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THE SYNTHESES OF POLYCYCLIC MOLECULES CONTAINING β-CARBOLINE UNITS BY THE PHOTOCHEMICALLY INDUCED RING CLOSURE OF ENAMIDES

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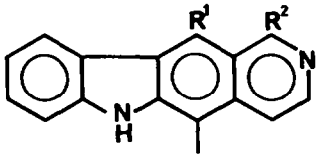
Abstract The syntheses of 5-methyl-5,8,9,14-tetrahydroindolo(2,3-c)indolo (2,3-g)quinolizin-6-one and 15-methyl-7,8,13,15-tetrahydroindolo(3,2-c) indolo(2,3-g)quinolizin-5-one from the photochemical cyclisation of 1-methylene-2-(N¹methylindole-2'-carbonyl)1,2,3,4-tetrahydro-β-carboline and 1-methylene-2-(N¹methylindole-3'carbonyl)1,2,3,4,-tetrahydro-β-carboline are described. Attempts to prepare indolo(2,3-c)isoquinolines from the photochemical cyclisation of 2-benzamidoindoles were unsuccessful.

Some arc-shaped planar polycyclic molecules such as the pyrido(4,3-b)-carbazole alkaloids ellipticine (1, R^1=Me; R^2=H) and olivacine (1, R^1=H; R^2=Me) intercalate into DNA, and exhibit activity against experimental tumours[1]. Indolopyridonaphthyridone alkaloids represented by nauclefine (2)[2] show little or no anticancer action, but many related molecules bearing a β-carboline nucleus do have biological activity, particularly in the central nervous system.

In an attempt to investigate these two types of biological effects we set out to synthesize polycyclic structures of the types (3) and (4) which incorporate features of both the pyrido (4,3-b)carbazole and the β-carboline alkaloids. In this we have been partly successful, thus the target molecules (3, R=Me) and (4, R=Me) have been prepared by reacting harmalan (5) with 1-methylindolyl-2-carbonyl chloride and 1-methylindolyl-3-carbonyl chloride in the presence of triethylamine and irradition of the respective enamides (6) and (7) with ultraviolet light.



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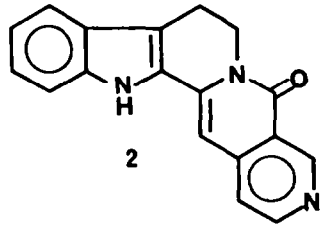

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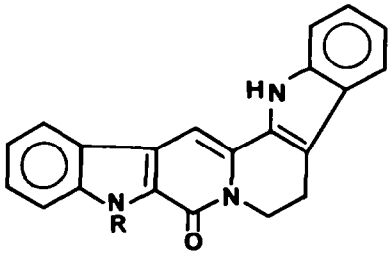

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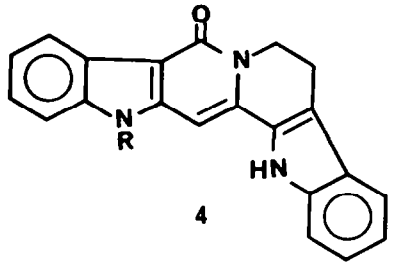

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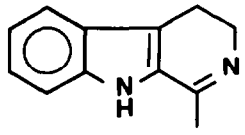
The initial reaction products are the dihydro compounds (8) and (9), but these readily dehydrogenate in the presence of air and silica to afford the appropriate hexacycles (3, R=Me) and (4, R=Me). Attempts to synthesize the des-methyl derivatives (3, R=H) and (4, R=H) along similar lines failed, principally because indolyl-2-carbonyl chloride and indoyl-3-carbonyl chloride tend to react with themselves in the presence of base rather than with harmalan.

Indolo(2,3-c)isoquinolines (11) exhibit anticancer properties[3] and their shape again suggests that they owe their activity to intercalation with DNA. The synthesis of these compounds is achieved via the cyclisation of 3-arylindolyl-2-isocyanates (10) which are themselves prepared by a Curtius rearrangement from the corresponding 3-arylindoyl-2-carbonylazides.

