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REARRANGEMENT IN THE REACTION OF OXINDOLE WITH *o*-NITROBENZYL CHLORIDE[1]

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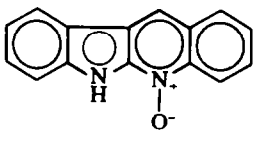
Abstract—The alkylation of oxindole with *o*-nitrobenzyl chloride produces three products, **5a**, **6**, and **10**. The N-hydroxyindoloquinolone **5a** probably arises by rearrangement of an initial alkylation product as shown in Scheme 1. The indoloquinolone **6** is formed by base-catalyzed elimination of *o*-nitrobenzaldehyde from the dialkylation product **10** and also apparently by a thermal process most simply considered as a 1,5-sigmatropic rearrangement of **10** → **12**.

The reaction of oxindole with *o*-nitrobenzyl chloride in ethanolic sodium ethoxide at room temperature was reported[2] to yield, after sublimation of the crude product, an "extremely stable compound," $C_{15}H_{10}N_2O$, which did not melt below 350°. This compound was proved not to be **1** or **2** by comparison with authentic specimens.[2] Structure **3** was also excluded because 4-methyloxindole and *o*-nitrobenzyl chloride gave a product similar to that from oxindole. The structure, **4**, finally proposed to account for the properties of this compound has the defect of requiring the anti-thermodynamic coexistence of the basic amide ion and the acidic imonium ion within the same molecule. There is yet another structure **6** for the product which has not been considered, and whose formation under the reaction conditions could be readily explained by the sequence in Scheme 1. Such a sequence, as far as compound **5**, has precedent in the general synthesis of N-hydroxyindoles from *o*-nitroaromatic compounds.[3] On re-examining this reaction, we find that it is more complex than originally thought.[2]



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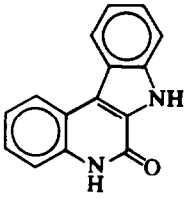

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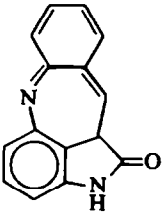

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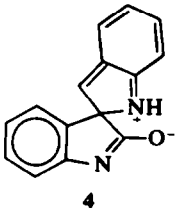

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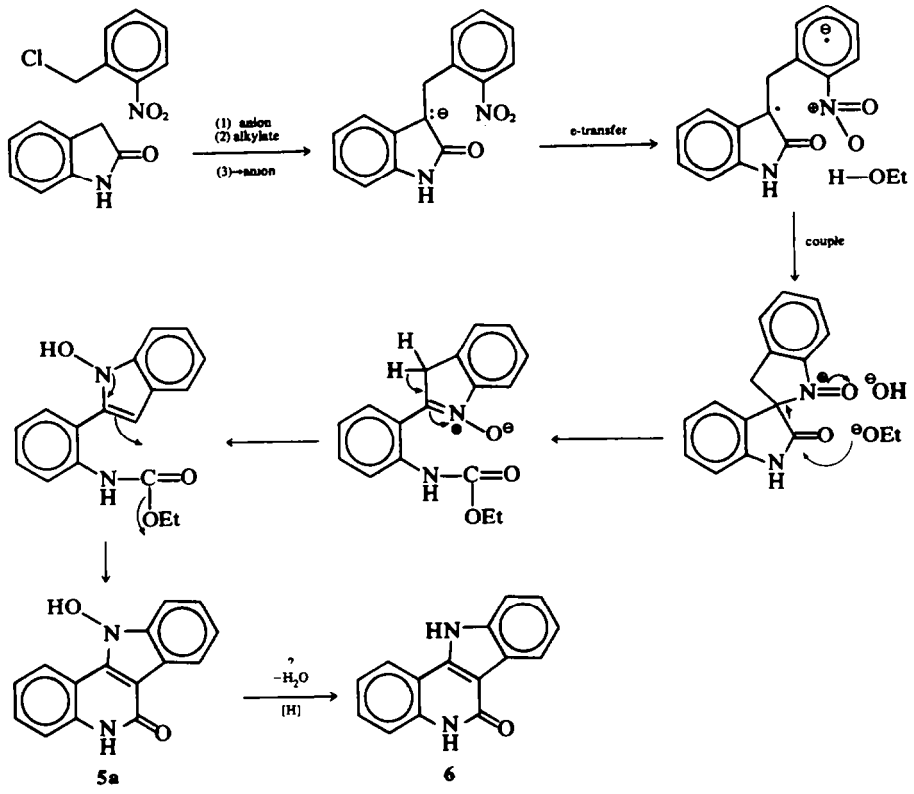
The major product of the reaction before sublimation is a compound, m.p. 248–250°, isolated by crystallisation. In the mother liquors was a small amount of the reported compound $C_{15}H_{10}N_2O$, but an amount too small to account for the yield after sublimation of the crude product. The 250° compound was found by analysis, mass spectroscopy, and integration of the ^{1}HMR spectrum to have the molecular formula $C_{22}H_{15}N_3O_4$ and, therefore, to be a product of dialkylation. A notable feature of the ^{1}HMR spectrum of this product was the two proton singlet at $\delta^{DMSO\text{-}d6}$ 5·79. When this 250° compound was sublimed at 200–250°, it was cleanly cleaved into *o*-nitrobenzaldehyde and the previously reported "extremely stable compound," $C_{15}H_{10}N_2O$.

