition was complete the solution was stirred overnight at room tempera-

ture. The yellow solution was concentrated at room temperature and on cooling deposited yellow crystals of the product (0.78 g, 81%), m.p. 279—280 °C (glacial acetic acid) (Found: C, 76.50; H, 3.8; N, 5.5. $C_{15}H_9NO_2$ requires C, 76.57; H, 3.85; N, 5.95%); $\nu_{max.}$ 3 215 (OH), 1 720 (CO) 1 680, (CO), 1 600 (Ar), 1 460 and 1 380 cm^{-1}; δ_H (220 MHz) 7.22—8.32 (8 H, m, ArH) 11.96 (1 H, s, exchangeable OH); Found: M^+, 235.0630 $C_{15}H_9NO_2$ requires M, 235.0631); m/z 235, (100%) and 207 ($M^+ - 28$).

10b,11-*Dihydro*-11-*hydroxy*-6H-*isoindolo*[2,1-a]*indol*-6-*one* (**12**).—The isoindoloindole (**11**) (200 mg, 0.85 mmol) was dissolved in tetrahydrofuran (10 ml) and methanol (3 ml). Sodium borohydride (350 mg, 0.9 mmol) was added in portions. After the addition was complete the suspension was stirred overnight under nitrogen and monitored by t.l.c. (chloroform–methanol 19:1). The solvent was removed under reduced pressure and cold water added slowly. The product was extracted with diethyl ether (3 × 15 ml) and the combined ether extracts washed and dried. The crude product was passed through a small flash column with chloroform–light petroleum (4:1) as eluant; (120 mg, 60%), light yellow needles (ethanol), m.p. 113—114 °C (Found: C, 75.85; H, 4.6; N, 5.9. $C_{15}H_{11}NO_2$ requires C, 75.9; H, 4.65; N, 5.9%); $\nu_{max.}$ 3 340 (OH), 1 710 (amide CO) 1 615, 1 465—1 480d and 1 220 cm^{-1}; δ_H (220 MHz) 6.24—7.68 (8 H, m, ArH), 5.35 (2 H, q, J 11 Hz, 10b-H, 11-H), and 5.16 (1 H, s, D_2O exchangeable OH); m/z, 237 (M^+) and 209 ($M^+ - 29$, 100%).

The indolinol (**12**) (25 mg, 0.1 mmol) was dissolved in dry benzene and phosphorus pentaoxide (17 mg, 0.12 mmol) was added in portions. After complete addition the solution was heated under reflux for 3 h (monitored by t.l.c., ethyl acetate–toluene) when the starting material had disappeared; the solvent was then evaporated under reduced pressure. Crushed ice was added and after 15—20 min the product was extracted with diethyl ether (2 × 10 ml). T.l.c. indicated that the product was a complex mixture and showed a light yellow spot corresponding to an authentic sample of the indoloindole (**19**). The product was separated by preparative t.l.c. and a yellow band was isolated; m.p. 151—152 °C (from ethanol) (lit.,[12c] 150—151 °C); $\nu_{max.}$ 1 720 (>N–C=O) 1 610 (CO), 1 450, and 1 370 cm^{-1}; (Found, M^+ 219.0682. $C_{15}H_9NO$ requires 219.0685), m/z 219, (100%) and 190 ($M^+ - 29$).

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