It occurred to us that a simpler route would be the photochemical cyclisation of amides (12) and to test this proposal 2-aminoindole[4] was reacted with benzoylchloride in pyridine to give a mixture of 2-benzamidoindole (12, R^1=R^2=H) and 2-benzamido-1-benzoylindole (12, R^1=H; R^2=COPh).

Irradiation of the monobenzoyl derivative caused only slow decomposition of the substrate and no cyclised products were isolated. The low field position (δ 10.55) of the indolic NH proton signal in the starting material suggests that this compound prefers to exist in the Z-form (13) in which hydrogen bonding predisposes the molecular geometry against ring formation. Such a problem is less likely in the case of the dibenzoyl derivative (12, R^1=H; R^2=COPh), but in this case photochemical irradiation served only to cleave off the N-benzoyl substituent.



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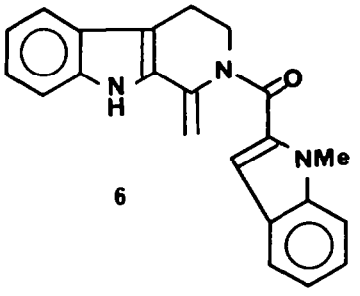

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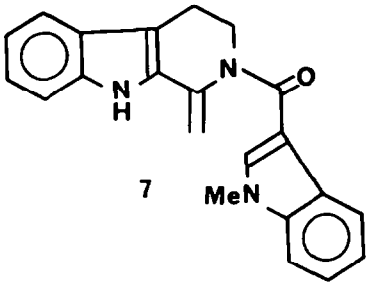

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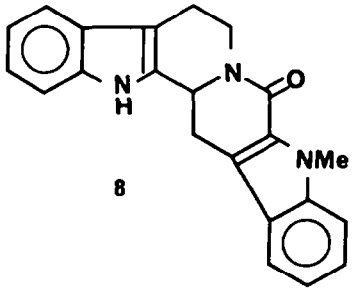

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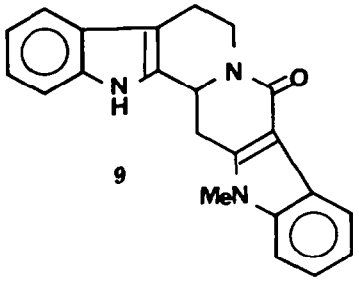

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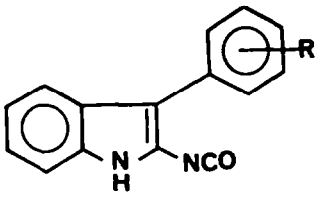

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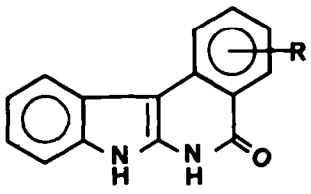

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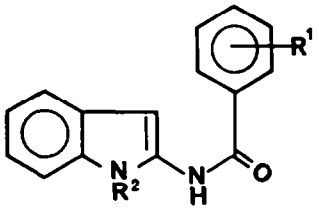

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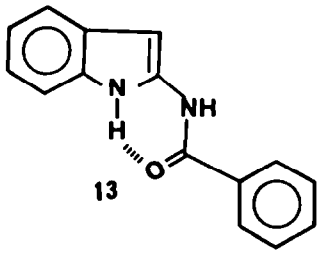

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EXPERIMENTAL

Unless stated otherwise ultraviolet spectra data refer to solutions in 98% ethanol and infra-red spectra were recorded as Nujol mulls. ^{1}H nmr data were obtained at 100 MHz, and photochemical reactions were carried out using 125 W or 400 W Hanovia lamps in a quartz immersion well.