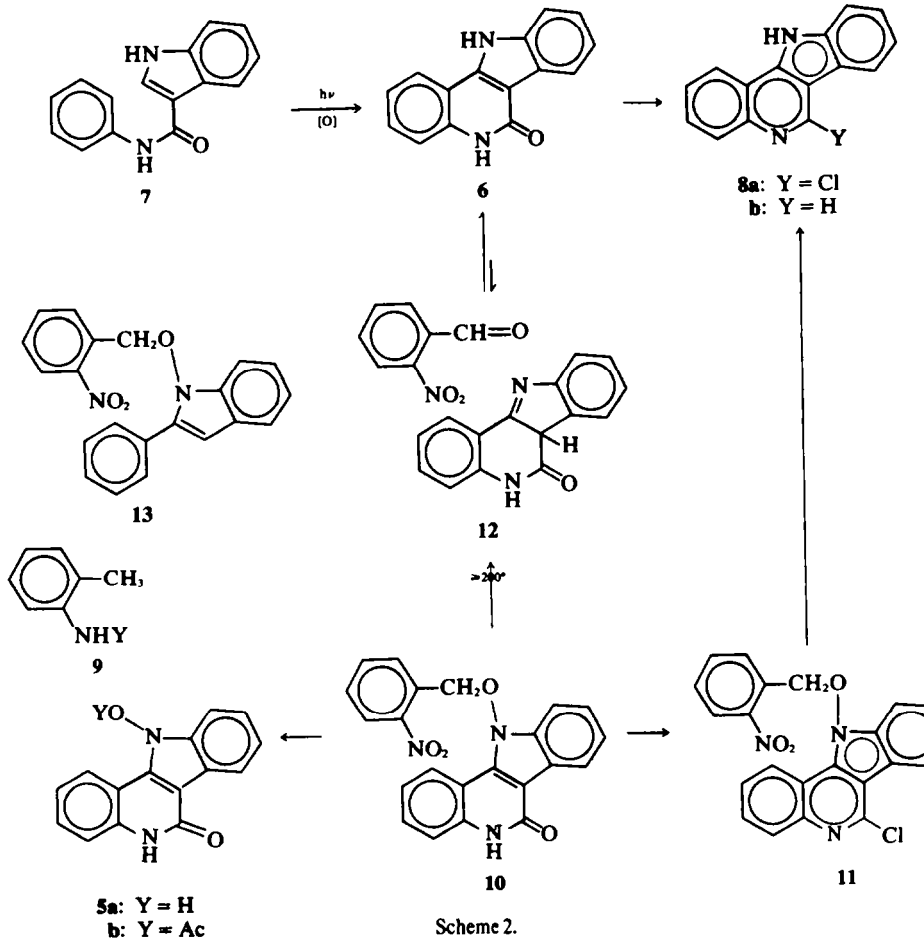
Evidence for the quinolone moiety in this latter compound was provided by its conversion with PCl_5–$POCl_3$ into a chloroindoloquinoline **8a** which was then reduced by P–HI to the known indoloquinoline **8b**. The final proof that the $C_{15}H_{10}N_2O$ compound was indeed the indoloquinolone **6** was provided by direct comparison with a sample synthesized by irradiation of indole-3-carboxanilide **7**.[4]