1-Methylene-2-(N'-methylindole-2'- carbonyl)-1,2,3,4-tetrahydro-β-carboline (6) 1-Methylindole-2-carboxylic acid (0.193 g, 1.1 mmol) was suspended in dry dichloromethane (8 cm^3) and two drops of dry dimethylformamide was added. Oxalyl chloride (0.1 cm^3, 0.146 g, 1.1 mmol) was introduced and the mixture was stirred at room temperature. The acid gradually passed into solution; this was accompanied by the steady evolution of gas. When bubbling had finally ceased, the resulting acid chloride solution was added carefully, over 20 min., to an ice cold solution of harmalan (0.2 g, 1.09 mmol) in dry dichloromethane (3 cm^3) containing triethylamine (0.25 cm^3). The reaction mixture was stirred for 75 min; thin layer chromatographic analysis (25% ethylacetate in petrol/silica) after this time showed that all starting material had been consumed. Removal of the solvent under reduced pressure was followed by flash chromatography using the eluent system described above. Co-evaporation of the product fractions gave the title compound as a pale-yellow gum. Yield = 244 mg (65%). ^{1}H nmr δ($CHCl_3$)* 8.75 (1H, bs, indole N-H), 7.1 - 7.7 (8H, m, aromatics), 6.65 (1H, s, H-3'), 4.65 and 5.05 (2 x 1H, 2 x d, (J= 2 Hz) exomethylene protons), 4.25(2H, t, (J=5 Hz, CH_2-N), 3.75 (3H, s, N'-CH_3), 2.95 (2H, t, (J= 5 Hz), -CH_2-); m/z (E.I.) (%): 341.1531 (M+, 78), 326(32), 313(42), 185(48), 184(33), 175(24), 174(35), 173(54), 158(100), 130(28), 89(70). $C_{22}H_{19}N_3O$ requires: 341.1528; λ_{max} (nm): 217, 305.

5-Methyl-5,8,9,14-tetrahydroindolo(2,3-c) indolo(2,3-g)quinolizin-6-one (3, R=Me) The enamide (6) (234 mg) was dissolved in analar grade benzene (500 cm^3) and the pale-yellow solution flushed with dry deoxygenated nitrogen for 35 min before irradiating with a 125 V medium pressure u.v. lamp. After 15 h, during which the progress of the reaction was monitored by t.l.c. and u.v. spectroscopy, the solution was evaporated down in the presence of silica. The resulting powder was applied to the top of a column of silica and subjected to flash chromatography with 45% ethylacetate in petrol as the eluent. The product fractions were combined, filtered and evaporated under reduced

pressure to yield the title compound as a yellow solid (140 mg, 59.6%): m.p. > 300°. ^{1}H n.m.r. δ[d^6-DMSO/(CD$_3$)$_2$CO]: 11.35 (1H, bs, N-H), 7.75 [1H, d, (J= 7Hz), H-1 or H-10], 6.7-7.5 (8H, m, aromatics), 4.25 [2H, t, (J=6 Hz), CH-N], 4.00 (3H, s, N-CH$_3$), 2.80 [2H, t, (J= 6Hz), -CH$_2$-]. ν_{max} (cm^{-1}): 3400, 1645, 1590. λ_{max} (nm): 228, 296, 315, 330 (sh) 348, 390. m/z 339.1373 (M+) $C_{22}H_{17}N_3O$ requires m/z 339.1371 [Found: C, 77.75; H, 5.0; N, 12.2 $C_{22}H_{17}N_3O$ requires: C, 77.85; H, 5.05; N, 12.4%].