The *o*-nitrobenzyloxy group lost from the 250° compound at 200–250° must have been attached to one of the two nitrogen atoms to account for the single NH peak in the ^{1}HMR spectrum. From its probable origin by alkylation of the nitrone or hydroxylamine oxygen at some stage in Scheme 1, the *o*-nitrobenzyloxy group should have been attached to the indole nitrogen of **6**. In confirmation, the quinolone NH–C=O group was shown to be present in the 250° compound **10** by reaction with PCl_5–$POCl_3$ which produced the chloroquinoline derivative **11** lacking a carbonyl group.

Hydrogenation of **10** in methanol-THF with Pd/C produced *o*-toluidine **9a** and the N-hydroxyindoloquinolone **5a**, both of which were characterized as their acetyl derivatives **9b** and **5b**. The 250° compound **10** was reconstituted by alkylation of the sodium salt of **5a** with *o*-nitrobenzyl chloride. Since **10** may well have been formed in this way via **5a** in the reaction with oxindole, a further examination of the crude oxindole reaction product for the presence of **5a** was made. TLC comparison and integration of the ^{1}HMR spectrum of acetylated crude product revealed it to consist of ~50% **10**, ~40% **5b**, and ~10% **6**, and therefore **5a** was present in the crude product in an amount comparable to that of **10**. The very low field ^{1}HMR absorption at $\delta^{DMSO\text{-}d6}$ 5·79 due to the benzylic methylene in **10** is associated with an extra deshielding effect of the indoloquinolone portion since the methylene absorption for the model compound 1-*o*-nitrobenzyloxy-2-phenylindole,



Scheme 1.



Scheme 2.

13, at δ^{DMSO-d_6} 5·20, although itself at quite low field, is upfield from that of **10**.

The clean thermal cleavage of **10** is presumably a suprafacial (7 electrons) 1,5-sigmatropic hydrogen shift to **12** followed by imine ⇌ enamine tautomerism. Although this cleavage occurs readily in the range of 200–250°, the indoloquinolone **6** present in the crude alkylation product before sublimation has not been formed in this way since **10** is stable in ethanol solution at reflux. Instead **6** apparently arises by base-catalyzed decomposition of **10**. Reaction of **10** in ethanolic sodium ethoxide at room temperature produced **6** and *o*-nitrobenzaldehyde. The elimination is therefore initiated by benzylic proton removal with the indoloquinolone anion as leaving group and not by removal of the NH proton of **10** with loss of *o*-nitrobenzyloxide.* In agreement, the N-hydroxy-indoloquinolone **5a** was inert to ethanolic ethoxide at room temperature.† Therefore, Scheme 1 is valid up to structure **5a**, but **5a** is actually transformed into **6** *via* the *o*-nitrobenzyloxy derivative **10** by both a base-catalyzed reaction and thermal reaction.*

The compound $C_{16}H_{12}N_2O$ obtained[2] from 4-methyloxindole and *o*-nitrobenzyl chloride presumably has the structure **6** with a methyl group at the position predicted by Scheme 1.

EXPERIMENTAL

The following instruments were used. IR, Beckman IR-5A and IR-20A (for spectra in KBr, absorption above 1850 cm^{-1} is not reported); UV, Cary 14; ^{1}HMR, Varian T-60 and HA-100 (s = singlet, d = doublet, m = multiplet, and b = broad); MS, Varian M-66.

M.ps (corrected) were determined either on a Reichert-Kofler microscope hot stage or else in a sealed capillary. In the series of compounds below, m.ps appreciably above 200° were not easily reproduced due to decomposition and/or sublimation, spectra and TLC were much better criteria of purity and identity. Silica gel GF_{254} (Merck, Germany) was used for thin and thick layer chromatography.

Reaction of oxindole with o-nitrobenzyl chloride. The literature procedure[2] was followed except for the work up. To a solution of Na (450 mg, 19 mg a) in abs EtOH (10 ml) was added a soln of oxindole (Aldrich, 1·33 g, 10 mmol) in abs EtOH (15 ml). This pale yellow soln was added at room temp with stirring to a soln of *o*-nitrobenzyl chloride (Aldrich, 1·60 g, 9·35 mmol) in abs EtOH (15 ml) over a period of 0·5 hr. The soln turned brown and within ~12 hr solid had precipitated. After 2 days the reaction mixture was acidified with 10% aq HCl, and the EtOH was removed at reduced pressure. The residual yellow-brown solid was triturated thoroughly with water, filtered and dried. The brown solid was triturated with 30 ml of 95% EtOH, filtered and dried to give a tan solid (707 mg). TLC in $CHCl_3$:MeOH (95:5) gave three spots R_f 0·63 **10**, 0·50 **6**, and 0·45 **5a**. Acetylation of a portion of the tan solid at room temperature, and integration of its ^{1}HMR signals at δ 2·84 ($CH_3C{=}O$ of **5b**) and 5·79 (OCH_2Ar of **10**) in conjunction with TLC intensities gave the proportion of **10**:**5a**:**6** in the crude product as ~50:40:10. Reversal of the order of addition (*o*-nitrobenzyl chloride added to oxindole + EtO^-) only changed the ratio of products **10**:**5a**:**6** to ~40:40:20.

(a) *Dialkylation product* **10**. A portion (40 mg) of the tan solid was recrystallised three times from pyridine after which the colourless crystals were washed with pet ether (b.p. 30–60°) and dried to yield off-white needles of **10** (22 mg), m.p. 248–250° with rapid heating, IR (KBr) ν_{max} 1660 (amide C=O), 1530 and 1340 cm^{-1} (NO_2); UV(MeOH) λ_{max} 225 (35,900), 250 (47,400), 295 (10,000), 312 (11,500), 325 (14,300), and 342 nm (15,800); ^{1}HMR (DMSO-d_6) δ 5·79 (2H, s, —O—CH_2—Ar), 6·91–8·42 (12H, m, ArH), and 11·89 ppm (1H, b, exchanges with D_2O, NH); MS *m/e* 385 (M^+) (Found C, 68·37, 68·63; H, 3·90, 4·01; N, 11·00, 10·74. $C_{22}H_{15}N_3O_4$ (385·4) requires: C, 68·57; H, 3·92; N, 10·90%). If the heat was raised slowly on the microscope hot stage, the compound often did not melt but instead was slowly transformed into the indoloquinolone **6**.

(b) *Isolation of indoloquinolone* **6**. The crude alkylation product (50 mg) was sublimed first at 210° (0·05 torr) for 2 hr to remove more volatile material, and then the residual solid was further sublimed at 240° (0·05 torr) to give reddish brown crude **6** (25 mg). The crude product was partially decolourized by soln in boiling MeOH, treatment with carbon, and evaporation of the filtrate. The residual solid was then recrystallised twice from HOAc, rinsed with ether, and dried to give colourless granules of 5,11-dihydro-6H-indolo-[3,2-c]-6-quinolone **6** (12 mg) which partially sublimed and decomposed but did not melt below 350° either on the hot stage or in a sealed capillary; IR (KBr) ν_{max} 1640 and 1615 cm^{-1} (amide C=O); UV (MeOH) λ_{max} 225 (42,900), 248 (50,700), 294 (10,700); 306 (11,700); 322 (17,500), and 336 nm (22,400); ^{1}HMR (DMSO-d_6) δ 7·10–7·70 (6H, m, ArH), 8·18 (1H, m, ArH), 8·26 (1H, m, ArH), 11·41 (1H, bs exchanges with D_2O, NH); and 12·55 ppm (1H, bs exchanges with D_2O, NH); MS *m/e* 234 (M^+) (Found: C, 76·69; H, 4·30; N, 12·22. $C_{15}H_{10}N_2O$ (234·3) requires: C, 76·91; H, 4·30; N, 11·96%). The compound was identical in all respects with an authentic specimen prepared as described below.