15-Methyl-7,8,13,15-tetrahydroindolo[3,2-c] indolo[2,3-g]quinolizin-5-one (4,, R=Me) 1-Methylindole-3-carboxylic acid (1.0 g, 5.7 mmol) was suspended in dry dichloromethane (25 cm^3) and oxalylchloride (0.5 cm^3, 5.73 mmol) was added. The suspension was stirred for 75 min. until the acid had gone into solution and no further gas evolution was observed. The acid solution was then added carefully over 15 min. to a cooled solution of harmalan (1.0 g, 5.4 mmol) in dry triethyl amine (3 cm^3) and dry dichloromethane (25 cm^3) After stirring in an ice bath for 90 min. the solution was evaporated to give a yellow-brown foam. No attempt was made to isolate the enamide (7) at this stage, as t.l.c. analysis (silica or alumina/ethylacetate) showed it to be unstable. Instead, the foam was dissolved in analar grade benzene and the mixture was filtered to remove triethyl-amine hydrochloride before being flushed thoroughly with dry deoxygenated nitrogen (1 h). The red solution was then subjected to irradiation with a 400 W medium pressure u.v. lamp for a total of 26 h. T.l.c. and u.v. analysis established that no further changes were taking place after this time and so the solution was evaporated down to give a red gum. Chromotography on alumina using ethylacetate as the eluent afforded the title compound as a canary-yellow solid. Yield = 280 mg, 15.2%: m.p./ > 300°. ^{1}H n.m.r. run at 140°C δ (d^6-DMSO): 7.0-7.8 (9H, m, aromatics), 4.55 [2H, t, (J = 7 Hz), -CH$_2$-N], 3.92 (3H, s, N-CH$_3$), 3.16 [2H, t, (J= 7 Hz), -CH$_2$-]; ν_{max}(cm^{-1}): 3200, 1650, 1590, 1580, 1570, 750; λ_{max} (nm): 208, 242, 262, 281(sh), 295(sh), 253(sh), 374, 400. m/z (E.I) (%): 339, 1376 (M+, 100), 338(47), [Found: C, 77.8; H, 5.1; N, 12.4 $C_{22}H_{17}N_3O$ requires: C, 77.85; H, 5.05; N, 12.4%.

2-Benzamidoindole - A solution of 2-amino-indole (0.57 g, 4.3 mmol) in dry deoxygenated pyridine (15 cm^3) was cooled on an ice bath and 4-dimethylaminopyridine (52.5 mg, 0.43 mmol) was added. Benzoylchloride (0.5 cm^3, 4.3 mmol) was then introduced dropwise with care. When addition was complete, the solution was stirred at room temperature for 1 hr before partitioning between ethylacetate (100 cm^3) and 2 M hydrochloric acid (100 cm^3). The organic phase was washed again with hydrochloric acid (100 cm^3) and then saturated brine (100 cm^3) before drying and evaporating down in the presence of silica. The silica-absorbed crude product was applied to the top of a 6 cm diameter silica column and subjected to flash chromatography using 15% ethylacetate in petrol as the eluent. The first 60 cm^3 of eluent were run to waste and thereafter 20 cm^3 fractions were taken. Fractions 21-40 were combined, filtered and evaporated to yield a pale-green crystalline substance which was identified as 1-benzoyl-2-benzamidoindole (200mg, 14%. Fractions 61-81 were similarly combined and evaporated to yield the title compound 2-benzamido-indole (360 mg, 35%); m.p. 187-189°. ^{1}H n.m.r. δ(CDCl$_3$-d^6-DMSO): 10.55 (2H, bs, N-H and N'-H), 8.01 (2H, m, ortho-benzoyl protons) 7.0-7.6 (7H, m, indole H-4, 5, 6 and 7, and benzoyl H-3', 4' and 5'), 6.28 [1H, dd, (J = 3Hz), (J = 1 Hz), H-3];* m/z (E.I.) (%): 236 (M+, 100), 105 (68), 77 (45), 51 (41); ν_{max} (cm^{-1}): 3430, 3320, 1650, 1540; Found: C, 76.33; H, 5.10; H, 11.63. $C_{15}H_{12}N_2O$ requires: C, 76.25; H, 5.12; N, 11.86%].

Data for 1-benzoyl-2-benzamidoindole - M.p. 141.5-144°. ^{1}H n.m.r. δ(CDCl$_3$): 11.30 (1H, s, N'-H), 8.00, 7.65-7.8 and 7.36-7.6 (11H, 3 x m, phenyl ring protons and indole H-4), 7.44 (1H, s, H-3), 7.16 and 6.87 [2 x 1H, 2 x t, (J = 8 Hz), H-5 and H-6], 6.33 [1H, d, (J = 8 Hz), H-7]; m/z (E.I.) (%): 340 (M+, 11) 105 (100), 77 (44); ν_{max}(cm^{-1}): 3290, 1680, 1670, 745, 730, 710, 700; [Found: C, 77.27; H, 4.82; N, 8.04. $C_{22}H_{16}N_2O_2$ requires: C, 77.63; H, 4.74; N, 8.23%]: λ_{max}(nm): 209, 234, 310.

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