Indole-3-carboxanilide **7**. A soln of indole-3-carboxylic acid (96 mg),[5] aniline (72 mg) and dicyclohexylcarbodiimide (138 mg) in CH_2Cl_2 (70 ml) was refluxed for 2 hr. After concentration to 25 ml, the precipitated dicyclohexylurea was filtered off, the filtrate was evaporated, and the residue chromatographed on two thick layer plates (20 g SiO_2 per 20 × 20 cm plate) with benzene:ether (1:1). The UV-quenching band at R_f 0·32 gave a colourless solid (73 mg). One recrystallisation from MeOH-pet. ether (b.p. 60–80°) and one from $CHCl_3$-pet ether (b.p. 60–80°) gave colourless plates of **7** (57 mg), m.p. 173–175° (reported,[6] 178·5–179·5°), IR (KBr) ν_{max} 1617 cm^{-1} (conjugated amide C=O); UV (MeOH) λ_{max} 235 (14,100), 258 (17,700), and 290 nm (17,700); MS *m/e* 236 (M^+).

Photocyclodehydrogenation of **7** *to* **6**. The procedure of Altmann and Winterfeldt[4] was modified.[7] A soln of anilide **7** (57 mg) in benzene (4 ml) and abs EtOH (1 ml) was irradiated in a Pyrex tube with a 450 W medium pressure Hannovia lamp for 3 days. The soln was concentrated to leave a pale yellow solid which was recrystallised from HOAc. After ether washing and drying, the spectroscopic properties (IR, UV, ^{1}HMR, MS) of the off-white crystals of indoloquinolone **6** (15 mg) were identical with those of the compound from alkylation of oxindole and with those reported.[4]

Chloroindoloquinoline **8a**. A soln of indoloquinolone **6** (20 mg), PCl_5 (40 mg), and $POCl_3$ (1 ml) was refluxed for 5 hr. The $POCl_3$ was then distilled at reduced pressure, and ice was added to the residue which was basified with 10% aq NaOH. Extraction with ether and then with $CHCl_3$ gave a colourless solid (16 mg). Recrystallisation from MeOH-pet ether (b.p. 60–80°) gave colourless needles of **8a** (12 mg), m.p. 280° with sublimation; IR (KBr) no amide C=O; UV (MeOH) λ_{max} 235 (33,500), 272 (49,800), 290 (18,300), and 325 nm (5080); MS *m/e* 252 (M^+). (Found: C, 71·24; H, 3·52. $C_{15}H_9N_2Cl$ (252·6) requires: C, 71·31; H, 3·59%).

Indole[3,2-c]*quinoline* **8b**. A mixture of chloroindoloquinoline **8a** (20 mg), red P (40 mg), 48% HI (1 ml), and HOAc (1 ml) was heated in a sealed glass tube at 155° for 11 hr. The reaction mixture was basified with 10% aq. NaOH and the precipitated colourless solid centrifuged. The solid was washed successively by decantation with water, aq. $Na_2S_2O_3$, water, and then dried. Two recrystallisations from MeOH-pet. ether (b.p. 60–80°) gave colourless granules of **8b** (6 mg). The analytical sample was sublimed at 220° (0·05 torr), m.p. ~310° with sublimation and decomposition in a sealed capillary (lit.[8] m.p. above 320° with sublimation), on the hot stage **8b** sublimes at 270°; IR (KBr) no

*It is not excluded that the thermal reaction of **10** above 200° is also just a base-catalyzed elimination with another molecule of **10** or even the *o*-nitro group of the same molecule acting as the base.

†When **5a** was sublimed at 260° (0·05 torr) it was partly converted into another compound, slightly less polar on TLC than **5a**, which was not investigated further.

amide C=O; UV (MeOH) λ_{max} 235 (33,900), 273 (48,400), and 290 nm (16,900); MS *m/e* 218 (M^+). (Found: C, 82·38; H, 4·73. $C_{15}H_{10}N_2$ (218·3) requires: C, 82·55; H, 4·62%).

Pyrolysis of pure dialkylation product **10**. A sample of **10** (95 mg, 0·25 mmol) was pyrolyzed in a glass tube at 260° (0·1 torr). Within 20 min *o*-nitrobenzaldehyde (20 mg, 53%), m.p. 39–41° was collected, identical (IR, ^{1}HMR, TLC, m.p. and mmp) with an authentic specimen. Continuation of the pyrolysis for another 13 hr gave a yellowish brown sublimate of **6** (57 mg, 97%). Treatment of a boiling MeOH soln of the sublimate with carbon gave, after filtration and evaporation, an off-white solid which was recrystallised twice from HOAc. The colourless solid (48 mg) was identical in all respects with authentic **6**.

When a mixture of **10** (2 mg) in abs EtOH (1 ml) was stirrred and refluxed for 45 min, evaporation of solvent left an off-white solid whose TLC showed a single spot corresponding to **10** and no spot corresponding to the more polar **6**.

Hydrogenation of **10**. A mixture of 5% Pd/C (40 mg) and MeOH (8 ml) was saturated with H_2 for 15 min before addition of a soln of **10** (60 mg) in dry THF (40 ml). The hydrogenation at room temp and atmospheric pressure was stopped after 45 min, and the catalyst removed by filtration. Concentration of the filtrate at 35° (45 torr) left a colourless oily solid which was triturated with ether. The ether soluble material was chromatographed on a thick layer plate (10 g SiO_2 per 10 × 20 cm plate) in $CHCl_3$: MeOH (95 : 5). The UV-quenching band at R_f 0·90 yielded almost colourless *o*-toluidine (16 mg). Acetylation with Ac_2O–Py gave crystalline N-acetyl-*o*-toluidine, m.p. 105–107° (lit.[9] 111°), identical with an authentic specimen.

The ether insoluble material from the hydrogenation was recrystallised twice from MeOH to give colourless granules of N-hydroxyindoloquinolone **5a** (21 mg), m.p. 318° (dec); IR (KBr) ν_{max} 1635 and 1605 cm^{-1} (amide C=O); UV (MeOH) λ_{max} 230 (40,800), 252 (55,000), 256 (inf 53,340), 282 (13,300), 294 (10,800), 310 (13,300), 324 (18,300), and 338 nm (22,500); ^{1}HMR (DMSO-d_6) δ 7·15–7·75 (6H, m, ArH), 8·26 (1H, d (J = 4), ArH), 8·68 (1H, d (J = 4·5), ArH), 11·45 (1H, bs, exchanges with D_2O, OH or NH), and 12·11 ppm (1H, b, exchanges with D_2O, NH or OH). Ms *m/e* 250 (M^+) (Found: C, 71·90; H, 4·14. $C_{15}H_{10}N_2O_2$ (250·3) requires: C, 71·99; H, 4·03%).

A soln of **5a** (25 mg), Py (2 ml), and Ac_2O (1 ml) was allowed to react at room temp for 3 hr and was then evaporated to dryness at room temp (0·1 torr). The residual solid was recrystallised four times from $CHCl_3$–MeOH to give colourless needles of N-acetoxyindoloquinolone **5b** (11 mg), m.p. 227–235° (dec); IR (KBr) ν_{max} 1790 (N—O—C=O)† and 1640 cm^{-1} (amide C=O); UV (MeOH) λ_{max} 225 (38,900), 248 (55,100), 295 (12,100), 310 (12,100), 325 (16,200), and 340 mm (17,000); ^{1}HMR (DMSO-d_6) δ 2·84 (3H, s, CH_3C=O), 7·30–8·00 (6H, m, ArH), 8·37 (1H, d (J = 4), ArH), 8·61 (1H, d (J = 3), ArH), and 11·75 ppm (1H, bs, exchanges with D_2O, NH); Ms *m/e* 292 (M^+) (Found: C, 69·87; H, 4·15; O, 16·51. $C_{17}H_{12}N_2O_3$ (292·3) requires: C, 69·86; H, 4·14; O, 16·42%).

Chloroquinoline **11** *from* **10**. A soln of **10** (25 mg), PCl_5 (50 mg), and $POCl_3$ (1·5 ml) was refluxed for 5 hr. After distillation of the $POCl_3$ at reduced pressure, ice was added to the residue which was then basified with 10% aq NaOH. Extraction with $CHCl_3$ gave, after washing with water, drying and evaporation, a colourless solid (20 mg). Two recrystallisations from $CHCl_3$-pet ether (b.p. 60–80°) gave colourless needles of **11** (17 mg), m.p. 200–202°; IR (Nujol) NH and amide C=O absent; UV (MeOH) λ_{max} 238 (40,300), 270 (59,500), 290 (21,100), and 325 nm (7670); ^{1}HMR (DMSO-d_6) δ 5·87 (2H, s, OCH_2Ar), 7·50–9·00 ppm (12H, m, ArH) (Found: C, 65·47; H, 3·44; O, 10·45. $C_{22}H_{14}N_3O_3Cl$ (403·7) requires: C, 65·51; H, 3·47; O, 11·91%).

Treatment of **11** with P and HI at 155° followed by sublimation of the crude product gave **8b** from reductive cleavage of both the chlorine and the *o*-nitrobenzyloxy groups.

Reconstitution of **10** *from* **5a**. A mixture of **5a** (8 mg), Py (0·5 ml), and NaH (2 mg) was stirred at room temp for 1 hr. To this Na salt of **5a** was added a soln of *o*-nitrobenzyl chloride (5 mg) in benzene (0·3 ml). After 13 hr at room temp with stirring, the liquids were removed by evaporation at room temp (0·1 torr) to leave a brownish solid. TLC ($CHCl_3$: MeOH, 95 : 5) showed spots corresponding to **10** (major) and **6** (minor). Two recrystallisations from Py gave **10** as an off-white solid (5 mg) identical in all respects with the product of reaction of oxindole and *o*-nitrobenzyl chloride.

Reaction of **10** *with* NaOEt–EtOH. To a soln of Na (28 mg) in abs EtOH (2·3 ml) was added **10** (23 mg), and the mixture stirred at room temp for 24 hr (all solid in soln after 12 hr). EtOH was evaporated in a stream of nitrogen. Extraction with ether gave, after washing with water and drying, an oily solid whose TLC ($CHCl_3$: MeOH, 95 : 5) showed the absence of **10** and the presence of two new spots corresponding to **6** and *o*-nitrobenzaldehyde. Two recrystallisations from MeOH gave colourless granules of the indoloquinolone **6** (7 mg) identical with the authentic sample. The mother liquors were chromatographed on a thick plate (10 g SiO_2 per 10 × 20 cm plate) in benzene : ether (90 : 10). The UV-quenching band at R_f 0·74 yielded long needles of *o*-nitrobenzaldehyde (2·5 mg), m.p. 39–41°, identical with an authentic specimen.

When the N-hydroxy compound **5a** (5 mg) was stirred with a soln of Na (5 mg) in abs EtOH (0·8 ml) at room temp for 14 hr, **5a** (4·5 mg) was recovered unchanged after acidification and extraction.

1-*o*-*Nitrobenzyloxy*-2-*phenylindole* **13**. The literature procedure[11] was followed. A mixture of 1-hydroxy-2-phenylindole[12] (25 mg), Py (1 ml), and NaH (10 mg) was stirred at room temp for 1 hr. A soln of *o*-nitrobenzyl chloride (25 mg) in benzene (0·5 ml) was added, and the reaction mixture was stirred at room temp for 14 hr. The solvents were removed at room temp and reduced pressure. The residue was partitioned between ether and water, and the material in the ether was chromatographed on a thick plate (10 g SiO_2 per 10 × 20 cm plate) in benzene : pet ether (b.p. 60–80°), 75 : 25. The yellow band at R_f 0·76 yielded a pale yellow oil (17 mg). Two recrystallisations from ether-pet ether (b.p. 30–60°) gave yellow needles of **13** (13 mg), m.p. 99–101°; ^{1}HMR (DMSO-d_6) δ 5·20 (2H, s, OCH_2Ar), 6·60 (1H, s, indole 3-H), and 6·80–8·10 ppm (14H, m, ArH); MS *m/e* 344 (M^+).

N-Acetoxy-2-*phenylindole*. N-Hydroxy-2-phenylindole (25 mg) was acetylated at room temp with Ac_2O (0·3 ml) and Py (0·5 ml) for 3 hr. Work up and chromatography on a thick SiO_2 plate developed in benzene yielded an oil (16 mg) which was recrystallised twice from ether-pet ether (b.p. 30–60°) to give off-white crystals, m.p. 76–78° (lit.[13] m.p. 79–80°); IR (KBr) ν_{max} 1800 cm^{-1} (N—O—C=O);† ^{1}HMR ($CDCl_3$) δ 2·13 ppm (3H, s, CH_3C=O); MS *m/e* 251 (M^+).

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†Such a high frequency is apparently characteristic of the acetate carbonyl stretching frequency in the group N—O—Ac.[10]

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